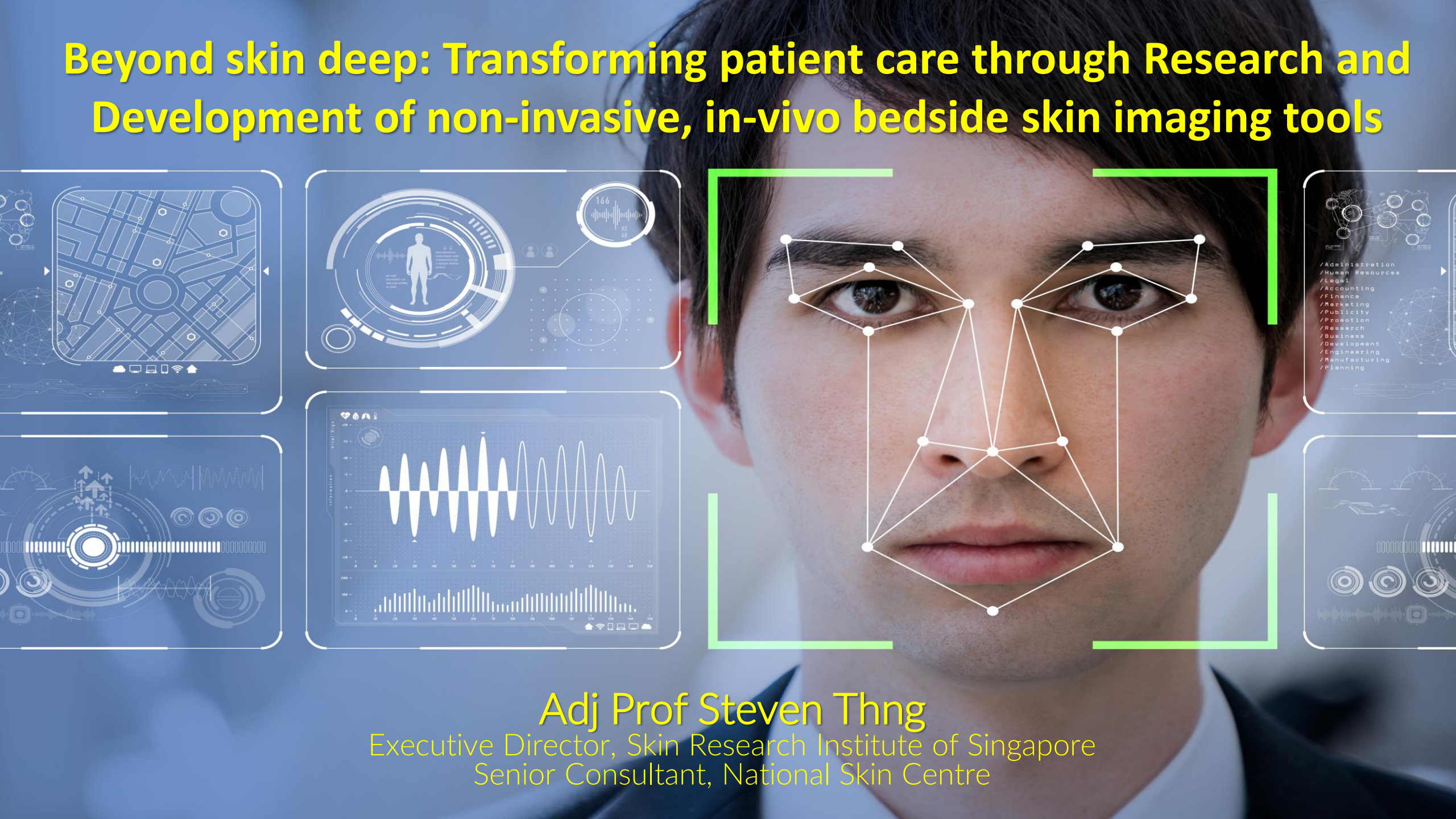
Beyond skin deep: Transforming patient care through Research and Development of non-invasive, in-vivo bedside skin imaging tools



Adj Prof Steven Thng

Executive Director, Skin Research Institute of Singapore

Senior Consultant, National Skin Centre


Research collaboration/funding
Galderma
Loreal
Clinuvel
ASLAN Pharma
JW Pharma
Johnson and Johnson
iTHERA
P&G
LVMH
Pola
Disclosures
No conflict of interest for this talk

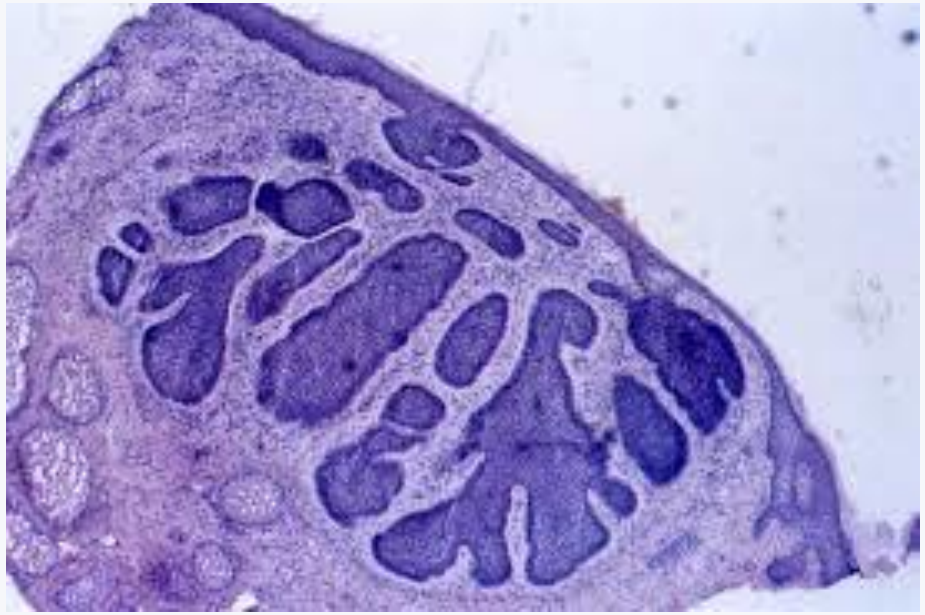

Why Skin Imaging in dermatology?

1960s

2021

What is this lesion?

Dermatology as it is “today”

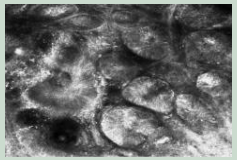
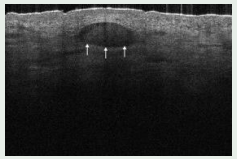
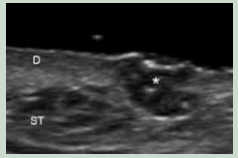


Dermatology as it is “today”

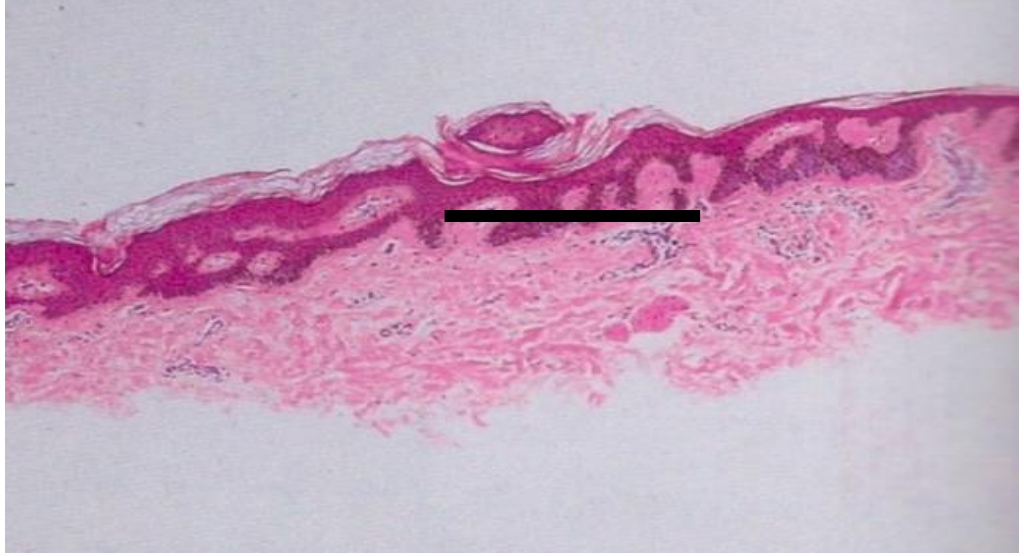
Some considerations of skin biopsy

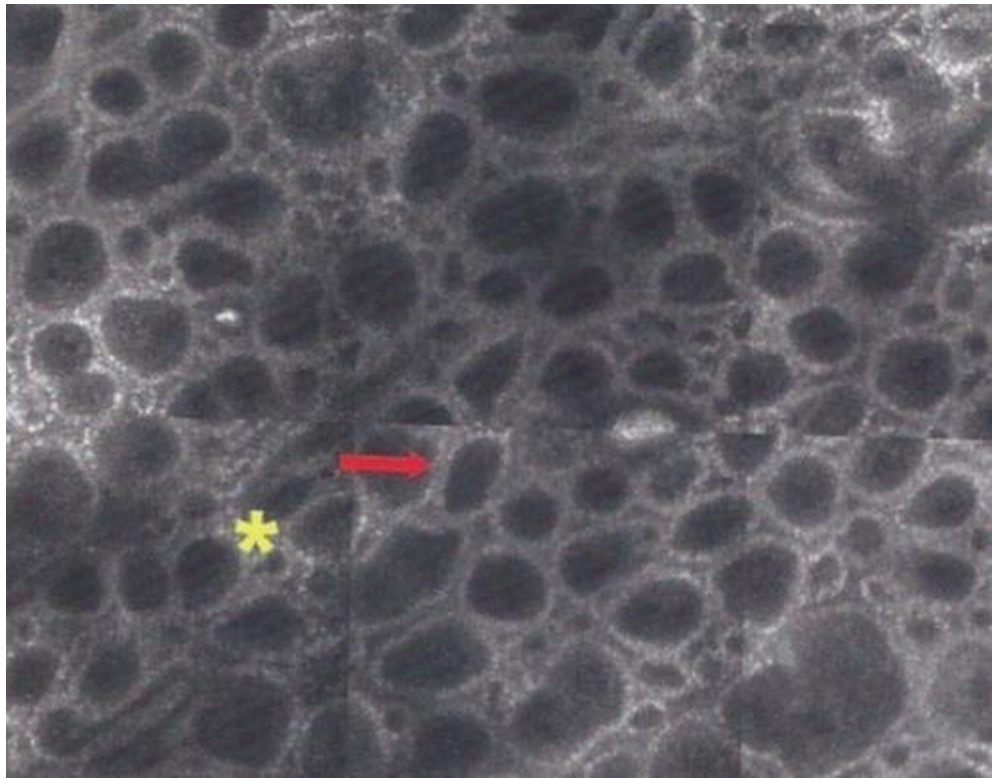
- Psychological stress
- Sampling error
- Scarring
- Repeated biopsy needed for follow up
- Biopsy cannot be done at the same site!

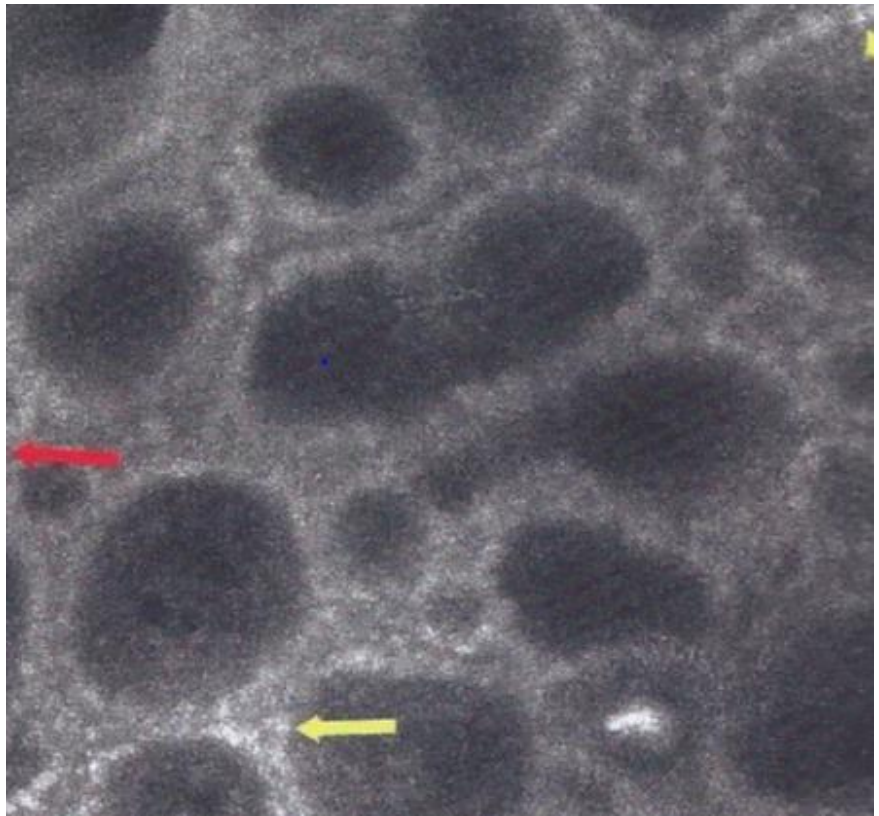
Main Skin Imaging Tools in 2010

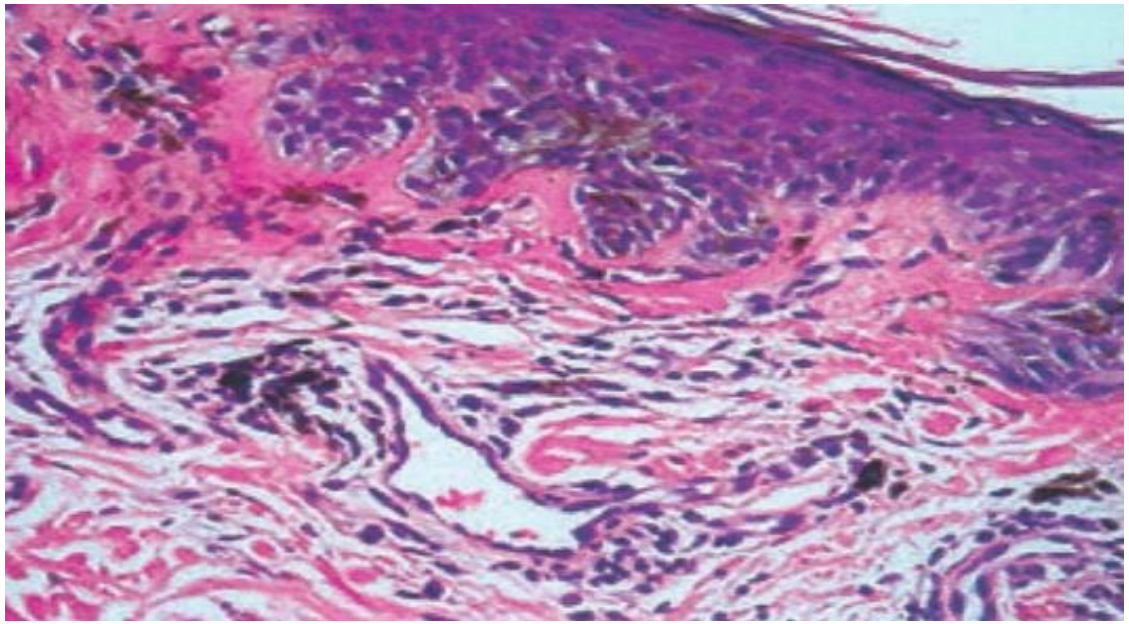
Imaging Tool	Advantages	Disadvantages
Reflectance confocal microscopy (RCM) 	▪ High cellular resolution (5-10 µm) ▪ Tissue morphology	▪ Limited penetration depth (150-200 µm) ▪ 2D imaging
HD Optical coherence tomography (OCT) 	▪ High cellular resolution (10-30 µm) ▪ Tissue morphology ▪ 3D imaging	▪ Limited penetration depth (1-3 mm)
Ultrasound 	▪ Good spatial resolution (100-200 µm) ▪ High penetration depth of up to a few cm ▪ Tissue morphology; blood flow (Doppler) ▪ 3D imaging	▪ Inability to differentiate hypoechoic tumor, inflammation or fat

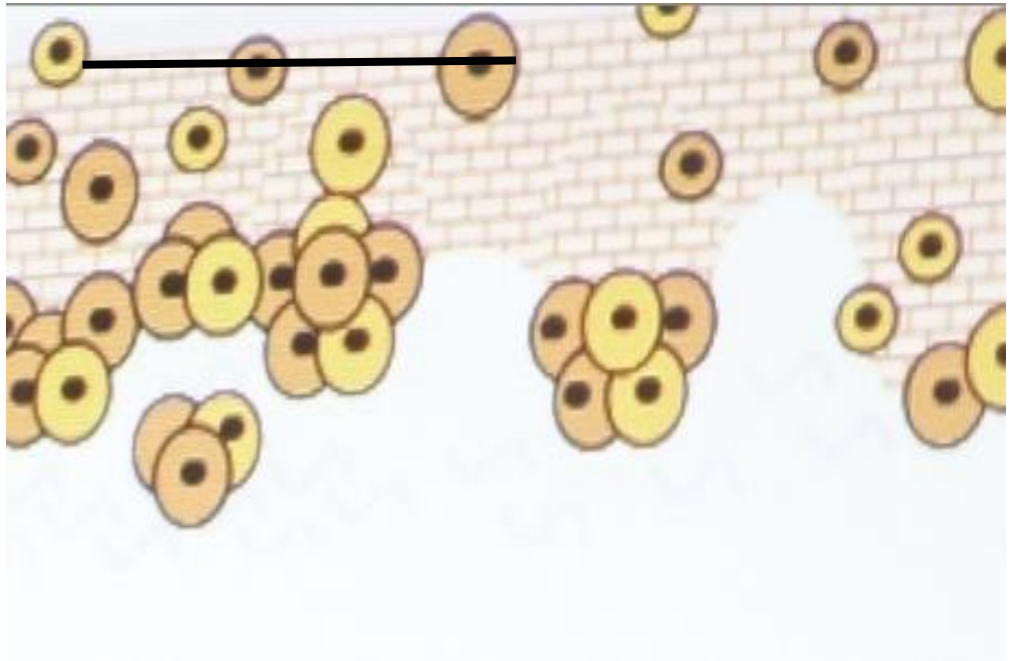
The In-Vivo Confocal

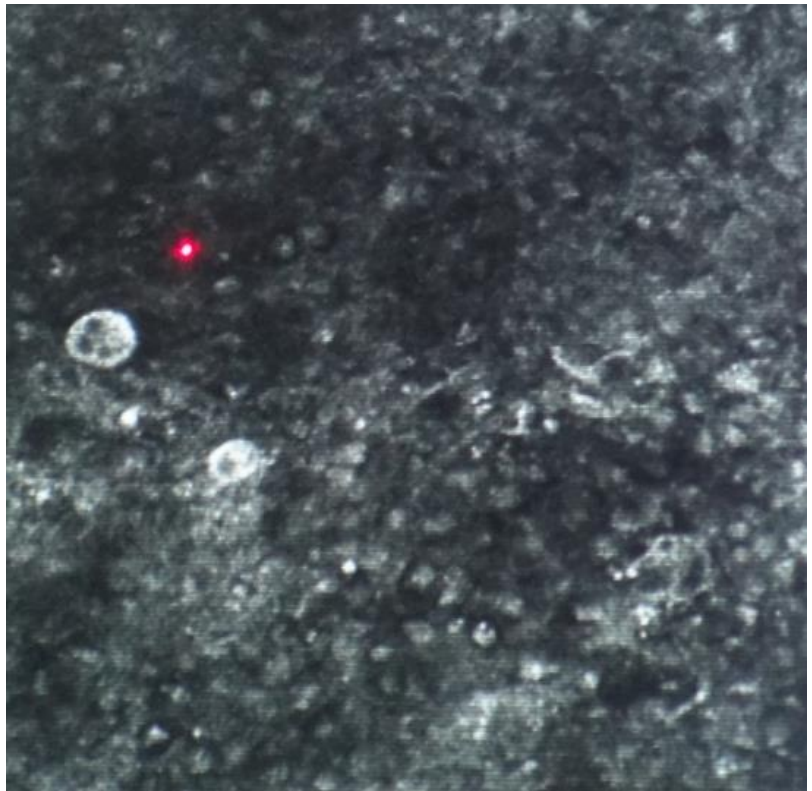


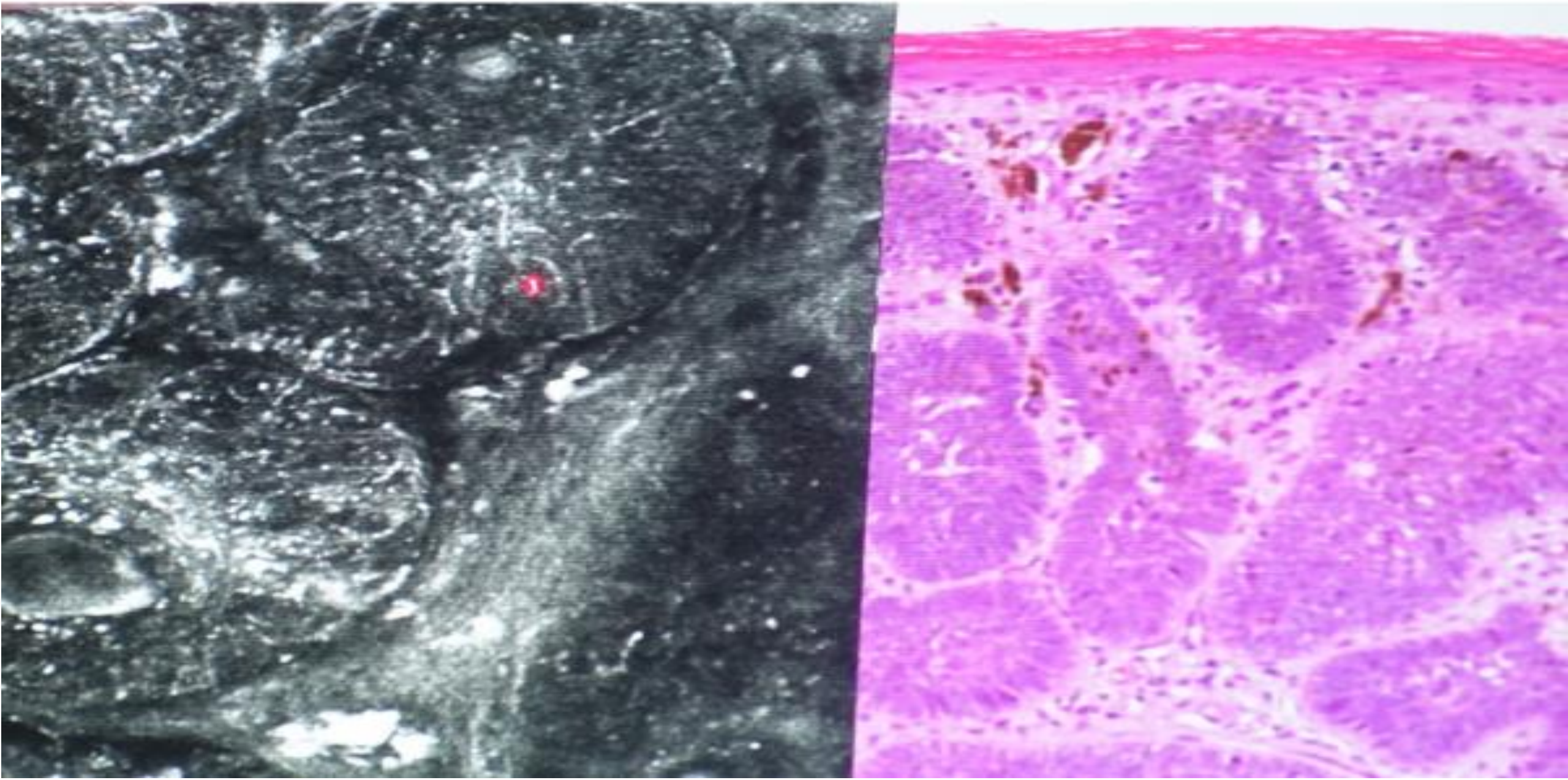




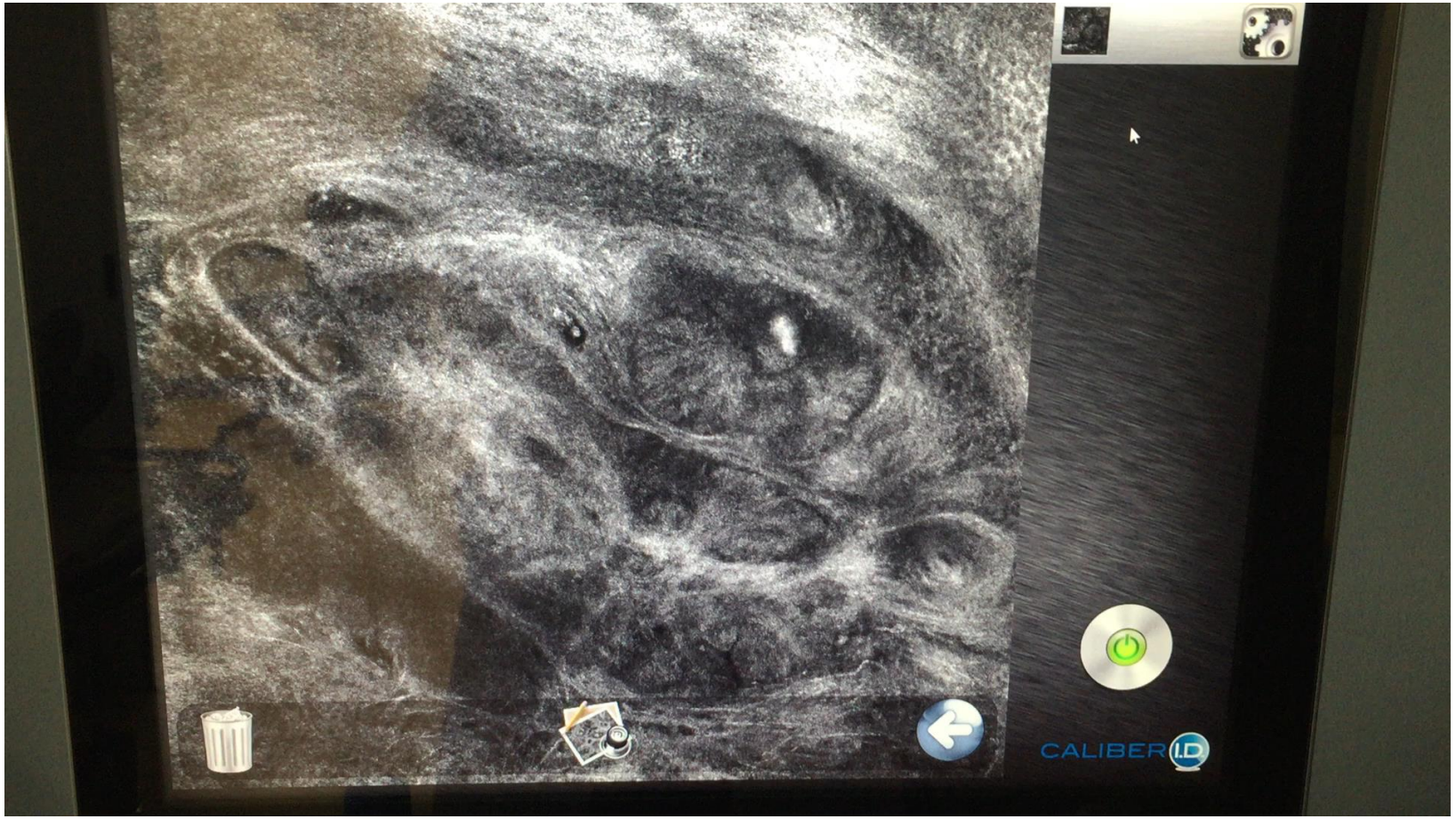




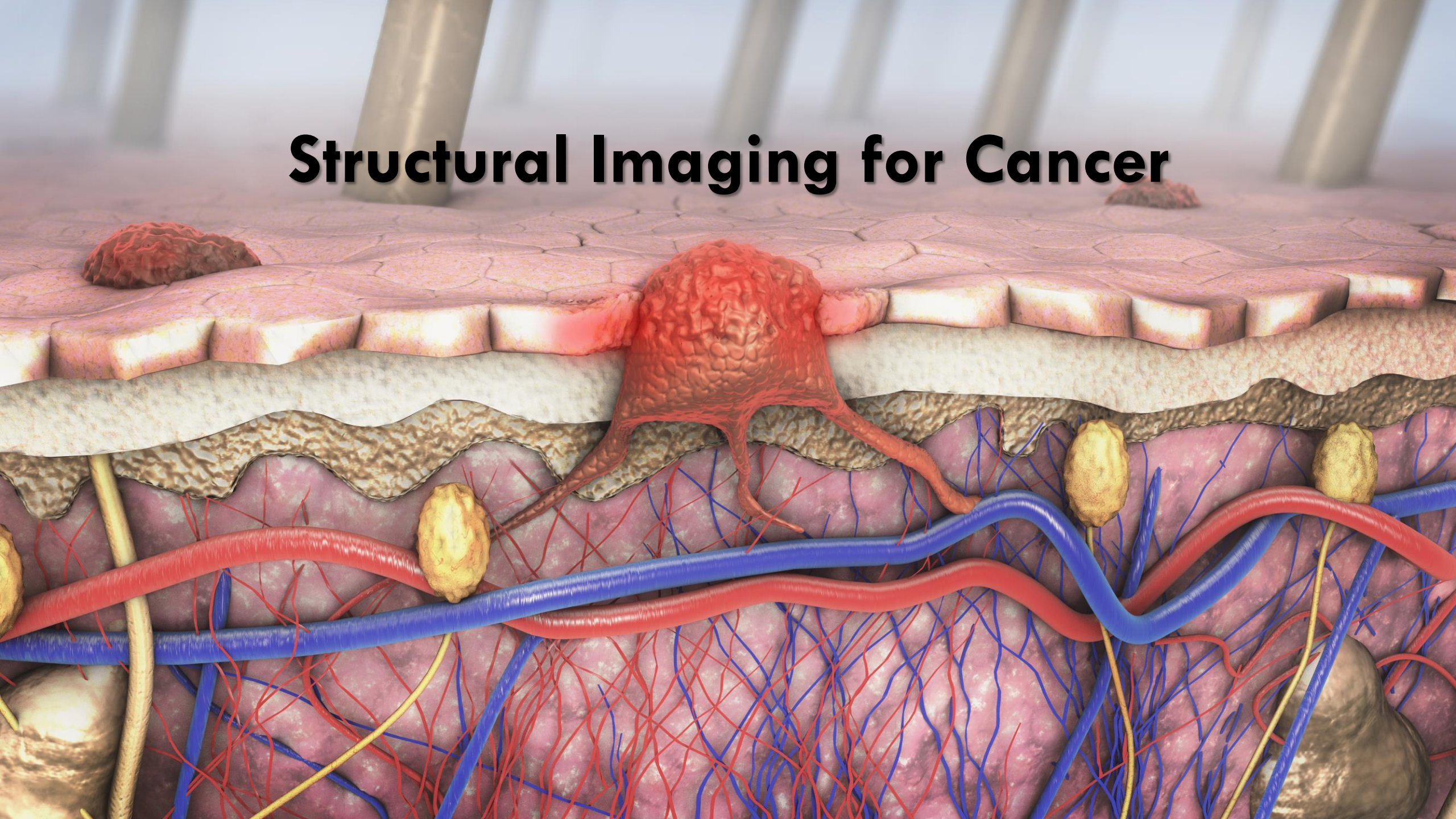




THE BEAUTY OF THE CONFOCALS



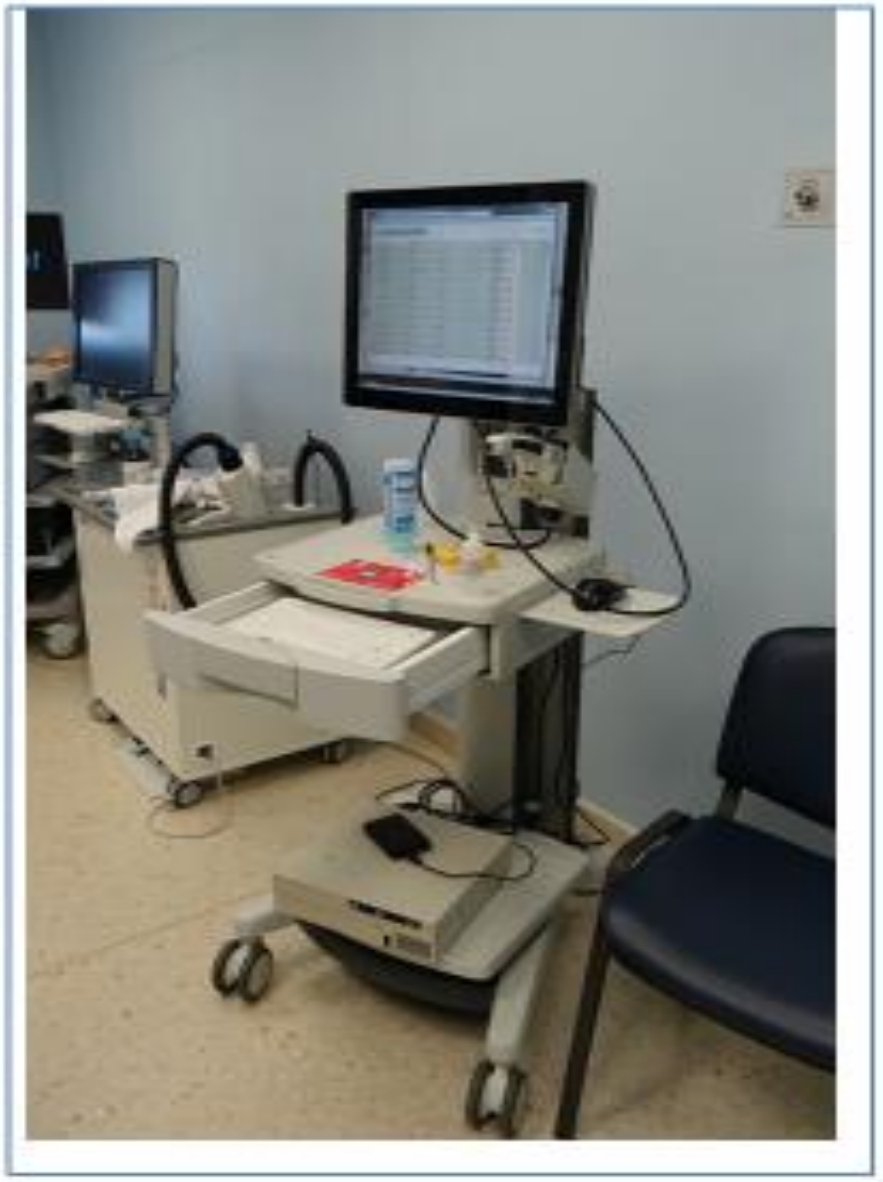
Structural Imaging for Cancer



Skin Cancer

- In-vivo confocal
  - Resolution of 1-5 micrometer
  - Visualize cellular level
  - Depth of up to 300 micrometer
- Diagnosis of BCC
  - Sensitivity of 91.3%
  - Specificity of 97%

Milind et al Lasers Surg Med 2017



Addressing Confocal Diagnostic Accuracy

Prospective clinical-pathological-Imaging study 2011 to 2012

- 415 lesions imaged
  - 91 cases of malignancies
    - **82 cases of BCC**
    - 8 cases of SCC
    - 1 case of melanoma

- Confocal Criteria for diagnosis of BCC:-
  - Tumor nests
  - Peripheral palisading
  - Vascularity
  - Clefting
  - *Loss of honeycomb pattern and pleomorphism of overlying epidermis*

- Increase specificity and decrease sensitivity
  - Employ top 4 criteria for confirmed diagnosis
  - Less than 4 criteria, biopsy.

Validation study of confocal imaging for BCC

- A total of 1031 cases enrolled
  - 1132 lesions imaged
    - 252 cases of malignancies
      - 223 cases of BCC
      - 21 cases of SCC
      - 8 case of melanoma

Confocal		Literature	Biopsy	
Sensitivity	98.8% (CI 93-99)	91%	Sensitivity	96.43% (CI 89-99)
Specificity	97.9% (CI 86-99%)	97%	Specificity	100%
PPV	98.55%		PPV	100%
NPV	98.67%		NPV	97%

PREVIOUS SKIN CANCER WORKFLOW

Clinical Diagnosis

2 weeks

Biopsy Result

2-3 weeks

Final excision

Fast, painless way of detecting skin cancer

Linette Lai Political Correspondent

Getting tested for skin cancer used to mean a painful biopsy, followed by a long, anxious wait for the results.

But doctors at the National Skin Centre (NSC) are now able to tell if someone has the disease simply by looking at his skin through a special machine.

Unlike a biopsy, no stitches are needed and a diagnosis can be made in as little as five minutes.

ST VIDEOS

British family whose daughter died in Negeri Sembilan files civil suit against resort operator

Spirited away: Carlos Ghosn's brazen disappearing act leaves questions unanswered

- Cost savings of $800,000 annually


100%
ZOOM


100%
ZOOM

What's next?

Current limitations of confocal service

- Performed by specially trained dermatologist
  - Costly and confined to certain days of the week

Ideal state:-

- Confocal performed by technician
  - Use of AI for diagnosis
  - Enable technology to be deployed across centres in Singapore and worldwide
  - Funded by NMRC Feb 2020-2023

Pellacani@Modena

Adams@NTU SCSE

Pushing the boundaries

From 2D to 3D reconstruction.

- Current surgical techniques is by **surgical margins** based on type of cancer, aggressiveness and site of cancer

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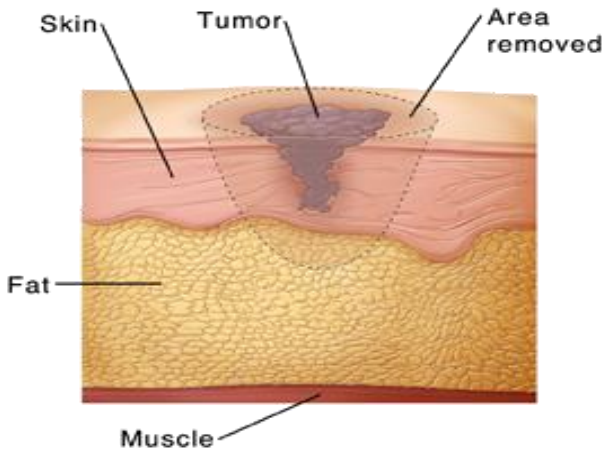

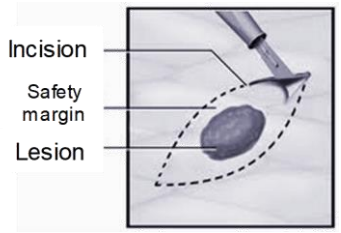

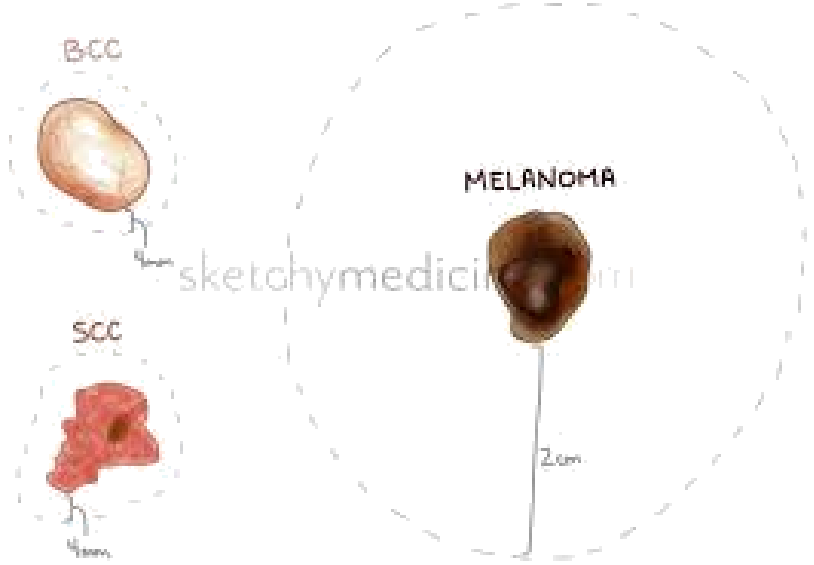

Pushing the boundaries

From 2D to 3D reconstruction.

- Current surgical techniques is by **surgical margins** based on type of cancer, aggressiveness and site of cancer

- MOHs Surgery
  - Not available in all centres
  - Time consuming, costly.

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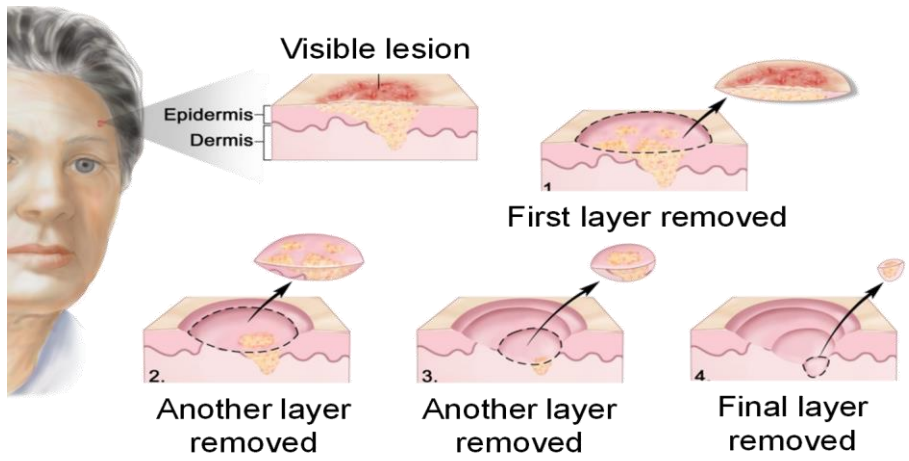
Moh's micrographic surgery (MMS)



Pushing the boundaries

From 2D to 3D reconstruction.

- Current surgical techniques is by **surgical ma** type of cancer, aggressiveness and site of cancer

- MOHs Surgery
  - Not available in all centr
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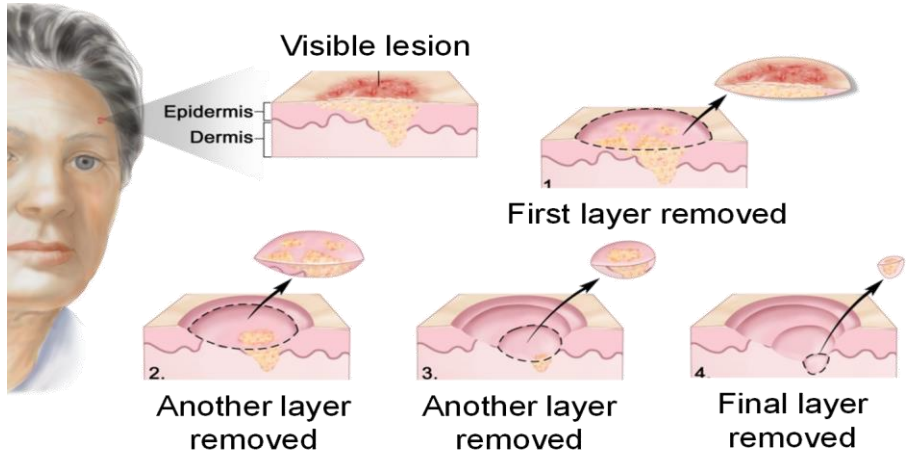
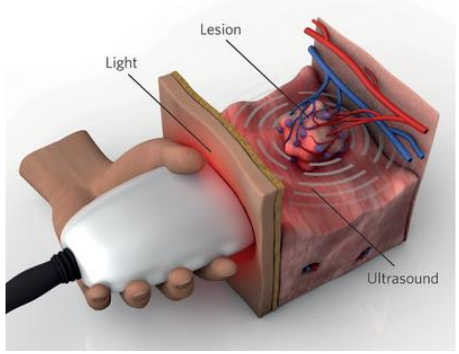
  .

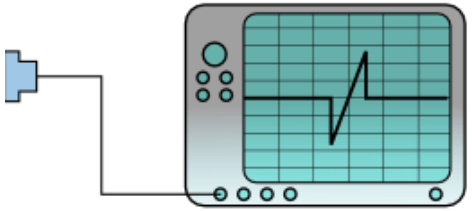
Pre-operative mapping to determine functional and physical structure of NMSC

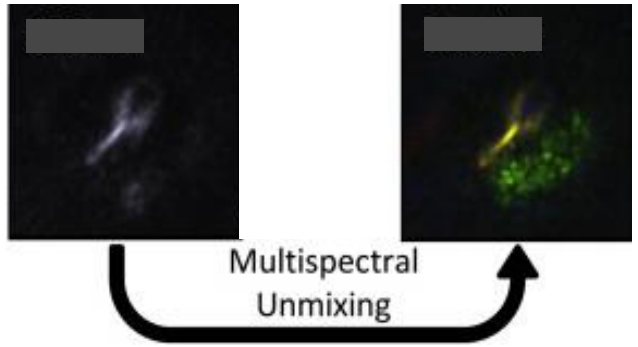
Moh's micrographic surgery (MMS)



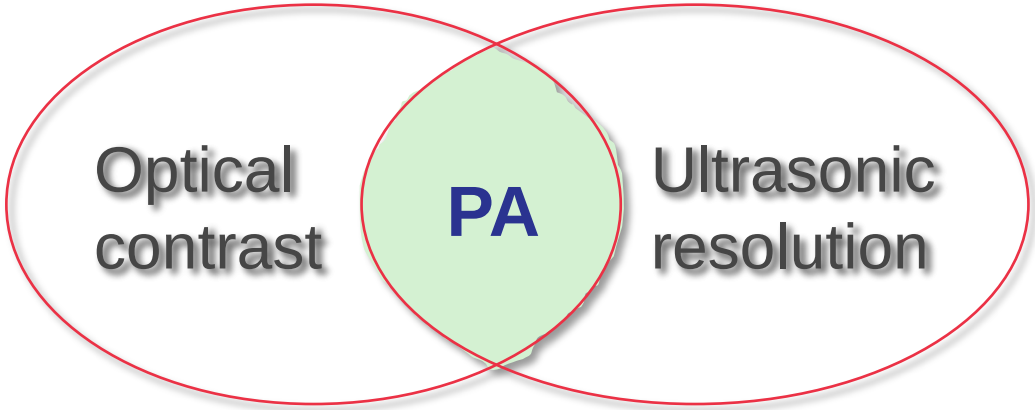
Photoacoustic (PA) Imaging Principle



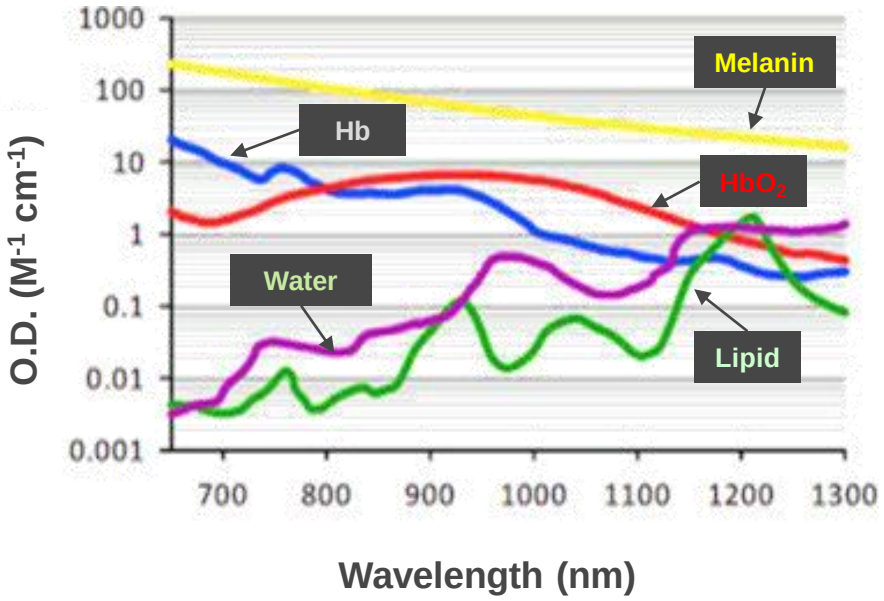




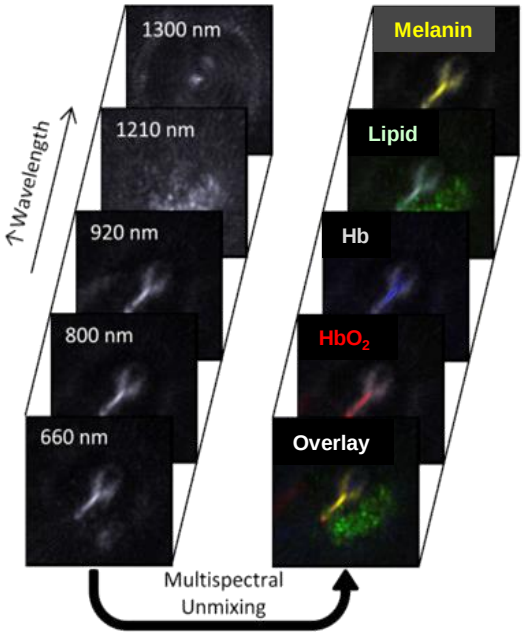
Laser pulse → Thermal expansion → Acoustic waves → Ultrasound detection → Image formation → Spectral decomposition



Multiple Endogenous Contrast



Absorption profiles of skin chromophores (Hb: deoxy-haemoglobin; HbO_2: oxy-haemoglobin)



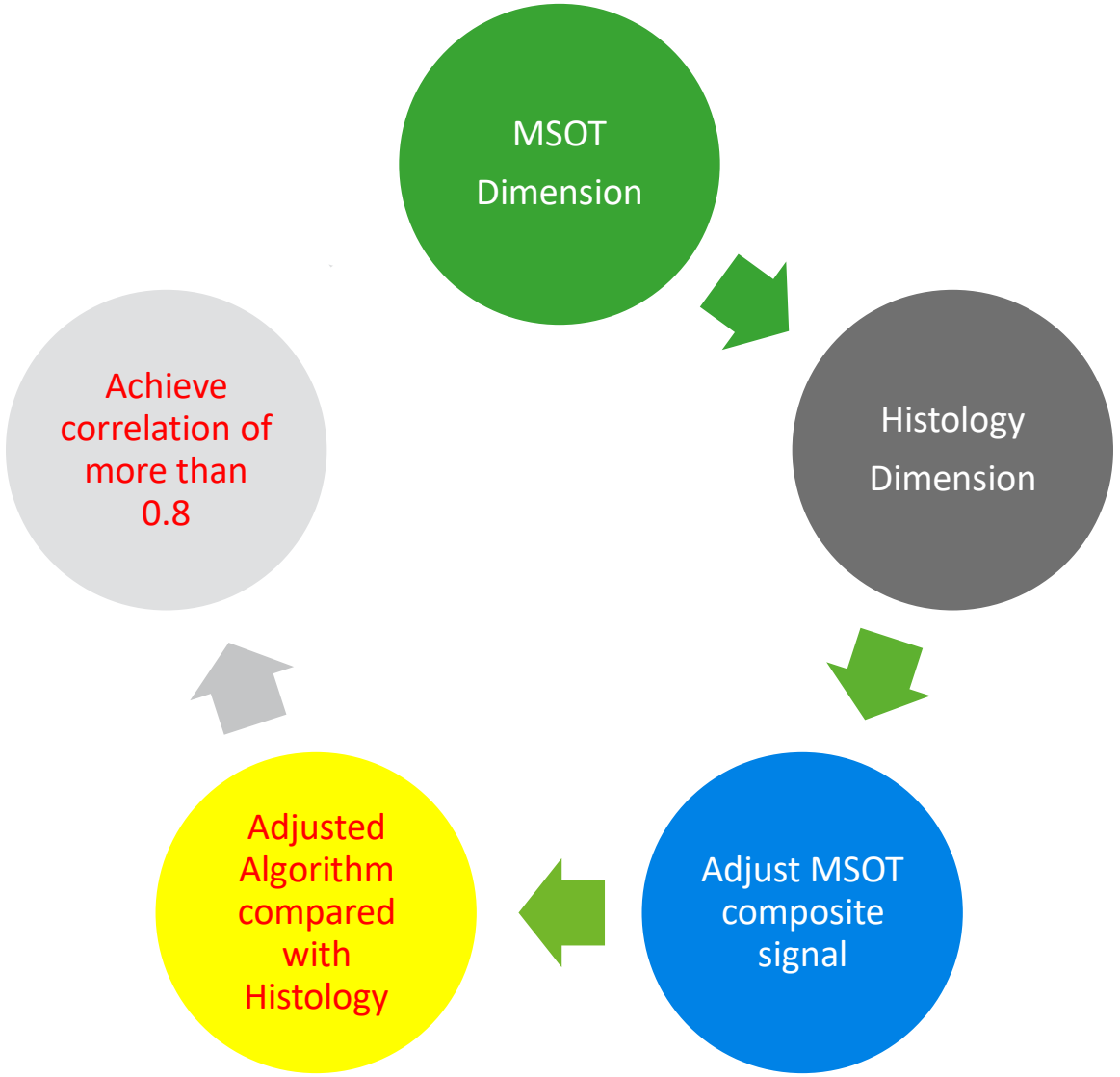
Multispectral MSOT images can resolve various skin chromophores

Journal of Investigative Dermatology 136(4):753-761

Developing Image Delineation Algorithm

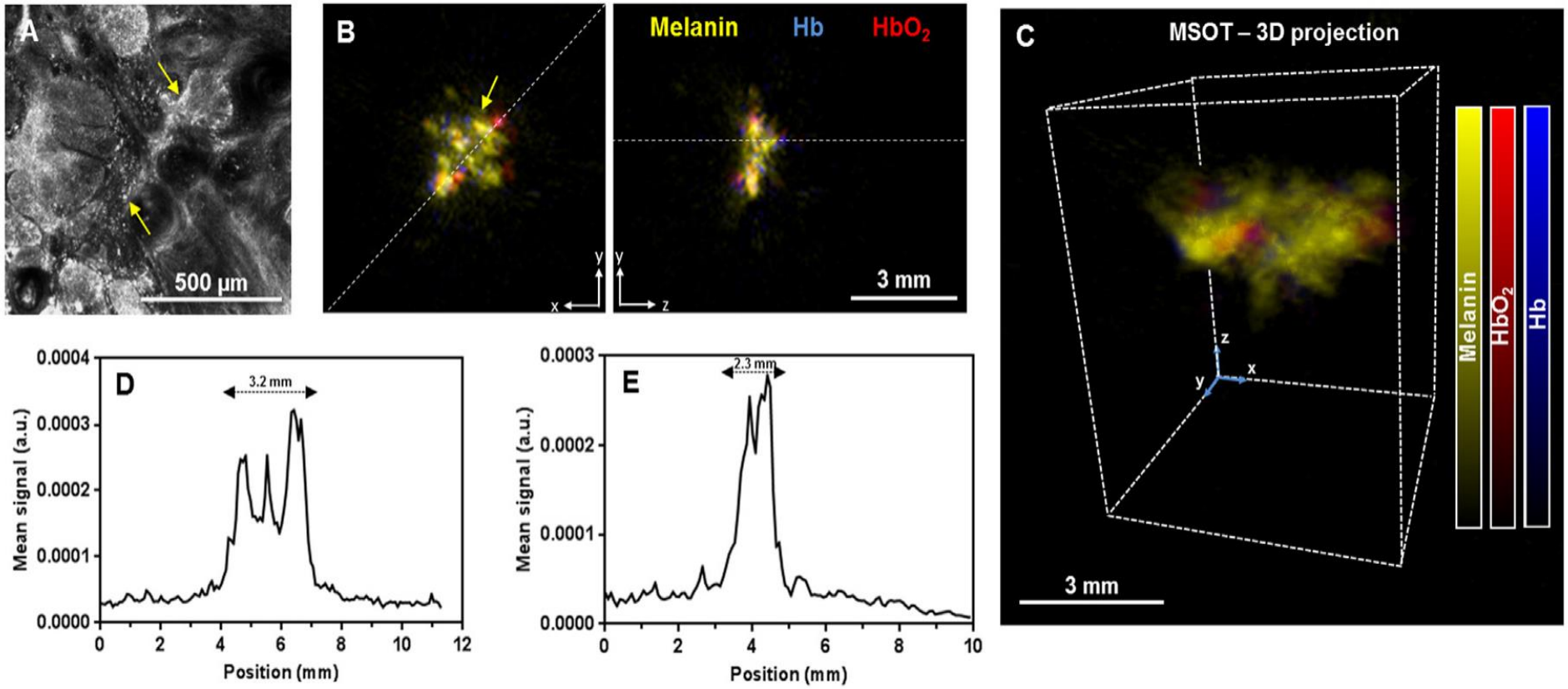
Refining the mapping of BCC in-vivo

- Study done in 2016[1]
- 21 patients enrolled
  - Using a composite of hemoglobin and melanin signals endogenously
  - Map out the dimensions of the tumor, compared with histology dimensions
  - Composite signals adjusted till correlation of more than 0.8 for length, breadth and depth.



1. ABE Attia, Thng et al. Photoacoustics 2017

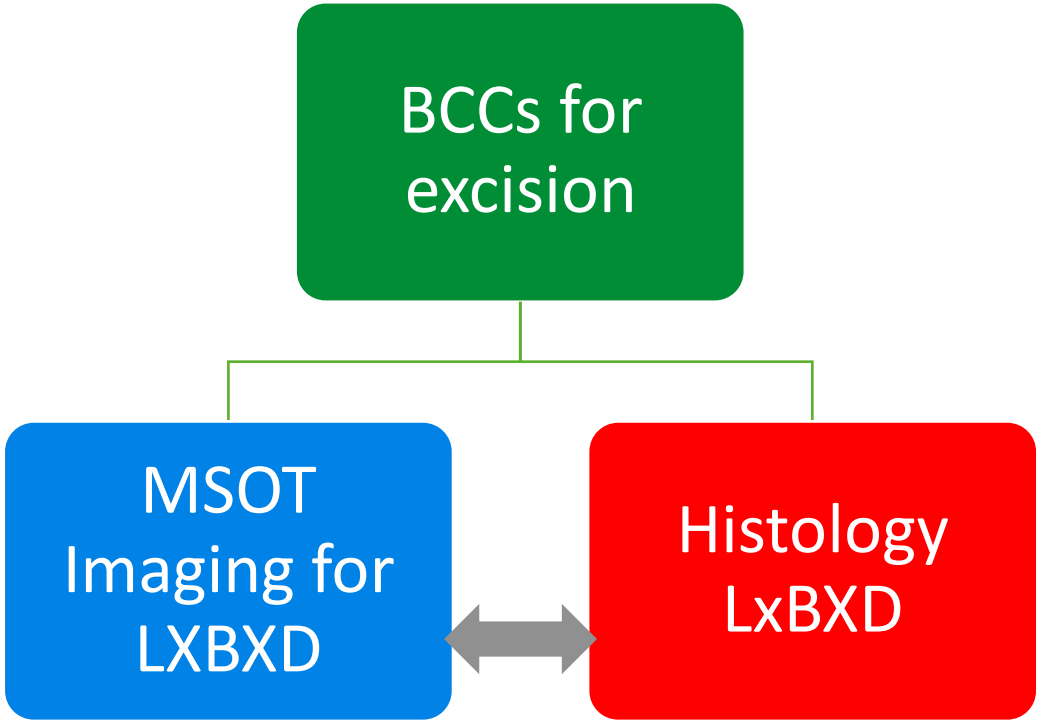
Mapping a pigmented BCC using a 3D probe



Validation Study and Results

Study Design

- Study Design:-
  - Prospective, clinic-pathological and imaging correlation study.
  - Patients with BCC scheduled for excision were imaged with MSOT and dimensions determined
  - Dimensions compared with histopathological measurements
- Statistical analysis
  - GraphPad Prism 6 software (GraphPad Software, San Diego CA)
  - Pearson's correlation coefficient, intraclass coefficient of correlation, and Bland-Altman method with 95% limits of agreement were employed to compare between tumor dimensions calculated by histology and vMSOT.



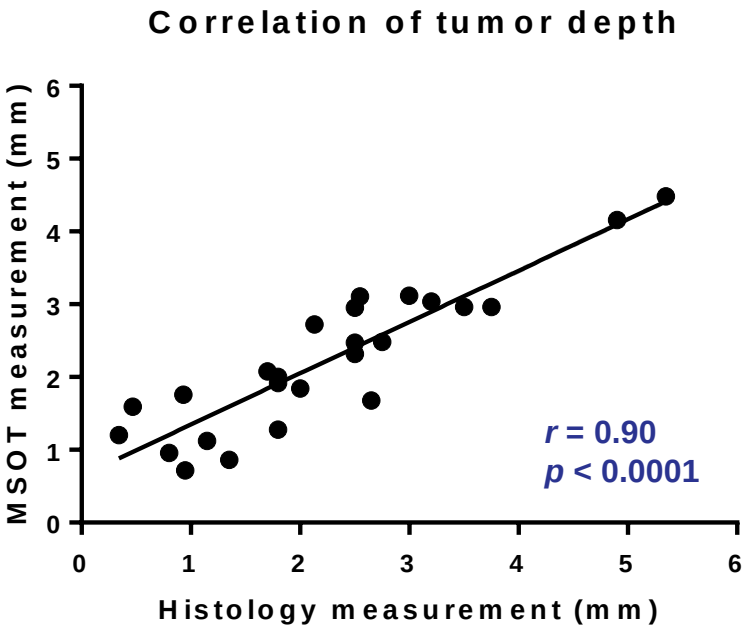
Chuah, Thng et al. JID 2018

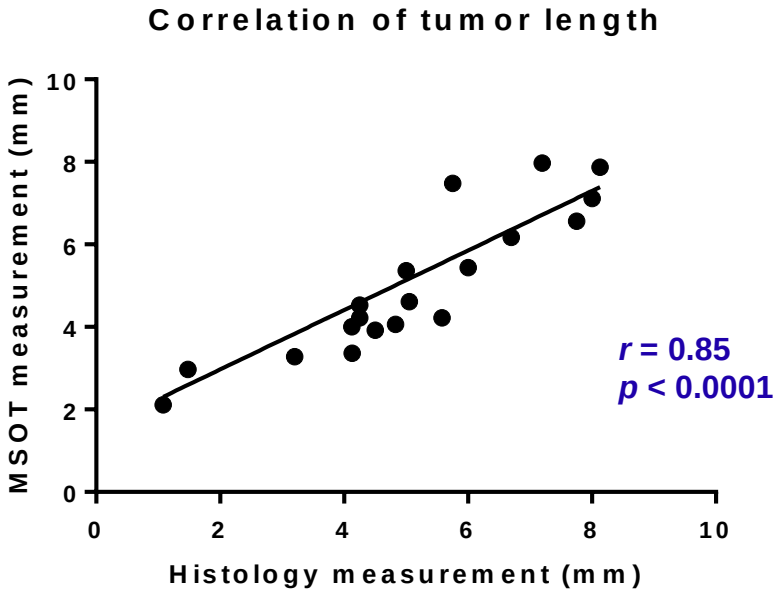
Results

- Study Population
  - 26 patients recruited
    - 6 cases were excluded as size if beyond the FOV of MSOT
    - 12 cases were female and 8 cases male
    - Site
      - 16 on face, 3 on trunk, 1 on limbs

Chuah, Thng et al. JID 2018

Results 1:- Correlation analysis





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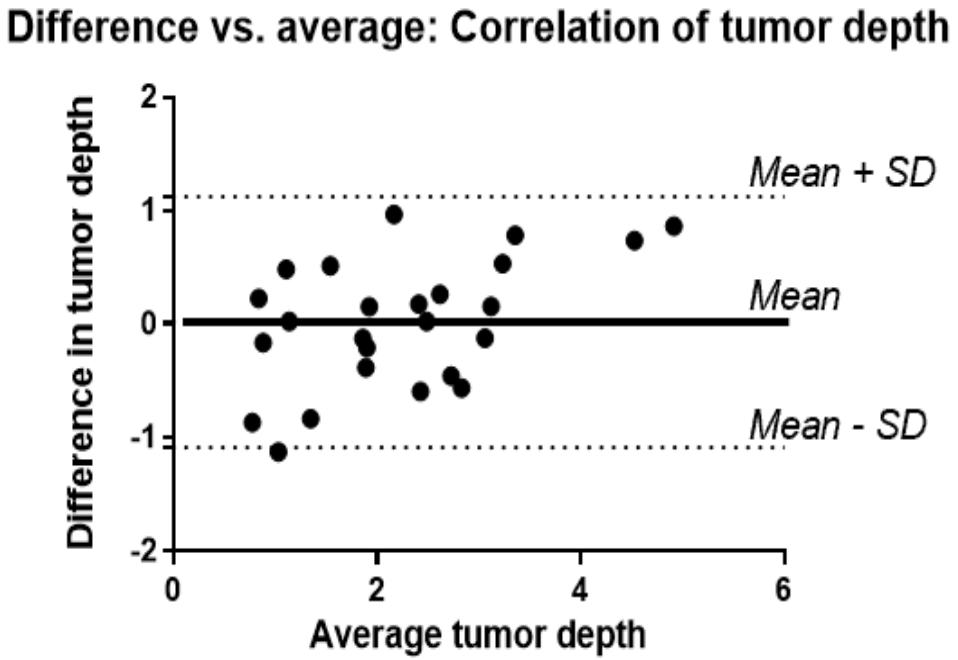
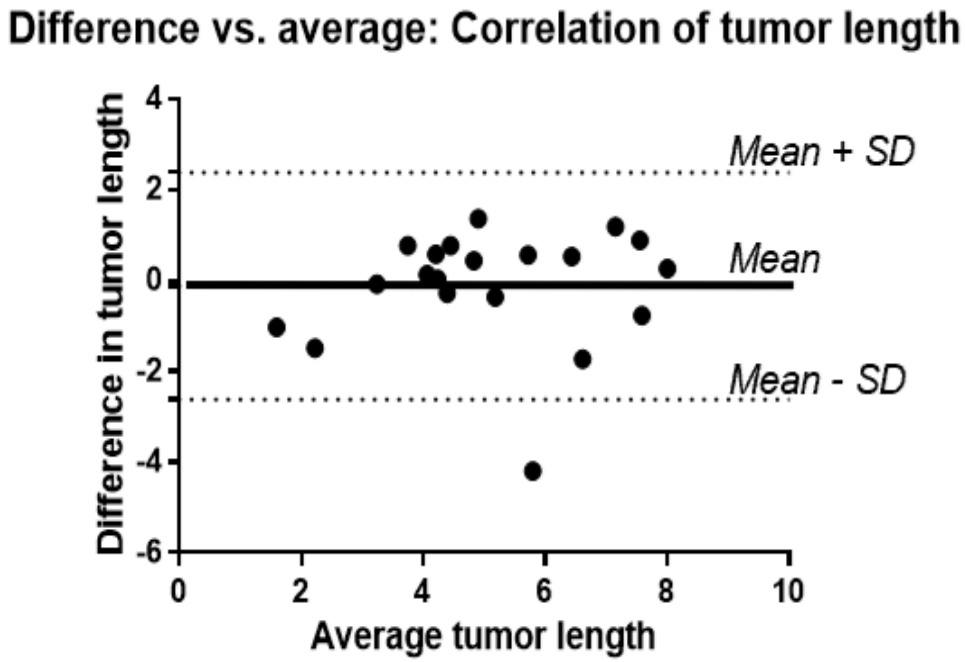
Results 1:- Correlation analysis (Bland-Altman plots)





Average difference of about 0.5 to 1 mm

Average difference of about 1mm - 2mm

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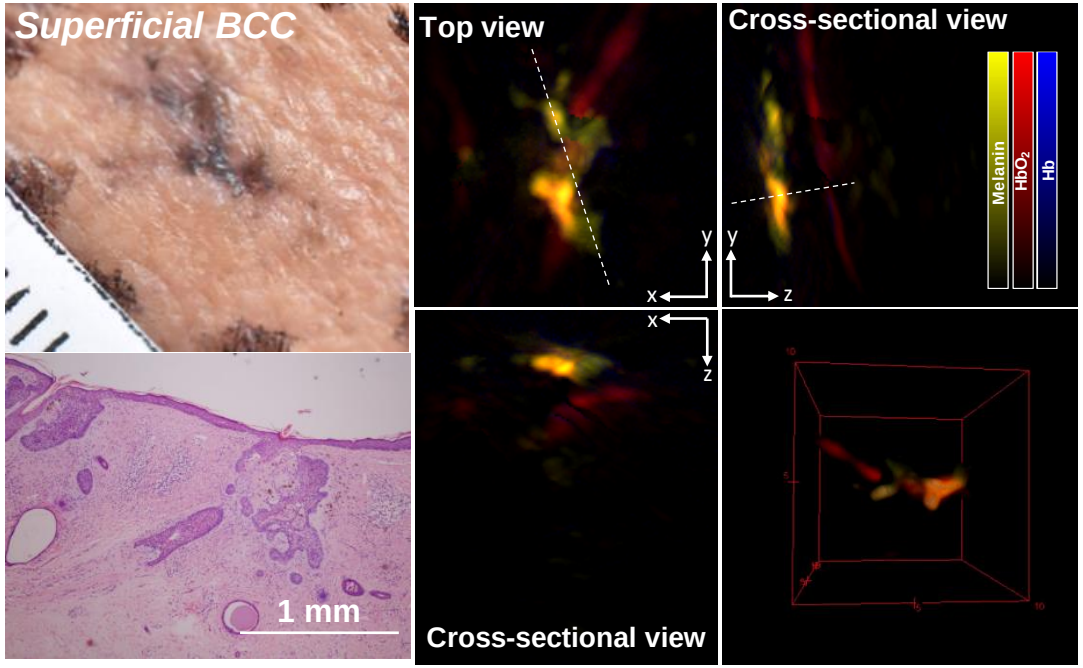
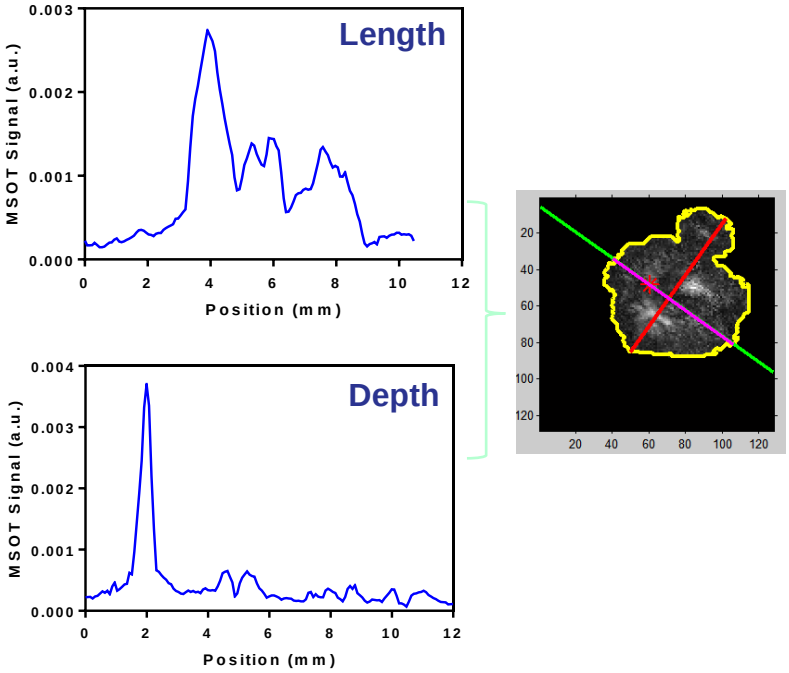
Case examples





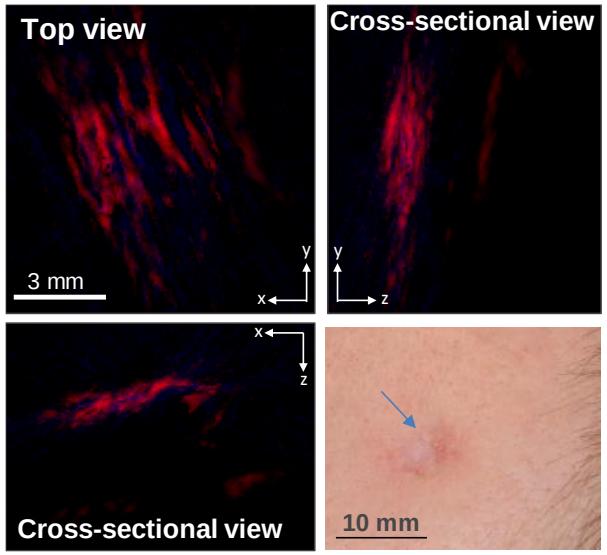
Dimension	MSOT	Histology
Depth (mm)	0.96	0.80
Length (mm)	5.78	5.00
Width (mm)	4.61	

MSOT correlate well with histology on tumor dimensions

Chuah, Thng et al. JID 2018

Imaging Across different Fitzpatrick skin phototypes

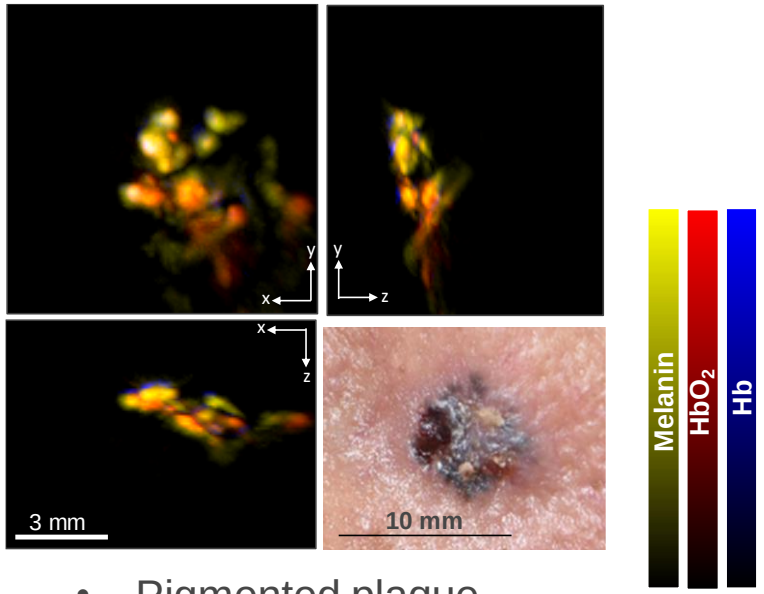
Fitzpatrick Type II



- Erythematous plaque

Dimension	MSOT	Histology
Depth (mm)	2.48	2.70
Length (mm)	4.22	5.20
Width (mm)	3.60	

Fitzpatrick Type IV



- Pigmented plaque

Dimension	MSOT	Histology
Depth (mm)	2.32	2.10
Length (mm)	7.56	7.50
Width (mm)	4.32	

Chuah, Thng et al. JID 2018

Discussion

- First in vivo clinical use of MSOT for 3D mapping and visualization of BCC through a composite of melanin and vascular signals.
- Real time, non-invasive, label-free, deep penetration
- MSOT measurements of lesion dimensions correlated well with histology
- Accuracy is better
  - In pigmented BCCs versus non-pigmented BCCs.
  - Tumor depth has better correlation than tumor length

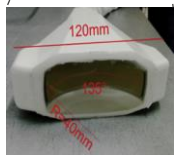
- MSOT is not accurate in very superficial BCC less than 0.5mm.
  - Unisotropic resolution at the peripheral regions of the FOV of the matrix array vMSOT detector. The lower detection limit of the vMSOT may lie between 0.47 and 1.28 mm.
- MSOT seems to be able to map BCCs accurately with margin of error of up to 0.5 mm (in depth) and 1.2mm (in length)
- Possible to be employed as pre-MOHs to reduce number of stages in MOHs.

Chuah, Thng et al. JID 2018

Future plans

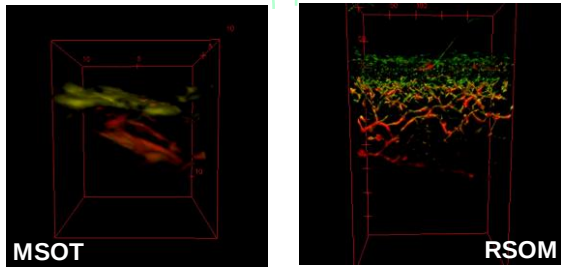
Multispectral Optoacoustic Tomography (MSOT)

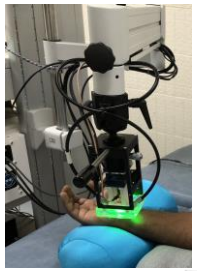
Clinical MSOT Experimental Imaging Platform (EIP)



2D probe ***3D probe***

Raster-scan Optoacoustic Mesoscopy (RSOM)



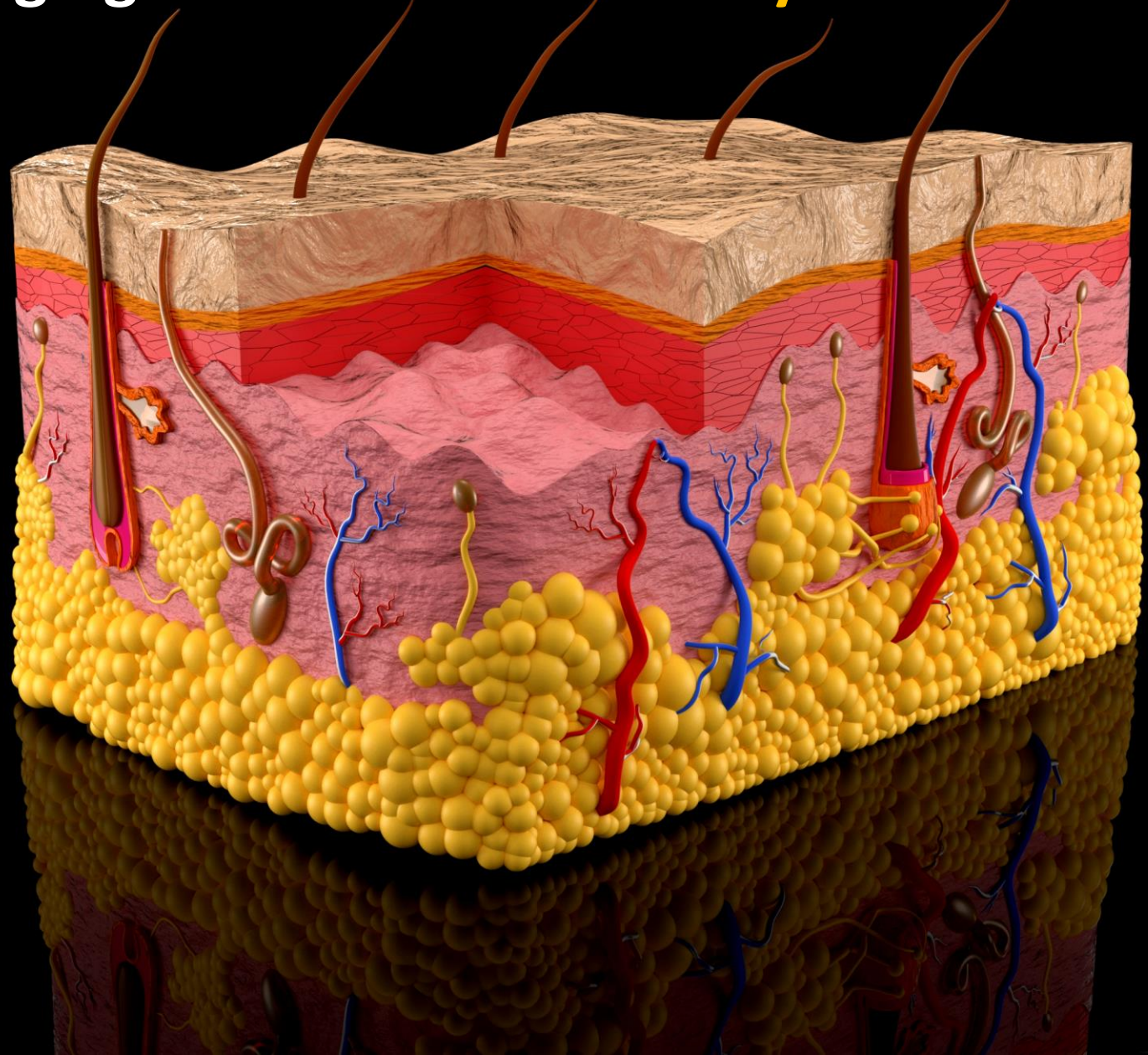


Clinical RSOM

Imaging modality	MSOT	RSOM
Spatial resolution (μm)	~ 80	~ 30
Penetration depth (mm)	10	2-3
Field-of-view (xyz, mm)	10 × 10 × 12	3 × 5 × 3
Label Free Imaging	Yes	Yes
Information derived	• Anatomical • Functional • Molecular	• Anatomical • Functional (for multi-wavelength)

NMRC funded research 2020-2023.

Structural Imaging for Skin Inflammatory Disorders – Vitiligo Stability



Vitiligo Grafting.

In National Skin Centre over the last 5 years

Segmental Vitiligo

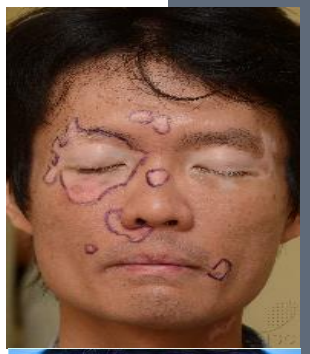
- Different pathogenesis from Vitiligo Vulgaris.
- Rapidly progressing phase, then stabilize

Complete to Excellent Repigmentation

95% of cases over the last 5 years

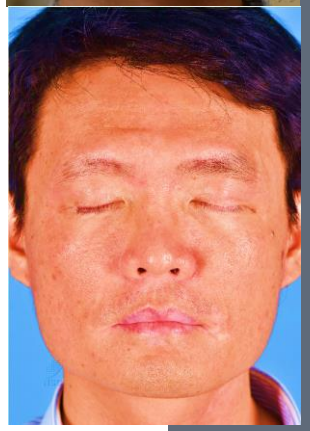
Partial Repigmentation

All cases had partial repigmentation and usually more than 50% repigmentation.



Vitiligo Vulgaris

- Auto-immune pathogenesis
- Waxes and wanes
- Stability is important



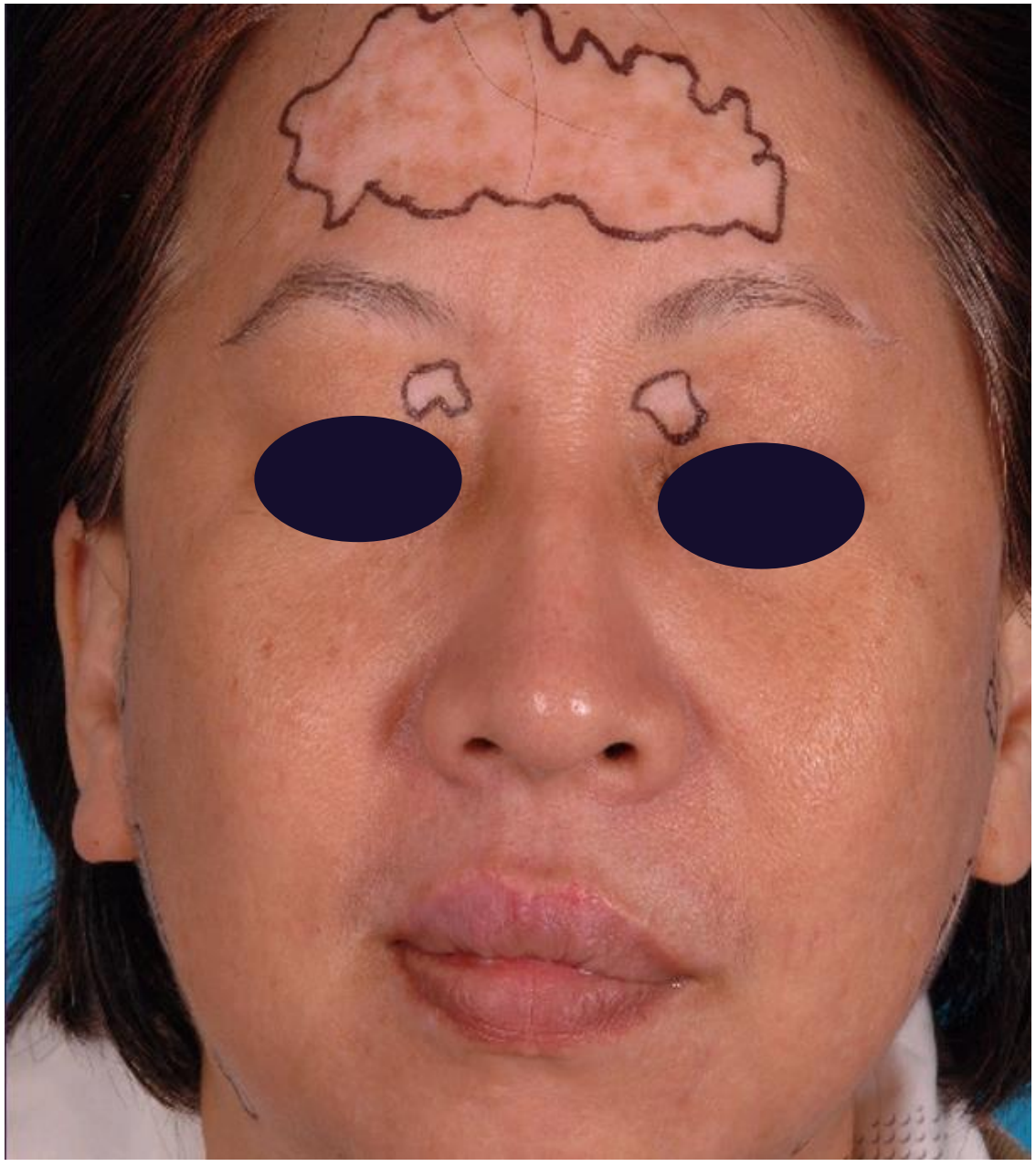
Complete to Excellent Repigmentation

70% over the last 5 years

None Responders

- **About 10% do not respond**
- Some developed active vitiligo 3-6 months post grafting

To graft or nor to graft…that is the question



Vitiligo Vulgaris

Selection of patients is of utmost importance!

- **Failure of conventional treatment**
  No significant repigmentation after 9 months of treatment.
- **Stable vitiligo**
  No new or expanding lesions in the preceding 12 months
- **Absence of koebner phenomena**
  Scars are not hypo/depigmented
- **No history of keloidal tendencies**
  Relative contra-indication
- **Positive test graft**
  Mainly for patients with vitiligo vulgaris

How do we better predict stability?

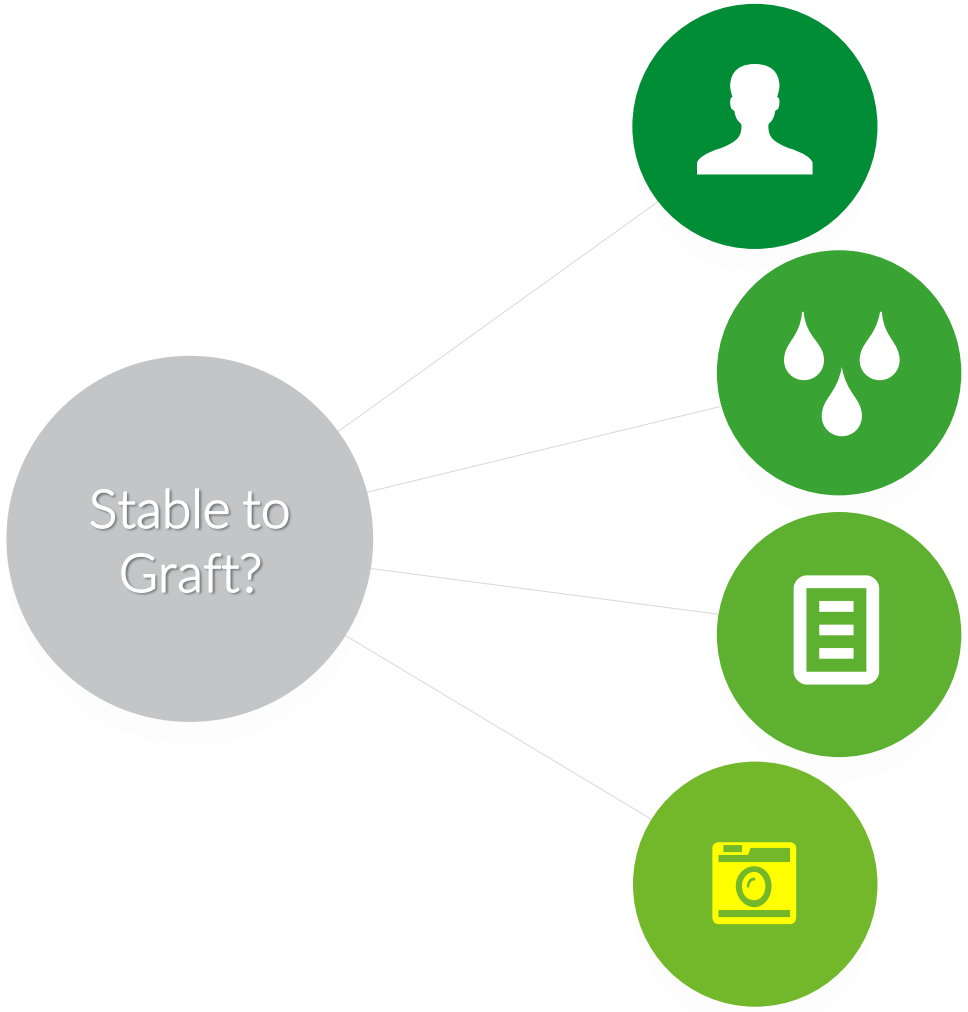
Prediction of Stability

Clinical Stability
Based on history and physical examination, range from 4 months to 3 years

Biochemical Parameters
Serum anti-oxidant status, homovanillic acid (HVA) and vanillylmandelic acid

Serological Studies
Presence ad titres of auto-antibodies to tyrosine hydroxylase, TRP1,2

Microscopic Studies
Peri-lesional skin looking for inflammatory cells, vacuolar changes in basal cells as well as degenerating melanocytes



Can Confocal be used to define Stability?

What can confocal tell us about vitiligo?

RCM and Prediction of Stability

Li et al. Indian Journal of Dermatology 2013

Study Design

- 125 patients recruited
- RCM performed at lesional, perilesional and normal skin
- VIDA score to assess stability as compared to RCM score
- RCM-Histo correlation in active vitiligo group

RCM Score

- Pigmentation status in the lesional skin:
- Status of the border of vitiligo lesion:
- Inflammatory cell infiltration:
- Melanocyte regeneration

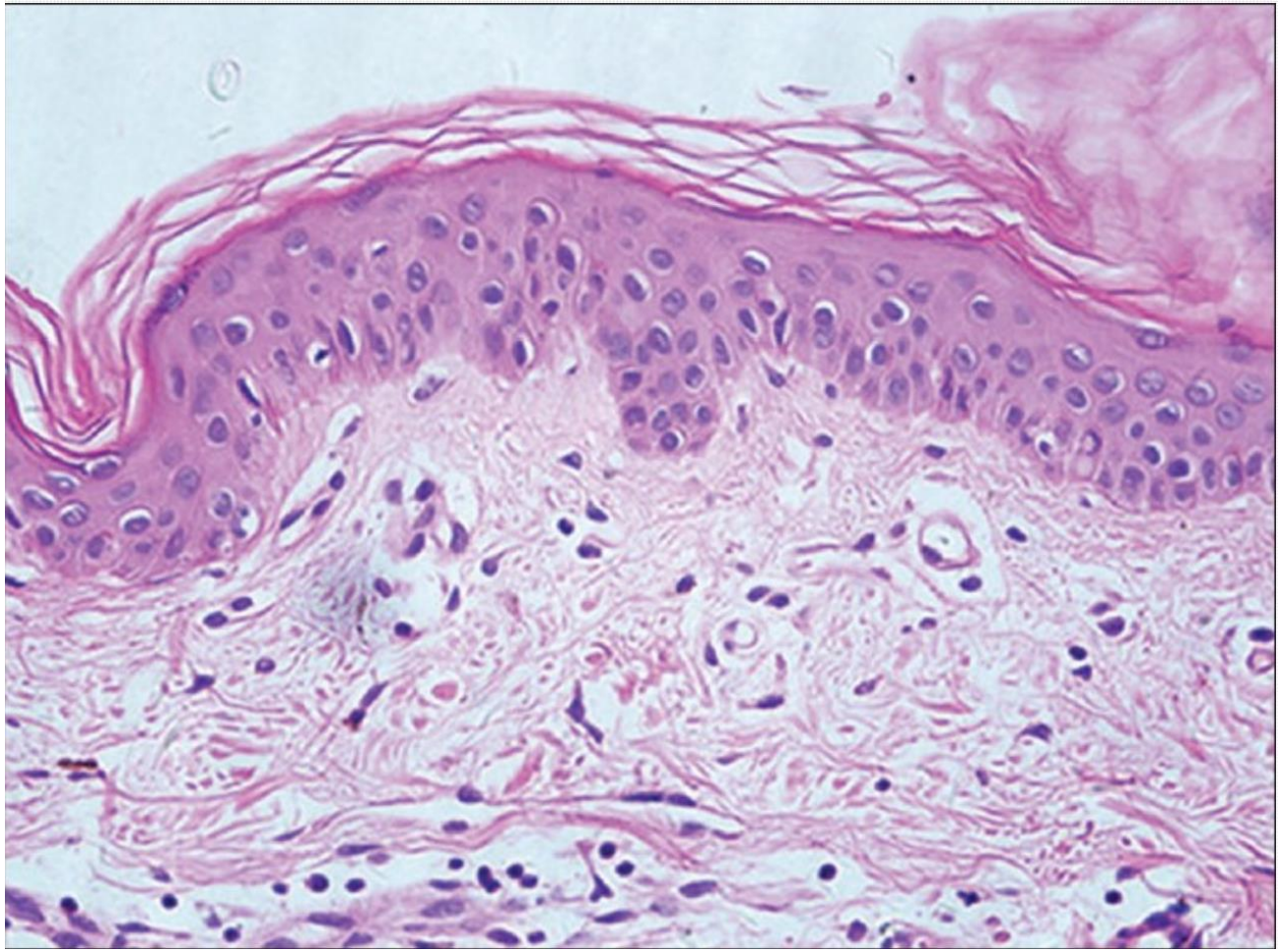
Total RCM score:

- <1 represented stable stage;
- ≥1 represented active stage;
- ≥2 represented rapid active stage

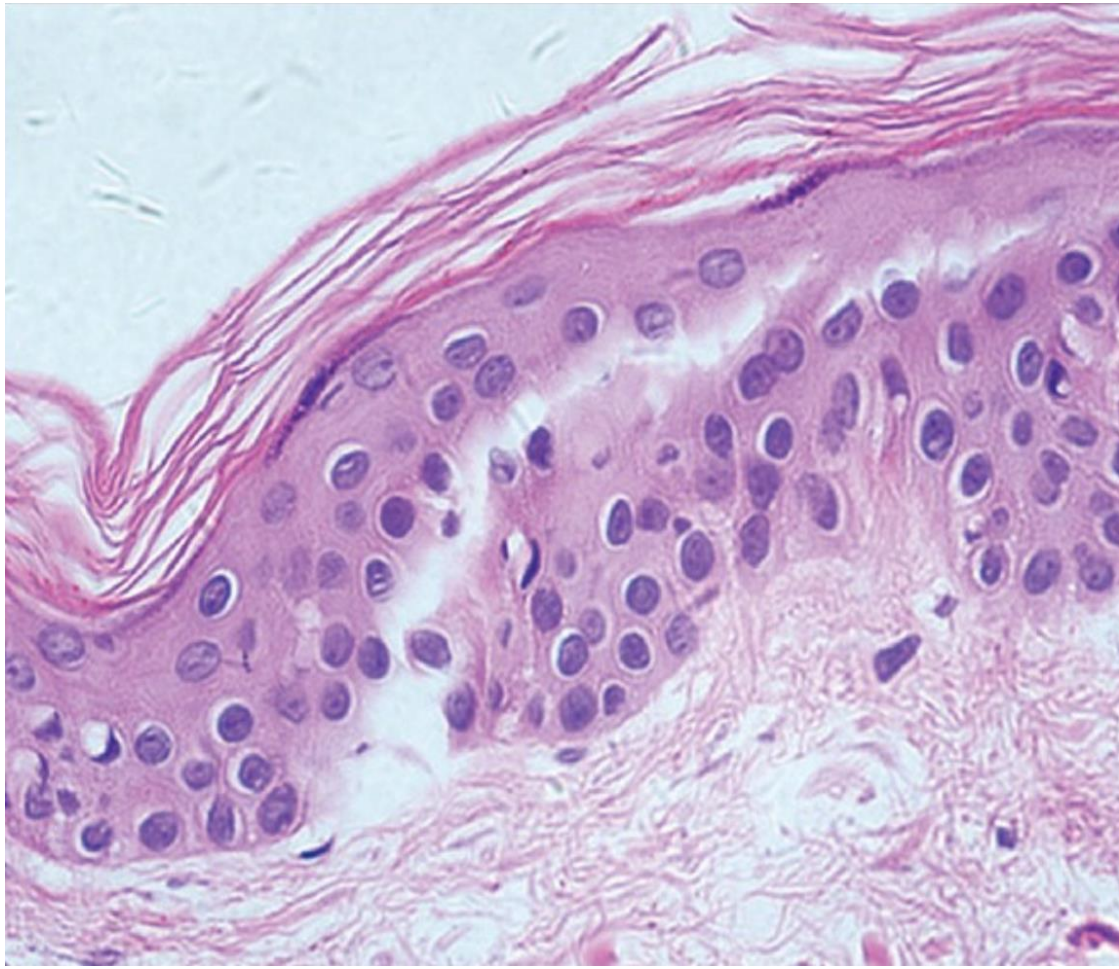
Group	VIDA (patients)	RCM (patients)
Rapid active stage group	30	26
Slow active stage group	40	37
Stable stage group	55	62

RCM and Prediction of Stability

Li et al. Indian Journal of Dermatology 2013



Cases when RCM revealed inflammatory cells



Cases when RCM revealed NO inflammatory cells

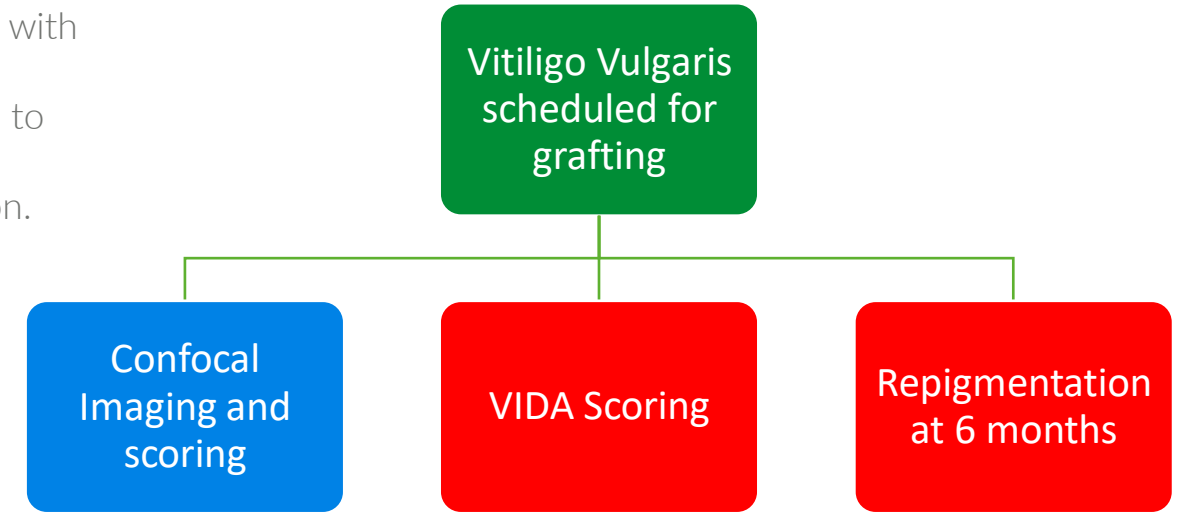
Can RCM Predict Response to Grafting?

RCM and Prediction of Response to Grafting

SY Chuah, TG Thng. Skin Research and Technology 2018*

Study Design

- Prospective study
- Patients with vitiligo vulgaris scheduled for grafting imaged with RCM
- Compare RCM scores with VIDA scores and with response to grafting
- Positive response defines by more than 75% repigmentation.



Assessments

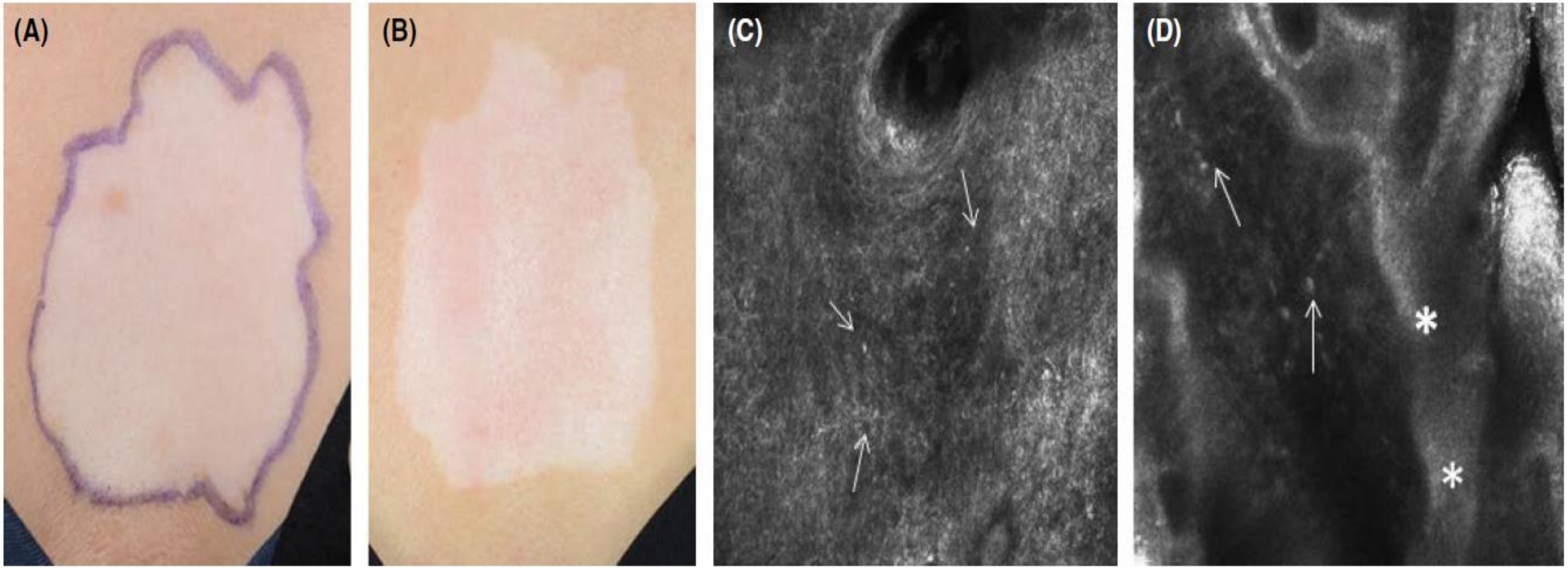
- RCM score
  - Done by 2 dermatologists independently
- VIDA scores done independently of RCM score.
- Response to repigmentation assessed by 2 dermatologists

Results

- 28 patients were enrolled over 1 year
  - 23 were included in assessment
  - 5 loss to follow up

RCM and Prediction of Response to Grafting

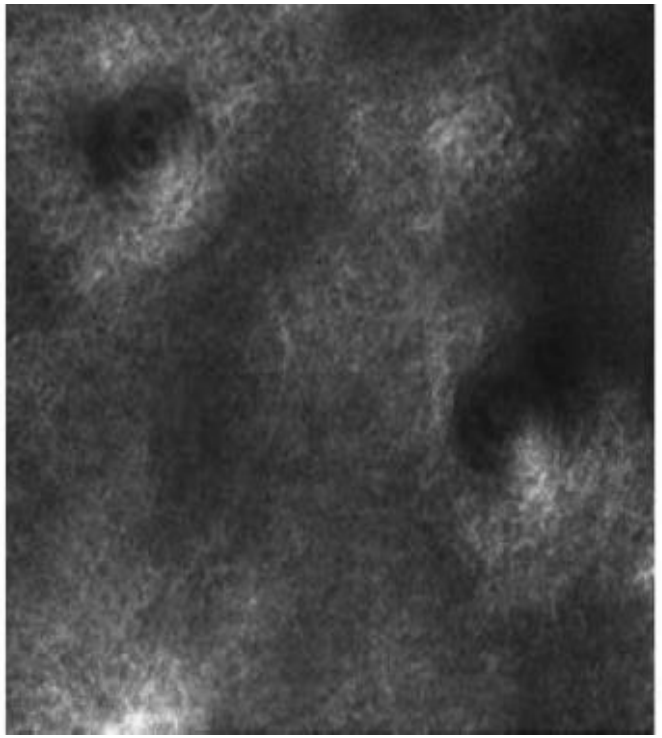
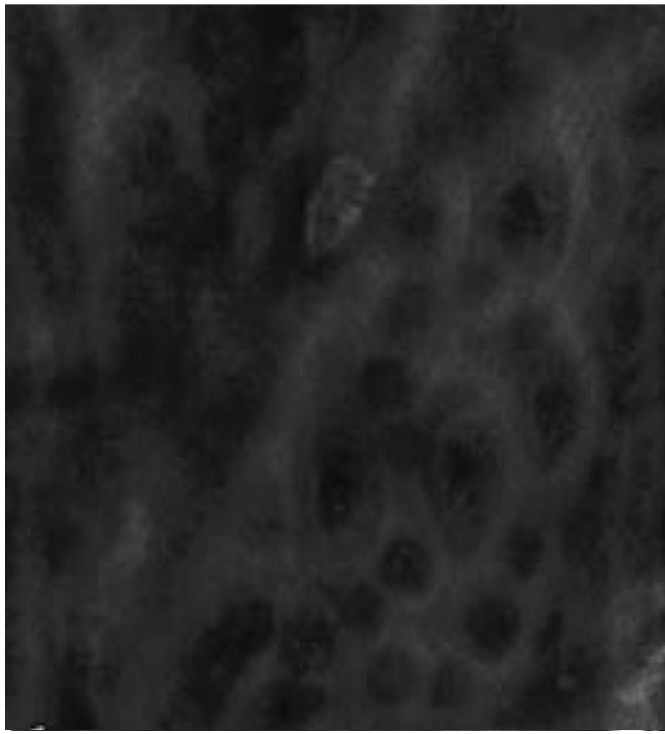
SY Chuah, TG Thng. Skin Research and Technology 2018



RCM and Prediction of Response to Grafting

SY Chuah, TG Thng. Skin Research and Technology 2018



RCM and Prediction of Response to Grafting

SY Chuah, TG Thng. Skin Research and Technology 2018

Predicting poor response to grafts:-

- VIDA has a very poor predictive value for failure of grafts
  - All 7 cases that failed has a VIDA score of 0. (Stable)

- RCM has excellent predictive value for failure of grafts
  - 6 out of 7 cases that failed has a RCM score of 1 and above.
  - 1 case of graft failure despite RCM score of 0. Could it be due to procedure?

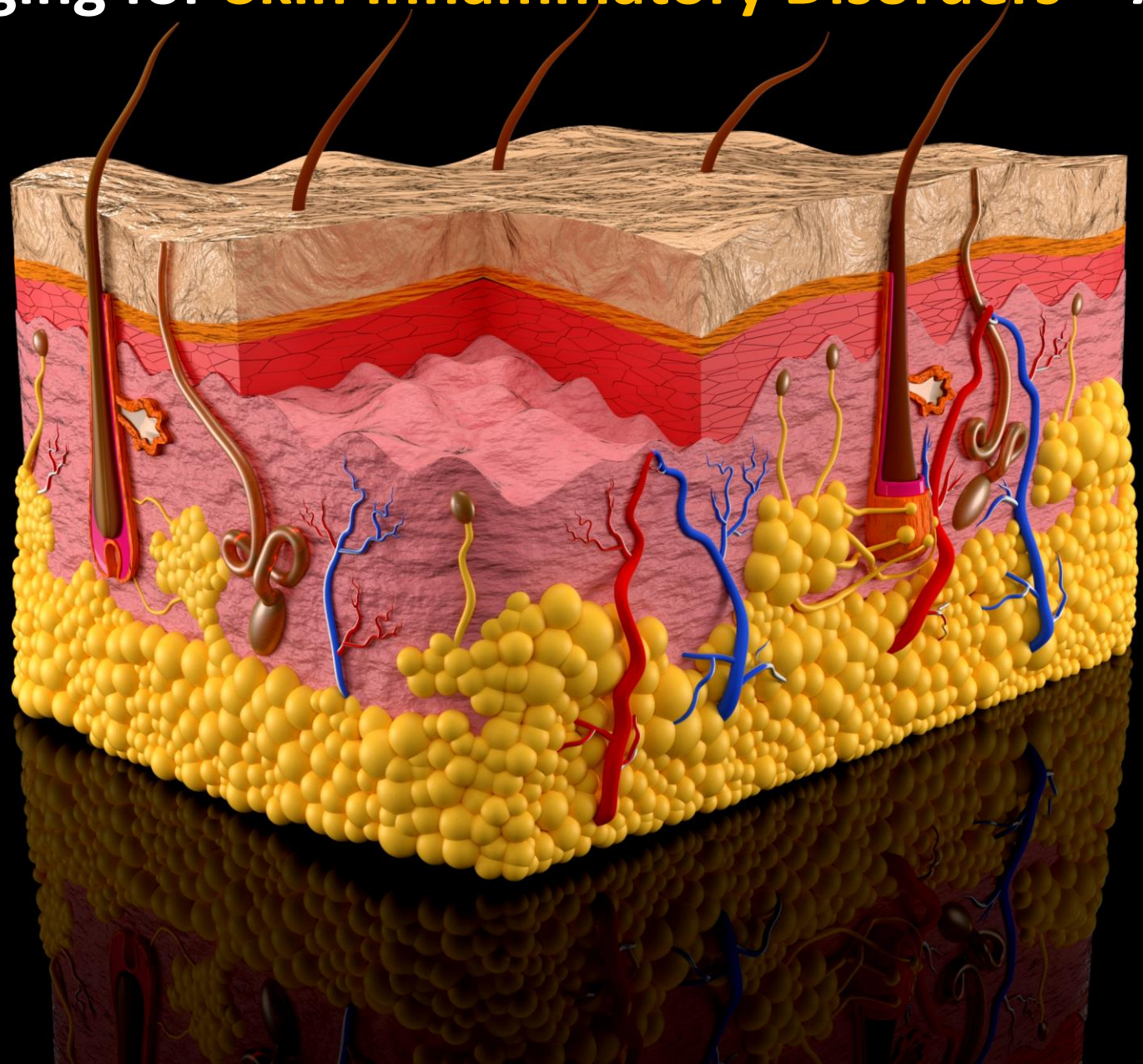
Predicting positive response to grafting

- RCM Score
  - For all cases scored by RCM to be stable, all achieved positive response to grafting
  - There were 6 cases that has features of active vitiligo on RCM but responded to grafting too*.

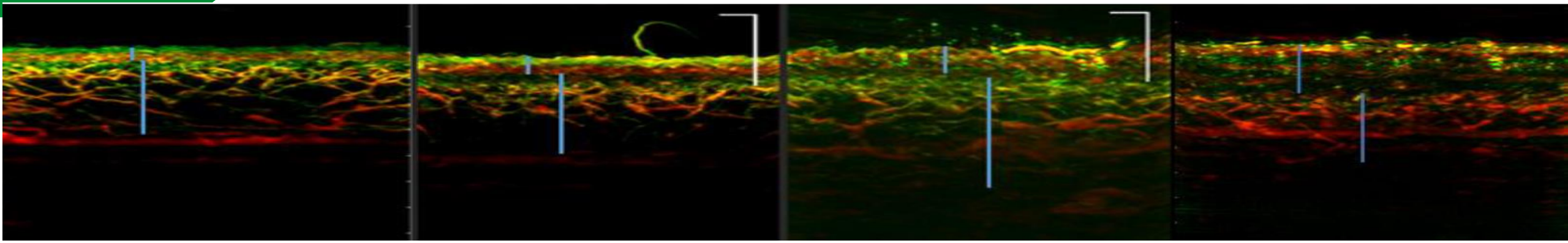
Overall RCM score for predicting response to surgery is good.

- If RCM score is stable, all patients will achieve good repigmentation outcomes
- If RCM score is more than 0 (indicates active vitiligo), likelihood of failure of grafts is 50%.

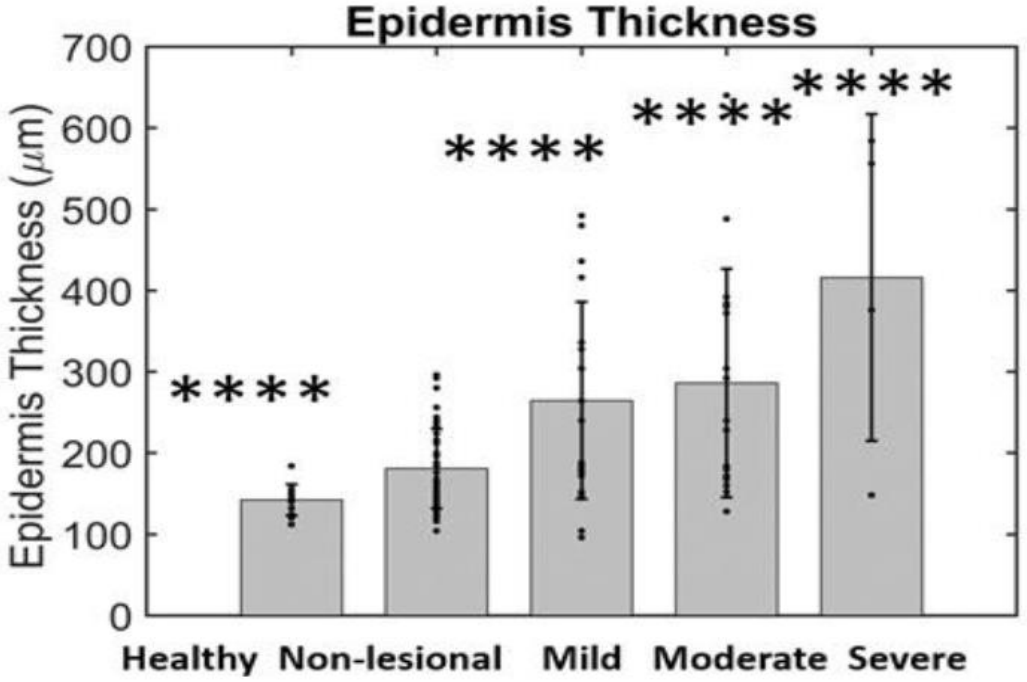
Structural Imaging for Skin Inflammatory Disorders – Atopic Dermatitis

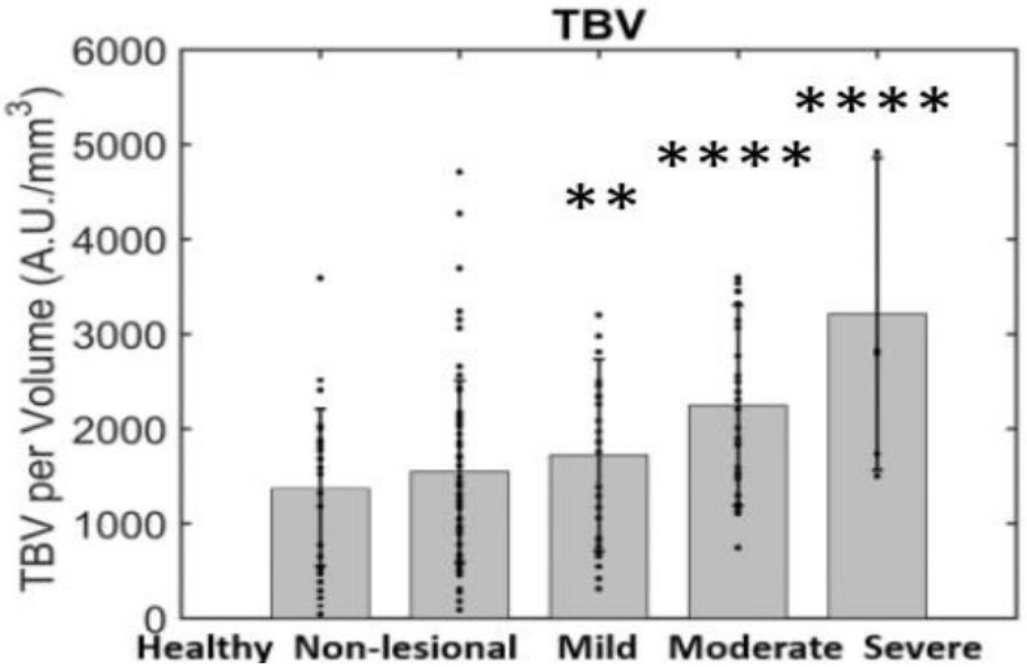


RSOM and AD

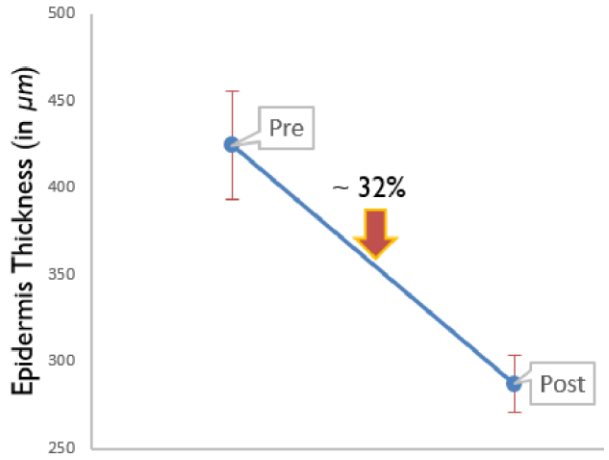


RSOM Eczema Four calculated metrics

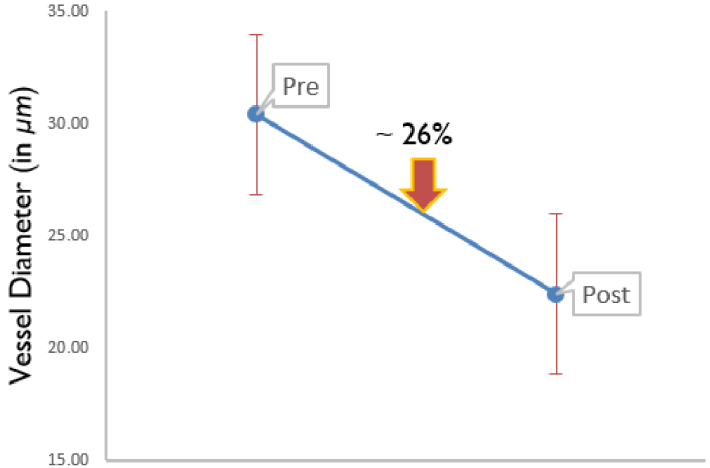




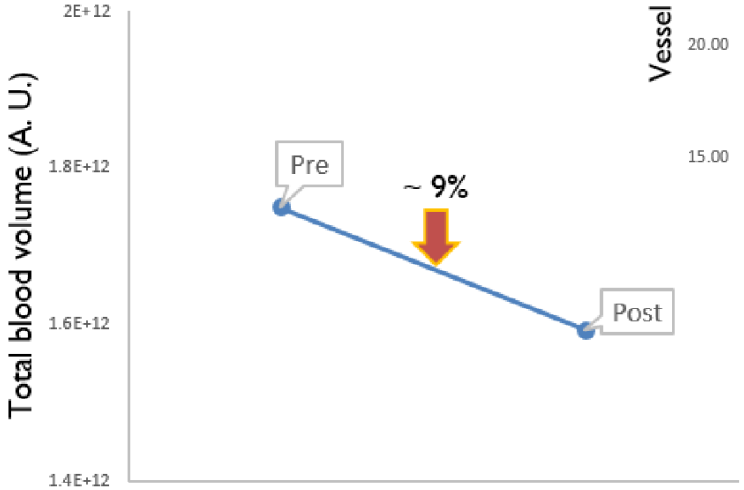
RSOM and AD



(a) Mean Epidermis Thickness



(c) Mean Vessel Diameter



(b) Total Blood Volume

Skin Composition Imaging

Why the need for Skin Composition Imaging?

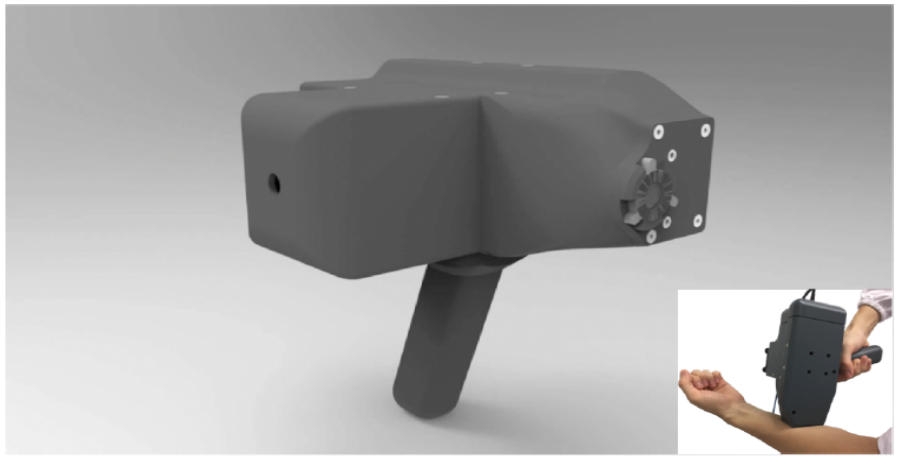
- Both skin structure and composition determines function of skin
- Structure is intact but functionally deficient
  - Atopic Dermatitis
    - Functional Barrier defect
    - Decreased expression of filaggrin
    - Downstream reduction in natural moisturising factors of the skin.
    - Current way to measure barrier defect is via trans-epidermal water loss (TEWL).

Can we measure the chemical composition of skin by the bedside to better understand/correlate composition with function and disease?

Skin Chemical Composition Imaging

HelioDerma for skin characterization

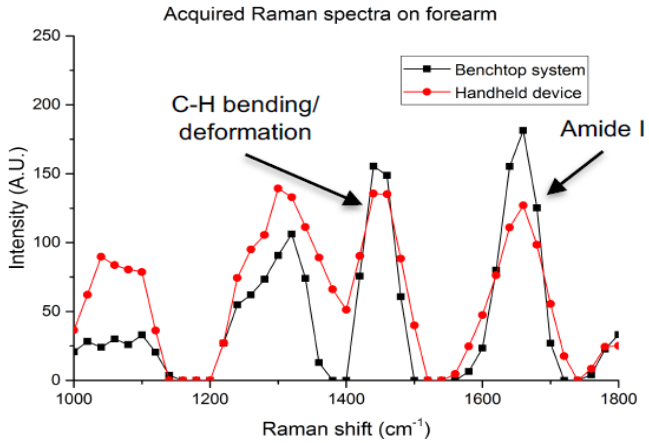
Singapore Bioimaging Consortium



Latest prototype

Skin-related biomarkers		
collagen	melanin	ceramide
elastin	triolein	cholesterol
keratin	urea	water
……	……	……

Raman spectral database

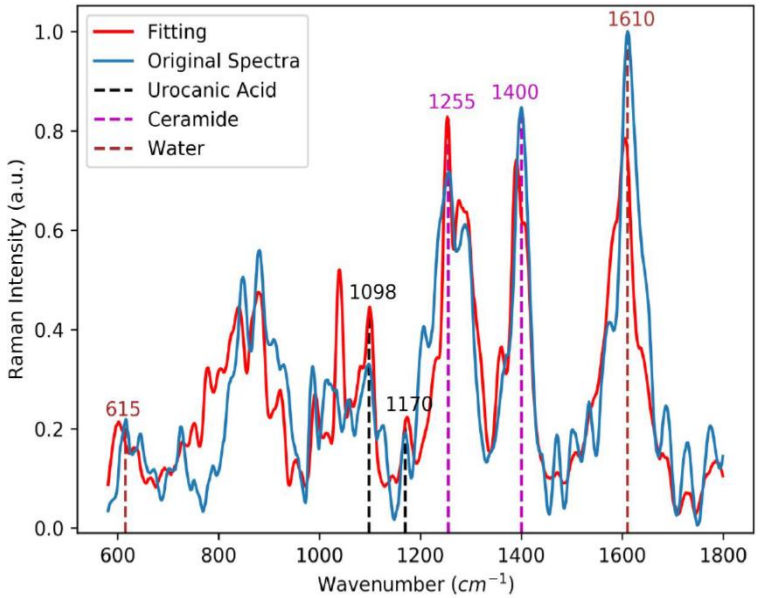


Competitive advantages

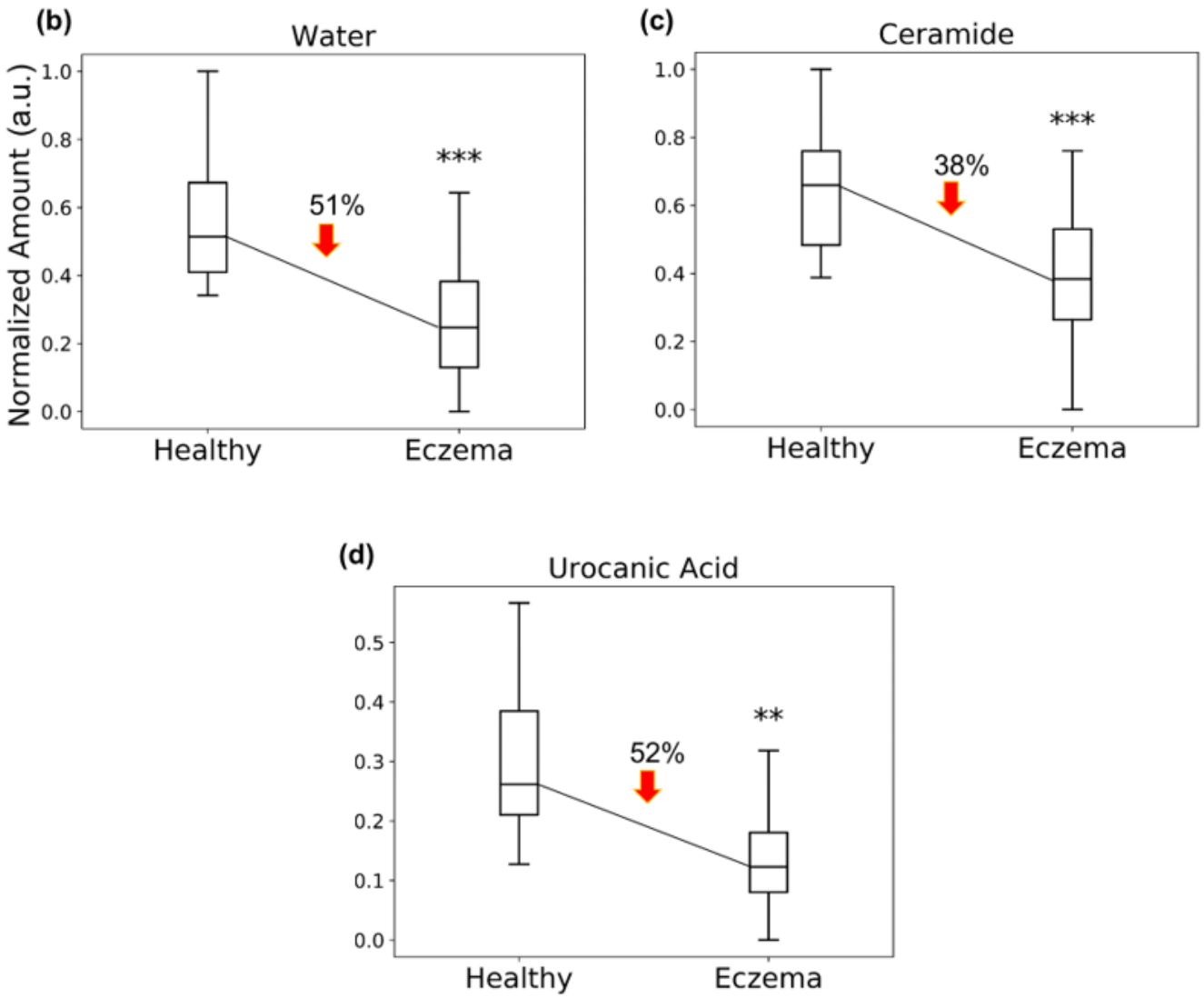
- Handheld for inaccessible regions
- Confocal for depth profiling
- Comparable sensitivity with benchtop systems
- Integrated Raman spectral database
- Advanced spectral unmixing algorithms for biomarker quantification

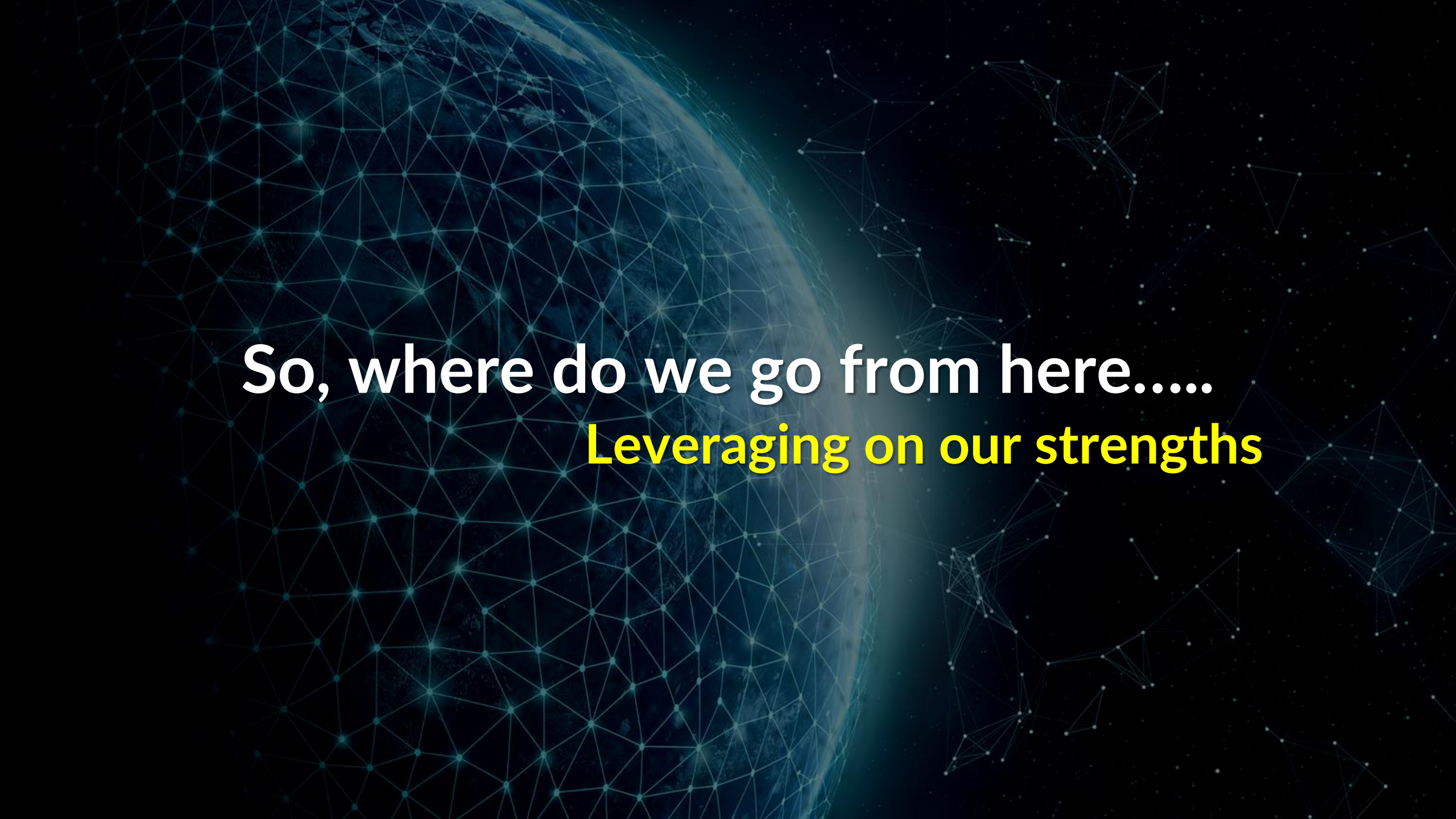
Fiber-based handheld confocal Raman spectroscopy system – Priority art filed (2017)

Raman Spectrum with Fitting and Functional Groups



Skin Components Boxplots




So, where do we go from here.....
Leveraging on our strengths

Integrating Different Components to Develop Disruptive Technologies

SENSOR SYSTEMS

- Surface sensors
- Biomarkers
- Environmental sensors.

STRUCTURAL IMAGING SYSTEMS

- 2D and 3D systems
- POC devices.

CHEMICAL COMPOSITION IMAGING SYSTEMS

- Reducing footprint and cost
- Consumer care systems

IMAGE ANALYSIS AND AI

- Diagnostics
- Quantifications
- Prognostics

APPS AND DATA MANAGEMENT

- Suite of capabilities and not one disease systems
- Database management

APPS

DISEASES

HEALTH

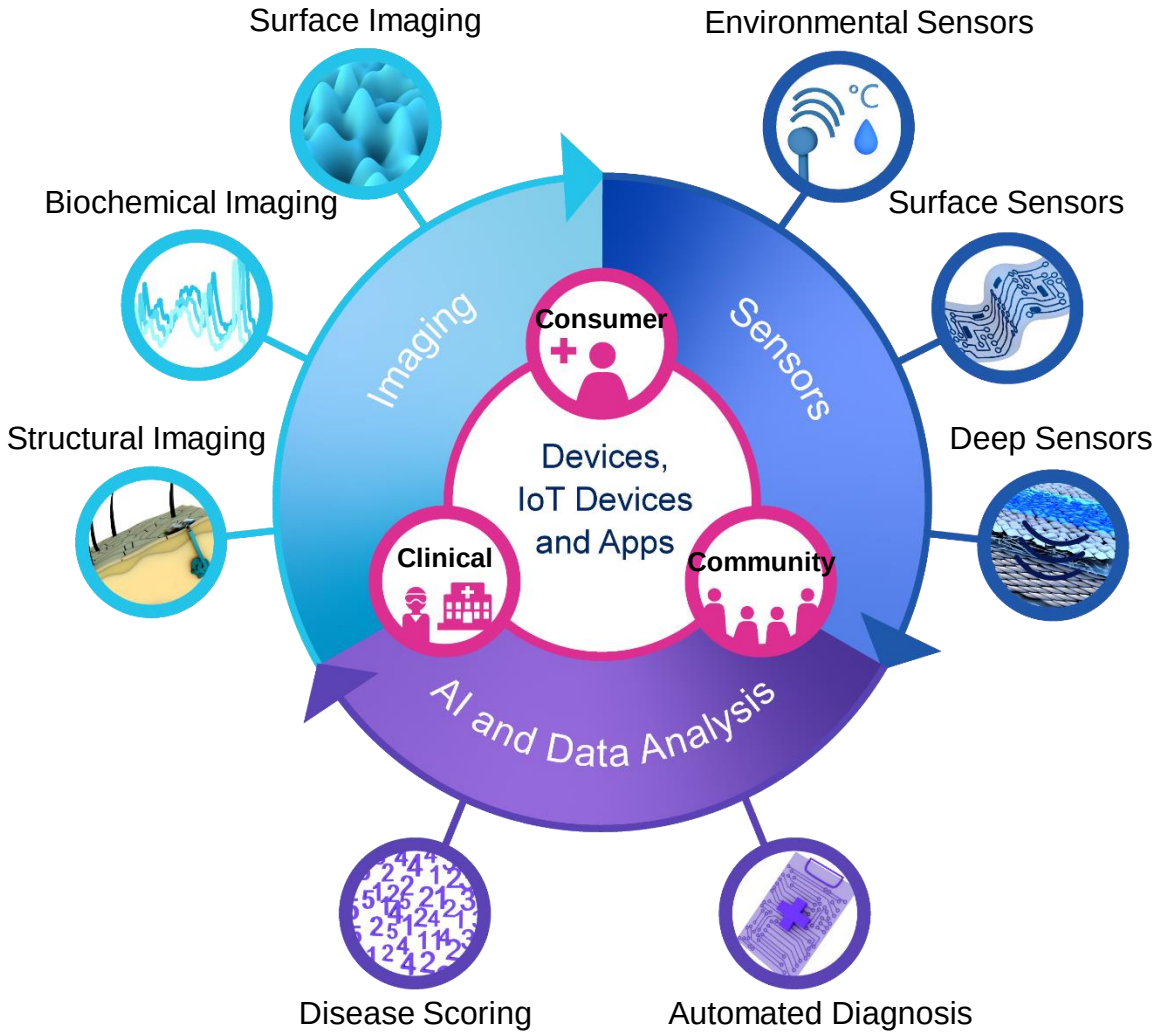
Hyper-personalised Monitoring Platforms for Health, Injury, and Disease

Vision: Skin as a "Window on Health"

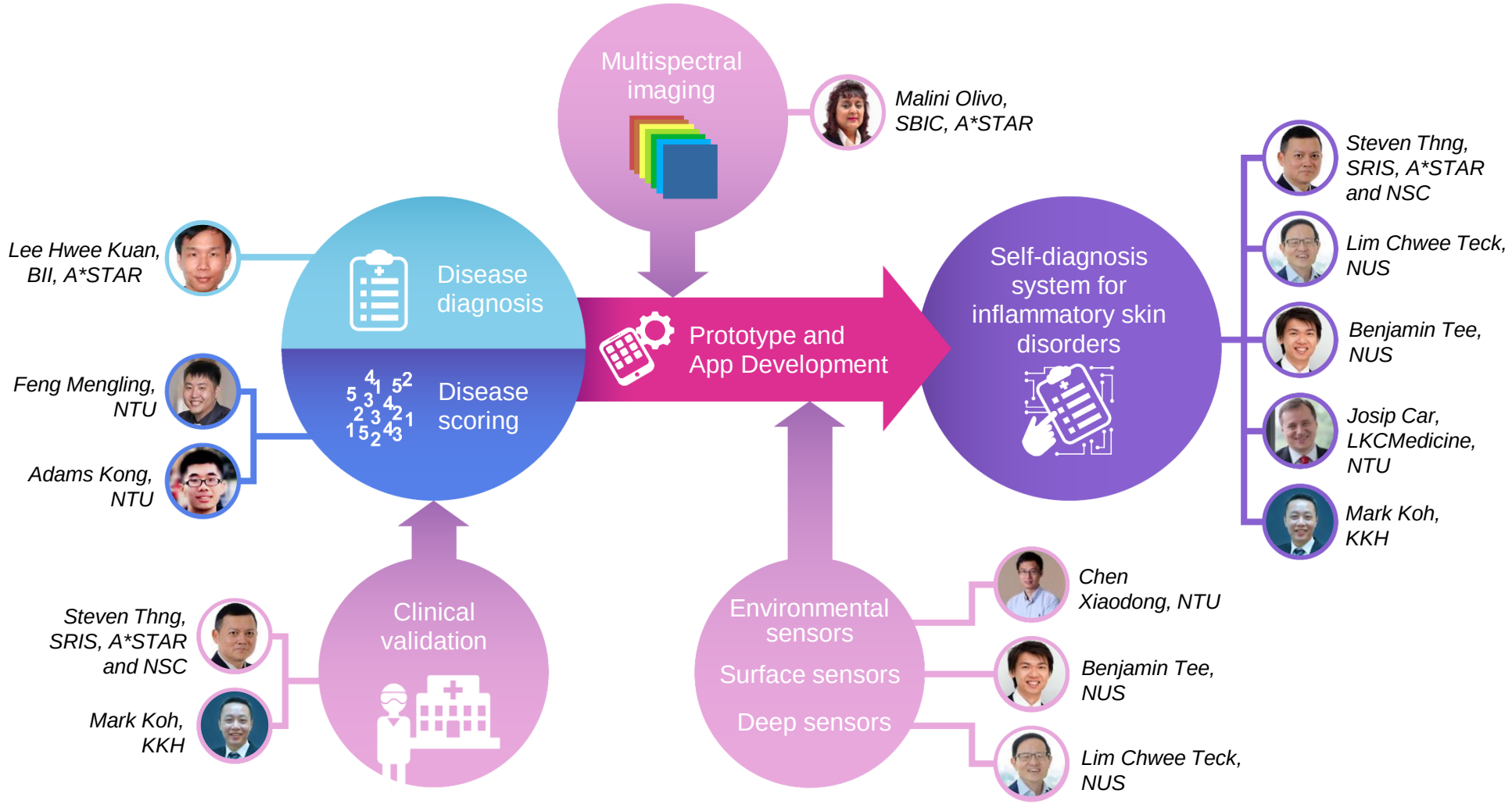
Skin health, especially **ageing and inflammatory skin conditions**, impose significant healthcare burden.

Treatment strategies do not account for **individual differences.**
Lack of **effective active management measures** on personal and community levels.

1st programme to **integrate all 3 fields of expertise. Creation of game-changing devices, IoT devices, and apps** that can impact skin health and beyond.



Vision: Skin as a "Window on Health"



COMMUNITY HEALTHCARE
Polyclinics, GPs, Pharmacies

CONSUMER CARE
Devices and Apps

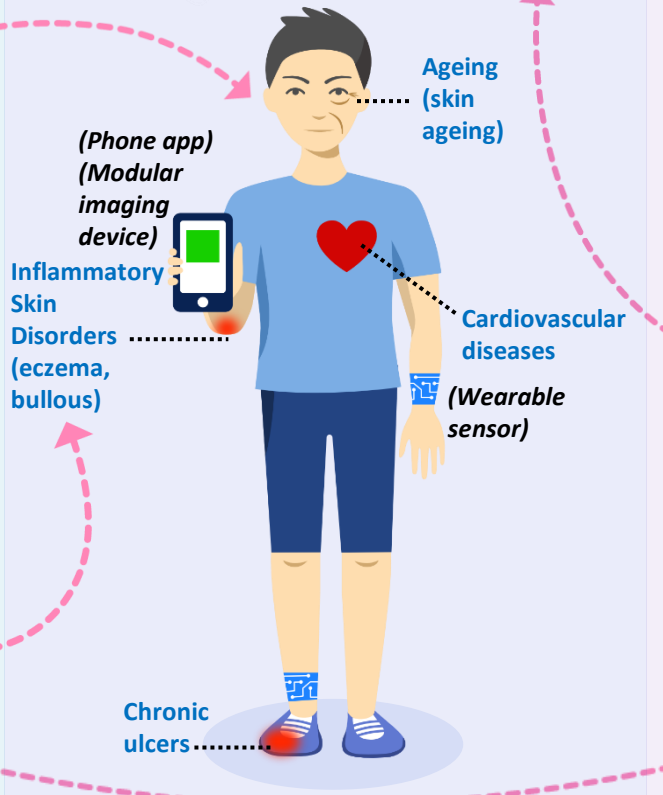
CLINICAL APPLICATIONS
Hospitals and Specialist Outpatient Clinics

Wearable systems

- Environmental, surface, and deep sensors
- Surface imaging
- AI for disease diagnosis, predictions, and recommendations

Pharmacy diagnosis booths

- Surface sensors
- Surface imaging
- AI for automated diagnosis and dispensing of medication

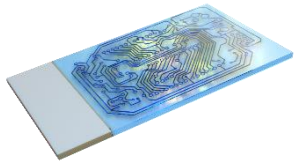


Hyperpersonalised monitoring of diseases

- Environmental, surface, and deep sensors
- Surface, structural, and biochemical imaging
- AI for disease scoring and monitoring

Polyclinic diagnosis systems

- Surface and deep sensors
- Surface imaging
- AI for automated diagnosis and disease scoring



Personalised therapies

- Surface and deep sensors (biomarkers)
- Surface, structural and biochemical imaging
- AI for disease scoring and personalisation of therapies

Virtual clinical trials

- Environmental, surface, and deep sensors
- Surface imaging
- AI for disease scoring and tracking


ADVENTURE

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Questions and Comments