Practical application of new technologies for melanoma diagnosis

Part I. Noninvasive approaches

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Learning objectives
After completing this learning activity participants should be able to identify new in situ technologies that may facilitate melanoma diagnosis; explain the advantages and disadvantages of each new in situ technology and how it could impact their patient population; and describe how these technologies can be incorporated into their practice, especially in the screening of patients at high risk of melanoma.

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Confirming a diagnosis of cutaneous melanoma requires obtaining a skin biopsy specimen. However, obtaining numerous biopsy specimens—which often happens in patients with increased melanoma risk—is associated with significant cost and morbidity. While some melanomas are easily recognized by the naked eye, many can be difficult to distinguish from nevi, and therefore there is a need and opportunity to develop new technologies that can facilitate clinical examination and melanoma diagnosis. In part I of this 2-part continuing medical education article, we will review the practical applications of emerging technologies for noninvasive melanoma diagnosis, including mobile (smartphone) applications, multispectral imaging (ie, MoleMate and MelaFind), and electrical impedance spectroscopy (Nevisense). (J Am Acad Dermatol 2015;72:929-41.)

Key words: MelaFind; melanoma; mobile app; MoleMate; Nevisense; spectroscopy; teledermatology.

Abbreviations used:

EIS:	electrical impedance spectroscopy
FDA:	US Food and Drug Administration
MSI:	multispectral imaging
SIA:	spectrophotometric intracutaneous analysis
SK:	seborrheic keratosis

OPPORTUNITY TO IMPROVE MELANOMA SCREENING EFFICIENCY

Key points

- **Melanomas may be difficult to distinguish clinically from nevi, particularly in high-risk patients**

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- **Numerous biopsy specimens associated with melanoma screening can be associated with significant costs and patient morbidity**

Making the clinical diagnosis of melanoma can be straightforward when confronted with a lesion that is markedly asymmetric with nonuniform pigmentation, particularly if there is history of recent change in appearance (ie, ABCDE of melanoma[1]) or if the atypical lesion is solitary or looks different from all other lesions (ie, ugly duckling[2]). However, in patients with numerous and clinically atypical nevi, it can be challenging to visually identify the lesion with the greatest histologically atypical features that may represent a new or developing melanoma. The number of nevi needed to remove in order to find 1 melanoma has been used as a measure of melanoma screening efficiency, with nevus to melanoma ratios ranging from 30 for general practitioners[3,4] to 4 to 12 for dermatologists[3,5-8] to 5 to 17 in specialized clinics seeing high-risk patients.[8-11] While lower nevus to melanoma ratios may indicate that fewer unnecessary biopsy specimens are being obtained, the optimal ratio for any practitioner or group of patients is unclear because removing too few nevi will likely be associated with missing some melanomas. On the other hand, unnecessary procedures may add significant cost to the medical system and morbidity for patients in the form of discomfort and scarring.

NONINVASIVE TECHNOLOGIES TO FACILITATE MELANOMA DIAGNOSIS

Key points

- **Noninvasive technologies may facilitate melanoma diagnosis and/or may minimize obtaining biopsy specimens from benign lesions**
- **Applications of new technologies may soon impact dermatology**

Noninvasive methods and technologies may facilitate early melanoma detection (Fig 1). [F1-4/C] Dermoscopy is a useful adjunctive tool that can help identify melanocytic lesions, increase confidence that a lesion may be benign or malignant, and increase diagnostic sensitivity in experienced users.[12] Serial dermoscopic photographs can be used (with devices such as MoleMax II) to observe individual lesions over time to identify potentially suspicious changes (rapid or asymmetric growth),[13-17] and the use of total body photography can increase the specificity of screening by confirming that most nevi are stable and not changing.[9,18-20] In addition to these conventional approaches, a number of noninvasive technologies have been developed that may facilitate a clinical diagnosis of melanoma. Reflectance confocal microscopy allows near-microscopic visualization of structures below the skin surface that approximates the resolution of histologic examination,[21,22] and several studies have shown its potential utility.[23-25] However, the large size and cost ($70,000-100,000) of instruments such as the Vivascope (personal communication with manufacturer, March 2015) will likely limit their current use to research applications, and this modality appears unlikely to make its way into community dermatology practices in the near future. These methods and technologies were reviewed in a continuing medical education article dealing with strategies for clinical management of patients with nevi that was published in the *Journal* in 2009.[26] Since that time, new information has been presented that addresses the applicability and efficacy of other technologies. In addition, Internet-based mobile applications (apps) have been developed for the detection of melanoma. We focus on these newer noninvasive technologies and their respective applications that are currently (or will soon be) commercially available and that may impact the practice of dermatology.

MOBILE (SMARTPHONE) APPLICATIONS

Key points

- **Smartphone-based applications for skin monitoring and melanoma detection are commercially available**
- **Many smartphone-based apps may not be reliable**

The near universal acceptance of the smartphone in developed countries has the potential to impact melanoma screening and early detection. Of 229 dermatology-related apps recently surveyed, 41 (18%) were related to self-surveillance/diagnosis and 8 (3.5%) related to teledermatology; half were free, and the others ranged in price from $0.99 to $139.99.[27] These include apps developed to assist patients in identifying melanoma on their skin. We reviewed apps that have been validated in published studies (Table I). Apps and accessories, including dermoscopes that can be mounted on the iPhone (Apple, Cupertino, CA), are also available to facilitate mobile teledermatology. These advancements in mobile technology could improve the detection rate and efficiency of self-skin examinations, leading to reduced time to diagnosis, mortality, and health care costs associated with melanoma. However, concerns have been expressed regarding the safety and accuracy of these mobile technologies.

In 2011, Health Discovery Corporation launched MelApp for the iPhone. It was one of the first mobile apps to use pattern recognition software and mathematical algorithms to provide melanoma risk

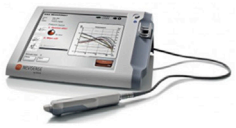
Technology	Study	Lesions (melanomas)	Sensitivity (%)	Specificity (%)
SIAscopy 	Moncrieff et al.[45]	348 (52)	83	80
	Haniffa et al.[47]	881 (31)	87	91
	Glud et al.[48]	83 (12)	100	59
	Tomatis[49]	1391 (184)	80	76
	Carrera[50]	1966 (287)	88	80
MelaFind 	Elbaum et al.[57]	246 (63)	95	68
	Friedman et al.[58]	99 (49)	98	44
	Monheit et al.[59]	1632 (127)	98	11
	Wells et al.[60]	47 (23)	96	8
	Hauschild et al.[63]	130 (65)	96	9
Nevisense 	Glickman et al.[68]	178 (12)	92	67
	Har-Shai et al.[69]	449 (69)	91	64
	Aberg et al.[70]	511 (16)	100	75
	Aberg et al.[71]	99 (13)	92	80
	Aberg et al.[72]	210 (62)	95	49
	Mohr et al.[73]			
	Algorithm 1	780 (103)	98	24
	Algorithm 2	715 (162)	99	25
	Malvehy et al.[74]	1946 (265)	97	34

Fig 1. Noninvasive imaging technologies and their performance in melanoma detection. Figures appear courtesy of (top to bottom) MedX Health Corp, MELA Sciences, and SciBase AB.

Table I. Mobile apps for melanoma detection

Study	Approach	No. of lesions	Melanomas	Sensitivity	Specificity
Robson et al[28]	AA	35*	2	50%	88%
Ferrero et al[29]	AA	93	93	11%	—
Wolf et al[31]		188	60		
App 1	AA			70%	40%
App 2	AA			69%	37%
App 3	AA			6.8%	94%
App 4	TD			98%	30%
Massone et al[33]	TD	18	2	100%	94%
Kroemer et al[34]	TD	104	6	100%	97%
Borve et al[35]	TD	69	12	61%†	—

AA, Automated analysis; *TD*, teledermatology.
*Fourteen of 35 lesions could not be analyzed by the app.
†Presented as diagnostic accuracy rather than sensitivity.

assessments for skin lesions. Robson et al[28] used the app to collect risk assessment data for 35 pigmented skin lesions from 31 patients who had been referred to their urgent skin cancer clinic. The app could not assess 40% of the lesions for technical reasons. When the low- and high-risk assessments reported by MelApp were compared with the histologic and/or clinical diagnoses for the remaining 21 lesions, the calculated sensitivity was 50% and the specificity was 88%. The authors concluded that mobile apps for the risk assessment of melanomas should be used with caution. MelApp is no longer available for download.

SkinScan also launched in 2011. Developed to analyze iPhone photos, it uses a proprietary fractal-based mathematical algorithm to build structural maps and determine the different growth patterns of skin lesions and the surrounding tissue. If SkinScan identifies a "high-risk" skin lesion, then the user is advised to visit the doctor "soon." The app recommends that "medium" and "low" risk skin lesions be tracked and shown to a physician during an annual skin examination. Ferrero et al[29] used SkinScan to evaluate 93 photos of biopsy-proven melanomas. The app reported 11% of the melanomas as high risk, 88% as medium risk, and 1% as low risk, and was unable to analyze some lesions (11% of total). In 2012, SkinScan was rebranded as SkinVision and the algorithm was modified. A clinical trial is planned in Europe to compare SkinVision with traditional diagnostic tools.[30] Given the recent changes in the regulation of mobile apps

(discussed below), the nevus analysis algorithm is currently unavailable in the United States.

In perhaps the largest study of its kind, Wolf et al[31] examined the accuracy of 4 (unidentified) smartphone apps that were used to evaluate images of 188 skin lesions, which included a total of 60 melanomas (44 invasive and 16 in situ) and 128 benign lesions (including nevi, seborrheic keratoses [SK], lentigos, dermatofibromas, and hemangiomas). The 4 apps were able to analyze 85% to 98% of the images, with sensitivities ranging from 7% to 98% and specificities ranging from 30% to 94%. The apps with the lowest sensitivities used automated algorithms to analyze the images; the best performing program missed 18 of 60 (30%) melanomas, whereas the app with the highest sensitivity used a store-and-forward form of mobile teledermatology (ie, images were analyzed by a remote dermatologist). In a related correspondence, Stoecker et al[32] questioned why the accuracy of this mobile teledermatology–based app exceeded what has been previously reported for teledermatology, and pointed out that the proportion of melanoma in situ to invasive melanoma lesions used in the study was much lower than is routinely seen in dermatology clinics or pigmented lesion centers—suggesting that the low sensitivity of smartphone apps is all the more worrisome.

Use of mobile teledermatology for melanoma screening

Key points

- **Mobile teledermatology appears to be feasible for melanoma screening**
- **Studies comparing mobile teledermatology with face to face dermatologic consultation and histopathologic examination are limited**
- **Smartphone apps are not designed to grade nevi or perform comparative analysis**

Several studies specifically evaluated the use of mobile teledermatology in melanoma screening. Massone et al[33] used a smartphone with a built-in 2-megapixel camera and pocket dermoscope to acquire clinical and dermoscopic images of 18 pigmented skin lesions (16 nevi and 2 melanomas) that were then forwarded to 2 independent (tele-) dermatologists for evaluation. Compared to the face to face diagnoses, the 2 teleconsultants correctly identified 89% and 91.5% of the lesions based on clinical and dermoscopic images, respectively. In a follow-up study, Kroemer et al[34] used a smartphone with a built-in 3.2-megapixel camera and pocket dermoscope to obtain clinical and dermoscopic images of 104 skin lesions (including 6 melanomas) from 80 patients. A single teledermatologist reviewed each set of clinical and dermoscopic images separately (1 month apart) and recorded a diagnosis. When differentiating benign from malignant skin lesions, the concordance between the teledermatologist and histopathology was 90% (κ value, 0.84) for both clinical and dermoscopic images. In addition, the teledermatologist and a face to face dermatologist were able to categorize all the melanomas as malignant melanocytic tumors. Considering all the lesions, the teledermatologist misdiagnosed 26 of the skin tumors, whereas the face to face dermatologist misdiagnosed 11 of the tumors. In a subsequent study, Borve et al[35] used a smartphone to capture clinical and dermoscopic images of 69 skin lesions (including 5 invasive melanomas and 7 melanomas in situ) scheduled for excision. The dermoscopic images were obtained using a dermoscope designed specifically as a smartphone attachment. The smartphone was also enabled with iDoc24 (iDoc24; Stockholm, Sweden), an app designed to facilitate mobile teledermatology. Two teledermatologists used a secure Internet platform (Tele-Dermis) to independently view the images. The authors reported that the diagnostic accuracy of the face to face dermatologic evaluation (67%) was similar to one of the teledermatologists (61%), but was statistically better than the other (51%). There was no statistical difference between the face to face dermatologist and the 2 teledermatologists when classifying lesions as benign or malignant.

These studies suggest that mobile teledermatology could potentially be used as a triage system for pigmented skin lesions, to screen referrals from primary care physicians, or be used in large-scale melanoma screening. In addition, such a platform may facilitate self-skin examinations. For example, Janda et al[36] provided a small group of high-risk patients with a mobile teledermoscope, which consisted of an iPhone 3 (with app preloaded) attached to a Handyscope (FotoFinder Systems; Bad Birnbach, Germany), and instructions for photographing and e-mailing the photographs to researchers. Patients selected both atypical and nonatypical appearing nevi, indicating the need for more training. Only 58 of 66 (88%) patient photographs were evaluable, with the remainder being of poor quality. In a follow-up study, 22 patients performed self-skin examinations assisted by mobile teledermatology and then underwent clinical examination; 1 melanoma and several nonmelanoma skin cancers were missed by patients and detected by the clinicians.[37] It was noted that patients tended not to select lesions in sexually sensitive areas or areas that are more difficult to

see. Patient omission of potential melanomas during lesion selection is further evidenced by Viola et al,[38] who found that a significant number of melanomas were incidentally identified by the consulting dermatologist in addition to the primary lesion of concern.

It is critical to note that smartphone apps and teledermatology are an adjunct to regular total body skin examinations, not a replacement for them. A limitation of mobile teledermatology is that clinical examination by the dermatologist is restricted to lesions of patient concern; face to face visits provide opportunities for complete skin examinations that may reveal skin cancers not noticed by the patient. Finally, another limitation of mobile apps is that they are generally not designed to grade nevus atypia or perform comparative analysis. They tend to provide an "all or nothing" answer on individual lesions (ie, nevus vs melanoma) without indicating the degree of irregularity or other potentially suspicious features. In addition, one of the major drawbacks over a face to face encounter is that these apps are not designed to compare lesions to one another, to identify the most atypical lesion (ie, ugly duckling), or to recognize atypical lesions that have shared features (ie, signature nevi).

Regulation of mobile technologies

Key point

- **The US Food and Drug Administration has regulatory authority over mobile apps, but the extent to which regulations will be enforced is unclear**

The US Food and Drug Administration (FDA), under the guidance of the US Congress, has expressed the intent to regulate mobile medical apps designed to diagnose, treat, mitigate, or prevent disease. In 2011, the FDA proposed guidelines to regulate mobile apps in accordance with existing regulated devices if the program (1) transforms the mobile device to function in a manner similar to existing FDA-regulated devices or (2) allows the device to connect or act accessory to preexisting FDA-regulated devices or programs.[39,40] Regulations for apps that pose minimal risk to patients and consumers but meet regulatory criteria for categorization as a "device" will not require submission for premarket review for approval by the FDA. These guidelines were officially issued in September 2013, and updated subsequently. Regulated mobile medical apps will include those that assist with self-management without providing specific treatment suggestions and devices that document, show, or communicate medical conditions to health care providers.[41] It is unclear how "minimal risk" will be defined and whether it will be applicable to devices used to rule out potential skin malignancy.

In summary, screening for melanoma with mobile devices appears feasible, with direct patient to physician teledermatology holding the most promise. However, barriers exist in the risk of missed malignancies (through the omission of malignant lesions not presented by the patient) and implementation of device regulations. Future investigation should focus on demonstrating the efficacy of mobile apps in melanoma detection as they are intended to be used by the population. If these apps prove unreliable, they may potentially cause harm to patients. We look forward to new developments that may enhance mobile technology and additional controlled studies that may validate it.

MULTISPECTRAL IMAGING: SPECTROPHOTOMETRIC INTRACUTANEOUS ANALYSIS (SIAsCOPY)

Spectrophotometric intracutaneous analysis technology and agreement with histologic features

Key points

- **SIAscopy uses chromophore imaging to determine microscopic architecture**
- **SIAscopy may assess melanin content and larger collagen structures more accurately than hemoglobin, but may not directly correlate with histology**

Spectrophotometric intracutaneous analysis (SIA) is a noninvasive multispectral imaging (MSI) technology intended for the evaluation of pigmented skin lesions and the detection of melanoma. A handheld scanner (SIAscope) illuminates 1.2 to 2.4 cm^2 areas of skin with wavelengths of light ranging from 400 to 1000 nm. Newer versions of the SIAscope are also capable of capturing dermoscopic images. Calibrated images are analyzed by a series of algorithms that extract information about the distribution, position, and quantity of several different chromophores (ie, eumelanin, hemoglobin, and collagen). Several studies have investigated the accuracy of SIAscopy in displaying the amount of melanin, blood, and collagen present in the epidermis and dermis. Claridge et al[42] found almost perfect correlation for melanin and a moderate correlation for hemoglobin. Subsequently, Matts et al[43] found that eumelanin measurements obtained by SIAscopy correlated with melanin density in histologic samples across all Fitzpatrick skin types. However, Terstappen et al[44] subsequently compared the SIAscopic images of 60 suspicious pigmented

skin lesions with their histopathologic features, and found that dermal melanin and collagen holes had no agreement with histologic results.

Early clinical studies using SIAscopy

Key points

- **Multiple studies have assessed the sensitivity and specificity of SIAscopy in melanoma detection**
- **SIAscopy may not be superior to dermoscopy**
- **SIAscopy is not well-suited for seborrheic keratoses, which may limit its utility in primary care settings**

Moncrieff et al[45] used a SIAscope to obtain images of 348 pigmented skin lesions (including 52 melanomas) referred for excision. The presence of dermal melanin, an erythematous blush from blood displacement, and a lesion diameter ≥6 mm favored a diagnosis of melanoma over benign lesions with 82.7% sensitivity and 80.1% specificity. In another study, Govindan et al[46] reported on SIAscopy in the screening of 886 lesions referred to a pigmented lesion clinic by general practitioners. The presence of only dermal melanin gave 94.4% sensitivity and 64% specificity for melanoma detection.

Several studies compared the performance of SIAscopy to dermoscopy. In a study by Haniffa et al,[47] dermatologists evaluated 881 pigmented lesions (including 31 melanomas) with a dermoscope and then reexamined each lesion using a SIAscope. The sensitivity and specificity of dermoscopy alone was 94% and 91%, respectively, and performance was not improved by the addition of SIAscopy. In another study, Glud et al[48] compared SIAscopy and dermoscopy in the evaluation of 83 lesions (including 12 melanomas) referred by nondermatologists for treatment. They reported that SIAscopy had higher sensitivity compared to dermoscopy (100% vs 92%), but lower specificity (59% vs 81%).

Several teams have developed new algorithms for MSI. Tomatis et al[49] developed a neural network classifier using a data set of 1391 lesions (including 184 melanomas) that was able to discriminate between melanomas and nonmelanoma lesions with a sensitivity of 80% and a specificity of 76%. Subsequently, Carrara et al[50] examined 1966 lesions (including 287 melanomas) excised for histopathologic diagnosis and 1940 nonexcised lesions that were not clinically suspicious by MSI and developed a classifier to differentiate the lesions as "excision-needing" or reassuring, based on the clinicians' management decisions. The system was able to emulate the clinicians with a sensitivity of 88% and a specificity of 80%.

These early studies suggested that SIAscopy might be useful for nondermatologists selecting skin lesions for referral because it does not require specific training and expertise. In addition, SIAscopy might be a good tool for training and archiving because it can also capture dermoscopic images. One problem with SIAscopy found in primary care settings is the low performance attributed to the high prevalence of SKs. Several studies[46,47,51] have reported on the negative effects SKs have on the sensitivity and specificity of SIAscopy.

MoleMate

Key points

- **Alternative algorithms and training programs were developed to improve the diagnostic accuracy of SIAscopy in primary care settings**
- **Molemate demonstrates equivalent sensitivity but reduced specificity compared to traditional diagnostic techniques**
- **MoleMate has received regulatory approval in the United States, European Union, and Canada**

Emery et al[52] used SIAscopy in the evaluation of 1211 lesions in 858 patients in primary care settings in the United Kingdom and Australia. The original SIAscopic diagnostic algorithm did not perform well in primary care settings because of the high prevalence of SKs and hemangiomas seen in that patient population; therefore, a primary care scoring algorithm was developed that would eventually be called MoleMate. The new algorithm added additional features (ie, the presence of collagen white dots, a cerebriform pattern, and blood vessels) and the patient's age to the Moncrieff scoring system[45] to aid in correctly differentiating SKs and hemangiomas from melanoma. The new algorithm proved to be more specific than the Moncrieff scoring system and dermoscopy using the 7-point checklist.

Several studies have shown that training of primary care practitioners can improve performance. Wood et al[53] reported that a short, computer-based course significantly improved SIAscopic feature recognition in a group of 25 primary care providers, whose median test scores improved from 74% to 86% after training. Watson et al[54] evaluated the effectiveness of the training program in a group of 18 general practitioners in the United Kingdom and another 30 in Australia. The United Kingdom and Australian groups

similarly improved their median test scores after completing the training program.

In a large randomized controlled trial, Walter et al[55] studied the evaluation by primary care physicians of 1297 patients presenting with pigmented skin lesions that were not immediately diagnosed as benign. Approximately half the patients were subjected to best practice (ie, clinical history, naked eye examination, and dermoscopy) while the remaining patients were evaluated using best practice in conjunction with MoleMate. Almost all (17/18) of the confirmed melanomas in the best practice group were correctly diagnosed, while (18/18) of them were correctly identified using best practice combined with MoleMate. For benign lesions, on the other hand, MoleMate was inferior to best practice in recommending a significantly higher percentage of lesions for biopsy.

MoleMate and its expanded features version (SIMSYS) is marketed by MedX Health Corporation (Mississauga, Ontario, Canada). These products received FDA approval in 2011, and have also received Health Canada clearance and CE Mark approval. MoleMate costs $6000 and SIMSYS costs $8000, but the latter adds the capability to store information on the patient, lesion location, and previous analysis (personal communication with manufacturer, March 2015). These systems are not broadly used in the United States by dermatologists, but may be having an impact in the cosmetics industry. MedX licensed a version of its technology to Proctor & Gamble for use in cosmetic point of sale counters to show consumers the condition of their skin before and after the use of skin products.

MULTISPECTRAL IMAGING—MELAFIND

MelaFind technology and early studies

Key points

- **MelaFind uses automatic image analysis and pattern recognition of skin lesions to determine morphologic disorganization**
- **Several studies suggest that MelaFind improves biopsy sensitivity but decreases specificity**

MelaFind (MELA Sciences; Irvington, NY) is a noninvasive MSI system that uses a handheld scanner to obtain 10 images using wavelengths ranging from visible to near-infrared (430-950 nm) that penetrate up to 2.5 mm beneath the skin surface.[56] First, the lesion is separated from the surrounding tissue based on differences in reflectance of blue (430 nm) light (image segmentation). Next, information regarding the presence and distribution of certain dermoscopic features (eg, asymmetry, blotchiness, etc) is extracted from the images. Finally, automated algorithms, based on linear classifiers, are used to analyze the data and ultimately determine the morphologic disorganization of the lesion. A proprietary database containing images of roughly 10,000 lesions (including >600 melanomas) was used in the training of the classifier. Each algorithm was designed to differentiate melanoma from one of the following: low-grade dysplastic nevus, congenital nevus, common nevus, SK, solar lentigo, and pigmented basal cell carcinoma. A given lesion is assigned 6 different scores, and if all the scores are above a set threshold value, then MelaFind recommends that a biopsy specimen of the lesion be obtained.

Elbaum et al[57] imaged 246 pigmented lesions (including 63 melanomas) that were considered suspicious for melanoma by skin cancer specialists and that were subsequently referred for biopsy. Two classifiers were used to define the threshold values that were used in separating melanoma from other lesions; a linear classifier yielded 100% sensitivity and 85% specificity, while a nonlinear classifier provided a sensitivity of 95% and a specificity of 68%. In a subsequent study, Friedman et al[58] independently presented 10 expert dermoscopists with dermoscopic images of 99 pigmented skin lesions (including 49 melanomas ≤6 mm) and compared their diagnostic performance and management decisions with those of MelaFind. The dermoscopists collectively demonstrated 39% sensitivity and 82% specificity in melanoma diagnosis and 71% sensitivity and 49% specificity in recommending that a biopsy specimen be obtained. MelaFind produced a sensitivity of 98% and a specificity of 44% in recommending a biopsy.

In a large multicenter study, Monheit et al[59] used MelaFind to evaluate 1632 pigmented lesions (including 127 melanomas) that were referred by dermatologists for biopsy. Melafind gave a sensitivity of 98% (2 melanomas were missed) and a specificity of 11% in recognizing the melanomas and recommending that a biopsy specimen be obtained. Melafind was compared to 39 dermatologists in an accompanying reader study consisting of 50 pigmented lesions (including 25 melanomas) selected from the initial pool of 1632 lesions. Dermatologists were presented with clinical history and dermoscopic images yielding a sensitivity of 78%, with fair interreader agreement (κ value, 0.22), but no specificity was reported (available in the package insert). In a follow-up study, Wells et al[60] randomly selected 47 of the 1632 lesions (which included 23

Table II. Comparison of dermatologist performance without and with use of noninvasive devices

Study	Approach	No. of lesions	Melanomas	Sensitivity	Specificity
MelaFind					
Rigel et al[60]	Clinical only	24	5	69%	54%
	Clinical plus device			94%	40%
Hauschild et al[61]	Clinical only	130	6	70%	56%
	Clinical plus device			78%	46%
Nevisense					
Har-Shai et al[67]	Clinical only	400	53	81%	84%
	Clinical plus device			98%	55%

melanomas) and provided clinical history and clinical and dermoscopic images to a panel of dermatologists who were blinded to the MelaFind results. The average biopsy sensitivity and specificity of the participating dermatologists was 80% and 43%, respectively, while sensitivity and specificity of MelaFind was 96% and 8%, respectively. Together, these studies suggest that MelaFind may have increased diagnostic sensitivity but reduced specificity for diagnosing melanoma compared to dermatologists. In addition, it may misclassify non-melanoma skin cancers because the technology is designed to assess overall structural disorganization of lesions rather than atypical cellular features.

Effect of MelaFind on performance of dermatologists

Key points

- **The utility of MelaFind for melanoma detection has been debated**
- **MelaFind as an adjunct to clinical examination increases provider sensitivity but decreases specificity**

Melafind has been criticized for its low specificity in melanoma detection, which comes at the expense of its high sensitivity. Cukras[61] expressed reservations about the low specificity of Melafind, suggesting that it may have limited utility; in achieving such high sensitivity it "almost always recommends biopsy." In regard to the study by Wells et al,[60] it was argued that randomly obtaining biopsy specimens of the subset of lesions at the same rate in the larger study would also achieve 94% sensitivity and 6% specificity. In the study by Monheit et al,[59] MelaFind also recommended obtaining a biopsy specimen for >90% (1472/1632) of the lesions.

Several recent studies have investigated the influence of MelaFind on the biopsy decisions reached by dermatologists. While the specificity of the device is low when used in isolation, dermatologists using MelaFind as a clinical adjunctive tool to assist in the decision to biopsy lesions of concern demonstrated improved specificity, which was still lower than their specificity without the device (Table II). Rigel et al[62] provided 179 dermatologists with the clinical history and clinical and dermoscopic images of 24 pigmented skin lesions (including 5 melanomas). After the dermatologists decided which lesions they would recommend for biopsy, they were provided the MelaFind recommendations and allowed to change their biopsy decisions. Knowledge of the MelaFind results improved their biopsy sensitivity from 69% to 94%, but their specificity declined from 54% to 40%. In addition, their biopsy recommendation rates associated with lesions that were not recommended by MelaFind for biopsy fell from 43% to 25%. The authors concluded that MelaFind can improve biopsy decision-making by dermatologists.

Recently, Hauschild et al[63] performed an online reader study in which 130 German dermatologists were provided the clinical history and clinical and dermoscopic images for 130 pigmented skin lesions (including 65 melanomas), with half of the dermatologists randomly selected to also receive MelaFind results for each lesion. For these lesions, MelaFind had a sensitivity of 96% and a specificity of 9%. The dermatologists without access to MelaFind results had a sensitivity of 70% and specificity of 56%, while those given the MelaFind results had a significantly higher sensitivity of 78% and lower specificity of 46%. The authors suggested that MelaFind could be an effective tool and reasoned that the reduced specificity associated with knowing the results was acceptable given the number of additional early melanomas that were detected by the dermatologists. Although not strictly used as such in the aforementioned studies, the high sensitivity of the device could be useful for ruling out melanoma given its high negative predictive value—although it should be noted that in the study by Monheit et al,[59] 2 of the lesions not recommended for biopsy by MelaFind proved to be melanoma.

Regulatory approval of MelaFind

Key points

- **MelaFind has received premarket approval from the US Food and Drug Administration and CE Mark approval in the European Union**
- **The US Food and Drug Administration has stipulated that MelaFind be used only by dermatologists to assist in biopsy decision-making**

MelaFind received premarket FDA approval in 2011, but because of concerns about the device's inability to detect nonmelanoma skin cancers and its low specificity, the FDA and MELA Sciences agreed to restrict its use with the following stipulations: (1) MelaFind is intended to assist the dermatologist with his/her decision to biopsy clinically atypical lesions by providing additional morphologic analysis; (2) lesions selected for analysis should not include those for which a melanoma diagnosis is considered likely as biopsy is already indicated; and (3) MelaFind is only to be used by a dermatologist who has completed a training program in the appropriate use of the device.[64] MelaFind also received approval in the European Union in 2011.

It has been reported that about 150 of the MelaFind devices have been distributed in the United States and Germany.[64] Under the company's physician lease agreement, a one-time fee of $10,000 is charged for installation of the device and training of personnel, along with an annual renewal fee of $2000 plus additional charges for each use.[65] Health insurance does not currently cover the service, and it is reported that patients are paying $25 to $175 for the first lesion evaluation and around $25 each for subsequent lesions.[64]

ELECTRICAL IMPEDANCE SPECTROSCOPY

Technology and initial studies

Key points

- **Electrical impedance spectroscopy measures the opposition to alternating electrical currents to determine differences in cellular properties**
- **Electrical impedance spectroscopy devices have improved (ie, TransScan, SciBase II, SciBase III, and Nevisense)**
- **Multiple studies have assessed performance of electrical impedance spectroscopy in melanoma diagnosis**

Electrical impedance spectroscopy (EIS) is a noninvasive diagnostic approach based on inherent electrical differences between benign and malignant tissues[66] that was initially investigated in breast cancer screening.[67] EIS measures electrical resistance within tissues subjected to alternating currents of various frequencies (1 kHz-2.5 MHz). Resistance to low frequencies is affected by the extracellular environment, whereas both the intra- and extracellular environments affect measurements at higher frequencies. Changes in cell shape, size, and membrane composition can be detected by EIS. Scanning uninvolved adjacent tissue allows determination of baseline electrical impedance of skin in a given area, which can then be compared to the electrical impedance of the lesion. An algorithm is used to classify the lesion based on data obtained from both the lesion and the adjacent skin.

Glickman et al[68] initially tested a TransScan device on human xenografted melanoma tumors in mice, and then used it to evaluate 178 suspicious skin lesions (including 12 melanomas) scheduled for excision. The device had a sensitivity of 92%, and specificity of 67%, although sensitivity improved with increasing melanoma depth. In a follow-up study, Har-Shai et al[69] used an updated version of TransScan to study 449 lesions (including 69 melanomas) scheduled for excision. The device failed to detect melanomas on the head and the neck because of electrical differences between these areas and the rest of the body. For lesions on the trunk and extremities, the EIS system had a sensitivity of 91% with a specificity of 64%, compared to dermatologists who had a sensitivity of 81% and a specificity of 84%. The addition of EIS to clinical examination improved the physicians' sensitivity to 98% but decreased their specificity to 55%.

Aberg et al[70] used the SciBase II EIS device (SciBase AB; Stockholm, Sweden) to evaluate 511 nevi and 100 skin cancers (including 16 melanomas) scheduled for excision. Scibase II had 100% sensitivity and 75% specificity in distinguishing melanomas from nevi, and 100% sensitivity and 87% specificity in distinguishing nonmelanoma skin cancers from nevi. In a follow-up study, Aberg et al[71] assessed 99 nevi and 13 melanomas, with the modification of using 2 different electrodes: a completely noninvasive circular electrode and a microinvasive spiked electrode. The small spikes penetrate the stratum corneum to reach the epidermis, and reduce biologic impedance variation that was problematic with earlier devices on the head and neck. The spiked electrodes demonstrated the best performance in distinguishing benign nevi from melanoma, yielding a sensitivity of 92% and a specificity of 80%. In a multicenter study, Aberg

et al[72] investigated the performance of SciBase II using disposable spiked electrodes and a new automated classification algorithm. The automated algorithm was trained on 285 lesions (including 135 melanomas) and then validated on a different set of 210 lesions (including 62 melanomas). The observed sensitivity was 95% and specificity was 49%, and sensitivity increased with melanoma thickness.

Further improvements were realized in the SciBase III device, which was used in a multicenter study by Mohr et al[73] of 681 patients with 751 lesions referred for excision. Based on experiences with SciBase II, 2 different algorithms were developed and evaluated. The first algorithm, in which 40% of the lesions were used for training and the remaining 60% for validation, gave a sensitivity of 98% for melanoma, 100% for nonmelanoma skin cancer, and 84% for severely dysplastic nevi; the overall observed specificity was 24%. The second algorithm, in which 55% of the lesions were used for training and the remaining 45% for validation, gave a sensitivity of 99% for melanoma, 98% for nonmelanoma skin cancer, and 94% for severely dysplastic nevi; the overall observed specificity was 25%. By comparison, the sensitivity was 100% and specificity was 8% for the referring dermatologists.

Nevisense

Key points

- **Nevisense has high sensitivity for both melanoma and nonmelanoma skin cancers**
- **Nevisense received the European CE Mark and approval by the Australian TGA, but has not yet received US Food and Drug Administration approval**

Results of performance of the newest SciBase iteration (Nevisense) in a phase 3 multicenter (5 US and 17 European sites) prospective, blinded clinical trial were recently reported by Malvehy et al.[74] In total, 1951 patients with 2416 lesions were enrolled in the study, with all lesions subsequently excised and evaluated by a panel of dermatopathologists. Ultimately, 473 lesions were excluded for various reasons (eg, investigator errors, lack of consensus diagnosis among the histopathologists, technical issues), which resulted in a total of 1946 evaluable lesions (including 265 melanomas). In addition, clinical and dermoscopic images of 1701 lesions (including 238 melanomas) were obtained for later evaluation by expert dermoscopists in a reader-type study. Nevisense classified melanoma with a sensitivity of 97% (9/265 melanomas were missed) and a specificity of 34%. Nevisense had 100% sensitivity for nonmelanoma skin cancers (48 basal cell carcinomas and 7 squamous cell carcinomas). The dermoscopists detected melanoma with a sensitivity of 49% to 61% and a specificity of 89% to 94%. Nevisense has received the European CE Mark and been approved by the Australian TGA, but has not yet been approved by the FDA for use in the United States. Pricing for Nevisense in the United States is not currently available (personal communication with manufacturer, March 2015).

RECOMMENDATIONS

Over the past few years, a number of noninvasive imaging applications and devices to facilitate melanoma detection have become available and are poised to impact the practice of dermatology. These new technologies offer the promise of improving early melanoma detection both by patients and physicians and reducing the practice of obtaining unnecessary biopsy specimens. Although multiple mobile apps have been developed for self-skin examination and appear feasible for skin screening and teledermatology, none of them (based on what is reported in the literature) have been adequately studied and/or shown to be sufficiently accurate and reliable to recommend at this point in time. MSI and EIS technologies have each led to next-generation devices that are easy to use in outpatient clinical settings. While these devices have some advantages and disadvantages, as summarized in Table III, they generally tend to have greater diagnostic sensitivity but lower specificity than has been reported for experienced dermatologists and dermoscopists. While dermoscopy by experienced practitioners appears to have a better sensitivity and specificity than any of the devices,[12] it is important to note that no trials have been conducted to compare the performance of dermatologists with or without dermoscopy against dermatologists using any of these newer devices in a true clinical setting. Another important consideration of the low specificity of these tools is that they are likely to recommend obtaining a biopsy specimen of lesions that are already difficult for dermatologists to diagnose (ie, clinically atypical nevi that are not clearly benign or malignant) and therefore may not be as helpful in patients with multiple atypical nevi. None of these devices scan the entire body, as would occur during a complete skin examination. It is also important to know that these devices require the lesion to be on a flat surface and accessible; lesions on the ears and under the nail plate, for example, are not evaluable. In addition, the trials of these devices excluded acral, mucosal, and genital lesions, as well

Table III. Comparison of new-generation noninvasive imaging devices

	MoleMate	MelaFind	Nevisense
Technology	MSI	MSI	EIS
Sensitivity	50%	>95%	>95%
Specificity	80-90%	10%	25%
Detection of NMSC	No	No	Yes
Detection of SK	No	No	Yes
Speed*	<1 min	1-2 min	5-10 min
Approval	US, EU, and Canada	US and EU	EU and Australia
Cost	$6000	Lease†	N/A

Note: MoleMate, MelaFind, and Nevisense are trademarks of their respective manufacturers.
EU, European Union; *N/A*, not available; *NMSC*, nonmelanoma skin cancer; *SK*, seborrheic keratosis; *US*, United States.
*Approximate time to evaluate single lesion.
†2013 leasing agreement stipulates $10,000 installation and training fee, $2000 annual renewal fee, and charges per lesion or patient session.

as lesions in hair-bearing areas. Finally, while these devices give a quantitative readout that is objective, there is a subjective component in which lesions the practitioner chooses to evaluate with the device.

In conclusion, while the performance of these devices is to some extent limited by the particular technology, their sensitivity and specificity for melanoma detection are largely determined by the threshold settings used for the algorithm classifiers. It is likely that the fear of missing a melanoma has led to classifier settings that favor high sensitivity at the expense of lower specificity. An interesting question to consider is what standards of performance the industry should be held for such devices in order to ensure patient safety and minimize harm. It is conceivable that the classifiers in these devices may be updated or modified for particular practice settings (such as primary care or general dermatology) and/or for particular patients based on melanoma risk factors, including numbers of nevi and clinically atypical nevi, and patient-reported history regarding individual lesions. Individual practitioners will have to contend with the practical considerations of evaluating how such applications and devices could be incorporated into their practices and be paid for, because their use is currently not covered by most health insurance plans.

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Answers to CME examination

Identification No. JA0615

June 2015 issue of the Journal of the American Academy of Dermatology.

March J, Hand M, Grossman D. J Am Acad Dermatol 2015;72:929-41.

1. e
2. c
3. b
4. a

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CME examination

Identification No. JA0615

June 2015 issue of the Journal of the American Academy of Dermatology.

March J, Hand M, Grossman D. J Am Acad Dermatol 2015;72:929-41.

Directions for questions 1-4: Choose the single best response.

A patient of yours seen 3 years ago with multiple nevi and a history of melanoma in situ had a difficult time getting an appointment, and decided to use a mobile app to check a few lesions she was concerned about. She called to tell you that the app (based on automated analysis) had not identified any of the lesions as high risk, and wondered if she still should come in for an examination.

1. What is the most appropriate thing to tell this patient?
   a. Automated analysis apps are the most sensitive and specific for melanoma detection, so she should be reassured
   b. The app she is using is an appropriate substitute for clinical evaluation, if she does not think the particular lesions have been changing in the past few months
   c. The majority of mobile apps available for download have been validated by clinical studies, and shown to be as effective as a dermatologist's examination
   d. She should confirm that the app she is using has been approved by the US Food and Drug Administration.
   e. It is unlikely that the app she is using has been validated in clinical studies, and it would be prudent given her history that she visit you for skin examination

The patient lives far away and is wondering if a teledermatology app would be better suited for her use in screening instead of the automated analysis app.

2. What is the most appropriate thing to tell this patient?
   a. Teledermatology apps are as sensitive as face to face clinical examinations because patients can usually identify the most suspicious lesions by self-skin examination
   b. There are a significant number of lesions that cannot be assessed with teledermatology but can be assessed by automated analysis
   c. Teledermatology apps may be a viable way to screen, but she should still plan on annual visits with a dermatologist for complete skin examination
   d. Teledermatology apps provide additional information in characterizing lesions that is otherwise not assessable by the naked eye
   e. Teledermatology has similar specificity as a clinical examination by a dermatologist

You are considering purchasing a new device for the noninvasive detection of melanoma, and have reviewed several devices based on new technologies.

3. Which device has both high sensitivity and the ability to also detect nonmelanoma skin cancers?
   a. MoleMate
   b. Nevisense
   c. Melafind
   d. MelApp
   e. There is no device with both of these features

4. What is likely to happen to your biopsy and melanoma detection rates when you use one of the devices as an adjunct to your clinical examination?
   a. Biopsy and melanoma detection rates will increase
   b. The biopsy rate will decrease while the melanoma detection rate will increase
   c. Neither rate will change
   d. Biopsy and melanoma detection rates will decrease
   e. The biopsy rate will increase while the melanoma detection rate will be unaffected