



Diagnostic tests

Scanning for melanoma

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Summary

Non-invasive diagnostic tools aim at increasing accuracy of melanoma diagnosis. Clinical naked eye observation in combination with dermoscopy can be regarded as the practical reference standard to identify lesions for histopathological evaluation. Pigmented lesions need to be evaluated in the context of patient history to identify risk factors for melanoma, followed by a dermoscopically-aided entire skin examination. Patients with identified risk factors should be further examined. Total body photography is widely used in the follow-up of high-risk patients (particularly those with numerous and dysplastic naevi) and can be coupled with digital dermoscopy or videodermoscopy. New non-invasive diagnostic aids comprise multispectral image analysis, reflectance confocal microscopy and computer assisted diagnostic systems. Also, molecular profiling of lesions is an emerging technique under investigation for melanoma diagnosis.

Key words: dermoscopy, total body photography, reflectance confocal microscopy.

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Introduction

Early detection of melanoma remains a significant challenge for clinicians. The critical issue is to remove all lesions that may be malignant while minimising the excision rate of harmless benign lesions. Since naked eye examination has a comparatively low sensitivity in melanoma detection, additional non-invasive diagnostic tools such as dermoscopy are being used in daily practice and have improved the sensitivity of diagnosis when applied by experts.^{1–3} The current diagnostic gold standard is visual inspection with dermoscopy followed by histopathological examination as required. A high number

of unnecessary surgical procedures are still performed.

A recent report dealing with primary skin cancer care in Queensland showed that 19.6 pigmented lesions are excised per melanoma.⁴

Several new non-invasive diagnostic tools aimed at increasing the accuracy of skin cancer diagnosis and thereby minimising unnecessary surgical procedures have emerged in recent years (Table 1). This expanding choice of diagnostic tools may cause confusion among doctors about what they are and how they can be used. Most systems offer a combination of diagnostic methods which may add to the uncertainty.

Clinical examination with visual inspection

A patient history to identify risk factors for melanoma as well as a full body examination aided by dermoscopy should be performed for every new patient. Since further evaluation is time-consuming, those individuals at risk, as well as lesions that are considered as atypical or suspicious, should be identified. A detailed history should include:

- age and sex
- personal history of melanoma or non-melanoma skin cancer
- family history of melanoma
- number of naevi
- presence of atypical or dysplastic naevi
- skin type
- tanning habits
- response to sun exposure and evidence of skin damage from the sun.^{5,6}

An inspection of the entire cutaneous surface should include the axillae, groin, the interdigital webs of the hands and feet, the nail apparatus and the scalp.

The ABCD acronym – Asymmetry, Border irregularity, Colour variegation, and large Diameter – supplemented with an E for Evolution, represents the clinical guideline for melanoma diagnosis. In contrast, the EFG acronym – Elevated, Firm and Growing progressively – is more appropriate for nodular melanomas that often have a more subtle clinical appearance.⁷ On physical examination, new and changing naevi should be detected as well as any 'ugly ducklings', that is, lesions that are

Table 1

Comparison of mole scanning methods

Method	Facts	Advantages	Main disadvantages
Visual inspection	ABCDE* rule is the usual clinical guide for most lesions, but EFG† is more appropriate for nodular lesions	Easy to perform	Limited sensitivity in melanoma diagnosis
Total baseline photography	Digital imaging in standardised positions Nearly whole skin surface visualised	Identification of 'ugly ducklings' Identification of new or evolving lesions	Only gives macroscopic information
Handheld dermoscopy	Visualisation of subsurface anatomic structures of epidermis and upper dermis Dermoscopes with polarised and non-polarised light are available	Well-established criteria Increases diagnostic sensitivity without diminishing specificity, when performed by specialists	Requires specialised training
Sequential dermoscopic follow-up		Automated diagnosis/teledermoscopy and combination with total baseline photography possible	Only preselected lesions can be compared dermoscopically Not suitable for nodular lesions
Multispectral image analysis	Light reflected in different skin depths is collected and analysed	Visual information of deeper skin layer compared with dermoscopy Automated diagnosis possible	Needs further evaluation in clinical trials
High-frequency ultrasound and optical coherence tomography	Vertical imaging of the skin	Monitoring of topical treatment possible	To date, not diagnostic aids
Reflectance confocal microscopy	Horizontal imaging of the skin with laser light that causes no tissue damage Melanin/melanocytes are a strong source of contrast	Quasi-histological resolution offers <i>in vivo</i> biopsy, monitoring of treatment, pre-surgical margin assessment	Requires specialised training Limited imaging depth To date, mainly used for research
Multiphoton laser scanning microscopy		Visualisation of cellular and subcellular structures	To date, mainly used for research

* Asymmetry, Border irregularity, Colour variegation, and large Diameter, supplemented with an E for Evolution

† Elevated, Firm and Growing progressively

dissimilar to the rest.

However, any one single visual inspection fails to detect small melanomas and amelanotic melanomas. Thus for high-risk individuals, six-monthly full cutaneous examinations supported by total body photography and dermoscopy as well as patient education for self-examination have been recommended by Australian guidelines.⁸

Total body photography

Total body photography is widely used in the follow-up of

high-risk patients, particularly those with numerous and dysplastic naevi. The technique can be performed with any camera, and a standard digital camera that provides good image quality for digital sectional body images is the most cost-effective option. To document nearly the entire body surface the patient should assume standardised positions under good light conditions. Images should be taken of the face, neck, area behind the ears, scalp (in bald individuals), anterior and posterior trunk, and the extremities (including palms and soles). Subsequent new or changing lesions that may be indicative of melanoma can be

Table 2

Overview of various mole scanning devices

Device	Standardised total body photography	Total body photography comparator	Macroscopic lesion images	Non-polarised dermoscopy	Polarised dermoscopy	Sequential dermoscopic imaging	Computer assisted diagnosis	Fully automated diagnosis	Teledermatology	Comments
EpiScope www.welchallyn.com				•						Handheld device
Dermatoscope Delta www.heine.com				•						Handheld device
DermoGenius basic www.biocam.de				•						Handheld device
DermLite Platinum www.dermlite.com					•					Handheld device
Molemax www.equipmed.com			•	•	•	•	•			Imaging system
Fotofinder www.fotofinder.de	•	•	•	•		•	•			Imaging system
DermoGenius Ultra www.biocam.de			•	•		•	•			Imaging system
MicroDerm www.visiomedag.com			•	•		•	•			Imaging system
Dermoscopix www.dermoscopix.com	•			•		•				Imaging software
Melanoscan www.melanoscan.com	•									Imaging system
MoleMap www.molemap.net.au	•			•		•			•	Imaging and patient history done by trained nurse
Db-Dermo Mips www.skinlesions.net					•			•		Automated diagnosis based on dermoscopy
MelaFind www.eosciences.com								•		Automated diagnosis based on multispectral image analysis

The features of the devices that are, in our estimation, most important are indicated by dots. For further detailed information on the devices and recent developments, follow the web links.

recognised in follow-up examinations by comparing the images with the patient's skin. Specific digital skin photography systems are available which facilitate standardisation of imaging and data storage (Table 2).

Total body photography has been reported to enable melanoma

detection at an early stage.⁹ However, small changes in naevi will probably be missed when only applying macroscopic imaging. A combined dermoscopic and total body photography approach is therefore recommended for patients who have atypical moles. Whereas digital dermoscopic images can

be obtained with dermoscopic lenses that can be attached easily to most commercially available cameras, various skin imaging devices offer a combination of total body photography and dermoscopy (Table 2). Some devices are also able to automatically compare two overview images and highlight new and changing lesions on the screen, though large-scale clinical studies of a high-risk population are needed to validate these findings.

Dermoscopy

Dermoscopy, also known as dermatoscopy or epiluminescence microscopy, has been widely adopted into everyday clinical use. It enables visualisation of subsurface anatomic structures of the epidermis and upper dermis. A dermoscope consists of a light source and a magnifying lens. While non-polarised dermoscopes require operation with an immersion medium, such as oil or alcohol, dermoscopes with polarised light do not.

Digital dermoscopy or videodermoscopy is also now widely used. As well as easy storage and retrieval, digital dermoscopic and clinical images can be sent electronically. This is called teledermatology or teledermoscopy (Table 1).

Numerous diagnostic algorithms have been proposed to assess a lesion including pattern analysis, ABCD rule, Menzies method, seven-point checklist and three-point checklist. All these algorithms have been proven to be of high specificity and sensitivity in the diagnosis of melanoma. The choice of which one to use should be made upon personal preferences.*

Dermoscopy, when performed by specialists, increases diagnostic sensitivity without diminishing specificity and has been shown to decrease unnecessary excisions.^{1-3,10} Two meta-analyses on studies published before 2000 verified that dermoscopy is superior to naked eye examination when used by experts.^{1,2}

Another study reported that even a one-day tutorial on dermoscopy can improve the ability of primary care physicians to correctly refer individuals with suspicious lesions to a skin lesion clinic.¹¹ A recent meta-analysis focused exclusively on studies that were performed in a clinical setting and found the relative diagnostic odds ratio (a measure for diagnostic accuracy) was 15.6 for dermoscopy compared to naked eye examination.³ This strong scientific evidence indicates that dermoscopy is presently the practical reference standard for non-invasive diagnosis of melanoma.

Follow-up examinations

Due to the impracticability of removing all lesions, follow-up is crucial so that melanomas which lack atypical features at the first visit are not missed. Suspicious lesions can be monitored

by serial dermoscopic and macroscopic imaging. Digital dermoscopic (and clinical) images are taken and linked to the body site via a computer. At the follow-up visit, the same lesion is photographed again for comparison. This is especially useful for patients with multiple lesions, and reportedly improves sensitivity in melanoma diagnosis.^{3,12} Re-examination after three months with subsequent follow-up visits every 6–12 months seems to be a useful strategy. For individuals with familial atypical multiple mole and melanoma syndrome, follow-up every three months is recommended.¹³

A major disadvantage of the method is, however, that only preselected lesions are monitored, whereas changes in a previously unsuspecting lesion or a *de novo* lesion might be missed. Follow-up should never be performed in nodular lesions, because if they are malignant they tend to grow faster than other melanoma types. Even short delays in treatment might increase the risk of a poor prognosis.

Teledermatology

Digital dermoscopic imaging enables primary care physicians to forward dermoscopic images (together with clinical information and macroscopic images) to specialists for a second opinion.¹⁴ Studies have shown good agreement between face-to-face diagnosis and diagnosis based on digital images.^{15,16} This is especially useful in remote areas, where referral is associated with considerable healthcare costs, and time for the patient.

Modern skin imaging devices combine dermoscopy and total body photography with teledermoscopic networks and computer-assisted automated diagnosis (Table 2). The company MoleMap, established by dermatologists, for example, offers a system in which a detailed examination followed by total body photography and comprehensive dermoscopic image capture is obtained by a specifically trained nurse. This information is then sent electronically to a dermatologist for expert analysis.

Multispectral image analysis

Multispectral imaging relies on the principle that light of different wavelengths, of the visible and infrared spectrum, penetrates the skin to different depths. When coupled with computer-based analysis, certain features not visible in macroscopic and dermoscopic analysis can be visualised.

Other non-invasive imaging tools

High-frequency ultrasound

High-frequency ultrasound provides a vertical image of the skin based on its different acoustic properties. However, because of the limited resolution, ultrasound alone is not a reliable diagnostic aid. It is more appropriately used for preoperative management in dermatology, for example, in assessing tumour thickness and vascularity.

* A detailed description of these algorithms can be found at www.dermoscopy.org/consensus/tutorial.asp

Optical coherence tomography

Optical coherence tomography is comparable to ultrasound, however it uses light instead of sound waves. It has better resolution than ultrasound but only penetrates to a depth of up to 1 mm, which approximately corresponds to the reticular dermis.

The resolution of optical coherence tomography does not reach the capabilities of reflectance confocal microscopy or histopathology, however cellular details can be viewed with the more modern devices. Although there are studies regarding the various features of skin cancer, reports of the diagnostic accuracy of optical coherence tomography are lacking. It seems that this technique might also play a role in other skin diseases in the future, such as contact dermatitis, psoriasis and bullous diseases, as well as monitoring of topical treatment.¹⁷

Reflectance confocal microscopy

Confocal laser scanning microscopy can be operated in fluorescence or reflectance mode, but reflectance confocal microscopy is more suitable for clinical applications. Reflectance confocal microscopy allows visualisation of the epidermis and papillary dermis at a quasi-histological resolution. Horizontal sections of a lesion can be scanned and viewed using a near-infrared laser. This method is ideally suited for melanoma diagnosis as melanin provides strong contrast and is easily visualised. Diagnostic algorithms for melanoma detection have been proposed and show improved diagnostic specificity and sensitivity.^{18–20} Furthermore, a glossary of terms commonly used in reflectance confocal microscopy has been published.²¹ This type of microscopy has also been used in non-melanoma skin cancer, Mohs surgery, *in vivo* surgical margin assessment and in follow-up of response to topical treatment. However, large-scale clinical studies are needed to assess the method's full clinical potential.

Multiphoton laser scanning microscopy

Multiphoton laser scanning microscopy works with a near-infrared laser beam which excites endogenous fluorophores. Nicotinamide adenosine dinucleotide phosphate (NADPH) is the primary source of autofluorescence. Like reflectance confocal microscopy, the multiphoton laser scanning microscopy provides horizontal sections of the skin allowing visualisation of cellular and subcellular structures. To date, it is mainly used as a research tool, rather than clinically.

Computer-assisted diagnosis

Automated diagnostic systems extract and analyse features of skin lesions and give a diagnosis. They have been shown to reach comparable levels of diagnostic specificity and sensitivity to that of expert dermatologists.²² To date, a few fully automated systems are available, some of which are integrated

in the software of videodermoscopy devices (Table 2). MelaFind uses multispectral imaging information from dermoscopic images. The MelaFind system is currently in the final stages of being granted US Food and Drug Administration approval and is anticipated to be available in the not too distant future. There is a tendency of these tools to over-diagnose melanoma. Further studies are required to assess the impact of automated instruments against human performance in the clinical field.

Molecular profiling

Molecular profiling is an emerging technique in melanoma diagnosis. A method that analyses RNA acquired from tape stripping of a suspicious melanocytic lesion is currently under investigation.

Conclusion

Although newer imaging techniques hold great promise, they cannot replace visual inspection and patient examination. Clinical naked eye observation in combination with dermoscopy can be regarded as the practical reference standard to identify lesions for excision. Histopathological analysis of lesions remains the gold standard in skin cancer diagnosis.

It is important to emphasise that pigmented lesions need to be evaluated in the context of a patient's entire skin examination. Although a general practitioner may easily make the decision to excise a suspicious lesion, there are a few clinical situations where a dermatologist's advice should be sought and further evaluation be performed. These include high-risk patients with multiple (atypical) naevi or naevi on specific anatomical locations such as palms, soles of the feet and under the nails, or on the genitals.

New non-invasive imaging techniques have great potential for monitoring lesion growth and response to treatment, as well as true margin assessment before surgery.

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Selected references are shown here. The full list of references is available with this article online at www.australianprescriber.com in Vol. 33 No. 5.

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Further reading

Selected dermoscopy books and online learning resources are listed with this article online at www.australianprescriber.com

Professor Soyer is co-founder and shareholder of e-derm-consult GmbH, a spin-off company of the Medical University of Graz, Austria, with emphasis on holistic solutions for teledermatology. He is also shareholder and consultant for MoleMap Australia by Dermatologists Pty Ltd.

Self-test questions

The following statements are either true or false (answers on page 163)

3. All patients with suspicious skin lesions need a full body examination at their first visit.
4. The ABCD rule is the appropriate clinical guide for assessing nodular lesions.

Book review

Dale and Applebe's Pharmacy Law and Ethics.
9th ed. Applebe G, Wingfield J.

London: Pharmaceutical Press; 2009. 553 pages.

Betty Chaar, Lecturer, Pharmacy Practice and Professional Ethics in Pharmacy, Faculty of Pharmacy, The University of Sydney

This very thorough examination of all legal aspects of the practice of pharmacy in the United Kingdom is the ninth edition of a popular text, widely used as a resource for pharmacists and in the training of future pharmacists in the UK. It is perhaps of less relevance to Australia, except that it could serve as a superb model for a similar text prepared in the Australian context of legal and ethical frameworks.

The book has benefited from years of revision, but also updates the reader about the 'plethora of legal changes that have been promulgated in recent years'. It is thoroughly researched, well indexed and is presented in a user-friendly style of headings and subheadings, with the added convenience of a summary at the end of each chapter, further reading suggestions and websites. The examples given to clarify complex issues are particularly useful to practitioners. Comparative analyses with other professions are also illuminating.

The majority of the 27 chapters are dedicated to explanation and examples of cases relating to various sections of the Medicines Act 1968. There are chapters about miscellaneous legislation relevant to the profession, explanation of the roles of various

bodies to which the profession is attached, and rules relating to registration as a pharmacist in the UK.

The chapter dedicated to professional conduct is limited in scope, by the authors' own admission, to the Royal Pharmaceutical Society's Code of Ethics. It does however clarify to the reader the exact status of the code and how pharmacists are bound by criminal, administrative and civil law as well as by the Code. In practical terms, the reader is taken through the principles and short explanations in clear unambiguous language, with references for further reading for those interested in more in-depth analyses of ethical principles underlying the Code.

The chapter on fitness to practise is of particular interest to those following the current roll-out of new legislation regarding pharmacy and other healthcare professions in Australia. The authors explain in detail the role of the various committees set up to address the diverse types and levels of misconduct and impairment, providing examples to elucidate stratification of jurisdiction and powers of these committees.

Although focused on the UK, this book is a valuable resource for those involved or interested in the legal and ethical framework of pharmacy practice outside Australia. It is an illuminating and helpful resource, not only because there are many similarities and universal practices in the pharmacy professions of western countries, but also in light of the current changes in Australian legislation.