The role of the expert pigmented lesion clinician in the age of Technology & AI

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International Dermoscopy Society

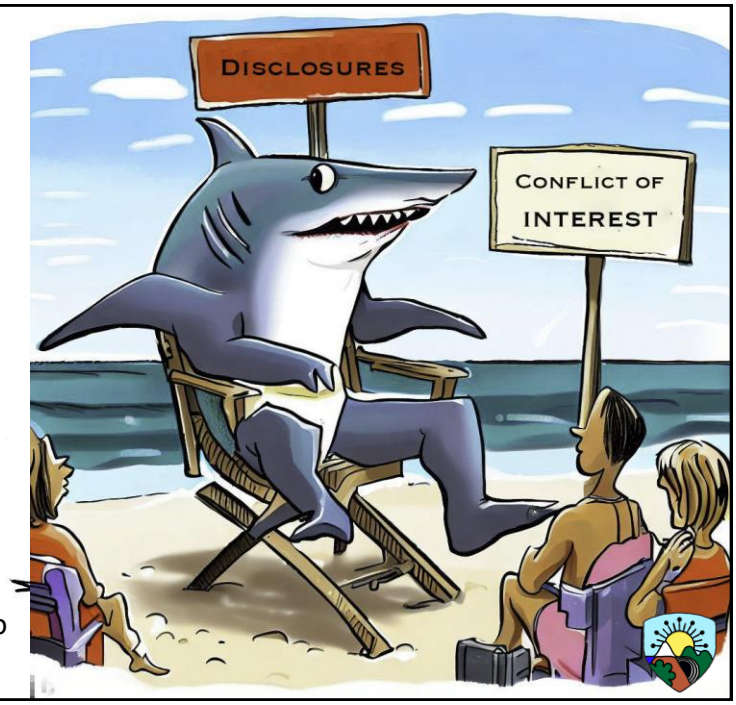
Welcome to dermoscopedia

AMERICAN DERMOSCOPY MEETING

1

Disclosures

- Canfield
- DermLite
- Heine
- FotoFinder
- Casio



Microsoft Bing AI image generator (no need for copyright)

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The role of the clinician in the age of technology

1. Morphology
2. Change (biology)
3. Integration of morphology & biology (genesis)
4. Interpretation & advancements

3

Human vision with dermoscopy is the gateway

4

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The role of the clinician in the age of technology

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     - Humans vision: analytical, differential, & comparative recognition
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     - ABCDs have helped but MMs can lack the clinical ABCDs or can resemble SKs
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     - AI Neural networks can match expert DA
  c. Clinicians recognize that MMs can be clinically and dermoscopically featureless
     - Monitoring (biology) has helped improve DA

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Towards Early Melanoma Detection:
Analytical Recognition

Analytical recognition

Comparative recognition

Differential recognition

- The Skin Cancer Foundation. The Many Faces of Malignant Melanoma brochure.
- Marghoob AA, Scope A. The complexity of diagnosing melanoma. J Invest Dermatol. 2009 Jan;129(1):11-3.

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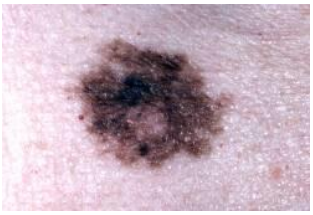
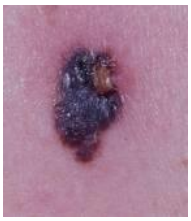
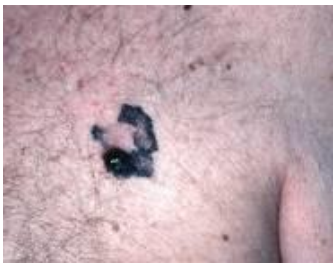
"ABCD" Mnemonic: 1985

- **A:** Asymmetry
- **B:** Border irregularity
- **C:** Color variegation
- **D:** Diameter ≥ 6 mm







- Freidman R, et al. CA Cancer J Clin. 1985;35:130-51. Photos courtesy of Ashfaq A. Marghoob, MD.

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ABCD: Sensitivity & Specificity

Early Diagnosis of Cutaneous Melanoma
Revisiting the ABCD Criteria

Naheed R. Abbasi, MPH, MD
Helen M. Shaw, PhD
Darrell S. Rigel, MD
Robert J. Friedman, MD
William H. McCarthy, FRACS
Iman Osman, MD
Alfred W. Kopf, MD
David Polsky, MD, PhD

Context The incidence of cutaneous melanoma has increased over the past several decades, making its early diagnosis a continuing public health priority. The ABCD (Asymmetry, Border irregularity, Color variegation, Diameter >6 mm) acronym for the appraisal of cutaneous pigmented lesions was devised in 1985 and has been widely adopted but requires reexamination in light of recent data regarding the existence of small-diameter (≤6 mm) melanomas.

Evidence Acquisition Cochrane Library and PubMed searches for the period 1980-2004 were conducted using search terms *ABCD and melanoma* and *small-diameter melanoma*. Bibliographies of retrieved articles were also used to identify additional relevant information.

Evidence Synthesis Available data do not support the utility of lowering the diameter criterion of ABCD from the current greater than 6 mm guideline. However, the data support expansion to ABCDE to emphasize the significance of evolving pigmented lesions in the natural history of melanoma. Physicians and patients with nevi should be attentive to changes (evolving) of size, shape, symptoms (itching, tenderness), surface (especially bleeding), and shades of color.

Conclusions The ABCD criteria for the gross inspection of pigmented skin lesions and early diagnosis of cutaneous melanoma should be expanded to ABCDE (to include "evolving"). No change to the existing diameter criterion is required at this time.

JAMA. 2004;292:2771-2776 www.jama.com

THE ABCD ACRONYM FOR melanoma screening was devised in 1985[1] to provide the lay public and primary health care professionals with a useful and memorable mnemonic to aid in the early recognition of potentially curable cutaneous malignant melanoma. The now well-known parameters of Asymmetry, Border irregularity, Color variegation, and Diameter

Table 1. Summary of Key ABCD(E) Sensitivity and Specificity Studies

Criteria Tested	Sensitivity, %	Specificity, %
A	57	72
B	57	71
C	65	59
D	90	63
E	84	90
≥1 Criterion	97	36
≥2 Criteria	89	65
≥3 Criteria	66	80
≥4 Criteria	54	94
All 5 criteria	43	100

- Abbasi NR, et al. JAMA. 2004;292:2771-6.

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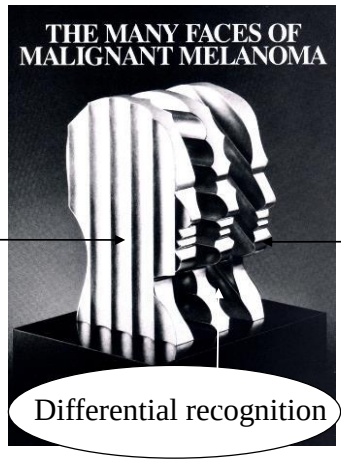
Towards Early Melanoma Detection:
Comparative Recognition



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Evolution / Change: Sensitivity & Specificity

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Table 1. Summary of Key ABCD(E) Sensitivity and Specificity Studies

Source	Total No. of Lesions	No. of Melanomas	Criteria Tested	Sensitivity, %	Specificity, %
Thomas et al,[4] 1998*	1140	460	A	57	72
			B	57	71
			C	65	59
			D	86	63
			E	84	90
			≥1 Criterion	97	36
			≥2 Criteria	89	65
			≥3 Criteria	66	80
			≥4 Criteria	54	94
			All 5 criteria	43	100
McGovern and Litaker,[10] 1992	192	6	BCD criteria applied jointly	100 (95% CI, 54-100)	98 (95% CI, 95-99)
Healsmith et al,[3] 1994†	165	65	≥1 of the ABCDEs	92 (95% CI, 82-96)	Not reported

Abbreviations: ABCD, Asymmetry, Border irregularity, Color variegation, Diameter greater than 6 mm; CI, confidence interval
*The authors used lesion diameter 6 mm or greater as the cutoff for this study and tested an E criterion (for horizontal enlargement).
†The authors tested E for elevation.

- Abbasi NR, et al. JAMA. 2004;292:2771-6.

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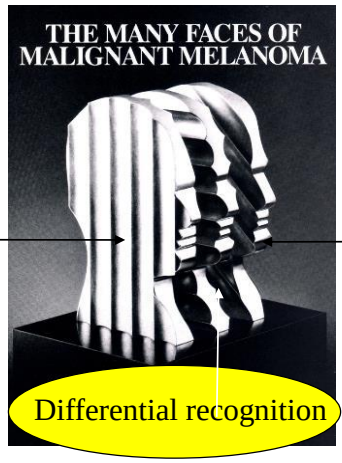
Towards Early Melanoma Detection:
Differential Recognition



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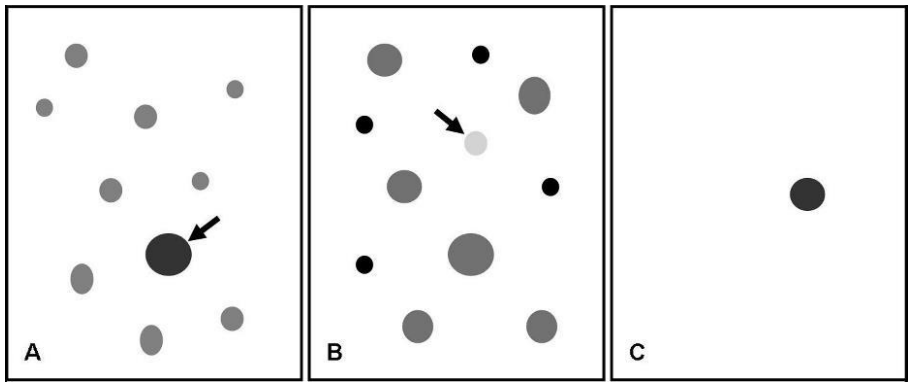
Ugly Duckling or Outlier Lesion

- Lesion/s that look different compared to their neighbors.



- Scope A, et al. The Melanoma Letter. 2007;25:1-3.

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Intra-Individual Signature Nevi

Evidence of a Limited Intra-Individual Diversity of Nevi: Intuitive Perception of Dominant Clusters Is a Crucial Step in the Analysis of Nevi by Dermatologists

consensus representation of nevus diversity in each individual. Nevus diversity is limited in each patient and constitutes an individual reference system, which we can intuitively perceive. This reference is probably crucial for nevus analysis and melanoma detection and opens perspectives for computer-aided diagnostics.

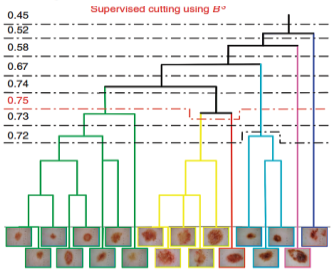

Figure 3. Hierarchical clustering of the similarity of nevi in a patient case, based on the nine experts' perceptions. This hierarchical tree displays the consensus degree of similarity between the 19 nevi of this individual. The higher the merging of two nevi in the tree, the more different their features were perceived by the nine experts. The highest B^3 value helps determine the partition level that best represents the expert-determined nevus diversity in this patient.

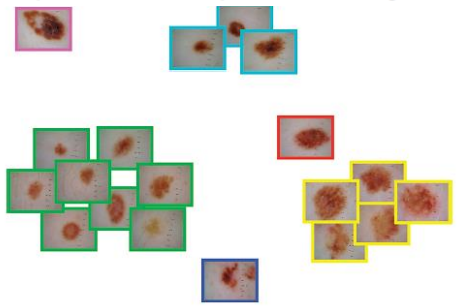

Figure 4. A multidimensional scaling (MDS)-derived visualization of the consensus clustering shown in Figure 3 (B3 ¼ 0.75). The more similar nevi (in terms of the number of experts who put them in the same cluster) appear closer together. Each image frame color represents a different cluster

- Wazaefi Y, et al. J Invest Dermatol. 2013;133:2355-2361.

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Ugly Duckling: Sensitivity & Specificity

Journal of the American Academy of Dermatology
Volume 56, Issue 2, Supplement 2, February 2007, Page AB143

The "ugly duckling" sign is sensitive for melanoma detection

- Sensitivity 89%
- Specificity 93%

- Scope A, et al. J Am Acad Dermatol. 2007;56:AB143.

15

Using these basic human functions we can identify subtle MM

- Case

16

The role of the clinician in the age of technology

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Think of technology as a supplement to your examination, not as a replacement!

Expert & technology is not a race to see who is the best but rather a race to help forge the most synergistic partnership aimed to help improve the care we deliver to our patients!

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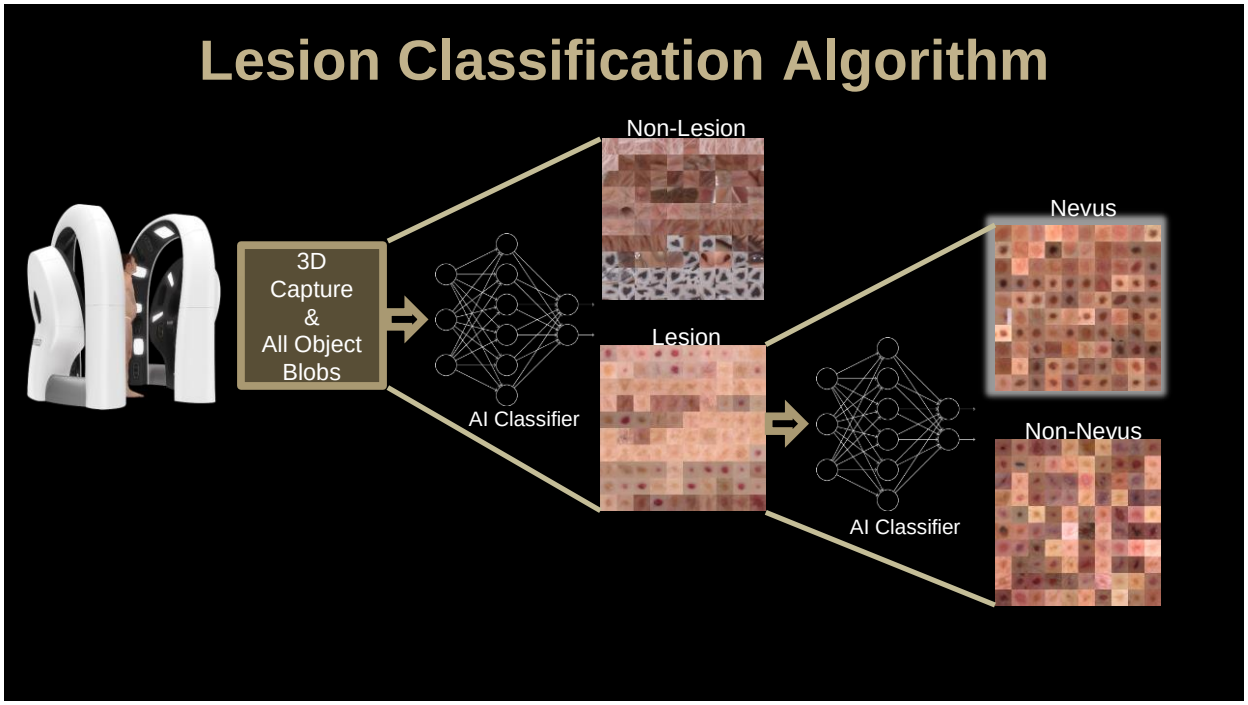
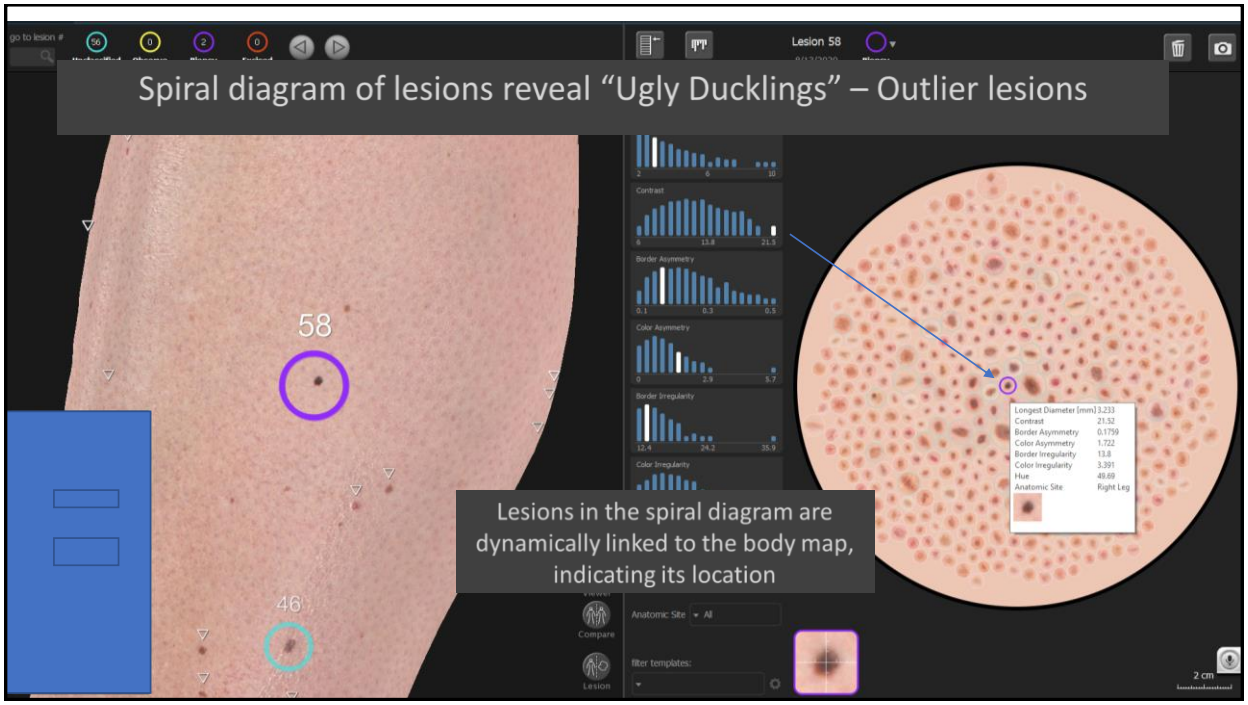

Lesion Classification Algorithm
Non-Lesion
3D
Capture
&
All Object
Blobs
AI Classifier
Lesion
Nevus
Non-Nevus
AI Classifier

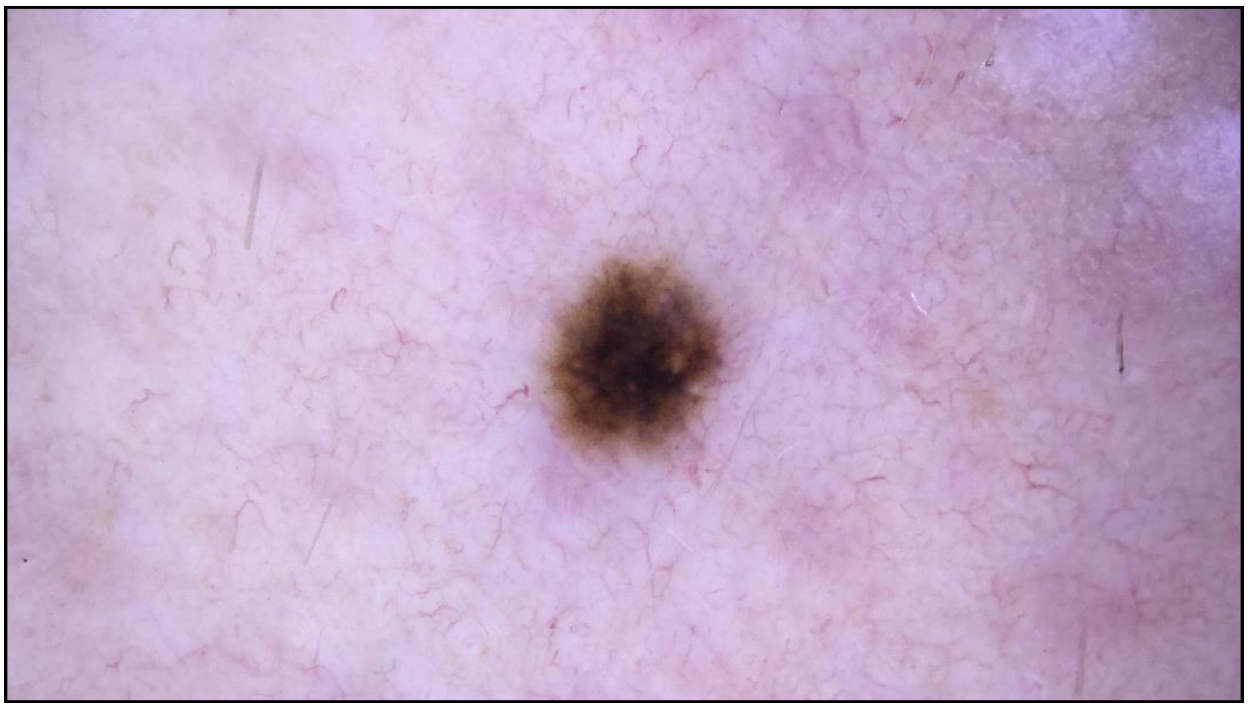
19


Automatic lesion detection
463
LESIONS

20


Spiral diagram of lesions reveal “Ugly Ducklings” – Outlier lesions
Lesion 58
58
46
Contrast
Border Asymmetry
Color Asymmetry
Border Irregularity
Color Irregularity
Longest Diameter [mm] 3.233
Contrast 21.52
Border Asymmetry 0.1759
Color Asymmetry 1.722
Border Irregularity 13.8
Color Irregularity 3.391
Hue 49.69
Anatomic Site Right Leg
Lesions in the spiral diagram are dynamically linked to the body map, indicating its location
Compare
Lesion
Anatomic Site All
filter templates:
2 cm

21



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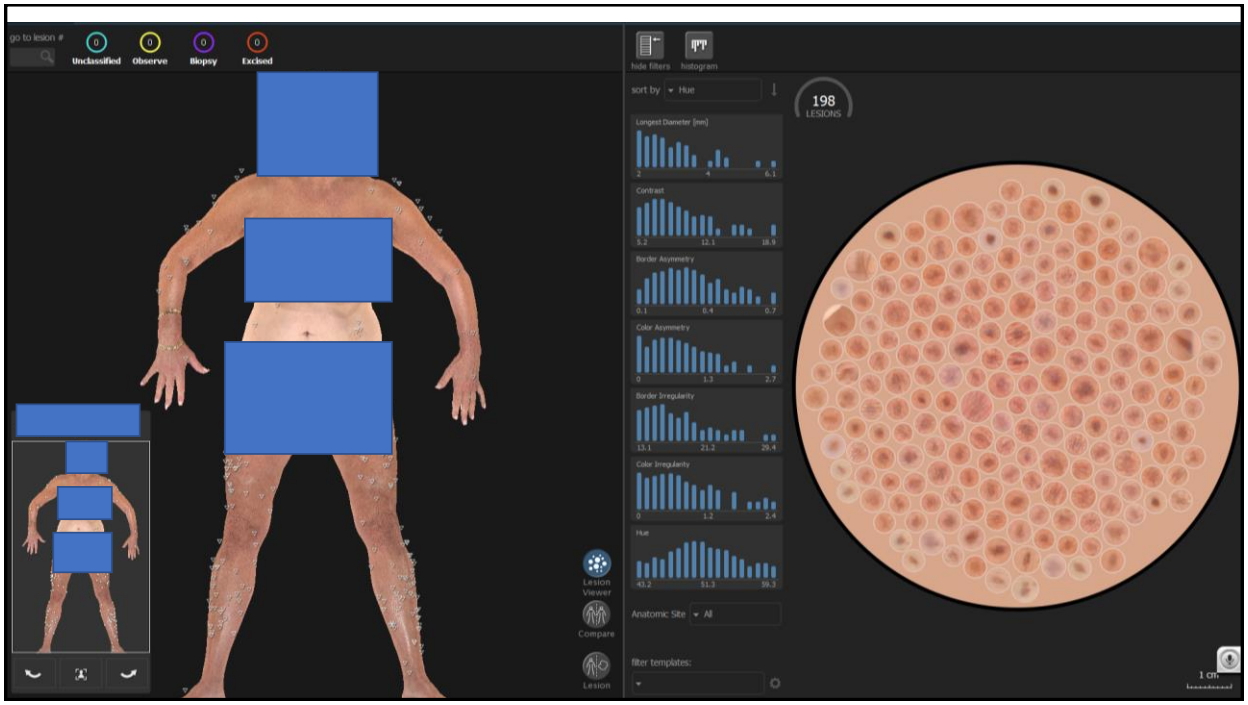
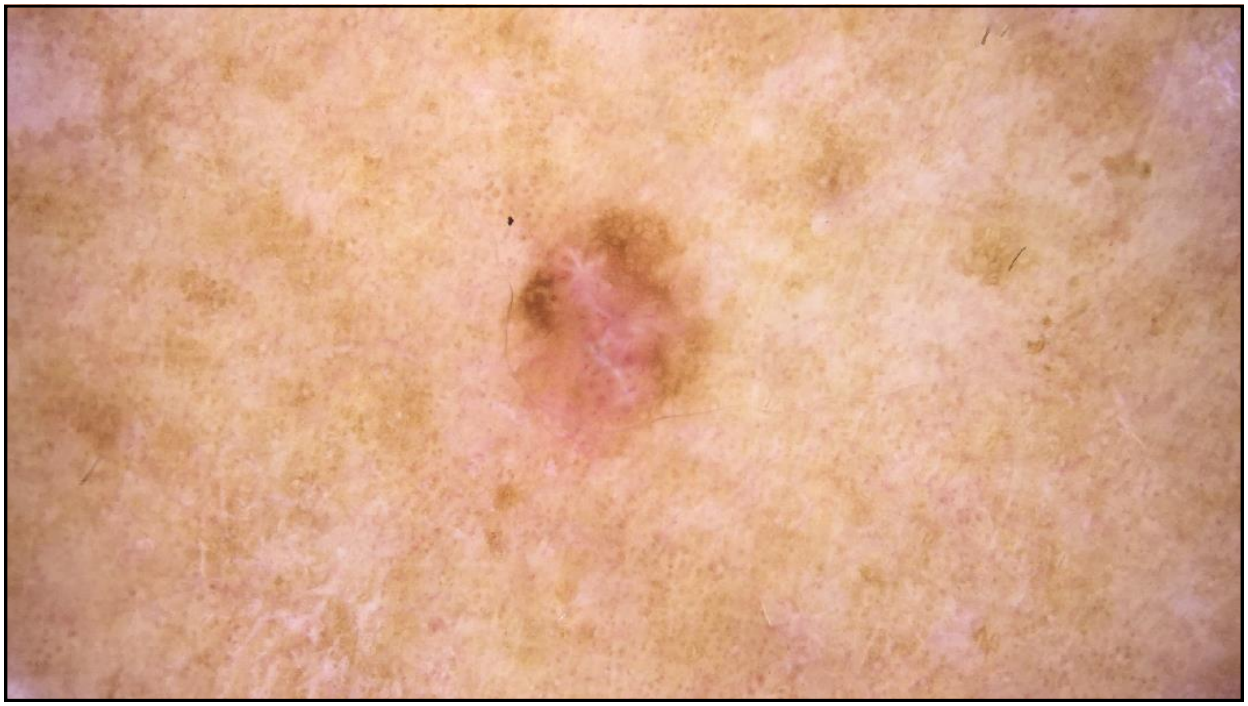

go to lesion #
Unclassified
Observe
Biopsy
Excised
hide filters
histogram
sort by
Hue
198
LESIONS
Longest Diameter [mm]
Contrast
Border Asymmetry
Color Asymmetry
Border Irregularity
Color Irregularity
Hue
Lesion Viewer
Compare
Lesion
Anatomic Site
All
filter templates:
1 cm

23


Spiral diagram of lesions may help reveal “Ugly Ducklings” – Outlier lesions
go to lesion #
Contrast
Border Asymmetry
Color Asymmetry
Border Irregularity
Color Irregularity
Hue
Lesion Viewer
Compare
Lesion
Anatomic Site
All
filter templates:
1 cm

24



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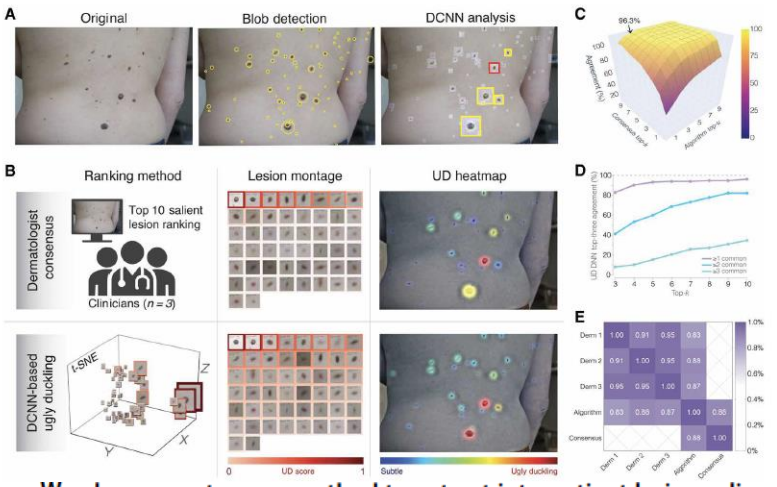
SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

CANCER

Using deep learning for dermatologist-level detection of suspicious pigmented skin lesions from wide-field images

Luis R. Soenksen[1,2,3,4,5,*], Timothy Kassis[6], Susan T. Conover[3], Berta Marti-Fuster[2,5], Judith S. Birkenfeld[2,5], Jason Tucker-Schwartz[2,5], Asif Naseem[2,5], Robert R. Stavert[7,8,9], Caroline C. Kim[10,11], Maryanne M. Senna[9,12], José Avilés-Izquierdo[13], James J. Collins[2,14], Regina Barzilay[16,17], Martha L. Gray[2,4,5,17]



cumbersome individual lesion imaging. We also present a new method to extract intrapatient lesion saliency (ugly duckling criteria) on the basis of DCNN features from detected lesions. This saliency ranking was validated against three board-certified dermatologists using a set of 135 individual wide-field images from 68 dermatological patients not included in the DCNN training set, exhibiting 82.96% (67.88 to 88.26%) agreement with at least one of the top three lesions in the dermatological consensus ranking. This method could allow for rapid and accurate assessments of pigmented lesion suspiciousness within a primary care visit and could enable improved patient triaging, utilization of resources, and earlier treatment of melanoma.

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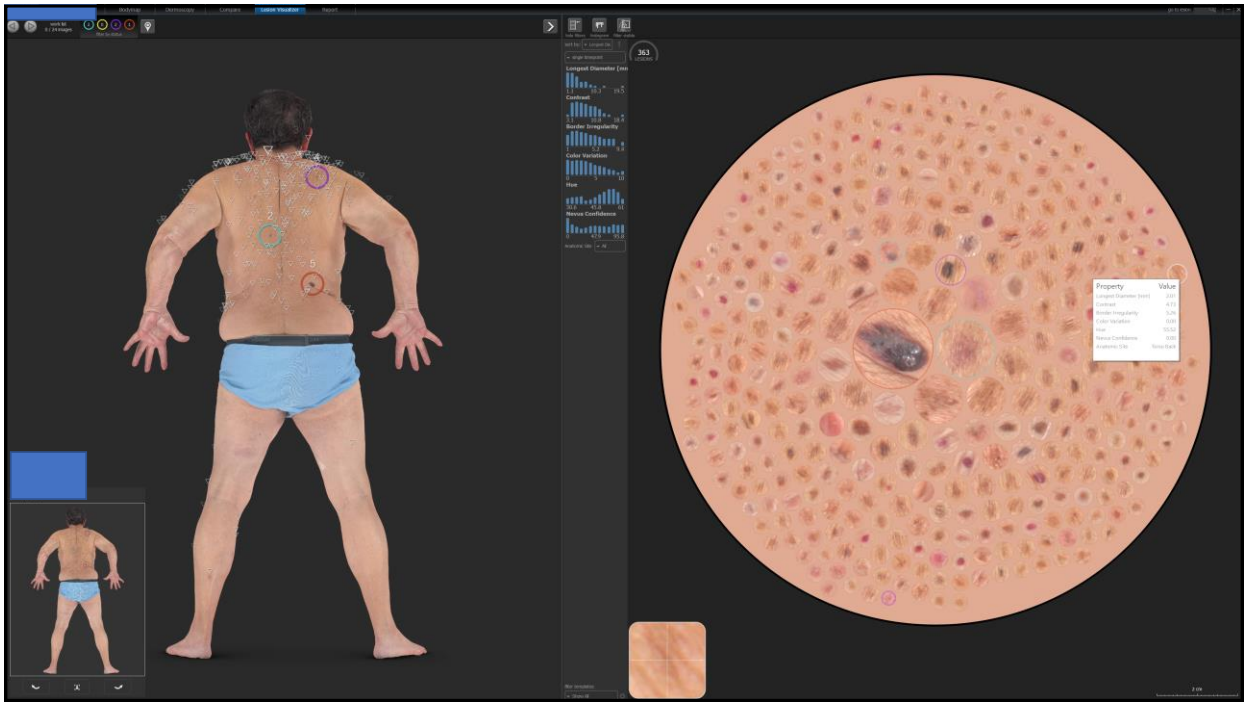

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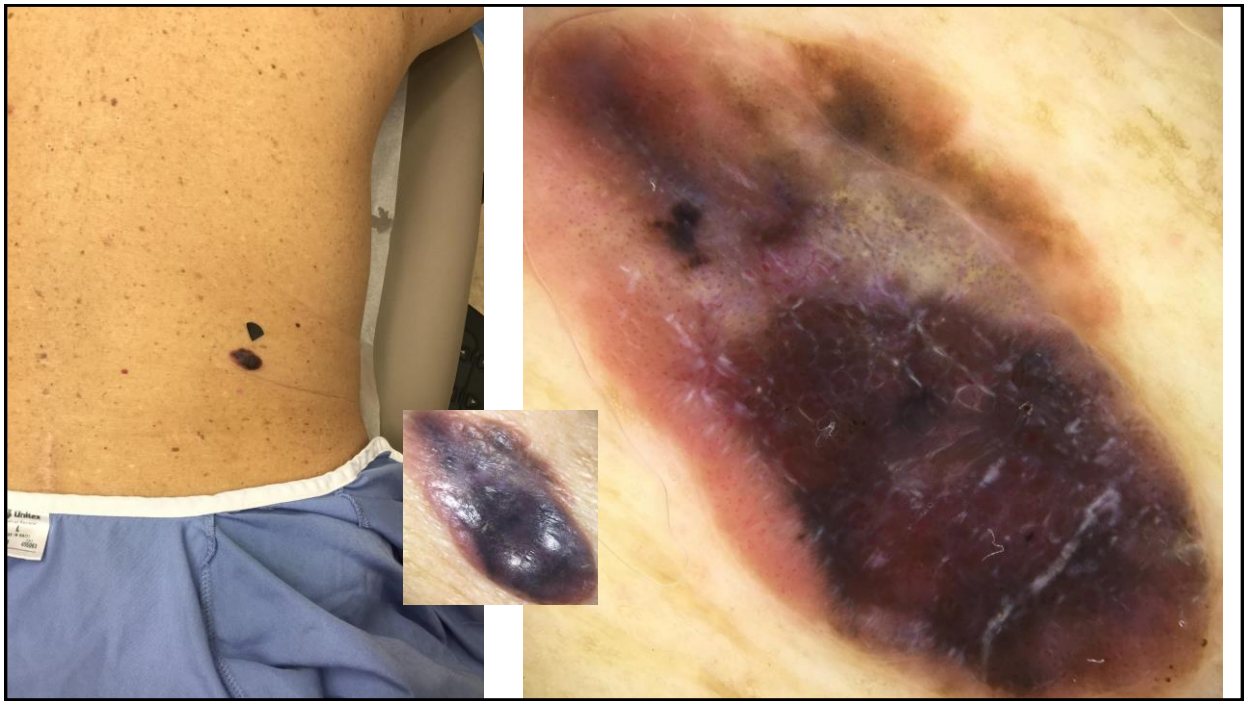

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3D Whole-body skin imaging for automated melanoma detection

Results: A total of 35 patients contributed 23,538 automatically identified skin lesions >2 mm in largest diameter (102–3021 lesions per participant). All were White patients and 23 (66%) were males. The median (range) age was 64 years (26–89). There were 49 lesions of melanoma and 22,489 lesions that were not melanoma. The AUC for the prediction model was 0.94 (95% CI: 0.92–0.96). Considering all lesions in a patient-level analysis, 14 (28%) melanoma lesions had the highest predicted score or were in the 99th percentile among all lesions for an individual patient.

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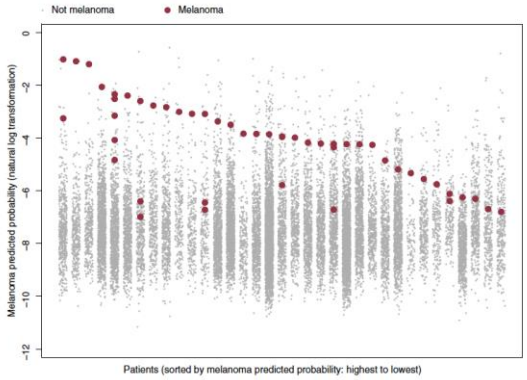

Using a model-based threshold associated with 95% sensitivity for melanoma detection, the model could reduce the number of lesions requiring examination by 75%.

This means that almost 6000 lesions were classified within the MM range!!! (B:M of 1:123)

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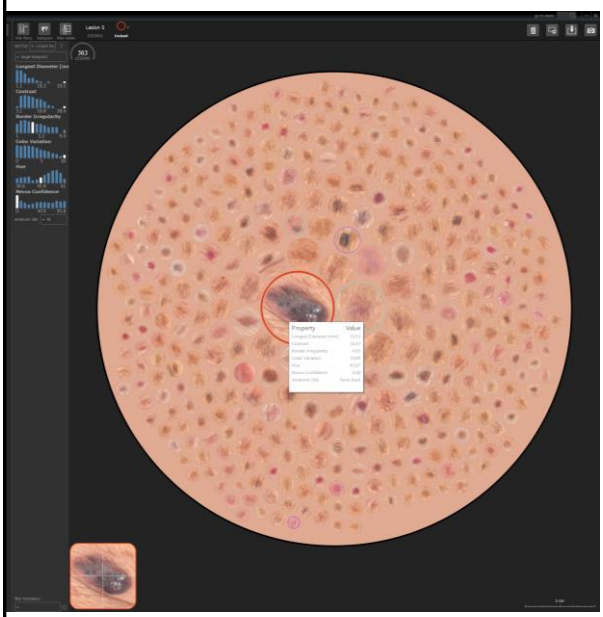

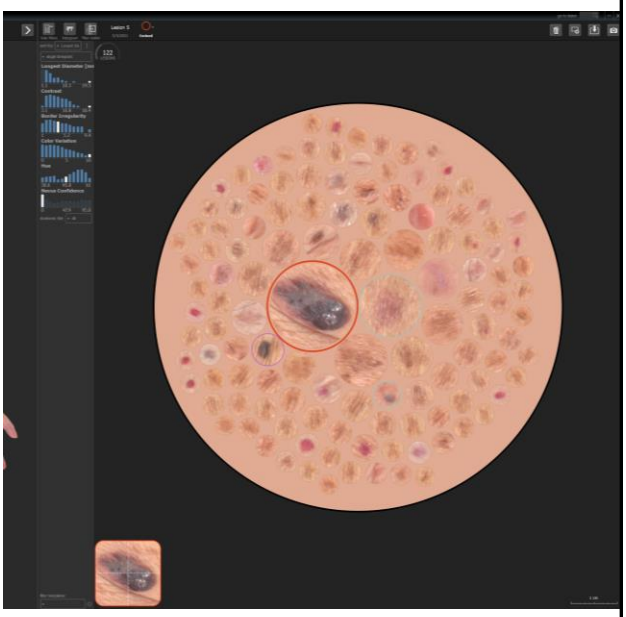

30

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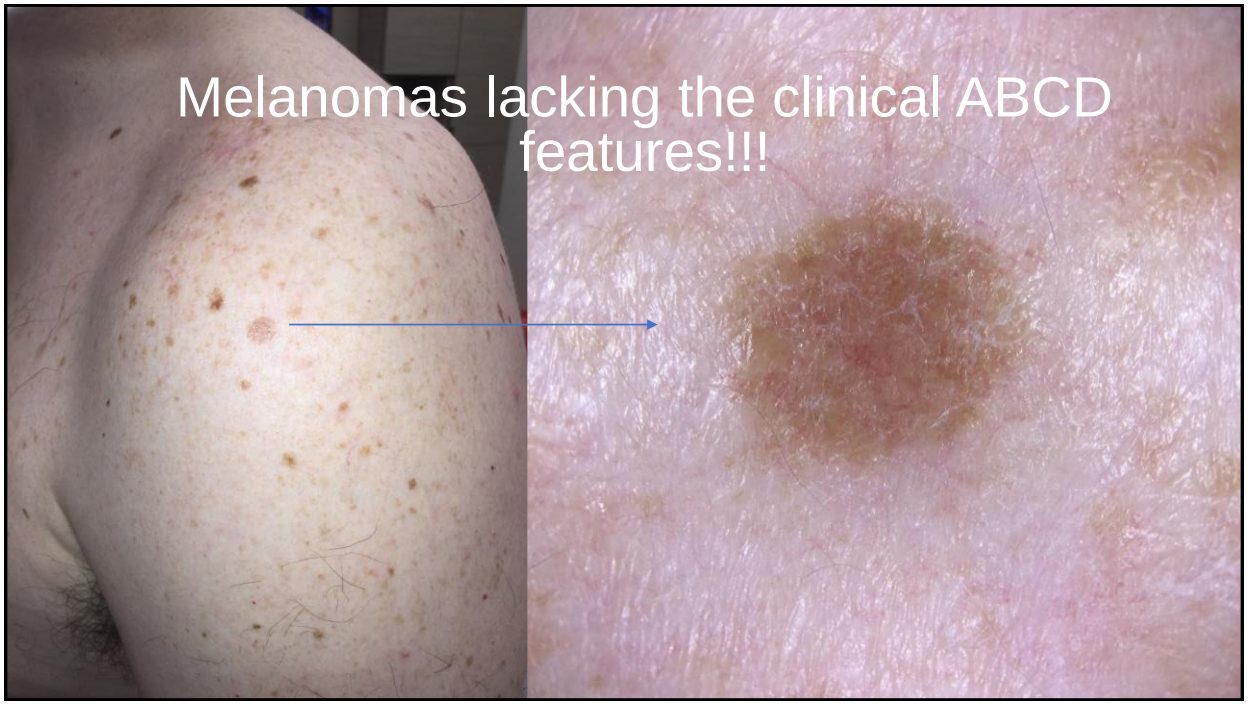

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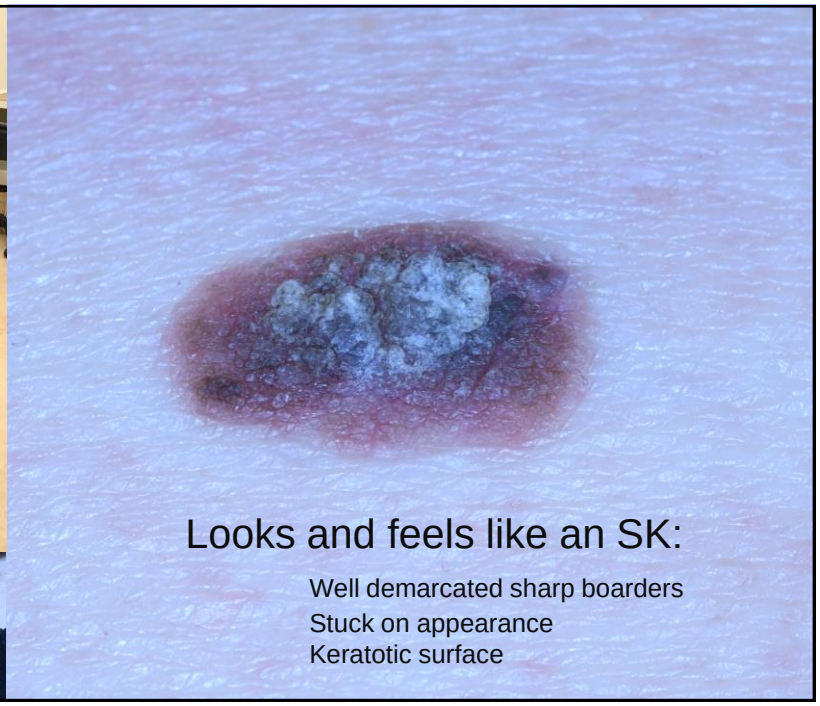

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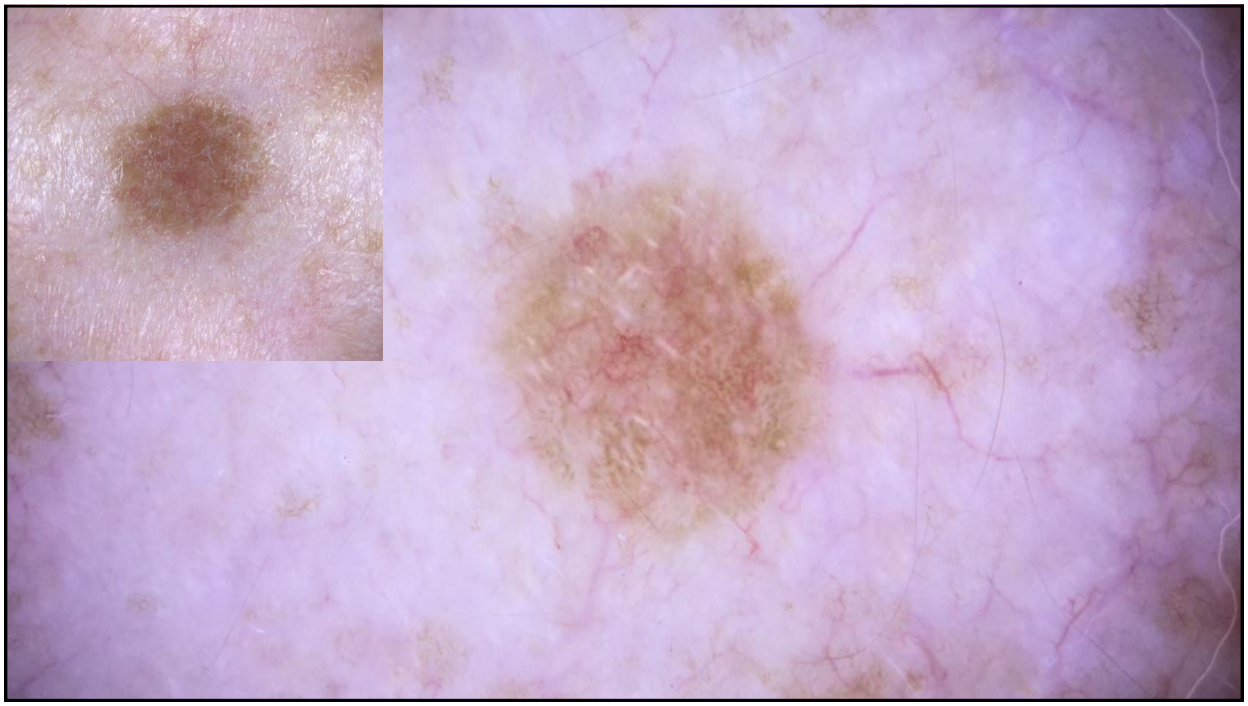

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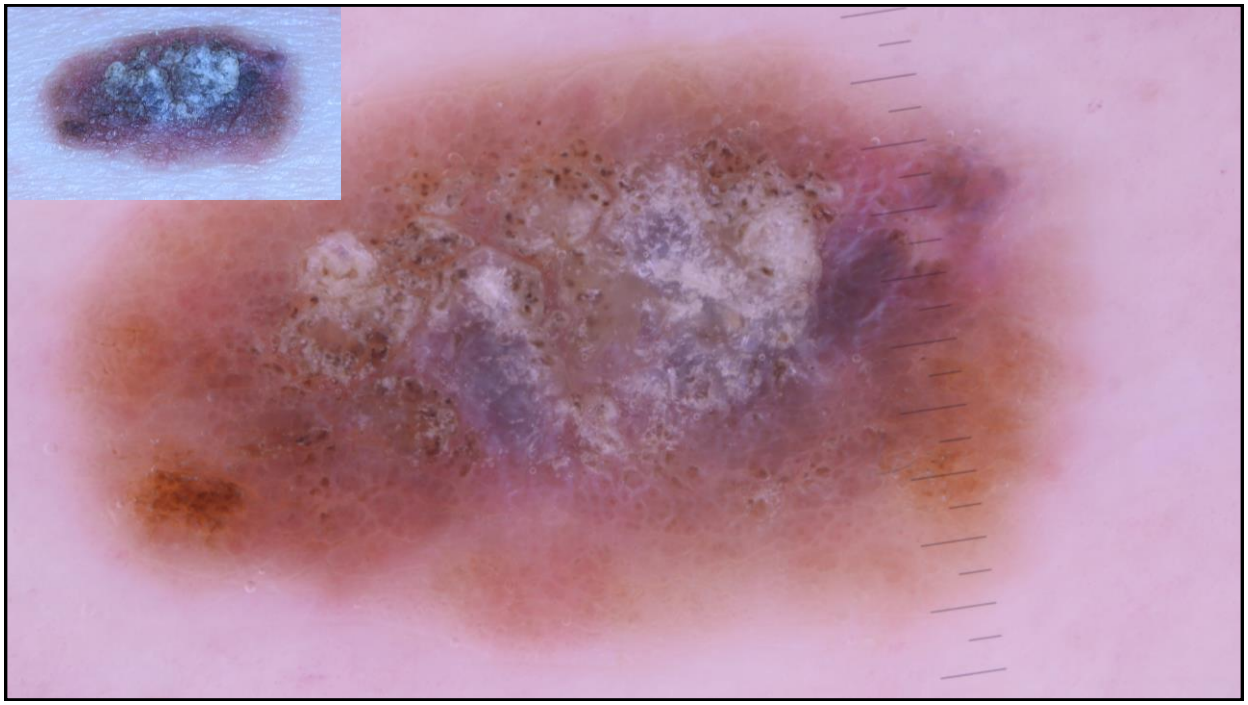

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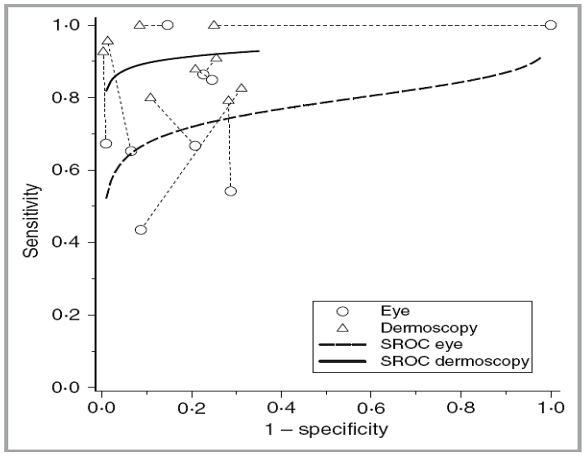
Diagnostic Accuracy: dermoscopy vs. naked-eye



There remains room for clinical improvement!

- ROC, receiver operating characteristic.
  Vestergaard ME, et al. Br J Dermatol. 2008;159:669-76.

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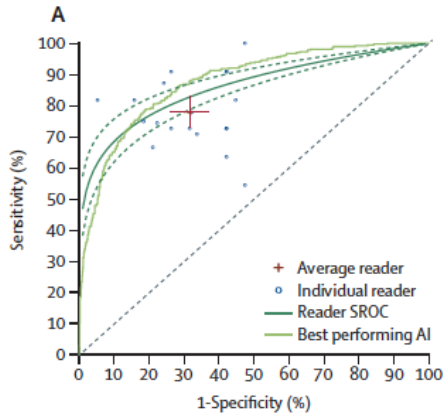
Validation of artificial intelligence prediction models for skin cancer diagnosis using dermoscopy images: the 2019 International Skin Imaging Collaboration Grand Challenge

Marc Combalia*, Noel Codella*, Veronica Rotemberg*, Cristina Carrera, Stephen Dusza, David Gutman, Brian Helba, Harald Kittler, Nicholas R Kurtansky, Konstantinos Liopyris, Michael A Marchetti, Sebastian Podlipnik, Susana Puig, Christoph Rinner, Philipp Tschandl, Jochen Weber, Allan Halpern*, Josep Malvehy*



Artificial intelligence for melanoma diagnosis

Philipp TSCHANDL *

teaching.[46] In conclusion, convolutional neural networks today are not inferior to dermatologists in basic image evaluation, but as rating an image is not matching a full clinical patient, or histologic, exam human-computer collaboration methodologies can be estimated to be the more successful path in the close future. For any application, the medical and scientific community should demand prospective clinical trials proving the benefit of CNNs in clinical practice.

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What is the significance of the insights we have made so far?

- Clinical expertise remains important and will remain so for the foreseeable future
- Technology offers the potential to elevate the expertise level of clinicians
  - Experts have a high threshold for biopsy: high specificity
  - Non-experts have a low threshold to biopsy: low specify

} Sensitivity similar

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Using these basic human functions we can identify subtle MM

- Case

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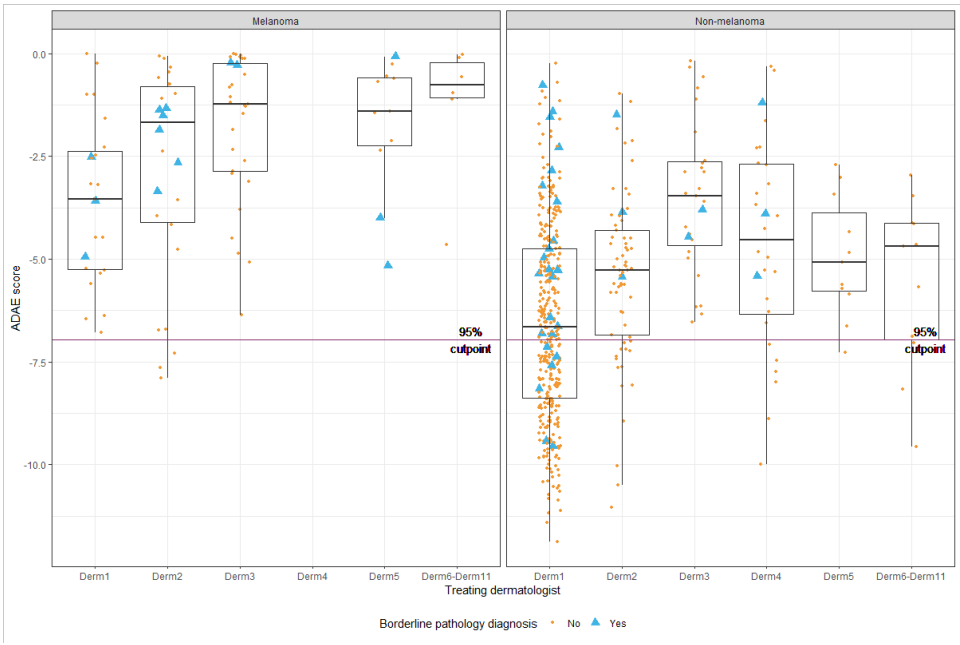
} Sensitivity similar

42

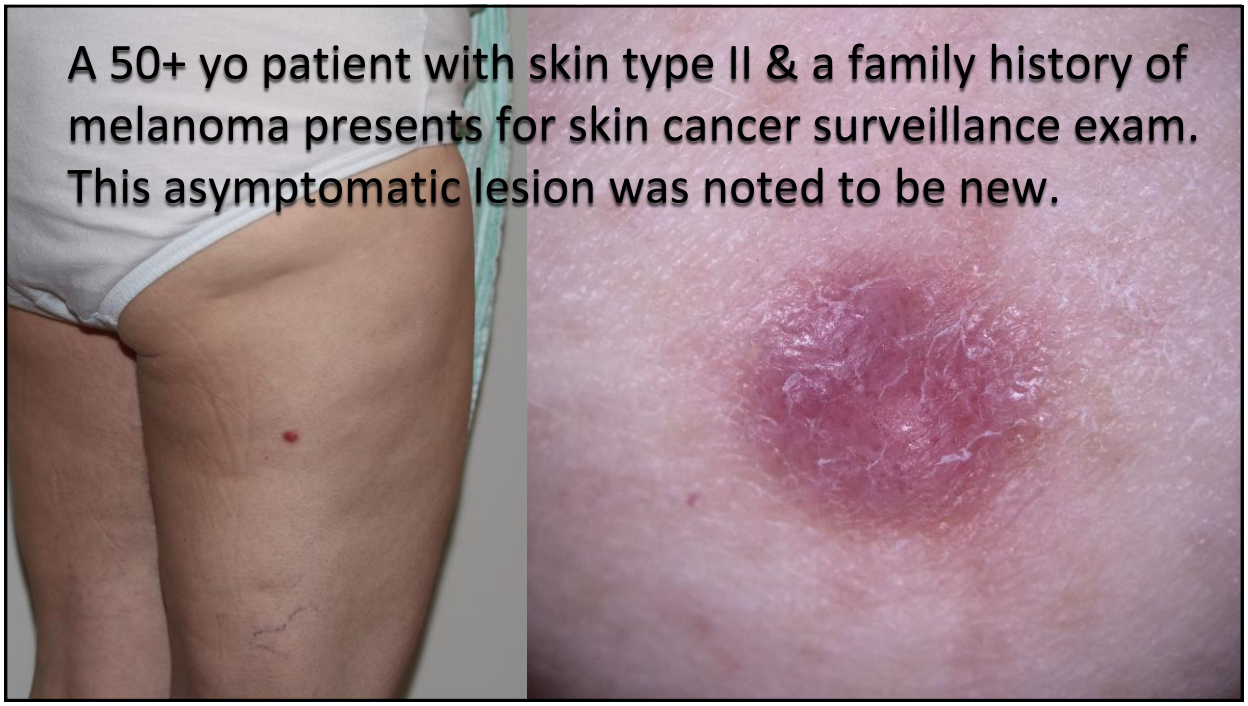


43

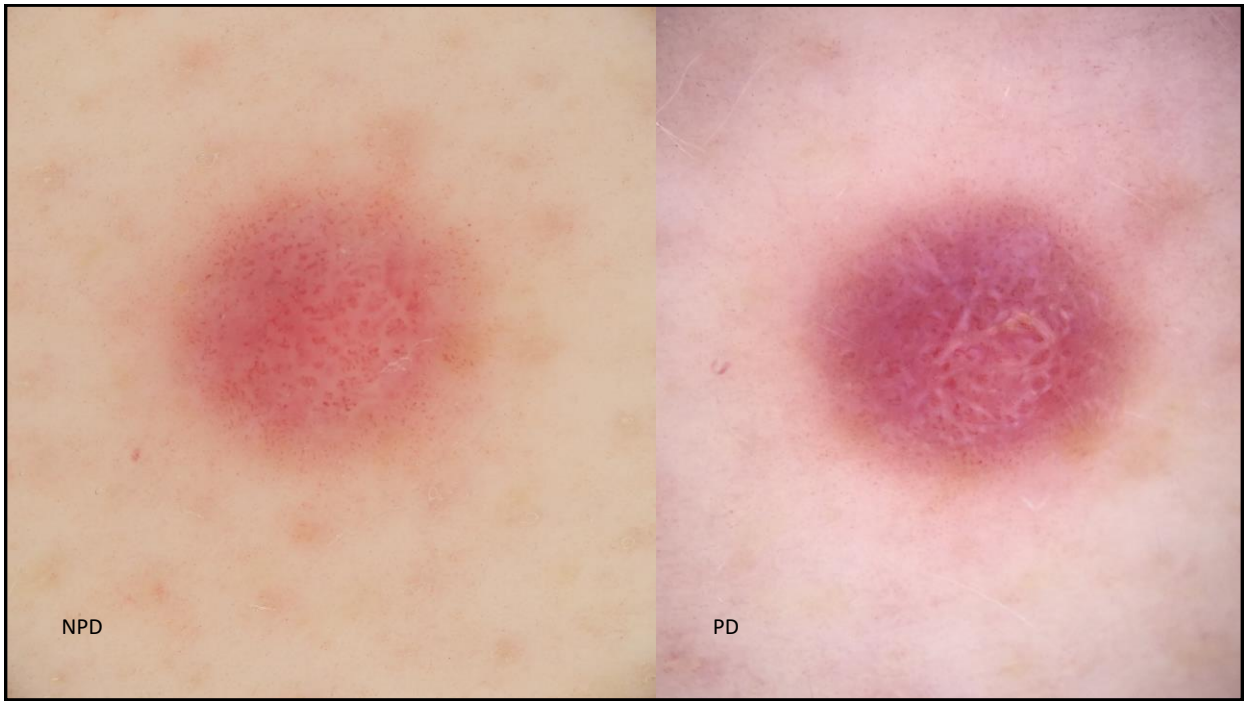
The limitations of AI

- Not able to detect some melanomas (which we are getting better at finding)
- Lower specificity resulting in excessive biopsies (expertise can impact this)

44


A 50+ yo patient with skin type II & a family history of melanoma presents for skin cancer surveillance exam. This asymptomatic lesion was noted to be new.

45


NPD
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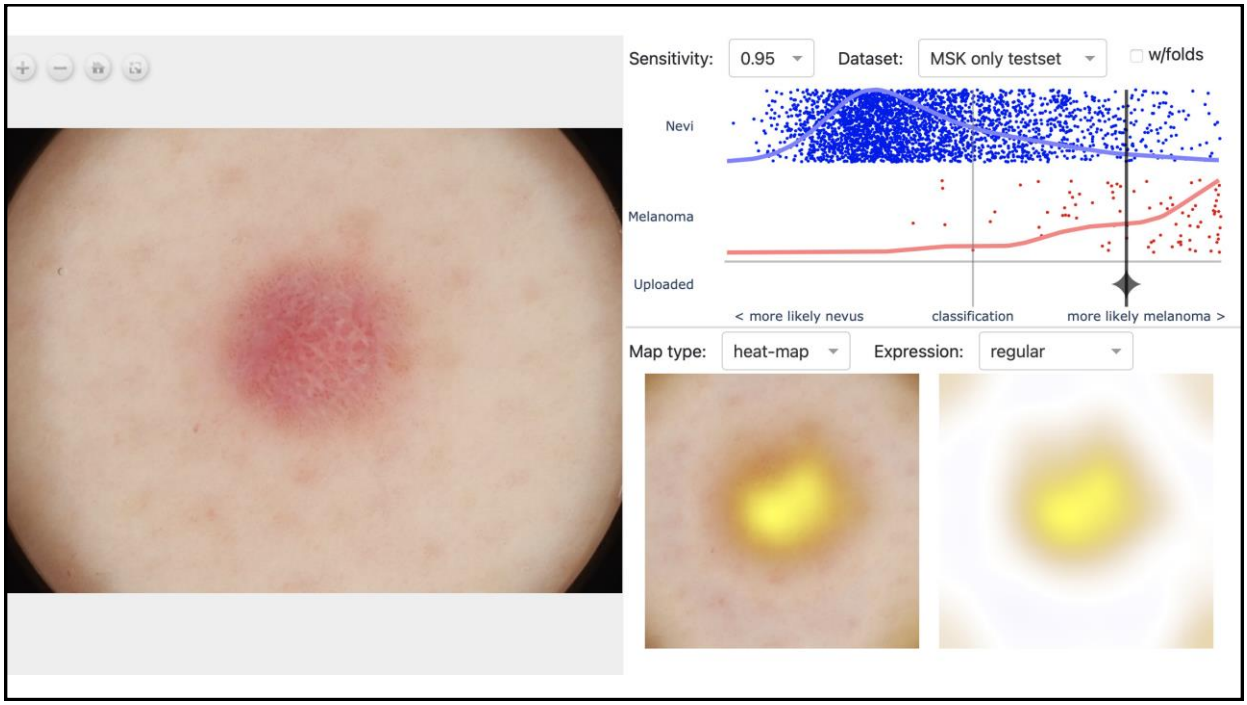
46



47

JAMA Dermatology | Original Investigation

Assessment of Diagnostic Performance of Dermatologists Cooperating With a Convolutional Neural Network in a Prospective Clinical Study

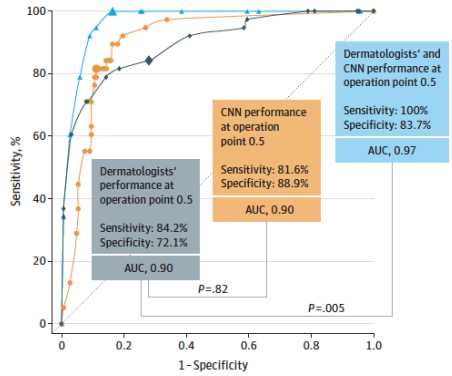
Human With Machine

Julia K. Winkler, MD; Andreas Blum, MD; Katharina Kommo
Albert Rosenberger, MSc; Holger A. Haenssle, MD

CONCLUSIONS AND RELEVANCE In this prospective diagnostic study, these findings suggest that dermatologists may improve their performance when they cooperate with the market-approved CNN and that a broader application of this human with machine approach could be beneficial for dermatologists and patients.

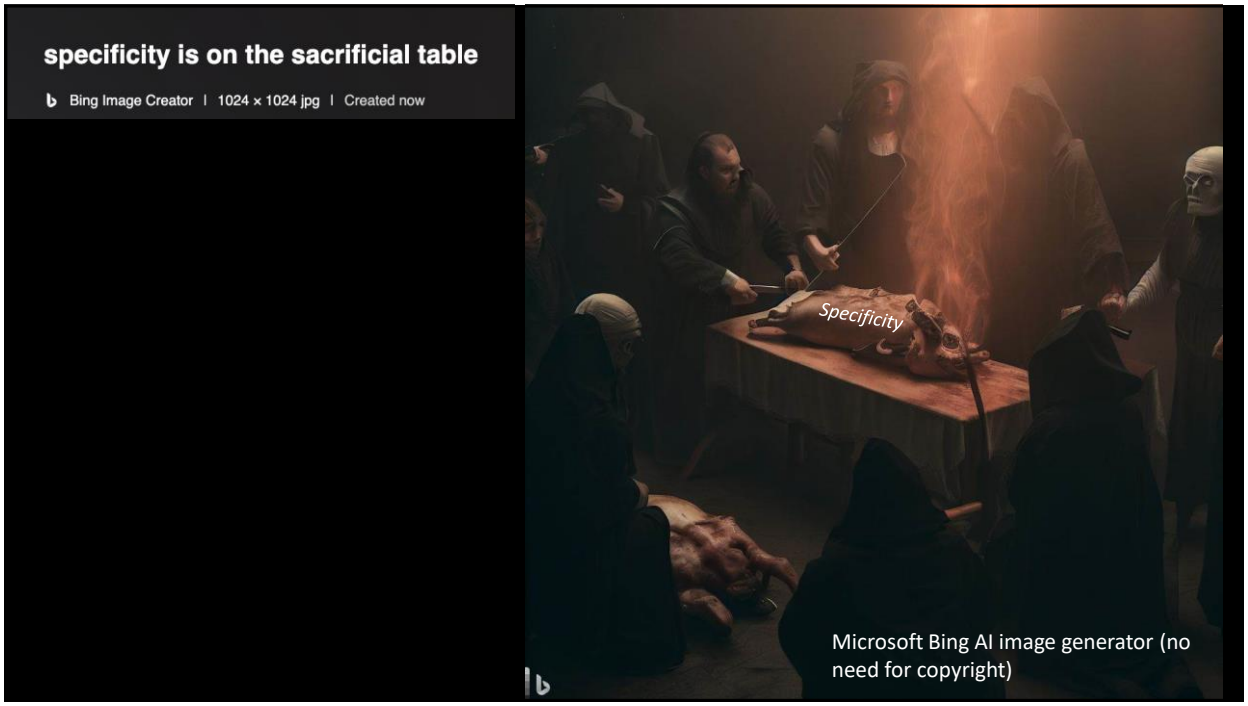
Table 2. Sensitivity, Specificity, and Accuracy of Diagnostic Classifications and Management Decisions of Dermatologists, Convolutional Neural Network (CNN), and Dermatologists Cooperating With CNN[a]

	Sensitivity	Specificity	Accuracy
Diagnostic classifications			
Dermatologists alone	84.2 (69.9-92.6)	72.1 (65.3-78.0)	74.1 (68.1-79.4)
CNN	81.6 (66.6-90.8)	88.9 (83.7-92.7)	87.7 (82.8-91.4)
Dermatologists with CNN	100.0 (90.8-100.0)	83.7 (77.8-88.3)	86.4 (81.3-90.3)
Management decisions			
Dermatologists alone	97.4 (86.5-99.5)	45.3 (38.3-52.4)	53.9 (47.5-60.3)
Dermatologists with CNN	100.0 (90.8-100.0)	55.8 (48.7-62.7)	63.2 (56.7-69.2)

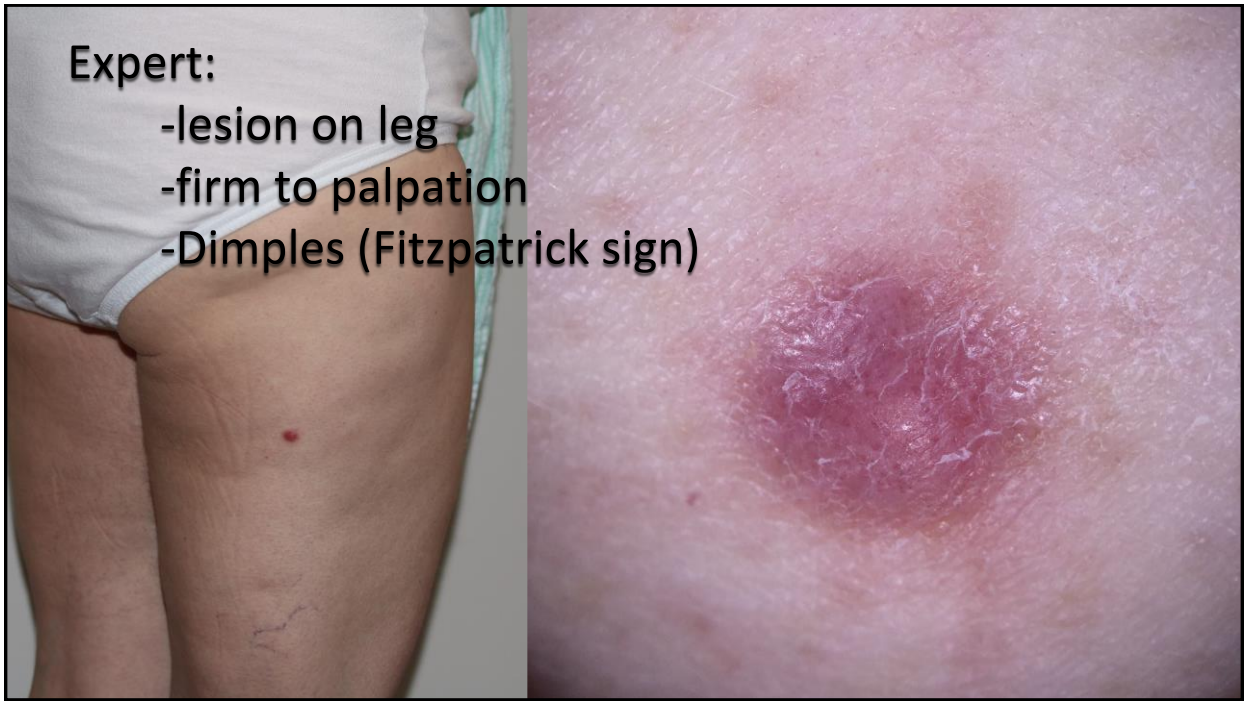


The CNN used was Moleanalyzer Pro (FotoFinder Systems). Sensitivities and specificities at the a priori operation point (cutoff for malignancy, ≥0.5) are depicted as larger symbols on the corresponding ROC curves. Abbreviation: AUC, area under the curve.

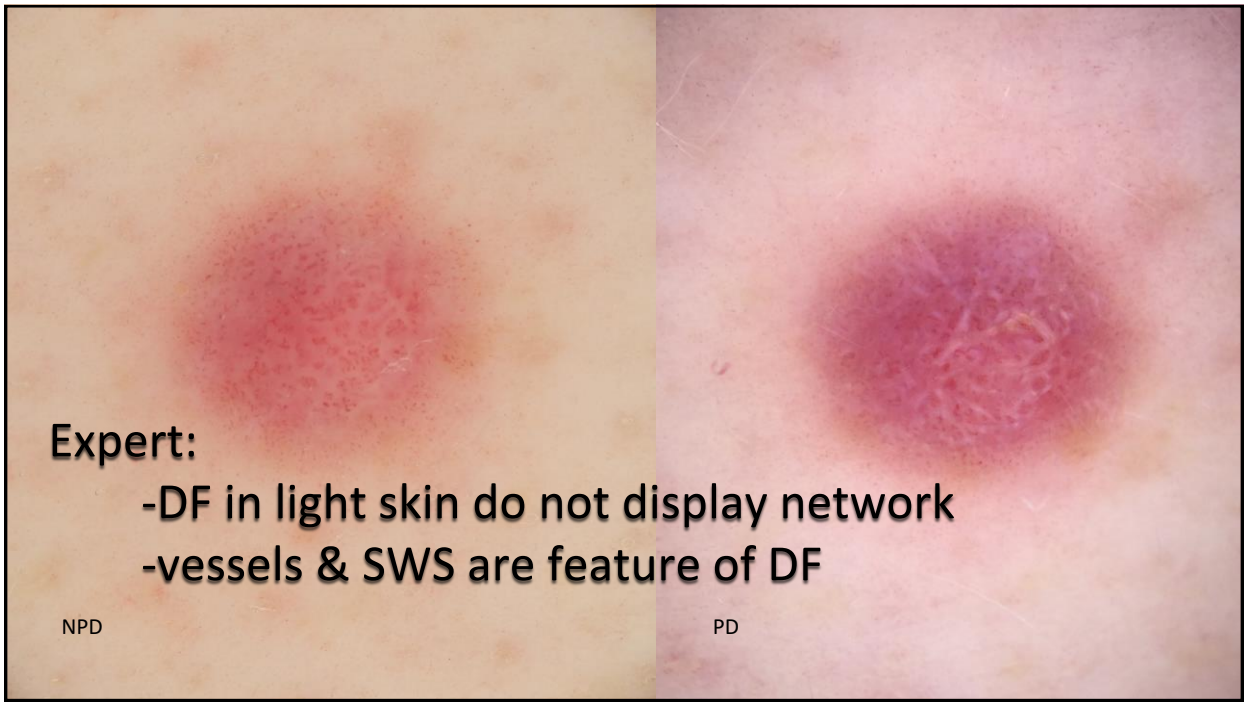
48


specificity is on the sacrificial table
Bing Image Creator | 1024 × 1024 jpg | Created now
Specificity
Microsoft Bing AI image generator (no need for copyright)

49

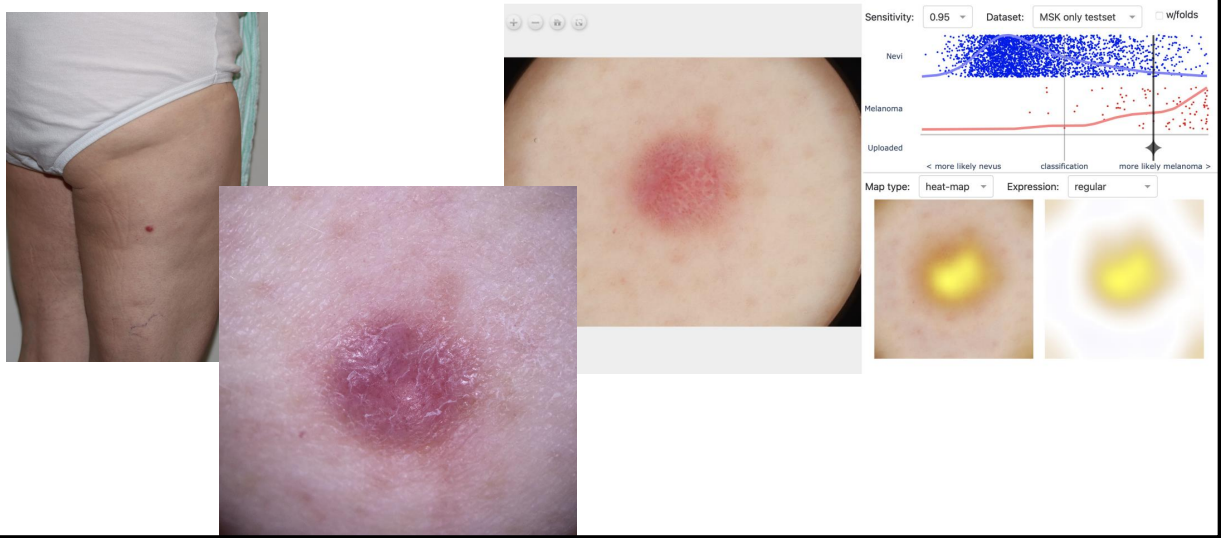

Expert:
-lesion on leg
-firm to palpation
-Dimples (Fitzpatrick sign)

50



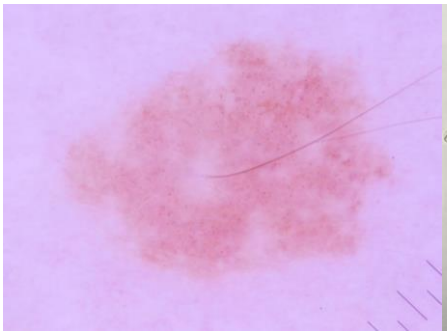
51

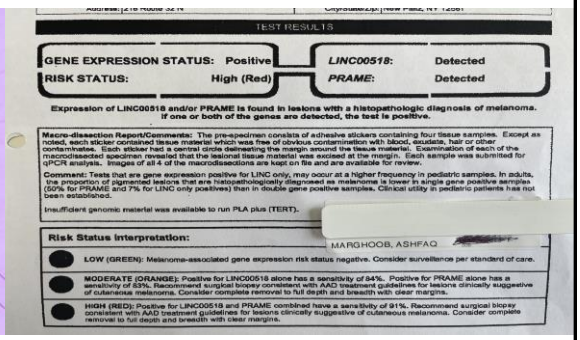
It's a DF despite what AI thinks!



52

All technology from RCM, electrical impedance, AI to GEP needs to be applied to a narrow group of appropriately selected lesions!





TEST RESULTS

GENE EXPRESSION STATUS: Positive — LINC00518: Detected

RISK STATUS: High (Red) — PRAME: Detected

Expression of LINC00518 and/or PRAME is found in lesions with a histopathologic diagnosis of melanoma. If one or both of the genes are detected, the test is positive.

Macro-dissection Report/Comments: The pre-specimen consists of adhesive stickers containing four tissue samples. Except as noted, each sticker contained tissue material which was free of obvious contamination with blood, exudate, hair or other contaminates. Each sticker had a central circle delineating the margin around the tissue material. Examination of each of the macrodissected specimen revealed that the lesional tissue material was excised at the margin. Each sample was submitted for qPCR analysis. Images of all 4 of the macrodissections are kept on file and are available for review.

Comment: Tests that are gene expression positive for LINC only, may occur at a higher frequency in pediatric samples. In adults, the proportion of pigmented lesions that are histopathologically diagnosed as melanoma is lower in single gene positive samples (50% for PRAME and 7% for LINC only positives) than in double gene positive samples. Clinical utility in pediatric patients has not been established.

Insufficient genomic material was available to run PLA plus (TERT).

Risk Status Interpretation:

MARGHOOB, ASHFAQ

LOW (GREEN): Melanoma-associated gene expression risk status negative. Consider surveillance per standard of care.

MODERATE (ORANGE): Positive for LINC00518 alone has a sensitivity of 84%. Positive for PRAME alone has a sensitivity of 83%. Recommend surgical biopsy consistent with AAD treatment guidelines for lesions clinically suggestive of cutaneous melanoma. Consider complete removal to full depth and breadth with clear margins.

HIGH (RED): Positive for LINC00518 and PRAME combined have a sensitivity of 91%. Recommend surgical biopsy consistent with AAD treatment guidelines for lesions clinically suggestive of cutaneous melanoma. Consider complete removal to full depth and breadth with clear margins.

9yo with unchanged lesion present since age 2.

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The role of the clinician in the age of technology

- Morphology
  a. Clinical expertise required to ID lesion/s at high probability for being MM
     - Humans vision: analytical, differential, & comparative recognition
     - Technology: AI Neural networks can classify lesions into risk categories, GEP…
  b. Clinical expertise required to decide which lesions need further evaluation & in differentiating nevi from MM
     - ABCDs have helped but MMs can lack the clinical ABCDs or can resemble SKs
     - Dermoscopy has helped in improving DA but its not 100%
     - AI Neural networks can match expert DA
  c. Clinicians recognize that MMs can be clinically and dermoscopically featureless
     - Monitoring (biology) has helped improve DA

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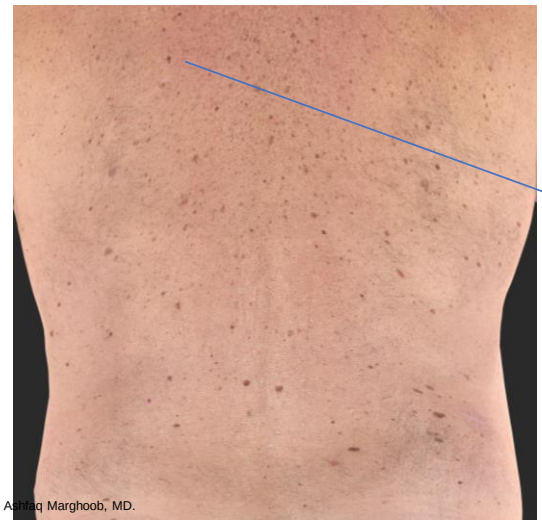
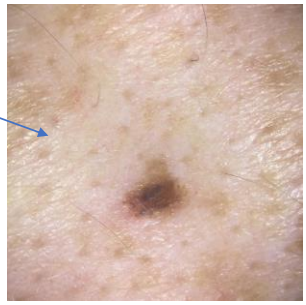
Clinically featureless MM





Photos courtesy of Ashfaq Marghoob, MD.

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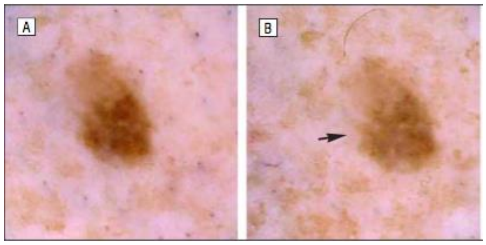
Sequential dermoscopy imaging helps in detection of so-called "featureless" melanomas

Identification of Clinically Featureless Incipient Melanoma Using Sequential Dermoscopy Imaging

Harald Kittler, MD; Pascale Guitera, MD; Elisabeth Riedl, MD; Michelle Avramidis, MD; Ligia Teban, MD; Manfred Fiebiger, MD; Rickard A. Weger, MD; Markus Dawid, MD; Scott Menzies, MBBS, PhD

Table 2. Positive Features of Melanoma per Lesion Seen in Baseline and Follow-up Images of Melanomas and Melanocytic Nevi*

No. of Positive Features of Melanoma	Melanoma	Melanocytic Nevi	*P* Value†
Baseline images	n = 91	n = 408	
0	56 (61.5)	279 (68.4)	.41
1	28 (30.8)	107 (26.2)	
>1	7 (7.7)	22 (5.4)	
Follow-up images, 1.5-4.5 mo	n = 34	n = 202	
0	21 (61.8)	152 (75.2)	.15
1	11 (32.4)	41 (20.3)	
>1	2 (5.9)	9 (4.5)	



- 61.5% of melanomas had no MM-specific structures at baseline.
- 61.8% of melanomas had no MM-specific structures at f/u of between 1.5-4.5 months!
- Only global changes helped identify these 'insipient' melanomas

ARCH DERMATOL/VOL 142, SEP 2006 WWW.ARCHDERMATOL.COM
1113

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The role of the clinician in the age of technology

1. Morphology
2. Change (biology)
3. Integration of morphology & biology (genesis)
4. Interpreter & advancements

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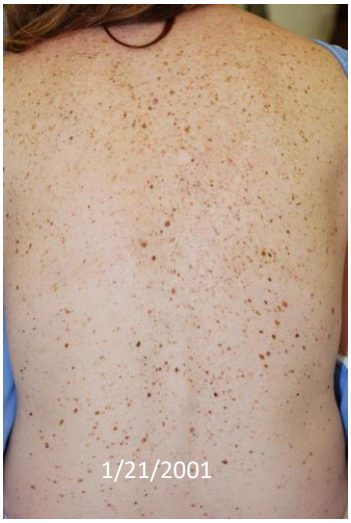
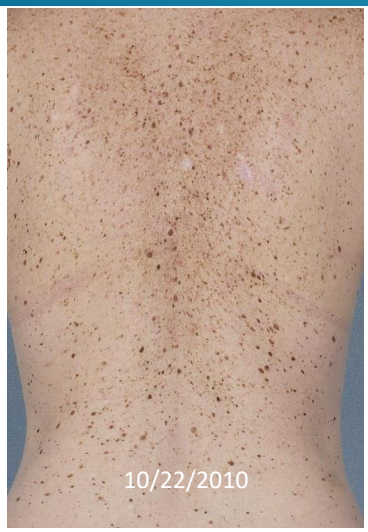
The role of the clinician in the age of technology

- Change (biology)
  a. Lack of change is a sign that the lesion is not a MM (or not a biologically relevant MM)
     - Results in few biopsies of nevi
  b. <1-3% of changing lesions prove to be melanoma since nevi do change

59

Most Nevi in Adults (Senescent Nevi) Are Remarkably Stable and Do Not Change (or Will Involute)





Photos courtesy of Ashfaq A. Marghoob, MD.

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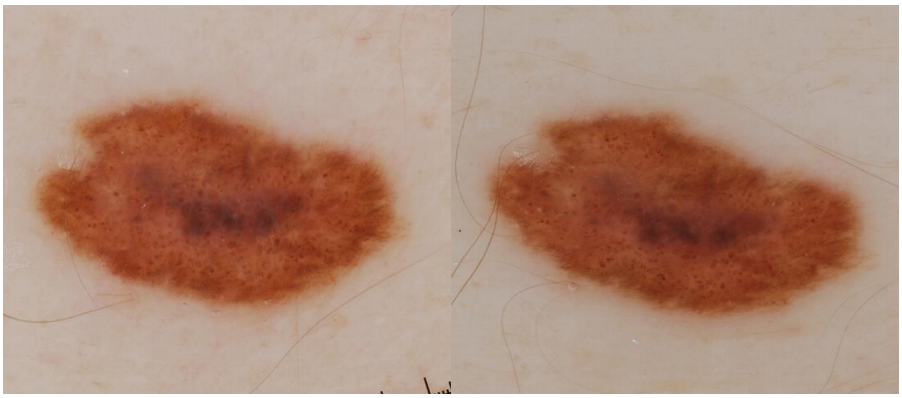
Followed for 8 years



No change

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TBP: reduces the number of unnecessary biopsies

Comparative Analysis of Total Body and Dermatoscopic Photographic Monitoring of Nevi in Similar Patient Populations at Risk for Cutaneous Melanoma

Agnessa Gadeliya Goodson, MD,* Scott R. Florell, MD,* Mark Hyde, PA-C,† Glen M. Bowen, MD,*† and Douglas Grossman, MD, PhD*†

BACKGROUND Our previous experience monitoring nevi in high-risk patients using serial digital epiluminescence microscopy (DELM) photography achieved low biopsy rates but was limited by melanomas presenting as new lesions or arising from nevi that had not been photographed.

OBJECTIVE To determine whether biopsy rates, efficiency of melanoma detection, and melanoma origin (de novo vs nevus derived) differed in a similar patient population monitored using total body (TB) photography.

METHODS One thousand seventy-six patients (including 187 from a prior cohort) underwent TB photography and were monitored using photographs obtained at the initial visit. Risk factors and median monitoring periods for these patients were comparable with those of patients previously monitored using DELM photography.

RESULTS Two hundred seventy-five biopsies were performed in 467 patients on follow-up visits. Of 12 melanomas detected on follow-u
new lesions, nine arose de novo,

CONCLUSIONS In our experienc
ing TB photography was associat
using DELM and facilitated dete
melanomas detected on follow-u

-Fewer nevi biopsied per patient

-Reduces the number of nevi biopsied for each MM found

Goodson et al	No TBP +dermoscopy	TBP +dermoscopy
Biopsies on follow up	1.1 per pt	0.59 per pt
Nevus:MM	45	17
% MM *de novo*	83%	75%

TBP, total body photography.
Goodson AG, et al. Dermatol Surg. 2010;36:1087-98.

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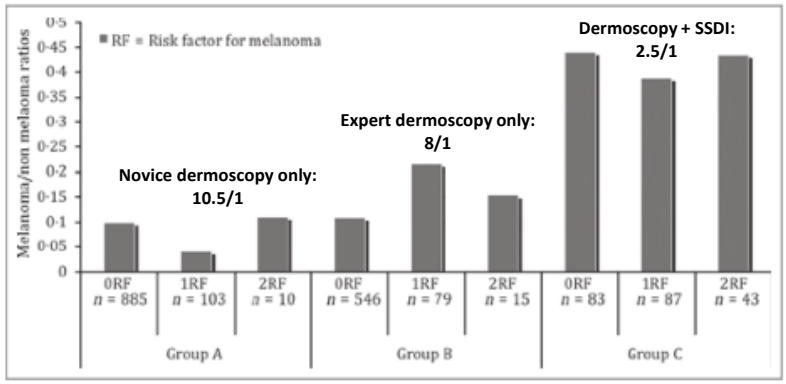
SDI reduces unnecessary biopsies of moles by 75%

46 dermatologists, 1-year study; equivalent sensitivity in all groups (91-95%); no diff. thickness

Availability of digital dermoscopy in daily practice dramatically reduces the number of excised melanocytic lesions: results from an observational study

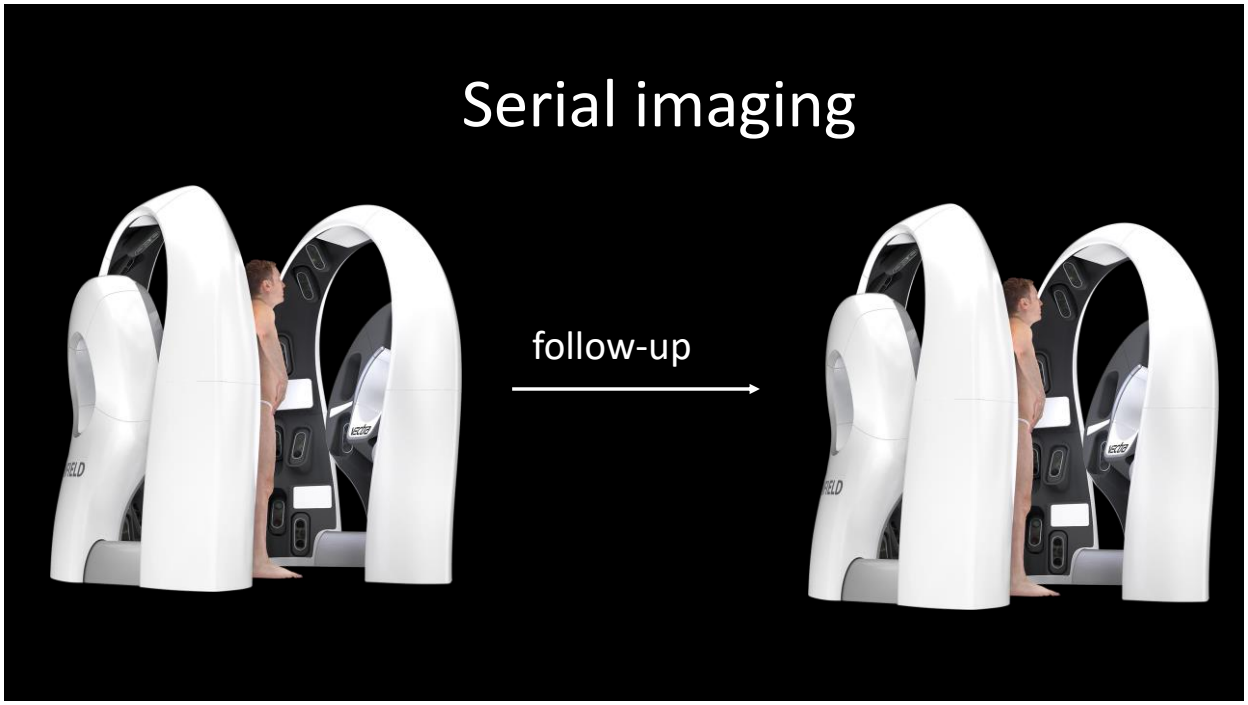
I. Tromme,[1]* L. Sacré,[1]* F. Hammouch,[2] C. Legrand,[3] L. Marot,[1] P. Vereecken,[1] I. Theate,[1] P. van Eeckhout,[1] P. Richez,[1] J.F. Baurain,[2] L. Thomas[4] and N. Speybroeck[5] on behalf of the DEPIMELA study group

PPV

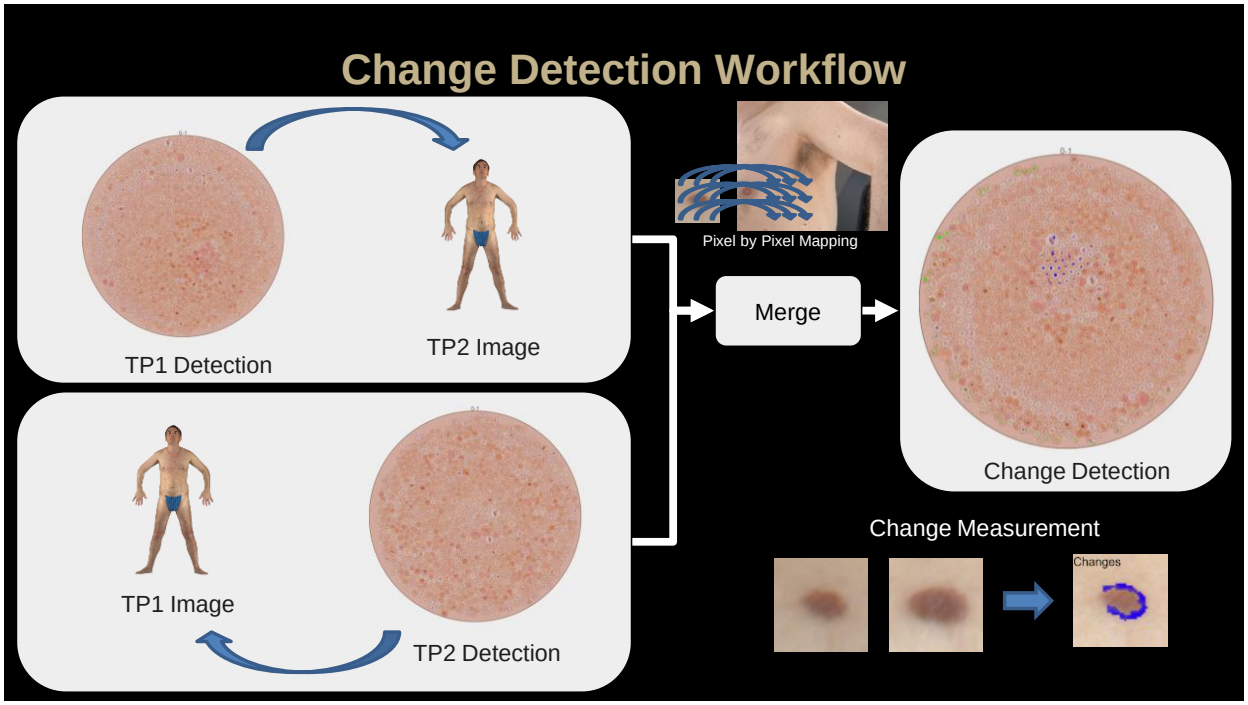


BJD. 2012

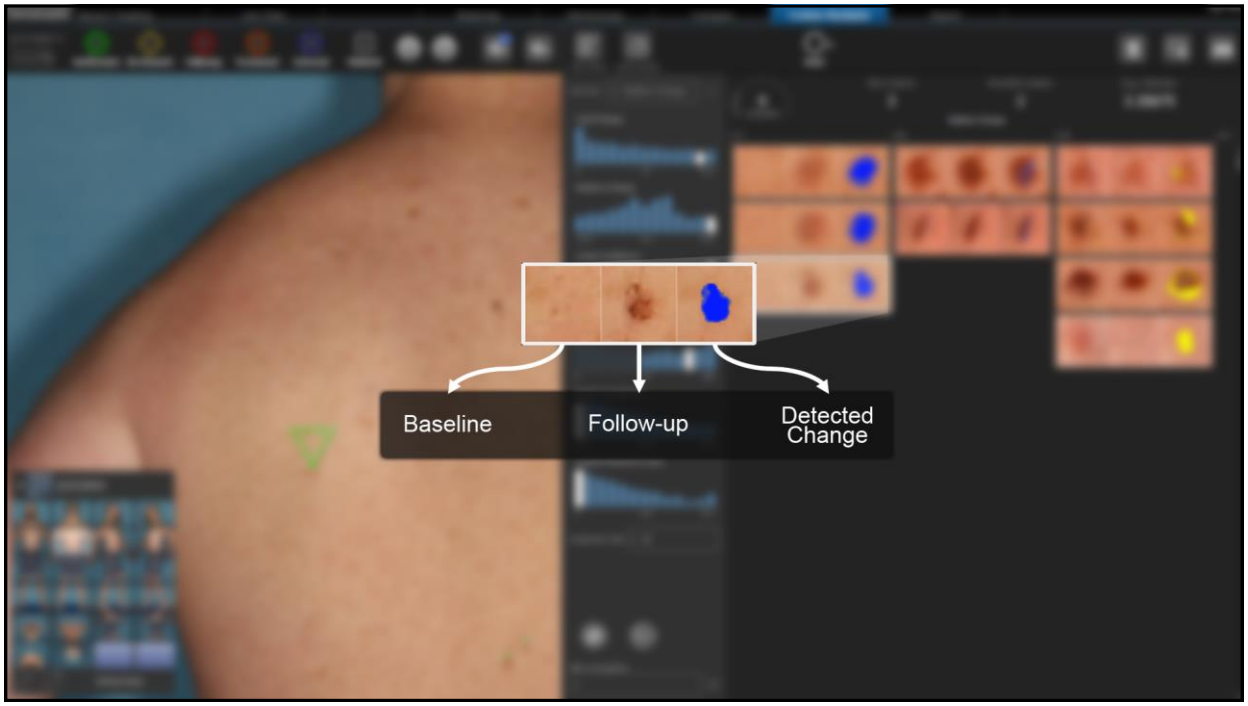
63


Serial imaging
follow-up

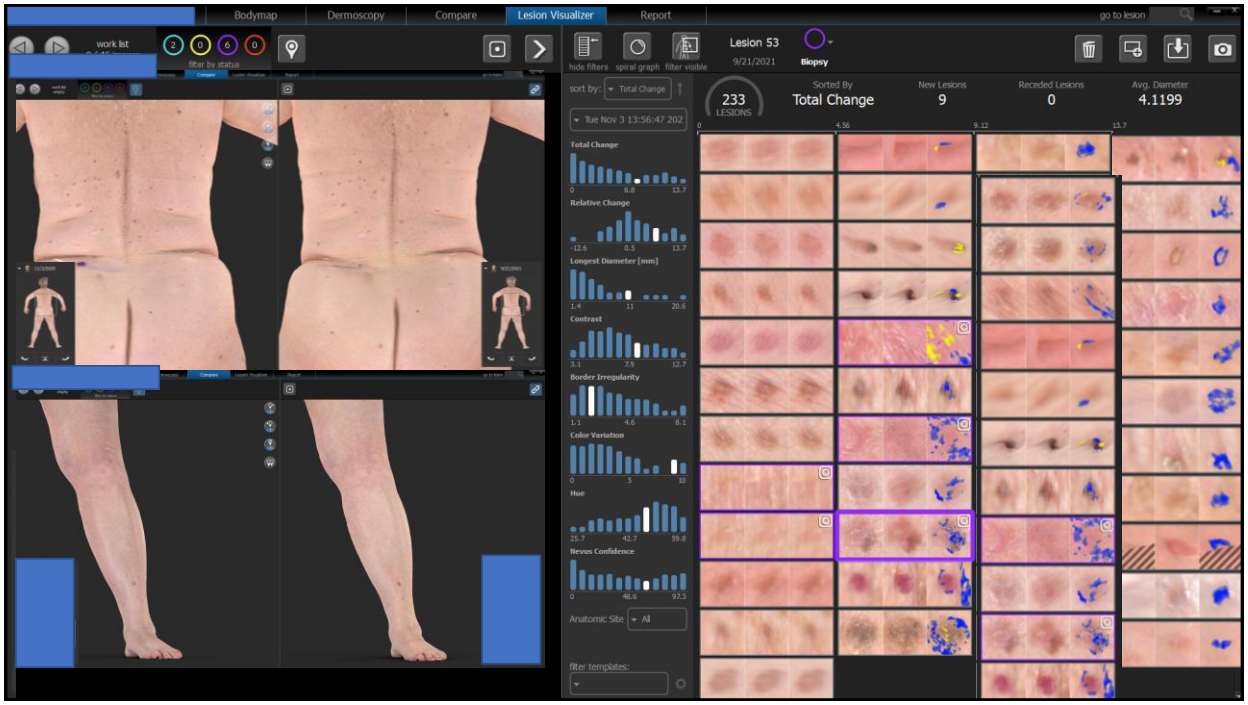
64


Change Detection Workflow
TP1 Detection
TP2 Image
Pixel by Pixel Mapping
Merge
Change Detection
TP1 Image
TP2 Detection
Change Measurement
Changes

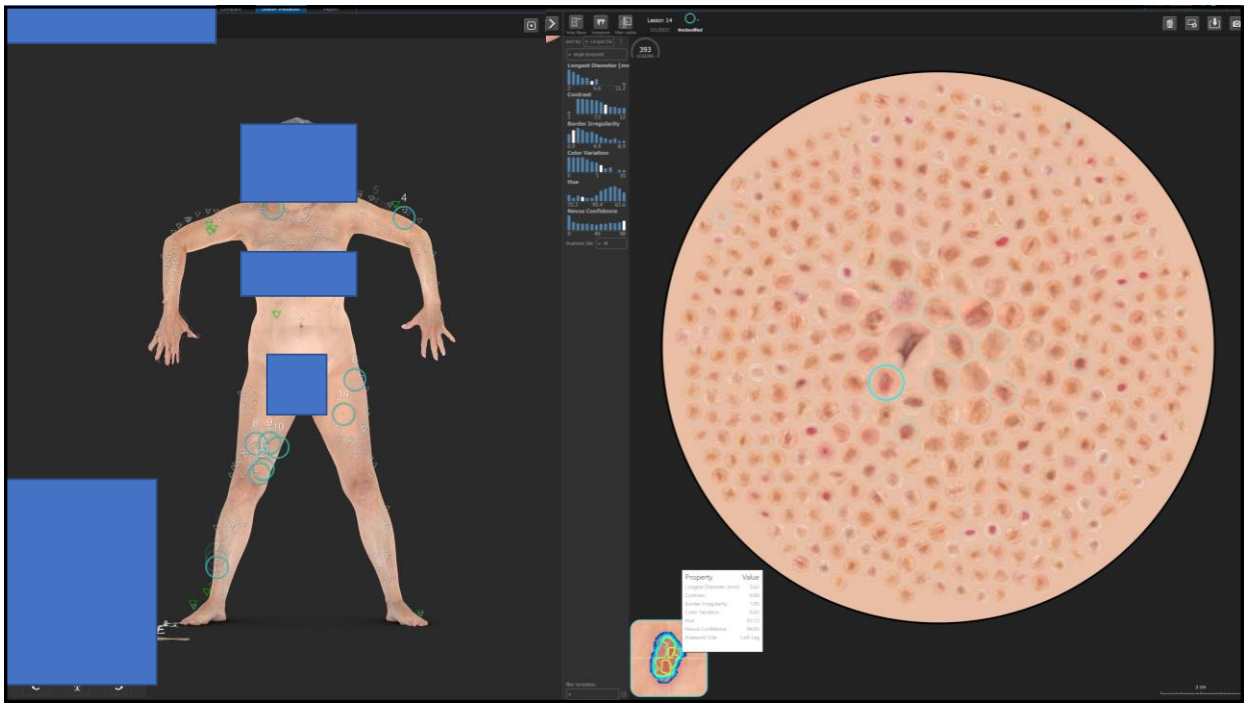
65


Baseline
Follow-up
Detected Change

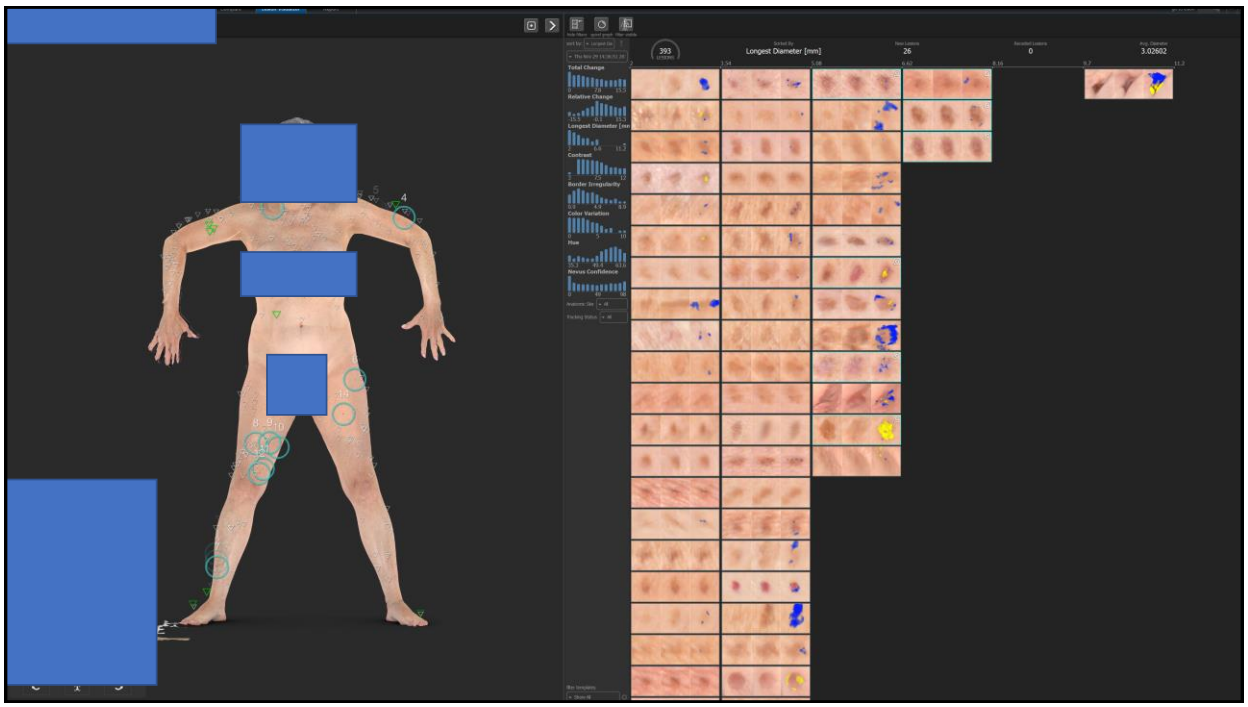
66


Bodymap
Dermoscopy
Compare
Lesion Visualizer
Report
Lesion 53
9/21/2021
Biopsy
233
LESIONS
Sorted By
Total Change
New Lesions
9
Receded Lesions
0
Avg. Diameter
4.1199

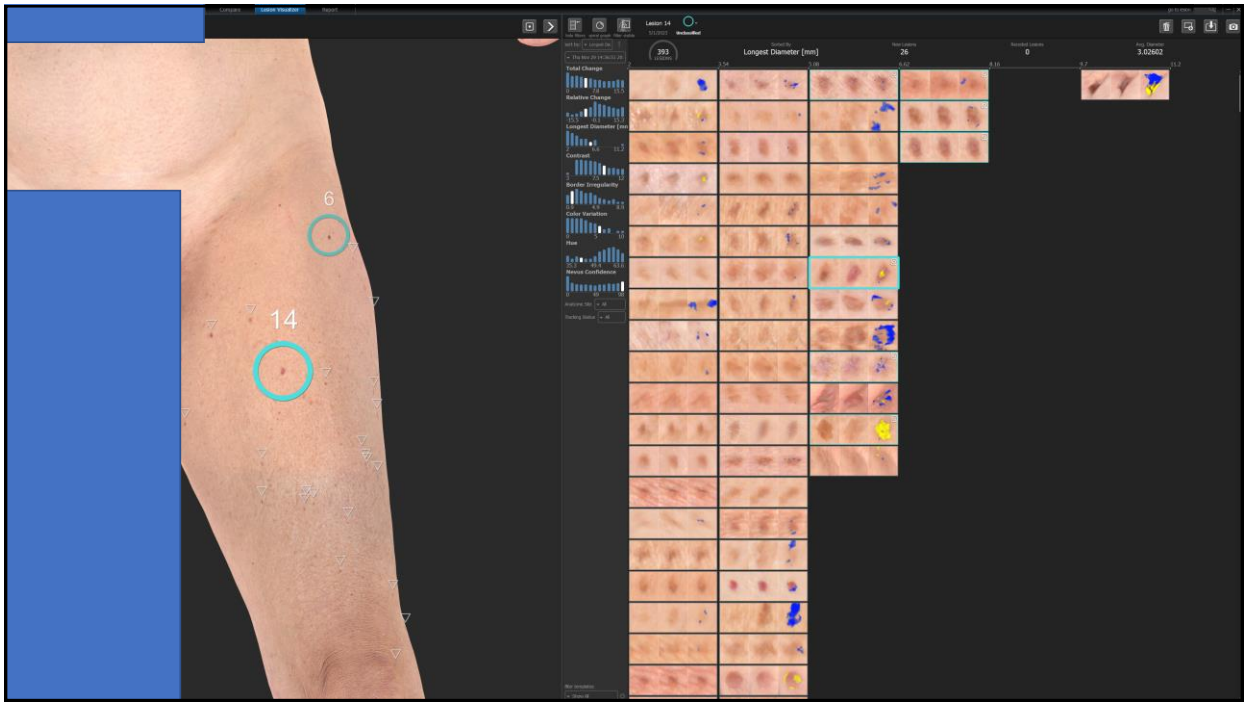
67



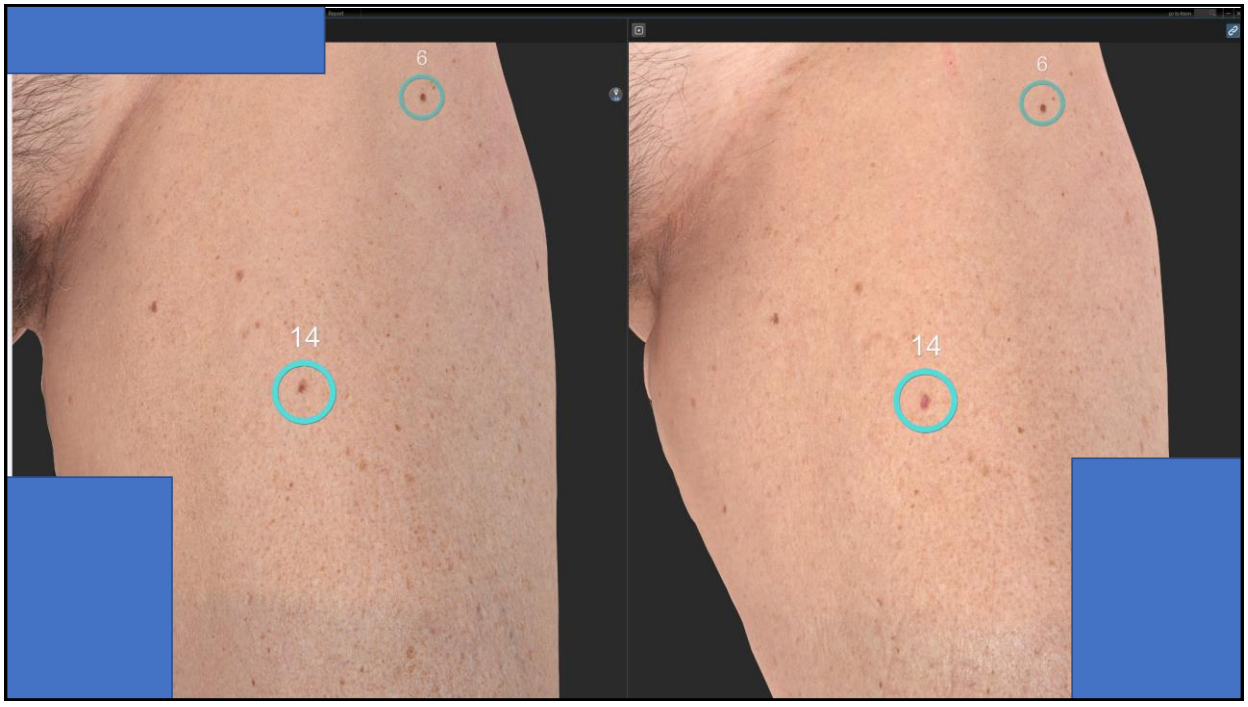
68



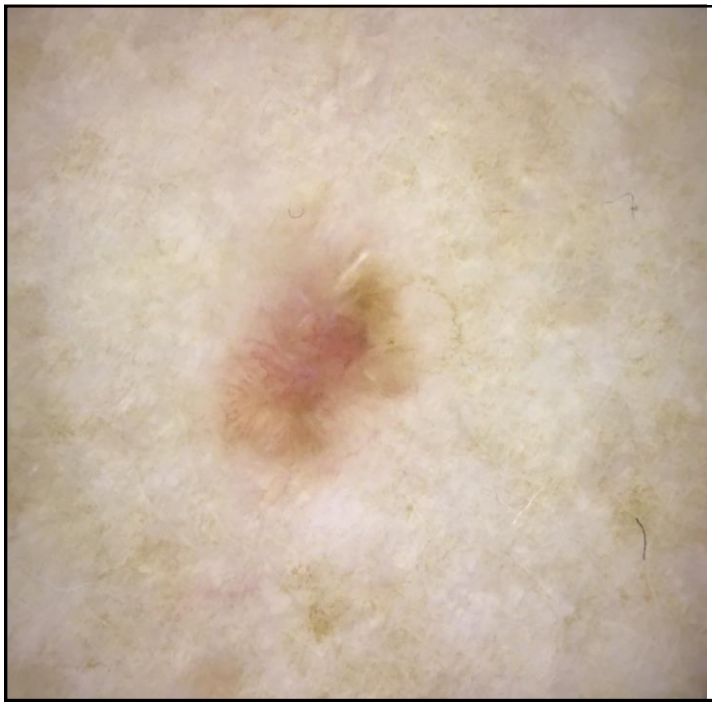
69



70



71



- Dermoscopy remains the main instrument to help decide which changed lesions require further investigation.

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The role of the clinician in the age of technology

- Change (biology)
  a. However, lack of change is a sign that the lesion is not a MM (or not a biologically relevant MM)
  b. <1-3% of changing lesions prove to be melanoma since nevi do change

Study	Year	# pts.	# lesions followed	Nevi followed/ patient	# changed	# melanoma	%MM/ changed
Schiffner	2003	145	272	1.9	95	0	0.0
Bauer	2005	196	2015	10.3	128	2	1.6
Robinson	2004	100	3482	34.8	193	4	2.1
Banky	2005	309			573	18	3.1

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The role of the clinician in the age of technology

1. Morphology
2. Change (biology)
3. Integration of morphology & biology (genesis)
4. Interpreter & advancements

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The role of the clinician in the age of technology

- Integration of morphology & biology (genesis) will be mission critical
  a. Addressing unnecessary biopsies (cost containment) while still finding relevant disease (context)
     - Lack of change, type of change, &/or rate of change may improve DA
  b. Perhaps discovering the true DN
  c. Addressing overdiagnosis
     - Differentiating aggressive from indolent MM

75

Type of change

- Nevi change:
  - Nevi with peripheral globules
  - Nevi with streaks
- Melanoma change
  - Type of change and not necessarily the rate of change is key

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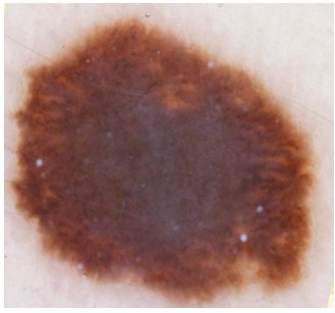
Streaks = radial growth phase of Reed's nevi



Argenziano G, Agozzino M, Bonifazi E, et al. Natural Evolution of Spitz Nevi. *Dermatology.* 2011.

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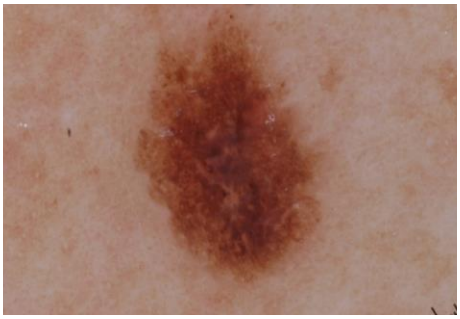
Peripheral globules = radial growth phase of some moderate DN (LAN)



Frequency and Characteristics of Enlarging Common Melanocytic Nevi

Harald Kittler, MD; Markus Seltenheim, MD; Markus Dawid, MD; Hubert Pehamberger, MD; Klaus Wolff, MD, FRCP; Michael Binder, MD

Objective: To analyze the frequency and characteristics of enlarging common melanocytic nevi.

Design: Cohort study using digital epiluminescence microscopy (ELM) for documentation and follow-up, with a median follow-up interval of 11.4 months.

Setting: A dermatology department at a university hospital in Vienna, Austria.

Patients: One thousand six hundred twelve melanocytic nevi appearing clinically as common nevi, obtained from 383 patients (mean [±SD] age, 34.2 ± 14.8 yr; 59.6% female).

Interventions: Follow-up examination and documentation by digital ELM.

Main Outcome Measures: Frequency of enlarging nevi according to age and comparison of ELM features observed in enlarging and nonenlarging nevi.

Results: Enlargement was found in 5.3% (n = 86) of nevi. The frequency of enlarging nevi was inversely related to age ($P<.001$), in that enlarging nevi were common in patients younger than 20 years and relatively rare in older age groups. Epiluminescence microscopy revealed a peripheral rim of brown globules in 48.8% (n = 42) of enlarging nevi. In contrast, a peripheral rim of brown globules was found in only 0.7% (n = 11) of nevi without enlargement ($P<.001$). Enlarging nevi that were excised in children and adolescents showed no histological signs of atypia. In older age groups, 48.1% of excised enlarging nevi that were clinically diagnosed as common nevi showed some histological signs of atypia. None of the excised enlarging lesions was histologically diagnosed as melanoma.

Conclusions: The frequency of enlarging common nevi is inversely related to age. In the absence of clinical signs of atypia, enlargement alone does not indicate malignancy. A peripheral rim of brown globules is a characteristic ELM feature of symmetrically enlarging melanocytic nevi.

Arch Dermatol. 2000;136:316-320

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Peripheral globules = radial growth

Baseline

6 months

14 months

36 months

50 months

10 years

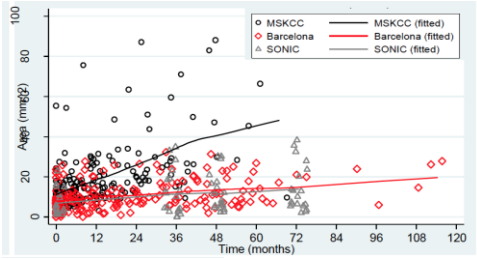
79

Original Investigation

Growth-Curve Modeling of Nevi With a Peripheral Globular Pattern

Shirin Bajaj, BA; Stephen W. Dusza, DrPH; Michael A. Marchetti, MD; Xinyuan Wu, BA; Maira Fonseca, BS; Kivanc Kose, PhD; Johanna Brito, MD; Cristina Carrera, MD; Vanessa P. Martins de Silva, MD; Josep Malvehy, MD; Susana Puig, MD, PhD; Sarah Yagerman, MD; Tracey N. Liebman, MD; Alon Scope, MD; Allan C. Halpern, MD, MSc; Ashfaq A. Marghoob, MD

	Growth Rate (per month)	CI, p-value
MSKCC	0.52mm²	95% CI: 0.43-0.61, p<0.001
Barcelona	0.12mm²	95% CI: 0.03-0.21, p=0.007
SONIC	0.13mm²	95% CI: 0.01-0.24, p=0.033
Average	0.27mm²	95% CI: 0.15-0.39, p=0.033



In those lesions that stopped growing (~20%), median time to growth cessation was at least 49.5 months, thus if a clinician

80

DERMATOLOGY PRACTICAL & CONCEPTUAL

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Growth rate of melanoma in vivo and correlation with dermatoscopic and dermatopathologic findings

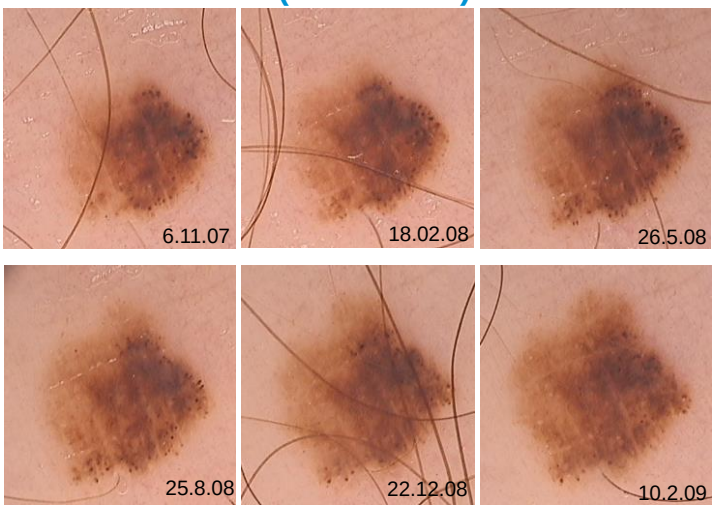
Jürgen Beer, M.D.[1], Lina Xu, M.D.[1], Philipp Tschandl, M.D.[1], Harald Kittler, M.D.[1]

Results: The median time interval between baseline and follow-up image was 12 months (range: 2–100 months). The majority of melanomas were in situ (n=28, 56%). The mean horizontal growth rate of all melanomas was 0.44 mm² (SD: ± 5.8 mm²/year). The histopathologic findings of numerous and large epidermal nests were associated with rapid growth. This histopathologic pattern corresponded to a pattern of clods ("globules") dermatoscopically. From a dermatoscopic point of view, melanomas with a main pattern of clods grew significantly faster (mean horizontal growth rate: 0.87 mm² 95% CI: 6.4-14.4 mm²/year) than melanomas with mainly a reticular pattern (4.8 0.4 mm² CI: 2.7-7.0 mm²/year) or with other patterns (0.21 mm² 95% CI: -0.5-5.6 mm²/year, p=0.01).

PG nevi growth rate: average 0.12-0.52mm² (depending on cohort) with fastest growth recorded at 2.26mm² !

81

Peripheral globules in melanoma = radial growth phase (MM 0.4mm)



82

Horizontal rate of growth of PG nevi and melanoma is the same

PG nevi	Melanoma
Grow symmetrically	Grow asymmetrically (63%)
No new features & no change in pattern	Often develop new features
Globules become sparser and smaller and eventually disappear	Globules do not disappear & if they do they are replaced by another MM specific structures
Growth cessation (50 months)	No growth cessation

CLINICAL AND LABORATORY INVESTIGATIONS
BJD British Journal of Dermatology

Slow-growing melanoma: a dermoscopy follow-up study

G. Argenziano, H. Kittler,* G. Ferrara,† P. Rubegni,‡ J. Malvehy,§ S. Puig,§ L. Cowell,¶ I. Stanganelli,** V. De Giorgi,†† L. Thomas,‡‡ P. Bahadoran,§§ S.W. Menzies,¶¶ D. Piccolo,*** A.A. Marghoob††† and I. Zalaudek‡‡‡

83

Integration of multiple technologies to evaluate suspect lesions

Clinical level [a,b]

- Confocal
- OCT
- Multi-spectra (SIAscopy)

Mechanical level [b]

- Electrical impedance

Molecular level signatures

- Tape strip for RNA[c]
- Dual photon spectroscopy (Raman)[d]

- *Example:*
  - *Changing lesion identified*
  - *Use GEP*
    - *If neg: follow*
    - *If pos: biopsy*

OCT, optical coherence tomography. a. Schuh S, et al. Cancers. 2022;14:1140. b. Ferrante di Ruffano, et al. Cochrane Database Syst Rev. 2018; 12:CD013186;c. Yao Z, et al. J Drugs Dermatol. 2017;16:979-986; d. Serebrennikova KV, et al. Biosensors (Basel). 2021;11:512.

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The role of the clinician in the age of technology

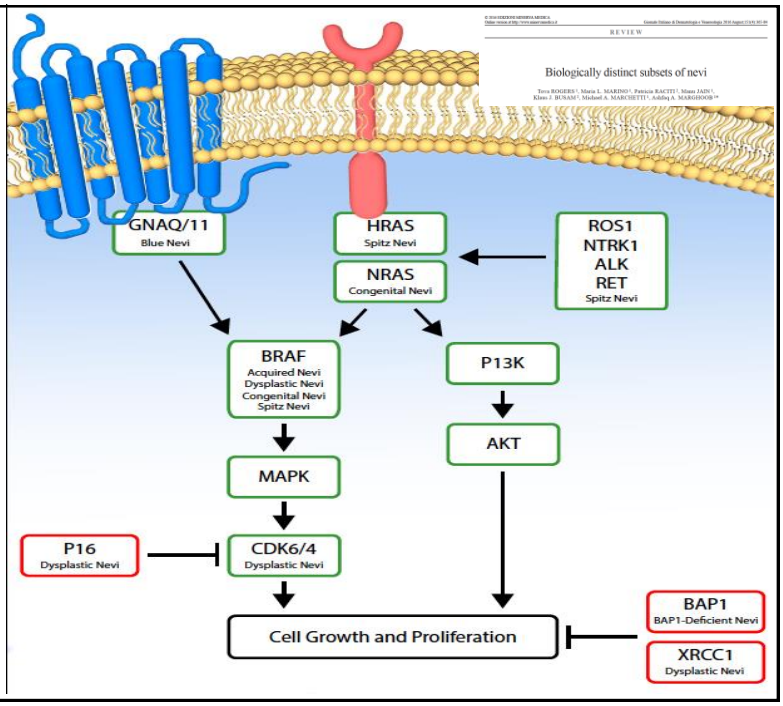
- Integration of morphology & biology (genesis) will be mission critical
  a. Addressing unnecessary biopsies (cost containment) while still finding relevant disease (context)
     - Lack of change, type of change, &/or rate of change may improve DA
  b. Perhaps discovering the true DN
  c. Addressing overdiagnosis
     - Differentiating aggressive from indolent MM

85

The knowledge of the existence of biologically distinct nevus subsets is likely to:

1. change the way nevi are classified

2. inform us about nevogenesis & melanomagenesis



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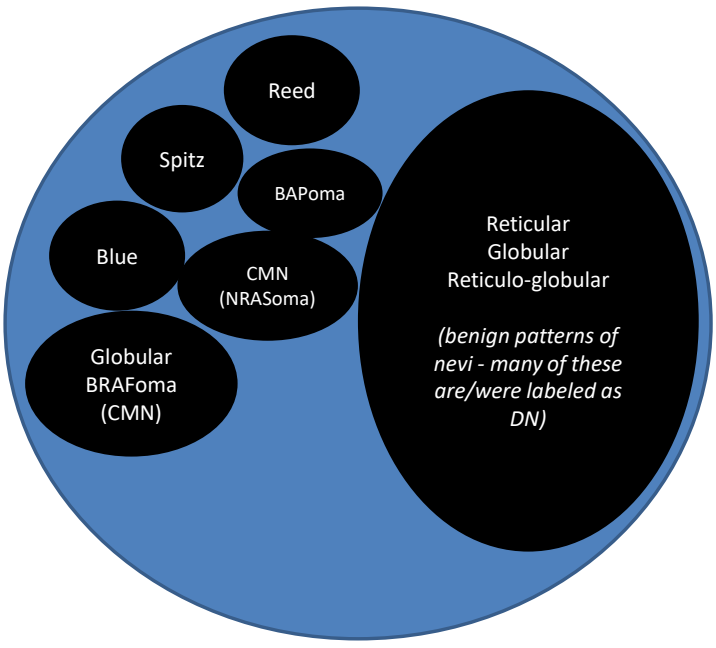

Left with a small subgroup of lesions that are <u>atypical</u>:

1. Clinically / dermoscopically
2. Biologically
3. Histopathologically
4. Molecularly

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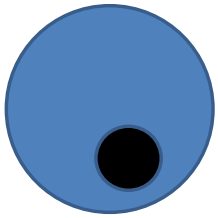

Questions :

1. Could a subset of these atypical lesions be the true DN (intermediary) lesion that has fueled so much debate over the decades?
2. Could a higher proportion of these nevi be on the evolutionary path to MM (precursor)?

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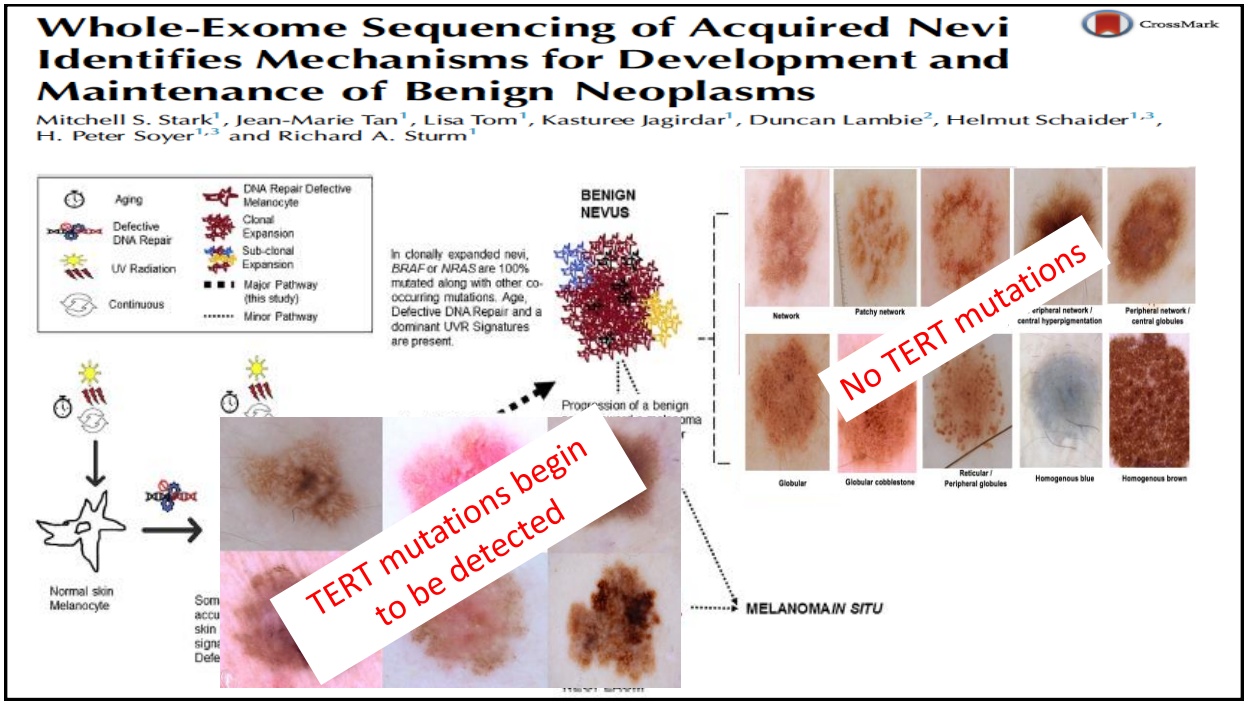

90

The role of the clinician in the age of technology

- Integration of morphology & biology (genesis) will be mission critical
  a. Addressing unnecessary biopsies (cost containment) while still finding relevant disease (context)
     - Lack of change, type of change, &/or rate of change may improve DA
  b. Perhaps discovering the true DN
  c. Addressing overdiagnosis
     - Differentiating aggressive from indolent MM

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Overdiagnosis of Melanoma

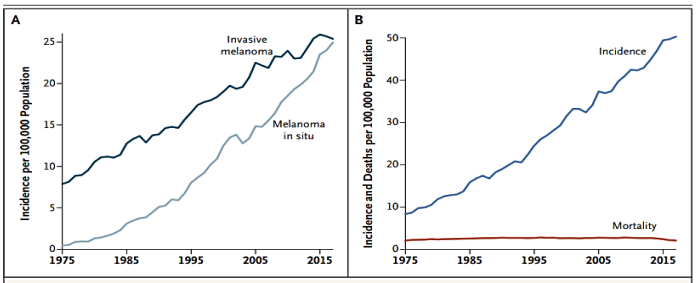

Figure 4. Summary Trends in Cutaneous Melanoma in the United States from 1975 through 2017.
Panel A compares the incidence of invasive melanoma with that of melanoma in situ. Panel B compares the incidence of melanoma with melanoma mortality. Incidence data are from the SEER Program, SEER 9 Registries (five states [Connecticut, Hawaii, Iowa, New Mexico, and Utah] and four metropolitan areas [Atlanta, Detroit, San Francisco, and Seattle]). All ages are included, and all incidence rates are age-adjusted to the 2000 U.S. standard population. Mortality data are from the National Vital Statistics System maintained by the National Center for Health Statistics.

The NEW ENGLAND JOURNAL of MEDICINE

SOUNDING BOARD

The Rapid Rise in Cutaneous Melanoma Diagnoses

H. Gilbert Welch, M.D., M.P.H., Benjamin L. Mazer, M.D., M.B.A., and Adewole S. Adamson, M.D., M.P.P.

"Unfortunately, new diagnostic technologies are now being used in skin examinations, which may further increase diagnostic scrutiny. The advent of the dermascope, a handheld device that magnifies skin abnormalities, has probably lowered thresholds to biopsy by highlighting subtle features in pigmented lesions. These features correlate poorly and inconsistently with biologic behavior but are nonetheless increasingly labeled as melanoma. Thus, the dermascope may have literally magnified the problem of overdiagnosis."

Welch H, et al. N Engl J Med. 2021;384:72-79.

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Estimating the magnitude of cancer overdiagnosis in Australia

Paul P Glasziou[1], Mark A Jones[1], Thanya Pathirana[2], Alexandra L Barratt[3], Katy JL Bell[3]

Cancer	Lifetime probability of diagnosis		Change in probability, 1982–2012	Overdiagnosis proportion†	Cancer diagnoses, 2012	Estimated overdiagnoses, 2012 (95% CI)
	1982*	2012				
Prostate	0.115	0.197	0.082	42%	20 759	8636 (8281–8991)
Melanoma						
Including in situ carcinomas	0.059	0.139	0.080	58%	14 436	8315 (8034–8596)
Invasive only	0.054	0.069	0.015	22%	7151	1552 (1331–1773)
Thyroid	0.0014	0.0052	0.0038	33%	661	483 (426–540)
Renal	0.011	0.019	0.008	42%	2045	861 (749–973)
Other invasive cancers	0.420	0.423	0.003	—	39 452	—

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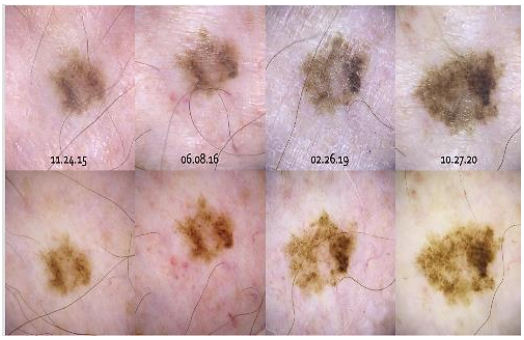
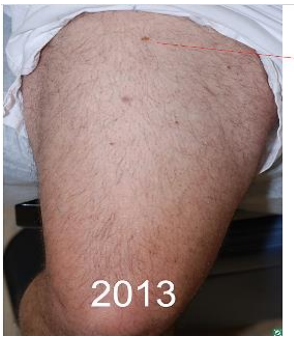
Indolent vs Aggressive Melanomas





5 years before biopsy
MM 0.2 mm: not NAM

4 years before invasive MM and metastasis developed (+SLNB)

SNLB, sentinel lymph node biopsy.
Photos courtesy of Ashfaq A. Marghoob, MD.

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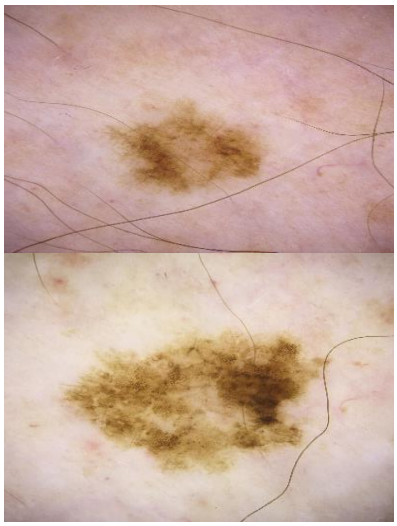
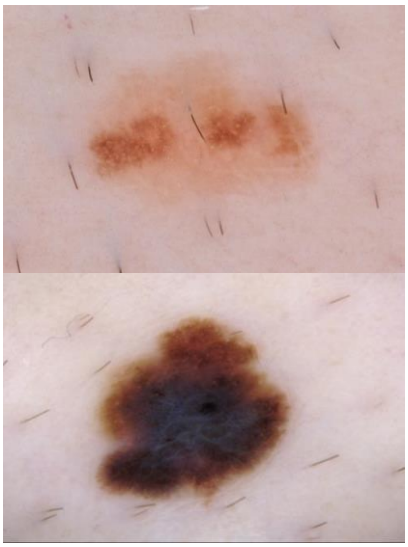
Can be predict which melanoma will become aggressive?





Photos courtesy of Ashfaq A. Marghoob, MD.

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Rate of growth of Melanoma: Dermoscopy

DERMATOLOGY PRACTICAL & CONCEPTUAL
www.derm101.com

Results: The median time interval between baseline and follow-up image was 12 months (range: 2–100 months). The majority of melanomas were in situ (n=28, 56%). The mean horizontal growth rate of all melanomas was 5.3 mm²/year (SD: ± 5.8 mm²/year). The histopathologic findings of numerous and large epidermal nests were associated with rapid growth. This histopathologic pattern corresponded to a pattern of clods ("globules") dermatoscopically. From a dermatoscopic point of view, melanomas with a main pattern of clods grew significantly faster (mean horizontal growth rate: 10.4 mm²/year, 95% CI: 6.4-14.4 mm²/year) than melanomas with mainly a reticular pattern (4.8 mm²/year, 95% CI: 2.7-7.0 mm²/year) or with other patterns (2.6 mm²/year, 95% CI: -0.5-5.6 mm²/year, p=0.01).

Beer J, et al. Dermatol Pract Concept. 2011;1:59-67.

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Predicting Aggressiveness: RCM criteria

In Vivo Melanoma Cell Morphology Reflects Molecular Signature and Tumor Aggressiveness

JIDOpen

Alessandra Marconi[1,7], Marika Quadri[1,7], Francesca Farnetani[2], Silvana Ciardo[2], Elisabetta Palazzo[1], Roberta Lotti[1], Anna Maria Cesinaro[3], Luca Fabbiani[4], Cristina Vaschieri[1], Mario Puviani[5], Cristina Magnoni[2], Shaniko Kaleci[2], Carlo Pincelli[1] and Giovanni Pellacani[2,6]

Melanoma is the deadliest type of skin cancer characterized by high cellular heterogeneity, which contributes to therapy resistance and unpredictable disease outcome. Recently, by correlating reflectance confocal microscopy morphology with histopathological type, we identified four distinct melanoma subtypes: dendritic cell, round cell, dermal nest, and combined-type melanomas. In this study, each reflectance confocal microscopy melanoma subtype expressed a specific biomolecular profile and biological behavior in vitro. Markers of tumor aggressiveness, including Ki-67, MERTK, nestin, and stemness markers were highest in the most invasive combined-type and dermal nest melanomas than in dendritic cell and round cell melanomas. This was also confirmed in multicellular tumor spheroids. Transcriptomic analysis showed modulation of cancer progression-associated genes from dendritic cell to combined-type melanomas. The switch from E- to N-cadherin expression proved the epithelial-to-mesenchymal transition from dendritic cell to combined-type subtypes. The dermal nest melanoma was predominantly located in the dermis, as also shown in skin reconstructs. It displayed a unique behavior and a molecular profile associated with a high degree of aggressiveness. Altogether, our results show that each reflectance confocal microscopy melanoma subtype has a distinct biological and gene expression profile related to tumor aggressiveness, confirming that reflectance confocal microscopy can be a dependable tool for in vivo detection of different types of melanoma and for early diagnostic screening.

Journal of Investigative Dermatology (2022) **142**, 2205–2216; doi:10.1016/j.jid.2021.12.024

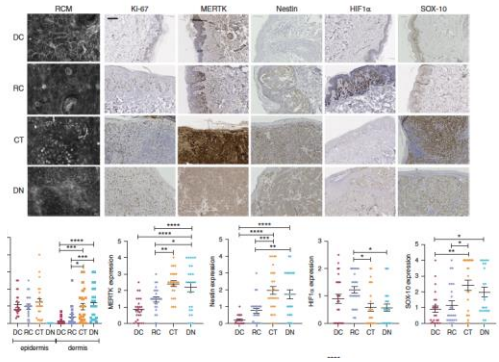

Figure-1

Marconi A, et al. J Invest Dermatol. 2022;142:2205-2216.

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Identifying the fast-growing melanomas: Molecular level

Molecular characterization of fast-growing melanomas

Caroline Gaudy-Marqueste, MD, PhD,[a] Nicolas Macagno, MD, PhD,[b] Anderson Loundou, PhD,[c] Eric Pellegrino, MSc,[d] L'houcine Ouafik, PhD,[d] Timothy Budden, PhD,[e] Piyushkumar Mundra, PhD,[f] Gabriela Gremel, PhD,[f] Victoria Akhras, MD,[g] Lijing Lin, PhD,[h] Martin Cook, MD,[f] Rajiv Kumar, PhD,[i] Jean-Jacques Grob, MD,[a] Eduardo Nagore, MD, PhD,[j] Richard Marais, PhD,[f] and Amaya Virós, MD, PhD[e]
Marseille, France; Manchester and London, United Kingdom; Heidelberg, Germany; València, Spain

Results: Two hundred patients were enrolled, among wom 70 had FGMM. The relapse-free survival was lower in the FGMM group (P = .014). FGMM had a higher number of predicted deleterious mutations within the 40 genes than nonFGMM (P = .033). Ulceration (P = .032), thickness (P = .006), lower sun exposure (P = .049), and fibroblast growth factor receptor 2 (*FGFR2*) mutations (P = .037) were significantly associated with fast growth.

Gaudy-Marqueste C, et al. J Am Acad Dermatol. 2022;86:312-321

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The role of the clinician in the age of technology

1. Morphology
2. Change (biology)
3. Integration of morphology & biology (genesis)
4. Interpreter & advancements

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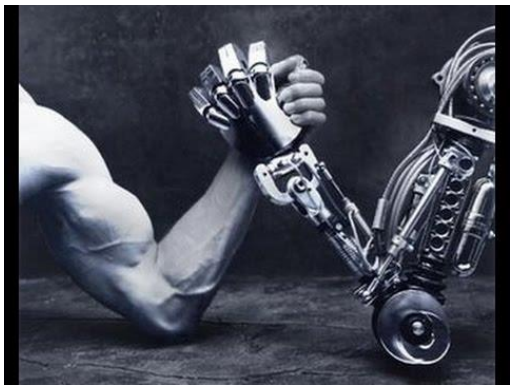
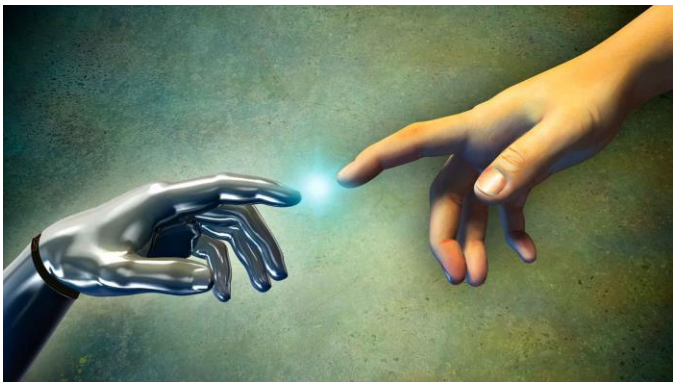
Man vs Machine OR, Man and Machine?





100

Technology requires a thinking clinician!

Technology can help risk stratify patients, risk stratify lesions into low risk and high/unknown risk categories OR direct human vision to areas to pay attention to!

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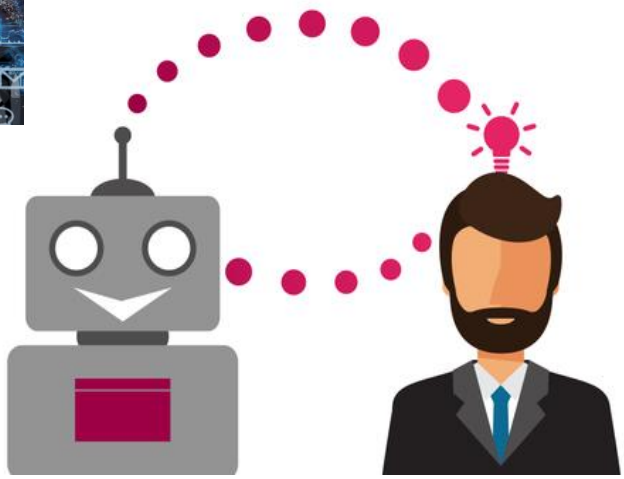
What technology to use when?

What combination of technologies to use to optimize sensitivity and specificity?



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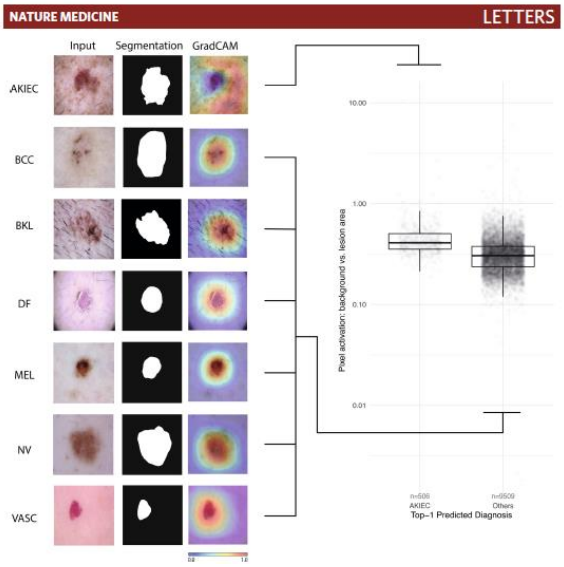
Human–computer collaboration for skin cancer recognition

Philipp Tschandl[1,17], Christoph Rinner[2,17], Zoe Apalla[3], Giuseppe Argen
Allan Halpern[6], Monika Janda[7], Aimilios Lallas[3], Caterina Longo[8,9], Josep I
Susana Puig[10,11], Cliff Rosendahl[14], H. Peter Soyer[15], Iris Zalaudek[16] and H



AI was consistently better at diagnosing AK compared to physicians.

The AI based its decision on background actinic damaged skin.

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ELSEVIER
Applied Animal Behaviour Science xxx (2004) xxx–xxx
www.elsevier.com/locate/applanim

Evidence for canine olfactory detection of melanoma

Duane Pickel[a], Glenda P. Manucy[b], Dianne B. Walker[c], Sandra B. Hall[d], James C. Walker[c,*]

[a] VONPICKEL K-9 Inc., 1386 Chaires Cross Road, Tallahassee, FL 32317-9724, USA
[b] Morninglo Goldens, 2401 Clara Kee Blvd., Tallahassee, FL 32303, USA
[c] Sensory Research Institute, B-340 NHMFL, Florida State University, Tallahassee, FL 32306-2741, USA
[d] Department of Statistics, Florida State University, Tallahassee, FL 32306-4330, USA

Accepted 27 April 2004

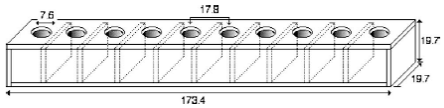
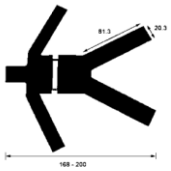


Fig. 1. Apparatus used for box testing. Dimensions are in centimeter.



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GENERAL DERMATOLOGY
BJD
British Journal of Dermatology

Invasive melanoma *in vivo* can be distinguished from basal cell carcinoma, benign naevi and healthy skin by canine olfaction: a proof-of-principle study of differential volatile organic compound emission*

C.M. Willis,[1] L.E. Britton,[1] M.A. Swindells,[2] E.M. Jones,[3] A.E. Kemp,[1] N.L. Muirhead,[1] A. Gul,[1] R.N. Matin,[4] L. Knutsson[5] and M. Ali[1]

Conclusions Invasive melanoma *in vivo* releases odorous VOCs distinct from those of BCC, benign naevi and healthy skin, adding to the evidence that the volatile metabolome of melanoma contains diagnostically useful biomarkers.

EDITORIAL
British Journal of Dermatology

Detection of skin cancer odours using dogs: a step forward in melanoma detection training and research methodologies

105

“Discovery consists of seeing what everyone else has seen and thinking what no one else has thought.”

Albert Szent-Giorgyi von Nagyrapolt
Nobel Prize laureate, 1937

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Sir Lucas Field, The Doctor, 1887

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