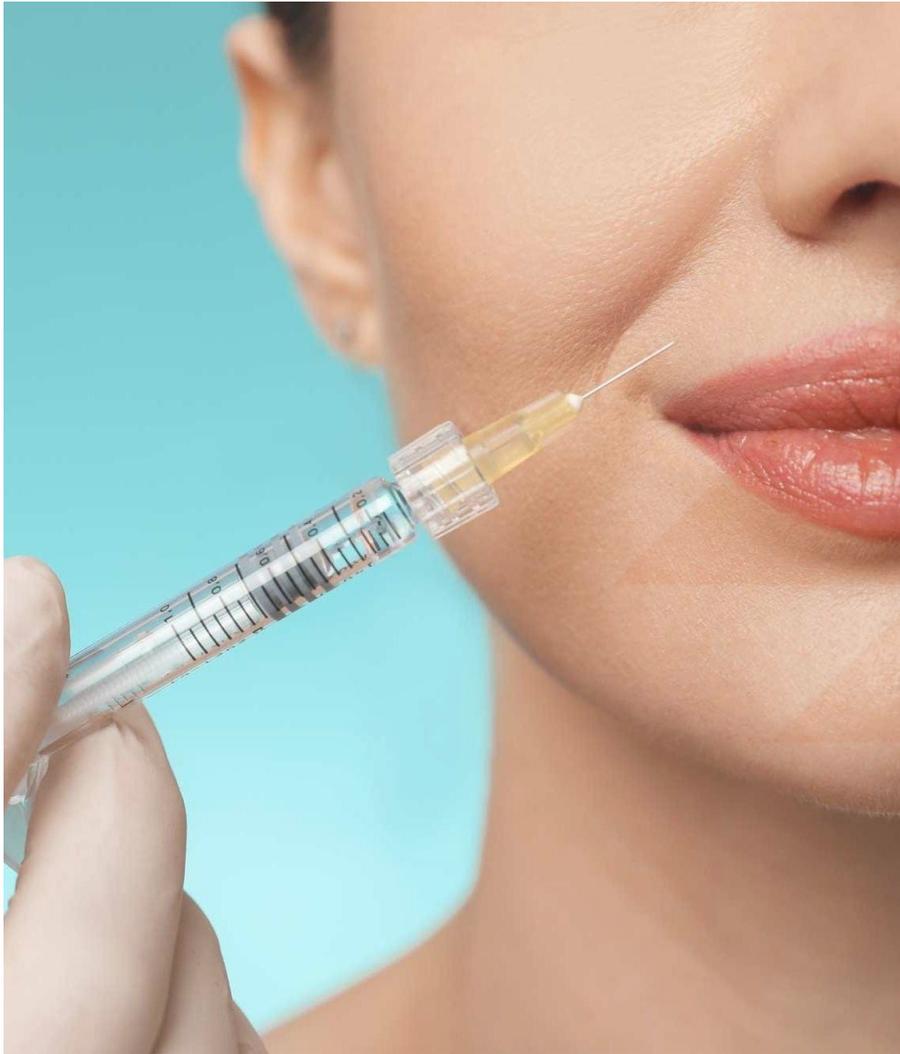


SGS proderm

# Aesthetic Dermatology – Clinical Testing of Injectables

Our ambition? Excellence.



# Contents

- About Us
- What are aesthetic dermatological injectables?
- Classification and regulation
- Study requirements:
  - Dermal fillers
  - Botulinum toxins
- Aesthetic: Effectiveness evaluation endpoints
- Instrumental measurements to support claims
- Imaging: State-of-the-art clinical photography

# SGS proderm in numbers



**28+ years study experience in dermatology, ophthalmology, oral hygiene and women's health**



**130+ hard working souls**  
**+20 freelance medical specialists (dermatologists, aesthetic specialists, gynecologists, dentists, pediatrician...)**



**2 clinical units**



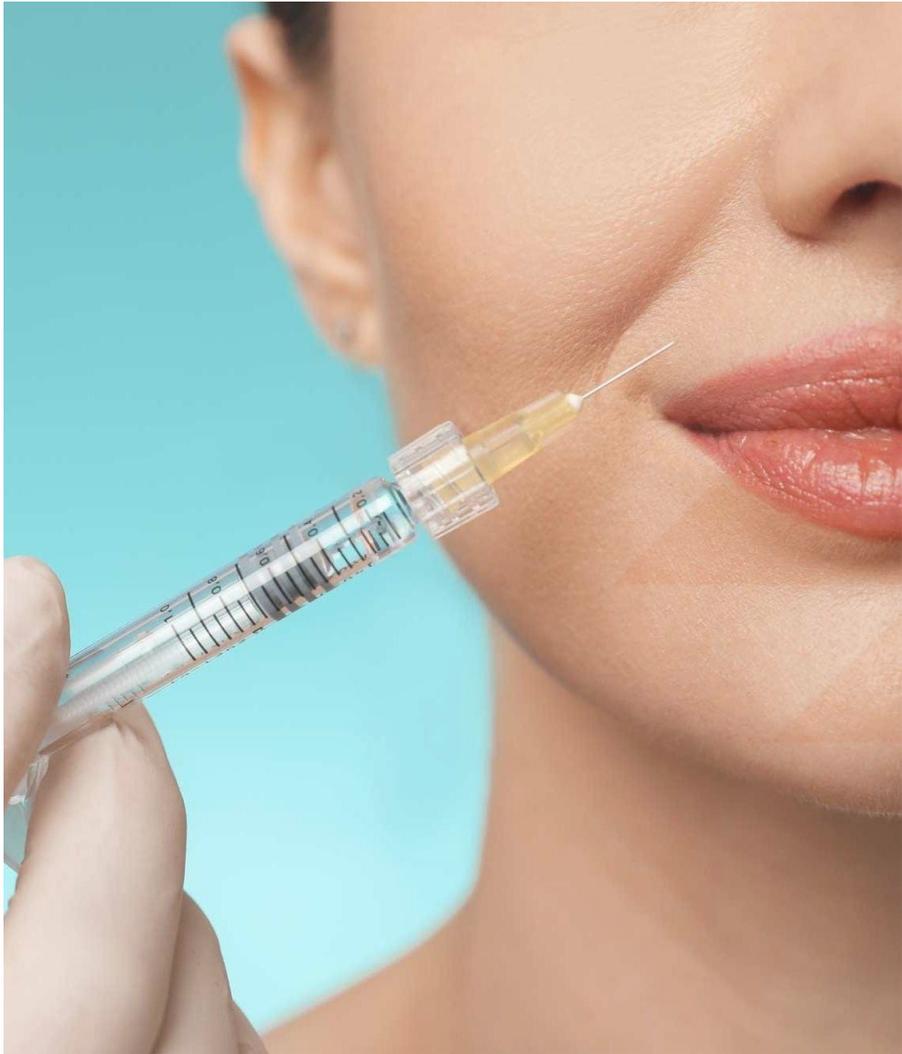
**6,500+ active subjects**



**50+ pre-qualified sites in Germany including Aesthetics**



**10,000+ enrollments p.a.**



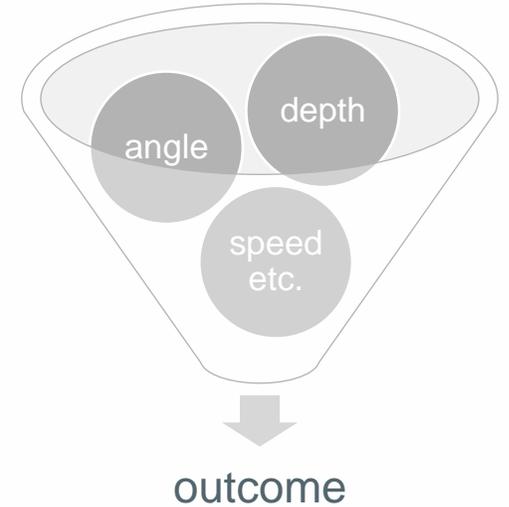
## What are aesthetic injectables?

- **Dermal fillers**
- **Neuromodulators (botulinum toxins)**
- Lipolytic agents (deoxycholic acid injection)
- PRP (Platelet-Rich Plasma)
- Sclerotherapy
- Collagenase injection
- Mesotherapy cocktails (injectable supplements)

# Injectables: Technical knowledge

Treatment outcomes are dependent on the skill of the physician performing the injection

- **access to experienced injectors is essential**





# Clinical Investigations of Dermal Fillers

# Dermal Fillers

*(Injectable implants, soft tissue fillers, wrinkle fillers, skin boosters)*

- Annex XVI to Regulation (EU) 2017/745 (MDR) -> dermal fillers are now medical devices (without an intended medical purpose)
- Safety and effectiveness must be clinically tested to EN ISO 14155:2020 standards.
- Must comply with the european commission's common specifications Annexes I and IV. C(2022)8626 and the commission implementing regulation (EU) 2022/2346



## Substance

- hyaluronic acid
- calcium, hydroxylapatite,
- poly-L-lactic acid
- collagen
- poly-methyl-methacrylate
- patient's own fat



## Aesthetic indications

- wrinkles and lines
- lip, cheek, etc. augmentation
- lipoatrophy
- contouring
- scars
- skin rejuvenation (booster)



## Injection sites

- face
- neck
- décolletage
- hands



## Risks

- unintentional intravascular injection leading to:
  - necrosis
  - visual impairment
  - blindness
  - stroke

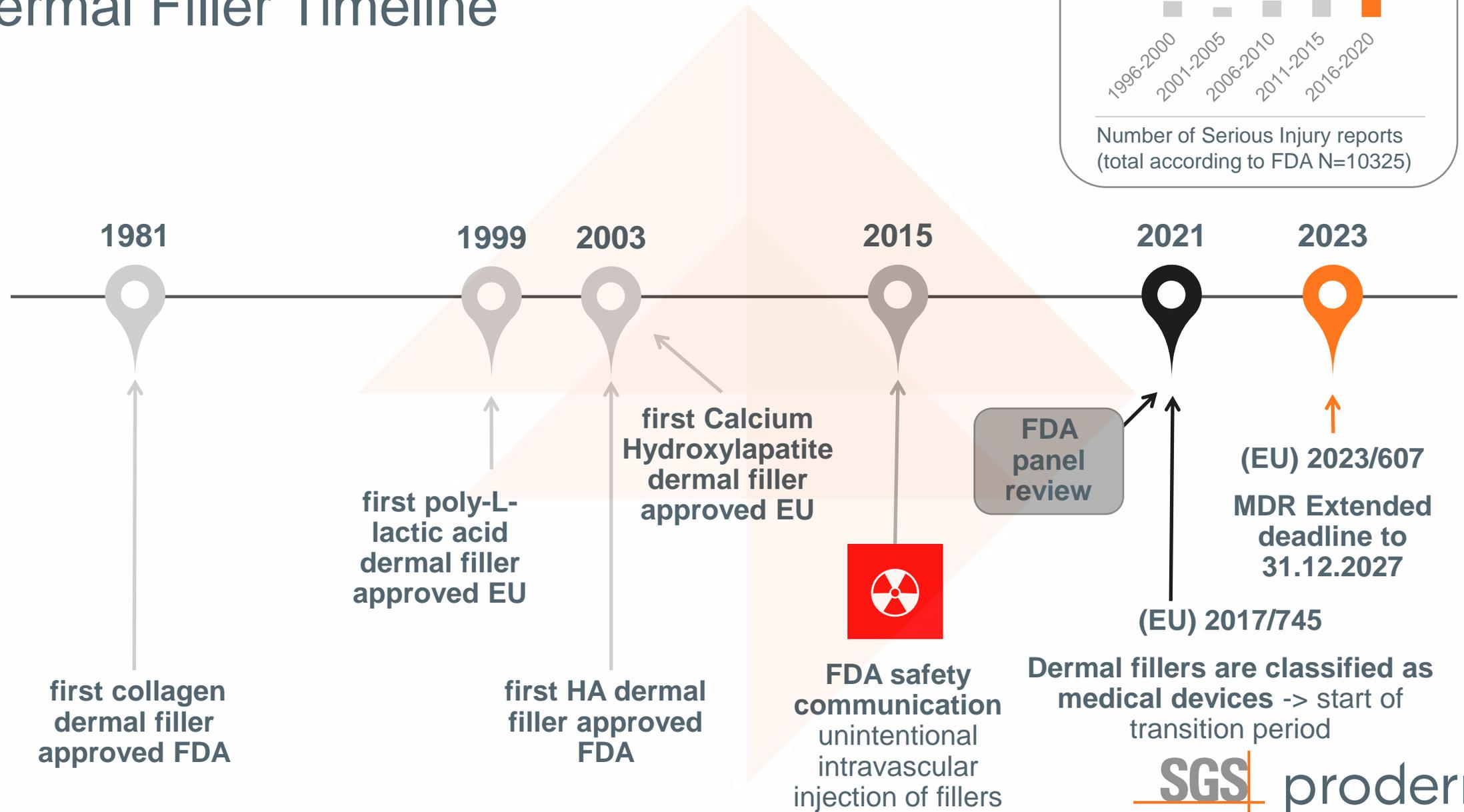
\*(this list is not exhaustive)



## Classification

class III Medical device (product without an intended medical purpose)

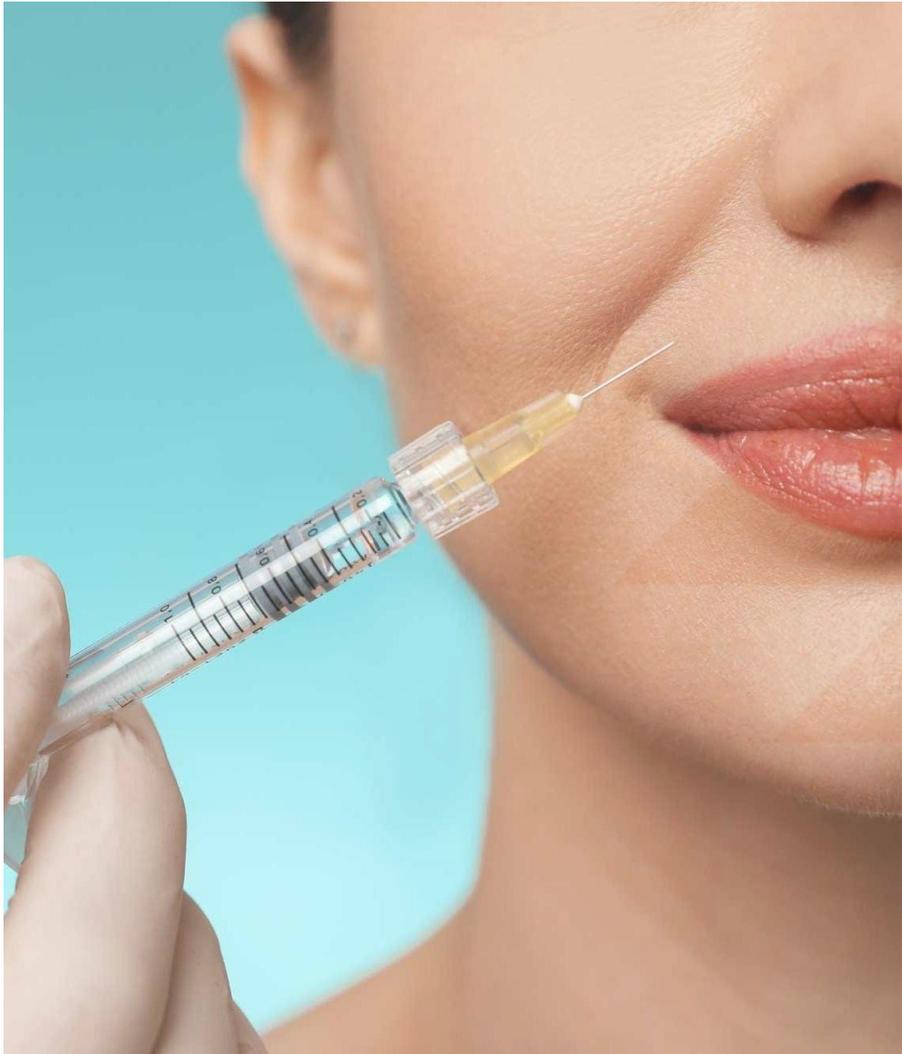
# Dermal Filler Timeline



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# Clinical Investigations of Medical Devices according to ISO

- ISO 14155:2020 comprises
  - Ethical Considerations
  - **Clinical Investigational Plan**
  - Investigator Responsibilities
  - Monitoring and Quality Control
  - Reporting and Documentation



## Dermal Fillers: Clinical Investigation Plan

- Study Objective: safety and effectiveness
- Study design
- Inclusion/Exclusion criteria
- Study procedures
- Effectiveness assessments
- Safety assessments

# Dermal Fillers: Clinical Investigation Plan

## Safety assessments



### ▪ Adverse Events (AE) Reporting

collect and document all reported adverse events, including their nature, severity, duration, and any necessary medical intervention.

### ▪ Systemic Reactions

refer to AEs that occur outside the injection site and may affect the whole body, i.e. allergic reactions, hypersensitivity reactions, or other systemic symptoms such as headaches etc.

### ▪ Local Tissue Responses

durability /stability of the dermal filler and the response of the surrounding tissues over time -> any product migration, nodule formation, granuloma formation, or tissue reactions.

### ▪ Injection Site Reactions

e.g. erythema (redness), swelling, tenderness, pain, itching, or bruising. These assessments help evaluate the immediate and short-term tolerability and local safety of the dermal filler.

### ▪ Vital Signs Monitoring

often monitored during or after the administration of the dermal filler to detect any acute changes or abnormalities.

### ▪ Follow-up and Long-term Safety

allows for the detection of any delayed adverse events, late-onset complications, or changes in the safety profile of the product.

### ▪ Ocular-related adverse events

i.e. visual disturbances, changes in color perception, impaired eyesight, or any other ocular symptoms that may arise during or after the use of the dermal filler. While ophthalmic tests (e.g. Visual Acuity Testing) may not be explicitly required by the EMA, investigators should exercise clinical judgment and consider the need for such tests.

Advisable to include ophthalmic assessments or consultations with ophthalmologists as part of the safety monitoring plan.



# Clinical Studies of Neuromodulators (Botulinum toxins)

# Botulinum toxins

(Neuromodulators, BoNT)

- As medicinal products, botulinum toxins are subject to a rigorous regulatory process that is overseen by the European Medicines Agency (EMA) and national regulatory authorities.



## Substance

- BoNT-A:** e.g. Botox (OnabotulinumtoxinA), Dysport (AbobotulinumtoxinA), and Xeomin (IncobotulinumtoxinA)
- BoNT-B:** e.g. Myobloc or Neurobloc (Rimabotulinumtoxin B)



## Aesthetic indications\*

- wrinkles and lines
- Off-label: brow lifts, facial asymmetry, body contouring, etc.



## Injection sites

- face:
  - glabellar
  - lateral canthal
  - forehead
  - upper lip
- neck, arms, legs



## Risks

- swelling
- localized bruising
- excessive muscle weakness
- unintended paresis of adjacent muscles
- botulism\*\*



## Classification

Medicinal products

\*Park MY, et al. Scientific review of the aesthetic uses of botulinum toxin type A. Arch Craniofac Surg. 2021;22(1):1-10.

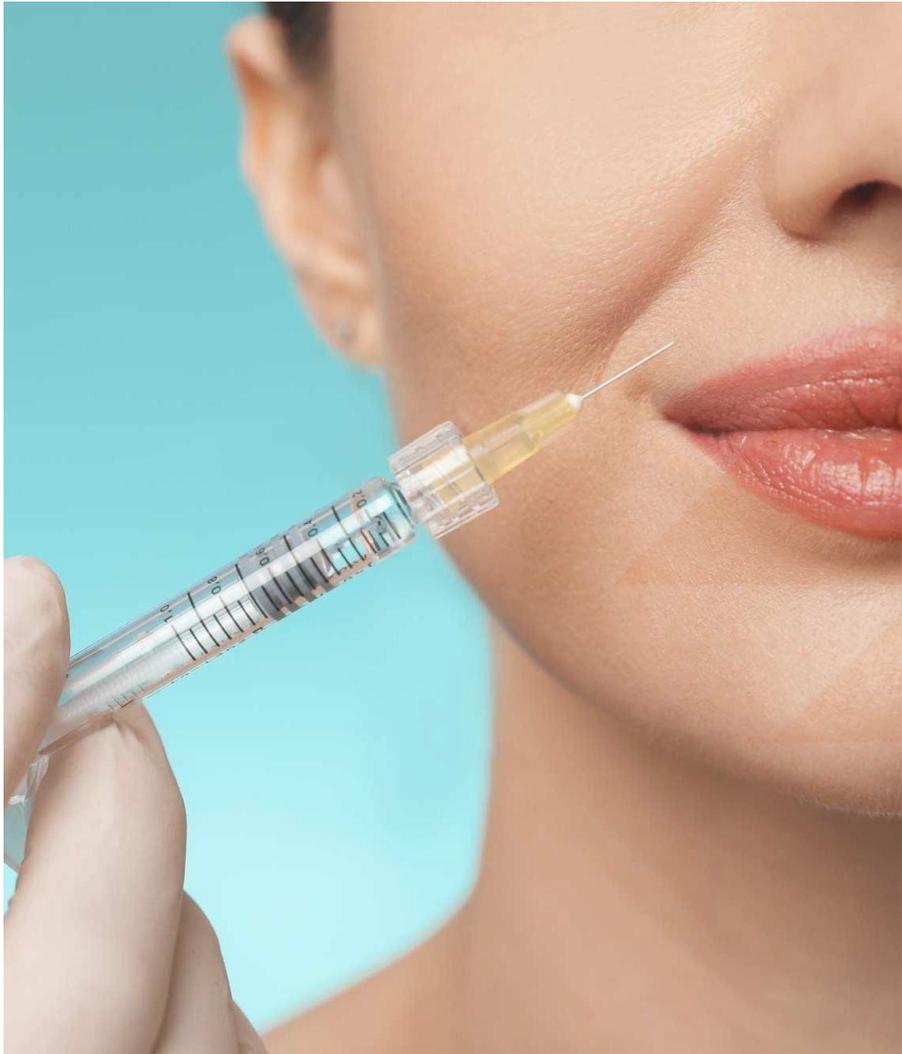
\*\* mainly as a risk associated with medical treatments due to the higher doses used, for a comprehensive list of AEs see: Landau M, et al. Botulinum toxin complications in registered and off-label aesthetic indications. J Cosmet Dermatol. 2020 Oct;19(10):2484-2490.

# EU Regulation of Medicinal Products

All clinical trials in the EU / EEA must have been carried out in accordance with the requirements set out in Annex 1 of Directive 2001/83/EC.

This means that:

- clinical trials conducted have to comply with EU clinical trial legislation (**Regulation (EU) No 536/2014 (CTR)** and **ICH guidelines**)
- clinical trials conducted outside the EU / EEA have to comply with ethical principles equivalent to those set out in the EEA, including adhering to international good clinical practice and the Declaration of Helsinki.



## Botulinum toxins: Clinical Study Plan

- Study Objective: Phase 1 / 2 /3
- Study design
- Inclusion/Exclusion criteria
- Study procedures
- Safety assessments
- Effectiveness assessments

# Botulinum toxins Clinical Study Plan

## Safety assessments



### ▪ Adverse Events (AE) Reporting

collect and document all reported adverse events, including their nature, severity, duration, and any necessary medical intervention.

### ▪ Systemic Reactions

refer to AEs that occur outside the injection site and may affect the whole body, i.e. allergic reactions, hypersensitivity reactions, or other systemic symptoms such as headaches etc.

### ▪ Immunogenicity Evaluation

via Serum Antibody Testing -> drug's ability to provoke an immune response -> neutralizing antibodies -> decrease the effectiveness of the treatment over time.

### ▪ Injection Site Reactions

e.g. erythema (redness), swelling, tenderness, pain, itching, or bruising.

### ▪ Vital Signs Monitoring

- monitored during or after the administration

### ▪ Follow-up and Long-term Safety

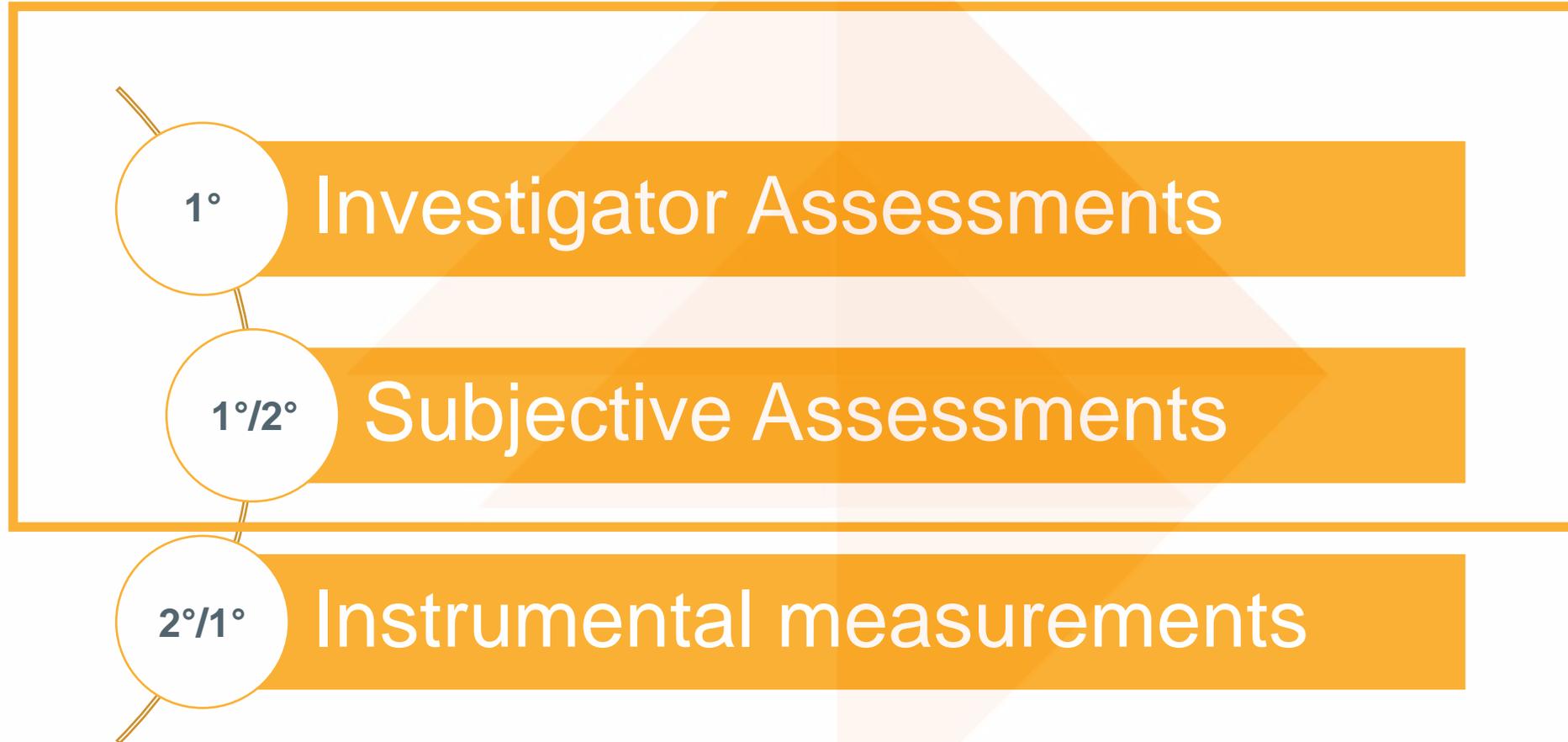
allows for the detection of any delayed adverse events, late-onset complications, or changes in the safety profile of the product.

### ▪ Physical Examinations

To look for **possible spread of toxin effects**.

e.g. muscle weakness, drooping eyelids, double vision, hoarseness or change or loss of voice, trouble saying words clearly, loss of bladder control, trouble breathing, and trouble swallowing.

# Aesthetics: Effectiveness Evaluation Endpoints



# Investigator Assessments (CLinROs)

## Aesthetic clinical rating scales

- **Purpose of Clinical Scales:** Objective, quantitative methods for evaluating the effectiveness and success of aesthetic treatments.
  - **Global Aesthetic Improvement Scale (GAIS):** internationally standardized and validated scale[1]. Used for classifying aesthetic improvement or change after aesthetic treatments. The GAIS is based on a five-step scale (Deterioration, No Change, Improvement, Significant Improvement, Major Improvement) and is a widely used method in aesthetic medicine, particularly in the minimally invasive area.
  - **Merz Aesthetics Scales™** : a comprehensive set of five scales designed to objectively measure aesthetic treatments. [2,3] The scales include assessments for forehead lines, glabellar lines, crow's feet, nasolabial folds, and overall facial volume loss.
  - **Allergan Scales:** validated photonumeric scales for: cheek smoothness, forehead lines, crow's feet, glabellar lines, nasolabial fold, facial skin texture, transverse neck lines, facial fine lines, infraorbital hollows, chin retrusion, lip fullness, perioral lines .
  - **The Wrinkle Severity Rating Scale (WSRS):** a valid and reliable instrument for quantitative assessment of facial skin folds, with good inter- and intra-observer consistency.[4] A commonly used, useful clinical tool for assessing the effectiveness of soft-tissue augmentation and other facial contouring procedures.

[1] Narins RS, et al. A randomized, double-blind, multicenter comparison of the efficacy and tolerability of Restylane versus Zyplast for the correction of nasolabial folds. Dermatol Surg. 2003;29(6):588-595

[2] Flynn TC, et al. Validated assessment scales for the upper face. Dermatol Surg. 2012;38(2 Spec No.):309-19

[3] Narins RS, et al. Validated assessment scales for the lower face. Dermatol Surg. 2012;38(2 Spec No.):333-42

[4] Day DJ, et al. The wrinkle severity rating scale: a validation study. Am J Clin Dermatol. 2004;5(1):49-52.

# Aesthetic Clinical Rating Scales: Area specific Scales

Indication	Treatment	Assessment Tool
Glabellar Lines (Frown Lines)	Neuromodulators	Glabellar Line Scale, [1]
Crow's Feet (Lateral Canthal Lines)	Dermal fillers Neuromodulators	Crow's Feet Wrinkle Scale, [1]
Forehead Lines	Neuromodulators	Forehead Line Scale, [1]
Nasolabial Folds	Dermal fillers	The Wrinkle Severity Rating Scale (WSRS)[2] ,The Lemperle Assessment Scale, [3]
Marionette Lines	Dermal fillers	Marionette Lines Grading Scale or the Merz Aesthetics Scales <sup>TM</sup>
Perioral Lines (Smoker's Lines)	Dermal fillers Neuromodulators	Allergan Perioral Lines Severity Scale (POLSS), The Wrinkle Severity Rating Scale (WSRS) or the Merz Aesthetics Scales <sup>TM</sup> , [4]
Lip Fullness	Dermal fillers	The Allergan Lip Fullness Scale [5]
Cheek Volume	Dermal fillers	The Merz Aesthetics Scale <sup>TM</sup> or the Midface Volume Deficit Scale (MVDS), [6]
Hand volume loss	Dermal fillers	Merz Hand Grading Scale (MHGS)[7]

[1] R Bazin, et al., SKIN AGING ATLAS, Vol 1 Caucasiens Type, Med'com éditions, 2007

[2] Day DJ, Littler CM, Swift RW, Gottlieb S. The wrinkle severity rating scale: a validation study. Am J Clin Dermatol. 2004;5(1):49-52.

[3] Lemperle G, et al. A classification of facial wrinkles. Plast Reconstr Surg. 2001 Nov;108(6):1735-50; discussion 1751-2

[4] Cohen JL, et al. An interrater and intrarater reliability study of 3 photographic scales for the classification of perioral aesthetic features. Dermatol Surg. 2014;40:663-670

[5] Werschler WP, et al. Development and Validation of a Photographic Scale for Assessment of Lip Fullness. Aesthet Surg J. 2015;35(3):294-307

[6] Baumann L, et al. Volumizing Hyaluronic Acid Filler for Midface Volume Deficit: Results After Repeat Treatment. Dermatol Surg. 2015 Dec;41 Suppl 1:S284-92

[7] Cohen, Joel L. MD; et al. A Randomized, Blinded Study to Validate the Merz Hand Grading Scale for Use in Live Assessments. Dermatologic Surgery 41(1):p S384-S388, December 2015.

# Subjective Assessments in Aesthetics

## Patient reported outcomes (PROs)

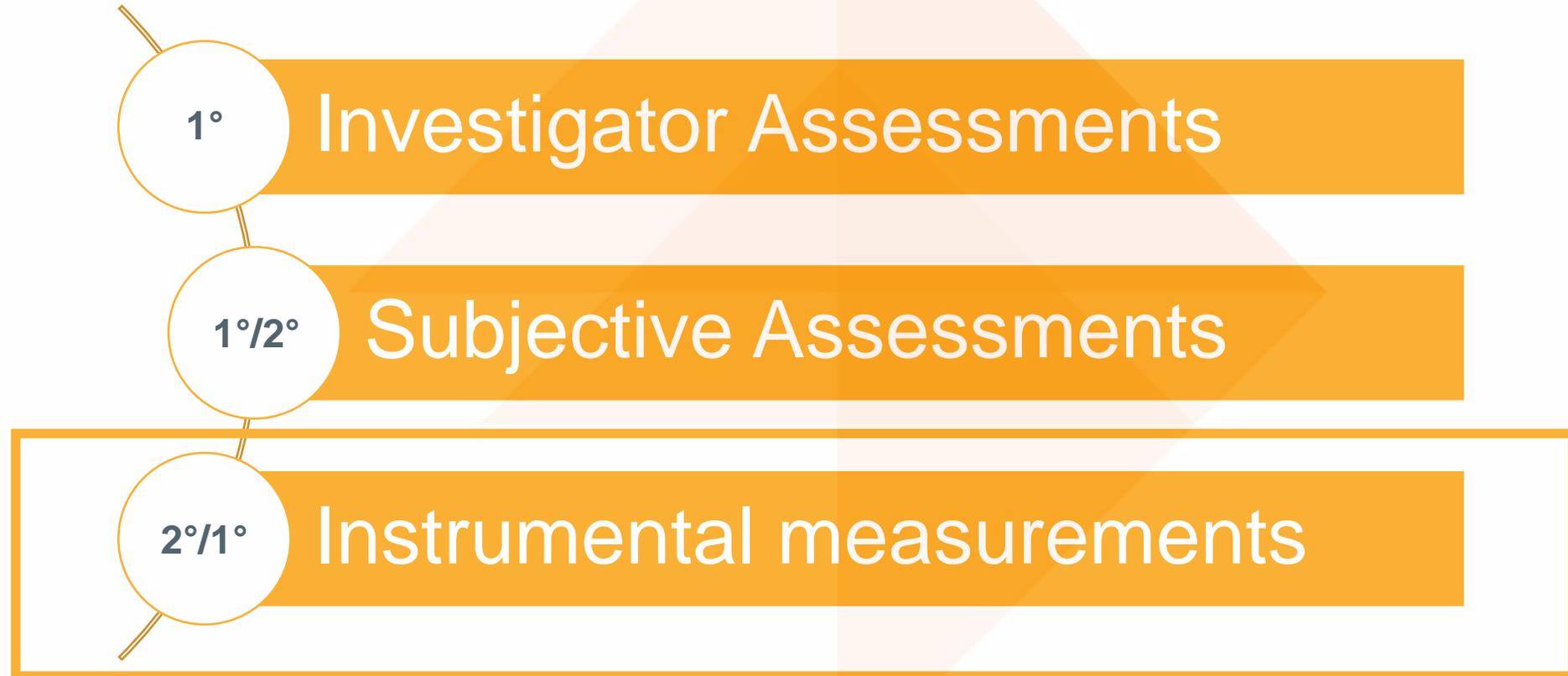
- **Subjective Global Aesthetic Improvement Scale (SGAIS):** This scale captures patients' self-perceptions of overall aesthetic improvement following treatment. It's a relative scale where patients can report their condition as 'worse', 'unchanged', 'improved', 'much improved', or 'very much improved'. It is frequently used due to its ease of use.
- **FACE-Q:** patient-reported outcome instrument composed of more than 40 independently functioning scales and checklists [1]. It is a very popular tool due to its comprehensive nature.
- **Facial Lines Outcomes (FLO-11) Questionnaire:** PRO to assess the impact of facial wrinkles on quality of life. Patients respond to questions about their worry, embarrassment, and satisfaction related to facial lines, both at rest and during facial expressions. [2]
- **Facial Line Satisfaction Questionnaire (FLSQ):** PRO to assess treatment expectations, satisfaction, impact, and preference in adults with upper facial lines.[2]
- **Subjective Patient Satisfaction Surveys:** may ask patients to rate their satisfaction with the treatment results, the process, and whether they would recommend the treatment to others. They are an invaluable tool for quality improvement.

[1] Klassen, Anne F. et al. FACE-Q Scales for Health-Related Quality of Life, Early Life Impact, Satisfaction with Outcomes, and Decision to Have Treatment: Development and Validation. Plastic and Reconstructive Surgery 135(2):p 375-386, 2015.

[2] Patel V, et al. Facial Line Outcomes (FLO-11) and Facial Line Satisfaction Questionnaire (FLSQ) Meet FDA Patient-Reported Outcome Guidance. Aesthet Surg J. 2020 Nov 19;40(12):NP710-NP711.

[3] US Food and Drug Administration. Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims. US Food and Drug Administration. 2009. <http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf>.

# Aesthetics: Effectiveness Evaluation Endpoints

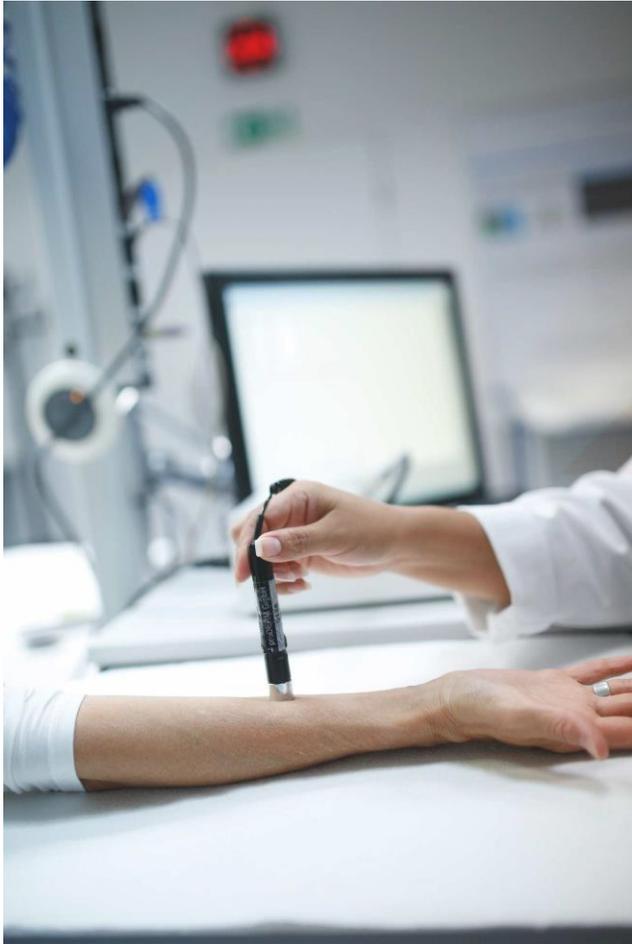




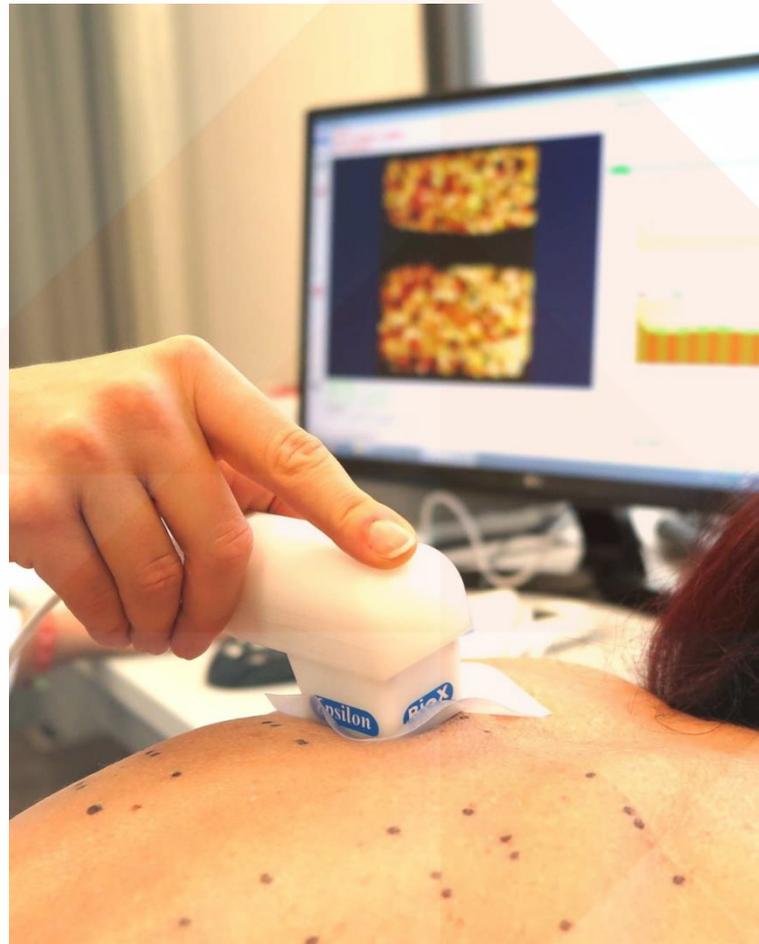
## Aesthetics Effectiveness: Instrumental Measurements

- Skin Dryness by Corneometer/Epsilon/ Moisturemeter
- Skin Dryness/Roughness by SquameScan or Corneofix/Visioscan
- Skin Sebum by Sebumeter/ Sebutapes/Sebufix/Lipbarvis/Swabs and Lipids
- Skin Elasticity by Cutometer, Cutiscan, Elastometer, DermalTorque/Ballistometer
- Skin Color by Chromameter/Spectrophotometer/ Mexameter
- Skin Thickness/Lipid/water ratio by Raman Spectroscopy

# Measurement of Stratum corneum Hydration



Corneometer



Epsilon

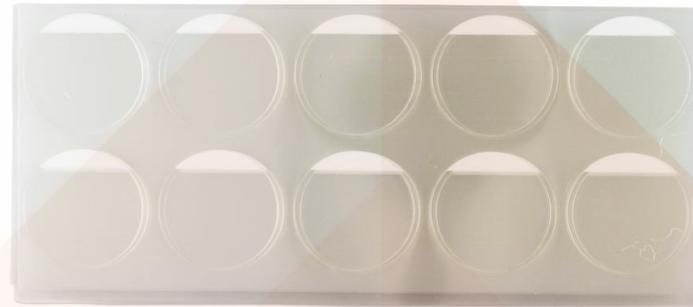


MoisturemeterD

# Measurement of the Stratum corneum Desquamation/Skin Dryness



SquameScan

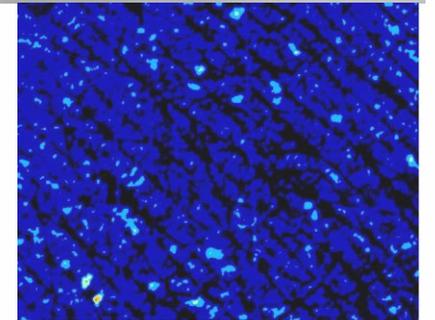


INCREASING SCALINESS LEVEL

D-Squame



Visioscan & Corneofix

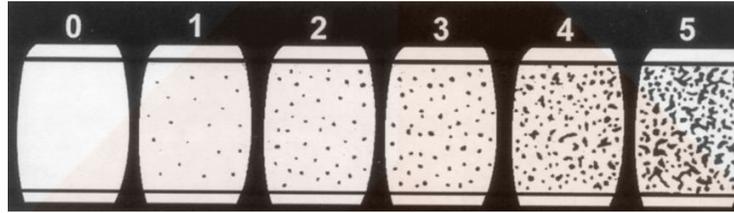


	Area [%]	Area [mm <sup>2</sup> ]
Class 1	66.18	19.06
Class 2	3.91	1.13
Class 3	0.13	0.04
Class 4	0.02	0.01
Class 5	0	0
All	70.24	20.24
Image area	100	28.8
Desquamation index	24.14	

# Measurement of Skin Sebum

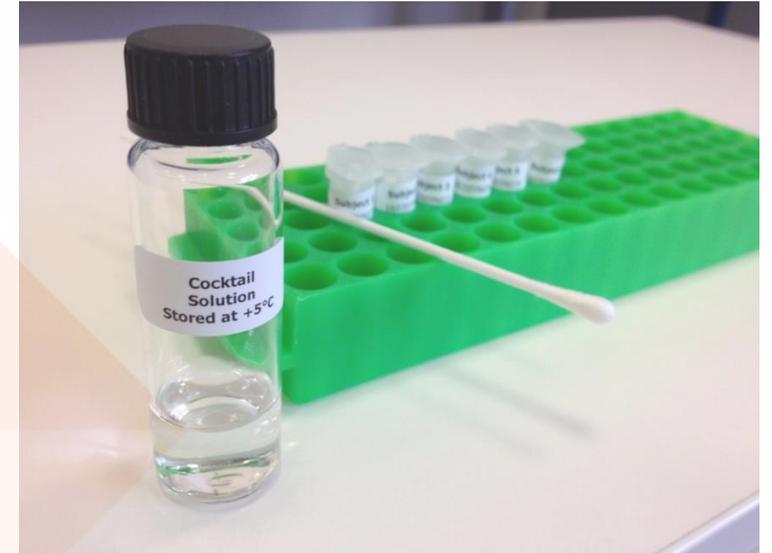


Sebumeter



## Sebutapes/Sebufix

- Removing sebum with Ethanol
- Sebutapes remain on the skin for 30 minutes an hour
- Determination of the basic sebum production ("casual levels").



Sampling and analysis from swabs / tape strippings

- Analysis of surface lipids
- Analysis of barrier lipids
- Lipidomics

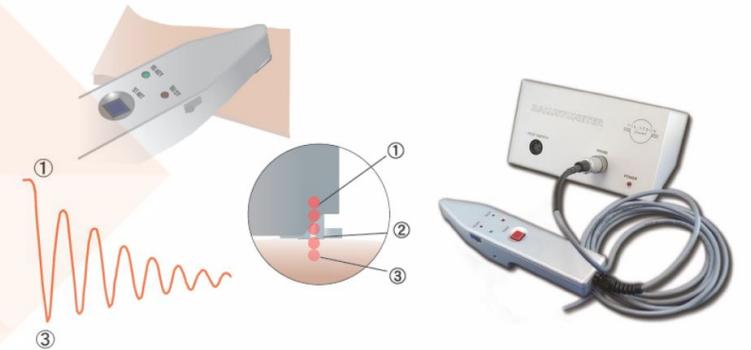
# Measurement of Skin Elasticity/Firmness



Cutometer



Dermal Torque Meter



Ballistometer

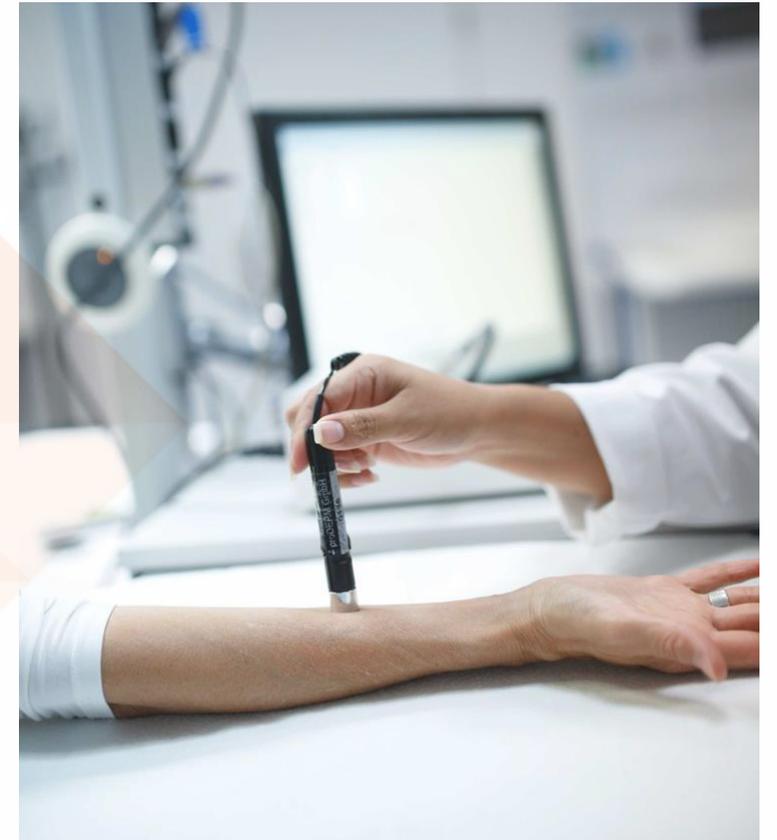
# Measurement of Skin Color



Chromameter

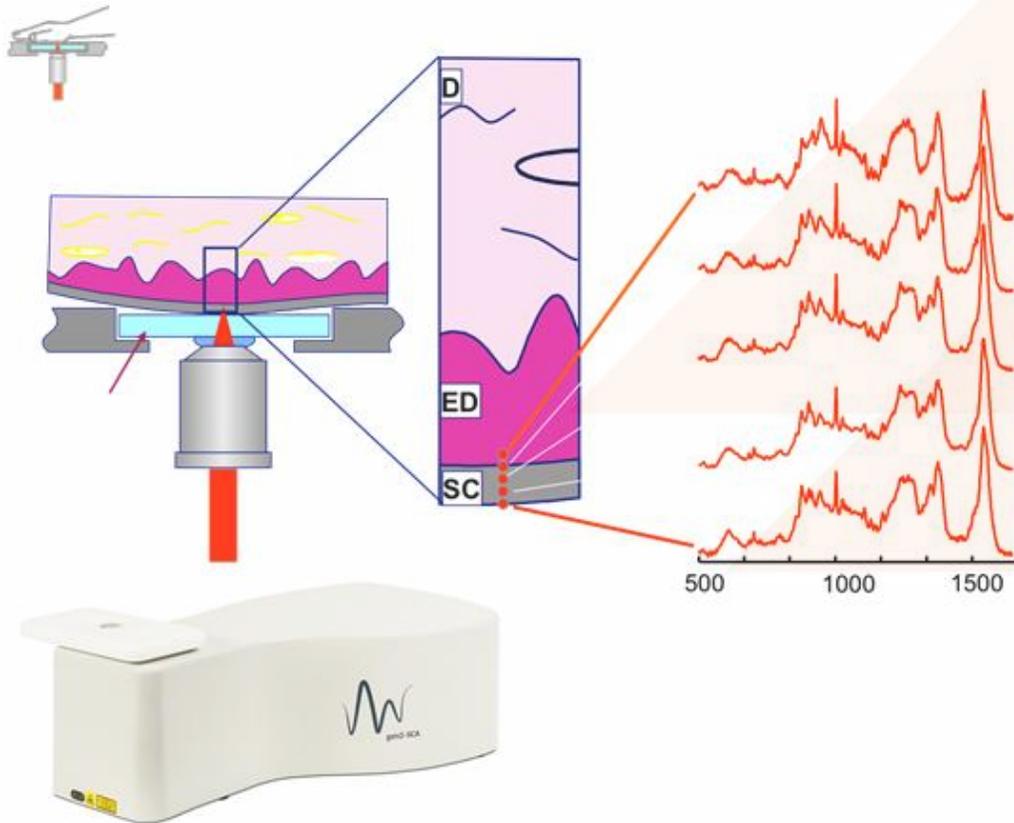


Spectrophotometer



Mexameter

# Confocal Raman Microspectroscopy (CRMS)



Raman spectroscopy enables non-invasive in vivo analysis of the molecular composition of the skin

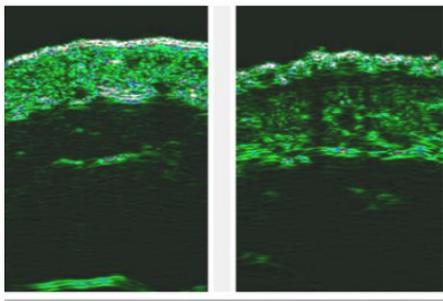
- In-vivo, non-invasive analysis of molecular concentration profiles
- Hydration of the skin, water content and distribution
- Natural Moisturizing Factors (NMF) & Barrier Lipids
- Skin penetration of biomolecules
- Collagen / Photoaging
- Lipid to protein ratio



## Aesthetics effectiveness: Images and Analysis Methods

- Imaging Techniques for Evaluation of Collagen
- LC-OCT (Stratum corneum, epidermal thickness, Keratinocyte distribution, Dermo-epidermal junction, Collagen, Melanin, Blood vessels)
- Skin roughness and wrinkle assessment by 3D skin measurements
- FLPI (vasodilation)
- Ultrasound
- Photography
- Image Analysis (roughness, pores, gloss, ...)

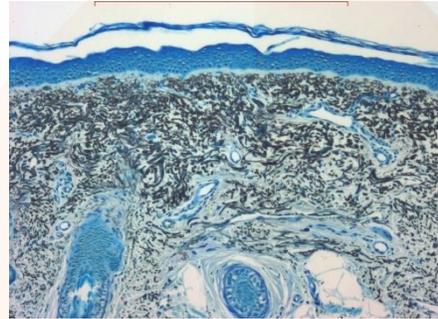
# Imaging Techniques for Evaluation of Collagen



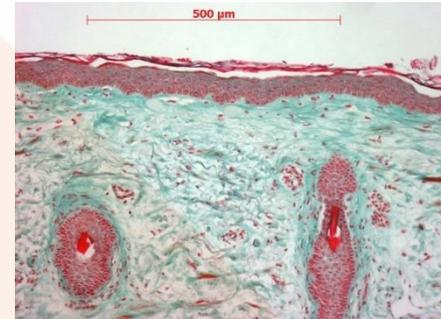
22Mhz-Ultrasound



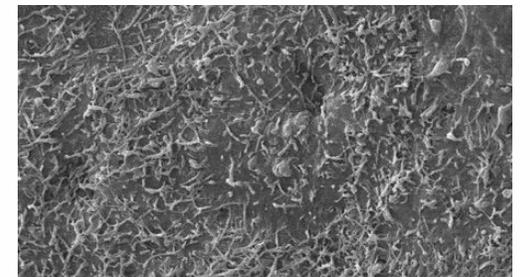
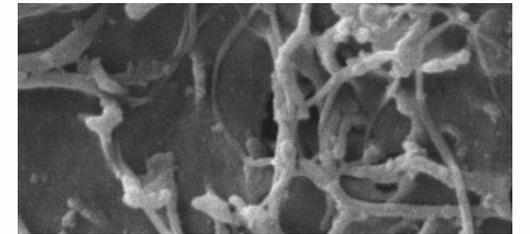
Vivosight (OCT)



Orcein staining from biopsies  
(black elastic fibers)



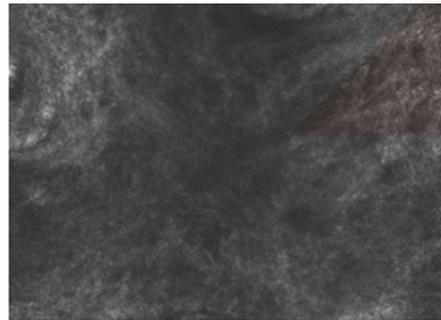
Masson-Goldner staining from  
biopsies (green collagen fibers)



TEM evaluation of suction  
blister roofs



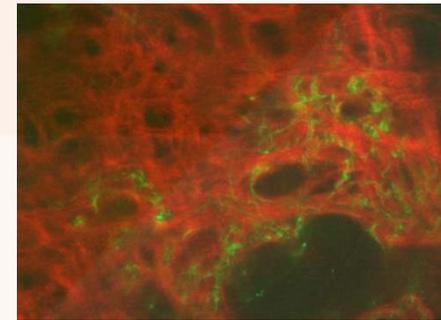
Confocal Microscopy  
(Vivascope)



Collagen image from  
Vivascope

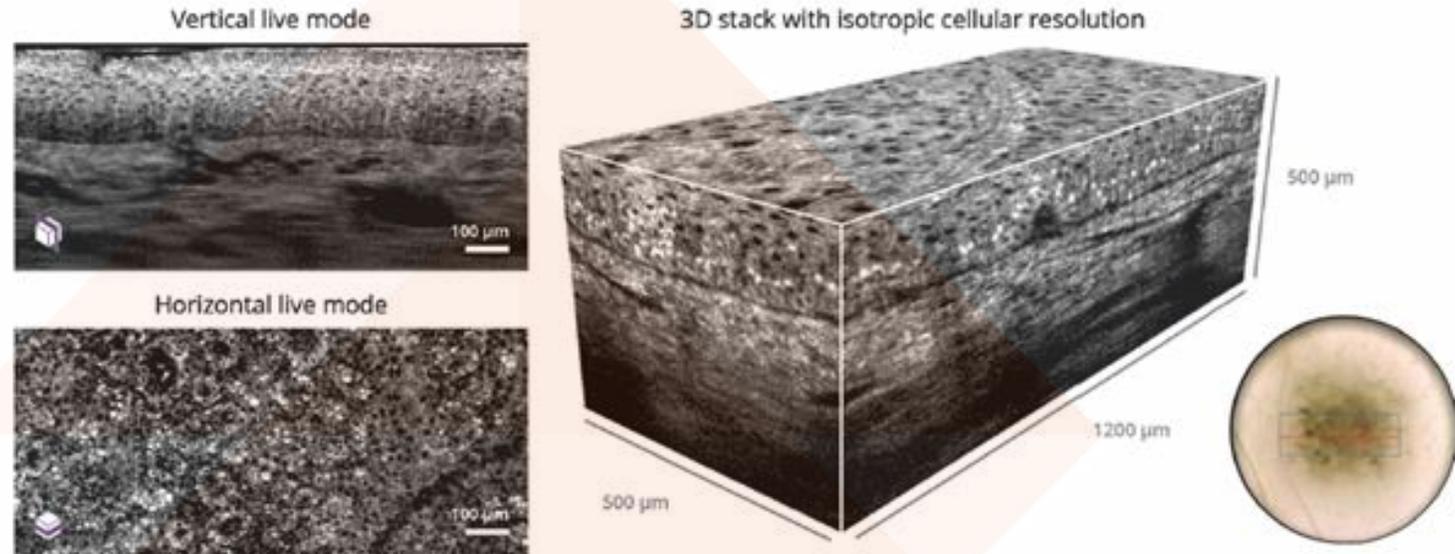


Multiphoton Tomograph



Autofluorescence of elastin  
and collagen crosslinks  
(green) and collagen SHG-  
signal (red)

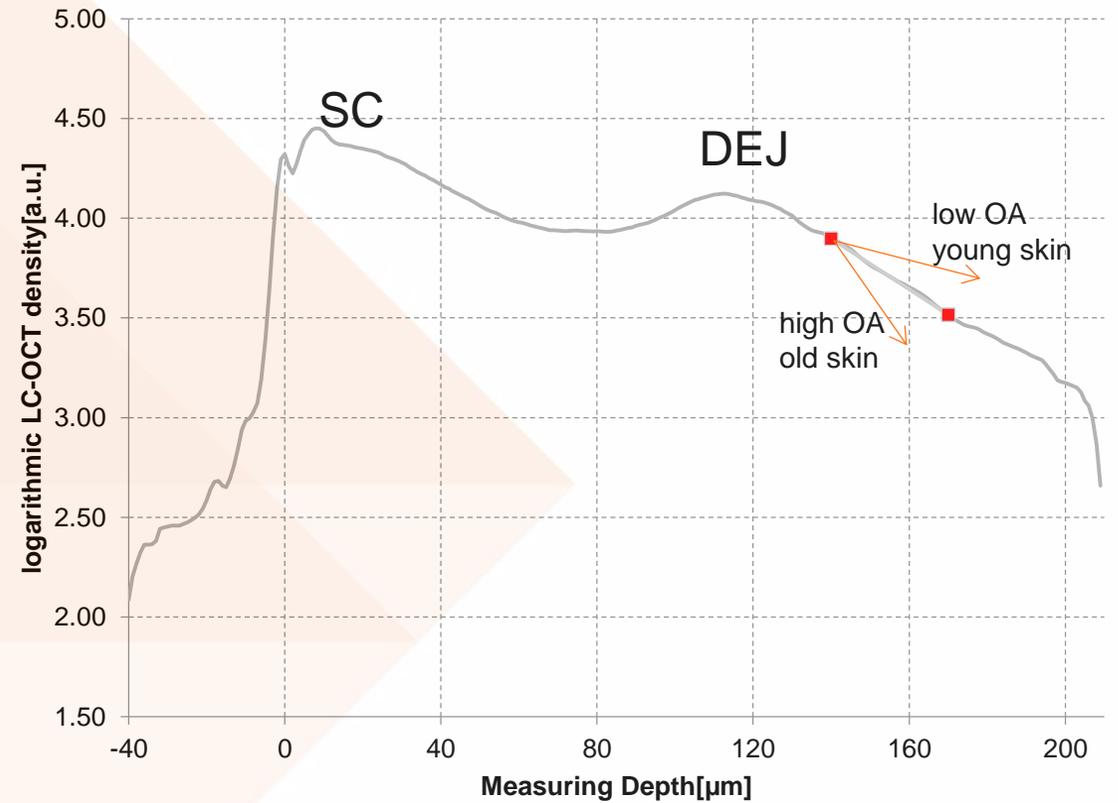
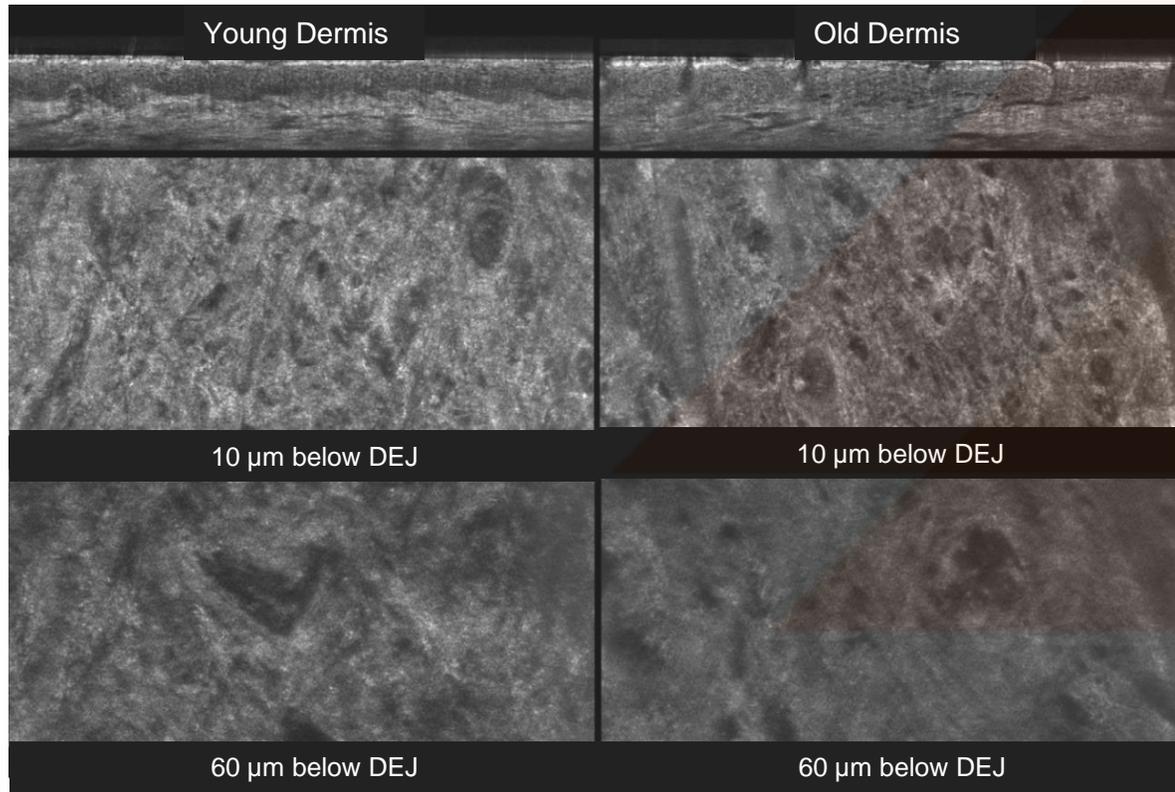
# Line-Field Confocal Optical Coherence Tomography (LC-OCT)



LC-OCT combines RCM and OCT technology

- Stratum corneum, epidermal thickness, Keratinocyte distribution
- Dermo-epidermal junction
- Collagen, Melanin
- Blood vessels

# LC-OCT – Optical Attenuation



Optical Attenuation: The negative slope of the LC-OCT signal in the upper dermis

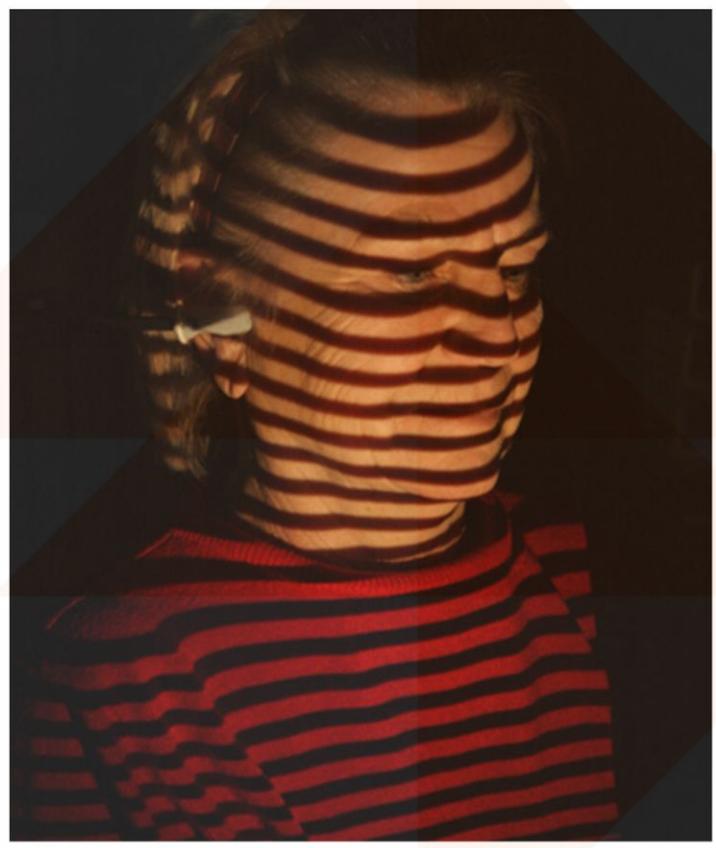
Young skin => high fibre reflection => low Optical Attenuation

Aged skin => low fibre reflection => high Optical Attenuation

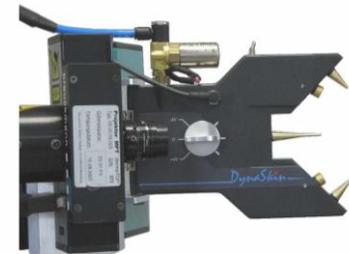
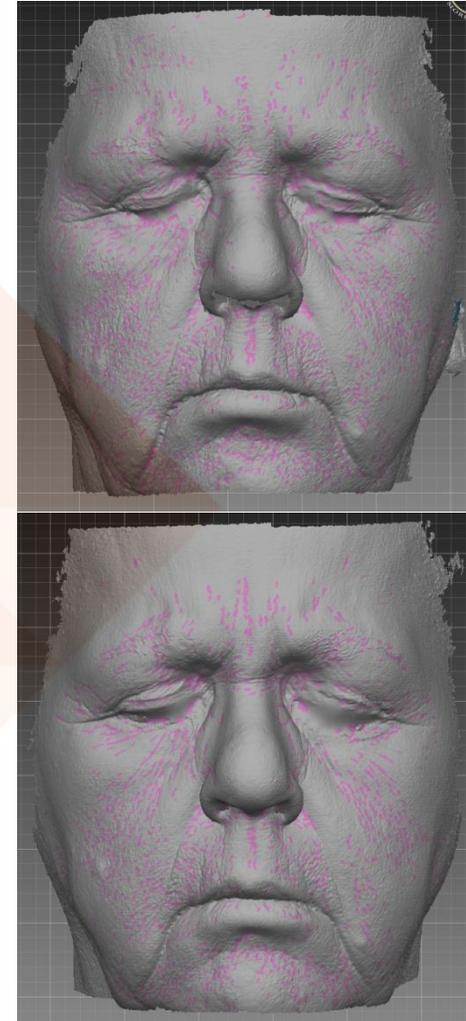
# Measurement of Facial Wrinkles/Skin Roughness/Skin Firmness by Fringe Projection



AEVA-HE



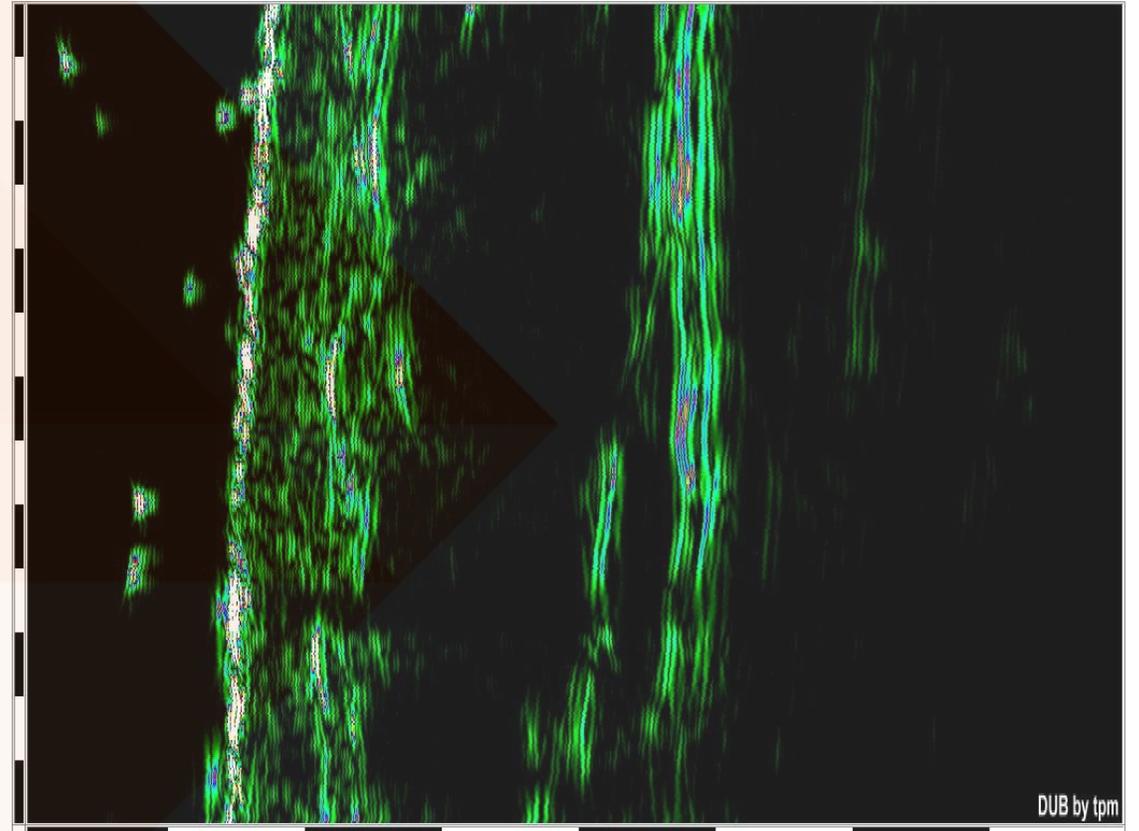
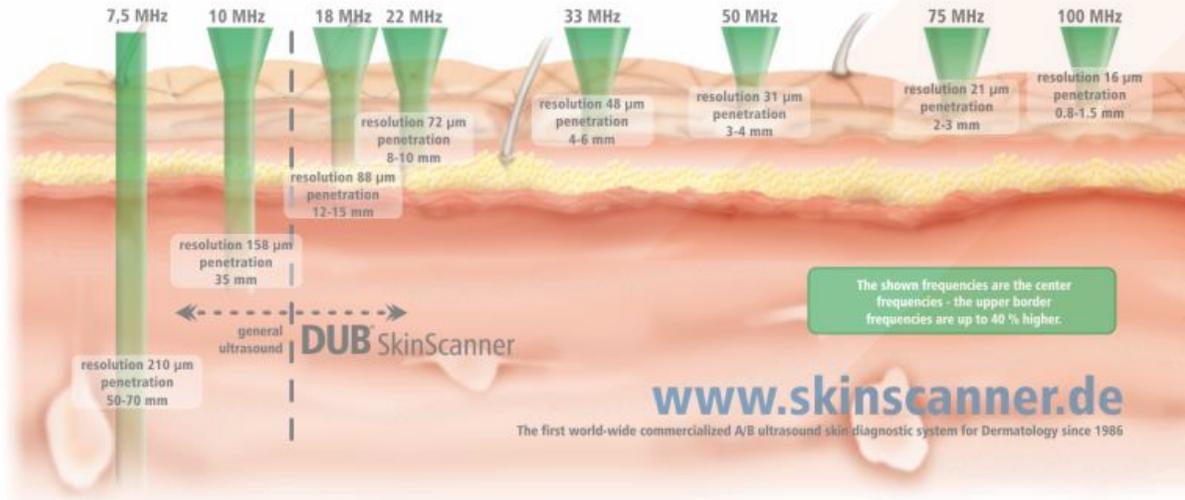
Fringes



Dynaskin add-on system for skin firmness

# Ultrasound

## Why we use different frequencies



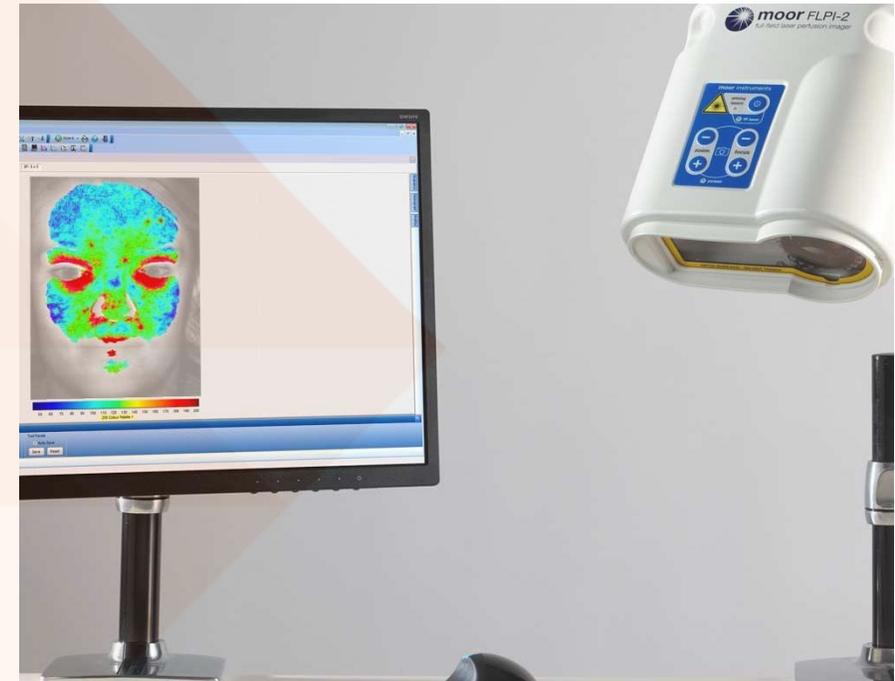
street: Im Dorf 15a • ZIP/city: DE-21335 Lueneburg • ☎ +49-4131-401555  
eMail: info@tpm-online.de • Web: www.digitalultrasound.de



<http://www.tpm-online.de/tpm/webneu/index.php/ultrasound-from-18-100-mhz.html>

# Measurement of Blood Perfusion

- Multiple setups (e.g. hand, face,...)
- Non-contact imaging of blood flow in microvessels in skin
- Resolution up to 580 x 752pixel
- Imaging area between 6 x 8 mm and 15 x 20 cm
- Test area according to set-up
- Measurement of single images as well as videos for kinetics possible



FLPI – Full Field Perfusion Imaging

# Standardized Photography



- **USR-CLiP (Unit For Standardized & Reproducible Clinical Photography)**
- Multiple setups (e.g. full-face, feet,...)
- Hasselblad camera full-format 50 megapixel
- Test area according to set-up



- **HiRIS (High Resolution Imaging System)**
- Multiple setups (e.g. hand, feet,...)
- Customized photography stand for standardized images
- 22 megapixel camera
- Test area according to set-up



- **MacIS XL (Macroscopic Imaging System XL)**
- Customized handheld system for standardized photography
- 21 megapixel camera
- Defined magnification
- Test area of 8 cm in diameter

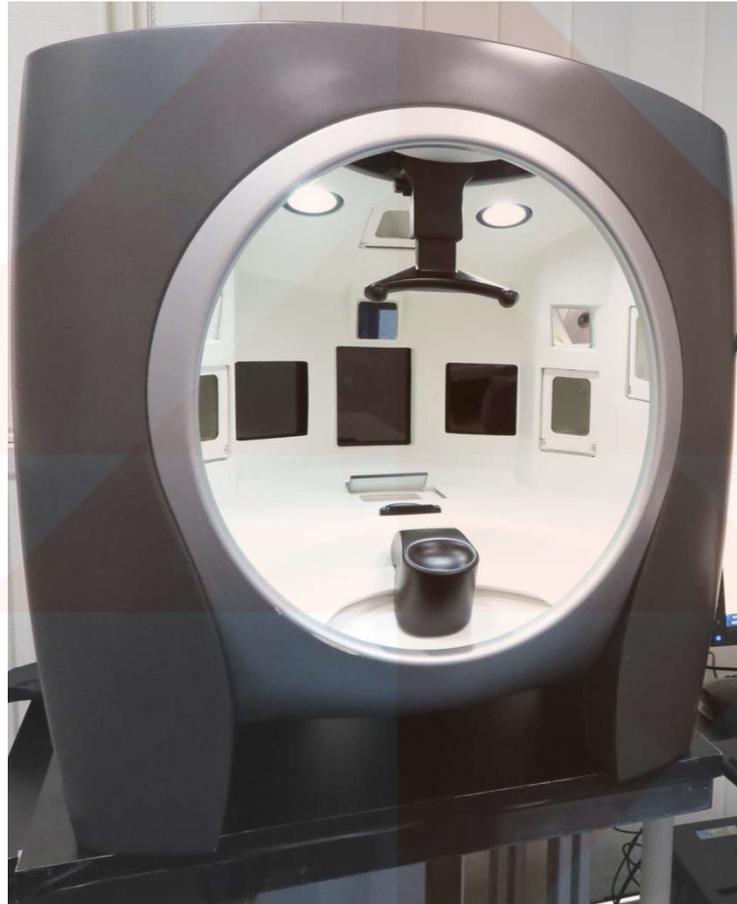


- **Dermlite Foto II Pro**
- Macroscopic images
- 22 megapixel camera
- Defined magnification
- Test area of 1.5 x 2 cm
- Non/Polarized and Cross-/Parallel-polarized illumination

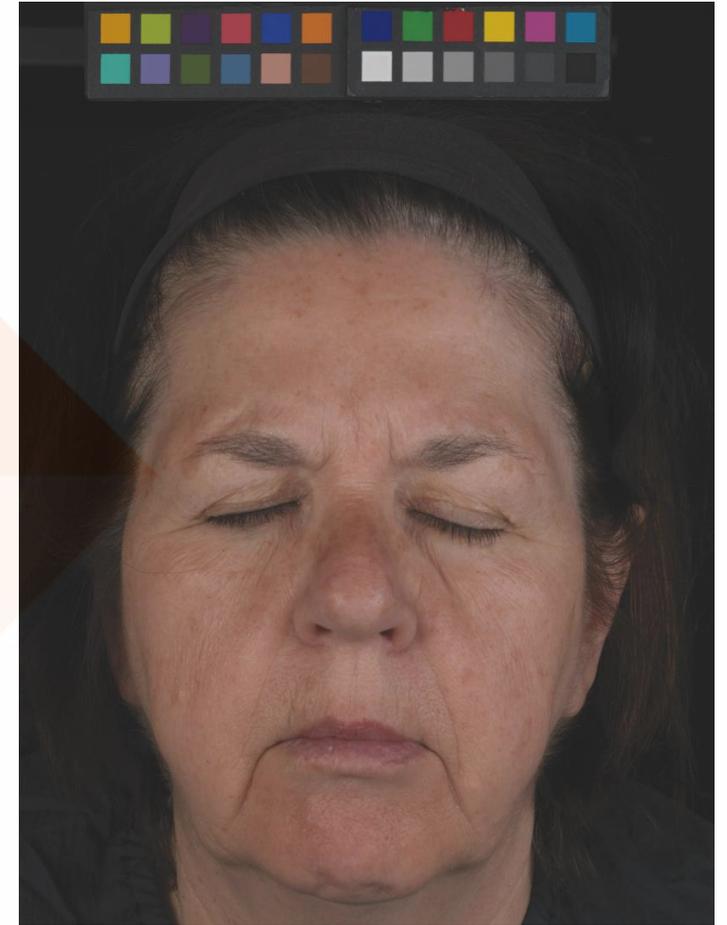
# Standardized Facial Photography



Colorface® Photobox

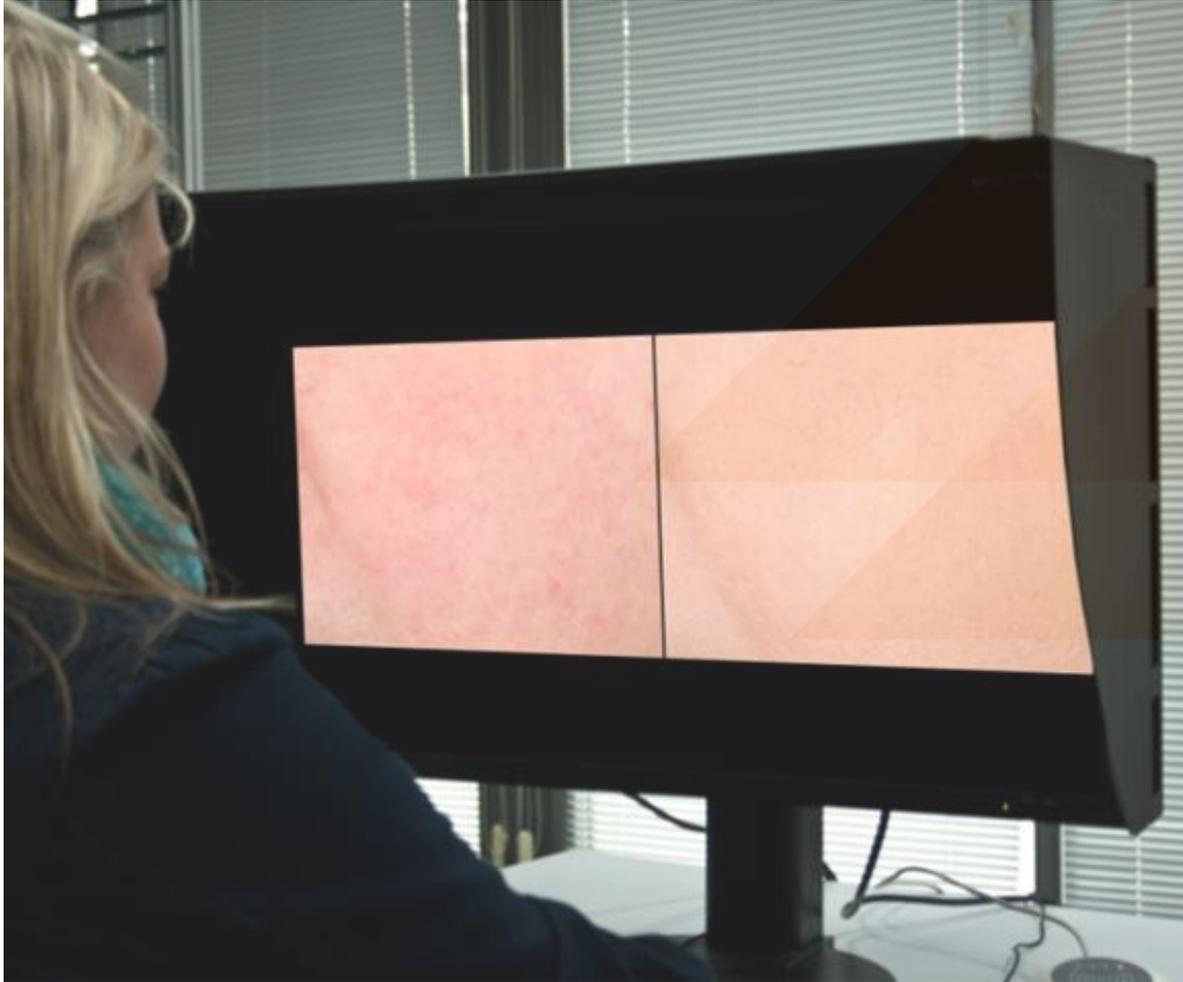


Visia CR2



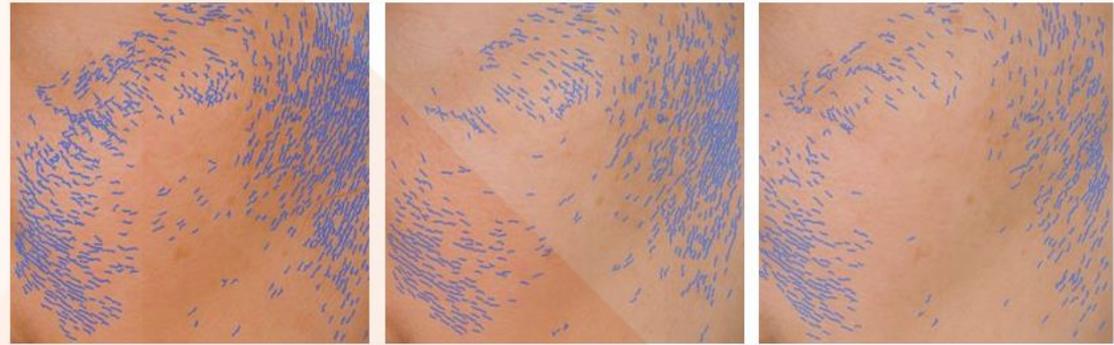
USR-Clip

# Color-Calibrated Monitors



- Presentation of images for expert rating
- High resolution
- High color accuracy - Adobe RGB color space

# Skin texture and Wrinkle Image Analysis

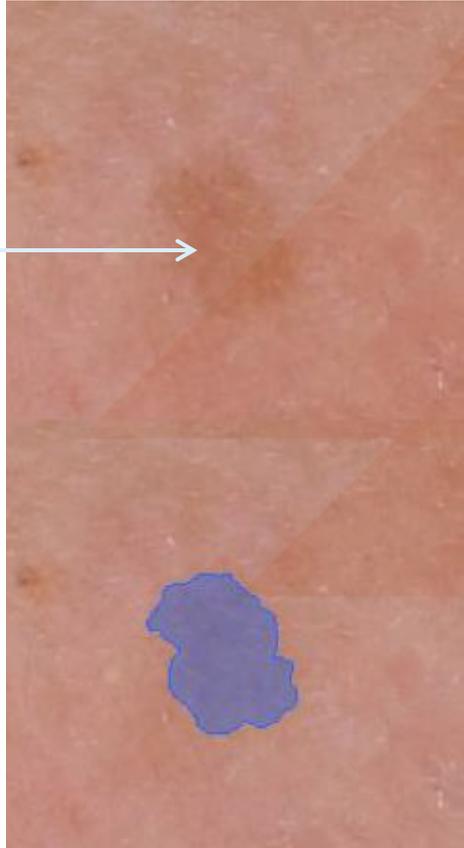


- Possible analysis parameters
  - surface
  - length
  - depth
  - volume

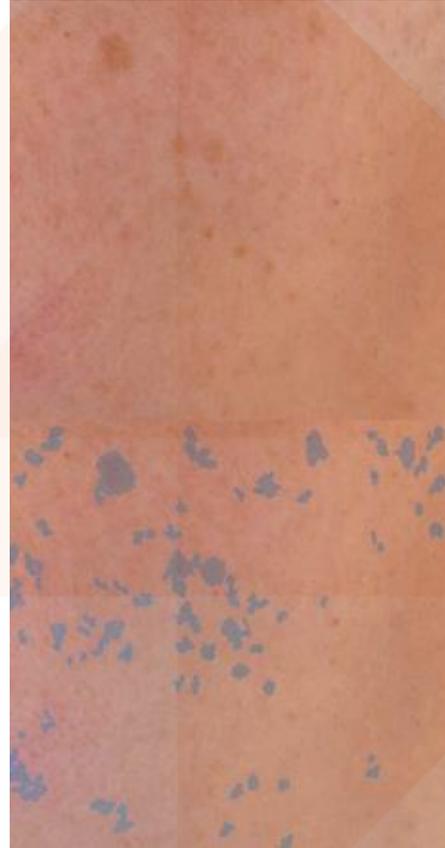
# Skin Texture/Roughness Pigmented Spots



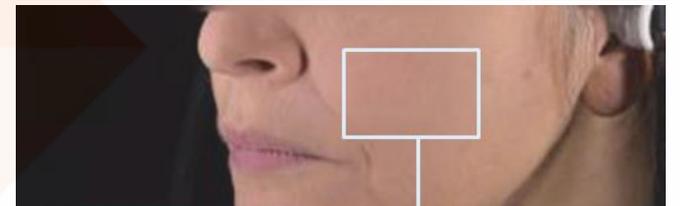
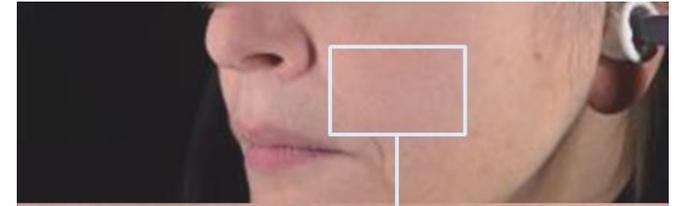
Colorface image (cross-polarized)



Single spot analysis



All pigment spots analysis



Skin Texture/Roughness

# Measurement of Pores



Parallel polarized image



Detected pores (green overlay)



Detail magnification

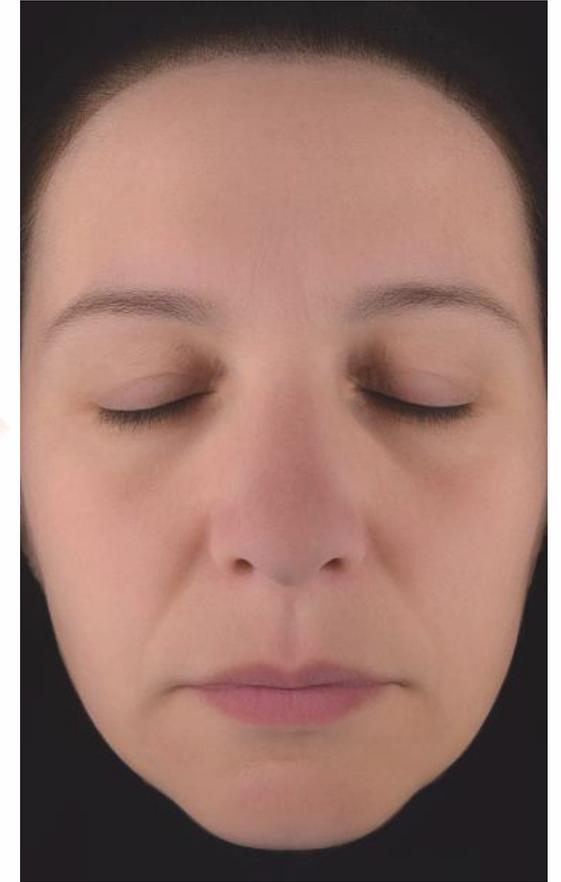


Automated segmentation of pores

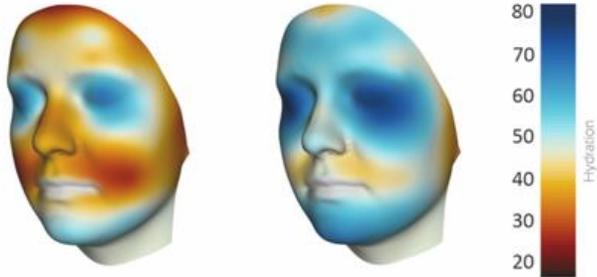
Newton Technologies



# Illustrations & Mean Face



# Mapping On Mean Face



Product effect mapping and hydration mapping

- Mean face representing a set of volunteers
- Average face can be used for marketing communication without having to worry about image rights
- Product effects can be mapped and visualized

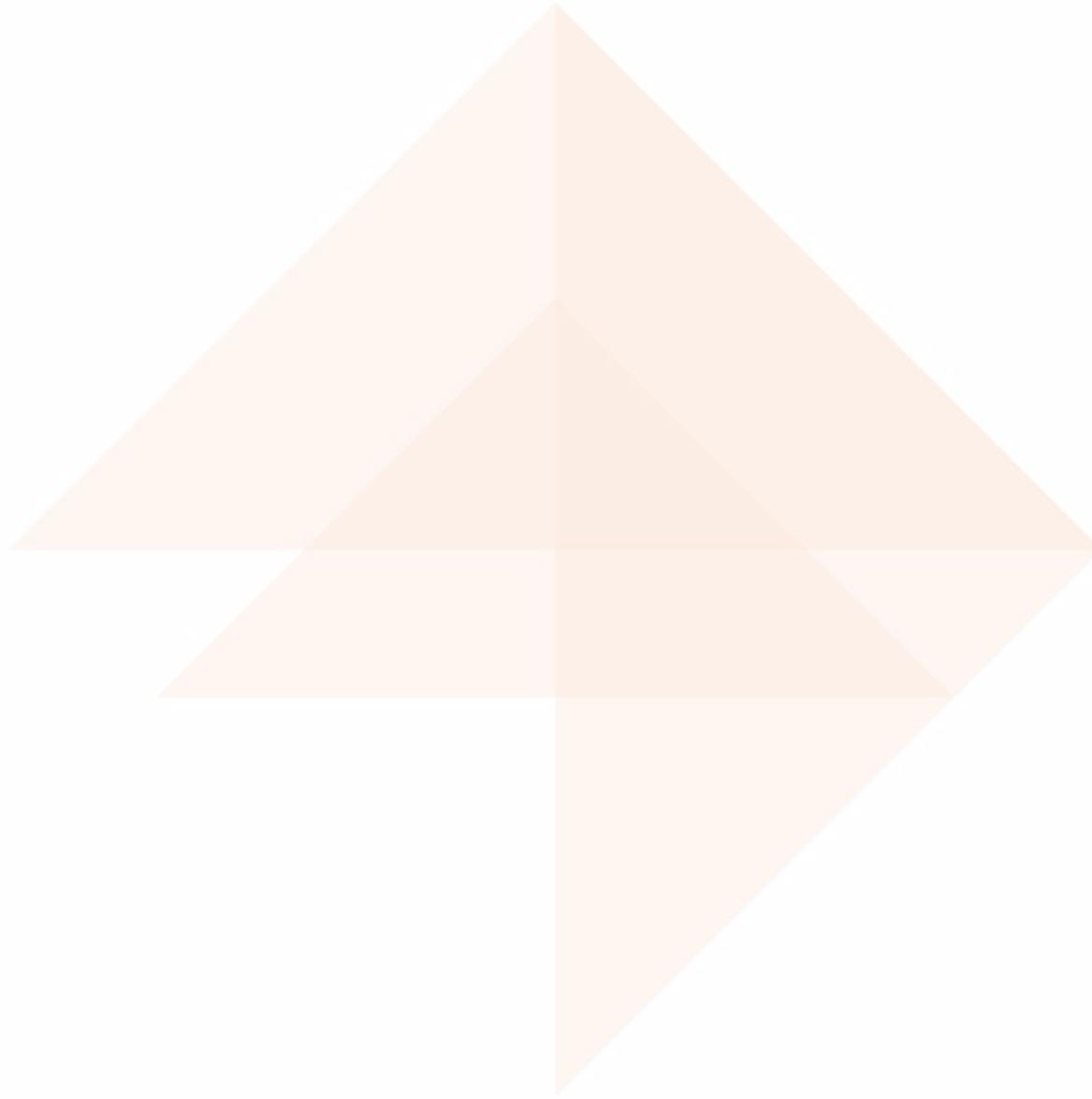


Thank you for your attention!

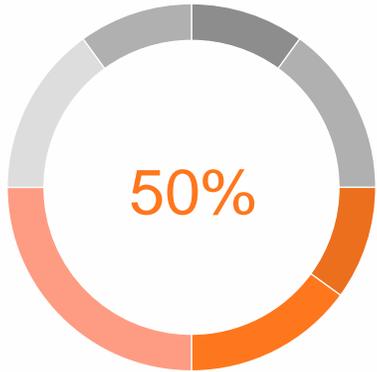
Web: <https://www.sgs-proderm.de/en/>

LinkedIn: <https://www.linkedin.com/company/sgs-proderm/mycompany/>

Contact: [gspringmann@proderm.de](mailto:gspringmann@proderm.de)



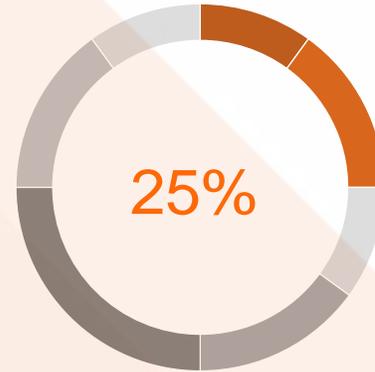
# Past Projects in Aesthetics



## Energy Devices

Radio frequency energy treatment, lasers, IPL, blue light

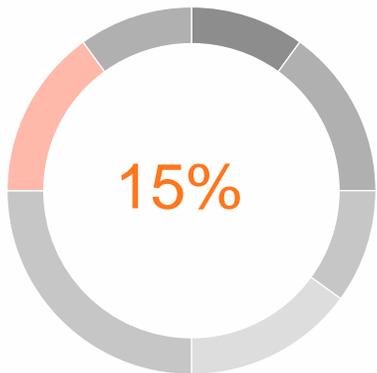
- PMCF studies
- medical device studies



## Injectables

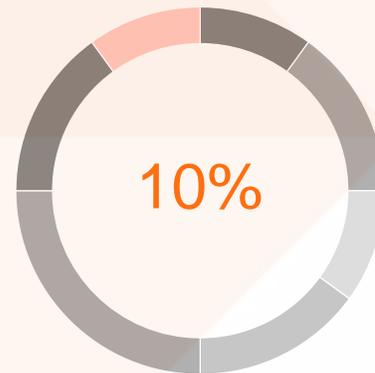
Botulinumtoxins and fillers

- Phase 1 studies
- PMCF studies
- medical device studies



## Peelings

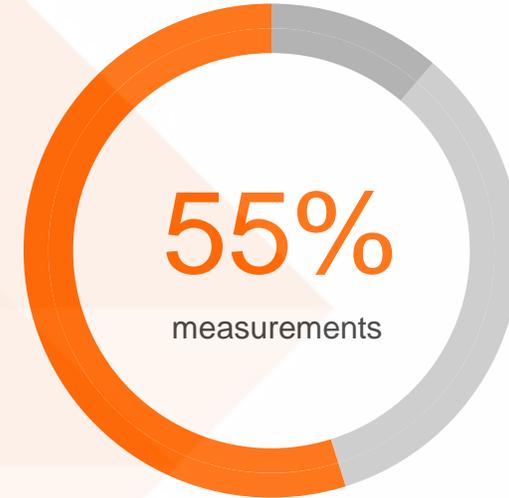
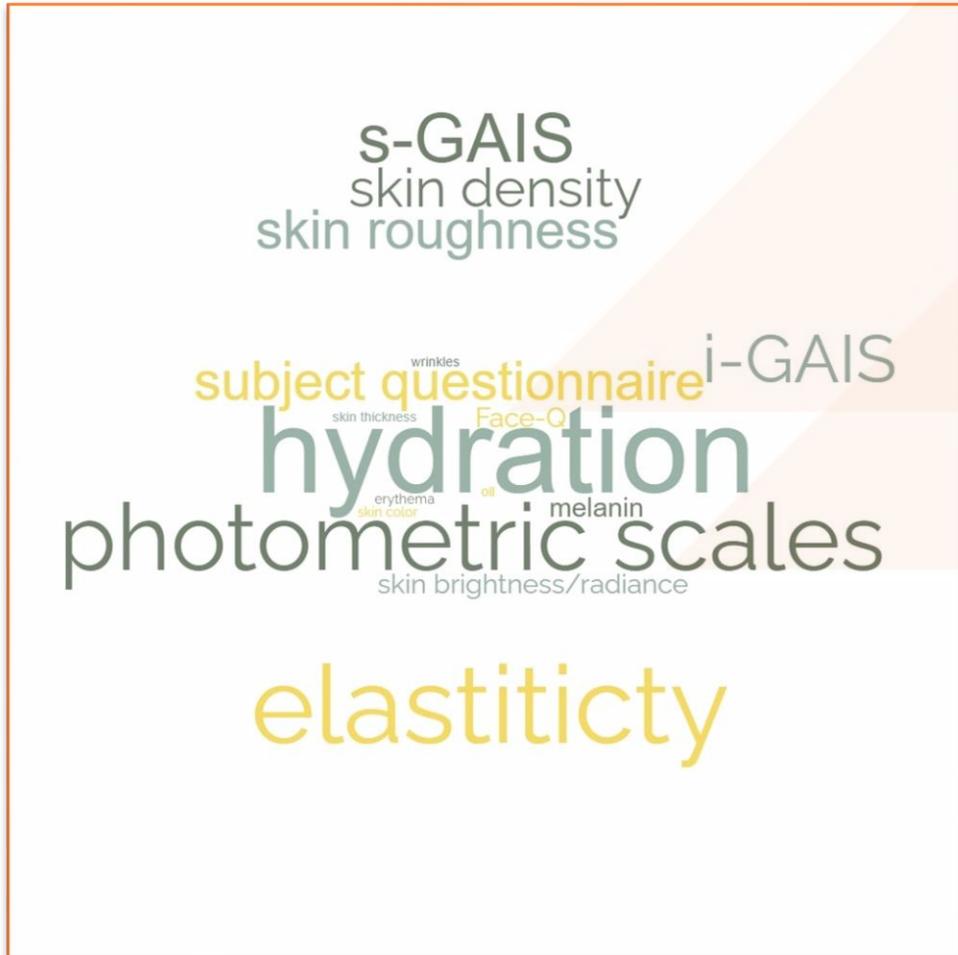
- Cosmetic studies



## Micro-needling

- Cosmetic studies

# Skin boosters: Evidence commonly used to support effectiveness claims



Composition of primary endpoints for EU clinical investigations