Individualized CXL in Ultra-Thin Corneas

The Sub400 Protocol

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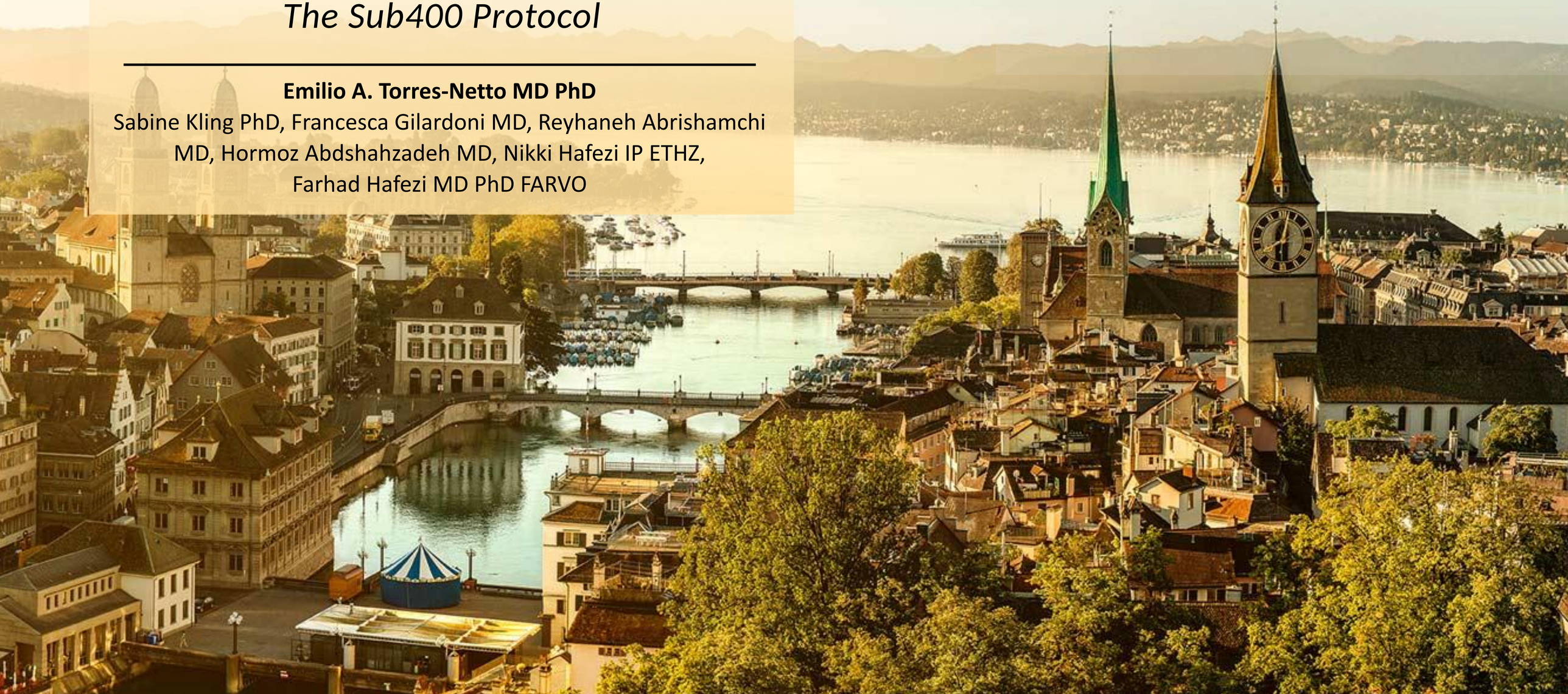
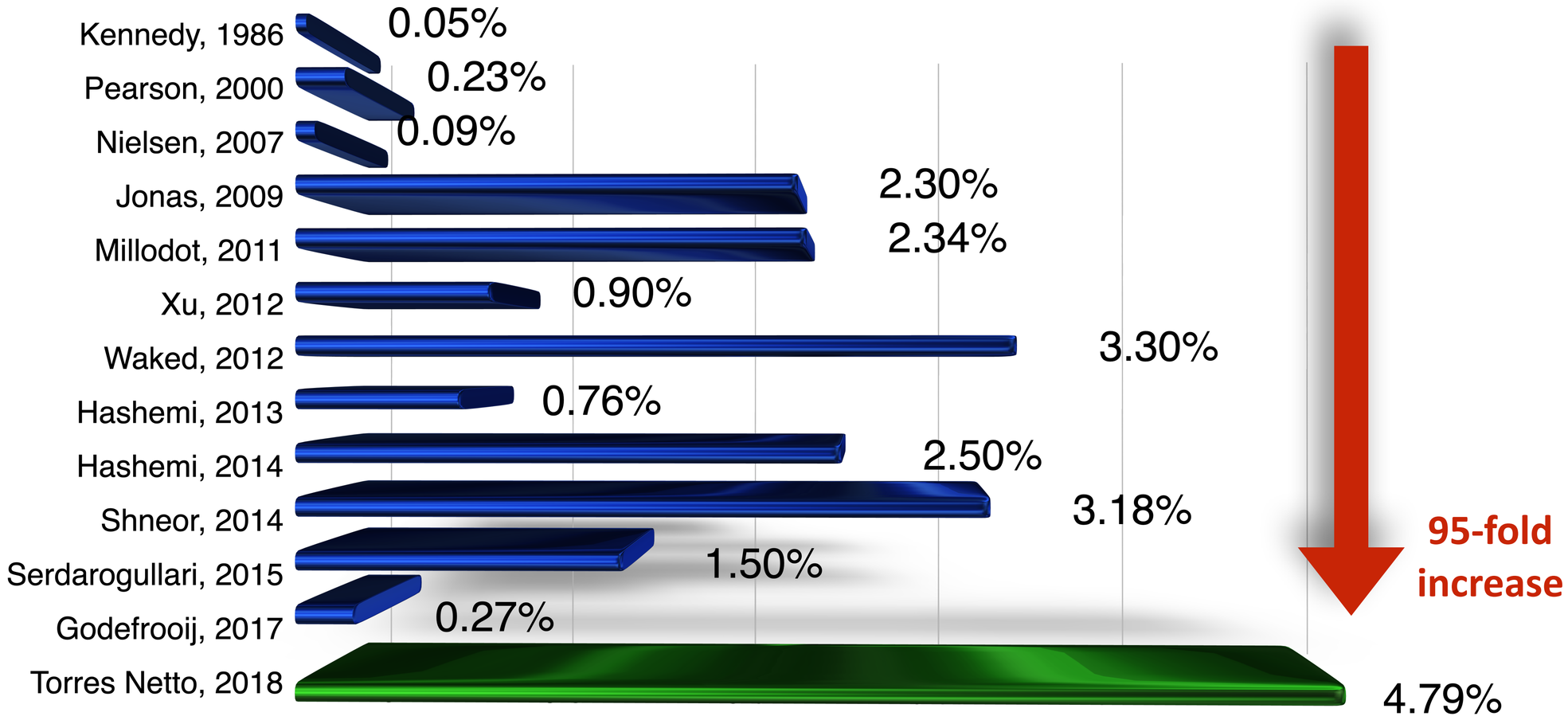
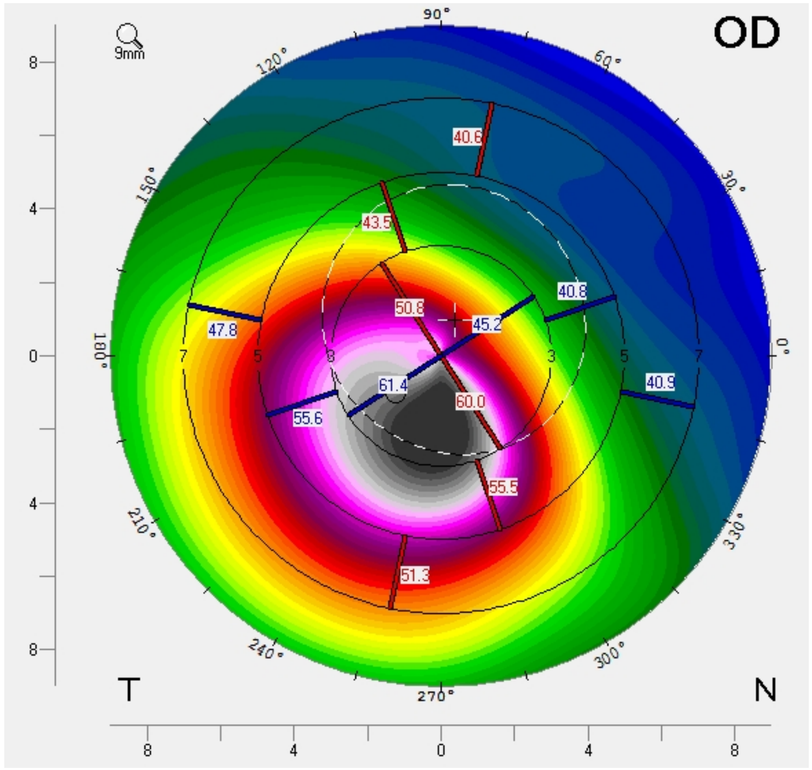


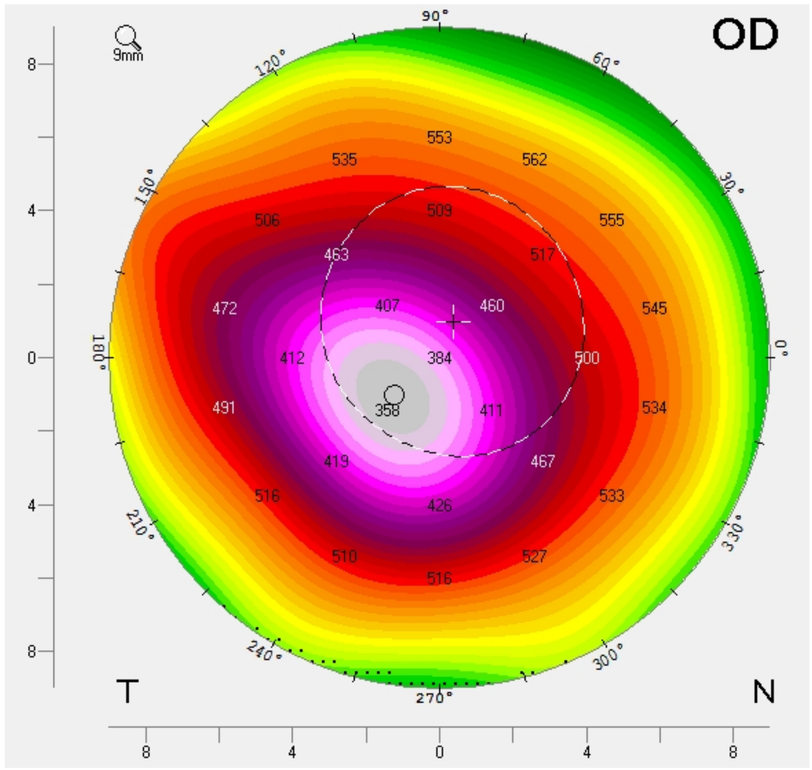
KC Prevalence reports worldwide



Adaptation of the CXL protocol for thin corneas

1. Background





thinnest point **356μm**
(with epithelium)

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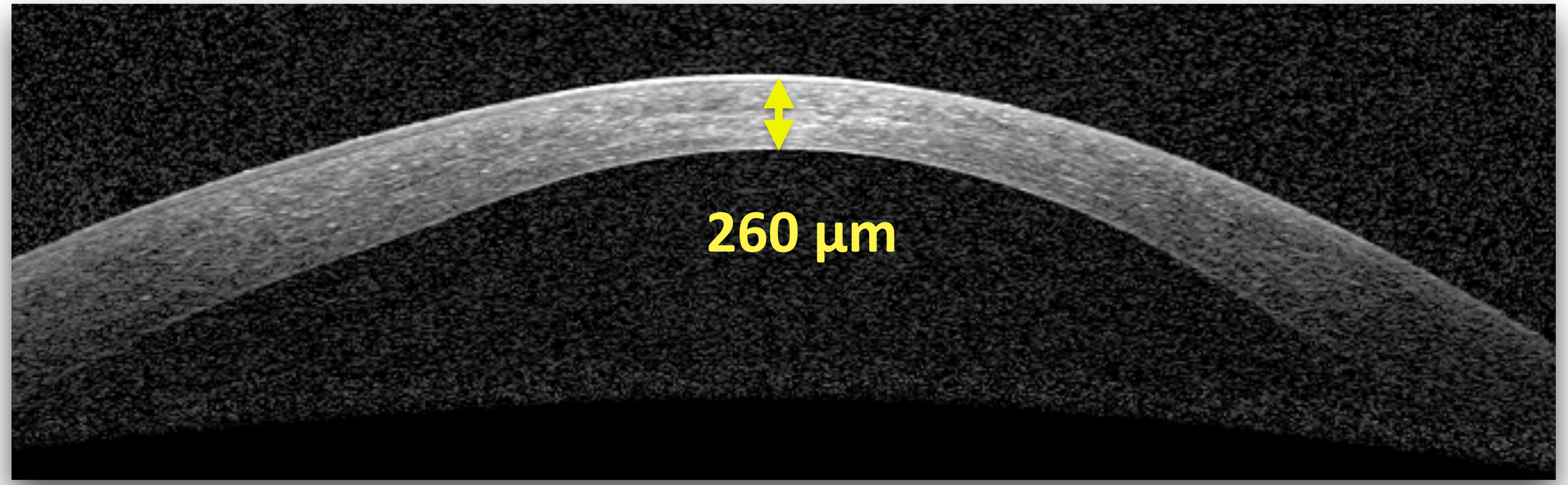
1. Background

Cornea of 260 µm - CXL?



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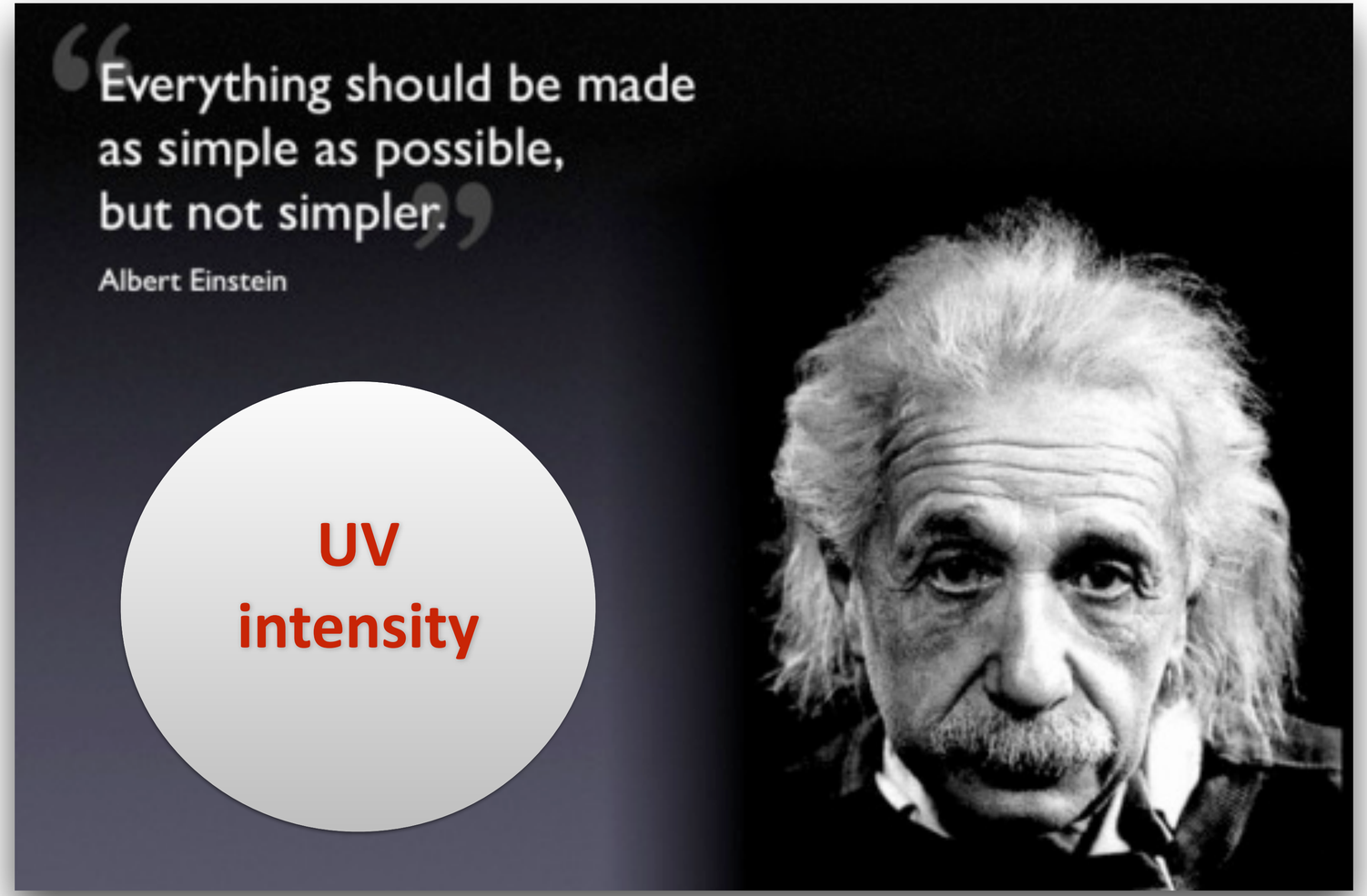
Adaptation of the CXL protocol for thin corneas

1. Background



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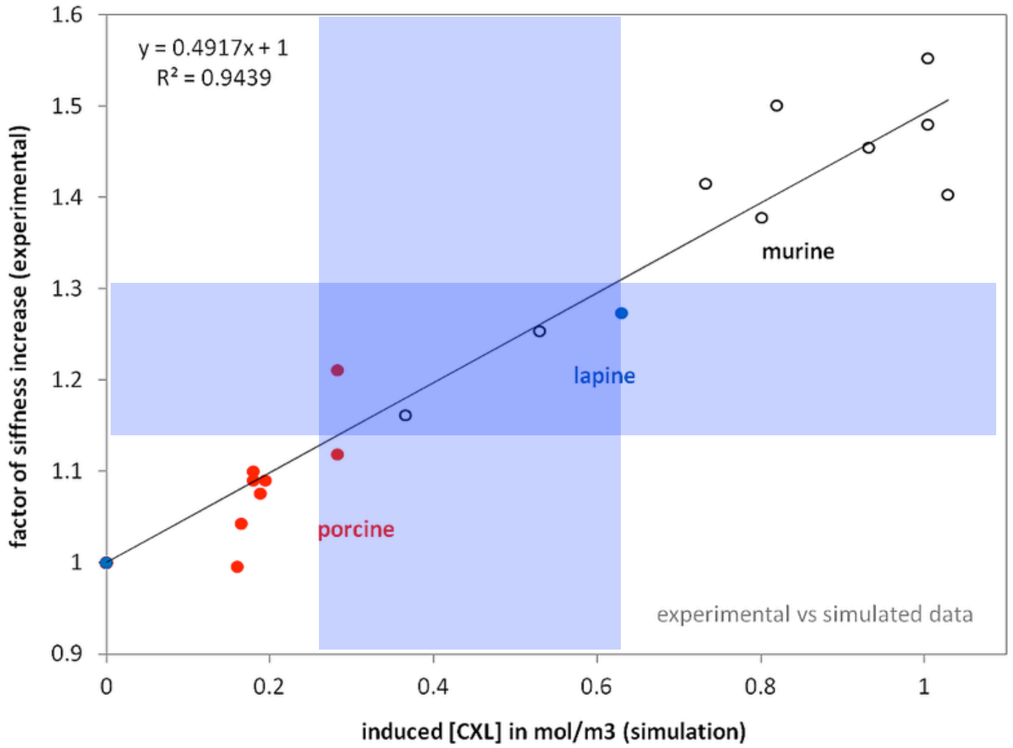
Do not adapt the cornea to the protocol.

Rather adapt the protocol to the cornea.

Predicting CXL efficacy with a model



Best range for CXL:

- significant stiffening
- no adverse effects

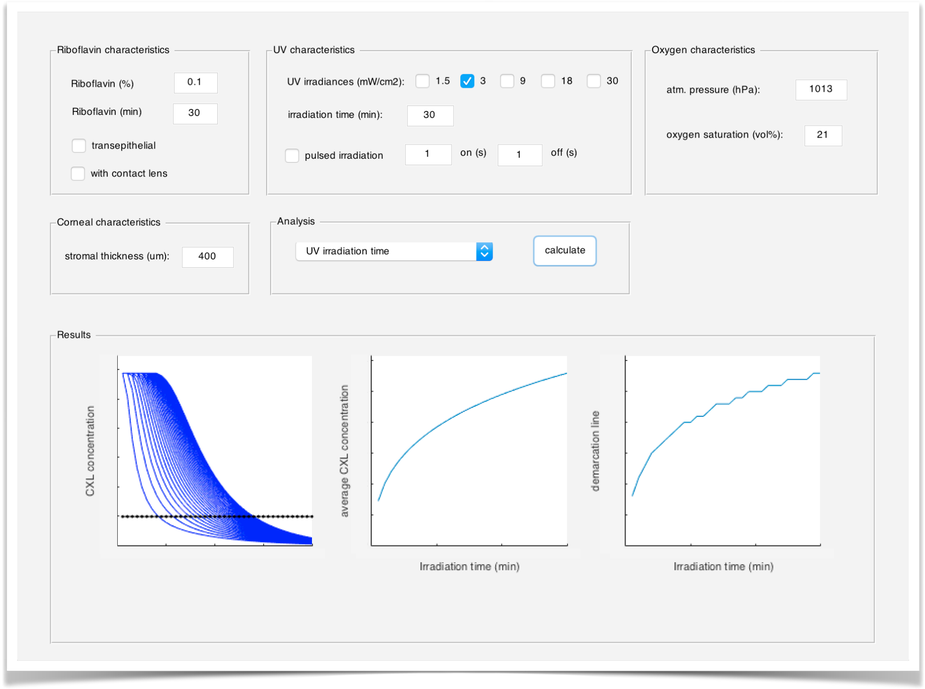
Linear relationship:
CXL-density determines the amount of corneal stiffening

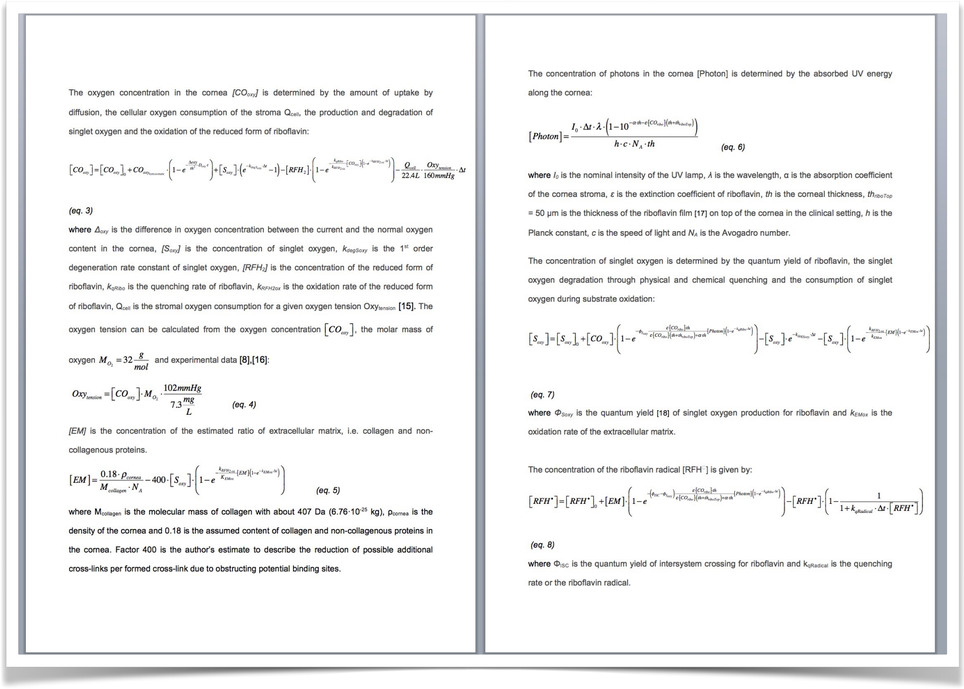
Kling et al., J Refr Surg, 2017

Nomogram for ultra-thin corneas

to individually settle irradiation time required for safe CXL treatment

1. Background





The oxygen concentration in the cornea $[CO_{corn}]$ is determined by the amount of uptake by diffusion, the cellular oxygen consumption of the stroma Q_{cell}, the production and degradation of singlet oxygen and the oxidation of the reduced form of riboflavin:

$$[CO_{corn}] = [CO_{corn}]_0 + CO_{corn_{source}} \cdot \left(1 - e^{-\frac{Sat^2}{\Delta_{corn}^2} \cdot t}\right) * [S_{corn}] \cdot \left(e^{k_{RFH_2Ox} \cdot [M]} - 1\right) - [RFH_2] \cdot \left(1 - e^{-k_{RFH_2Ox} \cdot [CO_{corn}] \cdot \left(1 - e^{-k_{RFH_2Ox} \cdot t}\right)}\right) - \frac{Q_{cell}}{22.4L} \cdot \frac{Oxy_{tension}}{160mmHg} \cdot \Delta t$$

(eq. 3)

where Δ_{Sorry} is the difference in oxygen concentration between the current and the normal oxygen content in the cornea, $[S_{corn}]$ is the concentration of singlet oxygen, $k_{degSorry}$ is the 1st order degeneration rate constant of singlet oxygen, $[RFH_2]$ is the concentration of the reduced form of riboflavin, k_{pRibo} is the quenching rate of riboflavin, k_{RFH2Ox} is the oxidation rate of the reduced form of riboflavin, Q_{cell} is the stromal oxygen consumption for a given oxygen tension $Oxy_{tension}$ [15]. The oxygen tension can be calculated from the oxygen concentration $[CO_{corn}]$, the molar mass of oxygen $M_{O_2} = 32\frac{g}{mol}$ and experimental data [8],[16]:

$$Oxy_{emission} = [CO_{corn}] \cdot M_{O_2} \cdot \frac{102mmHg}{7.3\frac{mg}{L}} \qquad \textit{(eq. 4)}$$

$[EM]$ is the concentration of the estimated ratio of extracellular matrix, i.e. collagen and non-collagenous proteins.

$$[EM] = \frac{0.18 \cdot \rho_{cornea}}{M_{collagen} \cdot N_A} - 400 \cdot [S_{corn}] \cdot \left(1 - e^{-\frac{k_{degSorry} \cdot [corn] \cdot \left(1 - e^{-k_{pRibo} \cdot t}\right)}{k_{pRibo}}}\right) \qquad \textit{(eq. 5)}$$

where $M_{collagen}$ is the molecular mass of collagen with about 407 Da ($6.76 \cdot 10^{-25}$ kg), ρ_{cornea} is the density of the cornea and 0.18 is the assumed content of collagen and non-collagenous proteins in the cornea. Factor 400 is the author's estimate to describe the reduction of possible additional cross-links per formed cross-link due to obstructing potential binding sites.

The concentration of photons in the cornea [Photon] is determined by the absorbed UV energy along the cornea:

$$[Photon] = \frac{I_0 \cdot \Delta t \cdot \lambda \cdot \left(1 - 10^{-\alpha \cdot th \cdot \varepsilon \cdot [CO_{corn}] \cdot \left(th + th_{RiboTop}\right)}\right)}{h \cdot c \cdot N_A \cdot th} \qquad \textit{(eq. 6)}$$

where I_0 is the nominal intensity of the UV lamp, λ is the wavelength, α is the absorption coefficient of the cornea stroma, ε is the extinction coefficient of riboflavin, th is the corneal thickness, $th_{RiboTop}$ = 50 µm is the thickness of the riboflavin film [17] on top of the cornea in the clinical setting, h is the Planck constant, c is the speed of light and N_A is the Avogadro number.

The concentration of singlet oxygen is determined by the quantum yield of riboflavin, the singlet oxygen degradation through physical and chemical quenching and the consumption of singlet oxygen during substrate oxidation:

$$[S_{corn}] = [S_{corn}]_0 + [CO_{corn}] \cdot \left(1 - e^{-\alpha_{corn} \cdot \frac{\varepsilon \cdot [CO_{corn}] \cdot th}{\varepsilon \cdot [CO_{corn}] \cdot th + \alpha \cdot th \cdot [Photon] \cdot \left(1 - e^{-k_{pRibo} \cdot t}\right)}}\right) - [S_{corn}] \cdot e^{-k_{degSorry} \cdot t} - [S_{corn}] \cdot \left(1 - e^{-\frac{k_{RFH2Ox} \cdot [EM] \cdot \left(1 - e^{-k_{pRibo} \cdot t}\right)}{k_{pRibo}}}\right)$$

(eq. 7)

where Φ_{Sorry} is the quantum yield [18] of singlet oxygen production for riboflavin and k_{EMox} is the oxidation rate of the extracellular matrix.

The concentration of the riboflavin radical $[RFH^{\cdot}]$ is given by:

$$[RFH^{\cdot}] = [RFH^{\cdot}]_0 + [EM] \cdot \left(1 - e^{-\frac{\left(\Phi_{Sorry} - \alpha_{corn}\right) \cdot \varepsilon \cdot [CO_{corn}] \cdot th}{\varepsilon \cdot [CO_{corn}] \cdot th + \alpha \cdot th \cdot [Photon] \cdot \left(1 - e^{-k_{pRibo} \cdot t}\right)}}\right) - [RFH^{\cdot}] \cdot \left(1 - \frac{1}{1 + k_{pRadical} \cdot \Delta t \cdot [RFH^{\cdot}]}\right)$$

(eq. 8)

where Φ_{ISC} is the quantum yield of intersystem crossing for riboflavin and $k_{pRadical}$ is the quenching rate or the riboflavin radical.

Kling et al., J Refr Surg, 2017

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Fixed Fluence (5.4 J/cm²)

400 µm

300 µm

Fixed Fluence (5.4 J/cm²)

400 µm

300 µm

Hipo-osmolaric

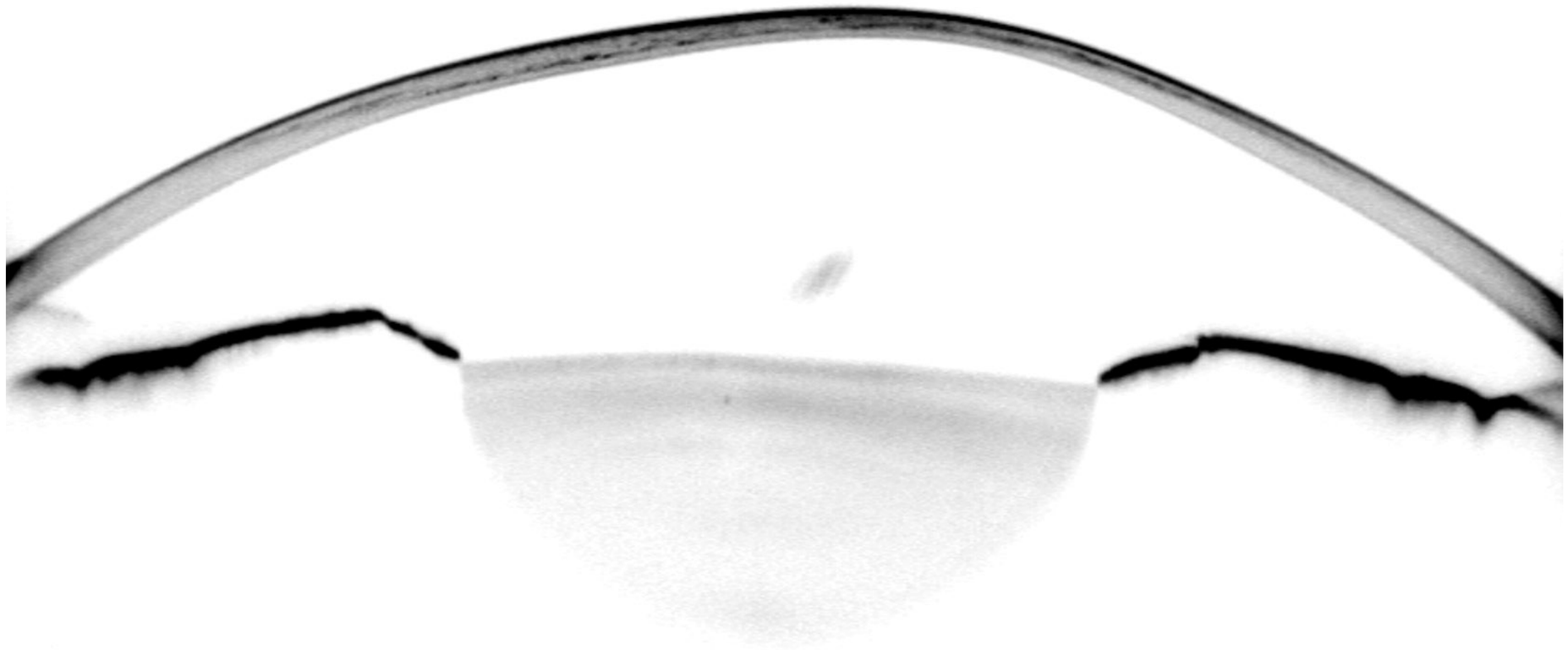
Contact lens-assisted

Individual Fluence

400 µm	300 µm	200 µm
		
3mW/cm² for 30’	*3mW/cm² for xxx’*	*3mW/cm² for xxx’*
5.4 J/cm²	xxx J/cm²	xxx J/cm²

Purpose

To analyse if individualized CXL with shorter irradiation times is able to stop keratoconus progression up to 12 months after treatment.



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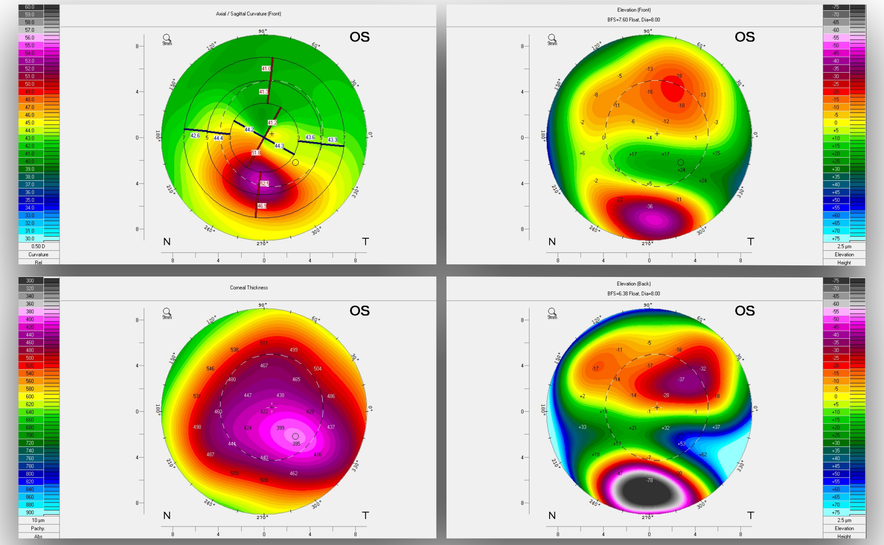
Methods

- **47 progressive keratoconus** eyes (ΔK_{max}>1D / year) of 35 patients
- Corneal thickness **≤ 400µm** directly before UV irradiation



Case Example 9

C X L

Individually adjusted irradiation time

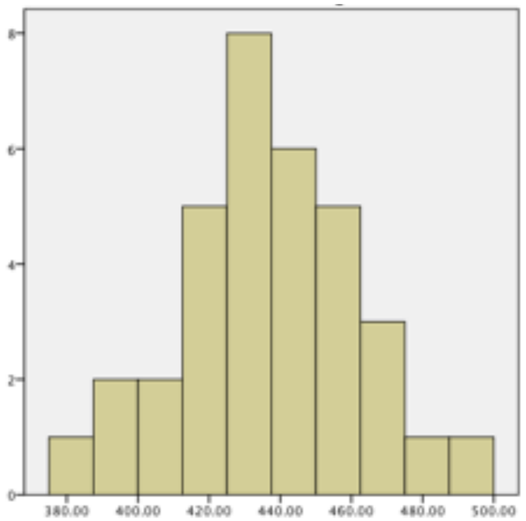
(irradiance 3mW/cm²)

Treatment Protocol

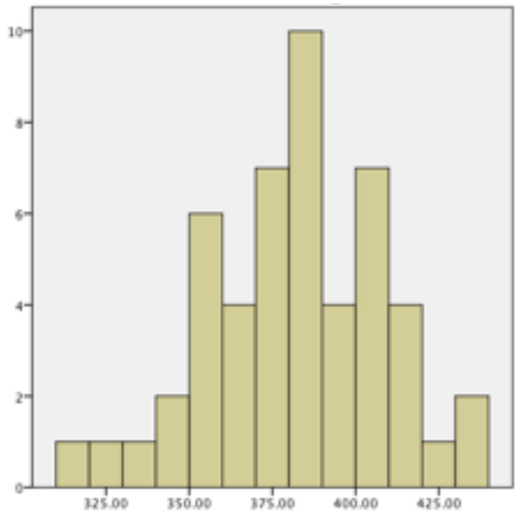
EPITHELIUM REMOVAL

SOAKING

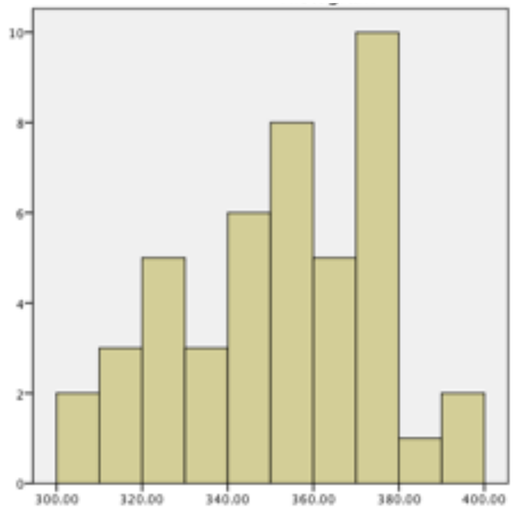
0.1% hypoosmolar riboflavin (30q2)



Pre-op thickness



Post-abrasio thickness



Post-ribo thickness

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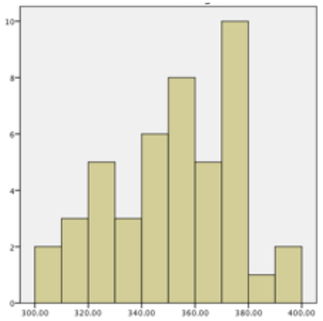
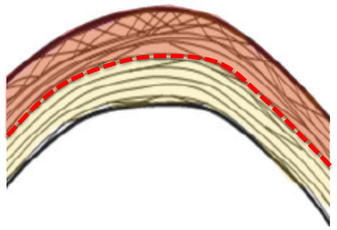
Treatment Protocol

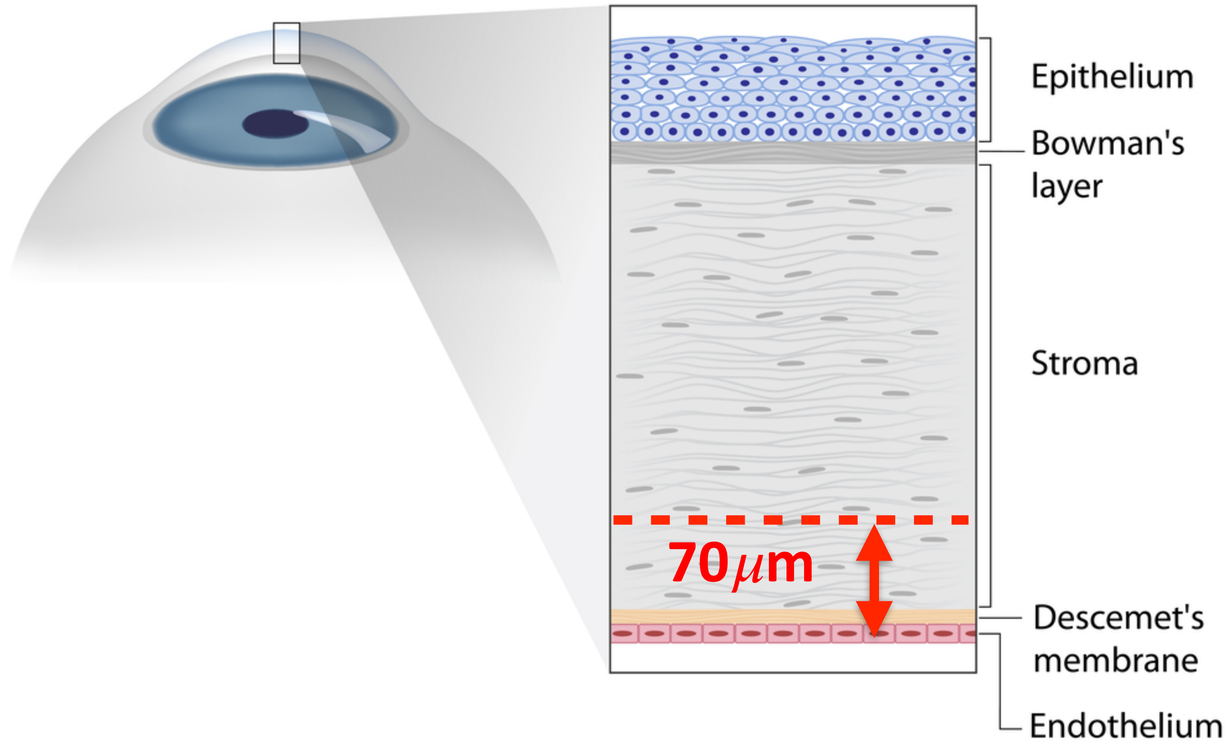
Post-ribo thickness



+



Desired demarcation line



Required UV irradiation time

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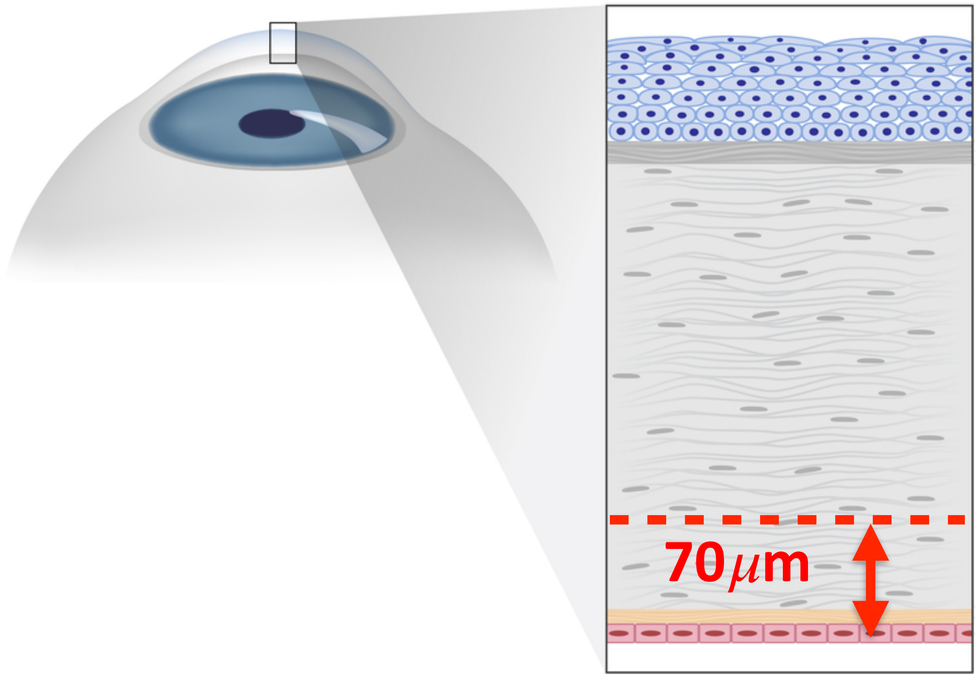
Treatment Protocol



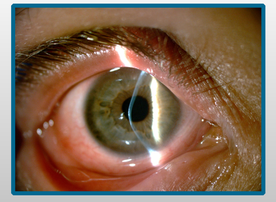
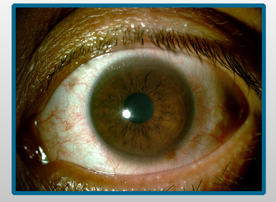
Required UV irradiation time

TABLE 2. Table Describing the Individual Fluence in Increments of 10 μm

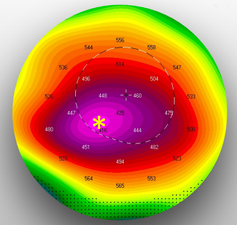
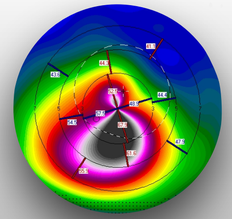
Individualized CXL		
Sub400 Protocol		
Minimum Stromal Required Thickness (μm)	UV Irradiation Duration (min)	Demarcation Line Depth (μm)
200	1	130
210	01:20	140
220	01:40	150
230	2	160
240	02:30	170
250	3	180
260	03:30	190
270	4	200
280	5	210
290	6	220
300	7	230
310	9	250
320	10	255
330	12	265
340	14	275
350	16	283
360	18	290
370	20	300
380	23	310
390	26	320
400	29	330

CXL = corneal cross-linking; UV = ultraviolet.

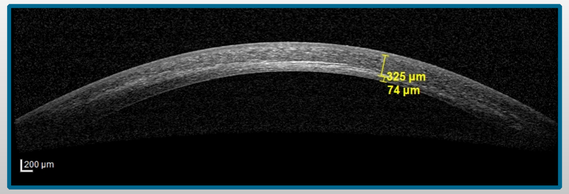
Follow-up

Clinical
1week, 6 and 12 month

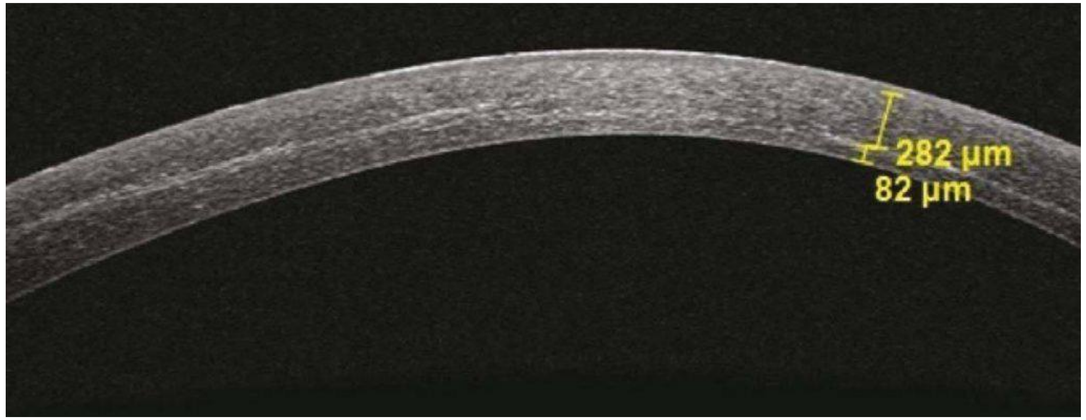



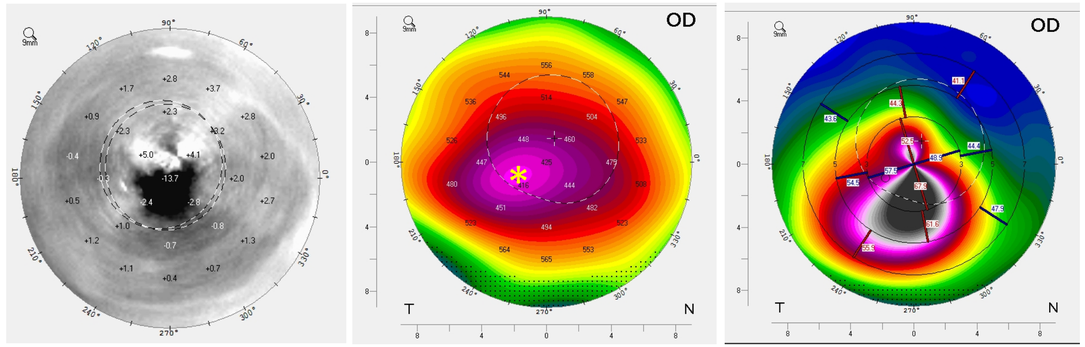
Scheimpflug
1, 12 month post-op

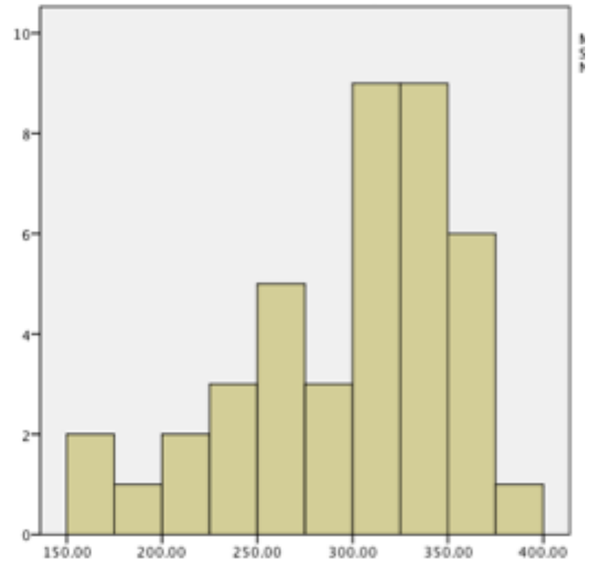


OCT
1 month post-op

Demarcation line at 1-month







Median demarcation line depth:

307 μm

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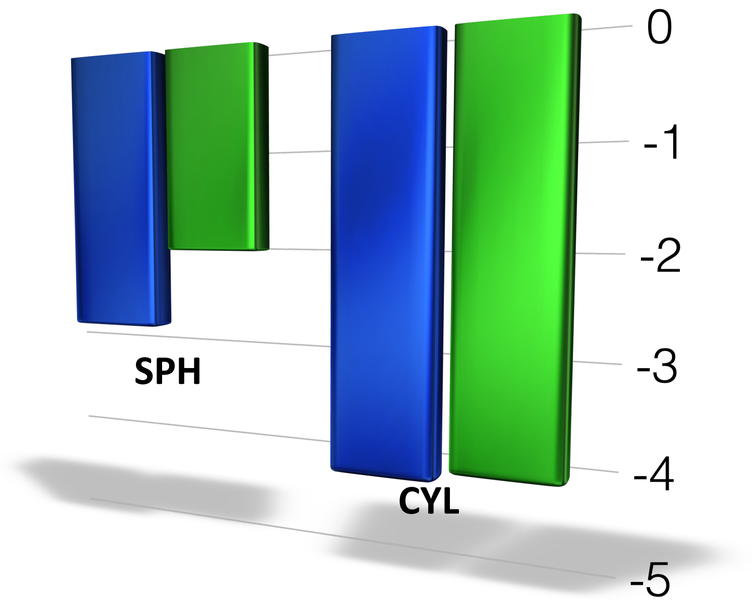
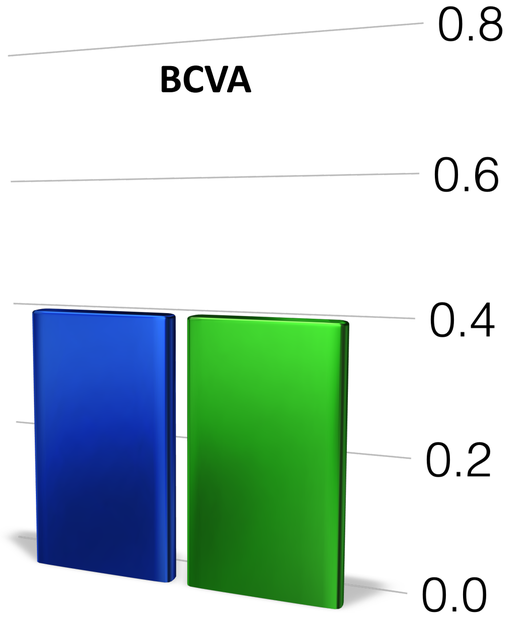
Refraction



Visual Performance



NO significant changes

Pre-op 1-year-post

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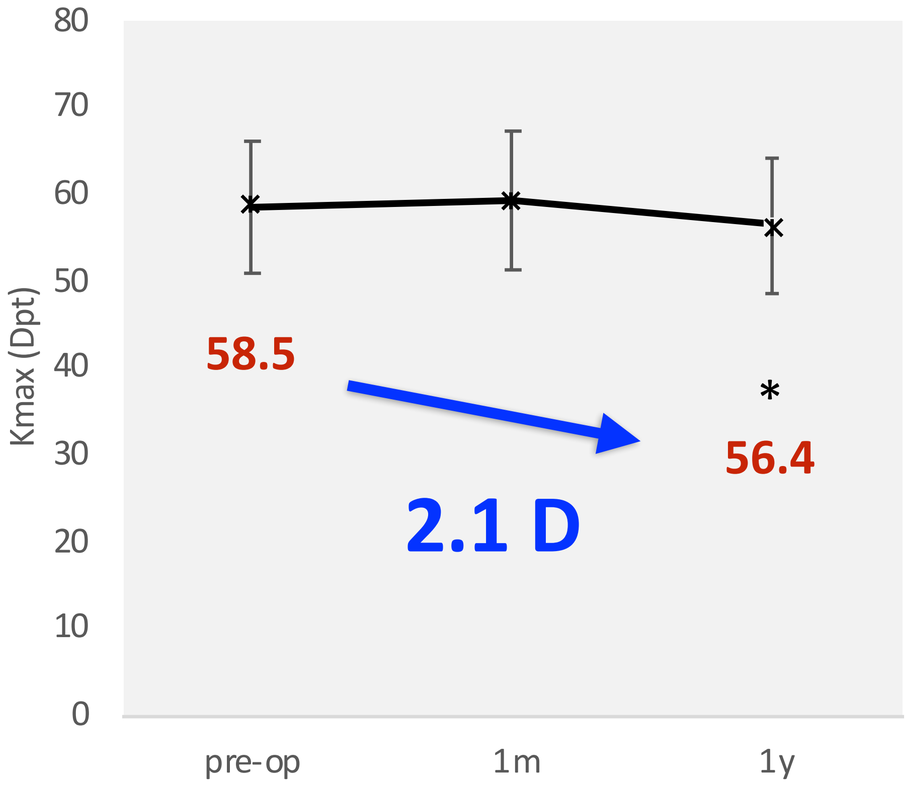
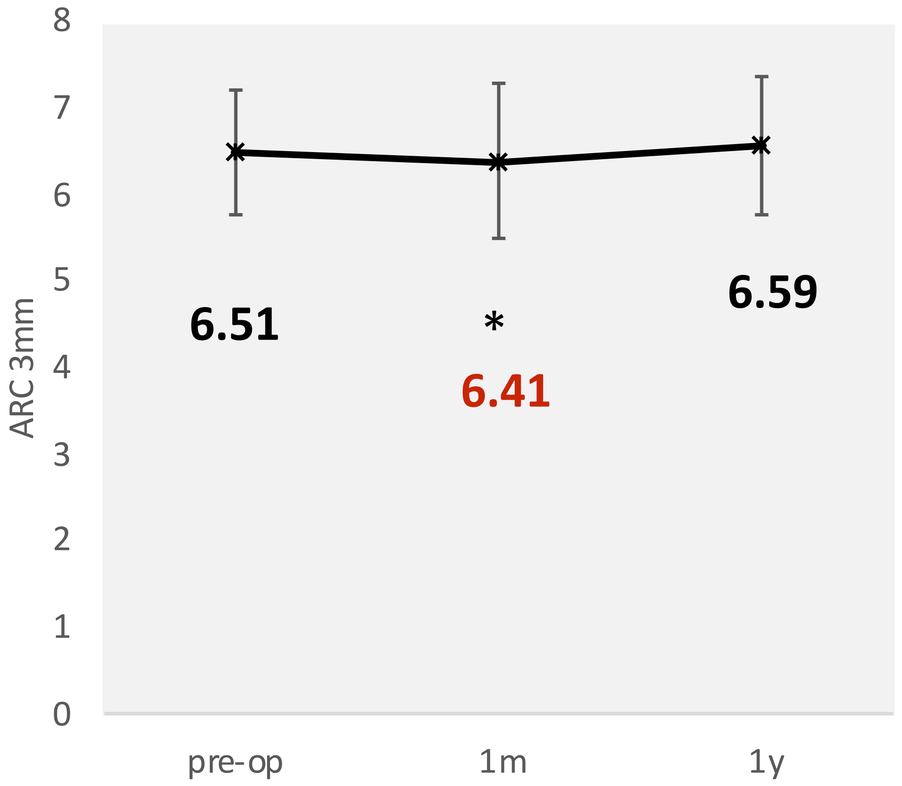
Individualized CXL - sub400 protocol

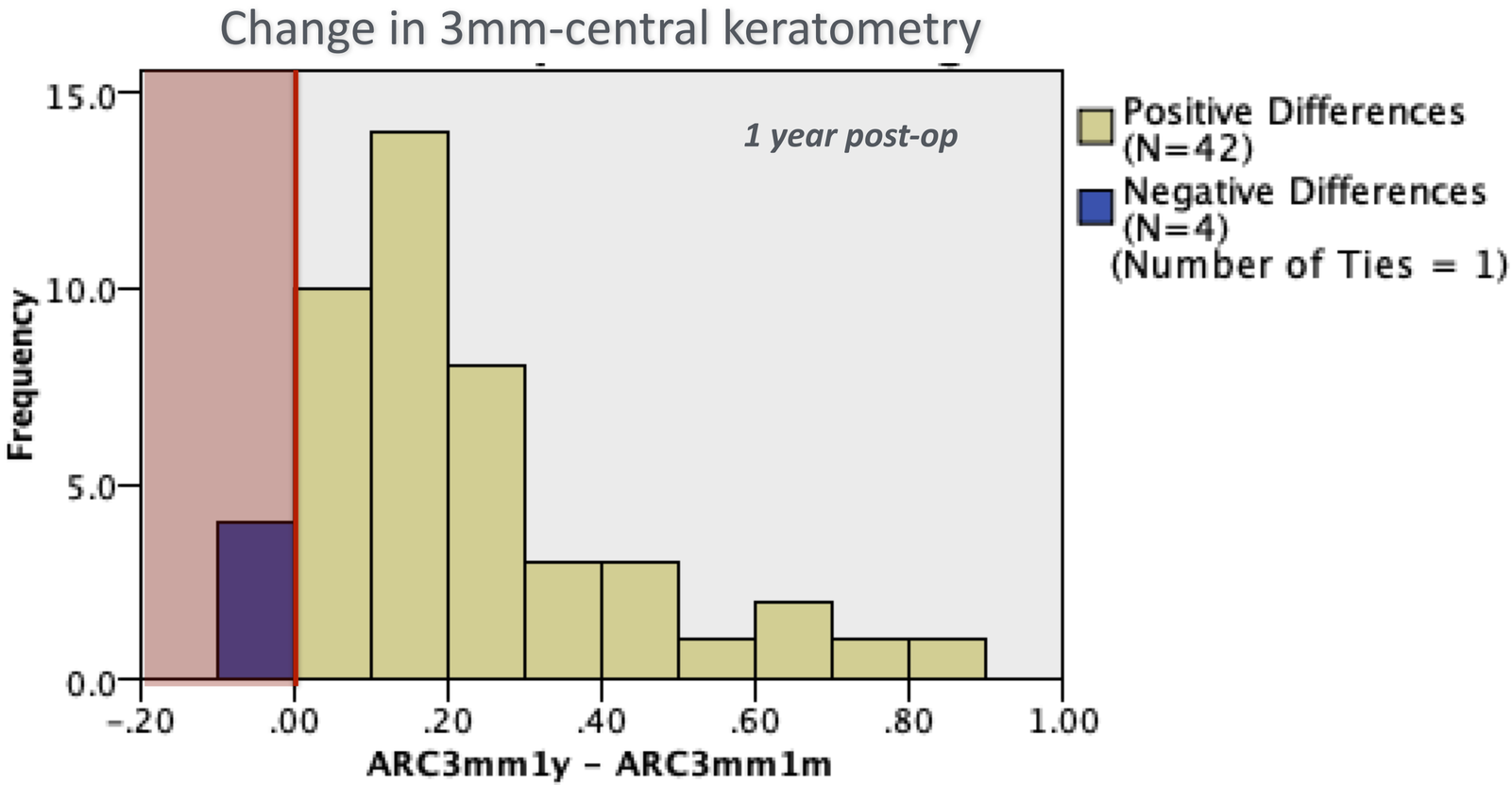
K Max



Central 3mm radius



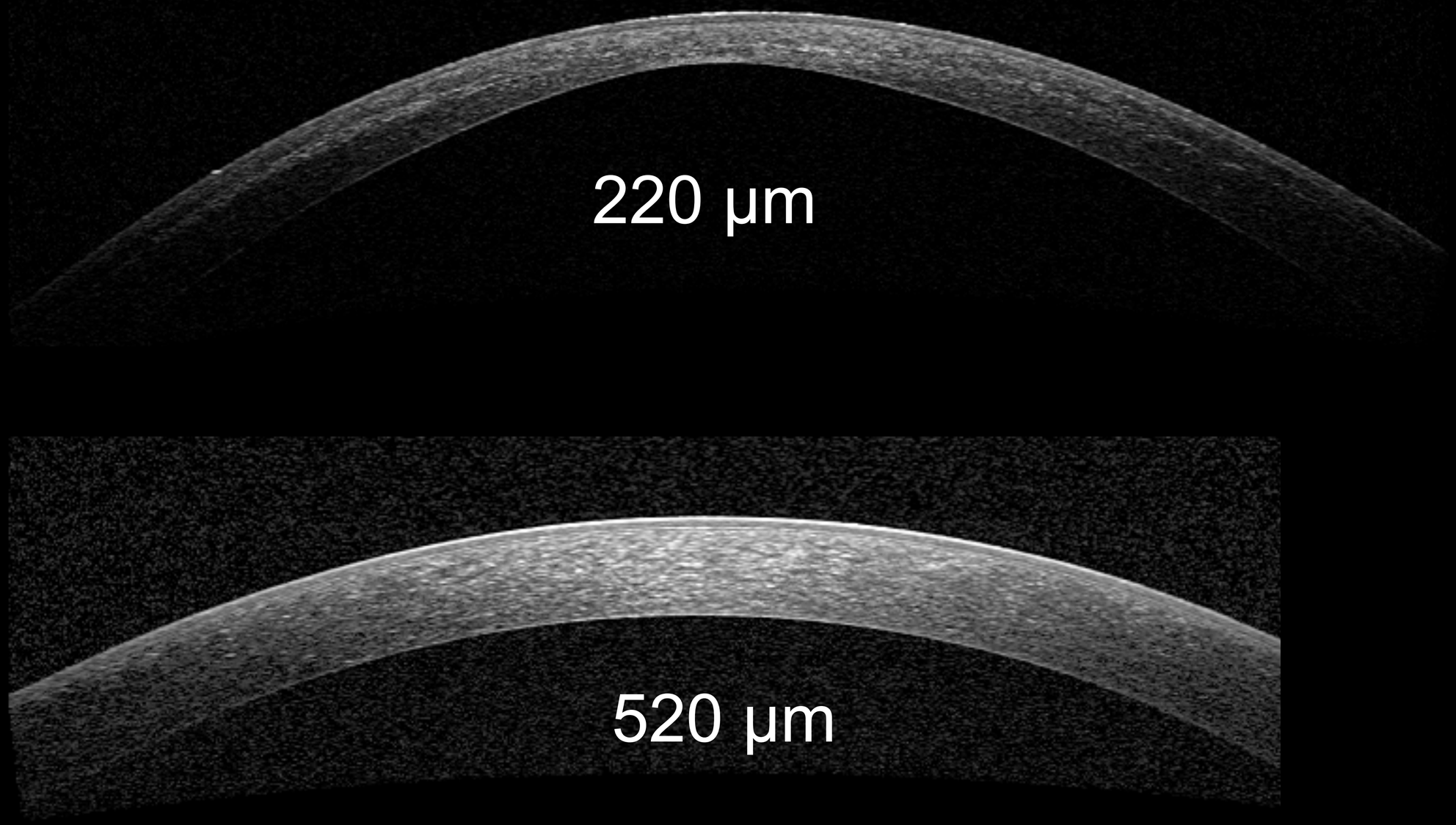
Individualized CXL - sub400 protocol



Median change: **-2.1D (Kmax)**

Failure rate: 8.6%

The sub400 protocol: Individualized CXL



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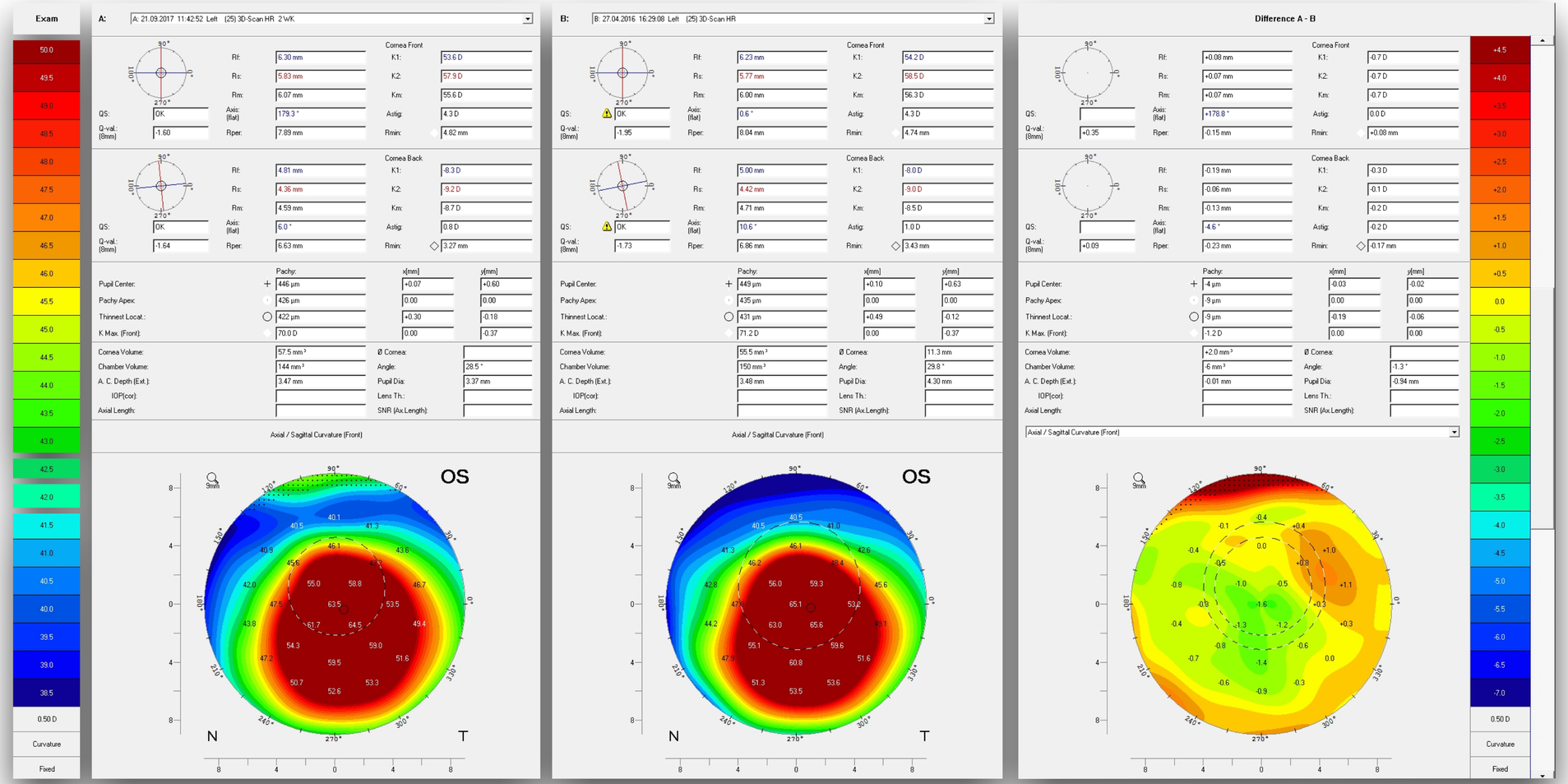
1. Background

2. Purpose

3. Methods

4. Results

1-year post-op



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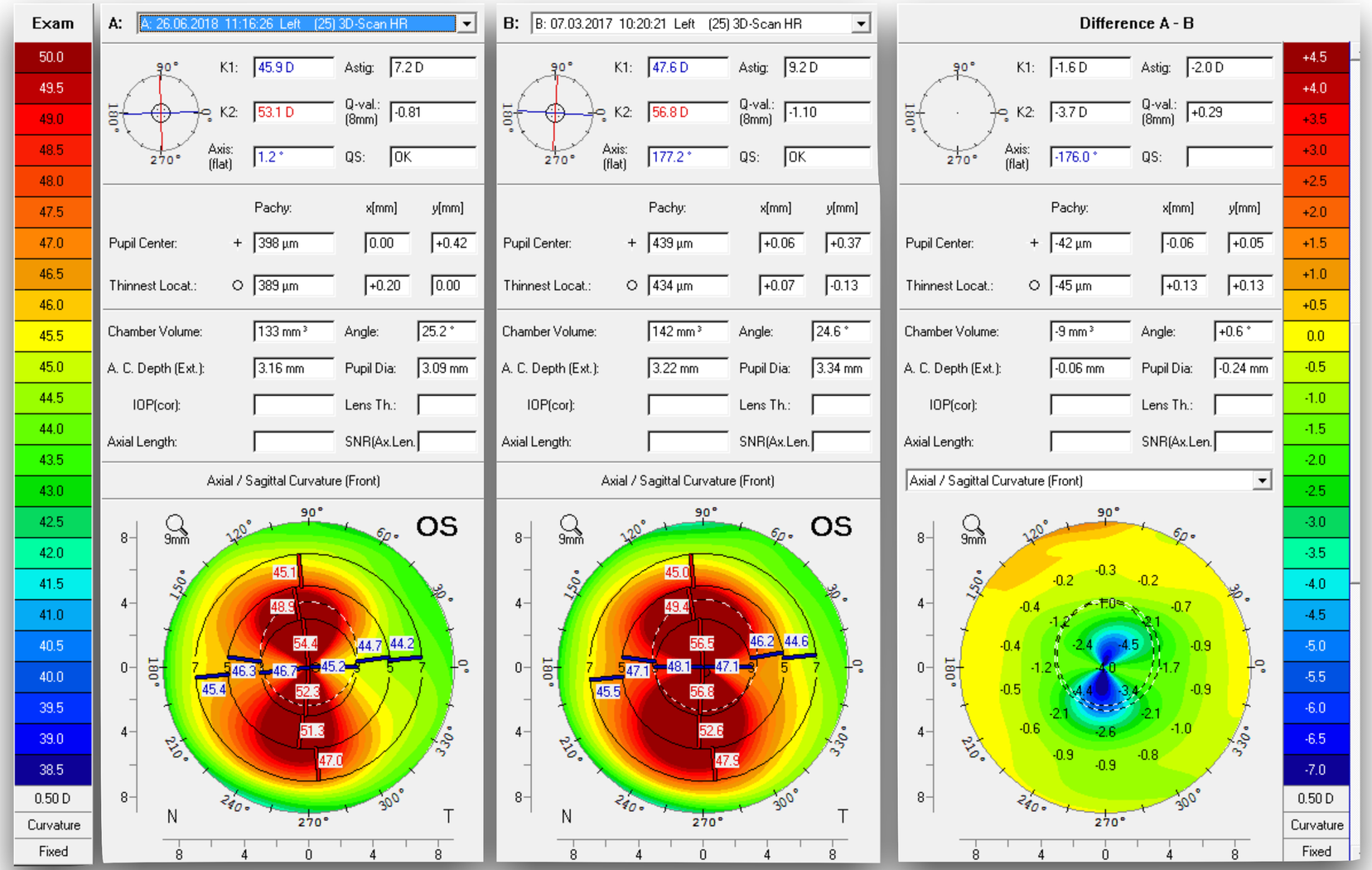
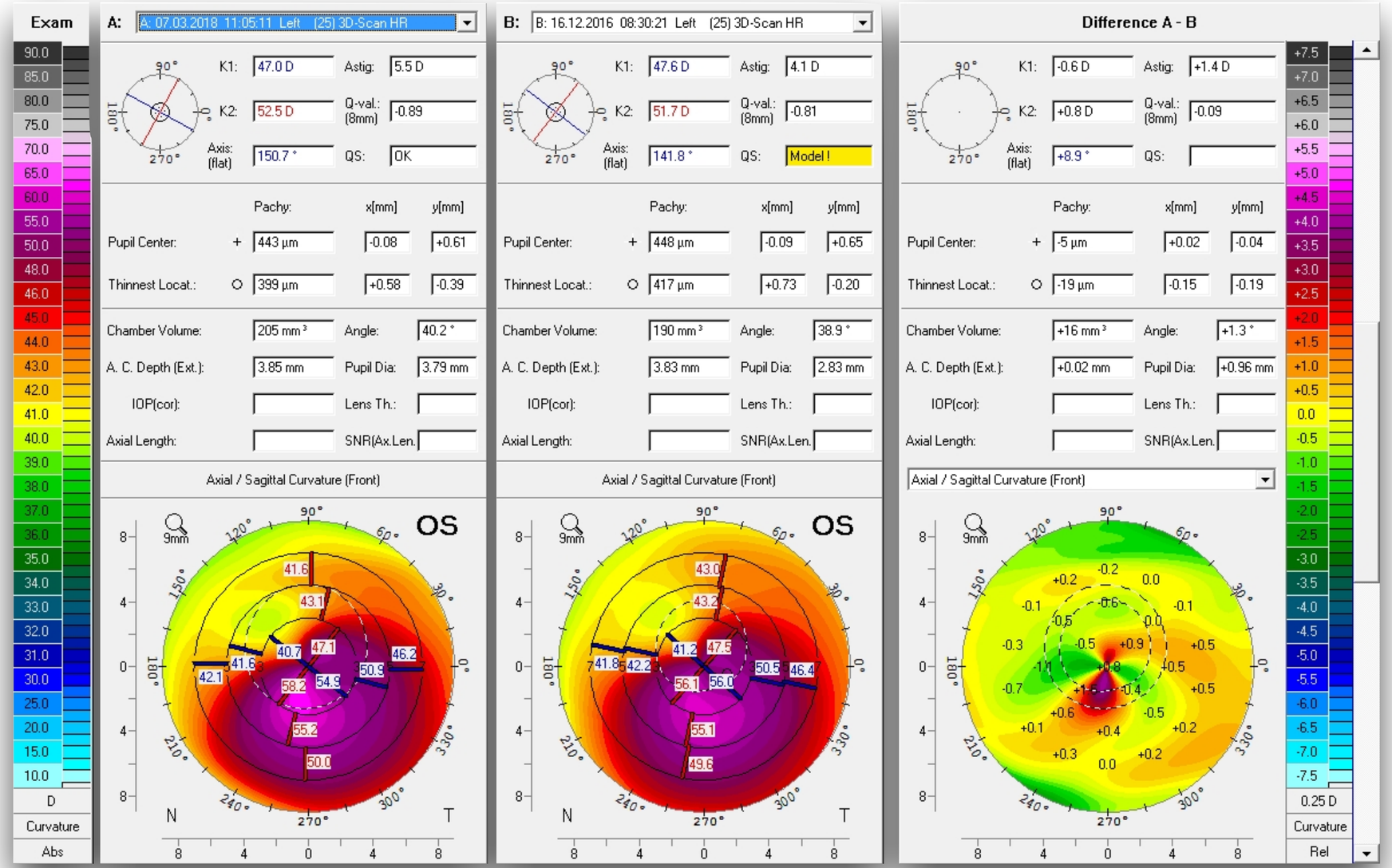
1-year post-op



1-year post-op



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Final messages

- **Individualized CXL with „Sub400 Protocol“ show promising results in halting KC progression in ultra-thin corneas;**
- **Treatments down to 220 um of stroma are possible**
- **Treatment makes sense if useful vision can be provided**
- **One-year failure rate is slightly higher than standard CXL (9% vs 7%);**
- **New nomogram is able to treat and brings new perspectives to treatment of ultra-thin corneas with keratoconus.**

THANK YOU

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