
RegenSight
a biomedical research company, introduces...
THERANOSTICS
Transforming **keratoconus** treatment.
Pioneering **Predictive**, **Personalized** and **Precision**
medicine in Ophthalmology.

KERATOCONUS: UNDERRECOGNIZED PATHOLOGY: A CORNEAL TOPOGRAPHY, SOON!

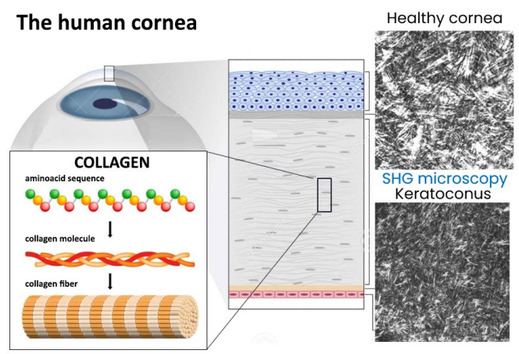
Keratoconus is the **most frequent** corneal dystrophy.
It is the **primary cause of corneal transplantation** in people under 40 globally.

Degenerative Corneal Disease

Microscopic studies of the keratoconus cornea show:

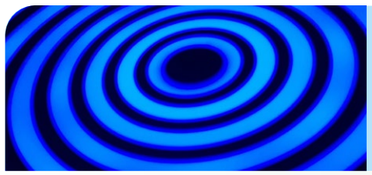
- disorganization of stromal architecture
- fragmented collagen fibers
- increased inter-fibrillar spaces

These factors **weaken** and **thin** the tissue, leading to corneal ectasia.[1,2]



WHEN	**Early onset,** typically in the second decade of life. Leads to progressive visual loss.
WHY	**Multifactorial disease** caused by genetic and environmental risk factors, which contribute to disease progression.[3]
UNDERRECOGNIZED	Previously considered rare,[4] keratoconus is now recognized to affect over 1% of the global population.[3]

Early detection and **prompt** treatment are crucial for preserving vision and emotional well-being in young patients.

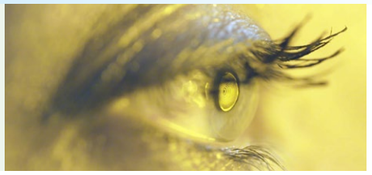


MAIN DIAGNOSTIC TOOL

Placido disc **corneal topography**. Non-invasive and accurate for detecting and tracking disease progression.

PROGRESSIVE DESEASE

Keratoconus typically has K_{max} **steepening of 0.7±0.8 D per year** (95% CI: 0.31 D - 1.14 D).[5,6]



>20 YEARS OF CORNEAL CROSS-LINKING: TIME FOR A REVIEW

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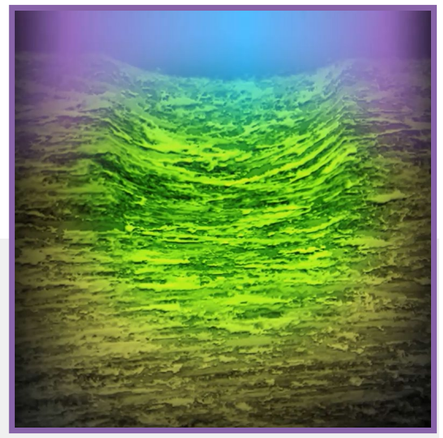
The procedure...

Corneal cross-linking (CXL) aims to halt keratoconus progression by generating new covalent chemical bonds between the stromal proteins, enhancing the biomechanical tissue strength.



... the photo-chemical mechanism of action...

The CXL procedure relies on a **photo-chemical** reaction involving:

- **riboflavin** as a photo-initiator
- **UV-A light** as a photo-activator

Photoiniziator	Photochemical Activation	Photochemical Reactions	Photopolymerization
(riboflavin, vit. B2)	(UV-A light)	(Riboflavin triplets, ROS)	(new covalent chemical bonds among proteins)

... the CXL protocols

Epithelium-off protocol (with corneal de-epithelialization): the gold standard.[7,8]
Removal of the epithelium is the cause of **severe adverse events** (infection and corneal scarring).[9,*]
Moderate adverse events are frequent (e.g., corneal haze ≥20%).

Epithelium-on protocol (transepithelial): **highly variable efficacy**. Less effective than epi-off.
Adverse events are mild and transient.

Riboflavin ophthalmic formulation
Numerous ophthalmic formulations available, with different compositions and manufacturing processes.[10]

UV-A light irradiation
Numerous irradiation protocols in use differing in UV-A light power density and energy dose.
There is no control over the homogeneity of the UV-A light beam.

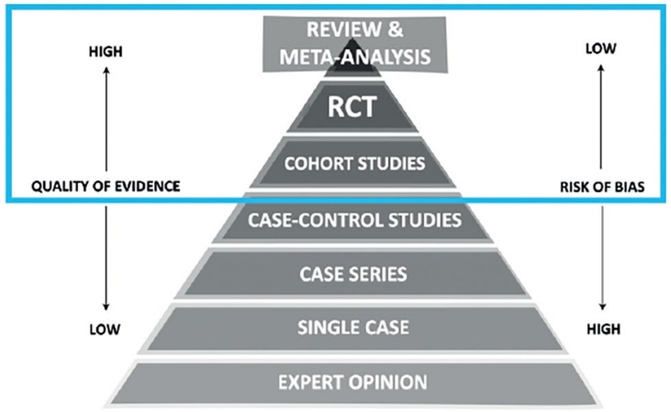
*Severe **adverse events** induced by CXL are infrequent (cumulative incidence: 1.2%).
They are always associated with **corneal de-epithelialization** or **incorrect treatment procedure** (i.e., inadequate amount of riboflavin or excessive UV-A light energy) and occur in the **first week** after treatment.[9]

THE CLINICAL EVIDENCES ON CXL ...

*«CXL may be effective in halting the progression of keratoconus for at least 12 months under **certain conditions**».*[11]

Meta-analysis studies,[7-9, 11-12] have shown a mean K_{max} flattening of 1.0 ± 0.8 D in 50% of cases treated with the epi-off CXL protocol.

A huge variability in outcomes has been found between protocols with lower efficacy after **epi-on than epi-off CXL.**



... the variables involved and the current limits of CXL...

NOT STANDARDIZED PROCEDURE

- numerous riboflavin formulations
- numerous UV-A light irradiation protocols
- empirical development of CXL protocols

HETEROGENEITY OF KERATOCONUS

- age
- disease stage
- corneal shape
- corneal curvature
- corneal thickness
- tissue anisotropy

UNCERTAIN THERAPEUTIC OUTCOME

- photo-chemical interaction between riboflavin and UV-A light not understood

... driving Regensight's research forward to elevate the gold standard

KEY FACTORS TO IMPROVE EFFICACY OF CXL CLINICAL OUTCOMES:

1. Adequate permeation of **riboflavin** into the cornea prior to UV-A light irradiation
2. Effective **UV-A light mediated photo-activation** of riboflavin in the cornea.

THE *RegenSight* SOLUTION:

MONITORING THE CORNEAL RIBOFLAVIN CONCENTRATION AND ENSURING ITS **EFFICIENT PHOTO-ACTIVATION** DURING CXL ARE CRUCIAL TO ACHIEVE THE DESIRED THERAPEUTIC OUTCOME FOR EACH PATIENT.

THE THERANOSTIC PLATFORM FOR CXL

CHROMO4VIS

UV-A MEDICAL DEVICE FOR THERANOSTIC GUIDED CORNEAL CROSS-LINKING

TRANSFORMATIVE TECHNOLOGY: THERANOSTICS

EXPONENTIAL & KEY-ENABLING TECHNOLOGIES

- **Placido disc with augmented reality**
- **Internet of Medical Things (IoMT)** for remote maintenance
- **Artificial intelligence (AI)** for continuous product improvement
- **Digital traceability** for clinical data storing

PRE-SET PROTOCOLS and unlimited add-on options

MAXIMUM RELIABILITY with double UV-A light monitoring system (precision ± 0.1 mW/cm^2)

Integrated interconnection with corneal iontophoresis for controlled delivery of riboflavin

RITSIGHT

0.22% RIBOFLAVIN OPHTHALMIC SOLUTION FOR CORNEAL CROSS-LINKING

UNIQUENESS THAT MEET SURGEONS' NEEDS

- **Exclusive solution** for all CXL protocols (epi-off, epi-on)
- **36 months** life cycle
- Storage at **room temperature** (4°C - 25°C)
- Indicated for **thin corneas** (minimum thickness 370 µm)

The only riboflavin validated for theranostic-guided CXL

DORSight

CORNEAL IONTOPHORESIS CONTROLLED DELIVERY SYSTEM FOR EXCLUSIVE USE WITH C4V CHROMO4VIS

UNIQUENESS

Corneal iontophoresis delivery system for fast and precise **patterned delivery of riboflavin in the cornea**. The device allows, through theranostic-guided UV-A light photo-therapy, for:

- **Enhancing precisely the regional biomechanics of the cornea**
- **Improving significantly the optical quality of the cornea**

THERANOSTICS: THE FUTURE...

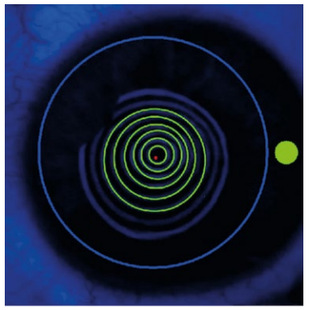
Improving efficacy and safety in keratoconus treatment

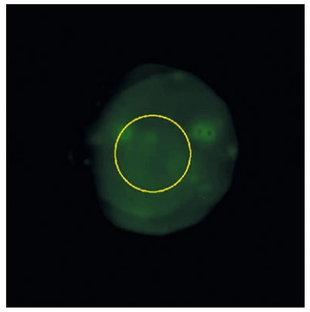
By integrating **THERA**py with molecular imaging diag**NOSTICS**, **theranostics** enables real-time monitoring of **corneal concentration of riboflavin** and its efficient **UV-A light mediated photo-activation.**

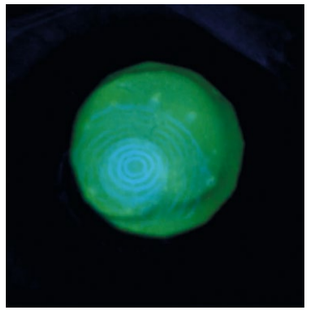
The technology has shown to significantly enhance the biomechanical strength of the human cornea (**pre-clinical validation**)[10,13-18] and to flatten the anterior corneal curvature (**clinical validation**)[19,20] with **predictive personalization and high precision**.

THE 4 PHASES OF THERANOSTIC-GUIDED CXL

1° CORNEAL FOCUSING 2° BASELINE MEASURE	3° RIBOFLAVIN DOSING PHASE	4° UV-A LIGHT PHOTO-THERAPY
assessing the corneal optical properties	assessing the amount of riboflavin permeating the cornea	treating and assessing treatment efficacy







The **riboflavin score** is an estimate of riboflavin corneal concentration

The **theranostic score** is an estimate of CXL treatment efficacy

C4V CHROMO4VIS allows the operator to proceed with UV-A light irradiation of the cornea when the **riboflavin score** is over the the preset threshold

The theranostic imaging biomarkers, **riboflavin score** and **theranostic score**, guide the surgeon in performing a treatment that **accurately** predicts the intended clinical outcome with **precision**.

... IS NOW WITH EVIDENCE

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From the *Proof of Concept* to theranostics validation [10,13-18]

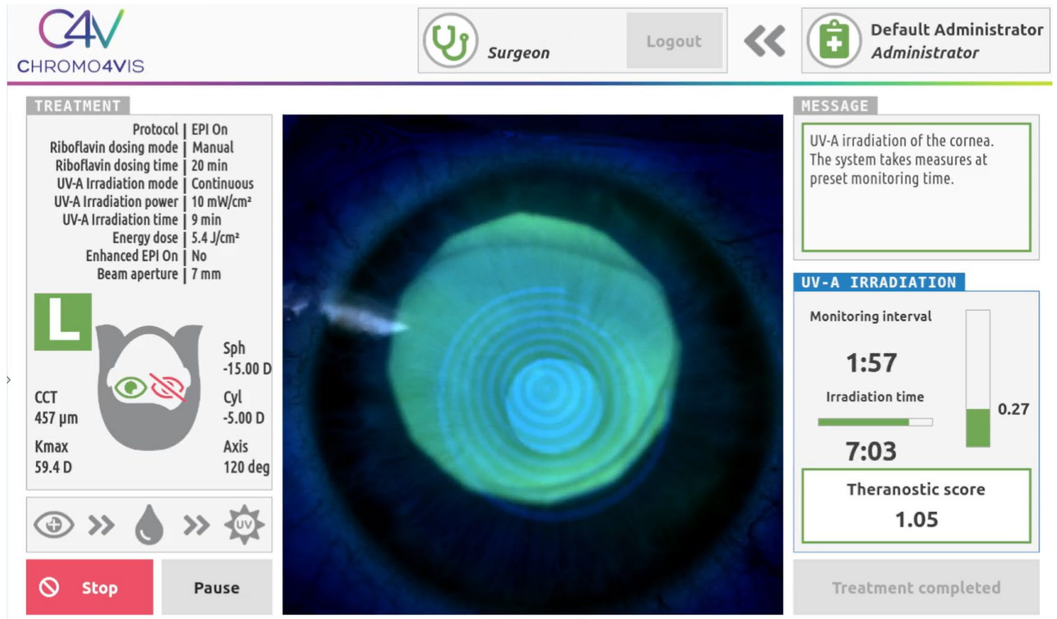
In a pre-clinical validation study,[17] theranostic-guided CXL was performed on eye bank human corneas with epi-off and epi-on protocols. A dynamic tonometry device was used to assess the deformation of corneal tissue induced by an air puff (*corneal elasticity*) before and 2 hours after CXL.

Table 2. Average values of corneal riboflavin concentration (±SD) during the dosing phase of Thera-CXL, mean corneal stiffness parameter (k_c, ±SD), maximum deformation amplitude (DA, ±SD) before and after Thera-CXL protocols, and average theranostic score in both protocols (±SD)

Parameter	Time (min)	Thera-CXL epi-on protocol (n = 12)	Thera-CXL epi-off protocol (n = 8)
Corneal riboflavin concentration (μg/cm³)	5	50 ± 19	344 ± 146
	10	73 ± 36	558 ± 235
	15	118 ± 68	—
	20	145 ± 77	—
Mean corneal stiffness (k_c, N/m)	Baseline k_c	41.4 ± 12.7	34.0 ± 5.0
	After treatment k_c	49.9 ± 11.2 (*P* = .03)*	41.7 ± 7.0 (*P* = .04)*
Maximum deformation amplitude (DA, μm)	Baseline DA max	635 ± 118	673 ± 86
	After treatment DA max	561 ± 104 (*P* = .03)*	610 ± 76 (*P* = .04)*
Theranostic score (d.n.)		0.7 ± 0.3	1.0 ± 0.2

d.n. = dimensionless number; Thera-CXL = theranostic-guided corneal crosslinking
*Statistically significant (paired *t* test)

A regression model incorporating the **theranostic score**, accurately predicted CXL efficacy in improving corneal elasticity, with 94% accuracy and 94% precision, regardless of the protocol used (epi-off or epi-on CXL).



The theranostic platform for CXL allows for the **precise delivery of riboflavin** and **UV-A light energy** tailored to each patient's cornea.

THE ARGO STUDY

ASSESSMENT OF THE**R**ANOSTIC **G**UIDED RIB**O**FLAVIN/UV-A CORNEAL

MULTICENTER, MASKED, RANDOMIZED CLINICAL TRIAL: UNIVERSITIES OF FIRENZE, MESSINA AND CATANZARO.

Objective: : To validate the **theranostic software** of the C4V CHROMO4VIS in predicting a K_{max} flattening at 12 months after CXL treatment.
Inclusion Criteria: Progressive keratoconus.
Stratification: Patients were stratified in **two CXL treatment protocols (epi-off and epi-on).**
Treatment: CXL was performed with **C4V CHROMO4VIS** and **RitSight**. The operators were unaware about the *cut-off* values of theranostic imaging biomarkers.

PRIMARY OUTCOME (1 YEAR)

The **accuracy** and **precision** of the theranostic imaging biomarkers in predicting CXL efficacy (determined as **K_{max} flattening greater than 0.1 D**) was **91%** and **95%**, respectively

Predictive ability of the theranostic imaging biomarkers in assessing the propensity of CXL treatment in flattening the K_{max} value at 1 year follow-up visit.

Predicted outcome / Theranostic biomarkers (cut-off values)	K_{max} change at 1-year >0.1 D flattening	K_{max} change at 1-year (≤0.1 D flattening)	Total
Riboflavin score >0.40 & Theranostic score ≥0.60	True Positives (n = 41) K_{max} change = -1.7±1.6 D	False Positives (n = 2) K_{max} change = +0.1±0.01 D (epi-off only)	43
Riboflavin score ≤0.40 and/or Theranostic score <0.60	False Negatives (n = 2) K_{max} change = -0.5 ± 0.2 D (epi-on only)	True Negatives (n = 2) K_{max} change = +0.2±0.2 D (epi-on only)	4
Total	**43**	**4**	**47**

SECONDARY OUTCOME (1 YEAR)

EFFICACY	SAFETY
K_{max} flattening: -1.5 ± 1.6 D (P< 0.01) Treatment **HALTS keratoconus progression**	**CDVA improvement: -0.1 ± 0.1 LogMAR** (P<0.001) Treatment **IMPROVES visual acuity**

Adverse Events:

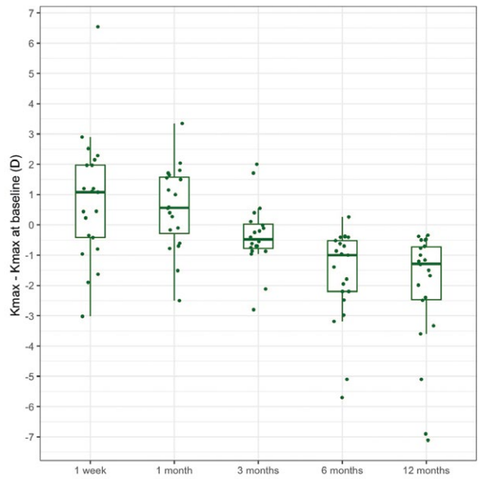
Only one type of adverse event recorded: **mild corneal haze** in 6% cases (state-of-the-art: ≥20%).[9]
The CXL procedure performed with C4V CHROMO4VIS and RitSight is **HIGHLY SAFE.**

CLINICAL VALIDATION OF THERANOSTICS

CROSS-LINKING FOR TREATMENT OF KERATOCONUS (REG.N.NCT05457647)[19,20]

K_{MAX} CHANGE IN TRUE POSITIVES OF STRATIFICATION GROUPS (1 year)

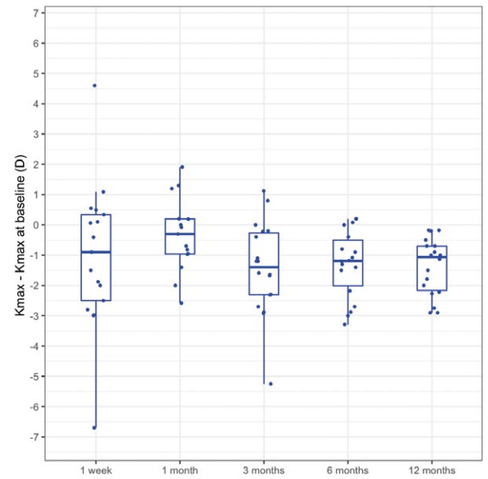
Theranostic CXL epi-off
K_{max} -2.1 ± 1.9 D



VS

State-of-the-art **CXL epi-off**
K_{max} -1.3 ± 1.4 D*

Theranostic CXL epi-on
K_{max} -1.3 ± 0.9 D



VS

State-of-the-art **CXL epi-on**
K_{max} -0.3 ± 1.5 D*

*References 7-9, 11-12

ANSWER TO STUDY HYPOTHESIS

The measurement of corneal **riboflavin concentration** and its **UV-A light mediated photo-activation** are the **primary factors** in determining the **therapeutic efficacy** of CXL.

Study Highlights

- Theranostics determines the efficacy of CXL procedure in real time, predicting its **therapeutic benefit**, which was confirmed at 12 months after treatment, with **high accuracy (91%)** and **precision (95%)**.
- **The clinical data** on efficacy of the CXL treatment performed with **C4V CHROMO4VIS** and **RitSight** are **superior compared with the state-of-the-art** CXL epi-off and epi-on protocols.

Conclusions

- Theranostics ushers in a new era in ophthalmology: **predictive**, **personalized** and **precision therapy**.
- Theranostics enables surgeons to personalize each CXL treatment based on the **predicted therapeutic benefit for every patient**.

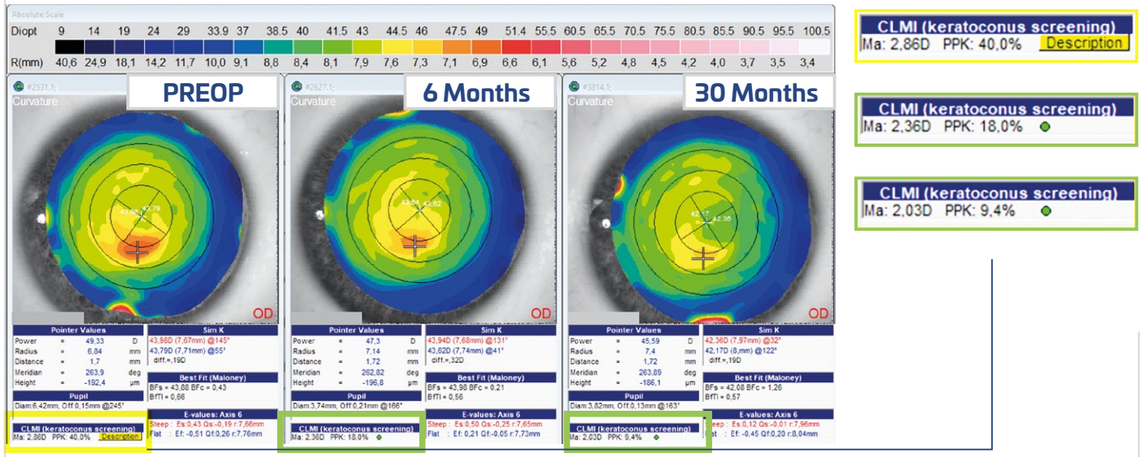
THE PARADIGM OF THERANOSTICS:

Clinical cases *(Images courtesy of Dr. Marco Lombardo)*

Keratoconus, 16 years

Theranostic-guided CXL
15 minutes RitSight application **(DE-EPITHELIZED CORNEA)**
UV-A light irradiation at 10 mW/cm^2 for 9 minutes

Riboflavin score= 1,71
Theranostic score= 0.85

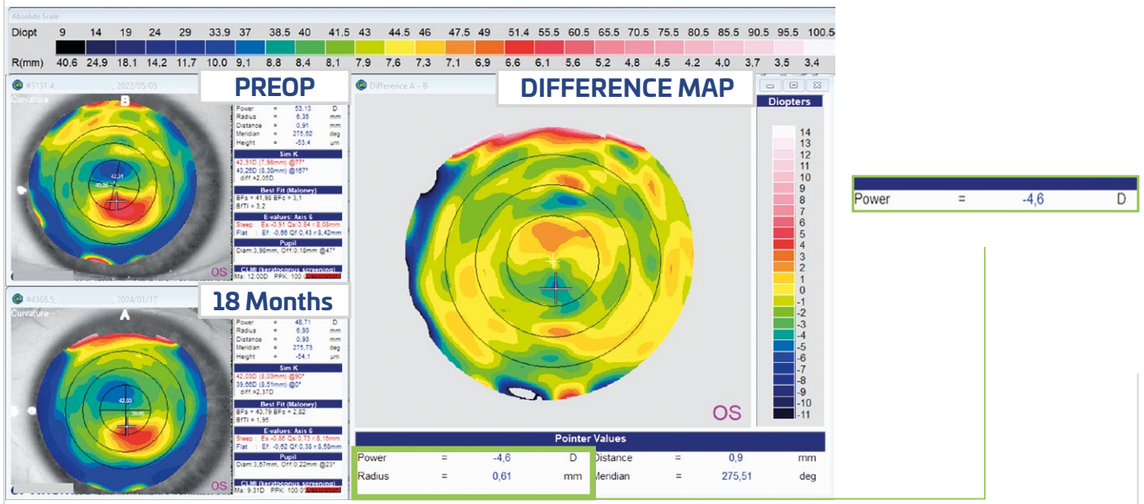


Clinical outcomes at 30 months follow-up: 3.7 D K_{max} flattening
The anterior corneal topography map normalized!

Keratoconus, 30 years

Theranostic-guided CXL
20 minutes RitSight application **(EPITHELIUM INTACT)**
UV-A light irradiation at 10 mW/cm^2 for 9 minutes

Riboflavin score= 0.48
Theranostic score= 0.72



Clinical outcomes at 18 months di follow-up: 4.6 D Kmax flattening
Visual acuity 20/20 with -5.25 sphere. **+6 EDTRS lines** gained from preoperatively (20/63 with 6.00 sphere)

EFFICACY IN REAL TIME

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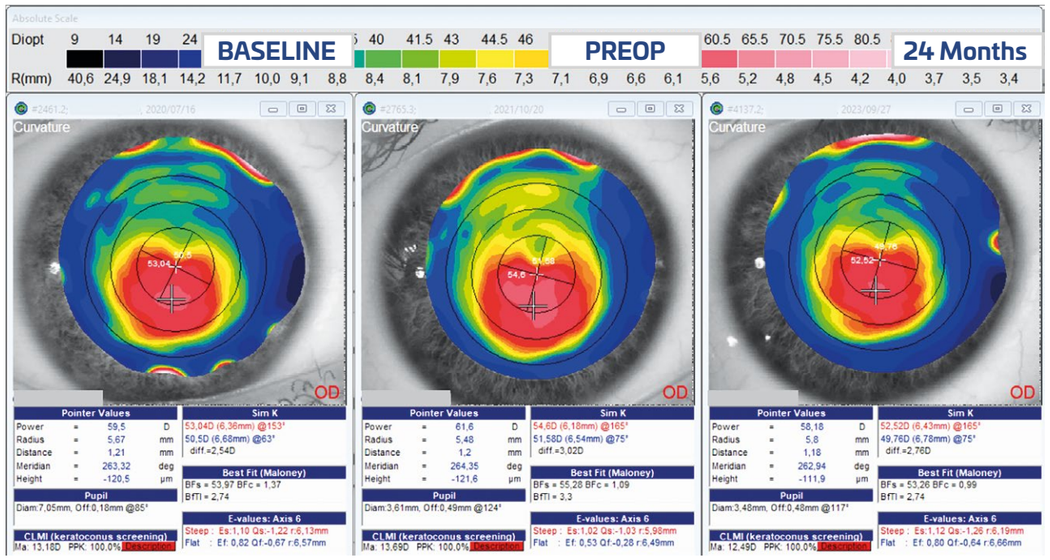
Clinical cases *(Images courtesy of Dr. Marco Lombardo)*

Keratoconus, 19 years. Treated by CXL epi-off in 2018
Evidence of progression (12 months: 2020-2021) 2.1 D K_{max} steepening

Theranostic-guided CXL
20 minutes RitSight application **(epithelium intact)**
UV-A light irradiation at 10 mW/cm^2 for 9 minutes

Riboflavin score= 0.70
Theranostic score= 0.90



Clinical outcomes at 24 months follow-up: 3.4 D K_{max} flattening
Retreatment with Thera-CXL effective and safe!

REGENSIGHT THERANOSTICS:

A TRANSFORMATIVE TECHNOLOGY ESTABLISHING THE NEW GOLD STANDARD IN KERATOCONUS TREATMENT

More clinical cases available at regensight.com

VISION ENGINEERING ITALY

Regensight is a Vision Engineering Italy's Company

Regensight elevates the gold standard for treatment of keratoconus at unparalleled level

Our value proposition

To be **patient centered** and **surgeon oriented.**

Our **goal** is to be representative of the **eye surgeons' needs** to **improve their patients' care.**

Social commitment

Regensight promotes **study** and **research** to improve the quality of life of patients with **keratoconus**.

The **Mario Lombardo research prize** is awarded annually to a **young researcher(under35)**, who is devoted to the study and research on keratoconus.

Certified quality

Regensight holds a UNI CEI EN ISO 13485:2021 quality management system for design, manufacturing management and marketing of ophthalmic active medical devices and related sterile accessories.

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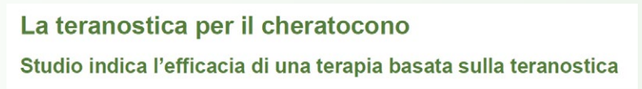
About us

CONCLUSIONS of META-ANALYSIS STUDY

*"Most effective method for **corneal cross-linking** is not known. **Theranostic UV-A device** measuring real-time corneal concentration of riboflavin, via acquisition and analysis of fluorescence emitted from riboflavin when illuminated by UV-A light (Marco Lombardo et al.) **to solve it**".*

Cochrane Eyes and Vision
(May 2022)



National press review on Regensight
Regensight (November 2023)

EU Startup News
(November 2023)

ESCRS iNovation

ESCRS iNovation Day
Emerging Company Showcase
(September 2024)

RegenSight
REGENERATE. IMPROVE

THERANOSTICS
SCIENTIFICALLY AND CLINICALLY VALIDATED

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This information is intended for healthcare professionals only.

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REGENERATE. IMPROVE

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Delivering life-changing therapies to patients with keratoconus