

# The era of technology in skin cancer diagnosis and management



J.Malvehy Hospital Clínic Barcelona. University of Barcelona Diagnosis Dermatologica, Barcelona

## Conflicts of interest

SPEAKER: Almirall, BMS, ISDIN, La Roche Posay, Leo, Novartis, Pierre Fabre, Roche, Sanofi

HONORARIA OR CONSULTATIONS FEES : Almirall, BMS, Biofrontera, GSK, ISDIN, La Roche Posay, Leo, Novartis, Polychem

GRANTS & RESEARCH SUPPORT: Almirall, Amgen, BMS, Biofrontera, Canfield, Cantabria, Fotofinder,

GSK, ISDIN, La Roche Posay, Leo, Mavig, Nevisense, Novartis, Polychem, Roche, iTOBOs (EU Grant)

Spouse/partner: Almirall, Amgen, BMS, Biofrontera, Canfield, Cantabria, Fotofinder, GSK, ISDIN, La Roche Posay, Leo, Mavig, Nevisense, Novartis, Pierre Fabre, Polychem, Roche

Other support (please specify): Abbie (educational activities), Lilly (educational activities), Novartis

Co-founder of Diagnosis Dermatologica sl and Athena Tech, Investor of Dermavision



## FOUNDING & COLLABORATIONS

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Agència de Gestió d'Ajuts Universitaris i de Recerca

## Research Team in AI. Dermatology Department. Hospital Clinic. Barcelona

#### **Clinical team**

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**D'Investigacior** 

Fundació

La Marató de TV3





## Skin Cancer Center in the Hospital Clinic of Barcelona



University Hospital Clinic of Barcelona



University of Barcelona



CEK. IDIBAPS. Fundació Clínic

#### Hospital Clínic de Barcelona



#### Fundació de Recerca Clínic Barcelona-Institut d'Investigacions Biomèdiques August Pi i Sunyer





IDIBAPS 2023: 2,000 rearchers; 2122 pub; 1,037 active competitive projects; 106 tesis; 86 patents; 12 spin-offs



Home

Research lines	
Members	Dermoscopy, digital dermoscopy, confocal microscopy and new photonic and physic technologies
Publications	Genetic epidemiology in melanoma and non-
Projects	Evaluation of immune response in melanoma
Transfer	Evaluation of minute response in metanoma

**Research lines** 

#### Giant congenital nevi

Identification of genetic prognostic profiles in melanoma

Study of the mechanisms involved in carcinogenesis and photocarcinogenesis in melanoma and non-melanoma skin cancer

News

# The Mission Skin Cancer Center



Quality assurance

## **The Skin Cancer Centre**

• Modern inpatient, ambulatory care and laboratory facilities necessary for the overall educational program for the different skin cancers

- Dermatopathology services
- Modern diagnostic radiology services,
- Resources for nuclear medicine imaging
- Blood banking, blood therapy facilities, facilities for clinical pharmacology and tumour immunology/biology.
- An advanced **oncology service (surgical, medical and radiotherapy)**.
- A set-up for regular multidisciplinary tumour conferences
- Set up for clinical trials on Good Clinical Practice base











#### **IDIBAPS y Fundación Clínic**



## Patients

- Patients atended yearly = 3,500
- Visits = 12,500 year
- New melanoma patients = 300 pts/yr
- Pts with systemic therapies = 200/ yr
- Complex Surgeries = 1500-1600 yr
- Clinical trials (ongoing) = 20-25



## Diagnostic of skin cancer

Diagnostic technologies 3D body scanner (Vectra 360) In vivo RCM (V1500, V3000); LC-OCT/OCT; US and ex-vivo CM microscopy (V2500)











1200 examinations of complex tumors per year Fast Mohs surgery (550 patients/year)

# Pigmented lesions Clinic (1980)

Fig. 15. Color variegation of early malignant melanoma.

Fig. 16. Color variegation of malignant melanoma. Note the pink-red component at lower

margin of lesion



Fig. 18. Early malignant melanoma, approximately six mm in diameter.



ig. 25. Dysplastic nevus measuring nine mm n diameter.



Fig. 12. Border irregularity of early malignant melanoma.



Fig. 13. Border irregularity of early malignant melanoma.

remembered by thinking of ABCD:

- A = Asymmetry.
- B = Border irregularity.
- C = Color variegation.
- D = Diameter generally greater than six mm.





Fig. 22. Progression of malignant melanoma: plaque with nodule.



Fig. 23. Progression of malignant melanoma plaque with amelanotic nodule.



Friedman RJ Rigel DS Kopf AW Cancer Journal 1986





Fig. 19. Early malignant melanoma, approximately eight mm in diameter.





Fig. 26. Dysplastic nevus with features of a

lark-target variant.





## **Diagnostic of Skin Cancer: Technology**



- Laboratory vs Patient (Medical Devices)
- In vivo vs ex-vivo

- Natural contrast or artifical contrast
- Imaging vs Quantitative

## **Qualitative methods (images)**

## Quantitaive

Total Body Scanners/ Dermoscopy Optical Coherence tomography (OCT) Confocal Microscopy (CM) LC-OCT

## Impedanciometry Multispectral analyses RAMAN



## **Diagnostic of Skin Cancer: Technology**



## Preclinical development

CE marked approval

## **Clinical adoption**

Enginering, laboratory

Start-up, clinical studies, regulatory

Vendors, education, reimbursement

10 yrs

## Tissue properties and photonics







## Dermatoscopes



**Dermoscopes** contain light-emitting diodes to provide illumination and are equipped with a magnification lens. However, PDs use two polarized filters to achieve **cross-polarization** 























# UV light dermoscopy

Dermoscopy with ultraviolet light utilizes the fluorescence emitted by skin lesions:

- Superficial micosis
- nail diseases
- *Demodex* mites
- scabies, and pigmented diseases
- Melanoma demmarcation for complete excision



A digital camera integrated dermoscope with a built-in near- UV wavelength (405-nm) light source (DZ-D100 device (Casio Computer Co, Ltd, Tokyo, Japan). It is also more easily accessible than Wood's lamps because eye protection and a darkroom are not required to obtain images.

Sano T, Minagawa A, Suzuki R, Koga H, Okuyama R. Dermoscopy with near-ultraviolet light highlights the demarcation of melanin distribution in cutaneous melanoma. J Am Acad Dermatol. 2020;23:S0190-9622(20)32281-7.

### Dermoscopy





### Dermoscopy



C



# High magnification microscopy of the skin up BAPS





# Super-high magnification dermoscopy at 400x magnification (D400)



Dusi D, Rossi R, Simonacci M, Ferrara G. Image Gallery: the new age of dermoscopy: optical super-high magnification. Br J Dermatol. 2018 May;178(5):e330.

# FLUORESCENCE-ADVANCED VIDEODERMATOSCOPY

- FAV is an optical electronic system consisting of a handheld probe and a monochromatic lightemitting source with a λ of 405 nm (±5 nm) and a fixed angle of incidence.
- Optical penetration depth varying from 200  $\mu m$  to 400  $\mu m$
- Visualization of subcutaneous structures to the point below the papillary dermis.
- To prevent light diffusion on the corneum stratus, glycerol is applied to the skin surface.
- The working mechanism underlying FAV exists in the ability of endogenous molecules to emit fluorescence after absorbing specific wavelengths.



Sanlorenzo M, Vujic I, De Giorgi V, et al. Fluorescence-advanced videodermatoscopy: a new method for in vivo skin evaluation. Br J Dermatol. 2017;177:e209-e10.

Scarfi F, Gori A, Silvestri F, et al. Fluorescence-advanced videoder- matoscopy: a promising and potential technique for the in vivo evaluation of vitiligo. Dermatol Ther. 2019;32:e12863.

# FLUORESCENCE-ADVANCED VIDEODERMATOSCOPY



Scarfi F, Gori A, Topa A, et al. Image Gallery: In vivo fluorescence-advanced videodermatoscopy for the characterization of skin melanocytic pigmented lesions. Pediatr Dermatol. 2019;180:e104. Cinotti E, Cortonesi G, Rubegni P. High magnification and fluorescence advanced videodermoscopy for hypomelanotic melanoma. Skin Res Technol. 2020;26:766–768.

## **OCT in Dermatology**





- OCT is a noninvasive, in vivo imaging method, which captures high-resolution (µm), 2D or 3D images of biological tissue (6x 6 mm ;2mm depth). Navigation in the skin with clinical image reference. Resolution (axial 10 µm; lateral 7.5 µm)
- OCT is an interferometric technique using relatively longwavelength light in the near-IR portion of the spectrum.

CLINICAL TRIAL



#### Optical coherence tomography of basal cell carcinoma: influence of location, subtype, observer variability and image quality on diagnostic performance\*

J Holmes <sup>(1)</sup>, <sup>1</sup> T. von Braunm**£**hl, <sup>2</sup> C. Berking, <sup>2</sup> E. Sattler <sup>(1)</sup>, <sup>2</sup> M. Ulrich, <sup>3</sup> U. Reinhold, <sup>4</sup> H. Kurzen, <sup>5</sup> T. Dirschka, <sup>6</sup> C. Kellner, <sup>7</sup> S. Schuh<sup>8</sup> and J Welzel<sup>8</sup>

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<sup>6</sup>Rivate Dermatdogy Office, Wuppertal, Germany
<sup>7</sup>S Benard-Hospital, Kamp Lintfort, Germany
<sup>8</sup>General Hospital Augburg Department of Dermatdogy and Allergology, Augburg Germany

#### Linked Editorial: Rossi et al. Br J Dermatol 2018; 178:994–996.

#### What does this study add?

- Lesion location does not affect diagnostic performance with OCT.
- Poor OCT image quality is associated with superficial scales and crusting, reducing diagnostic performance, but in these cases diagnosis with OCT is better than by clinical or dermoscopy examination alone.
- Observers' diagnostic confidence increases when using OCT and their performance reflects this.
- Diagnostic performance is consistent between trained observers.
- BCC subtype can be diagnosed from OCT images with moderate accuracy.



Fig 1. Example of a nodular basal cell carcinoma with typical characteristics, such as a poorly defined dermoepidermal junction (white line and white arrow), dark ovoid structures (+), ovoid structures with bright centre (black asterisk), black areas corresponding to cysts (white dashed circle) and surrounding bright stroma (white asterisk). Scale bar = 1.0 mm.



Fig 2. Superficial basal cell carcinoma (BCC). An example of tumour bulge intruding into the dermis (arrows) with an underlying dark border (asterisk), which are typical characteristics of superficial BCCs. Scale bar = 1.0 mm.



Fig 3. Infiltrative basal cell carcinoma (BCC). The characteristic feature of an infiltrative BCC is shown, the 'shoal of fish' (circle) consisting of clusters of narrow elongated dark structures (arrows). Scale bar = 1.0 mm.



Fig 4. Example of mediocre image quality due to presence of crusting/scales (arrows). Scale bar = 1.0 mm.

Optical coherence tomography of basal cell carcinoma: influence of location, subtype, observer variability and image quality on diagnostic performance. Holmes J, et al. Br J Dermatol. 2018 May;178(5):1102-1110

#### SHORT REPORT

## Dynamic optical coherence tomography of skin blood vessels – proposed terminology and practical guidelines

M. Ulrich,<sup>1,\*</sup> L. Themstrup,<sup>2</sup> N. de Carvalho,<sup>3</sup> S. Ciardo,<sup>3</sup> J. Holmes,<sup>4</sup> R. Whitehead,<sup>4</sup> J. Welzel,<sup>5</sup> G.B.E. Jemec,<sup>2</sup> G. Pellacani<sup>3</sup>



Figure 4 Correlations of schematic illustrations of the different shapes with real D-OCT images are presented.

## **Reflectance Confocal Microscopy**







**1. Non-invasive examination of skin** or native tissue in reflectance, that does not require the use of fluorescence, dyes or stains.

2. Contrast in the image correlates to naturally occurring variations in **refractive index of organelles and micro structures** within the skin.

3. Confocal images contain **information about nuclear, cellular and architectural detail**, similar to that seen in histology sections.

4. The pigment **melanin** within the epidermis has a high refractive index, in fact higher than keratin.

5. The confocal microscope images keratinocytes in the **epidermis**, **erythrocytes and leukocytes in capillaries within the papillary dermis and collagen bundles** within the dermis to a **depth of 100-200 µm at the 830 nm wavelength**.





67 years old lady consulting for stetic reasons for a ligh pigmented lesion on the face.Previous cryotherapy years before in another centre. Clinical image.





Dermoscopy exhibits a scar-like lesion probably due to previous cryotherapy. Non-specific light brown pigmentation

















x: 0.76 mm y: 1.24 mm z: 35.26 um Potencia del láser: 2.0 mW






x: -2.24 mm y: -0.76 mm z: 19.55 um Potencia del láser: 2.2 mW







x: -2.24 mm y: -0.76 mm z: 22.49 um Potencia del láser: 2.2 mW







x: -2.24 mm y: -0.76 mm z: 25.44 um Potencia del láser: 2.2 mW







x: -2.24 mm y: -0.76 mm z: 29.37 um Potencia del láser: 2.2 mW







x: -2.24 mm y: -0.76 mm z: 34.27 um Potencia del láser: 2.3 mW







x: -2.24 mm y: -0.76 mm z: 38.20 um Potencia del láser: 2.7 mW







Review Article	Clinical Trial	Epidemiology	Qualitative and Outcomes Research	Translational Research
Fast pathology': a review of ex vivo Confocal Microscopy	Long-term efficacy and safety of brodalumab for psoriasis after 120 weeks	Melanoma mortality in 31 countries from 1985 to 2015	Scalp Hair Assessment Patient-Reported Outcome™ for Alopecia Areata	Frontal Fibrosing Alopecia shows Th1 and JAK3 skewing
(p 1011)	(p 1037)	(p 1056)	(p 1065)	(p 1083)

WILEY

## Editor's Choice December 2020 John Ingram

### 'Fast pathology': a review of ex vivo confocal microscopy

Confocal microscopy (CM) permits high-resolution images of fresh, nonfixed skin specimens, which can be optically scanned in slices. Improvements in ex vivo CM allow visualization of cellular and architectural details, similarly to standard pathology. Digital staining with haematoxylin and eosin is incorporated in newer devices and immunostaining is also now possible. Currently, ex vivo CM is used mainly for intraoperative control of surgical margins of cutaneous tumours in Mohs surgery. However, new applications are being developed and, in their comprehensive review, Malvehy and coauthors describe the logistics, advantages and limitations of ex vivo CM.

Malvehy J, Pérez-Anker J, Toll A et al. Ex vivo confocal microscopy: revolution in



Squamous cell carcinoma with invasive areas (yellow triangles) and keratin pearl (blue triangle).

fast pathology in dermatology. Br J Dermatol 2020; **183**:1011–1025.

## Ex-vivo confocal microscopy





- Fast pathology in 5 minutes
- No damage of the tissue for regular pathology
- Surgical pathology in skin cancer and other tumours















H&E virtual staining. Fusion CM mode. Vivascope 4Gen.





## VivaNet Connectivity









FUNDACIÓ

BARCELON







BiomedicalOptics.SPIEDigitalLibrary.org

#### Line-field confocal optical coherence tomography for high-resolution noninvasive imaging of skin tumors

Arnaud Dubois Olivier Levecq Hicham Azimani David Siret Anaïs Barut Mariano Suppa Véronique del Marmol Josep Malvehy Elisa Cinotti Pietro Rubegni Jean-Luc Perrot



LC-OCT measures the echo-time delay and amplitude of light backscattered from cutaneous microstructures through low-coherence interferometry associated with confocal spatial filtering. Cross- sectional B-scan image is produced in real time at 10 frame /sec. With an isotropic spatial resolution of ~1  $\mu$ m, the LC-OCT images reveal a comprehensive structural mapping of skin at the cellular level down to a depth of ~500  $\mu$ m.

Line

Tube lens

Immersion

microscope



Arnaud Dubois, Olivier Levecq, Hicham Azimani, David Siret, Anaïs Barut, Mariano Suppa, Véronique del Marmol, Josep Malvehy, Elisa Cinotti, Pietro Rubegni, Jean-Luc Perrot, "Line-field confocal optical coherence tomography for high-resolution noninvasive imaging of skin tumors," *J. Biomed. Opt.* 23(10), 106007 (2018). doi: 10.1117/J.JBO.23.10.106007.

SPIE.

## Line-field Confocal Optical Coherence Tomography (LC-OCT)



B-scan image of healthy human skin (back of the hand), obtained with LF-OCT (Scale bar: 200µm)









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## Line-field Confocal Optical Coherence Tomography (LC-OCT)

#### Basal cell carcinoma



Melanoma

## **Consortium for research in LC-OCT**

**Hôpital Erasme – ULB** Veronique del Marmol Mariano Suppa Jovanie Razafindrakoto Florence Bourlond

Hôpital St Etienne Jean Luc Perrot

Hosp.Clínic Barcelona Josep Malvehy Susana Puig Javiera Pérez

**University of Siena, S. Maria alle Scotte Hospital** Pietro Rubegni Elisa Cinotti L. Tognetti

#### DAMAE

Maxime Cazalas Clothilde Raoux Nicolas Linard



## P116, L1







## P116, L1











## Measurement of photoageing: lineal confocal-OCT (LC-OCT)



3D LC-OCT quantification of epidermal characteristics in seven body sites on the same subject (27-year-old female, phototype II). The thickness of stratum corneum (SC) and stratum spinosum (SS) are reported in µm, whereas the undulation of the dermal- epidermal junction (DEJ, green layer) is expressed in percentage (Chauvel-Picard J et al)

Chauvel-Picard J, Bérot V, Tognetti L, Orte Cano C, Fontaine M, Lenoir C, Pérez-Anker J, Puig S, Dubois A, Forestier S, Monnier J, Jdid R, Cazorla G, Pedrazzani M, Sanchez A, Fischman S, Rubegni P, Del Marmol V, Malvehy J, Cinotti E, Perrot JL, Suppa M. Line-field confocal optical coherence tomography as a tool for three-dimensional in vivo quantification of healthy epidermis: A pilot study. J Biophotonics. 2022 Feb;15(2):e202100236. doi: 10.1002/jbio.202100236. Epub 2021 Oct 21. PMID: 34608756.

#### www.nature.com/scientificreports

### scientific reports

Check for updates

OPEN Non-invasive scoring of cellular atypia in keratinocyte cancers in 3D LC-OCT images using Deep Learning

> Sébastien Fischman<sup>1⊠</sup>, Javiera Pérez-Anker<sup>2,3</sup>, Linda Tognetti<sup>4</sup>, Angelo Di Naro<sup>4</sup>, Mariano Suppa<sup>5,6,7</sup>, Elisa Cinotti<sup>4,6</sup>, Théo Viel<sup>1</sup>, Jilliana Monnier<sup>6,8</sup>, Pietro Rubegni<sup>4</sup>, Véronique del Marmol<sup>5</sup>, Josep Malvehy<sup>2,3</sup>, Susana Puig<sup>2,3</sup>, Arnaud Dubois<sup>9</sup> & Jean-Luc Perrot<sup>10</sup>

> > . . . . . . . . . . .









Skin layers segmentation



Nuclei per layers (3D) Green: 1<sup>st</sup> top layer / Blue: middle layer / Red: bottom layer



Nuclei per layers (3D) Green: 1<sup>st</sup> top layer Blue: middle layer Red: bottom layer

Nuclei per size (volume) red: largest nuclei Green: intermediate blue: smallest Nuclei per atypia (Al score) red: highest atypia Green/yellow: intermediate blue: smallest atypia

### AI DETECTION OF BCC



### **PRE-SURGICAL MARGINS ASSESSMENT**





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## Multiphoton tomography

 Simultaneous excitation of endogenous fluorophores by two or more photons of low energy in the NIR



M. Kaatz, K. König. Multiphotonenmikroskopie und In-vivo-Multiphotonentomographie in der dermatologischen Bildgebung. Hautarzt 2010 Federica Arginelli et al. High resolution diagnosis of common nevi by multiphoton laser tomography and fluorescence lifetime imaging. Skin res and technol 2013

## **RAMAN** in skin cancer

- IR and Raman spectroscopy provide details regarding the chemical composition and molecular structure of substances in cells and biological tissues, and they are considered to be vibrational spectroscopic techniques.
- IR spectroscopy measures absorbed radiation, and can serve as a visualization tool to aid the pathologist in evaluating tissue specimens









Krafft C, Sergo V. Biomedical applications of Raman and infrared spectroscopy to diagnose tissues. Spectroscopy. 2006;20(5–6): 195–218 Lui H, Zhao J, McLean D, Zeng H. Real-time Raman spectroscopy for in vivo skin cancer diagnosis. Cancer Res. 2012 May 15;72(10):2491-500.

### Multispectral analyses of skin cancer

With the goal of diagnosing skin cancer in an early and noninvasive way, an extended near infrared multispectral imaging system can be used to evaluate deeper skin layers thanks to the higher penetration of photons at these wavelengths.









- Visual interpretation
- Computer vision analysis

Delpueyo X, Vilaseca M, Royo S, Ares M, Rey-Barroso L, Sanabria F, Puig S, Pellacani G, Noguero F, Solomita G, Bosch T. Multispectral imaging system based on light-emitting diodes for the detection of melanomas and basal cell carcinomas: a pilot study. J Biomed Opt. 2017 Jun 1;22(6):65006. Rey-Barroso L, Burgos-Fernández FJ, Delpueyo X, Ares M, Royo S, Malvehy J, Puig S, Vilaseca M. Visible and Extended Near-Infrared Multispectral Imaging for Skin Cancer Diagnosis. Sensors (Basel). 2018 May 5;18(5):1441.











## TOTAL BODY SCANNERS

### **3D TOTAL BODY PHOTOGRAPHY**





92 stereo cameras; polarised light; whole body 3D imaging system captures the entire skin surface in macro quality resolution with a single capture.
30 minuts IA: la nova evolució















lista de trabajo 0 / 29 imágenes

0 0 28 0 0 1

Dermoscopía

 $\langle 0 \rangle$ 

Female, 52 years old, personal history of melanoma in situ on right arm in 2002 (diagnosed in other center) and no familial oncological history.

2021, nodular BCC (scapular region) BCC superficial multifocal (lateral right back)

25/10/2021









## Skin cancer diagnostics: workflow of patients











MMSS 0,2 mm Breslow, 0 mit /mm2, III Clark.

## Intelligent Total Body Scanner for Early Detection of Melanoma



Al-based tools to provide holistic risk assessment for individual lesions, and risk stratification of patients to assist clinicians in monitoring for skin cancer.



## Consortium

The iToBoS project involves partners from 13 countries: Spain (5), Germany (3), France (2), Switzerland (1), Israel (1), Belgium (1), Greece (1), Ireland (1), Italy (1), UK (1), Hungary (1), Sweden (1) and Australia (1). For 48 months we will work to get the expected results for the benefit of scientific research.



The University of Queensland has received funding from the Australia's NHMRC under grant number APP2007014.



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\*Publicly released dataset of anonymised annotated TBP images will be used for an international challenge to foster use and development of new algorithms





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## Diagnostic of skin cancer in 2034



Imaging biomarkers: screening, risk, diagnostic, prognostic, predictive Deeper cellular resolution, molecular analyses, photonic nanotechnology, drug delivery....



- A number of technologies using imaging and physical properties are available for skin cancer diagnosis
- New technologies with faster examination and computed aided
- The combination of Deep phenotyping with machine learning can improve detection of skin cancer and risk stratification of patients

