

the Ophthalmologist™

In My View

The importance of passing good practices to new generations

10

In Practice

Four common misconceptions about later-stage cross-linking

26 – 28

NextGen

Novel gene vectors for retinal dystrophy patients

32 – 34

Sitting Down With

WIO alumni, Erin Shriver

50 – 51

Dry Eye Debate: The Progressive Practice

Four dry eye experts discuss their approaches to diagnosing and treating ocular surface disease

12 – 19



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References: 1. Craig JP, Nelson JD, Azar DT, et al. *Ocul Surf.* 2017;15(4):802-812. 2. Efron N, Jones L, Bron AJ, et al. *Invest Ophthalmol Vis Sci.* 2013;54(11):TFOS98-TFOS122. 3. *Ocul Surf.* 2007;5(2):75-92.

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To Pour From an Empty Cup

When it comes to mental health, physician wellbeing comes last on the list

Editorial



Mental Health Awareness Week in 2021 (May 10–16) feels more relevant than most. Over the last 12 months, ophthalmologists have faced untold personal and professional crises, as elective surgery were halted and resources were redistributed to frontline workers. When things returned to some kind of normality (a loose term, at best), some practices struggled to accommodate rapidly changing regulations – and rapidly growing wait lists – while others were forced to shut their doors for good.

But the places worst affected are often the hardest to see. In 2020, the British Medical Association investigated the personal impact COVID-19 on doctors' wellbeing. Seven thousand participants described how long working hours in unfamiliar settings, intensified conditions, worries about PPE, and fear of contracting the virus – and passing it on to their loved ones – had negatively affected their mental health. 43 percent said they had experienced work-related depression, anxiety, stress, burnout, emotional distress, or other mental health conditions since the pandemic started (1).

Though ophthalmology has been less directly impacted than some other specialties, the mark left upon it is no less serious (lest we forget, it was ophthalmologist Li Wenliang, who raised awareness of early COVID-19 infections in Wuhan).

For the sake of full transparency, this issue was supposed to look quite different; until a week ago, our feature was scheduled to explore the Orbis project addressing ROP in India. But, understandably, our contacts were occupied by the country's escalating second wave – a stark reminder that the pandemic has left no physician and no person untouched.

In honor of Mental Health Awareness Week (but whenever you read this), I ask you to be kind to yourselves. Speak to someone if you need to. Know that what you do and who you are matters. You can find a list of mental health resources on our Twitter page (<https://bit.ly/3uZfBmG>), as well as links to organizations campaigning to reduce the stigma around physician mental health. Studies have found that 35 percent of doctors do not seek regular health care for themselves (2). And that statistic has to change. Remember that these are (still) challenging times, and you deserve the same care you provide to your patients. Resting and recharging – however that may look to you – is an essential part of protecting your mental wellbeing.

Our thoughts go to our readers and their loved ones in India. I can only hope it passes soon.

References

1. BMA (2020). Available at: <https://bit.ly/3y1y11q>.
2. C Gross et al, *Arch Intern Med*, 160, 27 (2000). PMID: 11088080.

Phoebe Harkin
Deputy Editor



40



50

In My View

10 **Continuing Education**
Passing knowledge and good practices to new generations is vital – it gives teachers a real sense of achievement and, crucially, improves patient care, says Carol Shields

03 **Editorial**
To Pour From an Empty Cup
by Phoebe Harkin

Upfront
06 The latest news, views and research – from the link between dry eye and mental health to the recent findings challenging conventional wisdom around glaucoma treatment

Feature
12 **Dry Eye Debate: The Progressive Practice**
Four ocular surface experts explore the impact of COVID-19 on dry eye disease, their diagnosis and treatment protocols, and more

On The Cover



The latest dry eye roundtable panelists explain how to incorporate OSD management into a progressive practice



29

In Practice

- 20 **A Burning Issue**
Quick access to amniotic membrane transplantation increases chances of a successful outcome in blistering skin disorder patients, according to Charles Bouchard
- 26 **Busting Keratoconus Myths**
Kenneth A. Beckman shatters four common misconceptions about later-stage cross-linking for progressive keratoconus
- 29 **Let There Be (Laser) Light**
Promoting an evidence-based approach, the European Glaucoma Society Guidelines Committee has changed recommendations for the initial open angle glaucoma treatment

NextGen

- 32 **Unnatural Selection**
Stylianios Michalakis explains why novel gene vectors delivered by intravitreal rather than subretinal injection represent a lower-risk option for retinal dystrophy patients

Profession

- 36 **Inside the VISION 2020 LINKS Program**
Building long-term and long-distance ophthalmic partnerships to share knowledge, enhance education, and improve patient care worldwide
- 40 **Side by Side**
How twin sisters are breaking barriers to save sight in rural India
- 42 **The Negotiation Game**
The secret to a successful contract negotiation – according to doctor, lawyer, and founder of MDNegotiation Lisa Nijm
- 46 **Just for the Record**
Jason Handza offers five reasons why you should care about your electronic health records system

Sitting Down With...

- 50 **Erin Shriver, Clinical Professor, Oculoplastic, Orbital and Oncology Service, University of Iowa Hospitals and Clinics, Iowa City, USA**

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Easy Does It?

Not all patients with elevated eye pressure need treatment to prevent vision loss, according to landmark study

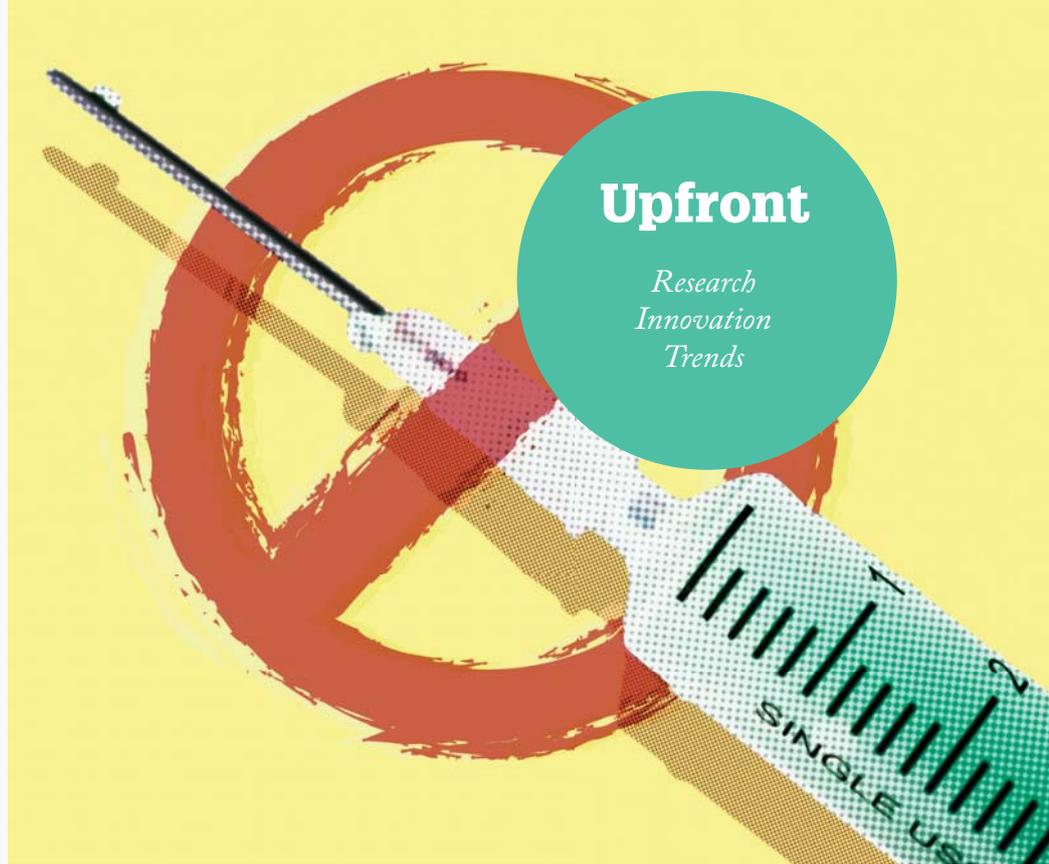
When it comes to ocular hypertension, conventional wisdom points to the need to act fast to protect vision. But recent findings suggest otherwise. The Ocular Hypertension Treatment Study (funded by the National Eye Institute and led by researchers at Washington University School of Medicine) recruited 1,600 patients who were at moderate to high risk for glaucoma because of elevated eye pressure. Half received daily treatment with eye drops, while the other half were observed without treatment. After seven years, when the treatment had been shown to be highly effective, patients in both groups were given drops. The team showed that preventive treatment reduced the incidence of glaucoma by 50 to 60 percent after five to seven years, but even with that substantial decrease, the total number of people who developed glaucoma remained relatively low, with only 25 percent going on to develop vision loss from glaucoma in at least one eye – much fewer than initially expected. The study suggests physicians can delay pressure-lowering treatment until early

damage is detected, without adversely affecting long-term outcomes. The next step? Determining which patients would benefit from preventative treatment. Michael A. Kass, the Bernard Becker Professor of Ophthalmology and Visual Sciences and lead author of the study, helped establish the five key risk factors: a patient's age, level of intraocular pressure, thickness of the cornea, a measurement of the appearance of the optic nerve head, and another measurement derived from standard visual field tests. "The five factors were determined using a multivariable risk model where they were entered one at a

time to see if they improved the predictive power, with all factors weighted to one standard deviation" explains Kass. While Kass does not consider a delay in pressure-lowering treatment risky, a high-risk person or a person who is concerned can start treatment before damage is detected. "This should cause the clinician and the patient to discuss the situation taking into consideration patient age, health status, life expectancy and personal preference."

Reference

1. WUSTL (2021). Available at: <https://bit.ly/3obGHEH>.



TIMELINE

Koji Nakanishi

The magical life of Japan's pioneering AMD researcher



Born in Hong Kong on May 11, 1925, Nakanishi gained his PhD in Chemistry from Nagoya University in Japan, before joining Columbia University in 1969



His group determined the structure of over 200 biologically active natural products, including ginkgolides (from the ancient ginkgo tree), insect hormones, antibiotics, and the human eye pigment involved in macular degeneration



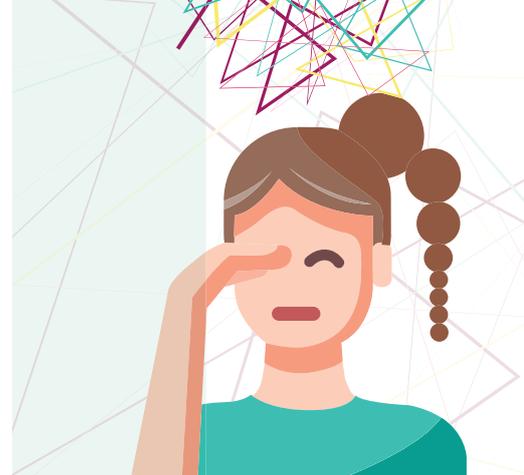
BUSINESS IN BRIEF

Find out what's been happening in the industry

- Claire M. Gelfman has been appointed as the new Chief Scientific Officer of Foundation Fighting Blindness. She will be overlooking the organization's scientific strategy with a focus on research initiatives accelerating new therapies for inherited retinal diseases, as well as early translational and pre-clinical research programs.
- Quantel Medical has launched a new website to share information on dry eye disease (DED). Mydryeyedisease.com aims to give patients a better understanding of the disease, symptoms and causes, and to help them choose the best treatment options. With monthly updates and seasonal topics, the website aims to be a practical tool for ophthalmologists to share with their DED patients.
- Santen has announced a global cooperation with Massachusetts Eye and Ear in Boston, USA, and Ulster University in Northern Ireland, UK, with the aim of researching, identifying, and developing new glaucoma treatments. Research will focus

on preventing and reversing optic nerve damage by exploring innovative therapeutic options for the visual nervous system.

- Oertli has introduced the latest generation of its OS 4 surgical platform for cataract, glaucoma, and retinal surgery. The new platform, with fully-automated user protection filter and a three-pump fluidics system, boasts more speed, precision, and safety. Visualization is improved with the use of two Power LED light sources, which provide 45 percent more light output.
- OPHTEC has introduced its new lens: the Precizon Toric and Precizon Presbyopic IOL. The IOL features a Transitional Conic Toric optic, designed for misalignment tolerance, and a Continuous Transitional Focus, providing a smooth near-to-far transition and a constant defocus between two sharp focal points, as well as a low rate of photic phenomena.



Coming Up Dry

Dry eye disease affects not only quality of life and productivity, but also mental health

A survey of adult patients with and without dry eye disease (DED) conducted by University of Southampton, UK, aimed to determine these groups' sociodemographics and relative quality of life (1). Unsurprisingly, results showed that DED negatively impacts patients' visual function and productivity, both at work and in other day-to-day activities. What's more, the survey found that those affected are more likely to suffer from anxiety and depression and miss more work. Comorbidities were also much more common in the DED group, with twice as many patients suffering from arthritis, hearing loss, and IBS. Based on the study, women and older people were more likely to suffer from DED.

Reference

1. P Hossain et al., *BMJ Open*, 11, e039209 (2021). PMID: 33664064.

Synthesizing more than 100 analogs of retinoids – including A2E, the fluorophore found in the outer segment membrane of photoreceptors – Nakanishi's research offered invaluable insight into the inner workings of animal vision and phototaxis



He received countless awards throughout his career, including the coveted Order of Culture medal from the Emperor of Japan

Passing peacefully on March 28, 2019, Nakanishi is remembered as an extraordinary chemist and a passionate amateur magician, who frequently entertained his audiences with live magic shows



Lessons from the Octopus Teacher

What does a color-blind octopus have in common with treating age-related macular degeneration?

A research project led by Shelby Temple, Honorary Professor at the School of Biological Sciences, Aston University and Bristol University, UK, measured the way octopus can detect polarized light, not visible to humans. Octopus are color-blind, but the study was able to show that they have developed the most sophisticated and sensitive polarization vision system of any animal that has so far been tested.

Temple explained: “We knew that octopus, like many marine species, could see patterns in polarized light much like we see color, but we had no idea that they could do so when the light was only 2 percent polarized – that was an exciting surprise, but even more surprising was when we then tested humans and found that they were able to see polarization patterns when the light was only 24 percent polarized.”

This discovery led to the development of a new medical device, which identifies



Octopus eye. Credit: Shelby Temple.

people at greater risk of developing age-related macular degeneration. The novel technology screens people for low macular pigments – carotenoids lutein, zeaxanthin and meso-zeaxanthin – which act as a natural defense against damaging violet-blue light. These pigments can only be acquired from diet – from foods such as cantaloupe, pasta, corn, carrots, orange and yellow peppers, fish, and eggs – and they offer long-term protection of the retina. Macular pigments prevent AMD by acting as antioxidants and by actively absorbing high-energy visible violet-blue wavelengths before they reach the retina. According to Temple: “Humans can perceive polarized because macular pigments in our eyes differentially

absorb violet-blue light depending on its angle of polarization, an effect known as Haidinger’s brushes. It’s like a super sense most of us don’t even know we have, revealing a faint yellow bow-tie shape on the retina. The more of these pigments a person has, the better protected they are against sight-loss.”

The new testing method enables eye care professionals to suggest appropriate lifestyle choices to people at more risk of developing AMD, like wearing sunglasses and eating more pigment-rich foods to help prevent their eyesight.

Reference

1. SE Temple, *J Exp Biol*, 224 (2021). PMID: 33602676.

Rough and Ready

Researchers identify a genetic mutation associated with the most common cause of glaucoma

After sequencing the protein-coding genes of more than 20,000 participants from 14 countries across Asia, Europe, and Africa, researchers believe they have

discovered a functionally defective gene associated with the most common cause of glaucoma: exfoliation syndrome. Patients with the systemic disorder, characterized by a progressive accumulation of abnormal protein material, were twice as likely to carry damaging mutations in the gene encoding for CYP39A1 – an enzyme that plays an important role in cholesterol processing. The findings suggest that defective CYP39A1 function is strongly associated with increased risk of exfoliation syndrome.

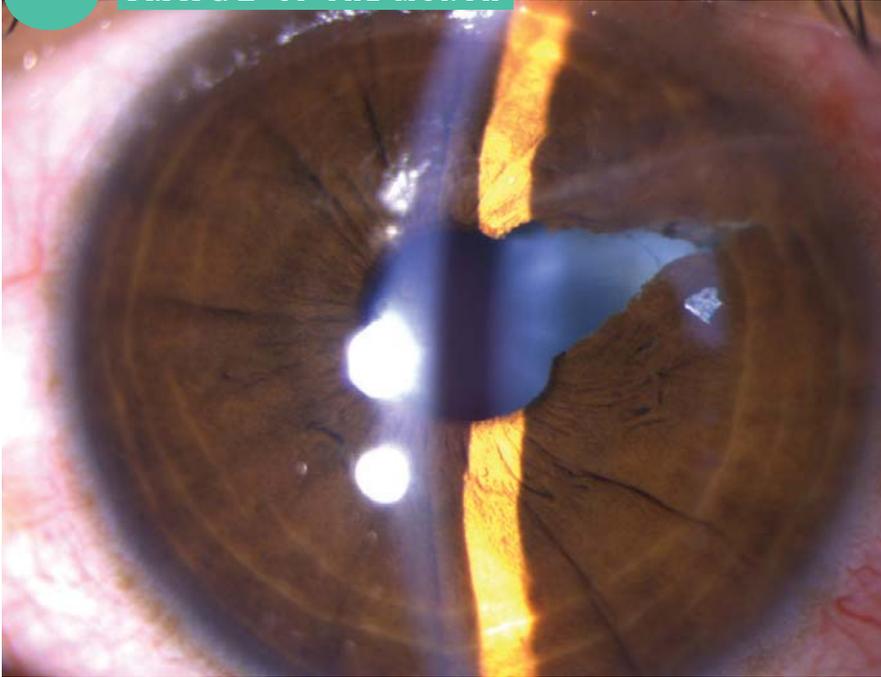
Why? Researchers hypothesize that, because cholesterol is found abundantly in all cells, any disruption to its processing could adversely impact normal functions. In this study (1), epithelial cells responsible for the aqueous humor were most affected by the mutation, with disruption ultimately leading to leakage of exfoliative material.

Reference

1. A*Star (2021). Available at: <https://bit.ly/3bgaW81>.



IMAGE OF THE MONTH

*Tiny Foreign Body*

This month's image shows a large self-sealed corneal wound, iris laceration, and traumatic cataract that cannot be explained by the tiny metallic foreign body lying over the iris. Indeed, another large foreign body was found embedded in peripheral retina.

Credit: Rami Abu Sbeit, a resident of ophthalmology, Hamad Medical Corporation, Qatar.

Would you like your photo featured in Image of the Month?
Send it to edit@theophthalmologist.com

QUOTE OF THE MONTH

"It's like we might do with any domestic cat - but with a lot more anaesthetic."

Surgeon David Williams on performing the world's first hood graft operation on 17 year-old, 93kg Sumatran tiger, Ratna, at Shepreth Wildlife Park, UK.

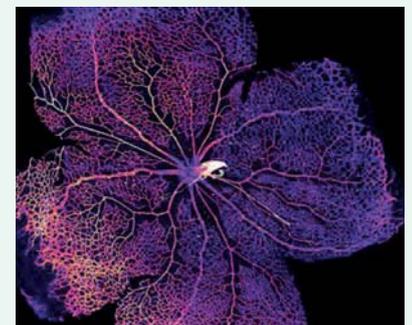
Telling the MacTel Tale

Newly discovered DNA mutations can help identify people with a genetic predisposition to early-onset MacTel

MacTel, a degenerative retinal disorder caused by slight changes to fundamental amino acid levels in a person's blood, is notoriously difficult to diagnose. Now, scientists at WEHI, University of Melbourne, Australia, have discovered that a rare DNA mutation in the *PHGDH* gene increases the risk of developing MacTel five-fold. In a study looking at 1,067 MacTel sufferers and 3,799 controls, researchers also identified seven other regions in the human genome responsible for increased risk of developing the disorder. With this knowledge, genetically predisposed individuals may now be identified early and offered them the best treatment options, potentially saving their vision. The team is now working on identifying other genes responsible for MacTel development.

Reference

1. R Bonelli et al., *Commun Biol*, 4, 274 (2021). PMID: 33654266.



Blood vessels in the retina. Credit: WEHI.

Continuing Education

Passing knowledge and good practices to new generations of ophthalmologists is vital – it gives teachers a real sense of achievement and, crucially, improves patient care

By Carol L. Shields, Director, Ocular Oncology Service, Wills Eye Hospital and Thomas Jefferson University, Philadelphia, Pennsylvania, USA

When I first came to Wills Eye Hospital in Philadelphia, it was a real eye-opener. My mentors and educators were outstanding; I listened to everyone who taught us and I attended all the lectures. Sometimes, trainees question what they're told to make sure they're using the right methods and tools, but that didn't happen to me. I trusted everyone at Wills Eye and knew I was getting the truth from the very start. It was the best learning experience I could have had.

These days, most technicians in my office will tell you that it is a challenge to work with me. I think fast and I work fast. Some say working with me is like a boot camp: we arrive early, we do a good job, we keep our patients happy, and we get great results. I will not stand for an image or an ultrasound done incorrectly. When I strive for the highest standards, it rubs off on everybody else – including my fellows.

I often think of the fellows who have worked alongside me. They have come from all over the world. Each one has been very different – and I think they have all been excellent. Some have become superstars, others have smaller solo practices, but they all seem happy with what they're doing. They survived the boot camp and they now thank me for “pushing them to be their best.” One of my favorite fellows, R. Joel Welch,



“I’m happy that my younger colleagues see me as building bridges for them. I keep every token of appreciation I get from the fellows with whom I’ve worked.”

gave me a laminated poem by Will Allen Dromgoole, “The Bridge Builder” and adjusted the protagonist from man to woman – and I treasure the sentiment behind it. I’m happy that my younger colleagues see me as building bridges for them. I keep every token of appreciation I get from the fellows with whom I’ve worked.

I am so proud of what we do for our patients. When they come to see me and my team, it is, perhaps, one of the most important days in their lives. We cannot give them any less than our absolute best – so that is what we do. I learned that from my mentors and I’m proud to pass it on to the next generations of ophthalmologists.

In My View

Experts from across the world share a single strongly held opinion or key idea.

The Bridge Builder

Will Allen Dromgoole

*An old woman going a lone highway,
Came, at the evening cold and gray,
To a chasm vast and deep and wide.
Through which was flowing a sullen tide
The old woman crossed in the twilight dim,
The sullen stream had no fear within;
But she turned when safe on the other side
And built a bridge to span the tide.*

*“Old woman,” said a fellow pilgrim near,
“You are wasting your strength with
building here;
Your journey will end with the ending day,
You never again will pass this way;
You’ve crossed the chasm, deep and wide,
Why build this bridge at evening tide?”*

*The builder lifted her old gray head;
“Good friend, in the path I have come,” she said,
“There followed after me to-day
A youth whose feet must pass this way.
This chasm that has been as naught to me
To that fair-haired youth may a pitfall be;
He, too, must cross in the twilight dim;
Good friend, I am building this bridge for him!”*

From: A Builder, 1900.



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References

¹US Patent NO: US8647383. ²Data on file, BVI, 2019.

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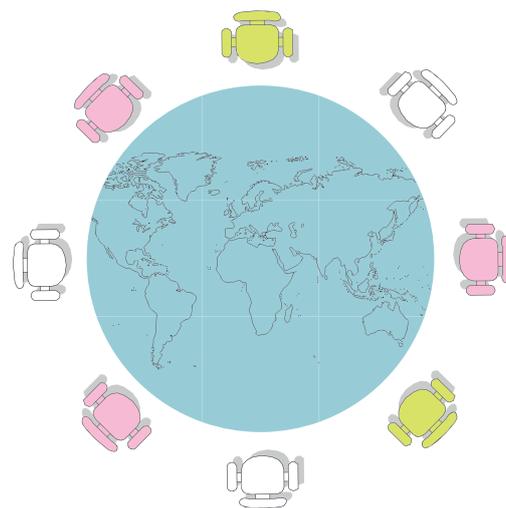
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DRY EYE DEBATE:

THE PROGRESSIVE PRACTICE

A timely roundtable, moderated by Elizabeth Yeu and featuring Laura Periman, Stefano Barabino, and William Trattler, explored ocular surface disease, including blepharitis, new products and technologies in the field, and the impact of COVID-19 on dry eye disease.





HOW IS DRY EYE MANAGEMENT INCORPORATED INTO YOUR PRACTICE?

Stefano Barabino: My Milan hospital practice gets patients referred from different parts of Italy, so I mostly see moderate to severe dry eye patients. We have a great collaboration with a laboratory of immunology, with which we detect expression of markers of the ocular surface inflammation, using cytometry. We conduct a lot of ocular surface inflammation research. In my private practice, I see patients with various ocular problems, and encounter patients with mild dry eye manifestation.

Laura Periman: Very recently, in June 2020 I opened the Periman Eye Institute, which has been purposefully designed to meet the needs of the dry eye patient – all we do is for these patients. We have a clinical research program, with a variety of trials that are Phase IIb, Phase III or Phase IV. Our patients are often referred from quite a distance, also internationally because we offer a very careful and mindful evaluation, with an integrated treatment plan for each patient.

William Trattler: At my practice, the Center for Excellence in Eye Care, we have 15 ophthalmologists, an optometrist, and we work across different ophthalmic subspecialties. My practice is specifically related to cataract surgery, refractive surgery, and cross-linking in keratoconus, and almost all patients I see for these procedures have dry eye disease (DED), so a major part of my practice is managing dry eye before and after surgery. I have been involved with DED management for quite a long time; some patients come to see me with just dry eye – with moderate to severe, very challenging manifestations of the disease, which are very frustrating for the patients. It is my job, and the job of the practice, to find appropriate solutions for them.

Elizabeth Yeu: I am also in a multi-subspecialty practice, with just over 20 clinicians, and with a strong OD base

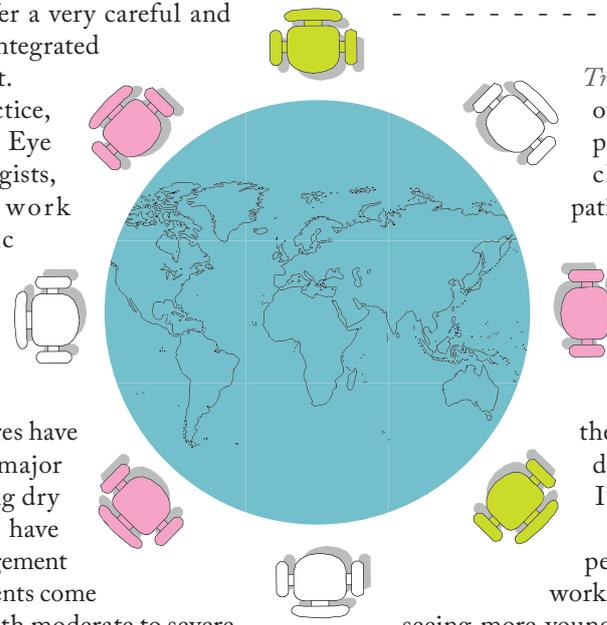
within our practice; they serve as true physician extenders, they practice medical eye care, and they serve as triage and primary care, for those patients who are first referred to us with dry eye. Cases that are referred to me are higher-level DED patients. They make up around 20 percent of my practice, with the remaining 80 percent made up of surgical cases. As Bill Trattler mentioned, dry eye before eye surgery is a huge risk factor for substandard patient satisfaction and concerns. Performing cataract and refractive surgery, we really have to be mindful of the number one refractive surface – the tear film – and my practice has high volumes of cataract and refractive surgery patients. I don't have as much experience with keratoconus patients as Bill Trattler, but it is very true that those patients also tend to get dry eye.

WHAT HAS CHANGED IN THE WAY YOU MANAGE YOUR PATIENTS' OCULAR SURFACE SINCE THE START OF 2020, WHETHER COVID-19-RELATED OR NOT?

Trattler: In 2020, we had to reduce our staff by around 30 percent. Many patients stopped coming in for routine check-ups and we have had more patients coming in with serious problems.

DED has been a huge issue in my practice since the pandemic started – it seems that I'm seeing more and more patients with dry eye every day. It has been a hugely challenging time. Nevertheless, there are many new technologies for the dry eye space just around the corner, so I'm excited about the future.

Barabino: What I have noticed – perhaps due to an increase of remote working and e-learning – is that we are seeing more younger patients who complain about dry eye symptoms. Many of them are teachers, academics – people who are forced to spend a lot of time in front of a screen all of a sudden. This is a more unusual population of our DED sufferers – we would normally mostly see older people, with other conditions.



Meet the panel:



STEFANO BARABINO,
HEAD OF THE OCULAR
SURFACE CENTER AT
THE SACCO HOSPITAL,
MILAN, ITALY



ELIZABETH YEU,
ASSISTANT
PROFESSOR AT
EASTERN VIRGINIA
MEDICAL SCHOOL
AND SURGEON WITH
VIRGINIA EYE
CONSULTANTS, USA,
WHO CHAIRED AND
MODERATED THE
ROUNDTABLE



WILLIAM TRATTLER,
CATARACT, CORNEAL AND
REFRACTIVE SPECIALIST
AT THE CENTER FOR
EXCELLENCE IN EYE CARE
IN MIAMI, FLORIDA, USA



LAURA M. PERIMAN,
DIRECTOR OF DRY
EYE SERVICES AND
CLINICAL RESEARCH
AT THE DRY EYE
CLINIC, SEATTLE,
WASHINGTON, USA

Another change is that we haven't been seeing patients on a routine basis, but rather when we really need to see them. In 2020 the access to our hospital was limited, so patients contacted us in various ways – they would send pictures, attend virtual appointments, and we made sure they felt in tune with their ophthalmologist, which is crucial for patients with a chronic disease, such as DED. It is very important for these patients' mental health to know that their eyes are well looked after.

Periman: Telemedicine is closely integrated into the way we care for patients. I have found it very important to be able to speak to patients without a mask, with my full face visible, and a virtual introduction has worked well for this. It enables me to establish a connection with patients who are in their familiar environment where they can relax. There was a worry among physicians that telemedicine would be impersonal, cold, and distant, and building a connection with a patient wouldn't be possible, but I have found the opposite to be true. Having initial discussions and risk evaluations online (all forms are completed electronically to minimize patients' time in clinic) creates engagement. I think that the way we ask questions helps to create an awareness of how lifestyles and habits contribute to DED. This really helps to open the realm of possibility of integrated care to patients. We create an integrated treatment plan, and the telemedicine introduction and online forms really prepare patients for what they can expect from the institute. We have trained patients to take fabulous photos, which help me to determine ahead of the visit what we might be dealing with, and I can tell patients what might happen when they come in – what imaging and testing they may expect.

WHAT IMPACT HAS MASK-WEARING HAD ON THE OCULAR SURFACE?

Periman: Ohio ophthalmologist, Darrell E. White, first coined the term “mask-associated dry eye” or “MADE” (1). It makes perfect sense: when you are wearing a mask, you have the flora

from your mouth and nose coming up into your eyes. As we begin to get a detailed ribosomal RNA analysis of patients' flora, we're going to see a lot more ENT flora around their eyes. It's not ideal – not what nature intended – so I'm expecting not only the turbulent airflow, but also the microbial flora to contribute to dry eye. I advise patients not to make the problem worse by getting eyelash extensions – that creates even more turbulent flow than just the mask alone. I have been showing patients how to tape their mask to prevent some of that turbulent air coming back into the eyes.

Trattler: As our practice is so focused on refractive surgery, we're seeing a huge interest in refractive surgery from patients who are frustrated with their glasses fogging, the dryness of their contact lenses. Some cataract patients are also getting frustrated with having to use their glasses together with a face mask. There is a general frustration with the airflow from mask using exacerbating DED.

Barabino: I don't know the exact mechanism yet, but it is certainly an issue for our patients and something we have noticed since the start of prolonged mask-wearing.

Yeu: I'm concerned that the use of glasses and contact lenses is going to worsen the air flow issues, as well as the microbial flora issues because of the direct aerosolization effect, evidenced by the fogging of the lenses. Droplets, instead of coming out, are getting stuck. This is why we might be seeing a much greater incidence of chalazia, blepharitis, and other conditions. Mask wearing has had a very unique impact – psychosocially and functionally. Usually, my refractive patients are coming in because they're not tolerating contact lenses, and they tend to have dry eyes to begin with; these days, they come in with mask intolerance, and they tend to start with a much healthier ocular surface. It has actually made a

difference as to how many patients with healthier ocular surface I'm seeing – they are getting DED symptoms for the first time, due to mask-wearing.

“I'm concerned that the use of glasses and contact lenses is going to worsen the air flow issues.”

OSD/DED NOMENCLATURE CAN BE COMPLICATED. WHICH TERMS DO YOU USE FOR WHICH CONDITIONS?

Periman: I'm probably guilty of interchanging terms, but in my opinion ocular surface disease seems to be the big umbrella term, from which you can get more specific, with many different possible aspects we can look at. Dry eye disease – of which there can be at least two dozen different conditions – are one subset, and then there are other ocular surface disorders, such as blepharitis, Meibomian gland dysfunction (MGD), neurological reasons, immunopathophysiology, allergic conjunctivitis, and more.

Barabino: I agree completely. Ocular surface disease is a disease of an entire system, encompassing many various underlying reasons. I've never seen a patient with severe DED without MGD. Sometimes I get patients referred with, for example, corneal ulcers, and general ophthalmologists might have used every solution they could think of, and nothing worked, for the simple reason: misdiagnosis – they missed the MGD. If you look at the whole system, you won't miss important signals.

Trattler: For a lay person, “dry eye disease” is often an easier term to understand, whereas we as clinicians have to figure out the exact reasons for why the patient's eyes are dry, taking all nuanced options into consideration, so we can focus our treatments on the exact aspect of our patient's condition. With patients, I tend to use the term “dry eye” and explain why their eyes are tearing even though their eyes are “dry” – it's always a fun part of the conversation!

Yeu: From a clinical perspective – when we are getting differential diagnosis, using terms like “external disease” or “ocular surface disease” makes sense – it encompasses various exacerbators. When I talk about “dry eye” with patients, it means specifically a dysfunction or imbalance of the tear film. Any other aspect of the disease for me falls into the external/ocular surface disease.

HOW DO YOU MANAGE YOUR PATIENTS FROM DED DIAGNOSIS? DO YOU HAVE A SET PROTOCOL FOR THE PRACTICE?

Trattler: There are many clinicians in our practice, and we each have our own separate strategies! It really depends on the patient – some have been treated for many years, others come in having never had any ocular disease treatment. Some patients present with collarettes, some are aqueous deficient, others might be neurotrophic. For me, there isn't one right answer on what to do – each patient is treated individually and I don't have just one protocol for what to do in each case. What I would say is that I often like to use an anti-inflammatory, and antiseptics for eyelashes and eyelid margins, as well as some warm compresses early on. I don't use specific questionnaire, but use targeted questions instead.

Periman: In my practice, we try to identify the co-conspirators and exacerbators early, and address them specifically, while also targeting inflammation. To me, inflammation is the bull's

“The ASCRS Corneal Clinical Committee has made recommendations to use the succinct “look, lift, pull and push” method, but I also get patients to look down now.”

eye of this “game,” and then we have to solve the Rubik’s cube of creating custom solutions for each patient – their risk factors are so different! I mentioned the video interview we conduct before seeing the patient in person. I can learn so much from this initial interview, seeing patients without their mask on. Co-contributors such as rosacea or dermatitis, psoriasis can help with the “sleuthing” and customization of the treatment. We conduct all the tests and use the results to guide therapy. Testing and examination give me a lot of answers and they fuel the process of trying to figure out how many components we

might be dealing with and what approach I might decide to use. These days, we have so many innovations we can use as additional tools – there are so many fabulous things coming to the fore, so I can see our protocols still shifting in the near future. Right now, we don’t use specific treatments for Demodex blepharitis, but I can see that changing very soon. Having many more ocular surface management tools available will make it so much easier for clinicians.

I use various symptom questionnaires, as each of them can give me different information: SPEED, OSDI, DEQ5, as ask about photophobia, impacts on mood. They are all validated questionnaire, and we imported questions into a form, which puts all the data into a spreadsheet for later analysis.

Barabino: My colleagues often mention to me that they don’t have time to diagnose DED, and because I see it every day, I have so much more opportunity and time to diagnose it correctly. I don’t agree with it; in my opinion, if you listen to your patients, and pay attention to ocular surface in slit lamp examination, use fluorescein and lissamine green, you get almost all the information you need to make the correct diagnosis. Fluorescein allows you to check for corneal damage, secondary to an inflammatory process, and with lissamine green you can see an alteration of the lead margin, so you can diagnose blepharitis, and if you see staining of the conjunctiva, you can probably diagnose dry eye with an autoimmune component. If you’re staining the superior part of the conjunctiva, it is probably limbal keratoconjunctivitis. Once you have the diagnosis, then you can start thinking about the appropriate treatment.

I like to use the Sande dry eye questionnaire. It only has two questions and gives you a good idea of the patient’s symptoms and

Stefano Barabino talks about the importance of seeing the ocular surface as a system

Barabino: It is tremendously important – and I emphasize this to my residents – that we see the ocular surface as a system, and check all components of it are working correctly. Sometimes we can get surprising results: some years ago, we examined patients with pterygium, which is a disease

of the conjunctiva, but when we actually looked at confocal microscopy images, we saw that in the center of the cornea there was an increase of immune cells being activated (2). Seeing the ocular surface in a systemic way is especially crucial ahead of any ophthalmic surgical procedure.

quality of life. I don't use it for all of my patients, but certainly for the ones taking part in clinical studies, and for those who are followed up by us for a longer time.

Yeu: I find the SPPED 2 questionnaire very useful – the ASCRS Corneal Clinical Committee came up with a great modified version to be used in the pre-operative setting for cataract and refractive patient populations.

I use meibography on every single patient. I see it as one of the greatest advancements we've seen – it gives me a clear point-in-time idea of what's going on with the patient's Meibomian glands, and MGD is such a large part of dry eye and ocular surface management.

HOW HAS YOUR EXAMINATION EVOLVED DURING THE PAST YEAR?

Yeu: With regards to the slit lamp exam, the ASCRS Corneal Clinical Committee has made recommendations to use the succinct “look, lift, pull and push” method, but I also get patients to look down now. I used to pay so much attention to the lower lid margin, looking for MGD, and I wasn't looking at the front of the lids – particularly the upper lid, which houses so much of the debris. I make sure to do this now.

Periman: I start my exam by looking at a person head to toe. Sometimes there are clues even in the way they're walking – you might suspect something like Parkinson's disease. When I get to the slit lamp exam, I use the “look, lift, push, pull” technique, and it's amazing

how much you can observe: there might be eyelid inefficiencies, laxity that you didn't appreciate previously, evidence of the floppy eye syndrome or evidence of keratoconjunctivitis. The staining pattern and the way that the tear film wets and spreads, as well as the tear meniscus height can

be very instructive. I also look at everyone's optic nerve through an undilated pupil – it's a force of habit.

Trattler: I look at the eye before putting the dye in, and I look at the tear meniscus – I find it very valuable. I also press on the lower lids to see secretions. Recently, I also started to get patients to look down, and carefully evaluate the upper eyelid and lashes. I have been surprised to see how common collarettes are – it's really changed the game for me, helping me to diagnose lid disease.

I find it important to keep fluorescein stain in for at least 2-3 minutes. Many clinicians are in a rush and only keep it in for 20 seconds, but you have to make sure that you see the stain throughout the entire cornea, so try to stick to this 3-minute mark.

Yeu: I also do my exam without any dyes as I want to see the natural tear film height and how it spreads across the inferior lid margin. I also pay much closer attention to blepharitis now than I did five years ago – there's a lot more information on this subject now.

To watch or read the rest of the discussion, including blepharitis management, innovations experts are most looking forward to trying, use of amniotic membrane, and much more, go to theophthalmologist.com and search for Dry Eye Debate: The Progressive Practice.

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A Burning Issue

In Practice

*Surgical Procedures
Diagnosis
New Drugs*

What all ophthalmologists need to know about two conditions they will probably never see: Stevens-Johnson syndrome and toxic epidermal necrolysis

By Charles S. Bouchard

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe and potentially lethal multisystem, mucocutaneous, immune-mediated adverse drug reactions (IM-ADR). These related conditions are as rare as they are serious, with an incidence of about 1 to 7 cases per million per year and an overall mortality rate of 20–25 percent (1, 2). Medications trigger SJS/TEN in greater than 80 percent of the adults who are diagnosed with it, and the onset typically occurs within a few weeks of administration of the culprit drug (3, 4). Antibiotics and anticonvulsants are among the most commonly implicated triggers.

Ocular involvement is associated with the vast majority of these cases. In fact, progressive conjunctival scarring and corneal damage are the most disabling long-term complications for SJS/TEN survivors (5). Secondary systemic complications often seen with SJS/TEN include

dermatologic, respiratory, genitourinary, and psychiatric disorders, including post-traumatic stress disorder. Due to the unusual nature of the disease, practicing ophthalmologists will rarely, if ever, see a case. However, it is imperative to understand the pathology and recognize symptoms so that a swift referral can be made to an ICU or dedicated burn unit in order to give these patients their best chance at a successful outcome.

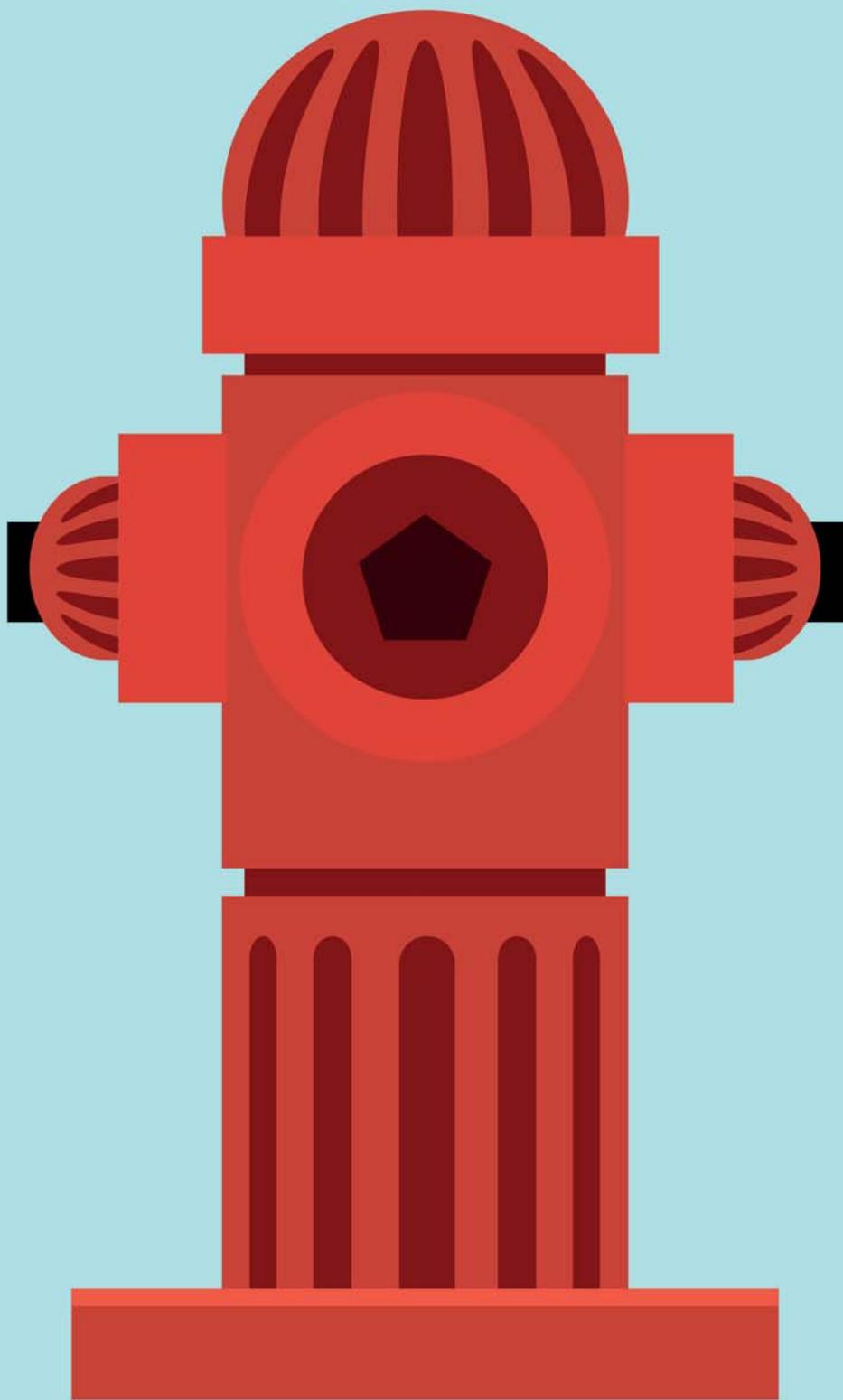
Diagnosis and referral

The management of SJS/TEN-associated ocular sequelae is extremely challenging. Because these conditions are so rare, the comprehensive ophthalmologist tends to be unfamiliar with the presenting signs of the disease, its acute management, and long-term consequences. There is a short window of opportunity during the acute stage when intervention may potentially avoid lifelong complications, which may include photophobia,

“It is imperative to understand the pathology so that a swift referral can be made to an ICU.”

intractable dry eye, chronic pain, corneal scarring, and severe vision loss – all of which are associated with diminished quality of life. And that’s why education is a major aim among those of us who are actively involved in SJS/TEN research and treatment.

Suspecting a diagnosis, immediately referring the patient to a regional burn center, and identifying the culprit drug are all critical to optimal management. The clinical presentation usually starts with a prodrome of fever, malaise, cough, rhinorrhea, and anorexia followed by mucositis and a painful generalized erythematous vesiculobullous rash with skin sloughing (6, 7). Early signs of ocular disease can be variable, ranging from conjunctival hyperemia to sloughing of the entire ocular surface



The AMT procedure

In the acute SJS/TEN patient with moderate-to-severe ocular disease involving the eyelid margin, cornea, and/or conjunctiva, a continuous 5 cm x 10 cm sheet of cryopreserved AM is separated from the nitrocellulose paper at one edge and draped over the eyelid margins in a vertical orientation with the epithelial basement membrane side up. The tissue can be secured with a running suture along the upper and lower eyelids or secured to the lid margins with

cyanoacrylate glue (Ethicon). [link to Bouchard video here] Cyanoacrylate glue is placed underneath the AM on the upper eyelid margin skin, several millimeters away from the eyelid margin. The AM is then held across the upper eyelid for 30 seconds with 2 forceps to ensure adhesion. A Desmarres retractor is used to lift the upper eyelid off the ocular surface, and a custom symblepharon ring is used to push the AM into the superior fornix and then the inferior fornix. This is done carefully to ensure the AM remains flat and unwrinkled under the symblepharon ring. A muscle hook is

used to flatten and spread the AM into the desired position, and cyanoacrylate glue is then placed on the skin of the lower eyelid several millimeters away from the eyelid margin, and the AM is draped over the glue. Excess AM beyond that which is attached to the eyelid margins is trimmed with scissors. Antibiotic ointment is applied over the eyelid and ocular surface, and the sterile drape is removed. At this point, the surgeon should ensure that the patient is able to close the eyelid and that there is no lagophthalmos secondary to the symblepharon ring.

“Other lid margin abnormalities that may develop include entropion, trichiasis, and punctal occlusion.”

and eyelid margin epithelium.

Underscoring my point about education: up to one-third of cases may be misdiagnosed, which also highlights the importance of gaining histological confirmation from a skin biopsy at the outset of the rash (8).

There is a well described genetic and ethnic predisposition to SJS/TEN. A significantly strong correlation was first found with the Han Chinese population in 2004. Carbamazepine (CBZ) induced SJS/TEN patients carried 100 percent of the HLA-B*1502 allele, and only 3

percent of HLA-B*1502 carriers tolerated CBZ. Based on its absence in Caucasian and the Japanese, the HLA-B*1502 allele seems uniquely limited to Han Chinese ancestral Asians and might be an explanation for the extremely high risk of CBZ-induced SJS/TEN in Southeast Asians compared with Caucasians and the Japanese (9). This knowledge has not only led to successful HLA-B*1502 screening programs in Taiwan, Singapore, and other parts of Southeast Asia (which have almost eliminated CBZ-associated SJS/TEN), but also furthered our understanding of the immunopathogenesis of SJS/TEN (10). Recent studies show that a network of susceptibility genes for SJS/TEN, such as TLR3, EP3, and IKZF1, may trigger the inflammation associated with several ocular complications (11, 12).

Ocular involvement SJS/TEN can be divided into acute and chronic

phases. The acute ocular symptoms manifest as inflammation of the entire ocular surface: cornea, bulbar and tarsal conjunctiva, and eyelid margin. This process runs the gamut from mild conjunctival injection to severe pseudomembranous conjunctivitis, corneal epithelial dysfunction, melting and perforation, and eyelid margin scarring. If inflammation persists, it may result in the chronic manifestations of the disease, such as symblepharon formation and forniceal shortening. In addition to the conjunctival inflammation, there may be damage of the mucin-producing goblet cells, lacrimal ducts, and meibomian glands, as well as keratinization of the ocular surface (6, 13). The most important prognostic factor in long-term outcomes of SJS/TEN is keratinization and scarring of the eyelid margins (14, 15). Other lid margin abnormalities that may develop include entropion, trichiasis, and punctal occlusion.

Patient management
Loyola University in Chicago, Illinois, USA, is the referral center for SJS/TEN cases that arise throughout



Figure 2 a-c: Once the AmnioGraft cryopreserved amniotic membrane (CAM) has been secured to the upper and lower eyelids, a Desmarres retractor is used to ensure that the CAM coats the internal surface of the upper and lower eyelids.

the Chicagoland area. We have been the go-to establishment for 25 years, due, in large part, to the work of Richard Gamelli, who established the main burn unit that is the hub of five similar units throughout the city. When patients are suspected of having SJS, they are sent directly to our burn unit. Though most ophthalmologists may see one SJS/TEN patient at the most throughout their career, we see 8–12 of these patients every year (16).

Because of the multisystem nature of the disease and the high mortality rate, patients with SJS/TEN should be managed in the ICU or dedicated burn units that have the capabilities to provide complex skin care and appropriate intensive care for more severe cases. This approach has been shown to improve outcomes (17). Stopping the culprit drug is also associated with a better prognosis for these patients; however, identification of the causal drug can be extremely challenging and often relies mainly on expert judgment – but every day of delay worsens the outcome (18).

Because of the frequent involvement of the eye in SJS/TEN, ophthalmologists need to be involved as early as possible. An initial ocular examination on all SJS/TEN patients should occur within 24 to 4 hours of admission. Unfortunately, patients don't always have the benefit of an ophthalmologist's input early in the process. In fact, only 66 percent of burn ICUs in the US consult ophthalmology for SJS/TEN patients (8, 13). Ocular involvement can be severe very early in the disease, even before extensive skin sloughing has occurred. Traditionally, the first two to six weeks following onset of symptoms is recognized as the acute stage. But ocular involvement in SJS/TEN can be fluid; a case that is moderate one day may become severe the next, making daily examinations crucial in the acute phase.

Ocular surface damage often represents the most

significant long-term complication of SJS/TEN. It has been reported that a majority of patients with late ocular complications find it difficult to read, drive at night, and use a computer for several hours at a time. The chronic ocular complications of SJS/TEN are caused by prolonged ulceration and ongoing inflammation that leads to scarring of the ocular surface. A major underlying cause of sight-threatening corneal complications is the continuous trauma caused by friction from the scarred mucosal surfaces of the eyelids. Even when patients do not lose vision, scarring in the fornix disrupts lacrimal gland function and causes dry eye syndrome – the most common complication.

Treatment evolution

The treatment of acute SJS/TEN involves a grading system of ocular severity (see Figure 1).

For Grades 0 and 1, daily saline (NaCl 0.9%) flushes should be performed and pseudomembranes debrided with a cotton-tipped applicator. Medical treatment should include

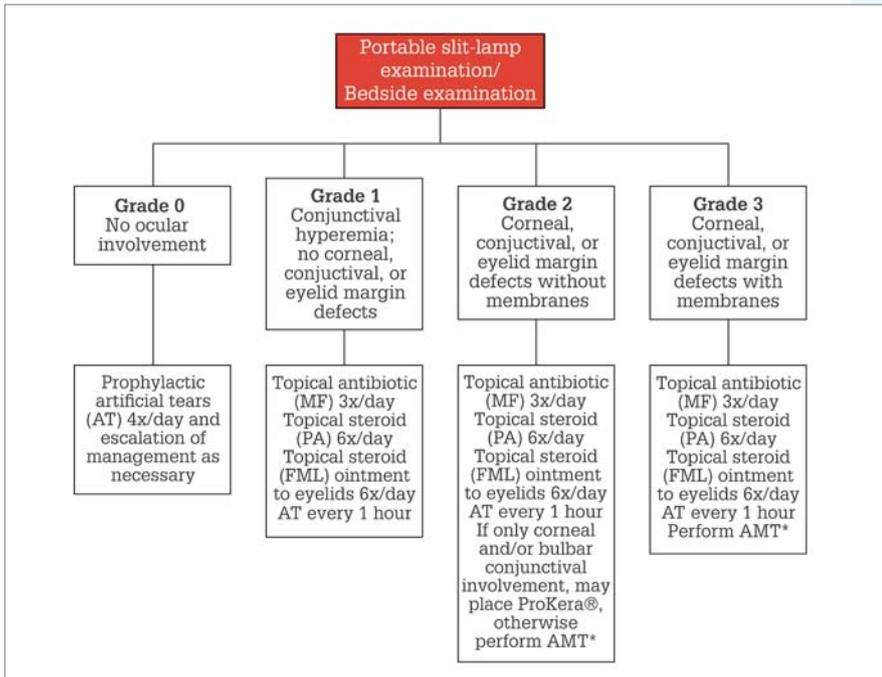


Figure 1. Flow diagram outlining the protocol for management of ocular manifestations in acute SJS/TEN. Moxifloxacin 0.5%; prednisolone acetate 1%; fluorometholone 0.1%; artificial tears; amniotic membrane transplantation.

moxifloxacin 0.5% drops (Vigamox) three times a day, topical steroid eye drops six times a day, and a steroid or antibiotic-steroid combination ointment to the eyelid margins four to six times a day. Cyclosporine 0.09% drops (Cequa, Sun Pharma) four times a day should also be considered. Preservative-free artificial tears should be used every one to three hours in between the other drops.

For grades 2 and 3, amniotic membrane transplant (AMT) is at the forefront of SJS/TEN management. This should be done within seven days of the onset of the skin rash, in cases with significant eyelid margin involvement +/- bulbar conjunctiva (see Figure 2) (19, 20). Systemic management is controversial, though drugs such as etanercept (a TNF- α receptor antagonist) and cyclosporine (an immunosuppressant) are showing promise in ongoing clinical trials, including one in which Loyola is a participant. Pulse systemic corticosteroid has been used in Japan since 2005 with beneficial results.

Amniotic membrane transplant (AMT) Amniotic membrane (AM) tissue has played a vital role in treatment of a variety of ocular surface conditions since 1940, when de Rött first reported on the use of fresh amnion and chorion as a biological dressing material for management of conjunctival defects (21). More recently, in 2002, John and colleagues reported the first use of AM in acute SJS (22).

Currently, there are two types of amniotic membrane tissue: dehydrated and cryopreserved. Cryopreserved AM (CAM) promotes regenerative wound-healing (23, 24, 25). The cryopreservation process allows CAM to retain key properties (heavy chain peptide [HC], hyaluronic acid [HA], pentraxin-3 [PTX3]) that are lost in the dehydration process. These biologic compounds are responsible for CAM's

anti-inflammatory and regenerative healing properties, such as tissue repair and remodeling (23, 24, 25, 26).

Early work with AM grafts for SJS/TEN focused on coverage of the entire ocular surface where both the ocular surface and the lid margins must be covered with AM to inhibit inflammation, scarring, and vision loss (22). A self-retained contact lens-like CAM device, known as Prokera (BioTissue), has also been used for isolated corneal epithelial defects without significant lid margin involvement (6, 7). BioTissue is currently the only company associated with cryopreserved AM.

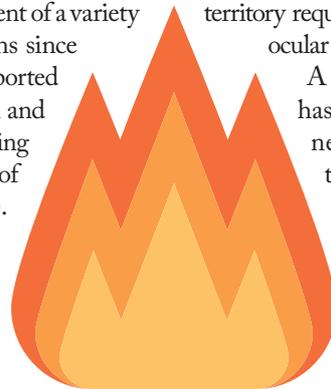
To effectively perform AMT for SJS/TENS patients in the vast majority of cases, we need a large enough piece of tissue to cover the upper eyelids and to coat and cover the internal surface on the inside—specifically, the upper part of the eyelid and the inside of the lower eyelid. This need is what makes cryopreserved AmnioGraft (BioTissue) indispensable to the process. There are no other AM tissue products available that are large enough to effectively cover all the territory required to manage severe acute ocular manifestations of SJS/TEN.

A major development that has taken AMT grafts to the next level in the SJS/TEN treatment hierarchy is the ability to perform the AmnioGraft procedure with cyanoacrylate glue instead of sutures. This obviates the need to send these very sick patients to the operating room. Instead,

when we secure the AM to the upper and lower eyelids with glue it can be done at the bedside (27, 28). The procedure that we use today is similar to the one described by Shanbhag and colleagues (28).

Treatment challenges

The biggest challenge inherent in the



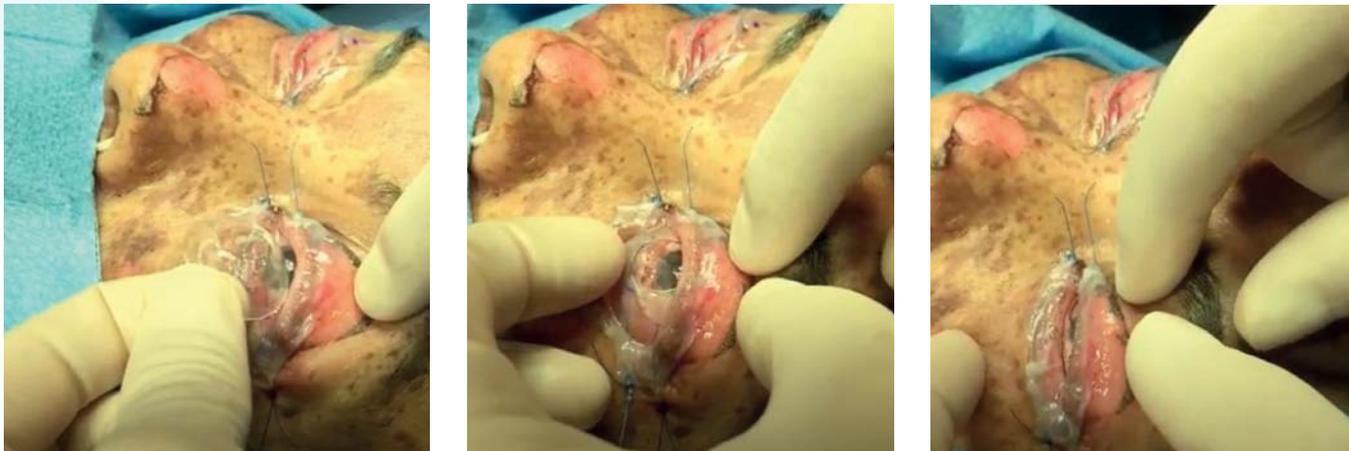


Figure 2 d-f: A Symblesphron ring is used to push the CAM further into the superior and the inferior fornix.

“The window of opportunity begins to close after the onset of ocular surface sloughing. After this acute period, intractable scarring sets in.”

use of AM for SJS/TEN treatment is that the procedure must be started within a week of the onset of the skin rash. If a patient undergoes AMT weeks later, the treatment is not as effective. Long-term results show that early use of AM in the acute phase of SJS/TEN is effective in mitigating severe vision loss (29). Despite a growing body of evidence describing early AMT as a means of preventing serious long-term sequelae, many patients still go untreated and thereafter experience

severe photophobia, painful dry eye problems, and blinding cicatricial ocular surface complications indefinitely. The sooner AMT is performed, the more effectively it can prevent scarring sequelae. The window of opportunity begins to close after the onset of ocular surface sloughing. After this acute period, intractable scarring sets in.

Resolution of the epithelial defects on the ocular surface reflects a favorable outcome. For more severe disease, multiple grafts may be necessary over a 2–4-week period. For chronic disease, multiple treatments have been reported to be effective in the management of ocular surface scarring, including Scleral PROSE contact lenses and mucus membrane grafting (MMG) for lid margin keratization (30, 31). Timely MMG can significantly alter the course of disease and not only preserve but improve vision in affected eyes (32). In one study, patients receiving suboptimal care during acute SJS presented later with severe ocular and visual morbidity; two-thirds of patients (99 percent without prior amniotic membrane grafting) presented more than a year after acute SJS with low vision or

blindness in 60 percent of eyes (33).

Keratoprosthesis (KPro) is probably the optimal surgical intervention for visual rehabilitation in end-stage ocular SJS/TEN. It can restore fairly good visual function; however, it is associated with complications and the need for repeat procedures (34). Patients with SJS/TEN tend to experience device retention and have more severe post-operative complications and a poorer visual prognosis relative to other indications.

Takehome

SJS and TEN are rare multisystem allergic drug reactions with significant ocular sequelae if left untreated within a narrow window of time using amniotic membrane grafting. Early recognition, diagnosis, and referral of SJS/TEN patients to a burn unit or ICU offers the patient the best chance for a favorable outcome.

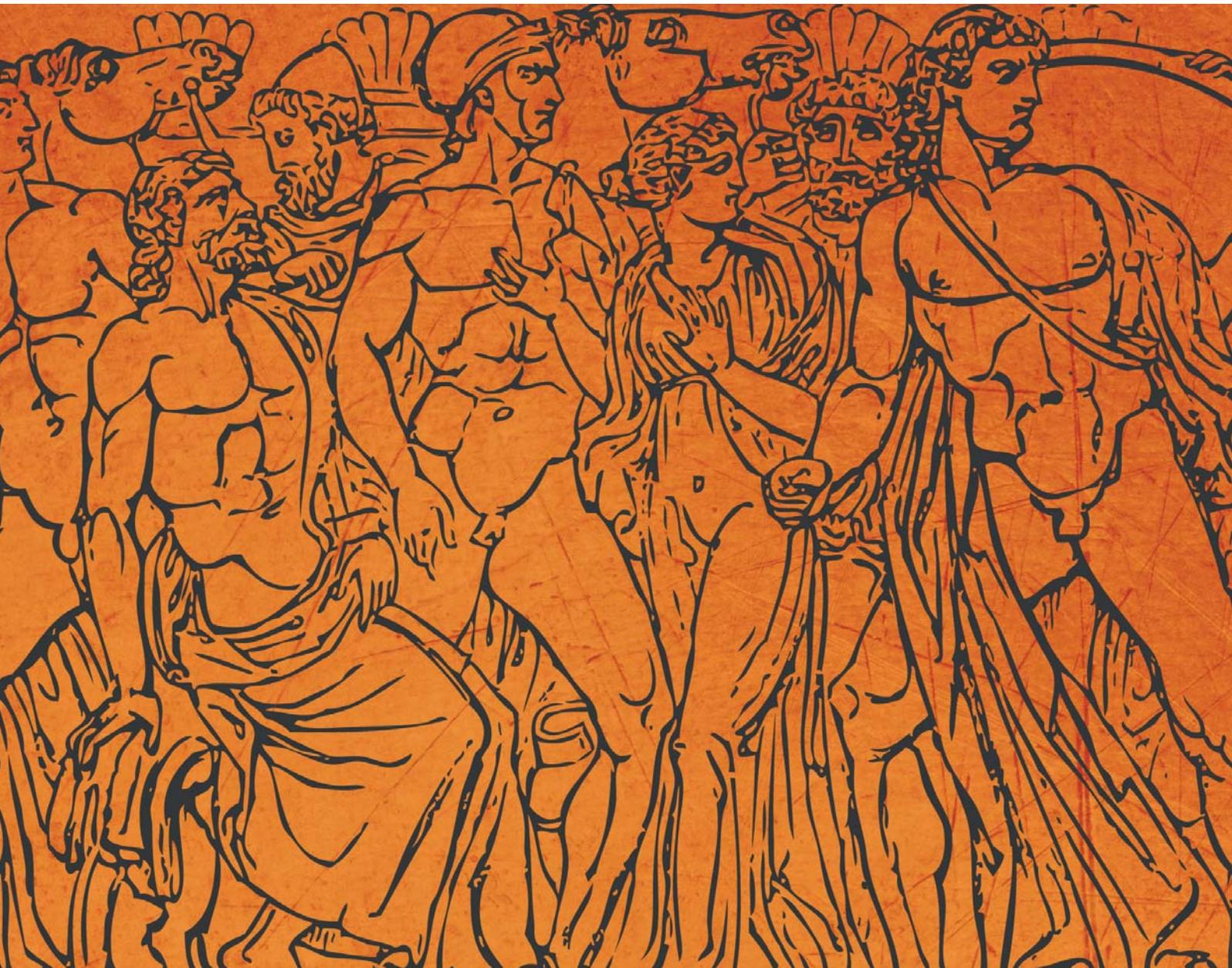
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See references online at: top.txt.to/a/burning/issue

Busting Keratoconus Myths

Four common misconceptions about later-stage cross-linking for progressive keratoconus

By Kenneth A. Beckman



Corneal collagen cross-linking slows or halts the progression of keratoconus. Ideally, patients should be treated early, before there is significant corneal damage. However, there are very good reasons to consider cross-linking instead of—or prior to—keratoplasty, even in cases with more advanced disease. Here, I'll address some of the misconceptions I've seen regarding older patients and those with more advanced disease.

Myth 1: Older patients don't progress
It is a commonly held belief that eyes with keratoconus will eventually undergo natural, age-related cross-linking and stop progressing by age 30 or 40. A corollary to this is the belief that cross-linking interventions don't work after this point and that any adult who continues to progress beyond their third decade should undergo keratoplasty. Though it is certainly true that we see the most significant and rapid progression in younger patients, there is evidence that progression continues beyond the 30s (1). I have personally seen plenty of patients over age 50 with corneas that continue to thin and steepen—and they have benefited from corneal collagen cross-linking. I don't believe anyone is "too old" for cross-linking if progression can be confirmed. In short, older patients do tend to progress, but often at a slower rate (2).

Myth 2: Vision can't be improved in patients with advanced keratoconus
Many doctors believe that a patient whose vision has decreased to 20/60 is a "lost cause" who would be better served by keratoplasty. They may feel confident in their ability to achieve near-20/20 vision with a graft and believe that would be more expedient than cross-linking. There are a couple of problems with this line of thinking. First, although the primary goal of cross-linking is to slow or halt progression, we also know that the corneal flattening achieved with the procedure does have some

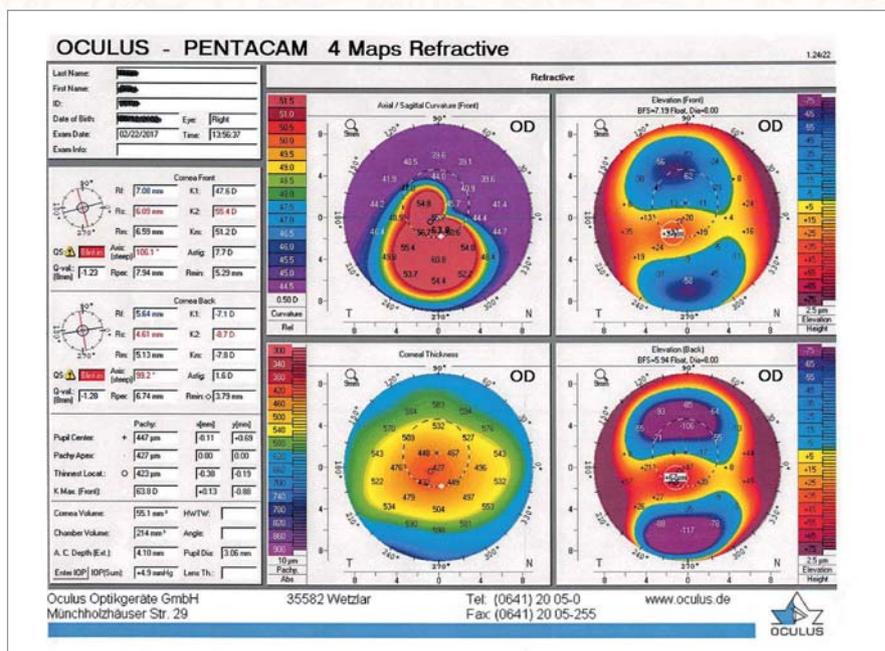


Figure 1. Cross-linking flattened this keratoconic cornea by 3.1 D, improving this teen's uncorrected visual acuity to 20/30.

impact on vision, with considerable individual variation (3). I have countless patients who have had dramatic visual improvement after cross-linking. Given this possibility, I would rather give patients the opportunity to see what effect the corneal flattening has on their visual function before proceeding to a transplant.

Additionally, I would rather address the visual acuity problems with cross-linking plus contact lenses than count on a perfect transplant result. As long as there is no scar in the visual axis, well-fitting scleral lenses are likely to provide very good visual acuity, even in cases of advanced keratoconus. In fact, I have seen many patients with steep cones who can only see 20/400 with glasses, but can get to 20/20 or 20/30 in a scleral lens—and I offer cross-linking to preserve this function. It's very possible their vision won't be any better than that with a transplant, anyway, and by cross-linking we spare them the surgical trauma and risks of infection,

glaucoma, cataracts, and graft rejection. Even in cases where I think a patient will ultimately need a graft, I would almost always recommend cross-linking first. Keratoconus can recur in the graft (4), so it makes me more comfortable to know the host cornea rim has been treated and is more stable.

I am particularly bothered by a rush to transplant in very young patients. I saw a 14-year-old male with progressive keratoconus for a second opinion in 2017. His K_{max} in the right eye (the worst eye) was 63.8 D (see Figure 1a), uncorrected vision was 20/100- and best-corrected acuity was 20/80. Although the visual acuity appeared to justify a keratoplasty, the cornea was crystal clear. I performed cross-linking and, by the three-month visit, his K_{max} had flattened by 1.1 D, improving the uncorrected vision to 20/30-2 and best-spectacle-corrected vision to 20/30. That would have been an outstanding result from a graft, but by avoiding the transplant, he has avoided so much hassle and risk. At his four-year

visit, the K_{max} had decreased to 60.7, for an improvement of 3.1 D since treatment (see Figures 1b and c). His uncorrected vision was 20/30 and his best corrected vision was 20/20-.

We have to keep in mind that teens are very active and more subject to trauma than adults. They may stop using their drops and cease to return for follow-up due to lifestyle or health insurance changes. They have a high likelihood of needing one or more repeat grafts in their lifetime. I believe we must consider not just the visual acuity but the lifetime risks of cross-linking versus transplant in deciding on the optimal course of treatment for young patients with progressive keratoconus.

Myth 3: If the patient has lost vision and is contact lens intolerant, it is time for a transplant

Cross-linking often reshapes the cornea enough to make a contact lens easier to fit and more comfortable. Several papers have now reported marked improvements in subjective and objective contact lens fitting and longer duration of tolerable wear after cross-linking, including among previously contact lens intolerant patients (5, 6). In some cases, this may give the patient the ability to shift to an easier and less expensive form of vision correction (such as glasses or soft contact lenses). But even in severe cases, where patients have lost best-corrected acuity, I find that almost everyone can be fit with advanced contemporary scleral lenses after cross-linking. It is key to work with an expert specialty lens practitioner. Again, my preference would always be to cross-link first and try the contact lens route to avoid a graft.

Myth 4: Increasing K_{max} after cross-linking is always indicative of progression

In rare cases, patients can continue to progress after cross-linking, especially if

the patient reached an advanced stage at a young age. Keratoconus patients should be followed closely after treatment for this reason. However, it is also important to know that K_{max} is not the only parameter one should monitor. As the cornea undergoes surface reconfiguration after cross-linking, steep areas of the cornea flatten but it is also possible for some flat areas to steepen before stabilizing. I like to look at the difference map, which subtracts the current topography from the original, to get a better understanding of how the entire cornea has changed with treatment.

In another teenage progressive keratoconus patient I treated, the Pentacam difference map (see Figure 2) confirms that the treatment was a success. Even though this patient's K_{max} appeared to "progress" from 65.3 D preop to 67.6 D by 15 months after cross-linking, his vision improved from 20/40 to 20/25. When I'm uncertain whether I'm seeing progression, it helps to remember that we are treating a patient and not a K_{max} value. If the patient's vision and quality of life is better, the K_{max} may be less important, provided the keratoconus has truly stabilized.

We have also seen some innovative algorithms that help in monitoring progression of keratoconus. The Belin-Ambrosio ABCD classification system has now been integrated into the Pentacam (but can be used with other devices) to determine when there is change beyond just measurement noise. It creates a composite score of four different parameters: Anterior (A) and posterior or back (B) radius of curvature (taken from a 3.0 mm optical zone centered on the thinnest point); minimum corneal (C) thickness; and best spectacle-corrected distance (D) acuity (7). While the ABCD classification system hasn't been specifically validated in eyes that have already been cross-linked, it has great potential to help us with decision making at all stages of the disease.

Fortunately, more patients are being treated early in the course of their disease now that cross-linking is more widely covered by insurance and more widely available around the world. However, we will continue to see advanced keratoconus patients in our practices, and I believe that most of these patients – provided they do not have central scarring – would benefit from cross-linking before considering a PK, regardless of their age, visual acuity, or contact lens tolerance.

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Let There Be (Laser) Light



Promoting an evidence-based approach, the European Glaucoma Society Guidelines Committee has changed recommendations for the initial open angle glaucoma treatment

By Augusto Azuara-Blanco

From 2019 to 2020, I chaired the European Glaucoma Society (EGS) Guidelines Committee with Carlo Traverso. The 5th Edition of the EGS guidelines was published in October 2020, after a superb team effort among a large number of colleagues (1). We aimed to promote evidence-based clinical practice and, to that end, followed GRADE methodology, including identification of key questions, critical evaluation of published literature, and formulation of recommendations. A key issue was the recommendation for an initial treatment for open angle glaucoma and the role of the laser as primary therapy.

The impact of the LiGHT trial Laser trabeculoplasty has been a valuable option for treating open angle glaucoma and ocular hypertension for several decades. The Argon Laser Trabeculoplasty Trial was a landmark trial in the US (2) that compared beta-blockers – the best medical treatment at the time – with argon laser trabeculoplasty

(ALT). Despite the evidence favoring ALT, medications remained the first and foremost choice in glaucoma treatment. This result might have been due to a number of factors, including the technical expertise required to deliver ALT, difficulties in changing established practice, and financial considerations (such as different reimbursement processes offered by healthcare providers and insurance companies). Whatever the reasons, ALT was not and has not been considered a first-line glaucoma treatment. Even to this day, patients with newly-diagnosed glaucoma usually start on medications. But the LiGHT trial may be changing this.

There have been a number of trials over the years highlighting evidence of the effectiveness of selective laser trabeculoplasty (SLT), but there has never been a landmark, decisive, high-quality trial until recently. Though smaller trials have value, there is always the concern of the potential risk of generalizability and bias, which may explain why – despite evidence showing

that laser is just as effective – medications have remained the primary therapy for glaucoma patients.

The LiGHT trial found that SLT was both more effective (including IOP control, disease

progression, and the reduced need for glaucoma surgery) and also more cost-effective than eye drops (3). Among the patients receiving SLT treatment, 74 percent did not require any eye drops at the end of the three-year follow-up. The trial, led by an international leader (Gus Gazzard of Moorfields Eye Hospital in London, UK) was very well designed and conducted, with a 700+ patient population and minimal attrition. These factors have significantly influenced the trial's well-received reputation. Its distinct impact is clear; after publishing the trial, the UK National Institute for Health and Care Excellence (NICE) decided to update their guidelines to suggest that lasers should be considered a first-line treatment (4). Thanks to the trial, surgeons are considering SLT now more than ever.



Lasers as first-line treatment

There have always been significant issues with patient compliance when it comes to medications. In my opinion, an increase in the proportion of patients with glaucoma and ocular hypertension who receive laser treatments will be associated with better patient outcomes. An exciting and novel laser technology by BELKIN Laser Ltd., direct selective laser trabeculoplasty (DSLTL), has the potential to revolutionize glaucoma care. The technology really is groundbreaking; delivering the treatment requires little expertise, and involves simply pressing a key and delivering the laser in seconds. Importantly, general ophthalmologists who may not feel that they are experienced enough in delivering ALT or SLT will be able to offer laser trabeculoplasty. A large multi-centre trial designed to compare SLT and DSLTL is currently ongoing and will be completed this year (5).

Moreover, DSLTL's non-contact delivery makes it patient-friendly and removes the risk of infection – a significant factor to consider in a post-pandemic climate.

But that's not to say medications will no longer play an important role in glaucoma treatment. After all, medications are also changing, and there are now more effective preservative-free eye drops that reduce adverse events and tolerability issues that were typical.

Other new considerations in the 2020 EGS Guidelines

One vital, qualitative aspect we wanted to deliver with the new guidelines was the patient's voice. In the previous (2016) edition of the EGS guidelines, we focused on the important questions to ask patients as well as patients' potential concerns, but this information was based on clinical opinion. For the new guidelines, we directly asked patients and patient representatives from a large

glaucoma charity (Glaucoma UK) to tell us about their most important concerns, their most common anxieties, and aspects vital to patients, such as the best ways for surgeons to break the difficult news that a patient has glaucoma. Though this section is only a couple of pages long, bringing the patient's voice to these guidelines was incredibly important.

*“We are all now
in an exciting time
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Another aspect that differs from previous versions of the guidelines is the quality-control process. We reached out to other glaucoma societies and were lucky enough to receive comments from the American Glaucoma Society, the World Glaucoma Association, and the Latin American Glaucoma Society. They all provided fantastic feedback, which also influenced some of the content of the recommendations. This international team effort is a big departure from previous guidelines, and it strengthens their validity.

The future

So far, the reaction to the guidelines has been overwhelmingly positive. However, only time will tell what the impact of the guidelines will be, as it takes time for people to take the recommendations into account and change their working practices. Though there is no such thing as a “perfect” set of guidelines, we are very confident in the strength of the methodology used!

We are all now in an exciting time in glaucoma management, with new options arriving frequently and better treatments following hot on their heels. Yes, there are still unmet needs in glaucoma treatment, but there is significant potential for improvement in the future.

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Unnatural Selection

Novel gene vectors delivered by intravitreal rather than subretinal injection may represent a lower-risk option for retinal dystrophy patients

By Stylianos Michalakis

NextGen

*Research advances
Experimental treatments
Drug/device pipelines*



Genetic mutations are not uncommon. Around the globe, five million people currently suffer from congenital retinal dystrophies caused by defects in specific genes. Though these errors may only alter a single element of a person's genetic blueprint, their effect can be devastating, often resulting in a loss of function in the photoreceptors or cells that form the retinal pigmented epithelium. To date, around 150 such defects have been identified.

But hope is on the horizon. In recent years, scientists have developed dedicated gene-delivery vehicles – vectors – that can be used to transport functional copies of the relevant gene into the defective retinal cells, essentially supplementing the missing function. These efforts have largely focused on vectors that are based on the genomes of adeno-associated viruses (AAVs). In collaboration with Hildegard Büning, a professor of the Infection Biology of Gene Transfer at Hannover Medical School (MHH), and an international team of researchers, my team and I have succeeded in constructing vectors that can be more easily and effectively introduced into retinal cells. Until now, it has been necessary to inject the viral vectors directly under the retina – a technique that requires highly skilled experts and facilities that are available only at specialized hospitals. Moreover, when using such an approach, there is always a risk of damage to the fragile retinal tissue itself. Another drawback of this method is that each injection reaches only a relatively small fraction of the target cells.

Using animal models, my colleagues and I have injected novel AAV constructs directly into the vitreous humor – and confirmed that these novel vectors can be transported into the light-sensitive photoreceptors in the retinal tissue (1). Our theory was strengthened by studies on human retinal tissue cultured in the laboratory, as well as studies with human retinal organoids (HROs), which are multilayer 3D models of the human retina

grown from human induced pluripotent stem cells (hiPSC) in culture (2). The novel AAV vectors resulted in high levels of gene expression in most major cells types of mature HROs, including photoreceptors. Finally, studies in a mouse model of achromatopsia – a complete lack of color vision – provided a first preclinical proof-of-concept for restoration of daylight vision after intravitreal gene supplementation with one of these novel vectors (1).

Origin story

So how do these novel vectors work? The key is to engineer specifically modified variants of the naturally occurring AAV serotypes commonly used so far. In our case, these vectors carry modifications in the capsid (the protein part of the viral vector) surface that endow novel properties and enable the vectors to cross multiple biological barriers and more efficiently infect (and transduce) target cells – for example, photoreceptors – in the retina. Biological complexity aside, the important point is that these novel vectors show higher efficiency across species and also work when tested on post-mortem human retina, which we can keep in culture for approximately 10 days.

To engineer modified variants, we used a procedure known as “directed evolution” – essentially mimicking what happens in nature (where variants with the most advantageous properties are chosen to overcome a given selection pressure) but under laboratory settings and conditions that accelerate the process. The aim? To select AAV variants that outperform other variants at a given task. In principle, you start with a high diversity of vector variants (aka a AAV variant library) – our library consists of five million distinct variants. Next, you screen those variants for beneficial properties using a specific selection assay (either in vitro or in vivo).

I think it's important to note that we did not invent directed evolution – nor are we the only group who applied it to engineer

“The general (or dogmatic) view is that selection pressure used should be logically and specifically linked to the desired outcome.”

novel vectors; however, we performed the selection process in a unique way, applying very high selection pressure.

The general (or dogmatic) view is that selection pressure used should be logically and specifically linked to the desired outcome. For our goal, this would mean applying the AAV library via intravitreal injection and then recovering vector variants (or their transcripts) from the photoreceptors after an incubation time of several days to weeks. And indeed, other researchers have done this in the past – with varying degrees of success. We decided to break with the dogma and applied the AAV library systemically (via tail vein injection) into live mice and then tried to recover AAV vector genomes from retinal cells (in particular, photoreceptors) after only a short incubation time (24 hours).

The high selection pressure is made more obvious when you explore the individual biological barriers that successful vector variants have to overcome, starting with the host immune system, systemic clearance, and the blood vessel endothelial cell barrier and retina-blood-barrier (RBB). Within the retina, vectors would need to escape from the retinal blood vessels and diffuse

into the retinal tissue. If entry from the choroidal blood vessels is assumed, then vectors should move through the Bruch's membrane, the retinal pigment epithelial cell barrier, the photoreceptor extracellular matrix, and the outer limiting membrane to finally enter the photoreceptor cells. If the entry pathway is the photoreceptor outer segment, then the connecting cilium would need to be overcome as well. If entry from the vitreal blood vessels is assumed, then vectors would need to penetrate through the inner limiting membrane, ganglion cell layer, the inner plexiform layer, the inner nuclear layer, and the outer plexiform layer to finally enter the photoreceptors at their synaptic endings. Upon cell entry, the vectors also need to traffic through and escape the endolysosomal vesicle system, uncoat and finally shuttle their genome through the nuclear membrane into the cell nucleus.

Despite the novel delivery method (and difficult journey), we reduced our selection time window for overcoming these biological barriers to just 24 hours.

The result was promising – surprisingly so. To be frank, I did not expect to be able to recover any AAV vector genome from retinal photoreceptors after systemic application, let alone with only 24 hours incubation time. Scientific curiosity drove me to try it – and now I am delighted I did! At least in the retinal universe, we had created a superhero vector.

From systemic to intravitreal injection – and beyond

Building on these promising preclinical results, we now aim to develop next-generation gene therapies for retinal disorders. One major goal will be to address conditions that require broad and highly efficient transduction of retinal photoreceptors, such as retinitis pigmentosa. Conventional AAV vectors used so far need to be delivered via subretinal injection in order to target photoreceptors. Such subretinal

injections are challenging and carry the risk of collateral damage to the fragile retina of the affected patients. To mitigate this risk, only small volumes of vector are administered in order to detach only a small part of the retina. However, due to limited spreading of the vector out of the subretinal bleb, only a small portion of the affected retina can be treated in this way. We now plan to leverage the novel AAV vector technology for intravitreal gene therapy of retinitis pigmentosa aiming to treat a large part of the retina, without the need for potentially damaging subretinal injections.

When using the vitreous humor as a target site, the risk for collateral damage caused by the surgery is markedly reduced, but the vector is now better exposed to the local immune system, which could result in a local immune response. However, we already have firsthand evidence that the modifications made in our novel vectors have also had a positive effect on the immune response. The novel vectors partially escape neutralization by anti-AAV antibodies – almost certainly the result of the tough selection process (1).

So, what's next? Though our results are promising, they do not necessarily speak to whether gene therapy will ever be able to fully restore lost or damaged vision, which, of course, depends on the specific underlying pathobiology. For some inherited retinal disorders, the disease progression (for example, the degeneration of photoreceptors) is rather slow. In those cases, supplementation of a healthy copy of the diseased gene – at an sufficiently early stage – could lead to a substantial restoration of vision. But with blinding disorders, even small effects from treatments can substantially improve a patient's life – while more significant effects allow them to have a more normal life.

Fortunately, our novel vectors are based on previously clinically-validated AAV

“The novel vectors partially escape neutralization by anti-AAV antibodies – almost certainly the result of the tough selection process.”

technology – so you could say they are improved versions of already known and widely used tools. We therefore believe that our technology can be more easily translated into the clinic; in fact, I expect to see the first clinical trial within the next couple of years.

When you work on the development of gene therapies, you always want to see your approach translated into clinical application. Success requires translational science and clinical development – and that's why my group continues to engineer further improved vectors. We can only hope we will have similar success addressing other remaining unmet needs in the future.

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POWER LIST:

The Path to Success Roundtable



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Cynthia Roberts,

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Inside the VISION 2020 LINKS Program

Profession

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Building long-term and long-distance ophthalmic partnerships to share knowledge, enhance education, and improve patient care worldwide

By M. Scott Hickman, Randal Avolio, Brenton Finklea, Ciku Mathenge, Jacquelyn O'Banion, Sadik Taju, and Marcia Zondervan

Two simple truths: i) there are currently too many blind people in the world, and ii) there are not enough ophthalmologists – in the right places and with the right skills – to prevent and treat unnecessary blindness. The shortage of ophthalmologists is especially acute in low-resource settings; the World Health Organization (WHO) recommends a minimum of one ophthalmologist per 250,000 people (1), but the number drops as low as one per 500,000 to 1,000,000 in many places on the African continent (2). Compare this to North America and Europe, where one ophthalmologist serves 20,000 people. Fifty-seven countries are considered to be in a health workforce crisis, and 36 of those are in Africa, where an additional 1.5 million health workers are needed.

The VISION 2020 LINKS Program aims to address the lack of ophthalmic human resources by providing a public health-oriented framework that pairs hospitals and training institutions in low and middle-income countries (LMICs) with training institutions in high-income settings to share learning, enhance ophthalmic education, and improve



Figure 1. Ciku Mathenge teaching small incision cataract surgery to current CAGO fellow Omair Ali at RIIO

“The first step is simply for the eye care staff in a low-resourced hospital or training institution to want a LINK.”



Figure 2. Steering Groups of RIIO and Wills Eye Hospital with SEE International staff.

patient care in a reciprocal manner so that both institutions benefit. The LINKS Program has been active in the UK since 2004 through the International Centre for Eye Health (ICEH) at the London School of Hygiene & Tropical Medicine (LSHTM) with great success, and has been conducted in the US via SEE International since 2018.

The VISION 2020 LINKS Program establishes and fosters needs-based partnerships that “provide training and support to develop the expertise of eye specialists overseas and enable them to prevent more people going blind” (3). It not only involves the subspecialist training of ophthalmologists between the two LINK partners, but also includes the whole eye care team, including mid-level cadres, nurses, management, information technology, and record keeping. In the US, SEE International oversees the LINK partnership between a US academic institution and a LMIC academic program, and in the UK, the ICEH overseas the LINKS partnerships. There are currently 30 active LINKS between the UK and other locations, mainly in Africa, plus two in the US. LINKS have a focus on surgical skills transfer, such as pediatric cataract surgery and

vitreoretinal surgery, and clinical skills transfer especially in glaucoma, diabetic retinopathy, and retinopathy of prematurity. Other areas include nursing care, patient flow, finance, management, and leadership. Costs incurred by a LINK are approximately \$25,000 per year (4), mainly in travel for the eye care teams to each other’s institutions for hands-on training.

The LINKing process

The first step is simply for the eye care staff in a low-resourced hospital or training institution to want a LINK. A Needs Assessment form is then filled out to start to identify the key priority needs of the LMIC partner and to enable the LINKS Program Manager at ICEH or SEE International to identify a suitable matching institution in the UK or USA.

Next is the establishment of a LINKS Steering Group with the main stakeholders for both institutions and then two formal Needs Assessment Exchange Visits; the UK or US institution eye care team visits the host institution, and the host institution visits the US or UK. After the exchange

visits, they develop a Memorandum of Understanding (MoU) and Activity Plan to state the intent to work together. Alongside the MoU, a three-year Activity Plan sets out who is doing what, when, for how long, and where the funding will be found. This is signed by senior leaders, such as the CEO and Medical Director of the Hospitals, the Dean of the Medical School and the Ministry of Health focal person for eye care. Once the MoU is signed, the VISION 2020 LINKS Program helps secure funding.

Monitoring of training is done by the LINK Steering Groups of each institution via the Activity Plan. Minutes of each LINK Steering Group Meeting are shared and an Annual Report with a financial and training summary is submitted to the VISION 2020 LINKS Program each year. Equipment, consumables, and training materials are the responsibility of each individual LINK partnership and should be well thought out before training begins.

Though the main objective of the LINK is to enhance training and human resource development, the

VISION 2020 LINKS USA

The first two LINKS established in the US – between the Rwanda International Institute of Ophthalmology (RIIO) in Kigali, Rwanda, and Wills Eye Hospital, Philadelphia, Pennsylvania, USA; and between Addis Ababa University (AAU) in Ethiopia and Emory University in Atlanta, Georgia, USA – are good examples of how LINKS work.

Before 2017, Rwanda didn't have an ophthalmic residency program, so any physician wishing to practice ophthalmology had to travel out of the country for training. Under the leadership of Ciku Mathenge at RIIO and Brad Feldman and Brenton Finklea at Wills Eye Hospital Center for Academic Global Ophthalmology (CAGO), RIIO and Wills both came to SEE International and expressed an interest in a LINK. RIIO had started the first ophthalmology residency program in Rwanda, and they expressed an interest in their Needs Assessment with residency program development, diabetic and cataract tracking programs, research development, and low vision. From here, Steering Groups were formed, site visits made, an MoU and three-year Activity Plan developed. Funding was found (facilitated by SEE International), and an evaluation of the program is ongoing. The three-year action plan can be seen in Table 1, with a more detailed description of ongoing activities in Table 2.

The second VISION 2020 LINK USA is currently forming between AAU and Emory University under the leadership of Sadik Taju of AAU and Jacquelyn O'Banion of Emory. This partnership's Needs Assessment is focusing on a retinopathy of prematurity (ROP) screening program and a diabetic retinopathy (DR) screening program. As most travel has

Year 1 (July 2018 -June 2019)	Year 2 (July 2019 -June 2020)	Year 3 (July 2020 -June 2021)
1. First-year training document for residents completed	1. Second-year training document for residents completed	1. New class of RIIO residents (year 1-3 curriculum defined)
2. Wills faculty assigned to RIIO residents as mentors	2. RIIO directors to Wills Eye Hospital for curriculum delivery and plans	2. Clinical rotation with Kibuye, Burundi (safety permitting)
3. CAGO fellows visit RIIO to assist with program development	3. MSICS course held in RIIO	3. CAGO fellows visit RIIO to ensure residency set in place
	4. RIIO residents visit Wills Eye for course	4. Review and revise MoU for next three-year cycle
	5. Wills steering committee visit RIIO for project review	

Table 1. RIIO/Wills Eye Three-Year Activity Plan

CAGO fellow March 2018	CAGO fellow visit December 2018	CAGO fellow visit February to March 2019	CAGO fellow visit February 2020
Introduction to clinical skills and diagnostic testing workshop.	Introduction to oculoplastics didactics + exam.	Worked with John Cropsey to educate Ophthalmic Technicians.	Review session for upcoming ICO exam.
Clinical introduction in neuro-ophthalmology.	Clinical skills: gonioscopy and Goldmann applanation tonometry.	Developed lecture series for review of the ICO examination at RIIO.	Provided lectures on various basic science topics and daily sets of practice questions.
Suturing course for residents.	MSICS and suturing.	CAGO fellows visit RIIO to ensure residency set in place.	Fellow provided one-on-one clinical skills development with new class of first year residents.
Residents and the fellow participated in a cataract outreach in which residents were shown how to perform retrobulbar and peribulbar blocks as well as the basic preparatory / sterile techniques of the OR.			

Table 2. RIIO/Wills Eye Academic Activities

been disrupted by the recent COVID-19 pandemic, this LINK is expected to grow in the near future. Currently, Emory is continuing to support AAU resident education through the development of an online lecture and grand rounds database providing AAU residents and faculty access

to the same educational activities as Emory residents. Additionally, Emory continues to support Ethiopian residency education with the annual ICO review course. Once COVID-19 permits travel within and between countries, ROP and DR LINKS activity will resume.

LINK partnership should ideally enable leveraging of governmental and non-governmental organizations to help in the purchase or donation of equipment and supplies. The funding of the initial Needs Assessment visit is done with the help of the VISION 2020 LINKS Program. Afterwards it is the responsibility of the institution to fundraise. A Toolkit makes the case for fundraising and the importance of the LINKS program, and it also explains whom to ask and how (3).

There are different ways of thinking about the lack of ophthalmologists in the world. One is through the patient perspective. A patient with avoidable blindness in this world still goes blind even if there is the best treatment in the world for the condition exists, but there is no ophthalmologist available to give that care. This blindness has many consequences: it impacts on income, quality of life, and can even bring early death. That is a harsh reality for someone with a condition as curable as a cataract. Another perspective is from the doctor. There are doctors in low-resource settings taking care of all the glaucoma, cataracts, pediatrics, macular degeneration, glasses, and trauma for a population of one million people. That is a very, very heavy burden to carry. "Train more ophthalmologists!" is easier said than done, but it is the goal of the VISION 2020 LINKS Program to alleviate this burden for the patients and to support institutions that train ophthalmologists where the shortages are most severe. To learn more about putting your institution to work to alleviate global blindness, please visit the websites of SEE International in Santa Barbara, California, and the International Centre of Eye Health in London, UK.

M. Scott Hickman is a Volunteer Professor of Ophthalmology at the



Figure 3. RIIO residents taking their first International Council (ICO) examination (all passed!).

University of Kansas, and the Medical Director of Ad Astra Eye in Lawrence, Kansas, and SEE International in Santa Barbara, California, USA.

Randal Avolio is the President and CEO of SEE International in Santa Barbara, California, USA.

Brenton Finklea is a cornea specialist and Director of the Wills Eye Hospital Center for Academic Global Ophthalmology, Philadelphia, Pennsylvania, USA.

Ciku Mathenge is Professor of Ophthalmology at the University of Rwanda and Director of the Rwanda International Institute of Ophthalmology in Kigali, Rwanda.

Jacquelyn O'Banion is an Assistant Professor of Ophthalmology and Director of Global Ophthalmology at Emory University and received a Master's degree in Public Health for Eye Care at the London School of Hygiene & Tropical Medicine, in London, UK.

Sadik Tajou is Assistant Professor

of Ophthalmology at Addis Ababa University and Head of Pediatrics and Strabismus at Menelik II Hospital, as well as lead investigator for retinoblastoma in Ethiopia.

Marcia Zondervan is Assistant Professor at the London School of Hygiene & Tropical Medicine and is the VISION 2020 LINKS Programme Manager, in London, UK.

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Chhaya and Chhavi Tiwary. Images were taken before the start of the COVID-19 pandemic.

Side by Side

How twin sisters are breaking barriers to save sight in rural India

Fifteen years ago, Mrityunjay Tiwari, working in the rural state of Bihar in India, saw a pressing need for local ophthalmic care – in other words, a clinic, staffed with trained healthcare workers – as well as an urgent need to help young girls with limited opportunities to gain education. In December 2005, Tiwari founded the Akhand Jyoti Eye Hospital (www.akhandjyoti.org) in Mastichak Village in Bihar, starting with just 10 beds. The hospital grew to 350 beds and now performs around 65,000 surgeries each year, with 80 percent of those offered to patients free of charge.

The hospital eventually entered into a long-term partnership with the international eye care charity, Orbis and, in 2019, was able to start a successful pediatric eye center – Children’s Eye Centre – the only such clinic in Bihar with a comprehensive pediatric screening program. The partnership also enabled access to training in pediatric eye care.

Tiwari decided to use the hospital as a platform for bringing wider societal change, addressing the community’s attitudes towards girls’ and women’s capabilities in a state where only 52

Chhaya Tiwary

Chhaya is a keen soccer player and an eye care professional. She was trained in low-vision rehabilitation at Dr. Shroff’s Charity Eye Hospital in Bihar. She says, “I provide rehabilitation for patients whose low vision cannot be improved, even after surgical intervention.”

Just two weeks after finishing her ophthalmic training, Chhaya approached the Akhand Jyoti Eye Hospital, single-handedly set up a clinic, and put together a team to provide low-vision rehabilitation services to adult and pediatric patients, including women and girls. During the COVID-19 pandemic, patient flow to the clinic has been reduced, but Chhaya is confident that operations will be back to full capacity when possible.



percent of women are literate – the lowest literacy rate in India.

The hospital started a vocational training program, combining eye health education with soccer practice, that allowed girls and young women to showcase their drive, ambition, and soft skills. The vision was

“Professional careers seemed unachievable to the two girls who were brought up by their grandmother.”

to empower underprivileged girls, bringing about gender equality and fighting against dowry, domestic violence, and economic inequality. The program stipulated that parents/guardians would allow girls to play soccer and agree not to marry them before they turn 21 years old. In exchange, young women would receive an eye care education, with the opportunity to become optometrists or junior doctors. As Tiwari has noted in the past, when patients receive eye care and ophthalmic referrals from qualified young women, it sends a strong message in a patriarchal society.

The sisters

Twin sisters Chhaya and Chhavi Tiwary were born in 1997 and grew up in a small village in rural Damodarpur, Bihar, without electricity or drivable roads. Every day, they walked three miles to and from school. Professional careers seemed unachievable to the two girls who were brought up by their grandmother – that is until they enrolled in the Akhand Jyoti Eye Hospital’s educational program. They graduated as optometrists alongside 11 other young women.

To watch a film detailing the sisters’ early life story, as told by them and their grandmother in 2019, go to www.akhandjyoti.org/stories-that-inspire/removing-blindness-of-the-mind.

The film shows the unimaginable barriers they had to overcome – including their father, vehemently opposed to female education, and a family tragedy – as well as their goal to eradicate avoidable blindness from Biha

Follow Chhavi Tiwary’s Twitter account @ChhaviTiwary to see the work she’s doing in Bihar, India.

For more information visit www.orbis.org.uk or @ukorbis on Twitter.



Chhavi Tiwary

Like Chhaya, twin sister Chhavi also trained in eye care and plays soccer. She attended paediatric counseling training at Dr. Shroff’s Charity Eye Hospital.

“I was the first candidate for the training in paediatric counseling at Dr. Shroff’s,” she says. “I learned that it is very important to build rapport with the patient while counseling them, explain the underlying causes [of their sight loss], and to provide necessary counseling. Initially, it was difficult for me to convince them the eye care worked [due to a lack of understanding about the effectiveness of surgery]. But now I can motivate the parents of child patients to have surgeries.”

A lack of access to eye health is an issue in many low-to-middle income countries, and Chhavi has been involved in outreach to rural communities; she comments, “I go to the field, identifying and counseling children and parents for surgical interventions.”

She recalls a home visit to see a child after an operation and remembers the child being gleeful to be able to look at the clear blue sky.

Chhavi says, “This training helped me understand the softer side of counseling, which helps me bond with people I am helping. I feel happy when I see someone, an adult or child, and they are back in the hospital for surgery after counseling.”

The Negotiation Game

The secret to a successful contract negotiation – according to doctor, lawyer, and founder of MDNegotiation Lisa Nijm

By Phoebe Harkin with Lisa Nijm

So, you aced your job interview and are offered a contract. You start reading and realize the terms are less than perfect. Maybe it's the salary, maybe it's the number of sick days; either way, you are not completely sold. Still, you want the job – so what do you do? You negotiate. But this is where it gets tough. How do you know what to push back against and what to accept? When to compromise and when to walk away? Lisa Nijm has (most of) the answers. Maybe because she is a rarity in the world of ophthalmology, holding the dual title of doctor and lawyer. Nijm has lectured on contract negotiation at over 40 residency programs across the country, and held workshops at some of the largest meetings in the US. In 2020, after seeing colleagues struggle with the fallout of negotiated contracts, she created an online resource for physicians to help them learn how to become better negotiators: MDnegotiation.com.

“My goal is not just to teach you how to negotiate one contract, but how to negotiate altogether, so you can utilize those skills in any scenario; low stakes or high,” says Nijm. “Negotiation skills are life skills. They aren't just for your first work contract; they are something that can be helpful throughout your career – and the rest of your life.” We ask Nijm for her tips on a successful contract negotiation,



Lisa Nijm

ask how young ophthalmologists can leverage their skills, and find out when to negotiate and when to walk away.

How do you become a good negotiator?

The truth is nobody is born a great negotiator, but you can learn how to become one. I like to think of negotiation as a muscle – and, like all muscles, you need to work it to make it stronger. Whether you realize it or not, you are negotiating on a daily basis. With your patients, your staff, your kids. It seems strange that we spend so long training on the medical side of practice, but receive little to no education regarding the business and legal aspects of medicine. This deficit puts us at a major disadvantage when it comes to high stakes negotiation, such as employment contracts.

What makes a successful negotiation?

Negotiation is fundamentally about building relationships. Many people think of negotiation as contentious – for me to win, someone else has to lose – but, in reality, the best negotiations occur when take the time to communicate and form a relationship. The first step of the process is understanding what the other party is looking for to come to an agreement. And as we grow our communication skills and learn how to be more attentive to the other party's needs on a more routine basis, those skills will become more natural to us as we enter into higher stakes negotiation. No ophthalmologist would go into surgery operating on the toughest monster of a cataract without having done cataract surgery previously; you would practice before you went onto something harder. That's exactly what I wish to teach physicians in regard to negotiation – learn these skills, practice, and build them so you are ready when it really counts. This is actually one of the reasons why younger ophthalmologists may have difficulties when starting out, because that job offer will often be their first high

stakes negotiation. To be successful, you want to have sharpened those skills over the years in low stakes scenarios in order to have developed the knowledge and the confidence needed to succeed when it becomes serious. In my negotiation workshop, I teach ophthalmologists the logical thought structure and process that they need to utilize to define your goals and come together with another party to reach an agreement.

What's the most common mistake people make when they enter these conversations?

Not going in prepared. By that I mean, not understanding how to position yourself in the negotiation. You need to be prepared with not only what your goals are, but with an understanding of what the other party's goals are. You have to evaluate the negotiation from all sides.

The second mistake is not looking at the bigger picture. You're not going to be able to get everything you want in a negotiation, so try to figure out how you can negotiate your wants as a package – rather than a single figure – that will make your offer more attractive to the other party. It's easier to reach an agreement on a package than a point.

Research has found that women are less likely to negotiate salary when applying for jobs. Do you think women tend to fare worse in contract negotiations?

The concept of women negotiators is really interesting. Research from the Harvard Business Review found 20 percent of women never negotiate and just accept whatever is on their contract. As a result, they end up earning anywhere from \$650,000 to \$1,000,000 less on average over the course of their career. Studies have come out as to why women don't give themselves enough credit in negotiation. Some of it has to do with skills, some to do with the perception that women have of

themselves, and some the external factors working against them. Because of this, women need to be especially cognizant of any factors that may affect the environment in which they're negotiating, and figure out ways to work around those. This is so common that I teach a specialized workshop for women negotiators that focuses on identifying these factors, overcoming counterproductive actions and boosting emotional intelligence.

What are your top tips for a successful negotiation?

Preparation is key. The majority of the negotiation occurs well before you even receive the final written contract; it starts at the interview. When you talk to a prospective employer, it is important to identify which areas they consider important to see if there is commonality with your own. How do you do that? By doing your research, coming prepared with the appropriate questions, and defining your goals; after all, if you don't, someone else will define it for you. But these questions don't mean anything if you don't listen to the answers. Too often we get caught up in what we're looking for and forget that, for an agreement to work, both sides have to have a vested interest in the outcome. Always be willing to hear the other side.

What should a prospective employee be looking out for?

Research has found that the top three areas young ophthalmologists regret not negotiating more is salary, vacation, and call schedule. I would highly suggest coming in with an idea of what the practice is like, what their expectations are of you, what they've looked for with past associates, what the typical call schedule is, and what the vacation package is like. On your part, go in with an understanding of your desired salary range and what is typically being offered in this area for some of these other benefits as well, because



there are many things in a contract that can make or break how happy you are day-to-day.

Are there any benefits that make up for potential loss in salary?

Yes, but the extent to which you are comfortable with that depends on your personal goals. To give an example, a colleague of mine once signed a contract that gave her zero sick leave. That meant anytime she was ill, she had to make up those hours by taking a vacation day or working a 70-hour week, which was a huge stress on her. I can understand how this happens. After so many years of schooling and so much debt, we often feel so lucky to have a well-paying job that we focus less on the other factors that come into play. And that's not to say you should downplay salary – it is certainly important – but, when you are in practice, other factors can make a big difference as to whether you are satisfied or not. It comes down to feeling

that you are being paid what you are worth. You can find data on average salaries from recruiters, residency programs, or online sites like doximity.com. You can also ask alumni to get an average range, taking into account location and subspecialty; that way you can get an idea if they are making a fair offer. Not every practice is trying to lowball you. So, if they are making you a fair offer, how much more would you expect a candidate to negotiate if you were on the other side of the table?

When do you compromise and when do you walk away?

Good question. That comes down to your BATNA – your Best Alternative To a Negotiated Agreement. The stronger your BATNA, the greater your ability to walk away from a negotiation. Again, you have to determine for yourself what you are willing to compromise on. Having other offers will give you more confidence to adjust your negotiation plan.

Pay discussions are often framed as inherently difficult. Do you have any tips on making it feel more positive for both parties?

First of all, get used to the idea that discussions on salary are expected, so shake off the negative associations you may have around money conversation. This is business and negotiations are an appropriate and expected part of that. The other thing is to remember that it is a team discussion. Bringing on new associates is expensive for practices, so they want you to want to be there – and if it is the right practice for you, let them know. When discussing salary, preface it by saying what you can bring to the practice, and how you can help it grow. Think of it as taking a more communal strategy than an individual one, with understanding that if all this works well, you are going to be on the other side of the table at some point interviewing some new associate in the exact same position. It helps to make it a positive experience for everyone involved.

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Any tips for overcoming negotiation anxiety?

The first step is recognizing your value. You would not be in this position unless you had something the other party is looking for, so don't underestimate yourself. The second thing is practice. I say this a lot, but the more you implement your negotiation skills, the more confident you will become – to the point your nervousness will go away. You have the tools that you need to be a great negotiator, and you will be with proper education and practice.

What can a newly qualified ophthalmologist bring to a practice?

A lot – so leverage your skills! Most young ophthalmologists have the advantage of having trained with cutting-edge devices, which is a huge benefit to practices that have not adopted these new technologies yet. The other thing you have to offer is you – and that's where personality can play a big part. Are you a "somebody" who is going to work hard, stay late to see patients, and be happy to come in on the weekends? For the first six months to a year when you start with a new practice, you are under a microscope. If you really want to put your best foot forward, you need to show the practice that you are going to do your best to help build your practice and in turn, help the overall practice survive, thrive, and grow.

What areas of the contract should young ophthalmologists focus on?

The role, the salary, the benefits, and the exit strategy. In any contract, you should have a good understanding of what the expectations are going to be for what you're getting in return. Part of that is knowing what will happen if things don't work out. Your first job might not be your last, so it's worth looking into things like restrictive covenants and tail coverage for malpractice insurance. Likewise, if the job does go the way you planned and you want to become a partner, you will also need to have an idea of what the transition from being an associate would

be like (typically two separate agreements in the US). Many residents tend to go back to their hometown, and bring their family. The kids move to a new school, everybody starts to get settled, and then something doesn't work out with the practice. If that's the case, is the contract written in a way that you are able to stay there or do you have to move? If you've done your due diligence, it may not work out that way – hopefully you end up on the partnership track – but, if not, you have to be aware of what could happen. It pays to think long-term.

Outside of financial gain, what are the advantages of being a better advocate for yourself and for others?

When somebody is a good negotiator, you end up with not only financial success, but with success in informing the long-lasting relationships that will help you along in your career. When parties are able to come together in an agreement – and base that agreement in a relationship of trust and understanding and confidence, you can work together to achieve mutual goals. And that goes a long way. You'll not only achieve financial success, but you'll be able to achieve happiness in your practice in understanding how to work with patients to get them to comply with care, so that they have better outcomes. It also makes it easier to keep your employees satisfied so that you are working together as a team to provide the best care for your patients. Becoming a better communicator and working out how to negotiate in a way that brings parties together – not apart – is equally beneficial in your personal life.

If you could give one piece of advice, what would it be?

Remember, negotiation is a muscle; you build it with practice. Take action and ownership of that skill. Invest the time in learning and practicing in an environment that's comfortable, so that you feel confident in your skills by the time you get to a high-stakes scenario.



Just for the Record

Five reasons you should care about your EHR system

By Jason Handza

It has been more than a decade since the US government introduced Meaningful Use legislation and the subsequent rush to implement electronic health records (EHRs). At this point, use of the technology is nearly ubiquitous across the field of ophthalmology. However, just because a practice has an EHR doesn't mean the system effectively supports the organization's strategic goals around quality, efficiency, and patient satisfaction. EHRs have evolved dramatically in recent years, and the system you bought over 10 years ago may no longer be fully meeting your needs today – whether you know it or not.

Here, I explore five areas where your

current system may be underperforming – and share how more sophisticated solutions may offer opportunities to improve.

Enabling documentation specificity
In the haste to onboard EHRs, specialty practices, including ophthalmologists, often opt for “off-the-shelf” solutions that are readily available for implementation. Unfortunately, generic ambulatory EHRs contain a great deal of information that is not relevant to ophthalmology. Even more problematic, these solutions don't contain critical information that ophthalmologists do actually need, including condition

lists and protocols. And that can cause physicians to spend critical time during the patient visit searching for information to document the episode, distracting them from the patient, causing frustration, and resulting in a less-than-optimal patient experience.

However, when an EHR is designed with ophthalmology in mind, it can deliver the detail needed without all the extraneous information. Going a step further, if the EHR uses adaptive template technology, it can generate pick lists that include only relevant choices based on patient history and problem lists, filtering out options that don't apply and eliminating findings



“However, when an EHR is designed with ophthalmology in mind, it can deliver the detail needed without all the extraneous information.”

that are not pertinent to the patient. When an EHR is customizable with templates and drop-down menus that can be tailored to provider preferences, it can boost efficiency even further. Robust technology, such as auto-

complete drawings of the eye based on exam findings, can also expedite this cumbersome aspect of ophthalmology documentation.

Ensuring robust data collection
A primary function of an EHR is to collect data, so when a solution falls short in this regard, it may limit opportunities for your practice. Conversely, when solutions are designed to capture the full detail of a patient encounter and identify when required content could be missing, it can support better quality reporting and stronger reimbursement. For example, with detailed data, your practice can determine whether you’re submitting the optimal quality measures for MACRA or whether there are others that better reflect practice performance. Once you determine the measures you want to send, real-time regulatory performance monitoring can identify whether a patient qualifies for those measures and then present you with data fields related to those measures during the patient encounter. In other

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words, you can collect the appropriate information while the patient is still in the room. Greater specificity can also yield more comprehensive coding, which is key to demonstrating medical necessity and receiving suitable reimbursement.

Fostering greater mobility

Over the last 10 years, there has been an explosion in cloud-based technology, which offers several benefits over traditional hosted options (where software is installed on a server located in the practice office). For example, cloud-based solutions offer the latest software features and functionalities without having to go through onerous upgrades. A vendor can make changes in the cloud and, when you next log into the system, new features are immediately available for use. And, of course, cloud-

based solutions also support greater access from any location. Providers that have multiple locations can travel freely between sites and have immediate access to patients' medical records without losing information in transit. Physicians can also respond to patient needs more quickly if they receive an urgent call outside of regular business hours, using laptops or mobile devices to securely access the system.

Elevating the patient experience

More than ever, patients want a service-focused healthcare experience, and they are willing to spend time seeking out those providers who deliver it. What does that look like for patients? Straightforward appointment scheduling, limited wait times, efficient appointments, and easy access to providers outside of office visits.

The Big Five

Five key areas where a new EHR could help improve performance

- Greater documentation efficiency and specificity
- Robust data capture for better quality reporting and stronger reimbursement
- Enhanced mobility for practices on the go
- Elevated customer experience with greater convenience and access
- A stronger referral pipeline to grow the practice over time



Traditional EHRs can struggle to enable such convenience, resulting in a suboptimal patient experience.

Modern options, however, can streamline patient access, allowing individuals to schedule appointments easily and check in remotely. They can also facilitate a connected care experience, with portals fostering more communication outside of the appointment and embedded telehealth solutions that support remote care for patients who are unable to visit the office. These EHRs can also help ease the payment process, allowing patients to make payments at the point of care or via their phone or tablet. When payment solutions are integrated with the EHR and practice management system, providers begin to offer services that not only drive patient payment but also increase satisfaction.

“Traditional EHRs can struggle to enable such convenience, resulting in a suboptimal patient experience.”

Strengthening the patient pipeline
For ophthalmologists, a solid referral network is critical to maintaining a thriving practice. The right EHR can nurture these relationships, helping you identify where referrals are coming from and then efficiently sharing information in a HIPAA-compliant manner to facilitate greater collaboration and ensure care continuity. You can also use referral data to uncover areas of opportunity to expand the practice, focusing marketing and communication efforts on referral sources that have the most potential for growth.

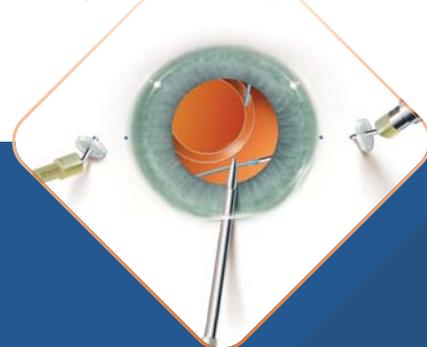
Recognizing the problem is the first step
If you want to stay competitive in today’s healthcare marketplace, merely having any old EHR is no longer good enough. Practices that acknowledge and address the disconnect between current functionality and what patients expect, need or deserve in the short and long term will be the first to embrace more efficient, higher-quality, patient-centric care – and the most likely to succeed.

Jason Handza is a vitreoretinal surgeon and Chief Medical Officer for Nextech. He is based in Trinity, Florida, USA.



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A professional headshot of Erin Shriver, a woman with long dark hair, smiling warmly. She is wearing a dark grey blazer over a black top and a gold necklace with a blue gemstone. The background is a plain, light grey color.

From Empowered to Empowering

Sitting Down With... Erin Shriver, Clinical Professor,
Jim O'Brien Gross and Donnita Gross Chair in
Ophthalmology Department of Ophthalmology & Visual
Sciences, Oculoplastic, Orbital and Oncology Service,
University of Iowa Hospitals and Clinics, Iowa City, USA

What sparked your interest in medicine?

When I was in junior high, I took a summer anatomy course at the University of California, Berkeley taught by medical students. They had completed their anatomy dissection course and shared a cadaver with us. I was hooked. The course really ignited my passion and appreciation for the human body. It was also my first opportunity to meet people of the same age who wanted to be physicians and it made me think that maybe I could be a doctor too.

Why did you decide to pursue a career in ophthalmology and oculoplastics in particular?

One patient changed my career path in medicine. As a third-year medical student, I was headed to a future in sports medicine until I observed the preoperative counseling for a middle-aged woman who was undergoing an orbital decompression for thyroid eye disease (TED). The otolaryngologist showed her a look book of pre-operative and post-operative photos and I was able to observe the remarkable transformation of this restorative procedure. I was first assistant on her surgery the next day with the otolaryngologist and an ophthalmologist. I knew I enjoyed working with women from my research experience with the Women's Health Initiative and, after that clinic and surgery experience, I decided I wanted to commit my life to helping TED patients (who are mostly women). I attended an International Ophthalmology Conference through the Proctor Foundation and decided ophthalmology was the perfect fit for me.

How has the field changed over the course of your career?

The growth of aesthetics within oculoplastics has been particularly pronounced. The technologies and principles available to us are helping both

our aesthetic and functional patients. My initial passion for thyroid eye disease (TED) has been reignited with the recent FDA approval of teprotumumab, a monoclonal antibody therapy which has dramatically changed how we treat TED patients. When I finished fellowship, I got involved with a Graves' disease support group and built a large TED practice, but I soon became frustrated with waiting and watching while the disease took its toll on patients. It was only once they were stable that we would typically intervene. I often felt helpless and lost my love for it. Thankfully, I now love seeing TED patients as I have a new tool that allows me to intervene sooner.

You're a passionate champion of women in ophthalmology; where does this come from?

Being a woman wasn't a strong part of my identity through medical school. I never thought that my gender affected me either positively or negatively. Although as a female physician, there are constant reminders from typically older male patients of my gender, it was a particular experience while interviewing for my oculoplastics fellowship that measurably affected my perspective. During an interview, a prospective fellowship preceptor told me: "You are smart and athletic, but I have never taken a woman as a fellow and I do not think I am ready to do so this year." In that moment, I realized that some leaders saw being a woman as a liability.

The person who took the fellowship from that preceptor deserved it – and he, in my opinion, was likely better qualified for the position. Had the preceptor only just said he picked someone else based on their overall qualifications, I would have completely understood. But he didn't – and, in a strange way, I appreciated his honesty because I wouldn't have wanted to work closely with someone for two years that had such strong feelings about women as fellows. Better yet,

“Being a woman wasn't a strong part of my identity through medical school.”

his rejection also steered me toward my fellowship at Bascom Palmer Eye Institute, where I went on to have a large number of amazing women role models.

The preceptor's words also gave me the impetus to attend my first Women in Ophthalmology (WIO) Summer Symposium during fellowship, which ultimately set my career into motion.

What would you consider to be your biggest professional and personal successes?

I am really proud of how much WIO has grown since I first got involved with leadership in the organization in 2012. I feel fortunate that so many other people are able to experience everything that I love about the organization. I am also extremely proud of my nine- and 11-year-old sons – and the young men they are becoming. My husband and I are thoroughly enjoying being parents and seeing them thrive in so many ways.

Who, outside of the scientific community, has been your biggest inspiration?

My aunt, Sandy Barbour, the Athletic Director at Penn State University. She is one of the few women Athletic Directors at a Division 1A university. She has demonstrated to me that if you love what you do and you throw yourself into it, you will be successful no matter what barriers you face.



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References: 1. Omeros survey data on file. 2. OMIDRIA [package insert]. Seattle, WA: Omeros Corporation; 2017. 3. Al-Hashimi S, Donaldson K, Davidson R, et al; for ASCRS Refractive Cataract Surgery Subcommittee. Medical and surgical management of the small pupil during cataract surgery. *J Cataract Refract Surg.* 2018;44:1032-1041.

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