Technological advances for the detection of melanoma

Advances in diagnostic techniques

Lauren Fried, BS, Andrea Tan, MD, Shirin Bajaj, MD, Tracey N. Liebman, MD, David Polsky, MD, PhD, and Jennifer A. Stein, MD, PhD
New York, New York

Learning objectives
After completing this learning activity, participants should be able to describe how total body photography can be used to identify early melanoma; explain how confocal imaging can reduce unnecessary biopsies; and discuss the status of artificial intelligence in melanoma diagnosis.

Disclosures
Editors
The editors involved with this CME activity and all content validation/peer reviewers of the journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

Authors
The authors involved with this journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

Planners
The planners involved with this journal-based CME activity have reported no relevant financial relationships with commercial interest(s). The editorial and education staff involved with this journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

Managing the balance between accurately identifying early stage melanomas while avoiding obtaining biopsy specimens of benign lesions (ie, overbiopsy) is the major challenge of melanoma detection. Decision making can be especially difficult in patients with extensive atypical nevi. Recognizing that the primary screening modality for melanoma is subjective examination, studies have shown a tendency toward overbiopsy. Even low-risk routine surgical procedures are associated with morbidity, mounting health care costs, and patient anxiety. Recent advancements in noninvasive diagnostic modalities have helped improve diagnostic accuracy, especially when managing melanocytic lesions of uncertain diagnosis. Breakthroughs in artificial intelligence have also shown exciting potential in changing the landscape of melanoma detection. In the first article in this continuing medical education series, we review novel diagnostic technologies, such as automated 2- and 3-dimensional total body imaging with sequential digital dermoscopic imaging, reflectance confocal microscopy, and electrical impedance spectroscopy, and we explore the logistics and implications of potentially integrating artificial intelligence into existing melanoma management paradigms. (J Am Acad Dermatol 2020;83:983-92.)

Key words: artificial intelligence; confocal microscopy; dermoscopy; electrical impedance spectroscopy; machine learning; melanoma; sequential digital dermoscopic imaging; total body photography.

From The Ronald O. Perelman Department of Dermatology, New York University School of Medicine.
Ms Fried and Ms Tan are cofirst authors.
Funding sources: None.
Conflicts of interest: None disclosed.
Accepted for publication March 22, 2020.
Reprint requests: Jennifer A. Stein, MD, PhD, The Ronald O. Perelman Department of Dermatology, New York University School of Medicine, 240 E 38th St, New York, NY 10016. E-mail: Jennifer.Stein@nyumc.org.
0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2020.03.121
Date of release: October 2020.
Expiration date: October 2023.

Scanning this QR code will direct you to the CME quiz in the American Academy of Dermatology's (AAD) online learning center where after taking the quiz and successfully passing it, you may claim *1 AMA PRA Category 1 credit*. NOTE: You must have an AAD account and be signed in on your device in order to be directed to the CME quiz. If you do not have an AAD account, you will need to create one. To create an AAD account: go to the AAD's website: www.aad.org.

Distinguishing early stage melanomas from atypical nevi remains a diagnostic challenge for dermatologists. Examination with the naked eye has limited diagnostic accuracy compared with examination using additional technologies.[1] For example, dermoscopy use enables higher sensitivity, decreased benign-to-malignant ratios, and the detection of thinner melanomas compared to examination with the naked eye.[2-5] For dermoscopically challenging pigmented lesions (ie, "borderline" lesions), novel noninvasive technologies can maximize accurate diagnosis while minimizing preventable morbidity and the cost of additional procedures. Herein, we discuss these technological imaging advancements in depth and provide an update on melanoma detection.

TOTAL BODY PHOTOGRAPHY

Key points

- **Total body photography facilitates the identification of new or changing lesions in patients with atypical nevi and has been shown to reduce the number of biopsy specimens obtained from benign lesions**
- **Automated total body photography enables rapid standardized image collection**
- **Three-dimensional total body photography is commercially available and allows 360° visualization of all body surfaces**

Background

For patients with extensive or atypical nevi, identifying malignant lesions is challenging; total body photography (TBP) has long been used to facilitate this process.[6] TBP involves capturing high-resolution baseline clinical full-body photographs for use as adjuncts to total body skin examinations (TBSEs) at subsequent visits. This can aid in the identification of new/changing lesions and reassure both the patient and the physician that a lesion has exhibited stability over time. TBP is most useful for patients with extensive or atypical nevi, patients who have undergone many biopsy procedures, or patients with extensive photodamage.[7]

Benefits

Referencing TBPs during the TBSE can help physicians identify new or changing lesions, which may contribute to earlier detection of cutaneous malignancy.[6,8] In a 5-year cohort study of 977 melanoma patients, 48% of 46 second primary melanomas were diagnosed by TBP.[9] Furthermore, comparison with baseline photographs can provide evidence of lesion stability and reduce unnecessary biopsy procedure. A study of high-risk patients in 2 pigmented lesion clinics saw a 3.8-fold reduction in nevus biopsy procedures after TBP incorporation.[10] A reduction in biopsy procedures is associated with decreases in both patient morbidity and costs to the health care system.[10] Implementation of TBP has also been shown to decrease cancer worry, which can improve patient quality of life and adherence to screening.[11] TBPs can also be referenced during self-skin examinations (SSE), wherein TBP utilization has been shown to improve sensitivity and specificity for detection of new/changing lesions.[12]

Automated TBP

While periodic TBP is a useful tool, obtaining photographs is time-consuming given the multiple body positions, angles, and lighting conditions that must be reliably reproduced. Automated TBP machines (Table I) use whole-body scanners with multiple cameras that simultaneously capture images from different angles. This facilitates rapid standardized image collection, reduces operator error, and does not require a manual photographer. Costs can range from $50,000 to $150,000, so dermatologists need to consider whether their patient population could benefit from these technologies (telephone communication, Canfield Scientific Inc, 2019).

Three-dimensional TBP

Canfield Scientific, Inc offers 2 automated 3-dimensional (3D) TBP devices, the VECTRA WB360 and the VECTRA WB180.[13] In the WB360 ($245,000), the patient holds 1 pose and 92 cameras simultaneously capture photographs from all angles. A digital 3D avatar of the patient is generated, allowing for 360° visualization of all body surfaces and manual annotation with dermoscopic images, easing incorporation of TBPs into the TBSE. The VECTRA WB180 ($135,000) comprises 46 cameras and generates 2 independent avatars of the patient's front and back. However, 3D-TBP is not currently widely used because of the costly equipment and the large device size, which may be difficult to incorporate into existing offices, though the WB180 occupies significantly less space.

Simplified TBP

Because formal TBP can be cost prohibitive, informal, more affordable solutions can be substituted. Smartphones and tablets can be used to import photographs of individual lesions or parts of the body directly into the electronic medical record. MoleMapper (Sage Bionetworks, Seattle, WA) is an example of a free iOS application that patients can download to store photographs on their smartphone for use during SSEs and TBSEs. Simplified TBP can be

Table I. Comparisons of total body photography, sequential digital dermoscopic imaging, and reflectance confocal microscopy

Technology	Key features	Advantages	Limitations and financial information
TBP	Clinical imaging of entire skin surface Automated TBP machines are offered by companies including Canfield Scientific (Parsippany, NJ), DermSpectra (Tucson, AZ), Fotofinder (Columbia, MD), and Melanoscan (Stamford, CT)	Facilitates identification of new or clinically changing lesions Standardized photographs can be taken by office staff or through outside TBP companies	Lengthy photograph acquisition times for manual photocapture Referencing TBPs may lengthen length of office visit CPT code for TBP for patients with dysplastic nevus syndrome or personal or family history of melanoma allows for physician reimbursement in some scenarios Automated units are large and can be expensive ($50,000-$150,000): 3D TBP VECTRA minimum space requirements: WB360: 112 in × 135 in × 105 in; WB180: 130 in × 84 in × 102 in
SDDI	Longitudinal dermoscopic imaging of individual suspicious lesions Images are captured using standalone cameras, camera lens attachments, dermoscopes with camera or smartphone compatibility, or specialized smartphone attachments	Allows short- or long-term monitoring of specific lesions for suspicious changes	Limited by patient compliance Cannot identify new lesions Photograph acquisition and comparison may lengthen office visits Many options for capturing and storing dermoscopic images at a variety of price points (<$40 for basic smartphone attachments to ~$2,000 for a dedicated dermoscopic lens for an SLR camera) SDDI is not covered by insurance and physicians are not eligible for reimbursement for utilization
TBP and SDDI	Each lesion mapped on total body photography has longitudinal dermoscopic imaging	Integration of both techniques Allows for identification of new lesions and dermoscopic surveillance of existing lesions Streamlines incorporation of TBP and SDDI into the TBSE	Lengthy photograph acquisition times for manual photocapture Large physical device size and high costs if using an automated unit Limited by patient compliance
RCM (Caliber Imaging and Diagnostics, Inc, Rochester, NY)	Real-time, in vivo imaging with visualization down to the papillary dermis and near-histologic resolution Image capture by a staff member takes ~5 min including setup and preparation Image size up to 8 mm × 8 mm	Can be used on borderline atypical cases or difficult amelanotic or facial lesions Can be used for presurgical mapping of tumor margins and postsurgical monitoring for LM/LMM (technique does not require additional training or technology) Leasing available	High equipment costs ($98,000 plus $5000 annual maintenance for the wide-probe RCM VivaScope 1500) Optional add-on handheld probe (VivaScope 3000) for difficult-to-image areas, such as the eyelid, for $52,500

Continued

Table I. Cont'd

Technology	Key features	Advantages	Limitations and financial information
		Separate CPT codes for confocal image acquisition and interpretation offer reimbursement comparable to that of a skin biopsy procedure with dermatopathologist review	Extensive image-based training needed to gain mastery
EIS (Nevisense, SciBase AB, Stockholm, Sweden)	Measures electrical impedance, with output scores differing between benign and malignant tissues	One disposable electrode per patient examination; each can be used for up to 10 lesions Measurement takes ~30 seconds	Nevisense tablet and electrode pen are $7500 Single-use electrodes cost $49 each EIS is not covered by insurance, and physicians are not reimbursed for utilization of the device EIS incorrectly classifies a high proportion of seborrheic keratoses as positive because of associated structural changes

3D, 3-Dimensional; *CPT*, Current Procedural Terminology; *EIS*, electrical impedance spectroscopy; *LM/LMM*, lentigo maligna/lentigo maligna melanoma; *SDDI*, sequential digital dermoscopic imaging; *SLR*, single-lens reflex; *TBP*, total body photography; *TBSE*, total body skin examination.

particularly useful in patients with many nevi concentrated in 1 area of the body (ie, the back).

Limitations

TBP can be time-consuming, and incorporation of photographs into the TBSE lengthens the examination. This emphasizes the importance of selecting patients who are most likely to benefit from TBP. Younger patients who are still developing new nevi may require reimaging over time to maintain a useful standard for comparison. More advanced devices can be costly and space-consuming, although the wide range of available imaging modalities allows providers to find a system that works best for their practice.

It is also important to prioritize patient privacy when choosing how to archive images in an era of increasing shared electronic medical record systems—some patients may feel uncomfortable with the possibility of numerous clinicians having access to TBPs.[14] In this case, physicians might consider alternative methods of image storage, such as local servers, secondary cloud-based storage locations, or patient-owned external storage devices.

SEQUENTIAL DIGITAL DERMOSCOPIC IMAGING

Key points

- **Sequential digital dermoscopic imaging allows for direct dermoscopic comparison of borderline lesions over time to monitor for suspicious change**
- **The use of sequential digital dermoscopic imaging has been demonstrated to reduce unnecessary biopsy procedures and can facilitate earlier detection of melanoma**
- **Many TBP units have incorporated sequential digital dermoscopic imaging**

Background

Dermoscopy use by trained clinicians improves diagnostic accuracy for melanoma compared with visual inspection alone.[15] Sequential digital dermoscopic imaging (SDDI) permits longitudinal dermoscopic monitoring of suspicious lesions and is especially useful for lesions lacking clearly benign or malignant dermoscopic features (Table I). Whereas the clinician may have otherwise obtained biopsy specimens from these equivocal lesions, 3-month SDDI offers a safe alternative through close monitoring for changes indicative of early-stage melanoma[16] (Argenziano et al[17] demonstrated 3 months to be the appropriate interval for short-term monitoring). SDDI can also be used together with TBP, and many TBP imaging systems have incorporated SDDI.

Benefits of SDDI

SDDI can facilitate the earlier detection of melanoma, particularly in early disease when tumors may lack classic dermoscopic features, and where the only clue to malignancy may be change over time.[18-20] In a 3-year prospective study of 212 high-risk patients, 15 of 17 melanomas were diagnosed solely by changes detected on SDDI, without exhibiting any melanoma-specific features.[21] Studies have shown a 3.3-fold reduction in unnecessary biopsy procedures and improved specificity for melanoma diagnosis with SDDI.[22,23]

SDDI with TBP

Although TBP and SDDI can be used independently, diagnostic advantages are greater when combined.[24,25] TBP allows for localization and identification of new lesions, while SDDI enhances surveillance of preexisting lesions. In 1 prospective study using both techniques, the median depth of the 75 melanomas detected was in situ.[26] Other studies have also reported detection of more in situ and overall thinner melanomas using these modalities.[25,27]

Limitations

Capturing and comparing dermoscopic images requires additional time and may lengthen visits. SDDI also requires additional follow-up visits, which may increase costs, particularly to patients with no insurance or high deductibles. However, lessening of health care expenditures may still be seen with reduction of unnecessary biopsy procedures. There is also a risk of patients being lost to follow-up—this approach is best used in reliable, compliant patients who can be trusted to return for follow-up imaging.[28,29]

REFLECTANCE CONFOCAL MICROSCOPY

Key points

- **Reflectance confocal microscopy offers in vivo near-histologic resolution with visualization of the papillary dermis**
- **Reflectance confocal microscopy is particularly useful for borderline atypical cases, difficult amelanotic or facial lesions, and presurgical margin mapping**
- **Reimbursement codes for confocal imaging and interpretation are available**

Background

Reflectance confocal microscopy (RCM) uses an 830-nm laser that is reflected back from within the skin to produce an image with cellular detail and in vivo near-histologic resolution at 30× (Fig 1; Table I).[30-34] Imaging depth is 200 μm to 300 μm, allowing for visualization of the papillary dermis.[33-35] Particularly useful in borderline atypical cases, RCM is a noninvasive technique that can be used in combination with dermoscopy to improve diagnostic accuracy and reduce unnecessary biopsy procedures.[36] It can also assist in presurgical mapping of tumor margins for lentigo maligna (LM)/lentigo maligna melanoma (LMM). Dermatologists can learn to interpret RCM images themselves or can upload images to a skilled RCM reader for interpretation.

Benefits in melanoma detection

RCM may aid in the management of difficult-to-diagnose melanomas. Used alone, a metaanalysis showed pooled sensitivity of 92.7% and specificity of 78.3% for melanoma detection.[37] However, RCM has greatest applicability when used for second-level evaluation in combination with dermoscopy for equivocal lesions. In this setting, RCM has been shown to improve diagnostic accuracy compared with visual inspection with dermoscopy, and to prevent removal of ≤70% of benign lesions.[36,38-41] Prospective studies demonstrated that the use of RCM with dermoscopy reduced the number needed to excise when evaluating equivocal lesions concerning for melanoma, translating to significant cost−benefit advantages.[39,42]

RCM can be particularly useful for difficult amelanotic lesions and for facial lesions such as LM/LMM.[43,44] Cinotti et al[45] found that RCM was more sensitive than dermoscopy for LM/LMM (80% vs 61%), particularly in cases of hypomelanotic or recurrent LM/LMM, and had higher interinvestigator agreement and confidence levels, though RCM was less specific (81% vs 92%).[45] The differential strengths of RCM and dermoscopy alone suggest that combination of the 2 modalities could improve diagnostic accuracy of clinically and dermoscopically challenging lesions.

Presurgical tumor margin mapping

RCM can assist in presurgical mapping of tumor margins for LM/LMM, which is challenging because of subclinical extension on cosmetically sensitive areas. Pellacani et al[46] found that RCM accurately determined LM tumor borders in 91% of cases compared to 26% when using dermoscopy, and Guitera et al[47] used RCM to identify

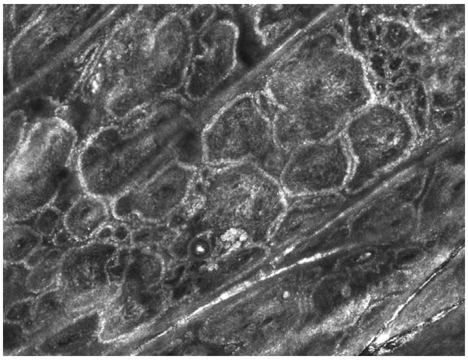

Fig 1. Reflectance confocal microscopy image of a common melanocytic nevus. This is an optical horizontal section through the dermoepidermal junction showing a regular arrangement of small basal cells and melanocytes. Image courtesy of Caliber Imaging and Diagnostics, Inc (Rochester, NY).

subclinical disease >5 mm beyond dermoscopically detected LM margins in 59% (29/37) of patients. Yélamos et al[48] found that handheld RCM combined with radial video mosaicing predicted slightly smaller defects than staged excision and reduced the need for scouting biopsy specimens preoperatively while sparing healthy tissue perioperatively.

Financial information

Caliber Imaging and Diagnostics (Rochester, NY) offers the wide-probe RCM VivaScope 1500, which retails for $98,000 ($5000/year maintenance). Whereas high costs and lack of reimbursement previously limited access mostly to academic centers, separate Current Procedural Terminology codes for confocal image acquisition and interpretation now offer reimbursement for RCM comparable to that of obtaining a skin biopsy specimen with dermatopathologist review.[49] Clinicians can be reimbursed for 1 or both procedures. A financial analysis using 2019 Medicare rates estimated a break-even point (after device cost plus maintenance fees) for image acquisition and interpretation at 2 to 3 cases per day.[50,51] These developments may encourage dermatologists to incorporate RCM into practice.

ELECTRICAL IMPEDANCE SPECTROSCOPY

Key points

- **Electrical impedance spectroscopy is an objective adjunct measurement for evaluating suspicious pigmented lesions**
- **High sensitivity and negative predictive value may help guide whether to obtain biopsy specimens from lesions that are clinically or dermoscopically suspicious for melanoma**
- **Electrical impedance spectroscopy often falsely detects seborrheic keratoses as positive, so clinicians must triage only melanocytic lesions for evaluation**

Background

Electrical impedance spectroscopy (EIS), marketed as Nevisense (SciBase AB, Stockholm, Sweden), is a minimally invasive device for melanoma diagnosis that uses a handheld probe with an electrode to apply alternating electric current to tissue and measure electrical impedance (Table I).[52] Disposable electrodes are equipped with gold-covered pins that painlessly penetrate to the stratum corneum, without impacting future histopathologic interpretation.[53] Differences in cell size, shape, orientation, and membrane composition result in intrinsic electrical differences between benign and malignant tissues, and the device generates a numeric score (0-10) and dichotomous output (negative/positive).[52,54]

Benefits in melanoma detection

EIS efficacy was assessed and the scoring system determined in a prospective clinical validation study of 1943 lesions (including 265 melanomas, 85% of which were in situ or early invasive) using an EIS score <4 for benign lesions and 4+ for melanomas.[55] The study reported 96.6% sensitivity, 34.4% specificity, and a negative predictive value of 98.2%. Similar to RCM, EIS is not intended for use in isolation, but rather in combination with dermoscopy and visual inspection. Rocha et al[56] evaluated the addition of baseline EIS measurements to short-term SDDI in a study of 160 clinically suspicious pigmented lesions, wherein lesions scoring 7 to 10 on EIS were considered high risk for melanoma and excised, while those scoring 4 to 6 were monitored for 3 months using SDDI.[56] Following this protocol, sensitivity was 100% (5/6 melanomas scored 7+ with EIS; the remaining melanoma [in situ] scored 6 but exhibited change on SDDI) and specificity was 69.5%, significantly higher than for EIS alone. The study found that need for SDDI would be reduced by 47% with EIS incorporation.

Svoboda et al[57] surveyed the impact of EIS results on clinicians' diagnostic accuracy and biopsy decisions, finding that EIS results led to a change in biopsy decision in roughly 25% of cases and improved both sensitivity and specificity.

Table II. Comparisons of convolutional neural network versus dermatologist performance in pigmented lesion classification using dermoscopic images

Study	CNN architecture	Total images (train and test), n	Dermatologists, n	AUROC	
				CNN	Dermatologists
Esteva et al[59]	GoogleNet Inception v3	129,450	21	0.91	—
Haenssle et al[60]	GoogleNet Inception v4	>100,000	58	0.86	0.79
Marchetti et al[61]	Fusion algorithm	2310	8	0.86	0.71
Yu et al[62]	VGG-16 model	724	2	0.84, 0.8	0.81, 0.82

AUROC, Area under the receiver operating characteristic curve; *CNN*, convolutional neural network.

Limitations

EIS incorrectly classifies many seborrheic keratoses as positive because of associated structural changes, so clinicians must triage only melanocytic lesions for evaluation.[55] In addition, although EIS has high sensitivity and negative predictive value, its sensitivity decreases with decreasing Breslow depth. This suggests potential to miss thin melanomas, which was demonstrated in the study by Malvehy et al,[55] wherein all 9 false negative results were for in situ (7/9) or T1a (0.4 mm and 0.6 mm, 2/9) melanomas.[55] Financial information appears in Table I.

ARTIFICIAL INTELLIGENCE AND MACHINE LEARNING

Key points

- **Convolutional neural networks are computer algorithms that can be trained to recognize melanoma and have the potential to serve as adjunct tools for clinicians to improve diagnostic accuracy**
- **Studies have reported comparable performances between convolutional neural networks and board-certified dermatologists in melanoma diagnosis**
- **Artificial intelligence could potentially transform the delivery of care and increase access to specialty services via telemedicine in the future**

Machine learning principles

The field of dermatology has witnessed unprecedented breakthroughs in artificial intelligence (AI) in recent years, especially regarding melanoma diagnosis. Machine learning can potentially create powerful, easily accessible tools that improve diagnostic accuracy, revolutionizing melanoma detection and patient care.

Convolutional neural networks (CNNs) constitute a branch of machine learning involving computer algorithms that are trained and refined for a specific task, such as image classification. In melanoma research, CNNs are trained to differentiate melanomas from benign lesions or keratinocytic carcinomas using large sets of labeled dermoscopic or clinical images. Computational filters detect features including size, edges, color, and contrast.[58] The algorithm improves itself whenever errors are encountered, allowing for progressive refinement and improving predictions for subsequent inputs. While the studies discussed in this section directly compare CNN performance to that of dermatologists, AI would be best used as an adjunct to clinical analysis by an experienced physician.

AI in melanoma diagnosis

In their landmark 2017 study, Esteva et al[59] showed that CNN performance was comparable or superior to most dermatologists in differentiating benign from malignant lesions (Table II). This CNN was trained on a dataset of 129,450 clinical images (including 3374 dermoscopic images); performance was compared to that of 21 board-certified dermatologists regarding melanoma and keratinocytic neoplasm classification using clinical images and melanoma classification using dermoscopic images.

Haenssle et al[60] subsequently compared diagnostic performance of Google's Inception v4 CNN architecture to an international group of 58 dermatologists using dermoscopic images; most dermatologists were outperformed by the CNN. Marchetti et al[61] reported the results of the 2016 International Symposium on Biomedical Imaging Challenge hosted by the International Skin Imaging Collaboration, a public archive of approximately 24,000 biopsy-proven skin lesions. The top-performing fusion algorithm out of 25 teams had a greater area under the receiver operating characteristic curve than that of 8 experienced dermatologists from 4 countries, with performance better than some but not all dermatologists. Similar results were also seen in the study by Yu et al,[62] which showed that the CNN performed similarly to dermatologists for dermoscopic diagnosis of acral melanoma.

Limitations

Although machine learning holds tremendous promise in melanoma detection, there are noteworthy limitations. As the logic at which CNNs arrive at their final diagnosis remains a black box, in cases where dermatologists and AI disagree there is no way to identify the point of discrepancy to facilitate improvement on either end.

Furthermore, the efficacy and output of these CNNs is only as good as the datasets on which they are trained. The strength of the network depends on dataset size and breadth, and each model may have different sensitivities, specificities, and biases depending on training images. This principle is important when considering implications of AI-predicted melanoma detection for patients with skin-of-color (SOC). As Adamson et al[63] noted, there may already be inherent bias in machine learning algorithms given the lack of SOC lesions, which can look different in darker skin types, in training datasets. Although melanoma incidence is higher among whites, the lack of SOC lesions suggests that no matter how well-developed the CNN algorithm it may underperform on lesions in patients with SOC. This blind spot in machine learning could potentially have grave consequences and exacerbate existing health care disparities if not addressed. To this end, the International Dermoscopy Society has studies aimed at collecting standardized dermoscopic images in patients with SOC. Future studies involving CNNs should include more photographs of patients with SOC in training datasets to help circumvent this bias.

Practical applications

AI could greatly expand access to dermatologic care. Given the near-ubiquity of mobile devices, smartphone applications may be practical future platforms for delivery of this technology, with numerous applications for skin cancer screening, education, mole mapping, diagnosis, and research available.[64,65] Few have been assessed for clinical efficacy, however, and those that have are unreliable and inaccurate with poor diagnostic sensitivity.[64,66] Although the US Food and Drug Administration proposed recommendations for mobile application regulations in 2015, there is a still an alarming lack of regulatory oversight.[64] Though there is no substitute for in-person skin examinations, reliable smartphone applications and dermoscopy attachments could be combined with AI and used as triaging tools for nondermatologists, improving delivery of specialized dermatologic care to patients in rural areas. Melanoma incidence and mortality in rural and remote communities is exponentially higher than in urban areas, likely because of limited access to dermatologists and socioeconomic barriers.[67-69] Such technological improvements may bridge access gaps and reduce melanoma mortality in remote areas. Although real-life applications still require rigorous study, AI technology is rapidly evolving, and dermatologists should remain cautiously optimistic about its use.

In conclusion, noninvasive diagnostic modalities, such as TBP, SDDI, RCM, and EIS, have helped optimize efficacy of early melanoma diagnosis while minimizing patient morbidity related to obtaining biopsy specimens of benign lesions. CNNs show promise in changing the medical landscape; harnessing this potential may revolutionize melanoma detection efforts and help address disparities in access to care. Still, readers should recognize that these are evolving technologies limited in function by the number of images available for training, and extensive research assessing real-life clinical utility is required before they can be adopted into practice.

REFERENCES

1. Kittler H, Pehamberger H, Wolff K, Binder M. Diagnostic accuracy of dermoscopy. *Lancet Oncol*. 2002;3:159-165.
2. Vestergaard ME, Macaskill P, Holt PE, Menzies SW. Dermoscopy compared with naked eye examination for the diagnosis of primary melanoma: a meta-analysis of studies performed in a clinical setting. *Br J Dermatol*. 2008; 159:669-676.
3. Carli P, de Giorgi V, Chiarugi A, et al. Addition of dermoscopy to conventional naked-eye examination in melanoma screening: a randomized study. *J Am Acad Dermatol*. 2004;50:683-689.
4. Carli P, De Giorgi V, Crocetti E, et al. Improvement of malignant/benign ratio in excised melanocytic lesions in the 'dermoscopy era': a retrospective study 1997-2001. *Br J Dermatol*. 2004;150:687-692.
5. Salerni G, Teran T, Puig S, et al. Meta-analysis of digital dermoscopy follow-up of melanocytic skin lesions: a study on behalf of the International Dermoscopy Society. *J Eur Acad Dermatol Venereol*. 2013;27:805-814.
6. Slue W, Kopf AW, Rivers JK. Total-body photographs of dysplastic nevi. *Arch Dermatol*. 1988;124:1239-1243.
7. Waldman RA, Grant-Kels JM, Curiel CN, et al. Consensus recommendations for the use of non-invasive melanoma detection techniques based on results of an international DELPHI process [e-pub ahead of print]. *J Am Acad Dermatol*. 2020. https://doi.org/10.1016/j.jaad.2019.09.046. Accessed June 10, 2020.
8. Feit NE, Dusza SW, Marghoob AA. Melanomas detected with the aid of total cutaneous photography. *Br J Dermatol*. 2004; 150:706-714.
9. Lallas A, Apalla Z, Kyrgidis A, et al. Second primary melanomas in a cohort of 977 melanoma patients within the first 5 years of monitoring. *J Am Acad Dermatol*. 2020;82: 398-406.

10. Truong A, Strazzulla L, March J, et al. Reduction in nevus biopsies in patients monitored by total body photography. *J Am Acad Dermatol*. 2016;75:135-143.e5.
11. Moye MS, King SMC, Rice ZP, et al. Effects of total-body digital photography on cancer worry in patients with atypical mole syndrome. *JAMA Dermatol*. 2015;151:137-143.
12. Oliveria SA, Chau D, Christos PJ, Charles CA, Mushlin AI, Halpern AC. Diagnostic accuracy of patients in performing skin self-examination and the impact of photography. *Arch Dermatol*. 2004;140:57-62.
13. Rayner JE, Laino AM, Nufer KL, et al. Clinical perspective of 3D total body photography for early detection and screening of melanoma. *Front Med (Lausanne)*. 2018;5:152.
14. Lakdawala N, Bercovitch L, Grant-Kels JM. A picture is worth a thousand words: ethical dilemmas presented by storing digital photographs in electronic health records. *J Am Acad Dermatol*. 2013;69:473-475.
15. Dinnes J, Deeks JJ, Chuchu N, et al. Dermoscopy, with and without visual inspection, for diagnosing melanoma in adults. *Cochrane Database Syst Rev*. 2018;12:CD011902.
16. Altamura D, Avramidis M, Menzies SW. Assessment of the optimal interval for and sensitivity of short-term sequential digital dermoscopy monitoring for the diagnosis of melanoma. *Arch Dermatol*. 2008;144:502-506.
17. Argenziano G, Mordente I, Ferrara G, Sgambato A, Annese P, Zalaudek I. Dermoscopic monitoring of melanocytic skin lesions: clinical outcome and patient compliance vary according to follow-up protocols. *Br J Dermatol*. 2008;159:331-336.
18. Skvara H, Teban L, Fiebiger M, Binder M, Kittler H. Limitations of dermoscopy in the recognition of melanoma. *Arch Dermatol*. 2005;141:155-160.
19. Kittler H, Guitera P, Riedl E, et al. Identification of clinically featureless incipient melanoma using sequential dermoscopy imaging. *Arch Dermatol*. 2006;142:1113-1119.
20. Menzies SW, Gutenev A, Avramidis M, Batrac A, McCarthy WH. Short-term digital surface microscopic monitoring of atypical or changing melanocytic lesions. *Arch Dermatol*. 2001;137:1583-1589.
21. Haenssle HA, Vente C, Bertsch HP, et al. Results of a surveillance programme for patients at high risk of malignant melanoma using digital and conventional dermoscopy. *Eur J Cancer Prev*. 2004;13:133-138.
22. Tromme I, Sacre L, Hammouch F, et al. Availability of digital dermoscopy in daily practice dramatically reduces the number of excised melanocytic lesions: results from an observational study. *Br J Dermatol*. 2012;167:778-786.
23. Menzies SW, Emery J, Staples M, et al. Impact of dermoscopy and short-term sequential digital dermoscopy imaging for the management of pigmented lesions in primary care: a sequential intervention trial. *Br J Dermatol*. 2009;161:1270-1277.
24. Berk-Krauss J, Polsky D, Stein JA. Mole mapping for management of pigmented skin lesions. *Dermatol Clin*. 2017;35:439-445.
25. Gasparini G, Madjlessi N, Delyon J, et al. Usefulness of the ''two-step method'' of digital follow-up in early stage melanoma detection in at high risk French patients: a retrospective 4-year study. *Br J Dermatol*. 2019;181:415-416.
26. Moloney FJ, Guitera P, Coates E, et al. Detection of primary melanoma in individuals at extreme high risk: a prospective 5-year follow-up study. *JAMA Dermatol*. 2014;150:819-827.
27. Salerni G, Carrera C, Lovatto L, et al. Benefits of total body photography and digital dermatoscopy (''two-step method of digital follow-up'') in the early diagnosis of melanoma in patients at high risk for melanoma. *J Am Acad Dermatol*. 2012;67:e17-e27.
28. Gadens GA. Lack of compliance: a challenge for digital dermoscopy follow-up. *An Bras Dermatol*. 2014;89:242-244.
29. Madigan LM, Treyger G, Kohen LL. Compliance with serial dermoscopic monitoring: an academic perspective. *J Am Acad Dermatol*. 2016;75:1171-1175.
30. Haroon A, Shafi S, Rao BK. Using reflectance confocal microscopy in skin cancer diagnosis. *Dermatol Clin*. 2017;35:457-464.
31. Mandel VD, Bombonato C, Pampena R, et al. Integration of dermoscopy and reflectance confocal microscopy for distinguishing melanomas from nevi of the breast area. *J Eur Acad Dermatol Venereol*. 2018;32:940-946.
32. Gonzalez S, Swindells K, Rajadhyaksha M, Torres A. Changing paradigms in dermatology: confocal microscopy in clinical and surgical dermatology. *Clin Dermatol*. 2003;21:359-369.
33. Calzavara-Pinton P, Longo C, Venturini M, Sala R, Pellacani G. Reflectance confocal microscopy for in vivo skin imaging. *Photochem Photobiol*. 2008;84:1421-1430.
34. Shahriari N, Grant-Kels JM, Rabinovitz H, Oliviero M, Scope A. In vivo reflectance confocal microscopy image interpretation for the dermatopathologist. *J Cutan Pathol*. 2018;45:187-197.
35. Paganelli A, Longo C, Pampena R, Piana S, Borsari S. Early diagnosis of skin melanoma metastasis by means of dermoscopy and confocal microscopy. *JAMA Dermatol*. 2018;154:1482-1485.
36. Lovatto L, Carrera C, Salerni G, Alos L, Malvehy J, Puig S. In vivo reflectance confocal microscopy of equivocal melanocytic lesions detected by digital dermoscopy follow-up. *J Eur Acad Dermatol Venereol*. 2015;29:1918-1925.
37. Xiong YD, Ma S, Li X, Zhong X, Duan C, Chen Q. A meta-analysis of reflectance confocal microscopy for the diagnosis of malignant skin tumours. *J Eur Acad Dermatol Venereol*. 2016;30:1295-1302.
38. Stanganelli I, Longo C, Mazzoni L, et al. Integration of reflectance confocal microscopy in sequential dermoscopy follow-up improves melanoma detection accuracy. *Br J Dermatol*. 2015;172:365-371.
39. Pellacani G, Pepe P, Casari A, Longo C. Reflectance confocal microscopy as a second-level examination in skin oncology improves diagnostic accuracy and saves unnecessary excisions: a longitudinal prospective study. *Br J Dermatol*. 2014;171:1044-1051.
40. Pellacani G, Witkowski A, Cesinaro AM, et al. Cost-benefit of reflectance confocal microscopy in the diagnostic performance of melanoma. *J Eur Acad Dermatol Venereol*. 2016;30:413-419.
41. Yélamos O, Manubens E, Jain M, et al. Improvement of diagnostic confidence and management of equivocal skin lesions by integration of reflectance confocal microscopy in daily practice: prospective study in 2 referral skin cancer centers [e-pub ahead of print]. *J Am Acad Dermatol*. 2020. https://doi.org/10.1016/j.jaad.2019.05.101. Accessed June 10, 2020.
42. Alarcon I, Carrera C, Palou J, Alos L, Malvehy J, Puig S. Impact of in vivo reflectance confocal microscopy on the number needed to treat melanoma in doubtful lesions. *Br J Dermatol*. 2014;170:802-808.
43. Guitera P, Menzies SW, Argenziano G, et al. Dermoscopy and in vivo confocal microscopy are complementary techniques for diagnosis of difficult amelanotic and light-coloured skin lesions. *Br J Dermatol*. 2016;175:1311-1319.
44. Borsari S, Pampena R, Lallas A, et al. Clinical indications for use of reflectance confocal microscopy for skin cancer diagnosis. *JAMA Dermatol*. 2016;152:1093-1098.

45. Cinotti E, Labeille B, Debarbieux S, et al. Dermoscopy vs. reflectance confocal microscopy for the diagnosis of lentigo maligna. *J Eur Acad Dermatol Venereol*. 2018;32:1284-1291.
46. Guitera P, Moloney FJ, Menzies SW, et al. Improving management and patient care in lentigo maligna by mapping with in vivo confocal microscopy. *JAMA Dermatol*. 2013;149:692-698.
47. Pellacani G, De Carvalho N, Ciardo S, et al. The smart approach: feasibility of lentigo maligna superficial margin assessment with hand-held reflectance confocal microscopy technology. *J Eur Acad Dermatol Venereol*. 2018;32:1687-1694.
48. Yélamos O, Cordova M, Blank N, et al. Correlation of handheld reflectance confocal microscopy with radial video mosaicing for margin mapping of lentigo maligna and lentigo maligna melanoma. *JAMA Dermatol*. 2017;153:1278-1284.
49. Levine A, Markowitz O. Introduction to reflectance confocal microscopy and its use in clinical practice. *JAAD Case Rep*. 2018;4:1014-1023.
50. Stein JA, Grant-Kels J. Advances in imaging. Presented at the 39th Annual Advances in Dermatology, NYU Langone Health, June 6-7, 2019.
51. Siegel DM. Reflectance confocal microscopy coding. Available at: https://caliberid.com/vivascope1500-Overview.html#. Accessed June 10, 2020.
52. Braun RP, Mangana J, Goldinger S, French L, Dummer R, Marghoob AA. Electrical impedance spectroscopy in skin cancer diagnosis. *Dermatol Clin*. 2017;35:489-493.
53. Welzel J, Schuh S. Noninvasive diagnosis in dermatology. *J Dtsch Dermatol Ges*. 2017;15:999-1016.
54. Glickman YA, Filo O, David M, et al. Electrical impedance scanning: a new approach to skin cancer diagnosis. *Skin Res Technol*. 2003;9:262-268.
55. Malvehy J, Hauschild A, Curiel-Lewandrowski C, et al. Clinical performance of the Nevisense system in cutaneous melanoma detection: an international, multicentre, prospective and blinded clinical trial on efficacy and safety. *Br J Dermatol*. 2014;171:1099-1107.
56. Rocha L, Menzies SW, Lo S, et al. Analysis of an electrical impedance spectroscopy system in short-term digital dermoscopy imaging of melanocytic lesions. *Br J Dermatol*. 2017;177:1432-1438.
57. Svoboda RM, Prado G, Mirsky RS, Rigel DS. Assessment of clinician accuracy for diagnosing melanoma on the basis of electrical impedance spectroscopy score plus morphology versus lesion morphology alone. *J Am Acad Dermatol*. 2019;80:285-287.
58. Zakhem GA, Motosko CC, Ho RS. How should artificial intelligence screen for skin cancer and deliver diagnostic predictions to patients? *JAMA Dermatol*. 2018;154:1383-1384.
59. Esteva A, Kuprel B, Novoa RA, et al. Dermatologist-level classification of skin cancer with deep neural networks. *Nature*. 2017;542:115-118.
60. Haenssle HA, Fink C, Schneiderbauer R, et al. Man against machine: diagnostic performance of a deep learning convolutional neural network for dermoscopic melanoma recognition in comparison to 58 dermatologists. *Ann Oncol*. 2018;29:1836-1842.
61. Marchetti MA, Codella NCF, Dusza SW, et al. Results of the 2016 International Skin Imaging Collaboration International Symposium on Biomedical Imaging challenge: comparison of the accuracy of computer algorithms to dermatologists for the diagnosis of melanoma from dermoscopic images. *J Am Acad Dermatol*. 2018;78:270-277.e1.
62. Yu C, Yang S, Kim W, et al. Acral melanoma detection using a convolutional neural network for dermoscopy images. *PLoS One*. 2018;13:e0193321.
63. Adamson AS, Smith A. Machine learning and health care disparities in dermatology. *JAMA Dermatol*. 2018;154:1247-1248.
64. Chao E, Meenan CK, Ferris LK. Smartphone-based applications for skin monitoring and melanoma detection. *Dermatol Clin*. 2017;35:551-557.
65. Marek AJ, Chu EY, Ming ME, Kovarik CL. Assessment of smartphone applications for total body digital photography-guided skin exams by patients. *J Am Acad Dermatol*. 2016;75:1063-1064.e1.
66. Rat C, Hild S, Rault Serandour J, et al. Use of smartphones for early detection of melanoma: systematic review. *J Med Internet Res*. 2018;20:e135.
67. Rollin A, Ridout B, Campbell A. Digital health in melanoma posttreatment care in rural and remote Australia: systematic review. *J Med Internet Res*. 2018;20:e11547.
68. Aneja S, Aneja S, Bordeaux JS. Association of increased dermatologist density with lower melanoma mortality. *Arch Dermatol*. 2012;148:174-178.
69. Stitzenberg KB, Thomas NE, Dalton K, et al. Distance to diagnosing provider as a measure of access for patients with melanoma. *Arch Dermatol*. 2007;143:991-998.