The Most Updated Keratoconus Management Guide

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International Keratoconus Academy of Eye Care Professionals
www.keratoconusacademy.com

Current & Future State of Keratoconus Detection and Monitoring

Presented By
Clark Chang, OD, FAAO, FSLS

Financial Disclosures – Clark Chang

- Allergan (C)
- Dompe Pharmaceutical (S)
- Eyenovia (C)
- Glaukos (Employment)
- Oculus (S)
- Visus Therapeutics (C)

C=Consultant, S=Speaker Bureau

Current & Future State of KC Management

Presented By
Bill Tullo, OD, FAAO, Dipl

Financial Disclosures – Bill Tullo

- Oculus (Employment)

How common is keratoconus (KCN)?

- Classically referenced: Prevalence

1:2,000* based on a registration study in Olmsted County, Minnesota, conducted between 1935-1982; diagnosis was based on the detection of scissors reflex with retinoscopy and keratometry outcomes!

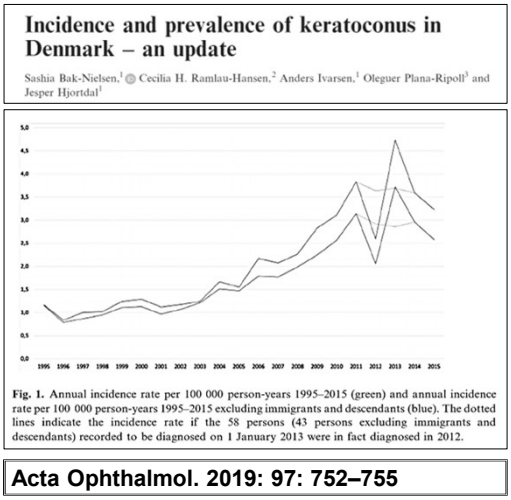
*Kennedy RH, Bourne WM, Dyer JA. A 48-year clinical and epidemiologic study of keratoconus. Am J Ophthalmol 1986;101(3):267-73.

AJO – 2017: Age-specific incidence and prevalence of keratoconus: a nationwide registration study

- Netherlands study: 4.4 million patients from a mandatory health insurance data base
- Prevalence of keratoconus in the general population was **1:375 !**
- Annual <u>incidence</u> (new cases) of keratoconus was **1:7,500**
- **<u>Conclusion</u>**:
  - "**Both the annual incidence and the prevalence of keratoconus were five-fold to ten-fold higher than previously reported**."

KCN Global Prevalence: Meta-Analysis

Reference	Prevalence	Geography
Kennedy et al. 1986	0.05% or 1:2000	US
Jonas et al. 2009	2.3%	India
Millodot et al. 2011	2.3%	Israel
Xu et al. 2012	0.9%	China
Hashemi et al. 2014	2.5%	Iran
Godefrooij et al. 2017	0.26% or 1:375	Netherlands
Torres Netto et al. 2018	4.79%	Saudi Arabia
Chan et al. 2020	1.2% or 1:84	Australia
Hashemi et al. 2020*	0.14% or 1:700	Global Meta-Analysis


Incidence and prevalence of keratoconus in Denmark – an update

Sashia Bak-Nielsen,[1] Cecilia H. Ramlau-Hansen,[2] Anders Ivarsen,[1] Oleguer Plana-Ripoll[3] and Jesper Hjortdal[1]

Fig. 1. Annual incidence rate per 100 000 person-years 1995–2015 (green) and annual incidence rate per 100 000 person-years 1995–2015 excluding immigrants and descendants (blue). The dotted lines indicate the incidence rate if the 58 persons (43 persons excluding immigrants and descendants) recorded to be diagnosed on 1 January 2013 were in fact diagnosed in 2012.

Acta Ophthalmol. 2019: 97: 752–755

Studies Outside of U.S. Suggest Prevalence May be Higher in Certain Populations

*Hashemi H, Heydarian S, Hooshmand E, et al. The Prevalence and Risk Factors for Keratoconus: A Systematic Review and Meta-Analysis. *Cornea*. 2020;39(2):263-270

Primary Ectatic Diseases

- Keratoconus
- Post-refractive surgery progressive ectasia
- Pellucid's Marginal Degeneration
- Keratoglobus

** Should be separated from other primary or secondary "thinning disorders",
ie, Terrien's marginal degeneration
Ie, Dellen, Inflammatory melts, post-trauma thinning

SPECIAL ARTICLE

Global Consensus on Keratoconus and Ectatic Diseases

José A. P. Gomes, MD, PhD, Donald Tan, MD, PhD,† Christopher J. Rapuano, MD,‡ Michael W. Belin, MD,§ Renato Ambrósio, Jr, MD, PhD,¶ José L. Guell, MD,‖ François Malecaze, MD, PhD,** Kohji Nishida, MD,†† and Virender S. Sangwan, MD‡‡, the Group of Panelists for the Global Delphi Panel of Keratoconus and Ectatic Diseases*

Background: Despite extensive knowledge regarding the diagnosis and management of keratoconus and ectatic corneal diseases, many controversies still exist. For that reason, there is a need for current guidelines for the diagnosis and management of these conditions.

Purpose: This project aimed to reach consensus of ophthalmology experts from around the world regarding keratoconus and ectatic diseases, focusing on their definition, concepts, clinical management, and surgical treatments.

Methods: The Delphi method was followed with 3 questionnaire rounds and was complemented with a face-to-face meeting. Thirty-six panelists were involved and allocated to 1 of 3 panels: definition/diagnosis, nonsurgical management, or surgical treatment. The level of agreement considered for consensus was two thirds.

Results: Numerous agreements were generated in definitions, methods of diagnosing, and management of keratoconus and other ectatic diseases. Nonsurgical and surgical treatments for these conditions, including the use of corneal cross-linking and corneal transplantations, were presented in a stepwise approach. A flowchart describing a logical management sequence for keratoconus was created.

Conclusions: This project resulted in definitions, statements, and recommendations for the diagnosis and management of keratoconus and other ectatic diseases. It also provides an insight into the current worldwide treatment of these conditions.

Key Words: keratoconus, corneal ectasia, consensus, corneal cross-linking, corneal transplantation

(*Cornea* 2015;0:1–11)

Keratoconus and ectatic corneal diseases have been recognized for more than 150 years.[1,2] Over the last 2 decades, there has been a revolution in the knowledge related to the diagnosis and management of these conditions. In terms of diagnosis, the advent of corneal topography, and more recently corneal tomography, has increased the ability of ophthalmologists to identify corneal ectasia at a much earlier stage than was previously possible.[3] As a result, the previously established prevalence of keratoconus of approximately 1/2000 among the general population[4] has been challenged with much higher prevalence rates found in many parts of the world.[5,6]

The surgical treatment for keratoconus reflects this evolution.[7] Alternative procedures, such as the use of intrastromal corneal ring segment(s) (ICRS),[8,9] corneal cross-linking (CXL),[10–12] therapeutic excimer laser treatments including phototherapeutic keratectomy[13] and photorefractive

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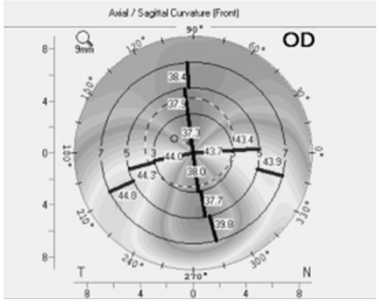
Supported by the Asia Cornea Society, The Cornea Society, EuroCornea, and the Panamerican Cornea Society (PanCornea).

Gomes JA, Tan D, Rapuano CJ, Belin MW, Ambrósio R Jr, Guell JL, Malecaze F, Nishida K, Sangwan VS; Group of Panelists for the Global Delphi Panel of Keratoconus and Ectatic Diseases. Global consensus on keratoconus and ectatic diseases. Cornea. 2015 Apr;34(4):359-69.

Consensus Publication Statements…..

- True unilateral keratoconus does not exist
- **Central pachymetry is the least reliable** indicator for diagnosing KCN
- **Thinning location and pattern** are aspects that distinguish KCN, PMD, and keratoglobus
- KCN and PMD are best differentiated by a combination of
  - Full tomographic corneal thickness map
  - Slit-lamp examination
  - Anterior curvature map
  - Anterior tomographic elevation map



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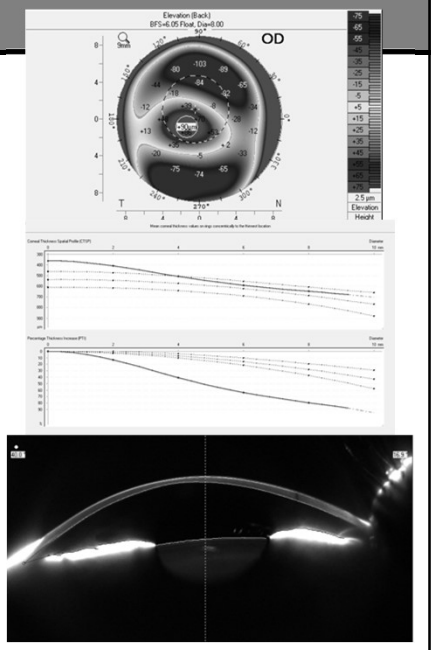
KCN - Early Diagnosis & Pearls

- Criteria "<u>mandatory to diagnose</u> KCN"
  - Abnormal **posterior elevation** (ectasia)
  - Abnormal corneal thickness **distribution**
  - Non-inflammatory corneal thinning
- Diagnosing <u>mild or subclinical</u> KCN
  - "Posterior corneal elevation abnormalities must be present"
  - "Best current and most widely available diagnostic test to diagnose early keratoconus is tomography (Scheimpflug or optical coherence tomography)"



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KC Progression & Monitoring Pearls

- Ectasia progression is defined by a consistent change** in <u>at least 2</u> of the following parameters
  - Progressive steepening of the anterior corneal surface
  - Progressive steepening of the posterior corneal surface
  - Progressive thinning and/or an increase in the rate of corneal thickness change from the periphery to the thinnest point

* "changes need to be **<u>consistent</u>** over time and **<u>above the normal variability</u>** (ie, noise) of the measurement system (this will vary by system)"

** "Although progression is often accompanied by a decrease in BSCVA, a **<u>change in both uncorrected visual acuity and BSCVA is not required</u>** to document progression"

Gomes JA, Tan D, Rapuano CJ, Belin MW, Ambrósio R Jr, Guell JL, Malecaze F, Nishida K, Sangwan VS; Group of Panelists for the Global Delphi Panel of Keratoconus and Ectatic Diseases. Global consensus on keratoconus and ectatic diseases. Cornea. 2015 Apr;34(4):359-69.

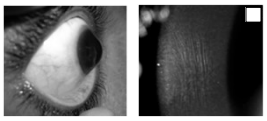
Possible KCN Signs and Symptoms

Look out for warning signs in medical history

- Family history of KCN
- Chronic eye rubbing and/or atopic eye diseases
- Systemic associations - Down syndrome - Connective tissue disorders

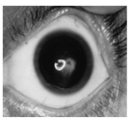
Listen carefully to subjective symptoms

- Reduced visual quality or loss of vision
- Glare, halo, ghosting, and/or monocular diplopia (especially at night)
- Frequent changes in glasses prescriptions or contact lens refits



Look out for refractive & keratometric anomalies

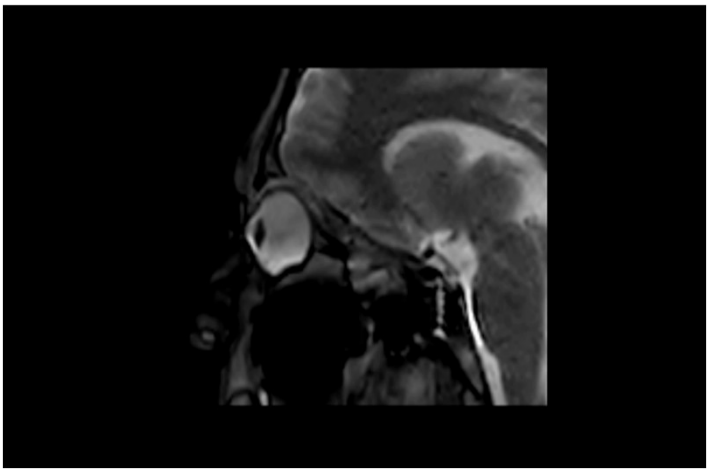
- Distortion of mires on keratometry
- Error messages on autorefractors
- Increasing astigmatism and/or high baseline astigmatism
- Unsatisfactory attempts at vision correction & progressive loss of UCVA & BCVA
- Unexplained amblyopia



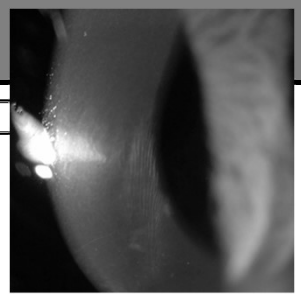
The American Academy of Ophthalmology Corneal Ectasia Preferred Practice Pattern recommends <u>prompt</u> referral of patients who have been diagnosed with progressive keratoconus to an ophthalmologist who can perform corneal cross-linking.[1]

1. Moussa, S., et al. Genetics in Keratoconus – What is New? Open Ophthalmology Journal. 2017; 11: 201–210. Published online 2017 Jul 31.

Possible KCN Signs and Symptoms

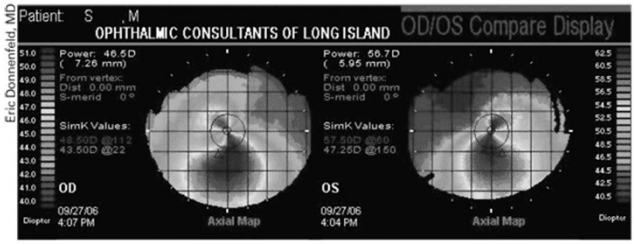


KC Detection - Past



- Central K > 47 D and/or **increases** in Ks
- (Frequent) **Increases** in Cyl
- High baseline Cyl (ie, >2D)
- (Frequent) **Increases** in Myopia
- Unexplained BCVA <20/20 or reduced Vr-QoL
- Irregular (scissor) reflex

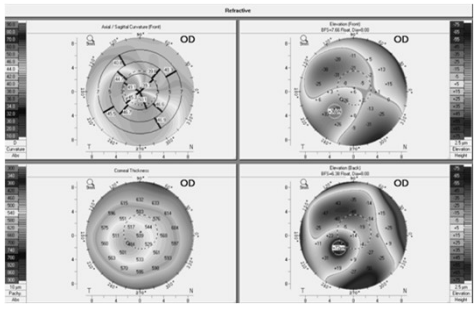
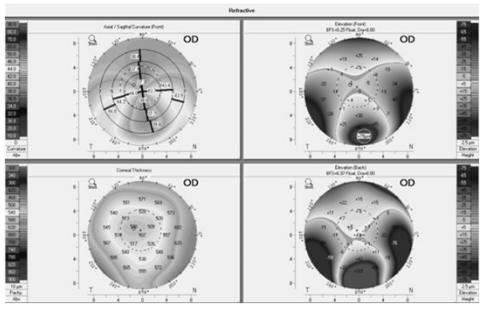
KC Detection – Past/Present



An eye like this, with skewed astigmatism, is a relative contraindication for a multifocal intraocular lens and limbal relaxing incisions, say experts.

- Central K > 47 D or **increases** in Ks
- Non-Orthogonal topo pattern
  - **Asymmetry** and/or radial skew
- I/S Ratio (Hemi-meridianal steepening)
  - At 6mm diameter, I/S ≥ 1.8 – 2.0 is likely abnormal
  - At 6mm diameter, I/S ≥ 1.5 is questionable
- **"Small" & consistent increases** in the above risk characteristics over time

KC Detection - Present

- Posterior elevation **>18mi** (myopia) & **>28mi** (hyperopia)
  - Anterior elevation >8mi
  - Elevation values are specific for BSF reference shape
- On pachymetry map
  - **Interocular asymmetry** at thinnest location **≥ 25mi** (less than **1%** population)
  - Apical decentration of > 0.8 mm or
  - > 50mi disparity between superior & inferior cornea
- Personally, rate of pachymetric distribution & changes over time are more weighted

KC Detection & Monitoring - Present

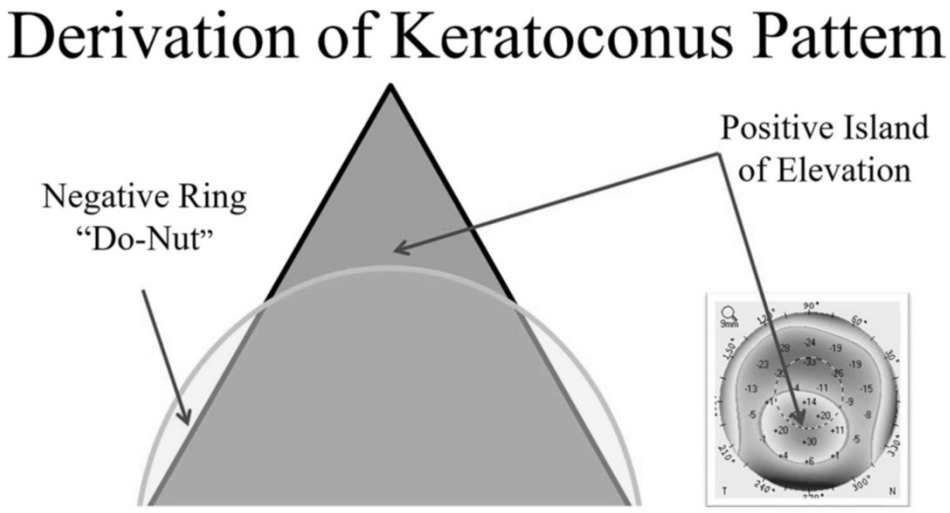
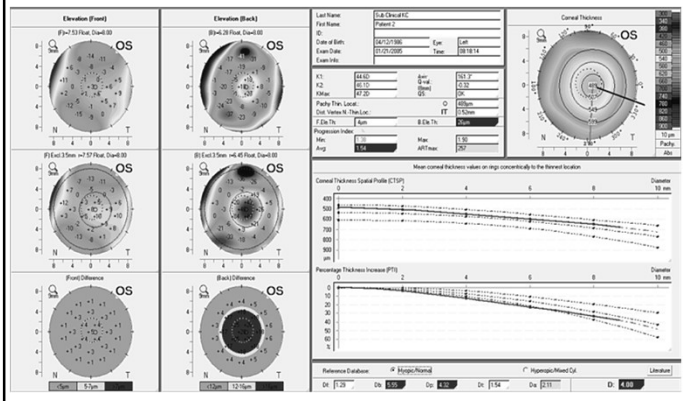
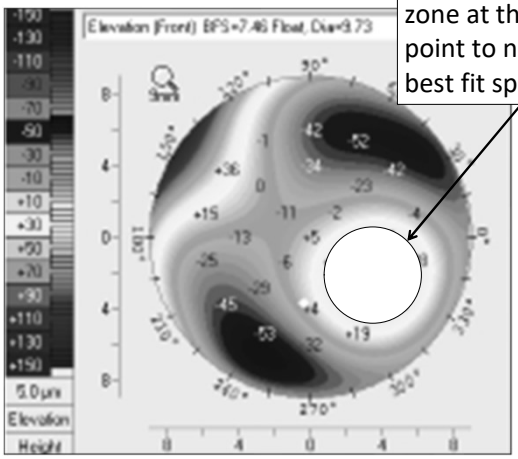


Figure adapted from "Belin MW, Jang HS, Borgstrom M. Keratoconus: Diagnosis and Staging. Cornea. 2022 Jan 1;41(1):1-11. "

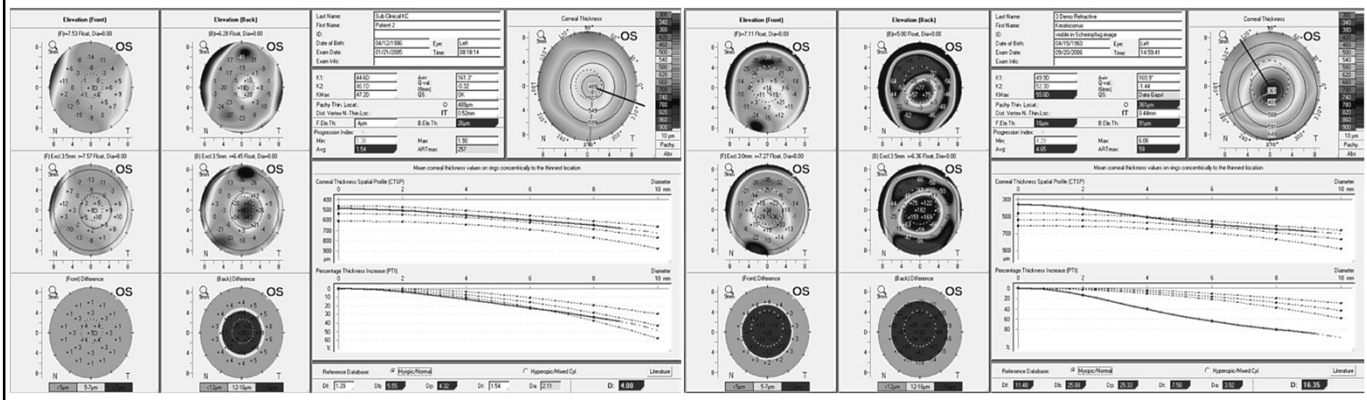
KC Detection & Monitoring - Present





Radius of Curvature
Measured at Thinnest Point

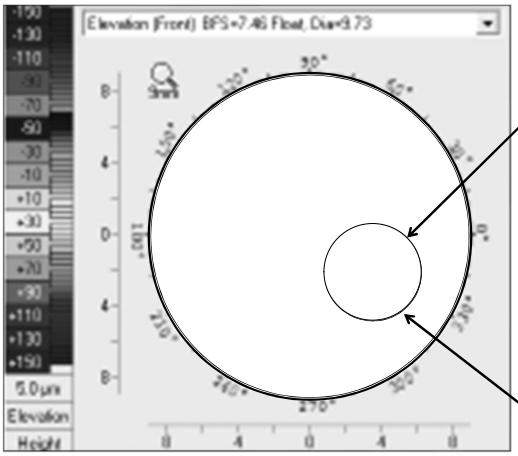
KC Detection & Monitoring - Present



Final "D" - Sensitivity 0.941 / Specificity 0.944

KC Detection & Monitoring - Present

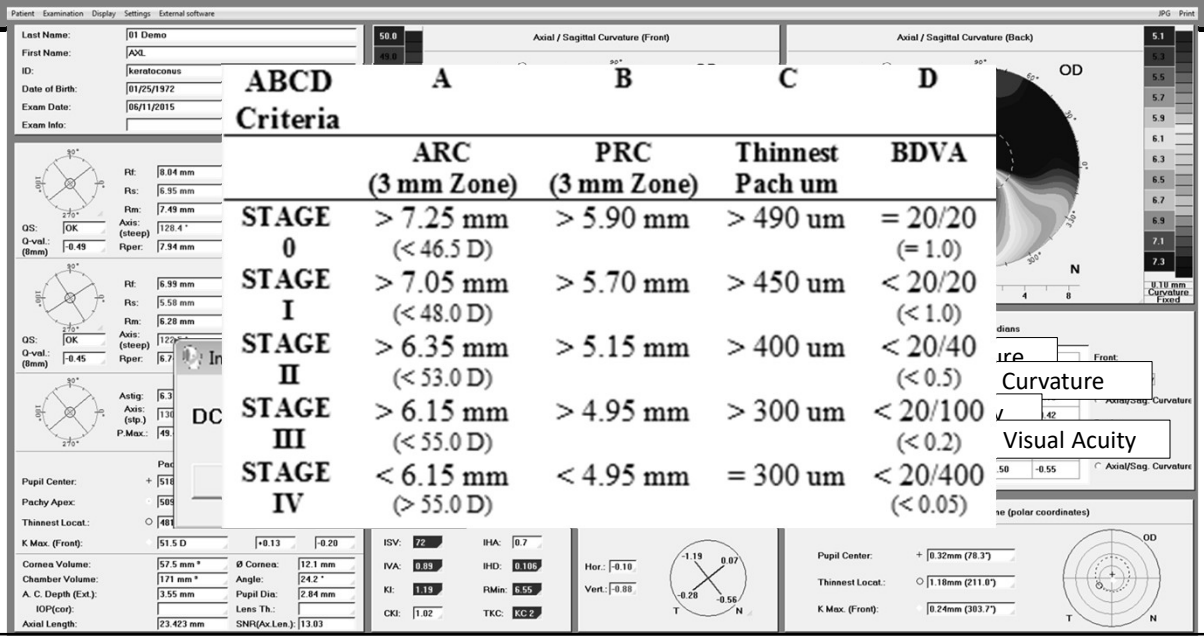
Radius of Curvature Measured at Thinnest Corneal Point



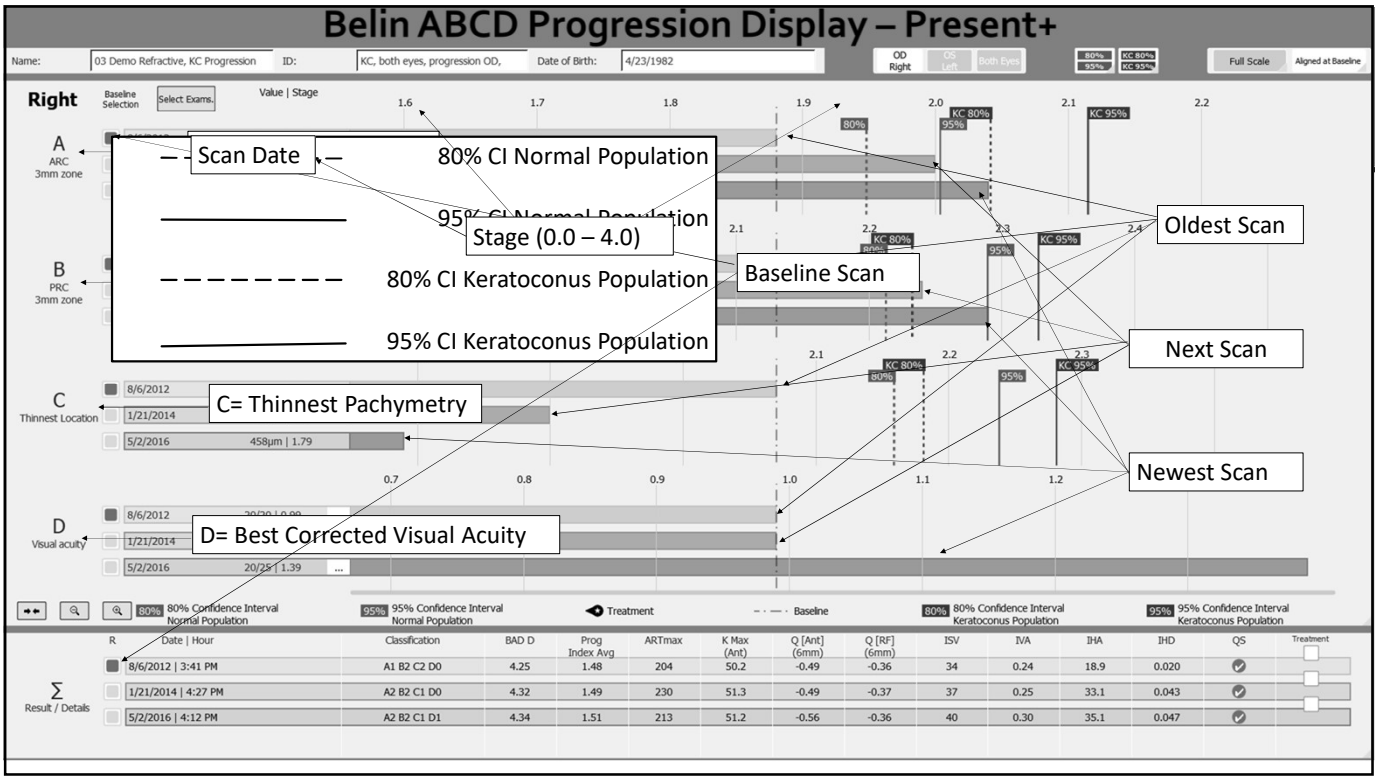
The Belin/Ambrosio excludes a 3mm-4mm zone at the thinnest point to normalize the best fit sphere.

The Belin ABCD Staging measures the ROC and pachymetry in this area to assess severity and track progression.

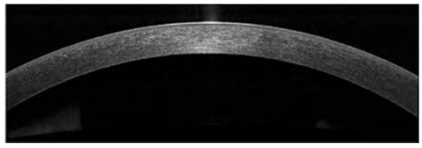
Topometric / KC Staging Display – Present+

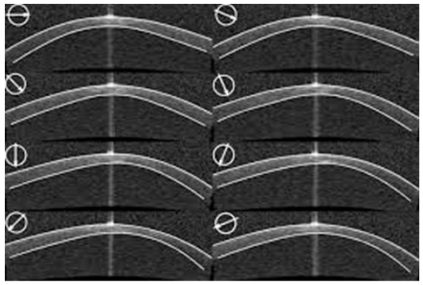


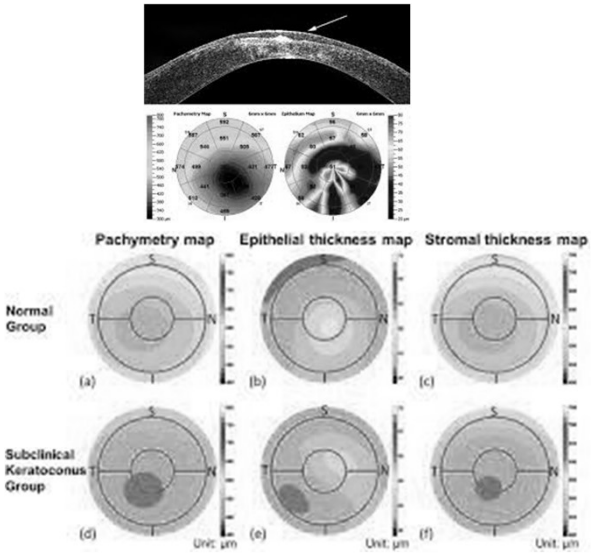
ABCD Criteria	A	B	C	D
	ARC (3 mm Zone)	PRC (3 mm Zone)	Thinnest Pach um	BDVA
STAGE 0	> 7.25 mm (< 46.5 D)	> 5.90 mm	> 490 um	= 20/20 (= 1.0)
STAGE I	> 7.05 mm (< 48.0 D)	> 5.70 mm	> 450 um	< 20/20 (< 1.0)
STAGE II	> 6.35 mm (< 53.0 D)	> 5.15 mm	> 400 um	< 20/40 (< 0.5)
STAGE III	> 6.15 mm (< 55.0 D)	> 4.95 mm	> 300 um	< 20/100 (< 0.2)
STAGE IV	< 6.15 mm (> 55.0 D)	< 4.95 mm	= 300 um	< 20/400 (< 0.05)



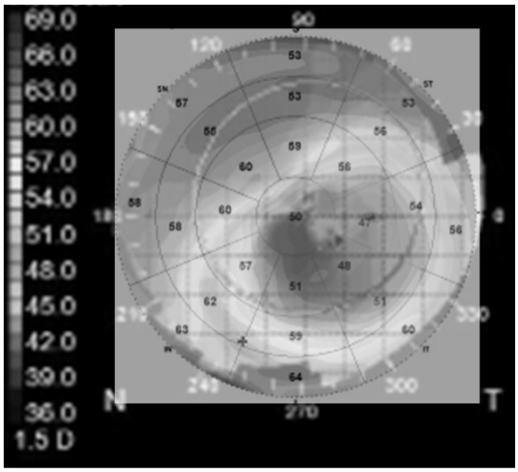
KC Detection – Present v Future

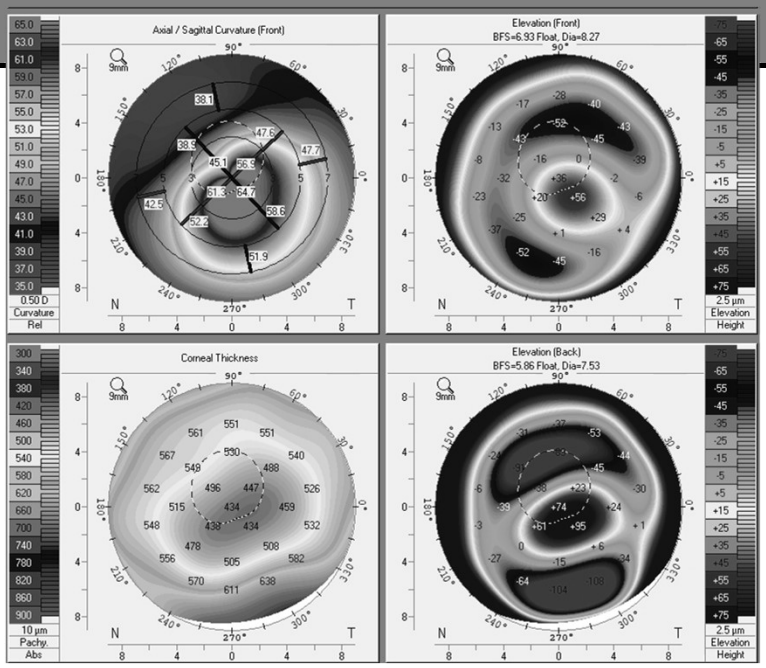






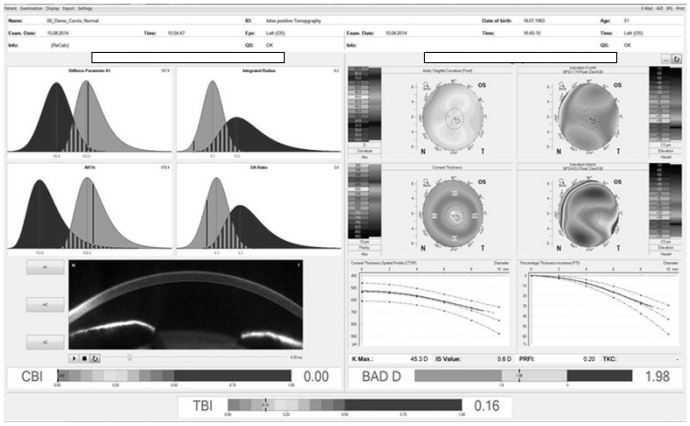
Keratoconus Case





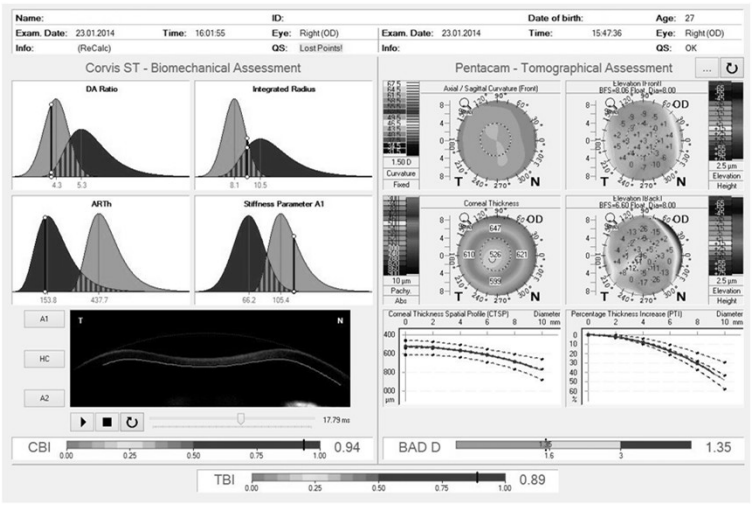
Slide Courtesy, Beeran Meghpara, MD
Wills Eye Hospital

KC Detection - Future



NOT FDA APPROVED in US

Tomographical / Biomechanical Assesment OD



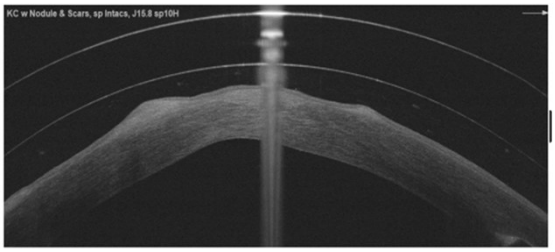
"Biomechanical changes likely occur before tomographic changes" – Cynthia Roberts OD, PhD

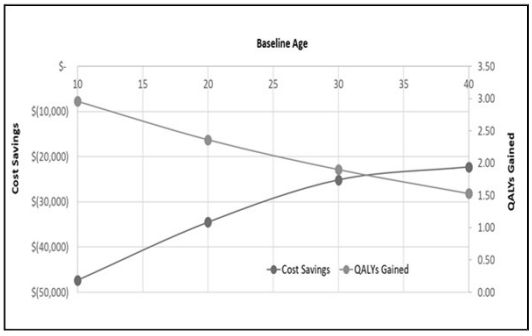
CBI (0.94) and TBI (0.89) already abnormal OD

NOT FDA APPROVED in US

Management Challenges

- Decline in quality-of-life with progression
  - Scleral CL improve BCVA & Vr-QoL[1]
  - High prevalence (40.6%) of depression in KCN especially with binocular CL use (GP and/or hybrid) [2]
  - Increased chair time in KCN management
- Cost of treatments over lifetime[3]
  - Conventional Tx (ie, Spec, CLs & tectonic surgery)
  - Medical treatment (new U.S. health economic data)
- Early Detection of KCN & KCN Progression
  - Preserving best visual potentials
  - Cost of technology
  - Routine pediatric screening for KCN





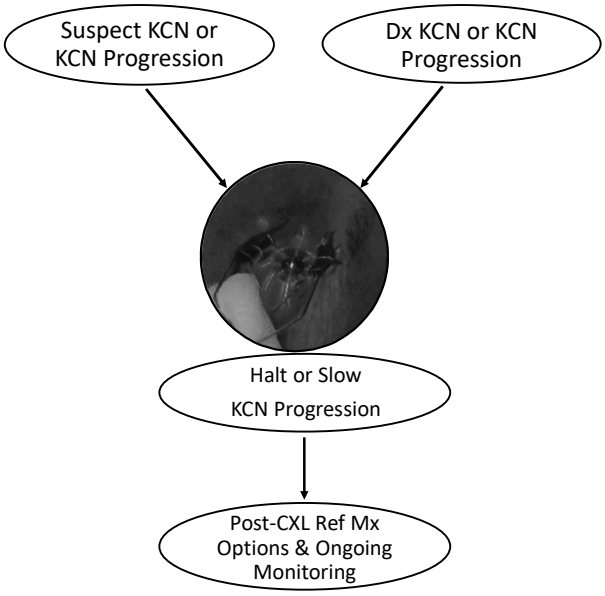
1. EO Kreps, K Pesudovs, I Claerhout, C Koppen. Mini-Scleral Lenses Improve Vision-Related Quality of Life in Keratoconus. Cornea. 2021 Jul 1;40(7):859-864
2. Al-Dairi W, Al Sowayigh OM, Al Saeed AA, Alsaad A. Depression Among Keratoconus Patients in Saudi Arabia. Cureus. 2020 Dec 6;12(12):e11932.
3. Lindstrom R, Berdahl J, Donnenfeld E. Cross-Linking versus Conventional Management for Keratoconus: A Lifetime Economic Model. *J Medical Economics* 2020.

Current & Future State of KC Management

Breaking Conventional KCN Cycle: Collaboration Opportunity

Keratoconus (KCN) is an ideal condition for collaboration between optometrists & ophthalmologists.

1. **The 1st challenge** is detecting KC early before vision is compromised
2. **The 2nd challenge** is to prevent further corneal changes and corresponding loss of vision that may lead to a corneal transplant
3. **The 3rd challenge** is helping patients see better, wherever they are in the KCN staging

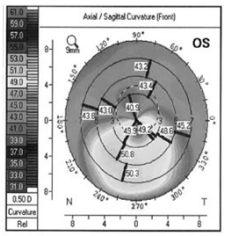


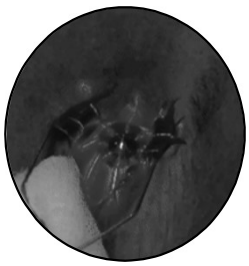
When to refer for additional testing?

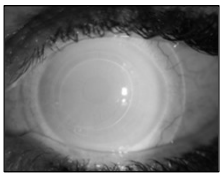
- 1. Frequent Refractive changes
- 2. Frequent CL refit
- 3. K ≥ 47D
- 4. Subjective visual complaints and worsening of symptoms
- 5. BCVA < 20/20 with no anatomical explanation
- 6. Family history
- 7. Medical Hx (ie, atopic eye disease, chronic eye rubbing)

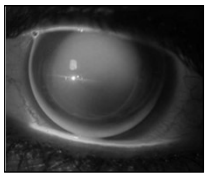
New KCN Mantra (Detect Early & Stabilize)

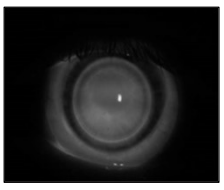
Diagnose **Early** ⇨ Stop Progression ⇨ **Maintain Best Possible BCVA Potential**











What Got Cross-linking Approved By FDA

Inclusion Criteria

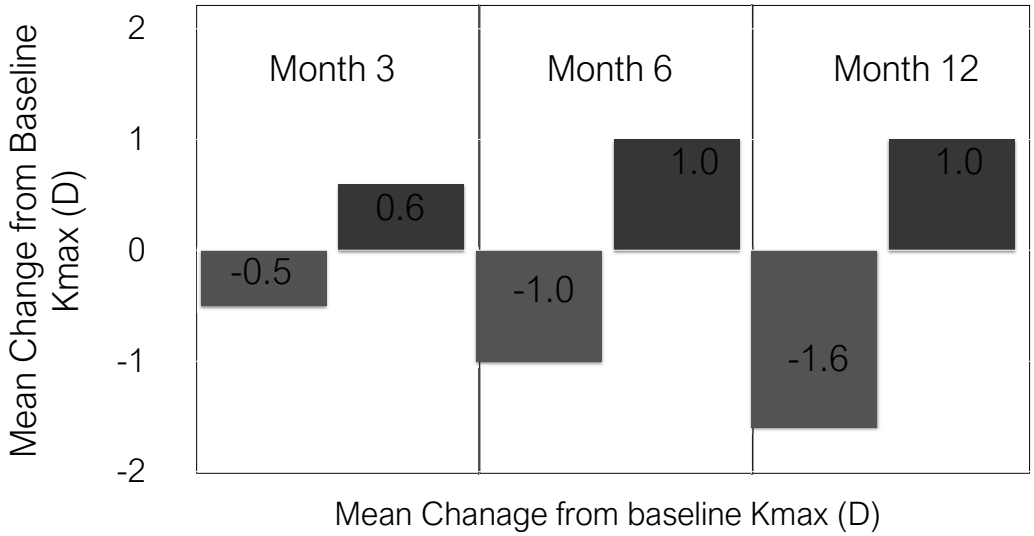
- 14 YO or older in age (up to 65 YO)
- Dx of KCN or ectasia s/p refractive surgery
- Axial topo consistent with KCN
  - K of 47 or greater
  - I:S ratio > 1.5
- BSCVA worse than 20/20 on ETDRS chart
- Corneal thickness **300 microns or greater**

Progression ≤ 24 Months

- Increase in 1 D in steepest K value, or
- Increase of 1 D in manifest astigmatism, or
- Myopic shift of 0.5 D on subjective manifest refraction, or
- Decrease of 0.1 mm in the back optical zone radius in rigid contact lens wearers

1. Hersh PS, Stulting RD, Muller D, Durrie DS, Rajpal RK; United States Crosslinking Study Group. United States Multicenter Clinical Trial of Corneal Collagen Crosslinking for Keratoconus Treatment. Ophthalmology. 2017 Sep;124(9):1259-1270.

Progressive KCN Mean Change Kmax (D)



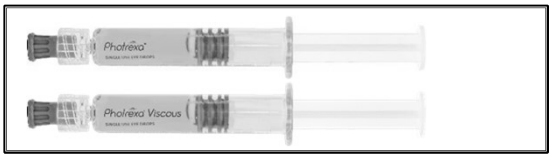
FDA-Approved CrossLinking Procedure & Platform

Indications

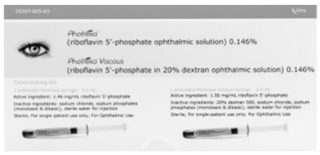
- Progressive Keratoconus & Corneal Ectasia Following Refractive Surgery (Post-LASIK Ectasia)

Approved Drug-Device Platform

- **Photrexa® Viscous** (riboflavin 5'-phosphate in 20% dextran ophth soln)[1]
- **Photrexa®** (riboflavin 5'-phosphate ophth soln)[1]
- **KXL®** ultraviolet light delivery system in corneal collagen cross-linking Procedures.[2]



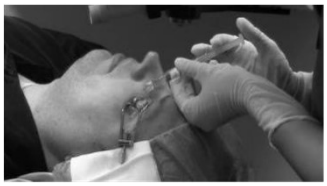
GMP API & GMP Manufactured



[1] Manufactured for Avedro. | [2] Manufactured by Avedro

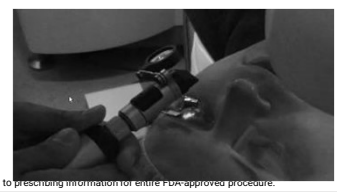
FDA-Approved Cross-Linking Procedure & Platform

1. Remove epithelium.

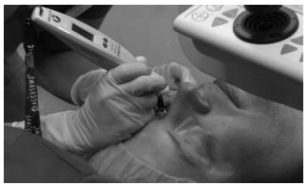


2. Soak cornea with **Photrexa® Viscous** (riboflavin 5'-phosphate in 20% dextran ophthalmic solution).

✓ 30 minutes



3. Check for flare.



4. Once flare is observed, measure corneal thickness.

✓ If corneal thickness is **less than 400 µm, instill 2 drops of hypotonic Photrexa®** *(riboflavin 5'-phosphate in ophthalmic solution)* **until the corneal thickness increases to at least 400 µm**.

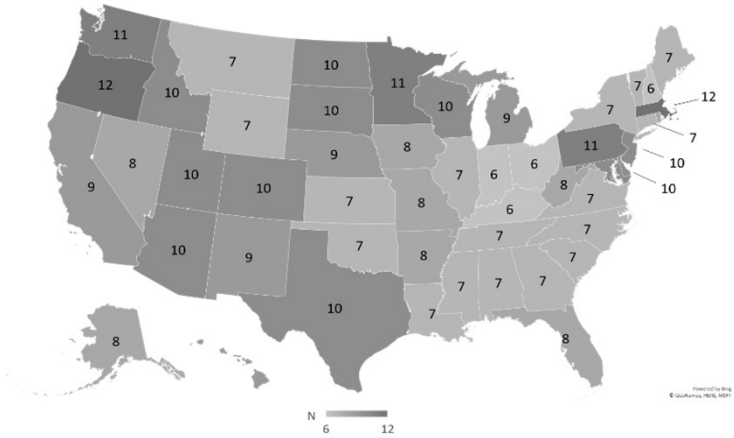
5. Irradiate for 30 minutes.

✓ Continue applying Photrexa® Viscous *(riboflavin 5'-phosphate in 20% dextran ophthalmic solution)* during irradiation.

Refer to prescribing information for entire FDA-approved procedure.

Patient Q&A: Insurance Coverage?

All **50 states** have more than **6 plans** that cover cross-linking



FDA-approved iLink is broadly covered in the U.S.

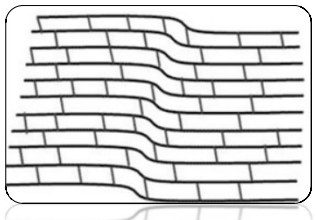
6 National and

62 Regional Health Plans

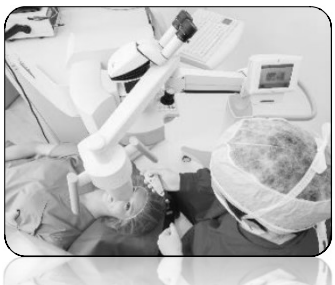
96% of Commercial Lives Covered

For a comprehensive up to date list of increasing approved carriers, please visit
www.livingwithkc.com

Patient Q&A: Does it "take away" keratoconus?



Aim of cross-linking is to halt or slow disease progression



Cross-Linking is <u>not</u> a refractive procedure

Post-op evaluation for visual correction & ongoing corneal monitoring are still recommended

Patient Q&A: Why do I need CXL?

1. CXL may improve lifetime outcomes & economic burdens

4,000 **Eyes individually simulated across 2,000 patients**

- *Mean age at baseline 31 yrs., mean follow-up 52.3 yrs.*
- *4:1 ratio of slow to fast progressors.*

26% **Reduction in rate of PK in iLink treated eyes vs. control**

- *Slow-progressors: 0.3% iLink and 8.7% control eyes underwent PK.*
- *Fast-progressors: 2.5% iLink and 92.7% control eyes underwent PK.*

28 Yrs **Fewer years spent in advanced stages of disease (AK 3 & 4)**

- *Drives impact on lost productivity; out-of-pocket costs (lens type).*

Lindstrom R, Berdahl J, Donnenfeld E. Cross-Linking versus Conventional Management for Keratoconus: A Lifetime Economic Model. *J Medical Economics* 2020.

Patient Q&A: Why do I need CXL?

2. CXL early may results in better QoL

REVIEW

Measurement of Quality of Life in Keratoconus

Himal Kandel, PhD, Konrad Pesudovs, PhD,† and Stephanie L. Watson, MBBS, PhD**

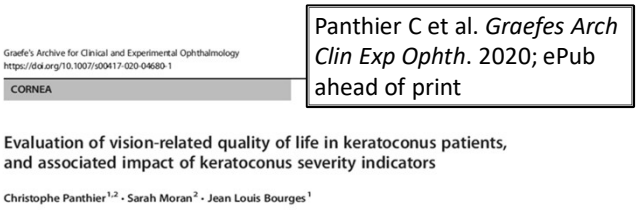
Purpose: To identify and assess the quality of questionnaires used to measure quality of life in keratoconus and guide selection of the most appropriate questionnaire for evaluating the impact of keratoconus.

Key Words: keratoconus, patient-reported outcomes, quality of life, questionnaire

(*Cornea* 2020;39:386–393)

Kandel et al *Cornea* 2020; 39:386- 393

- Many patients who have better visual acuity with contact lenses than with spectacles **may not be able to wear contact lenses all day.**[9,10]
- **Ocular pain and discomfort are significantly more in people with keratoconus wearing contact lenses**, particularly RGP contact lenses.[3,6]
- The impact of keratoconus on QoL therefore may be **disproportionate to the clinical measures** such as best corrected visual acuity.[8,12]



Graefe's Archive for Clinical and Experimental Ophthalmology
https://doi.org/10.1007/s00417-020-04680-1

CORNEA

Evaluation of vision-related quality of life in keratoconus patients, and associated impact of keratoconus severity indicators

Christophe Panthier[1,2] · Sarah Moran[2] · Jean Louis Bourges[1]

Panthier C et al. *Graefes Arch Clin Exp Ophth*. 2020; ePub ahead of print

- BCVA in the better eye is the most important factor contributing to patient's VR-QoL
- Clinicians should consider initially targeting the better eye, as this may have a greater impact on the patients' quality of life.
- **CXL contributed to higher VR-QOL scores**
  - **Early stages of KC: avoid deterioration of BCVA**
  - **In late stages of KC: decrease stress and anxiety concerning the progression of the disease**

Patient Q&A: Why do I need CXL?

3. Synergy with optical rehabilitation

- FDA-approved corneal cross-linking procedure offers
  - Coverage for over 95% of commercially insured lives
  - Proven safety and efficacy
  - Slowing or halting keratoconus progression may enable patients to continue to tolerate contact lenses[1]

FDA-approved CXL
Slow or halt progression to help preserve vision

Scleral Lenses
Vision Rehabilitation
Address vision needs

The proprietary **iLink** epithelium-off procedure incorporates **Photrexa® Viscous** (riboflavin 5'-phosphate in 20% dextran ophthalmic solution) *and* **Photrexa®** (riboflavin 5'-phosphate ophthalmic solution) which are photoenhancers indicated for use with the **KXL®** ultraviolet light delivery system.

1. Singh K, Bhattacharyya M, Arora R, Dangda S, Mutreja A. Alterations in contact lens fitting parameters following cross-linking in keratoconus patients of Indian ethnicity. *Int Ophthalmol*. 2018 Aug;38(4):1521-1530.

Patient Q&A: Couldn't I wait longer?

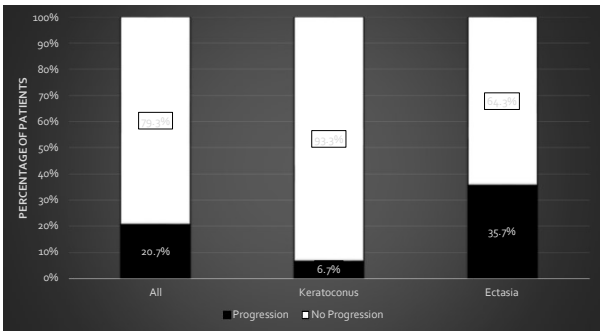
Further KC worsening may occur while progressive KC eyes wait to receive CXL

- **Shah et al (UK) [1]**
  - **All 46 progressive KC worsened with wait time made longer by COVID pandemic**
  - **Typical Avg wait time is 182 ± 65 days & COVID restrictions added at least 3 mo**
  - **Worsened keratometric indices & lost nearly 1 line of VA**
- **Goh et al (New Zealand) [2]**
  - **39.6% (n=38) of 96 eyes further worsened over 153 ± 101 days**
- **Chatzis et al (Switzerland) [3]**
  - **While waiting to document KC progressionin young KC patients (age 9 to 19 Yr)**
  - **88% (n=52) of 59 eyes were found to have Kmax ≥1D within 12 mo**
- **Romano et al (UK/Italy) [4]**
  - **25% of 104 eyes worsened in Kmax over 84.8 ± 62.9 days**
  - **Progressive KCN < 18 Yrs – Suggest no more than 6 weeks wait time**
  - **Progressive KCN > 18 Yrs – Suggest no more than 12 weeks wait time**

1. Shah H, Pagano L, Vakharia A, Coco G, Gadhvi KA, Kaye SB, Romano V. Impact of COVID-19 on keratoconus patients waiting for corneal cross linking. Eur J Ophthalmol. 2021 Mar 15:11206721211001315.
2. Goh YW, Gokul A, Yadegarfar ME, Vellara H, Shew W, Patel D, McGhee CNJ, Ziaei M. Prospective Clinical Study of Keratoconus Progression in Patients Awaiting Corneal Cross-linking. Cornea. 2020 Oct;39(10):1256-1260.
3. Chatzis N, Hafezi F. Progression of keratoconus and efficacy of pediatric [corrected] corneal collagen cross-linking in children and adolescents. J Refract Surg. 2012 Nov;28(11):753-8. doi: 10.3928/1081597X-20121011-01. Erratum in: J Refract Surg. 2013 Jan;29(1):72.
4. Romano V, Vinciguerra R, Arbabi EM, Hicks N, Rosetta P, Vinciguerra P, Kaye SB. Progression of Keratoconus in Patients While Awaiting Corneal Cross-linking: A Prospective Clinical Study. J Refract Surg. 2018 Mar 1;34(3):177-180

Patient Q&A: How Long does it last? 10-Yr Epi-Off CXL Outcomes in US

- In general, CXL appears to remain stable 10 years (N=30 eyes in 16 Px – 15 KC Eyes & 15 Ectasia eyes)
  - Stable topography
    - 77% of the entire cohort
    - 87% of keratoconus eyes
    - 67% of ectasia eyes
  - Stable BSCVA
    - 86% of the entire cohort
    - 100% of keratoconus eyes
    - 71.4% of ectasia eyes
- Progression was defined
  - Steepening of Kmax ≥2D
  - Worsening in VA (UCVA or BSCVA) ≥ 2 logMar lines
  - Belin ABCD Progression display

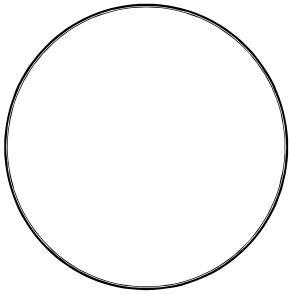


Courtesy, Steven Greenstein, MD

The CLEI Center for Keratoconus

Post-Op Considerations

- A bandage contact lens should be applied
- Similar to standard of care for postoperative management of PRK patients, post-op regimen varies but may include:
  - Antibiotic
  - Steroid
  - NSAID
  - Lubricating drops
  - Opioid (Vicodin, OxyContin, etc..)
- Treatment Emergent Adverse Events from Phase 3 (TEAEs)
  - **Majority of AEs reported resolved during the 1st month**
  - Resolved within 6-months: Corneal epithelium defect, corneal striae, punctate keratitis, photophobia, dry eye, eye pain, and decreased visual acuity

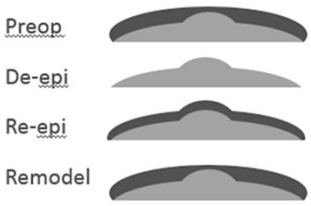


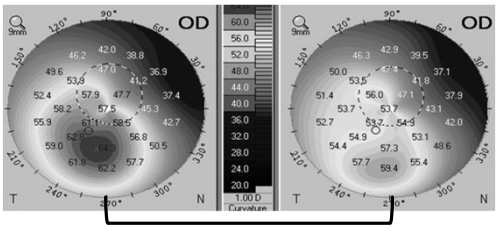
Phase 3 TEAE Examples - Progressive KCN

- Corneal Opacity (haze)
- Corneal Epithelium Defect
- Punctate Keratitis
- Corneal Striae
- Eye Pain
- Blurred Vision
- Reduced Visual Acuity

Post-op CL Fitting: When to Start?

- Initial apical epithelial hyperplasia & subsequent remodeling
  - Allow approx **4 weeks** after CXL before consider refit
    - Ideally, patient RTC at 4 weeks with habitual lens to examine fit & VA
    - If acceptable, wait longer to allow for more elevation self-adjustments
    - If non-functional or new CL wearer, consider CL fitting (or at least CL refraction)
    - **Many advanced contact lens options exist today. But regardless of lens design, increased contact lens follow-up needed during the first 12 months after CXL**





K_{max}

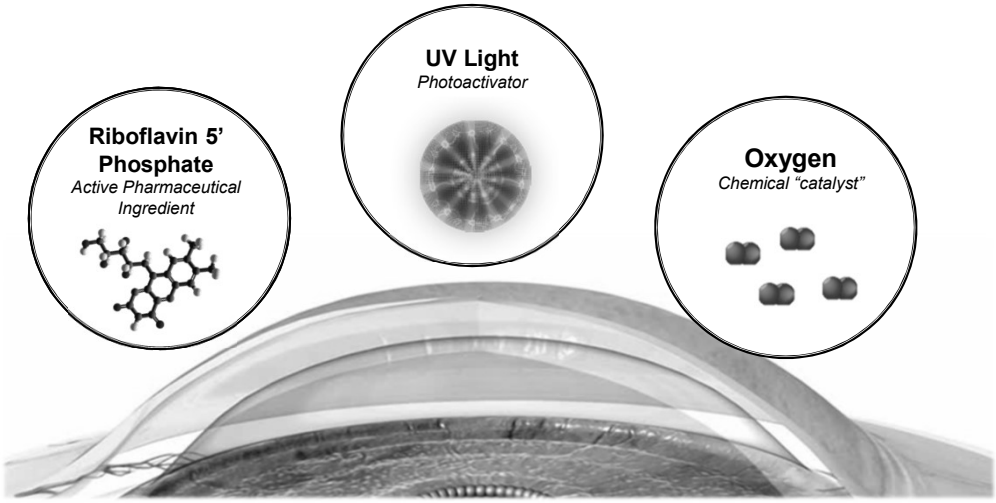
Summary of General Follow-Up Schedule

VISIT	PLAN
Day 1 to 1 Week	· Topical antibiotic, steroid · Frequent lubricants · No eye rubbing · Remove BCL once epithelium heals
Month 1	· OCT Imaging · Tomography / Topography · Vision assessment · **Contact lens refitting evaluation**
Month 3, 6, 12 **(Follow-ups potentially performed and billed by diagnosing physician depending on practice preference)**	· Continued evaluation utilizing tomography / topography · Vision assessment

No Global Period! Follow-up visits can be billed to insurance

Enhancing CXL Mechanism of Action

- Corneal collagen cross-linking combines UV light + Riboflavin (vitamin B2) drops
- *UV light and oxygen activate the pharmaceutical agent to form additional covalent bonds within the intracellular matrix of the collagen stroma (= corneal stiffening)*



US Phase III Pivotal Trial of Glaukos' Epi-on Cross-linking Therapy

Epi-on Treatment Demonstrated the Ability to Halt or Reduce the Progression of Keratoconus versus Observed Disease Progression in a Placebo-Control Arm

279 Eyes with Progressive Keratoconus
at 14 US Clinical Sites, 2:1 Randomization

189 Active Eyes	**90 Control Eyes**
• Epi-on Ophthalmic Solution • Supplemental Oxygen • Higher Energy, Pulsed UV	• Placebo Solution • No Oxygen Delivery • Sham UV Treatment

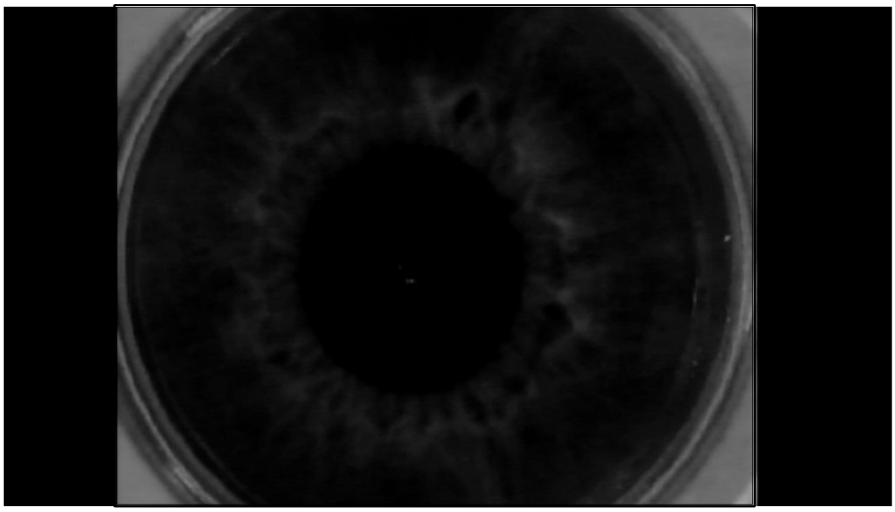
Primary Efficacy Endpoint:
Difference of ≥ 1 D between treatment groups in mean change in Kmax from baseline at month 6

Control eyes eligible for cross-over at month 6
All eyes followed an additional 6-months

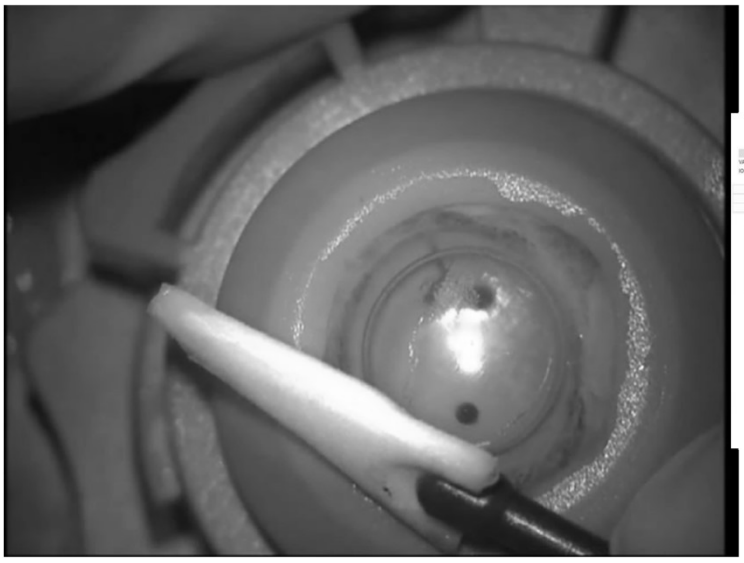
- **Achieved prospectively defined primary efficacy outcome, demonstrating Kmax treatment effect of -1.0D (p = 0.0004)**
- 98% of placebo randomized patients elected to cross-over to epi-on treatment
- Well-tolerated, majority of adverse events reported were mild and transient in nature, no change in corneal endothelial cell count over the course of the trial
- Forms the basis for planned regulatory submission (U.S. NDA) by Glaukos in 2022

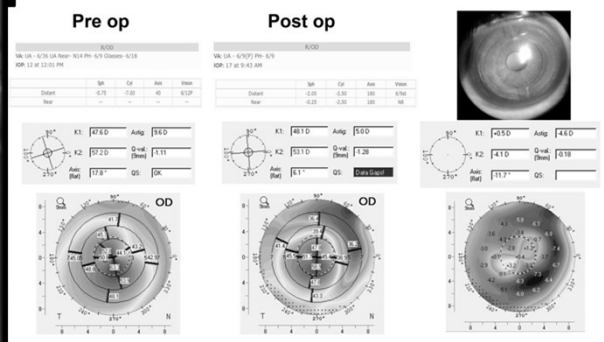
Epithelium-on cross-linking is Not approved by the US FDA

Intrastromal Ring Segment (ICRS)



Corneal Allogenic Intrastromal Ring Segments (CAIRs)



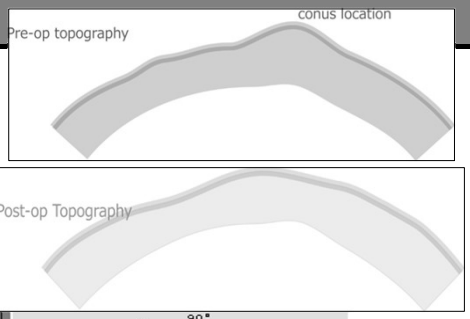


DR. SOOSAN JACOB, MS, FRCS, DNB

NOT FDA APPROVED in US

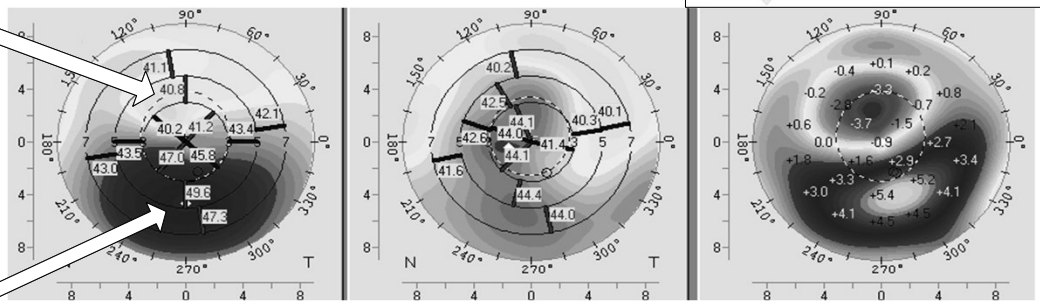
Refractive Corrections spCXL: TG-PRK

- TG-PRK Goals after CXL:
  - Ablation driven by individualized topo data to normalize anterior cornea
    - Pending remaining stromal bed thickness, may possibly further reduce residual HOA
  - Improve optical rehabilitation outcomes



Hyperopic Tx

Myopic Tx



NOT FDA APPROVED for KCN in US

Nattis A, Donnenfeld ED, Rosenberg E, Perry HD. Visual and keratometric outcomes of keratoconus patients after sequential corneal crosslinking and topography-guided surface ablation: Early United States experience. J Cataract Refract Surg. 2018 Aug;44(8):1003-1011.

Topo-Guided PRK + CXL: Early US Experience

- Treatment parameters under Topo-laser FDA limitations
  - Prefer 6.5OZ if RSB ≥ 300µm
    - If possible, treat all refractive error
  - If RSB < 300 µm, then reduce OZ to 6.0mm
    - Cyl up to -3D, and then sphere correction

- 12 Months results after TCAT/Topo-PRK
  - UCVA – mean 4 line improvement
  - CDVA – mean 2 line improvement
  - No adverse event reported, ie, No infections, scarring, excessive thinning after treatment or during follow-up

NOT FDA APPROVED for KCN in US

Nattis A, Donnenfeld ED, Rosenberg E, Perry HD. Visual and keratometric outcomes of keratoconus patients after sequential corneal crosslinking and topography-guided surface ablation: Early United States experience. J Cataract Refract Surg. 2018 Aug;44(8):1003-1011.

Reduction of Corneal Transplant Utilization

Oslo University Hospital

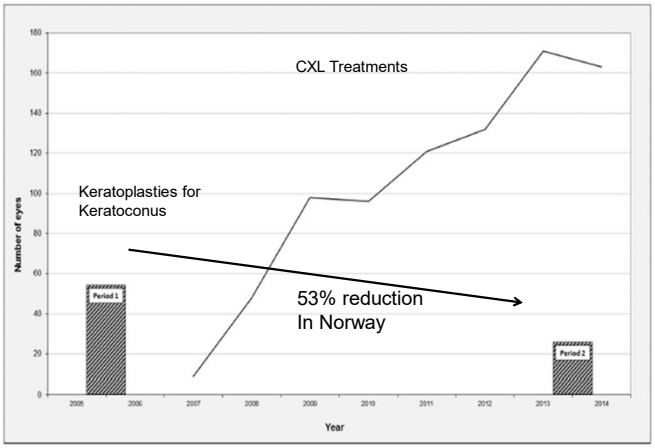


FIGURE 1. The annual number of CXL treatments from 2007 to 2015 (blue line), and the number of keratoplasties for keratoconus in period 1 (2005–2006) and period 2 (2013–2014).

Sandvik et al., Cornea 2015;34:991–995

Risk Factors For Corneal Transplantations

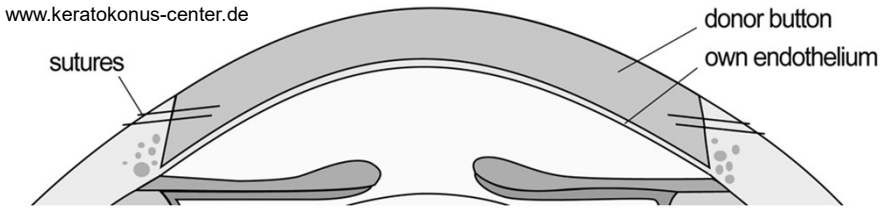
- **"Future research should examine if young patients with these conditions may benefit from more frequent follow-up and/or early CXL to reduce the need for subsequent keratoplasty." [1]**
- **N.B. – Atopic diseases & Down syndrome were not associated with higher risk of KP in the study[1]**

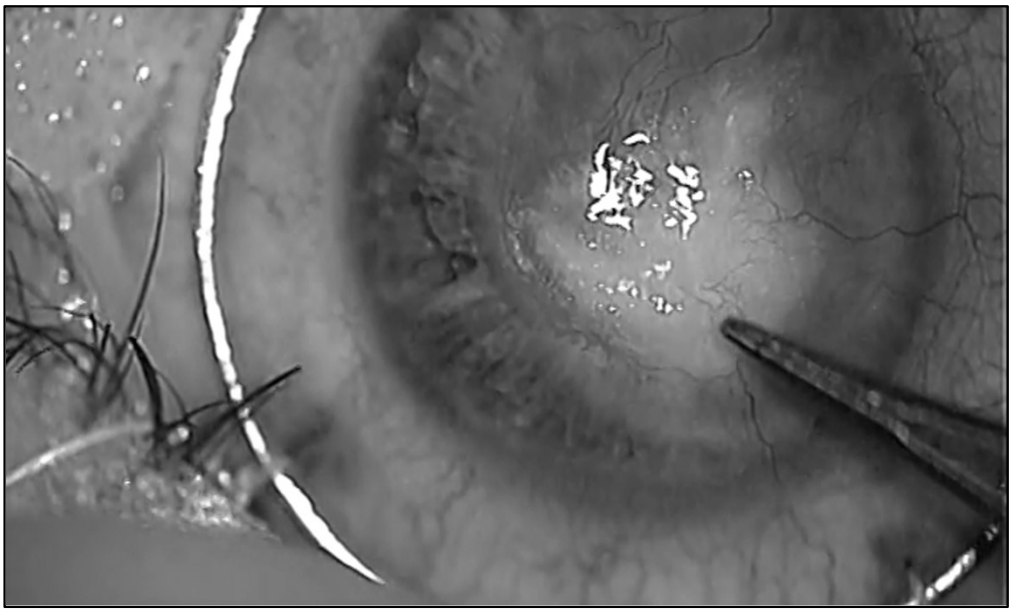
Logistic Regression Co-variates		Odds Ratio (95% CI, Univariate Model)	P value
Age (Reference 10 - 19 Yrs)			
	20 – 29 Yrs	1.87	< 0.001
	30 – 39 Yrs	1.81	<0.001
	40 – 49 Yrs	1.70	<0.001
Ocular Conditions			
	Corneal Hydrops	3.19	< 0.001
	Glaucoma	0.56	<0.001
	Contact Lens	0.70	<0.001
Systemic Conditions			
	Leber Congenital Amaurosis	2.23	0.059
	Sleep Apnea	1.63	<0.001
	Diabetes Mellitus	1.27	<0.001
	Depression	1.26	0.004

1. Thanitcul C, Varadaraj V, Canner JK, Woreta FA, Soiberman US, Srikumaran D. Predictors of Receiving Keratoplasty for Keratoconus. Am J Ophthalmol. 2021 Nov;231:11-18.

DALK vs PKP

- PKP carries lifelong risk of endothelial rejection, so DALK may benefit KC patients
  - Typically, younger with healthy endothelium
  - Higher cumulative risk
  - Endothelial protection over PKP still debated
  - Up to 25% of cases require PKP conversion
  - Injectable cell regeneration therapy in future?





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Questions?
Thank you

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