The use of noninvasive imaging techniques in the diagnosis of melanoma: a prospective diagnostic accuracy study

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Background: Early detection of melanoma is crucial to improving the detection of thin curable melanomas. Noninvasive, computer-assisted methods have been developed to use at the bedside to aid in diagnoses but have not been compared directly in a clinical setting.

Objective: We conducted a prospective diagnostic accuracy study comparing a dermatologist's clinical examination at the bedside, teledermatology, and noninvasive imaging techniques (FotoFinder, MelaFind, and Verisante Aura).

Methods: A total of 184 patients were recruited prospectively from an outpatient dermatology clinic, with lesions imaged, assessed, and excised. Skin specimens were assessed by 2 blinded pathologists, providing the gold standard comparison.

Results: Fifty-nine lesions from 56 patients had a histopathologic diagnosis of melanoma, whereas 150 lesions from 128 patients were diagnosed as benign. Sensitivities and specificities were, respectively, MelaFind (82.5%, 52.4%), Verisante Aura (21.4%, 86.2%), and FotoFinder Moleanalyzer Pro (88.1%, 78.8%). The sensitivity and specificity of the teledermoscopist (84.5% and 82.6%, respectively) and local dermatologist (96.6% and 32.2%, respectively) were also compared.

Limitations: There are inherent limitations in using pathology as the gold standard to compare sensitivities and specificities.

Conclusion: This study demonstrates that the highest sensitivity and specificity of the instruments were established with the FotoFinder Moleanalyzer Pro, which could be a valuable tool to assist with, but not replace, clinical decision making. (J Am Acad Dermatol 2021;85:353-9.)

Key words: artificial intelligence; atypical melanocytic nevi; dermoscopy; FotoFinder; MelaFind; melanoma; teledermoscopy; Verisante Aura.

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INTRODUCTION

Early diagnosis of cutaneous melanoma is crucial to ensure the timely excision of thin, highly curable lesions.[1,2] Dermoscopy can assist in early detection of melanoma and melanoma in situ; however, diagnostic accuracy has been shown to improve only when dermoscopy is conducted by experienced examiners,[3] and accuracy may be initially worse for clinicians inexperienced with this technique.

A number of noninvasive, computer-assisted methods have been developed for use at the bedside to facilitate a timely diagnosis of melanoma without the need for an expert dermatologist, including multispectral instrumentation, Raman spectroscopy, Reflectance confocal microscopy, and artificial intelligence with dermatoscopic algorithms.[4-9,10] These tools have shown improved sensitivity in distinguishing melanoma from benign skin lesions and diagnostic accuracy comparable to that of clinical examination.

MelaFind is a multispectral instrument that uses automatic image analysis to classify lesions by morphologic disorganization and recommends which lesions should be biopsied.[11] The software generates a score based on 75 morphologic features, including asymmetry and irregularity. MelaFind sensitivities in detecting melanoma ranged from 94% to 98% and had generally low specificity[4] (Table I).

Verisante Aura uses Raman spectroscopy, an optical method that correlates the spectrum of inelastic scattering of laser light within the skin, produced by changes induced in the molecular vibration of tissue biomolecules, with the molecular composition of the cells constituting the area examined. The resultant light spectrum is analyzed statistically, providing support for the diagnosis of skin cancer. For the diagnosis of melanoma, Lui et al[5] reported a sensitivity of 90% to 95% and specificity of 15% to 68% when comparing melanoma with nonmelanoma skin lesions. Histopathologic correlation was used to confirm to all skin cancer diagnoses, but lesions clinically diagnosed as benign were not biopsied unless they were deemed equivocal or patients provided consent for excision.

FotoFinder uses the Tuebinger Mole Analyzer, a computer-aided algorithm that can also be used to facilitate the recognition of melanoma from benign skin lesions. It assigns a score to lesions according to structural characteristics, and the score indicates the probability that the lesion is a melanoma. However, there is no threshold value to decide whether a lesion should be excised or biopsied. FotoFinder has recently developed Moleanalyzer Pro, which uses a deep-learning algorithm and complex machine learning to update the algorithm, with the goal of increasing sensitivity and specificity. However, this updated artificial intelligence–developed algorithm has not been tested in a clinical setting.

CAPSULE SUMMARY

- Several noninvasive techniques to identify melanoma have been identified, but not tested independently in a clinical setting.
- This study demonstrates that FotoFinder Moleanalyzer Pro had a sensitivity and specificity similar to that of the expert dermatologists and could be used in practice to complement clinical decision making.

Recently, there has been an increase in interest in artificial intelligence to diagnose melanoma and melanoma in situ. Independent studies have used different algorithms and repeated them with a high sensitivity and specificity, often either equal to or better than that of dermatologists assessing the same images by dermoscopy.[12-14] One of the limitations of the current research is the lack of studies that examine artificial intelligence in the clinical setting.[8] Evaluating images in isolation removes some of the multifactorial aspects of diagnosing lesions in the clinic. One study examined the diagnostic performance of MelaFind but was limited in its scope and conclusions because not all lesions imaged were biopsied, resulting in a lack of histopathologic confirmation.[9] Published diagnostic accuracy studies have compared the diagnostic accuracies of individual instruments with clinical examination, but we do not know of comparative prospective studies examining several instruments in parallel. Apart from 2 smaller studies,[11,12] these studies were not performed independently of the devices' manufacturers. We were unable to find any reports of independent head-to-head prospective diagnostic accuracy studies.

Most studies of skin lesions use a dichotomous method in which a lesion is considered a melanoma or not. This does not mirror clinical judgment, in which excision is the appropriate management for a clinically equivocal lesion. Weinstock et al[18] proposed a basic skin cancer triage to ensure timely diagnosis and excision of suspicious lesions by categorizing lesions in 1 of 3 ways: to further evaluate and biopsy the lesion ("act"), to reassure the patient that the lesion is benign ("ignore"), or to reevaluate the lesion at 2 and 6 months to decide whether it should be excised later ("watch"). The

Table I. Previously published sensitivity and specificity of selecting lesions for biopsy with MelaFind or Verisante Aura compared with that achieved by a dermatologist (with or without dermoscopy)

	No. of lesions	Dermatologist sensitivity, %	Dermatologist specificity, %	MelaFind sensitivity, %	MelaFind specificity, %	Verisante sensitivity, %	Verisante specificity, %	Financial support
Rigel et al[7]	24	69.0	54.0	94.0	40.0	N/A	N/A	MELA Sciences Inc
Hauschild et al[16]	130	69.5	55.9	96.9	9.2	N/A	N/A	Independent
Monheit et al[4]	1632	78.0	3.7	98.3	9.9	N/A	N/A	MELA Sciences Inc
Wells et al[8]	47	80.0	43.0	96.0	8.0	N/A	N/A	MELA Sciences Inc
Friedman et al[17]	99	71.0*	49.0*	98.0	44.0	N/A	N/A	Electro-Optical Sciences
Lui et al[5]	518	N/A	N/A	N/A	N/A	95–99	15–54	Verisante Technology Inc

N/A, Not applicable.
*With aid of dermoscopy.

decision to act, ignore, or watch a lesion was based on high- and low-risk lesion characteristics.[15] We hypothesized that clinical judgment plays an integral role in choosing lesions to excise and that existing diagnostic accuracy studies failed to incorporate this element in the study method. We questioned whether these noninvasive imaging devices can be used to assist the clinician in making this clinical judgment, ensuring the excision of all melanomas but limiting the number of unnecessary surgeries.

We conducted an investigator-initiated, nonindustry-sponsored, prospective diagnostic accuracy study comparing a dermatologist's diagnosis using clinical examination at the bedside and remote diagnosis using clinical and dermoscopic images (teledermoscopy) with 3 noninvasive smart-imaging devices to determine the relative accuracy of each in detecting melanoma.

METHODS

This study was a prospective analysis of patients from Atlantic Canada who were treated in the Pigmented Lesion Clinic in the Division of Clinical Dermatology and Cutaneous Science, Dalhousie University, Halifax, Nova Scotia. Patients were recruited from general dermatology clinics at the QEII Health Sciences Centre, from private community clinics, and on referral from family practices.

Study design and population

A standard clinical history included demographic data (sex, date of birth, and ethnicity), lesion-specific history (duration and change), and risk factors for melanoma (family history of melanoma, personal history of melanoma/melanoma in situ, history of sunburns, and history of blistering sunburns). Exclusion criteria included recurrent lesions or metastases; lesions less than 2 mm or greater than 2 cm in diameter; lesions not accessible to the devices; lesions located on scars, crusts, psoriasis, eczema, sunburn, or other skin condition; lesions covered by thick hair; and genitalic lesions not accessible to the devices. Exclusions also included lesions that had previously been biopsied or subjected to an ablative procedure, lesions located on mucosal surfaces, lesions that were obscured by foreign matter, ulcerated lesions, and lesions on the sole or palm, or within 1 cm of an eye. In addition, patients with a Fitzpatrick skin phototype of higher than III were excluded from the study because of the limitations of the machines used in diagnosing melanoma in patients with higher phototypes.

A total skin examination was performed, with an assessment of pigmentary characteristics (hair color, skin phototype, freckling tendency, an estimation of number of nevi, and the presence and number of atypical nevi). The target lesion was identified by the referring dermatologist as a lesion warranting further investigation, deemed to be clinically challenging. The target lesion was assessed clinically. Its size (measurement in its 2 greatest dimensions radially), color, and the use of side lighting where needed were recorded. Sun-exposed areas were considered to be areas of the body other than those not habitually exposed to the sun (chest, abdomen, back, buttocks, and thighs).

Macroscopic and dermoscopic images of the lesions were captured with a DermLite Cam V2

Table II. Demographic data

	Melanoma, No. (%)	Nonmelanoma, No. (%)
Mean age, y	62	48
Sex		
Men	37 (66.0)	63 (49.3)
Women	19 (33.9)	65 (50.7)
Fitzpatrick skin phototype		
I	2 (3.6)	3 (2.3)
II	33 (58.9)	78 (60.9)
III	21 (37.5)	45 (35.1)
IV	0	2 (1.6)
History of cancer		
Melanoma	11 (19.6)	15 (11.7)
Other skin cancer	13 (23.2)	23 (18.0)
Systemic malignancies	8 (14.3)	9 (7.0)
Initial clinical suspicion*		
Patient	32 (54.2)	94 (62.7)
Family member/friend	17 (28.8)	27 (18.0)
Family practitioner	2 (3.4)	15 (10.0)
Referring dermatologist	8 (13.6)	14 (9.3)

There were 59 melanomas from 56 patients and 150 nonmelanomas from 128 patients.
*Percentages of lesion warranting further assessments that were identified by patients, a family member or friend, their family practitioner, or a referring dermatologist.

Table III. Characteristics of patients receiving a diagnosis of melanoma histopathologically with Breslow depth, or melanoma in situ, the site of the melanoma, and relevance to sun exposure

	Count	Percentage
Type		
Melanoma in situ	27	45.8
Melanoma	32	54.2
Breslow depth, mm		
Mean	0.72	
Standard deviation	0.56	
Median	0.57	
Range	0.19—2.9	
Site		
Extremities	18	30.5
Trunk	25	42.4
Head and neck	14	23.7
Acral	2	3.4
Sun-exposed site		
Yes	58	98.3
No	1	1.69

(3 Gen Inc, San Juan Capistrano, CA). A clinical or dermoscopic diagnosis was recorded by 1 of 2 experienced dermatologists (P.R.H. or R.G.L.) using the basic skin cancer algorithm (excise, do not excise, or watch [the in-person diagnosis]). The lesion was then imaged with the Verisante Aura, MelaFind, and both the FotoFinder Tuebinger and Moleanalyzer Pro. Outputs were recorded as Verisante Aura (low, equivocal, or high suspicion for melanoma), MelaFind (high or low disorganization with a probability score of −5 to 9, with a score of >2 being suspicious for melanoma), FotoFinder Tuebinger, and Moleanalyzer Pro (probability score 0-1, with 0 indicating no suspicion for melanoma and 1 indicating a high suspicion for it). All lesions were excised regardless of the clinical diagnosis or the device outputs. Clinical and dermoscopic images of variable quality were also assessed remotely by an external expert (A.O.) in dermoscopy who used proprietary teledermatology software (DermEngine, MetaOptima). A.O. used the basic skin cancer algorithm (excise, do not excise, or watch) to categorize the diagnoses.

After excision, the skin specimens were processed in paraffin, sectioned, and stained with hematoxylin-eosin for routine light microscopy. They were reviewed independently by 2 dermatopathologists (T.Y.L. and S.P.), with a third dermatopathologist (N.M.W.) casting the deciding vote in cases in which there was disagreement in the pathologic diagnosis.

Statistical analysis

Descriptive statistics were used for patient data. The pathologic diagnosis was taken as the gold standard. Continuous variables were compared with Student t test and categoric variables by χ^2 test. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were calculated for the following: MelaFind, FotoFinder, Verisante Aura, in-person diagnosis, and teledermoscopic diagnosis (all compared with the gold-standard pathology diagnosis).

The analysis was carried out with SAS STAT (version 9.3, SAS Institute, Inc, Cary, NC).

RESULTS

Two hundred nine lesions were analyzed from 184 patients. Fifty-nine lesions from 56 patients had a histopathologic diagnosis of melanoma or melanoma in situ, whereas 150 lesions from 128 patients were diagnosed as benign. Patient demographics and lesion diagnosis characteristics are described in Tables II and III. Patients all had a Fitzpatrick skin phototype of between I and III. The mean age of patients with melanoma was 62 years (range 31-84 years), and the mean age of patients without melanoma was 48 years (range 17-86 years). There were 37 men and 19 women who received a

Table IV. Sensitivity and specificity of MelaFind, FotoFinder, Verisante Aura, dermatologist (clinical and dermoscopy), and remote dermatologist in diagnosing melanoma compared with histopathologic diagnosis*

Methods compared with gold standard	Sensitivity (95% CI)	Specificity (95% CI)
MelaFind	82.5 (72.6–92.4)	52.4 (44.2–60.6)
FotoFinder Tuebinger Mole Analyzer	83.1 (72.6–93.6)	75.2 (67.27–83.1)
FotoFinder Moleanalyzer Pro	88.1 (79.4–96.9)	78.8 (71.5–86.2)
Verisante Aura	21.4 (10.7–32.2)	86.2 (80.2–92.1)
Dermatologist	96.6 (91.91–101.31)	32.2 (18.4–46.0)
Teledermoscopic diagnosis	89.8 (79.6–96.2)	66.0 (57.8–73.5)

CI, Confidence interval.
*Sensitivity and specificity of the clinical decision to excise melanoma cases as made by the local dermatologist and by both the local and remote dermatologists.

Table V. Teledermoscopic decision based on clinical and dermoscopic images and on FotoFinder Tuebinger Results

	Total lesions, No. (%) (N = 209)	Melanoma, No. (%) (N = 59)	Nonmelanoma, No. (%) (N = 150)
Teledermoscopic decision			
Excise	104 (49.8)	53 (89.8)	51 (34.0)
Ignore	90 (43.1)	4 (6.8)	86 (57.3)
Reevaluate ("wait")	15 (7.2)	2 (3.4)	13 (8.7)
FotoFinder Tuebinger			
Excise	86 (41.1)	49 (83.0)	37 (24.7)
Ignore	123 (58.9)	10 (16.9)	113 (75.3)
Combined			
Excise	130 (62.2)	56 (94.9)	74 (49.3)
Ignore	79 (37.8)	3 (5.1)	76 (50.7)

diagnosis of melanoma, and there were 63 men and 65 women who received a diagnosis of benign lesions.

When using the basic skin cancer triage in deciding whether to excise a suspicious lesion, the local dermatologists achieved a 96.6% sensitivity and 32.2% specificity (Table IV). Of the 209 total lesions, 163 were recommended for excision. Of these lesions, 57 were melanoma and 106 were benign, resulting in an excision ratio of benign to melanoma of 2:1. Two melanomas were missed (1 melanoma with a Breslow depth of 0.58 mm, located on the front torso; and 1 melanoma in situ, located on the head/neck). Both of these melanomas were diagnosed by FotoFinder Moleanalyzer Pro as melanoma. There were 3 cases in which the local dermatologists recommended reevaluation, all of which were histopathologically diagnosed as benign.

The teledermoscopist (A.O.) achieved a sensitivity of 89.8% and a specificity of 66.0%. Of 209 total cases, the teledermoscopist recommended excision in 104 cases (Table V). Of those 104 cases, 51 were benign and 53 were melanoma (an approximately 1:1 benign to melanoma excision ratio). The teledermoscopist missed 4 melanomas (1 melanoma in situ, located on the back; 1 melanoma in situ, located on the foot; 1 melanoma with a Breslow depth of 0.22 mm, located on the arms; and the other with a Breslow depth of 0.93 mm, located on the back). Of the 15 cases in which the recommendation was to wait or reevaluate, 2 were melanoma.

As shown in Table IV, MelaFind had a sensitivity of 82.5% and specificity of 52.4%, Verisante Aura had a sensitivity of 21.4% and specificity of 86.2%, FotoFinder Tuebinger had a sensitivity of 83.1% and specificity of 75.2%, and FotoFinder Moleanalyzer Pro had a sensitivity of 88.1% and specificity of 78.8%, with an excision ratio of 1:1.

The teledermoscopist suggested excision in approximately 50% of the cases, and this included approximately 90% of the melanomas. The Verisante Aura and MelaFind indicated excision of 15.2% and 82.4%, respectively, which detected 17.7% and 90.6% of melanomas, respectively. FotoFinder Tuebinger recommended excision in 41.1% of cases and detected 83.0% of all melanomas. FotoFinder Moleanalyzer Pro recommended excision in 68.9% of cases and detected 84.2% of all melanomas.

DISCUSSION

We report an independent, peer-reviewed, prospective, diagnostic concordance study of the detection of melanoma and melanoma in situ, using clinical and dermatoscopic examinations, teledermoscopy, noninvasive imaging systems, and a basic skin cancer algorithm to reassure a patient, to reassess a lesion, or to excise a lesion. Our study supports previous studies that have shown a high sensitivity of some noninvasive devices in detecting melanoma. However, low specificity and low diagnostic accuracy indicate that some of these machines cannot replace a dermatologist's clinical experience

in selectively choosing which lesions to excise. In addition, there are multiple practical limitations to using these devices in a clinical setting, including size, location, and Fitzpatrick skin phototype.

The results of MelaFind and Verisante Aura were similar to those of previous studies in the diagnosis of melanoma (Table IV). MelaFind was approved by the Food and Drug Administration in 2011 after Monheit et al[4] reported its high sensitivity (98.4%), low biopsy ratio (10.8:1), and higher specificity (10.5%) compared with that achieved by nonspecialist clinicians (3.7%).[19] Winkelmann et al[6] summarized 7 studies that used multispectral digital skin lesion analysis (MelaFind, STRATA Skin Sciences Inc, Horsham, PA) in melanoma diagnosis. Sensitivity for the clinical diagnosis of melanoma and the need for surgical excision after viewing both the clinic images improved from 70% to 88% after the addition of multispectral digital skin lesion analysis; the specificity improved from 52% to 58%.[17] Other studies (Table I) support our results that MelaFind had higher sensitivity but lower specificity than that achieved by dermatologists in selecting lesions to biopsy for suspected melanoma.[7,8,16,17] Lesions assessed with Verisante Aura were identified as having low probability, high probability, or equivocal chances of being melanoma. Its high specificity indicates that many lesions were correctly identified as having a high probability of being melanoma, but its low sensitivity impedes its potential use as a screening measure. The low specificity of MelaFind and the low sensitivity of Verisante Aura could result in increased costs and unnecessary procedures, as well as missed melanoma diagnoses.

Our study has shown that adding computer analysis of dermoscopic images (FotoFinder) has complemented clinical diagnostic accuracy by reducing the number of missed melanomas. When the FotoFinder Tuebinger was used as an aid to the clinical diagnosis, both the melanomas that were missed by the local dermatologists were captured. When it was used to complement the remote dermatologist, the number of missed melanomas was reduced from 4 to 3. Of the 4 cases, 3 were listed as histopathologically challenging, with a diagnosis of melanoma favored, but not definitive. Seventeen cases initially diagnosed histopathologically as equivocal and suspicious for melanoma were also considered atypical on clinical examination, as well as on teledermoscopy, illustrating that the challenges faced by examining dermatologists may be shared by pathologists.

Evolving artificial intelligence tools are also likely to assist in the evaluation of pigmented lesions by less skilled clinicians.[5,7,8,16,17] Lui et al[5] acknowledged that Raman spectroscopy should be used to assist rather than replace a clinician to diagnose melanoma.[7] In addition, patients are sometimes more likely than primary care physicians or dermatologists to recognize a mole as being suspicious for melanoma (Table II). This supports the idea that a screening tool using artificial intelligence could be used in primary care offices to rapidly screen lesions of concern. Although there are some practical limitations in clinical utility, the relatively high sensitivity and specificity of the FotoFinder Moleanalyzer Pro in this study suggest that this device could be used as an aid in assessing pigmented skin lesions.

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