
OSI
Ocular Surface Insight
Issue 14
Beware of the Beast in Beauty
Lab on chip: biomarkers reality to clinics
An NHS trainee perspective on dry eye disease

Quantel medical

info@daybreakmedical.com
+44 (0) 208 894 6601

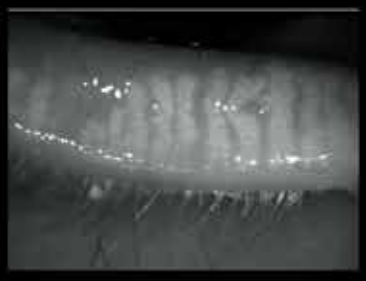
DAYBREAK MEDICAL

• ILLUMINATE •

# I.P.L. TREATMENT OF DRY EYE

## TREAT THE ROOT CAUSES OF DRY EYE

1. **M.G.D**
Meibomian Gland Dysfunction



2. **INFLAMMATION**
Rosacea and blepharitis

3. **DEMODEX**

c.stim™


+


## MULTIPLE CLINICAL RESULTS:

- Improved tear film quality
- Better meibum quality and expression
- Reduction in patient symptoms and neuropathic pain relief
- Reduced inflammatory markers in tears

LEARN MORE?

daybreakmedical.com

# Ocular Surface Insight

"Coming together is a beginning; keeping together is progress; working together is success."

Henry Ford

## Welcome to the latest issue of **OSI**.

We are very excited to announce that OSI will be running a 2-day conference on the 24-25 June in London. We have a fantastic group of speakers that are innovative experts in their field. We are also working in partnership with TFOS and MCLOSA with dedicated sessions in the programme. You can see more details about the content and speakers in the magazine and I would encourage you to keep checking our website for the full programme which will be available soon.

In this issue Sabrina Vaccaro and her team are sharing insights to an unusual case of corneal melting with fascinating photographs. Rohit Shetty and Dr Pooja Khamar are sharing their amazing work and day-to-day findings on biomarkers in clinic.

My colleague Radhika Rampart has written a thought-provoking piece about Artificial Intelligence in Cornea and Refractive Surgery.

We are also grateful to have Prof. Jennifer Craig's thoughts and views yet again in the OSI magazine for a Q & A regarding TFOS "A Lifestyle Epidemic: Ocular Surface Disease" study.

The strength of OSI lies with our great editorial board with active and interested contributors and readers. I hope to count on your continued contribution.

*Samer Hamada*

Samer Hamada,
MD, MSc, DO (hons), FRCSEd, FRCOphth

**osimag.co.uk**

# About us


## Ocular Surface Insight

**Editor in Chief**
Samer Hamada

**Published by**
VisionDuo Ltd.

**Sales & Advertising**
Denise Castell
denise@visionduo.com

**Business Development & Marketing**
Åsa Baudin
asa@visionduo.com

**Conference & Educational Events**
events@visionduo.com

**Accounts**
accounts@visionduo.com

Media No. 0001

Published March 2022




If you wish to receive your own future copies of OSI magazine, please email: subscriptions@visionduo.com.

***We stand with Ukraine!***

## Contributors

**Mr. Samer Hamada**
Consultant Lead
*Queen Victoria Hospital East Grinstead*
Director and Lead Consultant
*Eye Clinic London*

**Mr. Brian Tompkins**
BSC(Hons) FCOptom, FBLCA
Director & Optometrist
*TK & S Optometrists Ltd.*

**Dr. David Lockington**
Consultant Ophthalmologist
Cataract & Corneal Surgeon
*NHS Greater Glasgow & Clyde*

**Ms Vivian Ho**
Associate Consultant Ophthalmologist
*United Christian Hospital Hong Kong*

**Prof. Jennifer Craig**
Associate Professor
*The University of Auckland New Zealand*

**Dr. Sabrina Vaccaro**
*Ophthalmology Resident, Department of Ophthalmology*
*University of Magna Graecia, Catanzaro, Italy*

**Miss. Radhika Rampat**
MBBS BSc (hons) FRCOphth
Locum Consultant Ophthalmic Surgeon
*Corneo-Plastic Unit*
*Queen Victoria Hospital,*
*East Grinstead*

**Dr. Pooja Khamar**
Consultant Ophthalmologist & Lead Trainer
*Narayana Nethralaya Eye Institute Bangalore, India*

**Dr. Rohit Shetty**
DNB, FRCS, PhD (Netherlands)
Consultant Cornea and Refractive surgery
Vice Chairman
*Narayana Nethralaya Eye Institute*
*Bangalore, India*

**Dr. Jonathan Bonnar**
*Royal Victoria Hospital, Belfast , Northern Ireland*

**Miss. Elsa Lee**
*Institute of Ophthalmology, University College London*
*Guy's, King's, and St Thomas' School of Medicine,*
*King's College London*

**Dr. Keyur Patel**
BSc(Hons) OD Dip(IP)
DipGlauFAAO
FcoOptom FBCLA
*Director & Optometrist*
*TK & S Optometrists Ltd.*

# Contents




# What's in the news?

## Increased lacrimal inflammatory mediators in patients with keratoconus

This study aimed to characterize the tear film immunologic profile in keratoconus (KC) patients compared with healthy individuals (control group) and to investigate the correlation between the tear film immunologic profile and atopy, disease severity, and disease status over time.

The study involved 30 KC patients and 18 healthy individuals. Tear collection was obtained using microcapillary tubes. Tear film levels of fractalkine, granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon (IFN)-γ, interleukin (IL)-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IL-17A, IL-21, IL-23, interferon-inducible T-cell alpha chemoattractant (ITAC), macrophage inflammatory protein-1 alpha (MIP-1α), MIP-1β, MIP-3α, and tumour necrosis factor (TNF)-α were detected. Keratometric measurements and topographic patterns were used to diagnose and define disease progression. Tear immunologic profiles were compared, emphasizing the presence or absence of ocular allergy. Correlations between the cytokine profile, disease severity, and disease status were also analysed longitudinally in the KC patients.

The results from the study showed that Lacrimal cytokine concentrations were higher in the KC patients than they were in the controls in 14 of 21 cytokines analyzed. IL-6 was the most relevant cytokine found in KC patients, especially when associated with ocular allergy. There was no correlation between KC progression and the level of inflammatory cytokines when analysed longitudinally. KC severity correlated with IL-6 concentration, where the more severe KC presented a higher IL-6 concentration in tears.

Inflammatory activity seems to be involved in the pathogenesis of KC. Out of 21 cytokines, 14 were more concentrated in the tears of KC patients than healthy subjects. IL-6 was significantly higher in KC patients' tears and was related to disease severity. Disease progression did not correlate with cytokine levels when analyzed longitudinally.

Authors: Gustavo Souza Moura, Albert Santos, Marcos Antonio Cenedeze , Meire Ioshie Hiyane, Niels Olsen Saraiva Camara , Luciene Barbosa de Sousa, Lauro Augusto de Oliveira

Publication: Mol Vis. 2021 Dec 7;27:656-665.eCollection 2021.

## Impact of prolonged face mask wearing on tear break-up time and dry eye symptoms in health care professionals

The purpose of this study was to evaluate the impact of prolonged surgical face mask wearing on dry eye symptoms and tear film break-up time (T-BUT) in health care professionals.

A total of 33 health care professionals were included in the present cross sectional prospective study. In addition to a complete ophthalmological examination T-BUT measurements were performed twice for all participants in the morning (8 am) and in the afternoon (5 pm). The subjects also filled-in the ocular surface disease index (OSDI) questionnaire twice, before and after wearing the face mask, on the same day.

Sixty-six eyes of 33 participants (17 female and 16 male) were evaluated. The mean age was 33.6 ± 7.55 (24-48) years and mean total duration with mask on between the two evaluations was 514 ± 12.5 (495-526) minutes. The mean T-BUT was 9.3 ± 1.0 (3-16) seconds at 8 am and 8.3 ± 1.5 (3-14) seconds at 5 pm ($p = 0.01$). The mean OSDI score was 20.1 ± 8.3 (0-68.75) at 8 am and 27.4 ± 10.4 (0-81.25) at 5 pm ($p < 0.01$).

The authors concluded that use of a surgical mask for the entire workday was seen to worsen T-BUT and increase dry eye symptoms in healthy individuals. Ophthalmologists should be aware of the possibility of worsening of dry eye symptoms with the prolonged use of surgical face masks and consider modifications if necessary.

Authors: Mine Esen Baris, Suzan Guven Yilmaz, Melis Palamar

Publication: Int Ophthalmol. 2022 Feb 4;1-4.doi: 10.1007/s10792-022-02213-9.

BVI

# QUALITY OF VISION
# **UNCOMPROMISED** & **EXTENDED**

ISOPURE



Follow us

bvimedical.com

1605996-01

# What's in the news?

## Effects of aerobic exercise on tear secretion and tear film stability in dry eye patients

The study set out to analyse the effects of aerobic exercise (AE) on tear secretion and tear film stability in dry eye patients.

This study consisted of two parts, each part included 3 groups, namely dry eye without AE group, dry eye with AE group and pre-clinical dry eye with AE group. In part 1, we studied the variations of Schirmer I test and six tear compositions before and after AE (34 eyes in each group). In part 2, we studied the variations of tear meniscus height, first and average non-invasive tear breakup time (F-NITBUT and A-NITBUT), lipid layer thickness, number of incomplete and complete blinks, partial blink rate (PBR) and visual acuity before and after AE (30 eyes in each group).

In dry eye with AE group, Schirmer I test at 0 min after AE increased significantly compared to baseline ($P < 0.001$), the oxidative stress marker 8-hydroxy-2'-deoxyguanosine after AE decreased significantly compared to baseline ($P = 0.035$, $P = 0.045$), F-NITBUT and A-NITBUT after AE prolonged significantly compared to baseline ($P < 0.001$, $P = 0.007$, $P = 0.036$; $P < 0.001$, $P = 0.001$, $P = 0.044$), number of incomplete blinks and PBR at 10 min after AE decreased significantly compared to baseline ($P < 0.001$; $P < 0.001$) while number of complete blinks increased significantly ($P < 0.001$). Besides, significant differences were also found

between dry eye with AE group and dry eye without AE group at all above corresponding time point ($P < 0.05$).

The authors concluded that AE promotes tear secretion and improves tear film stability in dry eye patients. AE may be a potential treatment for dry eye.

Authors: Sun, Xiaofan Chen, Yanming Huang, Huan Zou, Wei Fan, Mei Yang, Rongdi Yuan
Publication: BMC Ophthalmol. 2022 Jan 4;22(1):9.doi: 10.1186/s12886-021-02230-9.

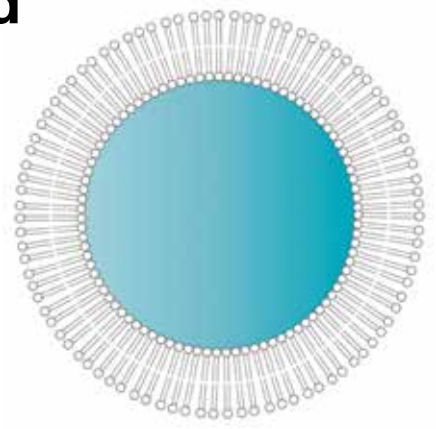
---

# What's in the news?

## Moxifloxacin releasing intraocular implant based on a cross-linked hyaluronic acid membrane

Intraocular antibiotic delivery is an important technique to prevent bacterial infection after ophthalmic surgery, such as cataract surgery. Conventional drug delivery methods, such as antibiotic eye drops, have limitations for intraocular drug delivery due to the intrinsic barrier effect of the cornea. Therefore, frequent instillation of antibiotic eyedrops is necessary to reach a sufficient bactericidal concentration inside the eye.

In this study, an intraocular implant, MXF-HA, that combines hyaluronic acid (HA) and moxifloxacin (MXF) was developed to increase the efficiency of intraocular drug delivery after surgery. MXF-HA is manufactured as a thin, transparent, yellow-tinted membrane. When inserted into the eye in a dry state, MXF-HA is naturally hydrated and settles in the eye, and the MXF contained therein is delivered by hydrolysis of the polymer over time. It was confirmed through in vivo experiments that MXF delivery was maintained in the anterior chamber of the eye at a concentration sufficient to inhibit Pseudomonas aeruginosa and Staphylococcus aureus for more than 5 days after implantation.



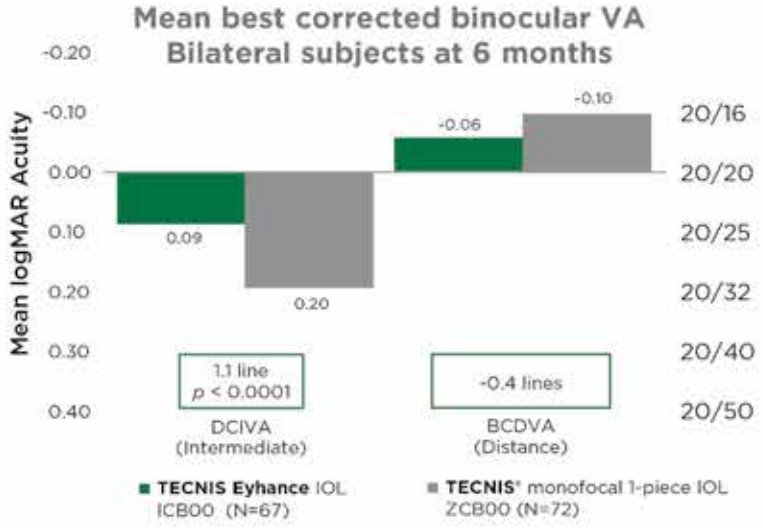
These results suggest that MXF-HA can be utilized as a potential drug delivery method for the prevention and treatment of bacterial infections after ophthalmic surgery.

Authors: Dong Ju Kim, Mi-Young Jung, Joo-Hee Park, Ha-Jin Pak, Martha Kim, Roy S Chuck, Choul Yong Park
Publication: Sci Rep. 2021 Dec 16;11(1):24115.doi: 10.1038/s41598-021-03605-0.

# TECNIS Eyhance IOL

A new generation of monofocal IOLs

## Improved intermediate vision




**TECNIS Eyhance** IOLs (ICB00) offer a statistically significant improvement in monocular and binocular intermediate vision vs. **TECNIS®** monofocal 1-piece IOLs (ZCB00).[1]

- Improved intermediate vision[1]
- 20/20 distance vision[1*]

## Give them more.

Enhance your patients' intermediate vision by using **TECNIS Eyhance** IOL.


**Reference**

1. Data on File, Johnson & Johnson Surgical Vision, Inc., Sep 2018. DOF2018CT4015.


*Based on a clinical study, N=134 achieved mean 20/20 monocular pooled distance BCDVA.

# Enhanced vision within reach.

**For healthcare professionals only.**

**Please read the Directions for Use for Important Safety Information and consult our specialists if you have any questions.**

TECNIS Family of IOLs | LEADING INNOVATION | HIGH-QUALITY OUTCOMES | EXCEPTIONAL SATISFACTION |

Bring Vision to Life.

**TECNIS**
Eyhance IOL

**See the Passion in Each Patient.**

Johnson & Johnson VISION

REGISTER HERE:

OSI

OCULAR SURFACE INSIGHT

# Dry Eye Masterclass & Symposium

**24 - 25 June 2022**

**Hard Rock Hotel**
**Conference Centre, London**

**Topics to include:**

Keynote Lecture: Molecules and hormones in Ocular Surface Disease

Keynote Lecture: Modern thinking in Ocular Surface Reconstruction

Artificial Intelligence in Ocular Surface Disease - more data needed!

TFOS Session: Dry eye awareness and update on diagnosis and management

MCLOSA Session: Decision making, in eye surface disease; persistent epithelial defect and ocular surface failure

Biologics; the new frontier in managing ocular surface and dry eye disease

Human inlays as a way forward in managing keratoconus and refractive errors

Can we stop permanent corneal deformation?

Updates on diagnostics of infectious keratitis and the management of bacterial and fungal keratitis

**Mr. Arthur Cummings**
**Prof. Rohit Shetty**
**Mr. Samer Hamada**
**Dr. Damien Gatinel**
**Prof. Christopher Liu**
**Prof. Jennifer Craig**
**Mr. Mohamed Elalfy**
**Miss. Artemis Matsou**
**Prof. Michael Mrochen**
**Prof. James Wolffsohn**
**Prof. Stephen Kaye**
**Mr. Sheraz Daya**
**Mr. David Lockington**
**Dr. Yan Ning Neo**
**Mr. Borja de la Sen-Corcuera**
**Mr. Damian Lake**
**Mr. Sajjad Ahmad**
**Dr. Pooja Khamar**

CPD and CET points applied for.

osimag.co.uk

# Corneal melting and perforation due to topical anesthetics abuse: a challenging case

Sabrina Vaccaro

By **Sabrina Vaccaro**[1], **Giuseppe Giannaccare**[1], **Andrea Lucisano**[1], **Vincenzo Scorcia**[1]

Department of Ophthalmology, University of "Magna Graecia", Catanzaro, Italy

## Introduction:

The use of topical anesthetics is a common practice in ophthalmology for performing both diagnostic and therapeutic procedures. However, their abuse can cause damage to the corneal epithelium and, in most serious cases, even corneal melting and perforation. The use of local anesthetic eye drops has been shown to damage epithelial organelles and to inhibit corneal epithelial cell migration. Scanning electron microscopy revealed that the apical cell attachment at the junction between endothelial cells is weakened with endothelial polymorphisms and focal necrosis. The clinical presentation can be variable, and sometimes findings common to other pathologies, such as bacterial, fungal and acanthamoeba keratitis, can be present thus delaying a proper diagnosis.
Here we present a case of corneal melting and perforation due to topical anesthetics abuse along with its management and outcomes.

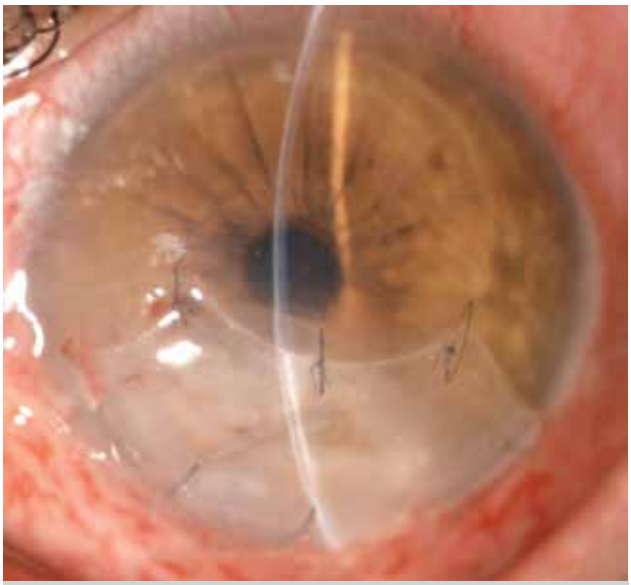


**Figure 1**: Slit-lamp photograph of the tectonic graft

## Clinical case

A 40-year-old male presented to our Department with intensive pain, photophobia, and decreased visual acuity in his right eye. Two months before, he had a bulbar trauma with a metallic fragment in the same eye that was removed. Upon presentation, slit lamp examination showed a paracentral corneal ulcer of 3 x 6 mm with diffuse thinning and perforation. A tectonic lamellar graft centered on the lesion was performed (Figure 1).

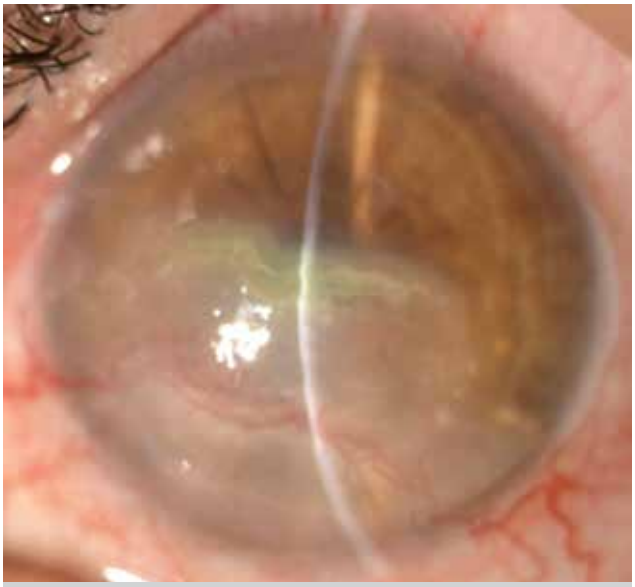


**Figure 2**: Slit-lamp photograph of corneal epithelial defect with diffuse stromal infiltration, oedema and corneal neovascularization

Despite postoperative course was regular, the patient continues to report an intense pain. Two months postoperatively, a corneal epithelial defect of new onset with diffuse stromal infiltration, oedema and corneal neovascularization appears (Figure 2). Corneal swab yielded no causative micro-organisms. Topical empirical broad-spectrum antibiotics were started, along with preservative-free lubricants and oral acyclovir 400 mg five times a day. Two weeks later, the clinical picture worsened with a recurrency of corneal perforation with iris prolapse. The patient was re-admitted to the hospital and a penetrating keratoplasty (PK) was performed. After discharged from hospital, the patient did not attend follow-up visits and a diastasis of the host-donor junction was detected with an overlying epithelial defect (Figure 3). The patient at first denied the use of the anesthetic but after intensive questioning on the matter, he admitted that a physician had initially given him the eye drop.
A conjunctival flap was made as described by Gunderson to prevent a further corneal perforation. To date, 19 months after the last surgery, clinical picture is stable (Figure 4).

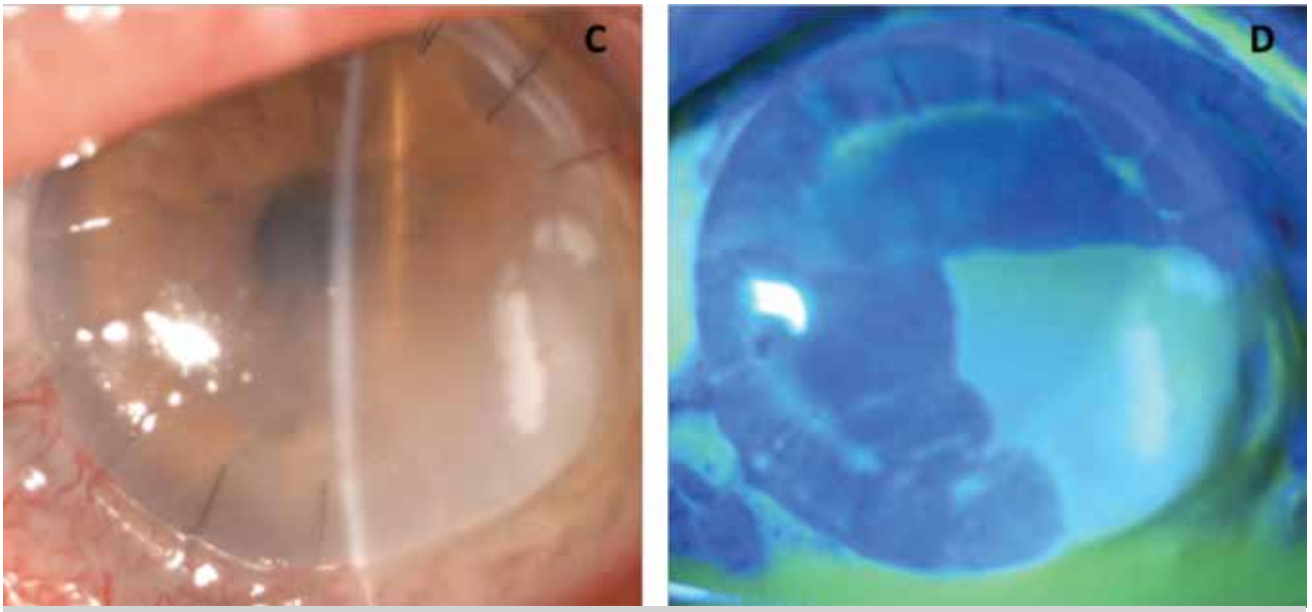



**Figure 3**: Slit-lamp photograph showing initial temporal diastasis with overlying epithelial defect (C). Corneal staining with fluorescein shows the epithelial defect (D)

## Discussion

The pathophysiology of topical anesthetic abuse keratopathy remains unknown. It is crucial for ophthalmologists to identify this condition to establish a prompt treatment. However, in most cases it is difficult because patients deny the anesthetic eye drops abuse.
At the same time, it is important to exclude the presence of infectious keratitis since some findings can be common to other pathologies, such as bacterial, fungal and acanthamoeba keratitis.
A distinctive feature is the disproportionate pain that the patient reports leading to an increased use of anesthetic that worsens further the corneal damage.
This pain can mimic an Acanthamoeba keratitis that is often characterized by pain out of proportion to findings.
Collecting a proper medical history is very helpful, including contact lens wearing, exposure to contaminated water and corneal trauma. Various studies report an association with manifestations of psychiatric illnesses, for this reason a psychiatric consultation must be considered in suspicious cases. Furthermore, ophthalmologist should inform pharmacists and doctors about the risk associated with the use of topical anesthetic eye drops in order to avoid the sight-threatening consequences of their abuse.

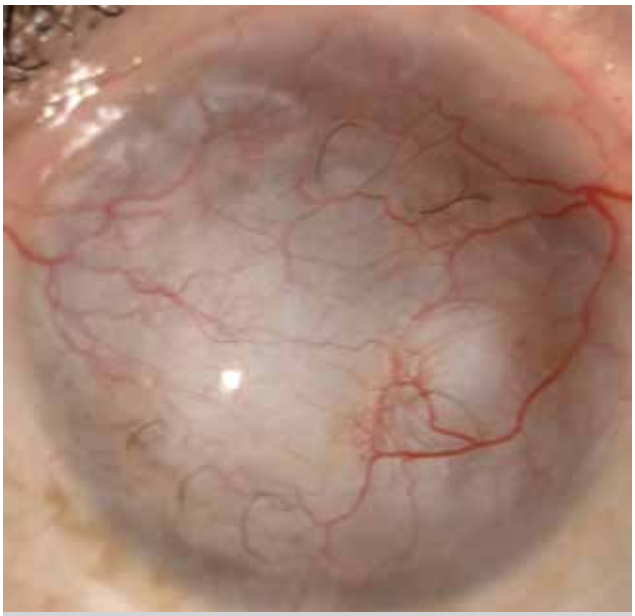


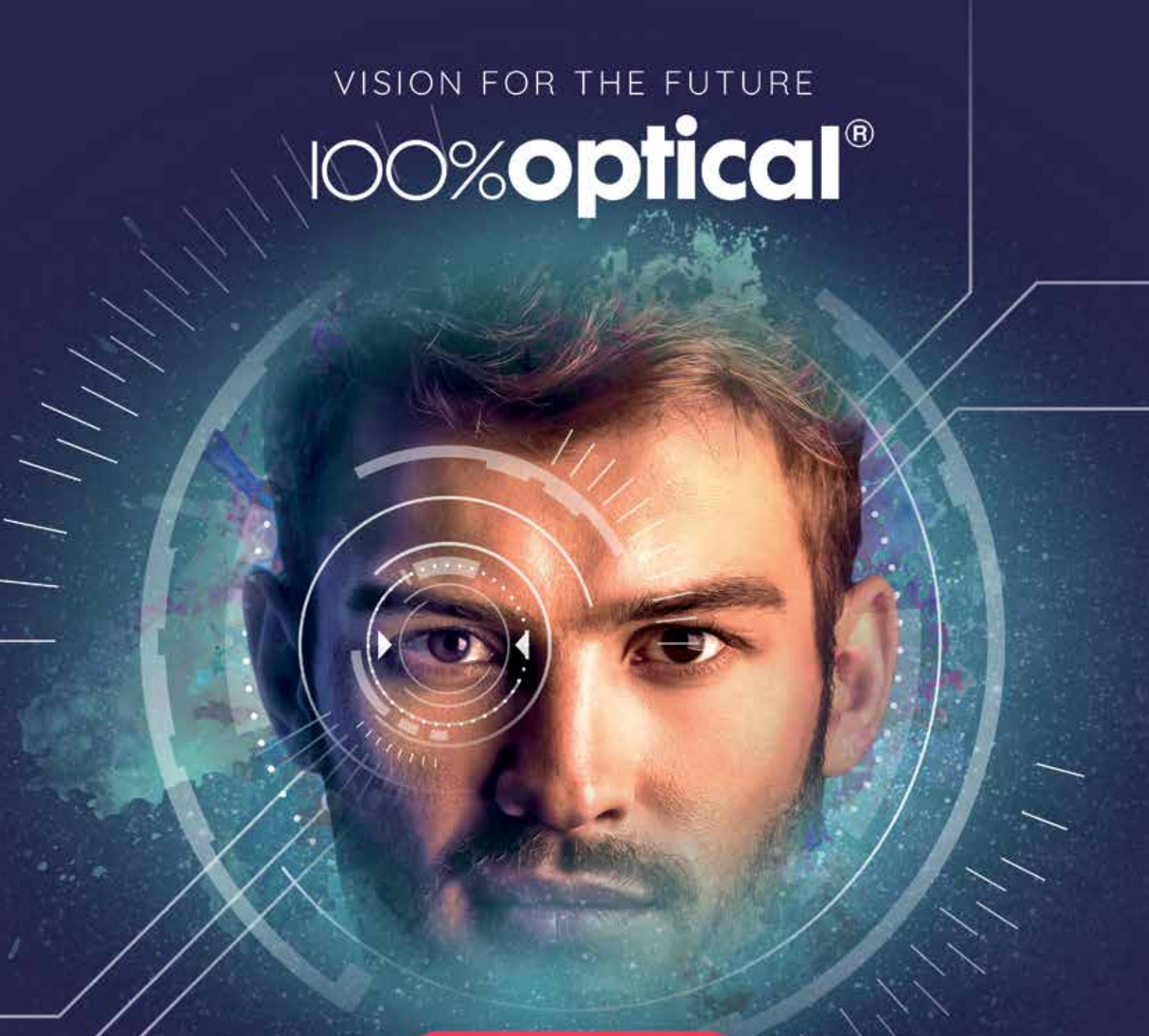
**Figure 4**: Slit-lamp photograph of right eye 19 months after Gundersen flap surgery that shows corneal conjunctivalization and neovascularisation

References:

1. Burns RP. Toxic effects of local anesthetics. JAMA. 1978 Jul 28;240(4):347.
2. Risco JM, Millar LC. Ultrastructural alterations in the endothelium in a patient with topical anesthetic abuse keratopathy. Ophthalmology. 1992 Apr;99(4):628-33.
3. Ansari H, Garibaldi DC, Jun AS. Anaesthetic abuse keratopathy as a manifestation of ocular Munchausen's syndrome. Clin Exp Ophthalmol. 2006 Jan-Feb;34(1):81-3.
4. Yagci A, Bozkurt B, Egrilmez S, Palamar M, Ozturk BT, Pekel H. Topical anesthetic abuse keratopathy: a commonly overlooked health care problem. Cornea. 2011 May;30(5):571-5.
5. Wu H, Hu Y, Shi XR, Xu F, Jiang CY, Huang R, Jia H. Keratopathy due to ophthalmic drug abuse with corneal melting and perforation presenting as Mooren-like ulcer: A case report. Exp Ther Med. 2016 Jul;12(1):343-346. doi: 10.3892/etm.2016.3296.
6. Yagci A, Bozkurt B, Egrilmez S, Palamar M, Ozturk BT, Pekel H. Topical anesthetic abuse keratopathy: a commonly overlooked health care problem. Cornea. 2011 May;30(5):571-5.
7. Pharmakakis NM, Katsimpris JM, Melachrinou MP, Koliopoulos JX. Corneal complications following abuse of topical anesthetics. Eur J Ophthalmol. 2002 Sep-Oct;12(5):373-8.

VISION FOR THE FUTURE

# 100%optical®



REGISTER FREE

## 23-25 APRIL 2022
## EXCEL LONDON

- Meet equipment manufacturers
- See the latest technology
- Learn from top practitioners

www.100percentoptical.com

#100optical @100optical

OFFICIAL UK PARTNER
Association of Optometrists

MEDIA PARTNER
Optometry Today

SPONSORS
Community Eyecare
Transitions
BAUSCH+LOMB See better. Live better.
SpaMedica
OCUCO
OptiLight
Johnson&Johnson VISION
EssilorLuxottica
CHARMANT

A Media 10 event

# Lab on chip: biomarkers reality to clinics

By **Rohit Shetty,** DNB, FRCS, PhD and **Dr Pooja Khamar**, MS, FCRS(NN), PhD

## Background

Ocular surface disease, such as dry eye disease, allergies and infections, are not only extremely common, but also have a significant impact on the patient's quality of life. Dry eye disease in particular often impairs the patient's functional vision, influences day-to-day activities and leisure pursuits and can manifest as reduced efficiency at work. It has also been significantly associated with both anxiety and depression and can be debilitating in its symptoms.[1]

Unfortunately, the symptoms and signs – or in other words, the subjective and objective clinical findings of dry eye disease – do not necessarily correlate.[1] The patients exhibiting significant distress oftentimes do not display proportionately severe clinical signs, and those with alarming signs and vision-threatening complications may often exhibit only mild symptoms.[1] Moreover, there is a considerable overlap between the clinical presentations of patients of dry eye, ocular surface infections and allergies, but each mandates different treatment.[1] A meticulous examination and accurate diagnosis are required, but at times inadequate in distinguishing them. In the event of an incorrect clinical diagnosis, prescription of antiallergic drugs or antibiotics that can be epitheliotoxic, can exacerbate dry eye disease.[1]

In the largest international survey of prescribing practices in dry eye disease, which explored how severity and subtype may influence the choice of management, the Tear Film and Ocular Surface Society (TFOS) concluded that evaporative subtypes were more commonly treated with lid hygiene, lid warming therapies, procedural dry eye therapies such as intense pulsed light, oral and topical antibiotics and nutritional supplements.[2] On the other hand, punctal occlusion, contact lenses, biologics and secretagogues were preferred in aqueous deficient disease.[2] However, research investigating the efficacy of management therapies by disease subtype is currently limited, and further studies are required to understand the relevance of biomarker tests in deciding the ideal management strategy.[2]

Detection of biomarkers in tear samples has opened up several unexplored avenues in the diagnosis, treatment and prognostication of diseases of the ocular surface, including allergy and dry eye. The utilisation of modalities such as ELISA (Enzyme-Linked Immunosorbent Assay), multiplex bead, multiarray and proteomic technology, has enabled analysis of small volume samples while simultaneously increasing detectable targets.[3] At present, tear osmolarity and matrix metalloproteinaise-9 (MMP-9) are the only biomarkers approved by the United States Food and Drug Administration (FDA) and have point-of-care measurement devices that are commercially available.[4] Multiplex cytokine assays validated for tumour necrosis factor (TNF)-α, interferon (IFN)-γ, interleukin (IL)-1β, and IL-6, have also been introduced.[5,6] In addition to these, we chose to include the following in our customized multiplex ELISA platform (Bio-M Pathfinder) - IL-17A, IL-10, sICAM1 (soluble intercellular cell adhesion molecule 1) and vascular endothelial growth factor (VEGF-A) for their putative role in the pathophysiology of dry eye disease.[7]

The technique of collecting tear fluid for analysis with the use of Schirmer's strips has been described in literature.[3] Based on this knowledge, we utilised the Schirmer's strips obtained from patients undergoing routine dry eye evaluation pre-operatively in our practice of refractive surgery. These samples were run through a customized multiplex ELISA platform (Bio-M Pathfinder). (Figure 1) The manner in which these results guided the course of our refractive surgery planning and patient outcomes, has been illustrated in the cases described below.

Figure 1


## WORKFLOW OF BIO-M PATHFINDER KIT

Tear samples were collected by using Schirmer's strips. These were bent at the preformed notch by 90° and then placed into the conjunctival sac at the junction of the middle and lateral thirds, allowing the paper to wet by capillary action for 5 minutes. The strips were collected in sterile 1.5 ml microcentrifuge tubes.

Tears were eluted from the Schirmer's strips by adding 300 µl phosphate buffer solution (extraction buffer) to the tubes. 50 µl of the resulting extract was added to each sample well of the cartridges obtained for measurement of the following markers - MMP9, IL6, TNFα, IL1β, IL17A and sICAM1. 1 ml of specific wash buffer was then added to the designated buffer well. The cartridges were loaded into the analyser system, which provided the measured value of the specific analyte based on the established internal references for each.

Figure 2

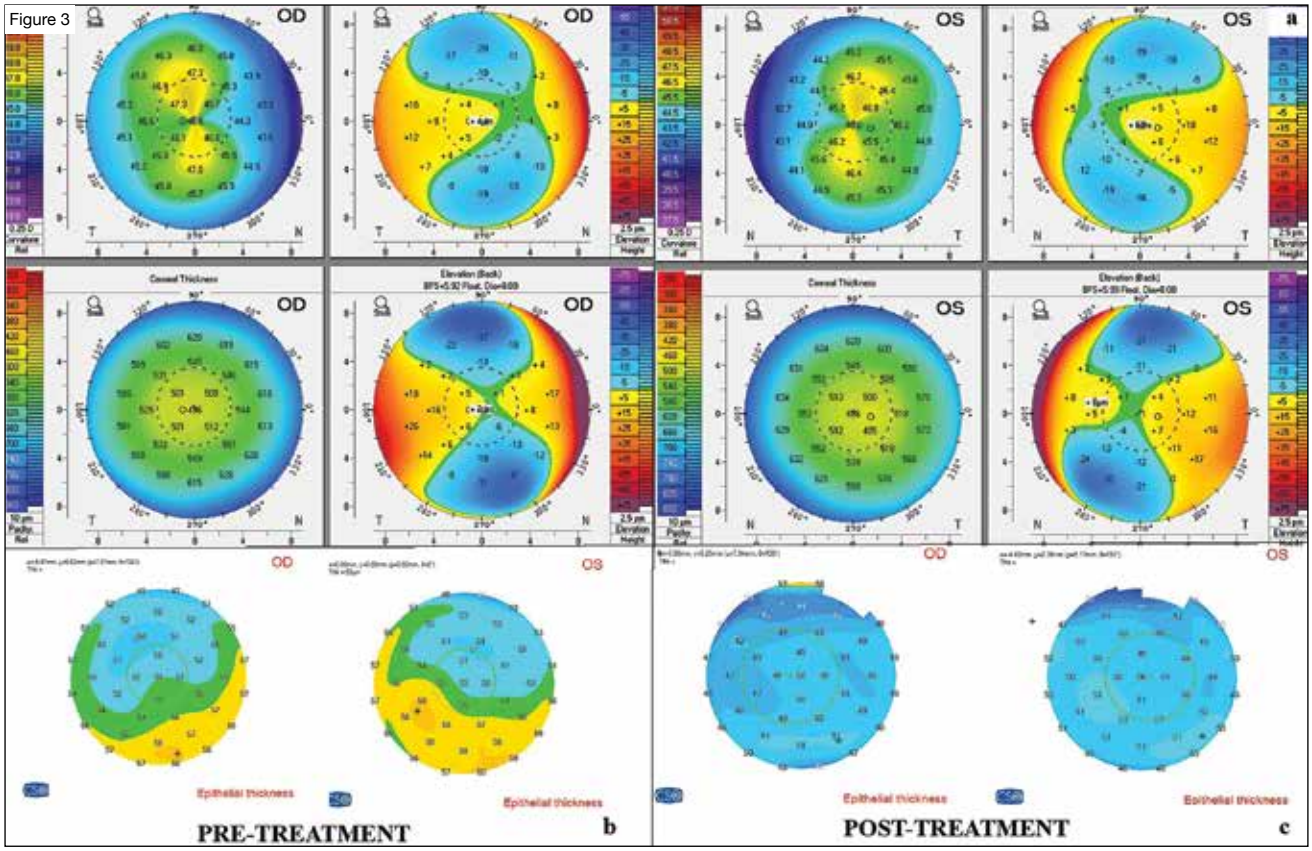
## CASE DISCUSSION

### CASE 1

A 28-year-old gentleman presented to the refractive service at our hospital, for consultation regarding undergoing refractive surgery. He had no significant ocular complaints related to dry eye, or systemic complaints indicating any inflammatory predispositions to developing dry eye. He did not report any relevant past ocular or systemic history.

On slit lamp examination, there was no evidence of meibomian gland disease. As part of the routine screening prior to refractive surgery, he underwent corneal topography using a rotating Scheimpflug camera (Pentacam, Oculus Optikgeräte GmbH), assessment of corneal biomechanics using Corneal Visualization Scheimpflug Technology (Corvis ST) and epithelial mapping using MS39 Anterior Segment Optical Coherence Tomography. While the topography and biomechanics were reported to be within normal limits, the epithelial mapping revealed significant irregularity in the thickness map. (Figures 3a, 3b)

Figure 3




The Schirmer's I test was performed and revealed values of 35 mm in the right eye and 32 mm in the left eye, while the Schirmer's II test reported 25 mm of wetting in each eye. The tear film break-up time (TBUT) was found to be >10 seconds in both eyes with no significant fluorescein staining of the cornea. He reported an Ocular Surface Disease Index (OSDI) of 8.71.

In consideration of the irregularity of the epithelial surface, we decided to run a diagnostic panel on the tears collected with the help of Schirmer's strips. The biomarker revealed significantly elevated levels MMP-9, while the rest of the biomarkers were reported to be within normal limits (Figure 4a). We decided to perform a procedural dry eye therapy in the form of thermal pulsation therapy for this patient.[7] Repeat imaging performed after 4 weeks revealed significant reguralisation of the epithelial layer. (Figure 3c) The biomarker analysis was repeated after 4 weeks and revealed significantly lowered MMP-9 levels. (Figure 4b) Considering the lowered level of inflammatory markers, we decided to go ahead with the proposed refractive surgery of photorefractive keratectomy.

## CASE 2

A 22-year-old student presented to the refractive service at our hospital, desiring to undergo refractive surgery. On evaluating her history, we discovered that she had vague, non-specific

Figure 4

NARAYANA NETHRALAYA

BEST

**Name:** **Age: 28 yrs** **Sex: Male**

**Date of Report: 06/01/2022**

| Test Parameter | Results | | Reference Interval |
|---|---|---|---|
| | Right Eye | Left Eye | |
| IL- 6 | 13.1 | 19.4 | >23.5 pg/ml |
| IL- 1b | 2.6 | 1.7 | >4.36 pg/ml |
| IL – 17 A | 9.3 | 6.1 | >6.82 pg/ml |
| MMP 9 | 129180 | 161807 | >49000 pg/ml |
| I CAM – 1 | 32062 | 34729 | >38031 pg/ml |
| TNF - a | 4.6 | 2.61 | >4.89 pg/ml |
| 1L-10 | 0.387 | 0 | - |
| VEGF- A | 203 | 320 | - |

a

NARAYANA NETHRALAYA

BEST

**Name:** **Age: 28 yrs** **Sex: Male**

**Date of Report: 10/02/2022**

| Test Parameter | Results | | Reference Interval |
|---|---|---|---|
| | Right Eye | Left Eye | |
| IL- 6 | 13.5 | 8.6 | >23.5 pg/ml |
| IL- 1b | 2.4 | 1.23 | >4.36 pg/ml |
| IL – 17 A | 7.8 | 5.92 | >6.82 pg/ml |
| MMP 9 | 3830 | 6822 | >49000 pg/ml |
| I CAM – 1 | 22231 | 30986 | >38031 pg/ml |
| TNF - a | 2.63 | 2.42 | >4.89 pg/ml |
| 1L-10 | 0.164 | 0.890 | - |
| VEGF- A | 423 | 409 | - |

b

Figure 5

NARAYANA NETHRALAYA

BEST

Name: Age: 22 yrs Sex: Female

Date of Report: 10/01/2022

| Test Parameter | Results | | Reference Interval |
|---|---|---|---|
| | Right Eye | Left Eye | |
| IL- 6 | 20.1 | 28.4 | >23.5 pg/ml |
| IL- 1b | 3.61 | 5.7 | >4.36 pg/ml |
| IL – 17 A | 2.46 | 5.43 | >6.82 pg/ml |
| MMP 9 | 76280 | 54391 | >49000 pg/ml |
| I CAM – 1 | 122062 | 134729 | >38031 pg/ml |
| TNF - a | 2.86 | 2.21 | >4.89 pg/ml |
| 1L-10 | 0.387 | 0.262 | - |
| VEGF- A | 119 | 246 | - |

a

NARAYANA NETHRALAYA

BEST

Name: Age: 22 yrs Sex: Female

Date of Report: 15/02/2022

| Test Parameter | Results | | Reference Interval |
|---|---|---|---|
| | Right Eye | Left Eye | |
| IL- 6 | 12.1 | 7.6 | >23.5 pg/ml |
| IL- 1b | 1.41 | 1.23 | >4.36 pg/ml |
| IL – 17 A | 1.8 | 2.12 | >6.82 pg/ml |
| MMP 9 | 10246 | 11254 | >49000 pg/ml |
| I CAM – 1 | 31082 | 29916 | >38031 pg/ml |
| TNF - a | 2.12 | 3.62 | >4.89 pg/ml |
| 1L-10 | 0.140 | 0.291 | - |
| VEGF- A | 223 | 609 | - |

b

symptoms indicating eye strain and ocular irritation. She did not report any relevant past ocular or systemic history.

The slit lamp examination and imaging performed on Pentacam, Corvis ST and MS39 were reported to be within normal limits. The Schirmer's I test reported scores of 28 mm in both eyes, while the Schirmer's II test values were found to be 18 mm in the right eye and 19 mm in the left eye. The tear film break-up time (TBUT) was found to be >10 seconds in both eyes with no significant fluorescein staining of the cornea. Her OSDI was reported to be 22.6.

Owing to the non-specific nature of her complaints, we performed a tear biomarker analysis with due consent for the same. The tear report revealed elevated levels of ICAM-1 with borderline levels of MMP-9 (Figure 5a).

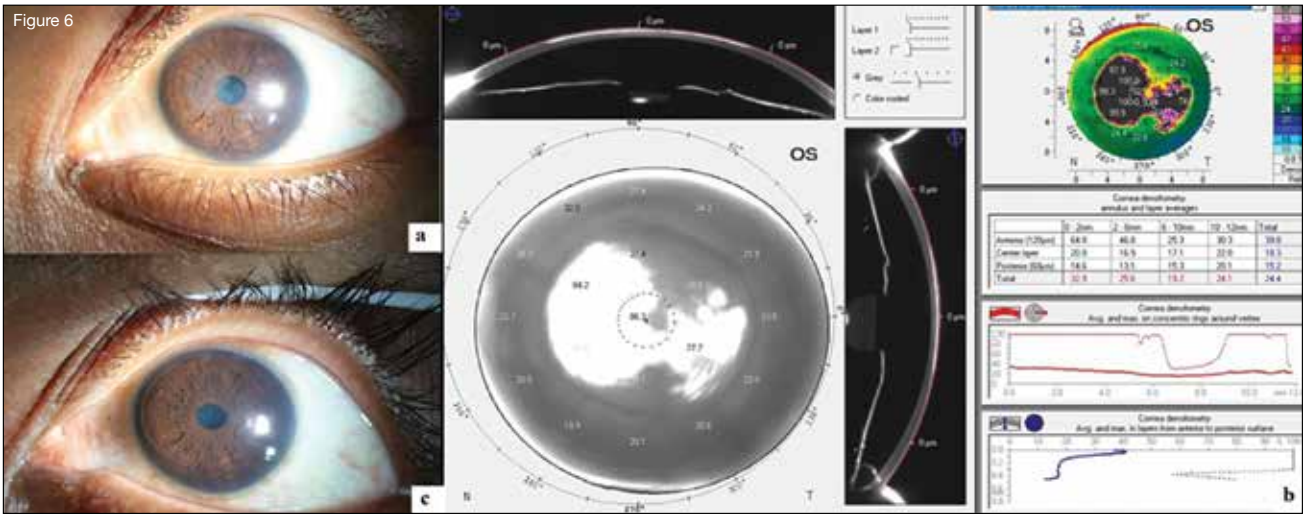
We decided to treat the subclinical inflammation prior to definitive refractive surgery, so as to ensure the accuracy of pre-operative corneal measurements due to stabilisation of the tear film and also reduce the likelihood of post-operative dry eye. The surgery was deferred for a month in which she was treated with lifitegrast 5% ophthalmic solution.8 On repeating the tear analysis after a month, the ICAM-1 levels were found to be lowered (Figure 5b), and we decided to proceed with the refractive surgery.

## CASE 3

A 26-year-old lady first presented to us with complaints of blurring of vision in both eyes. She had undergone photorefractive keratectomy (PRK) 6 months prior to presentation and had been diagnosed as a case of post-PRK haze. The slit lamp examination revealed grade 2 anterior stromal haze (Fantes et al9) involving the pupillary area (Figure 6a). On corneal tomography, an average densitometry of 64 GSU was reported in the anterior zone of the central 0-2 mm and 46.8 GSU in the anterior zone of the surrounding 2-6 mm (Figure 6b).

We planned a scar correction treatm ent with topography-guided custom ablation (T-CAT) for the patient. However, prior to undergoing the definitive procedure, we decided to investigate if any factors in the tear film may have contributed to the development of haze. Tear biomarker analysis revealed significantly elevated TNF-α and borderline levels of other inflammatory markers (Figure 7a). She was prescribed corticosteroid therapy in tapering doses for four weeks, along with adequate lubrication. After ensuring

Figure 6



lowered levels of TNF-α (Figure 7b), T-CAT was performed for definitive scar correction with judicious intra-operative use of mitomycin-C (MMC) 0.2%, allowed to act on the ocular surface for 30 seconds. Post-operatively, the patient was kept on a close follow up to monitor for haze. The post-operative clinical examination revealed significantly reduced density of the corneal haze, with no signs of recurrence of haze/scar. (Figure 6c)

## CASE 4

A 52-year-old gentleman presented to our Dry Eye Clinic with complaints of burning sensation, grittiness and eye strain for the past year. He had no known systemic or ocular illnesses or allergies. He had been receiving treatment in the form of lubricant eye drops (carboxymethylcellulose 0.5%, sodium hyaluronate 0.1%) and even immunomodulator eye drops (cyclosporine 0.05%) with no relief in symptoms.

His visual acuity was 6/6 in each eye, with a normal slit lamp and fundus examination. Dry eye examination was also reported normal – with a Schirmer's 1 of 32 in the right eye and 30 in the left eye, Schirmer's 2 of 24 in the right eye and 22 in the left eye and TBUT of > 10 seconds in both eyes. However, OSDI revealed his subjective symptoms to be significant, with a reported value of 70.62. The patient had evidence of meibomian gland disease. In order to understand whether his symptoms were purely psychosomatic in origin, we decided to perform a tear biomarker test to rule out any abnormalities in the same. The tear report revealed highly elevated values of MMP-9, along with raised iCAM-1, IL-1b and VEGF-A. (Figure 8a)

Intense pulsed light with low level light therapy has shown promising results in terms of lowering levels of MMP-9, IL-1b, IL-17, MMP9/TIMP1 ratio and ocular surface B-cell proportions.[10] On pursuing this course, we discovered dramatically lowered levels of all inflammatory mediators after three weeks of therapy. (Figure 8b) The patient had also improved symptomatically, and was then continued on a maintenance course of lubricating eye drops.

## DISCUSSION

The tear fluid is composed of lipids, mucins, water, salts and 1526 proteins identified via proteomics, thus making it a less complex body fluid as compared to serum or plasma.[12] The study of tear composition, as the final output or 'proximal fluid' of the lacrimal function unit (LFU), has thus been proposed to be an ideal source for analysing biomarkers associated with its various components.[12] Tear biomarker assays have therefore been deemed useful in various fields, especially as an objective tool for diagnosis and monitoring of dry eye disease among other conditions.

The introduction of tear biomarker assays may potentially revolutionize the practice of refractive surgery when implemented in the appropriate situations. With the help of the customized multiplex ELISA platform (Bio-M Pathfinder), we attempted to put this into practice.

The scope of the analysis is revealed in the cases summarised above. In the first case, a clinically normal patient was revealed to have irregular epithelium on imaging. The corneal epithelium has the ability to mask underlying stromal irregularities, and at times can undergo remodelling even in the absence of stromal changes. In either case, performing refractive surgery in the presence of pre-existing irregularity of the epithelium, can induce further irregular remodelling and result in regression, scarring or increased risk of ectasia, especially following high corrections.[12] We attempted to understand whether this picture was driven by inflammation or reflected in the tear biomarker levels, and discovered elevated levels of MMP-9 on tear biomarker analysis. As an intense inflammatory response has been noted in the acute phase of corneal wound healing following treatment with excimer laser, and this response is particularly high in PRK (photorefractive keratectomy) as compared to LASIK (laser-assisted intrastromal keratomileusis), we decided to treat the pre-existing inflammation before proceeding with the definite treatment.[13] This was done by performing thermal pulsation therapy, which has been shown to reduce ocular

Figure 7

NARAYANA NETHRALAYA

BEST

Name: Age: 26 yrs Sex: Female

Date of Report: 28/09/2021

| Test Parameter | Results | | Reference Interval |
|---|---|---|---|
| | Right Eye | Left Eye | |
| IL- 6 | 11.2 | 7.2 | >23.5 pg/ml |
| IL- 1b | 6.4 | 2.83 | >4.36 pg/ml |
| IL – 17 A | 5.67 | 4.87 | >6.82 pg/ml |
| MMP 9 | 23245 | 16789 | >49000 pg/ml |
| I CAM – 1 | 29810 | 32982 | >38031 pg/ml |
| TNF - a | 23.67 | 21.8 | >4.89 pg/ml |
| 1L-10 | 0.223 | 0.192 | - |
| VEGF- A | 223 | 209 | - |

a

NARAYANA NETHRALAYA

BEST

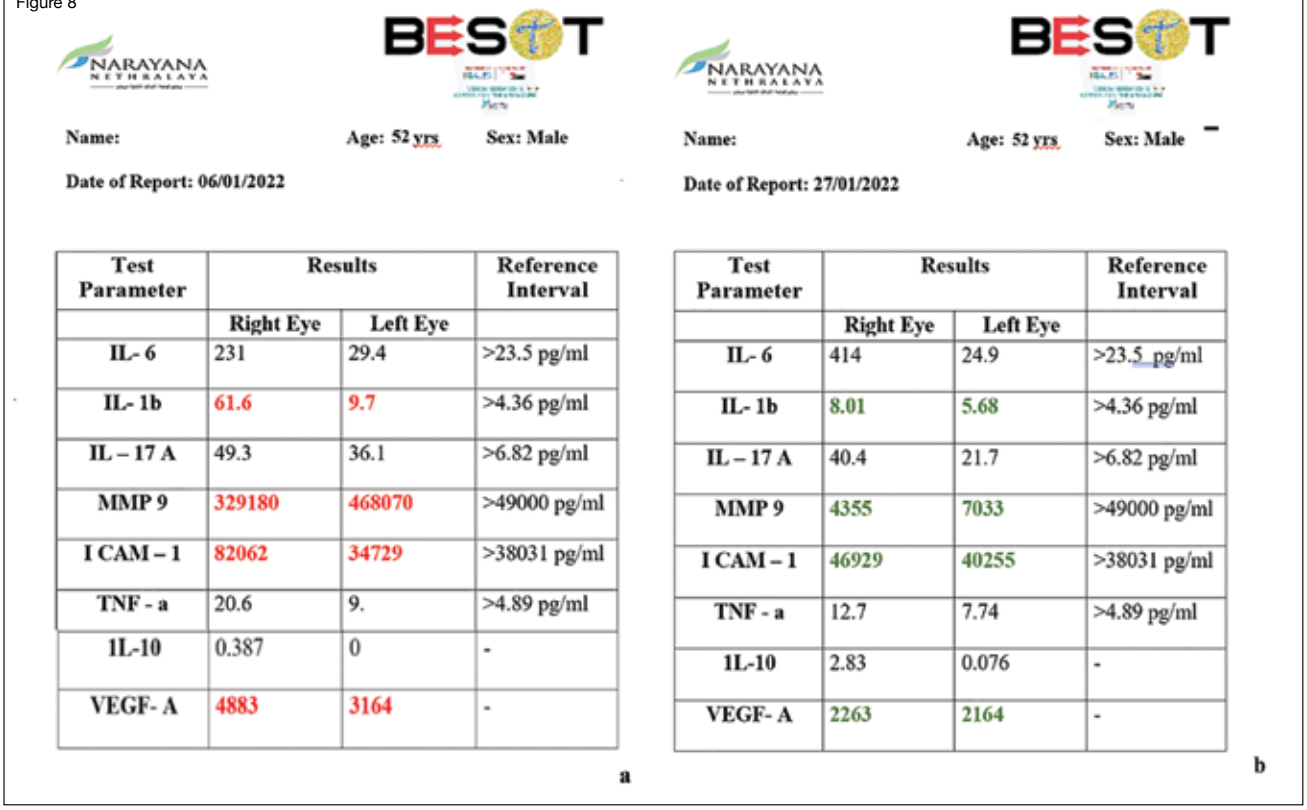
Name: Age: 26 yrs Sex: Female

Date of Report: 30/10/2021

| Test Parameter | Results | | Reference Interval |
|---|---|---|---|
| | Right Eye | Left Eye | |
| IL- 6 | 11.12 | 6.32 | >23.5 pg/ml |
| IL- 1b | 6.21 | 1.83 | >4.36 pg/ml |
| IL – 17 A | 2.86 | 3.19 | >6.82 pg/ml |
| MMP 9 | 11235 | 10986 | >49000 pg/ml |
| I CAM – 1 | 20345 | 14657 | >38031 pg/ml |
| TNF - a | 2.64 | 1.82 | >4.89 pg/ml |
| 1L-10 | 0.126 | 0.082 | - |
| VEGF- A | 218 | 189 | - |

b

Figure 8



Name: Age: 52 yrs Sex: Male

Date of Report: 06/01/2022

| Test Parameter | Results | | Reference Interval |
|---|---|---|---|
| | Right Eye | Left Eye | |
| IL- 6 | 231 | 29.4 | >23.5 pg/ml |
| IL- 1b | 61.6 | 9.7 | >4.36 pg/ml |
| IL – 17 A | 49.3 | 36.1 | >6.82 pg/ml |
| MMP 9 | 329180 | 468070 | >49000 pg/ml |
| I CAM – 1 | 82062 | 34729 | >38031 pg/ml |
| TNF - a | 20.6 | 9. | >4.89 pg/ml |
| 1L-10 | 0.387 | 0 | - |
| VEGF- A | 4883 | 3164 | - |

a

Name: Age: 52 yrs Sex: Male

Date of Report: 27/01/2022

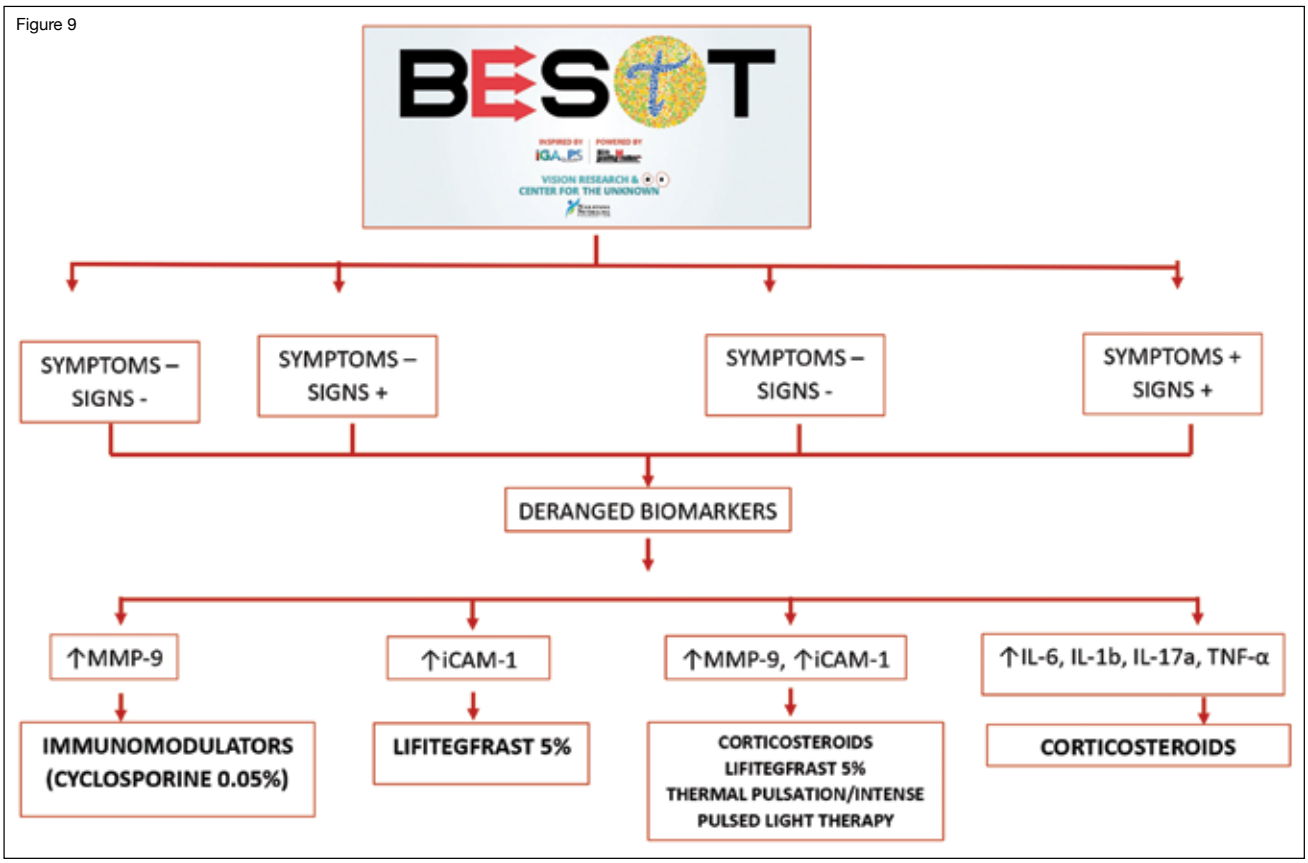
| Test Parameter | Results | | Reference Interval |
|---|---|---|---|
| | Right Eye | Left Eye | |
| IL- 6 | 414 | 24.9 | >23.5 pg/ml |
| IL- 1b | 8.01 | 5.68 | >4.36 pg/ml |
| IL – 17 A | 40.4 | 21.7 | >6.82 pg/ml |
| MMP 9 | 4355 | 7033 | >49000 pg/ml |
| I CAM – 1 | 46929 | 40255 | >38031 pg/ml |
| TNF - a | 12.7 | 7.74 | >4.89 pg/ml |
| 1L-10 | 2.83 | 0.076 | - |
| VEGF- A | 2263 | 2164 | - |

b

surface inflammation by stabilising levels of inflammatory markers such as MMP-9.7 In this scenario, we chose a surface ablation procedure (PRK) to regularise the corneal epithelial surface in addition to correcting the refractive error.

In the second case, the patient reported vague asthenopic symptoms, which did not translate to an abnormal dry eye evaluation. However, subclinical inflammation was revealed on biomarker analysis in the form of elevated levels of iCAM-1. Inflammation can be both the cause and result of an unstable tear film, contributing to a vicious cycle - increased osmolarity of the tear film can drive ocular surface inflammation, and the inflammatory cytokines themselves can subsequently lead to a reduction in the number of goblet cells and disrupt the corneal barrier.[14] Targeting specific inflammatory markers thus becomes an essential component of treatment and is not always addressed by mere prescription of artificial tears. In this case, we used lifitegrast 5% ophthalmic solution, which has been demonstrated to lower iCAM-1 levels.[8] This was done not only to offer symptomatic relief, but also reduce the pre-existing inflammation prior to refractive surgery.

Figure 9



In the third case, we decided to understand the role of tear biomarkers towards development of corneal haze following surface ablation procedures. The role of deficient nutrition, signs of dry eye or tear film instability, sunlight exposure etc. in the development of corneal haze following surgery as predictors of ocular surface inflammation, has already been delved into.15 As we now possess an instrument that enables direct measurement of ocular surface inflammation, we employed the same for assessment of inflammatory markers. As in the previous case, we ensured control of inflammation by lowering the elevated levels of MMP-9 with corticosteroid therapy prior to undertaking corrective laser surgery. Controlled release of inflammatory markers in the acute inflammatory phase following surgery, would prevent deposition of disorganized cellular material, abnormal extracellular stromal remodeling and resultant haze formation.[15] A more structured approach that we follow towards targeting specific biomarkers is highlighted in the flowchart below (Figure 9), also known as BESTT (Biomarker Enabled Specific Targeted Therapy).

It has expanded the scope of research and diagnostics in ophthalmology, such as – using tear VEGF levels as a biomarker for predicting severity of diabetic retinopathy[16] and degree of macular edema or efficacy of treatment in patients of retinal vein occlusions[17]. The possible correlation between tear levels of angiogenin and genesis of retinopathy of prematurity, has been studied.[18] Significantly different levels of carbonic anhydrase, lipase and antioxidants were noted in glaucomatous eyes, and each holds the potential to develop a specific and sensitive biomarker for glaucoma as a screening tool.[19]

Tear biomarker analysis has also opened up similar possibilities in the field of neurology, with respect to diseases such as multiple sclerosis[20], Parkinson's disease[21] and Alzheimer dementia[22].

With technological advances, increased scope of scientific and clinical research and non-invasive methods of sampling, tear fluid analysis is an attractive option not only for diagnosis of disease, but also for monitoring progression and guiding the course of treatment. Through this article, we attempt to highlight the manner in which the Bio M Pathfinder Kit serves to customise treatment approach for ocular surface conditions and improve patient outcomes. With further developments in the fields of proteomic, lipidomic and metabolomic detection, it promises to facilitate a more streamlined approach towards individualised care and predictive, preventive and personalised medicine in the near future.

# An NHS trainee perspective on dry eye disease

By **Jonathan Bonnar**

As an ophthalmology trainee, I read the account of Andrew Northover in the Autumn issue of OSI with sadness but also familiarity. Despite the more recent advances in the understanding and management of dry eye disease, it still seems to be considered somewhat of a hindrance in most ophthalmic clinics. The advice is usually that of regular lid hygiene and lubrication, followed by discharge. I can't help but think of the poor ophthalmology SHO seeing a patient with dry eyes for the 'Nth' time and trying to think of some new, untried lubricant which might save the day and feel sorry for both the patient and the doctor.

Three years ago, I developed a new found appreciation for the troubles that dry eye disease can cause. Following a bout of viral conjunctivitis, I have found myself bothered with dry eyes and surprised at how unpleasant it can be. I did what I had been taught, regular lid hygiene and lubrication. It did work, eventually, but took a long time and still relapses. It was during this period that I was fortunate enough to attend the European Association for Vision and Eye Research (EVER) conference where I learned a lot more about dry eye disease, its diagnosis and management. I learned about the DEWS II report and the self-perpetuating vicious circle of dry eye disease[1]. In my corneal rotation, I was pleased to find that the approach I had learned about was in practice with the use of topical steroids and some Ciclosporin, however most dry eye disease is not treated by corneal specialists. The majority of dry eye disease treated in NHS hospital eye services presents through eye casualties, where it is seen to by junior trainees, nurse practitioners and optometrists amongst others. Whilst the standard of care provided is good, they are hampered by an inability to effectively diagnose, counsel and manage patients due to time constraints in a busy casualty service where the dry eye patient is not imminently losing sight but is very much deserving and needing of attention. This may be combined with a lack of appreciation for the role of inflammation in the disease process[2]. It is by treating this inflammatory component that we can make a real change for patients.

Where learning medicine is a degree with formal education, ophthalmic training is more of an apprenticeship. If those above you are not actively managing and valuing the diagnosis and treatment of dry eye disease then that is not passed down to the younger generations. Dry eye disease management often seems to be experience-based rather than evidence-based care, as practitioners often use whatever they are comfortable with rather than necessarily following the evidence. Ocular surface problems are rife within the ophthalmologist's patient population not just due to dry eye disease, but also due to postoperative tear film disturbance and preservatives in topical medications, and that is before we think of the more unusual causes which have more systemic concerns such as Sjogren's syndrome, Parkinson's disease, sleep disorders and systemic medications. Whilst it seems to be such an innocuous disease, there are many systemic problems and chronic diseases which contribute to it, and these often carry their own burdens to the patient. With an increase in the awareness of dry eye disease and its impact on patients' day to day life, combined with improved diagnostics and treatments, this could go a long way to improving quality of life and compliance with other medications[3]. The first step to improving something is often to measure it, and so for this we need standardised outcome measures, both subjective and objective to allow audit and continual improvement in care.

I think that when a condition is going through a period of intense advancements such as in dry eye disease at present, then the younger generation of ophthalmologists have an opportunity to lead the way in bringing their new found knowledge and skills to those they work with. As they rotate through placements with different teams, even the VR surgeons might pick up new techniques and the latest thinking on the management of ocular surface disease. It is my hope that following robust studies and proof of safety and efficacy, we will soon have access to these new techniques and modalities to help our NHS patients. Diagnostics such as osmolality, MMP-9 measurements and meibography; treatments like LipiFlow and intense pulsed light and other new innovations have the possibility to change the paradigm of dry eye disease diagnosis and management and help a lot of patients[4–8].


References:

1. Craig JP, Nichols KK, Akpek EK, et al. TFOS DEWS II Definition and Classification Report. The ocular surface. 2017;15(3):276-283. doi:10.1016/J.JTOS.2017.05.008
2. Baudouin C, Irkec ß M, Messmer EM, et al. Clinical impact of inflammation in dry eye disease: proceedings of the ODISSEY group meeting. doi:10.1111/aos.13436
3. Zhang X, Vadoothker S, Munir WM, Saeedi O. Ocular Surface Disease and Glaucoma Medications: A Clinical Approach. Eye & contact lens. 2019;45(1):11. doi:10.1097/ICL.0000000000000544
4. Vunnava KP, Shetty N, Kapur KB. A review of meibography for a refractive surgeon. Indian Journal of Ophthalmology. 2020;68(12):2663. doi:10.4103/IJO.IJO_2465_20
5. Lanza NL, Valenzuela F, Perez VL, Galor A. The Matrix Metalloproteinase 9 Point-of-Care Test in Dry Eye. The ocular surface. 2016;14(2):189. doi:10.1016/J.JTOS.2015.10.004
6. Willcox MDP, Argüeso P, Georgiev GA, et al. TFOS DEWS II Tear Film Report. The ocular surface. 2017;15(3):366. doi:10.1016/J.JTOS.2017.03.006
7. Blackie CA, Coleman CA, Holland EJ. The sustained effect (12 months) of a single-dose vectored thermal pulsation procedure for meibomian gland dysfunction and evaporative dry eye. Clinical Ophthalmology (Auckland, NZ). 2016;10:1385. doi:10.2147/OPTH.S109663
8. Cote S, Zhang AC, Ahmadzai V, et al. Intense pulsed light (IPL) therapy for the treatment of meibomian gland dysfunction. The Cochrane Database of Systematic Reviews. 2020;2020(3). doi:10.1002/14651858.CD013559

# What's in the news?

## Analysis of Globular Cells in Corneal Nerve Vortex

Less was known about globular cells which were a type of dendritic cells (DCs) in cornea. We aimed to investigate the morphological and distribution characteristics of globular cells in corneal vortex and their clinical correlations with ocular surface.

Case records of patients who underwent in vivo confocal microscopy (IVCM) were evaluated retrospectively. The morphology and distribution features of globular cells in cornea nerve vortex and their co-existence status with Langerhans cells (LCs) were analyzed. Data of ocular surface symptoms and signs were collected and their correlations with globular cells distribution patterns and dendritic forms were performed. Dry eye patients without LCs were treated with preservative-free artificial tears, while patients with LCs were treated with artificial tears and fluoromethalone until the activated LCs disappeared.

A total of 836 eyes from 451 individuals were included. Three distribution patterns of globular cells in vortex were investigated, type 1 scattered globular cells (57.66%), type 2 large amounts of globular cells (≥50 cells) gathering in vortex and along some fixed vortex direction horizontally (13.52%) and type 3 no globular cells (28.83%). Their location and cell count altered slightly in the follow-ups but would not disappear. LCs could co-exist with globular cells and could fade after treatment. The type 2 distribution pattern was associated with older age ($p = 0.000$) and higher upper eyelid Meiboscore ($p = 0.006$). Dendritic globular cells had higher Meiboscore than Non-dendritic forms.

Globular cells had characteristic distribution patterns and biological features different from LCs. They were associated with long-term irritation of the meibomian gland dysfunction.

Authors: Ran Hao, Ziyuan Liu, Yilin Chou, Chen Huang, Dalan Jing, Haikun Wang, Shuang Gao, Xuemin Li
Publication: Front Med (Lausanne). 2022 Feb 22;9:806689.doi: 10.3389/fmed.2022.806689.eCollection 2022.

## A randomized multicenter clinical evaluation of sequential application of 0.3% and 0.15% hyaluronic acid for treatment of dry eye

We aim report the clinical efficacy of sequential applications of 0.3% and 0.15% unpreserved hyaluronic acid (HA) for the treatment of dry eye disease (DED).

Patients over 19 years of age with DED level 2 or higher, corneal fluorescein staining (CFS) score > 1, and tear break-up time (TBUT) < 10 s were included. Seventy-six patients were randomly assigned to the 0.15% HA group, 0.3% HA group, or combination group. Each group applied two drops of 0.15% or 0.3% HA, or a single drop of both 0.3% and 0.15% HA. Patients were evaluated using the ocular surface disease index (OSDI), CFS and conjunctival fluorescein stain score, TBUT, and blurring/discomfort after application at baseline, 4 weeks, and 8 weeks.

The result of the study showed that the combination group had the greatest improvement in CFS score from baseline to 8 weeks, compared with the 0.15% and 0.3% HA group ($p < 0.001$). The combined CFS-OSDI responder rates of the combination group (CFS score = 0 and OSDI ≥ 50% improvement at 8 weeks) were significantly higher than those of the 0.15% and 0.3% groups ($p = 0.037$). At 4 and 8 weeks, blurring after application in both the 0.3% and combination groups was significantly higher than in the 0.15% group, despite no difference between the 0.3% and combination groups. There were no differences in CFS and conjunctival staining score, TBUT, or OSDI within the three groups at baseline, 4 weeks, and 8 weeks.

The authors concluded that sequential application of 0.3% and 0.15% HA improved symptoms/signs in moderate to severe DED patients.

Authors: Jong Hwa Jun, Seung Pil Bang, Han Sang Park, Donghee Yoon, Ja Young Ahn, Seong Jae Kim, Hong Kyun Kim
Publication: Jpn J Ophthalmol. 2022 Jan;66(1):58-67.doi: 10.1007/s10384-021-00885-x. Epub 2021 Nov 29.

# Cornea and Ocular Surface in Systemic Diseases

By **Ruchi Shah, Cynthia Amador, Kati Tormanen, Sean Ghiam, Mehrnoosh Saghizadeh, Vaithi Arumugaswami, Ashok Kumar, Andrei A. Kramerov, Alexander V.**
Edited by **Elsa Lee**

**Pearls for Practice**

- Corneal pathologies offer a unique angle to unveiling systemic diseases
- Findings by ophthalmologists may alert to potentially life-threatening diseases
- Emerging treatments for corneal pathologies in these patients may be local or ocular-specific

**Summary**

This review of corneal and ocular surface involvement in systemic diseases encompasses manifestations, pathophysiology, and treatments on the horizon. Herein we describe the cornea in endocrinopathies and viral infections in light of their disease burden and the Covid-19 pandemic.

## 1. Introduction

Systemic diseases and associated corneal abnormalities are examined by categories, covering characteristic manifestations, molecular mechanisms, signalling pathways, and emerging treatments, with particular emphasis on diabetes mellitus due to the authors' research interests.

## 2. Endocrine diseases

### *2.1 Cornea in Diabetes mellitus*

Corneal complications are observed in 45–70% diabetic patients and often under-diagnosed. Although epithelial and neural complications are more symptomatic, diabetes affects the entire ocular surface.

#### *2.1.1 General traits*

##### *2.1.1.1 Diabetic epithelial keratopathy*

Diabetic epitheliopathy/keratopathy is manifested by abnormalities including fragility, stem cell dysfunction, altered basement membrane (BM) composition, delayed wound healing, impaired barrier function, oedema, recurrent erosions, and non-healing ulcers. Although often concomitant with diabetic corneal neuropathy (DCN), their cause-effect relationship is unclear.

###### *2.1.1.1.1 Mechanisms*

1. Altered epithelial cell adhesion and BM degradation are shown in human ex vivo diabetic corneas, with:
   - o reduced BM immunostaining for laminins, nidogen-1, and limbal fibronectin,
   - o increased expression of proteinases: MMP-3, MMP-10, and cathepsin F

   These impair epithelial cell migration and wound healing.
2. Decreased expression of stem cell markers in ex vivo and organ-cultured diabetic corneas indicate stem cell dysfunction which may be normalised by recent gene therapy
3. Growth factor and their signalling pathway alteration in humans and organ-cultures of diabetic cornea impair cell adhesion, wound healing, and lead to epithelial fragility and subbasal nerve loss:
   - o Elevated opioid growth factor (OGF), or [Met5]-enkephalin via ζ receptors (OGFR) dysregulates corneal epithelial proliferation and wound healing. In animal models, opioid antagonist Naltrexone increased cell proliferation and normalized OGF blood levels.
   - o Diminished activated epidermal growth factor receptor (EGFR) and downstream mediators of the pro-survival signalling pathways in the phosphatidylinositol-3-kinase (PI3K) – Akt kinase axis, and extracellular regulated kinase (ERK) may be due to upregulation of matrix metalloproteinase-10 (MMP-10), cathepsin F, and miR-146a; their inhibition reversed phospho-EGFR levels, accelerated wound healing, and normalised stem cell patterns. In animal diabetic corneas, Akt activation by SIRT1 upregulation or PTEN inhibition also accelerated epithelial healing.
   - o Increased hepatocyte growth factor (HGF) and decreased receptor c-Met expression impair cell migration, proliferation, and apoptosis.
   - o Elevated insulin-like growth factor binding proteins (IGFBPs) offset increased IGF-1 and disrupt cell survival.
   - o Decreased peptide thymosin β4 (Tβ4) impair wound healing.
   - o Nerve growth factor (NGF) levels changes are unknown.
   - o Decreased transforming growth factor (TGF)-β3 impairs healing
   - o Increase in MiR-146a and miR-424 (epithelial microRNAs/miRs, potent epigenetic regulators) inhibit EGFR and impair healing; inhibitors like antagomirs reversed this in animals.
   - o Advanced glycation end product (AGE) accumulation lower keratocyte attachment to the extracellular matrix, induce apoptosis, and retard epithelial wound healing.

##### *2.1.1.2 Neuropathy*

DCN manifests by reduced corneal sensation which is important for non-invasive diagnostics as it positively correlates with disease duration and DM stage. Histologically, reduced nerve fibre density and length in the inferior whorl, increased nerve tortuosity and thickness are observed, most notably in the sub-basal/

subepithelial nerve plexus. The mechanism of DCN remains unknown.

#### 2.1.1.3 Stromal change

Reduced keratocyte density, abnormal collagen fibril deposition, cross-linking due to AGEs, upregulated MMP-3 and MMP-10, and lipidomic changes reflect extracellular matrix remodelling.

#### 2.1.1.4 Endothelial change

Increased pleomorphism and polymegethism, decreased ECD, and Descemet's membrane with abnormally wide-spread collagen bundles are observed.

#### 2.1.1.5 Conjunctiva

Vascular dilation, capillary loss and tortuosity, and decreased goblet cells are common. Abnormal microbiome may warrant treatment with broad-spectrum antibiotics.

#### 2.1.1.6 Tear film changes

Diabetic inflammation and AGE accumulation in the lacrimal gland cause aqueous-deficient dry eye and tear film instability which contribute to epitheliopathy. Keratoconjunctivitis sicca severity correlates with diabetic retinopathy severity.

#### 2.1.1.7 Biomechanical change

The indicators corneal resistance factor (CRF) for tissue elasticity and corneal hysteresis (CH) for biomechanical integrity are increased and correlate with HB1Ac levels. Notably this may be protective for keratoconus.

### 2.1.2 Surgical complications

Diabetic patients account for most complications in cataract and vitreoretinal surgery, and keratoplasty. Contact lens wear may be a risk for epitheliopathy in DM.
In cataracts, there are increased post-operative endothelial cell loss and increased corneal thickness with eodema. In DSAEK and DMEK, diabetic donors are associated with higher risks of complications. Late-stage DM in donors is contraindicated for transplant.

### 2.1.3 Emerging treatments

#### 2.1.3.1 Insulin

Insulin eye drops in animals prevent sub-basal nerve loss and in humans significantly promoted corneal re-epithelialization
post-epithelial debridement in vitreoretinal surgeries in diabetic patients.

#### 2.1.3.2 Naltrexone

Ongoing trials study the effect of topical Naltrexone in normalising corneal sensitivity and healing.

#### 2.1.3.3 Gene and MicroRNA therapy

Adenoviral (AV) gene therapy has been used to normalize the expression of diabetes-altered genes c-Met, cathepsin F and MMP-10 in 3D organ-cultured human cornea and limbal stem cell cultures. Marked toxicity was noted in progenitor-enriched cultures of diabetic limbal epithelial cells. Subconjunctival injection in animals of miRNA antagomir promoted corneal nerve regeneration and autophagy. miRNAs typically have multiple intracellular targets and clinical translation is cautioned.

## 2.2 Cornea in Graves' Disease

In thyroid eye disease (TED), over 66% moderate to severe patients experience dry eyes and exposure keratopathy is a main complication. While corneal hysteresis is decreased, central corneal thickness remains unchanged. Systemic immunotherapies including rituxumab (anti-CD 20), TNF-α inhibitors, tocilizumab (anti-soluble IL-6 receptor) and cyclosporine (T lymphocyte inhibitor) are promising.

## 2.3 Addison's Disease

Ocular presentations in primary adrenocortical insufficiency are rare and include photophobia, ptosis, blepharitis and loss of eyelashes, keratoconjunctivitis, episcleritis, corneal ulcers, cataract, papilloedema, and limbal stem cell deficiency (LSCD).

## 2.4 Hyperparathyroidism

Primary hyperparathyroidism or secondary causes including chronic renal failure cause hypercalcemia and consequent calcium deposition in Bowman's layer/band keratopathy. In primary hyperparathyroidism, there is increased CCT and IOP; an unusual pattern of Vogt white limbal girdle with stromal deposits had been described.

# 3. Infectious Disease

## 3.1 Viral

### 3.1.1 SARS-Cov-2/COVID-19

SARS-CoV-2 can gain entry via ocular mucosa and infect ocular cells. Viral RNA is found in the cornea, conjunctiva, and ocular secretions of infected patients, whilst nucleocapsid protein antigens are found in the conjunctiva, trabecular meshwork, and iris of those infected. Viral entry receptors, angiotensin-converting-enzyme-2 (ACE2) and TMPRSS2, are expressed in the cornea and conjunctiva.
In diabetes, there is marked conjunctivitis; the diabetic ocular surface facilitates viral entry with impaired barrier, healing, and stem cell function. However, viral ocular surface tropism, cytopathic effects of the virus in cornea and innate signalling pathways involved are yet unknown.

### 3.1.2 Herpes Simplex Keratitis

Most HSK are caused by HSV-1 (90%). Anti-proinflammatory cytokines to lymphotoxin-α and -β, IL-17, TNF-a, may mitigate stromal keratitis. Most recently, topical 2% cyclosporine-A and 1% prednisolone acetate eye drops have been found to improve corneal opacity from herpetic stromal keratitis. A novel combination of prophylactic oral acyclovir and ascorbic acid has shown to reduce and prevent the recurrence of corneal epithelial herpetic keratitis.

### 3.1.3 Varicella Zoster Shingles/VZV

Herpes zoster ophthalmicus (HZO) is found in 10–20% VZV. The most severe eye-threatening complications of HZO are pan-uveitis and retinal necrosis. The US Centers for Disease Control recommends Shingrix® (recombinant glycoprotein E) vaccine for adults over 50.

### 3.1.4 Human T-Cell Leukemia Virus/HTLV-1

Targeting CD4+ T-cells, HTLV-1-associated uveitis increases complications including keratoconjunctivitis sicca and interstitial keratitis.

### 3.1.5 Epstein-Barr virus/EBV

EBV infection causes corneal endotheliitis on in vivo confocal microscopy and stromal keratitis with granular, ring-shaped opacities;

mononucleosis also causes delayed onset bilateral peripheral interstitial keratitis. Epithelial-mesenchymal transition (EMT) may lead to corneal fibrosis.

### *4. Conclusions*

Ophthalmologists may be the first point in uncovering systemic pathologies. Although many corneal abnormalities are not specific to systemic diseases, their recognition coupled with a holistic clinical picture may be instrumental to timely intervention. Exploring mechanisms of pathophysiology furthers the development of ocular-specific treatments.

**Table 1. Summary of Systemic Disease and Corneal Manifestations**

| Systemic Disease | Corneal manifestations |
|---|---|
| **Endocrine** | |
| Diabetes Mellitus | 1. Keratopathy:<br>1. compromised epithelial barrier function and wound healing<br>2. stem cell marker reduction,<br>3. decreased p38 and EGFR/ Akt signaling<br>2. Oedema;<br>3. neuropathy (loss of subbasal corneal nerves);<br>4. endothelial cell loss;<br>5. increased stromal rigidity with altered biomechanics due to AGE accumulation;<br>6. impaired tear film secretion |
| Graves' Disease | 1. Inflammation, irritation, and<br>2. dry eye due to corneal exposure caused by proptosis;<br>3. changes in corneal biochemical properties. |
| Addison's Disease | 1. Corneal ulcers,<br>2. keratoconjunctivitis,<br>3. limbal stem cell deficiency,<br>4. vision loss. |
| Hyperparathyroidism | 1. Band keratopathy due to calcium deposits in Bowman's layer, conjunctiva, and peripheral cornea.<br>2. Changes in endothelial morphology. |
| **Viral Infection** | |
| COVID-19 | 1. Dry eye, blurred vision, itching, redness, tearing, discharge, foreign body sensation,<br>2. conjunctivitis in a minority of patients. |
| Herpes Simplex Keratitis<br><br>Shingles | 1. Corneal blindness, ulcers, corneal opacification,<br>2. angiogenesis, and<br>3. corneal nerve loss. |
| Human T-Cell Leukemia | 1. Keratoconjunctivitis sicca,<br>2. interstitial keratitis,<br>3. corneal haze and opacities,<br>4. thinning and scarring of the peripheral cornea,<br>5. keratopathy and<br>6. neovascularization. |
| Virus HTLV-1 | 1. Keratoconjunctivitis sicca,<br>2. interstitial keratitis,<br>3. corneal haze and opacities,<br>4. thinning and scarring of the peripheral cornea,<br>5. keratopathy and<br>6. neovascularization. |
| Epstein-Barr Virus | 1. Stromal keratitis with granular, ring-shaped opacities,<br>2. delayed onset bilateral peripheral interstitial keratitis,<br>3. corneal endotheliitis (also seen in CMV infection),<br>4. epithelial-mesenchymal transition. |
| **Bacterial infection** | |
| Tuberculosis/TB | 1. Lid vulgaris,<br>2. conjunctivitis,<br>3. scleritis, episcleritis,<br>4. corneal phlycten,<br>5. interstitial keratitis. |

**Table 1.** Continued

| | |
|---|---|
| Syphilis | 1. Uveitis and syphilis keratitis, which may lead to decreased visual acuity and even permanent blindness. |
| Pseudomonas aeruginosa keratitis | 1. Contact lens-related ulcers, biofilm formation, bacterial keratitis, corneal edema,<br>2. liquefactive necrosis. |
| **Autoimmune and Inflammatory Diseases** | |
| Reumatoid Arthritis/RA | 1. Scleritis, episcleritis,<br>2. peripheral ulcerative keratitis,<br>3. keratoconjunctivitis sicca, and may be precursor to other rheumatic disease such as Sjo¨gren's syndrome. |
| Sjo¨gren's Syndrome | 1. Moderate to severe ocular dryness, thus causing corneal melt/perforation,<br>2. uveitis, scleritis, and in severe cases<br>3. limbal stem cell deficiency. |
| Systemic Lupus Erythematosus/SLE | 1. Inflammation may cause cataracts,<br>2. keratoconjunctivitis sicca (via secondary Sjo¨gren's syndrome and rheumatoid arthritis),<br>3. glaucoma,<br>4. discoid lesions of eyelids,<br>5. episcleritis, scleritis,<br>6. keratitis, and<br>7. uveitis. |
| Gout | 1. Keratitis and<br>2. corneal endothelial dysfunction. |
| Allergic Keratoconjunctivitis/AKC | 1. Punctate keratitis, corneal erosions, corneal ulcerations, epithelial defects,<br>2. Oedema<br>3. neovascularization,<br>4. scarring, and vision loss. |
| Vernal Keratoconjunctivitis/VKC | 1. Punctate epithelial erosions, shield ulcers,<br>2. stromal plaques, neovascularization,<br>3. keratoconus,<br>4. infectious keratitis, and<br>5. LSCD. |
| Multiple Sclerosis/MS | 1. Significant reduction of corneal nerve fiber density, branch density and length with axonal loss. |
| Granulomatosis with Polyangitis/GPA | 1. Bilateral peripheral ulcerative keratitis due to the presence of autoantibodies and inflammatory cells from limbal blood vessels,<br>2. limbal edema,<br>3. corneal thinning,<br>4. endothelial cell loss. |
| Sarcoidosis | 1. Corneal small nerve fiber loss and damage,<br>2. interstitial keratitis,<br>3. band keratopathy from calcium deposits in the Bowman's layer,<br>4. dry eye. |
| Cogan's Syndrome | 1. Bilateral peripheral subepithelial keratitis with nummular lesions,<br>2. deep stromal keratitis,<br>3. granular infiltration in peripheral cornea,<br>4. photophobia, excessive tear production, diminished visual acuity. |
| Immunobullous Disease | 1. Punctate epithelial erosions,<br>2. bilateral corneal perforations, corneal melting,<br>3. decreased corneal nerve density,<br>4. intraepithelial defects,<br>5. anterior stromal fibrosis,<br>6. corneal neovascularization. |

**Table 1.** Continued

| Genetic Diseases with Corneal Deposits | |
|---|---|
| Wilson's | 1. Kayser-Fleischer ring and sunflower cataract formation due to copper accumulation. |
| Cysgtinosis | 1. Formation of corneal crystals of cysteine deposits and photophobia, and<br>2. recurrent corneal erosions in some cases. |
| Fabry Disease | 1. Cornea verticillata (vortex keratopathy) due to whorl-like deposits in the epithelial and sub- epithelial layers, with<br>2. corneal haze and<br>3. conjunctival vessel tortuosity. |
| Meretoja Syndrome | 1. Corneal lattice dystrophy,<br>2. corneal ulcers,<br>3. dry eye, photophobia,<br>4. dysfunction of the meibomian glands,<br>5. early development of cataract. |
| Mucopolysaccharidosis (7 subtypes) | 1. Corneal clouding that appears as yellowish-grey granules deposited in all layers of the cornea, but mainly in the stroma,<br>2. increased keratocyte size and the<br>3. displacement of collagen fibrils. |
| Hyperlipoproteinemia | 1. Corneal arcus |
| **Other genetic disorders** | |
| Aniridia | 1. Aniridia-associated keratopathy,<br>2. conjunctival neovascularization, and corneal blindness caused by<br>3. limbal stem cell insufficiency. Altered Notch1 and Wnt signaling. |
| Ehlers-Danlos Syndromes (EDS) | 1. Kyphoscoliotic EDS (mutated PLOD1 or FKBP14 genes) is associated with scleral fragility, microcornea.<br>2. Brittle cornea syndrome (mutated ZNF469 or PRDM5 genes) can cause<br>1. corneal rupture, scarring, keratoconus, keratoglobus.<br>3. Classic EDS with mutations of COL5A1 or COL5A2 genes may result in thinner and steeper corneas. |
| Marfan syndrome | 1. Corneal flattening and thinning. |

References:

Ljubimov, Systemic diseases and the cornea, Experimental Eye Research, Volume 204, 2021, 108455, ISSN 0014-4835, https://doi.org/10.1016/j.exer.2021.108455. Available at: https://link.springer.com/article/10.1007/s00330-021-08311-z

MCLOSA & OSI

The Medical Contact lens & Ocular Surface Association

# Joint Virtual Symposium

## Reinventing the Horizon

Moderated by OSI Editor-in-Chief Mr Samer Hamada and Miss Artemis Matsou

Edited by **Elsa Lee** MSc Ophth MBBS

The curtains closed on the first Medical Contact Lens and Ocular Surface Association (MCLOSA) and Ocular Surface Insight (OSI), Joint Virtual Symposium in spirits of celebration. In connecting speakers and online attendees from across four continents, we bring colleagues and mentors a step closer to in-person gatherings. Please take a look at the speaker highlights, and clinical pearls to advance your practice.

### Symposium in Retrospect

**Panel 1: Ocular surface protection:**
**A superheroes approach**

**Samer Hamada – Early detection of ocular surface failure**
Early detection is essential; early manifestation might be obscure, but inflammation is normally present and can be treated.

Identifying early, in recognising advanced signs is key; these include active inflammation (redness, chemosis, chalasis), conjunctival congestion, conjunctivochalasis, corneal neovascularistion, ocular surface (OS) staining, lack of lustre appearance, disorganised epithelium, DED, LSCD, loss of limbal anatomy/palisades of Vogt effacement, and columnar keratopathy (typically seen superiorly extending inferiorly).

Ocular surface failure involves the failure of OS integrity, homeostasis, and regulatory systems (innervation, endocrine, vascular, immune regulation).

Ocular surface damage is often difficult to repair.

The clinical picture in OS damage is not static as stem cells travel faster inferiorly, and slower superiorly.

Corneal epithelial maps can be useful to highlight limbal hyperplasia, thinning, variable measurements, and focal irregularities.

Early Management involves

1. Protection: Lid malposition and fornix adhesion, wet not dry
2. Restoring homeostasis: control inflammation, optimise tear film and systemic conditions

**David Lockington –**
**How I approach Corneal melting and perforation**

Do not hope to be a superhero: have a plan and know what weapons are available; do the simple things well!

Keys:

1. Take good history: 4Is = injury, infection, inflammation, iatrogenic.
2. Appropriate examination: be wary, the eye may not always be watering/have reduced VA, shallow AC, Seidel's test, Pigment spot.
3. Medical management: always treat the hot eye (back up surgical with medical: Antibiotics, anti-virals, anti-MMP, steroids, immunotherapy; focus on the whole not just the hole).
4. Use objective imaging: serial minimum; topography/ AS-OCT, relieve the % thinning guesses.
5. Prevention before the perforation.

5 Principles for approaching corneal melt:

1. Take proper history to identify cause.
2. Examine with suspicion for perforation – concentrated fluorescein.
3. Imaging for accurate comparison.
4. Know medical and surgical options – switch off the inflammation above the eye.
5. Do no harm with treatments.

Aims for management:

- Preserve the globe
- Address cause to prevent further deterioration
- Visual rehabilitation - early and late
- Educate primary care/patient – in hospital

Management options

- Supportive
- Medical
- Surgical

Corneal glues

1. Indications and use:
   Early Definitive or temporizing = Cyanoacrylate, small perforations <1mm;
   treat surface dry and intact, debride, surgical spears,

large diameter contact lens; never regret taking patients to theatre!
2. Techniques for application: direct or use plastic to bridge gap
   Use insulin syringe flick away the main drop and use the remaining glue on bevel for neat seal
3. Glue works less well if inferior defect, as blink reflex dislodges glue

Conjunctival flaps
AMT: Single layer cuboidal epithelial cells, basement membrane, avascular stromal matrix
Primary closure
Scleral/corneal grafts

**Gok Ratnarajan – As seen by a glaucoma surgeon**

Glaucoma medication causes significant OSD, and is often underdiagnosed in busy glaucoma clinics. Topical toxicity impacts QoL and surgical success. Prostaglandin Associated Periorbitopathy (PAP) was discussed.

Glaucoma drops have conjunctival proinflammatory and proapoptotic effects (latanoprost and timolol).

Ocular surface optimisation is important for surgical outcomes in filtering surgery. Treat the asymptomatic; consider patients perspectives!

SLT is increasingly offered as 1st line treatment for those with OSD, poor compliance, not suitable for filtering surgery since LiGHT multicentre RCT, which compared selective laser trabeculoplasty and eye drops for first-line treatment of ocular hypertension and glaucoma.

MIGS improves OSD: MIGS is a safe adjunct with phaco, for mild to moderate disease; lowers IOP and reduces drop burden, prevent/delay filtering surgery.

Raman Malhotra – Ocular surface protection: Oculoplastic surgeon's perspective

BLInKS for TriPS:
- Blink
- Lagophthalmos
- Inturning eyelid/entropion
- Keratinisation
- Scarring
- Fornix
- Trichiasis
- Punctum
- Sac

There are four types of blink:
1. Twitch blink
2. Incomplete blink
3. Complete blink
4. Forced or voluntary blink

Cotton tip test positive for meibomian gland inversion is a good prognosis for surgical correction: ask if the patient is more comfortable when lid is everted.

Surgery
- Upper eye lid grey-line split
- Correction of curled tarsus
- Levator recession
- Anterior lamellar repositioning

Post-trabeculectomy eyelid retraction and periorbital volume and lagophthalmos, were discussed.

**Colin Williams - Chronic Disease and their psychological effects**

Hands-on advice on first line practical tips, to calm anxious patients were introduced.
Handling overwhelming emotions in others and ourselves by defusing/unhooking from unhelpful thoughts, grounding yourself in the present, continuing despite their presence. Diffusing and grounding skills were practiced.

**Fiona Carley**
**Contact lens induced limbal stem cell deficiency**

"He who studies medicine without books sails on unchartered sea, but he who studies medicine without patients does not go to sea at all." – William Osler

Two clinical cases were presented with diagnosis and differentials, diagnostic confirmation

Keys:
1. Consider diagnosis in the presence of typical features, and undertake appropriate diagnostic tests.
2. Contact lens-induced LSCD can be reversed, if recognised early.

**Prof Francisco Figueiredo - MCLOSA Kersley lecture: Chemical burns – through the eye of time**

Comprehensive evidence-based lecture on chemical burns from diagnosis and management, economic and humanistic burdens, to psychosocial effects and patient-centred reviews.

**Panel 2: Environmental factors effect on the ocular surface**

**Arthur Cummings - Work, hobbies and habits**

Updated definition of dry eye disease (DED):
a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film. This is accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles.

DED is not defined by symptoms! There is avariable prevalence of 5-50%.

Disruption of hyperosmolar stress is indispensable for rescue processes on the ocular epithelia – tear film layer stability, normalising osmolarity, and continuous biophysical protection; characteristically there is increased osmolarity, inflammation, loss of homeostasis.

Factors such as relative air humidity, temperature, illumination, video terminal time, air conditioning impact DED.

Clinical or traditional signs of dry eye disease are indicative of ocular surface damage but do not reveal etiology!

**Rohit Shetty - Hormones, immune system and nerves**

The interactions of CNS, immune and endocrine systems were explored.

Mask-associated dry eye, and hypo-osmolar ocular surface damage are on the rise.

Simplifying and expediting biomarker analysis, and considering nociceptive factors are key.
Lysyl oxidases (LOX) enzymes, for endogenous corss-linking was explored.

**Brian Tompkins - Contact lenses – Latest evidence**

Principles of CL: maintain ocular health and comfort.
Types of CL include Soft, RGP, hybrid, scleral. Features to consider include wettability, surface quality; soft lens technologies are considered e.g., plasma treatment, PVP, aquaform, mucomimetics, water gradients; smart surface and tear substitutes comparison was made from natural, semi-synthetic to synthetic across hydration, lubrication, mucoadhesion, mucomimicry, viscoelastic, and wound healing properties. Polyethylene glycol (PEG) lubricant for coating soft lenses was reviewed.

**Sabrina Shah-Desai - Cosmetics and Cosmetic Surgery (Beauty and the Beast)**

Cosmetic trends affect ocular surface diseases. Patient consumers are unaware of make-up risks e.g., preservatives at concentrations approved for consumer use are toxic to ocular surface and adnexal cells.

As aesthetic procedures become more socially acceptable, their impact on the ocular surface has been heightened and instantiated in:

- Periorbital dermatitis
- Type 4 hypersensitivity to nickel in mascara, CL solution, Kajal pencil, fragrance allergy, nail varnish, Thimerosal in CL solutions etc
- Chronic blepharitis secondary to micropigmentation permanent tattoos e.g. eye brows/eye liners
- DED and OSD due to topical anaesthetics
- Glitter eye shadow, makeup removal wipes, and dried mascara causing mild ocular discomfort, pre-corneal tear film instability, keratitis,
- Longer lashes channel airflow directly onto the eye surface with drying effect, and particle accumulation
- Cyanoacrylate based lash extension / glue contain latex and ammonia and high emission of formaldehyde
- Eyelash growth serums – Latisse containing prostaglandin analogues
- Periorbital botox leading to hypometric blink, OSD, and blepharitis
- Botox induced ptosis
- Dermal filler blindness – areas associated with irreversible sight loss and ophthalmoplegia
- Laser/skin tightening treatments; cicatricial ectropion
- Horizontal lid phimosis
- Recurrent congenital ptosis

**Amy Gallant-Sullivan**
**Eyes are the story – beauty and pharma**

Above-the-mask makeup has seen a surge in the pandemic. Mainstream products cause ocular irritation, allergy, contact dermatitis, meibomian gland and corneal epithelial cell toxicity, and contact lens dropout.

Despite the risks, there is widespread low cosmetic-related health awareness.

Patients' application processes impact diagnosis

Top 10 ocular-surface-offending ingredients are argireline (acetyl hexapeptide-3 / acetyl hexapeptide-8), benzalkonium choloride (BAK), carbon black, formaldehyde, isopropyl cloprostenate, parabens, phenoxyethanol, retinols, chlorphenesin, tea tree oil

Top 10 blunders in aesthetics are botox for Crow's feet, botox-in-a-jar, eyelid tattooing, eyelash extensions, eyelash tinting, eyeshadow powerder/glitter, OTC eyelash growth serums, retin-A, sharing makeup, and water-proof makeup.

**Andrena McElvanney - Therapeutic contact lenses – what is new?**

Amniotic membrane (patch and graft applications) and CL were explored.

Bandage contact lens (BCL) is versatile in an extensive range of indications. Omnilenz and its different specifications, were introduced.

Hydration, size adjustment, and lid tightening for fitting were explored to avoid lens extrusion.

**Panel 3: Sjogren's disease: How they see it?**

**Alaa Aldaadaa - An Oral Surgeons view**

Sjogren's disease oral presentation is key to incidental diagnosis.
Systemic consideration including neck swelling offer differential diagnoses.

Early diagnosis and referral is essential. Monitoring of dental caries, periodontal disease and salivary gland tumour e.g., Non-Hodgkin's lymphoma, are key considerations.

**Parwez Hossein - Contact lens related Microbial keratitis**

Contact-lens related infection can rapidly lead to severe corneal damage in a few hours, and perforation in a few days.

Chloramphenicol is only bacteriostatic; use quinolone in CL keratitis.

AS-OCT aids diagnosis and guides antimicrobial use.

Emergency therapeutic keratoplasty has value despite apparent poor prognosis in light of graft survival curves, as PK in advanced infection still lead to 5 lines of VA improvement at 1 year.

Showering in CL daily increases keratitis risk by over 7 times (dose-response relationship).

Despite advice from optometrists, patients continue to perform CL poor hygiene practices.

**Sophie Jones - Management of refractive surprise**

Refractive surprise is the failure to achieve intended post-op refractive target, resulting in anisometropia, dominance switch, patient dissatisfaction, and medico-legal implications.

Manage patient expectation before surgery, and identifying those at high risk is essential.

Risk factors include high myope (exclude staphyloma), younger age, ocular co-morbidities, poor pre-oeprative CDVA, surgical difficulties, and complications.

Prevention relies on accurate biometry: A-Constant optimisation and Correct IOL formula selection.

Factors influencing biometry accuracy include:

- Poor fixation (strabismus etc)
- Previous intraocular surgery: optical biometry to RPE, US biometry to ILM;
- consider optical AND US biometry in vitrectomised eyes, and compare with the other eye. Expect minor myopic shift after phacovitrectomy.

- Previous laser refractive surgery:

- Hyperopic surprise after myopic laser surgery

- Myopic surprise after hyperopic laser surgery

- Hyperopic surprise in previous radial keratotomy

- Overestimation of corneal power in keratoconus can lead to hyperopic surprise

Cataract surgery causes, and exacerbates pre-existing DED; optimise pre-peri and post-operatively is imperical
human error.

Principles of treatment:

1. Treat the patient not the refractive error!
2. Manage Post-op DED and HOA; Check for distended capsular bag, toric IOL rotation
3. Communicate pros and cons with patients

Surgical options:

1. Corneal: Laser refractive; LRI's antiastigmatic keratotomies;
2. Lens-based: IOL exchange, add-on implants, IOL fixation/rotation revision

Pearls:
- IOL Exchange: Early surgery preferable
- Add-on implants or corneal refractive surgery: stable refraction mandatory; wait 3 months

**Samer Hamada - Dry eye master class**

Masterclass agenda encompasses:

- TFOS DEWS II
- DED pathogenesis
- Diagnostics
- Role of questionnaire based assessment in your DED clinics
- External and systemic examination
- Optimizing slit-lamp examination-MGD grading, anterior blepharitis diagnosis
- Setting up a dry eye clinic
- When should I plan systemic investigation and connective tissue disorder work-up?
- Refractory DED
- Masquerades including Demodex
- Stepwise management – conventional to advanced therapeutics
- Dry eye in KC
- DED impact on Optical quality

# What's in the news?

## Association Between Skin Findings and Ocular Signs in Rosacea

The objective of this study was to report the most frequent signs in ocular rosacea and evaluate their association with skin findings.

Fifty-one patients diagnosed with rosacea by a trained dermatologist were evaluated by an ocular surface specialist. A complete ophthalmological examination was performed.

In the study, the prevalence of ocular signs in patients with rosacea was 74.5%. The average age at presentation was 50 years and women were more affected than men. The most common findings were lid margin erythema, meibomian gland dysfunction, and blepharitis. Fifteen patients had decreased visual acuity due to complications related to rosacea such as leukoma and corneal neovascularization. Interestingly, patients that had the lowest visual acuity presented with dermatological signs of papules and pustules (p=0.001) and rhinophyma (p=0.023). Two patients who showed subepithelial fibrosis and fornix foreshortening were diagnosed as having ocular cicatricial pemphigoid (OCP) by immunohistopathological analysis of conjunctival specimens.

In conclusion, ocular compromise is common in rosacea. This study shows that there might be a relationship between the severity of ocular involvement and certain subtypes of cutaneous disease. Rosacea and OCP may coexist. In cases that present with conjunctival fibrotic changes, a diagnostic biopsy is mandatory.

Authors: Francisco Lucero Saá, Federico Cremona, Pablo Chiaradia
Publication: Turk J Ophthalmol. 2021 Dec 28;51(6):338-343.doi: 10.4274/tjo.galenos.2021.05031.

# Spontaneous resolution of dislocated DMEK despite novel herpetic keratitis

By **Iain Davidson** MB BCh, **David Lockington** MB BCh BAO (Hons) FRCOphth PhD

## Introduction

Modern corneal lamellar transplantation in the form of Descemet's Membrane Endothelial Keratoplasty (DMEK) has resulted in rapid recovery of vision in patients with endothelial failure. However, this sutureless surgical intervention is associated with graft dislocation requiring re-bubbling procedures [15.6% in one Canadian series]. [1] It is not clear what intrinsic factors contribute to graft dislocation (aside from the learning curve). [2,3] Post-operative steroid use is known to predispose to ocular surface infection. [4] We wish to report a case of a dislocated DMEK complicated by novel herpetic infection in the immediate post-operative period and discuss our management strategy and subsequent outcome.

## Case report

A 67-year-old man with advanced Fuch's endothelial dystrophy presented to our corneal services with poor vision. He had left corneal scarring due to previous complicated intra-ocular surgeries. BCVA was OD 6/60, OS 1/60. He underwent uneventful combined right cataract surgery and DMEK, and was discharged on topical dexamethasone and chloramphenicol x4/day as standard. Day 1 review showed a centered graft. At week 1 review he stated his eye was uncomfortable and he admitted to rubbing it vigorously. IOP was 6mmHg with no wound leak, but a completely detached, freely mobile DMEK scroll was observed, and so he underwent a re-bubble procedure with air. He was also prescribed 40mg oral prednisolone to reduce inflammation. AS-OCT confirmed central graft attachment at week 1 post re-bubble.

At week 2 post re-bubble, he reported 2 days of pain and photophobia. Visual acuity was 1/60. There was a large geographic epithelial defect with dendritic pattern. New infraorbital skin vesicles were noted beneath his facemask, and herpes simplex virus (HSV) was confirmed on PCR testing. The topical dexamethasone was reduced to x2/day and he was prescribed systemic aciclovir 400mg x5/day and topical ganciclovir x5/day. The cornea was oedematous and the DMEK graft was now detached on AS-OCT imaging (central cornea thickness 1200um; see Figure 1A).

After 2 weeks of anti-viral treatment, the epithelial defect resolved, yet the vision remained poor and the cornea oedematous with persistent shallow DMEK detachment. Due to the risk of introducing HSV intra-ocularly from a further re-bubbling procedure, and the potential that the DMEK tissue was no longer viable due to inflammation, conservative management was continued (oral acyclovir 400mg x2/day and topical dexamethasone x2/day).

At 9 weeks post initial surgery (8 weeks post re-bubble; 6 weeks of HSK treatment) the patient experienced spontaneous graft reattachment with complete resolution of corneal oedema. Visual acuity was 6/12 UA with a comfortable white eye (pachymetry 585um). [See Figure 1B]

## Discussion

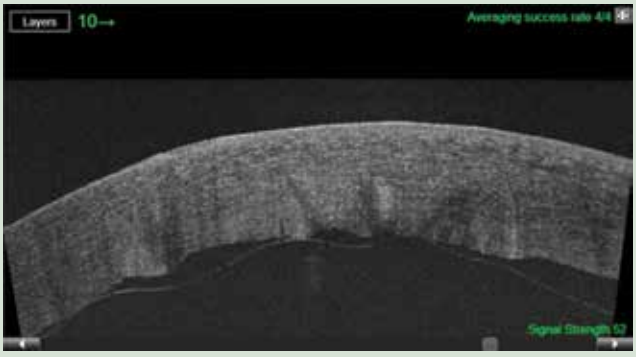
Steroid use following corneal transplantation has been associated with new herpetic infection (1.18% in PKP). [5] Infection can occur via intracorneal multiplication of virus after reactivation in ganglia, reactivation of latent-state virus in residual recipient cornea and/or reactivation of donor-recipient transmission virus. [5] New herpetic keratitis has also been reported after Descemet stripping automated endothelial keratoplasty for a failed graft. [6] Conversely, DMEK has been shown to be a successful intervention to address HSV-related endothelial failure. [7]

The literature is relatively silent regarding the impact of novel HSK infection on DMEK adherence and ultimate survival. A recent case report of focal DMEK detachment due to new HSK at 1 month post op resulted in eventual graft failure, requiring a repeat DMEK. [8] However, new HSK has been reported at first week following DMEK surgery which resolved within 2 days with anti-viral treatment. [9] Similarly, reactivation of HSK at 2 months post-DMEK was reported to resolve within 2 weeks of antiviral treatment. [10]

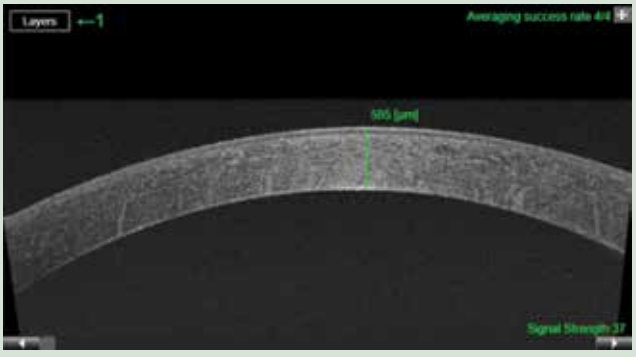
Melles' group have suggested that re-bubbling for DMEK graft detachment may result in similar visual outcomes as in uncomplicated DMEK, when performed within the first 6 to 8 postoperative weeks. [11] Furthermore, a large German study reported that the overall number of re-bubblings had no influence on the postoperative outcome after DMEK, if a re-bubbling becomes necessary. [12] In our case, we had concern that a further re-bubbling in the presence of active surface infection could result in intra-ocular infection. We assumed that the detached DMEK tissue may not survive the inflammation and infection and so opted to observe and treat conservatively.

Our unusual case of late spontaneous graft reattachment following treatment of a HSV geographic ulcer in a dislocated DMEK scenario should reassure the clinician that active or immediate surgical intervention is not always required. Surgical management of graft dislocation can be delayed in cases of DMEK detachment complicated with herpetic viral keratitis, with good outcomes, as in our case.

**Figure 1**: Composite figure of AS-OCT images showing persistent detachment of DMEK complicated with active HSK (A), which spontaneously resolved following medical management (B).



**A**. Week 2 post rebubble: Active herpetic infection
DMEK detachment, epithelial thinking, large geographic ulcer



**B**. Week 8 post rebubble and Week 6 after HSK treatment:
6/12 UA. Comfortable, no oedema, 585um

# For your eyes only: Custom-fit lenses can have a life-changing impact

By **Brian Tompkins** and **Dr Keyur Patel**

If you want a perfectly fitting suit, you don't buy off-the-peg. If you want the best possible pair of shoes, you get them made bespoke. Custom-fit is the best way to ensure total comfort – and it applies to contact lenses too.

Rather than relying on standard lenses and hoping they fit the shape of the eye, eye care practitioners can now create a 100 per cent bespoke lens which matches the exact contour of the surface of a patient's eye.

EyePrintPRO™ is effectively like taking a fingerprint of the eye. It's quick, painless and has life-changing benefits – with people who have struggled for years to get a lens to fit due to their keratoconus or other debilitating corneal disease now enjoying the benefits of a fully customised lens unique to them.

It uses impressions of the ocular surface to design specialized contact lenses that match the shape of each individual eye. This highly customized fit results in greater stability of the lens, improving comfort for many patients.

## The background

Christine Sindt, OD, FAAO, FSLS, developed the concept of EyePrintPRO in her early years as an optometrist. As she devoted her career to providing the best possible care to patients with diseased and irregular corneas, her ambition to advance the standard of contact lens care only grew.

After developing the EyePrint Impression Process, she partnered with Keith Parker, the president of Advanced Vision Technologies, to assist in the development of manufacturing this highly customized contact lens. Together, and with the help of many dedicated colleagues, they have greatly improved contact lens fitting technologies and delivered life changing vision and ocular comfort to many patients.

The EyePrint Prosthetics headquarters is located in Lakewood, Colorado. From this location, EyePrint Prosthetics' staff works closely with a tight-knit network of specially trained and certified practitioners across the globe. EyePrint Prosthetics teams up with some of the world's most esteemed practitioners to provide the highest standard of care to patients with extreme ocular conditions.

## How it works

All EyePrint Practitioners undergo training in the EyePrint Impression Process before they are certified and listed on the EyePrint referral network. Through this collaboration with EyePrint Practitioners, the EyePrintPRO has helped many patients who had no other options because of the irregularity of their ocular surface.

The flagship product, the EyePrintPRO, allows patients with ocular disease, complicated optics, and severely irregular ocular surfaces to experience the vision, comfort, and ocular health benefits of customized contact lenses. The numerous benefits of the EyePrintPRO are enabled through patented Elevation Specific Technology™ (EST).

The EyePrint Impression Process captures the exact shape of a patient's eye, providing a 3D model of the entire ocular surface. EyePrint Prosthetics utilizes EST to match the elevation differences of each individual eye with a perfect fitting contact lens.

## Ocular Impressions

The EyePrint Impression Process takes only minutes and acquires the most accurate data possible of the ocular surface. Using an FDA-approved ocular compound and an insertion tray, designed specifically to fit the ocular globe, the impression process captures all corneal-scleral irregularities and contours.

This simple, non-toxic process allows for more information to be obtained than high-tech, computerized topographical scanners. This provides the practitioner with the ability to fit the most complex of eyes.

## Custom Lens Production

After the impression process is complete, the EyePrint Practitioner sends the impression to EyePrint Prosthetics for scanning, designing, and manufacturing.
The proprietary EyePrint Scanning Process creates a virtual 3D model of the eye. The 3D model is then imported into specialized EyePrint Designer software, where a virtual lens is generated to parallel the unique ocular surface. Once the design is complete, the data is sent to a state-of-the-art manufacturing lab.

This advanced EyePrint technology identifies the details of the ocular surface for optimal design, vision, and comfort.

The final EyePrint contact lens is then shipped to the Certified EyePrint Practitioner for dispense.

## What it means in practice

We are proud to have been the first UK practice licensed to use EyePrintPRO. As eye care practitioners, the impression gives us more information than the very latest topographical scanners and allows us to fit complicated ocular irregularities with precision. Lenses are manufactured in a high oxygen permeable material with superior quality optics, giving patients the ultimate in comfort, health and vision.

EyePrintPRO uses the very latest 3D scanning technology. Rather than relying on standard lenses and hoping they fit the shape of an individual eye, we can now create a 100 per cent bespoke lens - exclusive to the patient.

EyePrintPRO is recommended for patients with keratoconus, irregular astigmatism, ocular surface disease (dry eye), trauma, extreme cases of deformed eyes, pellucid marginal degeneration, chemical burns, post-surgical corneas (including corneal transplants and post LASIK ectasia), pinguecula, pterygium, stem cell failure, or simply anyone looking for improved vision and comfort.

It has provided an incredibly effective solution to some of our most complex patients. Many have struggled for years to find a contact lens that affords them true comfort and freedom. Thanks to EyePrintPRO those struggles are over and they can enjoy a new lease of life.

If you want a perfectly fitting suit, you don't buy off-the-peg. If you want the best possible pair of shoes, you get them made bespoke. Custom-fit is the best way to ensure total comfort – and it applies to contact lenses too.

Rather than relying on standard lenses and hoping they fit the shape of the eye, eye care practitioners can now create a 100 per cent bespoke lens which matches the exact contour of the surface of a patient's eye.

EyePrintPRO™ is effectively like taking a fingerprint of the eye. It's quick, painless and has life-changing benefits – with people who have struggled for years to get a lens to fit due to their keratoconus or other debilitating corneal disease now enjoying the benefits of a fully customised lens unique to them.

It uses impressions of the ocular surface to design specialized contact lenses that match the shape of each individual eye. This highly customized fit results in greater stability of the lens, improving comfort for many patients.

## The background

Christine Sindt, OD, FAAO, FSLS, developed the concept of EyePrintPRO in her early years as an optometrist. As she devoted her career to providing the best possible care to patients with diseased and irregular corneas, her ambition to advance the standard of contact lens care only grew.

After developing the EyePrint Impression Process, she partnered with Keith Parker, the president of Advanced Vision Technologies, to assist in the development of manufacturing this highly customized contact lens. Together, and with the help of many dedicated colleagues, they have greatly improved contact lens fitting

technologies and delivered life changing vision and ocular comfort to many patients.

The EyePrint Prosthetics headquarters is located in Lakewood, Colorado. From this location, EyePrint Prosthetics' staff works closely with a tight-knit network of specially trained and certified practitioners across the globe. EyePrint Prosthetics teams up with some of the world's most esteemed practitioners to provide the highest standard of care to patients with extreme ocular conditions.

## How it works

All EyePrint Practitioners undergo training in the EyePrint Impression Process before they are certified and listed on the EyePrint referral network. Through this collaboration with EyePrint Practitioners, the EyePrintPRO has helped many patients who had no other options because of the irregularity of their ocular surface.

The flagship product, the EyePrintPRO, allows patients with ocular disease, complicated optics, and severely irregular ocular surfaces to experience the vision, comfort, and ocular health benefits of customized contact lenses. The numerous benefits of the EyePrintPRO are enabled through patented Elevation Specific Technology™ (EST).

The EyePrint Impression Process captures the exact shape of a patient's eye, providing a 3D model of the entire ocular surface. EyePrint Prosthetics utilizes EST to match the elevation differences of each individual eye with a perfect fitting contact lens.

## Ocular Impressions

The EyePrint Impression Process takes only minutes and acquires the most accurate data possible of the ocular surface. Using an FDA-approved ocular compound and an insertion tray, designed specifically to fit the ocular globe, the impression process captures all corneal-scleral irregularities and contours.

This simple, non-toxic process allows for more information to be obtained than high-tech, computerized topographical scanners. This provides the practitioner with the ability to fit the most complex of eyes.

## Custom Lens Production

After the impression process is complete, the EyePrint Practitioner sends the impression to EyePrint Prosthetics for scanning, designing, and manufacturing.
The proprietary EyePrint Scanning Process creates a virtual 3D model of the eye. The 3D model is then imported into specialized EyePrint Designer software, where a virtual lens is generated to parallel the unique ocular surface. Once the design is complete, the data is sent to a state-of-the-art manufacturing lab.

This advanced EyePrint technology identifies the details of the ocular surface for optimal design, vision, and comfort.

The final EyePrint contact lens is then shipped to the Certified EyePrint Practitioner for dispense.

## What it means in practice

We are proud to have been the first UK practice licensed to use EyePrintPRO. As eye care practitioners, the impression gives us more information than the very latest topographical scanners and allows us to fit complicated ocular irregularities with precision. Lenses are manufactured in a high oxygen permeable material with superior quality optics, giving patients the ultimate in comfort, health and vision.

EyePrintPRO uses the very latest 3D scanning technology. Rather than relying on standard lenses and hoping they fit the shape of an individual eye, we can now create a 100 per cent bespoke lens - exclusive to the patient.

EyePrintPRO is recommended for patients with keratoconus, irregular astigmatism, ocular surface disease (dry eye), trauma, extreme cases of deformed eyes, pellucid marginal degeneration, chemical burns, post-surgical corneas (including corneal transplants and post LASIK ectasia), pinguecula, pterygium, stem cell failure, or simply anyone looking for improved vision and comfort.

It has provided an incredibly effective solution to some of our most complex patients. Many have struggled for years to find a contact lens that affords them true comfort and freedom. Thanks to EyePrintPRO those struggles are over and they can enjoy a new lease of life.

# Q & A's with Prof. Craig

Edited by **Vivian Ho**

Prof. Craig

1 How did you come up with the study idea on investigating the impact of digital screen use and lifestyle factors on dry eye disease (DED) in the paediatric population[1]?

As recognised by the Tear Film and Ocular Surface Society whose latest global Workshop is focused on A Lifestyle Epidemic: Ocular Surface Disease, it's become increasingly apparent in recent years that many of our lifestyle choices serve as triggers for dry eye disease. This includes what we eat and drink, the medications or nutraceuticals we take, or the cosmetics we choose to apply. One key lifestyle factor that's become an intrinsic part of modern life, and even more so since the pandemic, is digital screen use.

The progressive nature of dry eye disease means that it's vital that we understand the impact of modifiable factors on the ocular surface so that we can offer evidence-based recommendations at the earliest stages, in an attempt to minimise any life-long impact of the disease. With this in mind, we felt it valuable to assess the eyes of children, as there's relatively little data available, yet we're seeing more children reporting dry eye symptoms than ever before.

Increasingly our youth are exposed to many of the same risk factors we're exposed to as adults. Digital screen use is common one, with screen use associated with poor blink habits. Incomplete blinking in itself has been linked with the development of meibomian gland dysfunction and dry eye so this is an area worthy of further research.

2 What sort of diagnostic tests did you use on the participants to evaluate whether they have DED?

We assess our participants using non-invasive or minimally invasive tests, so that we don't destabilise the tears more than necessary during assessment. This allows us to obtain the most accurate information about the eyes in a natural setting. We routinely start with capturing symptoms on a validated questionnaire (usually the OSDI and/or DEQ-5). We then perform clinical tests that might indicate a loss of tear film homeostasis. This includes measuring the non-invasive tear breakup time, and where possible, tear hyperosmolarity and ocular surface staining (cornea, conjunctiva and lid margin) with fluorescein and lissamine green. A diagnosis of dry eye disease, according to the TFOS DEWS II criteria, is made with a positive symptom score and any one of these global indices of tear film homeostasis.

We also collect non-invasive measurements such as tear meniscus height that can indicate presence of aqueous deficiency, and evaluate the lipid layer and perform infrared meibography to assess the likelihood of evaporative dry eye secondary to meibomian gland dysfunction.

3 How often do you use noninvasive tear break-up time (NIBUT) instruments in your studies to evaluate tear stability? Do you think all ophthalmologists should have access to a NIBUT instrument when evaluating their patients with dry eye disease?

We are fortunate to be able to use non-invasive measurements in all of our research studies. Based on the peer-reviewed literature, this is currently considered the best way to measure tear film stability. Scientific evidence shows that the very act of instilling fluorescein in the tears before assessing breakup time can destabilise the film and affect our measurements.

Ideally, ophthalmologists should use non-invasive instrumentation to assess dry eye disease, but it is recognised that this is not always available. Until such non-invasive measures are more widely available, fluorescein can be used, however, it's important that the volume instilled is minimised as much as possible. Using a yellow barrier filter on the slit lamp helps to improve visualisation of the fluorescence created by the blue light so that only tiny volumes of fluorescein are necessary to get a great view.

References:

1) Impact of digital screen use and lifestyle factors on dry eye disease in the paediatric population. The Ocular Surface 24, 2022; 64-66. Wang et al.
2) Modifiable lifestyle risk factors for dry eye disease. Wang et al. Cont Lens Anterior Eye 2021; 44:101409.

4 Are you surprised to see that some of demographic risk factors[2] of DED such as gender and ethnicity; or lifestyle risk factors such as outdoor activity or diet quality, did not have significant impact on the study participants?

These demographic features have certainly been noted as risk factors in adults but less so in children. Data from previous studies would suggest that, in youth, there's probably somewhat of a buffer in the system that provides the eye with the capacity to manage the impact of various risk factors, up to a point. As we age, gradual reductions in the tear film quantity and quality along with the impact of a cumulative lifetime exposure to challenging environments, can make the tear film more susceptible to destabilisation, and the ocular surface more vulnerable to damage.
The combination of factors can then, more readily, serve to trigger that self-perpetuating cycle of tear film instability and hyperosmolarity, and ocular surface inflammation and damage, described as the vicious circle of dry eye disease.

5 The study result showed greater digital screen exposure was associated with higher odds of DED, while increased sleep was a protective factor. Would you recommend children who suffer with DED to have these lifestyle modifications from now on especially during the current COVID-19 pandemic?

The literature, not only from our group, but from many researchers around the world, is certainly indicating that high levels of screen exposure are detrimental to ocular surface health. The risk of developing dry eye symptoms and dry eye disease increases with the greater number of hours spent on digital screens, which suggests that reducing screen time should be beneficial, although more research is needed in this area. Taking breaks from the screen helps to minimise digital eye strain, and an effort should be made to blink often and fully during screen use, to encourage optimal meibum flow and distribution, and to help protect the eye's surface. Reduced sleep is indeed a recognised risk factor for dry eye disease, with those sleeping less than 6 hours each night experiencing, on average, higher levels of dry eye symptoms than those who sleep for more than 6 hours. This would suggest that a good night's sleep can, along with many other benefits, help protect against the development of ocular surface dryness. Maintaining homeostasis of the tear film is vital to avoid the development of dry eye symptoms so it could be argued that a proactive approach to improving digital screen and sleep habits should be considered, for everyone, not just those suffering from DED.

# Artificial Intelligence in Cornea and Refractive Surgery: Are YOU ready?

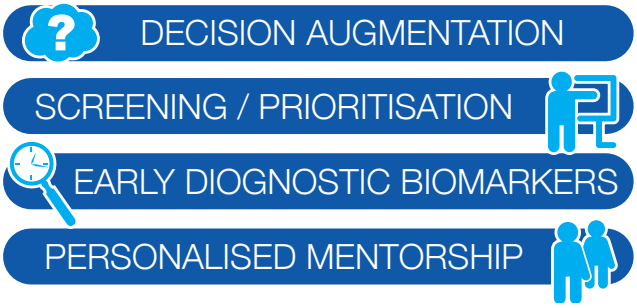
By **Miss Radhika Rampat,** MBBS BSc (hons) FRCOphth, Ophthalmic surgeon, Queen Victoria Hospital, East Grinstead.

### Artificial Intelligence (AI) is NOW…

It can be seen in the multitude of industries that have already been transformed by it. Whether you shout out 'Alexa' , 'Siri' or whether you drive in your Tesla - it is all around us. Advances in Imaging techniques combined with an acceleration during the pandemic has seen a recent boom in interest in Anterior segment disease specifically.

### I don't believe AI will replace us…

But it will become part of the tools we use to **diagnose and manage** our patients and more. For example, based on imaging alone the MS39 Anterior Segment OCT scan (CSO, Italy) can already tell us who has keratoconus (KC) based on an AI algorithm, but soon it could tell us who will go on to need crosslinking (CXL), or who may need re-bubbling after endothelial keratoplasty surgery. [1] We already have the start of **personalised mentorship** involving AI with ORBIS the flying eye hospital having online free access to a platform where you can upload medical retina or glaucoma cases.

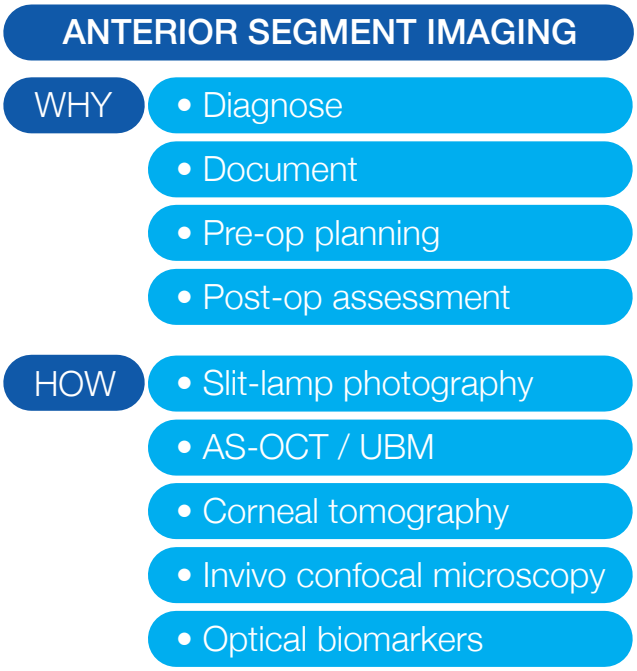



### So why exactly do we need AI ?

We have an increasing number of patients who are living longer, and we know resource poor countries don't have enough eye care givers for a given population, but the problem of long wait times is an issue here too. We are also more concerned with outcomes and patient satisfaction now than ever before. Despite all of this, we can deliver higher quality care if we just keep up with advancing technologies available at our fingertips, but this will have its own challenges.

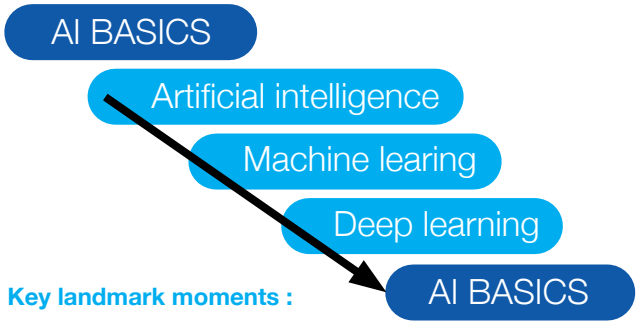
### Why did it take so long?

We already had AI but imaging had previously let us down - Imaging modalities have now improved at an astounding speed. AI researchers and clinicians are now moving their focus towards less explored ophthalmic areas - the anterior segment of the eye. We use imaging to diagnose, document, as well as for pre-op planning and post-op assessment. When you take Electronic Medical Record systems (EMR) and combine them with high quality imaging as well as faster computers - it is inevitable that we will benefit from a wealth of well-organised, anonymised medical datasets - but what do we do with them?




### Basic Principles

I want to demystify some of the basic principles and terminologies related to AI, particularly machine learning (ML) and deep learning (DL). Otherwise how can we help with clinical implementation of these AI technologies?




### Key landmark moments :

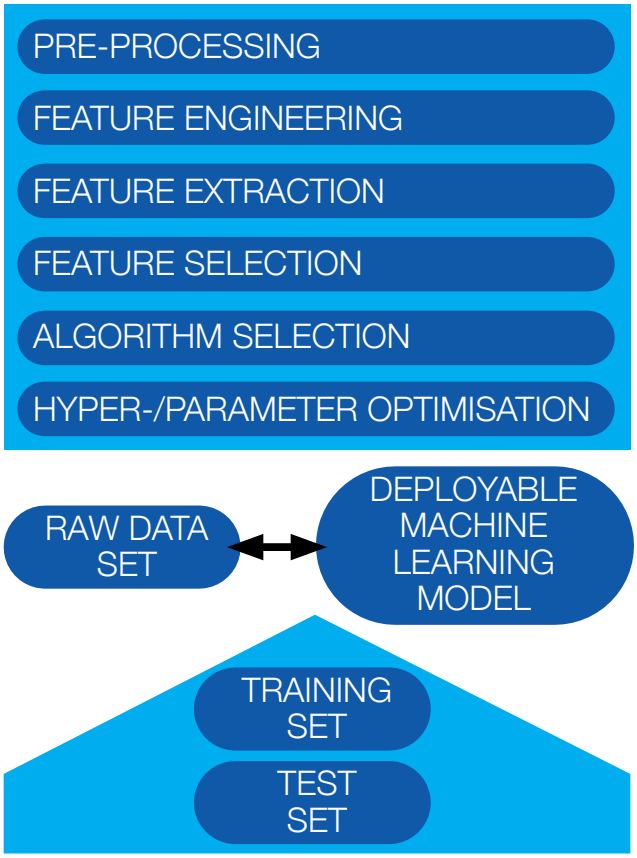
- Collaboration of Google Deepmind X Moorfields Eye Hospital (Mr Pearce Keane)
- Collaboration of Microsoft X Bascom Palmer Eye Institute (Dr Ranyah Habash)
- FDA approve AI diagnosis models (DR/ ROP)
- FDA see AI/ML-based Software as a Medical Device (SaMD)

Artificial intelligence - in the true sense of being human-like, has not yet been fully realised. When we say AI in medicine - we are really talking about Machine Learning. Instead of manually explicitly programming to say this is a photo of a bird or a dog because of a set of rules, the algorithm will start to look at features of the bird and dog and start to differentiate the two, giving more weight to certain features.

**Machine learning** focuses on creating algorithms which adapt to the presentation of new data so the learning is driven by the data. **Deep learning** basically refers to a subset of ML where there are several layers to the programming much like a human brain with multiple connected neurons. **AutoML** (Automated Machine Learning) is the next frontier - it refers to a situation where an ML/AI algorithm is 'ready to use' – not as a finished product but as a tool that can be used to build finished products without having to have expert knowledge.

Now that you know different subsets of AI - it is key that we learn the most common terms now that you are likely to start to read AI based articles.

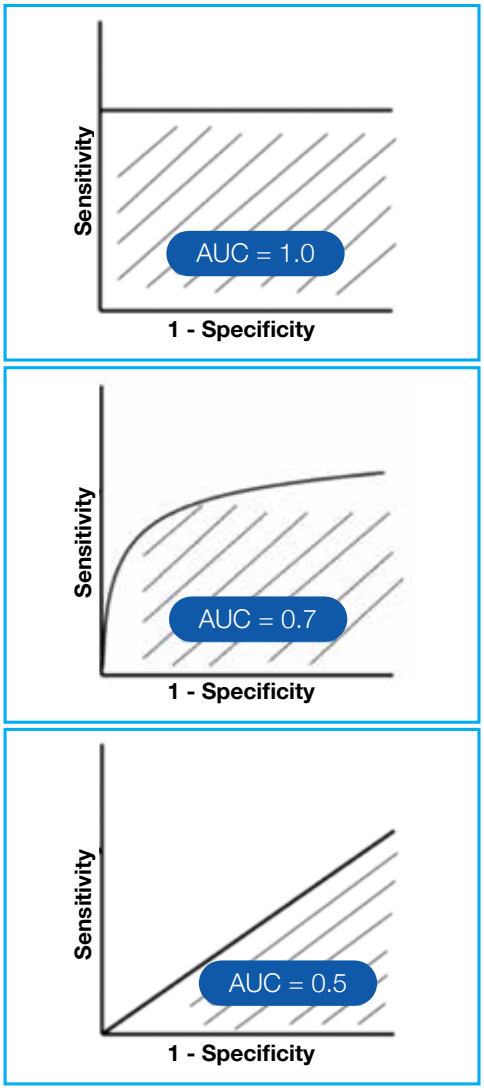
**GROUND TRUTH: Data labelled by clinicians.**
**TRAINING SET: Usually 75% of the eyes are kept aside to train the algorithm.**
**TEST SET: Usually 25% of the eyes are kept aside to train the algorithm.**
**VALIDATION: Data sent from external source to see if algorithm applicable to 'real-world' data.**



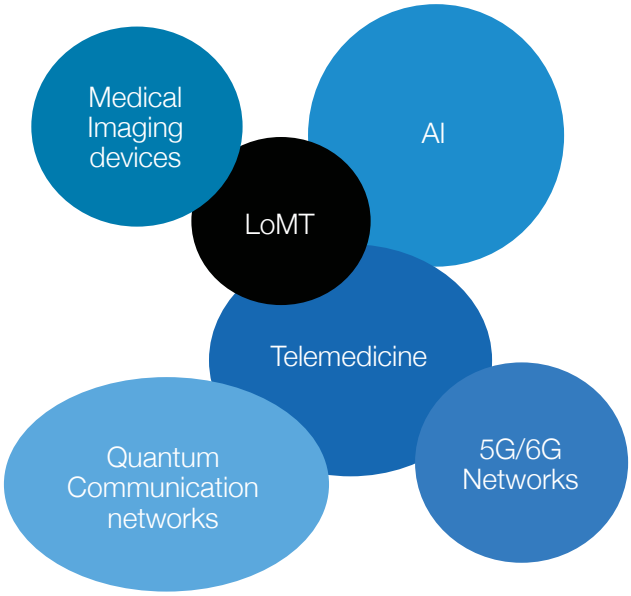

Experts such as data scientists are needed to clean the data, look at the variables or features they want to use, create the algorithm and then optimise the parameters so that they can maximise the predictive performance of their model – this is very time and resource intensive. For example, I was lucky to support part of the project testing the PEARL-DGS formula developed by Dr(s) Guillaume Debellemanière, Damien Gatinel and Alain Saad. It has taken approximately 3 years and over 3000 hours of development and testing. It is the newest and recently repeatedly proven to be the way to accurately calculate an IOL power – the first to be an open-source code ! [2,3] It's also free and accessible to all clinicians though it is to be used as a tool to support our current formulae as well as our clinical judgement and not replace it. (https://iolsolver.com/).

## What's the ROC?

When you come to reading an AI paper - a way they report results is using ROC curves to determine the performance of a given model at all thresholds. The AUC can be 0.5 which is no better than a random guess, 0.5-1 in the real word range and then 1 which is deemed 'perfect', but in reality could be a reflection of overfitting to the training data.




AI, telemedicine, 5G/6G networks, Quantum Communication Networks and IoMT are likely to all form part of the new healthcare revolution.



## Cornea

AI has been successfully used in the prediction of diagnosis of various corneal disorders, including Infectious keratitis, keratoconus, pterygium, endothelial diseases, and corneal graft-related complications, amongst others. In the most recent update from our Asia-Pacific Journal of Ophthalmology (APJO) article, you can see how artificial intelligence has been explored for anterior segment disease such as – diagnosis of Infectious Keratitis, Keratoconus, Fuchs Endothelial Dystrophy, IOL calculations, Cataract grading and more. [4]

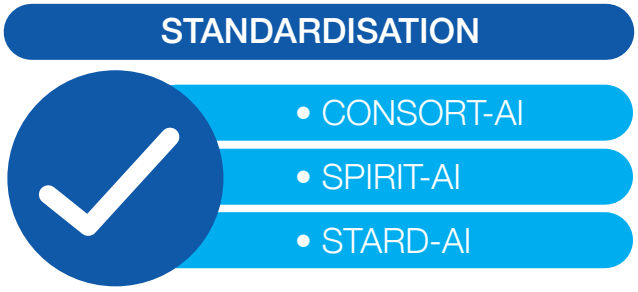
## Refractive

More than 20 million cataract surgeries were being performed pre-pandemic - and we are falling behind. AI-assisted telemedicine platforms have been proposed to screen, diagnose and grade cataracts, potentially serving as a model of care for global eye health. 5,6 The global burden of uncorrected refractive error estimated to be over 150 million, our ability to bypass subjective refraction and prescribe from an automated system has become an important goal - especially in resource poor areas. Previously, DL had been utilised in predicting refractive errors from fundus images but now beta-software installed on a wavefront aberrometer utilising the new LD/HD polynomials method allowed accurate AI-powered prediction of results achieved by subjective refraction.[7]

## Standardisation

Now that the global burden of anterior segment disease is apparent, we know there is an unmet need, especially in resource poor countries as well as within the NHS which is at breaking point. But Before AI is implemented in the real-world clinical setting - we must be aware that standardisation is key.

Standardisation of imaging techniques is much more difficult in the anterior segment - variability in magnification, contrast, angle/width of light beam, the transparent nature of cornea. We need a method that will achieve high image quality and usability. [8]




Standards also include those for reporting of diagnostic accuracy studies, protocol items recommended for interventional trials related to AI as well as guidance on the consolidated standard of reporting trials related to AI. AI guidelines aim to improve the transparency, consistency and applicability of AI-based research.[4]

There is of course trepidation over missed or incorrect diagnosis, falsely reassuring a patient and the medicolegal implication of it all. Cautious implementation with a safety net system will be warranted to ensure utmost patient safety.

## Are YOU ready for AI in your practice?

AI focuses on making connections between input and preferred output. Therefore, it is important to ensure we avoid the problem of 'rubbish in, rubbish out'.

An ideal input = high image resolution + high accuracy of data input (ground truth) + least interobserver variability + new technology (hand-held retinal cameras / slit-lamp adapters/ smartphones / cloud computing) to improve workflow.

**AutoML** will mean cost reduction and democratising ML, but there will likely be a model performance lag as it won't be as good as supervised or semi-supervised model development before it is optimised. Also there will be more of the 'black box' feel to it with even more reduced explainability.

I do not believe that we will be replaced as clinicians, but in fact use rigorously tested systems to support us so we in turn can spend that extra chair time with our patients - counselling them and listening to them. We can come up with a personalised management plan that will be best applicable to them and their condition(s).

I've been privileged to be involved in and have this international overview of what's happening right now in the world of AI for Anterior Segment Surgery - and it's very exciting.

References:

1. Zéboulon, P., Ghazal, W. & Gatinel, D. Corneal Edema Visualization With Optical Coherence Tomography Using Deep Learning: Proof of Concept. *Cornea* **40**, 1267–1275 (2021).
2. Gatinel, D., Debellemanière, G., Saad, A., Dubois, M. & Rampat, R. Determining the Theoretical Effective Lens Position of Thick Intraocular Lenses for Machine Learning-Based IOL Power Calculation and Simulation. *Transl. Vis. Sci. Technol*. **10**, 27 (2021).
3. Debellemanière, G. *et al*. The PEARL-DGS Formula: The Development of an Open-source Machine Learning-based Thick IOL Calculation Formula. *Am. J. Ophthalmol.* **232**, 58–69 (2021).
4. Rampat, R. *et al*. Artificial Intelligence in Cornea, Refractive Surgery, and Cataract: Basic Principles, Clinical Applications, and Future Directions. *Asia Pac J Ophthalmol (Phila)* **10**, 268–281 (2021).
5. Gao, X., Hao, L., Wang, J., Ma, G. & Zhang, T. Effect of Phacoemulsification Combined with Intraocular Lens Implantation on Inflammatory Factors, Oxidative Stress Response and Hemorheology in Diabetic Cataract Patients. *J. Coll. Physicians Surg. Pak*. **28**, 762–765 (2018).
6. Li, H. *et al*. An automatic diagnosis system of nuclear cataract using slit-lamp images. *2009 Annual International Conference of the IEEE Engineering in Medicine and Biology Society* (2009) doi:10.1109/iembs.2009.5334735.
7. Rampat, R., Debellemanière, G., Malet, J. & Gatinel, D. Using Artificial Intelligence and Novel Polynomials to Predict Subjective Refraction. *Sci. Rep*. **10**, 8565 (2020).
8. Sounderajah, V. *et al*. Developing Specific Reporting Standards in Artificial Intelligence Centred Research. *Ann. Surg*. **275**, e547–e548 (2022).

# The 105th Oxford Ophthalmological Congress

## Returns to an in-person meeting in 2022

Monday 4th July to Wednesday 6th July 2022

**The Doyne Lecturer**
Mr. Demis Hassabis
CBE FRS FREng FRSA

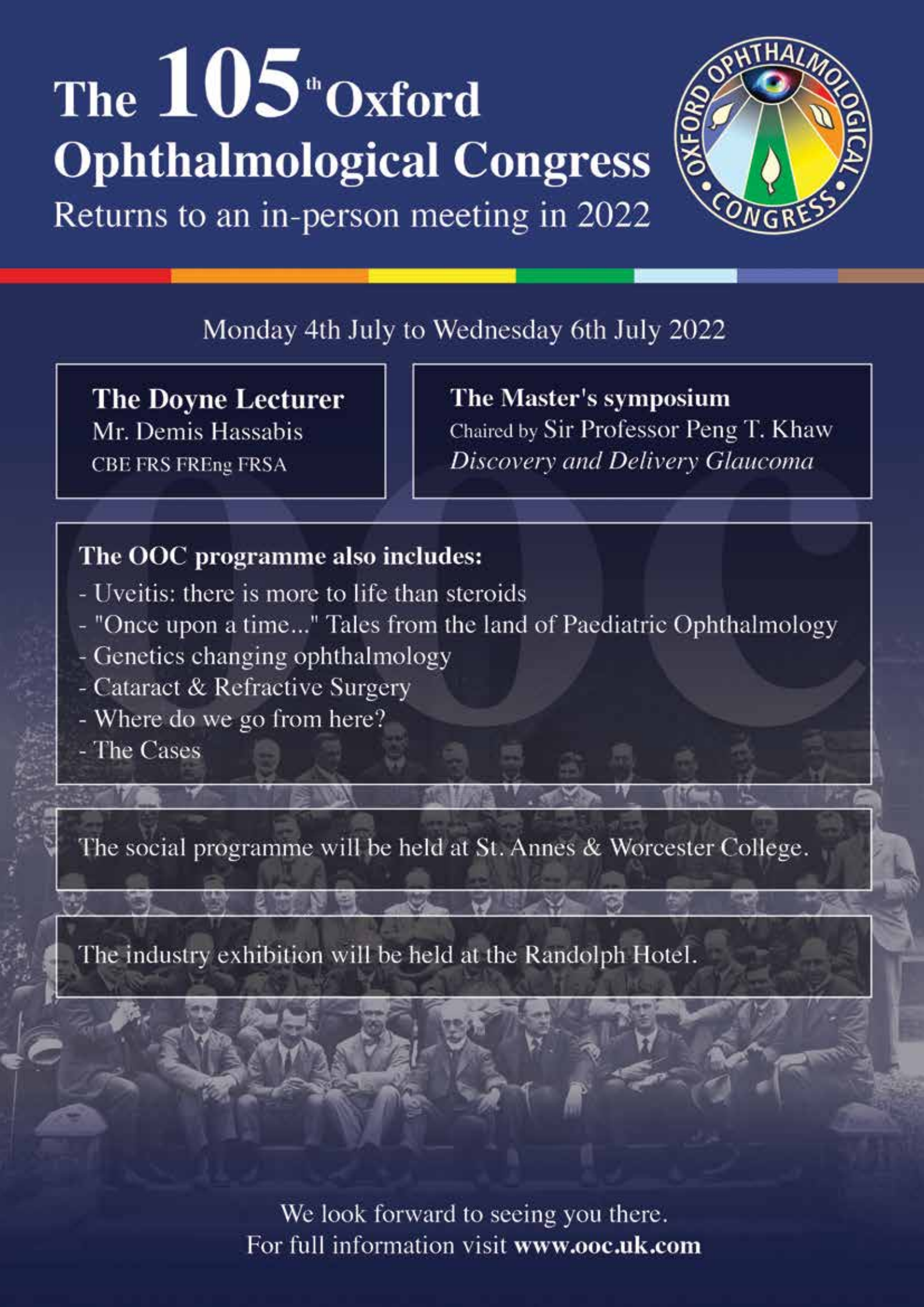
**The Master's symposium**
Chaired by Sir Professor Peng T. Khaw
*Discovery and Delivery Glaucoma*

**The OOC programme also includes:**

- Uveitis: there is more to life than steroids
- "Once upon a time..." Tales from the land of Paediatric Ophthalmology
- Genetics changing ophthalmology
- Cataract & Refractive Surgery
- Where do we go from here?
- The Cases

The social programme will be held at St. Annes & Worcester College.

The industry exhibition will be held at the Randolph Hotel.



We look forward to seeing you there.
For full information visit **www.ooc.uk.com**

## The Théa Dry Eye range:

# A MAJOR BREAKTHROUGH IN THE TREATMENT AND PREVENTION OF DRY EYE DISEASE

**Softacort® and Thealoz® Duo are two preservative-free preparations that work on different stages of the vicious cycle of Dry Eye disease**

## Softacort®
0.335% Hydrocortisone Sodium Phosphate

**Treats Dry Eye patients with mild, non-infectious conjunctival inflammation[1]**

**Reduces conjunctival redness, increases Tear Film Thickness, and improves symptoms of Dry Eye Disease with no significant effect on IOP[2]**

TREAT

DRY EYE


## THEALOZ® DUO
3% Trehalose, 0.15% Sodium Hyaluronate

**Effective prevention for moderate-severe Dry Eye patients[3]**

**Unique combination delivering significant OSDI improvements in moderate-severe Dry Eye patients[3]**

PREVENT

## USED TOGETHER, SOFTACORT® AND THEALOZ® DUO IMPROVE OUTCOMES IN DRY EYE DISEASE[2,3]

**Softacort® 3.35mg/ml eye drops, solution in single-dose container. Abbreviated Prescribing. Contains:** Hydrocortisone sodium phosphate. **Information:** Please refer to Summary of Product Characteristics before prescribing. **Presentation:** 3 sachets each containing 10 single-dose units of 0.4ml. A single-dose container contains enough to treat both eyes. **Indications(s):** Treatment of mild non-infectious allergic or inflammatory conjunctival disease. **Posology and method of administration:** Adults & the Elderly: 2 drops 2–4 times per day in the affected eye. Treatment will generally vary from a few days up to a maximum of 14 days. Consider gradual tapering off down to one drop every other day to avoid relapse. Children: safety and efficacy is not established. **Contraindications:** Hypersensitivity to active substance or excipients. Ocular hypertension including that caused by known glucocorticosteroids. Herpes simplex and other corneal viral infections at acute stage of ulceration, unless combined with specific therapeutic agents. Conjunctivitis with ulcerative keratitis even at the initial stage. Ocular tuberculosis, ocular mycosis, acute ocular purulent infection, purulent conjunctivitis, and purulent blepharitis, stye and herpes infection that may be masked or aggravated by anti-inflammatory drugs. **Warnings and precautions:** *Red eye:* Do not prescribe for undiagnosed red eye. *Ocular hypertension & cataracts:* Monitor patients at regular intervals during treatment – prolonged use of corticosteroids has been shown to cause ocular hypertensions especially for patients with previous IOP increase induced by steroids, and also cataract formation especially in children and the elderly. In children the ocular hypertensive response can happen more often, frequently and severely than in adults. *Immuno suppression:* Use of corticosteroids can result in opportunistic ocular infections due to delay or suppression or healing delay; and to the masking of symptoms. *Viral keratitis:* Not recommended but may be used if required only with a combined antiviral treatment and under close supervision. *Perforations and thinning of cornea/sclera:* Thinning of cornea and sclera (caused by diseases) may increase risk of perforations with use of topical steroids. Suspect a fungal infection with corneal ulcerations where a steroid has been used for a long time. Remove contact lenses when using Softacort. With blurred vision or other visual disturbances, consider referring patients for evaluating possible causes which may include cataract, glaucoma or rare diseases like central serous chorioretinopathy (CSR). Softacort contains phosphates. *Children:* Long-term continuous corticosteroid therapy may produce adrenal suppression. **Pregnancy:** Not recommended unless clearly necessary. **Lactation:** Risk to newborns/infants cannot be excluded. It is unknown if Softacort is excreted in human milk. **Driving & using machines:** Temporary blurred vision or other visual disturbances may affect ability to drive or use machines. Wait until vision clears before driving or operating machinery. **Undesirable effects:** Mild and transient burning and stinging immediately after instillation. Unseen with hydrocortisone, but have been observed with other topical corticosteroids: allergic and hypersensitivity reactions, delayed wound healing, posterior capsular cataract, opportunistic infections, herpes simplex infection, fungal infection, glaucoma, mydriasis, ptosis, corticosteroid induced uveitis, changes in corneal thickness, crystalline keratopathy, blurred vision. Very rarely, corneal calcification in patients with significantly damaged corneas. Prolonged use of corticosteroids has shown to cause ocular hypertension, especially with pre-existing or family history of increased IOP, and cataract formation. Children / elderly are more susceptible to IOP rise. Diabetics are more prone to sub capsular cataracts following topical steroids. In diseases causing thinning of the cornea, topical steroids could lead to perforation. **Overdose:** Rinse with sterile water. Discontinue treatment where prolonged overdosage causes ocular hypertension. Symptoms from accidental ingestion are unknown, however, consider gastric lavage or emesis. **Storage:** Do not store above 25°C. Keep the single-dose containers in the sachet, in order to protect from light. Discard any unused contents immediately after administration. **Legal category:** Prescription Only Medicine (POM). **Basic NHS Price:** £10.99 for a pack of 30 single-dose containers. **PL No:** 20162/0024. **Sale and Supply:** Thea Pharmaceuticals Ltd, ICS Innovation Way, Keele University Science & Innovation Park, Keele, Newcastle Under Lyme, ST5 5NT **Date of preparation:** 05/10/2018.

REPORT ADVERSE EVENTS TO THÉA PHARMACEUTICALS LIMITED AND WWW.MHRA.GOV.UK/YELLOWCARD OR SEARCH FOR MHRA YELLOW CARD IN THE GOOGLE PLAY OR APPLE APP STORE.


**References:** 1. Softacort Summary of Product Characteristics. 2. Kallab M *et al*, Adv Ther. 2020;37:329–341.
3. Chiambaretta F *et al.* Eur J Ophthalmol 2017; 27(1):1–9.



**Théa Pharmaceuticals Limited,** ICS Innovation Way, Keele University Science and Business Park, Keele, Newcastle under Lyme, ST5 5NT
**Head Office / Medical Information:** 0345 521 1290 **Email:** theasupport@theapharma.com www.thea-pharmaceuticals.co.uk MTDU022 JUL2021


Théa
let's open our eyes