Model-Based Prediction of Crosslinking Outcomes

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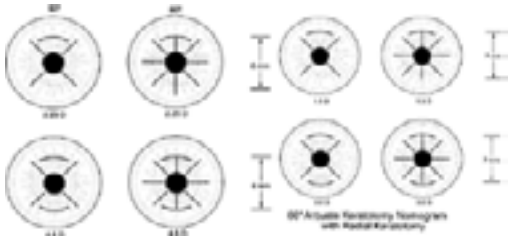
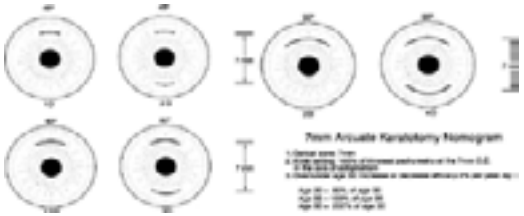
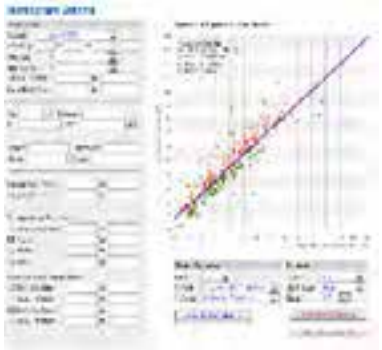
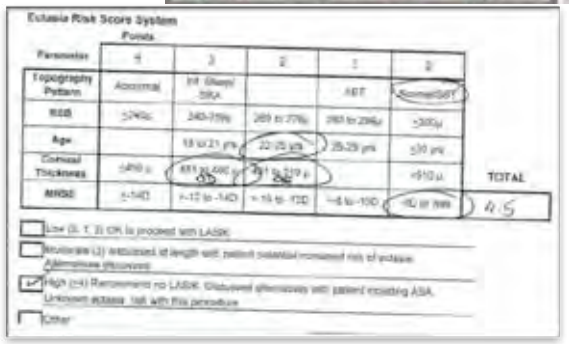
Disclosures: Intellectual property in biomechanical measurement & modeling (Cleveland Clinic/OptoQuest), Avedro (research), Ziemer (consultant), Zeiss (research)

Clinical Nomograms for Corneal Surgery Planning







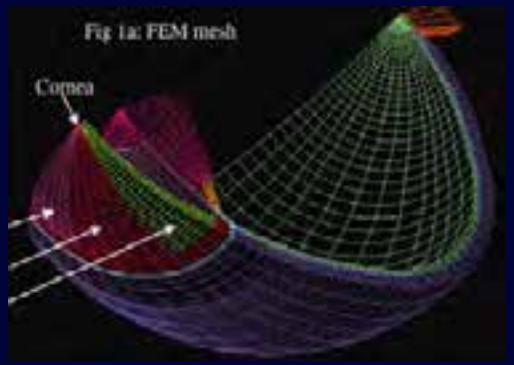


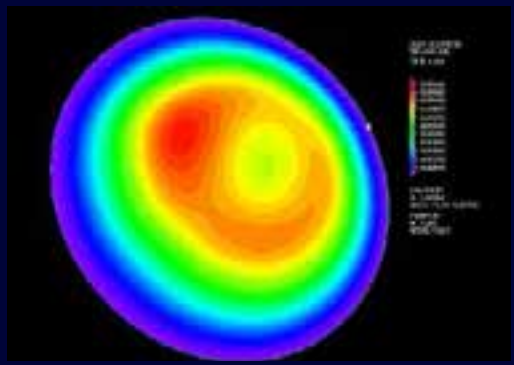
All share mechanistic pathways mediated by biomechanics;
Yet there is no unifying clinical decision pathway

The Cornea: An Ideal Target for Simulation-Based Medicine

- Exquisite structure-function relationship
- Accessible for measurement
- Clinical applications that appeal directly to structural mechanics

Macro-effects of CXL: Computational Modeling Analyses





Geometry

Material properties

FE Mesh

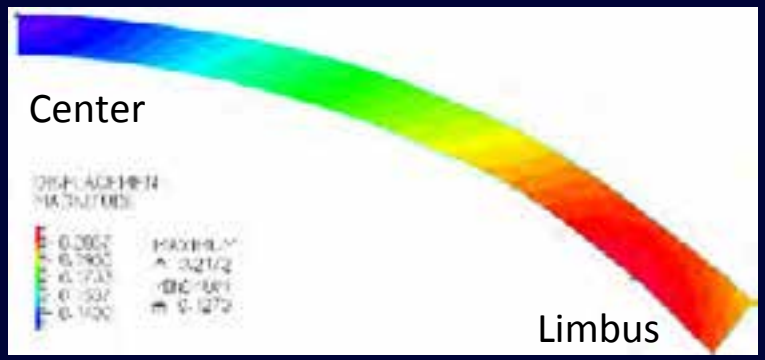
Simulation

Load

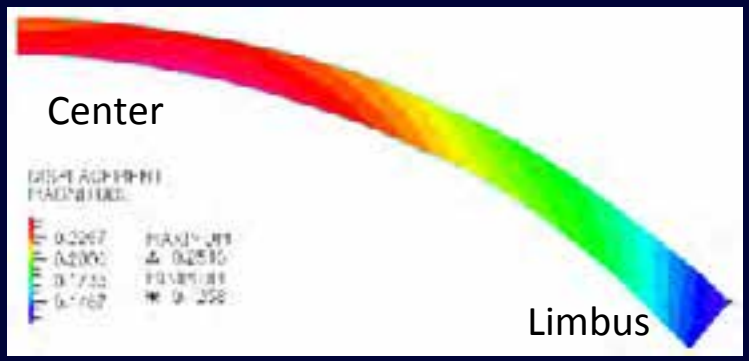
Stress/strain/shape & optical solutions

Displacements after myopic LASIK with different corneal material properties

High stiffness => overcorrection



Low stiffness=> undercorrection (± ectasia)



Sinha Roy and Dupps, JRS 2009

Modified treatment approaches for customization and optimization

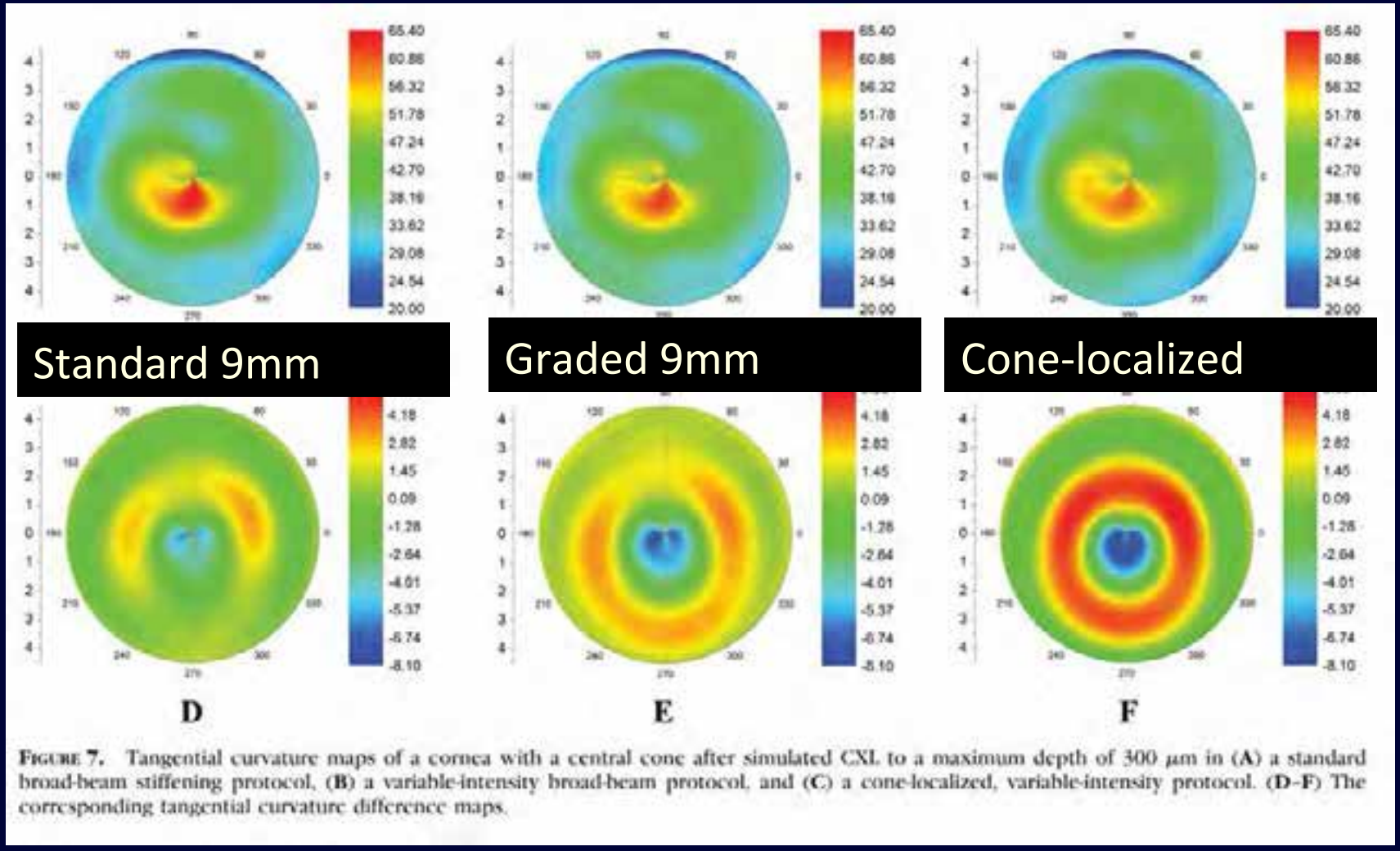


FIGURE 7. Tangential curvature maps of a cornea with a central cone after simulated CXL to a maximum depth of 300 μm in (A) a standard broad-beam stiffening protocol, (B) a variable-intensity broad-beam protocol, and (C) a cone-localized, variable-intensity protocol. (D–F) The corresponding tangential curvature difference maps.

Sinha Roy & Dupps, IOVS 2011

Response to modified treatment approach

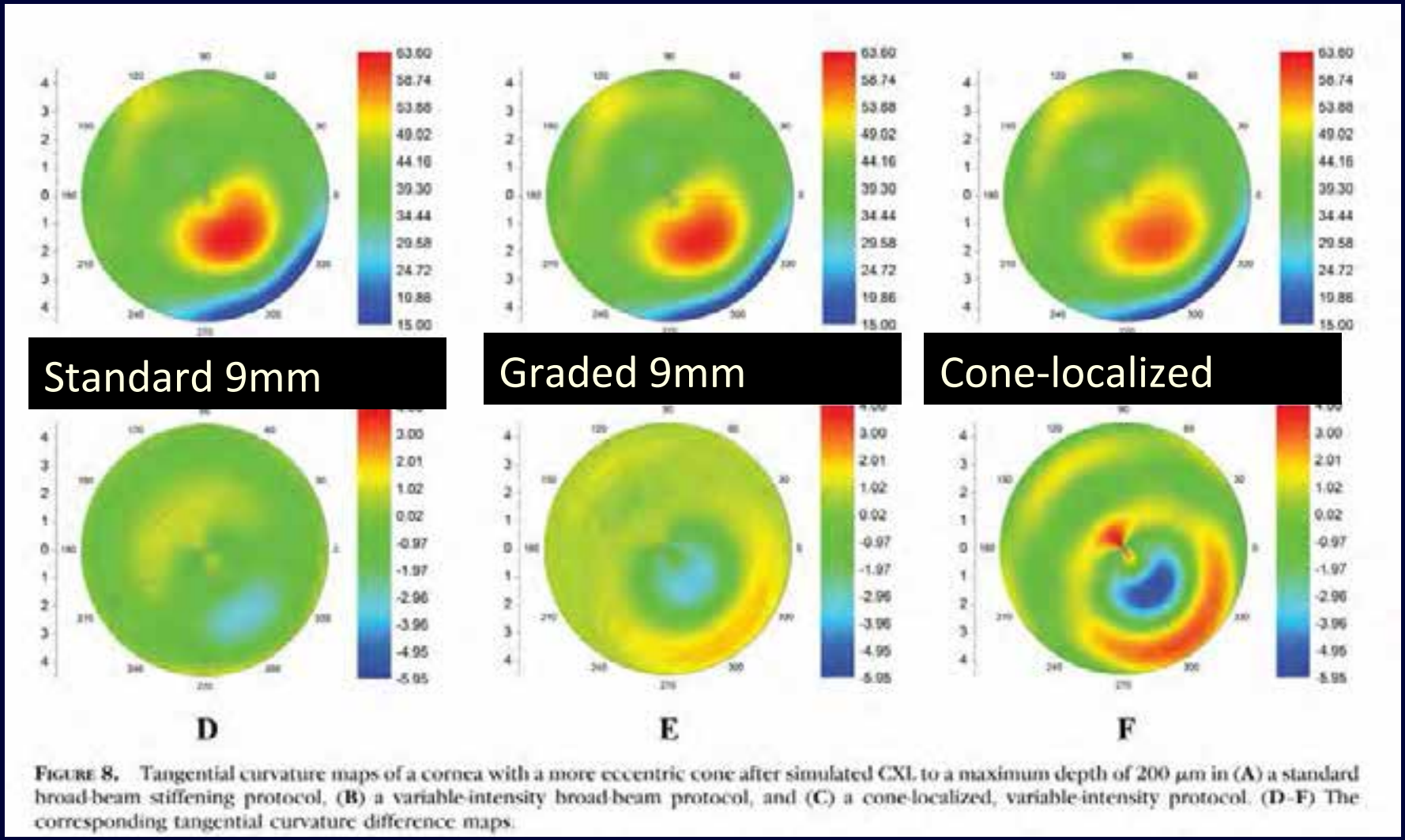
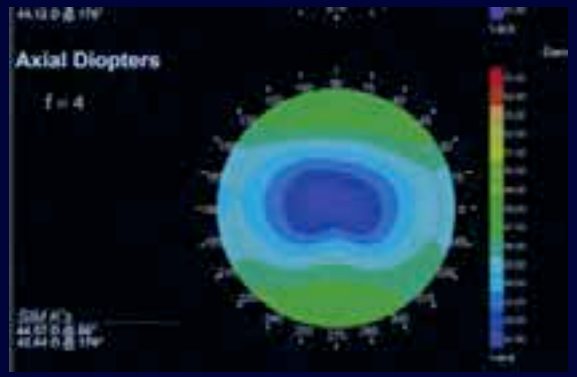


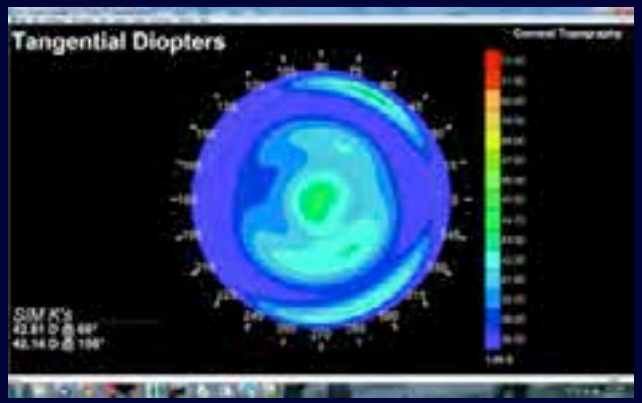
FIGURE 8. Tangential curvature maps of a cornea with a more eccentric cone after simulated CXL to a maximum depth of 200 μm in (A) a standard broad-beam stiffening protocol, (B) a variable-intensity broad-beam protocol, and (C) a cone-localized, variable-intensity protocol. (D–F) The corresponding tangential curvature difference maps.

Sinha Roy & Dupps, IOVS 2011

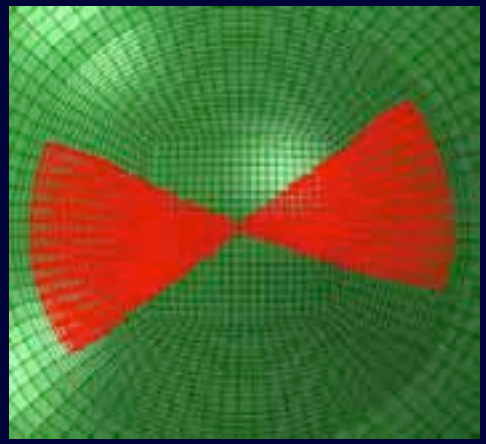
Virtual trials of novel non-ablative refractive treatments



Myopia



Hyperopia

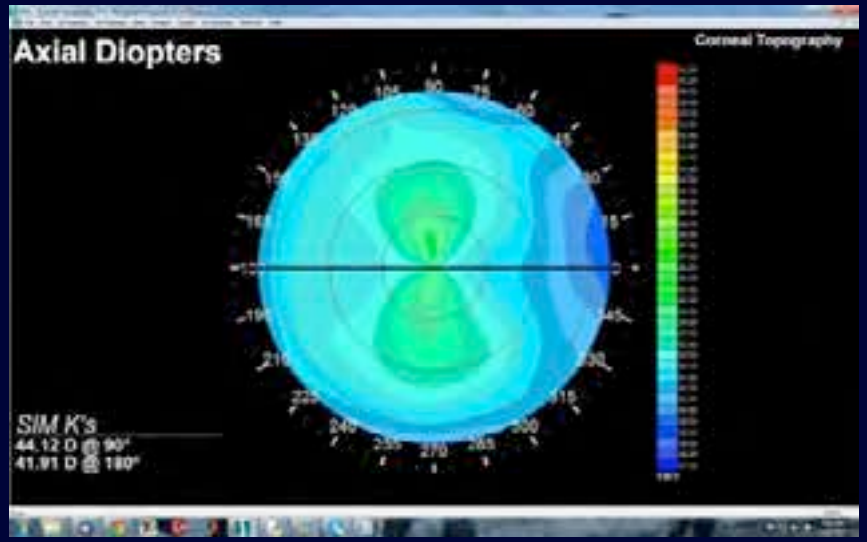


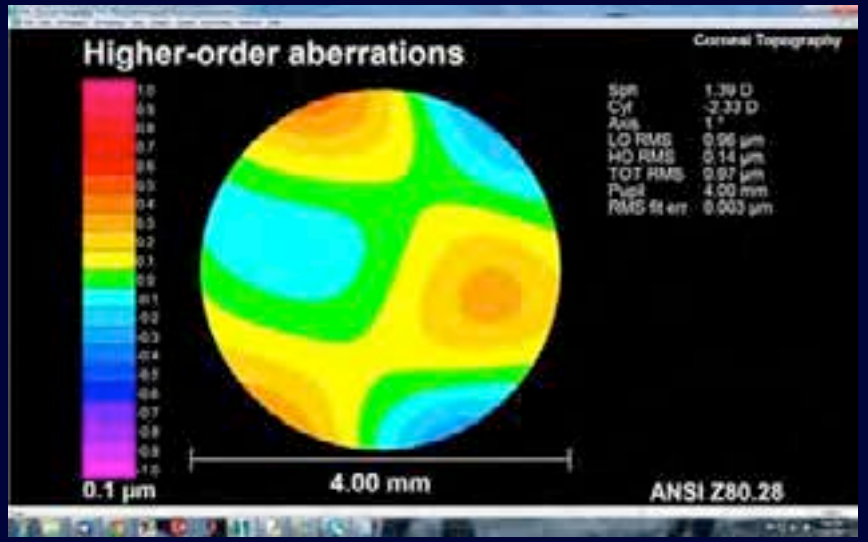
Astigmatism

Effect of stiffening factor with linear bowtie CXL pattern for astigmatism

Preop

Higher-Order Aberrations

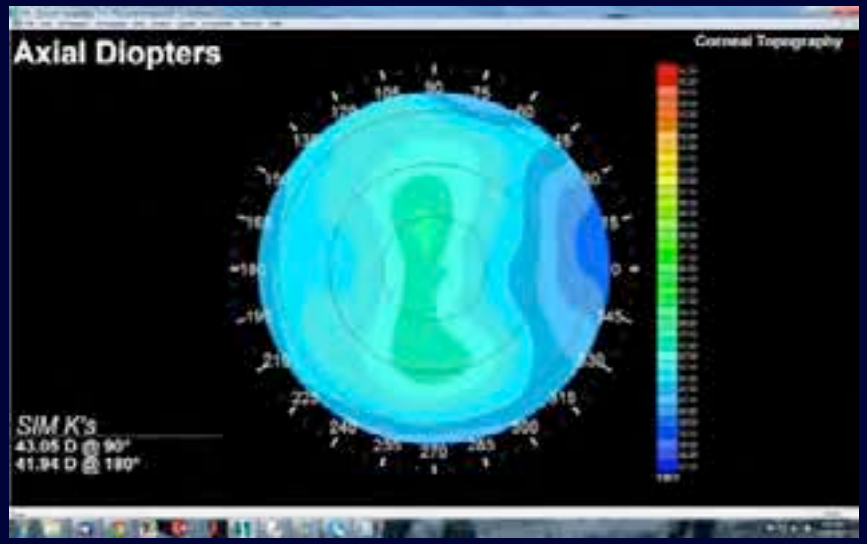


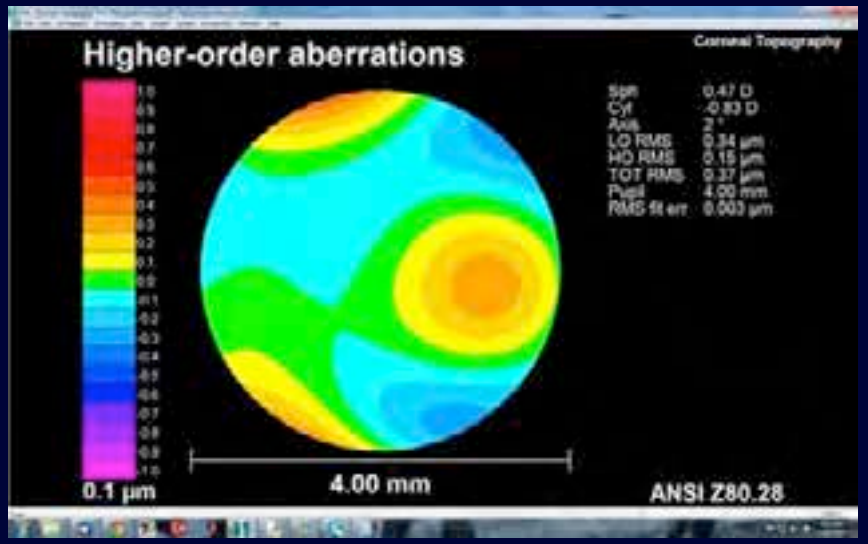


Seven et al, JCRS 2015

2x stiffening

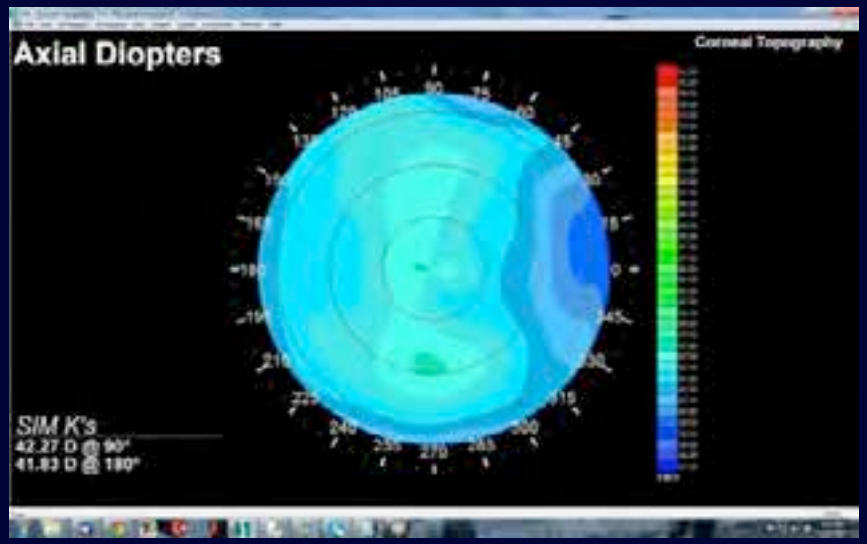
- Postop k=2
- Higher-Order Aberrations

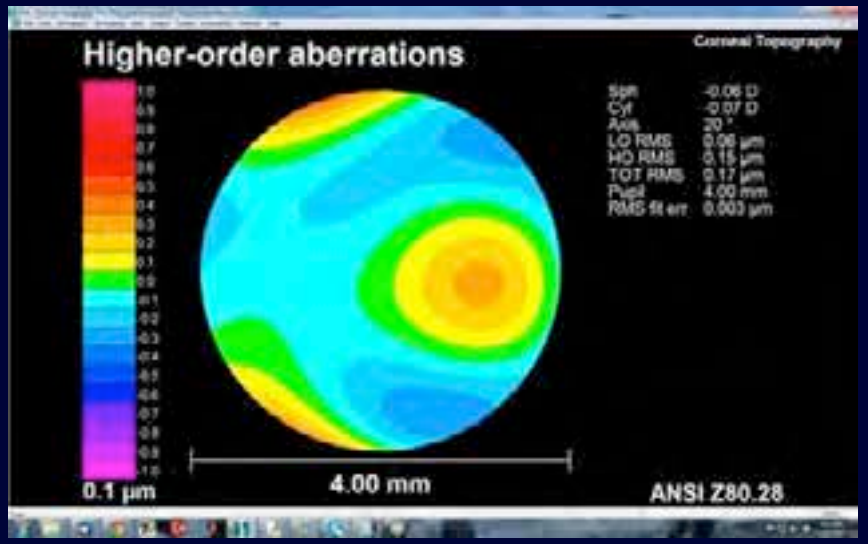




4x stiffening

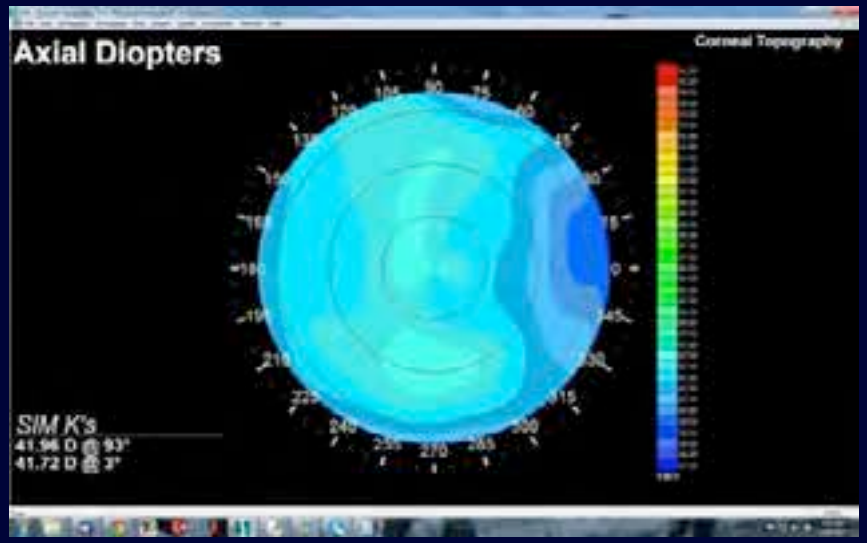
- Postop k=4
- Higher-Order Aberrations

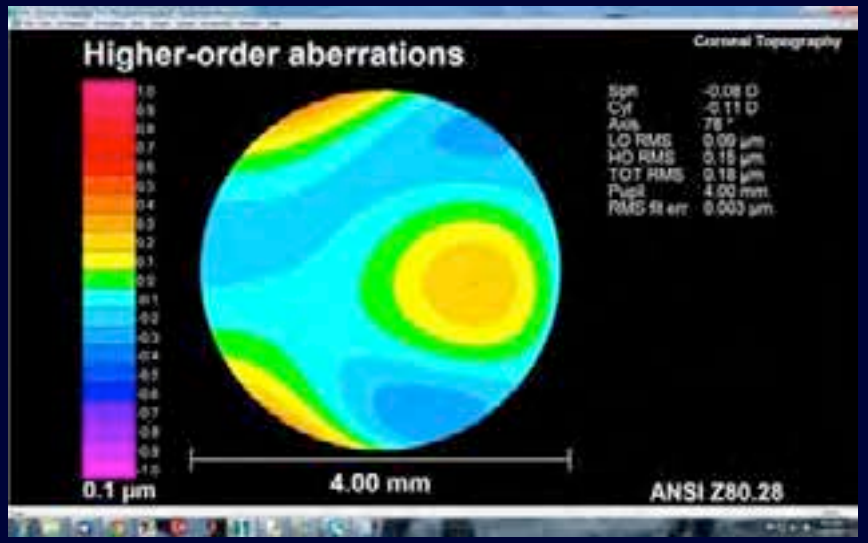




6x stiffening

- Postop k=6
- Higher-Order Aberrations



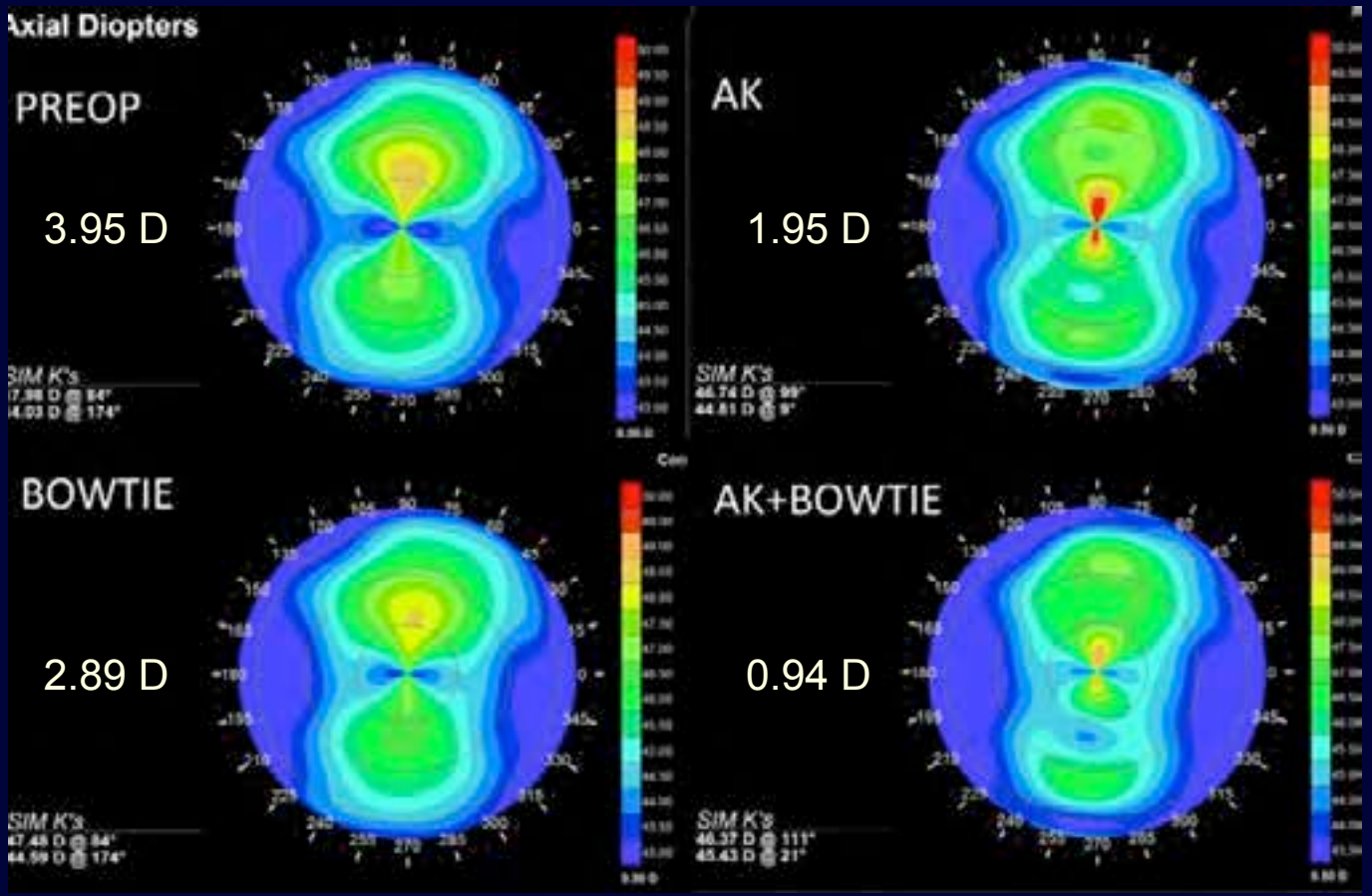


Virtual clinical trial in 10 patients

Patient				
1	-0.99	-0.92	-0.48	-1.1
2	-1.1	-1.04	-0.57	-1.12
3	-1.01	-0.99	-0.53	-1.12
4	-1.05	-1.02	-0.55	-1.1
6	-0.43	0.81	0.37	-1.09
7	-0.1	0.69	0.24	-0.74
8	-1.13	-1.07	-0.58	-1.15
9	-0.79	-0.78	-0.45	-1.1
10	-0.32	-0.29	-0.34	-1.2

Seven et al, JCRS 2014

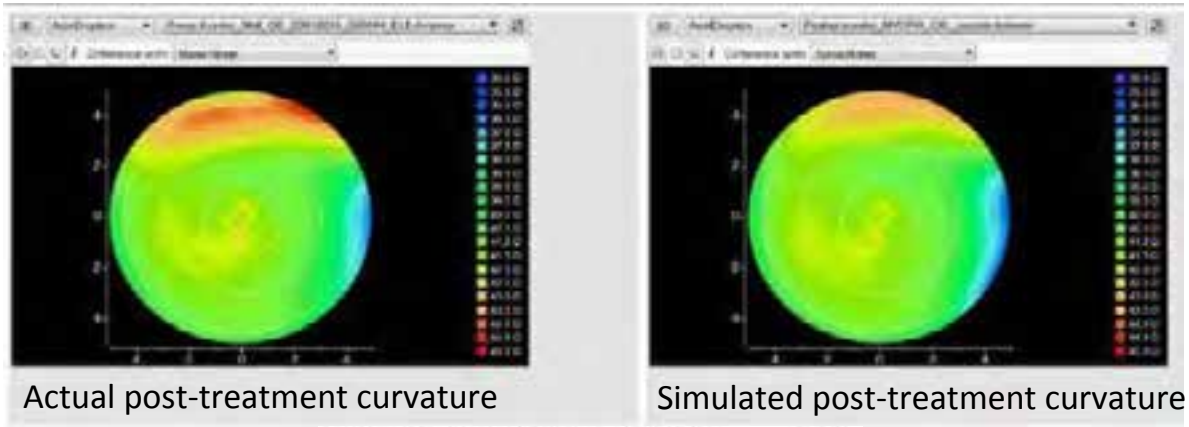
Combined astigmatic keratotomy/CXL



Seven & Dupps, J Med Devices, 2014

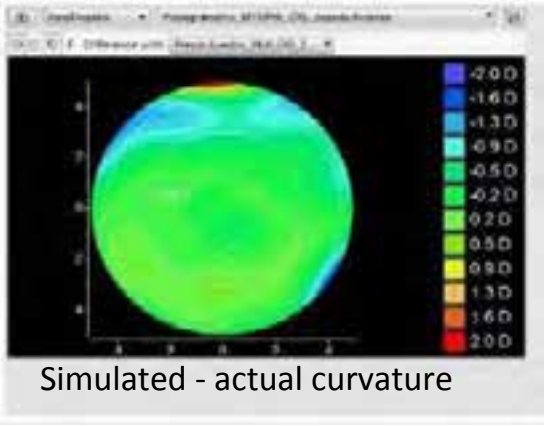
Masked Comparison of Simulated & Actual Central CXL Treatment Outcomes

Axial Curvature



Actual post-treatment curvature

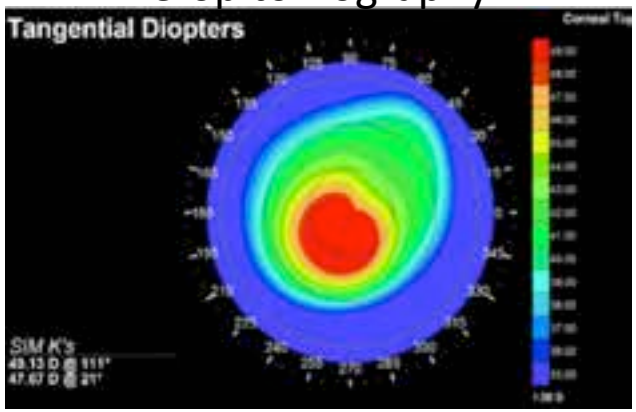
Simulated post-treatment curvature



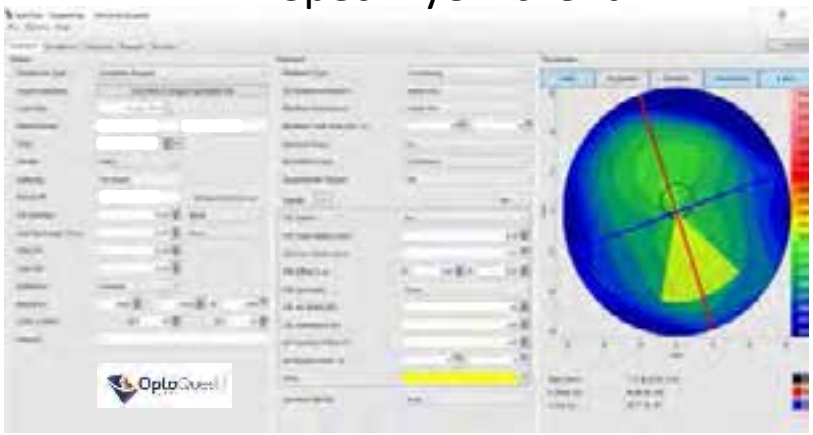
Simulated - actual curvature

Personalized CXL pattern design and pre-clinical simulation-based verification

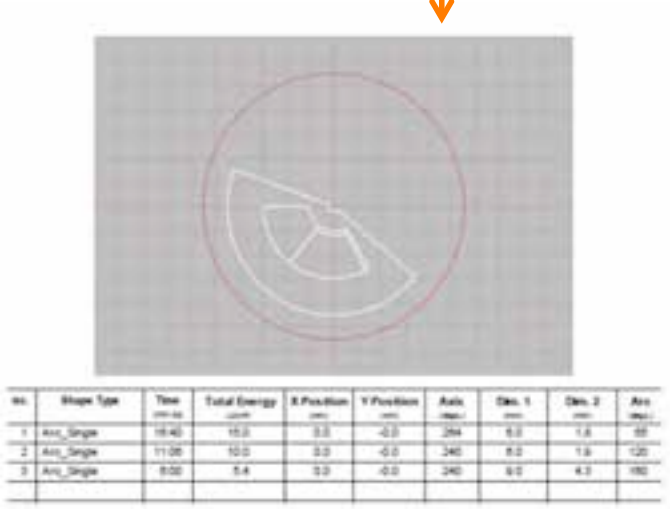
Pre-op tomography



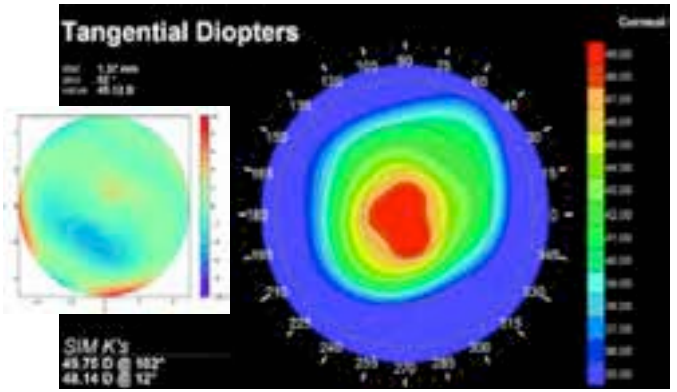
SpecifEye™ client



UV delivery plan



FEA-predicted outcome



Conclusions

- Computational modeling:
  - Addresses a need for rational treatment design in crosslinking treatment planning
  - Leverages full 3D corneal datasets and treatment specs in patient-specific structural simulations
  - Shows high potential for translational implementation with short solution times

Acknowledgments

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Ohio Third Frontier

OptoQuest

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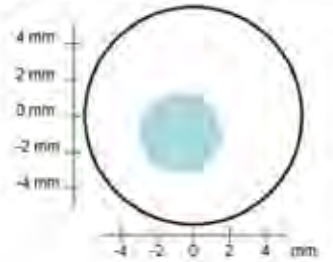
  - Cleveland Clinic Innovations Product Development Fund
  - Avedro, Inc.
  - The Pender Ophthalmic Research Fund

Research to Prevent Blindness

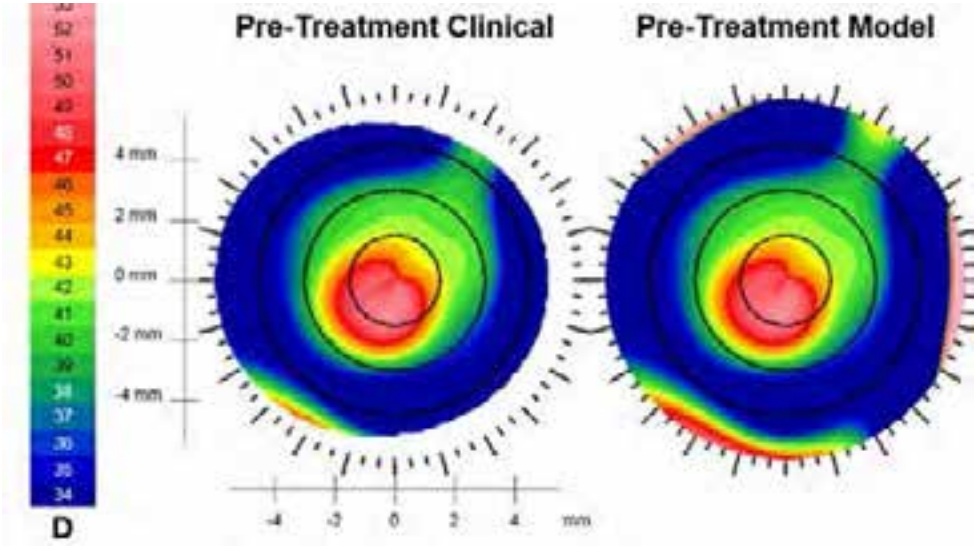
An “n of 1” virtual trial example

Patient Summary	
Patient Name:	
Patient ID:	6624
Gender:	Female
DOB:	
Laterality:	OD (Right)
Imaging Device:	Pentacam 1.20r29
QS:	OK
RMS Fit Error:	6.44 µm
IOP:	15.0 mmHg
Tonometer:	ORA
Estimated AEL:	21.29 mm
UDVA ◊ CDVA:	20/20 ◊ 20/20
MRx:	0.00 + 0.00 X 180
Surgeon:	William Dupps

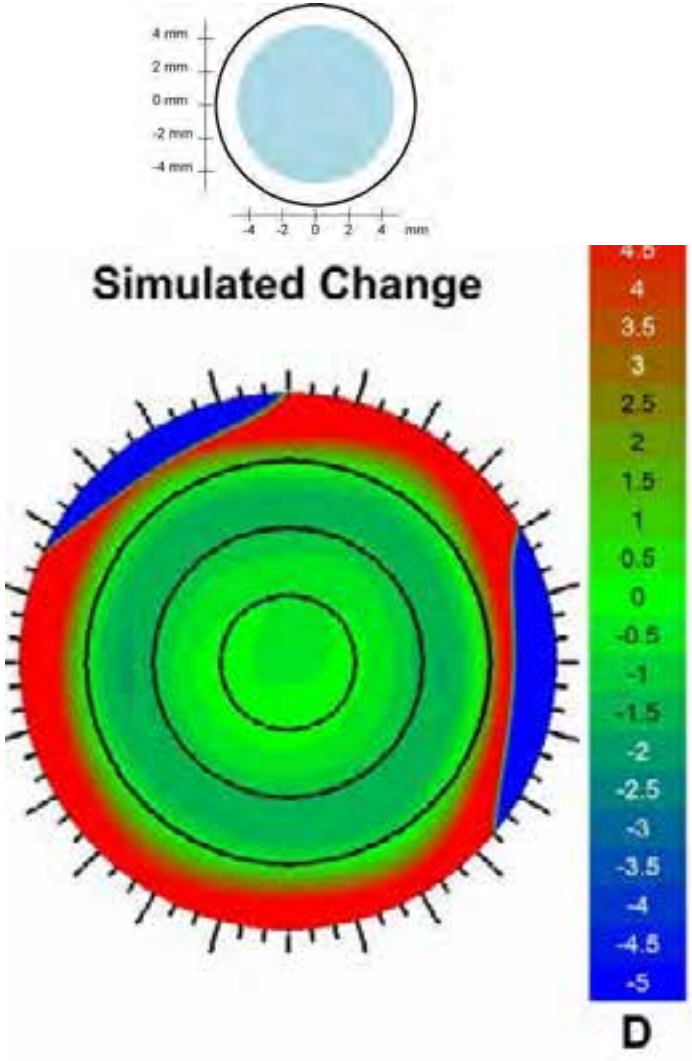
Treatment Summary	
Treatment:	Crosslinking
Treatment Device:	AvedroKxl
Epithelium:	Off
Riboflavin:	VibexXtra
Soak Time:	30 Minutes : 0 s
Illumination Type	Continuous

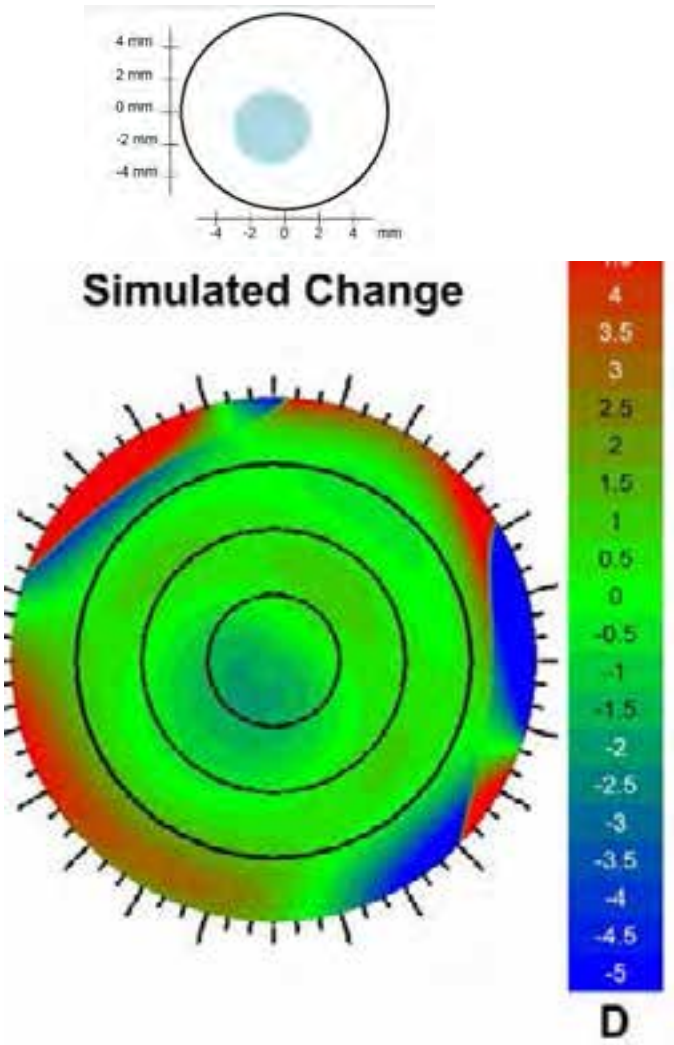


No	Pattern	Time (min : s)	Total Energy (J/cm²)	Offcenter (x,y) (mm)	Orientation (θ°)	Outer Radius (mm)	Inner Radius (mm)	Arc (θ°)
1	Circle	30 : 0	5.40	(-0.75, -1.00)	0.00	2.25	0.00	360.00

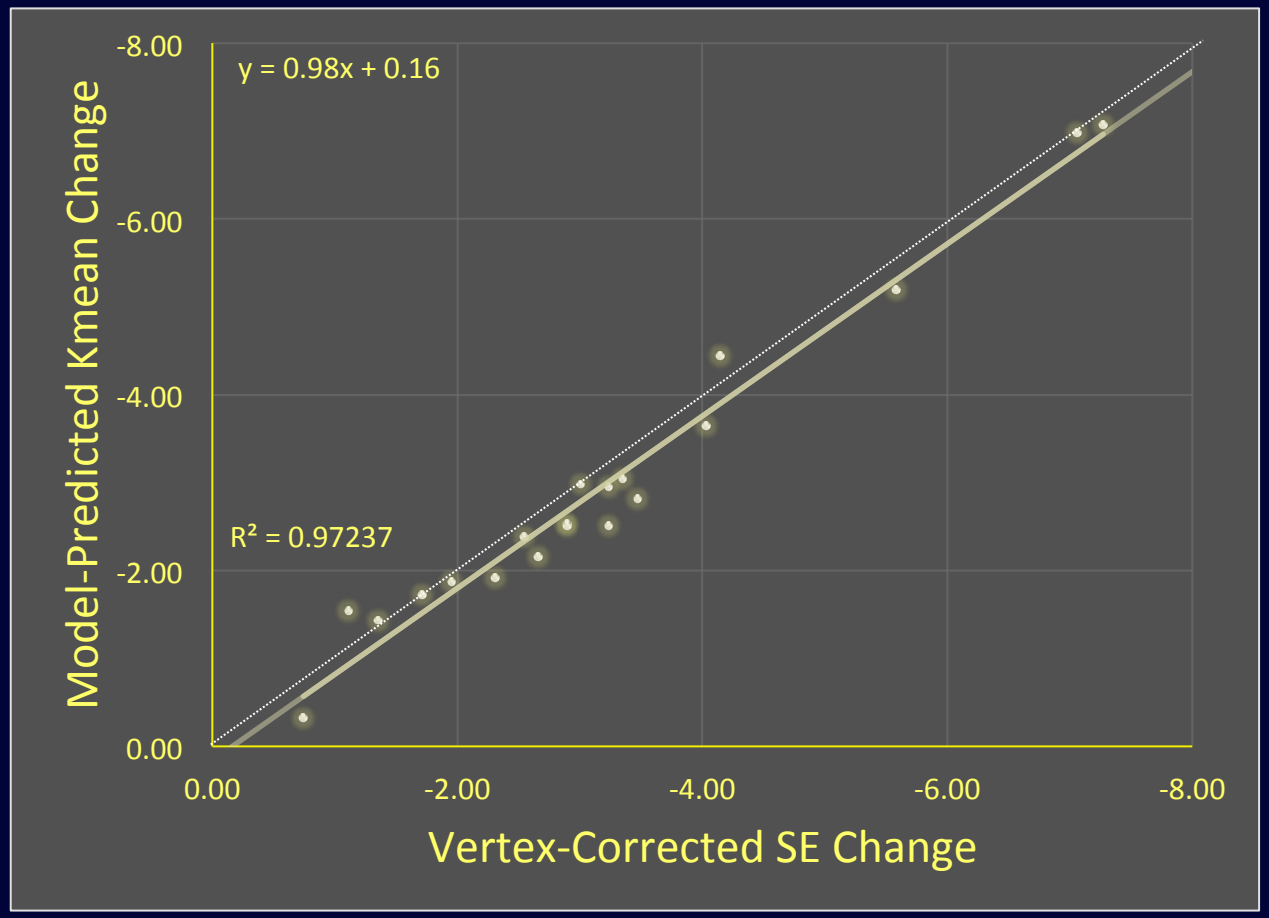


9mm CXL vs. elevation-centered spot





LASIK validation trial: prediction error in refractive change from FEA (n = 20)



Seven et al, IOVS 2016

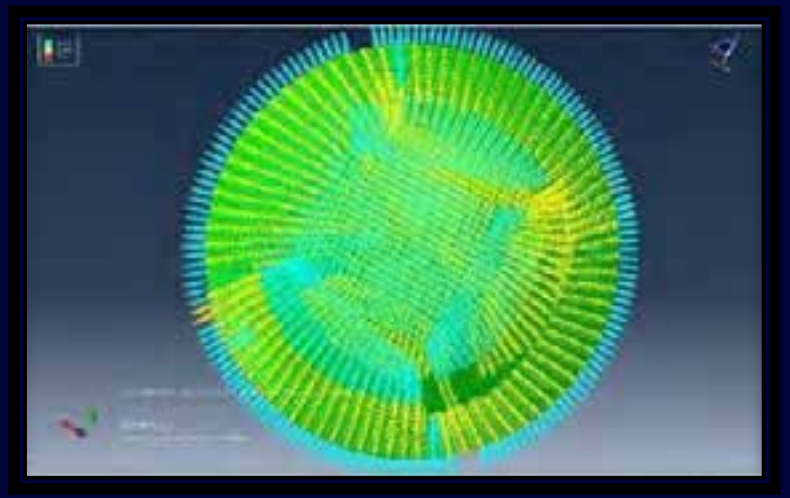
LASIK + adjunctive CXL

- Rationale
  - reducing risk of post-refractive surgery ectasia
  - prevention of postoperative refractive regression

- Clinical Evidence
  - results suggest early refractive outcomes similar to LASIK alone (Tomita et al, JCRS 2014)
  - less regression in hyperopic LASIK treatments (Kanellopoulos & Kahn, JRS 2012)
  - No direct data on benefit to ectasia risk

LASIK + adjunctive CXL

- Simulate LASIK and LASIK + CXL in 4 patient-specific models
- Mean correction -3.93 + 0.56 D
- CXL stiffening factor = 1.5x[1,2]
- Anisotropic material properties[3,4]
- Preferred fiber orientations assigned to each element



	Preop error (verification)	Postop error (validation)
Kmean (D)	**0.08 ± 0.20**	**0.26 ± 0.14**

1) Roy et al, Exp. Eye Res 2013
2) Seifert et al, Plos One 2014
3) Wollensak et al,. JCRS 2003
4) Hoeltzel et al, J Biomech Eng 1992
5) Meek et al, Prog Ret Res 2009

Keratometric and residual stromal displacement results: LASIK vs. LASIK + CXL

Difference in K_{mean} (D)	-0.19 ± 0.08 (p>0.05)

	LASIK IOP 15	LASIK + CXL IOP 15	LASIK IOP 30	LASIK + CXL IOP 30
1	194	183	393	371
2	206	195	419	396
3	205	194	416	394
4	270	254	547	516
		p<0.05		p<0.05

Seven et al, ARVO 2014