Introduction and Panel Overview

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Center for Devices and Radiological Health
Food and Drug Administration

General and Plastic Surgery Devices
Panel Meeting

July 28, 2022
Welcome!
Two Independent Panel Meetings

TODAY: General Issues Meeting

• Discuss **future devices** that analyze skin lesions

• Questions to be discussed:
  – Accuracy
  – Ground truth
  – Populations
Two Independent Panel Meetings

Tomorrow: Reclassification Meeting

• Discuss **two approved devices** (MelaFind and Nevisense)
• Approved for adjunctive use by dermatologists in assessing possible melanoma
• Currently Class III (high risk)
• Propose regulation as Class II (moderate-high risk)
Today’s Agenda

• Skin cancer
• Skin lesion analyzers (SLA)
• Use contexts
• Public speaker presentations
• Panel questions
Skin Cancer

• Skin cancer: 20% of individuals
• Early melanoma diagnosis critical
• Limited access to specialist care
• SLA may provide early detection
Skin Lesion Analyzers

- AI/ML-based devices to support lesion identification:
  - Assess visual appearance (photographs)
  - Assess physiological or biochemical changes
SLA Users

• Different users:
  – Dermatologists
  – Non-dermatologist healthcare provider
  – Lay persons
SLA Applications

• Different uses:
  – Specific lesion:
    • Is this lesion cancerous?
    • Is this lesion melanoma or BCC?
  – Screening: are any of my lesions suspicious?
Questions for General Issues Panel Meeting

1. Options for determining ground truth
   – Histology
   – Visual diagnosis by single or multiple dermatologists
   – Other means

2. Acceptable thresholds for sensitivity and specificity, based on
   – Target diagnosis (melanoma, BCC, SCC)
   – Intended user (dermatologist, primary care physician, lay person)

3. Health equity considerations
   – Variable incidence in different populations
   – Variable lesion appearance in different skin types
Thank you
Overview of Skin Lesions

Jennifer Bai, M.D.

Medical Officer
Office of Surgical and Infection Control Devices
Center for Devices and Radiological Health
Food and Drug Administration

General and Plastic Surgery Devices
Panel Meeting

July 28, 2022
Overview

• Skin Cancer
  – Epidemiology
  – Natural history and management of the most common skin cancers

• Typical workflow
  – Current practice
  – Skin lesion analyzers (SLA)
  – Clinical Considerations
Types of Skin Cancer

Skin cancer

Non-melanoma skin cancers (NMSC)

- Basal cell carcinoma (BCC)
- Squamous cell carcinoma (SCC)

Melanoma
# Epidemiology of Skin Cancers

<table>
<thead>
<tr>
<th>Skin Cancer</th>
<th>Estimated Cases Annually in US</th>
<th>Estimated Deaths Annually in US</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCC</td>
<td>3.6 million</td>
<td>Uncommon</td>
</tr>
<tr>
<td>SCC</td>
<td>1.8 million</td>
<td>Uncommon*</td>
</tr>
<tr>
<td>Melanoma</td>
<td>99,780</td>
<td>7,650</td>
</tr>
</tbody>
</table>

*Except in immunosuppressed patients (i.e., after organ transplant)


Basal Cell Carcinoma (BCC)

- Most common type of skin cancer
- Related to sun exposure
- Skin-colored papule with a pearly appearance
- Slow-growing, most often curable

Images with permission of DermNet NZ
Basal Cell Carcinoma (BCC)

• Most occur spontaneously
• Distinguished from similar appearing lesions by biopsy
• Treatment
  – Excision
  – 95-99% cure rates
• Rarely metastasizes (<0.1%)

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dermnetnz.org/imagedetail/10800?copyright=&label=
dermnetnz.org/imagedetail/2895?copyright=&label=
dermnetnz.org/assets/Uploads/amelanotic-melanoma-016__WatermarkedWyJXYXRlcm1hcmtlZCJd.JPG
Squamous Cell Carcinoma (SCC)

- 2nd most common skin cancer
- Scaly, thin erythematous lesion
- Often in sun-exposed areas
- Originates from epidermal keratinocytes

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dermnetnz.org/imagedetail/46228?copyright=&label=Cutaneous+squamous+cell+carcinoma&c
SCC

- Precursor: actinic keratosis
- Diagnosis confirmed by biopsy
- Treatment:
  - Excision: 95-99% cure rates
- Metastasis:
  - 2-6% rate
  - 5-year survival rate is 34%
  - Higher risk if immunosuppressed

SCC Mimics

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dermnetnz.org/imagedetail/20204?copyright=&label=
dermnetnz.org/imagedetail/9288?copyright=&label=
Melanoma

• Arises from melanocytes
• Can develop from nevi or normal skin
• Clinical exam:
  – **ABCD** (asymmetry, border irregularity, color variegation, diameter >6mm)
  – **E**: evolution
  – **F**: funny looking
  – **U**: “ugly duckling”

Images with permission of DermNet NZ
dermnetnz.org/imagedetail/27398?copyright=&label=dermnetnz.org/imagedetail/33005?copyright=&label=Acral+lentiginous+melanoma&caption=A%20Acral+lentiginous+melanoma
Melanoma

- Diagnosis confirmed by biopsy
- Thickness is critical for prognosis
- Treatment:
  - Localized: excision +/- lymph node biopsy
  - Metastatic: requires oncologic care
- High risk of metastasis and death

**Melanoma Mimics**

Images with permission of DermNet NZ
Melanoma Stage and Survival

• Cancer stage at time of melanoma diagnosis is critical, strong correlation to overall survival
• Average overall 5-year survival in US is 93.7%

<table>
<thead>
<tr>
<th>Stage</th>
<th>Diagnosed at Stage</th>
<th>5-Year Relative Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized</td>
<td>82%</td>
<td>99%</td>
</tr>
<tr>
<td>Regional</td>
<td>9%</td>
<td>71%</td>
</tr>
<tr>
<td>Distant</td>
<td>4%</td>
<td>32%</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Subtypes</th>
<th>% of Melanoma</th>
<th>Anatomic Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superficial Spreading Melanoma</td>
<td>70%</td>
<td>Any site, typically trunk or extremities</td>
</tr>
<tr>
<td>Nodular Melanoma</td>
<td>15-30%</td>
<td>Any site</td>
</tr>
<tr>
<td>Lentigo Maligna Melanoma</td>
<td>5%</td>
<td>Chronically sun-exposed sites</td>
</tr>
<tr>
<td>Acral Lentiginous Melanoma</td>
<td>2-3%</td>
<td>Palms, soles, under nails</td>
</tr>
<tr>
<td>Amelanotic Malignant Melanoma</td>
<td>0.4%</td>
<td>Any site, little/no pigment</td>
</tr>
</tbody>
</table>

Images with permission of DermNet NZ
1.dermnetnz.org/imagedetail/27398?copyright=&label=
2.dermnetnz.org/imagedetail/10625?copyright=&label=Nodular+melanoma&caption=Nodular+m%20elanoma
3.dermnetnz.org/imagedetail/9148?copyright&label
4.dermnetnz.org/imagedetail/33005?copyright=&label=Acral+lentiginous+melanoma&caption=A_cral+lentiginous+melanoma
5.dermnetnz.org/imagedetail/44050?copyright=&label=
Spectrum of Melanocytic Lesions

- Benign nevus
- Mildly dysplastic nevus
- Moderately dysplastic nevus
- Severely dysplastic nevus
- Melanoma in situ
- Invasive melanoma

Clinically considered “positive”/high risk
Typical Workflow for Skin Lesions

Patient

Dermatologist

Primary Care Physician (PCP)

Reassure
Typical Workflow for Skin Lesions

Patient

Dermatologist

Primary Care Physician (PCP)

Completely Benign

Benign but Potential for Developing Malignancy

Suspicious for Malignancy

Reassure

Monitor

Biopsy

Reassure
Approved Devices

• Two approved computer aided devices that utilize AI/ML for assessing pigmented lesions
  – MelaFind
  – Nevisense

• Intended use:
  – Adjunctive
  – **For dermatologists** only
  – To aid in a decision to biopsy
  – Limited to lesions suspicious for melanoma
Typical Workflow for Skin Lesions with SLAs

Patient

- SLA for Lay Persons
  - Dermatologist
    - SLA for Dermatologists
      - Completely Benign
        - Reassure
      - Benign but Potential for Developing Malignancy
        - Monitor
      - Suspicious for Malignancy
        - Biopsy
  - Primary Care Physician (PCP)
    - SLA for PCPs
      - Reassure
Clinical Considerations for SLAs

• Different indications
• Different intended users
• Different outputs
  – Binary (biopsy vs not biopsy)
  – Risk score
  – Diagnosis
Conclusion

• Early detection is important for melanoma
• SLAs may contribute to earlier triage of skin cancers
• Important to consider the accuracy and intended user
Thank you!
Skin Lesion Analyzer Device Landscape

Jianting Wang, Ph.D.

Biomedical Engineer, Acting Assistant Director
Light Based Energy Devices Team
Office of Surgical and Infection Control Devices
Center for Devices and Radiological Health
Food and Drug Administration

General and Plastic Surgery Devices Panel Meeting

July 28, 2022
Technologies for Evaluating Skin

• Physical examination aids
• Optical imaging modalities
• Non-optical modalities
• Skin lesion analyzer software
Physical Examination Aids

Dermatoscope (over the counter)

- Magnification and illumination
- May support image capture/storage
- Provides image for user to assess
- **Does not classify lesion or assess risk**

Image permission of DermNet NZ
https://dermnetnz.org/imagedetail/24629?copyright=&label=Irregular+shape%2Fstructure&caption=Irr
Digital Imaging with Structure Mapping

Advanced dermatoscope (Rx use)

• Multi-spectral light
• Provides image that highlights areas with high melanin, hemoglobin, collagen content
• User must assess image
• Does not classify lesion or assess risk
Multi/Hyper-spectral Imaging

MelaFind

- Optical – light based
- Assesses 3D morphological disorganization
- Artificial Intelligence (AI)/Machine-Learning (ML)-based analysis
- AI-based output: risk score on 10-point scale

- Approved to be used when a dermatologist chooses to obtain additional information for a decision to biopsy.

Images with permission of Strata Skin Sciences
Reflectance Confocal Microscopy (RCM)

- High resolution
- Provides image for user to assess
- Not widely used

- Example: VivaScope, cleared to provide *in vivo* images of tissue in unstained *epithelium and supporting stroma*

- Cochrane meta-analysis: dermatologists' performance with RCM

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>All lesions</td>
<td>76%</td>
<td>95%</td>
</tr>
<tr>
<td>BCC</td>
<td>94%</td>
<td>85%</td>
</tr>
<tr>
<td>Melanoma</td>
<td>92%</td>
<td>72%</td>
</tr>
</tbody>
</table>

*Image permission of DermNet NZ  dermnetnz.org/imagedetail/14188?copyright&label*
*Data: Dinnes J et al. Reflectance confocal microscopy for diagnosing cutaneous melanoma in adults. Cochrane Database of Systematic Reviews 2018*
Optical Coherence Tomography (OCT)

- High resolution
- Provides image for user to assess
- Not widely used

- Optical “ultrasound”-like images
- Example: VivoSight; cleared for 2D cross-sectional real-time imaging of external tissues

- Cochrane meta-analysis of OCT devices applied to skin cancer:

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCC</td>
<td>95% (95% CI 91-97%)</td>
<td>77% (95% CI 69-83%)</td>
</tr>
</tbody>
</table>

- Image with permission DermNet NZ: dermnetnz.org/imagedetail/13870?copyright=&label=+OCT&caption=+OCT
Electrical Impedance Spectroscopy (EIS)

- Nevisense
  - Assesses resistance to current
  - Impedance sampled in normal skin and lesion
  - Assesses difference in EIS signal
  - AI-based output: score on 10-point scale

Images with permission of Scibase
Nevisense 3.0 Clinical Reference Guide  scibase.com/uk/nevisense3/
Non-Optical Modalities

• High frequency ultrasound
  – Provides image to be assessed by user

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td>83% -100%</td>
<td>33%-73%</td>
</tr>
</tbody>
</table>

Non-Optical Modalities

- Raman spectroscopy
  - Assesses light shift induced by molecules
  - Signal requires software for interpretation

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SLA: Types, Uses, Users

• Software **in** a device, or Software **as** a Medical Device (SaMD)

• **Software input:**
  • Image: smartphone camera, dermoscopy
  • Other physical parameter: electrical Impedance, Raman spectroscopy
  • Supporting clinical data, e.g. skin type, history of lesion

• **Software output:**
  • Binary classifier (e.g., concerning, not concerning)
  • Multiclass classifier (e.g., nevus, melanoma, BCC, SCC)
  • Risk score, probability, etc.

• **Intended users:**
  • Dermatologists
  • Non-dermatology healthcare providers
  • Lay persons
SLA Software: Algorithm Development

- Artificial intelligence (AI) and machine learning (ML) to develop algorithm
- Three phases of development
  - Training phase
  - Validation/tuning phase
  - Testing phase
  - Device output compared to ground truth
  - Establishes sensitivity and specificity
  - Lock preset sensitivity; specificity follows
Skin Lesion Analysis Software

• Limitations and sources of bias:
  – AI/ML algorithm is only as good as the training provided
  – Datasets used (public or proprietary) may have limited
    • Skin phototype
    • Lesion types/diagnoses included
    • Lesion severity (e.g., lack borderline/challenging cases)

• Therefore, performance may not be generalizable
  – To full population
  – To all lesion types
Summary

• Wide range of technologies
  – Optical imaging
  – Non-imaging technologies
  – AI/ML algorithms

• Device use not limited to dermatologists
  – Dermatologists, non-dermatology providers, lay persons
  – Outputs: risk score, benign/malignant, diagnosis, etc.
Thank you!
Special Considerations:
Diagnostic Accuracy and Ground Truth

Henry Lee, M.D.
Medical Officer, Light-Based Devices Team
Office of Surgical and Infection Control Devices
Center for Devices and Radiological Health
Food and Drug Administration

General and Plastic Surgery Devices
Panel Meeting

July 28, 2022
Introduction

• Panel will be asked to comment on
  – Accuracy goals
  – Ground truth

• FDA will provide
  – Context for proposed accuracy
  – Context for proposed ground truth
Performance Benchmarks

• Assessment of output accuracy:
  – ≥ predefined sensitivity and specificity threshold (%)
  – ≥ performance of providers
    • Dermatologists
    • PCPs

• Assessing adjunctive effect on user accuracy:
  – Improves performance of the user
Accuracy of Dermoscopy for Melanoma

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Visual examination</strong></td>
<td>76% (66-85%)</td>
<td>75% (57-87%)</td>
</tr>
<tr>
<td><strong>Visual examination with dermoscopy</strong></td>
<td>92% (87-95%)</td>
<td>95% (90-98%)</td>
</tr>
</tbody>
</table>

# Accuracy of Teledermatology

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant vs. benign</td>
<td>94.9% (90.1-97.4%)</td>
<td>84.3% (48.5-96.8%)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>Range: 59% to 100%</td>
<td>Range: 30% to 100%</td>
</tr>
</tbody>
</table>

Accuracy of Lay People

• Limited studies
• No data for US laypeople
• Assume to have limited or no diagnostic skill
• Rely on output at face value
# Dermatologists and PCP

<table>
<thead>
<tr>
<th>Lesion Type</th>
<th>Specialty</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td>Dermatologist</td>
<td>67.2 - 100%</td>
<td>54 - 95.6%</td>
</tr>
<tr>
<td></td>
<td>Primary Care Provider</td>
<td>29 - 98%</td>
<td>49 - 98%</td>
</tr>
<tr>
<td>Squamous cell carcinoma (SCC)</td>
<td>Dermatologist</td>
<td>65.8%</td>
<td>95.6%</td>
</tr>
<tr>
<td></td>
<td>Primary Care Provider</td>
<td>42 - 69%</td>
<td>86 - 93%</td>
</tr>
<tr>
<td>Basal cell carcinoma (BCC)</td>
<td>Dermatologist</td>
<td>74 - 97%</td>
<td>87 - 98.9%</td>
</tr>
<tr>
<td></td>
<td>Primary Care Provider</td>
<td>79 - 89%</td>
<td>76 - 83%</td>
</tr>
<tr>
<td>Binary outcome (e.g. malignant vs. benign; biopsy vs. observation)</td>
<td>Dermatologist</td>
<td>65.8 - 94.8%</td>
<td>59.8 - 95.6%</td>
</tr>
<tr>
<td></td>
<td>Primary Care Provider</td>
<td>87.8 - 95.7%</td>
<td>57 - 90.6%</td>
</tr>
</tbody>
</table>
Ground Truth & Accuracy

- **Accuracy** – sensitivity and specificity compared to ground truth

**Ground truth** - true diagnosis, as established by a predefined method of assessing the lesion
Ground Truth Options

- **Biopsy** - traditional diagnostic benchmark
- **Non-invasive** - typically used for benign-appearing lesions
  - Clinical diagnosis by specialist (e.g. dermatologist)
  - Consensus diagnosis by panel of dermatologists
  - Stable lesion on follow-up
- **Hybrid model**
  - Biopsy suspicious lesions
  - Clinical diagnosis for benign appearing lesions
Variability and Accuracy of Histopathology

• Braun et al 2012
  – Substantial agreement among expert dermatopathologists: Kappa = 0.80

• Braun et al 2017
  – Local dermatopathologists compared to consensus panel
    • Sensitivity = 84.9%
    • Specificity = 98.1%


Conclusion

• Clinical accuracy varies by provider, specialty, and lesion type
• Input for regulating SLA:
  – Options for ground truth
  – Appropriate performance goals for accuracy
Thank you
Special Considerations:
Benefit/Risk and Prevalence

Scott L. Kominsky, Ph.D.
Biologist/Lead Reviewer, Cancer Diagnostics and Treatment Devices
Office of Surgical and Infection Control Devices
Center for Devices and Radiological Health
Food and Drug Administration

General and Plastic Surgery Devices
Panel Meeting

July 29, 2022
Benefit/Risk

Essential to determining reasonable assurance of safety and effectiveness:

1. Evidence of device safety and effectiveness
2. Nature and severity of the condition
3. Benefits and risks of alternatives
4. Risk management
## Benefit/Risk Assessment For SLA

<table>
<thead>
<tr>
<th>Benefits of SLA devices:</th>
<th>Risks of SLA devices:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Greater access to diagnostic information</strong> by increasing availability</td>
<td><strong>Increased healthcare utilization and more skin lesion biopsies</strong> due to false positive results</td>
</tr>
<tr>
<td><strong>Earlier testing</strong> to improve outcomes in skin cancer, especially melanoma</td>
<td><strong>Delay in diagnosis</strong> due to false negative results</td>
</tr>
<tr>
<td><strong>Enhanced assessment</strong> as an additional tool aiding clinical decisions, especially with borderline lesions</td>
<td><strong>Poor Positive Predictive Value</strong> when skin cancer has low prevalence in a given population</td>
</tr>
</tbody>
</table>
Performance Threshold

<table>
<thead>
<tr>
<th></th>
<th>BCC/SCC</th>
<th>MM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>≥ 80%</td>
<td>≥ 90%</td>
</tr>
<tr>
<td>Specificity</td>
<td>≥ 80%</td>
<td>≥ 70%</td>
</tr>
</tbody>
</table>

Potential performance goal

<table>
<thead>
<tr>
<th>Higher Sensitivity</th>
<th>=</th>
<th>Malignancy detection</th>
<th>=</th>
<th>Higher Specificity</th>
<th>=</th>
<th>Unnecessary Biopsies</th>
<th>=</th>
<th>Disease Outcome</th>
<th>Healthcare Resource Strain</th>
</tr>
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<td></td>
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</table>
Consideration of Target Diagnosis

- Consequences of false negative in cancer diagnosis > false positive
  - Sensitivity may be of greater clinical importance

- Consequences of false negative for melanoma > false negative for BCC/SCC
  - Different sensitivity/specificity thresholds may be appropriate for different target diagnoses
Consideration of User

- Primary care providers (PCPs) assess/treat > 50% of dermatological conditions
  - Diagnostic accuracy varies by training and experience
  - PCPs may have greater reliance on SLA
- Lay persons anticipated to have greater reliance on SLA
  - Not expected to have diagnostic skills

Different sensitivity and specificity thresholds may be appropriate for different users
Prevalence

• Skin cancer is more prevalent in certain populations
  • **High prevalence** in non-Hispanic white
  • **Low prevalence** in non-Hispanic black or Asian/Pacific Islander

• Device training/testing may utilize more skin cancer data from high prevalence populations

  Under-representation of low prevalence populations may affect generalizability of results
Potential Approaches

1. Train and test device using data having an equal representation of skin cancer lesions in both high- and low-prevalence populations
   - Increased time to accrue images $\rightarrow$ significant delay of device access to those at highest risk

2. Stepwise approach
   Initial training/testing using data sets from high-prevalence populations, followed by that from low-prevalence populations
   - Allows earlier device access to those at highest risk
   - May increase risk of false positive/negative results in lower prevalence populations
Summary

• **Weighing of Benefit/Risk**
  • Benefits
    • Greater access to diagnostic information
    • Earlier testing
    • Enhanced assessment
  • Risks
    • Increased healthcare resource utilization
    • Unnecessary skin lesion biopsies
    • Delayed diagnosis → poorer disease outcome
    • Poor positive predictive value in low prevalence populations

• **Consideration of Disease Prevalence**
  • Impact on diagnostic accuracy
  • Influence on device access
Questions for the Panel

Rudy Andriani, M.S.
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Center for Devices and Radiological Health
Food and Drug Administration

General and Plastic Surgery Devices
Panel Meeting

July 28, 2022
Question Overview

1) Ground truth: options

2) Accuracy: level of sensitivity and specificity

3) Ensuring generalizability to full US population
Definitions for Questions

**Ground truth vs accuracy:**

**Ground truth:** "gold standard" that will be used to determine the diagnosis of the lesion

**Accuracy:** measured sensitivity and specificity of device compared to the selected ground truth
Question 1: Ground Truth

In clinical trials for diagnostic devices, accuracy is assessed by comparing the device output to the ground truth. For skin lesions, particularly when ruling out malignancy, clinical practice has traditionally relied on histology for ground truth.

FDA has requested that histological diagnosis (core specimen processing with a consensus diagnosis from an expert dermatopathologist panel) be used for ground truth because it provides the greatest certainty in the diagnosis.

Device developers, however, cite concerns, both practical and ethical, in requiring biopsy of all lesions, particularly those that appear benign. They have proposed alternate means of defining ground truth, including consensus opinion of experts (of visual or dermoscopic examination of the lesion(s)), opinion of one expert (visual or dermoscopic examination), or other methods.
Question 1: Ground Truth

i. Should histological diagnosis be required for obtaining ground truth diagnosis in all lesions in SLA clinical trials?

ii. Are there scenarios for which alternate means or a combination (e.g., histopathology for suspected malignant lesions and consensus opinion of experts for suspected benign lesions) of ground truth would be acceptable?
Some SLA devices may be used for adjunctive use, meaning the output will be adjunctive information, to be used
• by a provider
• in concert with clinical and historical information,
• in reaching a management decision.
The provider may be a dermatologist or a non-dermatologist health care provider.

The table in the following slide provides proposed performance thresholds for sensitivity and specificity for melanoma, BCC, and SCC.
Question 2A: Performance Thresholds For Adjunctive Use

i. Should the performance thresholds of SLA devices intended for adjunctive use be a pre-defined sensitivity and specificity across all SLAs e.g., Table 5 (below), or should performance be compared to another metric, such as the performance of the study dermatologists without use of the SLA? Or, can adjunctive use performance be assessed by whether the SLA output improves the accuracy of the study dermatologists?

ii. If preset thresholds are preferable, are the proposed thresholds for sensitivity and specificity proposed appropriate? If not, what sensitivity and specificity thresholds do you propose?

<table>
<thead>
<tr>
<th>BCC/SCC</th>
<th>Sensitivity 80%</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Specificity 80%</td>
</tr>
<tr>
<td>MM</td>
<td>Sensitivity 90%</td>
</tr>
<tr>
<td></td>
<td>Specificity 70%</td>
</tr>
</tbody>
</table>
Question 2A: Performance Thresholds For Adjunctive Use

iii. Should the performance thresholds differ if the device is intended for use by dermatologists or by non-dermatology healthcare providers?

iv. Should the performance thresholds differ based on the target diagnosis (melanoma, BCC, and SCC)?

<table>
<thead>
<tr>
<th>BCC/SCC</th>
<th>Sensitivity 80%</th>
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<tr>
<td></td>
<td>Specificity 80%</td>
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<tr>
<td>MM</td>
<td>Sensitivity 90%</td>
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<td>Specificity 70%</td>
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Other SLA may be used as standalone devices, meaning that the output will be relied upon at face value to guide management.

Devices for lay users will always be standalone.
Question 2B: Performance Thresholds

Standalone Device

i. Should the performance thresholds of SLA devices intended for standalone use be a pre-defined sensitivity and specificity across all SLAs, or should performance be compared to another metric, such as the performance of the study dermatologists without use of the SLA?

ii. If preset thresholds are preferable, are the proposed thresholds for sensitivity and specificity appropriate? If not, what sensitivity and specificity thresholds do you propose?

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</table>
iii. Should the performance thresholds differ if the device is intended for use by lay users versus dermatologists or by non-dermatology healthcare providers? If so, what performance thresholds do you recommend for each?

iv. Should the performance thresholds differ based on the target diagnosis (melanoma, BCC, and SCC)? If so, what sensitivity and specificity thresholds do you propose?

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**Question 3: Performance in US Population**

Panelists should consider whether these SLA devices must be able to analyze skin lesions with an acceptable sensitivity and specificity in all patients prior to FDA clearance, or whether proof of performance data in higher-prevalence populations (e.g., non-Hispanic white individuals) can be provided to allow these high-prevalence populations access to this technology, followed by clinical studies in lower prevalence populations.

The potential benefit of a stepwise approach is that it may allow for earlier access to this technology for populations at high-risk, but it may increase the risk of false positive and false negative results in lower prevalence populations in whom the device has not been adequately trained and tested.

However, requiring SLA to be tested in patients with lower incidence before entering the market could delay the time to market due to extended enrollment times for statistically relevant numbers of darker skin individuals with skin cancer.
Question 3: Performance in US Population

Should FDA allow SLAs to be marketed based on study data from a limited US demographic (e.g., in higher incidence populations) with subsequent data collection in lower incidence populations to expand the indications for use?

Or, should the FDA require the training of AI/ML-based SLA technologies in all populations regardless of specific cancer incidence?
Question 3: Performance in US Population

Although the previous questions have focused on skin cancer, SLA may also be used for other lesions that have similar prevalence across all US demographics but look different in different Fitzpatrick skin types.

To ensure generalizability across the entire US population, should FDA require all AI/ML-based SLAs indicated for use beyond cancerous lesions to be trained and tested in a representative US population?