Filed Pursuant to Rule 433
Registration No. 333-151935
July 28, 2008

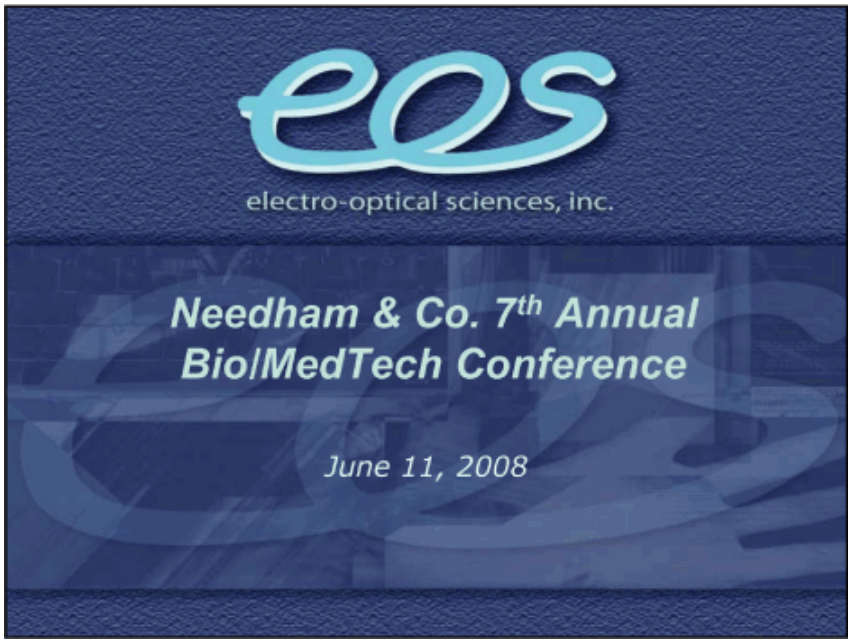
ELECTRO-OPTICAL SCIENCES, INC.
Free Writing Prospectus

Information contained in the following investor presentation and related articles and reports was used by Electro-Optical Sciences, Inc. (the "Company") in connection with certain investor presentations.

Forward-Looking Statements

Some of the statements contained in this free writing prospectus may constitute forward-looking statements within the meaning of the federal securities laws. Statements that are not historical facts, including statements about our beliefs and expectations, are forward-looking statements. These statements are not guarantees of future performance and involve risks, uncertainties and assumptions that are difficult to predict. More detailed information about factors that may affect our performance may be found under "Risk Factors" in the preliminary prospectus contained in the registration statement referred to above. Any forward-looking statements included in this free writing prospectus are based on information available to us on the date of this free writing prospectus. We undertake no obligation to update or revise any forward-looking statement, whether as a result of new information, future events or otherwise.

The Company has filed a registration statement (including a prospectus) with the SEC for the offering to which this communication relates. Before you invest, you should read the prospectus in that registration statement and other documents the issuer has filed with the SEC for more complete information about the issuer and this offering. You may get these documents for free by visiting EDGAR on the SEC Web site at www.sec.gov. Alternatively, the Company will arrange to send you the prospectus if you request it by calling (914) 591-3783.



Forward Looking Statements

This presentation includes "forward-looking statements" within the meaning of the Securities Litigation Reform Act of 1995. These statements include but are not limited to our plans, objectives, expectations and intentions and other statements that contain words such as "expects," "contemplates," "anticipates," "plans," "intends," "believes" and variations of such words or similar expressions that predict or indicate future events or trends, or that do not relate to historical matters. These statements are based on our current beliefs or expectations and are inherently subject to significant uncertainties and changes in circumstances, many of which are beyond our control. There can be no assurance that our beliefs or expectations will be achieved. Actual results may differ materially from our beliefs or expectations due to economic, business, competitive, market and regulatory factors.

MELA: Nasdaq CM

Why Melanoma?

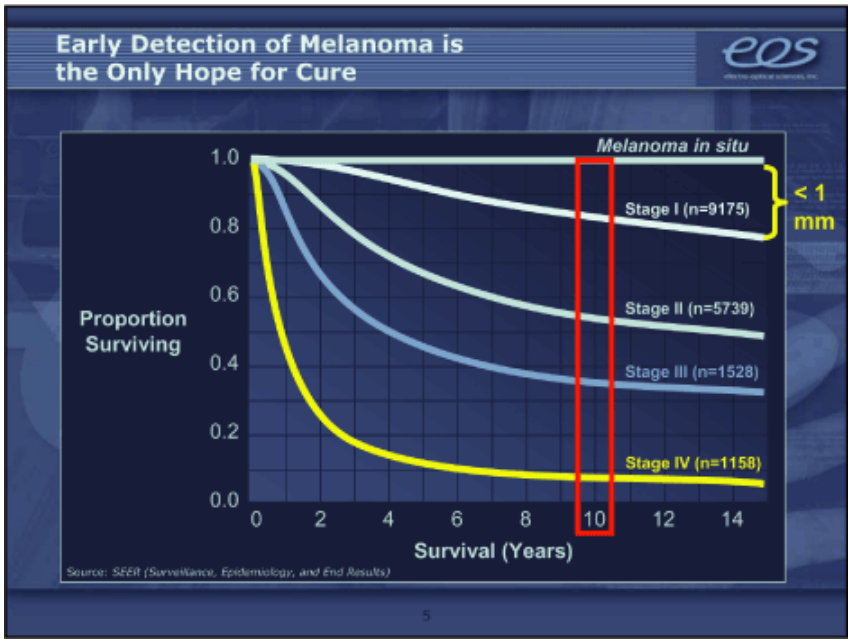
- Melanoma kills 1 US citizen per hour
- 80% of all skin cancer deaths
- 50% increase in mortality since 1973
- Fastest growing cancer 6% per year
- Most common cancer in women 25-29
- #1 cancer killer in women 30-35
- Affects all age groups
- No cure for late stage disease...must diagnose EARLY

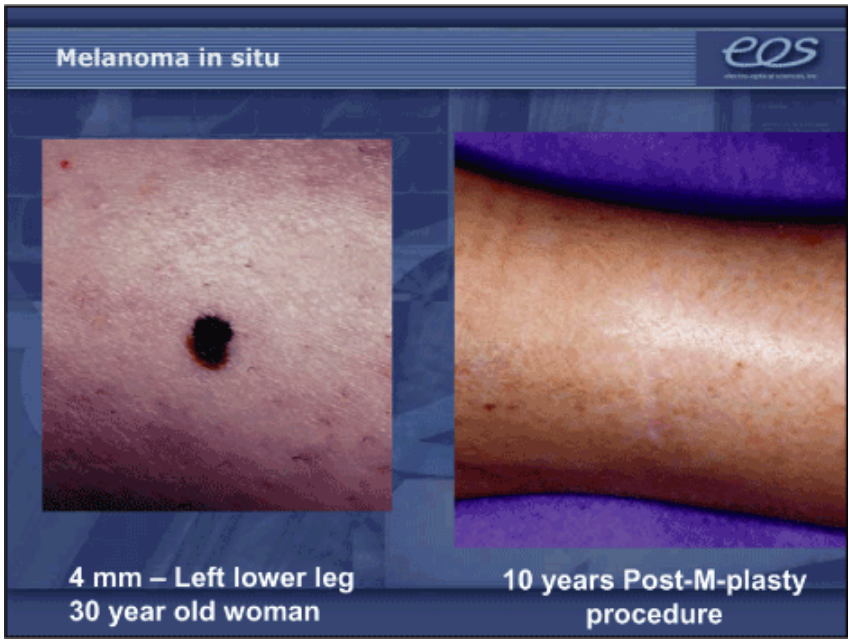
Impact of Melanoma Mortality vs Other Cancers

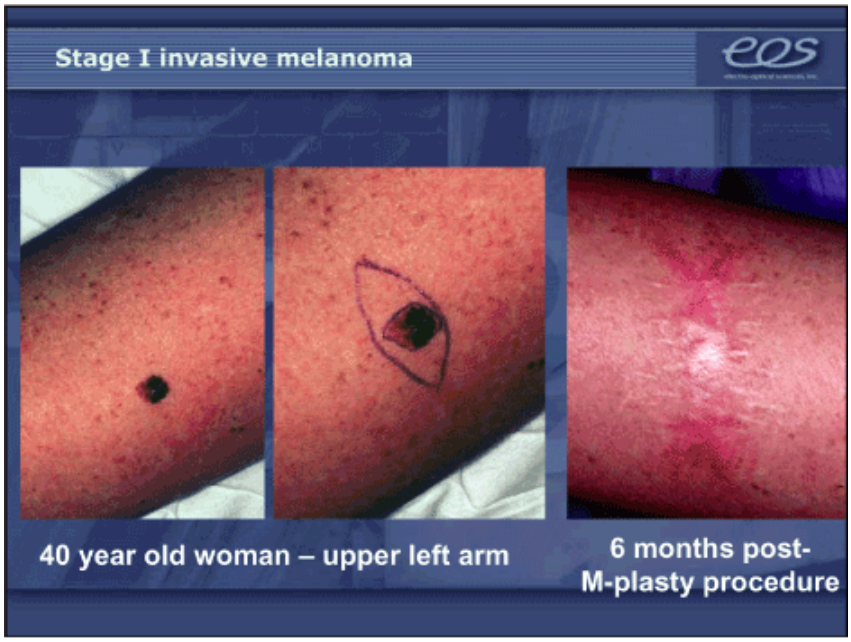
Due to **early age** of diagnosis and **lack of treatments that extend survival**, the impact of malignant melanoma on average years of life lost (AYLL) and lifetime earnings lost (LEL) is greater than that of other cancers assessed.

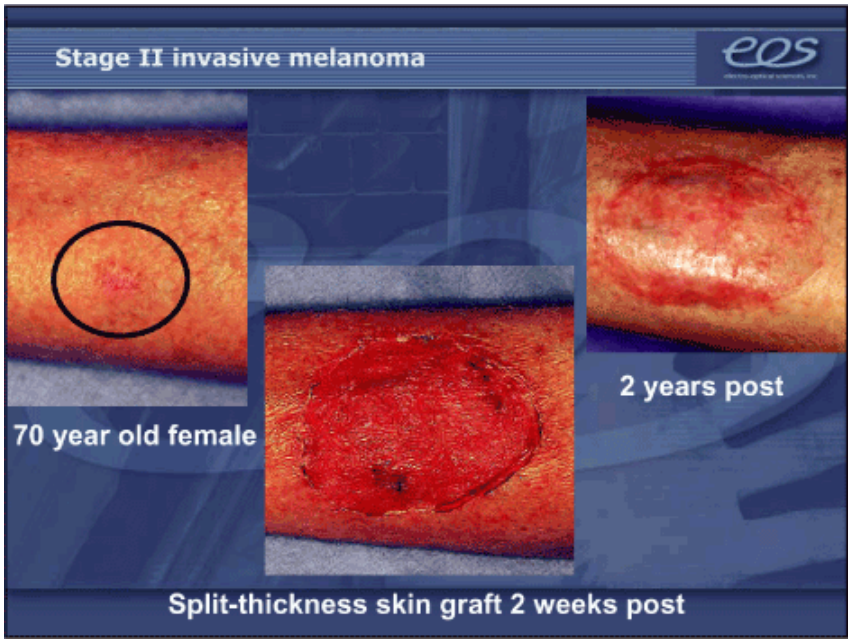
	Average Years of Life Lost (AYLL)	Lifetime Earnings Lost (LEL)
Melanoma of the skin	22.1	$831K
Liver & Intrahepatic bile duct	21.7	$769K
Oral cavity and Pharynx	20.3	$784K
Brain / Nervous System	19.7	$757K
Kidney & Renal pelvis	19.2	$699K
Lung & Bronchus	18.2	$652K
Pancreas	17.5	$612K
Colon & Rectum	17.1	$622K

D Taylor. 2008 ASCO Annual Meeting

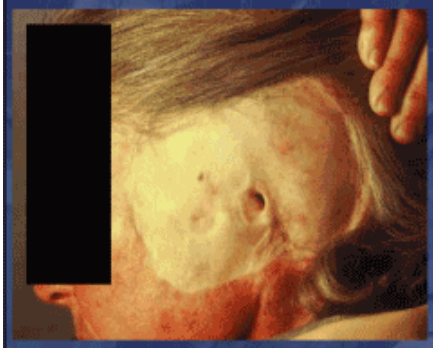

Early Detection of Melanoma is the Only Hope for Cure
Melanoma in situ
Stage I (n=9175)
< 1 mm
Stage II (n=5739)
Stage III (n=1528)
Stage IV (n=1158)
Proportion Surviving
1.0
0.8
0.6
0.4
0.2
0.0
0
2
4
6
8
10
12
14
Survival (Years)
Source: SEER (Surveillance, Epidemiology, and End Results)


Melanoma in situ
4 mm – Left lower leg
30 year old woman
10 years Post-M-plasty procedure

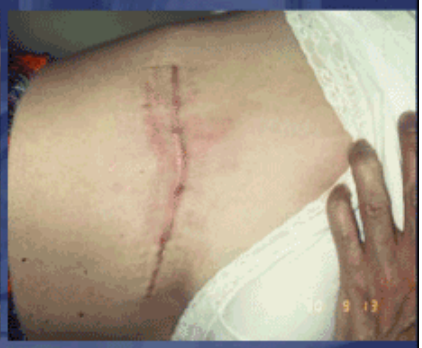

Stage I invasive melanoma
40 year old woman – upper left arm
6 months post-
M-plasty procedure


Stage II invasive melanoma
70 year old female
2 years post
Split-thickness skin graft 2 weeks post

Stage III Melanoma

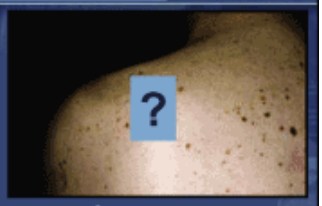


Stage IIIb - micrometastases



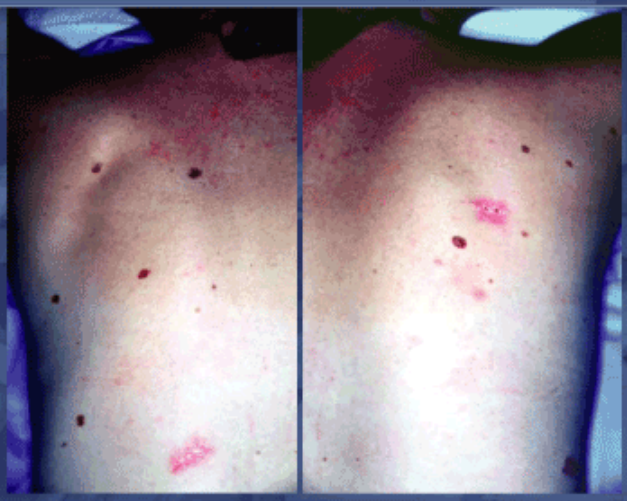
Stage IIIb – satellite metastases

Challenges Detecting Melanoma < 1 mm



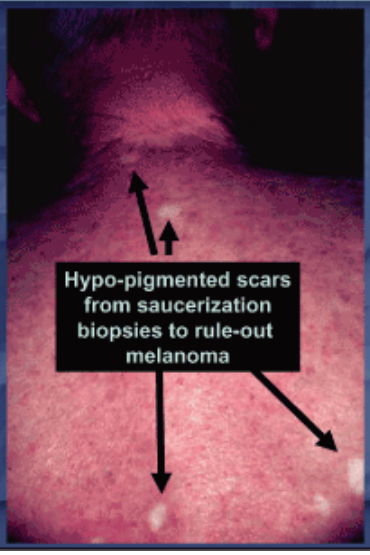
- VISUAL inspection – subjective
  - A B C D E
  - "ugly duckling"
- Can look like benign lesions
- Dermatology residence ~ 12 early stage melanomas seen
- Must biopsy to confirm suspicious
  - Pick the right ones
  - Experts miss 29% of small early stage melanomas
  - 50 to 100 false positives per every melanoma found
- "Biopsy" is a complete removal with margin
  - Pain, scar, itching
  - Anxiety waiting for results
  - Biopsy-avoidance behavior

Biopsies



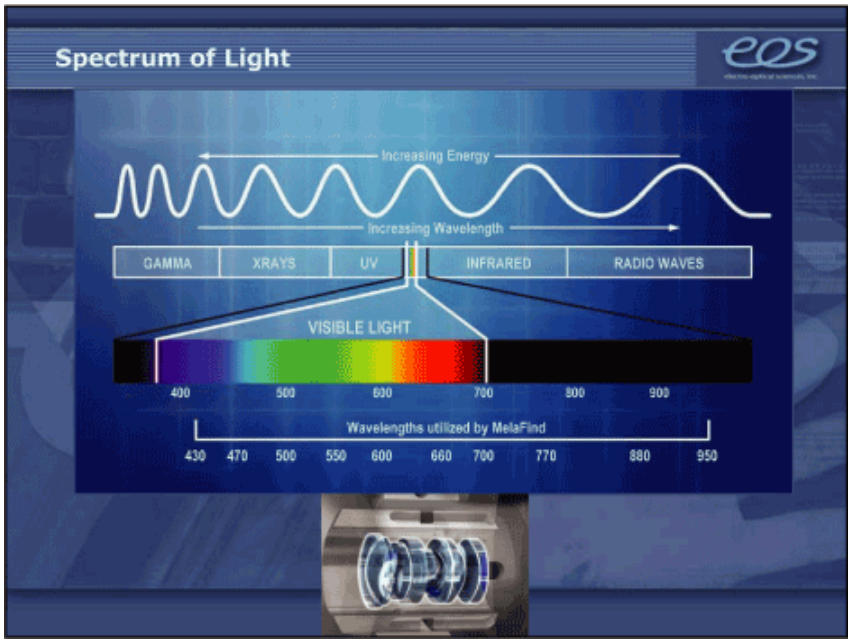
Dysplastic nevus syndrome – painful hypertrophic scars following excisional biopsies 4-6 weeks hence

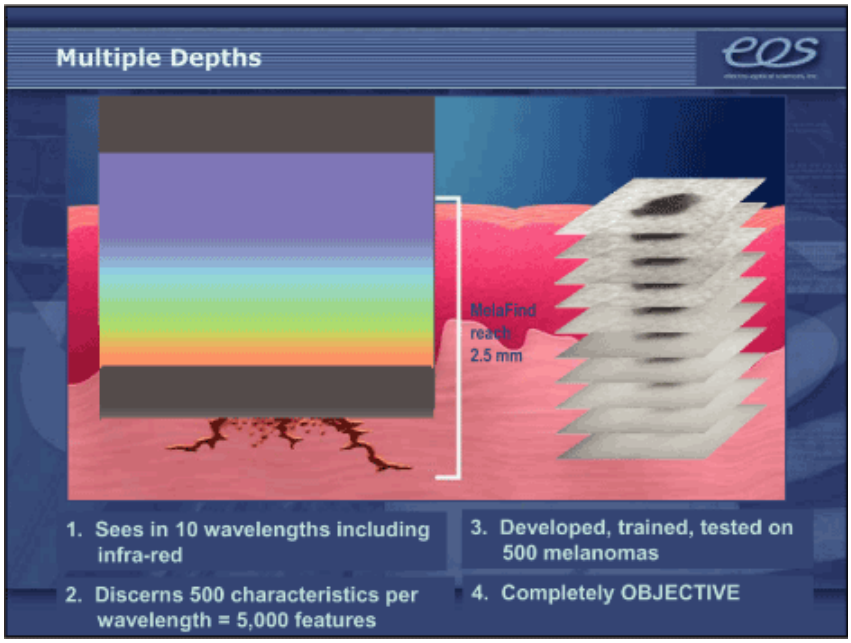
Biopsies to Rule-Out Melanoma

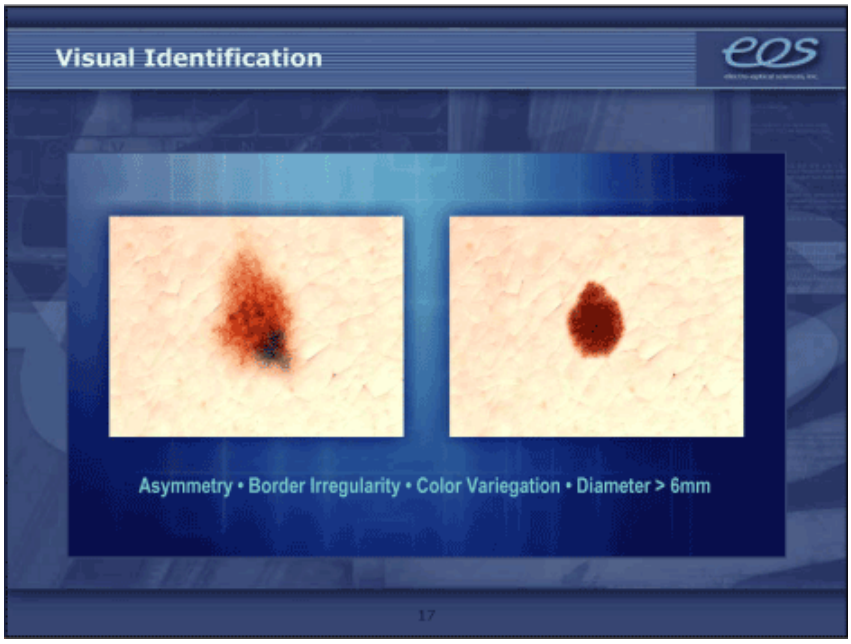


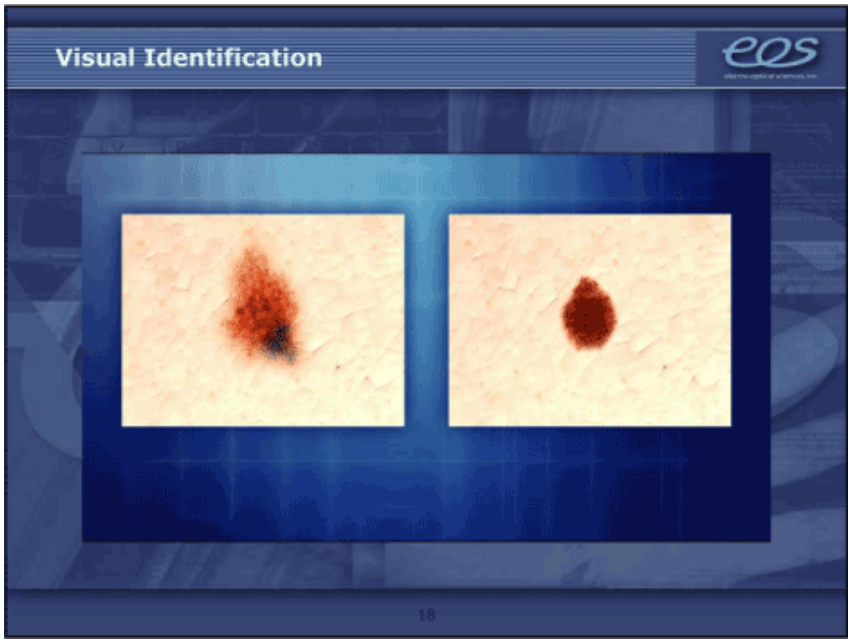

The MelaFind® System
MelaFind


Photon Path


Spectrum of Light
Increasing Energy
Increasing Wavelength
GAMMA
XRAYS
UV
INFRARED
RADIO WAVES
VISIBLE LIGHT
400
500
600
700
800
900
Wavelengths utilized by MelaFind
430
470
500
550
600
660
700
770
880
950


Multiple Depths
MelaFind
reach
2.5 mm
1. Sees in 10 wavelengths including infra-red
2. Discerns 500 characteristics per wavelength = 5,000 features
3. Developed, trained, tested on 500 melanomas
4. Completely OBJECTIVE


Visual Identification
Asymmetry • Border Irregularity • Color Variegation • Diameter > 6mm
17


Visual Identification
18

MelaFind® Phase 2 Data – Interim System*

Study 1

	N = 352 PSLs 28 melanomas	
	Experts	MelaFind
Specificity	28.4%	48.4%
	p < 0.0001	
Over-Biopsy Ratio	7.9 : 1	5.7 : 1
Missed Melanomas	MelaFind detected 28/28 melanomas	

** Software & algorithm development estimated to be 65% complete*

Dermatologist Sensitivity?

- 49 melanomas and 50 benign lesions matched by age, sex, and body location
- 10 expert dermoscopists
- Median size = 4.55 mm
- 21/49 = invasive melanoma (0.32 mm Breslow thickness)
- 28/49 = in situ melanoma
- Experts identified 35/49 melanomas
- MelaFind identified 48/49 melanomas

STUDY

The Diagnostic Performance of Expert Dermoscopists vs a Computer-Vision System on Small-Diameter Melanomas

Robert J. Friedman, MD; Dina Gutkowicz-Krusin, PhD; Michele J. Farber; Melanie Warycha, MD; Lori Schneider-Kels, MPH; Nicole Papastathis, BA; Martin C. Mihm Jr, MD; Paul Googe, MD; Roy Ring, MD; Victor G. Prieto, MD, PhD; Alfred W. Kopf, MD, MD; David Polsky, MD, PhD; Harold Rabinovitz, MD; Margaret Oliviero, ANP; Armand Cognetta, MD; Darrell S. Rigel, MD; Ashfaq Marghoob, MD; Jason Rivers, MD, FRCPC; Robert Johr, MD; Jane M. Grant-Kels, MD; Howin Tsao, MD, PhD

Objective: To evaluate the performance of dermoscopists in diagnosing small pigmented skin lesions (diameter ≤6 mm) compared with an automatic multispectral computer-vision system.

Design: Blinded comparison study.

Setting: Dermatologic hospital-based clinics and private practice offices.

Patients: From a computerized skin imaging database of 900 small (≤6-mm) pigmented skin lesions, all 49 melanomas from 49 patients were included in this study. Fifty randomly selected nonmelanomas from 46 patients served as a control.

Main Outcome Measures: Ten dermoscopists independently examined dermoscopic images of 99 pigmented skin lesions and decided whether they identified the lesions as melanoma and whether they would recommend biopsy to rule out melanoma. Diagnostic and biopsy sensitivity and specificity were computed and then compared with the results of the computer-vision system.

Results: Dermoscopists were able to correctly identify small melanomas with an average diagnostic sensitivity of 38% and a specificity of 82% and recommended small melanomas for biopsy with a sensitivity of 71% and specificity of 49%, with only fair interobserver agreement (κ=0.31 for diagnosis and 0.34 for biopsy). In comparison, in recommending biopsy to rule out melanoma, the computer-vision system achieved 98% sensitivity and 44% specificity.

Conclusions: Differentiation of small melanomas from small benign pigmented lesions challenges even expert physicians. Computer-vision systems can facilitate early detection of small melanomas and may limit the number of biopsies to rule out melanoma performed on benign lesions.

Arch Dermatol. 2009;145(4):476-482

DETECTION OF EARLY MALIGNANT melanoma (invasive and thin lesions) is one of the most effective ways of preventing mortality from this disease. Prognosis for patients with melanoma is dependent on early detection,[1,2] as evidenced by the 10-year survival rates as high as 99.3% that have been reported for thin melanomas smaller than 0.76 mm thick in the New York University melanoma database; these rates markedly decrease to 48% for lesions larger than 3 mm in thickness.[3] The effectiveness of this strategy is further confirmed because the reported marked reduction in mortality from melanoma, from 60% for those patients with melanoma diagnosed in 1960 to approximately 11% in 2005, is mainly due to early detection of thinner lesions followed by appropriate treatment.[4,5]

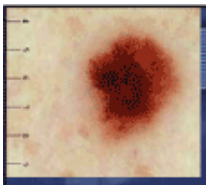
The incidence of melanoma in the general population is increasing in the United States and worldwide.[6] Several reports[7-9] have also indicated the presence of small melanomas, defined as those with diameters of 6 mm or smaller. The more prevalence of melanomas 6 mm or smaller warrants efforts to facilitate their identification

See also pages 469 and 533

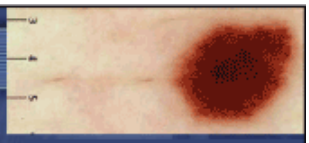
because many of these small melanomas may appear benign by clinical criteria and are therefore more difficult to diagnose.[7] In light of findings that smaller melanomas tend to be less deeply invasive than melanomas larger than 6 mm and, as such, are

Author Affiliations are listed at the end of this article.

Reader Studies

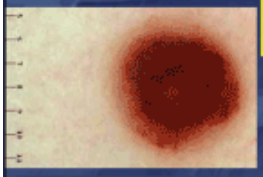


Front thigh – 43 yr old woman
9/9 experts said biopsy
MelaFind said no biopsy
Pathology – not melanoma
(low grade nevus)

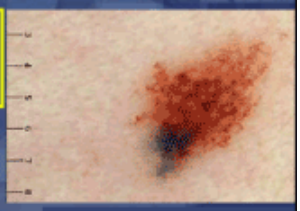


Foot - 13 year old boy
9/9 experts said no biopsy
MelaFind said biopsy
Pathology – melanoma *in situ*

Experts missed 29% of melanomas
Archives Derm, May '08



Foot – 38 yr old woman
5/9 experts said biopsy
MelaFind said biopsy
Pathology – 1.4 mm nodular melanoma

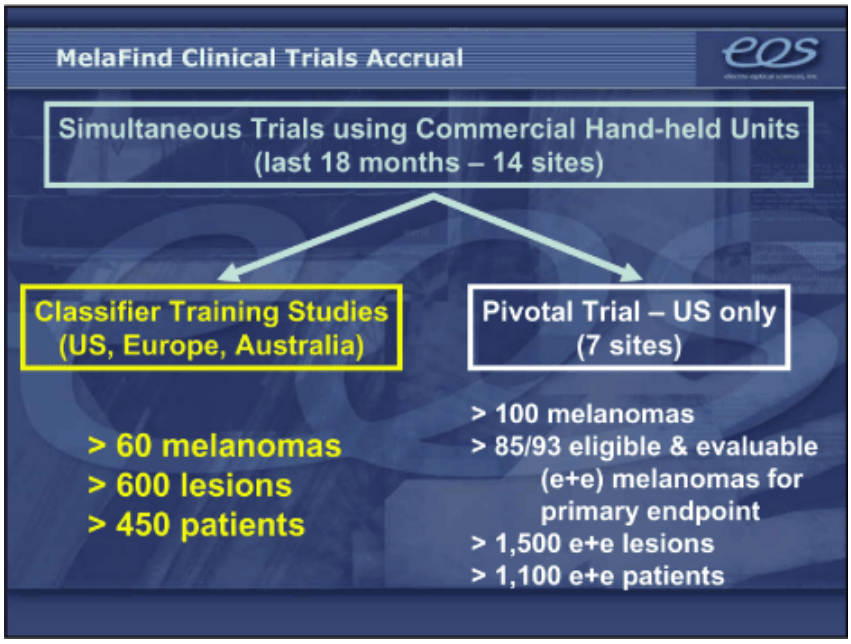


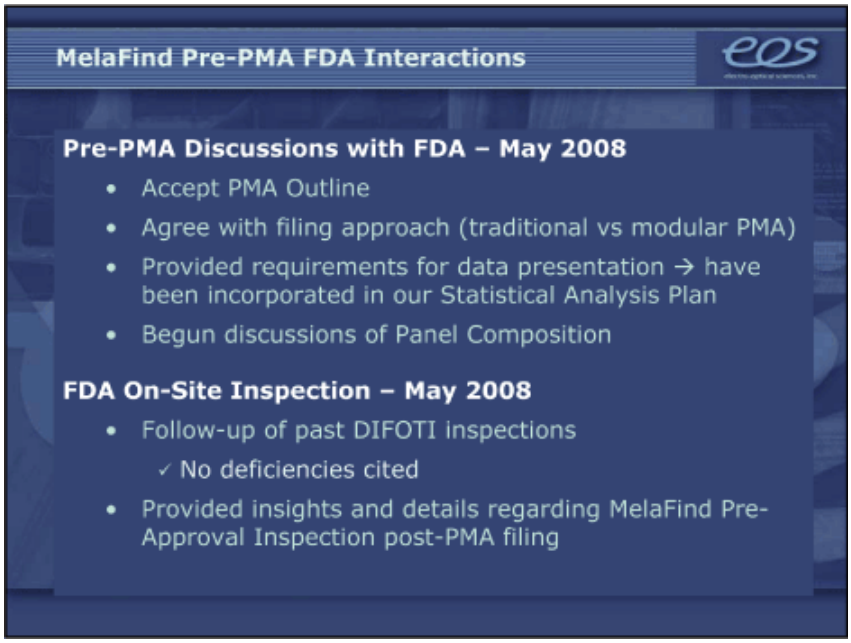
Face - 12 year old boy
9/9 experts said biopsy
MelaFind said no biopsy
Pathology – not melanoma
(congenital nevus)

Pivotal Trial Methods / Design

- Blinded study in patients undergoing biopsy of pigmented skin lesions
- 7 clinical sites in US
- Accrue until 93 melanomas; > 1,200 lesions
- Central dermatohistopath reference standard
- Clinical & dermoscopic pictures with standard cameras

MelaFind Pivotal Trial Endpoints – Protocol Agreement & Expedited Review	
Sensitivity	**Specificity**
≥ 92 / 93 biopsy-confirmed melanomas	p < 0.05 improvement vs study dermatologists


MelaFind Clinical Trials Accrual
Simultaneous Trials using Commercial Hand-held Units
(last 18 months – 14 sites)
Classifier Training Studies
(US, Europe, Australia)
> 60 melanomas
> 600 lesions
> 450 patients
Pivotal Trial – US only
(7 sites)
> 100 melanomas
> 85/93 eligible & evaluable (e+e) melanomas for primary endpoint
> 1,500 e+e lesions
> 1,100 e+e patients


MelaFind Pre-PMA FDA Interactions
Pre-PMA Discussions with FDA – May 2008
• Accept PMA Outline
• Agree with filing approach (traditional vs modular PMA)
• Provided requirements for data presentation → have been incorporated in our Statistical Analysis Plan
• Begun discussions of Panel Composition
FDA On-Site Inspection – May 2008
• Follow-up of past DIFOTI inspections
✓ No deficiencies cited
• Provided insights and details regarding MelaFind Pre-Approval Inspection post-PMA filing

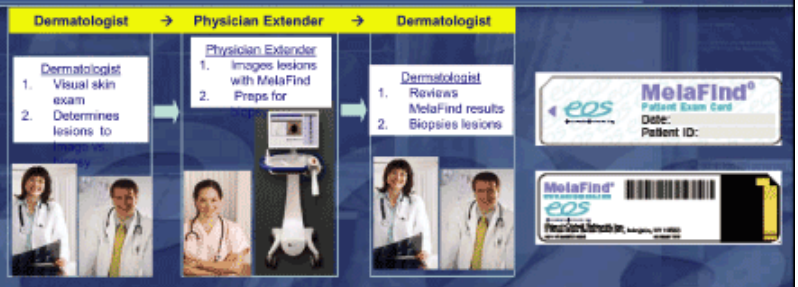
Busy 2H08...

- Auditing/closing of pivotal trial sites
- Classifier Training, Testing, & Selection
- Internet Readers Study:
  a. 90 physicians (dermatologists & PCPs)
  b. 130 lesions from the pivotal trial
  c. Principal Investigator
  d. Largest trial of its type
- Software Quality System Documentation
- Compliance Readiness
- PMA Compilation
- Unblindind & Analysis of Data
- PMA Filing

Ongoing / 3Q08

4Q08

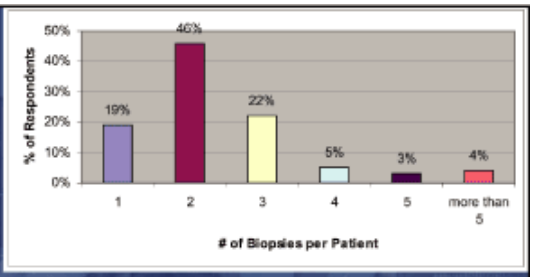
Commercialization Strategy – US Dermatologists



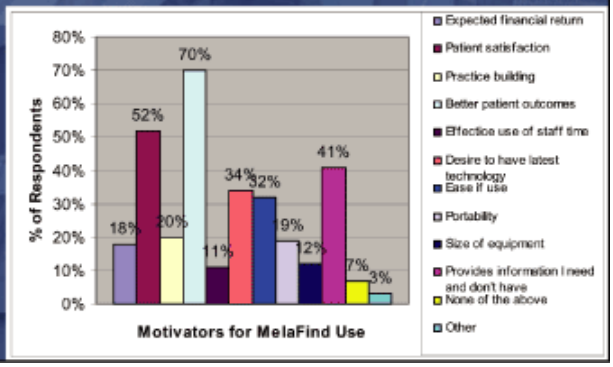
- EOS retains title to the MelaFind system
- Placed in dermatologist's office for a fee **$3K to $5K**
- Proprietary digital media card: **$50 → $100+**
  - ✓ Per-patient, per examination
  - ✓ Target **40** patients per week
- Focus on US dermatologists → initial **regional roll-out**
- Sales & marketing: evaluating potential partners *vs* initial "go-it-alone" strategy
- Additional revenues → annual software licenses, upgrades, etc.

Quantitative Research 180 dermatologists

How many biopsies do you typically perform per patient, per examination?
81% perform multiple biopsies per patient

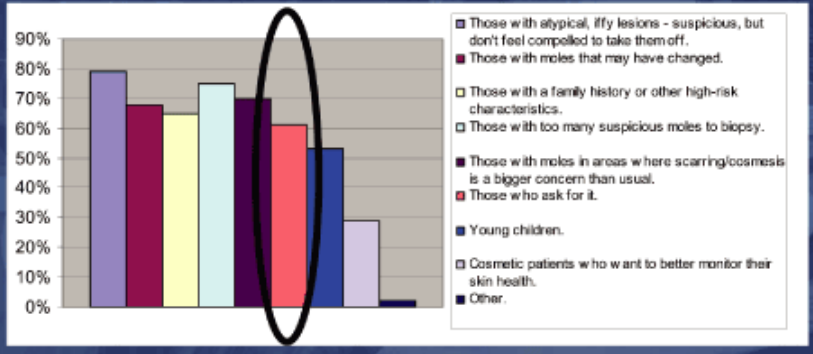


What are the greatest motivators for MelaFind use?
Better outcomes & patient satisfaction



Quantitative Market Research – 180 dermatologists

On what patient types might you use a product like MelaFind?



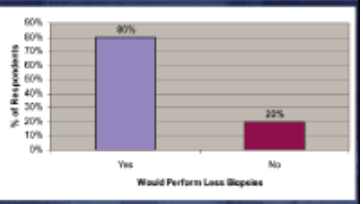
Over 60% of dermatologists in the survey see **> 150** patients/week

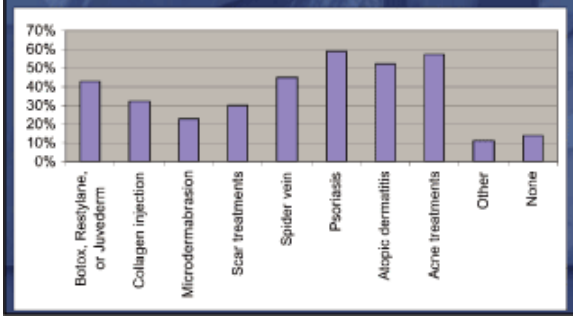
Mean uses per week = **33**; mean uses in high biopsiers = **44**/week

Nurses in qualitative research say **70** patients per week…why?

Burden of Biopsy Market Research (n=53 staff)

Average time by all caregivers	1st bx ($76-$90)	2nd bx (+$46-$60)
Shave biopsy	0:40:00	0:43:39
Punch biopsy	0:43:22	0:48:43
Excisional biopsy	0:51:33	1:02:59





- Respondents would used time saved on biopsies to perform a wide variety of procedures -- cosmetic and medical

Total responding = 44 (no medical assistants)

MelaFind Economics – reduced biopsies

Revenue without MelaFind:		Revenue with MelaFind:	
20 pts biopsied/wk:	$2,700	6 pts biopsied/wk:	$800
		Other procedures with biopsy time saved:	$1,600
		40 pts MelaFind/wk:	$2,000
		MelaFind operator:	($800)
TOTAL/wk:	$2,700	TOTAL/wk:	$3,600
TOTAL/yr:	$135,000	TOTAL/yr	$180,000

1. *Assumes only **$50** to practice for using MelaFind;*
2. *Does not include **additional procedures** performed due to NEW patients attracted to practice via MelaFind*

Consumer/Patient Qualitative Feedback

*"You hear so much about skin cancer these days… but the way doctors look at the skin is rather **primitive** and not an exact science."*

"The best trained dermatologist's eyes cannot go below skin surface but MelaFind can – why take a chance on cancer?"

*"**MelaFind will make me go to see a dermatologist** - a lot more people will be going to derms to check their moles out than what is happening…"*

*"I would like to have a MelaFind exam as a base – almost like a **mammogram**. Then depends on the results, I will go back to the doctor on a regular basis."*

*"I don't like needles - **I am likely to go to see my dermatologist more** often if my doctor has something like MelaFind."*

"I would absolutely ask my doctor about MelaFind. Absolutely."

*"I'd **expect my dermatologist to have MelaFind** because he always has the state of art, newest things in his office."*

"Everyone wants to go to a doctor who's technologically advanced."

*"If it's around $125; who cares if insurance covers it - **there is nothing under three digits in any dermatologist office**."*

"Everything in healthcare costs so much these days. $100-$150 seems reasonable and people can afford it."

*"I'd expect to pay around $300 for it – that's about how much I pay for an **x-ray**."*

Consumer Quantitative Market Research – I
n = 403 Patients

	"Melanoma Concerned"	"Skin Care Involved"
Skin Awareness	Extremely concerned with melanoma a/o prior experience with melanoma (self or family/friend)	Regular use of cosmeceutical products & procedures (Botox, fillers, laser, peels, etc.)

Financial Summary

Recent Financing History

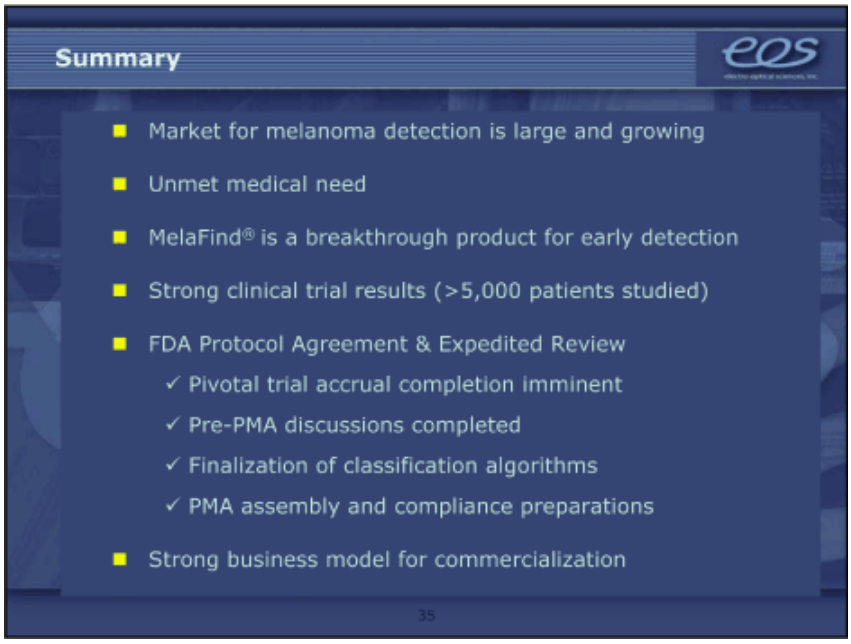
I.P.O.	November	2005	$21,311,500	$5.00 / share
PIPE	November	2006	$13,180,590	$5.70 / share
PIPE	August	2007	$11,501,023	$5.75/ share

Cash Position

March 31, 2008 ≈ $17.2 million

Shares Outstanding

December 31, 2007	15,401,882
Warrants & Options	2,938,970
Total Fully Diluted	18,340,852


Summary
Market for melanoma detection is large and growing
Unmet medical need
MelaFind® is a breakthrough product for early detection
Strong clinical trial results (>5,000 patients studied)
FDA Protocol Agreement & Expedited Review
✓ Pivotal trial accrual completion imminent
✓ Pre-PMA discussions completed
✓ Finalization of classification algorithms
✓ PMA assembly and compliance preparations
Strong business model for commercialization
35

Melanoma Research 2000, **10**, pp. 563–570

Precision of automatic measurements of pigmented skin lesion parameters with a MelaFind™ multispectral digital dermoscope

D. Gutkowicz-Krusin*, M. Elbaum, A. Jacobs, S. Keem, A. W. Kopf, H. Kamino, S. Wang, P. Rubin, H. Rabinovitz and M. Oliviero

Electro-Optical Sciences, Inc., 1 Bridge Street, Irvington, NY 10533, USA. Tel: (+1) 914 591 3783; Fax: (+1) 914 591 3785 (D. Gutkowicz-Krusin, M. Elbaum, A. Jacobs, S. Keem). The Ronald O. Perelman Department of Dermatology, New York University Medical Center, NY 10016, USA (A. W. Kopf, H. Kamino, S. Wang, P. Rubin). Skin and Cancer Associates, 201 N.W. 82nd Avenue, Bennett Medical Plaza, Suite 501, Plantation, FL 33324, USA (H. Rabinovitz, M. Oliviero).

The purpose of this study was to assess the precision of automatic computerized measurement of parameters that may be useful in the differentiation of malignant melanoma from benign pigmented skin lesions, and also to determine the feasibility of quantitative monitoring of skin lesions over time. Ten independent sequences of images were acquired with a MelaFind multispectral digital dermoscope for each of 12 benign or malignant pigmented skin lesions. The sequences of images were processed automatically to provide 10 independent measurements of the various parameters for each lesion. Parameters included lesion area, greatest 'diameter', perimeter, reflectance and asymmetry. The precision of each parameter determination was computed from the mean and standard deviation of the 10 measurements of that parameter. The relative errors in determining the lesion area, 'diameter' and perimeter were found to be 6%, 3% and 4%, respectively. Other lesion parameters that are used in differentiating melanomas from benign skin lesions were also analysed as a function of wavelength. In the blue band (about 430 nm) the relative error was about 7% for the mean lesion reflectance and about 7% for the asymmetry parameter. These results demonstrate the feasibility of using MelaFind for objective quantitative monitoring of changes in pigmented skin lesions over time. As suggested by some studies, such information is useful in the early detection of malignant melanoma. The results show that parameters obtained automatically from MelaFind images are sufficiently precise to allow pertinent parameters to be used to classify pigmented skin lesions.

Key words: computerized image analysis, early diagnosis, malignant melanoma, multispectral digital dermoscope, pigmented skin lesion

* To whom correspondence should be addressed

Introduction

The incidence of malignant melanoma is increasing. The lifetime risk for melanoma was 1 in 1500 in the United States in 1930; it has been projected that it would be 1 in 75 in the year 2000.[1] Melanoma carries a high mortality rate once it metastasizes, and in fatal cases results in an average loss of 17.1 years of life.[2] However, melanoma is curable if diagnosed early.[3]

Early detection of melanoma poses a challenge to both general physicians and dermatologists. The accuracy of clinical diagnosis by dermatologists ranges from 64–75%.[4] The use of a dermoscope may improve diagnostic accuracy; however, training and experience are needed to interpret the dermoscopic images.[5]

Further efforts towards early detection include the development of the clinical ABCD rules,[6] dermoscopic ABCD rules,[7] and a wide variety of computer-based image analysis systems.[8-12] All computer-based systems must perform certain essential functions. The first step is the digitization of photographic images or the direct acquisition of digital images of the skin lesions. The images must then be segmented to separate the lesion from the surrounding skin. Various lesion parameters are then computed from the segmented images, and parameters that are significantly different in melanomas and benign lesions are identified. These parameters can then be used for lesion classification,

i.e. for differentiation between melanomas and other pigmented cutaneous lesions. Thus, it is essential for the reliability of classification to determine the lesion parameters with high precision.

In the clinical setting, computer-based systems may provide diagnostic information, often based on a single-time examination of the lesion. However, there are indications that the history of a lesion may also provide important diagnostic information. In a recent paper, Kittler *et al.*[13] evaluated the performance of ABCD rules for dermoscopy combined with information about changes in the lesion size, colour or shape, as well as about ulceration or bleeding, within 1 year prior to excision. Of the 356 small (less than 1 cm in diameter) pigmented skin lesions, 73 were diagnosed by histopathology as melanomas. This study found that the frequency of reported changes was significantly higher for the melanomas. Together with the ABCD scores, this information (based on patients' reports) proved useful in differentiating melanomas from benign skin lesions.

Follow-up of pigmented skin lesions using digital epiluminescence microscopy was described by Braun *et al.*[13] The changes (in colour, size and architecture) in lesions were determined by visually comparing the digital images acquired over a period of 2 years. Two types of changes were documented: in colour only and in size and architecture. The latter type of change appeared to be correlated with 'dysplasia'.

A study by Menzies *et al.*[15] suggests that clinical history should be included in the diagnostic process. In this study, all nine melanomas that lacked characteristic dermoscopic features for melanoma had a history of change in colour, shape or size. These studies suggest that quantitative monitoring of changes in pigmented skin lesions should improve the diagnostic accuracy for melanoma.

In order to have reliable diagnostic value, assessment of the changes in the lesion should be objective and repeatable. This paper describes the MelaFind system developed by Electro-Optical Sciences, Inc. Our study was conducted to determine the precision of lesion parameter measurements with this system. The study results show that objective quantitative monitoring of pigmented skin lesions is feasible. The high precision of automatic parameter measurements with the MelaFind system also supports the feasibility of reliable classification of pigmented skin lesions.

Materials and methods

The MelaFind system

In our study we used the MelaFind multispectral digital dermoscope to acquire images of pigmented skin lesions. The system illuminates the skin with light in 10 narrow spectral bands in the visible and near-infrared. The illumination consists of filtered white light from a highly stable source. The filtered light is conveyed to the skin through a fibreoptic illuminator. A charge-coupled device (CCD) camera detects light in each of the 10 spectral bands used to illuminate the skin. Digital images acquired by the camera are then sent to a computer for processing.

The imaging system provides low noise, high resolution digital images at a high data transfer rate, with low distortion imaging over the entire field of view of about 2.5 X 2.0 cm. In the lesion plane, the pixel size is 20 X 20 μm. The monochrome CCD camera is contained in a unit mounted on an articulated arm that can be locked into position. The camera produces digital images 1280 X 1000 pixels in size. The illuminator is controlled by a stabilized power supply, the setting of which is adjusted automatically by the computer. Narrow interference filters, placed on a rotating wheel, are used to filter white light in bands from 430 nm to 950 nm. A fibre illuminator conveys the filtered light to the lesion, providing nearly uniform illumination at the skin surface. Non-uniformities of the illumination and the optical system, as well as the non-uniform response of the camera chip, are eliminated during calibration. Typically, the entire multispectral sequence of 10 images is acquired in less than 3 s.

The results reported here are from dermoscopic imaging, in which a layer of mineral oil is applied to the skin and a glass plate (at the front end of the camera unit) is placed over the oil layer. Slight pressure is applied, through the glass, to the skin throughout the imaging process, to minimize the problem of misregistration of images in different spectral bands. Based on the high repeatability of parameter estimation, misregistration is not important.

The system permits image data to be recorded in each spectral band over a large linear dynamic range, independent of skin type. In addition, each lesion image includes an image of a narrow strip of oil-free, diffusely reflecting calibration material, located along one edge of the field of view. The absolute reflectance of this material is known at each wavelength. The average image intensity in the strip region is used to obtain the absolute reflectance in every

pixel for every image in the multispectral sequence. This allows the colour calibration of the lesion images.

The database

Ten sequences of multispectral images were acquired for each of the 12 pigmented skin lesions. The 12 lesions consisted of one invasive melanoma (Breslow thickness 0.63 mm), one melanoma *in situ*, nine melanocytic naevi and one seborrhoeic keratosis. To ensure that the sequences were independent, the CCD camera was removed from the skin after each sequence, the lesion and surrounding skin were cleaned, oil was reapplied, and the camera repositioned on the lesion. Since air bubbles may affect the measured values of parameters such as reflectance, the operators previewed the images prior to acquisition and started again from the beginning of the procedure if bubbles were present. Since each sequence of images was acquired independently, the lesion location and orientation in the field of view of the camera varied from sequence to sequence. To reduce biases in the results, the lesion images were acquired using two different instruments at two different geographic locations (New York City and southern Florida) by five different operators.

Each sequence of multispectral images was analysed automatically. The first step in the image analysis is segmentation of the lesion from its surroundings in the field of view, as described previously.[12] The resulting segmentation mask, one for each sequence, was used to compute parameters such as area and perimeter, and also to segment images in all the spectral bands. The segmented spectral images were used to compute the wavelength-dependent lesion parameters. The 10 independent values of each parameter obtained for each lesion were then used to compute the average value of that parameter as well as the standard deviation. An example of a multispectral sequence of images for a melanoma *in situ* is shown in Figure 1, together with the segmentation mask for this sequence.

Results

Figure 2 shows the results of the lesion area measurements. The error bars shown in the figure represent one standard deviation. The lesions ranged in area from about 2 mm^2 for the smallest naevi to over 100 m^2 for the melanomas. The relative errors were similar and the average relative error was only about 6%. If on two examinations the lesion area changed by more than about 12%, this change would be statistically significant at the 95% confidence level.

Figures 3 and 4 show the results for lesion ‘diameter’ and perimeter measurements, respectively. The ‘diameter’ is defined as the longest distance between two points located on the lesion border, as determined by the segmentation mask; the perimeter is the length of the lesion border. Again, despite a wide range of values for these parameters, the relative errors were similar and averaged about 3% for the ‘diameter’ and about 4% for the perimeter. This is consistent with the results shown in Figure 1 concerning area, since the error in area measurement should be about twice the error of measuring a linear dimension.

The MelaFind images also allowed determination of the absolute reflectance for each pixel in each of the 10 spectral bands. Figure 5 shows the average lesion reflectance at 430 nm (blue band). Melanomas, seborrhoeic keratoses and some naevi reflect only a few per cent of the incident blue light and thus appear rather dark. The average relative error in reflectance measurement at this wavelength was about 7%.

Lesion reflectance varies considerably with wavelength. As shown in Figure 6, the average reflectance increases from a few per cent in the blue to about 30–40% in the infrared. Similarity in the average reflectance between melanomas *in situ* and naevi is not uncommon. In addition, seborrhoeic keratoses often appear as dark as invasive melanomas. Figure 7 shows the means of the spectral lesion reflectance for 33 invasive melanomas, 30 melanomas *in situ*, 183 naevi and 22 seborrhoeic keratoses from the MelaFind image database. It can be seen that the four lesions shown in Figure 6 are representative of their types.

Colour variegation is considered to be characteristic of melanoma and is included in the clinical and dermoscopic ABCD rules. Since lesions are not usually pigmented uniformly, the lesion reflectance may vary greatly from pixel to pixel. The ‘colour variegation’ parameter, defined as the standard deviation of the lesion reflectance, is shown in Figure 8. The results are of high precision and show that, regardless of the lesion type, the pixel-to-pixel variability in reflectance appears to be maximum in the red band (650–700 nm).

Lesion asymmetry has long been recognized as a characteristic of melanoma, as evidenced by its

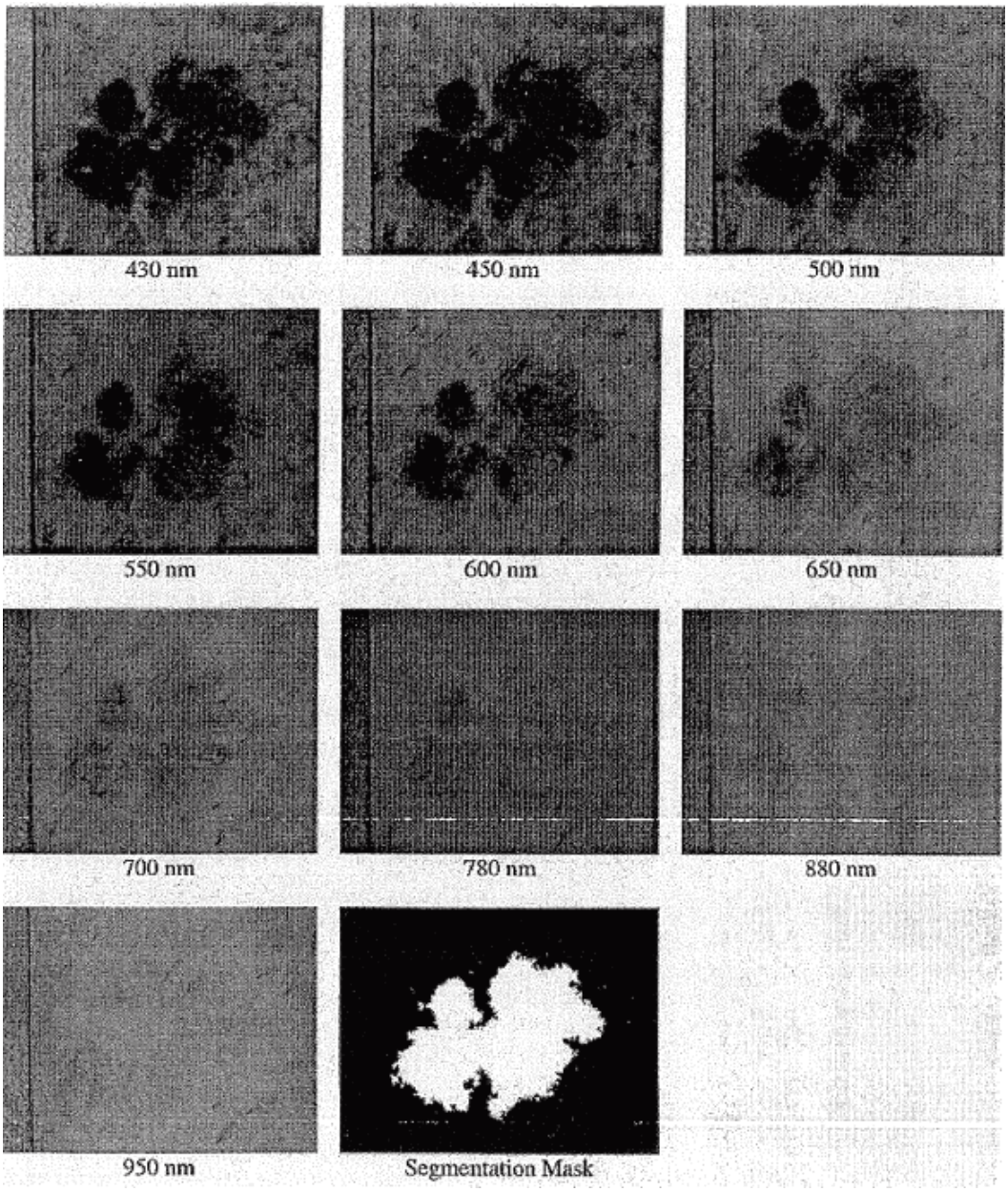


Figure 1. A sequence of multispectral images for a melanoma *in situ,* together with the automatically obtained segmentation mask for this sequence.

inclusion in the ABCD rules. The asymmetry parameter, shown in Figure 9, was computed as follows.[12] First, in each spectral band the two orthogonal principal axes in the segmented image were located and the image was then rotated to make these axes parallel to the image edges. The difference of intensities was then computed for every pair of pixels with locations that are mirror

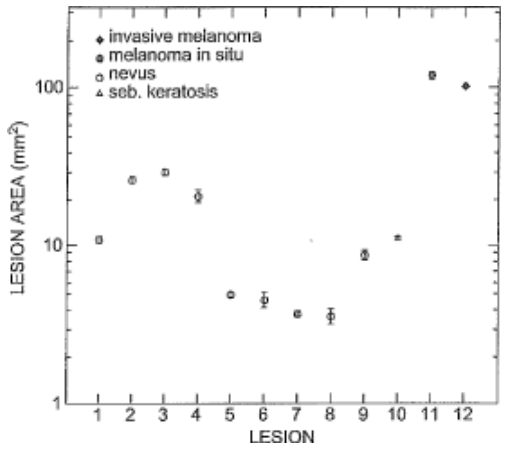


Figure 2. Automatic determination of the area of pigmented skin lesions. The error bars represent one standard deviation computed from 10 independent measurements for each lesion. The average relative error was about 6%. Changes in area in excess of 12% would be significant at the 95% confidence level.

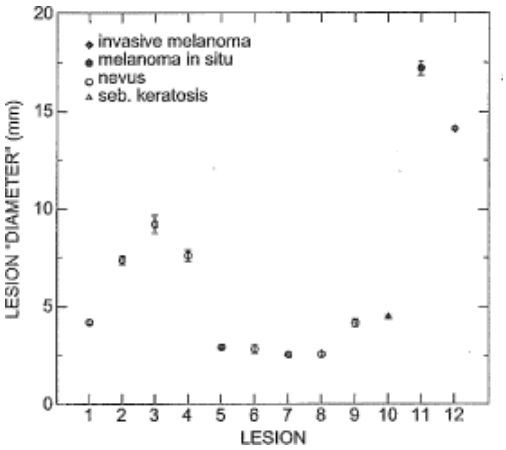


Figure 3. Automatic determination of the 'diameter' of pigmented skin lesions. The 'diameter' is defined as the longest distance between any two points on the lesion border. The error bars represent one standard deviation computed from 10 independent measurements for each lesion. The average relative error was about 3%. Changes in 'diameter' in excess of 6% would be significant at the 95% confidence level.

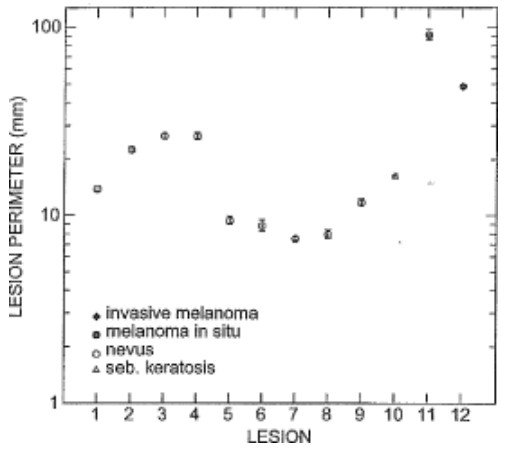


Figure 4. Automatic determination of the perimeter (the length of the border) of pigmented skin lesions. The error bars represent one standard deviation computed from 10 independent measurements for each lesion. The average relative error was about 4%. Changes in perimeter in excess of 8% would be significant at the 95% confidence level.

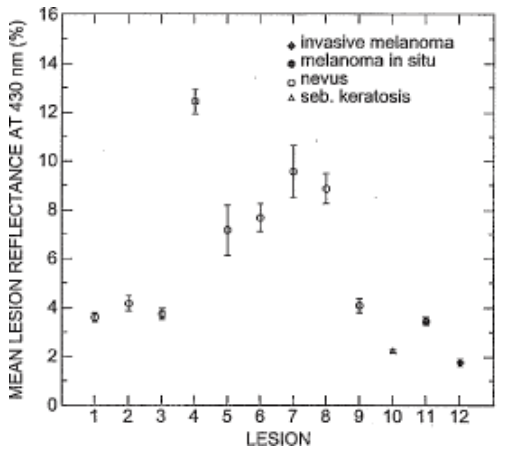


Figure 5. Automatic determination of the mean reflectance in the blue band (430 nm) of pigmented skin lesions. The error bars represent one standard deviation computed from 10 independent measurements for each lesion. The average relative error was about 7%. Changes in the mean reflectance in the blue band in excess of 14% would be significant at

the 95% confidence level.

images with respect to one of the principal axes. The asymmetry parameter for that axis is defined as the ratio of the sum of the absolute values of intensity differences and the total intensity in the segmented image. This normalization to the total intensity is necessary to ensure that the computed quantity is independent of the overall image brightness. It also makes the asymmetry parameter a measure of the fraction of the total lesion area that has different intensities on two sides of the principal

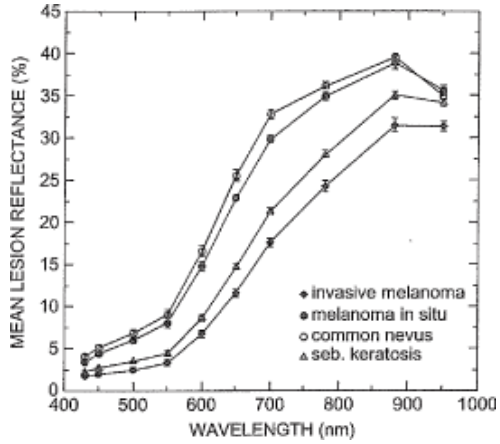


Figure 6. Automatic determination of the mean reflectance as a function of wavelength for four pigmented skin lesions. The error bars represent one standard deviation computed from 10 independent measurements for each lesion.

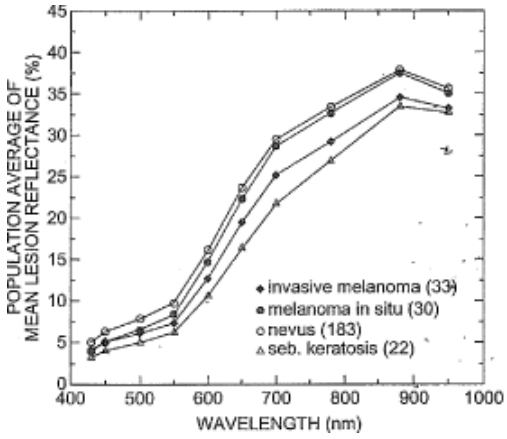


Figure 7. Population averages of the mean reflectance for melanomas (invasive and *in situ),* naevi and seborrhoeic keratoses from the MelaFind image database as a function of wavelength. These data show that the mean spectral reflectances of lesions shown in Figure 6 are similar to the population averages.

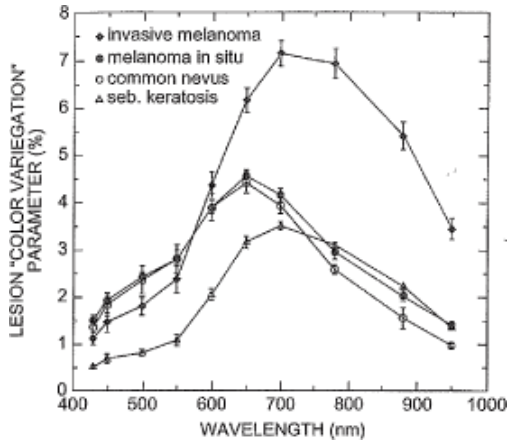


Figure 8. Automatic determination of the 'colour variegation' parameter as a function of wavelength for four pigmented skin lesions. For all the lesions shown, the 'colour variegation' parameter was maximum in the red bands (650-700 nm). The error bars represent one standard deviation computed from 10 independent measurements for each lesion.

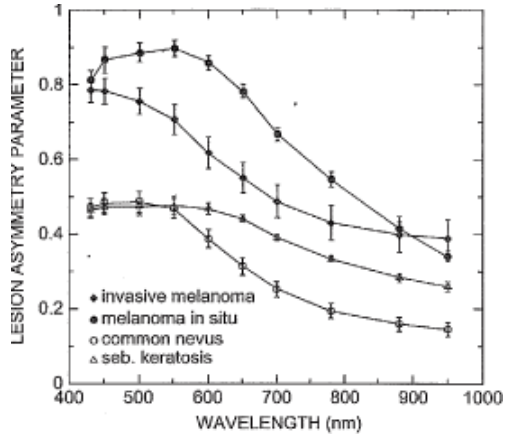


Figure 9. Automatic determination of the asymmetry parameter as a function of wavelength for four pigmented skin lesions. The error bars represent one standard deviation computed from 10 independent measurements for each lesion. The asymmetry parameter is very important for the differentiation between melanomas and other pigmented lesions.

axis. The lesion asymmetry parameter is the sum of the parameters computed for the two principal axes. The results for four lesions are shown in Figure 9. Clearly, this parameter varies with wavelength, and so does the relative error of its determination. The relative error for the 12 lesions used in this study was about 7% in the blue band (430 nm). The separation between the two malignant and two benign lesions seen in this figure does not in itself prove that the asymmetry parameter differentiates melanomas from benign lesions. However, the spectral asymmetry parameters did differ significantly between the populations of naevi (183) and melanomas (63) in the MelaFind image database.

Discussion

The monitoring of melanocytic skin lesions over time was discussed by Stolz *et al.*[16] The image acquisition system they used consisted of a handheld three-chip CCD camera (Sony). The field of view of the camera was 1.18 X 1.18 cm and the pixel size in the lesion plane was about 22.7 X 22.7 µm. Image segmentation was performed manually, moving the cursor along the lesion border. The relative error in area determination was reported to be less than 10%. The digital database also allowed side-by-side comparison of lesion images acquired at different times in order to determine visually changes in colour and dermoscopic structures. In 25% of the cases studied, these changes occurred without a significant change in lesion area. The authors concluded that monitoring lesions over time requires more than the measurement of the lesion area alone.

The MelaFind system for the acquisition of multispectral images of pigmented skin lesions and automatic analysis of such images allows objective determination of lesion parameters. In this study of the precision of parameter measurements the relative errors in determining the lesion area, 'diameter' and perimeter were 6%, 3% and 4%, respectively. Such an analysis was also carried out for lesion parameters that have been found to help in differentiating between melanomas and other pigmented skin lesions. For example, the lesion asymmetry in the blue band (430 nm) was determined with an error of about 7%. In addition, the colour of the lesion could also be determined quite reliably and objectively; the average relative error in the blue reflectance was about 7%.

The multispectral images acquired by MelaFind allow determination of lesion parameters as a function of wavelength as shown for asymmetry, as well as different measures of the reflectance distribution within a lesion. Such spectral representations may prove to be useful in following changes in lesion colour and architecture over time.

Conclusion

This study demonstrates the feasibility of using the MelaFind system for quantitative and objective monitoring of changes in pigmented skin lesions over time. As suggested by some other studies, this information is useful in the detection of early malignant melanoma. The demonstrated precision of automatic parameter measurements suggests that reliable classification of pigmented skin lesions with the MelaFind system may be feasible.

Acknowledgements

The authors thank Robert S. Bart MD for helpful discussions and Hal Woertzel for technical assistance. This research was supported in part by the NIH/NCI grants IR43CA60229 and IR43CA74628, and by the Christopher Columbus Fellowship Foundation.

References

1. Rigel DS, Friedman RJ, Kopf AW. The incidence of malignant melanoma in the United States: issues as we approach the 21st century. *J Am Acad Dermatol* 1996; **34**: 839–847.
2. Albert VA, Koh HK, Geller AC, Miller DR, Prout MN, Lew RA. Years of potential life lost: another indicator of the impact of cutaneous malignant melanoma on society. *J Am Acad Dermatol* 1990; **23**: 308–310.
3. NIH Consensus Conference. Diagnosis and treatment of early melanoma. *JAMA* 1992; **268**: 1313–1319.
4. Grin CM, Kopf AW, Welkovich B, Bart RS, Levenstein MJ. Accuracy in the clinical diagnosis of malignant melanoma. *Arch Dermatol* 1990; **126**: 763–766.
5. Binder M, Schwarz M, Winkler A, Steiner A, Kaider A, Wolff K, Pehamberger H. Epiluminescence microscopy. A useful tool for the diagnosis of pigmented skin lesions for formally trained dermatologists. *Arch Dermatol* 1995; **131**: 286–291.
6. Friedman RJ, Rigel DS, Kopf AW. Early detection of malignant melanoma: the role of physician examination and self-examination of the skin. *Cancer J Clinician* 1985; **35**: 130–151.
7. Stolz W, Riemann A, Cognetta AB, Pillet L, Abmayr W, Holzel D, Bilek P, Nachbar F, Landthaler M, Braun-Falco O. The ABCD rule of dermoscopy: a new practical method for early recognition of malignant melanoma. *Eur J Dermatol* 1994; **7**: 521–528.
8. Schindewolf T, Schiffner R, Stolz W, Albert R, Abmayr W, Harms H. Evaluation of different image acquisition techniques for a computer vision system in the diagnosis of malignant melanoma. *J Am Acad Dermatol* 1994; **31**: 33–41.
9. Binder M, Kittler H, Seeber A, Steiner A, Pehamberger H, Wolff K. Epiluminescence microscopy-based classification of pigmented skin lesions using computerized image analysis and an artificial neural network. *Melanoma Res* 1998; **8**: 261–266.
10. Green A, Martin N, Pfitzner J, O'Rourke M, Knight N. Computer image analysis in the diagnosis of melanoma. *J Am Acad Dermatol* 1994; **31**: 958–964.
11. Seidenari S, Pellacani G, Giannetti A. Digital video-microscopy and image analysis with automatic classification for detection of thin melanomas. *Melanoma Res* 1999; **9**: 163–171.
12. Gutkowicz-Krusin D, Elbaum M, Szwajkowski P, Kopf

AW. Can early malignant melanoma be differentiated from atypical melanocytic nevus by *in vivo* techniques? Part II: Automatic machine vision classification. *Skin Res Technol* 1997; **3**: 15–22.

13. Kittler H, Seltenheim M, Dawid M, Pehamberger H, Wolff K, Binder M. Morphologic changes of pigmented skin lesions: a useful extension of the ABCD rule for dermatoscopy. *J Am Acad Dermatol* 1999; **40**: 558–562.

14. Braun RP, Lemonnier E, Guillod J, Skaria A, Salomon D, Saurat JH. Two types of pattern modification detected on the follow-up of benign melanocytic skin lesions by digitized epiluminescence microscopy. *Melanoma Res* 1998; **8**: 431–437.

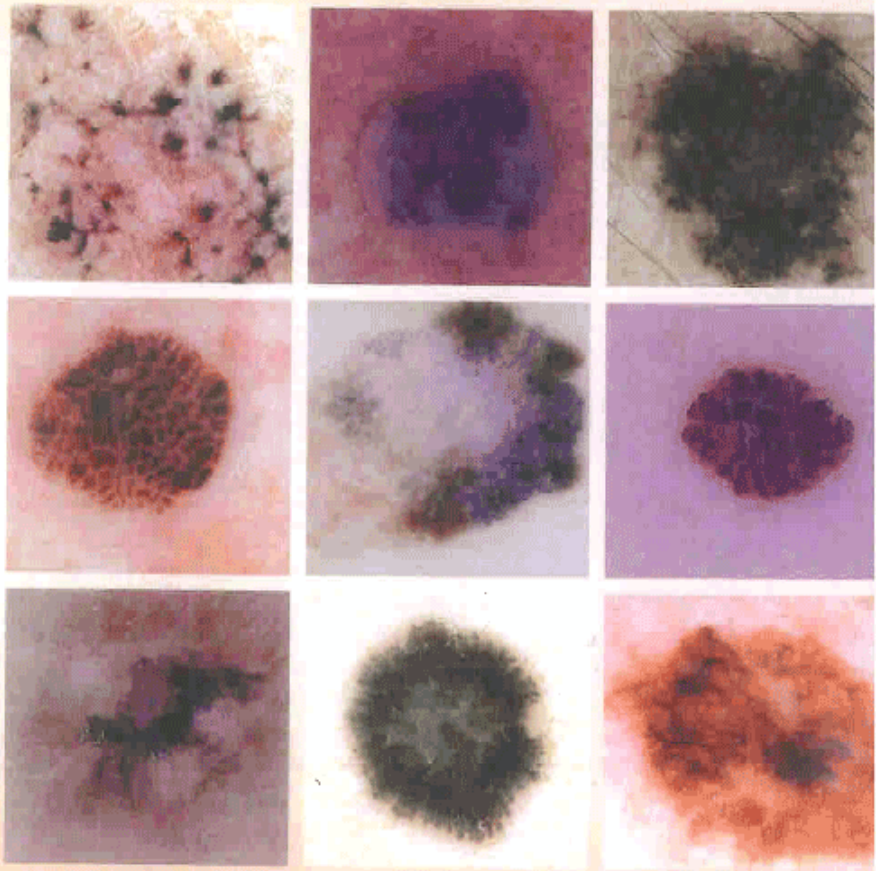
15. Menzies SW, Ingvar C, Crotty KA, McCarthy WH. Frequency and morphologic characteristics of invasive melanomas lacking specific surface microscopic features. *Arch Dermatol* 1996; **132**: 1178–1182.

16. Stolz W, Schiffner R, Pillet L, Vogt T, Harms H, Schindewolf T, Landthaler M, Abmayr W. Improvement of monitoring of melanocytic skin lesions with the use of a computerized acquisition and surveillance unit with a skin surface microscopic television camera. *J Am Acad Dermatol* 1996; **35:** 202–207.

(Received 20 October 1999; accepted in revised form 21 February 2000)

THE ENCYCLOPEDIA OF VISUAL MEDICINE SERIES

Atlas of DERMOSCOPY



Taylor & Francis
Taylor & Francis Group

Edited by
Ashfaq A. Marghoob MD
Ralph P. Braun MD and
Alfred W. Kopf MD MS(Derm)

CHAPTER 14

Automated diagnosis: illustrated by the Melafind® system

M. Elbaum

INTRODUCTION

MelaFind®, a registered trademark of Electro-Optical Sciences, Inc., is a multispectral dermoscopic imaging computer vision system, for objective, non-invasive detection of pigmented cutaneous melanoma (MM), as well as of high-grade dysplastic nevi (HGDN). The system is fully automated and is intended to serve as an objective 'consultant' to physicians. It will suggest to the physician to 'Consider biopsy — use clinical judgment' if it determines that an imaged pigmented skin lesion is either MM or HGDN. It will suggest 'Consider follow-up — use clinical judgment' if the score is below the 'Consider biopsy' classifier.

MelaFind is multispectral in that it employs light in a number of bands across the visible and infrared spectral region, to extract suitable information about the neoplasm from different depths within the lesion. It is a computer vision system in which the illumination of the lesion, creation of the image, extraction of the desired information, and reporting of the result to the operator are all done entirely under computer control. (For a more comprehensive review of computer vision for automated melanoma diagnosis, see reference 14.) MelaFind provides an objective determination of lesion status, as either positive or negative, independent of the diagnostic skills of the operator. It does so in near real time — less than a second is needed to capture the images, and about 1–2 min is required to provide a report to the operator.

MelaFind is in its final stage of testing prior to entering the market. The American Food and Drug Administration (FDA) has reviewed part of the Pre-Market Approval (PMA) application for MelaFind, and details of the clinical protocol are being discussed with the agency. This stage follows 2 years' testing of the feasibility of automated differentiation of pigmented lesions based on 35-mm color (red, green, blue) transparencies[1], and 3 years' development and testing of a prototype (the Spectral Lesion IMaging (SLIM) system)[2]. The current MelaFind system, intended for commercial use, is shown in Figure 14.1

PRINCIPLES OF OPERATION

'True positive' and 'true negative'

For MelaFind, as well as for physicians, truth of a 'positive' diagnosis of a pigmented skin lesion (PSL) is determined relative to the histologically positive lesion, on biopsy. Thus, a true positive lesion is one with a histological diagnosis of either MM (invasive or *in situ)* or HGDN (an architecturally disordered nevus with 'severe cytologic atypia'), while a true negative is a PSL with any other histological diagnosis.

This definition, in which melanoma is combined with HGDN into a single class, was recommended by the MelaFind Science Advisory Committee (SAC). (For list of members, see p.335.) The SAC felt that such a classification would best serve the interests of patients, given the current state of histopathology and the accepted standard of care by physicians.

Basis for lesion differentiation

Differentiation of a pigmented skin lesion is performed non-invasively on the basis of the multispectral digital dermoscopic images of the lesion that are acquired and analyzed, and the lesions then classified. To secure objectivity, the entire process is end-to-end automatic (no operator intervention).

The data used to classify the lesion consist of reflectance-calibrated digital images of the PSL that are acquired *in vivo*, in ten wavelength bands (see section below). Each image is calibrated so as to represent the reflectance distribution of the lesion in each band. These images contain patterns that arise from the wavelength-dependent absorption and scattering characteristics of light interacting with skin tissue[3,4]. The patterns differ for MM/HGDN, as opposed to other PSLs, the former tending to exhibit more heterogeneity and less symmetry than the latter. Hence, suitable algorithms for quantification of these differences are used to classify the lesion. In MelaFind, 'statistical pattern recognition' methods are used for PSL differentiation.

In statistical pattern recognition[5,6], each pattern is represented through a number of features (d) that constitute a pattern vector in a hyperspace. The features are considered as random variates, governed by feature-specific probability distributions.

The features defined in MelaFind are quantitative generalizations of those described qualitatively and subjectively by clinicians, who have noted that, when observed in white light, melanomas tend to be more heterogeneous and more asymmetrical than are benign neoplasms[7]. The image analysis that provides the d-dimensional pattern vector is described below, starting with image segmentation. The features themselves are discussed further under *Features for classification*, followed by discussion of the classifier structure and the feature selection process *(Lesion classification*, p.329).

Lesion image acquisition

The image acquisition process is under automatic control, and includes image 'pre-processing' procedures that detect several artifacts that could distort or degrade these images, as well as image calibration procedures that enable the images to be interpreted as maps of lesion reflectance in each of the ten wavelength bands.

Image formation

To create the patterns needed to differentiate between the classes, the 'dermoscopic' imaging method is employed[1,2,8], in which unwanted reflections of light at the upper surface of the skin (stratum corneum) are reduced, by placing a thin liquid layer (91% isopropyl alcohol) between the skin and the imaging instrument. This reduction occurs because the liquid improves the match between the optical refractive indices of skin and the glass 'front end' of the instrument.

To facilitate differentiation among lesions, MelaFind employs a multi spectral imaging system, in which the skin is illuminated by light, in each of ten different wavelength bands, in rapid succession. At each wavelength band, the skin has different reflection, absorption and scattering properties, so that the images of the skin taken at different wavelengths will generally be different. At wavelengths near 430 nm (blue), the dominant absorption is by the melanin contained inside pigmented skin lesions. However, light at this wavelength penetrates less deeply into the skin than does light at longer wavelengths[3,4]. Hence, deeper melanin-containing structures will be seen more readily at longer MelaFind wavelengths, e.g. 700 or 950 nm. Hemoglobin is another important contributor to the image structure, whose absorption also varies over the various wavelength bands.

The field of view and spatial resolution of the imaging system were selected on the basis of earlier research experience with dermoscopic images of pigmented skin lesions. The spatial resolution is on the order of 20 μm, at all wavelengths, with high signal-to-noise ratio. At this resolution, the wavelength-dependent texture of the lesion image can be analyzed, over different spatial scales. The MelaFind image format (1280 x 1000) enables lesions up to 2.2 cm in diameter to be accommodated in the field of view[1,2].

The imaging sensor selected for MelaFind MF 100/100A employs a complementary metal oxide semiconductor (CMOS) chip, with 10-bit intensity resolution. Illumination of the lesion in each of the ten wavelength bands is provided via banks of light-emitting diodes (LEDs), arranged as shown in Figure 14.2, that are adjusted during assembly (US Patent No 6,626,558). For image acquisition, the illumination conditions are adjusted under computer control, so as to optimize the dynamic range of the captured

image at each wavelength band, irrespective of skin pigmentation level. Such control is achieved by selecting the LED pre-charge voltage and current, and adjusting the duration of the illumination pulse, for each wavelength band separately, on the basis of the (low-resolution) preview image brightness. After assembly, the uniformity of the illumination field is measured and is required to be within specifications.

The light remitted from the lesion and surrounding skin is captured by the camera optics and is converted to digital images via the imaging sensor. The multi-step MelaFind calibration process compensates for the effects of various noise sources, such as dark current noise, and provides 'reflectance-calibrated' images. This calibration process also assures that, as hardware ages, repeatability of the imaging characteristics of the probe (both probe-to-probe and intra-probe) will remain adequate.

The MelaFind ten-image multispectral sequence for an invasive melanoma is shown in Figure 14.3, together with the segmentation mask that is subsequently generated automatically, as discussed below. The wavelength-dependent nature of the relationship between the image of the lesion and that of the surrounding tissue is immediately apparent here.

Image quality control procedures

The MelaFind system includes several image quality control procedures that aim automatically to detect and eliminate or reduce the influence of certain hardware faults or degradations, and/or image anomalies ('artifacts') that could affect the classifier outcome. Eight pre-processing software checks reside in each base unit, and are applied to every lesion image sequence; they respectively detect whether:

(1) Hardware status parameters may have changed beyond certain limits;

(2) The image may be too bright;

(3) The image may not be bright enough;

(4) Hairs may be present (of size exceeding a threshold value);

(5) One or more bubbles may be present over the lesion area;

(6) The lesion may extend too close to the image border;

(7) The size of the lesion is sufficient for processing;

(8) Unacceptable motion might have occurred during the image acquisition process.

Some of these software checks provide robustness with respect to procedural errors such as may be associated with inexperienced operators. A schematic description of the process through which this quality control software was developed is shown in Figure 14.4. In general, if the quality-control software detects a problem with any set of captured images, those images are rejected, the operator is notified and he/she is requested to repeat the image capture — or else to return the unit for servicing.

As an example, consider the bubble-detection algorithm (item 5 on the above list). The dermoscopic index-matching liquid, if not applied properly, can produce bubble artifacts such as seen in Figure 14.5a. Figure 14.5a and c are *in vivo* images of the same pigmented skin lesion, captured twice with a MelaFind MF-100 unit at a clinical test site.

The lesion was imaged twice because the MelaFind image quality check procedure automatically rejected the image on the first try, since bubbles were detected in Figure 14.5a. In Figure 14.5b, the portions of this image that were ascribed to bubbles by the bubble-detection algorithm are highlighted, in white with black contour. Because the image was rejected, the software automatically sent the operator a message stating that bubbles had been detected, requesting that another image of the lesion be taken. On the second try, the operator captured the image shown in Figure 14.5c. As is evident from Figure 14.5d, the bubble-detection algorithm found no bubbles over the lesion area in Figure 14.5c.

Segmentation

In the segmentation process, a decision is made regarding which pixels in the image belong to the pigmented lesion of interest and which do not. MelaFind performs segmentation automatically via an algorithm, without intervention by the operator. The principle underlying the method is that, irrespective of the color of the skin surrounding the lesion, there is a greater concentration of light-absorbing substances inside the lesion than outside

it, especially at short wavelengths (blue), where absorption by melanin is strong. Binary segmentation ‘masks’ are created, on the basis of the images in the blue and green bands, and the mask with a larger area is then applied to the images at all ten bands[9,10]. The location of the segmentation boundary is chosen on the basis of the histogram of signal intensities in the image, as described below.

Starting from a histogram of the signal intensities in an image, different algorithms can be used to generate the segmentation mask, which differ in the threshold that is selected. However, since the concentration of melanin in the surrounding skin varies with the patient’s skin type, history of sun exposure, etc., we have considered various mask thresholds, and have selected the one to use via a ‘supervised learning’ process (Figure 14.4).

As an illustration, three different thresholds in the intensity histogram are shown in Figure 14.6a, for one particular image. In Figure 14.6b, the corresponding masks that resulted from applying each of these three threshold levels for that image are shown, distinguished through different levels of gray shading. The type 1 mask emphasizes rates of change in melanin concentration. The type 2 mask is the one we used in our earlier work[1,2], and it continues to give the best results. The type 3 mask provided segmentations that were judged, in a preliminary survey of clinicians, to correspond most closely to their visual perceptions. However, such perceptions are influenced not only by melanin but also by hemoglobin concentrations.

The segmentation provided by MelaFind is robust, with respect to various degradations expected in the normal course of operation. As an example, although hair clipping is part of the protocol for use of MelaFind, residual hair often obscures the lesion image, as in Figure 14.7a. If segmentation of the lesion were to be attempted without effective removal of the hair from this image, the lesion mask shown in Figure 14.7b would result, which clearly is an invalid segmentation of the image. To generate the hair mask, a long-wavelength image is selected, in which band the contrast between the hair and the skin background is high. This image is subjected to an appropriate gradient transformation, with the result as seen in Figure 14.7c. Upon thus artificially removing the hair from the image, and then applying the usual segmentation algorithm, the intuitively valid lesion segmentation mask of Figure 14.7d results.

Features for classification

The initial choice of candidate features for use in lesion classification was motivated by the success of the ABCD paradigms for melanoma detection, both in clinical[11] and in dermoscopic[12] view. However, the candidate features go beyond those of the original ‘ABCD’ concepts. For example, instead of a single asymmetry measure (‘A’) on the color (red, green, blue) image, candidate parameters are considered that measure the asymmetry of the intensity distributions in the images at each of the ten wavelength bands[9,13]. As another example, instead of one candidate measure of the lesion border (‘B’), there are several — a border irregularity parameter, defined on the segmentation boundary, and ten border gradient parameters, for the images at each of the ten spectral bands. With ten spectral bands, the color variegation (‘C’) concept is generalized, and this measure of lesion heterogeneity used by physicians is refined further through calculation of the entropy of lesion reflectance at each wavelength. All of the features considered as candidates for use in lesion classification are required to be invariant to size, rotation or position of the lesion in the field of view.

MelaFind employs ‘GSR’ and ‘WMR’ features for classification[1,2]. The GSR features are calculated through algorithms that operate directly on the ‘gray-scale representation’ of the multispectral lesion images[1], for example in Figure 14.8a. These features generalize the ABCD concepts through various measures of asymmetry, blotchiness, border regularity, and lesion texture; for the algorithms that define GSR features, see US Patent No. 6,208,749[9].

The WMR features further generalize the ABCD concepts. They systematically characterize the heterogeneity and asymmetry of the lesion on different spatial scales, and are based on the multi-scale ‘wavelet maxima representation’ (WMR) of the images[2,10]. They provide various statistical measures of image texture at several wavelet ‘levels’ — each level representing a different scale of spatial structure. WMR feature values also vary with the wavelength of the light used to obtain the image. An example of the texture information elicited through the WMR at short wavelengths is provided in Figure 14.8b. The basic WMR features and methods used to extract them from the images are described in detail in US Patent No. 6,081,612[10].

More recently, the WMR features have been extended to include measures of their asymmetry, as

Table 14.1 The seven features selected for a non-linear classifier

Mnemonic	*Description*	*Band (nm)*
Wavelet features		
IL2b4W	density, interior, level 2*	600
IL3b7Q	entropy, interior, level 3†	770
ASY3IL2b3Y	quadrant maximum of entropy type 3, interior, level 2*	550
ASY3IL2b4Y	quadrant maximum of entropy type 3, interior, level 2*	600
GSR features		
txt630	texture type 6, 2 x 2 window	430
txt491	texture type 4, 5 x 5 window	920
txt593	texture type 5, 9 x 9 window	920

* Level 2 = 80 µm extent

† Level 3 = 160 µm extent

well as entropy measures. (For examples, see Table 14.1)

Robustness of features

Whereas a large number of GSR and WMR features can be defined, only such features are considered as candidates for use in the MelaFind classifier as satisfy a robustness criterion. This is a requirement that the value of the extracted feature be substantially the same when calculated from images of the same lesion acquired by different operators, with different MelaFind units, in different orientations, etc.

Lesion classification

Lesion differentiation is performed via a classifier that combines selected features (linearly or non-linearly) into a numerical score for each lesion. Below, we describe the nature of the MelaFind classifier.

Nature of the classifier

Lesion scores produced by the classifier are considered to be random variates that are governed by two probability distributions, one for lesions that are positive for the disease (‘melanomas’) and the other for those that are negative (‘non-melanomas’). The structure of the classifier is first defined, i.e. an algorithm is constructed that defines how to combine feature parameter values into a score.

Two types of classifier have been developed for MelaFind. The first type is a linear classifier, in which a linear combination of selected lesion features determines the score. The second type is a non-linear classifier, in which an exponential (Gaussian) transformation is applied to the features, that depends on their covariance. In either case, the coefficients of combination are determined through an iterative ‘supervised’ training process, employing a well-characterized lesion image database, for which the histopathology diagnoses are known. (The database is described in more detail in under Tests of performance.)

This training process selects from among a number of candidate classifiers, by searching for the ‘best’ separation between the score distributions for the ‘melanomas’ and for the ‘non-melanomas’ in the database. The measure of ‘best’ separation for the linear classifier is the highest specificity achieved at a fixed high level of sensitivity (usually 100% over the training set). For the non-linear classifier, the measure of ‘best’ separation is the area under the receiver operating characteristic (ROC) curve, which can be interpreted as an average sensitivity (where the average is taken over a range of specificity). In all cases, the known histopathology diagnosis serves as the truth standard.

Following training of the classifier, it is subsequently tested on an appropriately chosen ‘test set’ of lesions. The images in the ‘training set’ and the ‘test set’ are assumed to be representative of those of lesions in each of the two classes.

Feature selection

Automated search techniques are applied to candidate classifiers, each constructed with a different combination of features[9,10,14]. The process of feature selection begins with a list of approximately 1000 candidate features. A powerful search engine is then applied to test various combinations of these features (with the combination determined by the nature of the classifier, as detailed in the next subsection). The search has been automated, most recently with the aid of IBM's computer grid. (For a description, see for example www.gridtoday.com/03/0922/101 982.html).

Table 14.1 lists the features selected via the MelaFind search algorithms, for a seven-feature non-linear classifier. The seven features include four of the wavelet (WMR) type and three non-wavelet (GSR) features. All of the WMR features selected are from the lesion interior (as opposed to the region near the lesion border, or the region immediately outside the lesion border). Of the five scale sizes ('wavelet levels') over which WMR features are defined, the selected features are associated with scales of characteristic size 80 μm (level 2) and 160 μm (level 3). One of these is a wavelet density (number of wavelet maxima per unit area); while the other three are associated with measures of the entropy of the wavelet maxima coefficient distribution*. Entropy is a measure of the degree of disorder. The image of a melanoma, which tends to have a greater degree of disorder than non-melanomas, would be expected to have a greater entropy measure. The wavelength bands associated with the four selected WMR features range from 550 nm (yellow-green) to 770 nm (deep red).

The three GSR features that were selected are measures of lesion image texture. (By their design, GSR texture types 5 and 6 are measures of the variability in the area of dermal papillae, and in the length/width ratio of rete ridges[10].) One of the selected GSR features is a fine-grained measure of texture in the lesion image at 430 nm (blue). The other two are coarser textures of the lesion image at 920 nm (in the infrared), the band where light penetrates deepest into the lesion.

Classifier structure

We have utilized the linear classifier and the non-linear classifier for PSL differentiation. For the commercial system, we will select the one with the best performance in clinical trials.

Linear classifier The MelaFind linear classifier was utilized to attain maximum specificity, under the constraint of 100% sensitivity to MM, over the training set[1,2,9,10]; and minimum classification error in differentiation between invasive MM and *in situ* MM[14].

Multistep linear classifiers have been developed for use in MelaFind, such that, relative to the single-step classifier, the specificity is higher, while the sensitivity remains the same. As one example, consider the following three single-step linear classifiers:

(1) Classifier 1: trained on MM + HGDN vs. all other nevi;

(2) Classifier 2: trained on MM + HGDN vs. seborrheic keratoses;

(3) Classifier 3: trained on MM + HGDN vs. pigmented basal and squamous cell carcinomas.

The following three-step linear classifier is then defined (using a logical 'and' rule):

> If all three single-step classifier scores are above their thresholds, then the lesion is positive for melanoma (i.e. either MM or HGDN). Otherwise, the lesion is negative for melanoma.

Non-linear classifier The MelaFind non-linear classifier produces a score for each lesion based on the probability of melanoma or non-melanoma. This classifier is trained to minimize a weighted sum of the false-positive and false-negative misclassification errors. Because of its different structure, and since it addresses different performance requirements than the linear classifier, the computer search engines select different features for the two classifiers.

---

* Entropy measures are of the form $\sum p_i \ln(p_i)$ with $\sum p_i = I$, summed over all pixels in a region. The 'quadrant maximum of entropy' is the maximum (among four quadrants) of the single-quadrant entropy of the phase of WMR coefficients.

TESTS OF PERFORMANCE

Acquisition of the lesion image database

The lesion image database used for training and testing the MelaFind classifiers was acquired at 20 clinical sites, scattered across the USA and elsewhere. Thus, diverse patient populations are represented, and potential biases as to patient age, sex, geographic location, physician subjectivity, etc., are minimized. Table 14.2 is an alphabetized list of the clinical sites and the principal personnel who have contributed to the MelaFind image data collection effort, to date.

At each site listed, the same clinical protocol is used for data collection (after having been approved by the local Institutional Review Board). The protocol includes appropriate inclusion and exclusion

Table 14.2 Clinical sites and principal personnel contributing to the MelaFind® image database

Last name	*First name*	*Degree*	*Location*
Medical directors			
Cognetta	Armand	MD	Dermatology Associates of Tallahassee — Tallahassee, FL
Rabinovitz	Harold	MD	Skin and Cancer Associates — Plantation, FL
Technical director			
Gutkowicz-Krusin	Dina	PhD	Electro-Optical Sciences, Inc. — Irvington, NY
Science Advisory Board			
Callen	Jeffrey	MD	University of Louisville/ Associates in Dermatology — Louisville, KY
Kopf	Alfred W	MD	NYU Medical Center — New York, NY
Mihm	Martin (Chair)	MD	Massachusetts General Hospital — Boston, MA
Rigel	Darrell	MD	Rigel Dermatology Group — New York, NY
Sober	Arthur	MD	Massachusetts General Hospital — Boston, MA
Clinical collaborators			
Braun	Ralph	MD	University Hospital — Geneva, Switzerland
Callen	Jeffrey	MD	University of Kentucky/ Associates in Dermatology, PLLC — Louisville, KY
Cognetta	Armand	MD	Dermatology Associates of Tallahassee — Tallahassee, FL
Duvic	Madeline	MD	University of Texas, MD Anderson Cancer Center — Houston, TX
Friedman	Robert	MD	Private Practice — New York, NY
Grin	Caron	MD	University of Connecticut Health Center — Farmington, CT
Gross	Kenneth	MD	Skin Surgery Medical Group, Inc. — San Diego, CA
Halpern	Allan	MD	Memorial Sloan-Kettering Cancer Center — New York, NY
Lee	Peter	MD	University of Minnesota — Minneapolis, MN
Levine	Norman	MD	University of Arizona — Tucson, AZ
Monheit	Gary	MD	Dermatology Associates — Birmingham, AL
Nestor	Mark	MD	Skin and Cancer Associates — Aventura, FL
Peck	Gary	MD	Washington Cancer Institute, Washington Hospital Center — Washington, DC
Polsky	David	MD, PhD	NYU Medical Center — New York, NY
Rabinovitz	Harold	MD	Skin and Cancer Associates — Plantation, FL
Rao	Babar	MD	Robert Wood Johnson Medical School — New Brunswick, NJ
Schwartz	Jennifer	MD	University of Michigan — Ann Arbor, MI
Thomas	Nancy	MD	University of North Carolina, Chapel Hill — Chapel Hill, NC
Tse	Yardy	MD	Dermatology Associates — La Jolla, CA
Wolfe	Jonathan	MD	Burgoon Mackay and Schuler — Plymouth Meeting, PA
Dermatopathologists			
Mihm, Jr.	Martin	MD	Massachusetts General Hospital
Prieto	Victor	MD	University of Texas, MD Anderson Cancer Center
Googe	Paul	MD	Knoxville Dermatopathology Laboratory
King	Roy	MD	Knoxville Dermatopathology Laboratory

criteria. (For example, only pigmented skin lesions less than 2.2 cm in largest dimension, and that will be imaged with MelaFind prior to biopsy, are included in the study.) The protocol requires the use of an electronic case record entry form (eCRF), which must be filled in by the physician in charge. The data-collection software requires the physician to enter a diagnosis — 'melanoma' or 'melanoma cannot be ruled out' or 'not melanoma' — prior to imaging the lesion with MelaFind. If 'not melanoma' is selected, a reason for biopsy must be provided ('non-melanoma skin cancer,' 'patient request', 'patient discomfort', etc.). It also requires that, if dermoscopy was used, both the 'clinical' and the 'dermoscopic' diagnoses be entered. The eCRF is automatically included with the MelaFind image data sent (on compact disks) to EOS for processing.

The histopathology 'gold standard'

For developing and testing the MelaFind classifier, lesion histopathology provides the 'gold standard'. Thus, a key element of the MelaFind clinical protocol for data collection is the provision that the participating clinic send in representative sections of the biopsied lesion. These sections are then examined by at least two of the designated dermatopathologists (listed in Table 14.2) who participate in the study. Explicit rules are included for resolving discordant diagnoses, with particular regard to the known difficulty that pathologists experience in differentiating melanomas *in situ* from high-grade dysplastic nevi[15].

Database for training and testing classifier performance

The database used for MelaFind consists of images of PSLs and their associated histopathology diagnoses. This database is divided into two groups. The first group is denoted as the 'training set' and is used to train the classifiers. The second group of lesions (the 'testing set') provides a 'double-blind' test of the system, in which MelaFind differentiates the lesions without knowledge of any clinical or histopathology diagnosis.

For this database, the number of lesions within each histological category are shown in Table 14.3, first for the 1129 lesions in the 'training set' (179 MM + HGDN; 949 other PSL), then for the 477 lesions in the 'testing set' (37 MM + HGDN; 440 other PSL).

Table 14.3 Lesion categories in the image database used in training and testing Melafind® classifiers

	Number
Training set: 179 malignant melanomas (MM) plus high-grade dysplasic nevi (HGDN); 949 other pigmented skin lesions (PSL)	
Melanoma and HGDN	
invasive	43
in situ	65
HGDN	71
Total MM + HGDN:	179
Other pigmented skin lesions	
Nevus	
low-grade dysplasic nevus (LGDN)	591
congenital/congenital pattern	25
Spitz	11
blue	10
other	111
Subtotal	748
Keratosis	
seborrheic	84
solar	7
other	10
Subtotal	101

continued

Table 14.3 *continued*

	Number
Lentigo	
solar	33
other	25
Subtotal	58
Other categories	
pigmented basal cell carcinoma (PBCC)	32
dermatofibroma	6
hemangioma	1
angiokeratoma	1
acanthoma	1
other	1
Subtotal	42
Total other PSL	949

Testing set: 37 MM + HGDN; 440 other PSL

Melanoma and HGDN	
invasive	10
in situ	16
HGDN	11
Total MM + HGDN:	37
Other pigmented skin lesions	
Nevus	
LGDN	313
congenital/congenital pattern	11
Spitz	2
blue	5
other	39
Subtotal	370
Keratosis	
seborrheic	33
solar	2
other	1
Subtotal	36
Lentigo	
solar	10
other	7
Subtotal	17
Other categories	
PBCC	11
pigmented squamous cell carcinoma (PSCC)	2
dermatofibroma	3
hemangioma	1
Subtotal	17
Total other PSL	440

Results: hypothesis testing

We have tested the linear and non-linear classifiers in the context of two different hypotheses regarding performance of MelaFind, relative to that of physicians. Proof of either of these hypotheses will demonstrate the effectiveness of MelaFind as an objective diagnostic test, with performance exceeding that of expert physicians.

The linear classifier was trained to provide 100% sensitivity to MM + HGDN, while maintaining maximum specificity over the training set[1,2]. The non-linear classifier was trained, over the same training set, to provide maximum average sensitivity, the average being taken over the entire range of specificity. Resubstitution testing was used to validate the performance of each classifier. In addition, the 60/40 'bootstrap method' was used to 'cross-validate' the non-linear classifier[2].

The results we obtain with the non-linear classifier illustrate that it is applicable to the proof of the first hypothesis (Hypothesis A, below), while the performance of the linear classifier shows that it is applicable to the proof of the second one (Hypothesis B).

Hypothesis A

The average sensitivity of MelaFind exceeds that of the physician.

In mathematical terms: on average, the area under the receiver operating curve (AUC) for MelaFind exceeds that for physicians, with histopathology as the standard of truth.

Hypothesis B

The sensitivity of MelaFind to melanoma is at least 95%, at a confidence level of 95%, while the specificity of MelaFind is significantly greater than that of physicians.

The data available to date show that the non-linear classifier can provide an AUC (area under the curve on ROC curve) that exceeds the AUC for physicians. In Figure 14.9, smooth curves have been fit to the resubstitution ROCs*, for a non-linear classifier employing seven features, over the training set (top curve), and over the testing set (middle curve). The bottom ROC curve in Figure 14.9 represents the diagnoses entered by the physicians participating in the study (for the lesions in the same training set).

The data used to generate the physicians' ROC curve was determined by pooling the diagnoses entered for each lesion by the responsible physician, prior to imaging with MelaFind (and hence prior to biopsy). Each physician's diagnosis consisted of one of three entries: 0, 'melanoma'; 1, 'melanoma cannot be ruled out'; 2, 'not melanoma'. The data were pooled, and the (false-positive fraction (FPF), true-positive fraction (TPF)) pairs that resulted were then fit to the binormal ROC curve shown.

For each of the three ROC curves, the AUC is indicated in the legend, and the AUC for the

Table 14.4 Multistep linear classifier vis-à-vis physicians

	Number of MM + HGDN	*Sensitivity (%)*		*Number of non-(MM + HGDN)*	*Specificity (%)*	
		Nominal	*95% CI*		*Nominal*	*95% CI*
Training set						
Classifier	179	96.1	(92.1–98.1)	945	28.5	(25.6–31.4)
Physicians	179	88.3	(82.7–92.2)	945	21.0	(18.5–23.7)
Testing set						
Classifier	37	97.3	(86.2–99.5)	440	25.5	(21.6–29.7)
Physicians	37	97.3	(86.2–99.5)	440	17.3	(14.0–21.1)

MM, malignant melanoma; HGDN, high-grade dysplastic nevus

* To accommodate the statistical uncertainties associated with, sensitivity and specificity values (dependent on the number of lesions), we employ a smooth (binormal) curve fit to the resubstitution data. (The fit is accomplished via ROCKIT, available at http://www-radiology.uchicago.edu/cgi-bin/software.cgi).

MelaFind non-linear classifier exceeds that for the physicians, as required under Hypothesis A.

The results achieved with a three-step classifier are summarized in Table 14.4. As shown in the table, the sensitivity achieved with this classifier for the test set is the same (97.3%) as that of the physicians, but at higher specificity (25.5% vs. 17.3%). In this table, a physician's diagnosis is considered positive if it is either 'melanoma' or 'melanoma cannot be ruled out' — and negative otherwise. For the training set, the corresponding (FPF,TPF) point is represented by the large dot near the right side of the graph in Figure 14.9 (on the Physicians' ROC curve). Thus, initial indications are that the multi step linear classifier may provide the performance needed to prove Hypothesis B.

DISCUSSION

MelaFind is a computer vision system that creates multispectral images of PSLs and that is being 'taught' how to detect MM + HGDN, objectively on the basis of these images. The results reported here represent the first data, to our knowledge, that indicate the potential of an objective test for such lesions, relative to diagnoses by dermatologists on the same lesions.

Both for physicians and for MelaFind, sensitivity and specificity are defined relative to histopathology as the 'gold standard'. The values obtained for sensitivity and specificity represent estimates of 'biopsy sensitivity' and 'biopsy specificity' as opposed to diagnostic sensitivity and diagnostic specificity. Only the lesions that enter into the study are considered, i.e. without reference to prevalence of the condition. The sensitivity values obtained for physicians in the study must be viewed as an upper bound on their true 'biopsy sensitivity', because we do not know how many melanomas they missed. To determine their biopsy sensitivity, a multi-year longitudinal study would be required.

From two recent longitudinal studies[16,17], we estimate the biopsy sensitivity of specialist dermatologists to invasive and *in situ* melanoma is not greater than 94%. (The first of those studies[16] reported missing 14 melanomas — four *in situ* and ten invasive — identified during 9 years of patient follow-up. The second study[17] reported missing nine invasive melanomas in 6 years, based on the Cancer Registry data, which do not include melanomas *in situ.* Their reported biopsy sensitivity to invasive melanoma was 98%, whereas biopsy sensitivity to melanoma *in situ* was not determined.)

All of the lesions in our study were biopsied, yet the biopsy sensitivity of the physicians was less than 100%. This occurred because there were melanomas in the dataset, which the physician thought were not melanomas, but nevertheless ordered the lesions biopsied. The reason given for such biopsy was either patient concern or discomfort, or because the lesion was believed to be malignant, but not a melanoma.

For MelaFind, melanomas and high-grade dysplastic nevi are considered together as a single class — both in training the classifier and in testing it. This makes it difficult to compare our present results with those of our earlier publications[1,2], or with the work of others. Our earlier work concentrated on differentiation of true melanomas (i.e. either invasive or *in situ)* from nevi, especially severely atypical nevi.

ACKNOWLEDGMENTS

Portions of the work reported here were supported by grants to EOS from the National Cancer Institute under grant numbers R44 CA74628 and R44 CA90029, which support is gratefully acknowledged. We also thank the Christopher Columbus Fellowship Foundation for its 1998 Columbus Scholar award.

The following EOS staff members made important contributions to the development of MelaFind: Alexandru Bogdan, Michael Greenebaum, Dina Gutkowicz-Krusin, Adam Jacobs, Nikolas Kabelev, Sunguk Keem, Joanna Melman, Tomasz Momot and Steven Wicksman.

The author wishes to acknowledge major contributions to the MelaFind project by Drs Alfred Kopf, Harold Rabinovitz, Martin Mihm and Armand Cognetta, whose enthusiasm serves as an inspiration to the team. The author also wishes to thank each of the individual collaborators listed in Table 14.2, as well as their staffs, for their contributions to the work reported here, and special thanks go to Margaret Oliviero and Julie Tullos.

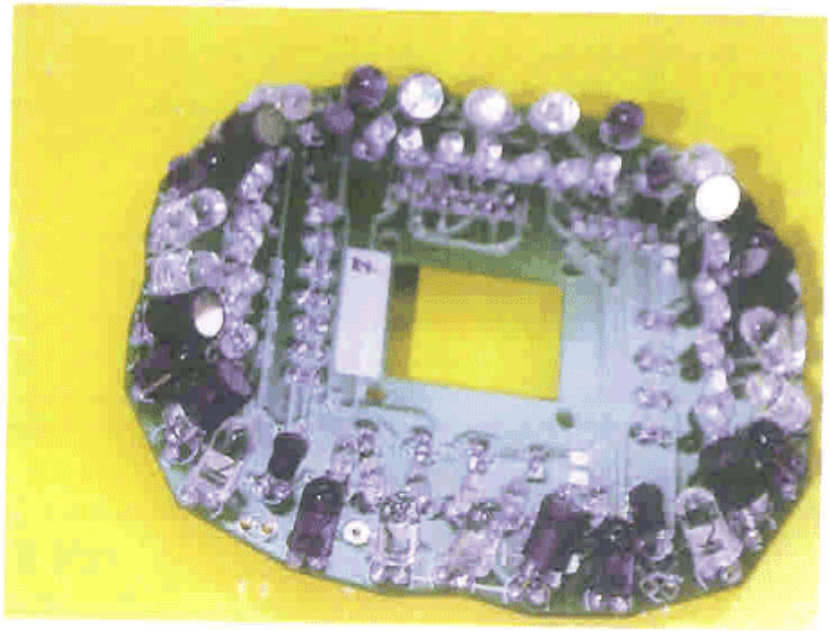
Finally, we gratefully acknowledge the guidance provided by the five members of Melafind Scientific Advisory Committee: Jeffrey Callen, MD (University of Louisville, KY); Alfred W. Kopf, MD (NYU Medical Center, New York, NY); Martin C. Mihm Jr (Massachusetts General Hospital, Boston, MA), Chair; Darrell Rigel, MD (Rigel Dermatology

Group, New York, NY); and Arthur J. Sober, MD (Massachusetts, General Hospital, Boston, MA).

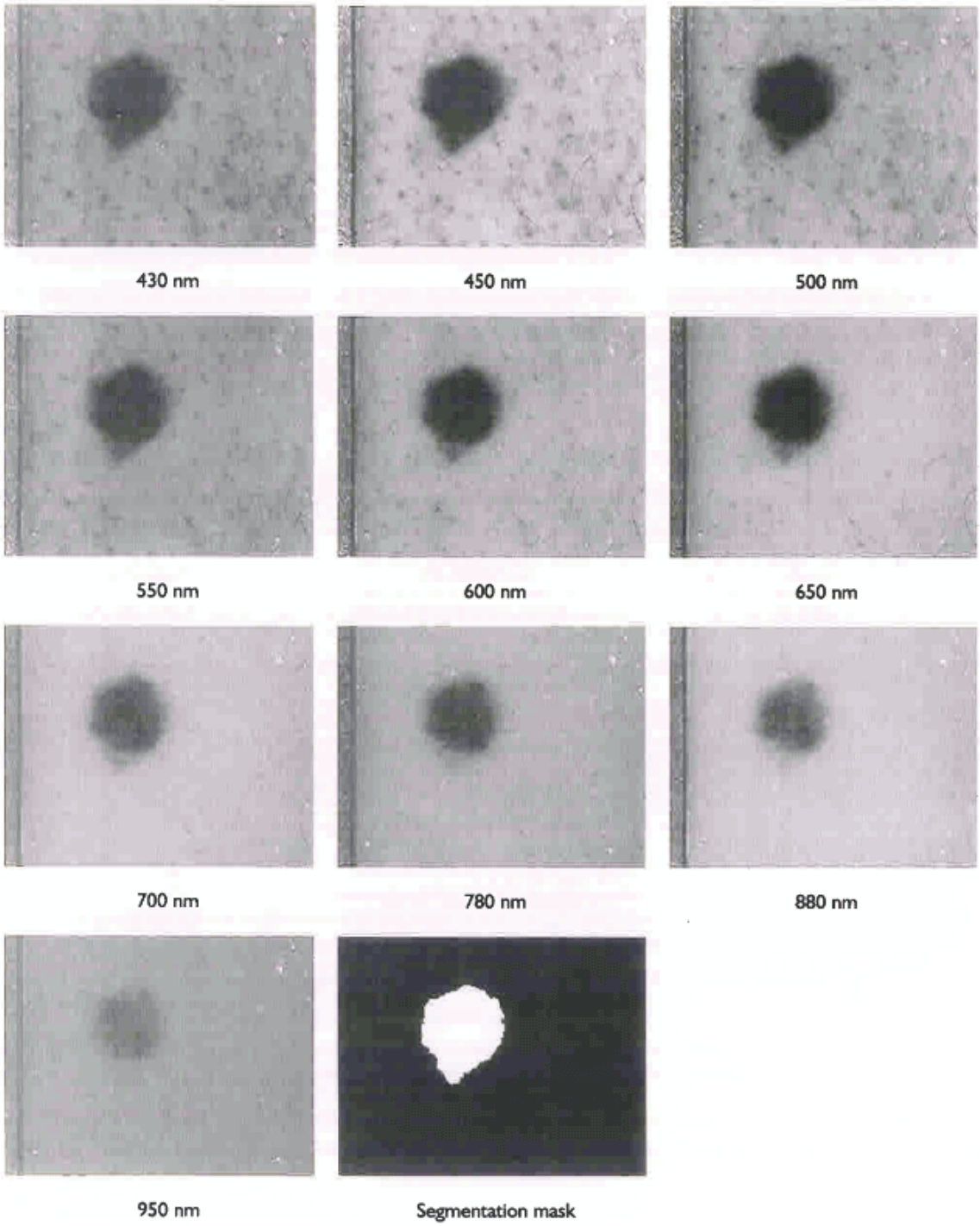
REFERENCES

1. Gutkowicz-Krusin D, Elbaum M, Szwajkowski P, Kopf AW. Can early malignant melanoma be differentiated from atypical melanocytic nevi by *in-vivo* techniques? Part II. Automatic machine vision classification. *Skin Res Technol* 1997;3:15–22
2. Elbaum M, Kopf AW, Rabinowitz HS, *et al.* Automatic differentiation of melanoma from melanocytic nevi with multispectral digital dermoscopy: a feasibility study. *J Am Acad Dermatol* 2001;44:207–18
3. Anderson RR, Parrish JA. The optics of human skin. *J Invest Dermatol* 1981;77:13–19
4. Jacques SL. Origins of tissue optical properties in the UVA, visible and NIR regions. In Alfano RR, Fujimoto JG, eds. *OSA Trends in Optics and Photonics. Advances in Optical Imaging and Photon Migration* Vol. 2,1996:364–71
5. Jain AK, Duin RPW, Mao J. Statistical pattern recognition: a review. *IEEE Trans Pattern Analysis and Machine Intelligence* 2000;22:4–37
6. Duda RO, Hart PE. *Pattern Classification and Scene Analysis.* New York: John Wiley & Sons, 1973
7. Friedman RJ, Rigel DS, Kopf AW. Early detection of malignant melanoma: the role of physician examination and self-examination of the skin. *Cancer J Clin* 1985;35:130–51
8. Friedman RJ, Heilman ER. The pathology of malignant melanoma. *Dermatol Clin* 2002;20:659–76
9. Gutkowicz-Krusin D, Elbaum M, Greenebaum M, Jacobs A. Systems and methods for the multispectral imaging and characterization of skin tissue. US Patent No. 6,208,749 B1 (March 27, 2001)
10. Gutkowicz-Krusin D, Elbaum M, Greenebaum M, *et al.* Systems and methods for the multispectral imaging and characterization of skin tissue. US Patent No. 6,081,612 (June 27, 2000)
11. Friedman RJ, Rigel DS, Kopf AW. Early detection of malignant melanoma: the role of physician examination and self-examination of the skin. *Cancer J Clin* 1985;35:130–51
12. Nachbar F, Stolz W, Merkle T, *et al.* The ABCD rule of dermatoscopy. High prospective value in the diagnosis of doubtful melanocytic skin lesions *J Am Acad Dermatol* 1994;30:551–9
13. Gutkowicz-Krusin D, Elbaum M, Jacobs A, *et al.* Precision of automatic measurements of pigmented skin lesion parameters with a MelaFind™ multispectral digital dermoscope. *Melanoma Res* 2000;10:563–70
14. Elbaum M. Computer-aided melanoma diagnosis. *Dermatol Clin* 2002;20:735–47
15. Cook MG, Clarke TJ, Humphreys S, *et al.* The evaluation of diagnostic and prognostic criteria and the terminology of thin cutaneous malignant melanoma by the CRC Melanoma Pathology Panel. *Histopathology* 1996;28:497–512
16. Bataille V, Sasieni P, Curley RK, *et al.* Melanoma yield, number of biopsies and missed melanomas in a British teaching hospital pigmented lesion clinic: a 9-year retrospective study. *Br J Dermatol* 1999;140:243–8
17. Duff CG, Melsom D, Rigby HS, *et al.* A 6 year prospective analysis of the diagnosis of malignant melanoma in a pigmented-lesion clinic: even specialists miss malignant melanomas, but not often. *Br J Plast Surg* 2001;54:317–21

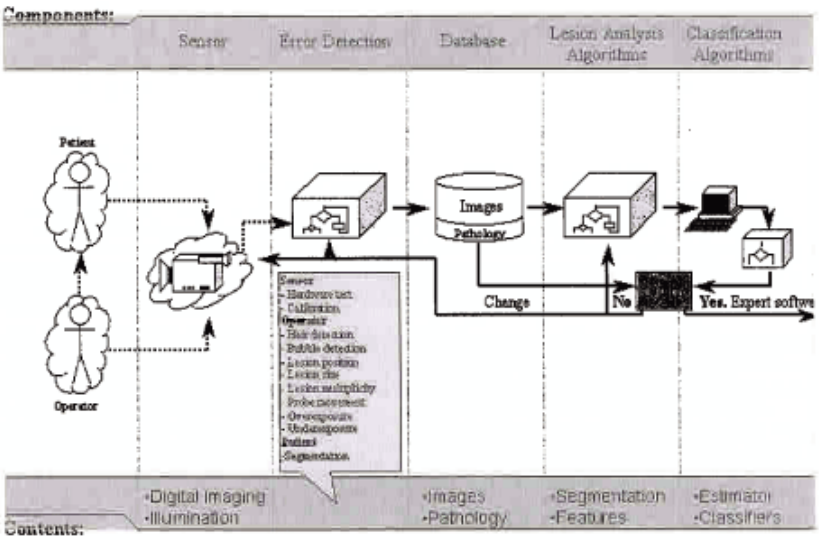
5 **Figure 14.1** Current MelaFind® System: (a) Probe and laptop computer in carrying case. (b) Hand-held MF-100/100A probe applied to a pigmented skin lesion



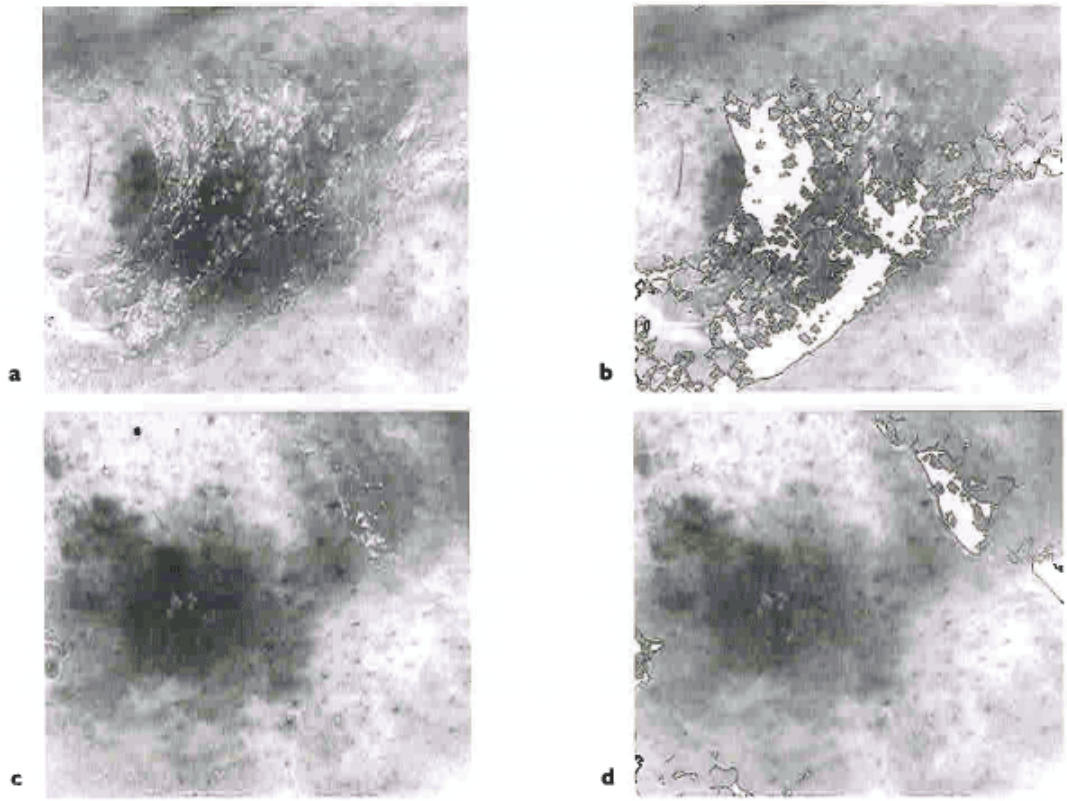
5 **Figure 14.2** MF-100 printed circuit board with attached, angled-in light-emitting diodes



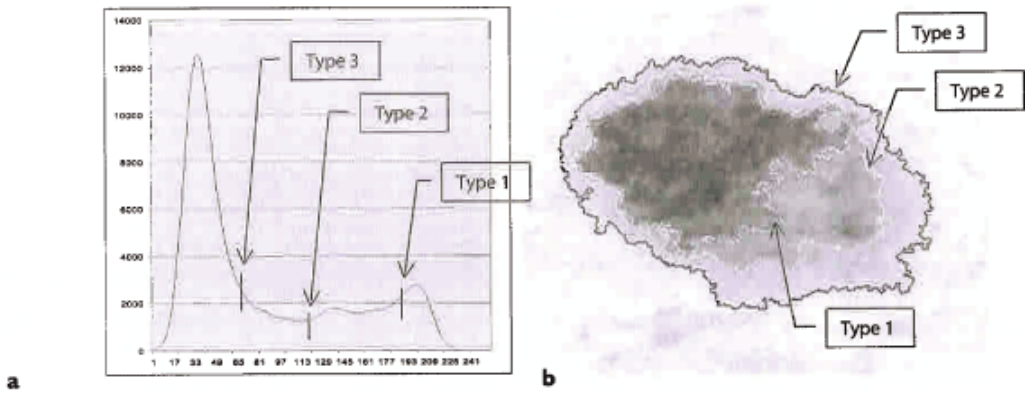
5 **Figure 14.3** A MelaFind® multispectral ten-image sequence (for an invasive melanoma) and the automatically generated segmentation mask for this sequence



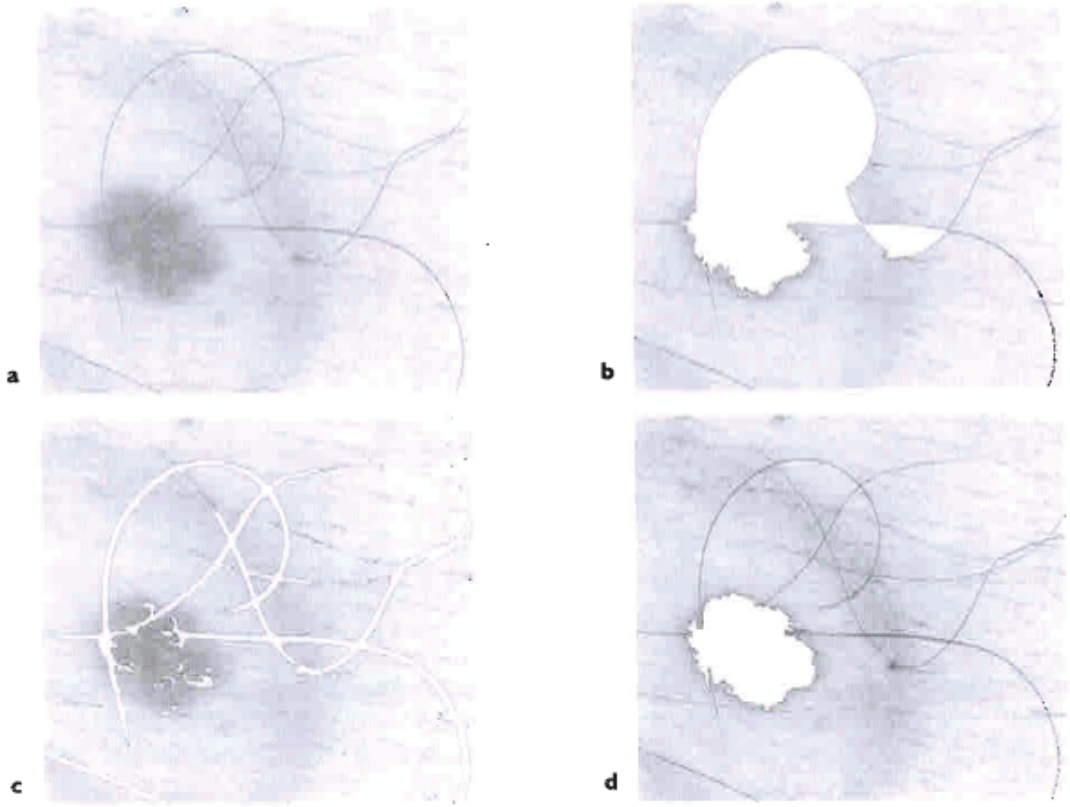
5 **Figure 14.4** 'Supervised learning' approach to development of quality control software



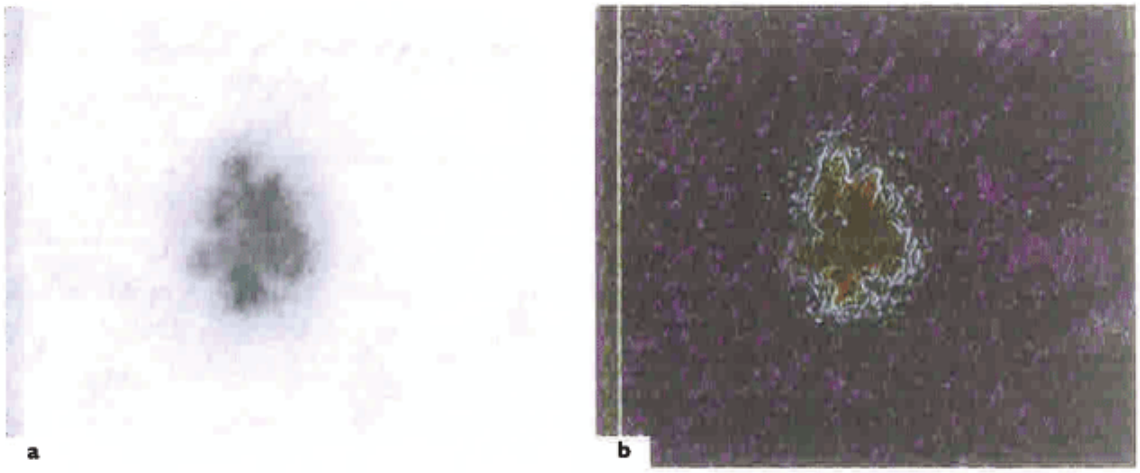
5 **Figure 14.5** Example of the bubble-detection algorithm at work. (a) Rejected lesion image. (b) The bubbles detected in image (a). (c) Accepted lesion image.(d) Bubble-detection result for image (c)



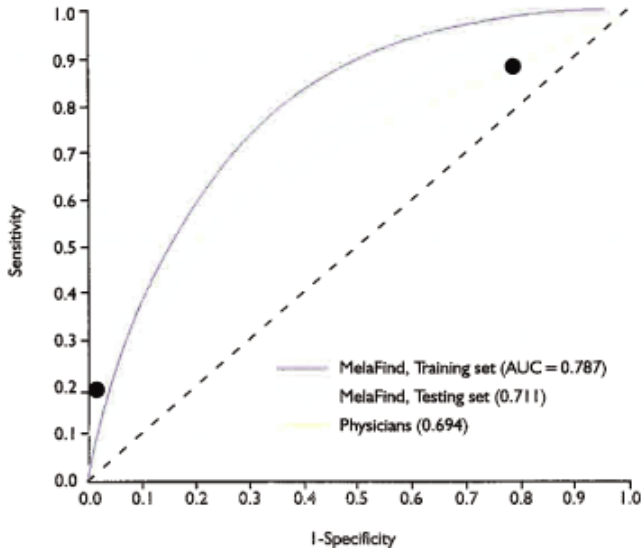
5 **Figure 14.6** Illustration of the dependence of the lesion mask on the segmentation threshold algorithm. (a) Histogram of image intensity at 430 nm, showing the three types of threshold. (b) The lesion image, with the three types of segmentation mask superimposed



5 **Figure 14.7** Illustration of lesion segmentation in the presence of residual hair. (a) Original skin image. (b) Invalid lesion mask, generated without hair removal. (c) Hair mask. (d) Lesion segmentation mask, generated with hair removal



5 **Figure 14.8** Illustration of a MelaFind® image and its wavelet transformation. (a) MelaFind dermoscopic gray-scale image of a melanoma at 430 nm (blue). (b) Pseudocolor representation of Wavelet transformation of the image in part (a)



3 **Figure 14.9** Non-linear classifier results vs. physicians' three-category diagnoses. Top: Melafind® - - resubstitution over training set: 179 (malignant melanoma (MM) plus high-grade dysplastic nevus (HGDN)) and 949 non-MM. Middle: MelaFind - - blind test on 37 MM + HGDN and 440 non-MM. Bottom: physicians' three-category diagnoses over the training set

STUDY

The Diagnostic Performance of Expert Dermoscopists vs a Computer-Vision System on Small-Diameter Melanomas

Robert J. Friedman, MD; Dina Gutkowicz-Krusin, PhD; Michele J. Farber; Melanie Warycha, MD; Lori Schneider-Kels, MPH; Nicole Papastathis, BA; Martin C. Mihm Jr, MD; Paul Googe, MD; Roy King, MD; Victor G. Prieto, MD, PhD; Alfred W. Kopf, MS, MD; David Polsky, MD, PhD; Harold Rabinovitz, MD; Margaret Oliviero, ARNP; Armand Cognetta, MD; Darrell S. Rigel, MD; Ashfaq Marghoob, MD; Jason Rivers, MD, FRCPC; Robert Johr, MD; Jane M. Grant-Kels, MD; Hensin Tsao, MD, PhD

Objective: To evaluate the performance of dermoscopists in diagnosing small pigmented skin lesions (diameter £ 6 mm) compared with an automatic multispectral computer-vision system.

Design: Blinded comparison study.

Setting: Dermatologic hospital-based clinics and private practice offices.

Patients: From a computerized skin imaging database of 990 small (£ 6-mm) pigmented skin lesions, all 49 melanomas from 49 patients were included in this study. Fifty randomly selected nonmelanomas from 46 patients served as a control.

Main Outcome Measures: Ten dermoscopists independently examined dermoscopic images of 99 pigmented skin lesions and decided whether they identified the lesions as melanoma and whether they would recommend biopsy to rule out melanoma. Diagnostic and biopsy sensitivity and specificity were computed and then compared with the results of the computer-vision system.

Results: Dermoscopists were able to correctly identify small melanomas with an average diagnostic sensitivity of 39% and a specificity of 82% and recommended small melanomas for biopsy with a sensitivity of 71% and specificity of 49%, with only fair interobserver agreement ($\kappa = 0.31$ for diagnosis and 0.34 for biopsy). In comparison, in recommending biopsy to rule out melanoma, the computer-vision system achieved 98% sensitivity and 44% specificity.

Conclusions: Differentiation of small melanomas from small benign pigmented lesions challenges even expert physicians. Computer-vision systems can facilitate early detection of small melanomas and may limit the number of biopsies to rule out melanoma performed on benign lesions.

Arch Dermatol. 2008;144(4):476-482

Author Affiliations are listed at the end of this article.

DETECTION OF EARLY MAlignant melanoma (in situ and thin lesions) is one of the most effective ways of preventing mortality from this disease. Prognosis for patients with melanoma is dependent on early detection,[1,2] as evidenced by the 10-year survival rates as high as 99.5% that have been reported for thin melanomas smaller than 0.76-mm thick in the New York University melanoma database; these rates markedly decrease to 48% for lesions larger than 3 mm in thickness.[1] The effectiveness of this strategy is further confirmed because the reported marked reduction in mortality from melanoma, from 60% for those patients with melanoma diagnosed in 1960 to approximately 11% in 2005, is mainly due to early detection of thinner lesions followed by appropriate treatment.[3,4]

The incidence of melanoma in the general population is increasing in the United States and worldwide.[3,4] Several reports[5-8] have also indicated the presence of small melanomas, defined as those with diameters of 6 mm or smaller. The mere presence of melanomas 6 mm or smaller warrants efforts to facilitate their identification

See also pages 469 and 533

because many of these small melanomas may appear benign by clinical criteria and are therefore more difficult to diagnose.[9] In light of findings that smaller melanomas tend to be less deeply invasive than melanomas larger than 6 mm and, as such, generally

have a more favorable prognosis,[10,11] efforts that focus on early detection of small melanomas could potentially reduce mortality from this disease.

Supplementing clinical examination with techniques such as dermoscopy is an effective strategy for improving the sensitivity of dermoscopy-trained dermatologists in melanoma diagnosis.[12] Although dermoscopy may be more effective than clinical examination in diagnosing thin malignant melanomas,[13,14] a study by Carli et al[15] demonstrated that dermoscopy did not improve diagnostic performance in identifying small (< 6-mm) melanomas. This finding indicates that additional diagnostic tools may be necessary to diagnose smaller melanomas more effectively.

Although many systems have been devised to facilitate the differentiation between histologically benign and malignant lesions, including dermoscopy and computer-assisted image analysis, this task continues to challenge even the most experienced dermatologist. The clinical ABCD criteria, initially described in 1985, remain an objective succinct algorithm for the early clinical recognition of melanoma.[1] Recently, E for evolving was added to the ABCD criteria to highlight the element of *change* as an important diagnostic feature of cutaneous melanoma.[11] The present study was designed to assess the sensitivity of dermoscopists in diagnosing small melanomas (£ 6-mm diameter) compared with a novel automatic computer-vision system.

METHODS

DATABASE

This study used cases from the digital dermoscopic database acquired by Electro-Optical Sciences Inc for the development and testing of MelaFind (Electro-Optical Sciences Inc, Irvington, New York), a computer-vision system for early detection of melanoma that is undergoing clinical testing. Twenty-six clinical sites in the United States and abroad have contributed to this database.

Only pigmented skin lesions (PSLs) were included in the database. The lesions were scanned using the multispectral computer-vision device before excisional or deep shave biopsy in toto. Approximately 80% of the lesions were biopsied to rule out melanoma, whereas the remaining lesions were biopsied mostly to rule out nonmelanoma skin cancer or because of patient concern. The diameter of eligible PSLs ranged from 2 to 22 mm. Previously biopsied, ulcerated, or bleeding lesions were excluded. Also excluded were lesions on mucosal surfaces and lesions that contained foreign matter (eg, tattoos).

Every case in the database consisted of multispectral dermoscopic images, a case record form with patient and lesion information (sex, age, and lesion location), prebiopsy diagnoses by the examining dermatologist, and a diagnostic histologic slide. Every slide was evaluated by 2 study dermatopathologists (from a panel of 4 dermatopathologists [M.C.M., P.G., R.K., or V.G.P.]) without knowledge of any additional clinical information; in cases of significant discordance in diagnoses, the slide was reviewed by a third study dermatopathologist. A lesion with at least 1 diagnosis of melanoma by the study dermatopathologists is considered melanoma. The histologic diagnoses distinguished invasive and in situ melanomas and high- and low-grade dysplastic nevi. Dysplastic nevi with severe cytologic atypia were considered high grade, and those with mild to moderate atypia were considered low grade.[16] These diagnoses provided a reference standard by which the diagnostic performance of dermoscopists and of the computer-vision system was evaluated.

MelaFind is a multispectral digital dermoscope that, for every lesion, acquires 7 images in the visible spectral bands and 3 images in the near-infrared spectral bands. All images are analyzed automatically for the following: (1) calibration to determine the fraction of the incident radiation that is reflected for every pixel in the image; (2) image quality control that determines whether the images are suitable for further analysis (eg, a lesion covered with too much hair is automatically rejected and the operator is asked to clip the hair and retake the image); (3) segmentation to create a lesion mask; (4) computation of lesion properties in different spectral bands; and (5) lesion classification.[17,18] The overall lesion classifier consists of 6 constrained linear classifiers, each trained to differentiate melanomas with 100% sensitivity from a particular type of lesion (low-grade dysplastic nevus, congenital nevus, common nevus, seborrheic keratosis, solar lentigo, and pigmented basal cell carcinoma). Thus, each lesion is characterized by 6 scores. A lesion is recommended for biopsy to rule out melanoma only if *all* scores are above the threshold value. On an independent testing set of 54 melanomas and 508 other PSLs not limited to small size, this classifier had biopsy sensitivity of 98% and specificity of 44%.

SELECTION OF LESIONS FOR THE STUDY

Small (£ 6-mm) lesions were selected for the study in July 2005 from the database of 1977 eligible and evaluable PSLs, including 202 malignant melanomas. The lesion diameter was determined automatically by the computer-vision system.[19] There were 990 (50% of the total) small lesions, of which 49 were melanomas; thus, 24% of all malignant melanomas were small. All PSLs were obtained either from the training database (75 small lesions, of which 38 were melanomas and 37 were matched non-melanomas) or from the blinded set of data (24 small lesions, of which 11 were melanomas and 13 were nonmelanomas).

All 49 small malignant melanomas were included in this study. The small nonmelanomas were stratified by patient age (1-30 years, 31–60 years, and 60 years or older), sex (female or male), and lesion location (head and neck, trunk, lower limbs, or upper limbs); 50 nonmelanomas were selected randomly to match the frequency of these characteristics in the melanoma sample. High-grade dysplastic nevi were excluded because no consensus exists on their management. The distribution of lesions in the study is given in **Table 1**.

STUDY PROCEDURE

Participants in the study (readers) received a CD-ROM with color dermoscopic images created using MelaFind multispectral images. A ruler was included in every image to allow readers to determine the lesion diameter independently. For some of the cases, standard dermoscopic images acquired with a Nikon Coolpix 4300 camera (Nikon) with a 3Gen dermoscopic attachment (3Gen.LLC) were also available. The equivalence of standard and computer-vision system dermoscopic images was visually assessed by 3 readers (A.W.K., H.R., and A.C.) on a set of 10 lesions (2 melanomas and 8 low-grade dysplastic nevi). Overall, the consensus of the readers was that the computer-vision system images are suitable for dermoscopic evaluation **(Figure 1)**.

For every lesion, information was provided about patient sex, age, and lesion location, whereas histologic information

Table 1. Description of Pigmented Lesions

Lesion Type	No. of Lesions[a]
Invasive melanoma	21
Breslow thickness, median (range), mm	0.32 (0.10-1.40)
Melanoma in situ	28
Low-grade dysplastic nevus	32
Congenital nevus	2
Blue nevus	1
Compound nevus	1
Intradermal nevus	2
Junctional nevus	1
Seborrheic keratosis	2
Hemangioma	1
Lentigo simplex	3
Solar lentigo	1
Lichen planus-like keratosis	1
Actinic keratosis	1
Basal cell carcinoma	2
Total No. of lesions	99
Total No. of patients	94

[a] Data are number of lesions unless otherwise indicated.

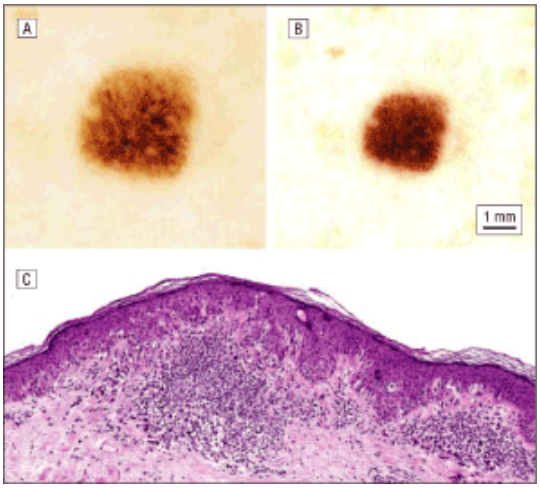


Figure 1. Dermoscopic images used for patient evaluation. A, Dermoscopic image of pigmented macule located on the leg. B, Machine-generated dermoscopic image of lesion in A. C, Histopathologic evaluation reveals a relatively broad asymmetric proliferation of mostly single and focally nested atypical melanocytes arranged along the dermoepidermal junction and at higher levels of the epidermis. A moderately dense lymphohistiocytic infiltrate is also evident in the subjacent dermis (hematoxylin-eosin, original magnification X 60). The histopathologic diagnosis was malignant melanoma in situ.

was not provided. The readers also received a form for recording their assessments of every lesion. All 10 readers were expert dermoscopists (9 dermatologists and 1 nurse practitioner specializing in dermatology), and their evaluations were performed independently.

EVALUATION OF DIAGNOSTIC PERFORMANCE

To determine diagnostic performance, each reader had to answer the following question: “Is this lesion a melanoma?” Individual responses were then compared with the histopathologic diagnosis, which served as the reference standard for the determination of the diagnostic sensitivity and specificity for each reader.

EVALUATION OF LESION MANAGEMENT DECISIONS

Diagnostic performance does not provide information about case management by dermatologists. To obtain such information, the readers were asked to answer the following question: “Would you biopsy/excise this lesion?” If the answer was yes, the readers had to specify the reason for biopsy. As with evaluation of diagnostic performance, histologic diagnoses were used as the reference standard to evaluate lesion management decisions. If readers indicated that they would biopsy the lesion because they were sure it was melanoma or to rule out melanoma, then the case was considered true positive (TP) if the histologic diagnosis was melanoma and false positive (FP) otherwise. If the reader would not have biopsied the lesion or would have biopsied the lesion to rule out nonmelanoma skin cancer, the case was considered true negative (TN) if the histologic diagnosis was not melanoma and false negative (FN) otherwise. These data allow determination of biopsy sensitivity and specificity of the readers.

DATA ANALYSIS

The diagnostic performance and lesion management decisions were analyzed by computing, for every reader, sensitivity (TP/[TP + FN]) and specificity (TN/[TN + FP]), as well as 95% confidence intervals, for these quantities. The interobserver variability was assessed using the κ statistic.[20] The average diagnostic sensitivity and specificity and average biopsy sensitivity and specificity were also computed, with 95% confidence intervals determined according to the Obuchowski[21] method, which takes into account correlations among the readers. For the averages, the other metrics of interest were positive predictive value (TP/[TP + FP]), negative predictive value (TN/[TN + FN]), and diagnostic accuracy (TP/[TP + FN + FP]). These variables were compared with the results of the automatic computer-vision system on the same set of small lesions.

RESULTS

Diagnostic sensitivity and specificity for all 10 readers (as well as averages) are displayed in **Figure 2** in the format of a receiver operating characteristic plot. The error bars in Figure 2 represent 95% confidence intervals, which were large because of the relatively small sample size for each reader. Despite these large confidence intervals, the interreader variability was even larger; the κ statistic was 0.31, indicating only fair agreement among the readers. On small lesions, the average sensitivity to malignant melanoma was only approximately 40%, but the associated specificity was high (approximately 80%). The median diagnostic sensitivity and specificity were similar, at 43% and 84%, respectively.

The fact that diagnostic sensitivity to melanoma was only approximately 40% does not imply that dermatologists do not treat approximately 60% of small melanomas; it only means that this is not a good measure of lesion management decisions. Information about such decisions can be gained from biopsy sensitivity and specificity **(Figure 3)**. The interreader variability on lesion management decisions was high: biopsy sensitivity ranged

from 37% to 88%, whereas specificity varied from 22% to 80% (κ = 0.34). However, for each reader, biopsy sensitivity was higher than diagnostic sensitivity. This is not surprising because some dermoscopically borderline lesions may be called benign but are nevertheless biop-sied to rule out melanoma. Because biopsy sensitivity is higher, it follows that biopsy specificity is lower.

The MelaFind database was randomly divided into the training and blind testing data sets. The biopsy sensitivity and specificity of MelaFind on the small lesions in the training set (38 melanomas and 37 nonmelanomas) was 100% and 46%, respectively. The biopsy sensitivity and specificity of the expert dermoscopist readers on average was 71% and 52%, respectively. On the small lesions in the blind testing set, the biopsy sensitivity of MelaFind was 91% (missed 1 melanoma in situ), with a specificity of 38%.

To increase the sample size of the small melanomas for a more robust statistical comparison of expert readers and computer-vision system, the small lesions from the MelaFind training and blinded data sets were combined. This pooling of data for MelaFind would be justified only if its results (sensitivity and specificity) are homogeneous for the 2 sets. Because of high sensitivity, the homogeneity assumption was tested using the Fisher exact test.[22] Based on the values of $P = .22$ for MelaFind sensitivity and $P = .75$ for MelaFind specificity, the null hypothesis of homogeneity is valid and data were pooled. On average, the expert dermoscopist readers had a biopsy sensitivity of 71%, with a specificity of 49%. The median biopsy sensitivity and specificity of the 10 dermoscopists was 74% and 50%, respectively. The biopsy sensitivity and specificity of MelaFind was 98% (missed 1 melanoma in situ) and 44%, respectively.

Detailed comparison of human and computer vision for the management of small PSLs (biopsy sensitivity and specificity) is presented in **Table 2**. It clearly demonstrates that for small lesions, the computer-vision system had significantly higher sensitivity than dermoscopists ($P < .001$), while the difference in specificities was not statistically significant ($P = .75$). In addition, the computer-vision system had statistically significant ($P = .02$) higher values of negative predictive value; the differences in positive predictive value ($P = .48$) and diagnostic accuracy ($P = .08$) were not statistically significant.

Sensitivity to invasive and in situ melanomas should also be considered separately; the results are given in **Table 3**. The 95% confidence intervals were large because of the small sample sizes. Nevertheless, it was clear that dermoscopists and the computer-vision system have higher sensitivity to invasive than to in situ melanomas. The data in Table 3 indicate that approximately 19% of small invasive melanomas and approximately 37% of small melanomas in situ may be left unbiopsied, even by expert physicians.

COMMENT

Reports vary in their assessment of the prevalence of melanomas 6 mm or smaller among the overall population of cutaneous melanomas.[5,7,8,10] In a retrospective review of small-diameter melanomas, Abbasi et al[11] concluded

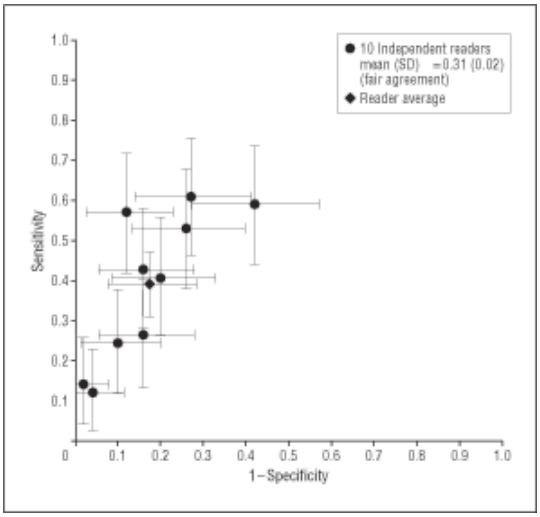
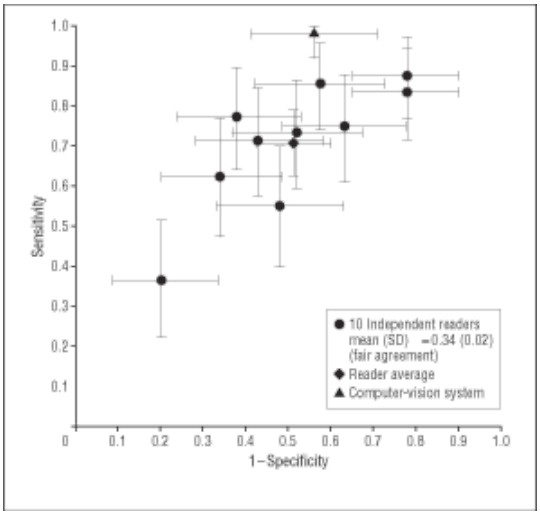


Figure 2. Diagnostic sensitivity and specificity of 10 dermoscopists on a set of 99 small pigmented skin lesions, including 49 melanomas. Error bars indicate 95% confidence intervals for each reader; the confidence intervals are smaller than interreader variability.



Figures 3. Biopsy sensitivity and specificity of 10 dermoscopists on a set of 99 small pigmented skin lesions, including 49 melanomas. Error bars indicate 95% confidence intervals for each reader; the confidence intervals are smaller than interreader variability. The result of the computer-vision system for the same set of lesions is also shown.

that the prevalence of small melanomas (£ 6 mm) ranged from less than 5% to 14%. The prevalence of small-diameter melanomas in our database, however, was much higher, at 25%, prompting us to evaluate this subset of lesions more closely. Although techniques of lesion recognition, such as dermoscopy, are gaining in popularity, the differentiation of early melanomas from benign PSLs continues to be plagued by uncertainty. This is especially true for the subset of small-diameter melanomas, which frequently display clinical and histologic discord.[23] The present study is one of the first, to our

Table 2. Small Lesion Management Decisions: Human vs Computer-Vision System[a]

	Baseline		Positive Predictive Value	Negative Predictive Value	Diagnostic Accuracy
	Sensitivity	Specificity			
Human	71 (63-79)	49 (40-58)	58 (51-64)	63 (52-74)	47 (39-55)
Computer-vision system	98 (92-100)	44 (29-59)	63 (56-70)	96 (79-100)	62 (53-70)
P value	< .001	.75	.48	.02	.08

[a] Data are given as average percentage (95% confidence interval) unless otherwise indicated.

Table 3. Average Sensitivity to Invasive and In Situ Melanomas[a]

Variable	Invasive Malignant Melanoma	In Situ Malignant Melanoma
Human diagnostic sensitivity	48 (36-59)	33 (22-44)
Human biopsy sensitivity	81 (71-91)	63 (52-74)
Computer biopsy sensitivity	100 (87-100)	96 (88-100)
P value for biopsy sensitivity	.11	.02

[a] Data are given as average percentage (95% confidence interval) unless otherwise indicated.

knowledge, to quantify diagnostic accuracy of dermoscopists in specifically identifying small melanomas. By comparing the diagnostic performance of dermoscopists with a computer-vision system, the design of this study gives insight into new methods of identifying small melanomas in early stages of development.

In our study, we determined diagnostic sensitivity and specificity and biopsy sensitivity and specificity. This approach uniquely allowed us to differentiate between diagnostic performance and lesion management decisions. Although the average diagnostic sensitivity for all 10 dermoscopists was only 39%, the average biopsy sensitivity was 71%. A similar disparity was seen between the average diagnostic and biopsy specificities of 82% and 49%, respectively, reflecting the fact that lesions suggestive of disease are often biopsied to rule out melanoma. Despite the high biopsy sensitivity of our readers, nearly 30% of melanomas smaller than 6 mm would not have been biopsied. Furthermore, only fair interobserver agreement (k = 0.31 for diagnosis and 0.34 for biopsy decision) indicates that dermoscopists differ in their evaluation of small PSLs, emphasizing the challenge in small melanoma diagnosis.

Only pigmented lesions scheduled for biopsy were eligible for inclusion in the database. Therefore, in the present study, the true biopsy sensitivity of examining dermatologists could not be determined directly. Thus, the pooled biopsy sensitivity was artificially high and specificity was relatively low. One could, in fact, take an extreme position that the examining physicians had 100% biopsy sensitivity and 0% biopsy specificity on the lesions in the database. The present study determined that the average biopsy sensitivity to small melanomas of the readers was 71%, and the corresponding specificity was 49%. However, only 2 small melanomas in situ were missed by *all* readers (ie, the combined biopsy sensitivity was 96%). At the same time, the combined biopsy specificity was 6% (only 3 lesions were TN for *all* readers). The combined biopsy sensitivity and specificity are, therefore, similar to the pooled high sensitivity and low specificity of more than 30 examining dermatologists, who contributed to the database using a variety of approaches to decide on lesion management. Thus, the sensitivity to melanoma can be increased by combining evaluations of lesions by multiple physicians but at the cost of reduced specificity. In practice, this means that, if a patient could consult 10 dermatologists about a single pigmented lesion, the probability that a small melanoma would be biopsied is 96%. However, if a patient is examined by a single dermatologist then the probability that a small melanoma would be biopsied is 71%.

Previously reported sensitivities and specificities for the clinical diagnosis of melanoma are higher than our findings, with sensitivities ranging anywhere from 58% to more than 90%[12,14,24-26] and specificities ranging from 77% to 99%.[26,27] One must take into account, however, that most published studies on diagnostic performance are not limited to small-diameter PSLs. This could explain why our results decreased below those frequently encountered in the literature. In a study[28] that evaluated only melanomas smaller than 7 mm in diameter, the diagnostic sensitivity was 44%, which is more consistent with our findings. Furthermore, variability in sensitivity measurements could reflect the different proportions of in situ and invasive lesions that are included in a given study on diagnostic performance. It is likely that dermatologists diagnose thicker more advanced lesions with greater sensitivity. In our study, 21 of the 49 small melanomas were invasive, with thicknesses ranging from 0.1 to 1.4 mm and a median thickness of 0.32 mm. Similar findings were reported by Kamino et al,[5] in which a sample of 30 small-diameter melanomas had thicknesses ranging from 0.25 to 1.4 mm. In our study, the diagnostic and biopsy sensitivity of expert dermoscopists in the evaluation of small-diameter invasive melanomas was 48% and 81%, respectively, significantly higher than the diagnostic and biopsy sensitivity for in situ melanomas, which was 33% and 63%, respectively.

A number of studies have also reported on the sensitivity of melanoma diagnosis when combining dermoscopy with naked-eye examination. In a study by Carli et al,[15] in which melanocytic lesions were segregated according to lesion diameter, dermatologists identified melanomas smaller than 6 mm with a sensitivity of 64% when using clinical and dermoscopic examination. However,

they found that the addition of dermoscopy to naked-eye examination did not provide a statistically significant improvement in sensitivity. In contrast, Bono et al[8] reported that the addition of dermoscopy to the clinical assessment of small-diameter melanomas allowed for a higher rate of recognition, from 49% with naked-eye examination to 72% with dermoscopic techniques. Others[12,29] have also reported improvement in the diagnostic accuracy with the use of dermoscopy, especially in small lesions. The discordant findings among these studies could be attributable to the different levels of expertise of examiners, to different proportions of invasive and in situ melanomas, and to differences in the prevalence of melanoma included in the sample. In a meta-analysis that evaluated the dermoscopic assessment of pigmented lesions, Kittler et al[14] surmised that, as the proportion of melanoma cases that composed a study subset increased, the diagnostic difficulty of the sample increased.

Our results must be examined within the context of the clinical presentation of small melanomas, which often make them more difficult to identify than larger-diameter malignant melanomas. Thomas et al[30] found that the specificity of melanoma diagnosis increases with the number of ABCDE criteria present. Small melanomas, however, do not always display the features typically used to diagnose malignant melanoma. Bergman et al[10] found that small melanomas have a different clinical presentation than large melanomas because smaller lesions do not always exhibit the characteristic ABCD features, and others[31,32] suggested that malignant melanomas do not display typical clinical and histologic features of melanoma until the lesions are larger than 5 mm. Because morphologic features that help distinguish melanomas from benign lesions may not be visible to the naked eye,[29] it is not surprising that, in light of their clinical presentation, small melanomas are missed much more frequently. The present study found that small melanomas are also difficult to diagnose by dermoscopic evaluation. Given these circumstances, emphasis should, thus, be placed on the E criterion when evaluating small pigmented lesions, which Abbasi et al[11] defined as evolving (ie, change over time in size, shape, color, surface features, or symptoms). In fact, Kamino et al[5] reported that the most frequent reason for excision of small melanomas was a new or changing lesion. Likewise, Helsing and Loeb[28] noted that a change in color was more frequently seen in small melanomas than in larger melanomas.

In conclusion, the differentiation of small melanomas from small benign pigmented lesions challenges even expert physicians. In comparing human evaluation with a computer-vision system, we found that the computer-vision system recommended biopsy for 98% of small melanomas (1 melanoma in situ missed), whereas dermoscopists, on average, would biopsy only 71% of small melanomas (29% missed, both in situ and invasive). By analyzing features indiscernible to the human eye, automated systems could assist dermatologists in the selection of lesions suggestive of disease for biopsy to rule out melanoma. Not only will the addition of such diagnostic tools limit the number of biopsies necessary to rule out melanoma on clinically suspicious yet histologically benign pigmented lesions, it will also aid in the detection and treatment of melanomas during the curable stages of development.

Accepted for Publication: December 7, 2007.

Author Affiliations: Department of Dermatology, New York University School of Medicine, New York (Drs Friedman, Warycha, Kopf, Polsky, and Rigel and Mss Farber, Schneider-Kels, and Papastathis), Electro-Optical Sciences Inc, Irvington (Dr Gutkowicz-Krusin), and Memorial Sloan-Kettering Cancer Center, New York (Dr Marghoob), New York; Departments of Dermatology (Drs Mihm and Tsao) and Dermatopathology (Dr Mihm), Massachusetts General Hospital, and Harvard Medical School (Dr Mihm), Boston, Massachusetts; Knoxville Dermatopathology Laboratory, Knoxville, Tennessee (Drs Googe and King); The University of Texas M. D. Anderson Cancer Center, Houston (Dr Prieto); Skin and Cancer Associates, Plantation (Dr Rabinovitz and Ms Oliviero), Dermatology Associates of Tallahassee, Tallahassee (Dr Cognetta), and Department of Dermatology, University of Miami School of Medicine, Miami (Dr Johr), Florida; Department of Dermatology, University of British Columbia, and General Hospital and British Columbia Cancer Agency, Vancouver (Dr Rivers); and University of Connecticut Health Center, Farmington (Dr Grant-Kels).

Correspondence: Robert J. Friedman, MD, Department of Dermatology, New York University School of Medicine, 124 E 72nd St, New York, NY 10021.

Author Contributions: Dr Friedman had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Friedman, Gutkowicz-Krusin, Farber, Warycha, Schneider-Kels, and Prieto. *Acquisition of data:* Gutkowicz-Krusin, Mihm, Googe, King, Prieto, Polsky, Rabinovitz, Oliviero, Cognetta, Rivers, and Tsao. *Analysis and interpretation of data:* Friedman, Gutkowicz-Krusin, Farber, Warycha, Schneider-Kels, Papastathis, Mihm, Googe, King, Prieto, Kopf, Rabinovitz, Oliviero, Rigel, Marghoob, Johr, and Grant-Kels. *Drafting of the manuscript:* Friedman, Gutkowicz-Krusin, Farber, Warycha, Schneider-Kels, Papastathis, and Prieto. *Critical revision of the manuscript for important intellectual content:* Friedman, Gutkowicz-Krusin, Farber, Warycha, Schneider-Kels, Papastathis, Mihm, Googe, King, Prieto, Kopf, Polsky, Rabinovitz, Oliviero, Cognetta, Rigel, Marghoob, Rivers, Johr, Grant-Kels, and Tsao. *Statistical analysis:* Gutkowicz-Krusin. *Obtained funding:* Friedman. *Administrative, technical, and material support:* Gutkowicz-Krusin, Farber, Warycha, Schneider-Kels, Papastathis, and Cognetta. *Study supervision:* Friedman, Kopf, Rigel, Grant-Kels, and Tsao.

Financial Disclosure: Dr Friedman is a shareholder, former director, consultant, and member of the Scientific Advisory Committee for Electro-Optical Sciences Inc (EOS); Dr Gutkowicz-Krusin is an employee of EOS; Mss Farber and Schneider-Kels and Dr Warycha received research support from EOS; Dr Mihm is a member of the Scientific Advisory Committee and the chief dermatopathologist for EOS; Drs Googe and King are dermatopathologists for EOS studies; Dr Prieto is a dermatopathologist for and is involved in a research project with

EOS; Dr Kopf is a former member of the Scientific Advisory Committee for EOS; Drs Polsky and Rabinovitz are consultants, principal investigators, and members of the Scientific Advisory Committee for EOS; Dr Cognetta is a principal investigator and member of the Scientific Advisory Committee for EOS; Dr Rigel is a consultant and member of the Scientific Advisory Committee for EOS; and Dr Grant-Kels will be a future investigator for EOS.

Funding/Support: Mss Farber and Schneider-Kels and Dr Warycha received research support from EOS.

Role of the Sponsor: Electro-Optical Sciences Inc provided data to the research team but had no role in study design, data analysis, data interpretation, or writing of the report.

Additional Contributions: Alicia Toledano, ScD, helped with statistical analyses and Nikolai Kabelev, BCSc, Joanna Adrian, MBA, and Mrinalini Roy, BA, of Electro-Optical Sciences Inc helped prepare the data for this study.

REFERENCES

1. Friedman RJ, Rigel DS, Kopf AW. Early detection of malignant melanoma: the role of physician examination and self-examination of the skin. *CA Cancer J Clin.* 1985;35(3):130–151.
2. Rigel DS, Friedman RJ, Kopf AW, Polsky D. ABCDE: an evolving concept in the early detection of melanoma. *Arch Dermatol.* 2005;141 (8):1032–1034.
3. Thompson JF, Scolyer RA, Kefford RF. Cutaneous melanoma. *Lancet.* 2005;365 (9460):687–701.
4. Rigel DS, Friedman RJ, Kopf AW. The incidence of malignant melanoma in the United States: issues as we approach the 21st century. *J Am Acad Dermatol.* 1996;34(5, pt 1):839–847.
5. Kamino H, Kiryu H, Ratech H. Small malignant melanomas: clinicopathologic correlation and DNA ploidy analysis. *J Am Acad Dermatol.* 1990;22(6, pt 1):1032– 1038.
6. Gonzalez A, West AJ, Pitha JV, Taira JW. Small-diameter invasive melanomas: clinical and pathologic characteristics. *J Cutan Pathol.* 1996;23(2):126–132.
7. Shaw HM, McCarthy WH. Small-diameter malignant melanoma: a common diagnosis in New South Wales, Australia. *J Am Acad Dermatol.* 1992;27(5, pt 1): 679–682.
8. Bono A, Bartoli C, Moglia D, et al. Small melanomas: a clinical study of 270 consecutive cases of cutaneous melanoma. *Melanoma Res.* 1999;9(6):583-586.
9. Sboner A, Bauer P, Zumiani G, et al. Clinical validation of the early diagnosis of melanoma. *Skin Res Technol.* 2004;10(3):184–192.
10. Bergman R, Katz I, Lichtig C, et al. Malignant melanomas with histologic diameters less than 6 mm. *J Am Acad Dermatol.* 1992;26 (3, pt 2):462–466.
11. Abbasi NR, Shaw HM, Rigel DS, et al. Early diagnosis of cutaneous melanoma: revisiting the ABCD criteria. *JAMA.* 2004;292(22):2771–2776.
12. Binder M, Schwartz M, Winkler A, et al. Epiluminescence microscopy: a useful tool for the diagnosis of pigmented skin lesions for formally trained dermatologists. *Arch Dermatol.* 1995;131 (3):286–291.
13. Ascierto PA, Palmieri G, Celentano E, et al. Sensitivity and specificity of epiluminescence microscopy: evaluation on a sample of 2731 excised cutaneous pigmented lesions: the Melanoma Cooperative Study. *Br J Dermatol.* 2000;142 (5):893–898.
14. Kittler H, Pehamberger H, Wolff K, Binder M. Diagnostic accuracy of dermoscopy. *Lancet Oncol.* 2002;3(3):159–165.
15. Carli P, De Giorgi V, Chiarugi A, et al. Effect of lesion size on the diagnostic performance of dermoscopy in melanoma detection. *Dermatology.* 2003;206(4): 292–296.
16. Arumi-Uria M, McNutt NS, Finnerty B. Grading of atypia in nevi: correlation with melanoma risk. *Mod Pathol.* 2003;16(8):764–771.
17. Gutkowicz-Krusin D, Elbaum M, Szwajkowski P, Kopf AW. Can early malignant melanoma be differentiated from atypical melanocytic nevi by in-vivo techniques? part II: automatic machine vision classification. *Skin Res Technol.* 1997; 3:15–22.
18. Elbaum M, Kopf AW, Rabinovitz H, et al. Automatic differentiation of early melanoma from nevi with multi-spectral digital dermoscopy: feasibility study. *J Am Acad Dermatol.* 2001;44(2):207–218.
19. Gutkowicz-Krusin D, Elbaum M, Jacobs A, et al. Precision of automatic measurements of pigmented skin lesion parameters with a MelaFind multispectral digital microscope. *Melanoma Res.* 2000;10:1–8.
20. Fleiss JL. *Statistical Methods for Rates and Proportions.* New York, NY: John Wiley & Sons Inc; 1981:225–232.
21. Obuchowski NA. Multireader, multimodality receiver operating characteristic curve studies. *acad Radiol.* 1995;2(suppl 1):S22–S29.
22. Fisher LD, van Belle G. *Biostatistics.* New York, NY: John Wiley & Sons Inc; 1993.
23. Annessi G, Cattaruzza MS, Abeni D, et al. Correlation between clinical atypia and histologic dysplasia in acquired melanocytic nevi. *J Am Acad Dermatol.* 2001; 45(1):77–85.
24. Soyer HP, Smolle J, Leitinger G, et al. Diagnostic reliability of dermoscopic criteria for detecting malignant melanoma. *Dermatology.* 1995;190(1):25–30.
25. Bafounta ML, Beauchet A, Aegerter P, Saiag P. Is dermoscopy (epiluminescence microscopy) useful for the diagnosis of melanoma? *Arch Dermatol.* 2001; 137(10):1343–1350.
26. Bono A, Bartoli C, Cascinelli N, et al. Melanoma detection: a prospective study comparing diagnosis with the naked eye, dermatoscopy and telespectrophotometry. *Dermatology.* 2002;205(4):362–366.
27. Wolf IH, Smolle J, Soyer HP, Kerl H. Sensitivity in the clinical diagnosis of malignant melanoma. *Melanoma Res.* 1998;8(5):425–429.
28. Helsing P, Loeb M. Small diameter melanoma: a follow-up of the Norwegian Melanoma Project. *Br J Dermatol.* 2004;151(5):1081–1083.
29. Steiner A, Pehamberger H, Wolff K. In vivo epiluminescence microscopy of pigmented skin lesions, 2: diagnosis of small pigmented skin lesions and early detection of malignant melanoma. *J Am Acad Dermatol.* 1987;17(4):584–591.
30. Thomas L, Tranchand P, Berard F, et al. Semiological value of ABCDE criteria in the diagnosis of cutaneous pigmented tumors. *Dermatology.* 1998;197(1): 11–17.
31. Howell JB. Spotting sinister spots: a challenge to dermatologists to examine every new patient at increased risk for signs of early melanoma. *J Am Acad Dermatol.* 1986;15(4, pt 1):722–726.

32. Schmoeckel C, Braun-Falco O. Diagnosis of early malignant melanoma: sensitivity and specificity of clinical and histological criteria. *Pigment Cell*. 1987;8:96–106.