EXPERT REVIEWS

Improving triage and management of patients with skin cancer: challenges and considerations for the future

Expert Rev. Anticancer Ther. 12(5), 609–621 (2012)

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Skin cancer is the most common malignancy in humans, thus representing a major health concern. Because of the increasing attention to skin cancer prevention, there has been a growing workload for dermatology clinics, with patients referred from primary care requiring assessment of suspicious skin tumors. This places a strain on limited specialist resources and can create a paradoxical situation wherein an early diagnosis becomes increasingly difficult for those patients who actually do suffer from skin cancer. The aim of these recommendations is to propose an updated, rational system of triage, involving improved accuracy of diagnosis and more timely management of skin cancer by both general practitioners and dermatologists.

Keywords: clinical diagnosis • dermatoscopy • dermoscopy • management • melanoma • skin cancer

Skin malignancy is a major global health concern owing to its high incidence in white populations, coupled with its potential morbidity and even mortality. The incidence of skin cancer generally increases for fairer-skinned populations living in sunnier geographies. In Italy, it is estimated that at least 15 people per 100,000 develop melanoma each year, whereas the incidence in Queensland, Australia, reaches over 50 per 100,000 [1]. Nonmelanoma skin cancer (NMSC) is a group of lesions other than melanoma that is mainly comprised of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). The incidence of BCC is at least ten-times greater than that of melanoma, and is the most frequent cancer affecting humans. Both the incidence and biologic aggressiveness of SCC stand in an intermediate position between melanoma and BCC [2].

Melanoma screening is particularly important and challenging for two reasons: the first is related to the potential mortality of melanoma if early diagnosis and removal is not carried out, and the second concerns the high incidence of its benign counterpart, the melanocytic nevus. In some instances nevi can mimic melanoma in clinical appearance and are present as multiple lesions in a vast number of individuals in the population. Consequently, even targeted screening for melanoma involves a great number of patients. In contrast to melanoma, BCC and SCC are much more common tumors but are not as biologically aggressive, and deaths from nonmelanoma skin cancer (particularly from metastatic SCC) are rare. Cure is effected in the vast majority of cases of NMSC by excision, but if not diagnosed and treated early, such NMSC can be locally destructive and lead to significant morbidity.

Recently, with an increasing emphasis on skin cancer prevention, there has been a progressive inundation of specialist dermatology clinics with patients referred from primary care, requiring assessment of possible skin malignancy. Waiting list times for dermatology clinics have typically increased, and dermatologists are faced with the task of assessing numerous referred benign lesions (including seborrheic keratoses, hemangiomas and benign nevi) in lower-risk patients in order to detect a relatively small number of malignancies [3]. This places a strain on limited specialist resources and can create a paradoxical and counterproductive situation wherein an early diagnosis becomes increasingly difficult for those patients who actually do harbor a skin cancer.

 10.1586/ERA.12.38 ISSN 1473-7140

The general purpose of these recommendations is to propose an updated, rational system of triage, involving improved accuracy of diagnosis and more timely management of skin cancers by both general practitioners and dermatologists. The guidelines are based on personal observations and recent advances in the management of benign and malignant skin tumors. The specific objectives of these recommendations are as follows:

- To improve the early diagnosis of melanoma and nonmelanoma skin cancer by primary care physicians and dermatologists;
- To reduce the number of unnecessary referrals of benign skin lesions to specialist dermatology clinics;
- To reduce the number of unnecessary removals of benign skin lesions in primary and secondary care;
- To reduce waiting list times for dermatologic and surgical clinics;
- To improve the overall quality of care for skin cancer management in both primary and secondary care.

Although the conditions of dermatological medical care may differ between areas and countries, these objectives will generally require the implementation of a multidisciplinary and multilevel approach to managing patients with skin malignancy. Three levels of management will be described below.

First level: the general practitioner

The first and essential actor in the triage of skin cancer is the general practitioner (GP). A European study found that approximately one in 200 patients who presented to a GP harbored an undiagnosed melanoma and one in 30 had an NMSC [4]. A smaller study based in a primary care skin cancer clinic setting in Western Australia found that in 349 consecutive patient consultations involving 244 patients, approximately one in 80 self-referred patients screened (by total body skin examination and dermoscopy) had undiagnosed melanoma and one in six had NMSC (one in eight had BCC, and one in 22 had invasive SCC or SCC *in situ*) [5]. The significant prevalence of skin cancer in white-skinned populations and the more frequent contact between individuals and their GP compared with dermatologists suggests that GPs are essential in the screening for melanoma and NMSC.

As a first step towards a more rational system of triage, an educational program should be implemented, with instruction of GPs carried out by dermatologists. This program should provide simple and effective diagnostic tools for the screening of melanoma and NMSC and establish a preferential management pathway for at-risk patients who are identified by the GP. During these training sessions and courses, GPs should be instructed in the most recent guidelines for the clinical and dermoscopic diagnosis of melanoma and NMSC, the epidemiology and risk factors for skin cancer, and especially be trained in a simplified and practical screening method for identifying suspicious lesions.

This screening method would involve instruction in the clinical (naked-eye) and dermoscopic recognition of melanoma and NMSC. Training should include an introduction to the dermoscopic features of BCC and SCC, as well as instruction in a basic dermoscopic screening algorithm for the diagnosis of melanoma, such as the three-point checklist [4,6]. The three-point checklist involves assessing a lesion for evidence of the three dermoscopic features of asymmetry of pigmentation pattern, atypical pigment network and/or blue-white structures. A score of 2 or 3 out of 3 has been shown to be 96% sensitive for the detection of malignancy (melanoma and pigmented BCC) by trained nonexperts, and has superior sensitivity compared with naked-eye assessment alone.

A useful technique to assist in the screening of patients is for the GP to stratify the patient according to age. A simplified approach for the triage of patients at risk for skin cancer is based on the following main indications that should prompt GP referral for specialist care:

- Patients younger than 15 years who have a pigmented lesion larger than 2 cm, or a rapidly growing papule or nodule;
- Patients aged between 15 and 50 years with multiple nevi on the arms (>20), an 'ABCD'-positive lesion or an 'EFG'-positive lesion ('ABCD' and 'EFG' are explained later in the text);
- Patients older than 50 years who have chronic actinic damage on visible skin.

In children (i.e., individuals under the age of 15 years) melanoma and NMSC are extremely rare events. Nevi in childhood are banal in the vast majority of cases, but there are two important exceptions: pigmented lesions that are greater than 2 cm in diameter, and pigmented or nonpigmented papular/nodular lesions that are fast-growing (Figure 1). In these cases, dermatological referral is necessary for two reasons. The first relates to the possibility of developing a melanoma within a congenital nevus. Most of the reported cases of childhood melanoma involve congenital nevi, with the potential risk of malignant transformation being proportional to nevus size. In particular, nevi that are less than 2 cm in diameter have an almost zero risk, whereas nevi larger than 2 cm develop melanoma in approximately one in 200 cases during the lifetime of the patient [7–9]. There is, however, some controversy about the risk for progression of congenital melanocytic nevi to melanoma. This is mainly due to an overestimation of atypical melanocytic proliferations developing in congenital nevi that are finally classified as melanoma. Of note, only 2% of patients with a giant congenital nevus develop melanoma, most of them before the age of 5 years. Therefore, prophylactic surgical treatment should be individualized depending on clinical suspicion of melanoma and cosmetic and functional results.

The second indication for seeking dermatological opinion in patients under 15 years of age is for rapidly growing papules or nodules. Pigmented or nonpigmented (reddish) palpable lesions in children that present with rapid, progressive growth for more than a month can be problematic because of the nature of the differential histopathological diagnoses. Besides rare *de novo* childhood melanoma, the differential diagnoses mainly include the more commonly encountered Spitz nevus or an atypical Spitz tumor. The latter is characterized by an intermediate biologic behavior between benign

nevi and melanoma. The management of these fast-growing lesions is prompt referral for assessment and possible removal [10–12].

In adult patients between 15 and 50 years of age, three particular subsets of patients should be referred for dermatologist care. The first group are patients affected by multiple (>50) common nevi on their whole cutaneous surface. These patients are at a higher risk for the development of melanoma compared with those harboring few nevi [13]. Rather than performing a full nevus count, a partial nevus count can be done as a quick and convenient alternative [14]. The latter involves the arms only and is considered high if there are 20 or more nevi present (Figure 2). A partial nevus count will generally be directly proportional to the total nevus count, but it should be used with caution as there are occasional patients who have a high number of nevi on their trunk but very few nevi on their arms. On a practical note, nevi less than 2 mm in diameter should be excluded from the above mentioned nevus count calculations. Patients with high nevus counts are best managed by a dermatologist experienced in dermoscopic diagnosis and digital mole mapping (i.e., short- and long-term monitoring; see below).

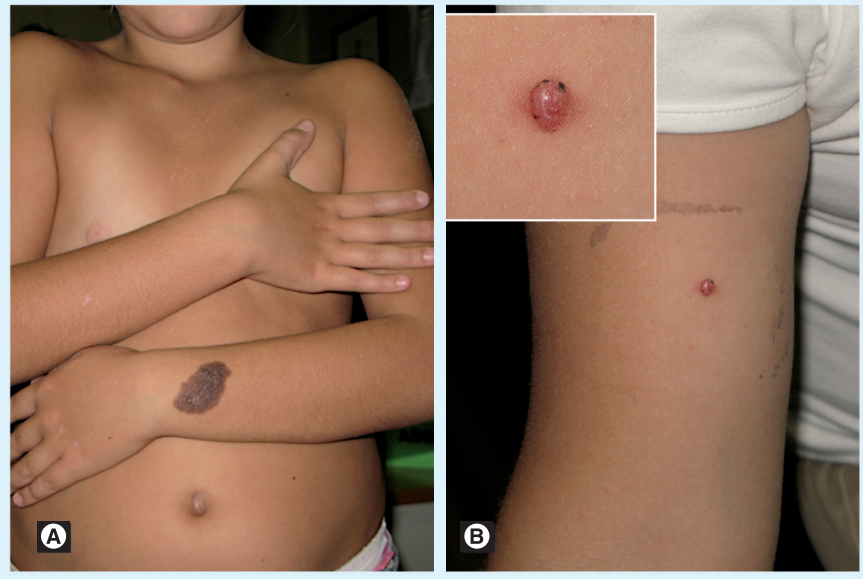

Figure 1. Children nevi requiring careful evaluation. (A) A pigmented lesion (congenital nevus) greater than 2 cm in diameter, and **(B)** a nonpigmented, fast-growing papular/nodular lesion (Spitz nevus). Under the age of 15 years these cases represent the two main indications for dermatological referral. The first relates to the possibility of developing a melanoma within a congenital nevus. The second concerns the problematic nature of the differential histopathological diagnosis of such fast-growing lesions.

The second subset are patients having one or more atypical lesions (Figure 2). The latter present clinically as flat pigmented lesions that are asymmetric in outline and large (>6 mm) in diameter. These lesions are often judged as positive by the ABCD rule of melanoma recognition, where 'A' represents asymmetry, 'B' represents notched or irregular borders (reminiscent of the geographic outline of an island), 'C' represents color variegation (including shades of brown, blue-gray, pink and red) and 'D' represents a diameter greater than 6 mm. Some authors have added 'E' to the ABCD algorithm, representing evolution and referring to a change in shape, size and/or color of the lesion over time [15,16]. Atypical melanocytic lesions should also be observed by dermoscopy to determine whether they possess any positive dermoscopic features of melanoma, which would prompt urgent referral to a dermatologist (see below).

A small subgroup of patients will have a large number of common nevi (>50) and numerous atypical nevi, in conjunction with a family history of cutaneous melanoma. This group of individuals with so-called 'dysplastic nevus syndrome' or FAMM (familial atypical mole and melanoma) syndrome are at very high risk for development of cutaneous melanoma and require dermatologist referral.

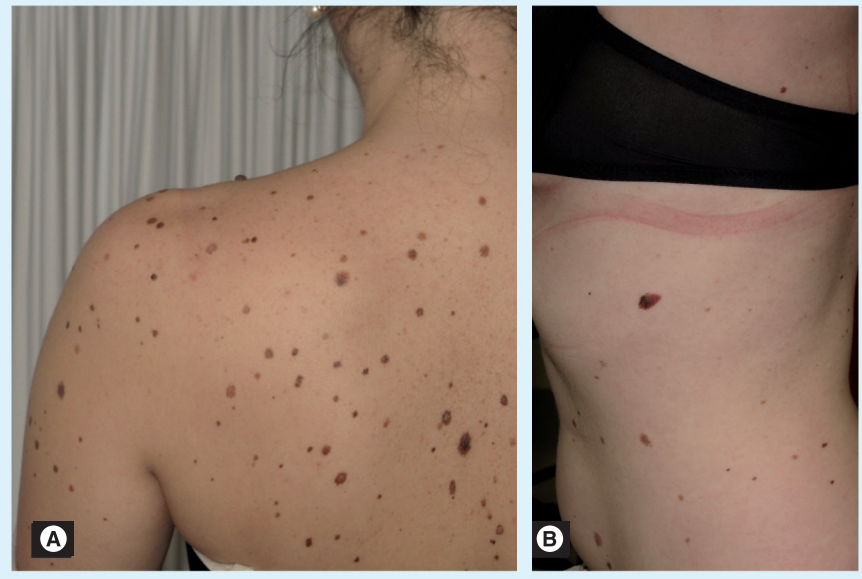

Figure 2. Young adults requiring specialist assessment. (A) A 35-year-old woman with multiple nevi on the back and arms. The presence of numerous nevi is a major risk factor for melanoma. Rather than performing a full nevus count, a partial nevus count on the arms can be done as a quick and convenient alternative. **(B)** An 'ABCD'-positive lesion (early invasive melanoma) on the trunk of a 42-year-old woman. Both patients require specialist referral.

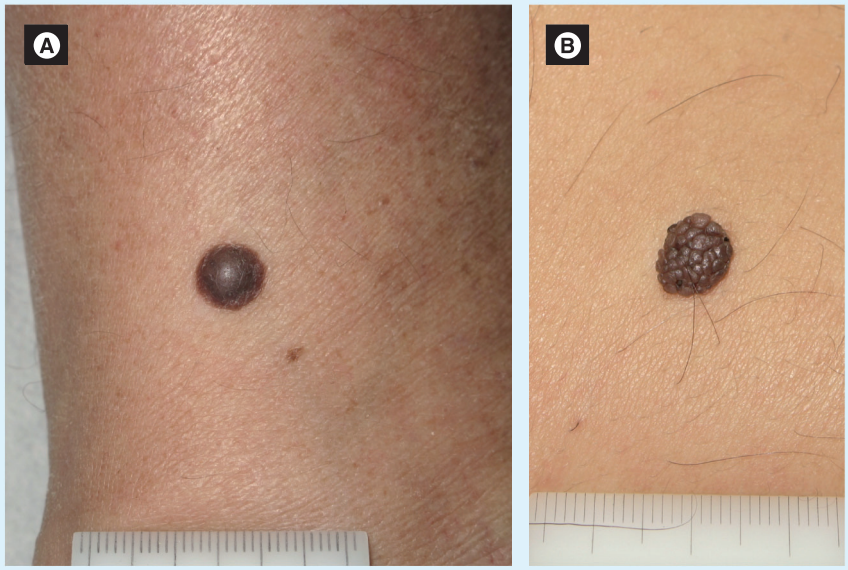

Figure 3. Nodular lesions. (A) An EFG-positive (i.e., elevated, firm and growing) melanoma on the leg of a 62-year-old man requiring urgent referral. Although elevated, the lesion shown in **(B)** is EFG negative because it has a soft consistency with a papillomatous surface and a long-standing history.

The third subset comprises those patients who possess a lesion that is EFG positive [17]. The EFG acronym summarizes the worrisome clinical characteristics of fast-growing skin malignancies, particularly nodular melanoma (NM). NMs often do not present with clinical features of the ABCD algorithm that are typical of superficial spreading melanoma, but instead typically demonstrate criteria of the EFG mnemonic [18]. A lesion is EFG positive if it displays the criteria of elevation ('E'), firmness on palpation ('F') and progressive growth ('G') for more than 4 weeks [17]. NM has a very aggressive biology and must be immediately reported to a specialist for urgent assessment. In addition to NM, fast-growing NMSCs, such as invasive SCC (including keratoacanthoma) or Merkel cell carcinoma, can also present as EFG-positive lesions that require prompt dermatologist review.

A possible differential diagnosis of NM is the dermal nevus, which also generally presents as a nodular lesion in adults. However, unlike NM, dermal nevi typically have a soft consistency, a papillomatous surface and, importantly, have a long-standing history with lesions often being present for many years (Figure 3).

Special attention should be given to those adult patients aged over 50 years who present with a skin cancer or equivocal lesion on an exposed site and/or who display evidence of chronic actinic damage (such as actinic keratoses and/or dermatoheliosis) on the typically sun-exposed sites of the face, neck, forearms and the back of the hands (Figure 4). In these situations, it is particularly important for the GP to classify the patient as 'high risk' and closely scrutinize their whole cutaneous surface, clinically and by dermoscopy. In these patients, the probability of finding a skin cancer on a covered skin site is relatively high. A recent study has reported that approximately one in ten patients who present with a suspicious lesion on a exposed location will have a skin cancer (melanoma or NMSC) on a covered location [19].

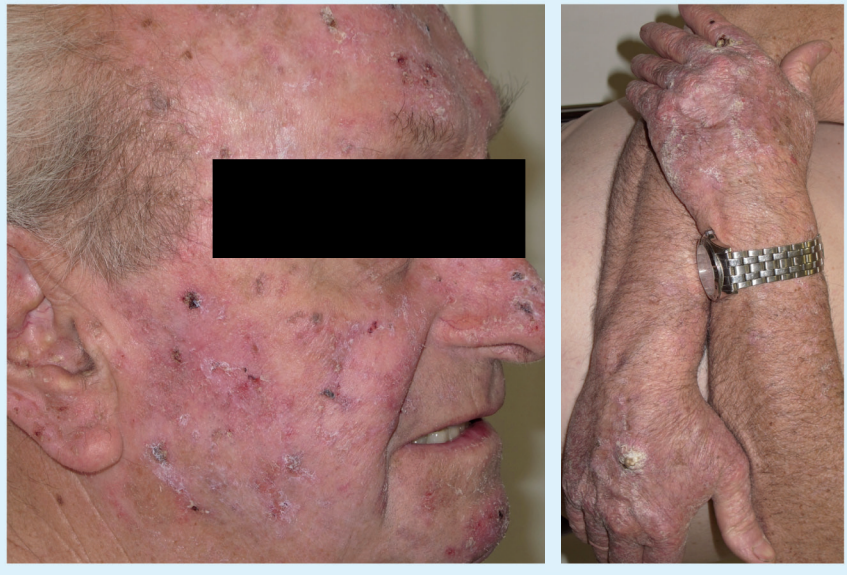

Figure 4. A 72-year-old man with severe chronic actinic damage (with numerous actinic keratoses) and equivocal/suspicious lesions on the typically sun-exposed sites of the face and the back of the hands. In patients such as this, the probability of finding a skin cancer on a covered skin site is relatively high.

During the inspection of the skin of these subjects, dermal nevi, seborrheic keratosis and cherry angiomas are frequently encountered. These benign lesions are very frequent in adult patients in this age group, and are usually easily identified by clinical and dermoscopic examination. Dermal nevi, as mentioned above, typically present clinically as long-standing, papular or nodular lesions with a soft consistency and papillomatous surface, and have comma vessels on dermoscopy. Seborrheic keratoses are characterized clinically by a rough 'warty' surface, easily removable greasy scales and a homogeneous yellow-brown pigmentation. Dermoscopically, seborrheic keratoses often possess multiple milia cysts, crypts, fissures and ridges, and a well-demarcated edge. Cherry angiomas are usually multiple, small papular lesions

that are bright red in color. On dermoscopy, the latter typically show well-demarcated reddish lacunes. In all of the cases listed above, specialist referral is not required but will be essential if the lesion does not present with the typical characteristics attributable to these three types of benign lesions, or if it has overtly suspicious features [20].

As mentioned above, suspicious melanocytic lesions are typically ABCDE or EFG positive clinically and/or have suspicious dermoscopic features, and if detected in this older age group would again prompt dermatologist referral. Also as stated above, individuals with numerous (>50) common nevi and/or multiple atypical nevi should also be referred for dermatology review.

Second level: the dermatologist

At the secondary level of care, patients referred from primary care screening centers would be consulted by dermatologists and other specialists involved in skin cancer management. Ideally, these specialists should form collaborative networks at the community or regional level for the interchange of expert advice and specialized care. In addition, centralized centers at the state or national level could be established for developing standardized clinical and diagnostic guidelines, organizing funding for educational campaigns and research, and so on. Indeed, such centers have already been established in countries such as Australia (e.g., Cancer Council Australia and the Australian Cancer Network). Standardization of the clinical diagnostic approach for dermatologists would include the following points.

Instrumentation

In order to optimize screening, specialists should be equipped with a manual (hand-held) dermatoscope. These are relatively inexpensive optical instruments that are capable of producing high quality images, which can be recorded by attachment to a digital camera. Dermoscopy improves the accuracy of diagnosis of a variety of skin lesions over clinical inspection alone while also having the advantage of being a relatively quick procedure for most patients [20–26]. With regard to the latter, a recent study estimated that the time required to complete a total body skin examination with manual dermatoscopy was in the order of 2–3 min [27]. Examination of all lesions by dermoscopy is particularly important for diagnosing early melanoma and NMSC, including melanoma that does not present as an 'ugly duckling' lesion by clinical inspection. These latter 'clinically featureless' melanomas may be pigmented or nonpigmented, and may be small, regular in shape and/or fairly uniform in color, in effect escaping clinical diagnosis because they lack the clinical ABCD criteria. However, these melanomas frequently have suspicious features on dermoscopy, which facilitates an early diagnosis [28].

In contrast to hand-held dermatoscopes, videodermatoscopes are digital tools that do not generally provide the high image quality required for precision in dermoscopic diagnosis, but are very useful for performing digital monitoring of patients with multiple nevi [29,30]. In effect, they aid in the detection of melanocytic lesions that develop dermoscopic change over time. Of note, videodermatoscopes are usually incorporated into more expensive computerized instrumentation, and nevus monitoring increases the time required for patient assessment [31].

Patient selection

As mentioned above, a significant problem of screening for melanoma in the general population is the extremely high prevalence of individuals with melanocytic nevi. Unselected screening of vast numbers of patients in the population becomes a practical impossibility with respect to available resources and cost. Targeted screening of higher-risk individuals has therefore been advocated [32]. Opportunistic full skin examinations of higher-risk patients by GPs and dermatologists may assist in the detection of skin cancer, including melanoma. For example, a US study estimated that more than 60% of melanoma patients had visited their family physician in the year prior to diagnosis for problems not related to the skin. Therefore, opportunistic screening of high-risk GP patients could potentially lead to an earlier diagnosis of

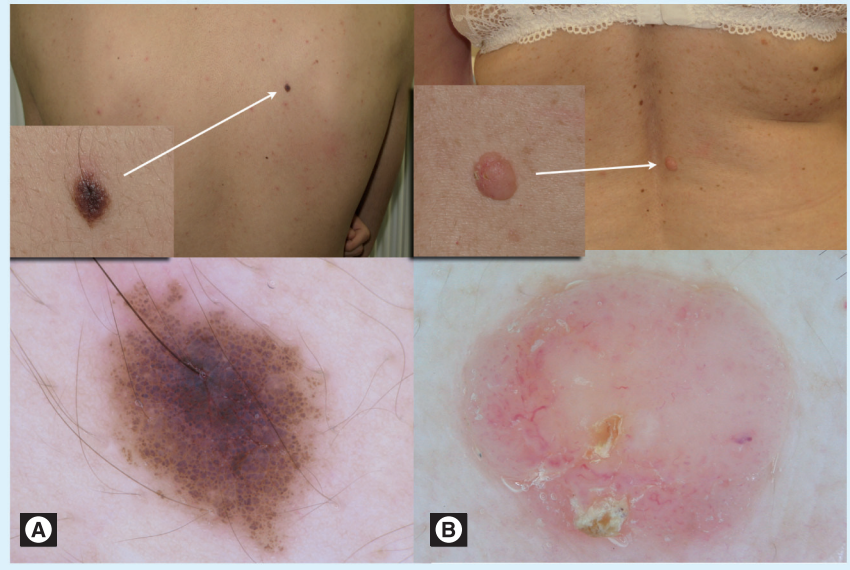

Figure 5. Solitary lesions. (A) A single pigmented lesion on the back of a 38-year-old man. Clinically and dermoscopically, the diagnosis of a small congenital nevus can be made with confidence, thus no excision or monitoring is needed. **(B)** A nonpigmented nodule on the back of a 66-year-old woman. The lesion is soft and slightly papillomatous, thus resembling a dermal nevus clinically. On dermoscopic examination, there is a combination of dotted and irregular vessels, with some vessels having an apparent 'comma' morphology. This lesion, therefore, belongs to a morphologic gray zone. Because it is a solitary and nodular lesion, the correct management is excision and not follow-up. Histopathologic examination revealed fibroepithelioma of Pinkus (i.e., fibroepithelial basal cell carcinoma).

such melanomas, with improved prognosis [33]. A second point concerns dermatologists: a recent clinical study has calculated that the risk of missing a skin cancer in patients who are seen by a dermatologist for a localized problem (which does not involve examination of the whole cutaneous surface) is in the order of one in 50 patients, while the risk of missing a melanoma is approximately one in 400 patients [19]. These sobering figures lead us to consider, at least for the specialist, the possibility of offering a total body skin examination to all patients, but if that is not feasible then it should be offered to patients in the following higher-risk groups:

- Patients with a personal history of any skin malignancy, or a family history of melanoma (in first-degree relatives);
- Patients under the age of 50 years who present with more than 20 nevi on the arms;
- Patients over the age of 50 years who present with evidence of chronic solar damage.

This scheme, a modification of a recent French study, allows a quick and effective selection of patient groups who are at increased risk of melanoma and NMSC [14].

Outcome of dermatologic triage

Once examined clinically and by hand-held (manual) dermatoscopy, patients will follow two distinct management paths depending on their risk profile: patients who have a single or few lesions, and patients with multiple nevi.

Patients with single or few lesions

Simply put, if a lesion appears benign it may be left, but if suspicious it should be removed. This approach, although apparently straightforward and obvious, is not so easily applied in daily practice owing to the high prevalence of lesions appearing slightly irregular on clinical or dermoscopic examination. Clinicians may choose to monitor such 'mildly atypical' melanocytic lesions in low-risk patients over time, but there are a few key problems with this approach. The yield of malignancy for slightly atypical lesions monitored in low-risk patients is very low, patient noncompliance with the follow-up regimen is a potential risk and the monitoring procedure limits access of other higher-risk patients to the screening facilities. In our view, monitoring is a specific procedure that helps reduce the number of unnecessary excisions in higher-risk patients, particularly those with multiple nevi (see below). By contrast, for low-risk patients with single (or a few) slightly atypical melanocytic lesions, a simple dichotomous approach (i.e., no further examination vs excision) can be adopted (Figure 5). The latter has a number of advantages; namely, to prompt excision of melanoma as early as possible, to avoid the problem of patients not returning for follow-up imaging and to acquire more appointment space for new, higher-risk patients to be screened.

In selected cases in higher-risk individuals, an alternate method to manage indeterminate or equivocal melanocytic lesions is short-term clinical and dermoscopic follow-up [30,34]. Short-term follow-up is useful in ensuring that the lesion being monitored follows a benign evolutionary course, thus helping to avoid unnecessary biopsy of benign lesions. Conversely, if there is any morphologic change in the lesion after short-term follow-up, then the lesion is removed for histopathologic testing. In this way, short-term monitoring aims to detect early melanoma that may otherwise have been missed.

In detail, short-term dermoscopic monitoring involves identification of equivocal melanocytic lesions that lack clear dermoscopic features of melanoma but which also lack the reassuring symmetry and monotony of pigmentation pattern and/or color which are features of benignity. These lesions could be described as 'mildly to moderately atypical' dermoscopically and in order to qualify for monitoring should be flat (macular) clinically, have a reticular pattern on dermoscopy, as well as no significant features of regression dermoscopically [35,36]. Clinically elevated lesions, or those having a multicomponent pattern or significant regression on dermoscopy should not be monitored. Short-term monitoring typically involves a baseline clinical and dermoscopic examination coupled with a review 3–4 months later to track the biologic behavior of the lesion. This procedure must be conducted with caution because melanoma can in some instances grow slowly and dermoscopic change might not be apparent after the 3–4-month monitoring interval [37]. Conversely, it is notable that approximately 17% of nonmalignant lesions monitored in the short term may show significant morphologic change (in size, shape, architecture and/or color), resulting in unnecessary removal [38]. It is an essential prerequisite for monitoring that patients comply with the follow-up protocol. The risk of noncompliance in lesion monitoring is not insignificant: for example, 12–16% of patients offered short-term monitoring did not return for follow-up review. Furthermore, it is noteworthy that Menzies *et al.* remarked: "a significant proportion of these [noncompliant] patients would have decided on surgical excision for management" [38].

In specialized academic and research centers and in selected clinics elsewhere, confocal laser microscopy (CLM) is also becoming available. CLM is a fairly recently introduced noninvasive imaging technique that generates black-and-white images in a horizontal plane at near-histologic resolution [39]. This diagnostic method is slower than dermoscopy and the equipment much more expensive, but CLM is particularly useful in challenging cases where a clear-cut dermoscopic diagnosis is difficult, especially in the context of flat lesions on the face and pink tumors [40–44].

Patients with multiple nevi

A patient with multiple nevi is identified by the presence of more than 50 common nevi in total (excluding lentigines or freckles, and common nevi less than 2 mm in diameter) and/or the presence of multiple clinically atypical moles. The latter are characterized by their relatively large diameter (>6 mm) and irregularity in shape and color. In addition to having numerous atypical nevi, patients with dysplastic nevus or FAMM syndrome are recognized by having a family history of melanoma. These patients are at a very high risk of developing melanoma and benefit from close, long-term monitoring of their lesions.

During the initial visit, the patient's nevi are each analyzed with the manual dermatoscope for any suspicious features. This is the traditional 'analytic' or morphologic approach for the dermoscopic diagnosis of melanoma. Next, the predominant dermoscopic nevus pattern of the patient is determined (i.e., reticular, globular or homogeneous dermoscopic pattern, or a combination thereof). By recognizing the predominant dermoscopic morphology of the patient's nevi – also called the 'signature' nevus pattern – the dermatologist can then identify any possible dermoscopic 'ugly duckling' lesion that differs from the others and should therefore be targeted for excision [45,46]. This is the 'comparative' dermoscopic approach for diagnosing melanoma (Figure 6). By adding the comparative to the analytic dermoscopic approach for recognizing melanoma, dermoscopists in a recent study were able to reduce the number of unnecessary removals of benign lesions by approximately 75% [47]. In other words, specificity for the diagnosis of melanoma was improved, which the authors found occurred without missing a case of melanoma.

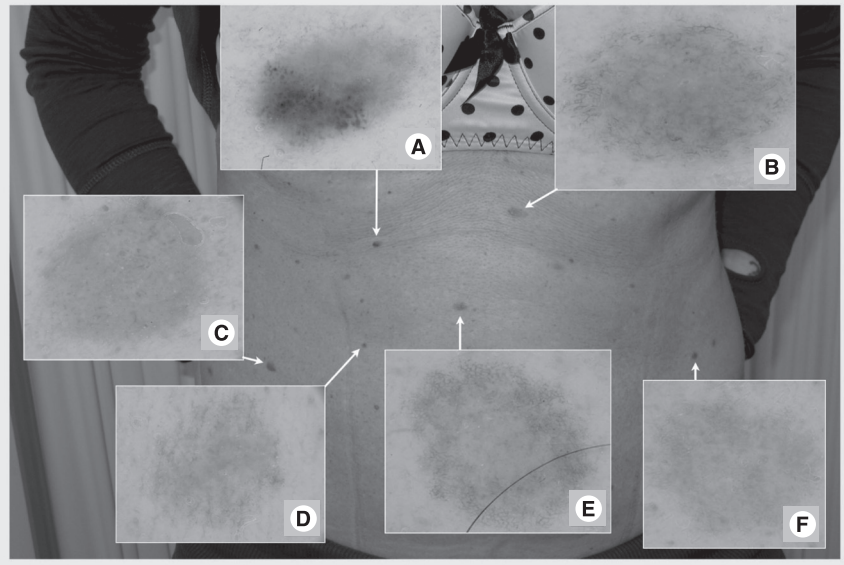

Figure 6. A 63-year-old woman with multiple melanocytic lesions on the trunk. Using the 'comparative' diagnostic approach, most lesions display a dermoscopically similar reticular/homogeneous pattern (lesions **B–F**), whereas lesion **(A)** exhibits a different ('ugly duckling') pattern. On closer 'analytic' dermoscopic examination the latter lesion shows a marked asymmetry of pigmentation pattern, with blue-white structures, irregular brown dots/globules and prominent dotted vessels. This lesion was therefore targeted for excision and histopathologically diagnosed as an early invasive melanoma.

Once the above process is completed at the first visit, patients with multiple nevi should be included in a long-term clinical and dermoscopic monitoring program for the detection of subsequent melanoma [48–52]. This is a time-consuming procedure but is justified for two main reasons: first, because a dermoscopically featureless melanoma such as an amelanotic/hypomelanotic melanoma or very early pigmented melanoma may already be present. Such melanomas can be very difficult to diagnose at the initial visit and typically lie covertly amongst other benign-looking lesions; and second, because patients with numerous nevi as mentioned above have a significant risk of developing a cutaneous melanoma at some subsequent time in their life. For patients with >50 common nevi and a number of atypical nevi (but without a family history of melanoma) this risk is approximately 3% [53], whereas for patients with dysplastic nevus or FAMM syndrome the risk is between 10 and 100% [48,52].

Before embarking on long-term monitoring, the specialist should first ensure that the patient is able to adhere to a strict follow-up regimen. If agreement between physician and patient is reached, the long-term monitoring protocol requires an initial (baseline) inspection of all nevi. In addition to this, videodermoscopic recording of a collection of lesions is carried out, usually consisting of those lesions having the most atypical appearance, although small and dermoscopically unremarkable lesions can also be monitored. This entire procedure is repeated after a 3-month interval. This first follow-up review facilitates the detection of any changes in the selected existing lesions on short-term videodermoscopic examination. Such lesions should be excised for histopathologic examination to exclude melanoma. Of note, patient compliance is typically significantly higher for short-term (3-month) as compared with longer-term (6–12-month) reviews [53]. In fact, Argenziano *et al.* found an 84% short-term (3-month) compliance rate, which dropped to 63% for medium-term (6-month) monitoring, and fell to a mere 30% for long-term (12-month) monitoring [53]. Therefore, assessment of the patient at 3 months improves compliance and thus reduces the potential risk of leaving a melanoma untreated (i.e., if the patient does not adhere to a longer-term follow-up appointment).

Following the 3-month review, if no suspicious lesions are identified, the patient should be followed on a 6–12-month basis, *ad infinitum* (Figure 7). It should be noted again that only clinically flat (nonpalpable) melanocytic lesions with a predominantly reticular pattern on dermoscopy are suitable for monitoring. Clinically elevated (palpable) equivocal lesions, or those with significant regression (>50% of the area of the lesion) or a multicomponent pattern on dermoscopy should not, as a general rule, be monitored. The latter is advocated as a safeguard against the possibility of delaying the diagnosis of potentially invasive melanoma, in particular an elevated NM with aggressive biologic behavior, or an invasive melanoma undergoing regression. In other words, elevated indeterminate lesions and those demonstrating significant regression should be excised at the outset, rather than monitored. Elevated lesions that are clearly benign (e.g., long-standing, soft dermal nevi or clear-cut seborrheic keratoses) do not require monitoring.

With regard to the detection rate of melanoma using the technique of long-term monitoring, a fairly recent Australian study involved long-term clinical (i.e., total body photographic) and dermoscopic monitoring of patients at high risk of melanoma [54]. The authors found that new or changed lesions were more likely to be melanomas in patients over the age of 50 years. With reference to new lesions, they found that in patients younger than 50 years, less than 1% of such lesions were diagnosed as melanomas histopathologically, whereas this figure climbed to 30% in those over 50 years. Regarding changed lesions, patients younger than 50 years had 3% of such lesions diagnosed as melanomas, whereas this figure increased to 22% in those older than 50 years. In addition, the authors concluded that close long-term monitoring of high-risk patients resulted in a higher proportion of early melanomas being found than would be expected without monitoring, coupled with a comparably lower biopsy rate of benign nevi (with cost savings and reduced morbidity associated with the latter).

Third level: the management of patient with melanoma

The next step concerns the clinical management of patients diagnosed with melanoma, who will undergo diagnostic and therapeutic protocols based on the stage of their disease. Fortunately, the majority of patients present with early-stage melanoma and can be managed satisfactorily by the local dermatologist. However, patients who present with difficult cases or who have advanced stages of disease are best managed in tertiary referral centers. These level III facilities, better defined as 'melanoma units', consist of multidisciplinary teams usually operating within a hospital setting. Melanoma units aim to offer patients a high level of professional input to optimize patient outcomes.

Staging

Once an initial excisional biopsy of a suspicious lesion is carried out and the histopathological diagnosis of melanoma is made, the patient's disease is staged. The purpose of staging is to select appropriate therapy and follow-up for patients with melanoma based on the relative risk of disease recurrence.

The most recent staging guidelines should be considered and histopathologic parameters such as ulceration and the number of mitoses per mm^2 of viable tumor taken into account [55]. However, the histological thickness of the primary melanoma, or Breslow index (expressed in mm), remains the most reliable prognostic parameter, and thus constitutes the mainstay for staging of the disease. Stages 0, I and II refer to the primary tumor, whereas stages III and IV are those in which melanoma has metastasized [101]. In particular, stage III involves regional lymph node or intransit skin metastasis, and stage IV involves remote (distant) metastasis. Longer-term survival rates (prognosis) correlate with the stage of the disease, with stage 0 patients having a near 100% 5-year survival rate, stage I 85–99%, stage II 40–85%, stage III 25–60% and stage IV only 9–15% [56].

The purpose of staging investigations is to detect, where possible, the presence of regional (primarily nodal) or visceral (distant) disease. The investigations will be tailored according to the risk profile of the patient at the time of the initial diagnosis of melanoma.

Sentinel node biopsy & surgical therapy

For patients with primary melanomas in the order of >1 mm thickness, sentinel lymph node biopsy (SLNB) has been advocated as a method to detect clinically unapparent regional lymph node micrometastases [57]. The sentinel lymph node is the first node to receive drainage from the primary tumor site. A radioactive tracer and patent blue dye are injected around the primary melanoma site and the location of the sentinel node identified using an intraoperative γ-probe. The surgeon then makes an incision at the latter site and the node is identified by its blue color. The node is removed and sent for histopathologic examination. SLNB is best performed together with wide local excision of the primary melanoma site, as the latter procedure may interfere with the ability to accurately locate the true sentinel node. Aside from supplying additional staging (prognostic) information pertaining to regional lymph node involvement, SLNB is controversial in that it has not demonstrated any significant therapeutic benefit [58–60, 101]. Indeed, there is evidence that radical lymphadenectomy performed after a positive SLNB does not confer a survival advantage compared with lymph node dissection performed at the time of clinically detectable lymph node metastases [57]. Special clinical situations requiring an individualized approach to the indication of SLNB are as follows: thin (<1 mm) melanomas with more than 1 mitoses/mm^2, very thick (>4 mm) melanomas, age of the patient (elderly and children) and pregnancy [61,101].

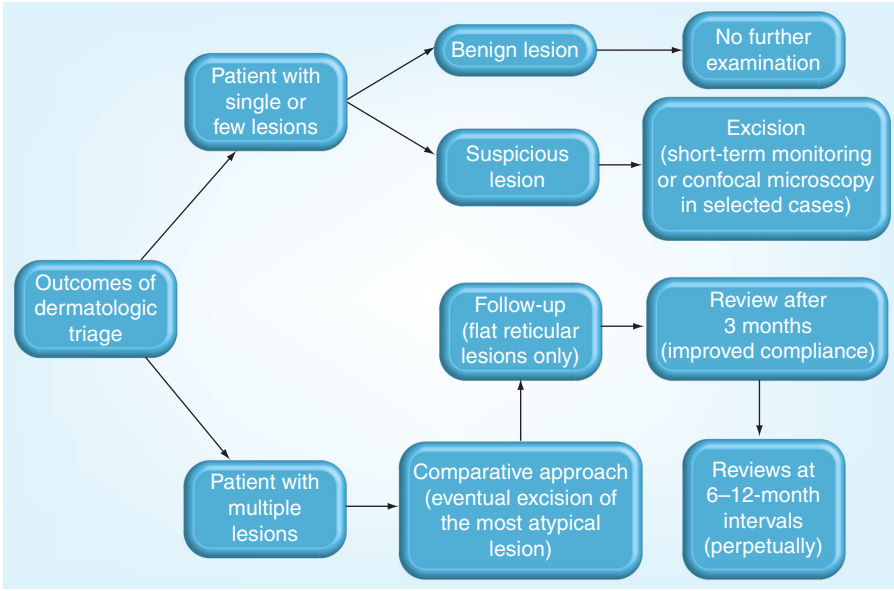

Figure 7. Workflow summarizing the two outcomes of the dermatologic triage.

Once the staging process is completed and it is verified that there is no evidence of disease involvement in regional and remote sites, definitive surgical treatment (re-excision) of the primary melanoma can be carried out. Excision margins are guided by the Breslow thickness of the melanoma. It is worth mentioning that some clinicians advocate complete excision with a narrow margin, noting that wider excision does not improve survival [62,63]. However, wider re-excision is currently practiced as a safeguard to reduce the incidence of local recurrence (i.e., persistence and regrowth of the primary melanoma due to inadequate initial excision) and/or local (satellite) metastases. Re-excision is usually performed together with the eventual SLNB and margins can be simplified to just three levels:

- Melanoma *in situ* requires excision with a 5-mm margin of uninvolved skin;
- Invasive melanoma with a thickness of less than 2 mm necessitates excision with a 1-cm margin;
- Melanoma thicker than 2 mm is excised with a 2-cm margin [64,65,101].

If, on the contrary, staging investigations reveal the presence of regional or distant disease, the management will be more complex and directed to the treatment of the metastases. Although some newer-generation drugs and other therapies have shown promise in the medical treatment of melanoma (interferon, ipilimumab and vemurafenib), the mainstay of treatment of disseminated melanoma remains surgical removal of metastases, as far as possible. This would include not only involved lymph nodes, but also, where feasible, excision of metastases (metastasectomy) from visceral organs.

Follow-up

The purpose of follow-up in patients with melanoma is to recognize at the earliest possible time any potential recurrence of disease, as well as to detect another possible primary melanoma. It is important to note that patients with a past history of melanoma are at a relatively high risk of developing multiple primary melanomas over their lifetime.

With regard to recurrence of disease, this may either involve persistence and regrowth of the primary tumor (i.e., due to incomplete excision) as mentioned above, or be due to metastases. The types of metastases that can occur are as follows:

- Satellite metastases, which are skin or subcutaneous lesions occurring within 2 cm of the surgical excision scar of the previous primary melanoma;
- In-transit metastases, which are skin or subcutaneous metastases located between 2 cm of such a scar and the regional lymph node basin;
- Distant metastases, which occur in lymph nodes, distant skin sites and the internal visceral, skeletal and the CNS.

The various protocols of follow-up for melanoma will differ based on the clinicopathological features of the primary lesion and on the stage of disease, and also in relation to the presence of any symptoms (e.g., due to brain or bony metastases). That said, it should be noted that the follow-up of patients with melanoma is a controversial topic, as there are currently no universally agreed-upon guidelines based on robust randomized trials. Therefore, we are not yet able to determine whether intensive follow-up involving frequent testing is actually more effective in improving patients' overall survival and quality of life compared with less-intensive follow-up.

Another problem concerns the choice of diagnostic tests to be performed. For example, it has been shown that follow-up chest x-ray (CXR) has a low yield for the detection of occult pulmonary metastasis. A study by Garbe *et al.* showed that of 2396 CXRs performed over a 25-month surveillance period for patients with stage I–III disease, only 14 (0.6% overall) patients had a CXR suspicious of metastasis, with 12 (0.5%) of these confirmed as true positives (i.e., metastasis) [66]. Furthermore, CXR is burdened by a number of false-positive results that then require further tests of higher specificity to be performed, such as computerized tomography (CT) [101].

The use of CT scanning of the chest compared with CXR alone offers a greater ability to detect pulmonary metastasis [67,68]. However, the potential risks associated with an increased exposure to ionizing radiation from CT need to be considered.

Ultrasonography is widely used in high-risk patients to detect nodal disease. There is an overwhelming consensus that ultrasound performed by experienced sonographers is superior to clinical examination (i.e., palpation) alone in detecting lymph node metastases [69]. However, it is unclear whether this early recognition translates to an improvement in survival [101]. If clinical examination or ultrasound reveals suspected nodal involvement, these patients should undergo ultrasound-guided fine-needle biopsy to confirm the suspicion of nodal metastases histopathologically.

PET imaging has greater sensitivity than CT in detecting metastases (including skin, deep soft tissue and viscera), with the exception of small lung metastases and brain tissue, which is best studied by MRI [70]. However, PET is also burdened with many false positives and should therefore be regarded as a level II method to be used for the confirmation of positive results on CT scanning [67]. PET imaging is particularly useful when used in conjunction with CT scanning prior to operating on melanoma patients who are at high risk for occult metastases [71].

In addition to performing the above investigations as required, melanoma patients must also receive education on the early detection of melanoma and NMSC, and have instruction on the technique of skin self-examination (usually performed monthly). A careful personal and family history must be taken, with possible examination of relatives, and a follow-up regimen arranged that is tailored to the stage of their disease. The follow-up regimen should include sequential clinical examination coupled with a complete dermoscopic inspection of all of the patient's pigmented and nonpigmented lesions in order to recognize the appearance of any subsequent early primary melanomas.

Multiple primary melanoma (MPM) patients comprise approximately 3–8% of all patients with melanoma, depending on the case study consulted [72]. MPM may be identified as either synchronous (two or more primary melanomas affecting the same patient at the same time) or metachronous disease (two or more melanomas that appear at different times in the patient's life). The diagnosis of MPM does not in itself appear to be a poor prognostic factor, with 10-year survival rates of these patients being reflected by the Breslow thickness of their most advanced primary melanoma and the presence or absence of regional lymph node metastases, rather than by multiplicity *per se* [72,73]. As mentioned above, patients already diagnosed with a primary melanoma should receive careful clinical and dermoscopic follow-up by their physician(s), as well as detailed instruction on the initial clinical signs of melanoma. These latter two factors should both contribute to an early diagnosis of any metachronous melanoma, with subsequent optimal prognosis.

Finally, the follow-up of patients with melanoma should be performed by a clinician experienced in the diagnosis of melanocytic lesions, primarily a dermatologist, given the importance of early recognition of a second or subsequent primary melanoma. Also, very often these patients (especially in younger age groups) have numerous moles, and therefore the diagnostic approach must be carried out according to the regimens mentioned above. In cases of suspected metastases (stages III and IV), the patient should be referred to a multidisciplinary tertiary referral center.

Expert commentary & five-year view

An updated and rational system of triage, involving improved accuracy of diagnosis and more timely management of skin cancers will require the implementation of a multidisciplinary and multilevel approach to managing patients with skin malignancy. As a first step towards a more rational system of triage, an educational program should be implemented, with instruction of GPs, who will be provided with a simple and effective diagnostic tools for the screening of melanoma and NMSC. A simplified approach for the triage of patients at risk for skin cancer is based on the main indications that should prompt GP referral for specialist care, described previously in the text.

At the secondary level of care, patients referred from primary care screening centers would be consulted by dermatologists and other specialists, who will be provided with a manual (hand-held) dermatoscope that allows rapid screening of most of the lesions of a given patient. A total body skin examination should be offered to the higher-risk groups stated previously.

Once examined clinically and by hand-held (manual) dermatoscopy, patients will follow two distinct management paths depending on their risk profile: patients who have a single or few lesions; and patients with multiple nevi. Short-term monitoring for patients with a single lesion (or a few lesions) should be limited to highly selected, higher-risk cases. Instead, a simple binary approach – 'no further examination versus excision' – should be implemented for lower-risk patients to achieve two main aims: to excise melanoma as early as possible; and to acquire more appointment space for new (higher-risk) patients who need to be screened. Higher-risk patients with multiple nevi should be included in a long-term clinical and dermoscopic monitoring program to decrease the number of unnecessary excisions of benign lesions and to improve the recognition of featureless melanoma or subsequent primary melanoma.

The third step concerns the clinical management of patients diagnosed with melanoma, who will undergo diagnostic and therapeutic protocols based on the stage of their disease. Fortunately, the majority of patients present with early-stage melanoma and can be managed satisfactorily by the local dermatologist. However, those patients who present with difficult cases or who have advanced stages of disease patients are best managed in tertiary referral centers.

Key issues

- A simplified approach for the primary-level triage of patients at risk for skin cancer is based on the following main indications:
  - Patients younger than 15 years of age with a pigmented lesion larger than 2 cm, or a rapidly growing papule/nodule;
  - Patients aged between 15 and 50 years having multiple nevi on the arms (>20), an ABCD-positive lesion, or an EFG-positive lesion;
  - Patients older than 50 years of age who have chronic actinic damage on visible skin.
- At the secondary level of care, dermatologists and other specialists should be provided with a manual (hand-held) dermatoscope that allows rapid screening of most of the lesions of a given patient.
- A total body skin examination should be offered to the following higher-risk groups:
  - Patients with a personal history of any skin malignancy or a family history of melanoma (in first-degree relatives);
  - Patients under the age of 50 years who present with more than 20 nevi on the arms;
  - Patients over the age of 50 years who present with evidence of chronic sun damage.
- Monitoring patients with a single lesion (or a few lesions) should be limited to highly selected cases. Instead, a simple dichotomous approach – 'no further examination versus excision' – should be implemented for lower-risk patients. This approach should prompt excision of melanoma as early as possible and make more appointment space available for new (high-risk) patients needing to be screened.
- By contrast, the higher-risk patient with multiple nevi should be included in a long-term clinical and dermoscopic monitoring program to decrease the number of unnecessary excisions of benign lesions and to improve the recognition of featureless melanomas or subsequent primary melanomas.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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