MAY 2019 # 33

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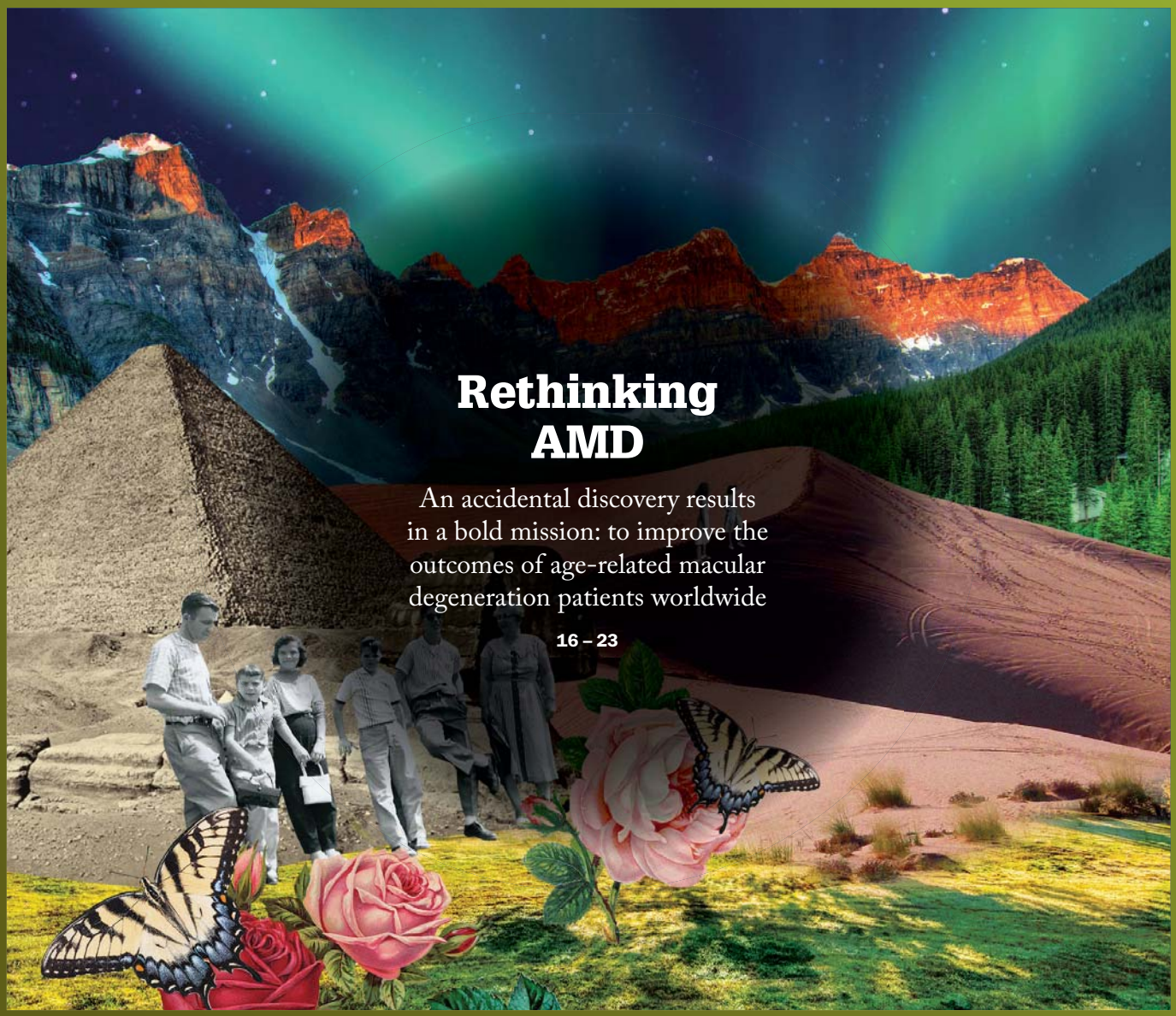

Rethinking AMD

An accidental discovery results in a bold mission: to improve the outcomes of age-related macular degeneration patients worldwide

16 – 23

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Image of the Month

A Horse Shoe Tear

This month's image shows a peripheral retinal detachment (120 degrees out). The detachment was missed during a routine eye test, but picked up using the ultra-widefield capability of an Optos device. The patient had laser treatment the next day, and his sight was saved.

Credit: Craig Wilcox, Classic Eyes, Dorset, UK

Do you have an image you'd like to see featured in The Ophthalmologist? Contact edit@theophthalmologist.com

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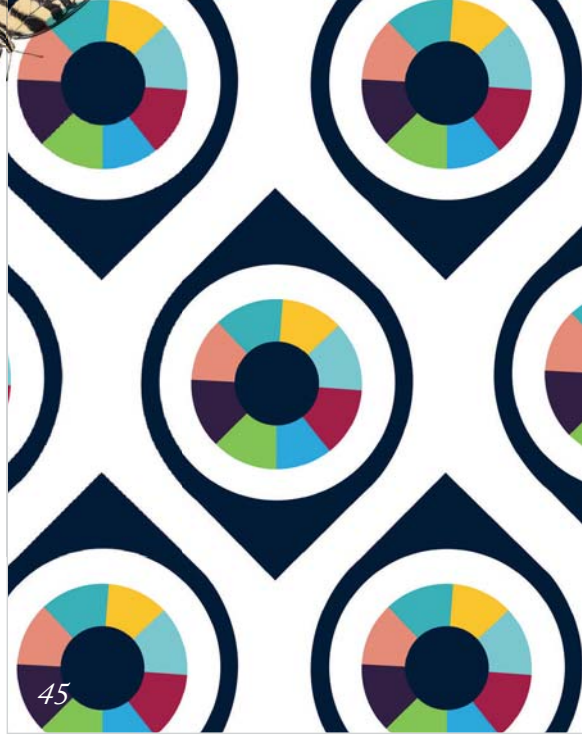

Upfront

In My View

On The Cover

The dark spot represents the deterioration of AMD patients' vision

the Ophthalmologist

Feature

In Practice

NextGen

Profession

Sitting Down With

the Ophthalmologist

ISSUE 33 - MAY 2019

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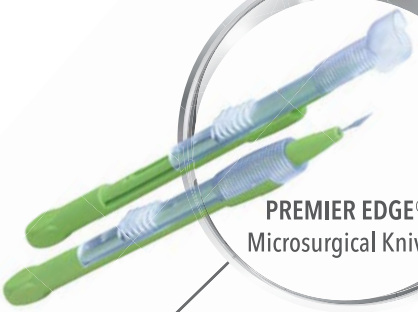

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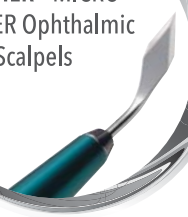

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Reality Check

Regular eye tests are important for us all – but they are vital for the world's children.

In a quick office poll, 60 percent of my co-workers declared that they have been for a professional eye test within the last two years – a percentage that should be closer to 100 given guidelines, the number of people sitting in front of computer screens, and the relative ease of accessing eye tests.

Screening children's vision is even more important. And though children in developed countries are likely to have their vision checked multiple times, increasing the chances of resolving any issues by the critical age of 4-5, the situation looks very different in developing countries. In India, there are currently no formal national vision and eye screening guidelines for children (1). In Nepal, children's eye screening relies on the work of volunteers.

Ophthalmologists certainly provide invaluable support in regions struggling to provide appropriate eye care; nominations to the Champions of Change category in our recent Power List (2) prove that point, as does our recent feature on ophthalmology in remote locations (3). But is there any way we can *all* do more?

I recently spoke to Rahul Ali, Country Director for Orbis India. He told me about the largest national network of Children's Eye Centers in the world – 33 in 17 states – which Orbis created, and about the Refractive Error Among Children (REACH) program that started in India in 2016, and is now being implemented in Nepal.

Ali also stressed how important comprehensive school-based screening is for children's education and future prospects – and for simply allowing them to enjoy being children. Seven-year-old Rabi from Nepal was diagnosed with myopia through an Orbis-supported screening program; his teacher immediately noticed how much more outgoing and interactive he became when his vision problems were properly addressed. When my son was recently asked what he wanted to be, he replied incredulously: "A kid!" – and with corrected vision Rabi is now able to fully embrace childhood.

Orbis is currently fundraising for the See My Future appeal (4), which aims to provide screening for 300,000 children in Nepal. I want to help change the eyecare landscape in Nepal – even in the smallest way – and I hope you will, too.

Aleksandra Jones
Editor

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2. *"The Power List 2019", The Ophthalmologist, 64, 16 (2019).*
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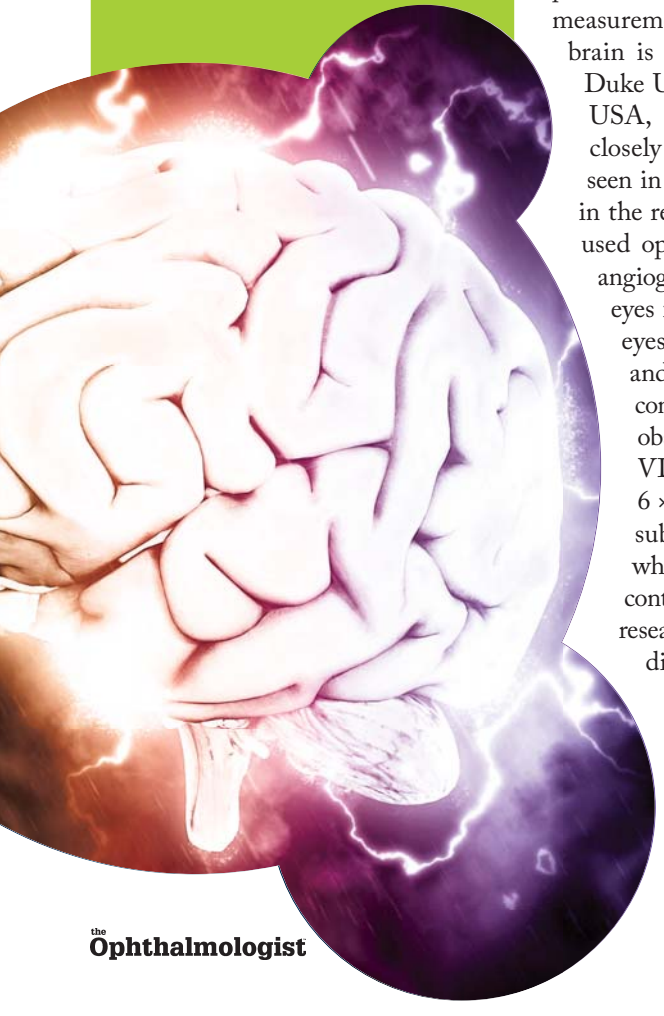
Upfront

Reporting on the innovations in medicine and surgery, the research policies and personalities that shape the practice of ophthalmology.

We welcome suggestions on anything that's impactful on ophthalmology; please email edit@theophthalmologist.com



Alzheimer's Window

OCT-A imaging points to a potential diagnostic tool in older people

Accounting for around two thirds of all dementia cases in older people, Alzheimer's disease (AD) places a huge burden not only on patients but also their carers and health systems all over the world. Research into novel treatments is ongoing, but the development of new tools to enable earlier diagnosis is another key focus.

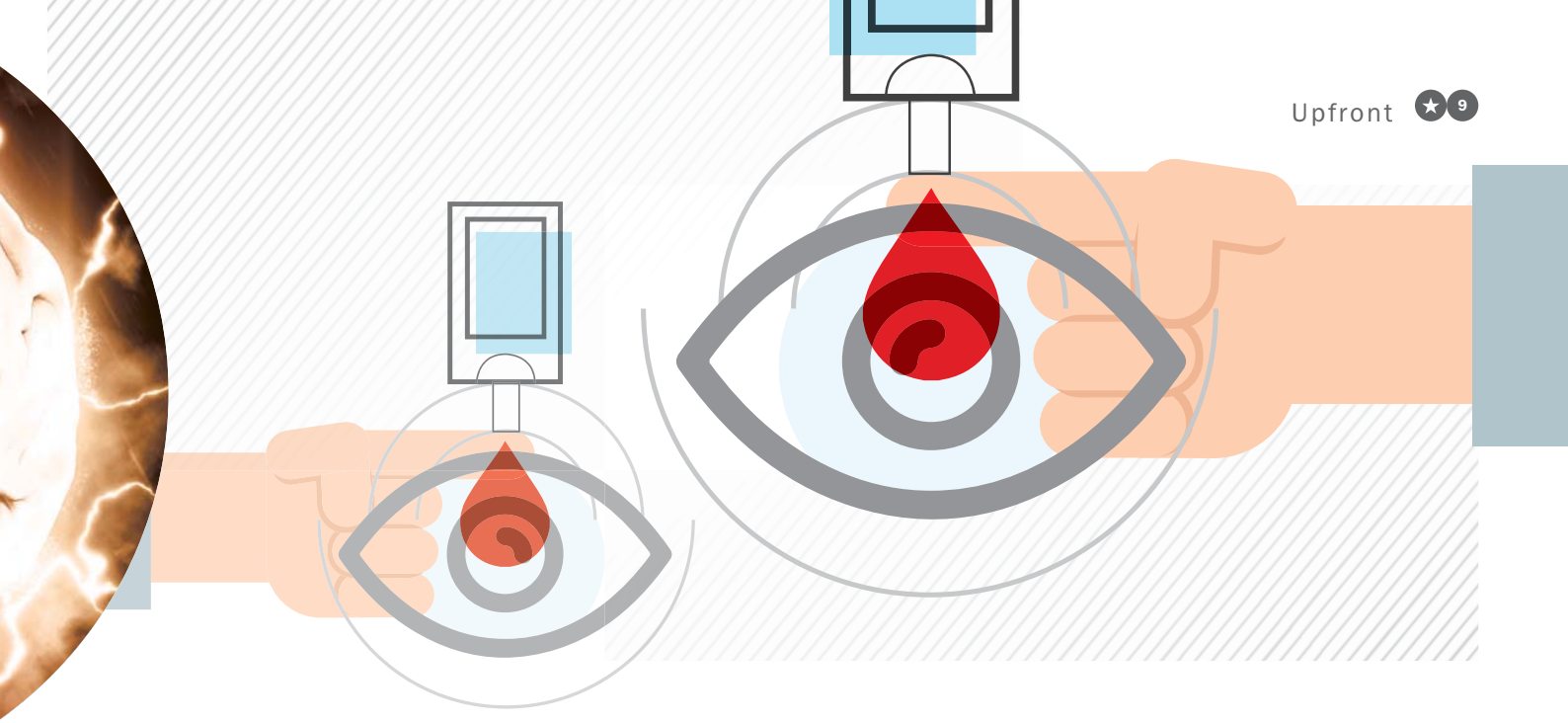
Cerebral microvascular changes are increasingly linked to AD and also mild cognitive impairment (MCI) – a potential early-warning sign of AD, but measurement of such changes in the brain is challenging. Researchers at Duke University in North Carolina, USA, decided to investigate how closely the microvascular changes seen in the brain would be mirrored in the retina. To that end, the group used optical coherence tomography angiography (OCT-A) to image 90 eyes from 52 AD participants, 79 eyes from 41 MCI participants, and 269 eyes from 142 healthy controls (1). The results? The team observed significantly decreased VD and PD (in 3 × 3-mm and 6 × 6-mm scans) using ETDRS subfields in AD participants when compared with MCI and control participants. However, the researchers did not see a significant difference between MCI and healthy controls.

Notably, the study excluded patients with other diseases, such as non-Alzheimer's dementia, high blood pressure, glaucoma and diabetes, so it is unknown whether the differences seen in OCT-A are unique to AD. Nevertheless, the researchers' objective remains unchanged. "The goal is to one day be able to diagnose Alzheimer's disease in the very early stages," says corresponding author Sharon Fekrat, Professor of Ophthalmology at Duke University.

For now, the team will continue collecting longitudinal data, as well as studying larger populations, both of which will be crucial in understanding how the retina's microvascular changes as the disease progresses. Moreover, Fekrat emphasises that, though OCT-A imaging may not offer the early diagnosis they were looking for, all is not lost: "We may have a non-invasive, inexpensive, and quick way to screen large numbers of people for Alzheimer's disease and enter these individuals into clinical trials," she says. And that can only be good news for other teams investigating potential therapies.

Reference

1. *SP Yoon et al., "Retinal Microvascular and Neurodegenerative Changes in Alzheimer's Disease and Mild Cognitive Impairment Compared with Control Participants", Ophthalmol Retina (2019).*



Eye-lets in T1D

How transient immune intervention unlocks transplant tolerance in type 1 diabetes

A recent preclinical study by the Diabetes Research Institute (DRI) at the University of Miami Miller School of Medicine has shed new light on islet transplantation for type 1 diabetes. By introducing an anti-CD154/CD40L blocking antibody, researchers found that islets transplanted into the eye survived long-term without continuous immunosuppression – and they also improved peripheral immune tolerance.

The researchers hope the work could unlock the potential of islet transplants for diabetes sufferers – without the downsides of immune suppression. "The best anti-rejection therapy we know of today is generalized – systemic – immune suppression," says Midhat Abdulreda, Assistant Professor of Surgery and lead author of the study. "Though drug advances have generally improved the survival of solid organ transplants, the side effects of chronic systemic immune suppression, such as cancer formation and stubborn infections that can lead to sepsis, can be life-threatening. This is what we're trying to eliminate."

The team split the participating mice into two groups, transplanting islets into the anterior segment of the eye of the experimental group, and into the kidney of the control group – all animals were then treated with CD154/CD40L-blocking antibody.

The results? Both groups experienced immunosuppression-free islet survival of more than 300 days. After 284 days in the kidney group and 412 days in the eye group, the researchers performed a second transplant of islets into the kidney (the kidney group also received a simultaneous nephrectomy to remove the first transplant) to evaluate peripheral immune tolerance. Promisingly, over 70 percent of the eye transplant group experienced more than 400 days' survival of the second islet transplant without continued immunosuppression, compared with just 30 percent of those who initially received islets in their kidney.

"Our preclinical studies in animals indicate that, without proper conditioning of the recipient, immune-mediated rejection of islet grafts from mismatched donors will be attacked in the eye. However, our recent findings suggested that conditioning the mouse recipients and a non-human primate (baboon monkey) with a relatively mild and transient immune intervention resulted in significant prolongation in survival of mismatched islet grafts, both in the eye and in the kidney," explains Abdulreda. "Our findings also showed a slight advantage of the eye, as a transplant site, in promoting better survival of mismatched islets upon a second transplantation in the same recipients. We don't fully understand the reasons for this yet, but we believe this makes the eye an attractive site for islet transplant, and worthy of future studies for potential human application."

Though excited about recent findings, Abdulreda acknowledges that the next step will be more challenging. "We're currently evaluating the safety and potential efficacy of implanting islets in the eye of legally blind diabetic patients in an FDA-approved clinical trial. This will be critical for future clinical studies building on our preclinical and translational research."

The team are also planning to evaluate the efficacy of localized immune intervention administered via eye-drops as an alternative to systemic immune suppression.

Reference

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White Out

Could nitisinone increase melanin production in patients with albinism?

Researchers at the National Eye Institute (NEI) believe that nitisinone may increase melanin production in people with oculocutaneous albinism type 1B (OCA-1B). Patients with OCA-1B experience decreased visual acuity, glare sensitivity and, in many cases, nystagmus, which further degrades image quality. OCA-1B is the most common form of albinism in the USA and it is characterized by a mutation in the gene that codes for tyrosinase. Tyrosinase breaks down the amino acid tyrosine and is the first enzyme in the pathway to melanin.

But what is it that makes melanin so important to the development of normal vision? "The truth is we really don't know," says Brian Brooks, clinical director at the NEI and lead author of the study. "There is something – likely something indirect – about the process of making melanin that can also affect the development of the cells of the retina. What's particularly odd is that the cells of the retina where we see developmental abnormalities clinically do not express the genes for making melanin. It's the neighboring retinal pigment epithelium and the melanocytes of the choroid that make the melanin," he explains. "A fair amount of excellent work has focused on the role of L-DOPA, which is an intermediate in the process of melanin production, which can exert some developmental effects on the retina – but that's just part of the story."

In an attempt to find out more, the pilot study followed three women and two men with OCA-1B over 18 months. Each patient was given a two milligram oral dose of nitisinone every day for 12 months, along with six additional months without the drug. Why nitisinone? "We know from basic biochemistry that one way to stabilize an enzyme is to increase the amount of its starting material or substrate. Nitisinone blocks the degradation of tyrosine, which has the side effect of raising its plasma levels. So, we are using a known side effect of this medication to flood the unstable tyrosinase enzyme with lots of tyrosine (substrate), making it more stable."

The results? Most participants experienced a slight darkening of skin and hair, and one participant experienced a slight darkening in skin color after sun exposure. Though the team was unable to detect clinically significant changes to melanin production or visual acuity, Brooks remains hopeful that nitisinone could benefit patients with OCA-1B. "We're confident for a couple of reasons. One, we saw the effect in mice and, two, it is not uncommon for younger patients to have more 'plasticity' in their visual systems. In our pilot study, the patient who showed the most change in his skin and hair melanin was on the younger side," he explains.

"That being said, I don't suggest ophthalmologists prescribe nitisinone to their patients with albinism outside of a well-monitored and controlled clinical trial," warns Brooks. "Although we did not see any serious adverse events in our pilot study, nitisinone can have significant side effects and patients need to be regularly monitored while they are on it."

Brooks and his team hope to build on this research by running the trial with younger patients. They also hope to look into nitisinone's efficacy on other forms of albinism.

Reference

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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).

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

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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; 2018. **3.** Walters T et al. *J Clin Exp Ophthalmol*. 2016;7(4):1-11.

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The CLASS of 2019

Safe, accurate, efficacious – is CLASS the new NPDS?

Trabeculectomy is a traditional and common surgical intervention for IOP reduction in patients with open-angle glaucoma. CO2 laser-assisted sclerectomy (CLASS) procedures are less common but, according to a recent study, no less effective. Now, researchers have directly compared trabeculectomy with CLASS (1). In an examination of 70 eyes – 37 in the trabeculectomy group and 33 in the CLASS group – the CLASS group reported a success rate of 97.2 percent, an increase on the 80 percent experienced by the NPDS group. We asked Juan Carlos Izquierdo, Chief of Glaucoma at the Oftalmosalud Eye Institute in Lima, Peru, and lead author of the study, to tell us more.

What inspired the CLASS study?

We were looking for a more controlled procedure, with a high rate of safety on one hand and with a similar efficacy to trabeculectomy on the other. That alternative was CLASS. Our experience with trabeculectomy showed good efficacy, but was associated with a relatively high rate of post-operative manipulations because of adverse events or complications, mostly associated with hyphotony or bleb-related complications. CLASS aims to solve both problems. As a non-penetrating procedure, the aqueous outflow is based on the natural flow without the major resistance to the outflow, and it includes an alternative absorption pathway – the intra-scleral (or suprachoroidal) pathway –which reduces the dependency on the bleb and, therefore, far fewer bleb-related complications are observed. Performing laser assisted deep sclerectomy also adds the benefits of the laser itself: the laser is accurate, simple to control and operate, and it is very reproducible. This gives confidence to the user and in turn, the patient.

Any other benefits?

CLASS has a good safety profile and very good efficacy, which has already been proven in the long-term. The main benefit for the patient is the unique combination of safety and efficacy, as the CO2 laser is highly absorbed by fluid. So, once we have achieved percolation, the laser is no longer effective, and we have reached the desired outcome of the procedure in a controlled intrinsic manner. As for efficacy, IOP reduction is very similar to the standard trabeculectomy, but with significantly fewer complications and medications needed in the post-op.

The last point I will mention is that for me, as a surgeon, a huge benefit is that the procedure is reproducible, which is key in planning the post-op treatment.

Was there an effect on visual acuity?

The feedback on visual acuity is already totally different compared with trabeculectomy. CLASS is performed safely, as you don't penetrate the anterior chamber, and in post-op the patient is in miosis, so the patient's impression is that it is simply a cataract surgery. In contrast, trabeculectomy patients have blurred vision due to the use of atropine – required to help maintain the anterior chamber – for at least two weeks post-operation. With CLASS, there is no promotion of cataract development in the long term as there is with trabeculectomy, and there is marginal improvement in BCVA. If we compare results between trabeculectomy and CLASS (measured according to the Snellen chart converted into the LOGMAR chart), we can see that in the trabeculectomy group, BCVA increased from 0.196 ± 0.27 to 0.20 ± 0.32 at 1-year post-op, while in the CLASS group, BCVA declined from 0.20 ± 0.2 to 0.07 ± 0.1 at 1-year post-op. These results show a small deterioration in the trabeculectomy group, and significant improvement in CLASS group. This is a good indication of improvement in visual acuity.

In the study, the post-CLASS group required less medication to control IOP than the trabeculectomy group – why?

Because of the difference in the control mechanism of aqueous outflow. The trabeculectomy operation generates a new drainage channel for aqueous outflow, which is not natural, so the body suffers from many unexpected changes and fluctuations resulting from the natural adaptation of the eye to significant change. In the CLASS group, there is a use of the natural process of aqueous outflow, but with a reduction to major resistance of aqueous outflow in that natural route. These less radical changes in the surgical solution lead to less trauma to the eye and the patient, and therefore to shorter adaptation process of the eye to the surgical outcome. Not only that, the trabeculectomy group is more likely to experience adverse events, which require a greater number of medications to stabilize the outcome.

What would you say to clinicians who are reluctant to try something other than trabeculectomy?

As surgeons, we must seek the best practice for each patient and, as such, we must be open to new technologies. There are so many out there – especially for glaucoma surgery – which we should test and validate to make sure they provide accurate and reliable results with safe and effective operation. We must then decide on the right approach for each patient. Just because we didn't learn about a certain procedure back in medical school doesn't mean it isn't good or shouldn't be considered – it only means we are getting older! Laser-based solutions are already the running promise of many ophthalmic applications, so I think it makes sense to add laser for glaucoma surgery to this portfolio.

Reference

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In My View

In this opinion section, experts from across the world share a single strongly-held view or key idea.

Submissions are welcome. Articles should be short, focused, personal and passionate, and may deal with any aspect of ophthalmology. They can be up to 600 words in length and written in the first person.

Contact the editor at edit@theophthalmologist.com

Trabs: Still on Top

MIGS has not superseded trabeculectomy

By Philip Bloom, Consultant Ophthalmic Surgeon at The Western Eye Hospital (Imperial College Healthcare NHS Trust) & The Hillingdon Hospital NHS Foundation Trust, London, UK

All current glaucoma treatments work via a reduction of intra-ocular pressure, a dose-related protective effect correlated to lowering not only the average pressure, but also its diurnal variation. Surgical and laser treatments may be more effective than medicines, the efficacy of which has to be reinforced daily by regular application related to a short, finite duration of action. Medicines, however, benefit from the possibility of treatment combinations using three distinct potential additive strategies – reduction in inflow and increase in either conventional (trabecular) outflow or non-conventional outflow.

Trabeculectomy has long been our default surgical glaucoma solution as it simply creates a semi-permanent, biological valve; much evidence supports it as a cheap, enduringly effective, and acceptably safe incisional treatment that is moderately independent of individual skill and technique. There is an attrition rate, however; complications are not infrequent and the results of the procedure can be frustratingly variable despite standardized surgical techniques. Dissatisfaction with side effects and complications of trabeculectomy led to the advent of glaucoma drainage devices and non-penetrating surgery; clearly these were not the answer as their routine use in the surgical control of glaucoma did not become widespread.

The advent of a variety of new surgical options represents a further attempt to refine the safety and efficacy of surgical intervention. The term MIGS refers to a number of ab interno glaucoma drainage procedures that do not require conjunctival incision and includes (amongst others) Goniosynechialysis, Endoscopic Cyclo-Photocoagulation (ECP), Trabectome, iStent, Cypass (now withdrawn), Hydrus, Kahook Dual Blade (KDB), ab interno Canaloplasty and Xen.

The wide range of options allows for a more logical and step-wise approach to surgery, and for a combination of treatments based on the mechanism of action. A further advantage of MIGS is the ability to combine surgery with phacoemulsification; phaco-trabeculectomy is no longer widely performed. For MIGS procedures performed in combination with cataract surgery, it is always challenging to isolate the effect of the procedure from that of cataract surgery alone. MIGS shows promise, but is as yet unproven and of uncertain longevity.

Some MIGS procedures offer the prospect of restoration of physiological trabecular outflow. But this potentially limits clinical efficacy because, in the presence of normal aqueous inflow, Schlemm's canal drainage routes seem to have a physiological "floor" of around 16 mmHg due to downstream resistance to flow. Further lowering would require additional aqueous suppression treatment, a real disadvantage if low IOP is needed or medication use is to be avoided. By contrast, both conventional and non-conventional outflow procedures potentially bypass this "choke-point," leading to lower IOPs but also raising the possibility of hypotony from over-drainage.

MIGS devices are unarguably expensive, largely due to development costs. Proponents argue that the extra cost is defrayed by reduced need for intensive

follow ups and better quality of life, but this is yet to be proven. Though this may be the case for a device such as the iStent, successful use of other devices, such as Xen, still requires extra follow up due to the common need for post-operative manipulations. Furthermore, devices that have a small unit effect may need to be implanted in costly multiples. If the effect is sub-optimal or if the device later fails, the health economics alter and may well ultimately favor conventional drainage surgery; at that point, the true price comparator is not drainage surgery but only the relatively cheap medications that MIGS spares.

Ultimately, the widespread adoption of MIGS will probably come down to an individualized assessment of safety versus efficacy. MIGS procedures that are inferior to trabeculectomy in efficacy will only be widely adopted if they have significant safety benefits. In early disease, there are many options and there is often time to try a variety of treatment options. In a patient with advanced glaucoma, it cannot be appropriate to offer a treatment of unproven efficacy or longevity.

It is apparent from the foregoing that the existence of MIGS raises the level of sophistication and complexity in glaucoma surgical management, making it more "granular," titratable and refined. Nonetheless, trabeculectomy continues to be our best single "fit and forget" option. The natural comparators for trabeculectomy are still other forms of "conventional" drainage, such as glaucoma drainage tubes, and maybe the recently released MicroShunt device, but to date trabeculectomy has yet to be bettered; 21st century trabeculectomy is an increasingly safe and effective procedure.

Joining Forces

Diabetic patients would be better served by coordinated care plan – and retina specialists must play their part

By Anat Loewenstein, Professor and Chairman, Division of Ophthalmology, Tel Aviv Medical Center, Sidney Fox incumbent chair of Ophthalmology, Vice Dean, Sackler Faculty of Medicine, Tel Aviv University, Israel

I recently attended the tenth edition of COPHy (Controversies in Ophthalmology: Europe) meeting, held this year in Dublin, Ireland. COPHy is an annual congress based on discussions of the latest, most debatable and divisive topics in the field of ophthalmology.

One of the sessions featured the Vision Academy, a global collaboration of experts who work together towards reaching a consensus and developing guidelines on debatable topics in the field of retinal disease, as well as sharing best practice patterns with retina physicians.

The debate on the need for coordinated care for patients with diabetes was of particular interest to me. It is well known that diabetic patients suffer from a range of systemic disorders, including cardiovascular, renal and neurological diseases (1, 2). Richard Gale from the University of York, UK, claimed that healthcare professionals involved in the treatment of patients with diabetes and diabetic eye disease are not currently communicating with each other. Emerging data show that an understanding of eye disease status can provide diabetologists with valuable prognostic information to help with the management of the systemic condition, in particular of other organs affected by diabetes.

Sobha Sivaprasad from the UCL Institute of Ophthalmology and Moorfields Eye Hospital, UK, argued that ophthalmologists do not have the capacity, expertise and resources to take into account other systemic complications of diabetes in the treatment of diabetic retinopathy. She mentioned multiple challenges of coordinated chronic disease approaches, including competing priorities, lowering of personal staff commitment, limited funding, reduced public understanding, and lack of communication across programs (3). The conclusion on this side of the debate is that monitoring is important, but it should be done independently.

The Vision Academy's perspective that I presented was this: diabetic retinopathy is a strong predictor for the development of comorbid conditions associated with diabetes – therefore, timely referral and discussion between healthcare professionals involved in the management of diabetes and its complications are essential to improve patient care.

The overall consensus seems to be that a greater understanding of the wider implications of diabetic retinopathy may provide the opportunity to improve communication between diverse healthcare disciplines.

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RETHINKING AMD

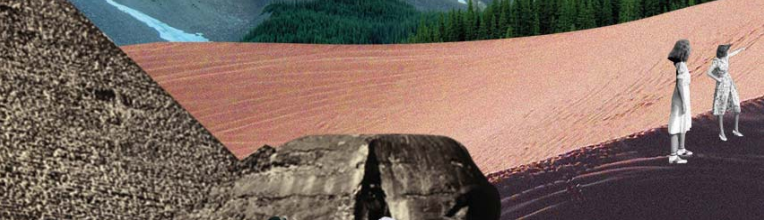
An accidental discovery, an aging population, a new approach to healthcare – this is the story of MacuLogix

Phoebe Harkin interviews Greg Jackson

In 1993, Greg Jackson was a graduate student at the University of Alabama at Birmingham. He was working in a laboratory with Cynthia Owsley, a pioneer in research on contrast sensitivity and driving – famous for her work into how vision changes with age. Owsley had become interested in night vision in older adults and passed the project on to Jackson. "As no one thought much of it back then, it was a perfect topic for a graduate student. I couldn't mess it up – or so it seemed!" says Jackson. There wasn't much information available on the subject: they knew that night vision worsened with age because of aging-related changes in the eye's optics, but it was unknown as to whether or not the retina was partly responsible for senescence of night vision. They started to investigate dark adaptation – the ability to adjust to darkness. "If you think about visual acuity as a proxy measure for daytime vision, dark adaptation is a proxy measurement for the ease or difficulty in which a person sees at night," explains Jackson, whose doctoral dissertation topic explored whether older adults had decreased ability to adjust to darkness because of senescence of the retina. To measure dark adaptation, you can present a flash of light to the eye and then repeatedly measure light sensitivity. Over time, the eye will detect progressively dimmer lights – much like how one can see progressively see fainter stars in the night sky. Notably, a young person's recovery time is significantly faster than an adult's over the age of 60.

"Of course, you couldn't just buy a dark adaptometer in those days," says Jackson. "Equipment had to be modified or re-programmed to measure dark adaptation." And so, with the help of a heavily modified Humphrey Field Analyzer, he started measuring patients' ability to dark adapt, and all was going smoothly.

A curious thing happened then: he flashed the light at one 72-year-old patient and waited for recovery. "Ten minutes went by. Then 18, then 20, then 25," Jackson says. "Still no recovery.



I started to panic, and by the time half an hour rolled around, I was ready to turn the machine off." He remembered sitting there in defeat, working out how he'd tell Owsley that he had not only broken the machine, but also wasted the patient's time. But then, 40 minutes into the test – 30 minutes longer than expected – the patient began to slowly recover. When he turned the machine off at 90 minutes, the patient – later to be known as "the first patient" – was still not fully recovered. "I couldn't believe it," says Jackson. "But it happened again… and again." The team collected five cases of patients with normal retinal health but clearly abnormal dark adaptation. Serendipity had struck – but Jackson didn't know it yet.

To get to the bottom of these cases, they sent the first patient to see two retina specialists – only to be told that there was nothing wrong. But how could that be true? They sent photographs to the Beaver Dam Reading Center, forerunner of the AREDS Reading Center at the University of Wisconsin, for evaluation. Again, they graded the patient as normal. No comorbid health problems, no further explanation. So what was it?

"Dark adaptation impairment can be used to identify clinical macular degeneration with 90 percent accuracy."

Friends in interesting places

Christine Curcio, one of Jackson's colleagues, was studying the retinas of patients with AMD around the same time. Curcio found that older adults generally lose more rods than cones, but when they develop AMD, their rods are affected significantly more – and earlier – than cones. It appeared that rods were almost acting as an early warning system for AMD in the retina. To test that theory, Jackson began measuring dark adaptation in AMD patients and found that their ability to adapt was massively delayed.

"At this point, that first patient was four years older – and had developed AMD," says Jackson. He went back and re-analyzed his early data and, sure enough, found that patients with the appearance of a normal retina but worse dark adaptation were more likely to develop AMD than their peers with better dark adaptation. They never published that data, but they didn't forget it either. Indeed, that initial study formed the foundation of later work – but it took Curcio to put the pieces together.

While researching the donor eyes of AMD patients, Curcio made a startling discovery: cholesterol deposition at the back of the eye, which can't be seen with imaging technology, is the forerunner to drusen – the defining feature of macular degeneration. Up until then, everyone believed drusen were focal. "Curcio upended that theory," says Jackson. "She found that when RPE becomes dysfunctional, it starts depositing cholesterol throughout the back of the macula – and she used microscopy on donor eyes to prove it." When cholesterol becomes sufficiently thickened, it becomes visible (a druse). In other words, by the time a clinician can see a druse, they're looking at the tip of an iceberg – and the damage is already well underway. Not only that, Curcio discovered that the cholesterol in a druse is the same type of cholesterol as that found in carotid arteries of patients with atherosclerosis. "And that was significant. As with atherosclerosis, this cholesterol causes oxidative stress and inflammation – stress that could be quenched with antioxidant supplements," Jackson says.

This knowledge, paired with the understanding that vitamin A was essential for dark adaptation, formed the basis of the team's next study: a small, randomized, controlled clinical trial where patients were supplemented with vitamin A. Jackson explains: "The test was never intended to treat the disease, it was meant to prove that the cholesterol layers serve as a barrier to vitamin A reaching the outer retina, essentially causing the localized vitamin A deficiency which impairs dark adaptation – and that's exactly what it did." And they finally determined why patients with AMD exhibited extreme dark adaptation impairment; even before a patient has drusen, they have cholesterol deposits at the back of the eye that are limiting vitamin A from getting to the outer retina. The result? Impaired dark adaptation. "And for those persons that do have

"If technology has enabled doctors to accurately diagnose and monitor glaucoma, then why aren't we using technology to find AMD?"

Figure 1. The full MacuLogix team.

Figure 2. Cynthia Owsley with Christine Curcio.

Figure 3. Jackson with Glenn Corbyn, the first doctor to buy an AdaptDx machine.

Figure 4. Bill Grace with the first prototype.

clinically identifiable macular degeneration, dark adaptation impairment can be used to identify the disease with 90 percent accuracy," says Jackson. They'd found the last missing piece of the puzzle and, just like that, Greg Jackson's life changed.

A fork in the road

"If you had asked me what career I wanted while working in Owsley's lab, I would have said, 'academic researcher,'" says Jackson. But something happened when he was doing the experiments. He ended up spending a lot of time with patients – four to six hours doing tests and filling in questionnaires. Invariably, he would end up hearing about how the patient had come to know that they had macular degeneration. "Many of them told me that they were unaware of their disease before they had severe vision loss in one eye," he says. Their stories always followed the same pattern: they would realize their visual acuity had dropped in one of their eyes, but they did not go to the doctor. When they finally did, they were diagnosed with AMD. "As I heard more and more stories, I couldn't shake the irony that I was using a modified visual field machine – the gold standard diagnostic for glaucoma – to measure dark adaptation," says Jackson. Then, one day, it hit him. "If technology has enabled doctors to accurately diagnose and monitor glaucoma, then why aren't we using technology to find and monitor AMD?" And that was the moment Jackson decided to build a modern, clinically-accessible dark adaptometer. He had a prototype. He had identified a need. Now all he needed was a buyer.

Nothing in life is so simple, however. And the first challenge Jackson faced was the test duration. With the laboratory prototype, it could take an hour to assess someone's dark adaptation, significantly longer than a routine clinical visit. "If I wanted doctors and patients to get on board with this idea, I would have to shorten the test – dramatically," he says. Even with this limitation, he approached industry. Jackson talked to every major company asking them about the opportunity and they all correctly told him that he was crazy. "No one wanted to take it on," he says. "I realized that I needed to change tactics." And so he decided to license the technology to an entrepreneur and commercialize it. They signed the license agreement in March 2004 to a company called Apeliotus Life Sciences, the forerunner to MacuLogix. With the help of John Edwards and Bill Grace, Jackson spent the next 10 years shortening the length of the test and optimizing the technology. Today, the device can test if someone has normal dark adaptation in six and a half minutes or less.

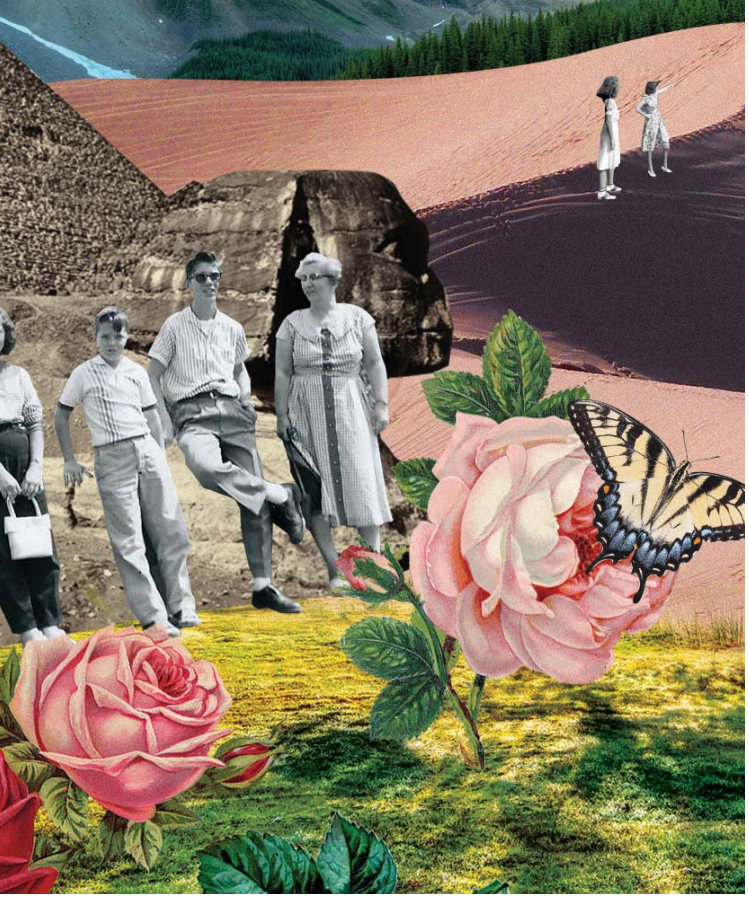
The second challenge was deciding how to explain dark adaptation. "Though dark adaptation isn't terribly complicated, it's complex enough that doctors might not understand if I was to say, 'The patient has a change in the slope of dark adaptation as expressed in log units of sensitivity change per minute,'" admits Jackson. To make dark adaptation easier to understand – and easier to explain – they decided to redefine the way they talked about it altogether. Thus, they invented the Rod Intercept (RI) – a single parameter to estimate the speed of dark adaptation. The Rod Intercept is simply the time in minutes by which nearly complete dark adaptation has occurred. "Faster times are better and slower times are worse. Simple."

The change in approach was effective. The team installed the first AdaptDx automated dark adaptometer to be used in a clinic in 2014, almost ten years to the day that the technology was licensed. It had been a long road – ten years of trial and error, breakthroughs and setbacks – but there was more to come. When Jackson started this project, he assumed his greatest challenge would be convincing doctors that dark adaptation was the best method to detect early AMD. As it turned out, the challenge was convincing them that early AMD was worth detecting at all.

Talking the talk…

"General ophthalmologists and optometrists rarely give bad news," says Jackson. Indeed, ophthalmologists work in one of the few specialties where most of the patients who walk into their clinics, walk out happy. Cataracts can be removed. Refractive errors can be corrected. Ocular surface diseases can be treated. But what about outcomes for AMD? "If you're a middle-aged optometrist or ophthalmologist in the United States, you probably didn't learn much about macular degeneration in medical school – and why would you?" asks Jackson. After all, there were no supplements or anti-VEGF injections back then. There was nothing an ophthalmologist could do to save a patient diagnosed with macular degeneration from losing their sight; severe vision impairment was a very real possibility. "In some ways, it makes sense that these same doctors did not tend to focus on managing AMD patients," he says. But it was exactly those doctors who Jackson needed to invest in his technology. To convince them, the original team had to reframe how they thought about AMD altogether.

There is a marketing theory that any type of disruptive technology – whether it be an Apple computer or a smart phone – requires an educational sell. "Steve Jobs had to tell people why they needed a computer in their life because they hadn't a clue. After all, why did a normal person need a computer back then?" asks Jackson. "Steve Jobs found a way to convince them." Jackson knew it was his job to sell dark adaptation. But how? They started with the very basics: reminding doctors of the prevalence of the disease. Many doctors were surprised that AMD is three more times prevalent than glaucoma. They would remind doctors that AMD is a progressive, chronic



disease with no cure, like diabetes. "When you start thinking about the disease that way, you become much more serious about prevention," says Jackson. "Because, like diabetes, early diagnosis leads to earlier treatment and better patient outcomes." Next, they had to educate them about the value of supplements, and how diet, exercise and comorbid disease management could help decrease the patient's risk of disease progression. And that brought Jackson and his team to the second part of their educational sell: how to identify AMD patients.

The hard sell

"These patients are already in your practice. They will be in your waiting room right now and you'll probably send each of them home without a diagnosis…" – that's exactly how Jackson used to begin his pitch to doctors in the early days. If a doctor didn't believe him, Jackson would propose a test, and ask them to pick patients over the age of 60 years old who they were absolutely sure did not have age-related macular degeneration. Jackson would offer to test them, and guarantee that at least 20 percent will fail.

"Typically, 30 percent of the patients failed," he says. "Long-overdue retinal images would be taken, and, in most cases, the diagnosis of AMD was confirmed. And the doctors would despair. How could they possibly have missed that many patients?" For Jackson, the answer was clear: the current method of identifying AMD is fatally flawed.

"Doctors have been taught to look for drusen during the clinical examination, but they are often missed," says Jackson. "Even the most keen-eyed ophthalmologist can miss a druse if they aren't looking for one. The first thing most ophthalmologists do is review their patient's visual acuity. If that patient has 20/20 vision, the ophthalmologist is more likely to miss a druse because they are not alerted that there is a problem. If they don't see a druse, they won't send them for a photograph. That's our current protocol for diagnosing macular degeneration. Is it any surprise that AMD patients are going unnoticed?"

"Like diabetes, early AMD diagnosis leads to earlier treatment and better patient outcomes."

The opportunity to outlive our eyesight

The magnitude of AMD under diagnosis alarmed Jackson. He was also shocked by some of his colleagues who were less surprised, contending that, if the disease is missed in its earliest stages, the patient is at very low risk of vision loss, and it will be caught later when AREDS2 supplements are indicated. Jackson's perspective was different; his focus was clearly set on AMD as a progressive, chronic disease: "Their five-year or even ten-year risk may be low at that point in time, but what is

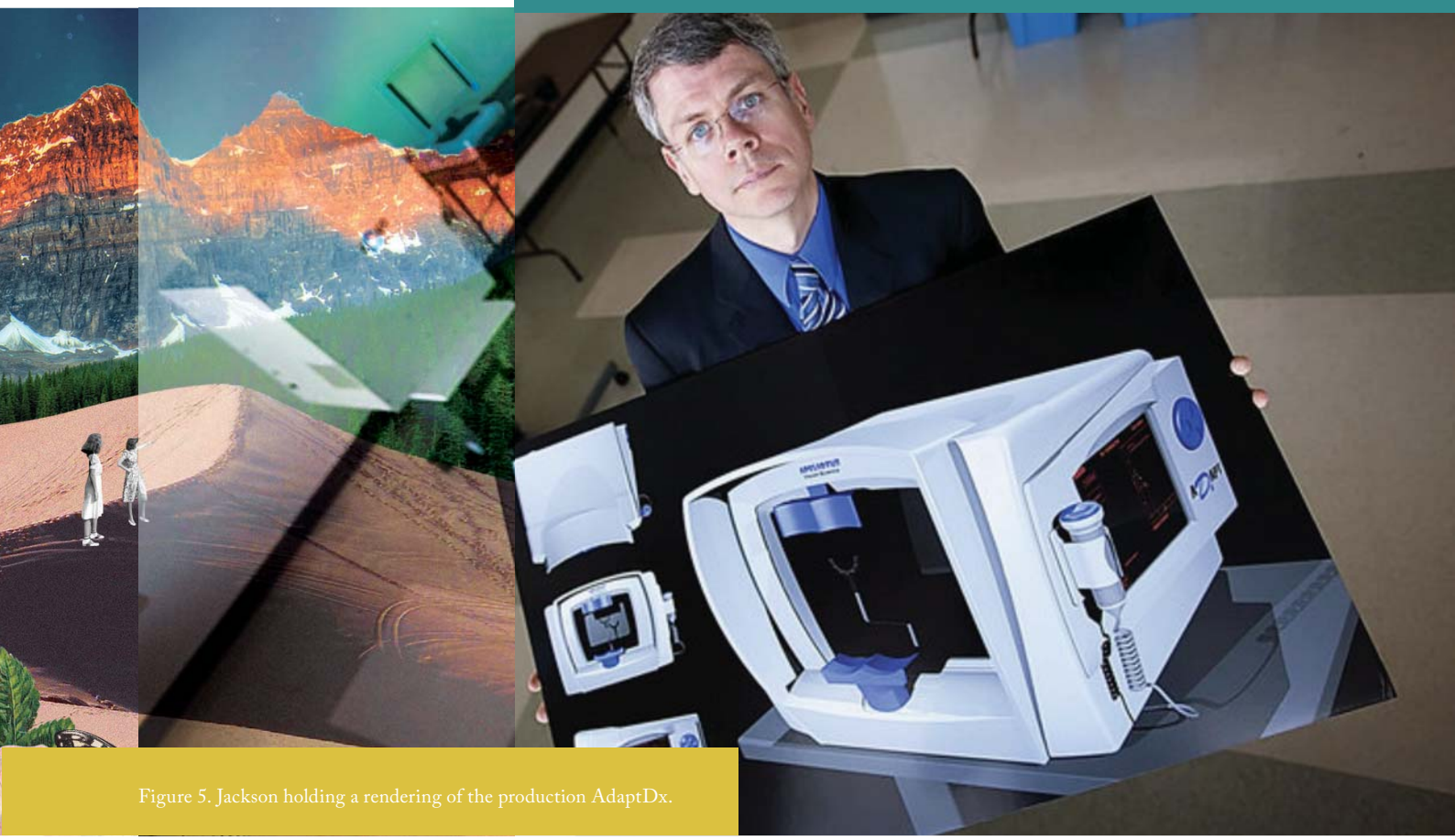


Figure 5. Jackson holding a rendering of the production AdaptDx.

their twenty-year, thirty-year or even forty-year risk of vision loss?" Some patients are diagnosed with early AMD in their 50s and so are likely to have the disease for multiple decades. Jackson believes that patients in the earliest stages of the disease may modify their risk of progression, but they must be given the diagnosis and education to give them an opportunity to preserve their sight. "As people continue to live longer, I felt it was vital to give AMD patients their best chance at outliving their eyesight."

Today, Jackson and his team are working hard as a company to educate doctors about AMD diagnosis and management. In fact, their company is built with the aim of eliminating blindness caused by AMD altogether. They have installed dark adaptation devices throughout the USA, and are now branching out into Europe, Canada and Australia. With every installation comes a new story of a doctor diagnosing a friend, a partner or even themselves. One employee asked for her parents to be tested after overseeing the installation of a device into the practice that provides eyecare to her family. Her mother failed the dark adaptation test and was subsequently diagnosed with AMD. Her mother now has the chance of a better outcome than her own parents, who previously lost vision in both eyes because of CNV. "If the doctor did not employ the technology, who knows how long it would have been before the diagnosis?" asks Jackson.

"Even the most keen-eyed ophthalmologist can miss a druse if they aren't looking for one."

Over the 18 years Jackson has been investigating dark adaptation, he has learned that a doctor's good days are the direct result of good patient outcomes. So, he's made it his personal mission to lessen the number of bad days – for patients and doctors. "Early adopters often tell me how this technology has helped patients enjoy better outcomes and it is their testimonials that are helping to spread the word about dark adaptation," says Jackson, with significant pride. This article marks a 15-year anniversary for MacuLogix. "Ten years of science and engineering, followed by another five realizing its true potential for patients and doctors," says Jackson. "Here's to the next 15!"

Gregory R. Jackson, PhD, is Co-founder and Chief Technology Officer at MacuLogix and inventor of the AdaptDx.

The Strong Case for NOV03

Dry Eye Disease (DED) is one of the most common ocular surface disorders – and Meibomian Gland Dysfunction (MGD) is one of its most common causes. MGD leads to an unstable lipid layer and tear film evaporation from the eye. Standard treatment options for DED include lipid-containing artificial tears and thermomechanical relief of the eyelids. But now a novel investigational new drug aims to treat evaporative DED by addressing the lipid layer instability. NOV03 (100 percent perfluorohexyloctane) is a preservative-free ophthalmic solution with unique properties and the first drug in development that targets DED associated with Meibomian Gland Dysfunction – but what advantages does it have over traditional aqueous eye drops usually prescribed or recommended for DED?

Simply better...

Firstly, NOV03 is water-free, which means that i) microbial growth is not possible, therefore ii) the product requires no preservatives, and iii) the product has no pH and consequently does not effect native tear osmolarity. The implicit suggestion that NOV03 should be better tolerated than standard DED products is supported by preclinical studies: repeated up to 4 times -daily instillation in rabbit eyes caused no irritation (1).

Secondly, the low surface tension of NOV03, an EyeSol®-based formulation, favors very effective spreading: an aqueous saline droplet "sits" on the cornea (contact angle: ~40 degrees), while EyeSol® droplets form a thin film on the tear film (contact angle: ~zero degrees) (1). Indeed, although EyeSol® droplet volumes are one-third those of saline, they cover a significantly greater corneal and eye surface area (1).

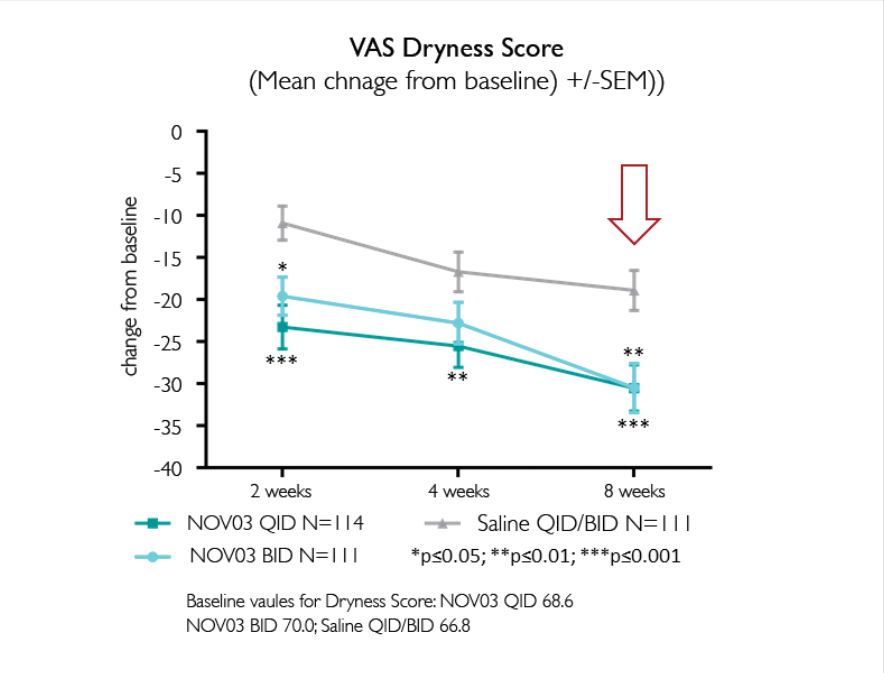


Figure 1. Symptomatic improvements associated with NOV03 are already significant at week 2 and 4 and remain significant throughout the study duration. Four daily administrations (QID) provide greater symptom control than a twice-daily regime (BID).

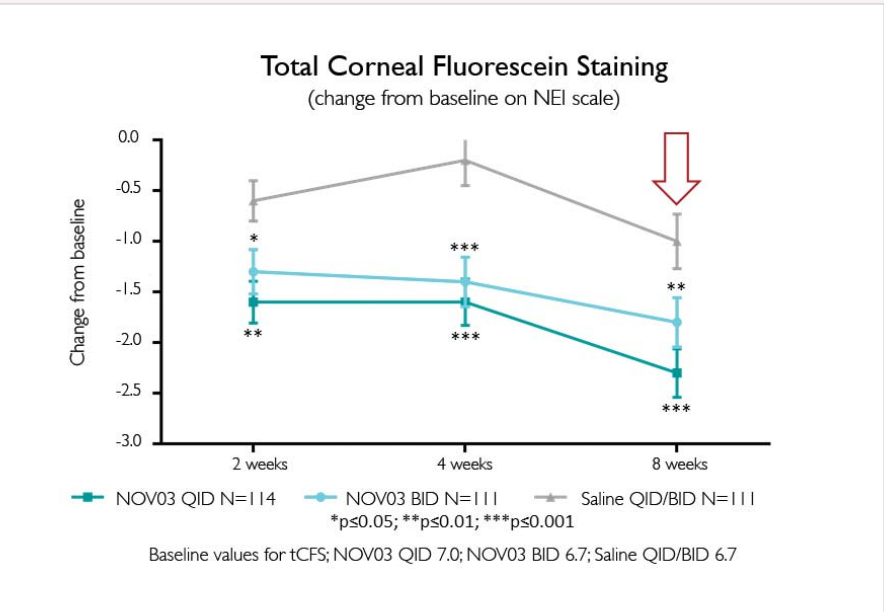


Figure 2. Corneal damage is significantly reduced by NOV03 administration, and the reduction is greater with a QID than a BID regime.

Thirdly, being amphiphilic, EyeSol® dissolves lipids and rapidly forms films on surfaces. Hence, NOV03 directly stabilizes the tear film without added surfactants, and has the ability to dissolve lipid deposits in blocked Meibomian glands (3). Preclinical studies show that topical EyeSol® formulations are sequestered in the tear film, where high levels persist for over 4 hours and penetrate into Meibomian glands, where significant levels persist for up to 8 hours (2). Thus,

the corneal coverage provided by NOV03 is not only rapid, but also durable.

A difference patients perceive

The above preclinical data are complemented by an increasingly large body of clinical evidence. We now know that perfluorohexyloctane administration improves MGD-associated DED by extending tear film break-up time, reducing corneal and conjunctival damage, increasing the number of expressible Meibomian glands, and improving Ocular Surface Disease Index (OSDI) values (4). Similarly, in patients with mild to moderate DED, NOV03 (four times daily) mediated >6 percent increase in tear film thickness and >13 percent increase in lipid layer thickness (5). And now a large US Phase II trial (Sidebar) further adds to the case for NOV03.

The SEECASE results are clear (6): excellent safety and tolerability, and outstanding efficacy (Figure 1, 2). Significant symptomatic improvements were apparent at two weeks and persisted until study completion; given that the study included only patients with relatively severe DED symptoms, this result is extremely encouraging. Also of note are the dose-dependent outcomes observed in SEECASE: the four times daily regime gives better outcomes than the two times daily regime (Figure 1, 2).

What I Saw in SEECASE

Joseph Tauber's referral-based dry eye center in Kansas City welcomes both DED and MGD patients. To date, he has participated in over 130 multi-center trials as principal investigator – including the SEECASE study. Here, he shares his thoughts with The Ophthalmologist.

MGD lacks both diagnostic and treatment tools; hence, therapy largely relies on home eyelid hygiene, although oral agents may improve Meibomian secretions in some patients. Similarly, DED treatments are poorly efficacious, slow-acting, and expensive. Overall, instead of fixing the problem, we only control the symptoms. And that leads to poor compliance – so, in many cases, the disease wins in the end.

SEECASE, however, was very interesting; by restricting recruitment to those with highly symptomatic disease, the trial set the efficacy bar quite high. The broad and significant improvement observed in the SEECASE treatment group therefore is extremely encouraging: we saw reduced severity and frequency of burning, stinging and dryness; reduced awareness of symptoms; and decreased corneal fluorescein staining. I was particularly struck by the proportion of patients willing to purchase the treatment they were receiving after the clinical trial was finished – on this measure, NOV03 had double the satisfaction rates of other products I have investigated. So my impression is that patients are extremely happy with NOV03.

In conclusion, clinical trials of DED products very rarely show simultaneous improvement in symptoms and signs – and it's even more uncommon to see improvements of the magnitude found in SEECASE. With data like these, we should be optimistic regarding the likely impact of NOV03 in DED associated with MGD.

SEECASE Phase II – Aiming High

This randomized, double-masked, multicenter US trial (n=336) enrolled highly symptomatic patients:

- low TBUT (5 seconds or less)
- MGD score 3 or more
- normal Schirmer ~15 mm
- OSDI ~55
- mild to moderate corneal damage

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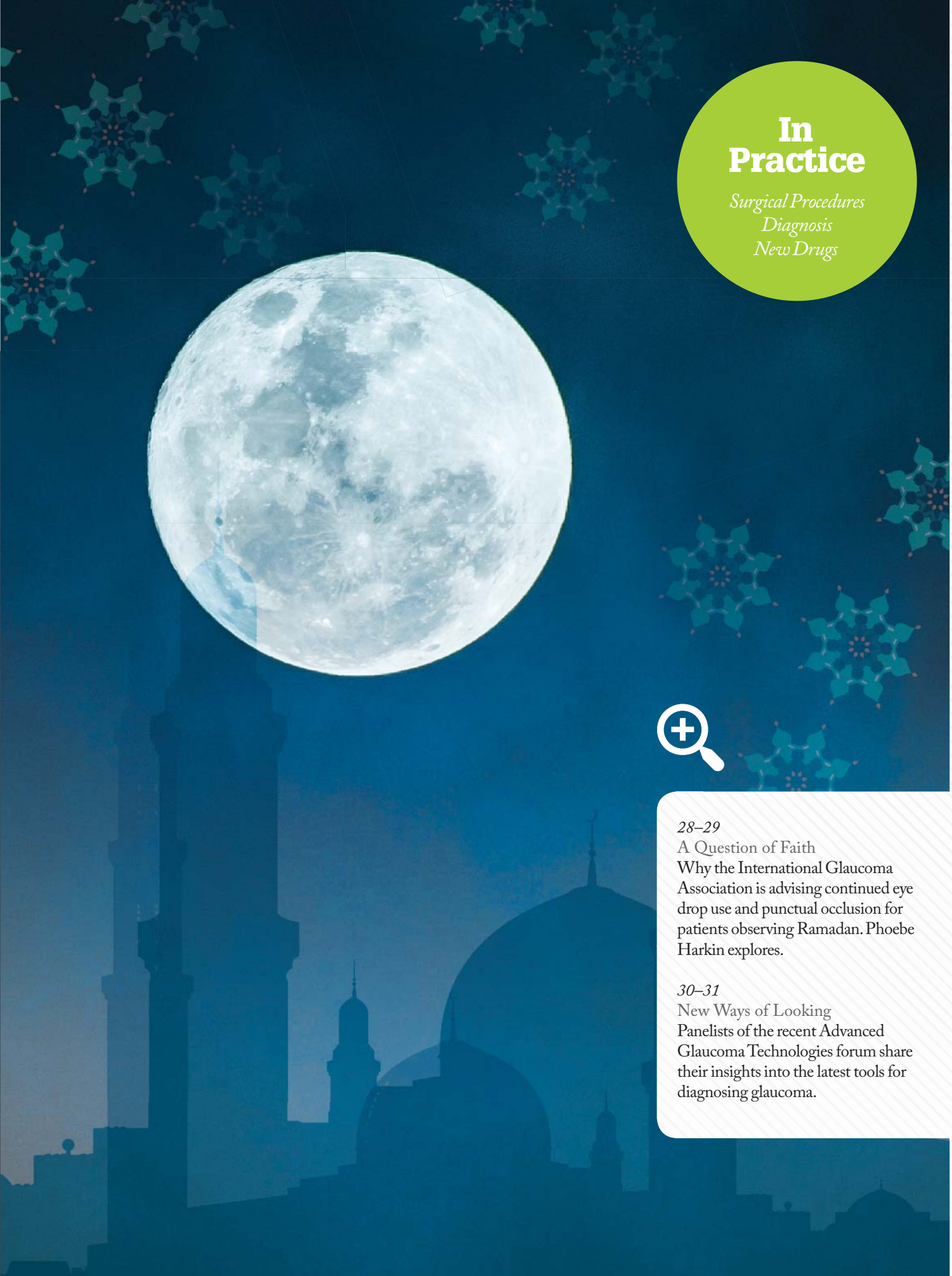


In Practice

Surgical Procedures
Diagnosis
New Drugs

A Question of Faith

How the International Glaucoma Association is advising continued eye drop use and punctual occlusion for patients observing Ramadan

By Phoebe Harkin

As May 5th approaches, ophthalmologists are asked to keep a close eye on their Muslim glaucoma patients. The reason? Ramadan, the ninth – and according to belief, the holiest – month of the Islamic calendar. Commemorating the first revelation of the Quran to the Prophet Muhammad, Ramadan is annually observed with a month of fasting. Although the dates shift depending on visual sightings of the crescent moon, it has been decided that Ramadan will fall between May 5 and June 5 this year. So what is the issue? A study has found that 63.7 percent of Muslims believe that the application of eye drops breaks fasting, with only 34.2 percent of Muslim glaucoma patients claiming they would continue taking their medication during this period (1). But that's not all.

"Even more worryingly, many of these patients stop using the drops altogether when they don't perceive any change to their sight. Of course, this is because changes are only apparent to the individual when significant sight loss has occurred, but the patient doesn't always know that," explains Subhash Suthar, Development Manager at the International Glaucoma Association (IGA). "It's distressing when patients realize that their vision has been damaged

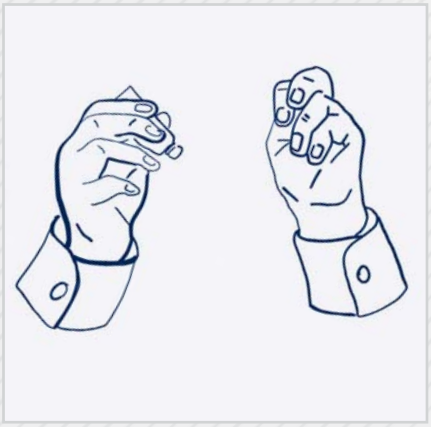
At a Glance

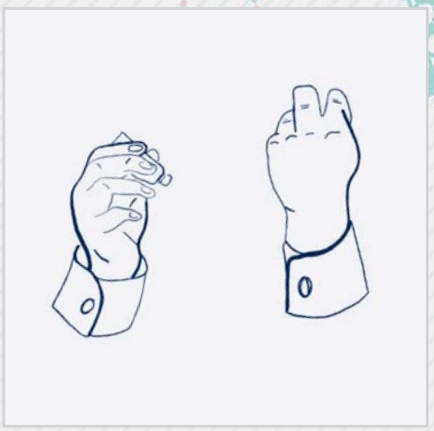
- *Ramadan is one of the Five Pillars of Islam, observed by Muslims worldwide*
- *During this month – beginning at dawn on May 5 and lasting until dusk on June 5 – Muslims refrain from eating and drinking in a bid to understand the true meaning of perseverance and tolerance*
- *This can have serious repercussions for glaucoma patients who stop using their drops for fear of breaking their fast; advanced disease, post-op patients, PXF and secondary glaucoma cases are most at risk*
- *To combat this, the IGA advises patients to practice punctual occlusion following instillation of morning and evening drops.*

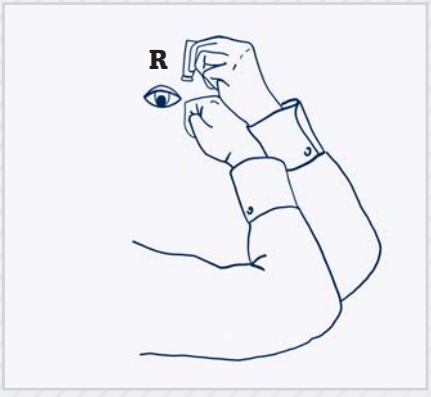
"I encourage doctors to remind their patients to continue taking drops during Ramadan." Ejaz Ansari

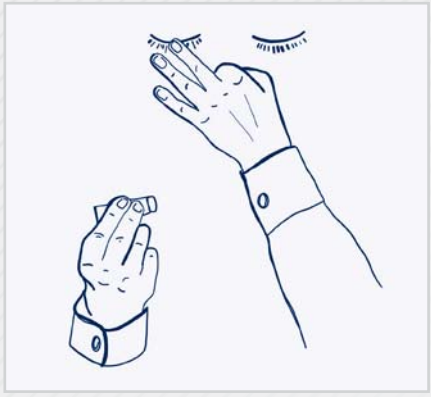
The IGA offers three key pieces of advice for ophthalmologists:

- Advise patients to continue using eye drops during Ramadan
- If patients remain doubtful, advise the use of morning drops at Suhoor and evening drops at Iftar
- Recommend punctual occlusion following instillation of drops (see figures)









by stopping drops during a follow-up appointment with their ophthalmologist or optometrist."

So how do we support patients during this period? "We want to reassure the Muslim community that drops can be taken before dawn and sunset (known as Suhoor and Iftar), when food and drink can be consumed," says Subhash. "We also suggest that patients close the tear duct – punctual occlusion – when taking eye drops as this means that fluid stays in the eye and does not drain into the throat and, as such, cannot be tasted. This is achieved by putting finger pressure at the corner of the eye next to the nose immediately after instilling drops."

The IGA has been working with the Muslim Council of Britain (MCB) to raise awareness of this issue among patients and ophthalmologists. Omer El-Hamdoon, MCB's Deputy Secretary General, has confirmed that all Islamic schools of thought agree that taking eye drops does not invalidate the fast. He adds that, although the chance of eye drops reaching the throat is unlikely, it can be avoided entirely with punctual occlusion (see figures above).

Professor Ejaz Ansari, Lead Clinician and Head of Glaucoma Services at Maidstone and Tunbridge Wells NHS Trust, has been working with the MCB and the IGA to promote the protocol. "Advanced glaucoma, post-op patients, PXF and secondary glaucoma cases are most at risk," says Ansari. "I encourage doctors to remind their patients to continue taking drops during Ramadan."

El-Hamdoon has the final word: "Islam advocates that people take care of their bodies – and that means protecting your sight."

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New Ways of Looking

In the past, ophthalmologists who suspected glaucoma had to rely on a visual field-testing machine, a tonometer, and an ophthalmoscope. Those were simpler times, but these are better ones

With Ike Ahmed, Earl Randy Craven, Marlene Moster, Constance Okeke, I. Paul Singh and Robert N. Weinreb

Today, our diagnostic tools do much more than simply rule glaucoma in or out: they help us stage the disease, estimate risk of progression, and measure any progression that does occur. In particular, data provided by modern tools helps us identify patients at highest risk – information which is key to glaucoma management and good clinical decisions. But, as is often the case, better information raises more questions than it answers; as Paul Singh says: "The more we learn, the more we realize how far we have to go." So where have we got to on this journey?

Identifying and staging

At present, identifying and staging glaucoma still requires both structural and functional information: today, these are mainly provided by optical coherence tomography (OCT) and visual field (VF) testing, respectively. In combination, these types of data help surgeons identify patients as early as possible in the course of the disease. Elucidation of the underlying disease mechanisms in a given patient, says Singh, can also guide management; for example, it can suggest a "watch and wait" strategy, thus saving aggressive therapy for those who really need it. "Understanding the relationship between structural and functional change," adds Marlene Moster, "helps us choose the right treatment for each individual patient." Only a minority of patients, she continues, are serious enough to justify a trabeculectomy; most can be classified into various categories that are more suited to one or another of the alternative approaches now available. "Glaucoma therapy can be personalized more than ever before," she says.

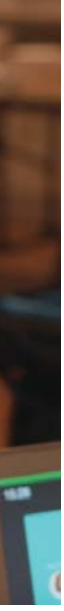
Constance Okeke has firm views on the diagnostic benefits of gonioscopy. "It's a key tool to guide MIGS selection – the angle helps you decide which procedure to use." She gives an example: a patient with a narrow angle and appositional closure. "Here, I would probably use a Trabectome procedure, because the hand piece tip allows me to not only open up the angle by goniosynechialysis, but also to follow up by removing the trabecular meshwork with a partial goniotomy so as to open up the outflow system." By revealing ocular pathology, such as pseudo exfoliation, pigment dispersion, or synechia, says Okeke, gonioscopy helps guide the surgeon regarding the choice of MIGS (e.g. goniotomy, stents or canaloplasty).

Progression risk and progression measurement

Estimations of progression risk, by contrast, rely on assessment of risk factors such as family history, disc hemorrhage,

At a Glance

- *The Advanced Glaucoma Technologies Forum took place in New York, USA, in October 2018*
- *An invited panel of glaucoma experts, chaired by Ike Ahmed, discussed many topics, including aqueous outflow and patient selection*
- *This article explores the topic of advanced diagnostic technologies used to identify and stage glaucoma.*



intraocular pressure (IOP), central corneal thickness (CCT), and corneal hysteresis (CH). All agree on the importance of IOP (See box: IOP), but Okeke emphasizes the utility of CH in determining how aggressively to treat a given patient, and Bob Weinreb agrees: "Corneal hysteresis is powerfully associated with risk of glaucoma progression – and is often overlooked." He suggests that, absent CH, the association between CCT and glaucoma progression actually may not exist.

Measuring glaucoma progression, however, requires both structural (OCT) and functional (VF) information. In the former context, Okeke suggests that OCT-mediated analysis helps indicate speed of glaucomatous change, and Weinreb notes that OCT angiography may be highly useful in monitoring patients with advanced disease. Regarding structural and functional analysis, the importance of testing macular OCT and VF is increasingly clear – Weinreb reminds us of work by Don Hood, Gus DeMoraes and Jeff Liebmann (1).

In conclusion

Ultimately, Randy Craven says, glaucoma diagnostics has benefited from a process of evolution: as problems arise, the ophthalmology community has addressed them, and so the field has advanced. "But we are still on the quest to find the magic number – the precise risk factor for each individual patient." Population-based studies, better OCT systems and other tools are helping us move towards this goal; ophthalmologists can now – with more confidence than ever before – judge how aggressively to treat a given patient. And this is unequivocally good; as Craven concludes: "We are no longer automatically opting for trabeculectomy – with all its downsides, including hypotony – rather, we are trying to do the right thing for each patient. That's personalized therapy, in a way."

IOP: How can it guide treatment? Some expert views

Randy Craven: "There are several ways of measuring IOP, which all work in different ways: for example, ORA, rebound tonometry, Goldmann tonometry, pneumotonometry. In each case, patient variations can interfere with the measurements – you end up adjusting Goldmann numbers in cases of thick corneas, for example. My habit now is to take measurements with three different instruments – when you see big differences between techniques, it actually tells you a bit more about the eye, such as how compliant or viscoelastic it is. Therefore, I rely on a group of pressure measurements from different machines – I don't know if I'm unique in that."

Marlene Moster: "We need 24/7 IOP measurements to really understand whether our treatments are effective or not. Moving towards implanting sensors in the eye will enable us to better understand how the individual is responding, and will help us make better surgical decisions for that patient."

Paul Singh: "We have to remember that IOP is just a number, a risk factor – it is not directly related to glaucoma. In fact, it's a moving target, which is why I find it's helpful to have other measurements. In particular, hysteresis provides information about the quality of the IOP measurements: for example, I'd be more concerned about low hysteresis and high IOP than about high hysteresis and higher IOP. So we shouldn't look at IOP in isolation – we need to take account of many other variables, including age, magnitude of pressure fluctuations, and rate of progression."

Ike Ahmed: "The incorporation of ocular biomechanics, specifically hysteresis measurements, assists risk analysis and helps us understand how the eye can handle a head of pressure. The ability to monitor pressure during out-of-office hours has been very revealing – when you see self-monitored IOP spiking in the patient's home, it is another indication that proactive, aggressive treatment may be required."

The Advanced Glaucoma Technologies Forum was hosted by The Ophthalmologist and supported by Ellex, Santen, Heidelberg Engineering, Reichert Ametek and Aerie Pharmaceuticals Inc.

Ike Ahmed is Assistant Professor at University of Toronto, Canada.
Earl Randy Craven is Associate Professor of Ophthalmology at Johns Hopkins University, Maryland, USA.
Marlene Moster is Professor of Ophthalmology, Wills Eye Hospital, Philadelphia, USA.
Constance Okeke is a glaucoma and cataract surgery specialist at Virginia Eye Consultants, and also an Assistant Professor of Ophthalmology at Eastern Virginia Medical School, Virginia, USA.
I. Paul Singh is an ophthalmic surgeon at Eye Centers of Racine and Kenosha, Wisconsin, USA.
Robert N. Weinreb is Distinguished Professor and Chair, Ophthalmology, University of California, USA.

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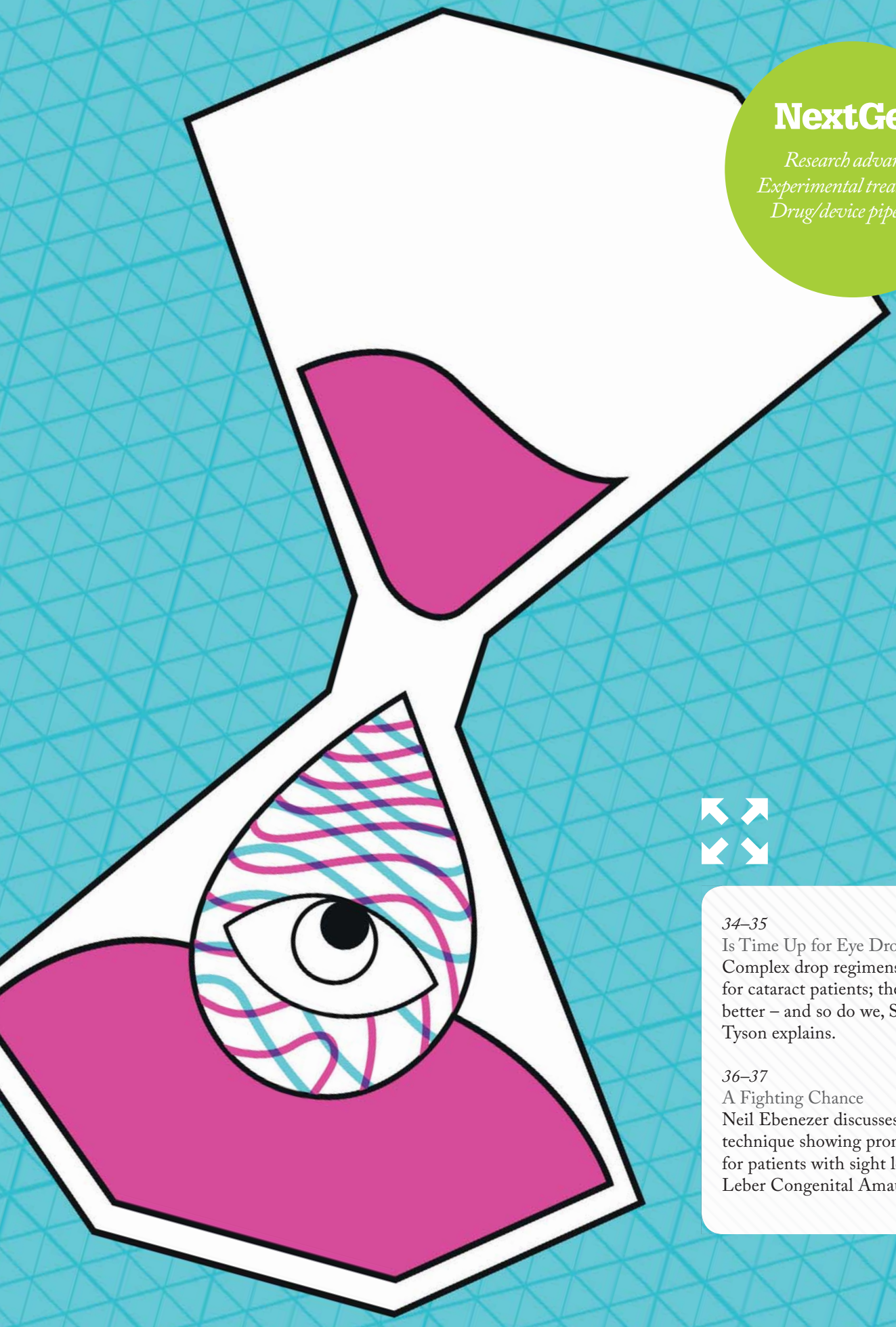


NextGen

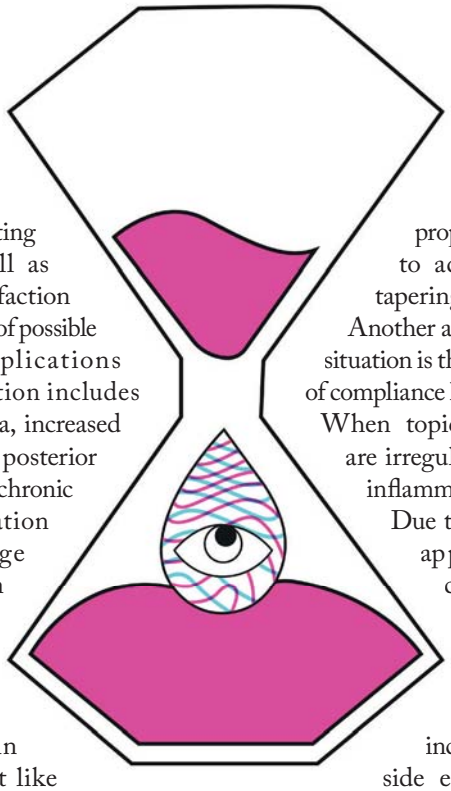
Research advances
Experimental treatments
Drug/device pipelines

Is Time Up for Eye Drops?

Complex drop regimens are difficult for cataract patients; they deserve better – and so do we

By Sydney Tyson

Cataract surgery is one of the safest and most widely performed ophthalmic procedures – and it plays a huge role in improving quality of life and reducing visual disability throughout the world (1). Nowadays, the technology used in cataract surgery is becoming increasingly advanced, further enhancing patients' postoperative visual results. Inflammation, however, is a common consequence of cataract extraction, and keeping it under control is paramount to preventing complications as well as ensuring overall satisfaction for patients (2). The list of possible postoperative complications caused by inflammation includes cystoid macular edema, increased intraocular pressure, posterior capsular opacification, chronic uveitis, fibrin formation and protein leakage from the breakdown of the blood-aqueous barrier (3, 4). Patients may experience mild to severe ocular pain and other discomfort like itchiness, burning, foreign-body sensation, and tearing (5). Surgeons routinely prescribe corticosteroid drops as part of their surgical strategy to reduce postoperative inflammation. Despite their ubiquity, topically administered drops are inherently problematic because of their method of delivery. Not only are they associated with poor bioavailability, but compliance is also notoriously suboptimal – the nature of drops versus human nature. It has been estimated that within two minutes of instillation, more than 80 percent of a drop is eliminated via the nasolacrimal drainage system (6). And that means less than 5 percent of a given dose reaches intraocular tissues (7).



At a Glance

- *Dextenza is an intracanalicular dexamethasone insert that provides sustained drug delivery to the ocular surface over a 30-day period*
- *FDA-approved for ocular pain following ophthalmic surgery – with an upcoming sNDA date for inflammation – it combats the key problems associated with topically administered drops; poor bioavailability, improper drop technique, potential toxicity and compliance*
- *Studies have found Dextenza increases bioavailability from 5 percent to 70 percent and decreases inflammation and pain after surgery –maintaining both for up to 45 days*
- *Patient-friendly approaches – like Dextenza – could replace problematic drug-delivery strategies in the future.*

The struggle is real

Patients have great difficulty with drops. They often repeat instillation, exposing the eye to potential toxicity associated with preservatives. Improper drop technique, like not washing hands, touching the bottle tip to the eye, missing the eye entirely or using an incorrect number of drops is common (8). When considering the age of the population undergoing cataract surgery and the common comorbidities, such as forgetfulness, arthritis and limited dexterity, it is clearly a daunting proposition for patients to adhere to complex tapering regimens (9, 10). Another aspect of this layered situation is the impact that a lack of compliance has on drug efficacy. When topical corticosteroids are irregularly used, rebound inflammation can occur (11). Due to their intermittent application, drug concentration varies over time, with peak –immediately after instillation –potentially increasing the risk for side effects and trough concentrations – before the next instillation – potentially producing insufficient pharmacologic effect.

A better way

Numerous companies are working on drug-delivery methods to overcome the many barriers to optimal drop administration. Ocular Therapeutix has introduced Dextenza, a sustained-release intracanalicular dexamethasone insert containing 0.4 milligrams of active drug. Placed by the surgeon into the canaliculus, the insert provides a sustained and tapered delivery of drug to the ocular surface over a 30-day period. Late last year, the FDA granted approval of Dextenza for the treatment of ocular pain following ophthalmic surgery. The insert contains only a fraction of the total dose of corticosteroid drops patients would typically administer postoperatively in a monthly course, so Dextenza may replace up to 70 topical drops. Research revealed that bioavailability increased from 5 percent to 70 percent with Dextenza (12, 13). The insert is placed by the surgeon, removing all compliance concerns and relieving the patient of the burden of a complex regimen of corticosteroid instillation and tapering. The insert does not contain preservatives,

eliminating concern regarding ocular surface toxicity. Over time the device softens, subsequently clearing through the inferior nasolacrimal canaliculus so there is no need for its removal. If necessary, it can be expressed or irrigated out.

The FDA's approval of Dextenza for pain indication was based on demonstrated efficacy in two randomized, vehicle-controlled phase 3 studies in which a statistically significantly higher incidence of subjects was pain free eight days after cataract surgery compared with the vehicle control group (12-14). Safety was also established in the two phase 3 studies as well as a third randomized, vehicle-controlled phase 2 study.

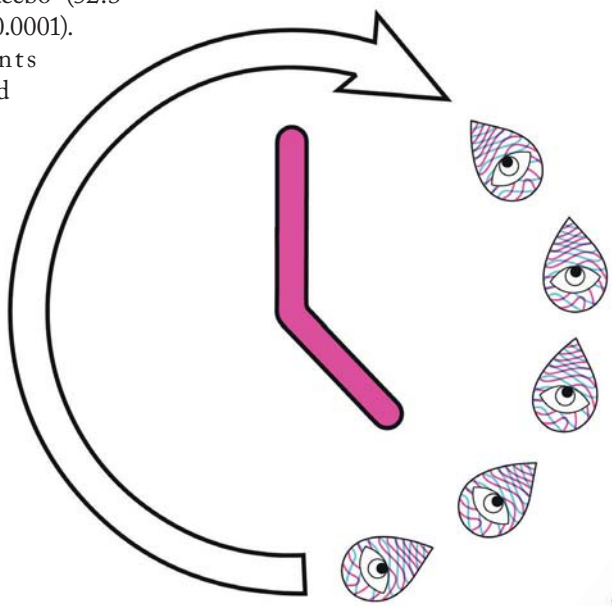
But what about inflammation?

In a phase 3C clinical study, I (along with other investigators) further evaluated the insert's effect on pain and inflammation (14). The 438 patients with planned clear corneal cataract surgery were randomized to receive Dextenza or placebo. The primary efficacy endpoints were complete absence of anterior chamber cells at day 14 and complete absence of pain at day eight. The onset of action was demonstrated immediately and 14 days after implantation, significantly more patients had an absence of anterior chamber cells in the treatment arm compared with placebo (52.3 percent vs 31.1 percent; $P < 0.0001$).

In addition, patients receiving Dextenza had decreased inflammation after surgery as early as day four and a decrease in pain as early as one day after surgery, both of which were maintained to day 45. The insert was well tolerated, with adverse events similar to placebo. Topical NSAIDs were not included in the trial and those that required rescue therapy were deemed a treatment failure. Interestingly, twice as many placebo patients required rescue therapy as Dextenza patients at day 14. Further, a small, qualitative survey found that treatment satisfaction with Dextenza is high (15).

The end of eye drops?

Ocular Therapeutix has now submitted a supplemental New Drug Application (sNDA) to the FDA for Dextenza seeking to expand the current indication to include the treatment of ocular inflammation following ophthalmic surgery. The company expects that the FDA review will be completed in the second half of this year. Antony Mattessich, the company's president and CEO, has stated its goal as making eye drop therapies obsolete. In connection with the approval and anticipated commercial launch of the product, Ocular Therapeutix has also submitted an application to Centers for Medicare and Medicaid Services for transitional pass-through payment status and an application for a permanent J-code. I for one am pleased. When we think about the precision of modern cataract surgery with its advanced technology and premium lenses, it seems counterintuitive that we still ask our patients to struggle through their confusing postoperative drop regimens. By replacing problematic drug-delivery strategies with patient-friendly approaches like Dextenza, we can finally say, "Eye drops: your time is up!"



Sydney L. Tyson is the President of Eye Associates and SurgiCenter of Vineland, New Jersey. Tyson reports that he has received research support from Ocular Therapeutix.

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A Fighting Chance

New technique shows promising results for patients with sight loss from Leber Congenital Amaurosis

By Neil Ebenezer

At the beginning of this year, I was delighted to see research from a clinical trial published in Nature Medicine (1) that showed promising results in preventing sight loss – or even restoring sight – for patients with a type of Leber Congenital Amaurosis (LCA). I'm proud that Fight for Sight funded the early stage research that helped enable this finding, which is what our charity is all about.

LCA is a disease of childhood and represents a group of rare inherited disorders that progressively affect the photoreceptors of the retina. People with LCA have severe sight loss at an early age, and it affects around two or three people in every 100,000.

Several different types of LCA have been identified to date – driven by mutations in genes that have been shown to be crucial for normal visual function, including RPE65 (LCA type 2) and CEP290 (LCA type10). Mutations in these genes can result in loss of an essential protein leading to visual impairment. Recently, the first viral gene therapy was approved for LCA type 2; it can improve patient vision in dim light, but there are no therapies for the other more common forms of LCA. And that's why it is so important that we fund research in this area.

This new gene-directed therapy involves using antisense oligonucleotides (short, synthetic, single-stranded DNA) to repair the genetic faults. The oligonucleotides that have been developed in this instance are specifically for LCA type 10, targeting the most common defect in a gene called CEP290. The oligonucleotide binds the RNA and blocks the effect of the fault, thereby allowing a normal protein to be produced to restore cell function. Much has already been written about using viral gene therapy to treat eye conditions, but this technology has the potential to provide an alternative technique that could transform the lives of some patients.

At Fight for Sight we funded initial research that was published in 2016 in Cell Stem Cell (2). The research was led by Mike Cheetham from the UCL Institute of Ophthalmology. By using cells derived from patients with LCA10 he developed a model of retinal organoids, or "mini retinas," which he grew in the lab to show that this oligonucleotide approach could efficiently target the mutation and restore function in photoreceptors. Following this proof of concept, Cheetham worked with the Dutch Biotech company ProQR to test potential drug candidates on human photoreceptors in these retinal organoids

At a Glance

- *New research, the early stage of which was funded by Fight for Sight, shows positive results in protecting sight for patients with a type of LCA*
- *The new therapy uses antisense oligonucleotides to repair genetic faults of LCA type 10, targeting a defect in the CEP290 gene*
- *Mike Cheetham from the UCL Institute of Ophthalmology led initial research published in 2016, developing retinal organoids using cells derived from LCA10 patients*
- *A clinical trial, involving five research organizations around the world, showed improvement in patients' visual acuity.*

– research that was recently published in Molecular Therapy Nucleic Acids (3). This work was essential because this therapy is specific to the human DNA sequence, and animal models do not recreate the disease. These mini-retinas could also be used to examine dosing and other potential effects, and have several advantages for studying pathogenic mutations over animal models. The output of this research better informed the subsequent clinical trial, to show potential doses and dosing frequency.

Based on this work, ProQR sponsored a clinical trial involving ten patients in three clinical centers in the USA and Europe. The study involved five research organizations around the world, including the UCL Institute of Ophthalmology. The patients received injections in the vitreous of their most affected eye, so that the treatment could diffuse to the retinal photoreceptor cells. The treated eye was compared with the untreated eye. The initial results were so encouraging that an interim report has just been published in Nature Medicine (1), reporting eight patients assessed at least three months after their first injection. The trial found that the product was safe, with no major adverse reactions. Importantly, the treated eyes showed significant improvements in light sensitivity and visual acuity that were not observed in the untreated eyes. After three months, five out of the eight patients showed improvement in visual acuity over 0.3 log10MAR, which is thought to be clinically meaningful. One patient responded exceptionally well, and reported improvement in the treated eye after six weeks. This patient self-reported that, for the first time in decades, lights were seen with increasing clarity and brightness, but only in the treated eye. After two months, the patient could read the first three lines of the standard ETDRS chart from a distance of one metre with the treated eye, but could not distinguish any letters with the untreated eye. Over the following months, he continued to improve.

Figure 1. The research findings could help lead to new treatments for patients such as Jackson, living with LCA, pictured here with his mother.

This was a combined phase one and two trial, which largely focused on safety, tolerability, and efficacy of the technique. The next stage will be to test the approach more widely in further trials before leading, we hope, to a therapy that could be available for patients with this condition.

The ultimate goal is not only the development of a treatment for people with LCA type 10, but also a therapeutic approach that could be applied to many other conditions including Stargardt disease, Usher syndrome and Fuchs endothelial corneal dystrophy. Ultimately, there are also possibilities for conditions outside the eye. An antisense therapy is already approved for spinal muscular atrophy, and there is hope for other conditions like Huntington's disease or dystrophic epidermolysis bullosa; basically, any condition where there is an appropriate genetic fault that can be rectified. These approaches, however, need dedicated research because each therapy is unique to the condition.

This is an exciting time for eye research. Many of these pioneering therapies are being trialled in the eye because it is contained and separate from the rest of the body – ideal. The developments we see over the next decade will be even more extraordinary than the previous ones. The fact that we are on the cusp of such breakthroughs means that, now more than ever, is the time to invest into vital eye research that will lead to the next big discovery.

Neil Ebenezer is the Director of Research, Policy and Innovation at Fight for Sight, UK.

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From the Ground Up

The long-term partnership transforming eye care in Myanmar

By Mitchell Brinks

International outreach first caught my interest in medical school, as I mapped out my career goals. I wanted an enjoyable rewarding career – and I knew that couldn't be measured in salary or surgical volume alone. I wanted to make an impact – and what could be more impactful than working with ophthalmologists in communities in the greatest need for our skills. The more I thought about it, the more international outreach seemed to offer the ideal solution: a chance to give my fellow humans one of life's greatest gifts – sight – and interact with people and cultures from all over the world. I knew then what I wanted to do. Since graduating, I've worked with underserved communities everywhere from Oregon, Washington and Alaska to Samoa, Cambodia, Bhutan and East Timor. I went on to become Assistant Professor of Ophthalmology at the Casey Eye Institute and, eventually, Director of the Casey International and Domestic Ophthalmology programs.

"Though Myanmar is a resource-rich country, more than a third of the population lives in poverty."

Five years ago, our faculty set our sights on an international, long-term partnership that best leveraged our institutional capacity. After an international search, we settled on a location – one of the poorest countries of Southeast Asia: Myanmar. Though Myanmar is a resource-rich country, more than a third of the population lives in poverty. It has one of the highest prevalence of blindness in the region, with a quarter million people blind from operable cataract alone. To put that in context, just a few years ago fewer than ten subspecialists served a population of 55 million – one oculoplastic, one retina, two cornea and two pediatric. While generous international partners from around the globe are now opening training opportunities for the many talented Myanmar ophthalmologists, there was no Myanmar run program in place to train subspecialist. We decided, as an institute, that the best way to make change was to start from the ground up.

What started as a glaucoma and oculoplastic skills transfer has developed into an altogether different task: assisting the growth of a nascent academic ophthalmology institution, and helping talented and committed local doctors build their vision of eye care of Northern Myanmar.

Today, the program in Mandalay incorporates many components of an effective US-based institution – including

At a Glance

- *The Casey Eye Institute has partnered with Siriraj Medical School and the Mandalay Eye & ENT Hospital to improve eye care in Myanmar*
- *The program – led by Mitchell Brinks and Yee Yee Aung– has links with four medical institutes in Southeast Asia: two in Myanmar; the Mandalay Eye and ENT Hospital and Shwe Yatu Tipitaka Eye Hospital, and two in Thailand; the Siriraj Medical School and BDMS/Bangkok Hospital System*
- *Alongside Ophthalmic Specialty Fellowships, the program offers mid-level personnel training, biomedical engineer training, pediatric screening, training for an Ocularist, Echographer, an improved health database and research capacity development*
- *The Casey/Myanmar partnership program has grown along with outreach partnerships in the South Pacific and the USA, as the team builds on its outreach programs in Oregon.*

Figure 1. Doctors Edmunds and Zaw.

Figure 2. Pediatric eye screening team in Myanmar.

subspecialists training junior faculty, ophthalmology residency development, academic research mentorship, and management development. It also includes staff training in data management, biomedical engineering, echography, Ocularist training, clinical technical work, and population eye health outreach. The project is now in its fifth year, and growing by the day.

I can't help but think how the program came to be. We knew we wanted to create a long-term plan with our partners in Myanmar and Thailand, but we weren't exactly sure what form it would take and that had to change. We were asking our colleagues to commit for the rest of their careers so we had to be sure of what we were doing. Short-term missions were an option but they didn't resonate with our career goals; we knew we were capable of more. In the end, we spent over a year sorting through what would become the foundation of our efforts: an education program that allowed us to replicate what we do at our university institution, elsewhere in the world. But, to do that, we needed help.

Figure 3. Ophthalmology chair David Wilson (left) and University President Joseph Robertson (right) with Sayadaw and Burmese monks.

The search begins…

Using our partner Bangkok Hospital as our base, we visited manyacademic centers and government hospitals throughout Southeast Asia until we found a structured and well-led training program that matched our program. In the end, we found two and they both became our program partners. The first was the Mandalay Eye, Ear, Nose and Throat Hospital, a government-run institution with a small faculty and residency program. The second partner site in Myanmar was a Buddhist monastery, Tipitaka Eye Hospital – literally the "Three Baskets" of Buddhist scriptures. It was led by a highly respected Sayadaw, or senior monk who had memorized the entire Buddhist literature – one of just a few in the whole country. The monastery hospital was, and is growing rapidly, giving our partnership the chance to help build new programs and bolster patient care. The government hospital was a different story. It was already well established and,

as a result, a bit less agile. Though I don't claim to be any kind of expert on Burmese culture or politics, I understand that in any international interaction, it takes a long time for both sides to build trust – and that's even more the case in a place like Myanmar where there has been an uncertain reception for bold ideas in the past. This seems to have changed and we've witnessed strong investment in health care and schools over the past few years.

So, in our project we adopted a slow growth strategy. We initiated meetings with different tiers of our respective intuitions – from ophthalmologists to technicians to instructors – all the way up to the president of our university. It was our way of guaranteeing vertical adhesion to the system on both sides. Of course, there were still niggles. We were aware that without a practical financial give-and-take basis for the relationship there may be less of an incentive to carry on. And that's why we worked with our partner sites to formalize and carefully delineate our plan in contract form. We all wanted to be clear on the plan and know how we would solve obstacles cooperatively, when they inevitable came to pass. Still, we knew we were asking a great deal from our partners. We were demanding their time, their trainees and their attention drawn away from their very heavy workload to engage with us during visits. At least one year went by before the overall cadre of ophthalmologists involved (both in the US and in Southeast Asia), were convinced that the partnership was worth investing in – but we did it, and the trust and capacity, is still improving today. We immediately began training sub-speciality ophthalmologists in oculo plastic surgery from the government hospital, along with developing management and operational protocols and clinical staff training programs at the monastery hospital. Everything else has grown from there.

Figure 4. University President Joe Robertson with Sayadaw and Ophthalmology chair.

Figure 5. Nurse aids and Mitchell Brinks (right).

Playing the long game

There are many ophthalmologists both from Myanmar and across the globe who choose to work for the betterment of eye care in Southeast Asia. These ophthalmologists selflessly taking on many patients, often seven days a week, and usually with little or no compensation. What they do is incredible, yet resources are can be limited – and collaboration is clearly beneficial among ophthalmologist in any country. Part of what makes long-term programs so appealing is that they give local hosts time to decide if a project is worth investing in and how they might fit in – and for visitors to better understand the local environment. It took us years to begin to understand how social, political and medical interactions play out between foreign and Myanmar ophthalmologists– unsurprisingly, they are more complex than the same interactions would be within the USA. At the same time, our program was gaining momentum. Ophthalmologists were becoming more and more invested in our program because we intended to be there for a long time. That was it. Short-term programs are well intentioned, but they take a lot of work on behalf of the local hosts, who then have to change their clinical and O.T. times and schedule to accommodate visitors – that doesn't happen as much with a long-term program. By creating a sustainable project, we were allowing trust to build over time – and that applies to our own faculty, too. The project gave surgeons the chance to get to know other surgeons, trainees to get to know other trainees, and technicians to know each other. It is these personal relationships that began to drive our work.

Where we are now

So far, our sub-specialty program has engaged in training an oculoplastic surgeon, glaucoma surgeon, vitreo retinal surgeon, uveitis specialist and neuro ophthalmologist, as well as a pediatric ophthalmologist and ophthalmic echographer. Alongside this, we've also helped connect our residents and are beginning to develop an academic library, enhance educational programs and understand the policy issues around non-profits working alongside us. We're even in the midst of training an ophthalmologist in public health, so they can take their knowledge back with them to Myanmar to steer long term planning in eye care. As you can imagine, a program of this kind – encompassing learners from different sites in a single channel – requires commitment from our team in Oregon. But it works. Why? Because our entire faculty is invested in the program. In fact, it's become part of the identity of our eye institute!

I often remind myself that where there is need, there is an opportunity to do good – and that's a belief shared by everyone in the program, both here in Oregon, in Myanmar, in Thailand and in the South Pacific.

One of our glaucoma surgeons is a good example of this. Having anticipated a meet and greet the afternoon of her arrival in Mandalay after 20 hours travel, she was asked if she would see a three year old boy with glaucoma. The boy had high pressures and the very large eyes common in advanced glaucoma. The only chance for this child was to operate without delay. Fortunately, our surgeon was also specifically trained in pediatric glaucoma.

Under normal circumstances, there would be no-one willing to operate on such a case…. but the hospital staff offered to do everything they could to make such an operation possible. The surgeon, Beth Ednunds, and the Myanmar doctors and staff were able to

Working Overseas

Myanmar came to the fore because of the diverse mix of like-hearted ophthalmologists willing to work together on the project. That was important because we knew that no matter how much we hashed through our plans, long-term growth would depend on the trust and respect we would build together. The ophthalmologists leading the project in Mandalay (Dr Yee Yee Aung) and Bangkok (Dr Ngamkae and Dr Somsran) are invariably thoughtful, open, and committed to the success of the project.

My team and I are currently writing a series of articles on the ethical principles around international partnerships – something every ophthalmologist working overseas has to think about. US physicians in particular are used to working in highly regulated environments. In fact, it is often these environments that allow us to produce our best work. The problem with this lies in maintaining these supportive dynamics when we leave our home countries and go to unregulated environments. Without strict rules, people can go off track, either because they are too ambitious in their desire to help, or not self-evaluating enough to evaluate what it and is not effective care – no matter how good the intentions. Our advice is that when people cross international boundaries, it is important they continue adhering to the principles that made them great in their own country and accept that ultimately it is the host's country, the host's patients and the host's decision as to what they would like to happen. As visiting ophthalmologists, it is our job to manifest their vision, while respecting our own principals on how it should be done.

Figure 6. Mandalay Eye Hospital.

Figure 7. Chair Laurel at Mandalay.

Figure 8. Mandalay faculty with Julie Falardeau.

improvise and successfully completed the surgery in both eyes. The surgery worked – the next day the eye pressures were down, the boy's eyes were clear and bright and his parents were delighted to see him playing with a toy car and smiling at them. It was a beautiful coming together of everything we had hoped for. Even though it was two years ago, she still hasn't lost her enthusiasm or motivation – and it's all because she had the opportunity to use her skills and make a difference.

The partnership's future

People often ask what the ultimate goal for this project is. I would say there are two. The first is to demonstrate that successful long-term partnerships can be the rule for successful and rewarding international collaborations – not the exception. Our program offers proof that it's possible to do things on a large scale, with a modest amount of time because, in actual fact, our host and partner Myanmar ophthalmologists do the vast majority of the work – planning, supplying, organizing, seeing patients, doing surgery and managing follow up – rather than us; the visiting ophthalmologists. But by investing our time and energy in long-term planning, we can do a lot more and feel good about it. We can clearly see that these relationships we've forged with colleagues in Myanmar and Thailand will remain part of our lives for many years to come. Interestingly, long-term partnerships aren't more difficult or more expensive to set up than short-term partnerships – they just take a little more planning and preparation.

The second goal is to provide ophthalmologists with ways to get the most out of their career by delivering their skills to those who need them most. The truth is, as much as medicine is a wonderful profession, economics and bureaucratic demands can wear away at even the most dedicated physician. Programs like ours are an antidote to that. Going to a place where you can do so much for so many reminds us why we got into medicine in the first place. It helps us rediscover that original inspiration and motivation, and allows us to be creative in the way we approach certain situations. We know that going to Myanmar can be a big step for some ophthalmologists – either because they're new graduates, have family obligations at home or simply aren't ready to cross so many time zones. We've found that our outreach program in the South Pacific, or even the one here throughout our home state of Oregon fit well for many faculty. There are quite a few people here at home who aren't much better off than those we visit overseas. We've actually found that the pleasant setting and family-oriented culture of less urban locations in the Pacific islands seems to lessen the challenge of leaving homes,

So that's where we are now. As I reflect on our partnership, I can't help but think of a moment three or four years into the Fellowship Training Program, when our team went out for dinner in Mandalay. As I looked around the table – seeing the happy cadre of young Myanmar ophthalmology specialists talking and laughing – I marveled at the self-supporting culture of talented doctors that this partnership had helped reach their goals. Seeing this group of dedicated and talented sub-specialists – most no older than 35 – I could envision the future of tertiary eye care in Mandalay. And it looked really good.

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It's A Conversation, Not A Conversion

The art and psychology behind successful FLACS consultations

By Blake Williamson

Approximately 65 percent of patients undergoing cataract surgery in our practice choose to have femtosecond laser-assisted cataract surgery (FLACS) – a relatively high conversion rate, given the low mean household income in the market in which I practice. It's not a new thing either. We've been consistently reaching this high conversion rate since we launched FLACS, and we've done it without any level of effort I'd consider extraordinary. On the contrary, it was a very natural and organic fit for our practice and the mindset of our team. So how is this possible? I believe it's due to a number of factors, including effective internal and external marketing, the way we structure refractive packages and our workflow. However, by far the most important factor is how my partners and I personally view the value of the laser. Put simply, we believe this technology helps us better serve patients. If we didn't, we wouldn't offer it. It's not that manual is bad; I actually think manual surgery is fantastic! I know that I can perform an excellent manual cataract surgery and I have colleagues who I would trust to perform excellent manual surgery, as well. But I also know that I chose the laser for my own mother and that's what I would want if I were having cataract surgery. This simple, non-emotional, non-political fact forms the foundation of how I talk about FLACS to patients. We don't give patients a "hard sell" and we don't tell them the laser is safer or that they will necessarily see better by choosing the laser. We don't need to do that. Instead, we simply talk about the laser's precision, reproducibility, and automation. As a surgeon, I believe that precision matters, so an honest conversation about femtosecond laser technology follows easily from that belief.

I believe too many surgeons get caught up focusing on what technology doesn't do instead of focusing on what it does do. I imagine many surgeons were soured by their experience with first-generation lasers, just like they were with first-generation presbyopia-correcting IOLs. But a decade has passed and lasers are better now. I personally believe FLACS is safer and better than manual surgery – and newer research backs it up. Plenty of studies with modern lasers and newer software versions have shown safety data that FLACS is superior to manual (1); however, I understand there are also large meta-analysis studies that have found them to be equivalent. I believe this will follow a similar trajectory as the evolution of extracapsular surgery to phacoemulsification. In the beginning, even when the data wasn't overwhelmingly in support of phaco, early pioneers pushed on because they intuitively knew it was better. They saw it every day in their own ORs. They just felt it. The patient's visual goals are also an important part of the conversation, because FLACS is automatically included in each of our refractive, advanced-technology packages.

Package rates

I like to keep it simple by offering patients just three packages. Keeping it simple helps our patients avoid "paralysis by analysis," where too many options make it too difficult to come to a decision. Our three options for cataract surgery include:

- Option 1: Manual cataract surgery with a monofocal lens and no astigmatism correction. Patients

At a Glance

- *FLACS is as safe and effective as manual cataract surgery – but some practices struggle with its integration, with uptake relying on effective internal and external marketing, well-structured refractive packages and optimized practice workflow*
- *Successful conversions often start long before the patient even walks through the door, by planting the seed with primary eye care doctors who are referring patients for surgery*
- *Once the patient is on-board, surgeons should stress the undeniable benefits of FLACS: precision, reproducibility and automation*
- *Don't be afraid to talk costs at the initial consult – it puts the patients at ease and gives them the information they need to make a measured decision, saving you and your refractive counselor's time.*

should expect to need bifocal glasses after surgery. I always make a point to mention that it is good and safe surgery, even if the patient starts out the consult by expressing interest in FLACS and advanced IOLs. I do this because I sleep comfortably at night knowing that no patient can ever say that I "talked them into" upgrading to FLACS.

- Option 2: FLACS with astigmatism correction, whether that be with astigmatic keratotomy or a toric lens. This option also includes ORA intraoperative aberrometry (Alcon). We tell patients that with this option they will likely be able to see at distance without wearing spectacles or contact lenses, but will need reading glasses for their up-close vision.
- Option 3: FLACS with correction for astigmatism and a presbyopia-correcting IOL. We tell patients this will greatly reduce their need for glasses at all distances. Option 3 includes ORA, as well as a LASIK touch-up within the first year if needed. Patients like knowing they have that safety net; it increases their confidence in reaching their refractive goals.

Honing the message

Some practices have struggled with FLACS conversion because they present patients with the option just once, discuss it too late in the decision process, fail to provide enough context or fail to make a recommendation. We believe in including discussions of laser cataract surgery early and often – ensuring there are no surprises.

Successful conversions start long before the patient even walks through the door, by planting the seed with primary eye care doctors who are referring patients for surgery. The seven optometrists who work for Williamson Eye and our referring optometrists outside the practice all know my views on the value of the femtosecond laser…and they share those views as I've used FLACS to operate on them personally or their loved ones in several instances. So it's one of the things they will mention when they first diagnose a patient with cataract. They have also told me they enjoy seeing these patients postoperatively because of the fast visual recovery and "wow" effect. When a patient schedules a cataract surgery consultation with us, they get an information packet that includes a pamphlet about the laser we use (Catalys, Johnson & Johnson Vision), as well as the available IOL options.

Figure 1

We are proud of our advanced technology options and don't hesitate to promote them within the practice. For example, we have custom-made, seven-foot-tall banners next to every check-in station educating patients about the Catalys laser and other technologies that we use (Figure 1). Every single person who comes into Williamson Eye Center sees those banners, whether they are here for an eye exam, dry eye treatment or bringing in a relative for LASIK surgery. I also have posters in the exam lanes on either side of the eye chart featuring the laser and advanced IOL options. Most importantly, we have created a video about FLACS to standardize the information patients receive about what the femtosecond laser is and how it helps us better meet their needs. We have many ophthalmologists, optometrists and staff members at our practice, so the video helps ensure that patients' awareness of FLACS isn't dependent on how passionate or articulate one person is compared with another. The eight-minute video was filmed and produced by students from the local university so not only was it very economical, it was personalized to us, as opposed to the cartoon animation videos the laser company provides. Each of our surgeons has a speaking part (all of which were carefully scripted to convey the exact message we wanted) and the video features the procedure, an animation comparing the automation of the femtosecond laser with a manual cataract surgery and an overview of our three package options.

Patients watch the video on a large iPad after their workup (Figure 2), just before they see the surgeon. They also receive an oversized "menu" of the package options that reiterates what the video covers (Figure 3). When I walk in the room, I can feel confident that the patient is well educated about the different options, and I can tailor our conversation to my findings and answer their questions about surgery. Often, when I walk into a room the patient says "I'd like a number two!" The conversation is very streamlined from that point.

In talking about the package options, I like to use the analogy of buying a car or a new computer, because those are purchases many people would have made in the past few years. On a new car, you can choose from several trim packages. On a computer, you can get different software and features based on whether you plan to use it for gaming, for browsing or for work. I tell them that cataract surgery is similar in that there are options to customize vision based on your lifestyle and your visual goals. All the options are safe and effective, but your choice centers on how much – or how little – you want to wear glasses. I also express the finality of this procedure by telling them it's similar to a heart valve in that the implant will never come out. They can't come back for an upgrade in five years, so

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*Comparison based on results from individual pivotal trials and not head to head comparative studies.

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Figure 2

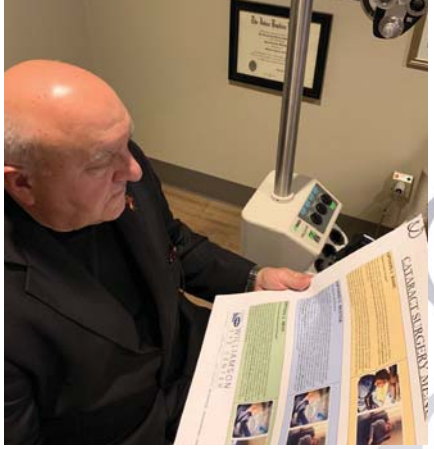

Figure 3

it's critical they choose the best technology for their visual goals.

The cost conversation

Many surgeons dread discussing pricing and avoid it completely, preferring to let a patient counselor handle that part of the conversation. This works for some, but not others. Initially, I thought that would be my approach, but I quickly realized that avoiding the cost conversation wasn't equipping my patients with the realities they needed to make the decision and it wasn't setting up my counselor for success either. Often, they would have a great discussion with me about presbyopia IOL solutions, only to get to my counselor and experience sticker shock when they found out the lenses they want are more than they can afford. They leave upset, my counselor feels like she's failed and sometimes these patients even end up at other practices.

Given this experience, I changed my approach. The bottom line is most cataract surgery candidates already take for granted they're going to see well, so they have two basic questions left on their mind: Will it hurt? And how much does it cost? That's what they are wondering throughout the entire hour-and-a-half diagnostic work-up. So when they finally get to me, I'd rather just address the elephant in the room by answering both of those questions. This puts the patients at ease and gives them a baseline understanding of cost so they can make a decision about value.

Here's how my consult usually goes:

- I ask about how they like to use their eyes and what their visual goals are
- I talk about what else is wrong with their eyes besides cataract, like dry eye, macular degeneration or diabetic retinopathy and how these diseases will still be there after surgery (which lowers expectations)
- If they have astigmatism, I tell them that's one of the only things I "can fix" at the time of cataract surgery and that doing so will reduce their need for bifocals
- I explain what they're a candidate for
- If it sounds like they're interested in option 2 or option 3 (and it's medically appropriate), I walk them through what those premium packages include and don't include
- I touch on price, explaining that while I can't give them an exact number because it depends on their insurance, the ballpark monthly price for those who finance the surgery is X and the ballpark total cost if they pay for everything up front is Y
- I like to relate that monthly payment number to something mundane in their life like a round of groceries or a cable bill. They are often paying more for their internet than we are asking them to pay for their vision, which really puts things into perspective
- I reinforce that many patients take advantage of the no-interest financing we provide that allows them to pay by the month (but of course, they always have the option to pay in full)
- I also let them know that even with option 2 and 3, the non-refractive portions of the surgery will still be covered by insurance and that often this makes up the majority of the total cost

Figure 4

With this approach, most patients are able to make a decision right away. As I walk out, I tell my teammate: "Hey, she's interested in option 2. This is what we're going to do." The counselor will then get into a lot more details about insurance coverage and deductibles, payment plans, and so on. If patients aren't ready to make a decision at that moment, we reassure them they can take all the time they need to discuss this with their family and research their options. Their biometry and history and physical is generally performed two weeks after the consult, which gives me time to clean up their ocular surface and gives them time to consider their options without feeling rushed.

Clinical pearls

Marketing FLACS doesn't end with the patient's decision about what type of surgery to have. It's also important that surgeons continue to refine their laser settings and techniques to actually deliver the highest level of precision possible and meet expectations for visual outcomes. To me, the primary clinical advantage of FLACS is that it automates and standardizes many of the variables in manual cataract surgery, similar to femtosecond laser LASIK compared with old microkeratomes. My father taught me early on that in refractive surgery, "automation" is a good word and "variables" is a bad word. For instance, the capsulotomy size can be set very precisely, after accounting for some stretch. I like to set mine at about 4.9 millimetres, so that I end up with a capsulotomy of about 5.1 millimetres, sufficient to consistently cover the edge of the optic for all 360 degrees around. This provides at least some level of standardization for the effective lens position (ELP) and also reduces the potential for lens tilt when implanting a toric IOL. My capsulotomies are perfect and free floating 99 percent of the time. No human being can do that in less than one second, 2,000 times in a row, year in and year out.

In addition to size, a well-centered capsulotomy is very important for ELP. I prefer to use the Catalys laser's scanned capsule setting (Figure 4) to center the capsulotomy on the capsular bag where it will sit, rather than on the pupillary center. I often choose to make anterior penetrating astigmatic keratotomy (AK) incisions. Not only do I find these to be more effective and consistent than intrastromal non-penetrating incisions, but I also like having the ability to titrate the AKs intraoperatively, choosing to open them or not based on the intraoperative aberrometry measurements.

Although many surgeons will have preferred settings for routine cataracts, it is important to adjust settings for unusual cases. For instance, in a case with a denser nucleus, I increase the fragmentation to debulk the nucleus and reduce my phaco time. For white or black cataracts, as well as those with any corneal scarring, I increase the laser energy settings to ensure that I can penetrate through the corneal opacity and achieve a complete capsulotomy. The laser can't treat what it can't see, so achieving good fragmentation can be difficult in these cases, but having a perfect capsulotomy is always useful – especially when dealing with the densest cataracts. Finally, it is absolutely essential to diagnose dry eye before surgery so patients know that the surgery didn't cause it. Once you start really looking, you may be surprised to find that almost all cataract patients have dry eye, whether they present with complaints or not. Our workup includes point-of-care osmolarity and MMP-9 testing on all cataract evaluations, as well as tear break-up time with the HD Analyzer (Visiometrics) and a careful evaluation of the lids and meibomian glands.

We typically schedule patients within two to three weeks of their consult, so I immediately start almost all patients on preservative-free tears. For the vast majority of patients with inflammation and hyperosmolarity, I also prescribe an immunomodulator and loteprednol for a couple weeks before surgery. Those with MGD may get thermal pulsation therapy or blepharoexfoliation. For patients with significant irregular astigmatism, I delay surgery to four weeks or more, so that we can repeat their topography and biometry after a longer course of dry eye therapy. Dry eye treatment alone can rule in or rule out advanced technology IOLs for these patients.

Done right, FLACS can be a lot of fun to integrate into your surgical processes and practice marketing. Together with advanced technology IOLs, the laser presents an opportunity to give patients the kind of visual outcomes and lifestyle benefits that many of us would choose for our own eyes. Let's make sure our patients know that too.

Reference

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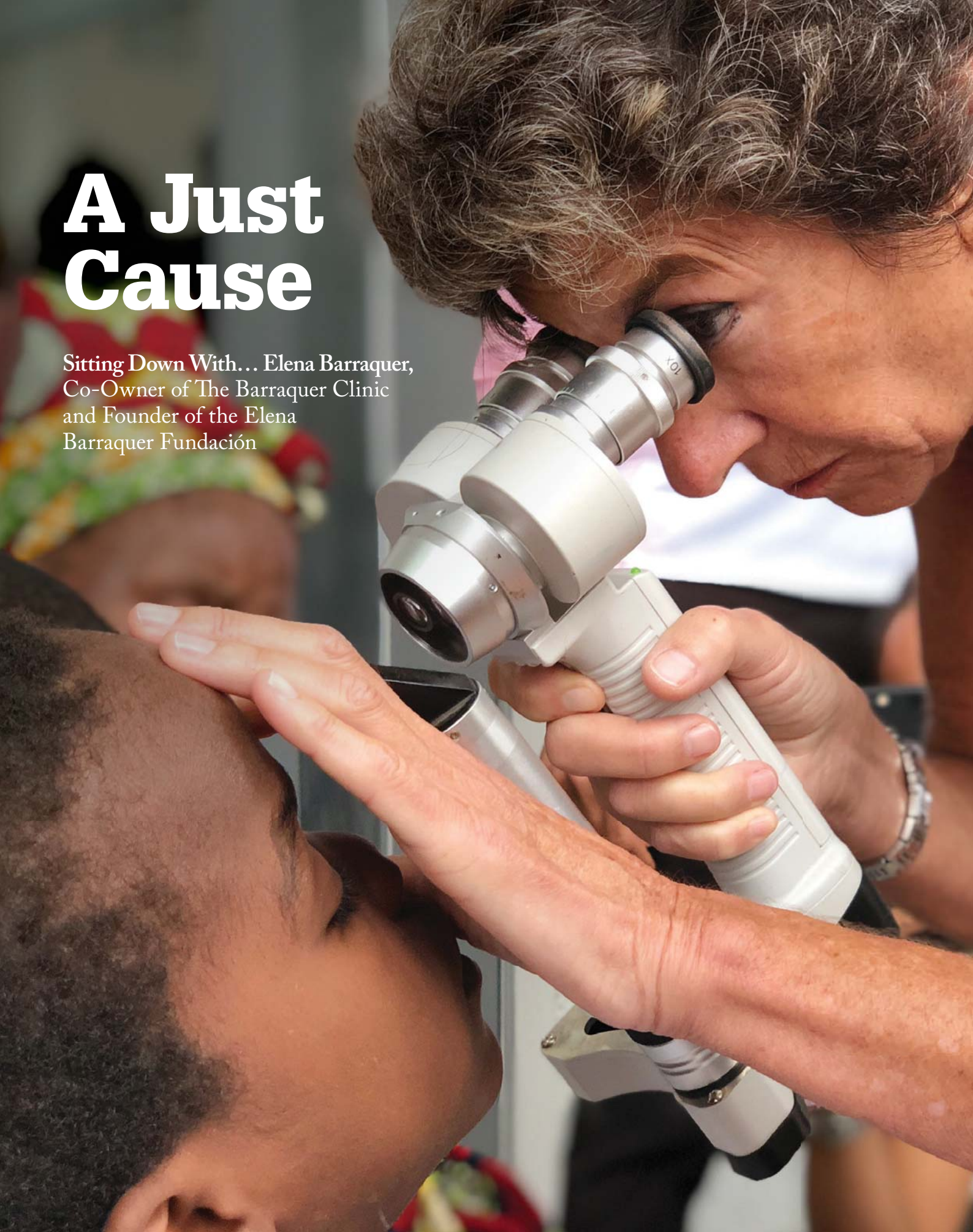
Blake Williamson is a third-generation ophthalmologist at Williamson Eye Center in Baton Rouge, USA. He is a speaker and consultant for Alcon and Johnson & Johnson Vision.

A Just Cause

Sitting Down With… Elena Barraquer, Co-Owner of The Barraquer Clinic and Founder of the Elena Barraquer Fundación



What is the best part of being an ophthalmologist?
Being able to give someone back their sight, because very often that means giving them back their life, too. When we travel on our missions, many of the people in need of cataract surgery are of working age. Last year in Mozambique, I operated on a man who was once a professional driver. He hadn't driven in two years because he couldn't see. By returning sight to people like him, you give them the ability to work and feed their families again. You give them dignity.

Tell us more about the Elena Barraquer Fundación.
It's a charity I started almost two years ago that offers eye care to communities without access to it. Ophthalmologists are coming from all over the world to work with us, which is what I always wanted. I certainly wouldn't want the foundation to die with me, or suffer if I was not able to travel as often as I do right now. I want enthusiastic young doctors to join the foundation and continue my work, when I'm no longer able to do it.

What are the barriers to medical care in these countries?
Patients don't have money – that's it. Cataract extractions, as we do them in developed countries, have become quite expensive. You don't only need costly instruments but also the disposable materials to run these instruments, which are even more expensive in the long run. Some of the hospitals we visit don't even have sterile gloves to use for the operations, so when we travel, we bring everything – up to 500 kg of materials every time!

How many missions do you get to do a year as a foundation?
This year we have treated over 2,217 patients. Every expedition, we perform about 200 or 250 surgeries. When I was in Angola last October, I did 251. We average about eight missions a year. This year, we have nine planned, all of them with two surgeons because we have come to realize they are more cost effective that way.

"Every year, there is something new – especially in the IOL space – to improve the results of cataract operations, giving patients more independence from glasses."

Do any moments stand out?
There are so many that I sometimes think I should write a book. The most recent memorable moment was in Angola. The banks there are not allowed to use their local currency to buy things from foreign countries because of government restrictions. And that means they cannot buy the disposable materials needed for cataract extractions, so for six months, there were no operations anywhere in the country. You can imagine the queues of patients waiting for us. It was heart breaking.

Looking at the bigger picture, your work goes beyond saving sight…
Yes. Some years ago, we did a very small, basic study on the economic impact of one of our one-week missions in Cape Verde. We worked out that restoring sight to those patients brought back $20,000,000 to the country. That's because it's not just the patients who can resume a normal life, it is their children – particularly girls of school age – who can, too. An educated child has a huge impact on the socioeconomic development of a country.

What legacy would you like to leave?
To continue the work of my foundation and to help eradicate preventable blindness by cataracts. We should all be doing something to prevent that – not just ophthalmologists. I think that the ophthalmic industry should collaborate with us.

What's exciting you in ophthalmology right now?
Every year, there is something new – especially in the IOL space – to improve the results of cataract operations, giving patients more independence from glasses. And that's very exciting. Vitro retinal surgery has changed even more. When I was a resident, retinal operations were boring because it was difficult to reach the retina, they didn't have the surgical aids to be able to do the wonderful, almost miraculous, things we can do today.

Any advice?
When you are young, go to as many conferences and read as many journals as you can. Things change so quickly that if you don't keep up with new things, you will fall behind.

If you weren't an ophthalmologist, what would you do?
When I see something I feel is unjust, I want to do something about it. So, for that reason alone, I would be a lawyer – to represent lost causes. I would have loved to be a musician because I love to sing and play guitar – I just don't do it very well.

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INDICATIONS AND IMPORTANT SAFETY INFORMATION FOR THE TECNIS® MULTIFOCAL FAMILY OF 1-PIECE IOLs

Rx Only

INDICATIONS: The TECNIS® Multifocal 1-Piece intraocular lenses are indicated for primary implantation for the visual correction of aphakia in adult patients with and without presbyopia in whom a cataractous lens has been removed by phacoemulsification and who desire near, intermediate, and distance vision with increased spectacle independence. The intraocular lenses are intended to be placed in the capsular bag. **WARNINGS:** Physicians considering lens implantation should weigh the potential risk/benefit ratio for any conditions described in the Directions for Use that could increase complications or impact patient outcomes. Multifocal IOL implants may be inadvisable in patients where central visual field reduction may not be tolerated, such as macular degeneration, retinal pigment epithelium changes, and glaucoma. The lens should not be placed in the ciliary sulcus. Inform patients about the possibility that a decrease in contrast sensitivity and an increase in visual disturbances may affect their ability to drive a car under certain environmental conditions, such as driving at night or in poor visibility conditions. **PRECAUTIONS:** Prior to surgery, inform prospective patients of the possible risks and benefits associated with the use of this device and provide a copy of the patient information brochure to the patient. The long term effects of intraocular lens implantation have not been determined. Secondary glaucoma has been reported occasionally in patients with controlled glaucoma who received lens implants. Do not reuse, resterilize or autoclave. **ADVERSE EVENTS:** The rates of surgical re-interventions, most of which were non-lens related, were statistically higher than the FDA grid rate for both the ZMB00 (+4.00 D) and ZLB00 (+3.25 D) lens models. For the ZMB00, the surgical re-intervention rates were 3.2% for first eyes and 3.3% for second eyes. The re-intervention rate was 3.3% for both the first and second eyes in the ZLB00 group. **ATTENTION:** Reference the Directions for Use for a complete listing of Indications and Important Safety Information.

REFERENCE: 1. JJV Data on File 2018. Validity of investigator initiated studies by Machat and Dell (DOF2018CT4021).

See the Passion in Each Patient.

Johnson & Johnson VISION