FEBRUARY 2020 # 41

the Ophthalmologist™

Goodbye, Dry Eye?

Experts in ocular surface disease present their solutions to a burning issue.

OMIDRIA now has a unique permanent J-code (J1097)[1]

Less stress, pure success ...in your O.R. day[2]

OMIDRIA® (phenylephrine and ketorolac intraocular solution) 1% / 0.3% is added to ophthalmic irrigating solution used during cataract surgery or intraocular lens replacement and is indicated for maintaining pupil size by preventing intraoperative miosis and reducing postoperative ocular pain.

The data are compelling and consistent—OMIDRIA makes cataract surgery better for you and your patients

Published and presented clinical data and manuscripts in preparation report that in post-launch (i.e., not included in current labeling), prospective and retrospective, double-masked and open-label, cohort and case-controlled, single and multi-center studies, the use of OMIDRIA statistically significantly:

- Prevents intraoperative floppy iris syndrome (IFIS)[3]
- Prevents iris prolapse[3]

Compared to steroids*:

- Reduces cystoid macular edema (CME)[4,5]
- Decreases breakthrough iritis[4]
- Reduces pain photophobia[4]

*OMIDRIA used intraoperatively with postoperative NSAIDs (no steroids) when compared to postoperative steroids with or without NSAIDs (no OMIDRIA).

Compared to epinephrine:

- Decreases complication rates[6]
- Decreases use of pupil-expanding devices (PEDs)[6-11]
- Enables performance of surgery and postoperative care without the use of steroids—allowing NSAID-only anti-inflammatory therapy[4,5,7]
- Shortens surgical times[6,7,9,10]
- Reduces need for opioids (i.e., fentanyl) during surgery while decreasing VAS pain scores[12]
- Prevents miosis during femtosecond laser-assisted surgery[11,13]
- Improves uncorrected visual acuity on day after surgery[6]

VAS = visual analog scale

OMIDRIA inhibits the release of inflammation-causing prostaglandins, preventing miosis and reducing postoperative pain[14]

OMIDRIA is separately reimbursed under Medicare Part B and by many Medicare Advantage and commercial payers.† Contact your OMIDRIA representative today or visit omidria.com to learn more.

†Based on currently available information and subject to change without notice. Individual plan coverage, payment, policies, and procedures may vary and should be confirmed by the facility. Omeros does not guarantee coverage or payment.

IMPORTANT SAFETY INFORMATION

OMIDRIA must be added to irrigating solution prior to intraocular use.

OMIDRIA is contraindicated in patients with a known hypersensitivity to any of its ingredients.

Systemic exposure of phenylephrine may cause elevations in blood pressure.

Use OMIDRIA with caution in individuals who have previously exhibited sensitivities to acetylsalicylic acid, phenylacetic acid derivatives, and other nonsteroidal anti-inflammatory drugs (NSAIDs), or have a past medical history of asthma.

The most commonly reported adverse reactions at ≥2% are eye irritation, posterior capsule opacification, increased intraocular pressure, and anterior chamber inflammation.

Please see the Full Prescribing Information for OMIDRIA at www.omidria.com/prescribinginformation.

You are encouraged to report Suspected Adverse Reactions to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

References: 1. HCPCS quarterly update. CMS.gov. Available at: https://www.cms.gov/medicare/coding/hcpcsreleasecodesets/hcpcs-quarterly-update.html. Accessed August 9, 2019. **2.** Omeros survey data on file. **3.** Silverstein SM, Rana V, Stephens R, et al. Effect of phenylephrine 1.0%-ketorolac 0.3% injection on tamsulosin-associated intraoperative floppy-iris syndrome. *J Cataract Refract Surg.* 2018;44(9):1103-1108. **4.** Visco D, et al. Study to evaluate patient outcomes following cataract surgery when using OMIDRIA with postoperative topical NSAID administration versus a standard regimen of postoperative topical NSAIDs and steroids. Presented at: 28th Annual Meeting of the American College of Eye Surgeons (ACES), the American Board of Eye Surgery (ABES), and the Society for Excellence in Eyecare (SEE), Caribbean Eye Meeting; February 1-5, 2019; Cancún, Mexico. **5.** Walter K, Kauffman L, Hess J. Rate of pseudophakic cystoid macular edema using intraoperative and topical NSAIDs alone without steroids. Manuscript submitted for publication. 2019. **6.** Rosenberg ED, Nattis AS, Alevi D, et al. Visual outcomes, efficacy, and surgical complications associated with intracameral phenylephrine 1.0%/ketorolac 0.3% administered during cataract surgery. *Clin Ophthalmol.* 2018;12:21-28. **7.** Al-Hashimi S, Donaldson K, Davidson R, et al. Medical and surgical management of the small pupil during cataract surgery. *J Cataract Refract Surg.* 2018;44:1032-1041. **8.** Bucci FA Jr, Michalek B, Fluet AT. Comparison of the frequency of use of a pupil expansion device with and without an intracameral phenylephrine and ketorolac injection 1%/0.3% at the time of routine cataract surgery. *Clin Ophthalmol.* 2017;11:1039-1043. **9.** Visco D. Effect of phenylephrine/ketorolac on iris fixation ring use and surgical times in patients at risk of intraoperative miosis. *Clin Ophthalmol.* 2018;12:301-305. **10.** Matossian C, Teves N. Clinical outcomes of phenylephrine/ketorolac intraocular solution versus epinephrine in cataract surgery in a real-world setting. Manuscript submitted for publication. 2018. **11.** Walter K, Delwadia N, Coben J. Continuous intracameral phenylephrine-ketorolac irrigation for miosis prevention in femtosecond laser-assisted cataract surgery: reduction in surgical time and iris manipulation. *J Cataract Refract Surg.* 2019;45(4):465-469. doi: 10.1016/j.jcrs.2018.11.004. **12.** Donnenfeld E, Shojaei R. Effect of intracameral phenylephrine and ketorolac 1.0%/0.3% on intraoperative pain and opioid use during cataract surgery. Manuscript submitted for publication. 2019. **13.** Gayton JL. Effect of early phenylephrine and ketorolac injection 1% / 0.3% (Omidria®) usage on pupil diameter in traditional and femtosecond laser assisted cataract surgery. E-poster presented at: 15th International Congress on Vision Science and Eye; August 10-11 2017; London, UK. **14.** OMIDRIA [package insert]. Seattle, WA: Omeros Corporation; 2017.

OMIDRIA

(phenylephrine and ketorolac intraocular solution) 1% / 0.3%

Glaucoma: Going the Distance

Through innovative methods of educating, screening and diagnosing the world's population, we can win the battle against glaucoma

I was genuinely excited to hear that The Ophthalmologist team selected Glaucoma Management as a key theme for the first half of 2020. This complex condition has benefited from amazing progress in recent years, but there is still much to do in the prevention of vision loss in glaucoma patients worldwide.

Glaucoma is highly prevalent – and rising (1). Unfortunately, there are significant shortages of skilled doctors in regional areas, who would not only be able to provide a diagnosis, but also the continuity of care that is so essential in glaucoma management.

The emphasis has to be put on early disease detection and comprehensive screening, which demands increased awareness and ongoing education of patient populations, as well as health and social care professionals. We are now able to disseminate information via internet channels, such as YouTube, using specific educational tools. For example, my MIGS University Video Series on the iGlaucoma YouTube channel reaches people in Africa, Asia, Australia and Europe, as well as North America.

Telemedicine and artificial intelligence will inevitably provide a significant advantage, by making use of a healthcare workforce that can screen patients anywhere – and using the data they provide in increasingly effective and novel ways.

Well-established diagnostic methods are not going away anytime soon, but I can see how newer technologies, such as corneal hysteresis, optical coherence tomography angiography (OCT-A) and implantable IOP monitoring devices, can aid in providing more accurate diagnoses. I'm personally excited about the prospect of a diagnostic test that shows retinal cell apoptosis in the optic nerve using fluorescent labeling...

Real innovation – and spreading the word about those advances (as in The Ophthalmologist's Special Series on Glaucoma Management) – will become our most effective weapons in the battle against glaucoma over the next decade and beyond. With all available resources dedicated to initiating conversations at all levels, we can prevent irreversible vision impairment.

Constance Okeke
Glaucoma and Cataract Specialist
Partner, CVP Physicians – Virginia Eye Consultants

SPECIAL SERIES
Glaucoma Management

Reference

1. *National Eye Institute, "Glaucoma Data and Statistics" (2019). Available at: https://bit.ly/30umcr7.*

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On The Cover

Hot, itchy, uncomfortable – dry eye can feel like sand in your eye, as illustrated by this month's dune-inspired cover

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A Hot Topic(al) for DME

Could a novel formulation technology offer an injection-free alternative for diabetic macular edema patients?

About half of all patients with diabetic retinopathy (DR) go on to develop DME. But as those patients will know, current treatment options can present a significant burden, requiring either regular injections or surgery. Moreover, there is a lack of suitable treatments for early DME patients – and a low benefit-to-risk ratio for mild DME sufferers.

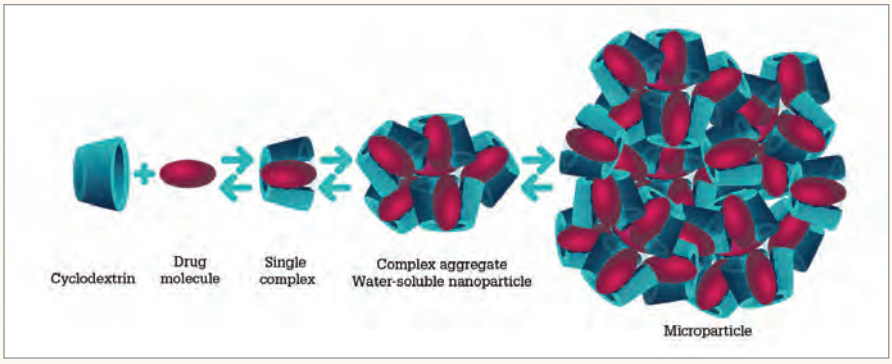
So why aren't there more treatment options for these patients? Well, one of the more obvious options – conventional eye drops – pose a number of hurdles for drug manufacturers, including limited solubility of drugs in such formulations, rapid clearance from the eye, and difficulty delivering drugs to the retina.

Now, a novel formulation approach could help overcome current limitations: solubilizing nanoparticle (SNP) technology.

These complex nanoparticles, which benefit from the unique characteristics of a compound called cyclodextrin, enhance drug solubility in aqueous tear fluid. Typically, the residence time for an eye drop is between two and four minutes – but SNP technology increases residence time to 8 to 12 hours. Moreover, it allows a much higher drug concentration, and the drug–cyclodextrin complexes are able to more easily penetrate the mucous layer of the eye, enabling sustained drug release and increased bioavailability.

In a recent Phase II study, the efficacy of Oculis' OCS-01 – based on SNP technology – was tested for the treatment of DME. The results will be presented at the Angiogenesis, Exudation, and Degeneration 2020 meeting, taking place on February 8, 2020 in Miami, USA. If positive, it could represent a step forward in DME treatment.

"Recently, a lot of the research focus has been on developing injectables, but we really believe topicals are important for DME," says Riad Sherif, CEO of Oculis. "Essentially, the technology gives ophthalmologists another tool in their toolbox, and gives patients another treatment option. We believe that by creating a topical treatment for DME, we can really help doctors to act quickly and improve the vision of patients."



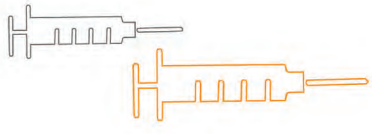
TIMELINE

A Brief History of Botox

A 70-year overview of Allergan's most profitable product

1953
Physiologist Vernon Brooks discovers that botulinum toxin type A blocks the release of acetylcholine causing temporary muscle "relaxation."

1960s
Alan B. Scott, an ophthalmologist, theorizes its muscle-relaxing effects might help in the treatment of strabismus.



BUSINESS IN BRIEF

A round-up of this month's acquisitions, approvals and the beginning of Ophthovation…

Hope for uveitic ME patients
Bausch Health has acquired an exclusive license for the commercialization and development of Clearside's XIPERE (triamcinolone acetonide suprachoroidal injectable suspension) – an investigational treatment for macular edema (ME) associated with uveitis – in the US and Canada. NDA resubmission to the FDA is expected to occur in the first quarter of 2020.

$7.5M grant for glaucoma therapies
Q_BioMed's partner – Mannin Research – has received a $7.5M grant from the German state of Saxony to develop glaucoma therapies. The grant will address the unmet needs of more than 12 million Europeans who suffer from the disease by funding the development of novel pharmaceuticals and biologic treatments for glaucoma.

Implant-free ELT going stateside
ELT Sight has acquired the IP and assets of MLase AG's excimer ophthalmic laser system for glaucoma surgery. Meeting currently unmet treatment needs, the ExTra ELT laser system performs implant-free, microinvasive glaucoma surgery to lower eye pressure. With the system already CE certified, the company plans to begin clinical studies in the US in early 2020.

Eylea competitor gets J-code
After being given the green light from the EMA's main advisory committee, Beovu – Novartis' follow-up to Lucentis for wet AMD treatment– has recently been issued a permanent J-code from CMS. The code, J0179, could enable more timely reimbursement of Beovu and improve access.

The start of Ophthovation
AAO and ASCRS have finalized plans for their Ophthovation business conferences, which aim to advance ophthalmic innovation. In direct competition with the Ophthalmology Innovation Summit (OIS), the meetings will be held every year prior to the annual meetings of each party, with the first planned for May 14, 2020.

The One Percent

Fight For Sight unites the UK's leading ophthalmologists to highlight a severe research funding gap

The UK government has announced it will only invest one percent of grant funding in eye research – despite 20 percent of the population experiencing serious sight loss, drawing blindness in their lifetime. In response, Fight for Sight has joined forces with 12 of the country's top researchers to call for a national plan on sight loss, drawing attention to what is being called, the "1:20 funding gap."

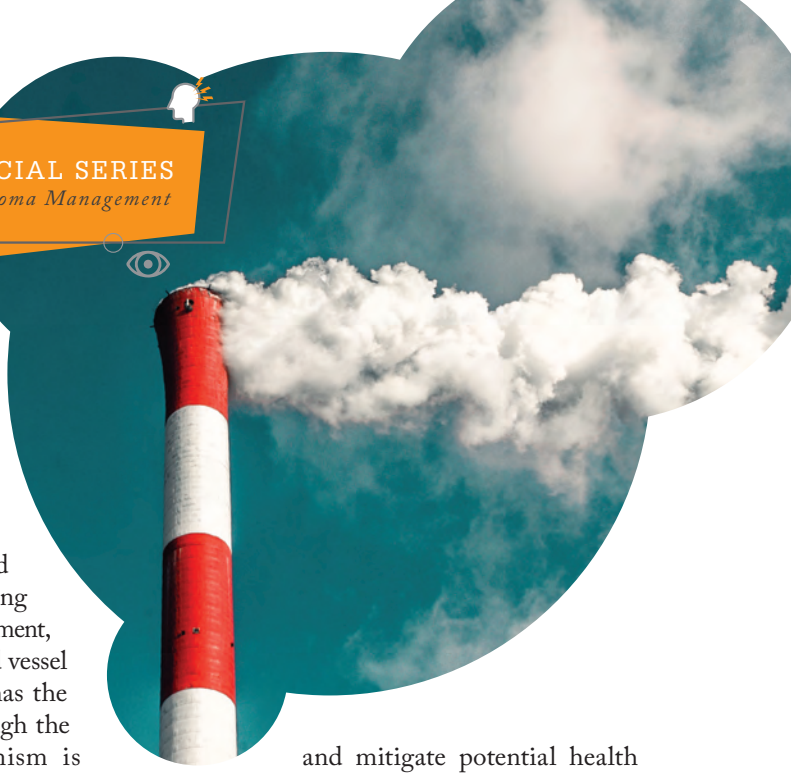
The charity will be conducting a major study this year to determine the economic and personal impact of sight loss, and will use the findings to lobby decision-makers later in the year. Rubina Ahmed, Fight for Sight's Head of Research, calls the gap shameful: "The amount of funding currently is not fit for the scale of the challenge, with hundreds of eye diseases and millions of people affected globally. Science and technology have the answers – the only barrier is the funding to make it happen."

1989
The FDA approves botulinum toxin type A for the treatment of both strabismus and blepharospasm. That same year, Allergan acquires Scott's company and changes the drug's name to "Botox."

1992
Jean Carruthers publishes a paper claiming Botox was "a simple, safe procedure" for the treatment of brow wrinkles.

Today
Botox is now well-known in the cosmetic world and has been used for the treatment of hyperhidrosis, chronic migraine and in pediatric patients with spasticity. Sales of the drug have soared past the $1 billion mark, with cosmetic use accounting for about half of this.

SPECIAL SERIES
Glaucoma Management



Choked Up

Poor air quality is associated with increased risk of glaucoma

Air pollution carries significant health risks: lung cancer, heart disease, acute respiratory infections… but what about glaucoma? A UK study found that those living in neighborhoods with higher amounts of fine particulate matter pollution were 6 percent more likely to have glaucoma than those in less polluted areas (1). The researchers focused on particles less than 2.5 µm in diameter – widely recognized as having major adverse effects on health – in the study of 111,370 individuals. The team compared participants' IOP and macula thickness with the number of toxic particulates reported at their home address, to find the association.

Paul Foster, Professor of Ophthalmic Epidemiology and Glaucoma Studies at UCL and Consultant Ophthalmic Surgeon at Moorfields, who led the study, likens the effect to that of a migraine. "It is well known that migraines increase the risk of developing glaucoma two- to three-fold. This is because they cause spasms in blood vessels in the eye and around the optic nerve – and we believe that pollution may act in a similar fashion," he says. "Glaucoma has two broad mechanisms by which damage is thought to occur: constricting blood vessels and exacerbating inflammation. At the moment, we think that the blood vessel mechanism probably has the greater impact. Although the neurotoxicity mechanism is still rather speculative, there is good reason to believe that this actually does happen."

The findings echo prior studies that found people in urban areas are 50 percent more likely to have glaucoma than those who live in rural areas, which also suggests that air pollution may be a key contributor to glaucoma risk. Though Foster cannot confirm yet that the association is causal, his team plans to continue the research to explore whether air pollution causes glaucoma, studying the short- and longer-term effects of air pollution on ocular blood flow, while trying to understand the toxic effect of micro particles of metals on the retina. He offers this advice to those hoping to reduce their exposure and mitigate potential health risks: "The first step is awareness that air pollution is ranked as the world's number one environmental threat to health. Each of us needs to make choices around transport, heating, cooking, and energy consumption, and try to live cleaner, greener lives. By creating clearer evidence around the risks of pollution, we can hopefully influence national and international policy."

Reference

1. *S Chua et al., "The Relationship Between Ambient Atmospheric Fine Particulate Matter (PM2.5) and Glaucoma in a Large Community Cohort", Invest Ophthalmol Vis Sci, 60, 4915 (2019). PMID: 31764948.*

Written in Blood

Is a simple test for early detection of melanoma in the eye on its way?

Early melanoma detection, both of the eye and skin, can dramatically increase the chances of successful treatment. Unfortunately, nevi at the back of the eye are quite common and tend to mimic early signs of the disease. Now, scientists have discovered microRNA biomarkers in the blood that can differentiate between benign nevi and melanoma, as well as identify whether the cancer has metastasized.

"Our research aimed to facilitate the clinical decision process by providing a simple blood test that will enable monitoring of nevi and reduce the need for intense surveillance," said Mitchell Stark, the lead author of the study from the University of Queensland Dermatology Research Centre, Australia. The test would be used by optometrists, GPs and specialists to monitor biomarker levels in the blood over time and alert them to high-risk patients that may need further tests. The next step is to validate the findings with an independent study and assess the clinical utility of the test.

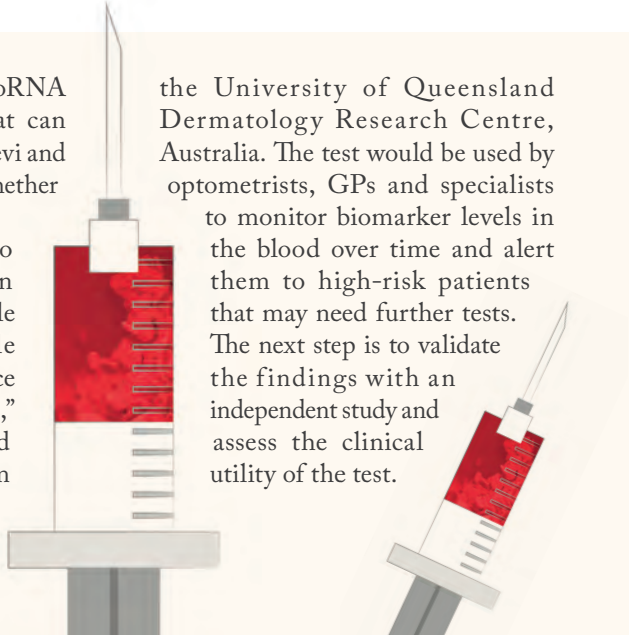
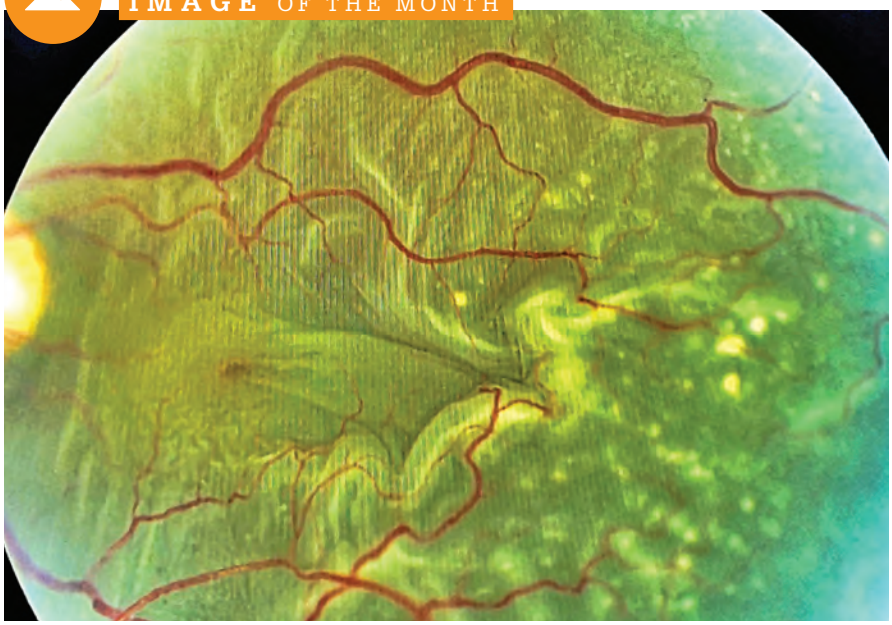


IMAGE OF THE MONTH



The Deep Sea

The image shows a total retinal detachment (RD) with proliferative vitreoretinopathy, which can develop in untreated rhegmatogenous retinal detachment cases, as well as 5-10 percent of patients who underwent RD surgery.

Credit: Sim Sreyneang, Resident of Ophthalmology, University of Health Sciences, Cambodia.

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

QUOTE OF THE MONTH

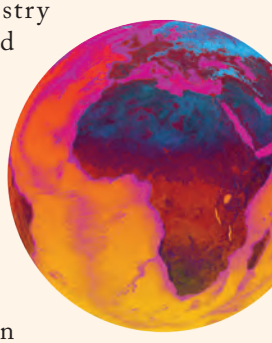
"AI has rightly been compared with electricity in the sense that it will permeate and find applications in essentially all areas of human endeavor, including ophthalmology."

Stephen Odaibo, retina specialist and AI engineer, co-founder of RETINA-AI.

Glaucoma: A Family Affair

Researchers discover the genetic risk factors for POAG associated with African ancestry

Despite the fact that primary open-angle glaucoma (POAG) is more prevalent and has a higher degree of clinical severity among African populations compared with European or Asian populations, individuals of African ancestry remain understudied in genomic research for blindness.



Researchers of a recent genome-wide association study (GWAS) aimed to tip the balance by looking at the association between African ancestry and genetic risk factors for POAG. The study, which included 26,295 participants, found that the amyloid-β A4 precursor protein-binding family B member 2 (APBB2) locus was significantly associated with POAG among individuals of African but not of European or Asian ancestry. If this single-nucleotide polymorphism is validated in more populations, it could have an impact on risk assessment and therapeutic strategies.

Reference

1. *GGLAD Consortium, "Association of Genetic Variants with Primary Open-Angle Glaucoma Among Individuals with African Ancestry", JAMA, 332, 1682 (2019). PMID: 31688885.*

In My View

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

The Sum of Our Parts

Physicians must band together to overcome the current challenges in ophthalmology

By Debbie Osborn, Executive Director of the Connecticut Society of Eye Physicians, the Connecticut ENT Society, the Connecticut Urology Society and the Connecticut Dermatology and Dermatologic Surgery Society, USA.

I've worked with a number of medical societies over the last 20 years, and I've picked up on a recurring theme: quality. In short, it has become an increasingly difficult task to balance quality with cost in healthcare. The USA administration – whether it is headed by Obama, Trump or someone else – makes changes that it believes will ensure healthcare quality, but – in reality – the impact of such changes on physicians across the country is rarely well understood. Time and time again, the administration fails to reach out to the medical community, viewing those within it as simple bystanders. But they are far from bystanders – they are the front line.

In my experience, everybody in healthcare is connected, and if one part of the system goes rogue, it has a direct effect on how physicians practice medicine elsewhere. Unfortunately, in recent years we've stopped trusting medical professionals, and forced them to practice defensive medicine. One example: the introduction of a new electronic medical records program. This particular decision has not only meant doctors have had to learn a whole new system – they now also have to deal with the inevitable: programs failing, which makes it difficult for them to defend their decisions if or when the records come into question. All of this contributes to increasing pressure on physicians, which has led to the high level of burnout and early retirement that we see today. It's great to advocate for patients – and we should certainly continue to do so – but we also need to advocate for physicians because, while they are busy taking care of people, no one is taking care of them.

One key problem that needs to be tackled, both in the medical community and general society, is the move away from being part of a support network or group. Rather than joining forces with those of a similar mindset or in a similar situation, we have become much more focused on individualism. But this simply does not work in medicine, where it's crucial that physicians focus not only on their own specialty, but also consider healthcare in general terms.

Last year, the societies I am involved with testified on more than 40 different pieces of healthcare legislation. We got involved with the opioid crisis, insurance and liability issues, and looked at the impact that these components will have on the healthcare delivery system as a whole. It is through such joined-up approaches that we can really begin to face the current challenges in ophthalmology. I believe it is essential for physicians to belong to some sort of organization – perhaps a society that will fight some of these battles for you, and work to unite people with a common voice.

Thankfully, I am starting to see the rise of medical societies once more, as people begin to realize that they simply cannot do it all alone. I believe it's extremely important for people to have support from a network. Physicians, in particular, need that community and collegiality. They need to know that there are others out there with the same questions and problems. No one can (or should have to) shoulder the pressure alone.

"Rather than joining forces with those of a similar mindset or in a similar situation, we have become much more focused on individualism."

Why Sight Is a Gender Issue

Women are the disproportionate victims of avoidable blindness – but, for that to change, women and girls need to be put at the center of global advocacy work

By Ian Wishart, CEO of The Fred Hollows Foundation, Australia.

Blindness discriminates. Around 20 million women are blind, comprising 55 percent of the global total; however, four out of five lose vision unnecessarily, because they face barriers to seeking the treatment they need. It's easy to see why women are more likely to be blind than men: nine out of 10 live in poverty. Setting aside the significant cost barriers, many women in the world also face cultural barriers and gender discrimination, which all impact on their ability to access the most basic eye healthcare.

In some areas, women can only visit an eye clinic if accompanied by a chaperone. In other instances, men – often viewed as the breadwinners in the family unit – will be prioritized for healthcare ahead of women. Discrimination can be as simple as men pushing in front of women in queues at eye screening camps. Young girls often miss out on school because they are expected to stay home and look after a blind parent or grandparent.

Women are also disproportionately affected by trachoma (the world's leading cause of infectious blindness), accounting for 75 percent of all people diagnosed with advanced cases of the disease. The fact that we have 20 million women blind, with another 120 million visually impaired, is unacceptable. Worse, if we don't act soon, rates of blindness will triple by 2050. We can't afford to stand by and let generations of women bear a disproportionate burden of avoidable blindness.

Through the She Sees initiative, The Fred Hollows Foundation is committed to closing this gender gap in vision – and thus unlocking the potential of millions of women and girls. Restoring sight to women has far-reaching benefits – improving lives and delivering economic returns as girls finish school and women enter the workforce. Through She Sees, The Fred Hollows Foundation is seeking to raise $20 million over the next five years to combat avoidable blindness for women and girls. She Sees places women and girls at the center of programs, services, partnerships, and global advocacy work. These activities must be guided by a clear understanding that all women and girls must have access to eye care, and effectively engage with services.

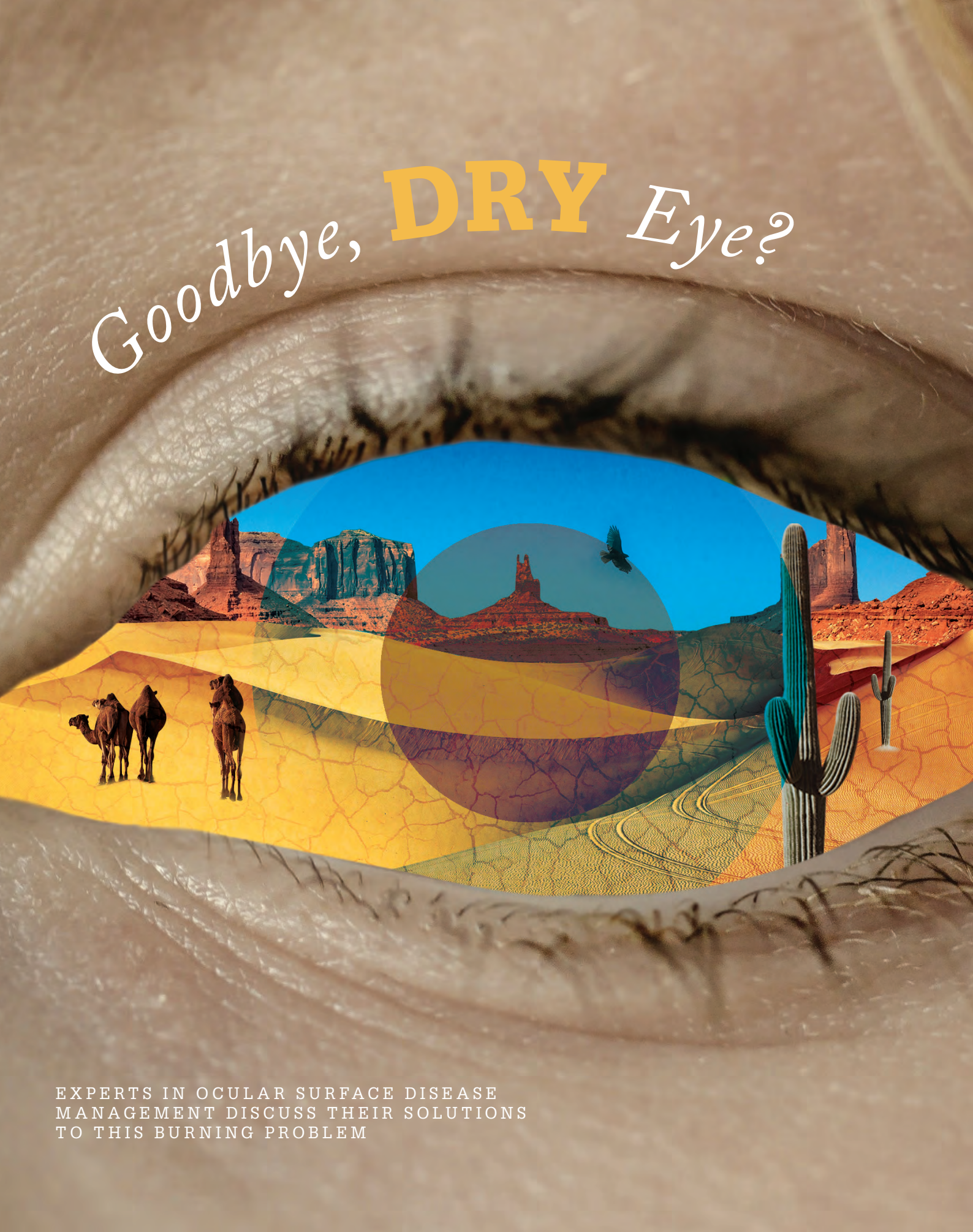
The Fred Hollows Foundation is developing creative programs that specifically target women where they work, and where they live. For example, in Pakistan and Bangladesh, The Foundation is working with local hospitals and health agencies to train outreach health workers who deliver maternal and child health services in eye care. This training allows the workers to find women and children with eye health issues and refer them to local specialist services. The Foundation is also training more women as health workers because, in many regions, women are more likely to access services when they are run by women.

"The fact hat we have 20 million women blind, with another 120 million visually impaired, is unacceptable."

In Bangladesh, there are more than three million women working long shifts in garment factories six days per week. Maintaining an intense focus on repetitive tasks for such long periods of time creates eye health problems. But, if detected early, they are treatable. And so, we have established eye centers at factories, and trained women to help identify colleagues needing eye care.

In Pakistan and Nepal, gender equity programs are already in place. Many female agricultural workers in remote areas of Pakistan injure their eyes while harvesting, so eye care training has been provided for first responders. Taking eye programs to places where women work increases the chances of early detection and ongoing contact with services. In turn, this proactive approach allows women to continue to earn an income and support their children and families. In other words, women's equality in eye care is fundamental to women's equality in life.

Goodbye, DRY Eye?



EXPERTS IN OCULAR SURFACE DISEASE MANAGEMENT DISCUSS THEIR SOLUTIONS TO THIS BURNING PROBLEM

After Dark

Nocturnal lagophthalmos plays a substantial role in dry eye manifestation and treatment outcomes… And it's time we start taking it more seriously.

By Laura M. Periman

For years, dry eye specialists have encountered patients whose symptom severity is conspicuously worse in the morning. In response, we developed practical tips to help patients avoid desiccating stresses at night. These recommendations frequently involve instructing the patient to avoid turbulent air across the faces (fans, AC, forced air heat), allergens and mites. Many of these patients follow our instructions diligently and still wake up dry, inflamed and in pain. Fortunately, in recent years, we've gained important insight into several of the underlying mechanisms contributing to this problem. We have subsequently identified nocturnal lagophthalmos – or insufficient eyelid seal – as a more prevalent and influential compounding factor than previously believed.

ADJUSTING THE ALGORITHMS

Recent research establishes that compromised lid seal – a condition wherein a patient's eye lids remain partially open during sleep – potentially affects up to 79 percent of all symptomatic dry eye patients across diverse demographic groups (1). Interestingly, patients with asymptomatic dry eye show comparatively and significantly less lid seal failure, and the severity of a patient's lid performance failure correlates heavily to the degree of dry eye symptom severity observed. Given this understanding, it is crucially important that we adjust our diagnostic algorithms to identify dry eye and MGD patients with poor lid functionality – those patients who are particularly susceptible to nocturnal lagophthalmos. For these patients, avoiding fans, allergens and other commonplace aggravators simply isn't adequate. When the eyelids' protective biomechanics are insufficient, they leave the ocular surface exposed at night, and desiccating stress is inevitable without a more specific and robust treatment strategy. Proactively addressing this problem is important, as desiccating stress is a known trigger for chronic inflammation leading to chronic dry eye disease (2).

LID LIGHT LEAKAGE

The "Korb-Blackie Lid Leak Test" is a simple and effective way to identify dry eye and MGD patients with insufficient lid seal (3). The test can be carried out in any exam room with basic equipment. In a dark room, gently place a muscle light or transilluminator at the upper tarsus of a closed eye and direct the light toward the interpalpebral fissure. If light escapes between the eyelids, the patient's lid seal is inadequate. The more light that "escapes" the interpalpebral fissure, the higher degree of dysfunction and greater exposure to desiccating stress at night (see Figure 1). In our practice, we record this in the EMR as "lid seal insufficiency," grading the condition negative, mild, moderate or severe based on the amount of light leakage.

We can also use a simple and effective "snap test" to manually assess a patient's lid position. A snap test is performed by gently pulling the patient's upper and lower eyelids away from the globe in a pinch like fashion then releasing. Lids that snap into place quickly are elastic and likely healthy, while lids that are slow to normalize may indicate excess laxity, functional lid malpositions, abnormal lid wiper mechanics and potentially, insufficient nocturnal lid seal. We pull on the upper lid superiorly and temporally from the globe (see Figure 2). Excessive amounts of upper lid laxity and distractibility from the globe are highly suggestive of floppy eyelid syndrome (FES). In these patients, we order a sleep study to identify obstructive sleep apnea (OSA), which is often associated with FES (5). In severe cases of FES, surgical repair may be required (6).

The pathophysiology of FES is interesting and multifactorial. Recent research suggests that floppy eyelids are associated with physical influences introduced over time: specifically, sleeping preferences – even face-down may exert tractional forces on the eyelid(s) (7). Ischemic damage is well described in obstructive sleep apnea and is associated with chronic inflammation. Additionally,

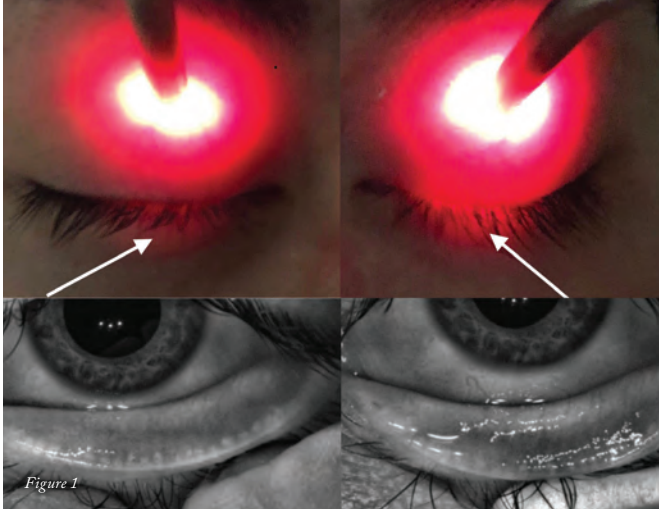


Figure 1

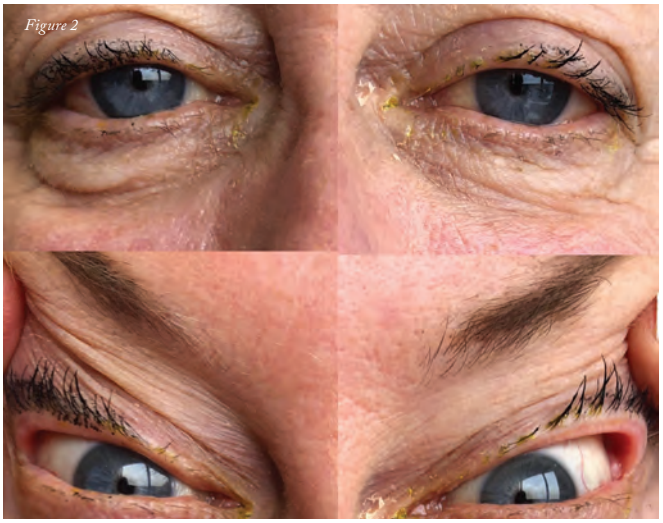


Figure 2

a post-surgical FES repair tissue analysis series demonstrated very high amounts of metalloproteinases in the tissues. One common theory is that the hypoxic episodes associated with obstructive sleep apnea create a smoldering inflammation which, over time, destroys the elastin fibers (8) and collagen fibers of the eyelids thereby creating the lid laxity, lash ptosis, and papillary conjunctivitis characteristic of FES (9). Treatment of OSA with CPAP has been reported to result in improvements in FES (10) and this is consistent with our clinical observations.

CONTROLLING THE CASCADE

If a patient's lid seal insufficiency and dry eye signs/symptoms are mild, I may advise them to use preservative-free OTC lubricating gels and ointments. However, for patients with moderate or severe signs and symptoms, I use a silicone medical-grade vaulted sleep mask developed for dry eye and MGD patients (such as eyeseals, Eye Eco), and specially designed to work with CPAP devices. By creating a comfortable seal around the periocular region, moist protection of the ocular surface is recreated. My patients report that the mask helps them sleep better and that their morning symptom severity is reduced. Some MGD patients report improved symptoms with night mask wear particularly if there is a component of allergy to dust mites. Clean the masks every morning in a simple soap that is free of perfumes, triclosan and colorants (such as diluted Dr Bronner's soap). In the MGD cases with excessive lid laxity, we have clinically observed that customizable thermal expression modalities, such as TearCare or iLux, provide a therapeutic advantage as the LipiFlow activators can be less likely to remain in optimal position on lax eyelids during treatment.

With the abundance of diagnostic and treatment strategies, we are able to reduce or prevent the desiccating stress-induced chronic inflammation cascade that characterizes dry eye. It is only by recognizing and minimizing the impact of nocturnal lagophthalmos that a protective ocular surface environment can be recreated – one that reduces symptom severity and helps our broad range of prescription, nutrition supplemental, and in-office treatment modalities work more effectively.

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Disclosures: Periman is a speaker for Allergan, Lumenis, Novartis and Sun Pharmaceuticals. She also serves as a consultant for Alcon, Eyedetec, Eyevance, Science Based Health, Sight Sciences, TearLab and Visant.

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A Nose for OSD

Could a new nasal spray be a panacea for dry eye sufferers?

By Elizabeth Yeu

With an estimated 16 million adults suffering from dry eye disease (DED) in the US alone, there is huge appetite for more effective and easy-to-use therapeutic options. The news of the OC-01 nasal spray being released by Oyster Point Pharma was welcome news to me, as I feel it will have a real impact on my patients' outcomes. The spray promises to overcome a number of challenges in ocular surface disease (OSD) management, namely by offering both physicians and patients a unique delivery system.

One of the key factors that contributes to OSD is the tear film. It is crucial that both the quality of the tear film and the architectural health of the ocular surface are improved in dry eye patients to help maintain a normal baseline of ocular surface. It is here where the neurostimulation pathway comes into play – enabling meibum egress and helping to create a more complete tear film. The primary cause of meibomian gland dysfunction (MGD) is the fact that we just aren't very good at blinking in today's society – whether this is because we're staring at visual devices for extended periods of time or because of contact lens wear. This poor-quality blink leads to pressure build up in the meibomian gland because the meibum is not being expressed properly, leading to pressure atrophy and destruction of the ocular surface architecture.

Neurostimulation that enables the release of meibum is therefore an extremely helpful tool to combat dry eye. Medical devices, such as the TrueTear from Allergan, have enabled neurostimulation of the glands in the past and can be useful as an adjunctive therapy for those suffering from DED. However, there have been challenges with the reimbursement pathway for such devices and the TrueTear is currently not covered by insurance in the USA. In my opinion, durable medical devices in ophthalmology are also just not that common. In addition to these issues, there are ergonomic challenges in getting the device into the proper position, especially for our older patients who already have digital arthritis and proprioception difficulties. Taking all of these factors into account, there is clearly a need for more therapeutic options that can benefit a broader population of patients with dry eye.

Earlier this year, Oyster Point Pharma announced the enrollment of their first subject in a Phase III clinical trial of the OC-01 nasal spray for dry eye disease. OC-01 is a highly selective nicotinic acetylcholine receptor (nAChR) agonist that re-establishes tear film homeostasis by stimulating the Lacrimal Function Unit – the glands and cells responsible for natural tear film production. So far, the OC-01 nasal spray is a really promising product. The phase two data demonstrate that it shows no negative side effects or adverse events as related to the eye. There is also no burning or foreign body sensation or any of the other concerns that can happen with some other known pharmaceuticals. In my opinion, this nasal spray can be used in many ways as both a primary therapy as well as an adjunctive therapy.

The beautiful thing about using a nasal spray is that the delivery system spares the ocular surface. If someone is having an acute flare with significant itching or discomfort, adding a drop can actually be more uncomfortable. Nasal sprays are already commonly used by patients who, in my experience, tend to be much more receptive to using a nasal spray over eye drops. Eye drops are also less favorable for women as an approach because it causes makeup to "run." As silly as that may sound, it can affect compliance with treatment for a huge target population that is affected by dry eye.

Personally, I would use this nasal spray for any patient, but especially those using artificial lubrication more than twice a day. It does not mean that we won't use other interventions, nor does it mean we're not going to use adjunctive anti-inflammatories to help quell the T cells and take care of acute flares, but I believe this spray could be a truly effective primary or adjunctive therapy.

Considering less than 10 percent of my own patients are completely under control with prescription therapy alone, being able to offer this therapy option will only help to improve patient satisfaction with their treatment. I think the use of this nasal spray means we're finally going to enter an exciting era where a single panacea therapy could help address the different challenges of dry eye more effectively.

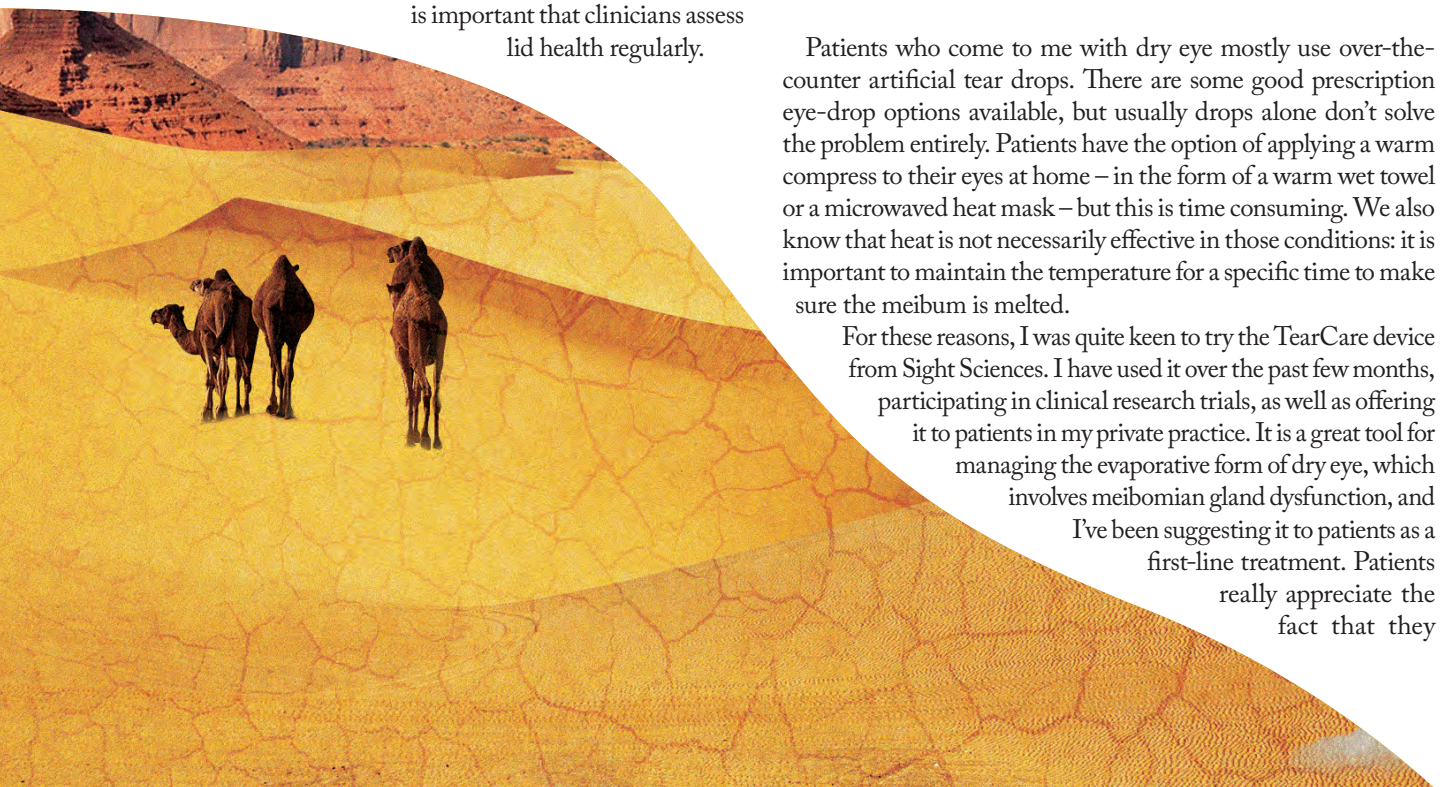
Elizabeth Yeu is Assistant Professor at Eastern Virginia Medical School, Cornea, Cataract and Refractive Surgeon with Virginia Eye Consultants, VA, USA.
Disclosure: Elizabeth Yeu is a member of Oyster Point Pharma's medical advisory board.

The Importance of Ocular Hygiene

Dry eye disease does not appear overnight – creating awareness of the need for life-long ocular surface management is vital

By Jennifer Loh

Dry eye is a very common problem in my practice. Patients usually come through my door with a different complaint, but it turns out that they suffer from an ocular surface problem, meibomian gland dysfunction, or evaporative tear disease. I could identify some form of this condition in almost all of my patients. Some have a very mild form of OSD and are asymptomatic, and in others it is more advanced, but I believe in all patients it needs to be treated at a young age, so that they do not think that they got the condition overnight, as many currently do – it happens over many years, in a similar way to tooth decay. It is important that clinicians assess lid health regularly.



"THERE ARE SOME GOOD PRESCRIPTION EYE-DROP OPTIONS AVAILABLE, BUT USUALLY DROPS ALONE DON'T SOLVE THE PROBLEM ENTIRELY."

Patients who come to me with dry eye mostly use over-the-counter artificial tear drops. There are some good prescription eye-drop options available, but usually drops alone don't solve the problem entirely. Patients have the option of applying a warm compress to their eyes at home – in the form of a warm wet towel or a microwaved heat mask – but this is time consuming. We also know that heat is not necessarily effective in those conditions: it is important to maintain the temperature for a specific time to make sure the meibum is melted.

For these reasons, I was quite keen to try the TearCare device from Sight Sciences. I have used it over the past few months, participating in clinical research trials, as well as offering it to patients in my private practice. It is a great tool for managing the evaporative form of dry eye, which involves meibomian gland dysfunction, and I've been suggesting it to patients as a first-line treatment. Patients really appreciate the fact that they

"I AM USUALLY THE FIRST PERSON TELLING MY PATIENTS ABOUT OCULAR SURFACE DISEASE, OR DRY EYE, EVEN THOUGH SO MANY OF THEM WOULD HAVE BENEFITTED FROM BEING TREATED EARLIER."

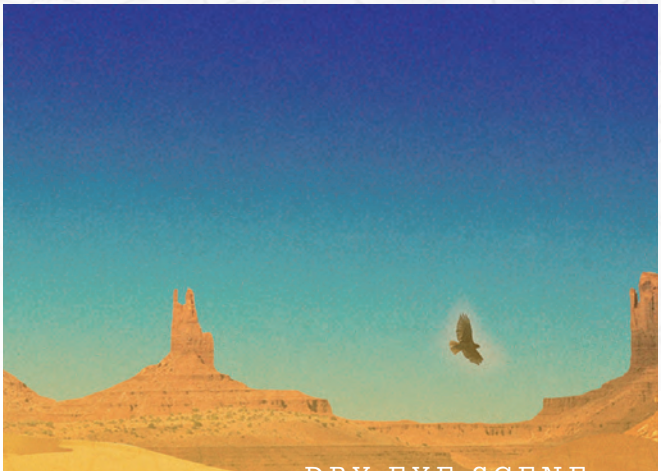
are not required to apply prescription medication every day, and they tend to see a very quick improvement. I make it clear that using TearCare is not a cure, but a continuous process. Just like taking care of our teeth throughout our lives and going to the dentist twice a year – it is equally important for my dry eye patients to take care of their ocular hygiene.

There are other devices that I have used that work in a similar way, but what I like about TearCare is its portability, and the fact that it is customized for the particular patient's needs. The electronic part of the device, the Smart Hub, is kept by the physician, and it is connected to the disposable, patient-specific component, called the Smart Lid, attached to the upper and lower eye lids of both eyes. The Smart Hub sends signals to the Smart Lid to provide a constant, consistent source of heat. The Smart Lid communicates with the Smart Hub, which adjusts and maintains the temperature. It is a sophisticated device, but for the patient is looks and feels like a simple sticker that they put on their eye lids, which provides a comfortable experience.

The device is really easy to use, both for the physician, and for the patient. It allows me to target the glands, and if I can see that one gland is more plugged than the other, I can manually target it with extracting forceps.

I am usually the first person telling my patients about ocular surface disease, or dry eye, even though so many of them would have benefitted from being treated earlier. I feel that it is now vitally important to raise public awareness of this issue. There are many great technologies available to treat this condition – and new ones will continue being developed – but very few patients know about meibomian gland and dry eye treatments, and I would really like this to change.

Jennifer Loh specializes in cataract and refractive surgery, and the management of dry eye disease, pterygium and glaucoma. She practices at Loh Ophthalmology in Miami, Florida, USA.



DRY EYE SCENE – A SELECTION OF DEVICES DESIGNED TO ALLEVIATE DRY EYE SYMPTOMS

- *iLux* from Alcon is a meibomian gland dysfunction (MGD) treatment system, which was introduced to the market in February 2019. The iLux device features a Smart Tip patient interface, which applies light-based heat and compression under direct visualization.
- *LipiFlow* by Johnson and Johnson Vision is a system used for thermal pulsation treatment. It assists in clearing gland blockages by heating and massaging the inner and outer lid. Patients receive in-office treatments that last 12 minutes, with activators placed under and over the eye lids, avoiding contact with the ocular surface.
- *NULids* is a medical device system designed for home use. It features a soft, daily disposable brush that massages the eye lids for 15 seconds per eye, once a day.
- *E>Eye* from ESW Vision aims to alleviate dry eye symptoms by generating a polychromatic light. It is used by an eye care professional, who places a metal eyewear protection on the patient's head, and applies a series of five flashes under the lower eyelid.
- Allergan's *TrueTear* intranasal tear neurostimulator aims to increase tear production using tiny pulses of energy. The device is aimed at adult patients with severe dry eye symptoms. It wirelessly connects to a phone app, which tracks the device use and intensity levels.

No "I" in Dry Eye

Diagnosing and treating dry eye is the physician's responsibility – but success demands involvement from the whole team

By Patti Barkey

When implementing any new technology into an established practice, the more time spent educating staff prior to roll-out with patients, the greater the chance of success. This same theory applies when it comes to building a successful dry eye practice; the whole team needs to be included in the process.

SETTING THE STAGE

Staff members play varying but equally important roles in facilitating the right diagnosis, such as gathering critical information, helping to educate patients about ocular surface disease and the treatment options, paving the way for the doctor to have an efficient consultation, and following through on the physician's recommendations. We know, for example, that most cataract patients have some form of ocular surface disease (1). But it is highly inefficient for the cataract surgeon to be the first person to discuss this with the patient or begin to investigate the extent to which it will affect their cataract surgery choices and outcomes. Instead, staff should play a key role in proactively gathering the diagnostic information the doctor requires.

At our practice, we start every workup with a version of the Standard Patient Evaluation of Eye Dryness (SPEED) questionnaire – with additional questions about allergy and autoimmune disease. Any positive results are then built into the patient's chief complaint and lead to further testing.

Typically, we will image the meibomian glands using a dynamic meibomian imaging device (LipiView II, Johnson & Johnson Vision). We also test for the tear film marker MMP-9 using the Quidel InflammaDry test and for tear osmolarity using the TearLab device. We will then look at the LipiView interferometry, which measures the lipid layer thickness and can tell us whether there is a full or partial blink. During the slit lamp exam, the physician performs a diagnostic meibomian gland expression, using a Q-tip or the Korb meibomian gland evaluator. With all this information in hand, the physician can make a clear diagnosis of the type(s) of dry eye the patient has.

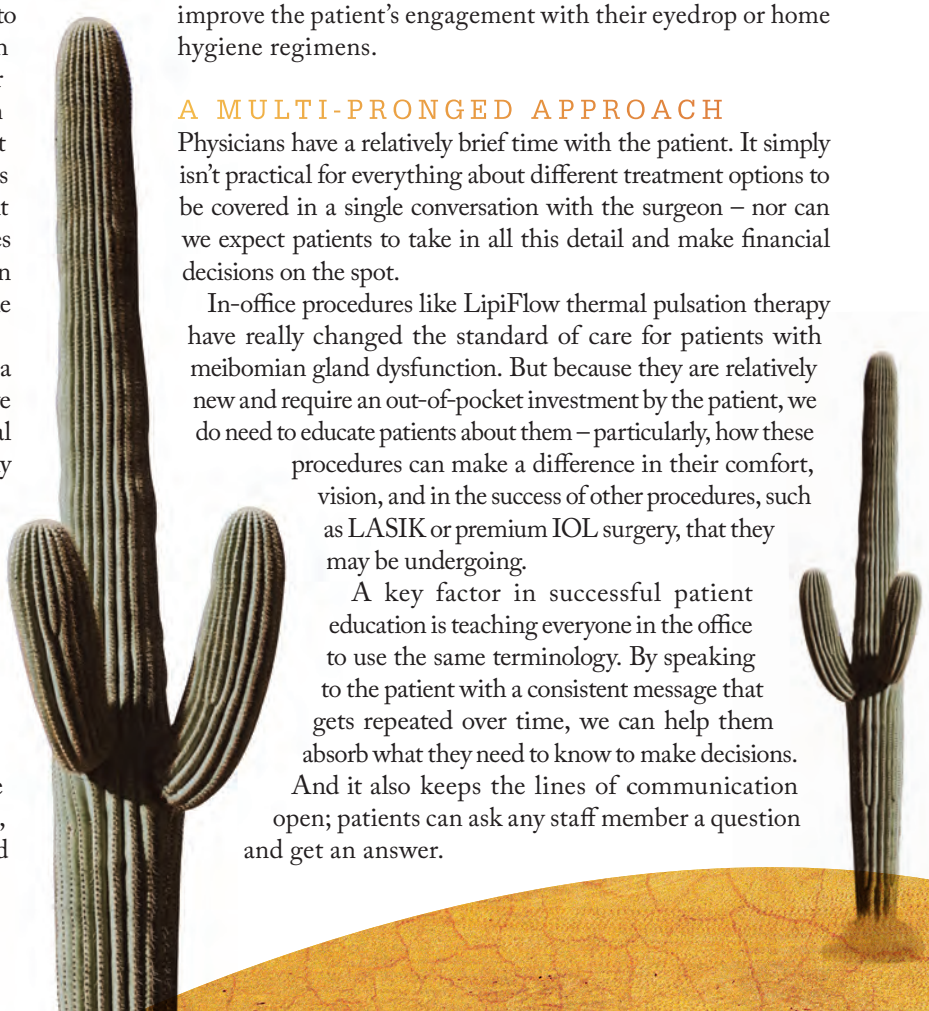
In addition, diagnostic testing can also help us to educate patients. Meibography images can be a powerful way to show patients the difference between normal, healthy glands, and their own. A positive MMP-9 test can help us emphasize the importance of getting inflammation under control, so that patients get the best possible outcome from their investment in a premium IOL. Imaging and testing can also help to improve the patient's engagement with their eyedrop or home hygiene regimens.

A MULTI-PRONGED APPROACH

Physicians have a relatively brief time with the patient. It simply isn't practical for everything about different treatment options to be covered in a single conversation with the surgeon – nor can we expect patients to take in all this detail and make financial decisions on the spot.

In-office procedures like LipiFlow thermal pulsation therapy have really changed the standard of care for patients with meibomian gland dysfunction. But because they are relatively new and require an out-of-pocket investment by the patient, we do need to educate patients about them – particularly, how these procedures can make a difference in their comfort, vision, and in the success of other procedures, such as LASIK or premium IOL surgery, that they may be undergoing.

A key factor in successful patient education is teaching everyone in the office to use the same terminology. By speaking to the patient with a consistent message that gets repeated over time, we can help them absorb what they need to know to make decisions. And it also keeps the lines of communication open; patients can ask any staff member a question and get an answer.



In our practice, when the patient calls to make an appointment for a dry eye evaluation, the call center staffer might say, "Well, we have a lot of new things available for dry eye right now. I'd love to have one of our counselors give you a call and talk to you about some of the treatments we offer prior to your appointment." From my experience, patients are usually very receptive to this and are grateful for the information. If a practice already has patient counselors for refractive or cataract surgery, I'm a huge advocate of using those counselors for dry eye as well. An initial call from the counselor plants the seed with the patient about the advanced diagnostics we use, and the new treatment technologies that might be recommended for them.

When they come to the office, the technician performing the testing will be introducing dry eye concepts, and educating patients about their test results as they go through the workup. Our technicians are also trained to listen for trigger words – if the patient does mention anything unusual, the technician knows to probe for more information about which drops they are using and why the patient is using them. The answer may be an indication that the patient is using the wrong product – for example, a vasoconstrictor for redness instead of treating the chronic dry eye or allergy – and provides us with the opportunity to introduce alternative treatments or a better choice for an over-the-counter drop.

Next, the patient counselor will meet with the patient in person to continue the education process. Counselors won't diagnose a patient, but they might say, "It looks like you have signs and symptoms of dry eye, let's review some of the available technologies that the doctor may recommend to you." Because a diagnosis hasn't been made at this point, nothing is certain, and our counselors are careful to communicate this to patients.

It is important that patients feel like they're in an environment where staff members throughout the office care about their dry eye. Part of this is ensuring that they feel no symptom has been dismissed and that staff are ready to offer solutions and resources. Therefore, when the physician finally examines the patient, they are ready to hear the diagnosis and treatment recommendation without feeling overwhelmed or pressured.

I also believe physicians should make recommendations based on the standard of care for their practice, without regard for the patient's race, gender or perceived financial status. The counselor can follow up immediately afterwards with information about Care Credit or other financing for the exact recommended treatment. If the plan involves more than one type of treatment — Blephex blepharoexfoliation and LipiFlow thermal pulsation therapy, for example — we typically bundle that into a single monthly payment for the patient.

THE PERSONAL TOUCH

A great benefit of getting the staff involved in patient education is that they can share their personal experiences in an authentic way. Our team members with dry eye are given the opportunity to have the treatments themselves, meaning they have first-hand knowledge – and this resonates with patients. Even those who don't have dry eye find it easy to talk about the procedures that we do because they have seen the repeated successes with our patients.

A team-based approach, in which everyone in the practice plays a role in educating patients, is one that works not only for dry eye, but for any service where we are asking patients to make a decision that involves their financial commitment – including corneal refractive surgery, premium IOLs, MIGS devices for glaucoma, and aesthetics.

There are a number of training resources available for doctors and staff who want to get more involved in patient education. I'm obviously an advocate of the Dry Eye University program (see Figure) and the online Dry Eye Access platform, but there are many other resources available, such as in-person training opportunities at professional meetings or through industry, podcasts from Dry Eye Coach, and a wealth of journal articles on the topic. Any practice that wants to make a commitment to getting staff off the sidelines and participating as full members of the dry eye team has a wide range of opportunities to learn more about how to engage staff and talk to patients about this important condition.

Patti Barkey is Chief Executive Officer of Bowden Eye & Associates in Jacksonville, Florida, and the creator of Dry Eye University and co-creator of Dry Eye Access. She is a certified ophthalmic executive and ophthalmic coding specialist.
Disclosure: Barkey has worked as a consultant for Johnson & Johnson, Allergan, Care Credit, Blephex and Alcon.

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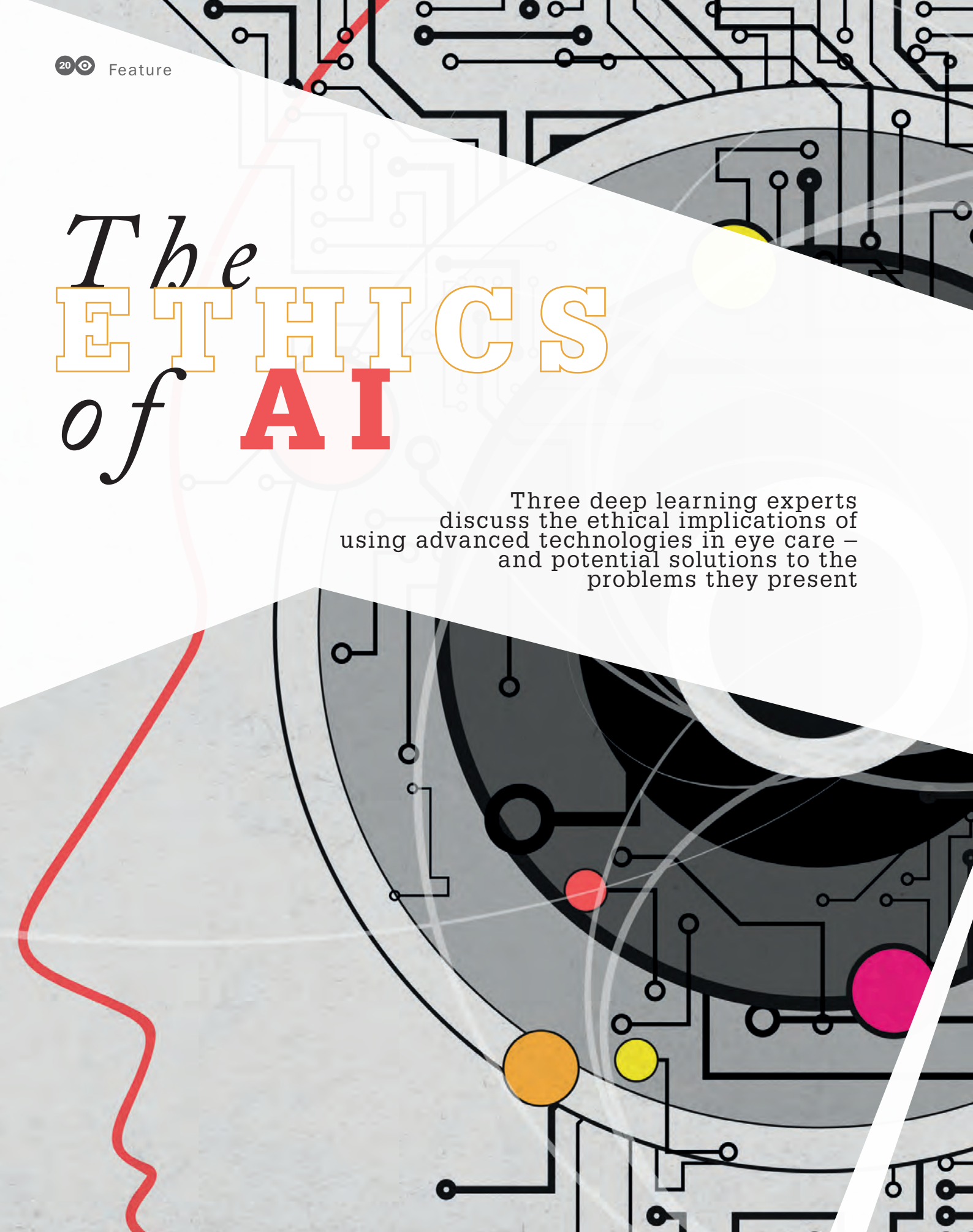
The ETHICS of AI

Three deep learning experts discuss the ethical implications of using advanced technologies in eye care – and potential solutions to the problems they present



Meet the AI Gurus

Pearse Keane is an NIHR Clinician Scientist at the UCL Institute of Ophthalmology, and Consultant Ophthalmologist at Moorfields Eye Hospital NHS Foundation Trust in London, UK.

Stephen Odaibo is a retina specialist, computer scientist, mathematician, full-stack AI engineer and co-founder of RETINA-AI in Texas, USA.

Daniel Ting is a Vitreoretinal Specialist at the Singapore National Eye Center, Assistant Professor of Ophthalmology at Duke-NUS Medical School, Singapore, and Adjunct Professor at the State Key Laboratory of Ophthalmology at Zhongshan Ophthalmic Center in China.

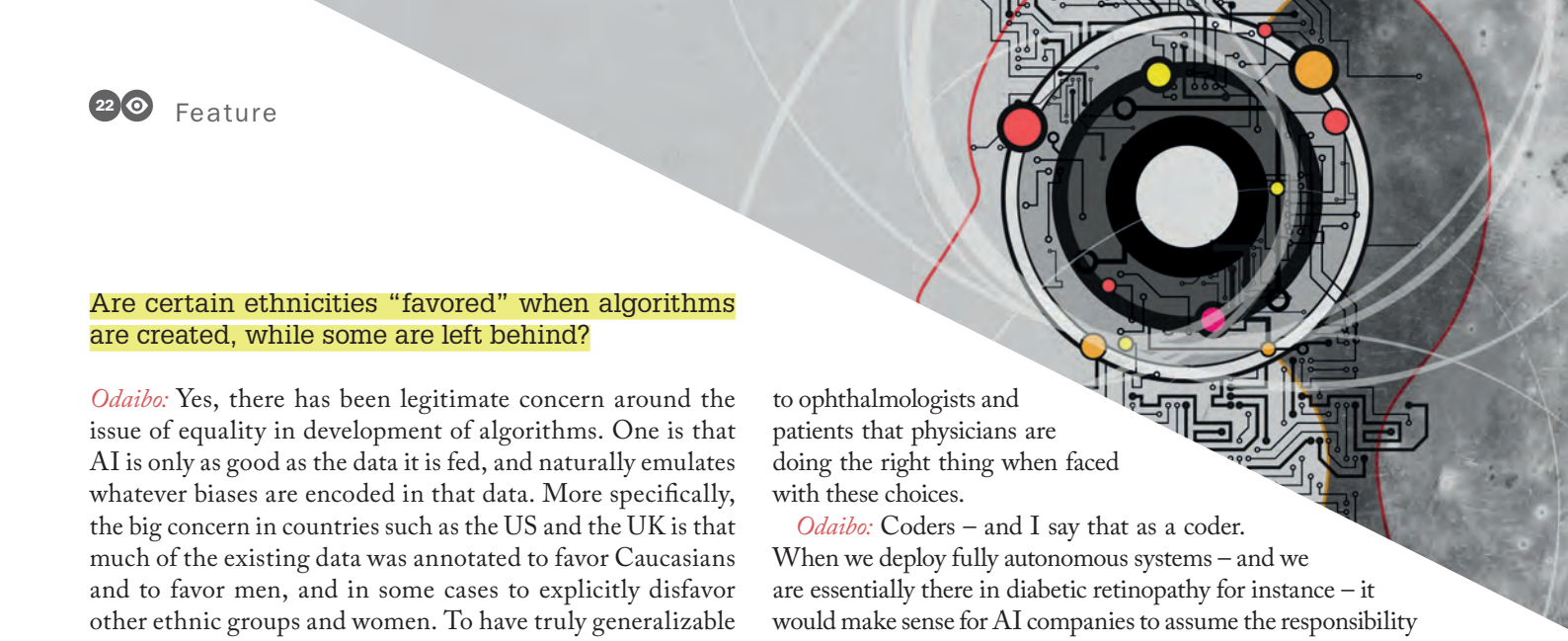
Is AI and deep learning being developed predominantly in and for industrialized countries?

Keane: There are huge barriers for the implementation of some of these technologies, but at the same time, there are also lots of opportunities. What I think you'll see is a confluence of improved telecommunications. As we start to see the rollout of 5G, for example, we will see increasing use of cloud-based infrastructure there may offer advantages to low and middle-income countries – though a lack of legacy infrastructure has to be taken into consideration. It might be the case that some of these countries can leapfrog more developed areas and start to do exciting things with these technologies.

One of the things I'm particularly interested in is automated deep learning systems. My team recently published a paper showing how healthcare professionals with no coding experience were able to train AI systems using deep-learning platforms. While those systems can't be used for direct patient care (in part because they would have to go through a robust regulatory process), you could imagine that this approach would allow the proliferation of novel clinical research applications for AI in both low and middle-income countries, and the developed world.

Odaibo: I have a privileged view into this being a dual citizen, both American and Nigerian, and being active in both countries. Developing countries have some notable advantages in terms of data, costs, readiness and willingness to implement AI solutions. Industrialized economies also clearly have advantages, such as well-developed regulatory systems, infrastructure, and established data systems. Each advantage can potentially resemble or be a disadvantage and vice versa. For instance, the absence of existing electronic medical records systems in developing countries provides an opportunity to "leapfrog" by starting out with AI-ready next generation EMR systems that are truly continuous learners, and are unencumbered by impeding static legacy systems. On the other hand, the relative dearth of existing electronic data does mean starting nearly from scratch for a lot of developing countries.

Ting: The ethical dilemma of applying AI in healthcare is widely debated. For developing countries, I see a huge potential role for AI to accelerate the standard of care, especially in countries with a shortage of eye specialists. At present, most deep learning systems are found in developed countries, which is unsurprising, given the availability of the technical expertise and clinical datasets. In 2019, my group collaborated with Zambian and UK ophthalmologists to report on the feasibility of using deep learning to screen for diabetic retinopathy in the African population. The findings were published in the Lancet Digital Health (Bellemo et al, 2019). Of course, the question is then whether the local community has the capacity and expertise to treat those who require treatment. These are some of the medical and ethical questions one may need to ask. If there is an insufficient number of doctors to treat a particular disease, is there a role to screen for a particular disease in the specific population? To clinically deploy an AI algorithm, it is always important to build a robust ecosystem surrounding it. This ecosystem requires medical, technical and financial support from multiple stakeholders.



Are certain ethnicities "favored" when algorithms are created, while some are left behind?

Odaibo: Yes, there has been legitimate concern around the issue of equality in development of algorithms. One is that AI is only as good as the data it is fed, and naturally emulates whatever biases are encoded in that data. More specifically, the big concern in countries such as the US and the UK is that much of the existing data was annotated to favor Caucasians and to favor men, and in some cases to explicitly disfavor other ethnic groups and women. To have truly generalizable algorithms that are fair, the distribution of training data has to be representative of the population, and, furthermore, has to be explicitly engineered to not be biased – because representative but biased data will yield a biased algorithm.

Ting: The AI algorithms are often created in developed countries such as US/Europe that are predominantly Caucasian, whereas in Asia (like Singapore), we have a multi-ethnic population consisting of people of Chinese, Malay and Indian origin. Given that the AI algorithm may be developed using certain populations, it is always important to test the generalizability of the algorithm against other populations.

What happens when the algorithms get something wrong? Who would be deemed responsible: producers, coders, or practitioners?

Keane: It depends if you're talking about an autonomous system or a decision-support system. If it is an autonomous system, then medical liability will be with the manufacturer of the AI system. If it is a decision-support system, it is the doctor who makes the final decision, which complicates things. In the US, if a doctor treats a patient according to the current standard of care, then they are usually protected against claims of medical malpractice – but if they do something that goes against the standard of care, then they may assume some legal liability.

The whole promise of AI is that it allows us to personalize our treatment of individual patients beyond the standard of care. As a doctor, you can be put in a tricky position. You have a patient, and you know the standard of care is X, but the AI system is telling you to do Y. If you do what the AI systems tells you and the patient reacts badly, you could be in a difficult situation legally. On the other hand, suppose that same doctor decides to go with the standard of care, despite the AI system telling them otherwise. If things go wrong for the patient, they could sue the doctor because the AI system told them to do Y, and they did X. In both scenarios, the doctor could be legally liable. It is a very difficult situation and, ultimately, one that professional bodies need to advise on. Guidelines would offer reassurance to ophthalmologists and patients that physicians are doing the right thing when faced with these choices.

Odaibo: Coders – and I say that as a coder. When we deploy fully autonomous systems – and we are essentially there in diabetic retinopathy for instance – it would make sense for AI companies to assume the responsibility that physicians currently assume. In a nutshell, AI companies will need malpractice insurance.

Ting: This is a question that I don't think we have a good answer to at the moment. In my personal opinion, I think the practitioners should ultimately have the responsibility to override the system if the wrong diagnosis is given by the AI software. Many newspaper headlines and research have reported that AI can perform better than humans, and in some cases that may be true. Nevertheless, in the healthcare setting, I always think that physicians should be the gatekeepers who assess and utilize all the different health technologies to improve patients' care. The clinical decision should be made based on the patient's clinical presentation, examinations and investigations. AI should always be treated as an assistive tool, instead of the sole decision-making tool for medical diagnoses. Furthermore, prior to adoption of any AI software, the physicians should also carefully appraise all the evidence that are available in the literature, the same way we assess any new drug released into the market.

If AI is used for analysing results/images, is it likely to increase the number of referrals? Are the world's healthcare systems prepared for such an increase?

Keane: AI is not magic. While it has the potential to be a powerful tool, it cannot solve complex diseases in isolation. It will only ever work in the context of good patient pathways and widespread adoption by healthcare professionals, and even in situations where you've got a good pathway, there could be other social, cultural or public health barriers to its success. I think it is important that we take a nuanced view of this.

Odaibo: It will most certainly increase the number of referrals, but I believe it is good to know who out there needs care, and what the stage of their disease is, regardless of the capacity to address it. The first step to solving a problem is knowing about the problem.

Ting: I think the application of AI is likely to increase the number of referrals to tertiary eye care settings. Hopefully

these will not be false positive referrals, although this could also happen if the operating threshold of the AI algorithms are not set properly. Some healthcare systems may not be ready to cope with this, especially in those countries with long waiting times.

What regulations exist already for implementing AI/deep learning around the world, and what still needs to be done in this area?

Keane: Systems certainly cannot be used on patients until they've received regulatory approvals from the appropriate regulator. The way AI systems will be regulated is likely to evolve in the coming years, as the FDA and others learn about the complexities – especially the issue of dealing with systems that learn "on the job" or have the potential to change their accuracy as they're exposed to more data. Currently algorithms are trained with data, but then they're locked in place, so they're not changing performance in real life. However, in the future algorithms could change over time – although that's currently very far from being a reality in the healthcare setting.

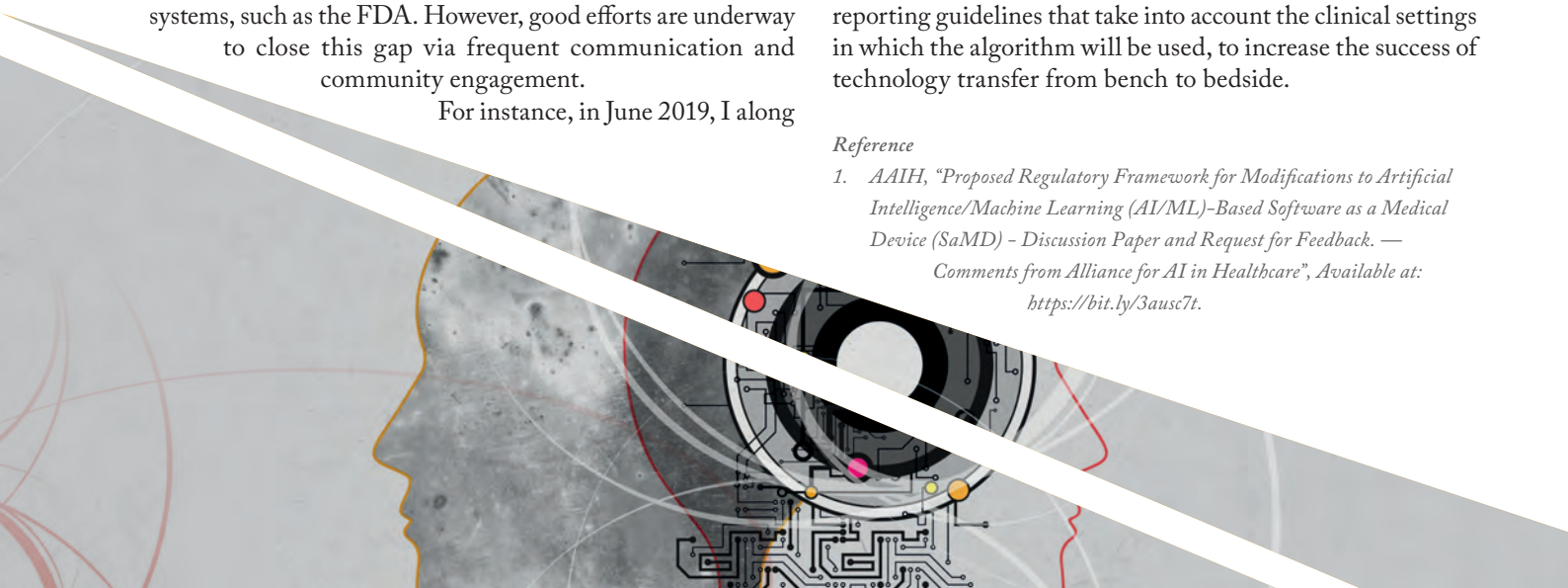
It is important to combine our excitement and enthusiasm for this new technology with caution and realism that it won't automatically cure everything. Before we even start to talk about referrals, we have to make sure that these algorithms are robustly, clinically validated because although they have great potential, there are a lot of ways in which they could go wrong. We need to bring the same level of rigour to the validation of algorithms as we would to a new drug or surgical procedure.

Odaibo: Much work is needed in the area of appropriate regulation that helps and improves the health of the public. The biggest barrier is knowledge, as this is a highly interdisciplinary area that does require some level of algorithmic understanding on the part of regulators. There is clearly a knowledge gap around the world in this area, including in the most developed systems, such as the FDA. However, good efforts are underway to close this gap via frequent communication and community engagement.

For instance, in June 2019, I along with a number of other healthcare AI experts helped draft the Alliance for AI in Healthcare's feedback to the FDA. This FDA-initiated feedback request was regarding a draft of its Regulatory Framework for AI Software as a Medical device (1). Such efforts demonstrate a sincere desire by the FDA to understand all facets of this important emerging field.

> "Currently algorithms are **trained** with data, but then they're **locked** in place, so they're not **changing performance** in real life."

Ting: At present, the FDA has already published a guideline to treat AI algorithms as medical devices. In the guideline, it states that the AI algorithm will need to be submitted and appraised based on the intended use. The WHO has also published recommendations on digital interventions for health system strengthening. The STARD guideline has always been the method we use to report a new diagnostic device, whereas the CONSORT is used for reporting clinical trials results. Nevertheless, it will be important to create new AI reporting guidelines that take into account the clinical settings in which the algorithm will be used, to increase the success of technology transfer from bench to bedside.



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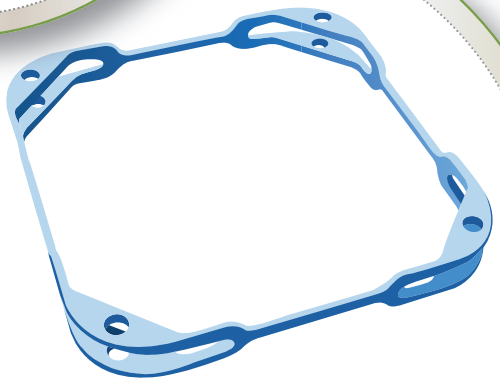

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Through the Looking Glass

Virtual reality is adding a new dimension to common ocular degenerative diseases

By Karim F. Damji

I have a strong interest in how virtual reality (VR) and augmented reality (AR) technology could play a role in my practice as an ophthalmologist and help the patients we see at the Eye Institute of Alberta. Typically, when I talk with patients about the conditions that they are living with, I'm limited to paper brochures and videos to help demonstrate what to expect with and without treatment.

At the end of 2019, the Department of Ophthalmology & Visual Sciences at the University of Alberta and the Eye Institute of Alberta held its second annual Eye Ball Gala to raise awareness and support for patient care and research. At this event, we had the opportunity to premiere a new virtual experience we called Through the Looking Glass. Through this immersive VR experience, guests at the gala had an opportunity to explore Wonderland and complete tasks while patterns of vision loss were simulated representing what can take place with untreated ocular degenerative diseases such as macular degeneration, cataracts, glaucoma, diabetic eye disease and inherited retinal conditions.

Education

We partnered with Edmonton-based company KOVR to develop Through the Looking Glass, with generous grant support from the Odd Fellow Rebekah Visual Research Foundation of Alberta. What we quickly discovered was that the application of this virtual experience extends to many areas of a patient's journey. What started off as a way to show others what life is like when living with an ocular disease has turned into an opportunity for further education to help patents and their families gain a better understanding of what it means to live with vision loss. This is important because it's not only patients' eyesight that's affected, it's also the challenges that arise for the family and other loved ones when someone is facing visual impairment.

In Through the Looking Glass, the user enters Wonderland and picks one of three mirrors, each representing a different condition. In this program, we were able to simulate glaucoma (which starts with impairment at the periphery of the visual field), macular degeneration (which impacts the center of the visual field) and cataracts (characterized by blur and glare). The condition deteriorates as the user continues through their journey, making it challenging to navigate as vision loss proceeds.

Aaron Clifford, senior producer at KOVR, commented that the world created by Lewis Carroll was an obvious choice. "Everything in Wonderland is about perception," he noted. "I can't think of a more perfect way to express how our perceptions can affect us in our daily lives."

Personal experience

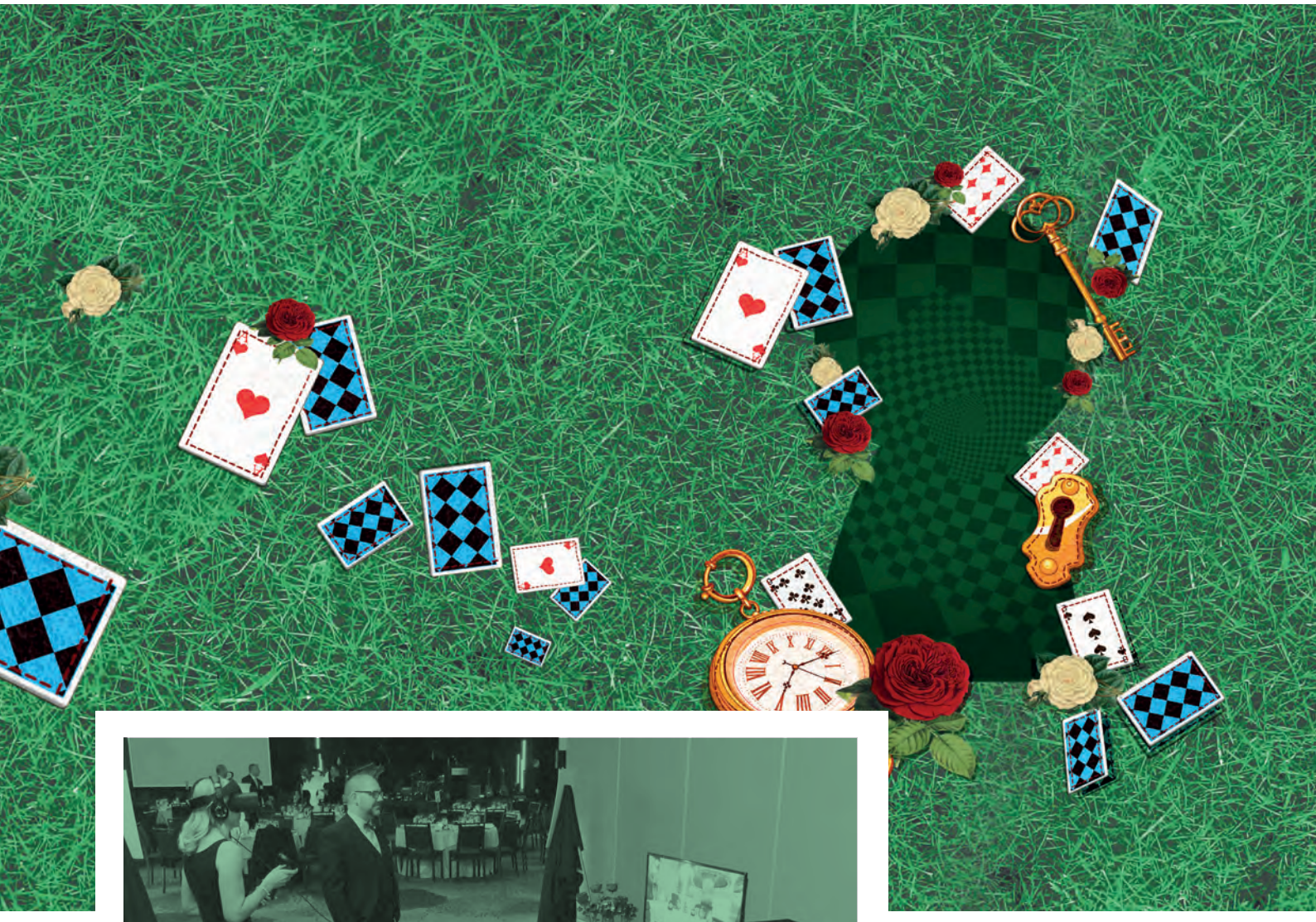
The applications of this program are numerous. We created Wonderland as an entertaining and fun environment for the event, but we can trim away the theme and still have a highly accurate VR depiction of three common ocular patterns of vision loss. Not only can we share this with patients and their loved ones to show what to expect as their conditions progress, but we can use this program to simulate different treatment options to discover the best strategies for patients.

"In Through the Looking Glass, the user enters Wonderland and picks one of three mirrors, each representing a different condition."

During the development process for this VR program, we consulted with researchers, doctors, technicians, and patients, along with holding critical review demonstrations with a large group of medical students at the University of Alberta. Ocular diseases are highly individualized, so not everyone will experience a condition in the same way. However, in speaking with our patients and having them try the simulations for themselves, they were able to provide us with feedback to create a more accurate depiction.

Future applications

In the future, we're envisioning a more AR-focused approach that permits users to experience these conditions in real-time



and in real environments. Through a technologically enhanced set of glasses, we can overlay the simulations of the conditions onto environments, such as their homes, that patients will need to navigate as part of their daily lives.

Never before have we been at a point in technology where we can provide such a realistic, intimate representation of what a person experiences when faced with ocular degenerative disease. Fortunately, many of the conditions I assist patients with are curable or treatable. The first step in addressing any health issue is education. The better educated the patients and their families are, the more empowered they are to participate in treatment and follow-up.

Through this program, we're taking a step in the right direction to better educate people about common ocular conditions. Patients and family members will be able to better understand what the condition is, how it will affect their lives and what treatment plans are best for their individual circumstances.

Karim F. Damji is Professor and Chair, Department of Ophthalmology & Visual Sciences, University of Alberta, Clinical Section Head for Ophthalmology, Edmonton Zone, Alberta Health Services, Australia.

The Beauty of Choroid Clarity

From differentiating disease states to demarcating the full extent of the abnormal vascular network, the advantages of swept-source OCT for the visualization of choroidal structure are many

By Rubens Belfort, with Eduardo A. Novais, Andre Romano, Heloisa Nascimento and João Rafael Dias

For a retina specialist, accurately diagnosing and effectively managing conditions of the choroid is, in many ways, the "final frontier" of posterior segment diseases treatment. Understanding the nuances and impact of choroidal diseases is crucial to our understanding of broader intraocular health, however, until recently, our working knowledge of this pivotal area has been relatively limited by the imaging technologies available to us. Swept-source optical coherence tomography (SS-OCT) is a new and exciting technology that offers us the ability to better visualize the choroid, as well as other "deep" physiological structures in the posterior segment with remarkable clarity. SS-OCT is also advantageous when cataract, vitreous haze, hemorrhages, and other opaque media are present, as it can produce a high-fidelity image under challenging conditions. Commercially available SS-OCT technology uses a longer, ~1050 nm wavelength and has less variation in sensitivity with depth (sensitivity roll-off) compared with spectral-domain (SD) OCT. This improved immunity to ocular opacity and deeper penetration into the choroid (1, 2) allows improved visualization of the choroid, both on cross-sectional as well as en face OCTA imaging (3, 4).

In our practice, we currently use SS-OCT to image the choroidal area and differentiate etiologies in patients with uveitis, which is often difficult to accurately visualize when media opacity is present. Specifically, I have begun investigating the use of SS-OCT to image patients with suspected toxoplasmosis or viral retinitis; diseases that, given the additional information now available to us, I believe directly affect (or are affected by) the choroidal structure. Here, I will share some insights and interesting cases wherein SS-OCT offered me and my colleagues a detailed view of the posterior segment, and played a pivotal role in our increased understanding of disease manifestation. It is also worth noting that the use of SS-OCT has allowed us to explore different choroidal patterns in primary and secondary ocular infections, such as in patients with positive and negative IgM anti-toxoplasma circulating antibodies.

Differentiating between toxoplasmosis and viral retinitis

SS-OCT may be able to help clinicians quickly and confidently differentiate between toxoplasmosis and viral retinitis by analyzing the choroidal region in greater detail. As recently as 2017, research was done by Invernizzi and colleagues on the use of OCT technology to identify distinguishing characteristics of these diseases (5). However, intraretinal edema can often attenuate the OCT signal, masking choroidal features underneath this region. This issue is more common when using

"I now suspect that the choroid plays a larger role than previously thought in diseases that trigger cellular retinal infiltration."

SD-OCT. With SS-OCT, we can acquire images with higher signal quality and make informed diagnostic decisions. SS-OCT has already shown us the significant role of the choroid in many so-called "classic" and "pure" retinitis cases.

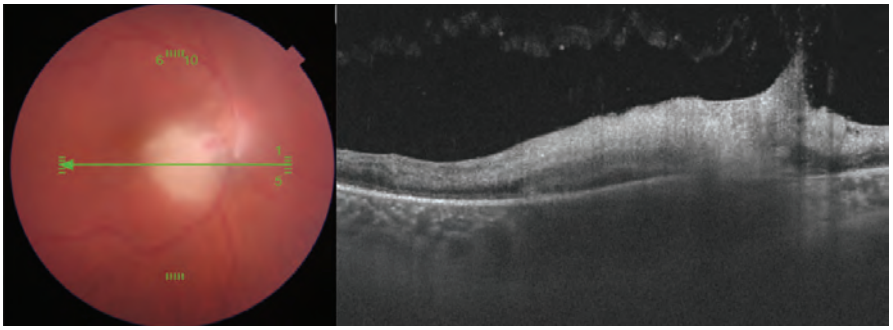
Specifically, two choroidal attributes, as identified by OCT scans, are associated with toxoplasmosis in the retinochoroidal region: hypo-reflectivity of the choroid beneath the necrotic focus, and the absence of hyperreflective septa within the choroid (see Figure 1). OCT scans from patients with viral retinitis, such as CMV and herpes, meanwhile, demonstrate that viral induced retinal necrosis does not affect underlying choroid (Figure 2). Although some degree of choriocapillaris alteration is present, the choroidal architecture is largely preserved. With this information in hand, it is much easier to make an informed diagnostic decision where the possibility of either disease is confirmed. Without a clear view of the choroid's anatomy, it would be substantially more difficult to make this diagnosis with certainty, and manage the disease accordingly.

Identifying the role of the choroid in toxoplasmosis

In addition to helping clinicians differentiate between disease states, the advanced imaging capabilities offered by new OCT technology can help us identify potential new associations and interactions during disease progression. For instance, a 29-year-old female was diagnosed with toxoplasmosis in April of 2018. She displayed a significant vitreous reaction, with a mild macular lesion on SD-OCT and a very small cyst in the fovea (see Figure 3). Her visual acuity was 20/40. The patient was treated and recovered, achieving 20/20 vision. Prophylactic course of anti-toxoplasmic medication to prevent recurrences was prescribed. At five months post-visit, the patient displayed no symptoms and scans appeared normal (see Figure 4). The patient decided to discontinue the treatment and, unfortunately, she presented a severe recurrence nine months later. She returned to our practice with 20/160 vision. Using SS-OCT (DRI OCT Triton from Topcon) to acquire multimodal imaging, we identified an abnormal thickness at the scleral-choroidal junction (see Figure 5). I now suspect that the choroid plays a larger role than previously thought in diseases that trigger cellular retinal infiltration. Fortunately, the deep tissue penetration made possible by swept-source technology creates new opportunities to understand the full range of physiological interactions present during posterior segment disease.

OCT-A application in toxoplasmosis

Unlike dye-based angiography, OCT-A is a non-invasive image modality that allows for the appreciation of depth-



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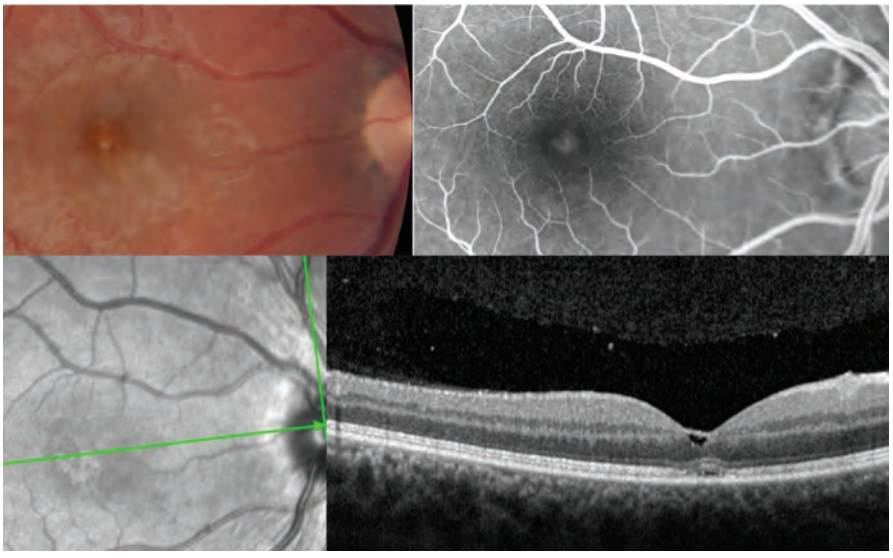

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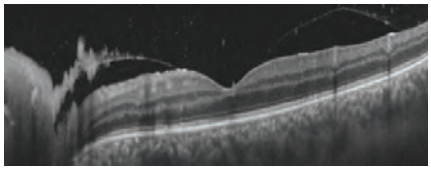

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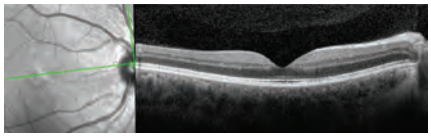

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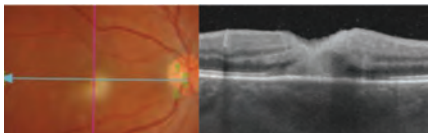


Figure 5.

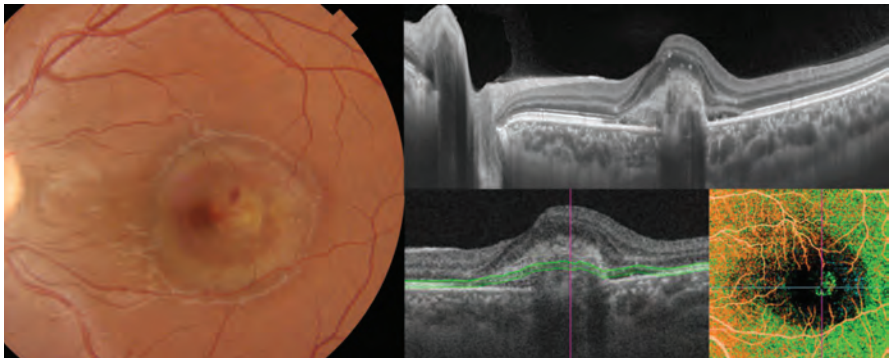
resolved spatial relationships of fundus vasculature. It also enables detailed en face visualization of the retinal and choroidal vessels separately, without the risk of adverse effects associated with the intravenous dye (6, 7). Choroidal neovascularization (CNV) is a potential complication that can cause severe visual loss in patients with posterior uveitis. Thus, the precise and early diagnosis of this sight-threatening disease is mandatory. The sensitivity of OCT-A to identify the neovascular complex may vary, as some clinical features such as hemorrhage, fluid, or fibrotic tissue may block OCT-A signal, preventing visualization of the CNV. However, as previously published by Novartis and colleagues, SS-OCT-A is better able to identify and demarcate the full extent of the abnormal vascular network (8). Thanks to this new technology we now have a powerful tool to better understand the natural history of CNV in posterior uveitis, avoiding the use of medications in many cases, as often symptoms disappear without interference.

A specific case where SS-OCT angiography was valuable in this process involved an 18-year-old pregnant female patient who experienced vision loss of 20/200 in one of her eyes after recovering from toxoplasmosis, and was referred to us for the possibility of disease recurrence.

Using our SS-OCT device's B-scan functionality, we discovered a subretinal hyperreflective lesion associated with subretinal fluid, and irregularity of the ellipsoid zone. A lack of vitreous cells and retinal edema, in conjunction with the presence of subretinal hyperreflective material, suggested the patient was suffering from a non-toxoplasmic infection. SS-OCT angiography clearly distinguished a type two choroidal neovascularization, and treatment with anti-VEGF was executed accordingly (see Figure 6).

Potential novel applications on the horizon

As SS-OCT and OCT-A are new technological developments, we are still in the pioneer stages of leveraging their capabilities to the fullest, and I expect that posterior segment researchers worldwide will continue to develop new and interesting ways to derive more clinical value from them. As an example, research presented at ARVO 2019 in Vancouver, Canada, demonstrated that patients with active inflammatory bowel diseases – such as Crohn's disease and ulcerative colitis – frequently display a thicker choroid and smaller foveal-vascular zone (FAZ) during the active disease



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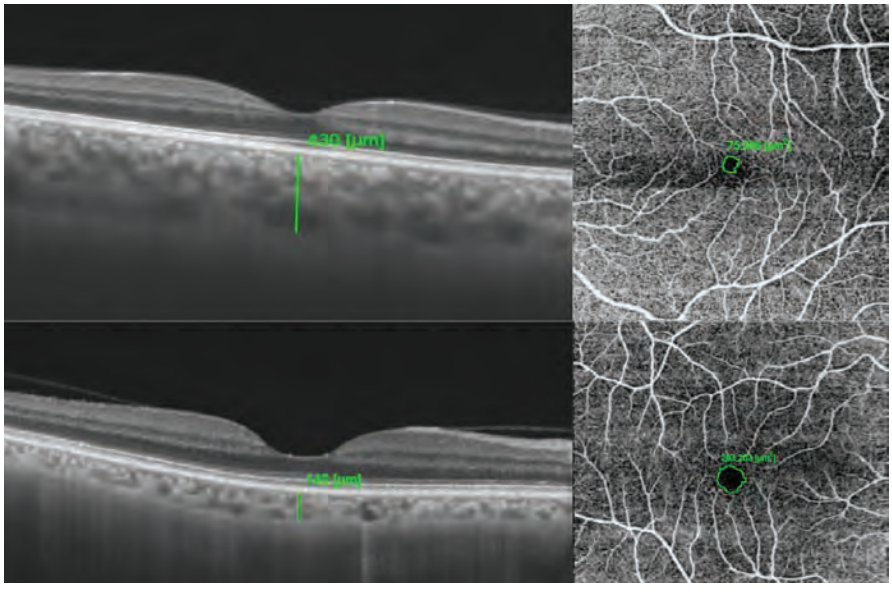

Figure 7.

in comparison to the remission phase of disease (see Figure 7) using SS-OCT, which is able to render the choroid in great detail (9). In this study, many patients with active disease possessed 20/20 vision and showed no signs of inflammation. Without the image clarity offered by SS-OCT, researchers would have likely missed this key detail, along with the opportunity to identify this interesting association in autoimmune manifestation.

The arrival of new imaging technologies offers retinal specialists high-resolution images that are undoubtedly beautiful to behold. But it's critical to note that while new imaging devices offer us beauty, they also offer us concrete clinical value – if we make the effort to use them in new and creative ways. Taking advantage of an unprecedented choroidal clarity, and the insights that come with it, is just one way to leverage the full potential of this new technology, and it is exciting to see how practitioners will continue to apply and derive value from SS-OCT.

Rubens Belfort is Head Professor of Ophthalmology at the Federal University of Sao Paulo, Brazil. Belfort is a member of the National Academy of Medicine in Brazil and directs the Philanthropic Vision Institute.

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Dousing the Post-Cataract Flames

Anti-inflammatories that reduce patient adherence or offer a more reliable delivery mechanism are driving the evolution of postoperative regimens

By Rochelle Nataloni

Despite surgical advances, ocular inflammation after cataract surgery is a reality that, if managed ineffectively, can have a significant impact on patient comfort, recovery, and final visual outcome (1). And it doesn't take a great deal of surgical trauma to alter the blood-aqueous barrier, resulting in protein leakage, cellular reaction, and subsequent inflammation in the anterior chamber. Diabetes, use of tamsulosin, a history of iritis, or extended phaco time are just some of the many factors that can increase the risk of inflammation following cataract surgery (2). Even low-grade inflammation, if uncontrolled, can lead to conditions such as cystoid macular edema (CME), which can ultimately cause permanent vision loss.

Topical anti-inflammatory drugs, such as corticosteroids, have been the foundation of postoperative inflammation control for half a century. With the introduction of topical non-steroidal anti-inflammatory drugs (NSAIDs), which are thought to complement steroids and provide additional inflammation control, it has become common for surgeons to employ both steroids and NSAIDs to control and prevent inflammation resulting from cataract surgery (3).

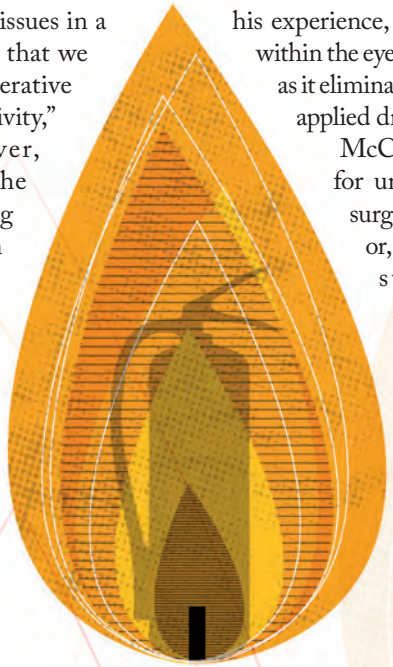
Advances in drug-delivery options have since expanded post-cataract inflammation management, and regimens are beginning to shift in response (See: A timeline of novel corticosteroid options). Cataract surgeons Dave Patel and Cathleen McCabe cite sustained-release drugs that remove the adherence burden from patients, and innovative delivery mechanisms that improve intraocular penetration among the options that are reshaping their post-cataract inflammation control strategy.

"Advances in drug-delivery options have expanded post-cataract inflammation management."

Critical control

According to Patel, quelling inflammation after cataract surgery is now more important than ever because of heightened patient expectations: "Today, cataract surgery is so efficient and technology has advanced to such an extent that patients are seeking faster, easier recovery options. They have these elevated expectations, because we've become so good at doing cataract surgery." As one of the most commonly performed surgeries in senior populations, Patel remarks that surgeons have become more proactive in trying to reduce recovery time – with a key objective being to aggressively treat and minimize post-surgery inflammation.

McCabe adds that the aim of inflammation control is to make sure that the ocular tissues are not surrounded by inflammatory mediators. "We want to make sure we provide a medication that, in essence, bathes tissues in a healing environment so that we can control any postoperative discomfort or light sensitivity," she explains. However, she also emphasizes the value in thinking long term: "Inflammation can cause scarring of ocular tissues, such as posterior synechia or even peripheral anterior synechia, as well as scarring of the anterior capsule, the iris, or the cornea. If there's enough inflammation after surgery, the capsular bag can contract; in the long term, this can lead to swelling in the retina – CME – which can affect visual function."



For routine cataract cases, Patel says he has long implemented an anti-inflammatory regimen of topical steroids, including Pred Forte (prednisolone acetate suspension 1 percent; Allergan), Lotemax (loteprednol etabonate suspension 0.5 percent; Bausch + Lomb), or Durezol (difluprednate emulsion 0.05 percent; Novartis), used four times a day for about three weeks. However, Patel adds that in his experience, delivering the steroid within the eye itself has the best effect as it eliminates the risk of a topically applied drug not penetrating.

McCabe's typical regimen for uncomplicated cataract surgery is similar: Durezol, or, if a patient is a known steroid responder, Lotemax, as well as Prolensa (bromfenac ophthalmic solution 0.07 percent, Bausch + Lomb). "Another way of providing a post-operative anti-inflammatory effect

is to use Omidria (phenylephrine ketorolac intraocular solution 1 percent/0.3 percent, Omeros) at the time of cataract surgery," she says. Combining Omidria with a sustained-release steroid formulation, she adds, could allow patients to avoid topical anti-inflammatories altogether.

Special considerations

When prescribing a week-long regimen of multiple postoperative eye drops, it's important to consider the likelihood of patients being able to manage. "It's crucial to have a good understanding of your patients and their dynamic outside of the office. For the most part, this is a geriatric population, so their memory might not be perfect. They may not remember to use the medication; or sometimes they have arthritis and administering the drug is challenging," explains Patel. On top of this, it is common for patients to have comorbidities – such as diabetes or retinal membranes – that require more aggressive or longer-term steroid use. McCabe tends to employ a "belt-and-suspenders" approach for more challenging cases (for example, when she is worried about non-compliance or a predisposition to inflammation-associated complications), which relies on a layered combination of steroidal products.

Surgical factors also need to be considered in the decision and may lend themselves to a more customized approach for inflammation control. "Patients who have had a lengthy surgical process – those who require manipulation of the iris, or patients who had complications such as a posterior capsular break – will have prolonged or excessive inflammation," explains Patel. "Similarly, patients who have had previous bouts of uveitis or inflammation tend to have a more robust inflammatory response to surgery or injury, so they require a lot more steroid treatment as well."

Patel points out another anatomy-related obstacle when steroids are delivered

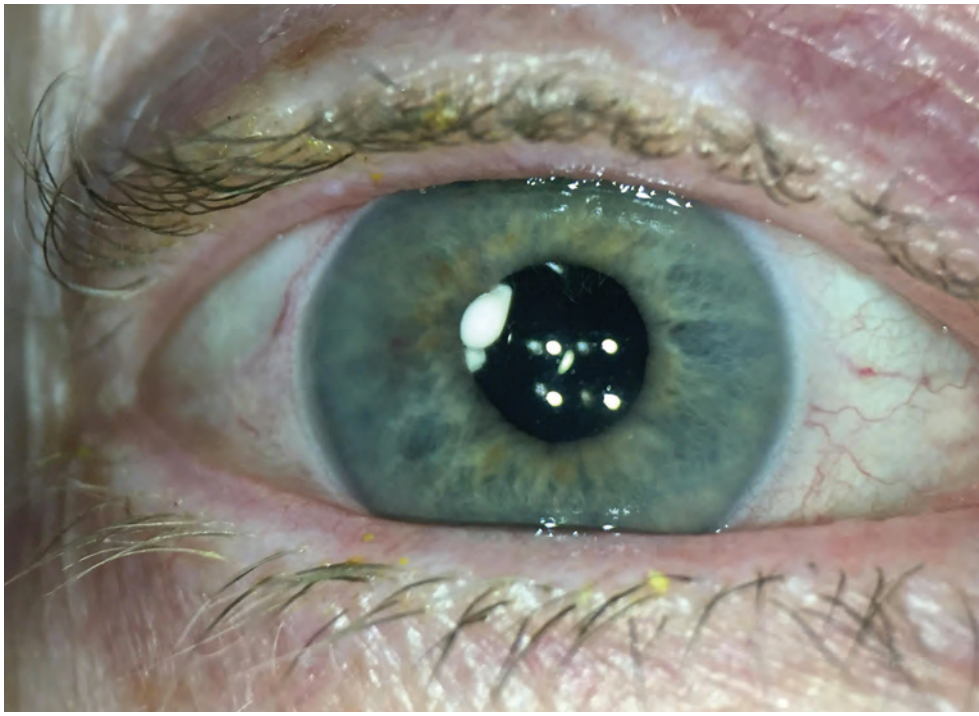


Figure 1. In some cases, Dexycu may be visible at the pupillary margin in the immediate postoperative period. Image courtesy of Dave Patel.

A timeline of novel corticosteroids

Years of research and development have led to several novel ophthalmic corticosteroid options that minimize or eliminate the patient's role in reducing postoperative inflammation:

- In February 2018, Dexycu (dexamethasone intraocular suspension 9%, EyePoint Pharmaceuticals) became the first and only FDA-approved intraocular corticosteroid, administered as a single injection to treat postoperative inflammation.
- In August 2018, the FDA approved Inveltys (loteprednol etabonate ophthalmic suspension 1%, Kala Pharmaceuticals), a twice-daily topical steroid for the treatment of inflammation and pain after ocular surgery.
- In November 2018, Dextenza (dexamethasone ophthalmic insert 0.4 mg, Ocular Therapeutix) was approved as an intracanalicular insert to treat postoperative ocular pain.
- In June 2019, the Dextenza insert was approved for the treatment of ocular inflammation.
- Most recently, in February 2019, Lotemax SM (loteprednol etabonate ophthalmic gel 0.38%, Bausch + Lomb) was approved for the treatment of postoperative inflammation and pain after ocular surgery.

topically; getting the right amount of drug in the eye. "Some patients may have corneas that do not process the steroids as expected. When this happens, we're really not sure how much of the drug is active within the eye once it's delivered on the surface (4)."

Ultimately, patients who are poorly adherent to their postoperative drop schedule tend to have a prolonged visual deficit because the inflammation can limit the quality of vision. Patel also highlights the additional risk of inflammation within the retina causing secondary effects, like macular edema. "The idea is really to prevent the nidus of inflammation, and using the steroids more aggressively has been shown to result in patients having better visual outcomes — and more steady outcomes — avoiding complications like retinal or macular edema."

Both surgeons said they have generally been successful using topical steroids to counteract inflammation, and that their typical regimens tend to be effective. However, plans that rely so much on patient adherence are inherently somewhat unreliable. Thus, Patel and McCabe argue that surgeons should welcome the array of FDA-approved options now available to mitigate some of this variability.

Alternative administration modes

Patients with a history of inflammatory conditions or risk factors that might predispose them to a more substantial postoperative inflammatory reaction (for example, anterior uveitis, diabetic macular edema, epiretinal membrane, prior retinal surgery, or retinitis pigmentosa) may benefit from an alternative approach. McCabe has begun to favor sustained-release options, such as Dexycu (dexamethasone intraocular suspension 9%, EyePoint Pharmaceuticals), or Dextenza (dexamethasone ophthalmic insert 0.4 mg, Ocular Therapeutix). Dexycu is injected into the ciliary sulcus at the end of cataract surgery, where it delivers a bolus of dexamethasone that tapers over the first few weeks after surgery, when it dissolves completely (see Figure 1). Dextenza is inserted into the lower lid tear canaliculus at the end of cataract surgery, where it elutes dexamethasone onto the ocular surface and gradually resorbs after about 30 days (see: Tackling drug delivery).

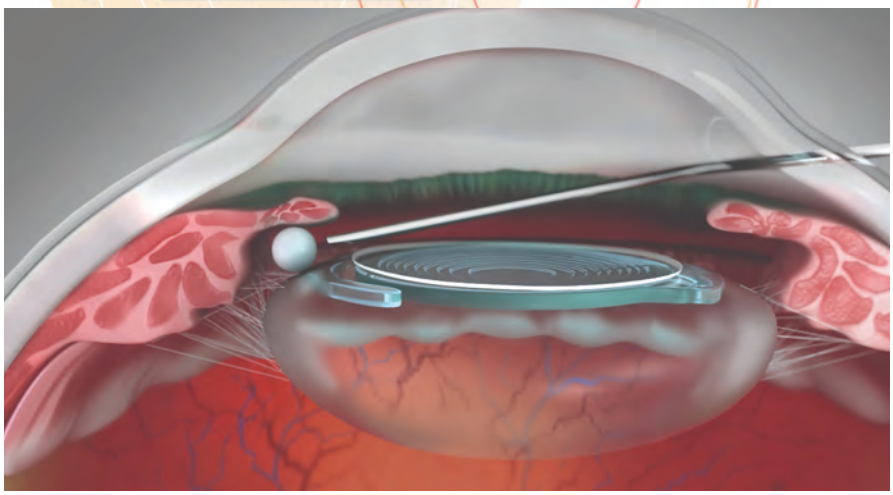


Figure 2. The bioerodible, sustained-release Dexycu is delivered behind the iris at the end of surgery. Image courtesy of EyePoint Pharmaceuticals.

"If I think there's a higher risk of inflammation postoperatively, I will use something that's less dependent on patient compliance. And that even includes when I think the patient might not be able to afford the drops. The idea is to insert something in the OR, so I don't have to rely on their ability to access the drug or to put the drug in," says McCabe. "In addition to eliminating compliance issues, putting the medication in the eye has some real advantages, such as providing constant dosing. Instead of peaks and troughs that may happen if there's a missed dose here or there, with an implant or insert we know that it's always there, and the dosage is tapered throughout the course."

Patel started out using Dexycu only in high-risk eyes, but he noted that there are many other clinical scenarios in which Dexycu may be useful, including routine cases. "I've also utilized Dexycu in eyes that are undergoing combination cataract and glaucoma surgery, because they tend to have more reaction within the chamber, requiring more steroids, or more frequently dosed steroids," he says. "I've chosen to use this intracameral formulation in the hopes that it can better control the inflammation, and resolve patients' post-surgical care in a rapid fashion."

"The advantage with Dextenza versus eye drops is that it may enable the patient to have a shorter duration of treatment, and patients are not required to administer it," says Patel. "However, with Dextenza, an enzymatic process has to take place for it to penetrate into the anterior chamber of the eye, which is no different than with the topically applied drugs. My concern with Dextenza is the possible variability of effect. We're not really sure how much of that drug is released, depending on the patient's anatomy, so we are essentially theorizing that it's a slow, sustained release, when in fact the concentration may be variable, depending on the eye being dry or lubricated, and how much of the implant is exposed within the tear duct."

So what now? It is clear that cataract

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Tackling drug delivery

A number of innovations in corticosteroid drug formulations have enabled improved delivery to the eye, including molecules with improved penetration and sustained-release drugs.

Better penetration

Changes to the formulation of an established ophthalmic steroid, loteprednol etabonate, aim to improve penetration into the eye and reduce dosing:

- *Inveltys.* Using mucus-penetrating particle (MPP) technology the company refers to as AMPPLIFY, Inveltys is able to better penetrate through ocular surface mucin barriers. According to preclinical data, it delivers 3.75 times more loteprednol etabonate to the aqueous humor compared with a traditional suspension. It is also differentiated from other topical corticosteroids by its indicated dosing schedule – twice daily, versus three or four times a day for other options (4).
- *Lotemax SM.* Similarly, Lotemax SM delivers loteprednol etabonate in a submicron particle size for faster drug dissolution in tears (5, 6), providing two times greater penetration to the aqueous humor compared with Lotemax Gel (7). The enhanced penetration enables less frequent dosing (three times per day), and ultimately, less reliance on patient adherence to the drop schedule.

Sustained-release

Two formulations of dexamethasone are designed to be placed by surgeons — one directly into the eye, one into the lower punctum — effectively removing patients' involvement in postoperative steroid administration:

- *Dexycu.* Formulated using the proprietary Verisome sustained-release technology, Dexycu is a cohesive, bioerodible liquid steroid depot injected into the ciliary sulcus at the end of cataract surgery, where it delivers a tapering dose of dexamethasone for about 21 days (see Figure 2). In controlled clinical studies, Dexycu provided a significant anti-inflammatory effect that began early and was sustained throughout the postoperative period (8, 9).
- *Dextenza.* Another dexamethasone delivery system, Dextenza uses a resorbable hydrogel device inserted at the end of surgery into canaliculus of the lower lid, where it remains in place for about 30 days, delivering a tapered dose of medication to the ocular surface (10).

surgery has come a long way: from extracapsular extraction and weeks of recovery to micro incisions and spectacle independence. Now that the surgery itself is so refined, one key to giving patients the best surgical experience and outcome is minimizing postoperative inflammation. It seems counterproductive to leave this crucial part of the process literally in the hands of patients, when options with less variability now exist. Novel anti-inflammatories will hopefully drive the future of postoperative treatment regimens and help provide patients with the best visual outcomes after cataract surgery.

Rochelle Nataloni is a medical writer, specializing in healthcare communications.

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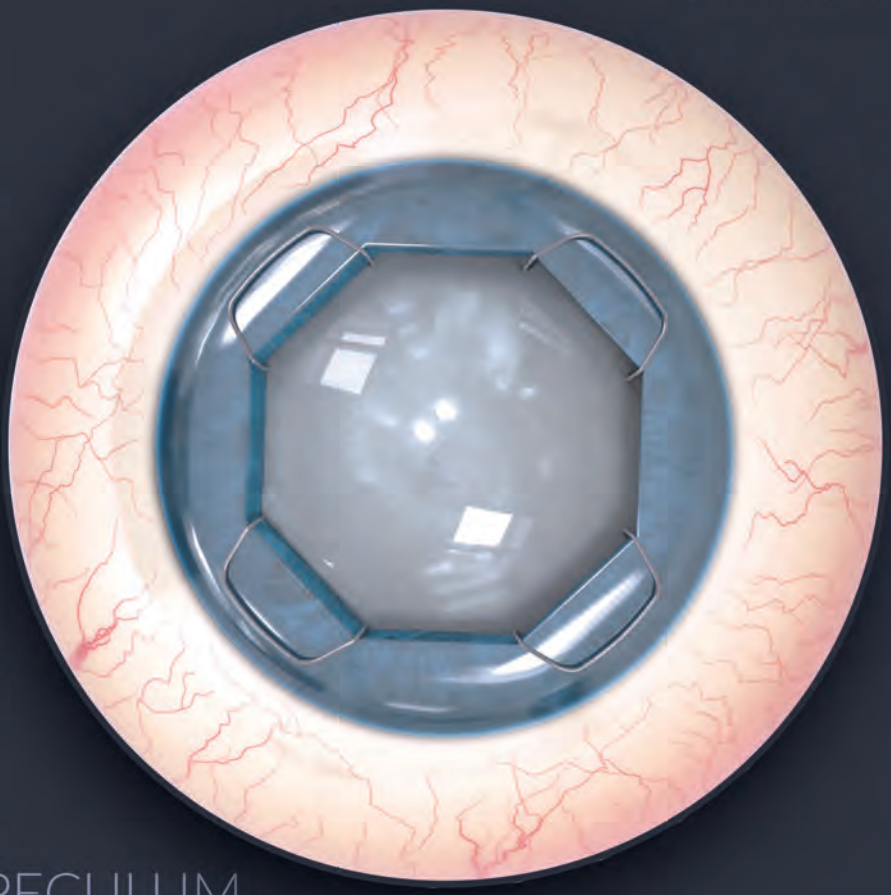

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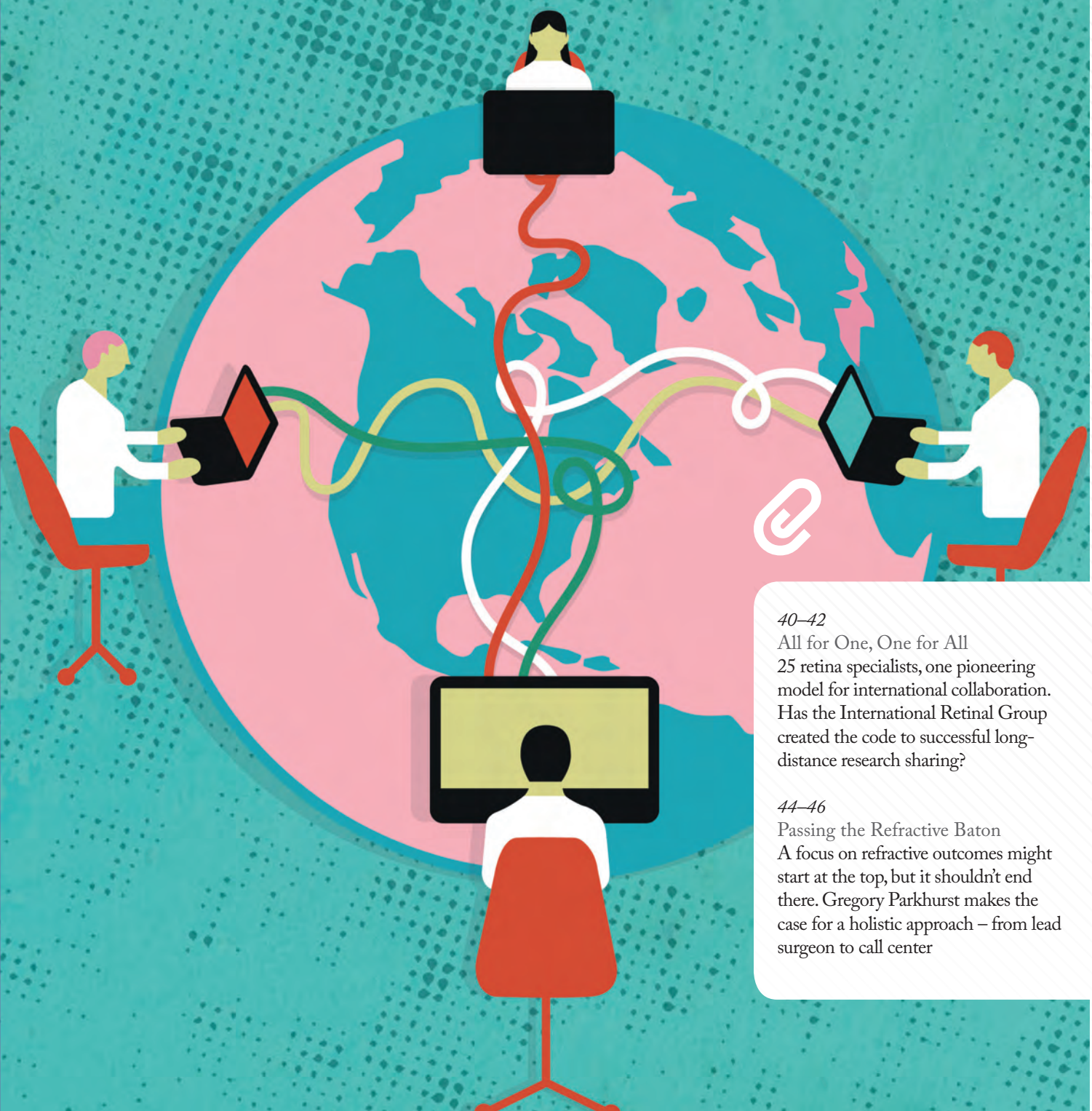


All for One, One for All

25 retina specialists, one pioneering model for international collaboration – this is the story of the International Retina Group

By Matias Iglicki and Dinah Zur

In 2016, Allergan launched the International Retina Panel: a mentorship program aimed at individuals who had shown excellence in clinical practice and research. For three years, Dinah and I worked alongside other passionate clinicians analyzing clinical cases and presenting our findings at conferences worldwide. Those same clinicians became our colleagues and in time, our friends. 12 months into the program, we realized we weren't ready to walk away from the network we had created. We decided to turn it into something else. A year later, we formed the International Retina Group (IRG): a collaborative network made up of 25 delegates from 14 countries – 12 retina surgeons and 13 medical retina specialists, with expertise in uveitis, imaging and epidemiology.

Our model is not completely unique – there are other collaborative networks in ophthalmology – but we are the only one (at least, the only one we know of) whose members don't hail from the same country, and the only one that operates without private funding. This has its advantages and disadvantages. While we are an independent group and we want to stay independent, financial support gives you the freedom to pursue bigger projects. We hope to secure altruistic funding ourselves in the future. But at the end of the day, the focus is on improving patients' lives, not our own careers. If we could offer advice to any researchers hoping to do something similar, let it be this: don't just do research for research's sake, do it for the purpose. Believe that what you are doing matters – and have a mentor.

During our time with Allergan, we were lucky to be mentored by Jayakrishna Ambati and Anat Loewenstein, who continued to act as our mentor after the course ended. Anat Lowenstein has been invaluable to the IRG. She has an excellent eye and every single correction, comment and suggestion she makes is taken on board. She offers productive feedback in as little as two or three days and has – we have no doubt – increased our chances of being published, by lending her input. But it is more than that. A mentor can also teach you essential "soft" skills, such as how to manage conflict. We are grateful for her support.

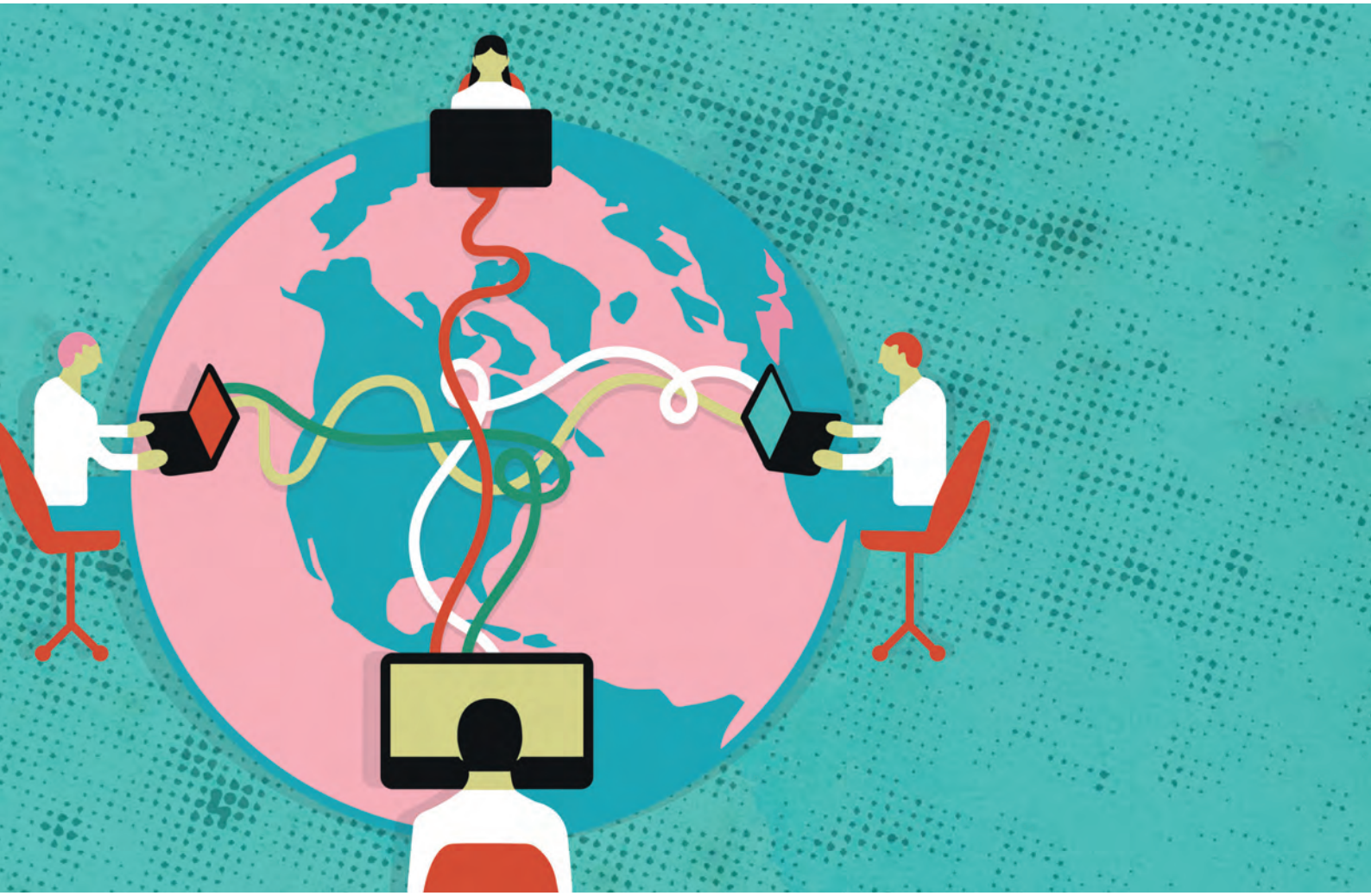
The way we work is simple [see box Collaboration Model]. The main research author has an idea which they share with the rest of the group, who then decide if it is worth pursuing. The main author sends a protocol and people choose whether or not to contribute – not every member has to contribute the same way. Some cannot send patient data, but they can take part in other ways, by running the statistical analysis, helping to write the paper or critical review, which is equally important. We usually set a deadline of a month for this part. Then comes the writing. When we all work together, we typically write a paper in three or four days. The time goes by quickly when you enjoy what you do. Once the manuscript is written, the main author then sends the manuscript to everyone in the group. Once our comments have been collated, we send the final draft to Anat Loewenstein, who has the final say. If she makes a suggestion, we take it on board – we know her supervision is key to our success.

"There is no big secret to making it work. You simply have to love what you do."

It's always 5 o'clock somewhere…

As you'd expect with such an international group (our members are spread from Australia to Argentina), productivity for us doesn't happen between 7 am and 7 pm. Since we are all practicing physicians, we do most of our research after clinic, between 7 pm and 7 am. The exception to the rule is the weekly call Dinah and I have every Saturday. We typically talk at 9 pm Dinah's time (in Israel), 3 pm my time (in Argentina). On the whole, time zones are irrelevant. We just work when we have the time. It goes without saying that if you are going to commit to working on a project in your free time, you have to be passionate about it – otherwise it is not going to happen. We have found the best way to get a paper done is by enjoying the journey. It may take six or seven months before the paper is published.

If you don't enjoy the process, it will take a lot longer and you will resent it, which is why we make a point of enjoying every meeting for what it is. We ask about each other's families, how the children are, and then we get to work. Those meetings are used to discuss everything from statistical analysis to the best journal for each paper. It is very international, open and collaborative, and through



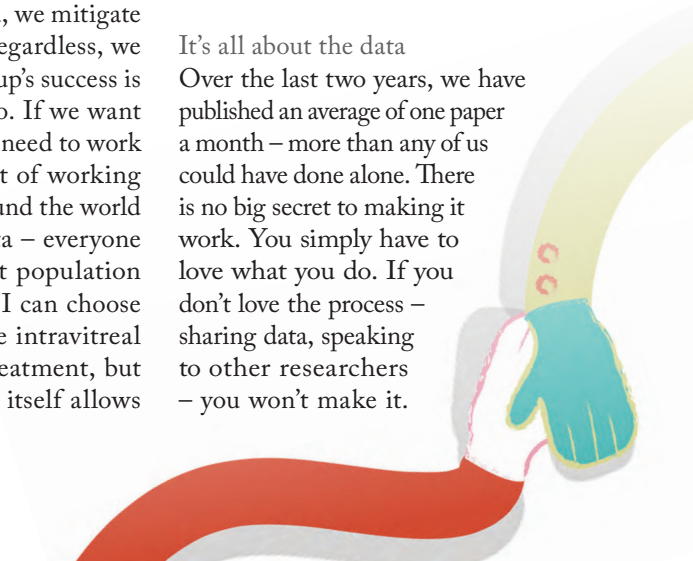
making sure every opinion is valued, everyone is happy with the outcome. Of course, that does not necessarily mean we always all agree! Not everyone contributes every time, and that is okay. Sometimes people will say: "If you don't take my revision, please leave me out of the paper," and we respect their wishes. Ultimately, our network is based on friendship, and preserving that friendship is crucial.

Pack mentality

People tend to assume that there must be competition in a group this large, but that is not the case. Allergan wisely chose delegates from all around the world – one or two per country – and in cases where there were more, for instance, three in Australia, they worked in very different places. And for good reason. No matter how well you get along, when you work in the same field, there will be times when you inevitably fight for the same positions. By working all over the world, we mitigate any conflict of interest. Regardless, we take the view that the group's success is our individual success, too. If we want to truly be productive, we need to work together. Another benefit of working with researchers from around the world is the diversity of our data – everyone brings a different patient population to an issue. For example, I can choose Ozurdex (dexamethasone intravitreal implant) as a first line treatment, but Dinah cannot, so that in itself allows us to study diverse patient populations undergoing a variety of local treatment regimens. Our papers cover a range of retina topics, from choroidal tumors to the impact of the dexamethasone implant on diabetic macular edema.

It's all about the data

Over the last two years, we have published an average of one paper a month – more than any of us could have done alone. There is no big secret to making it work. You simply have to love what you do. If you don't love the process – sharing data, speaking to other researchers – you won't make it.



Collaboration model

- Idea
- Group discussion
- Email protocol
- Send data
- Run statistical analysis
- Write paper
- Review
- Send to journal

Our network only works because of the people; each and every member of the group has a close relationship with everyone else. If you would like to do something similar, find people that you that you like and trust – and don't be afraid to share data. People can be possessive – rightly or wrongly – but you have to think of the bigger picture: improving patients' lives. The saying goes: "we are stronger together" and it is true! Take advantage of other people's skills, and combine your advantages. Take Dinah and myself for example: Dinah is excellent at referencing, whereas I love English grammar. We are both very open for improvement, which is a bonus.

By writing these papers, we hope to answer the questions we ask ourselves as clinicians. The paper we are currently working on came about that way. Dinah noticed that there was some kind of scar or subretinal exudate on the macula of DME patients who had undergone vitrectomy as a first-line treatment. We were afraid this would lead to irreversible vision loss, but instead of just saying "This is very bad," we decided to follow up on those patients. We saw that the reflectivity would decrease over time so we hypothesized that this may be due to inflammation in diabetic eyes without the scaffold of the vitreous. Interestingly, when we imaged the same patients a few months later, the sign had disappeared. It was only by sharing our experiences that we were able to see that this wasn't something to worry about.

Your own experiences are a great source of research inspiration. We made a WhatsApp group for IRG members so we could consult about difficult cases. What often starts as a "Hey, has anybody seen this before?" can lead to a new study. Ultimately, it is comforting to be able to share our findings with other physicians, so we can share them, in turn, with our patients.

There you have it: our blueprint for international collaboration. We hope it works as well for you as it has for us. Our thanks go to Allergan for getting us together for the first International Retina Panel meeting in 2016. We might have created the social and scientific network, but they gave us the tools – and we will continue to use them wisely. Good luck!

Matias Iglicki is a Retinal Surgeon and Researcher from the University of Buenos Aires, Argentina. Dinah Zur is a Retina Specialist at Tel Aviv Medical Center and a Clinical Senior Lecturer at Tel Aviv University, Israel.

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A Refractive Outlook for All

A focus on refractive outcomes might start at the top, but it shouldn't end there

By Gregory D. Parkhurst

As ophthalmologists, we like to consider our surgical skill as the essential component in achieving great outcomes and high patient satisfaction after cataract surgery. But without a team of people gathering information and helping to educate patients along the way, building a successful refractive cataract surgery practice would not be possible.

My practice, Parkhurst NuVision, is centered on a refractive philosophy that permeates through every position – from the lead surgeon to the call center. Simply put, we believe that everyone ought to have the opportunity to see their best without being dependent on prosthetic eyewear.

Every year, we shut down our clinic for a day to talk about this philosophy. We share five-star reviews and celebrate successes with the whole staff. We've also started the Parkhurst NuVision Eye2Eye Global Initiative, which is similar to the Toms Shoes' corporate responsibility model. For every patient who undergoes refractive surgery with us, we fund an operation through the Himalayan Cataract Project or charitable work elsewhere around the world. Our team members are incredibly excited and motivated to know they are not only making an impact to the patient in front of them, but also helping to cure a blind person elsewhere in the world.

The start of the journey

We are an optometric referral practice, and our patients' education on cataract surgery and IOL options begins well before they walk through our doors. Typically, an optometrist who already has a relationship with the patient starts the conversation by explaining: "Some of the procedures you're going to hear about are fully covered by insurance. Others are partially covered, but there might be a few thousand dollars on top of what insurance pays. The surgery center is going to discuss all your options with you."

To streamline the education process, we have implemented a new QR code communication tool, available from Ocular Innovations. Our referring optometrists have business cards with a QR code that links to our practice. All the doctor has to do is say, "I'm going to refer you to Dr Parkhurst. You can

"Our patients' education on cataract surgery and IOL options begins well before they walk through our doors."

open up your phone camera and scan this QR code." The patient is then automatically sent a series of short custom videos created by our team (Figure 1). Not only is this an efficient way to ensure patients consistently get critical information in advance, but it also conveys a high-tech impression for both us and the referring practice.

First contact

We have a call center team that receives all phone and website inquiries, and proactively reaches out to patients whose optometrists have faxed us a referral form. The physical layout of our office allows our entire team to be connected through a central hallway, so the call center team is not detached from the rest of the practice. That way, if a patient has a question that needs to be answered by a doctor, the phone agent can walk down the hall and grab a doctor to resolve the issue quickly.

For many cataract patients, this initial contact is brief. They already know that they have a cataract, they need surgery, and will have a consultation with us. But if they bring up specific procedures or technologies, the call center staff will tell them, "We actually perform eight different modern treatments. One of the reasons you should come to see us is because we're going to do a number of diagnostic tests. You'll meet with the doctor and they'll help you decide which of the different options is the best fit for your eyes."

The in-office experience

When a patient walks through the door at our practice, they are greeted by someone who's paying attention to them. Because we have the call center team handling calls in the back, the front desk receptionist's job is strictly to welcome patients.

The front desk then hands the patient to our "ophthalmic navigators" – we prefer using this term over "technician" because their job is to navigate patients through the diagnostic work-up of their eyes. The navigator has been trained not only to perform the relevant tests, but also to show the patient the results and, in the process, give them a mini anatomy lesson. This is important because invariably, patients think a cataract is something like a pterygium — a growth or film over the eye. If patients think a cataract is external, they don't understand why after surgery they would need an implant, let alone a premium lens. Therefore, the navigator's role is essential in helping the patient understand the problem, before we start discussing the solution.

Weighing up the options

The next person the patient sees is usually one of my in-house optometrists, all of whom have completed a residency in anterior segment and refractive surgery. They continue the process of educating patients on what a cataract is and what types of IOLs we might be considering. Part of that process is gathering information about the patient's profession, hobbies, and how they tend to use their eyes.

Assessment of the patient's preexisting refractive error is a major factor in our decision making. A myope who removes his glasses to read has a very different life experience than a hyperope, high myope, or someone wearing progressive spectacles or multifocal contact lenses — and we need to recognize that in making IOL and refractive target choices. Throughout this process, the navigator and the optometrist are searching for information that will help them narrow down the list of IOL possibilities for that patient, so that we can present just a couple of options.

Presenting the choice

Before choosing from our wide range of

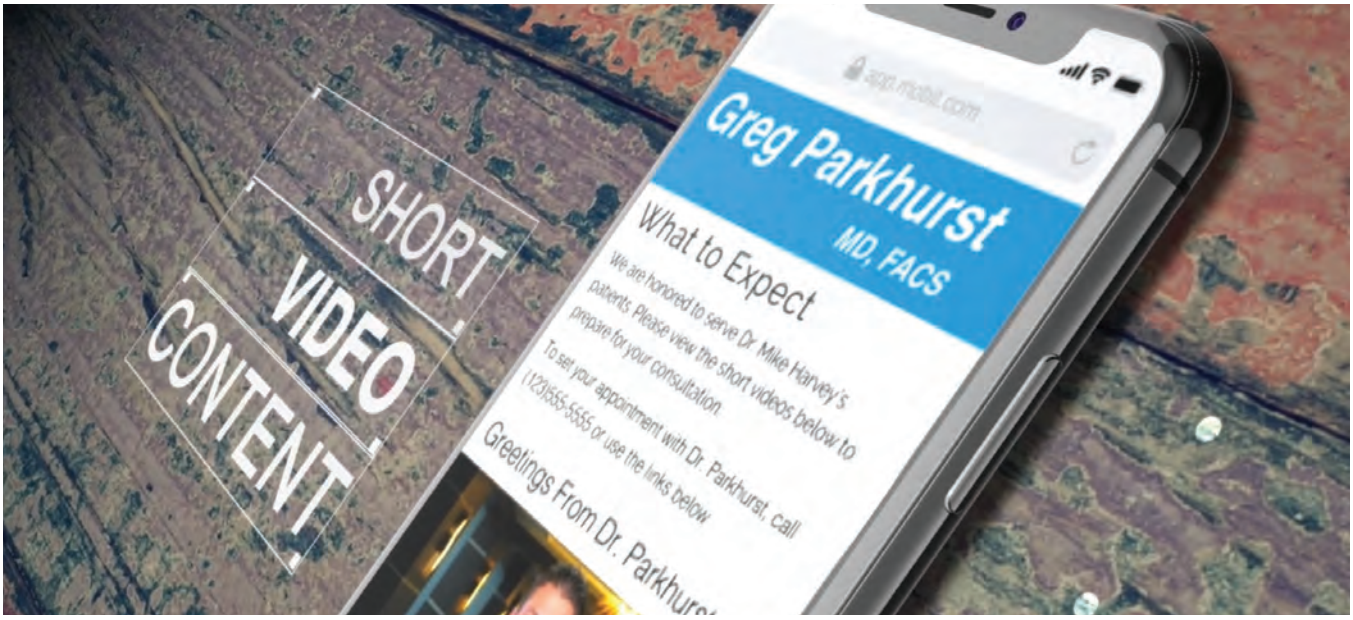

Figure 2. Using QR scanning, referring optometrists are able to easily direct patients to short educational videos created by the practice.

refractive IOLs, we ask ourselves a series of questions:

- Is there something besides cataract, for example epiretinal membrane or macular degeneration, that will affect this patient's visual potential?
- Does this patient have so much astigmatism that we need to use a toric IOL to correct it?
- Which distance is more important to the patient's daily life – near or intermediate?
- Do they need a high add power for near activities?

For patients with other complicating factors, I often suggest that we either maximize their distance vision or their near vision with a monofocal platform. For patients without significant ocular comorbidities, who want more spectacle independence, we now have two great options that are both suitable, depending on the desires of the patient. The TECNIS Symfony (Johnson & Johnson Vision) EDoF platform offers a continuous range of vision in all lighting conditions, although patients may not be able to do fine or sustained near tasks without reading glasses. I sometimes consider a "personalized vision" approach, in which we combine two different IOLs, such as an EDoF in the dominant eye, and a mid-add multifocal in the nondominant eye, to achieve specific goals for the patient. In other instances, we consider the new trifocal PanOptix (Alcon), which reaches distance, intermediate, and near targets. In addition to these already FDA approved IOLs, we are also clinical investigators for a small aperture IOL (IC-8, AcuFocus), and a new accommodating IOL (SC-9, CORD LLC), so those are also potential choices, depending on the patient's goals, and suitability for enrollment.

Closing the loop

The patient counselor is the last step of the journey, helping the patient by reviewing logistics, going over insurance coverage, and scheduling appointments for surgery, as well as postoperative follow-up. They also use simple tools to demonstrate what the expected outcome is for the patient, for each of the different IOL options presented by the doctor. This helps to set expectations and confirms that the patient has understood the difference between the available treatment choices.

After the consultation, we always communicate back to the optometrist who referred the patient, letting them know which type of surgery the patient will be having, and when they can expect to see them for postoperative care.

With this process, our entire team is involved in educating patients, navigating their choices, and helping us continue to build a strong refractive cataract practice.

Gregory Parkhurst is Medical Director of Parkhurst NuVision in San Antonio, Texas, USA. He serves on the Medical Advisory Board for Ocular Innovations, Inc.

He is an investigator for CORD and AcuFocus, and a consultant for J&J and Alcon.

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Sitting down with… Keith Martin, Ringland Anderson Professor and Head of Ophthalmology, University of Melbourne; Director, Centre for Eye Research, Australia and President, World Glaucoma Association

Why did you decide to focus on ophthalmology?

I have always been a keen musician and when I was a medical student, I was lucky enough to interview Jeffrey Tate – a highly successful orchestral conductor who initially trained in medicine. I asked him what he would have done if he'd stayed in medicine and, without a moment's hesitation, he said: ophthalmology. He talked about the balance between medicine and surgery, the precision required, and the sheer beauty of the eye as a structure. I'd had very little exposure to ophthalmology as a medical student – I was fascinated by neuroscience and thought I would become a neurologist. But that conversation really stuck in my mind. A few years later, after realizing that neurology wasn't for me, I thought I'd try ophthalmology for six months – that was 24 years ago!

"I have always been a keen musician and when I was a medical student, I was lucky enough to interview Jeffrey Tate – a highly successful orchestral conductor who initially trained in medicine."

Who were your most important teachers?

Some of my most influential mentors have been clinician-scientists with a passion for translation. Ophthalmology legend Peter Watson was a huge early influence on me – with his pioneering work spanning glaucoma, scleritis, corneal transplantation and ocular immunology – and he remained a close friend and mentor of mine until his death in 2017. Harry Quigley at Johns Hopkins University gave me my first break in glaucoma research and taught me to be rigorous and questioning. And Peng Khaw not only provided fantastic fellowship training in pediatric glaucoma at Moorfields Hospital London, but has also continued to provide wise guidance as my career has developed. He's also been an ongoing masterclass in ophthalmic advocacy.

How has ophthalmology changed over the course of your career?

Progress is often driven by technology, and the technological changes we have seen in ophthalmology have been nothing short of astounding. We now have better tools to assess the structure and function of the eye non-invasively than we have for any other part of the body. We can assess the retina at single-cell resolution and measure responses to just a few photons of light, all with instruments that are part of routine clinical care. Surgical technology has also made enormous progress and we now have the first-ever licensed gene therapy being used to treat patients with inherited eye disease. And this is just the start – we live in interesting times for ophthalmology.

What have been your proudest achievements?

Many of my proudest achievements have, of course, been related to my family. But aside from these, there are a number of clinical and scientific achievements that I'm proud of. On the research side, co-founding a gene therapy company from my lab in Cambridge and seeing that project being taken forward towards clinical development for glaucoma has been a great learning experience. Clinically, seeing some of the babies I've treated with congenital glaucoma becoming happy and successful young adults has been pretty amazing. But I hope my most useful contributions are still to come.

"Clinically, seeing some of the babies I've treated with congenital glaucoma becoming happy and successful young adults has been pretty amazing."

What are you working on right now?

My work is focused on developing new strategies to protect and repair the optic nerve. We are using gene therapy and other approaches that we hope will reduce vision loss and blindness in people whose glaucoma is progressing despite effective treatment to lower their intraocular pressure. We are currently collaborating with experts in brain and spinal cord repair to work out how to guide regenerating

optic nerve axons back to their central targets. Also, I have recently moved from Cambridge to become Director of the Centre for Eye Research Australia and Chair of Ophthalmology at the University of Melbourne, and I've been enjoying the challenge of helping drive translational research – not just in glaucoma, but across many other areas of unmet need within our specialty.

What is your ultimate goal for this field – for patients and clinicians?

I think we are finally moving into an era when reducing eye pressure will not be the only established treatment for glaucoma. I believe that clinical trials to test therapies that protect – and ideally enhance – optic nerve function are not just possible, but essential. Looking further ahead, I think restoring some useful visual function to those blind due to optic nerve disease will pose huge challenges, but these are not insurmountable.

The ultimate goal of glaucoma treatment is simple – to minimize the effect the disease has on the quality of life of our patients. I believe that we will develop technologies with the potential to make glaucoma-related

blindness a thing of the past. But in a world where cataract still remains the leading cause of blindness, it is worth remembering that it is not what we can do – it is what we actually do that matters.

What advice would you give to those following in your footsteps?

We are lucky to have some really talented clinician-scientists in our field. I hope and expect to see them leading our field, not following!

Dextenza®

(dexamethasone ophthalmic insert) 0.4 mg
for intracanalicular use

NOW USE UNIQUE BILLING CODE J1096

The only sustained-release steroid approved for the treatment of inflammation and pain following ophthalmic surgery

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- Designed to deliver a tapered dose[1]
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- Insert can be removed via saline irrigation or manual expression, if necessary[2]
- Physicians rated DEXTENZA as easy to insert[3,4]*

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INDICATION

DEXTENZA is a corticosteroid indicated for the treatment of ocular inflammation and pain following ophthalmic surgery.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

DEXTENZA is contraindicated in patients with active corneal, conjunctival or canalicular infections, including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella; mycobacterial infections; fungal diseases of the eye, and dacryocystitis.

WARNINGS AND PRECAUTIONS

Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Steroids should be used with caution in the presence of glaucoma. Intraocular pressure should be monitored during treatment.

Corticosteroids may suppress the host response and thus increase the hazard for secondary ocular infections. In acute purulent conditions, steroids may mask infection and enhance existing infection.

Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex).

Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal culture should be taken when appropriate.

Use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation.

ADVERSE REACTIONS

The most common ocular adverse reactions that occurred in patients treated with DEXTENZA were: anterior chamber inflammation including iritis and iridocyclitis (10%); intraocular pressure increased (6%); visual acuity reduced (2%); cystoid macular edema (1%); corneal edema (1%); eye pain (1%) and conjunctival hyperemia (1%).

The most common non-ocular adverse reaction that occurred in patients treated with DEXTENZA was headache (1%).

Please see brief summary of full Prescribing Information on adjacent page.

*73.6% of physicians in Study 1, 76.4% in Study 2, and 79.6% in Study 3 rated DEXTENZA as easy to insert.

References: 1. Sawhney AS et al, inventors; Incept LLC, assignee. US patent 8,409,606 B2. April 2, 2013. **2.** DEXTENZA [package insert]. Bedford, MA: Ocular Therapeutix, Inc; 2019. **3.** Walters T et al. *J Clin Exp Ophthalmol*. 2016;7(4):1-11. **4.** Tyson SL et al. *J Cataract Refract Surg*. 2019;45(2):204-212.

Ocular Therapeutix™