Modeling as a Tool for Ectasia Risk Analysis

William J. Dupps, Jr., MD, PhD
Ibrahim Seven, PhD
Ophthalmology, Biomedical Eng. & Transplant
Cole Eye Institute & Lerner Research Institute
February 25, 2017

Disclosures: Intellectual property in biomechanical measurement & modeling (Cleveland Clinic/OptoQuest), Avedro (research), Ziemer (consultant), Zeiss (research)
LASIK (and PRK) are among the most commonly performed procedures worldwide.

**FDA collaborative QOL Study (Eydelman, AAO 2014)**
- >96% satisfaction at 3 months
- 1 of 990 lost ≥2 lines of best-corrected vision
Corneal ectasia after refractive surgery

- Rare: Incidence 0.04 - 0.6% (Pallikaris et al, 2001)
- The most perplexing issue in refractive surgery
- Corneal steepening and irregular astigmatism
- Loss of best-corrected acuity
- Risk assessment challenging
Current ectasia risk assessment

Randleman et al, Ophth 2008
Challenges in Ectasia Risk Analysis

- **Scarcity** of cases
  - Negative reporting bias
  - Lack of central registry

- **Sparsity of data** for documented cases
  - Missing risk drivers (preoperative tomography)
  - Poorly conditioned probabilistic models with low external validity

- **Binary** approach to risk presence
  - Limits ability to quantify disease propensity

- **Probabilistic vs. mechanistic**
  - Statistical associations do not necessarily reflect mechanism, limited for *de novo* risk assessment

- Provocative hypothesis testing unethical
Case Study: Post-LASIK ectasia

- 34 yo male with myopic astigmatism
  - Central corneal thickness 498, 495
  - Flap thickness 98, 95
  - Max ablation depth 95, 92
  - PTA: 42, 40 (Santhiago et al, AJO 2014)

OS -6.25 + 2.00 x 065

OD -6.75 + 2.00 x 084

Vadhati et al, J Refract Surg 2016
Result: Post-LASIK ectasia OD
A Computational Approach to Ectasia Risk Analysis

1. Tomographic imaging
2. Import surfaces
3. Create FE mesh
4. Material property entry
5. Load
6. Surgical design and simulation
7. Analytics and Reporting
8. SpecifEye™

SpecifEye™ Analysis Report

SpecifEye™ Ectasia Analysis

The analysis includes detailed visualizations and numerical data for pre-treatment and post-treatment simulations, allowing for comprehensive risk assessment.
Verification of preoperative geometry

Pentacam

SpecifEye (8th order Zernike fit) – Plotted in VOL-CT
Microstructure-based corneal material model

Isotropic matrix with depth-dependent properties

Collagen fibrils with crimp and angular density functions

Baseline material constants from iFE of experimental inflation data

\[ W = W_{\text{isotropic}} + W_{\text{fiber}} + W_{\text{volumetric}} \]

\[ W_{\text{fiber}} = \frac{1}{\Pi} \int_0^{\Pi} \Phi(R_{\text{cornea}}, \varphi; \theta) W_{\text{fiber}}(R, \varphi; \theta) d\theta \]

\[ \Phi(R_{\text{cornea}}, \varphi; \theta) = \cos^{2n}(\theta) + \sin^{2n}(\theta) + c_1 \quad \text{for } 0 < R_{\text{cornea}} < 4.5 \text{ mm} \]

\[ \Phi(R_{\text{cornea}}, \varphi; \theta) = \sin^{2n}(\theta - \varphi) + c_2 \quad \text{for } 4 \text{ mm} < R_{\text{cornea}} < 5.5 \text{ mm} \]

Pinsky et al, 2005
Vadhati et al, 2015
Freed & Doehring, 2005
Freed et al, 2005
Grytz & Meshke, 2009

Pinsky et al., 2005
Aghamohammadzadeh et al., 2004
Max principal strain comparison

Preop | Preop scaled | LASIK simulation | Actual postop

OS

OD
Superior-inferior component of strain (anterior surface)
Von Mises Stress

A
von Mises stress - preoperative

B
von Mises stress - postoperative
Provocative loading of preop model: simulated change in max curvature ($K_{\text{max}}$)

Evolution of $K_{\text{max}}$ vs IOP

$K_{\text{max}}$ location

IOP 10  IOP 15  IOP 20

OD  OS
Large Scale Computational Analysis of Structural Risk in LASIK and PRK

- Tomography-specific models of 40 eyes
  - Group 0: Normal preoperative LASIK candidates (10)
  - Group 1: Atypical topographies (8)
  - Group 2: Disqualified but not keratoconus (10)
  - Group 3: Manifest keratoconus (10)
- Each eye subjected to 6 virtual surgeries (n=280)
  - PRK 4D, 8D myopia
  - LASIK 4D, 8D with 100 or 160 um flaps
- Geometric and strain outcomes analyzed along with putative clinical risk factors
  - Strain surrogates for ectasia risk

Dupps & Seven, Trans Am Ophthalm Soc 2016
### Subject characteristics

<table>
<thead>
<tr>
<th></th>
<th>Normal (Group 0) n = 10</th>
<th>Atypical (Group 1) n = 8</th>
<th>Disqualified (Group 2) n = 10</th>
<th>Keratoconus (Group 3) n = 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>$K_{\text{max}}$ (D)</td>
<td>44.14 ± 1.70</td>
<td>45.84 ± 1.93</td>
<td>44.61 ± 1.29</td>
<td>52.27 ± 8.09</td>
</tr>
<tr>
<td>$K_{\text{max}}$ Distance (mm)</td>
<td>0.90 ± 0.59</td>
<td>1.99 ± 1.48</td>
<td>0.83 ± 0.61</td>
<td>1.09 ± 0.77</td>
</tr>
<tr>
<td>$K_{\text{mean}}$ (D)</td>
<td>43.23 ± 1.62</td>
<td>43.40 ± 1.40</td>
<td>43.65 ± 1.34</td>
<td>45.62 ± 3.26</td>
</tr>
<tr>
<td>Anterior Corneal Astigmatism (D)</td>
<td>0.82 ± 0.40</td>
<td>3.14 ± 3.16</td>
<td>0.90 ± 0.56</td>
<td>2.79 ± 2.63</td>
</tr>
<tr>
<td>CCT (µm)</td>
<td>567 ± 32</td>
<td>565 ± 26</td>
<td>510 ± 26</td>
<td>510 ± 56</td>
</tr>
<tr>
<td>Thinnest Point Value (µm)</td>
<td>563 ± 32</td>
<td>559 ± 28</td>
<td>505 ± 27</td>
<td>494 ± 63</td>
</tr>
<tr>
<td>Thinnest Point Distance (mm)</td>
<td>0.65 ± 0.24</td>
<td>1.15 ± 0.95</td>
<td>0.82 ± 0.30</td>
<td>1.03 ± 0.43</td>
</tr>
</tbody>
</table>
Model verification
Maximum principal strain (MPS)
Mean MPS for anterior residual stroma

- Higher for known ectasia (Group 3) than normal (Group 0) for all pre- and postoperative comparisons ($P<.008$)
- Preoperative mean MPS also differentiated normal eyes (Group 0) from the clinically disqualified eyes (Group 2, AUROC = 0.90, 95% CI 0.68 – 0.99, $P<.001$)
Highest MPS for entire central 5mm stroma

- Metric defined by peak strain wherever it occurs ("weakest link" hypothesis)
- Higher variance
- Peak strains in LASIK occur in the flap because of circumferential severing of fibrils, does not reflect differences in residual bed
Predicted postoperative refractive error as a function of surgically induced strain change
Clinical nomograms for surgery planning

All corneal procedures share a mechanistic pathway mediated by biomechanics but no unifying clinical decision pathway.
DQ’d for LASIK

**Treatment Summary**

- **Treatment:** LASIK
- **Attempted Correction:** -6.00 + 0.00 X 170
- **Procedure Type:** WavefrontOptimized
- **Flap Laser:** AmoIntraLase
- **Flap Diameter:** 9.00 mm
- **Flap Thickness:** 110.00 μm
- **Hinge Orientation:** 90.00°
- **Ablation Device:** AlconWaveLightAllegretto
- **Optical Zone:** 6.50 mm
- **Treatment Diameter:** 9.00 mm

**Simulated Change**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kmean (3mm) (D)</td>
<td>-5.44</td>
</tr>
<tr>
<td>Ksteep (D)</td>
<td>-5.79</td>
</tr>
<tr>
<td>Kflat (D)</td>
<td>-5.81</td>
</tr>
<tr>
<td>Astigmatism (D)</td>
<td>0.02 @ 089°</td>
</tr>
<tr>
<td>Sph. Aberration (μm)</td>
<td>11.29</td>
</tr>
<tr>
<td>V. Coma (μm)</td>
<td>-0.14</td>
</tr>
<tr>
<td>H. Coma (μm)</td>
<td>-0.19</td>
</tr>
<tr>
<td>Pachy Min. (μm)</td>
<td>-90</td>
</tr>
<tr>
<td>Pachy Apex (μm)</td>
<td>-93</td>
</tr>
<tr>
<td>MRx</td>
<td>5.66 + 0.07 X 091</td>
</tr>
</tbody>
</table>

**SpecifEye™ Analysis Report**

- **Patient Name (First, Last):** Disqualifedeye2 Demo
- **Patient ID:** 25208244
- **Gender:** Unspecified
- **DOB:** 01-01-1983
- **Laterality:** OD (Right)
- **Imaging Device:** Penlacam 1.20r28
- **QSC:** OK
- **RMS Fit Error:** 1.93 μm
- **IOP:** 15.0 mmHg
- **Tonometer:** None
- **Axial Eye Length:** 25 mm
- **CDVA / UDVA:** 20/20 / 20/20
- **MRx:** -6.00 + 1.75 X 091
- **Surgeon:** ...

**Treatment Summary**

- **Treatment:** LASIK
- **Attempted Correction:** -6.00 + 0.00 X 170
- **Procedure Type:** WavefrontOptimized
- **Flap Laser:** AmoIntraLase
- **Flap Diameter:** 9.00 mm
- **Flap Thickness:** 110.00 μm
- **Hinge Orientation:** 90.00°
- **Ablation Device:** AlconWaveLightAllegretto
- **Optical Zone:** 6.50 mm
- **Treatment Diameter:** 9.00 mm

**Predicted Outcome**

- **Universal Nomogram**
  - Pre-Treatment Clinical: 41.98
  - Pre-Treatment Model: 36.54
  - Simulated Outcome: 37.27 @ 089°
  - Simulated Change: -5.44
- **Surgeon-Specific Nomogram**
  - Pre-Treatment Clinical: 41.06 @ 089°
  - Pre-Treatment Model: 35.20 @ 079°
  - Simulated Outcome: 2.08 @ 089°
  - Simulated Change: 0.02 @ 089°
- **Simulation-Based**
  - Pre-Treatment Clinical: 486 @ (-0.84, -0.63)
  - Pre-Treatment Model: 396 @ (-0.30, -0.20)
  - Simulated Outcome: 5.55 + 1.76 X 091
  - Simulated Change: 5.66 + 0.07 X 091

The results obtained from this analysis are not intended as a medical recommendation and should not be deemed definitive or considered a guarantee of outcomes. Physicians are solely responsible for their conclusions involving the use of SpecifEye. OptoQuest assumes no liability.
DQ’d for LASIK

<table>
<thead>
<tr>
<th>Summary</th>
<th>05 May, 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Name (First, Last):</td>
<td>Disqualifiedeye2 Demo</td>
</tr>
<tr>
<td>Laterality:</td>
<td>OD (Right)</td>
</tr>
<tr>
<td>Age:</td>
<td>32 Years</td>
</tr>
<tr>
<td>Flap Thickness:</td>
<td>110.00 µm</td>
</tr>
<tr>
<td>Flap Laser:</td>
<td>AmoIntraLase</td>
</tr>
<tr>
<td>Attempted Correction:</td>
<td>-6.00 + 0.00 x 170</td>
</tr>
<tr>
<td>Pachy Min.:</td>
<td>486 @ (-0.70, -0.50)</td>
</tr>
<tr>
<td>Pachy Apex:</td>
<td>492 µm</td>
</tr>
<tr>
<td>PSTA:</td>
<td>33.2%</td>
</tr>
<tr>
<td>PTA:</td>
<td>40.1%</td>
</tr>
<tr>
<td>RSB:</td>
<td>295 µm</td>
</tr>
<tr>
<td>K Max:</td>
<td>43.31 D</td>
</tr>
<tr>
<td>CLMI:</td>
<td>0.82 @ (-0.1, -0.3)</td>
</tr>
<tr>
<td>ORA CH:</td>
<td>12.0</td>
</tr>
<tr>
<td>ORA CRF:</td>
<td>12.0</td>
</tr>
<tr>
<td>Custom ORA Variables:</td>
<td></td>
</tr>
<tr>
<td>CorvisST Variables:</td>
<td></td>
</tr>
<tr>
<td>Vetratlas Elastography:</td>
<td></td>
</tr>
</tbody>
</table>

### SpecifEye™ Ectasia Analysis

#### Pre-Treatment Model vs Simulated Outcome vs Simulated Change

<table>
<thead>
<tr>
<th>Strain Type</th>
<th>Pre-Treatment Model</th>
<th>Simulated Outcome</th>
<th>Simulated Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Strain</td>
<td>2.66%</td>
<td>3.21%</td>
<td>0.55%</td>
</tr>
<tr>
<td>Maximum Strain</td>
<td>2.76% @ (-0.55, -0.69)</td>
<td>3.56% @ (-0.14, -0.83)</td>
<td>0.79%</td>
</tr>
</tbody>
</table>

#### Pre-Op vs Post-Op

**Susceptibility Score**

- **Lower**: Moderate
- **Higher**: Higher

**Surgically Induced Strain Change**

- **0**: 20.80%
SpecifEye™ Ectasia Analysis

05 May, 2016

**Summary**

- Patient Name (First, Last): Smileectasia Normal
- Laterality: OD (Right)
- Age: 35 Years
- Attempted Correction: -3.00 + 1.00 X 155
- Pachy Min.: 482 @ (-0.30, -1.10)
- Pachy Apex: 490 µm
- PSTA: 7.2%
- PTA: 6.5%
- RSB: 328 µm
- K Max: 46.31 D
- CLMI: 4.89 @ (0.8, -2.7)
- ORA CH: 12.0
- ORA CRF: 12.0

Custom ORA Variables:
- CorvisST Variables:
- Vectralis Elastography:

**Pre-Ops and Post-Ops**

- **Pre-Ops:** Cross Section, Anterior Stroma
- **Post-Ops:** Cross Section, Anterior RSB

**ABSOLUTE STRAIN**

<table>
<thead>
<tr>
<th></th>
<th>Pre-Treatment Model</th>
<th>Simulated Outcome</th>
<th>Simulated Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Strain</td>
<td>2.70%</td>
<td>2.89%</td>
<td>0.18%</td>
</tr>
<tr>
<td>Maximum Strain</td>
<td>2.79% @ (-1.64, -0.27)</td>
<td>3.04% @ (-0.55, -0.14)</td>
<td>0.25%</td>
</tr>
</tbody>
</table>

**SUSCEPTIBILITY SCORE**

- Pre-Op: Lower, Moderate, Higher
- Surgically Induced Strain Change: 0% to 6.77%
Conclusions

- Candidate susceptibility metrics based on model-derived strain were higher in eyes with confirmed ectatic predisposition (for pre- and postop states).

- The metric was effective at differentiating normal and at-risk eyes in ROC analyses, was highly correlated to corneal thickness-based risk metrics, and predicted variance in simulated refractive outcomes after LASIK and PRK.

Dupps & Seven, TAOS 2016
Conclusions

- 1st large-scale structural analysis of post-refractive surgery ectasia risk, incorporates entire 3-dimensional geometry of cornea rather than a subset of derivatives.
- Strain is an effective marker of known ectasia risk and correlates to predicted refractive error after myopic photoablative surgery.
- Limitations:
  - Lack of knowledge of patient-specific material properties, an important driver.
  - Modeling the acute response (plus static wound healing component).
  - Additional validation in actual post-refractive surgery ectasia cases required.
Acknowledgments

- Ocular Biomechanics & Imaging Lab
  - Ibrahim Seven, Ph.D.
  - Ali Vahdati, Ph.D.
  - Abhijit Sinha Roy, Ph.D.
  - Matthew Ford, Ph.D.
  - Donn Hardy, M.S.
  - Josh Lloyd, M.S.
  - Brent Hughes, M.S.

Support
- NIH R01 EY023381
- Ohio Third Frontier Innovation Platform Award TECH-013
- RPB Career Development Award
- NIH/NCRR K12/KL2RR024990
- National Keratoconus Foundation
- Cleveland Clinic Innovations Product Development Fund
- Avedro, Inc.
- The Pender Ophthalmic Research Fund
**Relationship of patient and surgery specific risk variables to absolute strain**

<table>
<thead>
<tr>
<th>Linear Regression Model and Results:</th>
<th>Constant</th>
<th>Coefficient</th>
<th>P value</th>
<th>R-squared</th>
</tr>
</thead>
<tbody>
<tr>
<td>$K_{\text{max}}$ (D)</td>
<td>0.01770</td>
<td>0.000203</td>
<td>&lt;.001</td>
<td>9.0%</td>
</tr>
<tr>
<td>$K_{\text{max}}$ Distance (mm)</td>
<td>0.02734</td>
<td>-0.000087</td>
<td>.7</td>
<td>0%</td>
</tr>
<tr>
<td>Anterior Corneal Astigmatism (D)</td>
<td>0.02651</td>
<td>0.000385</td>
<td>&lt;.001</td>
<td>4.9%</td>
</tr>
<tr>
<td>CCT (µm)</td>
<td>0.05112</td>
<td>-0.000045</td>
<td>&lt;.001</td>
<td>29.5%</td>
</tr>
<tr>
<td>Thinnest Point Value (µm)</td>
<td>0.04882</td>
<td>-0.000041</td>
<td>&lt;.001</td>
<td>29.9%</td>
</tr>
<tr>
<td>Thinnest Point Distance (mm)</td>
<td>0.02594</td>
<td>0.001437</td>
<td>.001</td>
<td>3.9%</td>
</tr>
<tr>
<td>Residual Stromal Bed Thickness, RSB (µm)</td>
<td>0.04282</td>
<td>-0.000043</td>
<td>&lt;.001</td>
<td>86.7%</td>
</tr>
<tr>
<td>Percent Stromal Tissue Altered, PSTA (%)</td>
<td>0.02172</td>
<td>0.000221</td>
<td>&lt;.001</td>
<td>71.7%</td>
</tr>
</tbody>
</table>
Predicted postoperative refractive error by group and surgery type