South Beach Symposium
medical + aesthetic dermatology
CELEBRATING 20 YEARS
OF PREMIER MEDICAL & AESTHETIC DERMATOLOGY EDUCATION

REIMAGINING
MEDICAL AND
AESTHETIC
DERMATOLOGY

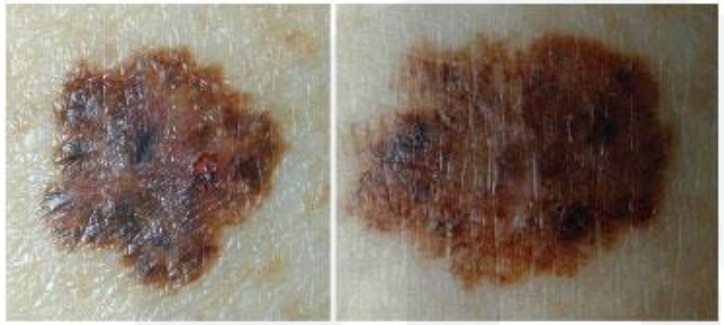
Non-Invasive Detection for Melanoma

Laura K. Ferris, MD, PhD

Professor of Dermatology

University of Pittsburgh

Making biopsy decisions for pigmented lesions

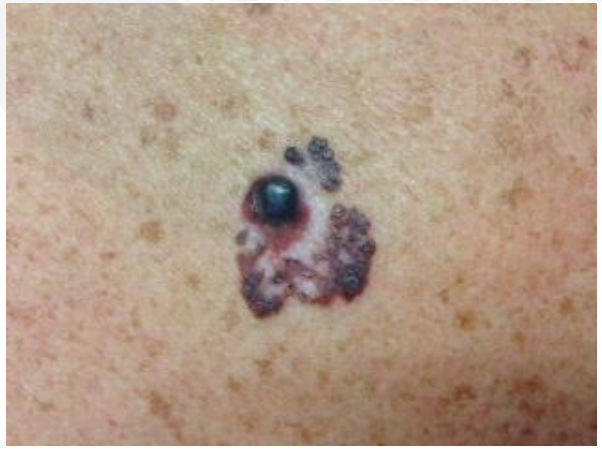


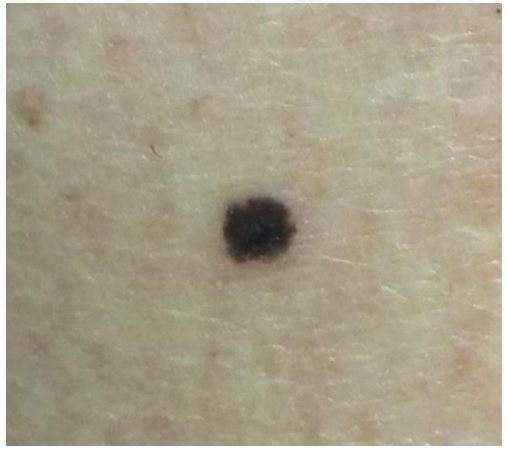
Non-melanoma

Melanoma

How good are we?

- Reader studies:
  - ❖ Sensitivity 65-82%
- NNB: 2.2 – 30.5 (mean 13.2 for US Dermatology practitioners)





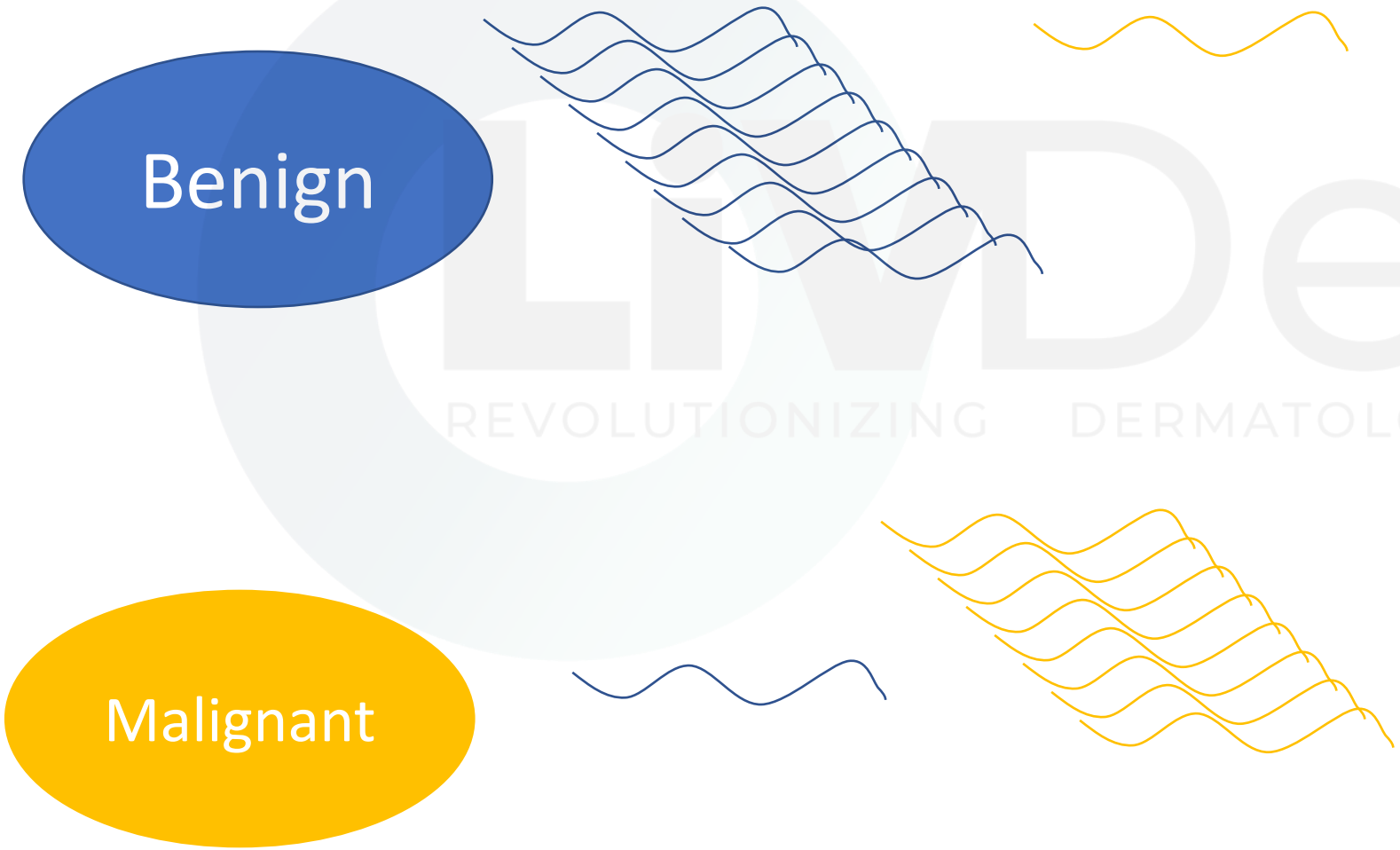
Approaches

Genetic analysis

Physical properties

- Visual
- Conduction

Gene expression profiling (GEP)



Applications in melanoma:

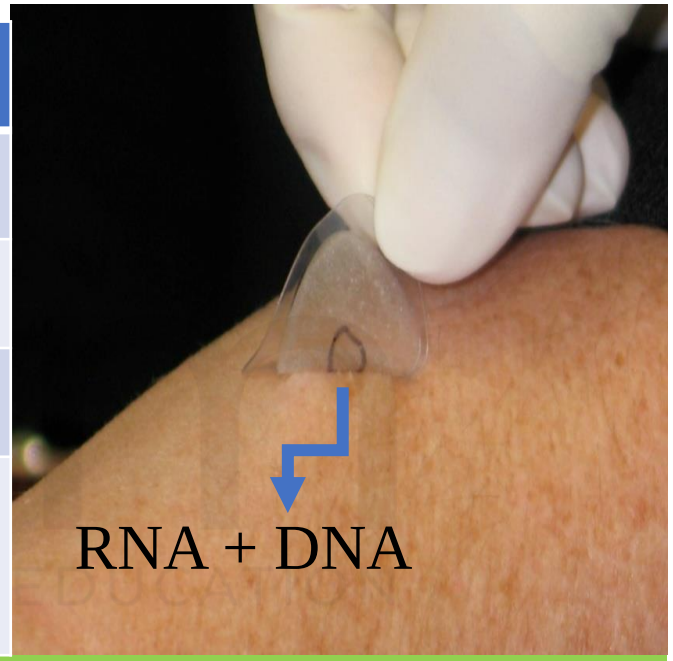
Non-invasive test to help:

1. **Distinguish melanoma from nevi**
2. Classify histologically equivocal biopsied melanocytic lesions
3. Predict which tumors are at highest risk of metastasis

PLA for non-invasive diagnosis of melanoma

J Am Acad Dermatol 2017;76:114-20.
JAMA Dermatol. 2017 Jul 1;153(7):675-680

Genetic finding	% histologic melanoma
LINC (RNA) +	7%
PRAME (RNA) +	50%
LINC ***and*** PRAME (RNA) +	93%
TERT promoter mutation (DNA) present	79%



SENSITIVITY:

- 97% of melanomas express LINC, PRAME, and/or TERT

SPECIFICITY:

- 48% of non-melanomas are negative for LINC, PRAME *AND* TERT

Luan et al. *Cell Death and Disease* (2019)10:855
https://doi.org/10.1038/s41419-019-2090-3

Cell Death & Disease

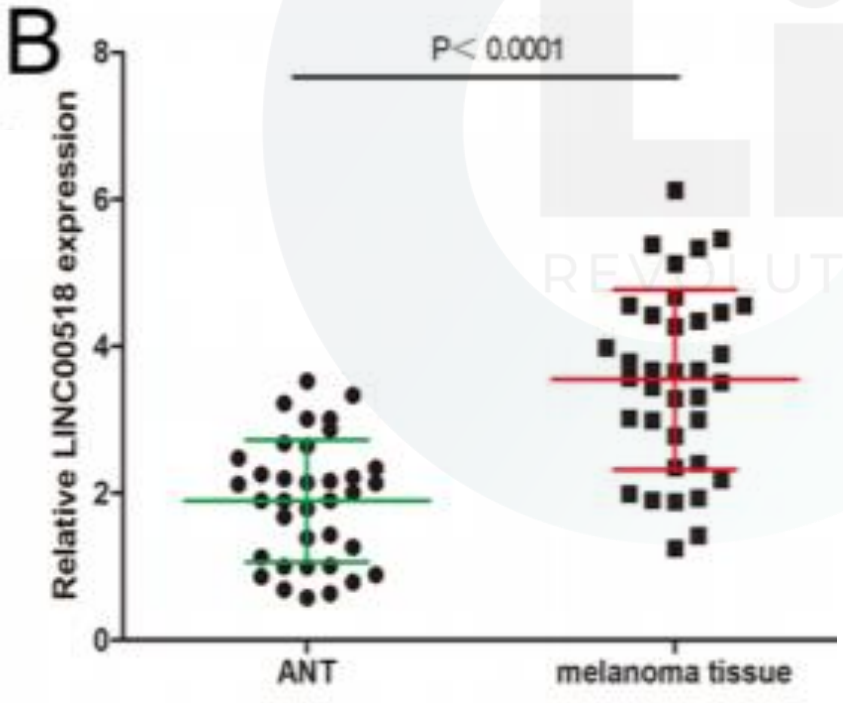
ARTICLE Open Access

Long noncoding RNA LINC00518 acts as a competing endogenous RNA to promote the metastasis of malignant melanoma via miR-204-5p/AP1S2 axis

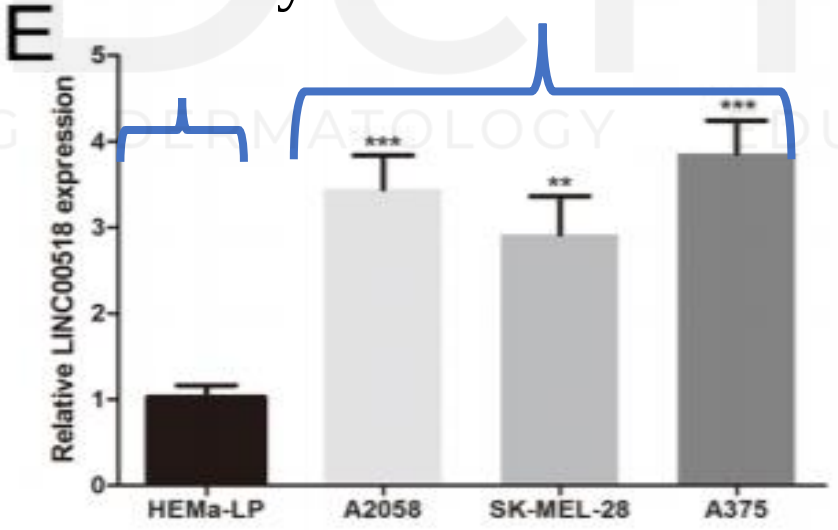
Wenkang Luan[1], Yuting Ding[2], Shaojun Ma[1], Hongru Ruan[1], Jinlong Wang[1] and Feng Lu[1]

LINC00518

- promotes melanoma invasion and metastasis
- Higher expression associated with lower melanoma survival



Primary melanoma



LINC00518 in multiple cancers

cancers

MDPI

Article 2020 Dec 21;12(12):3867

LncRNA *LINC00518* Acts as an Oncogene in Uveal Melanoma by Regulating an RNA-Based Network

Cristina Barbagallo [1], Rosario Caltabiano [2], Giuseppe Broggi [2], Andrea Russo [3], Lidia Puzzo [2], Teresio Avitabile [3], Antonio Longo [3], Michele Reibaldi [3], Davide Barbagallo [1], Cinzia Di Pietro [1], Michele Purrello [1] and Marco Ragusa [1,*]

frontiers in Oncology

ORIGINAL RESEARCH
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BBA - Molecular Basis of Disease 1865 (2019) 708–723

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BBA - Molecular Basis of Disease

journal homepage: www.elsevier.com/locate/bbadis

ELSEVIER

Down-regulated expression of LINC00518 prevents epithelial cell growth and metastasis in breast cancer through the inhibition of CDX2 methylation and the Wnt signaling pathway

Hong-Bin Wang[a,1], Hong Wei[b,1], Jin-Song Wang[a], Lin Li[a], An-Yue Chen[a], Zhi-Gao Li[a,*]

LINC00518 Promotes Cell Proliferation by Regulating the Cell Cycle of Lung Adenocarcinoma Through miR-185-3p Targeting MECP2

Xu Han†, Jixiang Wu†, Yajun Zhang, Jianxiang Song, Zhan Shi and Huiwen Chang*

PRAME (PReferentially expressed Antigen in MElanoma) in melanoma vs. nevi (IHC)

Melanoma Type	In Situ Only	Invasive	Total
Superficial spreading	12/12	37/41	49/53
Lentigo maligna	24/27	15/17	39/44
Acral	7/7	10/11	17/18
Nodular	NA	9/10	9/10
Other *	2/2	6/8	8/10
Subtotal †	45/48	77/87	122/135
Desmoplastic ‡	NA	7/20	7/20
Total	45/48	84/107	129/155

83% PRAME +
(90% of non-desmoplastic melanoma)

Type of Melanocytic Nevus	Diffuse (4+) IHC PRAME Expression	Focal (1 or 2+) IHC PRAME Expression
Common acquired nevus	0/40	4/40 (1+)
Dysplastic (Clark's) nevus	0/60	10/60 (1+)
		1/60 (2+)
Blue nevus	0/10	0/10
Spitz nevus	1/10	1/10 (1+)
Deep penetrating nevus	0/3	0/3
Traumatized/ recurrent nevus	0/15	1/15 (2+)
		1/15 (1+)
Congenital nevus	0/2	0/2
Nodal nevus	0/5	0/5
Total	1/145	18/145

13% PRAME +

Am J Surg Pathol. 2018 November ; 42(11): 1456–1465

Utility of *TERT* promoter mutations for cutaneous primary melanoma diagnosis

Nancy E. Thomas, MD, PhD[*,†], Sharon N. Edmiston, BS[*,†], Yihsuan S. Tsai, PhD[†], Joel S. Parker, PhD[†,‡], Paul B. Googe, MD[*,§], Klaus J. Busam, MD[¶], Glynis A. Scott, MD[‖,**], Daniel C. Zedek, MD[*,§], Eloise A. Parrish, MS[†], Honglin Hao[*], Nathaniel A. Slater, MD[*], Michelle V. Pearlstein, MD[*], Jill S. Frank, MS[†,††], Pei Fen Kuan, PhD[‡‡], David W. Ollila, MD[†,††], and Kathleen Conway, PhD[*,†,§§]

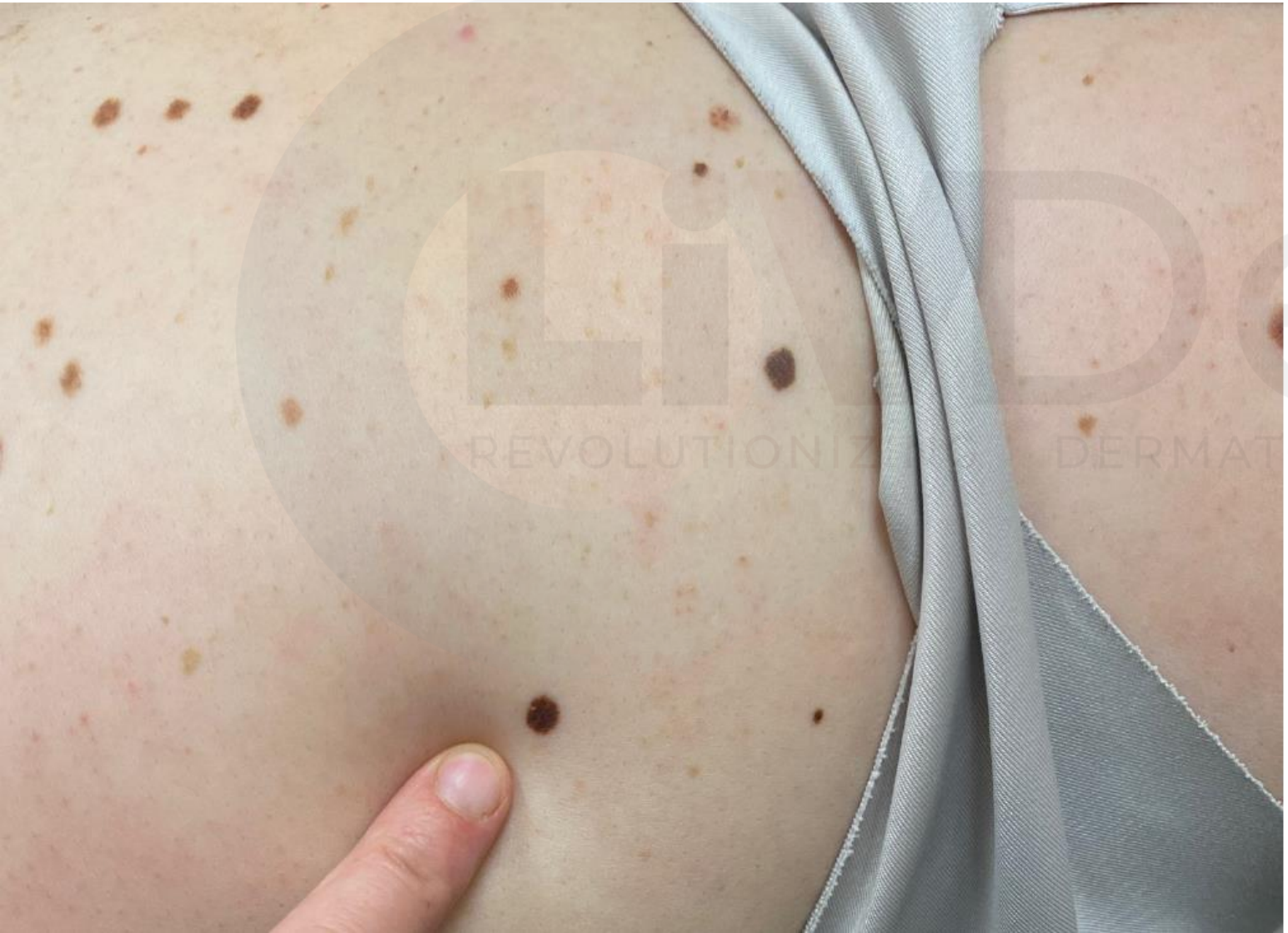
- *TERT* (telomerase reverse transcriptase) – maintains telomeres; mutations lead to uncontrolled replication and proliferation of cancer cells

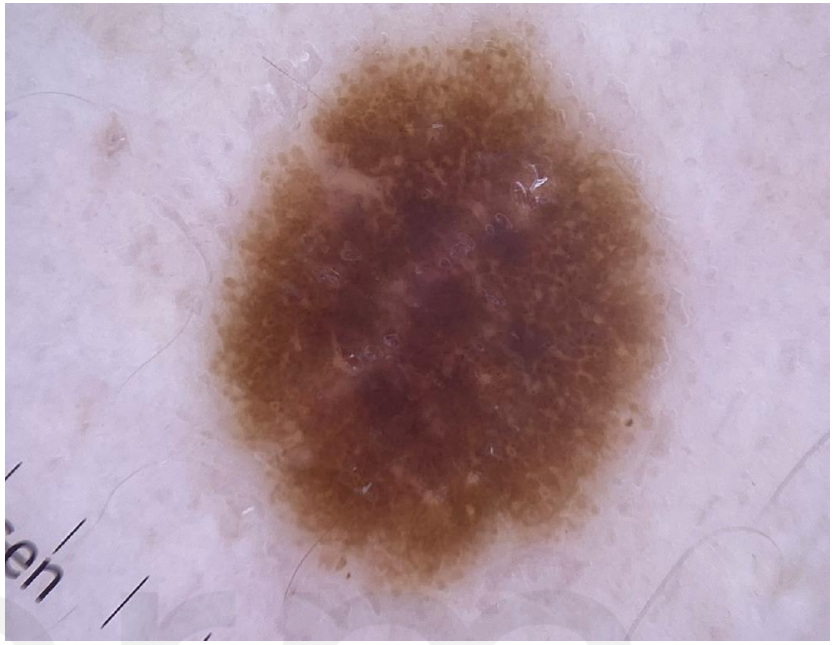
- *TERT* promotor mutations identified in:
  - 67/87 (77.9%) melanomas
  - 1/72 (1.4%) nevi

Lower rates of TERT positivity in:
- Acral melanoma
- Non-white race
- Younger patients
- Non-sun damaged skin
- Lower extremity lesions

Am J Dermatopathol. 2019 April ; 41(4): 264–272.

38 yo F, h/o MMIS
10 biopsies in past 13 months





PLA:

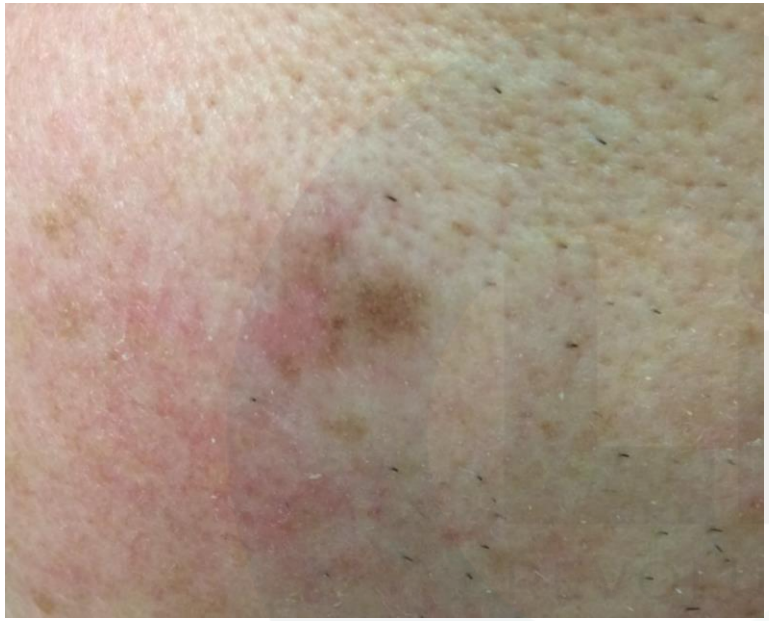
LINC: Detected

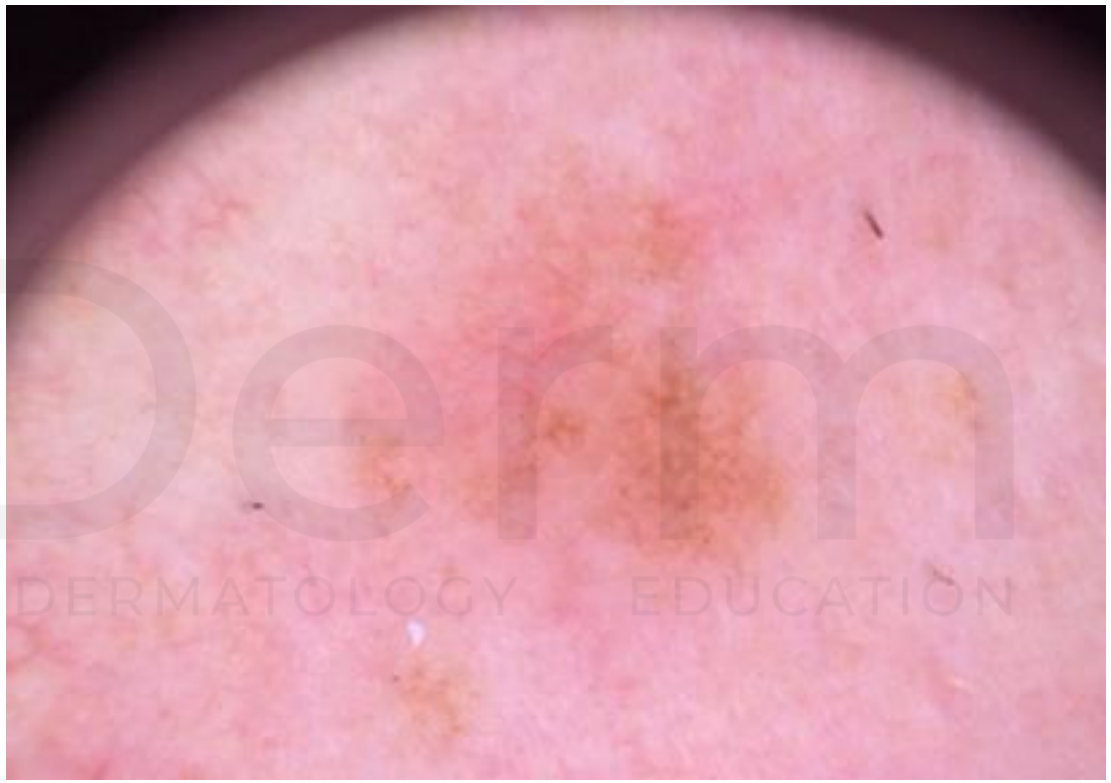
PRAME: Not Detected

Pathology:

EARLY EVOLVING MALIGNANT MELANOMA IN-SITU ARISING IN ASSOCIATION WITH A DYSPLASTIC COMPOUND NEVUS

Lesion on cheek, no change per patient





PLA:

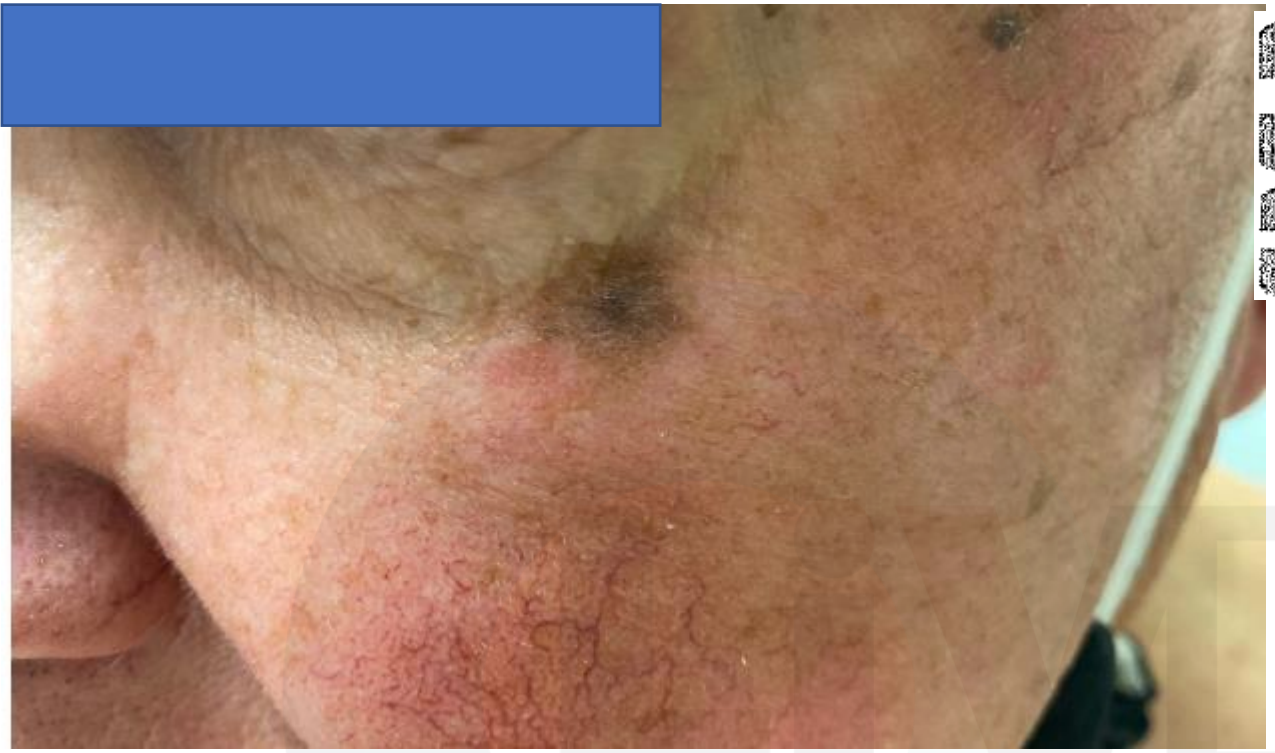
LINC: Detected

PRAME: Not Detected

TERT promoter mutation: Not Detected

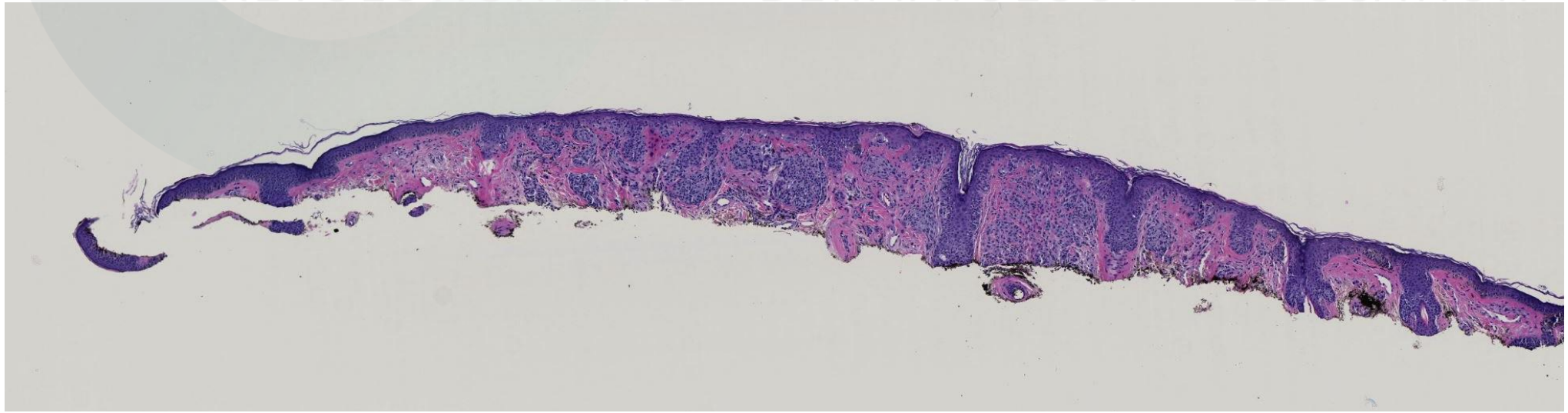
Pathology:

EARLY EVOLVING MALIGNANT MELANOMA IN-SITU ARISING IN ASSOCIATION WITH A DYSPLASTIC COMPOUND NEVUS



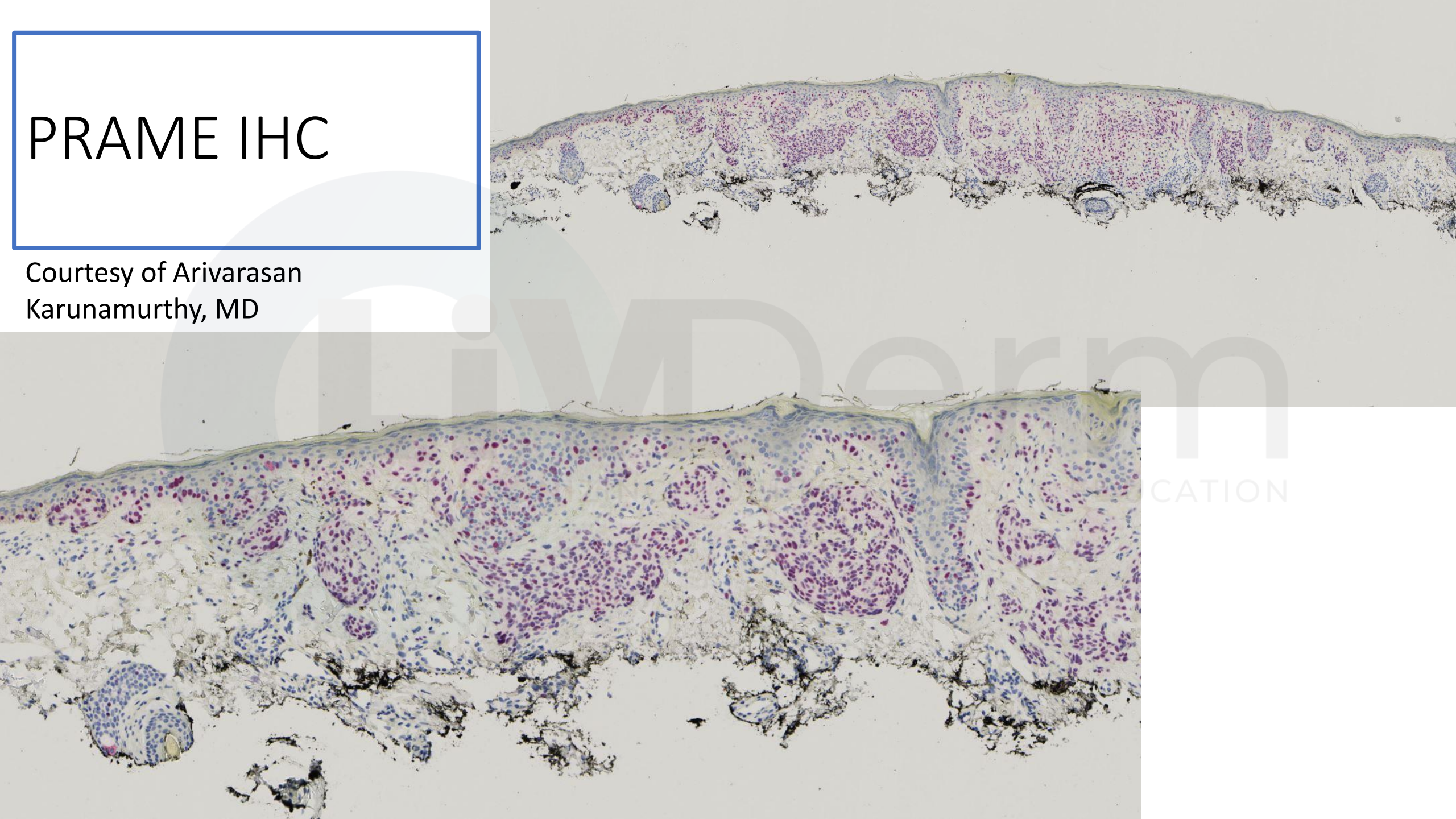
GENE EXPRESSION RISK STATUS: MODERATE (ORANGE)		LINC00518:	Not Detected
		PRAME:	Detected
MUTATION RISK STATUS: -		TERT Promoter:	Not Detected

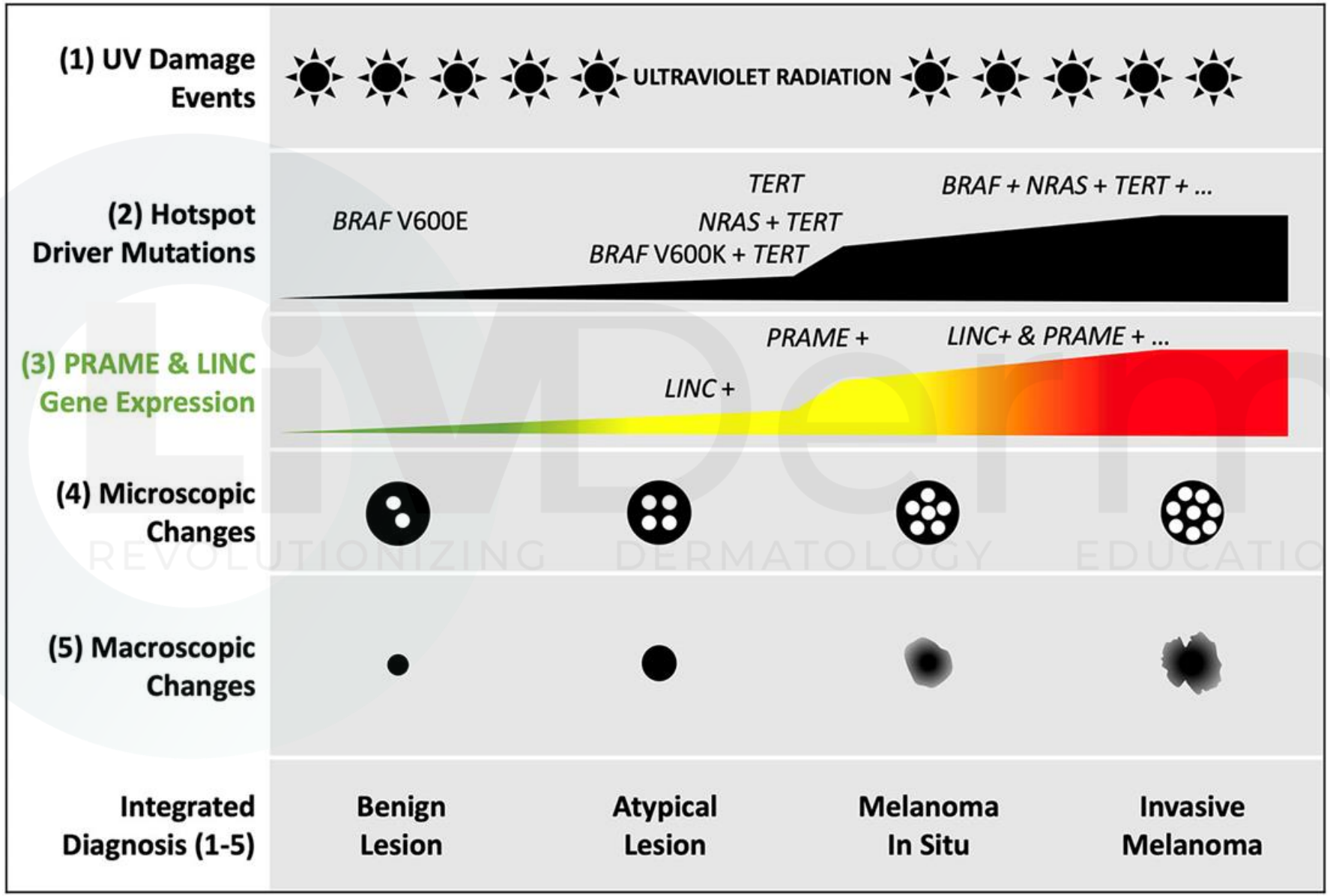
FINAL DIAGNOSIS:
SKIN, LEFT CHEEK, SHAVE:
A. MALIGNANT MELANOMA, LENTIGO MALIGNA TYPE
B. THE DEPTH OF INVASION (Breslow's thickness) IS 0.5 mm AT LEAST.
C. SURFACE ULCER IS NOT IDENTIFIED.
D. MITOTIC COUNT IS LESS THAN 1 PER 1mm2.



PRAME IHC

Courtesy of Arivarasan Karunamurthy, MD





Dermatol Online J. 2019 May 15;25(5).

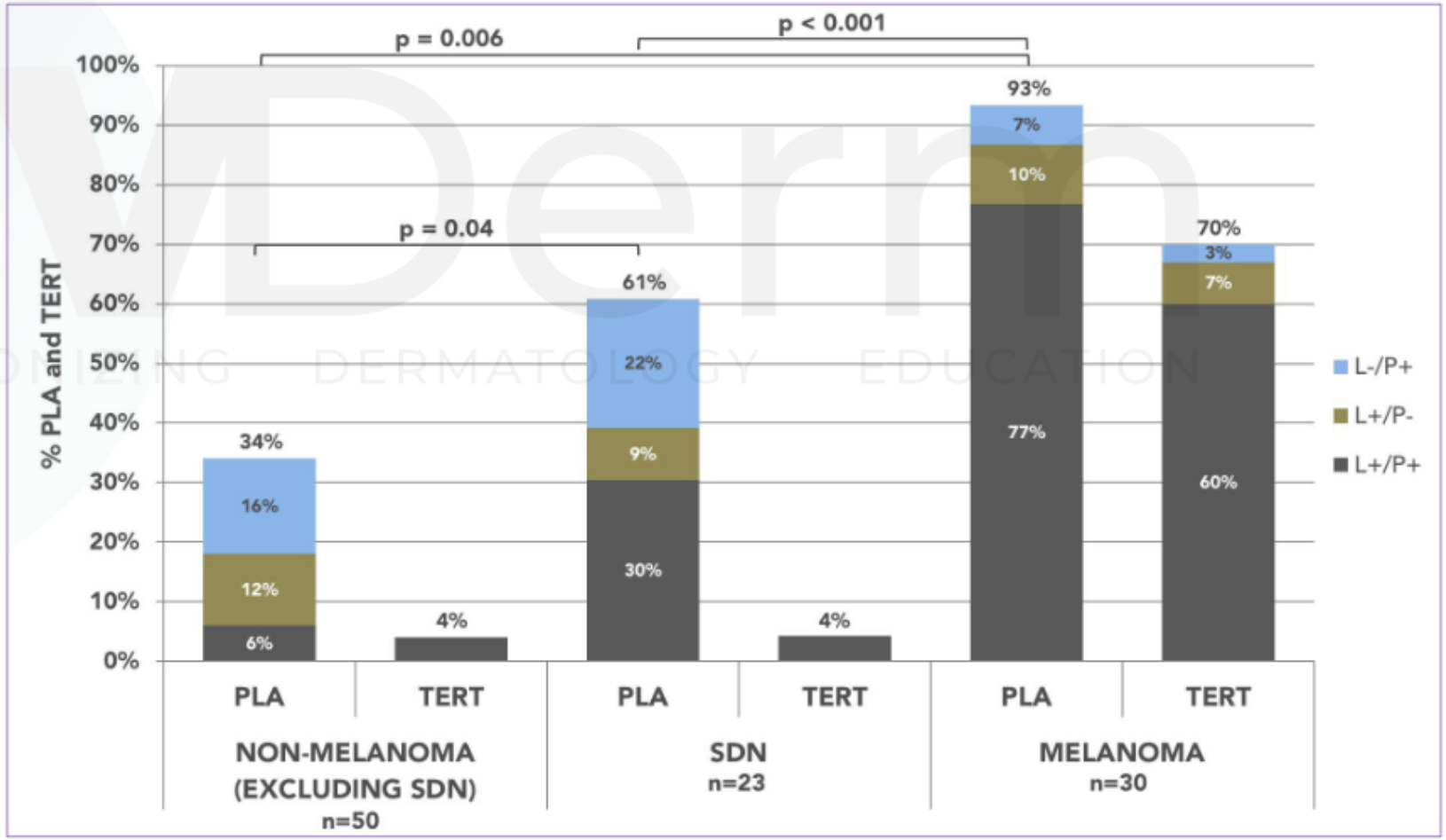
Risk Stratification of Severely Dysplastic Nevi by Non-Invasively Obtained Gene Expression and Mutation Analyses (SKIN, March 2020)

Severely dysplastic nevi:

- Commonly express LINC and/or PRAME
- *Rarely* carry TERT promoter mutation

Melanoma

- Most express LINC and/or PRAME *AND* TERT promoter mutation



What about negative PLA lesions?

- 1781 PLA negative patients
  - Clinical follow up on 69%
  - 10 (0.8%) diagnosed in next ~ 1 yr with melanoma (in situ, stage I)

- 304 PLA negative patients, retested 6-12 mo later
  - 34 (11%) were PLA positive, all biopsied
  - 3 (1%) melanomas (all in situ)

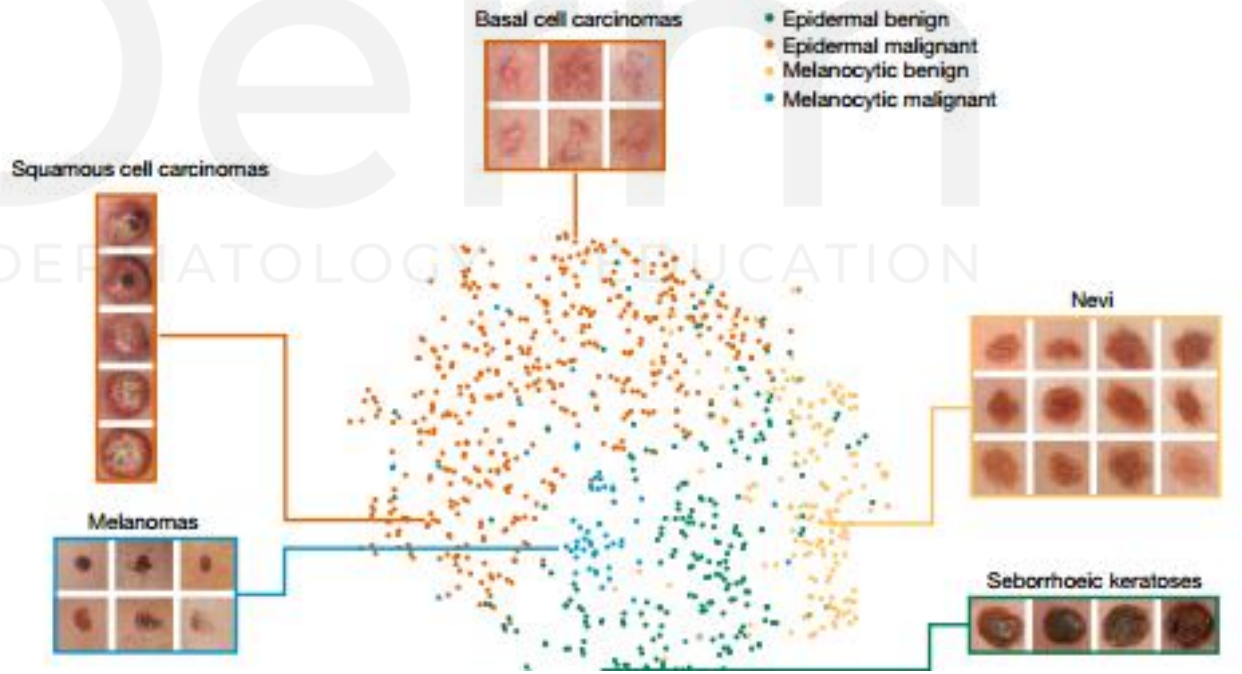
Negative predictive value >99%

SKIN The Journal of Cutaneous Medicine, September 2021

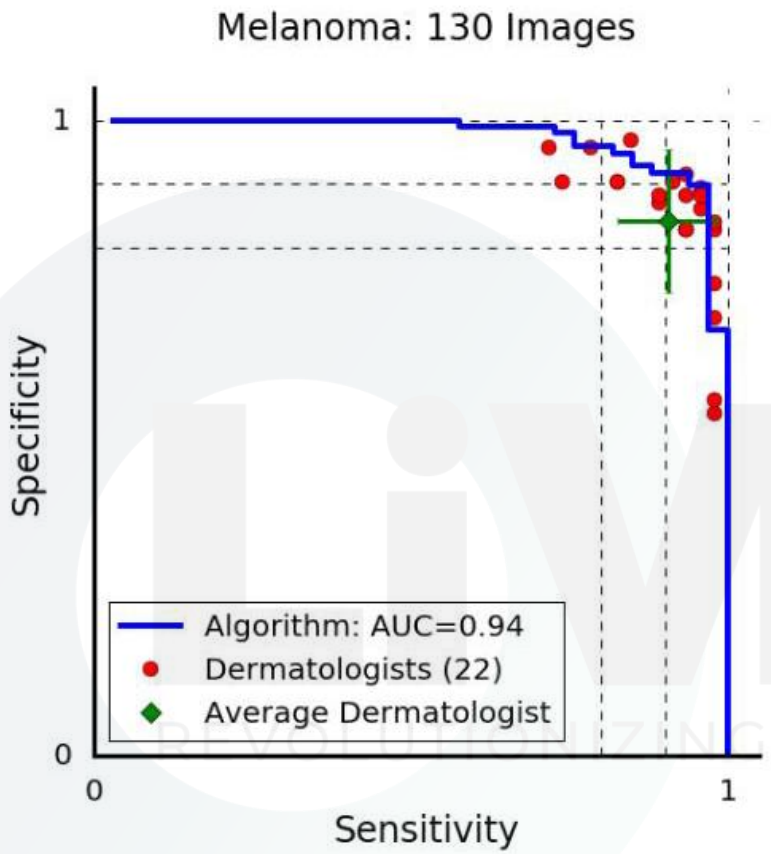
Dermatologist-level classification of skin cancer with deep neural networks

- Trained on >100,000 skin lesion images of >2,000 diseases
- Compared accuracy to dermatologists
  - Melanoma vs nevi
  - BCC / SCC vs SK
  - NOT SK vs melanoma!

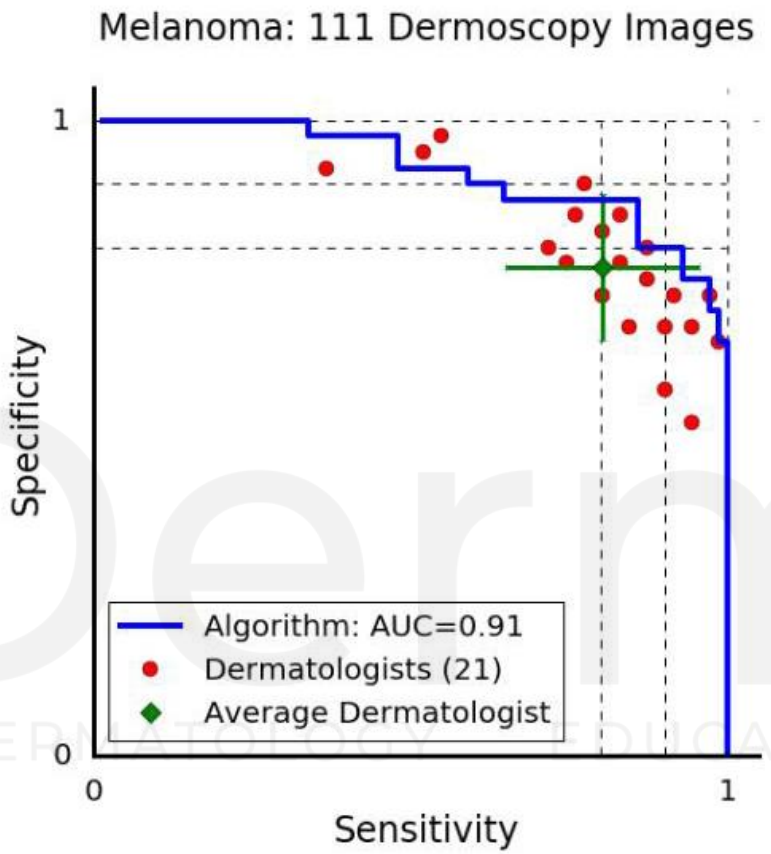
Clinical or dermatoscopic images



Nature. 2017 Feb 2;542(7639):115-118.



33 melanomas, 97 benign nevi



71 melanomas, 40 benign nevi

Red dot above the curve = Dermatologist outperformed computer

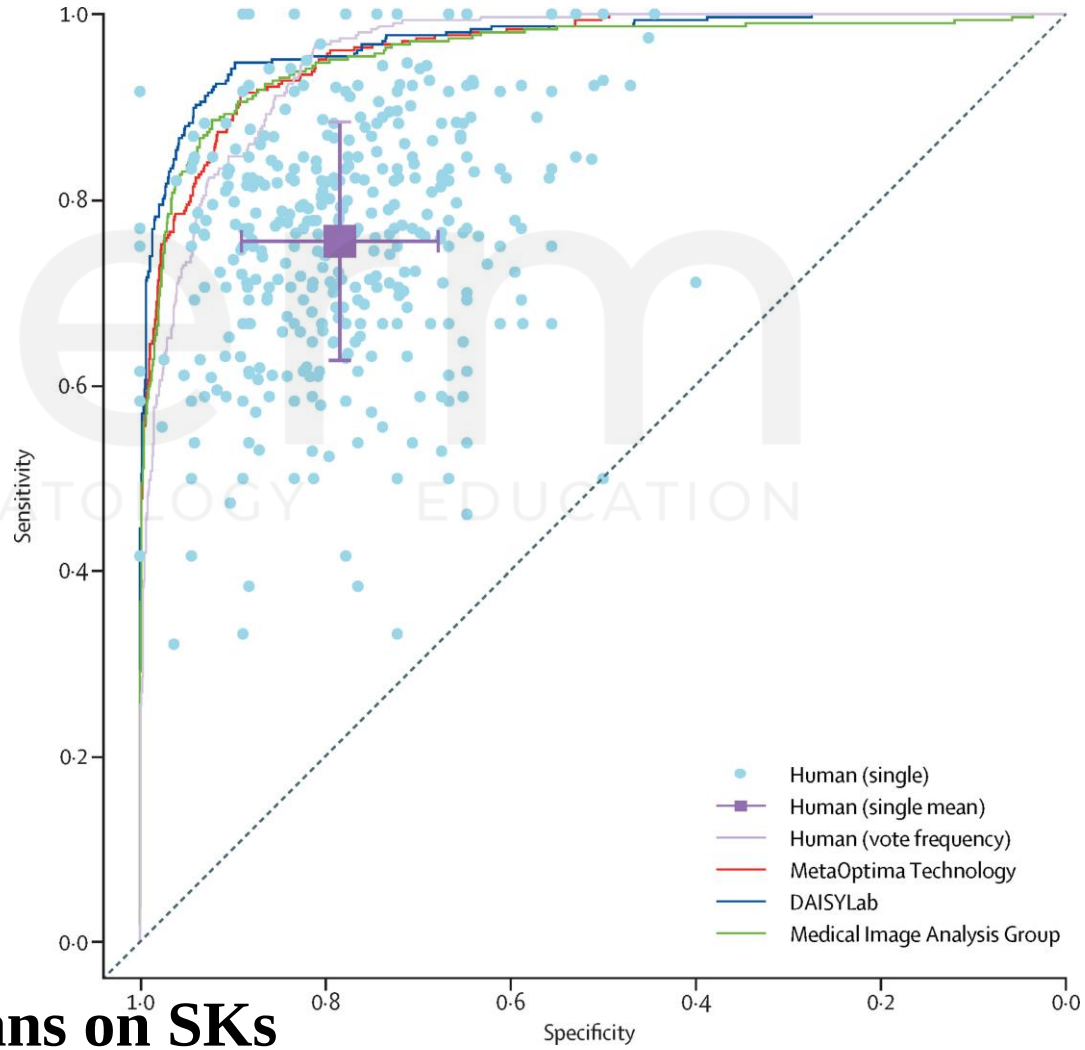
Red dot below the curve = Computer outperformed the dermatologist

No data on lesion thickness

Nature. 2017 Feb 2;542(7639):115-118.

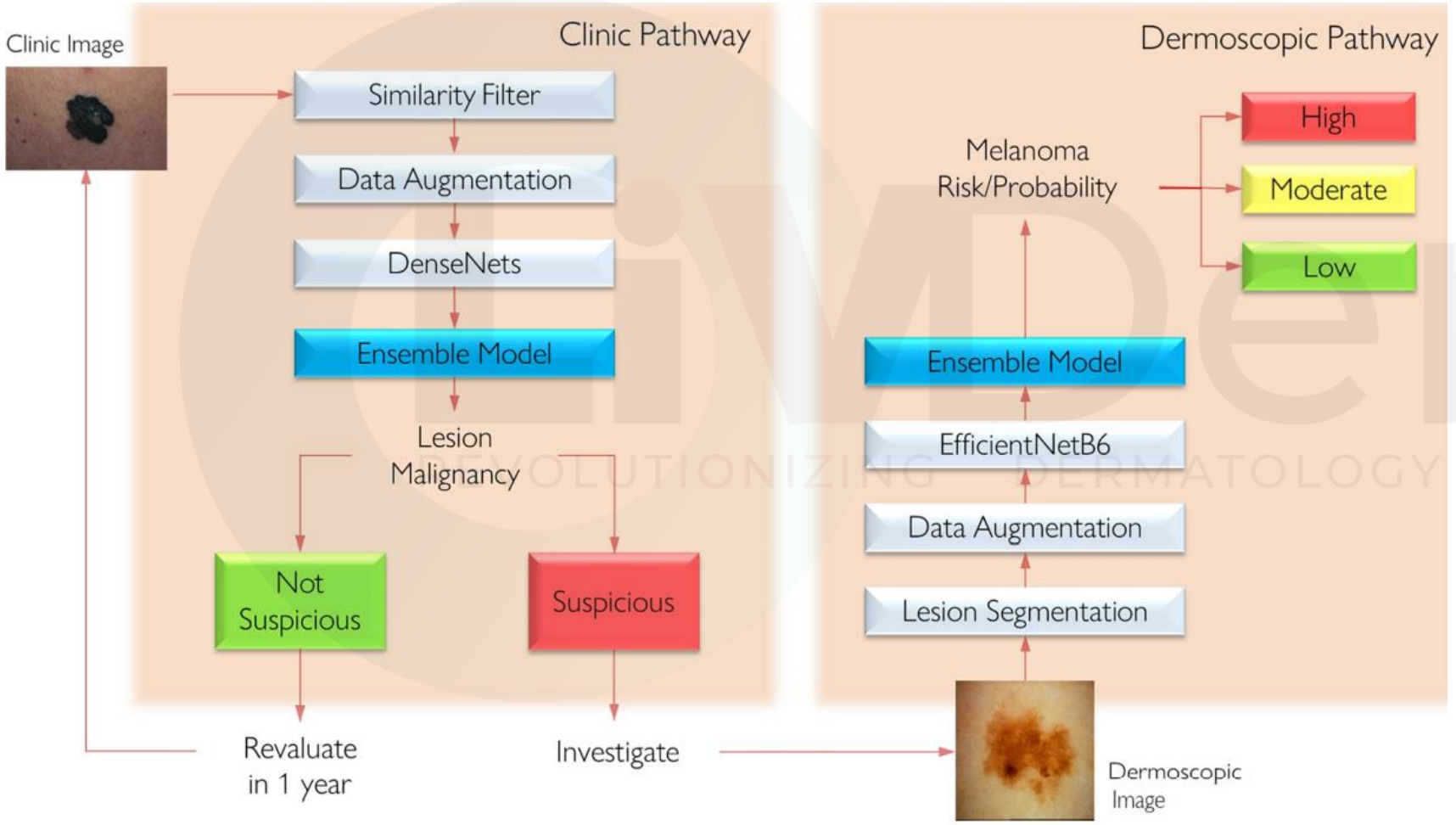
Discrimination of malignant from benign pigmented skin lesion

	Sensitivity	Specificity	Negative predictive value	Positive predictive value
All human readers (n=511)				
Melanoma	73·1% (65·8–79·6)	92·8% (91·3–94·2)	96·4% (95·3–97·4)	56·6% (49·7–63·2)
Expert readers (n=27)				
Melanoma	67·8% (60·3–74·8)	94·0% (92·5–95·2)	95·8% (94·6–96·8)	58·9% (51·7–65·8)
All algorithms (n=139)				
Melanoma	67·3% (59·7–74·2)	97·0% (96·0–97·9)	95·9% (94·7–96·9)	74·2% (66·6–80·9)
Top three algorithms (n=3)				
Melanoma	81·9% (75·4–87·3)	96·2% (95·1–97·2)	97·6% (96·7–98·4)	73·6% (66·9–79·6)



Top 3 algorithms also performed equivalent to humans on SKs

AI for melanoma diagnosis in primary care- the future?



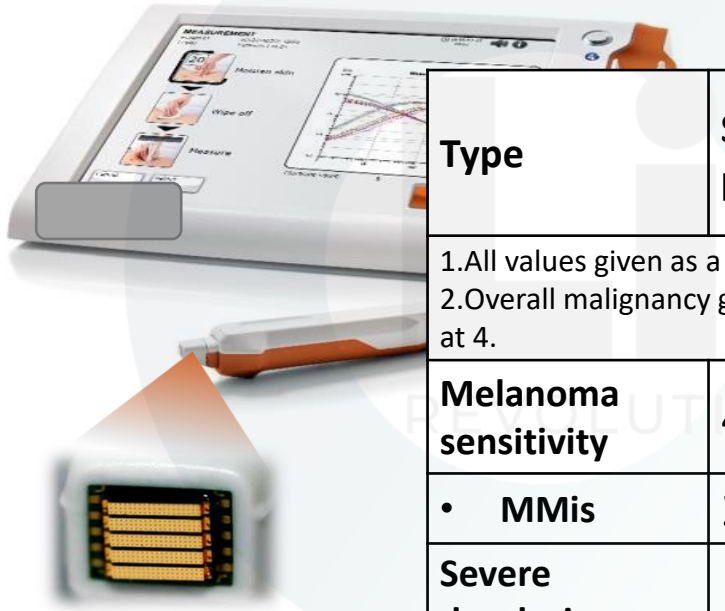
Trained using database of available and generated clinical and dermatoscopic images

- Sensitivity : 90%
- Specificity: 85-89%
- PPV: 59-65%
- NPV: 97%

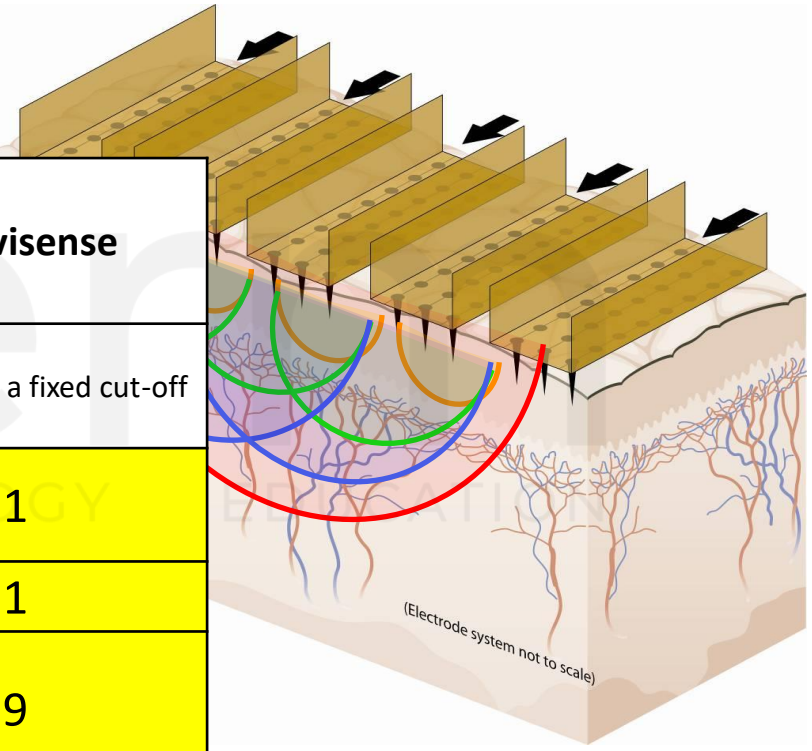
CAD system pathways developed to provide outputs for clinical and dermoscopy images to primary care physicians.

PLOS ONE | September 22, 2021

Electrical Impedance Spectroscopy (EIS)
FDA approved 2017 for use by dermatologists



Type	Seven-point	Malignancy grading	Local pathology	Nevisense
1.All values given as a percentage. NA, not applicable. 2.Overall malignancy grading as determined by the visual classification board with a fixed cut-off at 4.				
Melanoma sensitivity	49·2	70·6	84·5	97·1
• **MMis**	28·7	55·4	73·3	94·1
Severe dysplasia sensitivity	12·1	38·3	NA	83·9
Overall specificity	94·2	81·4	98·0	35·8



Br J Dermatol. 2014. Nov;171(5):1099-107.
FDA report.

NOTE: sensitivity 57.1% in patients <30 years of age (small n)

MELAFIND- What can we learn?

- Sensitivity comes at the cost of specificity
- Limited utility: Recommends biopsy of about 90% of lesions
- Extremely expensive optics/ machine
- Fixed classifier- cannot "learn" in real time →need FDA reapproval
- Product no longer available / supported

	Sensitivity	Specificity
MelaFind	97%	9%
Readers	72%	51%

Threshold	Sensitivity (95% CI)	Specificity (95% CI)
≥ -3	100.0% (97.9-100%)	0.8% (0.4-1.4%)
≥ -2	99.4% (96.9-100%)	1.3% (0.8-2.0%)
≥ -1	98.9% (95.9-99.9%)	3.6% (2.7-4.7%)
≥ 0	98.3% (95.1-99.6%)	10.8% (9.2-12.5%)
≥ 1	93.1% (88.3-96.4%)	29.8% (27.4-32.2%)
≥ 2	75.4% (78.4-81.6%)	60.0% (57.4-62.5%)
≥ 3	54.3% (46.6-61.8%)	81.8% (79.7-83.8%)
≥ 4	30.9% (24.1-38.3%)	91.4% (89.9-92.8%)
≥ 5	15.4% (10.4-21.7%)	96.1% (95.0-97.0%)
≥ 6	7.4% (4.0-12.4%)	98.8% (98.2-99.4%)

Monheit et al, Arch Dermatol. 2011 Feb;147(2):188-94. MelaFind Package insert

Human vs Machine – key differences in determining if a lesion is benign or malignant

Parameter	Human	Machine
Context	Consider all lesions on the skin, patient history, risk factors	Lesion in isolation; only the lesion the user chooses to evaluate
Objectivity	• Shaded by experience, fear of missing melanoma, incentive to biopsy or not • Favor biopsy of benign over missing malignant	• Objective • Can choose to maximize sensitivity vs. specificity
Learning	Years: one patient / paper/ textbook at a time	Can train classifier in hours / days
Features evaluated	• Uses set criteria to evaluate a lesion • Can usually explain "why"	• Can identify and use new features and process large amounts and layers of data • Cannot always explain "why"

Sensitivity and specificity are just one factor: must consider how tools designed to improve melanoma detection should best be integrated into clinical practice!