P090012
MelaFind®
MELA Sciences, Inc.

FDA Presenters:

Atiq Chowdhury, MS
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General and Plastic Surgery Devices Panel Meeting

November 18, 2010

PMA Review Team

- Atiq Chowdhury, MS – Lead Review
- Neil Ogden, MS – Overview, Non-Clinical and Clinical Review
- Richard Felten, MS – Non-Clinical Review
- Roxolana Horbowyj, MD, FACS – Clinical Review
- Max Robinowitz, MD, FACP – Clinical Review
- Peter Rumm, MD, MPH, FACPM
- Amor Khachemoune, MD, FAAD – Clinical Review
- Patricia Brown, MD, FAAD – Clinical Review
- Bipasa Biswas, MS – Statistical Review
- Hong Cheng, MD – Post-Approval Study

FDA Presentation

- Introduction
- Background on Protocol Agreement (Protocol 20031)
- FDA Regulations Used for P090012
- Clinical Studies Overview
- Statistical Overview
- Clinical Conclusions
- Post-Approval Study
- Panel Questions

Rationale for Bringing to Panel

- First-of-a-kind device
- Sponsor Requested Panel
- Input needed from Panel to determine risk/benefit of device

Sponsor's Proposed Indications for Use

MelaFind® is indicated for the evaluation of clinically atypical cutaneous pigmented lesions (those having one or more clinical or historical characteristics of melanoma, such as asymmetry, border irregularity, color variegation, diameter greater than 6 mm, evolving, patient concern, regression, and "ugly duckling"), when a physician chooses to obtain additional information before making a final decision to biopsy to rule out melanoma. MelaFind® is a non-invasive objective multi-spectral computer vision system designed as a tool to aid physicians in the detection of early (e.g., non-ulcerated, not bleeding, or less than 2.2 cm in diameter) melanoma.

MelaFind® is not a screening device and is not indicated for non-pigmented lesions, banal pigmented lesions, lesions that are clinically identified as definite melanomas, or lesions on special anatomic sites (i.e., acral, mucosal, subungual).

Device Description

MelaFind is a system that has:

- A dermoscope that uses 430 nm (blue) through 950 nm (near infrared) light to image the skin through a thin layer of liquid (alcohol or oil)
- A complementary metal oxide semiconductor (CMOS) digital camera inside the probe to capture images
- A computer that connects to the dermoscope as well as to a display monitor and removable storage media
- Predefined software statistical pattern recognition algorithms that differentiate among pigmented skin lesions to provide a fixed-threshold binary output:

  MelaFind = 1 = positive

  MelaFind = 0 = negative

FDA Presentation

- Introduction
- Background on Protocol Agreement (Protocol 20031)
- Diagnostic and Adjunctive Test Characteristics
- Clinical Studies Overview
- Statistical Overview
- Clinical Conclusions
- Post-Approval Study
- Panel Questions

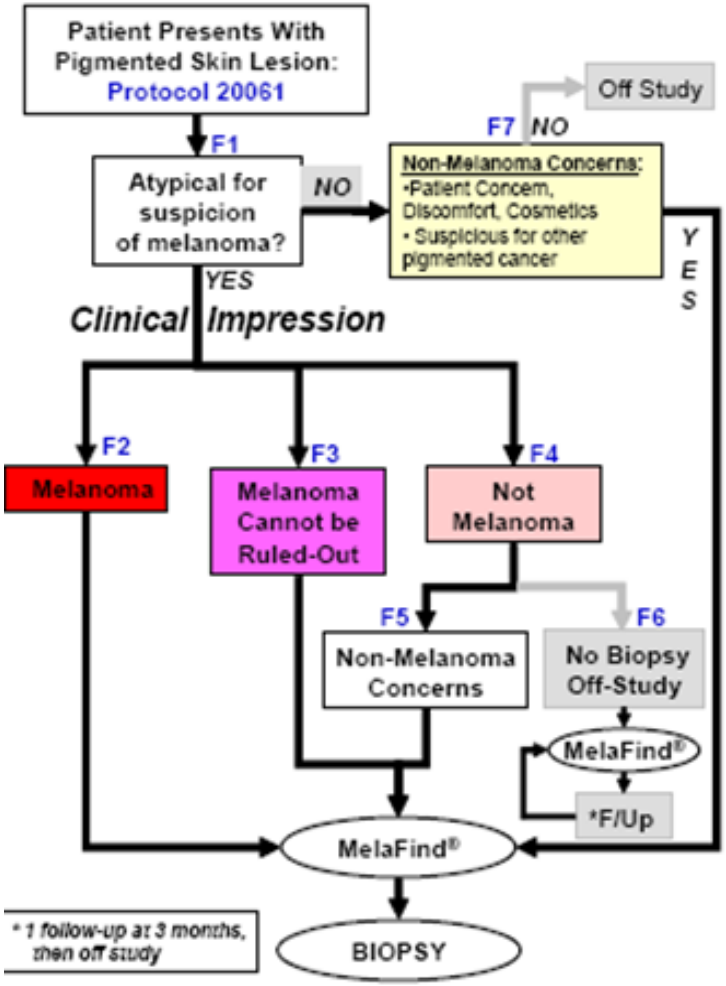
Protocol Agreement

- On October 20, 2004, FDA and the sponsor signed a Protocol Agreement based on Clinical Protocol 20031 (subsequently revised to become Protocol 20061).
- The Primary Aims (Sensitivity and Specificity) and the decision steps in lesion management were established to support MelaFind's claim to rule-out melanoma in atypical lesions suspicious of melanoma to reduce the number of unnecessary biopsies.
- Sensitivity and specificity were recognized as appropriate metrics for evaluating safety and effectiveness.

Protocol Agreement (cont)

- In the absence of clinical data, the FDA and the sponsor could not decide upon a mutually agreeable proposed indications for use for the agreement meeting.
- The panel will not be asked to address whether the sponsor had met the items of the protocol agreement but will be asked about the risk/benefit implications of the items.

Protocol Agreement (cont)



- Lesions atypical for suspicion of Melanoma (F1).
- Clinical diagnosis “Melanoma” (F2).
- Clinical diagnosis “Melanoma cannot be ruled-out” (F3).
- Clinical diagnosis “Not Melanoma” (F4).
- Undergoing biopsy for “Non-Melanoma Concerns” (F5 and F7).
- The sponsor initially proposed that “Uncertain” lesions from the F4 that are NOT biopsied would be followed (F6). However, no follow up group was enrolled.

Figure 1: Population Schema of Protocol 20061

Impact of Issues

- The FDA review team believes the following issues impact our ability to evaluate the risk/benefit for the device for its proposed indications for use:
  - Handling and Analysis of data considered ineligible and non-evaluable
  - Lack of enrollment in the 3-month follow up group (F6) – additional data to evaluate whether MelaFind was able to effectively rule-out melanoma from the “Not Melanoma” (F4) Group by comparing the MelaFind result to the dermatologist’s decision for a 3 month follow-up
  - F6 is a subset of F4. F4 = F5 + F6
  - Data to help determine if MelaFind could safely and effectively rule-out melanoma to reduce unnecessary biopsies in atypical lesions suspicious of melanoma
  - MelaFind was to be studied on **only** atypical lesions suspicious for melanoma to rule-out melanoma in order to reduce the number of unnecessary biopsies

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FDA Regulations Used for PMA P090012 MelaFind

Max Robinowitz, MD, FACP
Office of In Vitro Diagnostic Device Evaluation & Safety (OIVD)

General and Plastic Surgery Devices Panel Meeting
November 18, 2010

Overview of Why & How FDA regulates

- Food, Drug & Cosmetic Act
- The FDA regulation & guidance
- Characteristics of medical devices that function as diagnostic tests
- Regulatory classification for MelaFind

Medical Device Definition

FD&C Act 21 U.S.C. 321 Sec.201(h)

- “are intended to regulate medical devices to allow the public to receive the benefits that medical research & experimentation provide while at the same time protecting the public from increasingly complex devices which pose serious risks if inadequately tested or improperly designed or used”
- "an **instrument, apparatus, implement, machine, contrivance**, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:

- **intended for use in the diagnosis of disease or other conditions**, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, …..”

Diagnostic Devices = Function as Diagnostic Tests

FDA Statistical Guidance for Diagnostic Tests

- Diagnostic tests are a **combination** of physical product, system, assay, reagents, software, diagnostic algorithm, operator, clinician who orders and interprets results.
- **Same** diagnostic test may have **more than one indication for use --- each requiring validation by independent clinical studies.**
- The **indication for use** includes the recommended conditions for the pre-test, test and post-test interpretation.

FDA Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests

- **Diagnostic test** is used for patients with signs or symptoms to classify disease, condition or state of heath
- **Performance characteristics** are established **against a clinical reference standard in the intended use population for the labeled indications for use of the new test.** E.g. histopathology
- **Performance measures** could be
  - sensitivity-specificity pair
  - positive and negative predictive value
  - diagnostic likelihood ratio positive and negative.
- **Screening tests** are also diagnostic tests except the context in which they are applied in practice is what sets them apart. Screening tests are applied to asymptomatic individuals on a large scale.

Stand-alone Diagnostic Test

- Stand-alone test is used to **establish** the diagnosis of a disease or condition.
- Stand-alone test **clinical validation** =
  - Demonstration of **performance** in **comparison to a reference test or clinical diagnosis**
  - Demonstration of superiority or non-inferiority, **not just additional information**
  - **A positive device result over-rules the pre-test clinical diagnosis,** e.g. surgical path cancer result
  - **A negative device result is less strong support to over-rule the pre-test clinical diagnosis,** e.g. sampling error may result in false negative

Adjunctive Diagnostic Test

- Adjunctive test is
  - **not** a stand-alone test
  - intended use is **to provide additional information to another diagnostic test**
  - **The clinician may over-rule the adjunctive test**
- **Clinical validation** should determine if sufficient additional information is added to improve diagnostic performance (**not a random test**)
- The adjunctive test's **overall benefit depends** & **varies with what other Dx test or clinical data it is added to and circumstances for the application of both tests**

Safety of the Diagnostic Test

FDA Regulation 21 CFR 860.7

(4)(d)(1) There is a reasonable assurance that a device is **safe** when it can be determined, based upon **valid scientific evidence**, that the **probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions & warnings against unsafe use, outweigh any probable risks**. The valid scientific evidence used to determine the safety of a device shall adequately demonstrate the **absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses & conditions of use.**

THIS SLIDE WAS LEFT OUT DURING PRESENTATION

Effectiveness of Diagnostic Test

- **Effectiveness of diagnostic test** = quality of the diagnostic **information**
  - "in a **significant portion of the target population**, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use & warnings against unsafe use, will provide **clinically significant results**." (ref: 21 CFR 860.7)
  - Likelihood of false results & their consequences

- How well does the diagnostic test meets the intention-to-diagnose (ITD) analysis?
  - intended use
  - indications for use
  - when used according to the manufacturer's instructions for use

THIS SLIDE WAS REVISED FOR ACCURACY AFTER PRESENTATION – SEE TRANSCRIPT PAGE 101

FDA Categorization of the MelaFind

- MelaFind is intended to function as a diagnostic medical device.
- The **reference diagnosis** for MelaFind results are the histopathology diagnoses of the biopsied lesions.
- The sponsor intends MelaFind to be used as an **adjunctive diagnostic test** when used by dermatologists as additional information and does not over-rule the clinician
- MelaFind would function as a **stand-alone diagnostic test when the MelaFind result over-rules the pre-test clinical diagnosis**

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MelaFind - P090012
MELA Sciences, Inc.

US - FDA Clinical Analysis

General and Plastic Surgery Devices
Panel Meeting
November 18, 2010

Presented by
Roxolana Horbowyj, MSChE, MD, FACS
CDRH / ODE / DGRND

Outline

- Background
  - Brief Device Description
  - Proposed Indication for Use: Key clinical components
- Clinical Studies
  - Protocol 20061: Pivotal Study
    - Design
    - Outcome assessment
  - Protocol 20063: On-line Reader Survey
    - Design
    - Outcome assessment
- Summary Clinical Comments

Brief Device Description

MelaFind is a system that has

- A dermoscope that uses 430 nm (blue) through 950 nm (near infrared) light to image the skin through a thin layer of liquid (alcohol or oil),
- A complementary metal oxide semiconductor (CMOS) digital camera inside the probe to capture 10 multi-spectral (from blue to near infrared) 1280x1024 pixel digital images of a pigmented skin lesion under computer control.
- A computer that connects to the dermoscope as well as to a display monitor and removable storage media,
- Predefined software for image analysis with statistical pattern recognition algorithms that use a 75-feature linear classifier and 'sequential feature forward search' with the area under the curve of the ROC on the training data' to display a binary output:

  MelaFind = 1 = positive (melanoma, melanoma-in-situ, high grade dysplastic nevi and atypical melanocytic proliferation / hyperplasia)

  MelaFind = 0 = negative

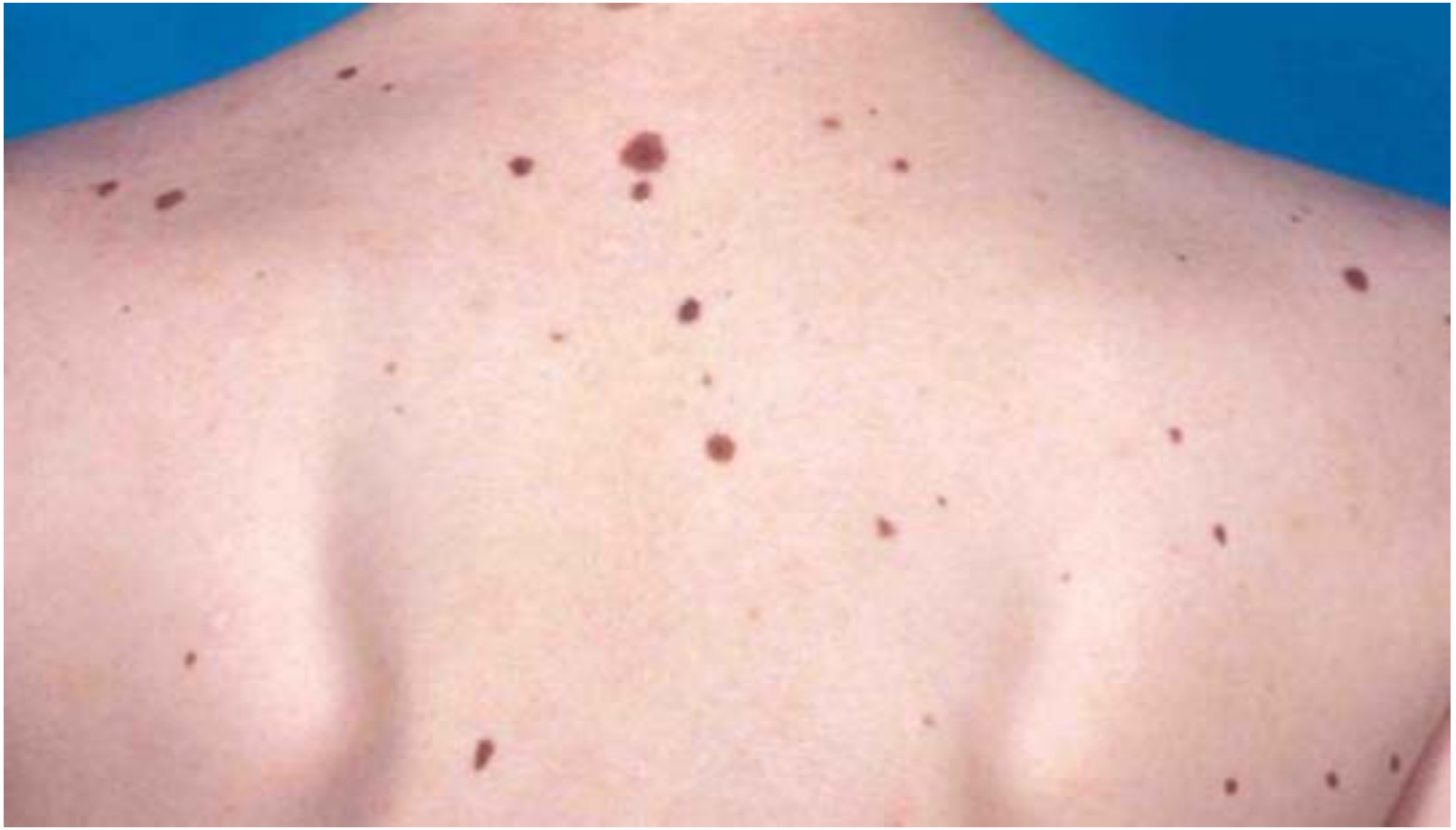
Comment: The training data ROC for determining binary input has not been presented.

Key clinical components of MelaFind
Proposed Indications for Use

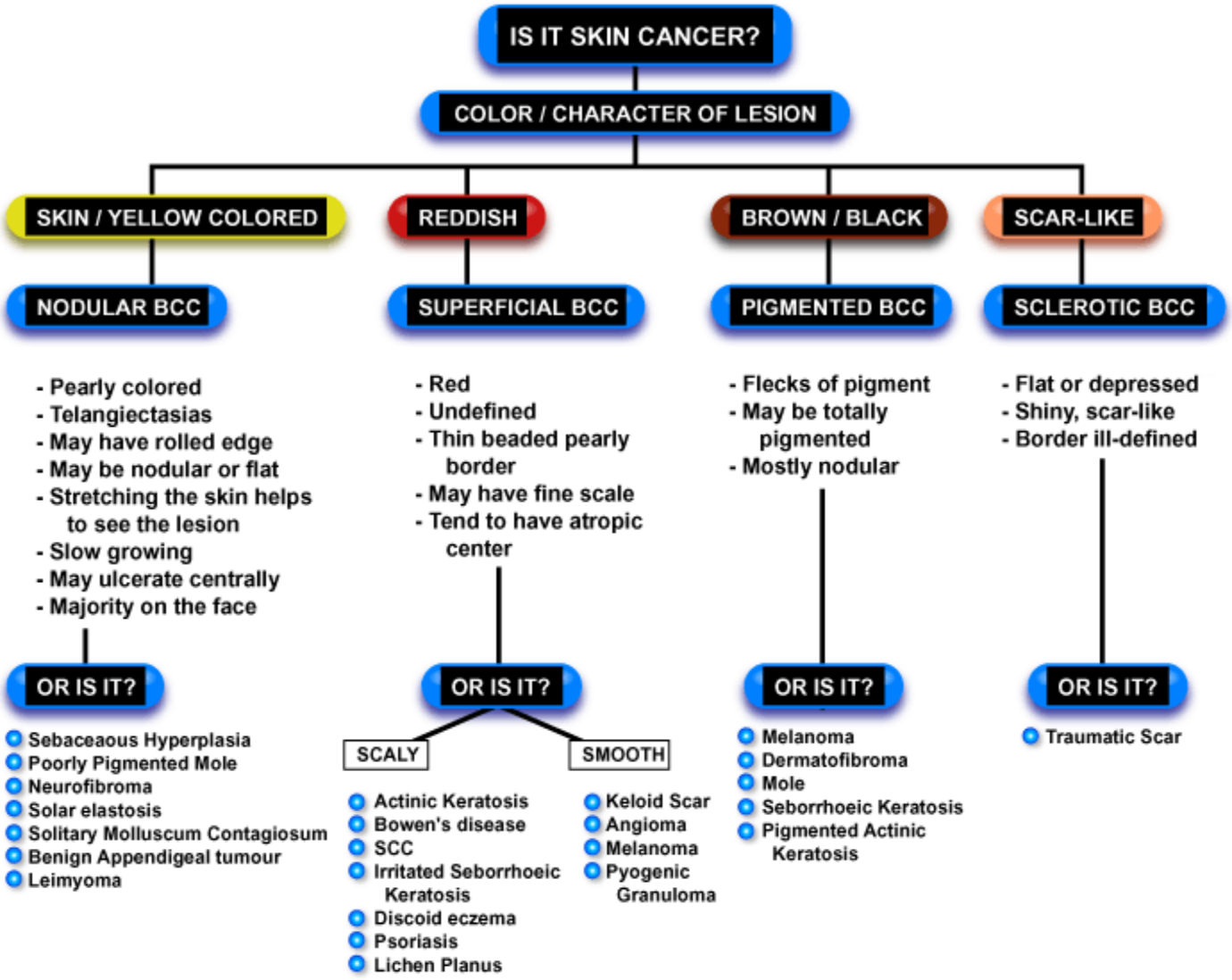
- Indicated for use
  - For evaluation of clinically atypical cutaneous pigmented lesions (those having one or more clinical or historical characteristics of melanoma, such as asymmetry, border irregularity, color variegation, diameter greater than 6 mm, evolving, patient concern, regression, and "ugly duckling"), when a physician chooses to obtain additional information before making a final decision to biopsy to rule out melanoma.
  - In detection of early (e.g., non-ulcerated, not bleeding, or less than 2.2 cm in diameter) melanoma.
- Not indicated for use
  - as a screening device
  - on non-pigmented lesions, banal pigmented lesions, or lesions that are clinically identified as definite melanomas, or lesions on special anatomic sites (i.e., acral, mucosal, subungual).

Comment: A proposed Indications for Use is expected to be supported by the data presented.

Pigmented Skin Lesions

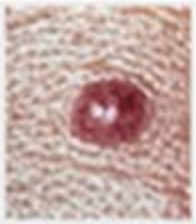


Ref: http://atlasgeneticsoncology.org/Kprones/FamilialMelanomID10088.html



Ref: http://www.skincancerguide.ca/prevention/is_it_skin_cancer.html

Pigmented Skin Lesions

Normal Mole	Melanoma	Sign	Characteristic
		Asymmetry	when half of the mole does not match the other half
		Border	when the border (edges) of the mole are ragged or irregular
		Color	when the color of the mole varies throughout
		Diameter	if the mole's diameter is larger than a pencil's eraser

Photographs Used By Permission: National Cancer Institute

Ten Leading Cancer Types for Estimated New Cancer Cases, United States, 2009

Estimated New Cases*

Males				Females		
Prostate	192,280	25%		Breast	192,370	27%
Lung & bronchus	116,090	15%		Lung & bronchus	109,350	14%
Colon & rectum	75,590	10%		Colon & rectum	71,380	10%
Urinary bladder	52,810	7%		Uterine corpus	42,160	6%
Melanoma of the skin	39,080	5%		Non-Hodgkin lymphoma	29,990	4%
Non-Hodgkin lymphoma	35,990	5%		Melanoma of the skin	29,640	4%
Kidney & renal pelvis	35,430	5%		Thyroid	27,200	4%
Leukemia	25,630	3%		Kidney & renal pelvis	22,330	3%
Oral cavity & pharynx	25,240	3%		Ovary	21,550	3%
Pancreas	21,050	3%		Pancreas	21,420	3%
All Sites	**766,130**	**100%**		**All Sites**	**713,220**	**100%**

Ref: http://www.cancer.org/acs/groups/content/@nho/documents/document/acspc-024113.pdf

Table 1. Tumor–Node–Metastasis staging categories for cutaneous melanoma (American Joint Committee on Cancer 2010).

Tumor	*Breslow thickness*	*Ulceration status/mitoses*
Tis	NA	NA
T1	≤1.0 mm	T1a: without ulceration and mitoses <1/mm^2 T1b: with ulceration or mitoses ≥1/mm^2
T2	1.01–2.0 mm	T2a: without ulceration T2b: with ulceration
T3	2.01–4.0 mm	T3a: without ulceration T3b: with ulceration
T4	>4.0 mm	T4a: without ulceration T4b: with ulceration
Node	*Number of metastatic nodes*	*Nodal metastatic burden*
N0	0	NA
N1	1	N1a: micrometastasis† N1b: macrometastasis‡
N2	2–3	N2a: micrometastasis† N2b: macrometastasis‡ N2c: in-transit metastases/satellites without metastatic nodes.
N3	4+ metastatic nodes, or matted nodes, or in-transit metastases/satellites with metastatic nodes	
Metastasis	*Site*	*Serum LDH*
M0	No distant metastasis	NA
M1a	Distant skin, subcutaneous or nodal metastases	Normal
M1b	Lung metastasis	Normal
M1c	All other visceral metastasis	Normal
	Any distant metastasis	Elevated

†Micrometastases are diagnosed after sentinel lymph node biopsy.
‡Macrometastases are defined as clinically detectable nodal metastases confirmed pathologically.
LDH: Lactate dehydrogenase; NA: Not applicable.
Data from [11].

MelaFind Clinical Studies

Protocol No.	Protocol Title	Protocol Version Date	Dates of Accrual	MelaFind® System Configuration	Study Objectives	Use of Data
20011	Patient Examination with MelaFind™ System Developed by Electro-Optical Sciences, Inc. (EOS)	16-Apr-01	12-Apr-01 to 25-Jul-08	Portable Case/ Cart	To acquire data needed for the continuing development of MelaFind®	Development of MelaFind® image analysis algorithms
20012	Non-invasive Breslow Thickness Measurement for Cutaneous Melanoma with MelaMeter™	2-Aug-01	30-Nov-01 to 28-Jul-04	Portable Case	To acquire data needed for the continuing development of MelaFind® and associated MelaMeter™ software	Development of MelaFind® image analysis algorithms
RCP2007-05	Benign Pigmented Skin Lesions: Melanin Localization and Quantification with MelaFind®	11-Jun-07	26-Sep-07 to 14-Apr-08	Cart	To acquire data needed for the continuing development of MelaFind® and to investigate the feasibility of melanin localization and quantification from MelaFind® images of benign pigmented skin lesions	Development of MelaFind® image analysis algorithms
20031-A	Evaluation of Pigmented Skin Lesions with MelaFind® System	30-Aug-04	12-Nov-04 to 5-Jul-05	Cart with Clinical Cameras	To demonstrate that MelaFind is safe and effective, using sensitivity to melanoma and specificity as metrics*	Development of MelaFind® image analysis algorithms
20031-B	Pilot Roll-in Study for Protocol 20061: Evaluation of Pigmented Skin Lesions with MelaFind® System	30-Jan-06	20-Dec-06 to 14-Jul-08	Cart with Clinical Cameras	To allow users to gain experience with both MelaFind® and the study methodology, prior to being initiated on Pivotal Trial Protocol 20061, while acquiring data needed for the final development of MelaFind® image analysis algorithms	Final development of MelaFind® image analysis algorithms
20061	Evaluation of Pigmented Skin Lesions with MelaFind® System	19-Dec-05	31-Jan-07 to 7-Jul-08	Cart with Clinical Cameras	To demonstrate that MelaFind® is safe and effective, using sensitivity to melanoma and specificity as metrics	Prospective testing of MelaFind® image analysis algorithms

*Protocol 20031-A was originally designed as a prospective pivotal trial of MelaFind® and stopped. It was later amended to become Protocol 20031-B and designated as a roll-in study for Protocol 20061

Protocols 20031 and 20061

Differences include:

- Definitions of "Evaluable Cases" - In Protocol 20061 (P20061) lesions could be non-evaluable whether or not CRF data and central dermatohistopathology diagnosis were available, if an acceptable MelaFind® image could not be obtained because
    1. *Image not acquired by MelaFind® , or*
    2. *Image disqualified by MelaFind® quality control algorithms,*
- Secondary endpoints
- Pathologies included in MelaFind Output = 1

Data analysis plan did not address assessment of 'Intent to Diagnosis' compared to 'Evaluable' populations: methods of handling data for biopsied lesions that were subsequently considered not eligible or evaluable.

Protocol 20061 - Pivotal Study

- Enrolled patients at 7 (3 academic and 4 community) geographically diverse sites in the US with 23 board certified dermatologists highly experienced in managing pigmented skin lesions.
- Masked MelaFind output, dermatologists assessment and dermatopathologists diagnosis to each other.
- Compared study lesion assessment by:
  - MelaFind:
    - 1 (positive) or
    - 0 (negative)
  - Dermatologist:
    - Is melanoma or
    - Cannot rule-out melanoma or
    - Is not melanoma
  - Dermatopathologist: histologic diagnosis

Protocol 20061 - Pivotal Study Design
Primary Objectives

'To demonstrate that MelaFind's sensitivity to malignant melanoma, among lesions with dermatological diagnoses of "Melanoma cannot be ruled out" or "Not melanoma", is at least 95% at a 95% confidence level.'

'To demonstrate that, along with this high level of sensitivity, the specificity of MelaFind for lesions that are not malignant melanoma, among lesions with dermatological diagnoses of "Melanoma cannot be ruled out" or "Not melanoma", is superior to the specificity of study dermatologists.'

Comment: A clinically significant difference in biopsy rate of lesions with dermatological diagnoses of "Melanoma cannot be ruled out" or "Not melanoma", was not a component of 20061 sample size determination or primary objective assessment.

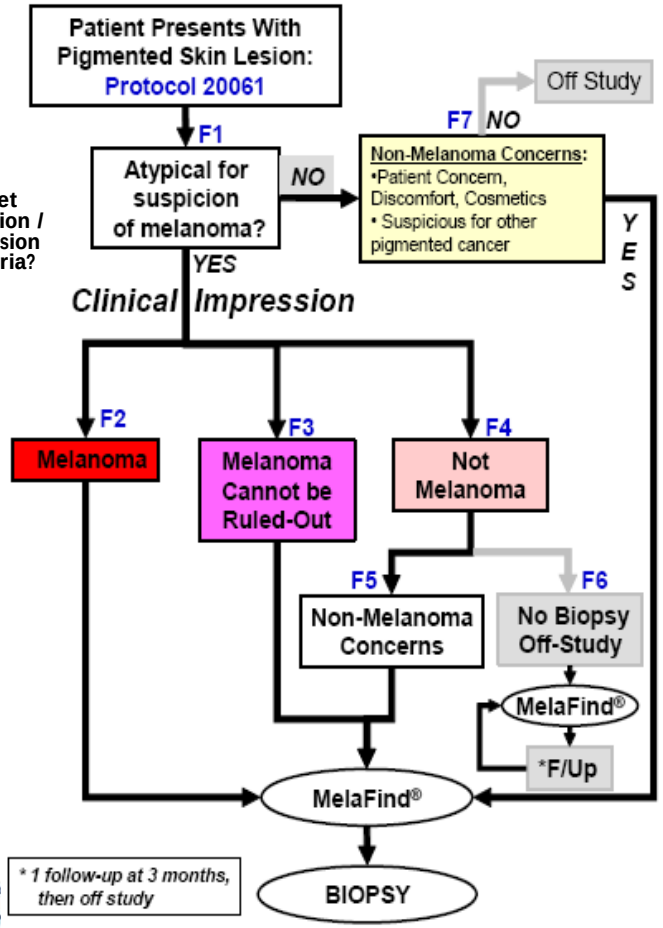
Prospective statistical plan did not pre-specify primary objective assessment confidence interval assessment to be one-sided or two-sided. FDA Statistical review will discuss the impact of 1-sided compared to two-sided assessment.

Safety and Effectiveness objectives were not independently defined.

'Malignant melanoma' in the primary objective refers to dermatopathology of melanoma and melanoma in situ, whereas MelaFind = 1 is based upon dermatopathology of melanoma, melanoma in situ, atypical melanocytic hyperplasia and high grade dysplasia.

Protocol 20061 - Pivotal Study Design
Inclusion Criteria, Procedure and Follow-up

Figure 6. Protocol 20061 – Study Population Schema



Ref: PMA Attachment 12-1, p. 11

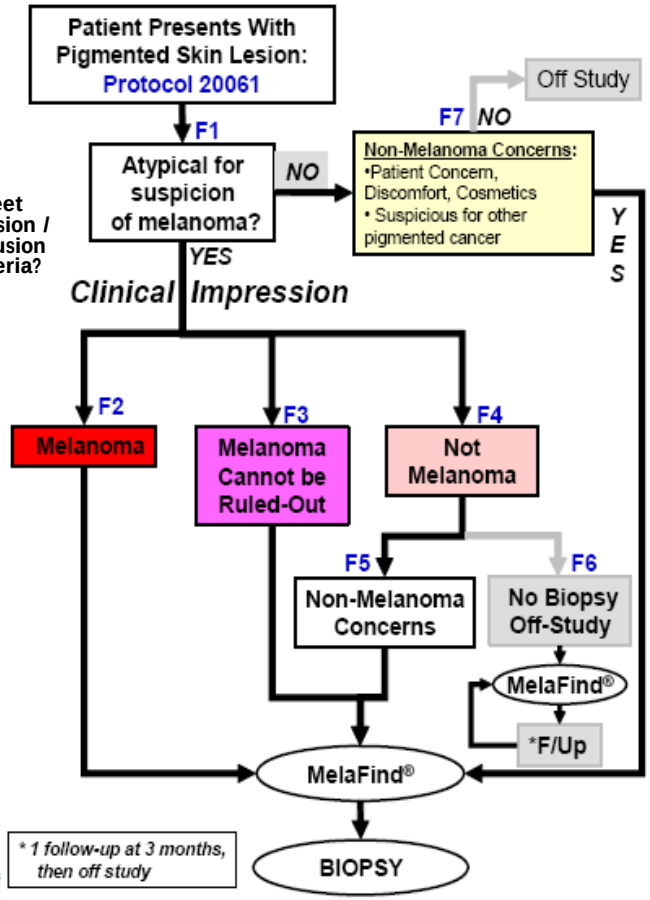
Inclusion criteria:

- Lesion is pigmented (i.e., melanin, keratin, or blood)
- Pigmented area diameter is 2 to 22 mm
- Lesion accessible to MelaFind probe
- Examining dermatologist clinical management decision to
  either
  - Lesion biopsy *in toto*,
  or
  - Lesion follow-up in 3 months
- Informed consent form signed

Comment: Inclusion criteria did not explicitly include a skin lesion on the basis of atypia or suspicion for melanoma, e.g.: ABCDE criteria

Protocol 20061 - Pivotal Study Design
Exclusion Criteria, Procedure and Follow-up

Figure 6. Protocol 20061 – Study Population Schema



Ref: PMA Attachment 12-1, p. 11

Exclusion criteria:

Lesion is

- on skin that is not intact: (e.g., open sores, ulcers, bleeding)
- within 1 cm of the eye
- on mucosal surfaces (e.g., lips, genitals)
- on palmar hands
- on plantar feet
- on or under nails
- on or in an area of visible scarring
- previously biopsied, excised, or traumatized
- contains foreign matter (e.g., tattoo, splinter, marker)

Comment: exclusion criteria did not explicitly exclude a skin lesion on the basis a lack of atypia or suspicion for melanoma, e.g.: ABCDE criteria

Enrolled and Biopsied lesions deemed ineligible or non-evaluable for P20061

Of 1831 enrolled (Intent-to-diagnose, ITD) lesions, 1632 were eligible and evaluable (E&E) because

- 18 were ineligible:
  - 1 patient withdrew from the study;
  - 3 cases were determined to be ineligible at the clinical study site;
  - 14 cases were determined to be ineligible during central dermatohistopathology review;
- 171 were non-evaluable:
  - 19 cases non-evaluable due to missing or inadequate histological slides
  - **162 cases non-evaluable due to unsuccessful imaging attempts**
    - 65 cases because of operator errors,
    - 36 cases because of MelaFind® or standard camera malfunctions,
    - 61 cases due to causes that could be either operator errors or MelaFind® malfunctions.

27 non-evaluable lesions were dermatopathologically diagnosed as melanoma.

Comment: This presentation focuses primarily on the E&E population. The FDA Statistical review further compares E&E and ITD population outcomes.

Protocol 20061 - Pivotal Study Outcomes
Lesion Accounting by Site

Table 12.4. Lesions Enrolled at Clinical Study Sites

Site No.	Lesions Enrolled*		Eligible and Evaluable Lesions	MM	HGDN**	Non-MM/HGDN**	Ineligible	Non-Evaluable
	Biopsy Arm	Follow-Up Arm						
1	224	0	203	27	12	164	1	20
2	369	0	316	38	9	269	4	49
3	632	0	561	25	7	529	5	66
4	264	0	250	19	7	224	0	14
5	191	0	159	9	6	144	2	30
6	43	0	37	1	3	33	4	2
7	108	0	106	8	4	94	1	1
TOTAL	**1831**	**0**	**1632**	**127**	**48**	**1457**	**17**	**182*****

*Excludes mis-registrations

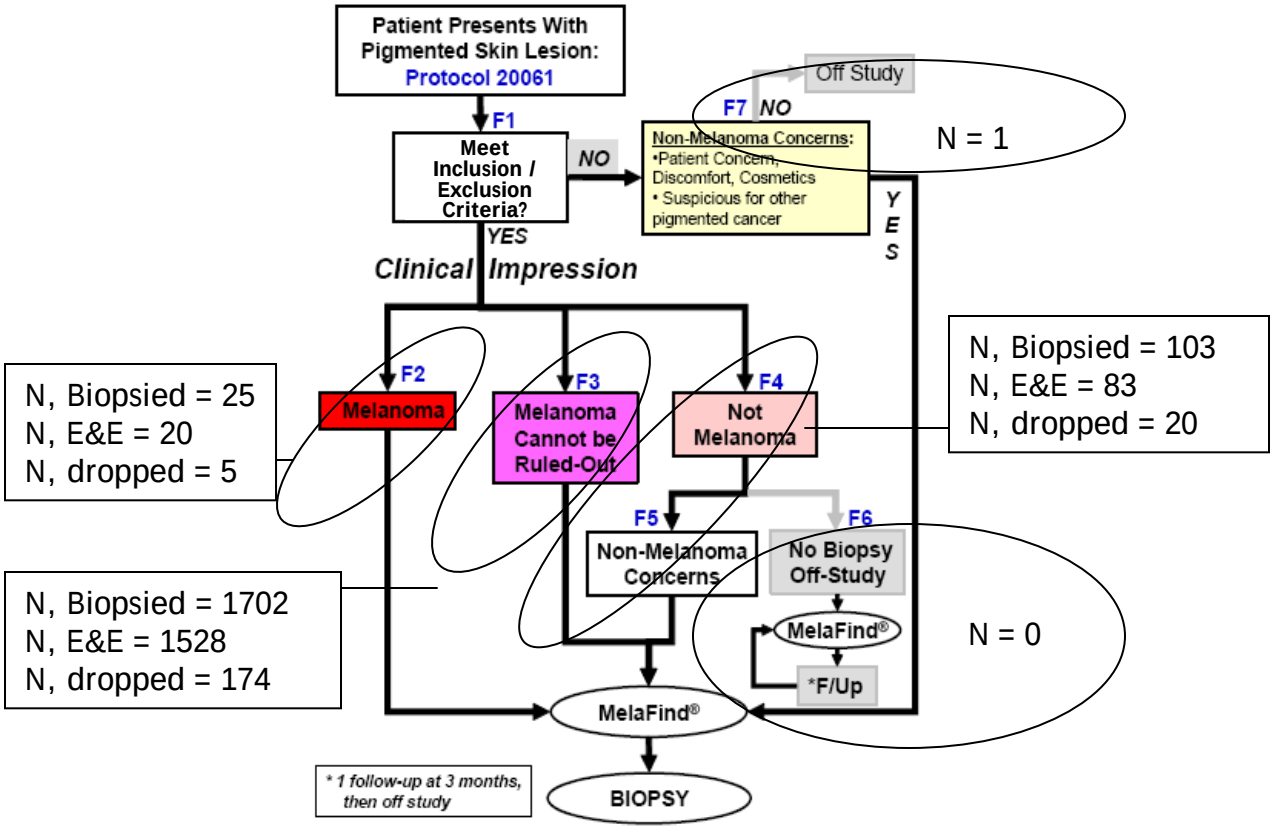
**Includes Atypical Melanocytic Proliferation/Hyperplasia (AMP/AMH)

***Includes the withdrawal, which rendered the lesion non-evaluable

Comment: Non-evaluable lesions were most common at sites with highest enrollment. No lesions were enrolled into the follow-up arm. This limits data for support of labeling for clinical practice with management that includes option for follow-up as well as biopsy.

Protocol 20061 – Lesion Disposition

Figure 6. Protocol 20061 – Study Population Schema



Comment: Cohort sizes were notably different. 10.9% (1632/1831) biopsied lesions became ineligible and non-evaluable for primary objective analysis. No lesions were enrolled to be followed rather than biopsied (F6); F3 and F4 are not surrogates for F6 because F3 and F4 were sufficiently atypical for suspicion of melanoma to warrant biopsy.

Protocol 20061 – eligible lesions with slides that completed central pathology, n = 1794

Dermatopathology N = 1794	Melanoma	High grade dysplastic nevus	Atypical melanocytic proliferation / hyperplasia	Other
Evaluable	**127** (8%)	**43** (3%)	**5** (0%)	**1457** (89%)
Unevaluable	**27** (17%)	**2** (1%)	**1** (1%)	**132** (81%)
Total	**154**	**45**	**6**	**1589**
% of Total Unevaluable	**27 / 154 = 17.5%**	**2 / 45 = 4.4%**	**1 / 6 = 16.7%**	**132 / 1589 = 8.3%**

Comment: 154 eligible lesions were malignant melanoma by dermatopathology; 27 of 154 (17.5%) were unevaluable.

Unevaluable lesion and patient characteristics, lesion distribution in F3, 4, and 5 cohorts are unknown.

The FDA Statistical Review will discuss the impact of unevaluable lesions on statistical outcome.

Protocol 20061 – Patient Characteristics for All Biopsied Lesions, n = 1831

- Gender: Males: 638 (46.1%) and Female: 745 (53.9%)
- Patient Age, 7 – 97 enrolled: 107 of 1831 lesions were in patients < 21 years old; none of these were melanoma.
- Anatomic location: lesions were most commonly on the posterior torso, anterior torso or extremity
- FitzPatrick Skin Type: most lesions were in patients with FitzPatrick Skin Type 2 and 3
- Geographic location: 1459 of 1831 lesions were in the US 'sun belt'

Comment: Covariate analysis has not been presented to allow assessment of significance of potential covariates such as patient age, lesion location or the full range of FitzPatrick Skin Type (1 – 6) and MelaFind use.

Melanoma Risk Factors for Patients with Eligible and Evaluable Lesions, n = 1632 (ref: Table 12.12)

- Personal history of basal cell carcinoma
- Personal history of squamous cell carcinoma
- Personal history of dysplastic nevi
- Personal history of melanoma
- Family history of melanoma
- Fitzpatrick Skin Type
- Natural red/blonde hair
- Blue/Green Eyes
- Outdoor summer jobs as a teenager
- Sunburns prior to age 20
- Sunburns prior to after age 20
- Number of Nevi >/= 2mm
- Atypical pigmented skin lesions
- Use of tanning beds
- History of UVA/UVB treatment

Of 127 patients with eligible and evaluable melanomas, 57 (45%) had no risk factors for melanoma. Covariate analysis not presented.

Protocol 20061 - Pivotal Study Outcomes
Clinical and Historical Characteristic Prevalence

Table 12.10. Prevalence of Clinical and Historical Characteristics of Melanoma among Eligible and Evaluable Lesions

Clinical Characteristic	Histological Diagnosis		
	Any (n = 1632)	MM/HGDN* (n = 175)	Non-MM/HGDN* (n = 1457)
Asymmetry	1257 (77.0%)	151 (86.3%)	1106 (75.9%)
Border irregularity	1196 (73.3%)	144 (82.3%)	1052 (72.2%)
Color variegation	1251 (76.7%)	153 (87.4%)	1098 (75.4%)
Diameter > 6mm	677 (41.5%)	123 (70.3%)	554 (38.0%)
Evolving**	540 (33.1%)	91 (52.0%)	449 (30.9%)
Patient concern	561 (34.4%)	78 (44.6%)	483 (33.2%)
Regression	90 (5.5%)	22 (12.6%)	68 (4.7%)
Ugly duckling	734 (45.0%)	114 (65.1%)	620 (42.6%)
*Includes diagnoses of Atypical Melanocytic Proliferation/Hyperplasia (AMP/AMH)			
**2 values of "Unknown" excluded from analysis			

Comment: MelaFind proposed indication for use is for lesions with these characteristics; 11 of 1632 E&E lesions had none of these characteristics. P20061 included 2-22mm diameter lesions. 41.5% E&E lesions had diameter >6mm. Data has not been presented stratified for diameter > or </= 6mm.

Dermoscopic evaluation

Table 12.11. Prevalence of Dermoscopic Characteristics of Melanoma among Eligible and Evaluable Lesions with Dermoscopic Evaluation by Examining Clinicians

Dermoscopic Characteristic	Histological Diagnosis		
	Any (n = 645)	MM/HGDN* (n = 88)	Non-MM/HGDN* (n = 557)
Multicomponent pattern	184 (28.5%)	29 (33.0%)	155 (27.8%)
Streaks/pseudopods	41 (6.4%)	11 (12.5%)	30 (5.4%)
Blue-white veil	34 (5.3%)	6 (6.8%)	28 (5.0%)
Branched streaks	59 (9.1%)	11 (12.5%)	48 (8.6%)
Assymetry	395 (61.2%)	62 (70.5%)	333 (59.8%)
Multiple colors	430 (66.7%)	66 (75.0%)	364 (65.4%)
Regression structures/peppering	97 (15.0%)	27 (30.7%)	70 (12.6%)
Atypical dots/globules	162 (25.1%)	24 (27.3%)	138 (24.8%)
Atypical network	242 (37.5%)	41 (46.6%)	201 (36.1%)
Atypical vasculature	40 (6.2%)	8 (9.1%)	32 (5.7%)
Border sharpness	63 (9.8%)	8 (9.1%)	55 (9.9%)
Scar-like depigmentation	37 (5.7%)	12 (13.6%)	25 (4.5%)

*Includes diagnoses of Atypical Melanocytic Proliferation/Hyperplasia (AMP/AMH)

Comment: Dermoscopy was performed in 645 of 1632 (39.5%) eligible and evaluable lesions.

Covariate analysis not presented for assessment of potentially significant covariate impact of dermoscopy on outcomes of MelaFind use.

Protocol 20061 – Eligible & Evaluable Lesion Histology

Table 12.6. The Histological Reference Standard for all Eligible and Evaluable Lesions

Lesion Type (n = 1632)	Lesion sub-type	n	%
Melanoma	**127**		**7.8**
	Invasive	70	4.3
	in situ	57	3.5
Atypical Melanocytic Hyperplasia/Proliferation	**5**		**0.3**
Nevus	**1258**		**77.1**
	Dysplastic, high-grade	43	2.6
	Dysplastic, low-grade	998	61.2
	Congenital/Congenital pattern	37	2.3
	Blue	16	1.0
	Spitz/Reed/Spindle Cell	10	0.6
	Other	154	9.4
Keratosis	**119**		**7.3**
	Seborrheic	93	5.7
	Solar/Actinic	16	1.0
	Other	10	0.6
Lentigo	**76**		**4.7**
	Solar/Actinic	31	1.9
	Other	45	2.8
Pigmented Basal Cell Carcinoma	**23**		**1.4**
Pigmented Squamous Cell Carcinoma	**10**		**0.6**
Other	**14**		**0.9**

} = Primary Endpoint MelaFind = 1

Comment: MelaFind = 1 includes Melanoma, Melanoma in situ, High Grade Dysplasia and Atypical Melanocytic Hyperplasia / Proliferation.

Study lesion mitoses data were not reported.

Protocol 20061 – Eligible & Evaluable Lesion Histology

Table 12.7. Eligible and Evaluable Melanomas

Melanoma Type (n = 127)		
Melanoma invasive	**n = 70**	**55.1%**
Superficial Spreading	60	85.7%
Lentigo Maligna Melanoma	7	10.0%
Nodular	2	2.9%
Unclassified	1	1.4%
Melanoma *in situ*	**n = 57**	**44.9%**
Superficial Spreading	31	54.4%
Lentigo Maligna	25	43.9%
Unclassified	1	1.8%

Comment: Eligible and evaluable lesions were pre-dominantly superficial spreading type. Subtypes of the 27 unevaluable melanomas are unknown. Performance data on other melanoma subtypes is limited.

Protocol 20061 - Eligible & Evaluable Lesion Breslow Thickness

Table 12.8. Breslow Thickness of Eligible and Evaluable Invasive Melanomas

Breslow Thickness	n = 70
Mean	0.41 mm
Std. Deviation	0.20 mm
Median	0.365 mm
Range	0.12 - 1.2 mm
Number of lesions <1 mm	68 (97.1%)
Number of lesions 1 - 2 mm	2 (2.9%)
Number of lesions 2.1 - 4 mm	0
Number of lesions >4 mm	0

Comment: Inclusion / exclusion criteria did not limit enrollment to T1 (<1mm thick) lesions.

Protocol 20061 does not provide data for assessment of MelaFind output on lesions thicker than 1.2mm, does not provide data representative of the T1 – T4 spectrum of melanoma w/o ulceration.

MelaFind proposed Indications for Use and Instructions for Use are not specific for T1 lesions.

Protocol 20061 – Primary Endpoints
F3 & 4 Eligible & Evaluable Lesions, n = 1612
Pathology: melanoma

Table 12.15. Primary End Points and the Results of the Pivotal Trial

Dermatologist Assessment: F3 or F4	Measured Value	Primary End Point	End Point
MelaFind® sensitivity to melanoma	98.25%	95% LCB ≥ 95%	95% LCB = 95.1% - Per one-sided test
MelaFind® specificity	9.49%	p < 0.05	p = 0.022 - Per two-sided test
Study clinician specificity (pre-biopsy)	3.71%		

E&E		Melanoma, n=114			Non-Melanoma, n=1498	
F3 & F4		Dermatologist			Dermatologist	
N = 1612 lesions		+	–		+	–
MelaFind	+	111	1		1272	68
	–	2	0		143	15

Comment: Dermatologist sensitivity = 99.1%. The clinical significance of the 5.8% difference in specificity is unclear; a clinically significant difference in specificity was not prospectively defined.

Protocol 20061: MelaFind = 1

Eligible & Evaluable Lesions, n = 1632

Pathology = melanoma, high grade dysplasia & atypical melanocytic hyperplasia / proliferation

20061 ('pivotal'): MelaFind	Melanoma (F2)	Melanoma Cannot Be Ruled Out (F3)	Not melanoma (F4)	Non-atypical pigmented lesion (F7)	All Populations
E&E	n = 20	n = 1528	n = 83		
Sensitivity	100.0% (14/14)	98.1% (156/159)	100.0% (2/2)	NA	98.3% (172/175)
Specificity	0.0% (0/6)	10.4% (142/1369)	18.5% (15/81)	0.0% (0/1)	10.8% (157/1457)
PPV	70.0% (14/20)	11.3% (156/1383)	2.9% (2/68)	0.0% (0/1)	11.7% (172/1472)
NVP	NA	97.9% (142/145)	100.0% (15/15)	NA	98.1% (157/160)

Comment: Amongst E&E lesion cohorts, while the sensitivities and negative predicative values of MelaFind were comparably high, specificities and positive predictive values were low and variable.

Clinical outcomes of MelaFind use under conditions that are extrapolated from study conditions (lesions identified by experienced dermatologists for biopsy) to lesions proposed for MelaFind Indications for Use and found in practices that include option for follow-up as well as biopsy are unclear.

Clinical outcomes are likely influenced by the proposed conditions of use; however, the proposed conditions of use have not been studied.

Protocol 20061 – Retrospective biopsy rate based upon stand-alone MelaFind output for E&E lesions

Group	Population								
	Atypical						Not Atypical		All Pigmented Lesions
	Melanoma (F2)		Melanoma Cannot Be Ruled Out (F3)		Not melanoma (F4)		Non-atypical pigmented lesion (F7)		All Populations
N, Lesions from Patients Enrolle	25		1702		103		1		1831
N, Lesions Enrolled	25		1702		103		1		1831
N, Lesions Biopsied	25		1702		103		1		1831
N, Eligible and Evaluable Lesions	20		1528		83		1		1632
MelaFind =	1	0	1	0	1	0	1	0	
Lesion	Is MM/HGDN/ AMP/AMH	Is not MM/HGDN/ AMP/ AMH	Is MM/HGDN/ AMP/AMH	Is not MM/HGDN/AMP/ AMH	Is MM/HGDN/ AMP/AMH	Is not MM/HGDN/AMP/ AMH	Is MM/HGDN/ AMP/AMH	Is not MM/HGDN/AMP/ AMH	All Diagnoses
By Physician (MD)	20	0	1528	0	0	83	0	1	1632
By MelaFind (MF)	20	0	1383	145	68	15	1	0	1632
By Dermatopathology (DP)	14	6	159	1369	2	81	0	1	1632

Comment: Because the E&E F3 ('melanoma cannot be ruled out') cohort is 76 times larger than the F2 ('melanoma') and 15 times larger than the F4 ('not melanoma') cohort – data is not directly additive and due to different risk-for-melanoma in the cohorts, biopsy rate is assessed per cohort:

F2: 0 / 20 = no difference in number of biopsies per stand-alone MF output = 1 or dermatologist

F3: 145 / 1528 = 9.5% fewer biopsies per stand-alone MF output = 1 than per dermatologist

F4: 68 / 83 = 82.0% more biopsies per stand-alone MF output = 1 than per dermatologist

MelaFind proposed indication for use is for atypical pigmented lesions not clinically identified as melanoma, e.g., F3 and F4; no data has been presented to support reliable patient or lesion selection and to validate selective use outcomes in practices with management that includes option for follow-up as well as biopsy.

Protocol 20061 – Non-melanoma Skin Cancers

Group		Population								
		Atypical						Not Atypical		All Pigmented Lesions
		Melanoma (F2)		Melanoma Cannot Be Ruled Out (F3)		Not melanoma (F4)		Non-atypical pigmented lesion (F7)		All Populations
N, Lesions from Patients Enrolle		25		1702		103		1		1831
N, Lesions Biopsied		25		1702		103		1		1831
N, Eligible and Evaluable Lesions		20		1528		83		1		1632
	MelaFind =	1	0	1	0	1	0	1	0	
	Lesion	Is MM/HGDN/ AMP/AMH	Is not MM/HGDN/ AMP/ AMH	Is MM/HGDN/ AMP/AMH	Is not MM/HGDN/AMP/ AMH	Is MM/HGDN/ AMP/AMH	Is not MM/HGDN/AMP/ AMH	Is MM/HGDN/ AMP/AMH	Is not MM/HGDN/AMP/ AMH	All Diagnoses
Melanoma Type	*in situ*	4	NA	52	NA	1	NA	0	NA	57
	Invasive	9	NA	61	NA	0	NA	0	NA	70
Melanoma Breslow Thickness	< 1 mm	8	NA	60	NA	0	NA	0	NA	68
	1 - 2 mm	1	NA	1	NA	0	NA	0	NA	2
	2.1 - 4 mm	0	NA	0	NA	0	NA	0	NA	0
	> 4 mm	0	NA	0	NA	0	NA	0	NA	0
HGDN		1	NA	41	NA	1	NA	0	NA	43
AMP/AMH		0	NA	5	NA	0	NA	0	NA	5
Dysplastic nevi, low grade		NA	5	NA	978	NA	15	NA	0	998
Other nevi		NA	0	NA	189	NA	28	NA	1	218
Non-melanoma skin cancers		NA	0	NA	23	NA	10	NA	0	33
Other non-melanocytic lesions		NA	1	NA	179	NA	28	NA	0	208
by DP & MD & MF		NA	0	NA	0	NA	15	NA	0	15
by DP & MD & not MF		NA	0	3	0	NA	66	NA	1	70

Comment: Protocol 20061 criteria included lesions with pigment i.e.: melanin, keratin, or blood.

33 E&E pigmented non-melanoma skin cancers: 23 basal cell and 10 squamous cell carcinoma

MelaFind output = 0

F3: 23 / 1528 = 1.5% more missed biopsies per stand-alone MF output = 0 than dermatologist

F4: 10 / 83 = 12% more missed biopsies per stand-alone MF output = 0 than dermatologist

MelaFind proposed indication for use is for atypical pigmented lesions not clinically identified as melanoma, e.g., F3 and F4.

MelaFind output = 1 for pigmented non-melanoma skin cancers = false negative for skin cancer.

Covariate analysis has not been presented to allow assessment of potential significance of patient, lesion (e.g.: pigment characteristics), user or other diagnostic test covariates on outcomes of MelaFind use in any population.

Protocol 20063 – e-Reader Survey Design

On-line internet based survey to

1: Determine and compare biopsy/referral sensitivity and specificity of MelaFind to the average biopsy/referral sensitivity and specificity of dermatologists.

Hypothesis: MelaFind® has biopsy/referral sensitivity at least as good as the average of dermatologists.

2: Compare the biopsy/referral sensitivity and specificity of MelaFind to the average biopsy/referral sensitivity and specificity in each of three groups of physicians: pigmented skin lesion experts, general dermatologists, and primary care physicians.

3: Compare biopsy/referral performance and diagnostic performance using areas under the corresponding receiver operating characteristic (ROC) curves that illustrate the trade-offs between sensitivity and specificity between three groups of physicians: pigmented skin lesion experts, general dermatologists, and primary care physicians.

3.1: Determine the interobserver variability in each of the above metrics within each of the caregiver groups.

Protocol 20063 – e-Reader Study Design Inclusion / Exclusion Criteria

Physicians participating in this study were considered eligible if:

1) a board certified dermatologist/internist:
   1. Primary Care Physician (PCP) – defined as a board certified physician who delivers primary care service to adult patients. This category includes internists, general practitioners, family practitioners, and geriatricians.
   2. Pigmented Skin Lesion Expert (PSLE) – defined as a board certified dermatologist who spends at least 25% of his/her clinical time evaluating pigmented skin lesions.
   3. General Dermatologist (GD) – defined as a board certified dermatologist who spends less than 25% of his/her clinical time evaluating pigmented skin lesions.
2) not a pediatrician;
3) did not participate in studies under MELA Protocols 20061 or 20081; and,
4) completed survey for at least 78 (60%) out of 130 lesions in the study.

Protocol 20063 – Reader Study Design
Physician - Reader Characteristics

Dermatologist type was determined by answers to an Intake Survey.

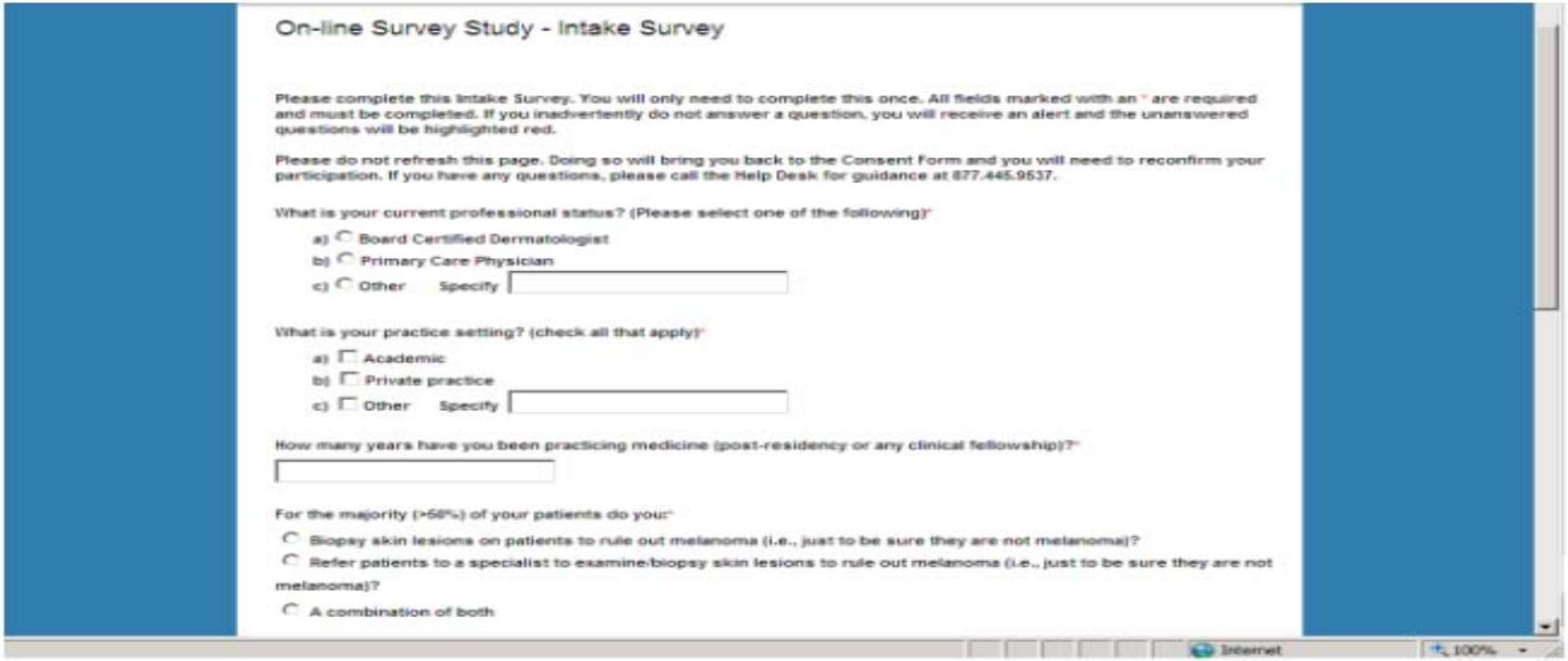


Figure 3. On-line Console: Intake Survey

Table 3. Characteristics of Participating Physician Readers

Physician reader characteristic	PCP N = 45 n (%)	GD N = 46 n (%)	PSLE N = 64 n (%)
Years practicing			
Mean (SD)	16.5 (9.0)	14.5 (10.2)	11.5 (7.7)

Protocol 20063 – Reader Survey Design
Lesion Inclusion / Exclusion Criteria

- Included 130 of the total of 1632 lesions in Protocol 20061 (pivotal) study: less than 10% of the 1831 enrolled lesions,
  - Lesions were selected with goal for 1 to 1 melanoma to non-melanoma ratio - not the prevalence of disease in the pivotal study.
    - 65 melanomas randomly selected by the statistician from among 97 of 127 pre-selected melanomas
    - 65 non-melanomas selected by the study's medical director (not independent third party as per protocol) based upon image quality review to match the frequency of different non-melanoma histological types represented in Protocol 20061, as well as match the age and anatomic site of the selected melanomas
- Excluded diagnosis of severely dysplastic nevus (severe atypia, n for high grade dysplasia = 0) or atypical melanocytic hyperplasia / proliferation - because 'there is currently no consensus on the clinical management of lesions in these categories'.

Protocol 20063 – Reader Survey Design
Lesion Characteristics

Table 8. Breslow Thickness

Breslow Thickness	n = 36
Mean	0.42 mm
Std. Deviation	0.23
Median	0.39 mm
Range	0.12 - 1.20 mm
Number of lesions < 1 mm	35 (97%)
Number of lesions 1 - 2 mm	1 (3%)
Number of lesions 2.1 - 4 mm	0 (0%)
Number of lesions > 4mm	0 (0%)

Comment: Invasive melanomas reviewed in Protocol 20063 were thin with a median Breslow thickness of only 0.39 mm. Only 1 melanoma was thicker than 1 mm.

Figure 4. On-line Console: Case Survey

Comment: Each of the 130 study cases began with a full case history and images (Figure 4). Participants were instructed to adjust their computer monitor settings to 1024 x 768 resolution to maintain consistency between computers. Monitor and color intensity do not appear to have been not standardized in the protocol.

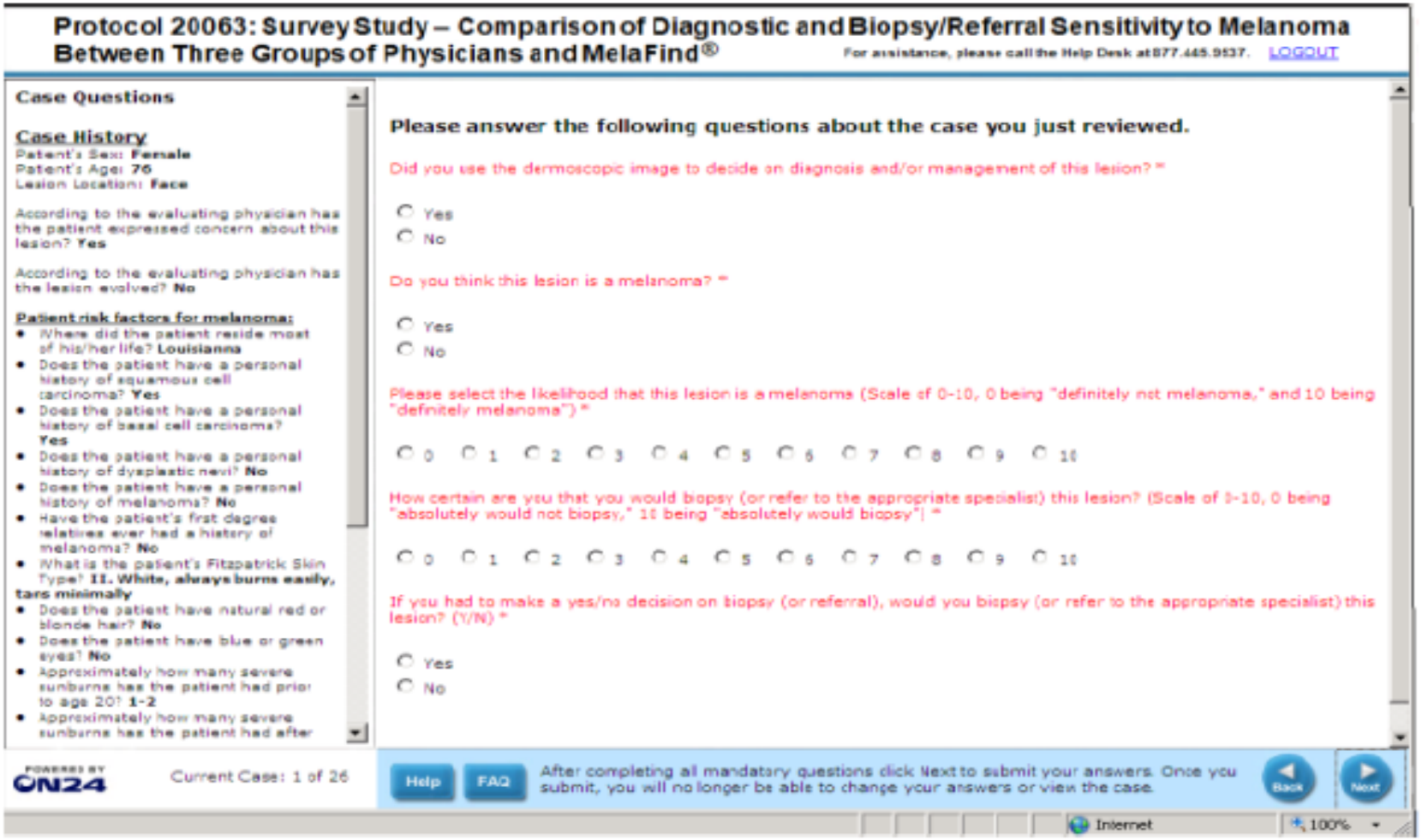


Figure 5. On-line Console: Case Questionnaire

If a physician did not indicate that he/she would biopsy the lesion due to concern that it is a melanoma, his/her response on the corresponding 11-point scale was to be set to 0.

If a physician indicated that he/she does not think that a lesion is melanoma, his/her response on that corresponding 11-point scale was to be set to 0.

Protocol 20063 – Reader Study Data

For MelaFind: Responses consisted of the dichotomous outcome of the *recommendation for biopsy (Y/N).*

For a study physician:

- *Biopsy/referral sensitivity:* estimated as the proportion of the melanomas that the physician would biopsy or refer to the appropriate specialist (i.e., *Question #5 = Yes*).
- *Biopsy/referral specificity:* estimated as the proportion of the other lesions (non-melanoma, non-severely dysplastic nevus and non-atypical melanocytic hyperplasia/proliferation) that the physician would not biopsy or refer to the appropriate specialist (i.e., *Question #5 = No*).
- *Diagnostic sensitivity:* estimated as the proportion of the melanomas that the physician identifies as melanoma (i.e., *Question #2 = Yes*).
- *Diagnostic specificity:* estimated as the proportion of the other lesions (non-melanoma, non-severely dysplastic nevus and non-atypical melanocytic hyperplasia/proliferation) that the physician does not identify as melanoma (i.e., *Question #2 = No*).
- *Receiver operating characteristic (ROC) curves:* estimated based on responses to the *11-point scales on how likely the lesion is a melanoma* as indicated by the physician, *and how certain the physician is that he/she would biopsy (or refer) the lesion.*

Protocol 20061 and 20063 Comparison of Methods of determining 'need for biopsy'

MelaFind: 1 (positive) or 0 (negative)
Dermatopathologist: histologic diagnosis

20061 (Pivotal) Study: real-time patient & lesion assessment
- All enrolled lesions deemed to need biopsy; No lesions not considered to need biopsy enrolled
– Stratified by dermatologists on a 3-point scale:
  - Is melanoma or
  - Cannot rule-out melanoma or
  - Is not melanoma

20063 (Reader) Survey: patient history and skin lesion image reviewed and stratified by
- General and pigment lesion expert dermatologists; Primary Care Providers (PCPs) excluded for Objective 1
- General and pigment lesion expert dermatologists and PCPs for Objectives 2 and 3

On a 2-point scale: yes / no, or
On an 11-point scale: 0 through 10

Comment: Due to different methods of skin lesion rating: 2-point vs 3-point vs 11-point, different conditions of rating: after decision for biopsy (20061) vs before decision for biopsy (20063), and different physician backgrounds, clinically, the Reader survey data is not applicable to pivotal study data interpretation.
FDA Statistical Review will discuss statistical study outcomes.

Summary Clinical Comment

T classification	*Thickness (mm)*	*Ulceration Status/Mitoses*
T1	≤1.0	a: w/o ulceration and mitosis <1/mm^2.
		b: with ulceration or mitoses ≥1/mm^2.
T2	1.01–2.0	a: w/o ulceration.
		b: with ulceration.
T3	2.01–4.0	a: w/o ulceration.
		b: with ulceration.
T4	>4.0	a: w/o ulceration.
		b: with ulceration.

[a]*Reprinted with permission from AJCC: Melanoma of the skin. In: Edge SB, Byrd DR, Compton CC, et al., eds.: AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010, pp 325-44.*

1. *MelaFind is categorized as a diagnostic device: stand-alone or adjunctive, depending on user experience and or preference.*

Two (n = 2) study lesions were 1 – 2 mm thick; maximum study lesion thickness was 1.2mm; mitoses data not reported.

Protocol 20061 data is not representative of the T1 – T4 spectrum of melanoma w/o ulceration. MelaFind proposed Indications for Use and Instructions for Use are not specific for T1 lesions.

Summary Clinical Comment

2. As to '…use when a physician chooses to obtain additional information before making a final decision to biopsy to rule out melanoma.'

All enrolled lesions had final decision to biopsy; no data has been presented for device use 'when a physician chooses to obtain additional information before making a final decision to biopsy to rule out melanoma.'

3. Based upon retrospective biopsy rate assessment, Protocol 20061 lesions with clinical assessment of 'not melanoma' have 68 / 83 = 82.0% more biopsies per stand-alone MF output = 1 than per dermatologist.
4. Clinical outcomes of MelaFind use under conditions extrapolated from study conditions (lesions identified by experienced dermatologists for biopsy) to lesions proposed for MelaFind Indications for Use and found in practices that include option for follow-up as well as biopsy are unclear, but are likely influenced by the proposed conditions of use. MelaFind has not been studied under the proposed conditions of use.

Summary Clinical Comment

5. As to use ‘for evaluation of clinically atypical cutaneous pigmented lesions (those having one or more clinical or historical characteristics of melanoma, such as asymmetry, border irregularity, color variegation, evolving, patient concern, regression, "Ugly duckling“)’

Whether high or low risk for melanoma, most enrolled lesions had some of these characteristics. Covariate analysis has not been presented to allow assessment of potential significance of patient, lesion, user or other diagnostic test, e.g.: dermatoscopy, covariates on outcomes of MelaFind use in any population.

6. As to ‘use for evaluating clinically atypical cutaneous pigmented lesions diameter greater than 6 mm’.

Lesions with 2 to 22 mm diameter were included; 41.5% of lesions had diameter >6mm. Data has not been presented stratified for < 6 and >/= 6mm to allow assessment of MelaFind performance for the indicated diameter: 6 to 22mm.

7. No data has been presented to support reliable patient or lesion selection and to validate outcomes of the proposed selective use in practices with management that includes option for lesion follow-up as well as biopsy.

Summary Clinical Comment

8. Patient Age: 107 of 1832 lesions were in patients < 21 years old. Covariate analysis has not been presented to allow assessment of potential significance of patient age and MelaFind use.

9. FitzPatrick Skin Type: most lesions were in patients with FitzPatrick Skin Type 1 – 3; Covariate analysis has not been presented to allow assessment of potential significance of the full range of FitzPatrick Skin Type (1 – 6) and MelaFind use.

10. As to the Reader survey & Pivotal study correlation

Reader survey data is not clinically applicable to pivotal study data interpretation due to substantive differences that have not been established to be poolable as to

- Methods of skin lesion rating: 3-point vs 2-point and 11-point scales,
- Lesion rating conditions: after decision for biopsy (20061) / before decision for biopsy (20063) and
- Evaluator backgrounds.

FDA Presentation

- Introduction
- Background on Protocol Agreement (Protocol 20031)
- FDA Regulations Used for P090012
- Clinical Studies Overview
- Statistical Overview
- Clinical Conclusions
- Post-Approval Study
- Panel Questions

General and Plastic Surgery Devices Advisory Panel Meeting

MelaFind by MELA Sciences

FDA Statistical Review

Bipasa Biswas
Diagnostic Devices Branch
Division of Biostatistics
Office of Surveillance and Biometrics
FDA, Center for Devices and Radiological Health

Outline

- Protocol 20061, Pivotal Study

  -Study design

  -Results

  -Concerns with study in Protocol 20061
- Protocol 20063, Reader Study

  -Analysis of reader study

  -Concerns with study in Protocol 20063
- Summary of studies in Protocols 20061 and 20063

Protocol 20061, Pivotal Study

- 23 dermatologists with expertise in early melanoma detection and management of pigmented skin lesions examined 1384 patients.
- Only atypical lesions that underwent biopsy were enrolled in the study.
- 1835 lesions registered for the study (1384 patients).
  - 22 lesions excluded (4, 1, and 17 because of registration error, patient withdrawal, and ineligibility)
- 1813 eligible lesions (1375 patients).
  - 19 had no pathology results.
- 1794 eligible lesions with pathology results(1364 patients).
  - 162 lesions were un-evaluable by MelaFind (155 failed QC or had no image file; 7* were acquired during phantom self-test failure week)
- 1632** eligible and evaluable lesions (1257 patients).
  - 20 lesions with dermatological diagnosis of “Melanoma”
- 1612 eligible and evaluable lesions with dermatological diagnosis of ‘Melanoma cannot be Ruled Out’ or ‘Not Melanoma’ (1242 patients).

* 7 MelaFind results were not missing in the electronic data provided by sponsor.
**1631 of these 1632 atypical lesions were initially screened for suspicion of melanoma.

MelaFind results on all eligible lesions with histopathology available (n=1794)

		Melanoma	Not Melanoma	Total	%
MelaFind	+	125	1347	1472	82.1%
	Un-evaluable	**27**	**135**	**162**	**9.0%**
	-	2	158	160	8.9%
	Total	154	1640	1794	100%

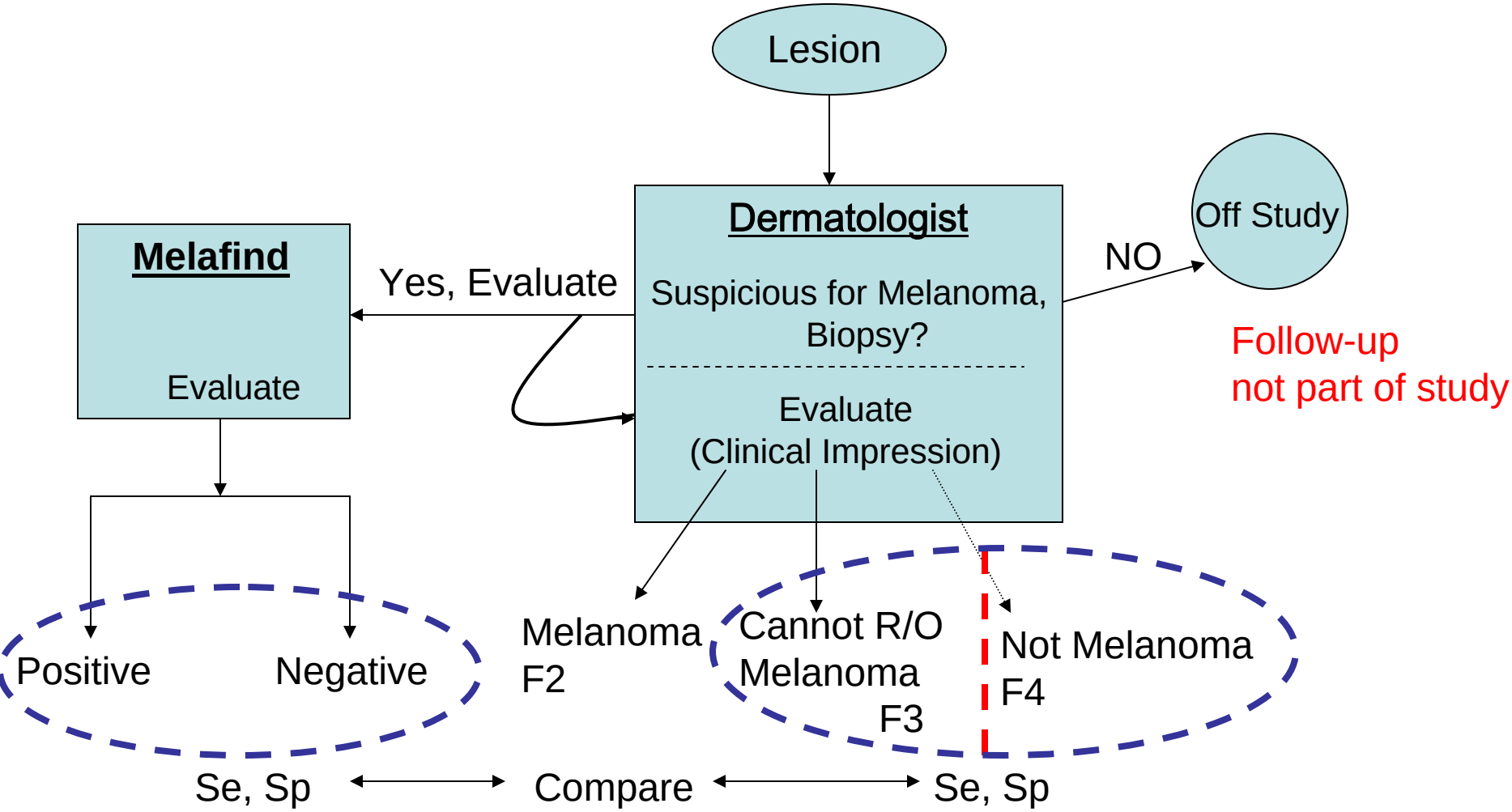
Predictive value of MelaFind –: 1.3% (2/ 160)

Predictive value of MelaFind +: **8.5%** (125/1472)

Predictive value of un-evaluable: **16.7%** (27/ 162)

Predictive value of Un-evaluable MelaFind Result significantly > than predictive value of positive MelaFind Result ($p < 0.002$)

Study Sample



Sensitivity and Specificity of the dermatologists

- **Biopsy/referral sensitivity** for each dermatologist is estimated as the proportion of the melanomas that the dermatologist would biopsy.
- **Biopsy/referral specificity** for each dermatologist is estimated by the proportion of other lesions (non-melanoma, non-severely dysplastic nevus and non atypical melanocytic hyperplasia/proliferation) that the dermatologist would not biopsy.
- **Diagnostic sensitivity** for each dermatologist is estimated as the proportion of the melanomas that the dermatologist identifies as melanoma.
- **Diagnostic specificity** for each study dermatologist is estimated by the proportion of other lesions (non-melanoma, non-severely dysplastic nevus and non atypical melanocytic hyperplasia/proliferation) that the dermatologist does not identify as melanoma.

Primary Aims, Protocol 20061

- **Primary analysis population**
  - excludes lesions for which investigator diagnosis is "MELANOMA“ (F2),
  - includes lesions for which investigator diagnosis is "Melanoma CAN NOT be ruled out“ (F3) or "NOT Melanoma” (F4).
- **Primary hypotheses to be shown:**
  - MelaFind’s sensitivity is at least 95% at a 95% confidence level.
  - MelaFind’s specificity is superior to specificity of study dermatologists.

Sensitivity for Melanoma, N = 114 (F3-F4 Eligible and Evaluable Lesions)

		Melanoma			Non-Melanoma	
		Dermatologist			Dermatologist	
		+	–		+	–
MelaFind	+	**111**	**1**		1272	68
	–	**2**	**0**		143	15

	Sens	95% CI		90% CI	
MelaFind†	98.3%	**94.1%**	99.7%	**95.0%**	99.5%
Investigator†	99.1%	95.7%	99.9%	96.3%	99.9%
Difference*	– 0.9%	– 5.5%	3.3%	– 4.4%	2.4%

95% Sensitivity: **met** with 90% CI (1-sided 95% LCB),
not met with 95% CI (2-sided 95% LCB).

†CI computed with Blythe-Still-Casella method
*CI is exact based on inverting 2 one-sided tests using standardized statistic

Specificity for Melanoma, N = 1498 (F3-F4 Eligible and Evaluable Lesions)

		Melanoma			Non-Melanoma	
		Dermatologist			Dermatologist	
		+	–		+	–
MelaFind	+	111	1		**1272**	**68**
	–	2	0		**143**	**15**

Sponsor Analysis

	Spec*	95% CI**	
MelaFind	9.5%	6.1%	12.9%
Investigator	3.7%	0.8%	6.7%
Difference	5.8%	0.9%	10.6%

Specificity Diff > 0: met with 95% CI (2-sided 95% LCB),

Average Specificity across examiners. ** CI for average from Student's t-distribution with 22 degrees of freedom

Specificity for Melanoma, N = 1498 (F3-F4 Eligible and Evaluable Lesions)

		Melanoma			Non-Melanoma	
		Dermatologist			Dermatologist	
		+	–		+	–
MelaFind	+	111	1		1272	68
	–	2	0		143	15

FDA Analysis

	Spec†	95% CI††	
MelaFind	10.6%	9.7%	13.2%
Investigator	5.5%	4.5%	7.3%
Difference	5.1%	3.3%	7.7%

Specificity Diff > 0: met with 95% CI (2-sided 95% LCB),

†Pooled estimate of Specificity.††95% Bootstrap percentile intervals.

Intention to Diagnose (ITD) Lesions Analysis (n=1770), Protocol 20061

- An intent to diagnose analysis was performed on all lesions with dermatological diagnosis “Melanoma cannot be Ruled Out” or “Not Melanoma”, that were eligible and had a pathology available (n=1770). The missing un-evaluable results by MelaFind are considered negative for this analysis.

		Melanoma			Non-Melanoma	
		Dermatologist			Dermatologist	
		+	–		+	–
MelaFind	+	112	1		1278	68
	Un-evaluable (missing)	22	0		113	16
	–	2	0		143	15

	Sens	95% CI	Spec	95% CI
MelaFind	82.5%	(75.6%, 88.3%)	17.6%	(16.0%, 20.0%)

Sensitivity + specificity=100.1 %, (95% CI 92.7% to 106.6%)
MelaFind was not statistically significantly better than chance.

Concerns with Protocol 20061

- In the pivotal study, there is inadequate data to determine the performance of MelaFind on all clinically atypical lesions (non-suspicious and suspicious for melanoma) because enrolled atypical lesions were screened for suspicion, and the performance of MelaFind was evaluated on these lesions.
- MelaFind was un-evaluable for 9.0% (162/1794) of the lesions and the predictive value of MelaFind un-evaluable result (16.7%) is significantly greater than the predictive value of MelaFind positive result (8.5%) ($p<0.002$).
- Including un-evaluable lesions by MelaFind in the primary aim analysis changes performance of MelaFind and it is not significantly better than chance. (Sensitivity + Specificity =100.1%; 95% CI: 92.7% to 106.6%)

Protocol 20063, Reader Study

- Sixty-five melanomas were selected at random by the Emory statistician from among 97 melanomas that were eligible, evaluable and met the image quality.
- "308 eligible and evaluable non-melanomas from Protocol 20061 were selected at random from the pool of 1457 available lesions. These 308 lesions were then subjected to image quality review by the Medical Director. Of the resulting pool of 236 non-melanomas, 65 were selected to match the frequency of different histological types represented in Protocol 20061"
- A total of 155 physicians in three categories Primary Care Physicians (PCPs) 45; General Dermatologists (GDs) 46 and Pigmented Skin Lesion Experts (PSLEs) 64 evaluated the selected lesions.

Aims of the Reader study

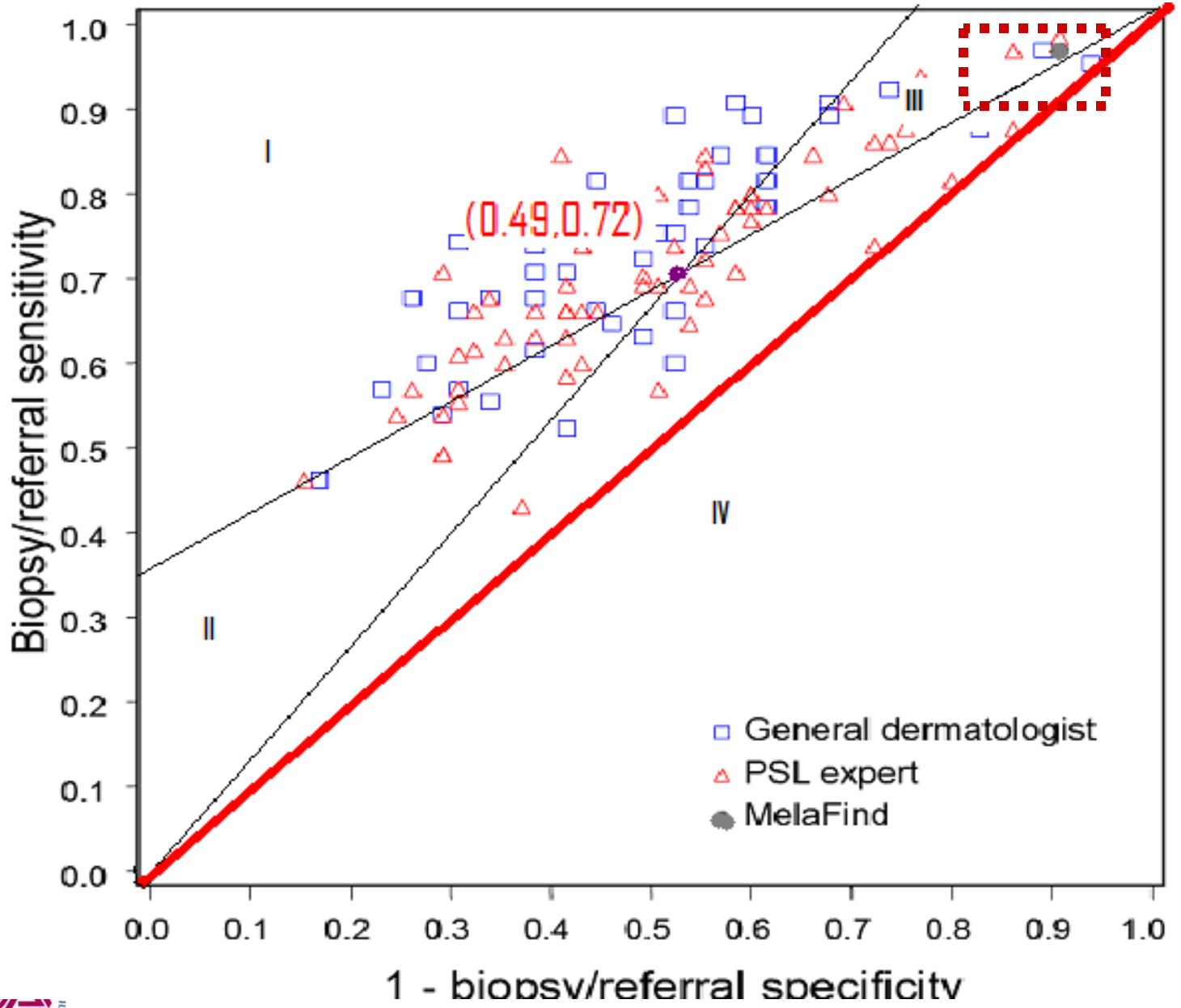
- To determine and compare the biopsy/referral sensitivity and specificity to the average biopsy/referral sensitivity and specificity of general dermatologists and pigmented skin lesions experts.
- To compare the biopsy/referral sensitivity and specificity of MelaFind to the average biopsy/referral sensitivity and specificity of the three physician groups.
- To compare the area under the ROC curve based on a 11 point scale (0 to 10) of the three groups of physicians.
- To determine inter-observer variability within each physician group.

Comparison of biopsy/referral sensitivity and specificity of MelaFind to All Dermatologists

	Sensitivity	95% CI	Specificity	95% CI
Survey Derms (GDs and PSLEs)	72.0%	(66.0%,78.0%)	51.0%	(43.0%, 58.0%)
MelaFind	97.0%	(90.0%,99.0%)	9.0%	(4.0%, 19.0%)
Difference	25%	(18.0%, 32.0%)	-42.0%	(-51.0%,-31.0%)

	MelaFind	Survey Dermatologists
Likelihood ratio positive= sensitivity/(1-specificity)	1.07	1.47
Likelihood ratio Negative = (1-sensitivity)/specificity	0.33	0.55

Analysis of the results obtained for primary aim



Region I: Both PPV and NPV better for test than average of dermatologists.
Region II: PPV is better; NPV is inferior to average of dermatologists.
Region III: NPV is better; PPV is inferior to average of dermatologists.
Region IV: Both PPV and NPV are inferior; overall region of inferiority than average of dermatologists.

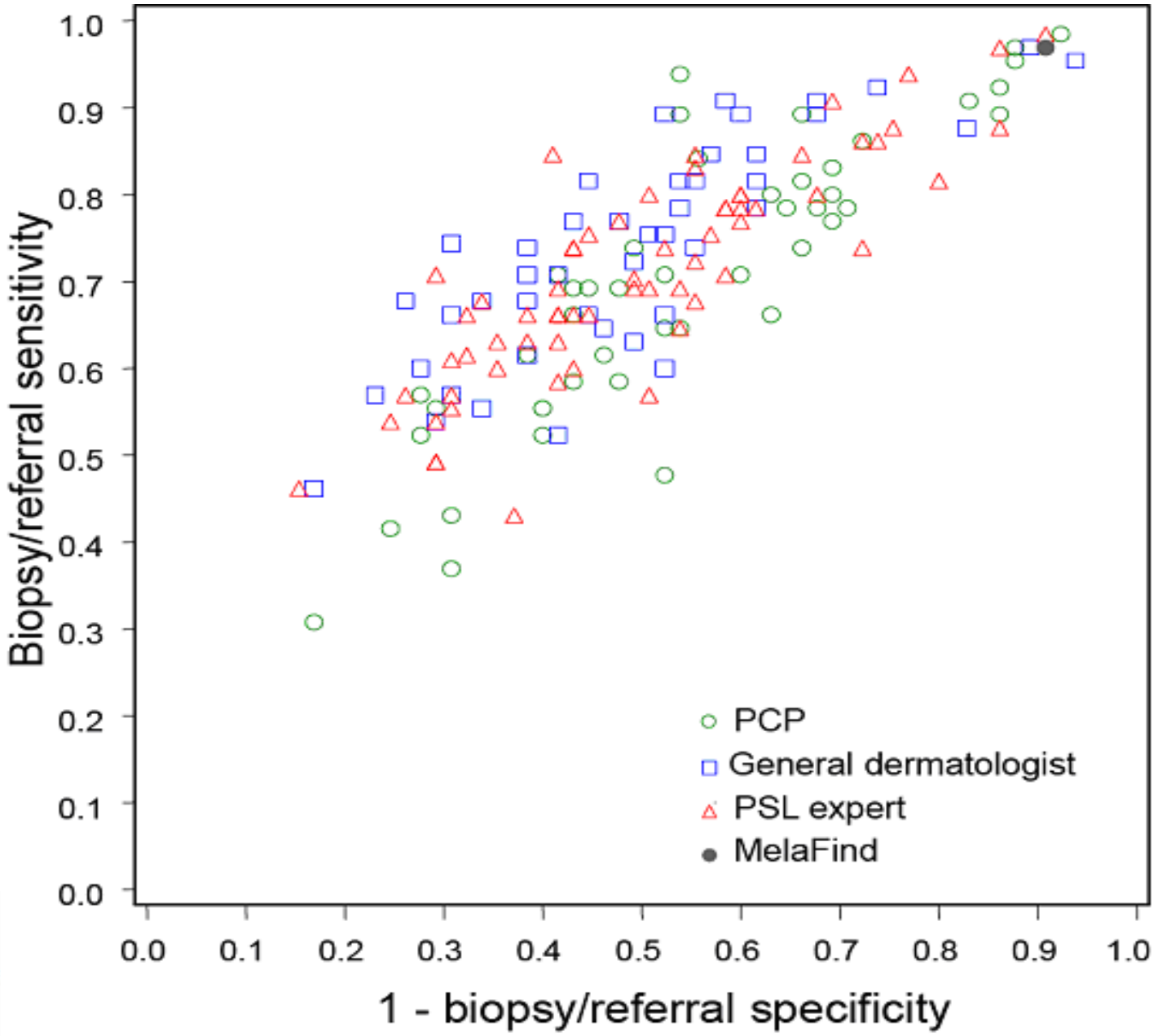
Interpretation of the graph

- The performance of MelaFind is in region III in comparison to the average of the survey dermatologists (GDs and PSLEs).
- The performance of MelaFind is at the upper right corner with sensitivity 97.0% (95% CI: 90.0% to 99.0%) and specificity 9.0% (95% CI: 4.0% to 19.0%).

Biggerstaff BJ (2000). Comparing diagnostic tests: a simple graphic using likelihood ratios. Statistics in Medicine, 2000; 19:649-663.

Comparison of biopsy/referral sensitivity and specificity of MelaFind to the three groups of Clinicians

	Sens	95% CI	Spec	95% CI
MelaFind	97.0%	(90.0%,99.0%)	9.0%	(4.0%,19.0%)
PCP	71.0%	(64.0%,78.0%)	45.0%	(37.0%,53.0%)
Difference (MF-PCP)	26.0%	(19.0%,34.0%)	-36.0%	(-46.0%,-25.0%)
GD	73.0%	(67.0%,80.0%)	51.0%	(43.0%, 60.0%)
Difference (MF-GD)	24.0%	(16.0%, 31.0%)	-42.0%	(-53.0%, -31.0%)
PSLE	71.0%	(65.0%, 77.0%)	50.0%	(42.0%, 58.0%)
Difference (MF-PSLE)	26.0%	(19.0%, 33.0%)	-41.0%	(-51.0%, -30.0%)


Biopsy/referral sensitivity
1 - biopsy/referral specificity
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
PCP
General dermatologist
PSL expert
MelaFind

Performance of MelaFind in comparison to the Survey Physicians

A likelihood ratio was calculated for each physician in the reader study and a graph was plotted for each physician and the regions in comparison to each physician was divided into four regions.
Where
Region I: Both PPV and NPV better for the test than the physician.
Region II: PPV is better; NPV is inferior to the physician..
Region III: NPV is better; PPV is inferior to the physician..
Region IV: Both PPV and NPV are inferior; overall region of inferiority than the physician.
.

MelaFind's performance in comparison to all physicians

Regions

I	II	III	IV	Total
8	1	130	16	155

Compared to all physicians in the reader study, MelaFind was superior (performance in region I) only to 8 **(5%)** out of 155 physicians and inferior (performance in region IV) to 16 (**10%)** of 155 physicians.

Concerns with Protocol 20063, Reader study

- Non-melanoma lesions selected in the reader study were not a random subset of the lesions in clinical study 20061, which could have biased study results.

- The melanomas and the non-melanomas were selected based on image quality and there could be potential for selection bias.

Concerns with Protocol 20063, Reader study (cont)

- The un-evaluable lesions by MelaFind in the clinical study (20061) were excluded from the reader study. Performance of the study physicians can not be generalized to the intent to diagnose/biopsy population.
- Jointly, the sensitivity and specificity of MelaFind in the selected set of lesions does not indicate that MelaFind is superior to the average of the performance of the dermatologists (GDs and PSLEs). In fact MelaFind was observed to be inferior to 16 (10%) of the 155 physicians (GDs, PSLEs and PCPs) and superior to only 8 (5%).

Summary of clinical studies in Protocols 20061 and 20063.

- Only a subset of intended use population studied (20061) (atypical lesions initially screened for suspicion of melanoma and sent for biopsy)
  - No performance data on device used by non dermatologist
- 9.0% (162/1794) of eligible lesions with pathology had un-evaluable MelaFind result.
  - The predictive value of MelaFind un-evaluable (16.7%) is significantly greater than the predictive value of MelaFind positive result (8.5%) ($p<0.002$).
- Including un-evaluable lesions in the primary analysis changes performance of MelaFind significantly. MelaFind's estimates were significantly no better than chance when all un-evaluable lesions are included in the primary analysis (Sensitivity + Specificity =100.1%; 95% CI: **92.7%** to 106.6%).

Summary of clinical studies in Protocols 20061 and 20063 (cont)

- The primary analysis finding of sensitivity was not robust. It barely met using the 1-sided 95% lower confidence bound. It would fail if the 2-sided 95% lower confidence bound was used.
- It would fail if one more melanoma had been missed using either 1-sided or 2-sided 95% lower confidence bound. The number of melanoma lesions eligible (154), eligible and evaluable (127), and analyzed in the primary analysis (114) were all greater than the number stated in the agreement (93).

Summary of clinical studies in Protocols 20061 and 20063.

- Reader study (20063) was performed on a subset of lesions from the eligible and evaluable lesions in the pivotal study already screened for suspicion of melanoma. The reader study excluded lesions un-evaluable by MelaFind. The results of the reader study cannot be generalized to the intent to diagnose/biopsy population.
- Non-melanoma lesions selected in the reader study were not a random subset of the lesions in clinical study 20061, which could have biased study results
- Jointly, the sensitivity and specificity of MelaFind in the selected set of lesions does not indicate that MelaFind is superior to the average of the performance of the dermatologists (GDs and PSLEs). In fact MelaFind was observed to be inferior to 16 (10%) of the 155 physicians (GDs, PSLEs and PCPs) and superior to only 8 (5%).

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- Statistical Overview
- Clinical Conclusions
- Post-Approval Study
- Panel Questions

P090012
Clinical Conclusions

Pivotal Study, Protocol 20061
Reader Study, Protocol 20063

Peter Rumm, MD, MPH, FACPM

Deputy Director

Division of Surgical, Orthopedic, and Restorative Devices
Office of Device Evaluation

General and Plastic Surgery Devices
Panel Meeting
November 18, 2010

MelaFind Protocol 20061 Clinical Concerns

1) **Inadequate data to evaluate the risk/benefit** (number of unnecessary biopsies to potentially find melanomas) of MelaFind performance in clinical use on clinically atypical lesions use - versus the standard lesion management of care.

- There is currently no data or adequate instructions for use to support the use of MelaFind results in order to guide the clinical decision to determine whether to biopsy or to not biopsy an atypical lesion.
- There is inadequate data to determine any true value added for MelaFind for use by a dermatologist or other provider.

MelaFind Protocol 20061 Clinical Concerns

2) Selection Biases:

- Enrolled atypical lesions were dependent upon individual dermatological assessment of whether that atypical lesion was suspicious of melanoma. The enrolled atypical lesions were further selected upon MelaFind's ability to evaluate the lesion.
- Sub-groups F2, F3, and F4 do not represent the real world classification of atypical lesions since sub-groups are suspicious of melanoma, and may be classified differently among physicians (i.e. another physician's F4 sub-group may include lesions from the F2 and F3 sub-groups).
- Inclusion of the "Not Melanoma" (F4) sub-group is not clinically informative since it only includes 1 lesion that was a melanoma (a single melanoma in situ that was already pre-selected as a suspicious and/or atypical lesion, and was biopsied).

MelaFind Protocol 20061 Clinical Concerns

3) No Clinical Benefit demonstrated for use by a dermatologist:

- When detecting Melanomas and High-Grade Lesions, MelaFind's diagnostic biopsy ratio was **7.6:1** compared to the dermatologist's **7.9:1**.
- Used independently, MelaFind missed 2 melanomas in an enriched population of melanomas when making the decision to biopsy an atypical lesion.
- Among the eligible and evaluable (EE) atypical lesions that were screened for suspicion of melanoma, MelaFind had a Positive Predictive Value (PPV) of 11.7%.

MelaFind Proposed Indications for Use Concerns

4) Sponsor's proposed Indications for Use defines the user to be at the physician or healthcare provider level:

- Protocol 20061 studied MelaFind use only with board certified dermatologists who were considered experts.
- There is data regarding a study testing the capabilities of MelaFind when used by a physician or healthcare professional on an atypical lesion prior to making a decision whether or not the atypical lesions should be biopsied.
- The data provided in Protocol 20061 does not support the use of MelaFind for non board-certified dermatologist use.

MelaFind Proposed Indications for Use Concerns

5) The sponsor intends to educate physicians on selecting the appropriate atypical lesions on which MelaFind is to be used.

- There is no current data demonstrating that the sponsor can educate a physician to properly identify atypical lesions for MelaFind use.

MelaFind Proposed Indications for Use Concerns (cont)

6) MelaFind's indication, *a tool to aid in the detection of early melanoma for physicians*. MelaFind's indication for detection of early melanoma is not supported by the data.
   - Protocol 20061 demonstrated MelaFind diagnostic results of a pre-selected atypical lesion by a dermatologist.
   - No data is presented to demonstrate that MelaFind can aid in the detection of early melanoma for physicians.
   - The indication at usage is misleading because MelaFind is not solely aimed at detecting early melanoma, but also lesions such as high-grade dysplastic nevus (dysplastic nevus with severe atypia), and atypical melanocytic proliferation/hyperplasia.
   - MelaFind cannot differentiate between early melanoma and other melanoma.

MelaFind Proposed Indications for Use Concerns (cont)

- Melanomas in this study were deemed to be early lesions by the sponsor.
  - The proposed IFU defines early melanoma as non-ulcerated, not bleeding, or less than 2.2 cm in diameter.
  - The NIH Consensus Development Conference Statement on Diagnosis and Treatment of Early Melanoma, January 27-29, 1992 defines early melanoma as: melanoma in situ and thin invasive lesions less than 1 millimeter in depth.

MelaFind Protocol 20063 Clinical Concerns

- Selection Bias:
  - Lesions selected in the reader study are a subset of the E&E lesions in Protocol 20061 which were initially screened for the suspicion of melanoma.
  - Lesions selected had a 1:1 ratio of melanoma and non-melanoma.
  - Lesion selected were based on image quality.
  - Excludes the 157 (8.66%) lesions that had no MelaFind result (failed QC, no image file) and HGDN lesions – this includes 27 “un-evaluable” melanomas.

MelaFind Protocol 20063 Clinical Concerns

- The use of photographs of lesions (plus some supportive information on the history of the lesion) has not been demonstrated to be truly comparable to the full history and physical examination of lesions by providers.
- Results of this study cannot be used to support any conclusions, including being able to measure potential biopsy/referral sensitivity of physicians from the atypical lesion population of Protocol 20061.

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Post-Approval Study Considerations for MelaFind MELA Sciences

Hong Cheng, MD, PhD, MPH

Division of Epidemiology
Office of Surveillance and Biometrics / CDRH

General and Plastic Surgery Devices Advisory Panel
November 18, 2010

Reminder

- The discussion of a PAS prior to FDA determination of device approvability should not be interpreted to mean FDA is suggesting that the device is safe and effective.

- The plan to conduct a PAS does not decrease the threshold of evidence required by FDA for device approval.

- The premarket data submitted to the Agency and discussed today must stand on its own in demonstrating a reasonable assurance of safety and effectiveness and an appropriate risk/benefit balance.

General Principles for PAS

- Objective is to evaluate device performance and potential device-related issues in a broader population over an extended period of time after premarket establishment of reasonable device safety and effectiveness.

- Post-approval studies **should not** be used to evaluate unresolved issues from the premarket phase that are important to the initial establishment of device safety and effectiveness.

PAS – Established Need

- Gather essential postmarket information
  - Longer-term performance including effects of re-treatments & approved product changes
  - Real-world device performance (patients and clinicians)
  - Effectiveness of training programs
  - Sub-group performance
  - Outcomes of concern in the post-market setting (safety and effectiveness)
- Account for Panel recommendations

Important Post Market Issues

- It is important to note that Post-approval studies **should not** be used to evaluate unresolved issues from the premarket phase.

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- Pamela Reynolds – BIMO Review
- Alan Gion– Manufacturing Review
- Tania Schuppius – Project Manager
- Yolanda Adams – Staff support

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Back-Up Slides (Statistical)

Sensitivity for Melanoma on all Lesions

("Melanoma", "Melanoma cannot be Ruled Out", "Not Melanoma")

		Melanoma			Non-Melanoma	
		Dermatologist			Dermatologist	
		+	–		+	–
MelaFind	+	124	1		1279	68
	–	2	0		143	15

	Sens	95% CI		90% CI	
MelaFind†	98.4%	94.6%	99.72%	95.5%	99.6%
Investigator†	99.2%	96.1%	99.96%	96.7%	99.9%
Difference*	–0.8%	–5.0%	3.0%	-4.0%	2.1%

†CI computed with Blythe-Still-Casella method

*CI is exact based on inverting 2 one-sided tests using standardized statistic

Specificity for Melanoma on all Lesions

("Melanoma", "Melanoma cannot be Ruled Out", "Not Melanoma")

		Melanoma			Non-Melanoma	
		Dermatologist			Dermatologist	
		+	–		+	–
MelaFind	+	124	1		1279	68
	–	2	0		143	15

	FDA Analysis			Sponsor's Analysis		
	Spec†	95% CI††		Spec*	95% CI **	
MelaFind	10.50%	9.77%	13.19%	9.37%	6.01%	12.73%
Investigator	5.51%	4.56%	7.32%	3.69%	0.78%	6.59%
Difference	4.98%	3.4%	7.62%	5.68%	0.90%	10.46%

†Pooled estimate of Specificity.††95% Bootstrap percentile intervals. Average Specificity across examiners. ** CI for average from Student's t-distribution with 22 degrees of freedom

Sensitivity for Melanoma/HGDN/AMP/AMH on all Lesions ("Melanoma", "Melanoma cannot be Ruled Out", "Not Melanoma")

		Melanoma			Non-Melanoma	
		Dermatologist			Dermatologist	
		+	–		+	–
MelaFind	+	170	2		1233	67
	–	3	0		142	15

	Sens	95% CI		90% CI	
MelaFind†	98.3%	95.1%	99.5%	96.0%	99.4%
Investigator†	98.9%	96.0%	99.8%	96.7%	99.7%
Difference*	–0.6%	–4.0%	2.6%	–	

†CI computed with Blythe-Still-Casella method

*CI is exact based on investing 2 one-sided tests using standardized statistic

Specificity for Melanoma/HGDN/AMP/AMH on all Lesions ("Melanoma", "Melanoma cannot be Ruled Out", "Not Melanoma")

		Melanoma			Non-Melanoma	
		Dermatologist			Dermatologist	
		+	–		+	–
MelaFind	+	170	2		1233	67
	–	3	0		142	15

	Spec †	95% CI ††		Spec*	95% CI **	
MelaFind	10.8%	10.1%	13.5%	9.9%	6.0%	13.8%
Investigator	5.6%	4.7%	7.5%	3.7%	0.7%	6.6%
Difference	5.2%	3.5 %	8.0%	6.2%	1.0%	11.5%

†Pooled estimate of Specificity.††95% Bootstrap percentile intervals. Average Specificity across examiners. ** CI for average from Student's t-distribution with 22 degrees of freedom

Results of difference in biopsy/referral AUC in the three physician groups

	AUC	95% CI
PCP (n=45)	0.59	(0.55, 0.64)
GD (n=46)	0.65	(0.59, 0.71)
PSLE (n=64)	0.63	(0.58, 0.68)
GD-PCP	0.05	(0.03, 0.07)
PSLE-PCP	0.03	(0.02, 0.05)
PSLE-GD	-0.02	(-0.04, -0.00)

Concerns with Protocol 20061

- Protocol 20061 undercounts all atypical lesions:

		Melanoma			Non-Melanoma	
		Dermatologist			Dermatologist	
		+	–		+	–
Mela Find	+	124	[1]		1279	[68]
	–	2	[0]		143	[15]

  - Brackets denote undercounts of all atypical lesions for purpose of comparing diagnostic sensitivity / specificity of dermatologist with MelaFind sensitivity / specificity.

MelaFind performance on all Lesions (Eligible and Evaluable Lesions, N=1632)

		Melanoma			Non-Melanoma	
		Dermatologist			Dermatologist	
		+	–		+	–
MelaFind	+	124	1		1279	68
	–	2	0		143	15

Prevalence of melanoma = 7.8%

	MelaFind	Dermatologist
PPV	8.5%	8.1%
NPV	98.8%	98.8%
Biopsy ratio	10.8:1	11.9:1*
Number Needed to Test (NNT)	11.8	12.9

* Biopsy ratio for dermatologist is based on all 1632 lesions

Performance of MelaFind in comparison to the Physicians

Regions

MelaFind's performance in comparison to PCPs

I	II	III	IV	Total
3	1	37	4	45

MelaFind's performance in comparison to GDs

I	II	III	IV	Total
2	0	38	6	46

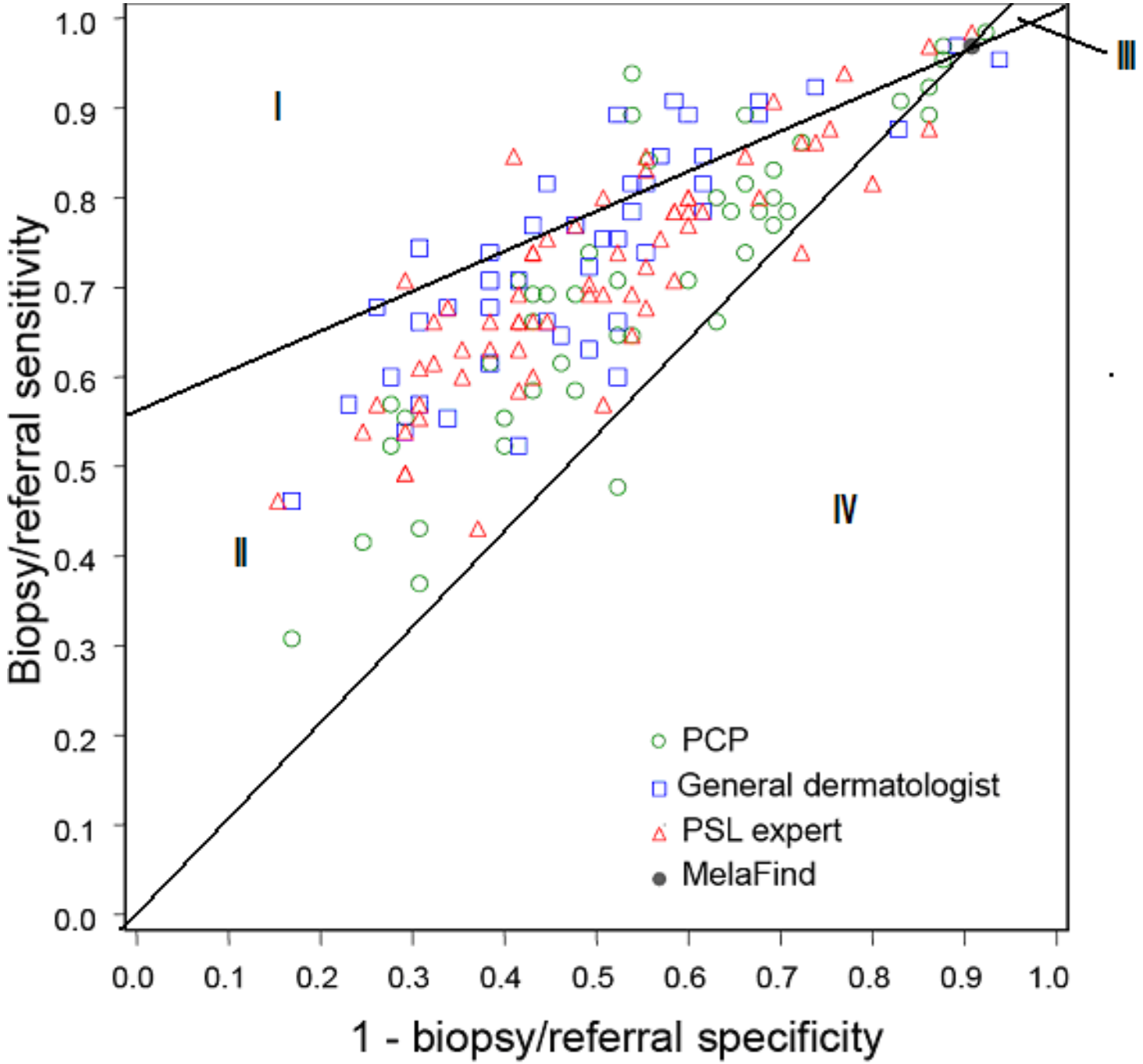
MelaFind's performance in comparison to PSLEs

I	II	III	IV	Total
3	0	55	6	64

MelaFind's performance in comparison to all Physicians

I	II	III	IV	Total
8	1	130	16	155

Compared to all physicians in the reader study, MelaFind was superior only to 8 (5%) out of 155 physicians and inferior to 16 (10%) of 155 physicians.


Biopsy/referral sensitivity
1 - biopsy/referral specificity
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
I
II
III
IV
PCP
General dermatologist
PSL expert
MelaFind

More ITD Analyses

Sensitivity for Melanoma, N = 114 (F3-F4 Eligible and Evaluable Lesions)

		Melanoma			Non-Melanoma	
		Dermatologist			Dermatologist	
		+	–		+	–
MelaFind	+	**111**	**1**		1272	68
	–	**2**	**0**		143	15

	Sens	95% CI		90% CI	
MelaFind†	98.3%	**94.1%**	99.7%	**95.0%**	99.5%
Investigator†	99.1%	95.7%	99.9%	96.3%	99.9%
Difference*	– 0.9%	– 5.5%	3.3%	– 4.4%	2.4%

95% Sensitivity: **met** with 90% CI (1-sided 95% LCB),
not met with 95% CI (2-sided 95% LCB).

†CI computed with Blythe-Still-Casella method
*CI is exact based on inverting 2 one-sided tests using standardized statistic

Specificity for Melanoma, N = 1498 (F3-F4 Eligible and Evaluable Lesions)

		Melanoma			Non-Melanoma	
		Dermatologist			Dermatologist	
		+	–		+	–
MelaFind	+	111	1		**1272**	**68**
	–	2	0		**143**	**15**

Sponsor Analysis

	Spec*	95% CI**	
MelaFind	9.5%	6.1%	12.9%
Investigator	3.7%	0.8%	6.7%
Difference	5.8%	0.9%	10.6%

Specificity Diff > 0: met with 95% CI (2-sided 95% LCB),

Average Specificity across examiners. ** CI for average from Student's t-distribution with 22 degrees of freedom

Specificity for Melanoma, N = 1498 (F3-F4 Eligible and Evaluable Lesions)

		Melanoma			Non-Melanoma	
		Dermatologist			Dermatologist	
		+	–		+	–
MelaFind	+	111	1		1272	68
	–	2	0		143	15

FDA Analysis

	Spec†	95% CI††	
MelaFind	10.6%	9.7%	13.2%
Investigator	5.5%	4.5%	7.3%
Difference	5.1%	3.3%	7.7%

Specificity Diff > 0: met with 95% CI (2-sided 95% LCB),

†Pooled estimate of Specificity.††95% Bootstrap percentile intervals.

E & E Lesions Analysis (n=1612), Protocol 20061

- An intent to diagnose analysis was performed on all lesions with dermatological diagnosis “Melanoma cannot be Ruled Out” or “Not Melanoma”, that were eligible and evaluable and had a pathology available (n=1612). The missing un-evaluable results by MelaFind are excluded for this analysis.

		Melanoma			Non-Melanoma	
		Dermatologist			Dermatologist	
		+	–		+	–
MelaFind	+	111	1		1272	68
	Un-evaluable (missing)	23	0		119	16
	–	2	0		143	15

	Sens	95% CI	Spec	95% CI
MelaFind	98.3%	(94.1%, 99.7%)†	10.6%	(9.7%, 13.2%)*

Sensitivity + specificity=100.1 %, (95% CI 92.7% to 106.6%)*

†Blythe-Still-Casella 95% CI; *95% Bootstrap percentile CI.

*95% sensitivity not met

Intention to Diagnose 1 (ITD) Lesions Analysis (n=1770), Protocol 20061

- An intent to diagnose analysis was performed on all lesions with dermatological diagnosis “Melanoma cannot be Ruled Out” or “Not Melanoma”, that were eligible and had a pathology available (n=1770). The missing un-evaluable results by MelaFind are considered negative for this analysis.

		Melanoma			Non-Melanoma	
		Dermatologist			Dermatologist	
		+	–		+	–
MelaFind	+	112	1		1278	68
	Un-evaluable (missing)	22	0		113	16
	–	2	0		143	15

	Sens	95% CI	Spec	95% CI
MelaFind	82.5%	(75.6%, 88.3%)†[1]	17.6%	(16.0%, 20.0%)*

Sensitivity + specificity=100.1 %, (95% CI 92.7% to 106.6%)*

MelaFind was not statistically significantly better than chance.

†Blythe-Still-Casella 95% CI; *95% Bootstrap percentile CI. [1]95% sensitivity not met.

Intention to Diagnose 2 (ITD) Lesions Analysis (n=1770), Protocol 20061

- An intent to diagnose analysis was performed on all lesions with dermatological diagnosis “Melanoma cannot be Ruled Out” or “Not Melanoma”, that were eligible and had a pathology available (n=1770). The missing un-evaluable results by MelaFind are considered positive for this analysis.

		Melanoma			Non-Melanoma	
		Dermatologist			Dermatologist	
		+	–		+	–
MelaFind	+	112	1		1278	68
	Un-evaluable (missing)	22	0		113	16
	–	2	0		143	15

	Sens	95% CI	Spec	95% CI
MelaFind	98.5%	(94.9%, 99.7%)†[1]	9.7%	(8.2%, 11.3%)*

Sensitivity + specificity=109.1 %, (95% CI 106.1% to 112.0%)*

†95% CI computed with Blythe-Still-Casella method.

*95% Bootstrap percentile CI. [1]95% sensitivity not met.

Intention to Diagnose 3 (ITD) Lesions Analysis (n=1770), Protocol 20061

- An intent to diagnose analysis was performed on all lesions with dermatological diagnosis “Melanoma cannot be Ruled Out” or “Not Melanoma”, that were eligible and had a pathology available (n=1770). The missing un-evaluable results by MelaFind were multiply imputed non-informatively within bootstrap resampling.

		Melanoma			Non-Melanoma	
		Dermatologist			Dermatologist	
		+	–		+	–
MelaFind	+	112	1		1278	68
	Un-evaluable (missing)	22	0		113	16
	–	2	0		143	15

	Sens	95% CI	Spec	95% CI
MelaFind	97.1%	(93.7%, 99.3%)*[1]	10.7%	(9.1%, 12.2%)*

Sensitivity + specificity=108.8 %, (95% CI 103.9% to 110.5%)*

*95% Bootstrap percentile CI. [1]95% sensitivity not met.