OCTOBER 2017 # 14

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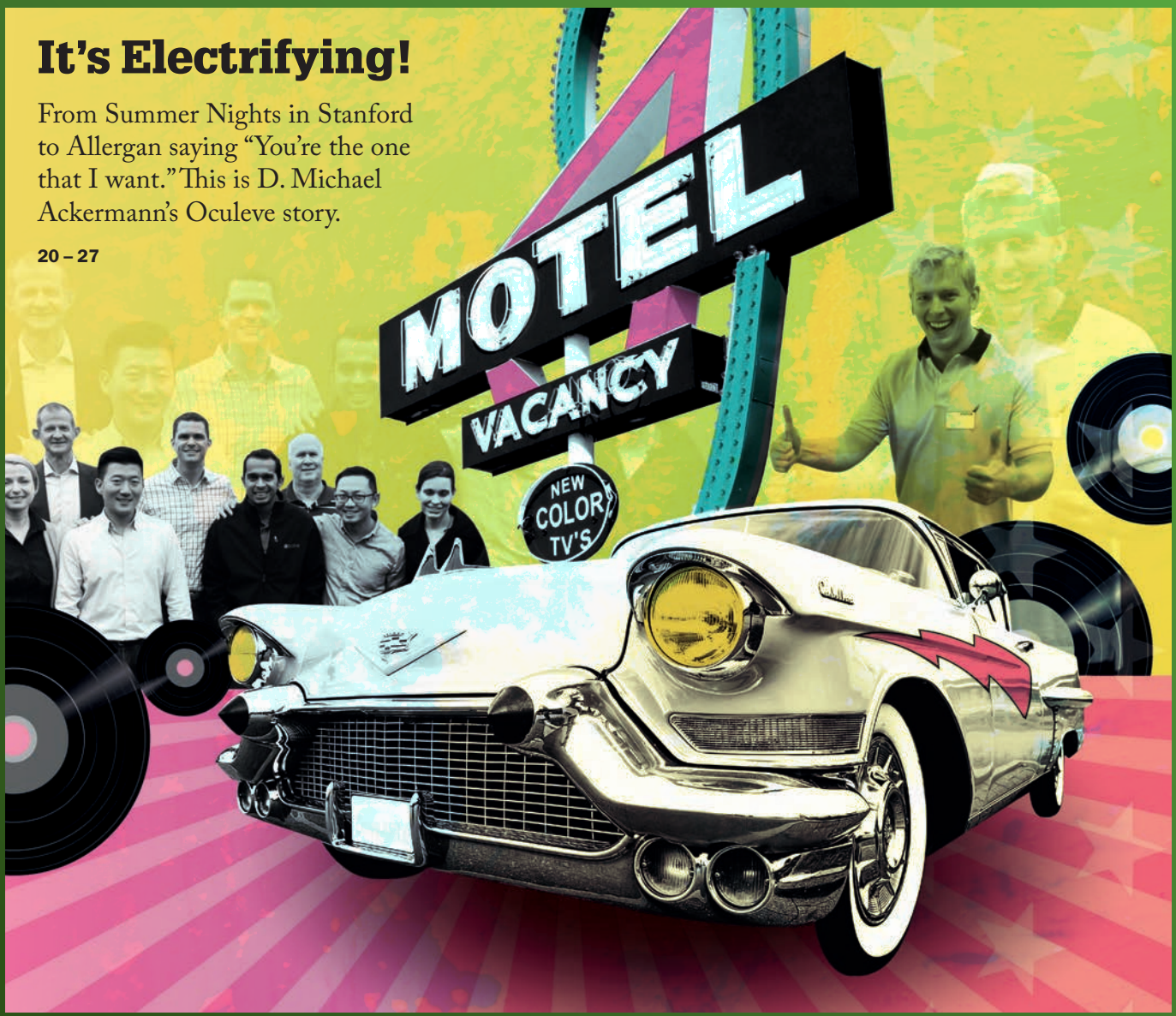
20 – 27



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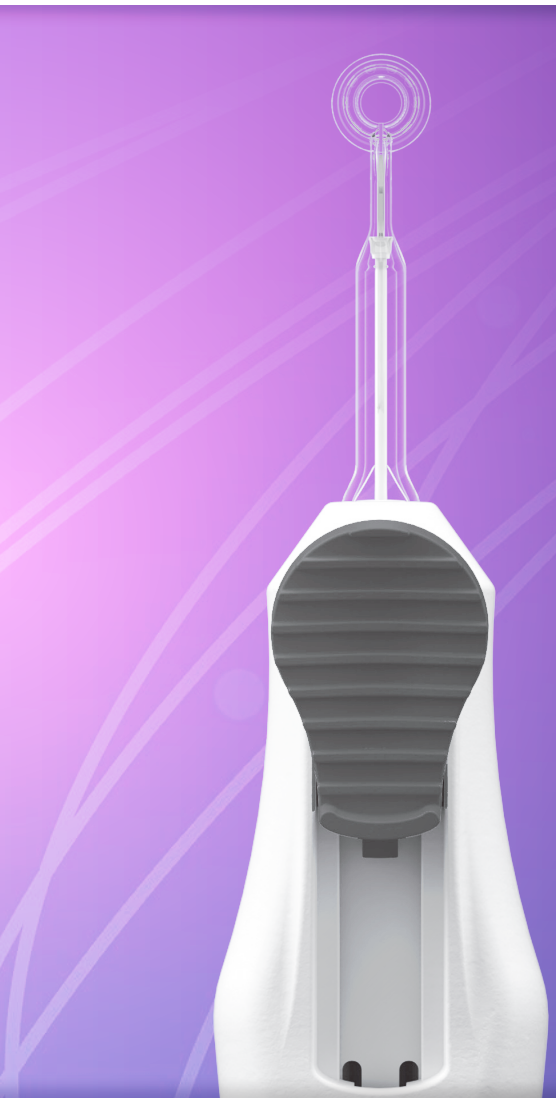

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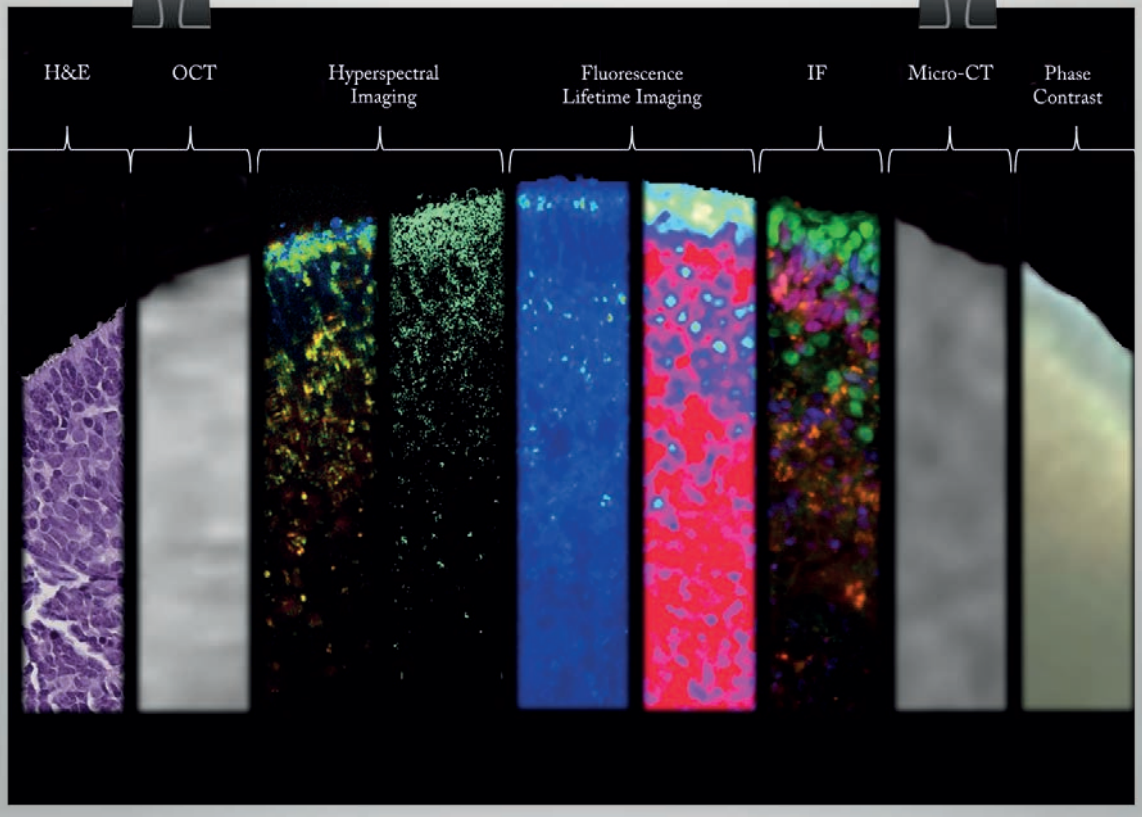

Live-imaging Retinal Genesis

Andrew Browne, a former resident at the University of Southern California Roski Eye Institute, USA, sent us this composite image of a mature 3D retinal organoid. In their study, the team used a range of non-invasive imaging techniques to study the growth and development of the retinal organoids, which were derived from human pluripotent stem cells (hPSCs). "This composite highlights the seven different imaging modalities used in the study, in which fluorescence lifetime imaging and hyperspectral imaging provided new insights into, and techniques to understand, organoid biology," says Browne. Credit: AW Browne et al., Invest Ophthalmol Vis Sci, 58, 3311–3318 (2017).

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

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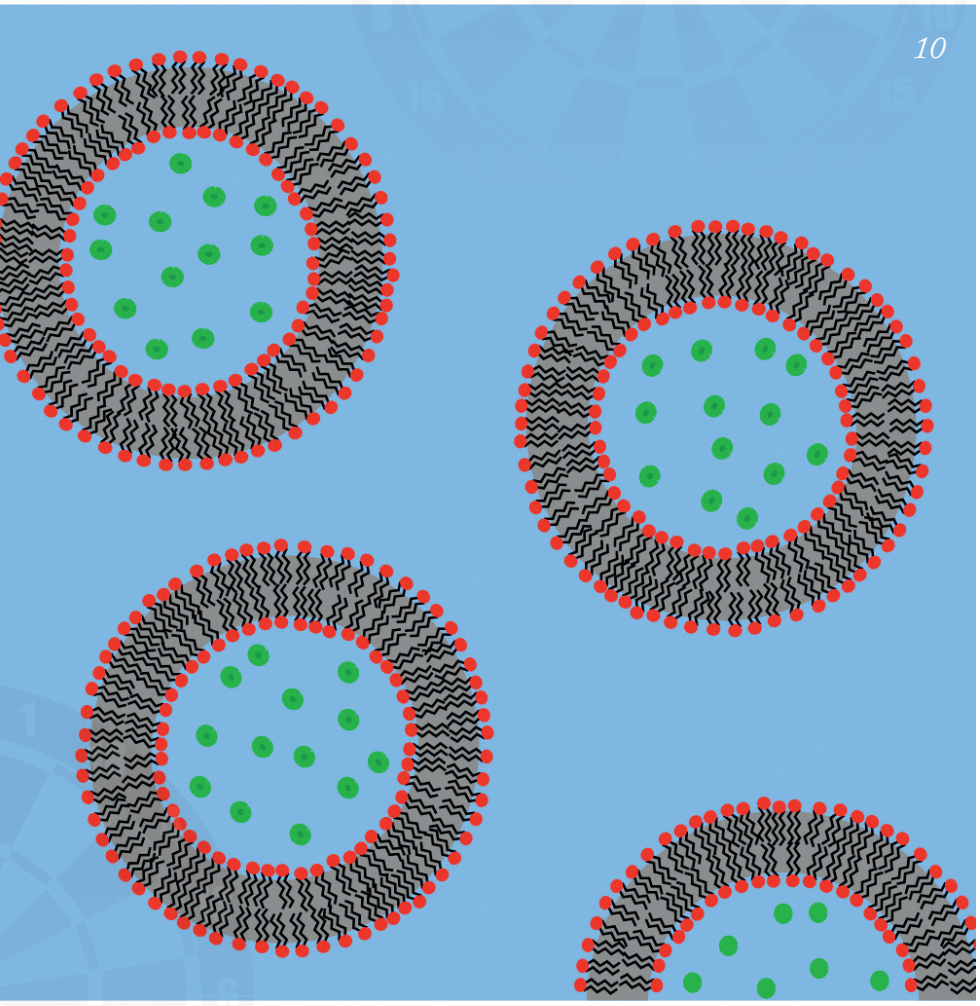

On The Cover

Our designer Hannah Ennis takes inspiration from the musical Grease. Go Greased Lightnin'!

Upfront

the Ophthalmologist

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When the World Changed Forever

The IBM PC changed computing forever. What might be ophthalmology's equivalent?

I'm a 'Xennial'– the microgeneration born between 1977 and 1983. I am not a 'digital native.' I remember the time before the all-pervasive Internet, when home computers had cassette drives. As I grew up, I watched the world change: portable music, personal computers, mobile telephones, and the magic that is the smartphone.

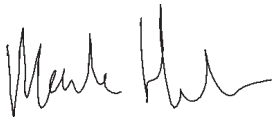
The nice thing about consumer technology is that the cost of entry has kept going down. Though it won't be as sophisticated as an iPhone X, we can now buy a practical smartphone for $30. But when it comes to stem cell and gene therapies (which is incredible stuff), I do worry about how long it will take before they become available to the many rather than the few. The handful of gene therapies on the market today can run into 6 or 7 figure costs – per patient. Cell therapy could cost more; it currently requires cells to be acquired, cultured, engineered, purified (all ex vivo) then placed back in to the patient. If it's the cornea, that's relatively straightforward. If it's in the retina, it's anything but. Will anyone other than the rich gain access to the best treatments?

If we return to the computer analogy, the 'PC moment' happened in 1981 when IBM launched the first PC, which cost $1,565. Just one year earlier, IBM's cheapest computer cost $5,120, and if you wanted to buy an IBM computer in 1980 that was as capable as the PC, that would cost closer to $20,000. By waiting one year, you got the same power, for less than an eighth of the price. So what might be ophthalmology's next PC moment?

It might be figuring out the growth factors that can recruit stem cells to repair the damage in the eye, as Sheraz Daya alludes to on page 51. If that's achievable, how many years or decades until it's possible?

We're seeing ophthalmic surgical robots with such exquisite maneuverability and precision that it will soon be feasible for almost every retina surgeon to perform some of the most demanding retinal procedures – like those demanded by subretinal application of gene or cell therapies. Wider adoption of these will enable more procedures to be performed, which is followed by some sort of economy of scale. The ex vivo lab-based portion will become a kit that a technician can use, and the robots will certainly speed surgical throughput. Today, such a robot costs about €500,000 (although an intraoperative OCT can cost $450,000, and a femtosecond laser for cataract surgery can cost almost as much). How long will it be before the surgical robots have their own PC moment, dropping in price, so every surgeon can use one? And will that help unlock the gene and stem cell revolution for everyone?

Mark Hillen
Editor



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

The Biomarker Breakdown

Could AMD be diagnosed through blood plasma analysis?

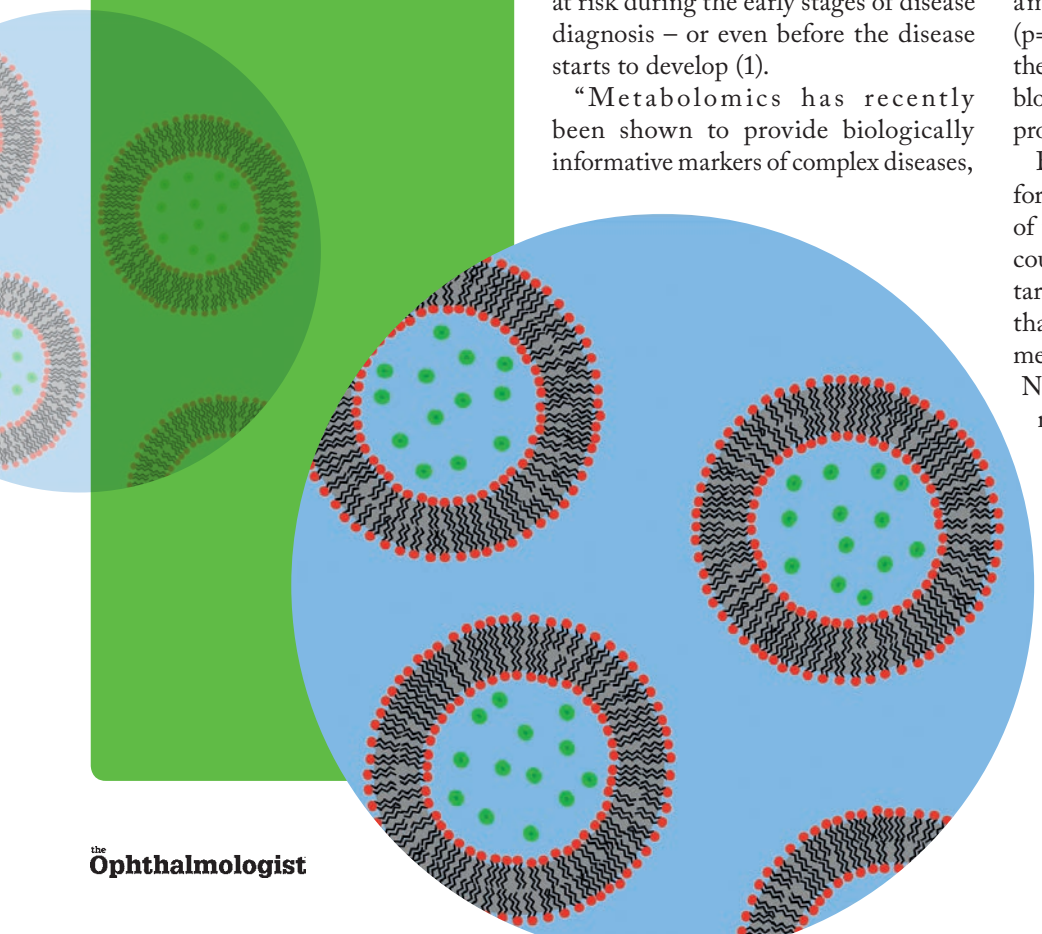
It's a classic "chicken and egg" scenario. When retinal diseases like age-related macular degeneration (AMD) strike, early diagnosis and intervention give the best prognosis and visual outcomes. But in reality, retinal disease cannot be diagnosed until structural changes are seen, and some patients only present at ophthalmology clinics when the visual symptoms – and the underlying pathology – are at an advanced stage. Now, a team from Massachusetts Eye and Ear Hospital, Boston, USA, are proposing that metabolomics analysis might hold the key to identifying those at risk during the early stages of disease diagnosis – or even before the disease starts to develop (1).

"Metabolomics has recently been shown to provide biologically informative markers of complex diseases, such as Alzheimer's, so we decided to research the role of metabolomics in AMD to find biomarkers for diagnosis and prognosis in this disease," says Deeba Husain, co-senior author on the corresponding paper (1).

In the study, the team took blood plasma samples from 90 patients with AMD (30 each with early, intermediate and late stage disease) and from 120 patients with normal macular health. The samples were analyzed using ultra high-performance liquid chromatography coupled to tandem mass spectrometry. They found that a total of 87 metabolites, mostly from glycerophospholipid metabolism, differed significantly between patients with AMD and the controls. Of these, 48 were significantly different across the different stages of AMD. "We were surprised to find that glycerophospholipid metabolism specifically seems to have a strong association with AMD – this pathway was highly enriched among the significant metabolites ($p=4.7 \times 10^{-9}$)," says Husain, who believes the results could form the basis of the first blood biomarker for early diagnosis and prognosis of AMD.

But their results aren't just important for diagnosing disease. "The detection of very significant metabolite pathways could lead to finding a new druggable target for treatment," says Husain. "And that could lay the path for personalized medicine in the management of AMD."

Next steps for the team include a large multicenter study to validate their findings, as well as a long-term follow-up study to better define the role of glycerophospholipid metabolism in disease progression. *RS*



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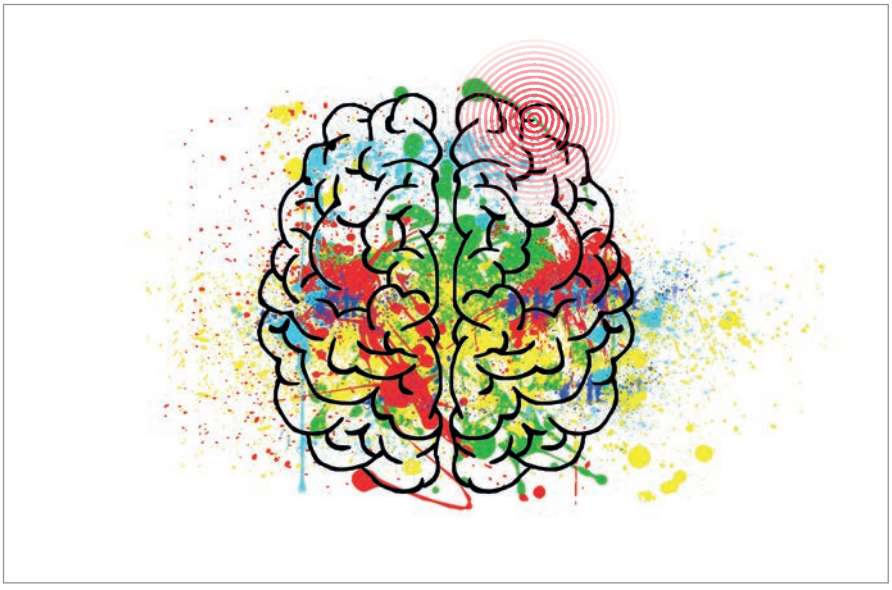
Detecting Dementia

Looking to the retina to find a biomarker for frontotemporal degeneration



Everyone is familiar with Alzheimer's disease (AD) – it's the most common cause of dementia (1). But few are familiar with frontotemporal degeneration (FTD); another dementia that's characterized by neuronal atrophy in the frontal and temporal lobes. Despite its relative obscurity, it's almost as common as AD in people under the age of 65, but it is poorly understood (2).

Certain forms of FTD share a characteristic with AD – tauopathies, or the accumulation of tau protein. Tau accumulates and forms inclusion bodies in neurons, resulting in neurofibrillary tangles that lead to cellular dysfunction and eventual cell death.

"There is an urgent need to find biomarkers for patients with FTD who have a tauopathy," says Benjamin Kim, assistant professor of Ophthalmology at University of Pennsylvania's Scheie Eye Institute, USA. Inspired to find a solution, Kim and his team turned to data published by a fellow lab at the University of Pennsylvania that showed that mice with a mutation in the microtubule-associated protein *Rp1* gene had photoreceptor abnormalities that were detectable by OCT (3). "Proper microtubule function is critical for photoreceptors," says Kim. "Because tau is also a microtubule-associated protein – which evidence suggests is also expressed in photoreceptors – we hypothesized that patients with a tauopathy might also have photoreceptor abnormalities detectable by OCT."

In their cross-sectional study, they examined the retinae of 27 patients with FTD (46 eyes) and 44 controls (69 eyes) using spectral-domain OCT (SD-OCT) (4). Of those with FTD, 19 (31 eyes) were identified as having probable tauopathy based on cerebrospinal fluid (CSF), genetic and clinical analyses. What structural differences did they find? Significantly thinner outer retinal layers (ORL) in patients with FTD compared with controls (132 vs. 142 µm, p=0.004), as well as significantly thinner outer nuclear layers (ONL; 88.5 vs. 97.9 µm, p=0.0030 and ellipsoid zones (EZ; 14.5 vs. 15.1 µm, p=0.009); patients in the tauopathy subgroup also exhibited thinning of these layers (p=0.01). The group also identified an association between the degree of thinning and results from MMSE (a screening examination for dementia), suggesting that outer retina thinning may correlate with disease severity.

"Our results of photoreceptor thinning were in line with our hypothesis, but it was surprising that there was no inner retinal thinning, as this has been seen in several other neurodegenerative diseases," says Kim. "We find our data exciting because we are seeing that dementia patients with different brain pathology may also have specific, different retinal abnormalities as well."

Ultimately, the team hopes that OCT analysis of the retina could be used as a biomarker for patients with FTD who have a tauopathy, but must first learn how OCT findings change over time in relation to disease. "We are now in an era where therapies specific to tau are being tested; if the use of OCT could become a validated biomarker, it would help increase the chance of finding treatments for these patients." *RS*

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2. *DJ Irwin et al., "Frontotemporal lobar degeneration: defining phenotypic diversity through personalized medicine", Acta Neuropathol, 129, 469–491 (2015). PMID: 25549971.*
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Screen the World

A global look at ROP screening

Retinopathy of prematurity (ROP) is a significant cause of childhood blindness — in 2010, 20,000 children became blind or severely visually impaired due to ROP, and that number is set to increase (1). Interventions such as laser therapy, cryotherapy and anti-VEGF drugs can improve visual outcomes, and screening helps save sight: premature babies should be screened within a few weeks of birth to monitor for the presence – and severity – of retinopathy. But how many countries actually have ROP screening programs and guidelines? And how were these developed? To find out more, an international research team asked ophthalmologists in 141 countries to complete an online survey about ROP services in their nation (2). Here are the findings:

- Of the 141 countries contacted, 92 (65 percent) completed the survey. The lowest response rate was from African countries.
- A total of 78 countries (85 percent) reported having ROP screening in some centers.
- Of the 14 countries that reported having no ROP screening, one was European, two were Asian, and 11 were African.
- Of the countries that completed the survey, 68 (88 percent) reported having defined screening guidelines; 31 of these were developed through collaborations between pediatric and ophthalmology societies, with the remainder being produced by ophthalmologists alone (15 countries) and local hospitals (18 countries) – four were unspecified.
- Seven countries reported only having one or two screening centers: Azerbaijan, Bosnia and Herzegovina, Lithuania, Montenegro, Myanmar, Bahrain and Qatar.
- Three countries only have one or two ophthalmologist screeners: Montenegro (one screener for a population of 626,000, and 3,400 births per year), Macedonia (one for a population of 2,080,000, and 10,600 births per year) and Bosnia and Herzegovina (two for a population of 3,870,000, and 15,800 births per year).

The authors conclude that their findings will allow "Ministries of Health and other agencies and organizations involved in the prevention of blindness in children to direct their efforts to those areas most in need as services for preterm infants expand in low-income countries." *RS*

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The Chronic

IRISS registry 24-month data shows when it comes to DME, there's chronic and then there's *chronic* – and treatment outcomes differ accordingly

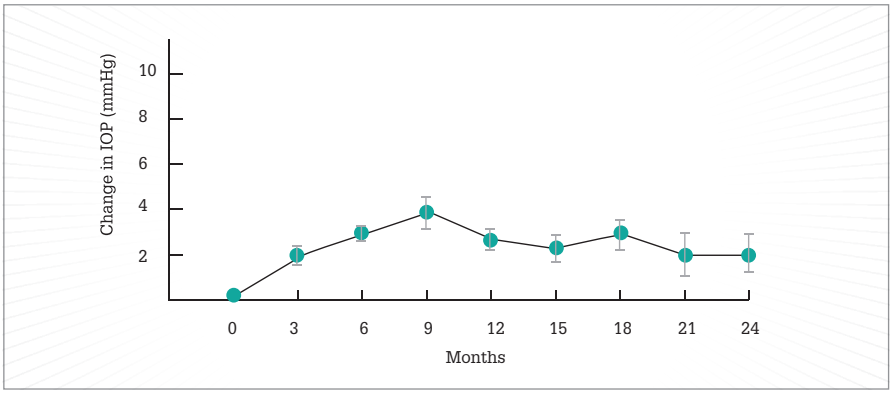

Figure 1. Mean change in IOP. Error bars represent the standard error of the mean.

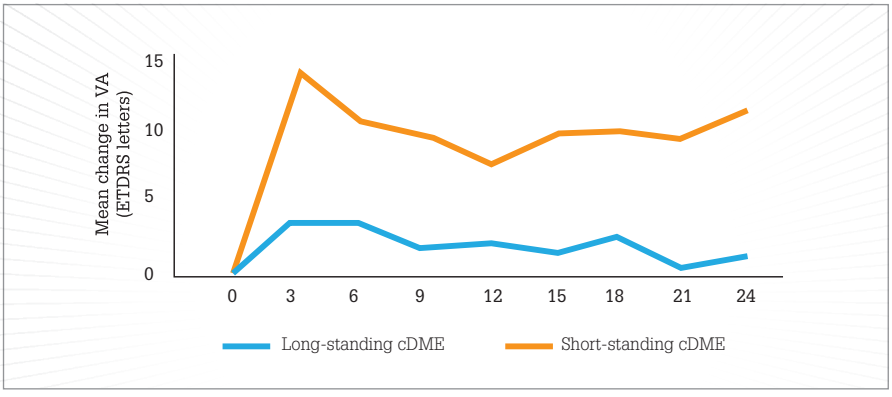

Figure 2. Earlier Iluvien use (i.e. in short-standing chronic DME [cDME]) was associated with better visual acuity outcomes than use in patients with long-standing DME.

An argument rattles on through the ages: what's the value of a clinical trial, if real-world results don't match up? There are many reasons for the disparity – the two main ones being i) careful trial patient selection that doesn't match the characteristics of real-world patients, and ii) closer supervision and dose adherence in the trial than in practice. But when it comes to long-acting implanted formulations of drugs, the second point is moot; patients should continue to receive therapeutic doses of the drug for the lifetime of the implant. And what if the population in the real world was very different to the clinical trial? It was against this background that the five-year, international, multicenter prospective open-label Iluvien Registry Safety Study (IRISS) (1) was performed in 593 eyes (from 563 patients with a [chronic] diagnosis of diabetic macular edema [DME], mean age 67.5 ± 10.7 years, 56.3 percent male) to answer the question: does the sustained-release fluocinolone acetonide 190 µg intravitreal implant work to treat DME in the real world – and for how long?

When it comes to treating patients with DME and using steroids over an extended period of time, there are two main safety signals that ophthalmologists look out for: raised intraocular pressure (IOP) and the development of cataract. At baseline, 82.6 percent of patients were already pseudophakic, and of the 97 patients who were phakic at baseline, 24 received concurrent cataract extraction with Iluvien injection. Mean DME duration at baseline was 4.49 ± 3.3 years, and mean IOP was 15.6 ± 3.86 years (and 5.2 percent of patients had IOP > 21 mmHg at baseline – which would have disqualified them from participating in the Phase III FAME trial (2) that formed the basis for Iluvien's registration approvals).

Two years after Iluvien was administered, what did the IRISS investigators find? A small (1.9 mmHg) increase in mean IOP (Figure 1) – much like FAME, but despite the wider patient population treated – with no clinically significant change in cup-to-disc ratios being observed. Visual acuity stability or improvement after Iluvien administration was rapid, and sustained over two years and, importantly in patients with chronic DME, earlier Iluvien use was associated with better VA outcomes with fewer IOP-related events (Figure 2). This finding may seem counter-intuitive when faced with the FAME trial, in which patients with chronic DME did better on Iluvien than those with non-chronic DME; however, in IRISS, the patient populations were very different – all patients had chronic DME, and the cutoff between long-standing and short-standing DME (Figure 2) was three years. Longer chronic disease, unsurprisingly, results in poorer outcomes. Finally, no statistical difference (p=0.584) was noted in vision improvement between phakic and pseudophakic eyes. *MH*

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That's One in Your Eye

Nerf guns are fun. But not when they cause ocular trauma

The Nerf story is an interesting one. It began in 1970 with the launch of a foam ball with the slogan "Throw it indoors; you can't damage lamps or break windows. You can't hurt babies or old people." That range soon expanded to NERF blasters – toy plastic guns that shoot plastic-tipped foam darts, and has further grown to include sucker-tipped bullets, foam swords, melee weapons – and, it turns out, traumatic hyphema, if they hit your eye.

Mukhtar Bizrah and Seema Verma are, respectively, Registrar and Consultant ophthalmologists at Moorfields Eye Hospital's Accident and Emergency Department, and have seen the damage that a Nerf bullet can do to the eye (1). Two adults and an eleven-year-old boy presented to Moorfields' A&E with at least 1 mm of traumatic hyphema – representing significant ocular trauma. Both adults experienced hyphema and uveitis, whereas the child had "formed hyphema, corneal edema, anterior uveitis, localized angle recession and commotio retinae."

They also identified further potential dangers: one of the patients was hit with a third-party bullet that has a harder plastic tip than the original part. There's also a cottage industry of 'mods,' with plenty of YouTube videos showing people how to alter their Nerf guns to fire bullets harder and faster. The manufacturers, Hasbro, state, "Nerf foam darts and foam rounds are not hazardous when used properly [...] Consumers must never aim Nerf blasters at a person's eyes or face, should only use the foam darts and foam rounds designed for specific Nerf blasters and never modify darts or blasters." Bottom line: if you're playing with Nerf guns, consider protective eyewear. And they can definitely hurt babies. *MH*

Reference

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Treat the World

A global look at the rates of ROP and treatment

What?
A retrospective cohort study on extremely preterm infants to compare the rates of retinopathy of prematurity (ROP) and its treatment in high-income countries participating in the International Network for Evaluation Outcomes (iNeo) of neonates (1).

Who?
Preterm infants (weighing <1,500 g at 240 to 276 weeks gestation) admitted to neonatal units between 2007 and 2013 in Australia, New Zealand, Canada, Finland, Israel, Japan, Spain, Sweden, Switzerland, Italy (Tuscany), and the UK.

How?
A total of 48,087 infants were included in the study. All data obtained from eye examinations was recorded using the International Classification of ROP, and the highest stage of ROP and treatment for advanced stages with laser or intravitreal anti-VEGF were analyzed. Information on survival past 32 weeks post-menstrual age was also collected.

Findings

- Mean survival to at least 32 weeks was 81.8 percent; the highest survival rates were reported in Japan (91.8 percent) and the lowest in Spain (67.8 percent).
- Across all countries, screening data was available for 95 percent of surviving infants, with mean rates of ROP varying between 25.2 and 91.0 percent.
- Of the screened infants, 24.9 percent received retinopathy treatment. The highest treatment rates among screened infants were reported from Japan (30.4 percent) and the lowest from Switzerland (4.3 percent).
- Non-receipt of antenatal steroids, male sex, lower gestational age, lower birth weight for gestation, and delivery by caesarian section were risk factors associated with ROP treatment in surviving infants, but multiple births was not.
- Japan was found to have a higher relative risk for ROP and retinopathy treatment compared with all other iNeo countries.

Conclusions
The authors write that their findings show considerable variation in the rates of ROP and its treatment and that, to understand the differences in outcomes, "networks should adopt common definitions to describe pathology and improve consistency in interpretation, minimize the amount of missing data, and perhaps record an expanded dataset." *RS*

Reference

1. *BA Darlow et al., "International variations and trends in the treatment for retinopathy of prematurity", Br J Ophthalmol, [Epub ahead of print], (2017). PMID: 28270489.*

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

It's Our Duty to 'Do' Diversity

A diverse workplace is worth having – so how do we go about achieving it?

By Cynthia Matossian, founder and Medical Director of Matossian Eye Associates, Mercer County, New Jersey, and Bucks County, Pennsylvania, USA

There should be no place for discrimination. My family has experienced it – both maternal and paternal grandparents had to flee Armenia during the Ottoman Empire expansion when Christians were being ethnically cleansed; it's why I grew up in Lebanon before moving to the US at the age of 12.

I've experienced it too – one of the most memorable examples was when I bought the practice that became Matossian Eye Associates. After completing my training program, I joined a practice for a year, and learned how things should and, importantly, how things shouldn't be done. I wanted to start my own practice and do things in a very different way. I found two brothers, practicing EENT – eye, ear, nose and throat – and bought the ophthalmology section from them. They were horrified that a woman was buying their ophthalmology practice – and so shocked that they refused to honor my signature, when we were finalizing the contract in front of our respective attorneys, because I was a woman! My husband (who has nothing to do with medicine, let alone ophthalmology) had to countersign. This was New Jersey – in 1987.

The benefits of having a diverse workplace are now well-known: a collection of people with different backgrounds, experiences, points of view and approaches to the tasks at hand is far better than one that could be described as a monoculture. The question is: how do we ensure a more diverse workplace, and that no person is discriminated against, left behind, or treated to their detriment? The answer lies in mentorship and support.

I recently attended the Women in Ophthalmology meeting in California, where women ranging from medical students to department chairs, residents to private practice owners were present. The diversity led to wonderful dialogue about factors important to each of these groups; we all learned from each other and gained an understanding of the breadth, depth and complexity of our field. There were presentations of clinical studies, scientific posters, and talks on a myriad of topics. For example, the latest meeting had presentations on how to say, "no," on how to negotiate a contract, and on medical procedures, such as cataract surgery and intravitreal injections.

These meetings give women a podium to voice their concerns, experience camaraderie, and learn how to address certain topics, including unequal pay, how to network with industry, achieve chairmanship position, get better grants and start a solo practice. They give women a forum to discuss these issues and hopefully to come up with options and positive solutions, with the idea of helping them understand what is needed to get invited onto the panels, or to be a speaker, moderator, or a presenter.

Over the last thirty years I have definitely seen more women coming into ophthalmology, and it's been such a welcome change. When I started out, there weren't many women ophthalmologists at all, let alone women chairmen, or women who owned practices or were senior partners in practices. Now,

the residency program intake in US ophthalmology departments comprises about 50 percent women, and it's much more common to see women who are departmental chairmen or who have leadership positions in large organizations, including industry. Not only are there more women in the field, but ophthalmology has changed in many other ways; when I started, most women ophthalmologists were either comprehensive ophthalmologists or pediatric ophthalmologists – it was almost unheard of for women to go into retina, ocular trauma or anterior segment surgery. But now that's completely changed, and we see many women in all of these sub-specialties within ophthalmology. And I will say that this trend has been for the benefit of our profession – and our patients.

Trust the Doctors to Deliver

The benefits of a clinician-led approach to research

By Berthold Seitz, Director of the Department of Ophthalmology at Saarland University Medical Center, Homburg/Saar, Germany, and Director, International Council of Ophthalmology Fellowships

The traditional model of company-led research can be rather slow to bring a drug or a product to market, and in many cases, the main reason can be summed up in one word: bureaucracy. There certainly can be a speed advantage when it comes to clinician-led research (CLR). However, not all CLR is equal, and there are good ways and bad ways of practicing it. Done right, it can be a fast, powerful, effective and credible means of developing a product and providing the clinical evidence that's required to bringing it to market.

The critical aspect is independence: whenever a company performs in-house research, there's always a perception of bias (rightly or wrongly) that the final result will be in favor of the company's product. A better model is industry-funded CLR projects that are completely independent of company oversight. If the clinician describes the purpose of the study, it makes the results more appropriate to the community. To me, these results are more believable, and I find them more easily and immediately applicable to my patients too. In my view, the 'translational' aspect of clinical development is far easier with CLR.

I'm Director of the International Council of Ophthalmology's fellowship program. We work with industry – in this case, Allergan – to fund research fellowships that support research that recognizes innovation advances, and the scientific understanding and clinical management of ophthalmic diseases. The award is open to ophthalmologists from all specialties and all countries. We have jury members for all of the subspecialties, and two best-rated applications from each subspecialty go to a final jury, and then a final decision is made who will get the $50,000 to do research in a different department for one year. And Allergan has no impact on the decision – and this is a really generous and a well-received gesture, and is an example of how I'd like to see all CLR funding work. I also think fellowship applications should come with a statement from the applicant's program director that he or she is allowed to resume their previous position once they return from the fellowship – nobody wants someone to be in the position that their career ends because their former boss doesn't want to give back their last position!

Andrew Carnegie once said of teamwork: "It is the fuel that allows common people to attain uncommon results." If you don't have a good team that's ready, willing and able to do the tasks you delegate to them, then all the funding in the world won't help you. My approach is to ensure that every member of my (160-strong) team is able to at least one thing better than me, to delegate, and when it comes to CLR, have an excellent, full-time study coordinator! It also helps if everybody involved is on the same level, and in the same place. At Saarland University, I am a clinical professor of the Department of Ophthalmology, but I'm at the same professional level as the electrical engineering professor of the Institute of Experimental Ophthalmology. We work closely together in the same building: he is on the fourth floor, I am on the first. If we need to meet to discuss something, he just comes down, brings some of his people, I bring some of my people, and we get on with the task at hand. If the clinician was at one location, and the research lab was 100 km away – I just don't think that will work for the best. CLR, wherever possible, should be conducted under the same roof.

Of course, there will always be situations where a more traditional, company-led, internal approach might be a better option. But when it comes to speeding translation from bench to bedside, and generating data that's credible to fellow clinicians, I strongly believe that independent CLR research is the best way to do this.

Peer-Reviewed Study Shows Optometrists and Ophthalmologists Frequently Miss Macular Degeneration

By Jeffry Gerson, OD, and Mark F. Pyfer, MD

A recent study published in JAMA Ophthalmology revealed how frequently optometrists and ophthalmologists fail to diagnose age-related macular degeneration (AMD) (1). The cross-sectional study, which included 1288 eyes (644 adults) from patients enrolled in the Alabama Study on Early Age-Related Macular Degeneration (ALSTAR) (2,3), revealed that doctors are missing AMD about 25 percent of the time. Also quite concerning is that 30 percent of the undiagnosed eyes in the study had large drusen, a known risk factor for wet AMD (1).

Understanding The Study

The authors set out to determine to what extent AMD is under-diagnosed by primary eye care physicians when the disease is actually present. In the study, they reviewed the medical records of 644 adults 60 years or older who were enrolled in ALSTAR. To be eligible, the person's medical record from the most recent comprehensive dilated examination did not indicate a diagnosis of AMD in either eye, and the medical record notes did not contain terms that signified the signs of AMD. Each patient in the ALSTAR study had digital color fundus photos taken, which were reviewed by masked, trained graders who determined the presence or absence of AMD findings according to the Clinical Age-Related Maculopathy Staging (CARMS) system (4). The types of AMD-associated lesions also were noted.

The results revealed that one of four eyes studied was not diagnosed with AMD during the dilated fundus examination, despite these eyes having macular characteristics indicative of AMD in the fundus photos. Approximately three-fourths of the 320 undiagnosed eyes had 10 or more small drusen (249 [77.8 percent]) and/or intermediate drusen (250 [78.1 percent]), with 96 (30.0 percent) of undiagnosed eyes having large drusen.

Who Overlooks AMD?

"As this study reveals, even the most experienced and well-trained primary eye care doctors can miss AMD, which may result in severe vision loss," says Jeffry Gerson, OD. "In fact, the prevalence of undiagnosed AMD in the study was not different for ophthalmologists versus optometrists."

Although the study authors say reasons for the missed diagnoses remain unclear, they point out that improved AMD detection strategies may be needed in primary eye care since many of these patients would have been candidates for therapeutic intervention with nutritional supplements.

"Current technology may lead to a sense of complacency, and does not always enable us to detect AMD early enough. This is easily overcome when dark adaptation testing is available," says Dr. Gerson.

The authors also call attention to potential treatments for earlier stages of dry AMD that will likely be developed in the coming years.

"While there is no cure for early AMD, it is important to diagnose the disease as early as possible to increase monitoring, educate patients and start measures that may slow progression. We can recommend lifestyle changes, such as smoking cessation, exercise and a healthy diet including antioxidant vitamins, and UV light protection with sunglasses as a start," says Mark F. Pyfer, MD. "Doctors who have the tools needed for earlier detection have a tremendous opportunity to help their patients, and advance their practices."

> *"Dark adaptation testing with the AdaptDx is a straightforward adjunct to OCT, fundus photography and standard clinical examination."*

The Road To Improved Outcomes

The challenge is that many cases of AMD are overlooked based on the absence of structural findings using some of the most advanced technology. For example, Ocular Coherence Tomography (OCT) is essential for detecting and managing many retinal diseases, but it only looks at structure. "Depending on interpretation, the OCT scan of a patient with a few small drusen is often normal and potentially underestimates the extent of disease," says Dr. Pyfer. "By the time photoreceptor ellipsoid layer thinning is visible on OCT, macular function may be significantly impaired." He adds: "Dark adaptation testing with the AdaptDx is a straightforward adjunct to OCT, fundus photography and standard clinical examination. This functional test allows you to detect AMD at least three years before it becomes clinically evident" (5). Several

Testing dark adaptation function with the AdaptDx® can help diagnose AMD at least three years earlier than drusen are visible.

peer-reviewed studies have shown that dark adaptation function is dramatically impaired from the earliest stages of AMD, with increasing impairment as the disease progresses (6,7).

In a recently published study, subjects with impaired dark adaptation were twice as likely to develop clinically evident AMD and eight times as likely to advance beyond the earliest stage of AMD (8). The only commercially available automated dark adaptometer, called the AdaptDx, measures a patient's Rod Intercept (RI) time. RI is the number of minutes it takes for the eye to adapt from bright light to darkness at a standard threshold stimulus level. The AdaptDx test provides a clear and objective measurement of retinal function with 90 percent sensitivity and specificity (9). An RI of less than 6.5 minutes indicates normal dark adaptation consistent with healthy photoreceptor function. An RI greater than 6.5 minutes indicates impaired dark adaptation, most often due to AMD in patients over age 50, unless there is a pre-existing hereditary retinal degeneration or significant vitamin A deficiency, which is rare in the United States.

"This study is a real eye-opener that clearly shows that, without the necessary technology, ODs and MDs are not always able to deliver the level of care that we would want for ourselves, our families and, of course, our patients," says Dr. Gerson. "The good news is that new technology can make it easier for us to walk out of the exam room with greater confidence in our diagnosis and our patient's prognosis."

Jeffry Gerson, OD, FAAO, practices at Grin Eye Care in Olathe, KS. He is a fellow of both the Academy of Optometry and Optometric Retina Society. Mark F. Pyfer, MD, FACS, is a cataract and refractive surgeon at Northern Ophthalmic Associates in Jenkintown, PA. He serves on the teaching faculty at Wills Eye Hospital in Philadelphia.

Did You Know?

- Up to 78 percent of AMD patients have substantial, irreversible vision loss at first treatment, including 37 percent who are legally blind in at least one eye (10,11)
- Unlike macular pigment optical density (MPOD) testing or genetic tests, the AdaptDx does not measure AMD risk. This easy-to-perform test is diagnostic of AMD, indicating that disease is already present

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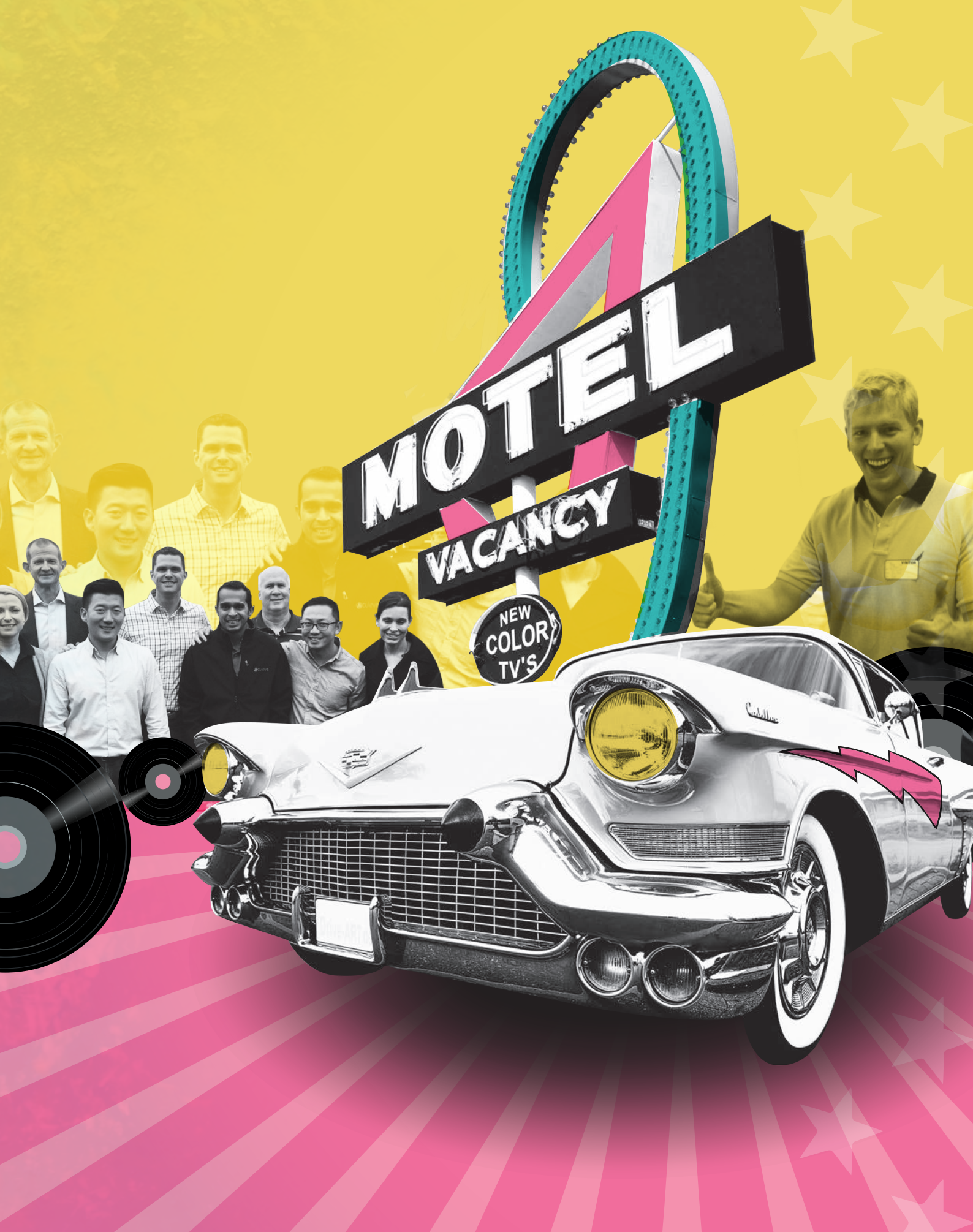
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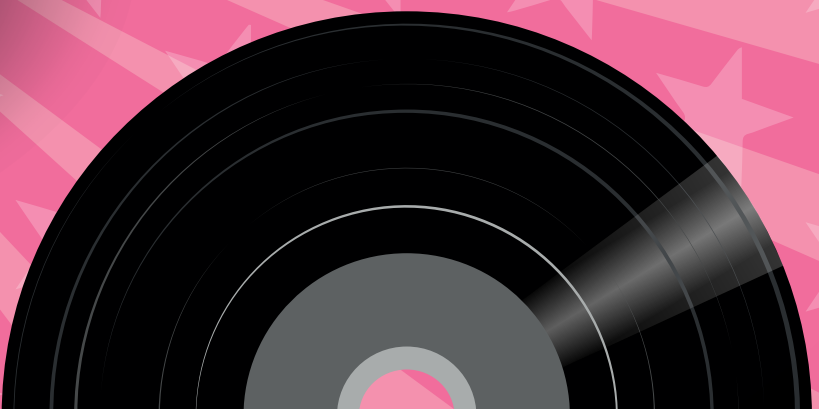
It's Electrifying!

The behind-the-scenes story of Oculeve

By D. Michael Ackermann



The Stanford Biodesign Fellows

When The Ophthalmologist approached me to tell the story of Oculeve, I first had to explain to them that it all started somewhere odd: heart-rate sensing baby monitors. I was a Biomedical Engineering undergraduate at Vanderbilt University in Nashville, Tennessee, and very interested in the field of electronic medical devices. In my junior year, I started a company with a business student with the intention of making… something. In terms of medical devices, we both knew that we didn't have the skills to develop something in the regulated medical device field, so we came up with the idea of developing a baby monitor (microphone in one device, speaker in the other) with an additional twist: a heart rate monitor to combat sudden infant death syndrome. If the baby's heart rate dropped below a certain level, an alarm would go off in the parent's unit and they could rush in and tend to the child.

The relevance? It was part of the learning experience. We worked on it for a year and a half, until the end of college, and had an absolute ball doing it. But at the end of our days at Vanderbilt, I gained a position in graduate school, my business partner had received an excellent job offer, and we decided to fold the company and move on. But the experience never left me. When I got to graduate school at Case Western Reserve University in Cleveland, Ohio, the environment wasn't particularly conducive to entrepreneurship (though that has changed since), and that meant I ended up focusing on being a good scientist – and I turned to neuroengineering and neurostimulation.

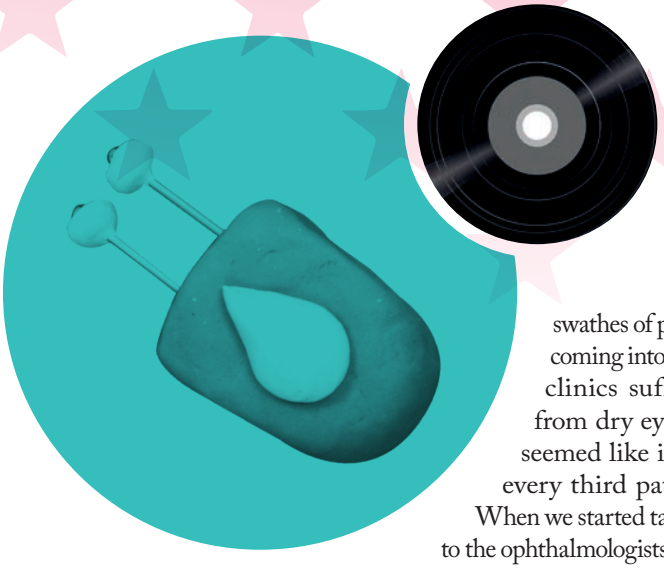
California Dreamin'!

Next, I headed to Stanford University in California (see Box: Go West!), where I had managed to secure a place on its Biodesign Fellowship Program. And that's where the Oculeve story really gets going.

The Stanford Biodesign Fellowship is an interesting program. Twelve fellows (eight in my day) are split into teams of four, with each team typically consisting of post-training physicians, scientists and engineers. Teams are normally assigned to a particular clinical area, and for my group, that area was ophthalmology. At the time, all I knew about ophthalmology was that I had two eyes and that they were important to me. What we ended up doing was spending a month in the autumn in the Stanford Ophthalmology clinic, plus a bit of time in local private practices as well, all to observe unmet needs.

Eyeing up unmet needs

Mark Blumenkranz ran the department at the time, and he and the other physicians in the department were immensely generous with their time. We came in, hoped we weren't too disruptive, and observed their care both in the clinic and in the operating room (OR). When we first got there, we immediately wanted to go into the OR, because you got to wear blue scrubs and feel like a surgeon – we got to 'play' doctor for a moment, and we thought that the OR was where the action was going to be. Over that month, our team identified 350 unmet needs – but few were identified in the OR; most were in the clinic. Why? Mostly because the patients in the OR already had solutions to their problems – surgery. We did identify some things that might improve efficiencies in OR workflow and so on, but the clinic was the area that seemed to have the greatest unmet needs. Even in my first week, I'd noticed that irrespective of whether it was the retina clinic, the glaucoma clinic, or whether it was a primary or secondary diagnosis, huge



swathes of people coming into these clinics suffered from dry eye – it seemed like it was every third patient. When we started talking to the ophthalmologists, they explained that there were a number of options but, in many cases, there wasn't really something that could help. There was also an emotional aspect: you could tell that the ophthalmologists were frustrated that there were many patients that they couldn't help as much as they wanted to. The patients still needed a lot of 'chair time' and were often very unhappy too.

"Huge swathes of people coming into clinics suffered from dry eye – it seemed like it was every third patient."

Ideas and iterations

The next step was essentially brainstorming. We had a room, a whiteboard, pens, and us. No ideas were stupid, they all got put on the board. At the end of the process, we had filled three of the walls with ink – and had come up with a couple of hundred ideas on how to address dry eye. Some were really quite ridiculous, but one by one, we started narrowing them down until we had a few things that were worthy of further investigation. The neurostimulation approach was one of them. The first neurostimulation idea was a pacemaker-like device for the lacrimal gland, with a lead that ran up through the neck and into the orbit. We were rather pleased with ourselves, and shared the idea with Chris Ta, Stanford's cornea chief. We told him, "Look, we had this idea…", showed him a rough prototype, and asked him what he thought. After his blood pressure returned to somewhere in the normal range (fortunately he didn't pass out), he said: "Yeah, I think you need to try again, and whatever you do, don't show this to my patients!"

We went back and iterated the concept several times with rough prototypes and feedback from physicians and patients. I think the first time that we started getting some nodding heads was when we came up with the concept of a small injectable pacemaker-like device that would be placed adjacent to the lacrimal glands and pace it. We realized at this point that such a device would be destined for patients with severe dry eye, but that there was a very real chance that it would work, and it was something that could be done in a procedure room in the clinic rather than the OR.

Raising money

For the next year, I incubated the company on Stanford campus and partnered with a couple of new people: a Stanford postdoc by the name of Jim Loudin, a faculty member you might have heard of: Daniel Palanker – and, of course, Mark Blumenkranz. Over the next year, we were able to raise a little bit of money first through business plan competitions – $50,000 or so – before raising $200,000, primarily through a seed investment from venture capital firm Kleiner Perkins Caufield & Byers. We were able to use that capital to pretty quickly get ourselves into the clinic and ultimately raised about $700,000 in seed capital. We hired a small staff of five and we were able to not only do

Go West!

Towards the end of my degree program, I had a dilemma that I just couldn't answer: do I stay in academia, or go into industry? My PhD mentor allowed me to spend a handful of months at Boston Scientific in Los Angeles, to try and get a sense of how things work in industry. I learned two things for certain: I didn't want to remain in academia, but I didn't think I wanted to start working for a big company either.

What really motivated me to move to the West Coast was my now-wife Kjerstin. I met her while in LA, and frankly, I became very motivated to return to the West Coast after completing my studies in Cleveland. So I started looking, and there was a Stanford Biodesign Fellowship program that was not only closer to the woman who I had fallen in love with, but also seemed to be a great match with my interest. And I thought it might actually give me an opportunity to learn how to do things better the next time around with a company.

The Oculeve team.

"I think the idea of neurostimulation – using electricity – was something that was more than a little foreign to ophthalmologists."

quite a bit of the development for the implantable device, but also get into the clinic by using some off-the-shelf products, namely a percutaneous stimulator used in anesthesia when seeking nerves for nerve block. Using that device, much to our delight, we found that we could stimulate tear production.

I think the idea of neurostimulation – using electricity – was something that was more than a little foreign to ophthalmologists. We needed to perform a small study to demonstrate the safety of the device and, frankly, to demonstrate to ourselves that it was working in the way we hoped it would. I was the very first patient, or rather, a 'normal' subject in that particular study.

From prototype to product

Prototyping is fun – especially in the early stages. The overall process takes a lot of time (it is highly iterative, after all), but the feeling that you're honing the design and materials to a point where you can bring a medical device that could help many can only be described as exciting. We started off by literally pulling things together in the lab and connecting them up – often even making things with tape and cardboard! Computer aided design (CAD) was certainly used later in the process, but we felt that the physical prototypes were appropriate for the early stages of innovation. There's little point caring about the look and feel of early prototypes: if it's likely that you're going to have to make some important changes later on based on what you find, then it doesn't make a lot of sense to invest a lot of time in the prototype. "Quick and dirty" was the order of the day: we were doing something to get immediate feedback. When we finally had something to show people that got them to nod their heads, it was a little piece of plastic packaging that I'd cut, and given some shape with a small amount of modeling clay.

The professional product design started in earnest in our second year at Stanford. We got lucky. Janusz Kuzma is an incredible mechanical engineer in the implantables space. He's a Polish Australian who did the design for the very first cochlear implant – and for several generations of them after that. He has been a lead mechanical designer on several products that are now on the market, not just cochlear implants, but the spinal cord stimulators too. Janusz had retired, and moved to Sydney, Australia, with his wife – but then decided that he regretted the decision to retire. I knew him by reputation and a colleague of mine in the neurostimulation space said that he thought Janusz was getting a little bored. Jim Loudin, the postdoc, and I flew out to Sydney and we spent a few days convincing Janusz to join us – and to do so without salary at first (just stock options) until we had some cash to pay him! We were amazingly lucky that he came on board. Thanks to Jim (on the electrical side) and Janusz (on the mechanical side), we were able to develop a beautiful human-quality implantable device in a really short period of time – just over half a year. And the process was a lot of fun.

Luck, Link and Letting Go: Lessons Learned from the Oculeve Experience

Be willing to follow the best idea – whether it's the one you're working on or not. Making that transition from the implant to the nasal stimulation program wasn't an easy decision to make. We had invested a lot of time, effort and money into the program by that point. Despite that, letting go was the right decision.

There is an element of luck when it comes to raising money – and part of that is that sometimes you can be lucky when it comes to the investors and their experience in the business. When you accept somebody's investment, you're establishing a long-term and influential relationship with someone, their experience and their opinions, not just their capital. Looking back, we were lucky to have the investors we did.

Be like Bill Link. One thing that resonates from him is that he's a very genuine person – both personally, and in business. He's courteous and respectful, recognizes the work of everyone within the organization from top to bottom; in short, he treats people right.

The Allergan core leadership.

An about turn led to an acquisition

Before long, we had implanted close to 40 patients, and found first, that the safety was great. The efficacy was also great – in some patients, but not all. Clearly, we had more work ahead – par for the course with medical device development. Another thing we observed was that despite being a unilateral implant, we were getting bilateral tearing. It was clear that it was working through a different mechanism than we had supposed: we were activating a reflex. Jim and I were in Mexico (where the clinical trials were being performed) thinking about how to really maximize this reflex process, when we thought. "Well, you get a lot of tearing through the nose…" We looked at each other and immediately returned to the hotel to start searching patents and the literature. We couldn't believe that we were the first to think of this. Physiologically, it's a remarkable concept: you stimulate a point in the nose, it activates the anterior ethmoidal branch of the trigeminal nerve that innervates the lacrimal gland, and you get an increase in tear production. Much of what we'd done had to be torn up and we started again – but it was worth it.

Allergan approached in April 2015. I believe Allergan's CEO, Brent Saunders, had talked to a number of physicians (including some clinical investigators of ours) at ASCRS that year, and had decided to place a phone call to us about an acquisition. We then had a very difficult decision to make. We were in the process of raising our Series C financing (of around US$30 million) and we were fortunate to be offered some very competitive terms by some of the venture capitalists involved. At that point, we had been very stealthy with regard to what we were doing – we weren't talking publicly about nasal stimulation, for two reasons. We were trying to get a head start, one, in terms of intellectual property filings, and two, it was such a goofy idea, we wanted to have the data to back it up, so that when people started learning about it, they were presented with hard clinical data, rather than a concept and a CAD render of a device. The dilemma was: if we entered a due diligence process with Allergan, and the deal fell through, then it would put a bit of a black eye in the Oculeve program in terms of raising financing. Allergan and Brent couldn't have been any classier about it. We explained the situation to them, and they decided very quickly about whether they wanted to move forward with the deal – and promised that if the deal didn't work out, they would provide financing at the best terms we were offered. It made us feel

Chris, Jim and Janusz.

a lot better dealing with them. Then, for the next two years, essentially, they left our team unencumbered to get on with it. In the areas that they did get involved, almost without exception, it was to add value.

One of the best examples of this was in the clinical development. Allergan has a huge research and development group, and they probably have more dry eye expertise than anywhere else on the planet. Michelle Senchyna (who went on to be the Allergan lead on Clinical Development for TrueTear) did a great job of extending our knowledge of the basic clinical science and helped generate some very compelling clinical data showing that TrueTear activates all three layers of the tear film: mucin, aqueous and meibum. The company also really shaped the commercial plans too – and added a ton of value to the program. At the end of April, the FDA granted Allergan marketing authorization for Oculeve TrueTear. We had made it – both literally and figuratively.

What's next

While TrueTear's commercial story is just beginning, my Oculeve story is over. I stepped down from my position at Allergan soon after the marketing authorization, and the first thing I did was take a really long vacation with my family.

What's next, in some respects, is more of the same. I'm joining a small company called Oyster Point Pharma (OPP), as Chairman of the board. OPP was actually a spin-out of Oculeve, and we're developing a pharmaceutical treatment for dry eye. I'm also working on an earlier-stage drug treatment for blepharitis – it's far too early to say if this project will have a future, but what I can say is that it's lots of fun to be back at the earliest stage again. Hopefully this time, I won't repeat the mistakes I made last time. It's a hell of a lot of fun and an incredible journey bringing a new treatment to market. I've met and worked with some great people, and I can't imagine doing anything else right now.

D. Michael Ackermann is Chairman of the Board at Oyster Point Pharma, Inc., and formerly the Vice President of Neurostimulation at Allergan, and President and CEO of Oculeve Inc.

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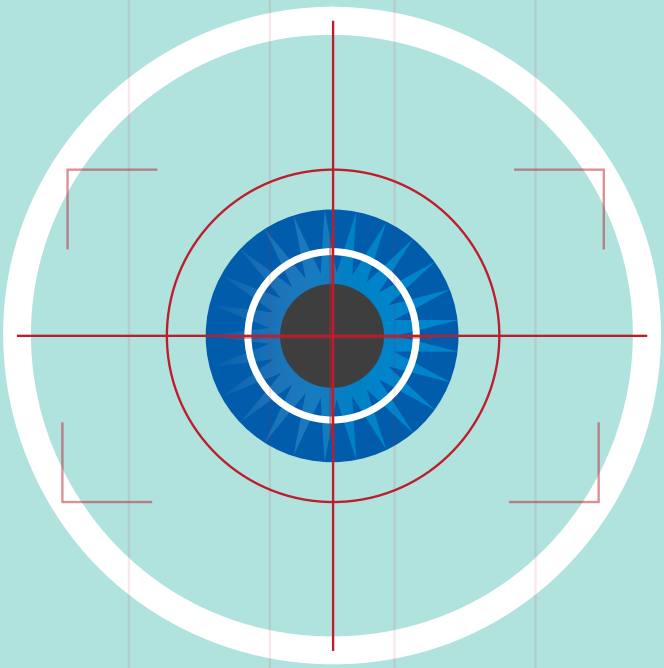

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Normal Tension Glaucoma: Are We Missing It?

Prevention is better than cure – especially when there is no cure

By Tony Realini

In clinical practice, we frequently encounter patients who present with almost all of the diagnostic findings of primary open-angle glaucoma (POAG) – but whose intraocular pressure (IOP) is in the normal range. It is a challenging clinical scenario because, for decades, we believed elevated IOP was the defining diagnostic feature of glaucoma. Today, it's recognized that elevated IOP is not integral to a diagnosis of glaucoma when optic nerve damage is observed in the absence of other explanations for disc abnormality and/or visual field loss (1). Yet, the myth that elevated IOP must be present for a diagnosis of glaucoma persists, which means that many clinicians frequently fail to detect normal tension glaucoma (NTG) until it reaches an advanced stage. If a clinician fails to suspect NTG in patients whose IOP lies within the normal range (12–22 mmHg), they may decide not to perform a careful optic nerve exam, and thereby miss the early signs of glaucomatous optic neuropathy (2).

Without high IOP, NTG is harder to detect and more challenging to manage than high tension POAG (HT-POAG) in several important ways. In a large epidemiologic study assessing the prevalence of glaucoma, it was found that an estimated 30 percent of patients diagnosed with OAG had NTG (3–4), and Asian populations appear to be particularly prone to NTG; the Japanese Tajimi study cited a POAG prevalence of 3.9 percent, of which 92 percent had NTG (3,5). In this article, I will examine the differences between NTG and HT-POAG and outline strategies for optimal detection and management.

NTG: Does it exist?

The first question to consider is: does NTG exist as a distinct disease entity? It is worth noting that the term NTG was coined to describe patients who had all of the typical optic nerve and visual field findings of POAG except for elevated IOP. Thus, it is not surprising that NTG and HT-POAG share many of the same risk factors. Granted, some are more common in NTG, such as migraine and poor circulation/vascular dysregulation, than in POAG (Box 1: Risk Factors for Glaucoma). Likewise, some clinical findings, such as disc hemorrhage, acquired pits of the optic nerve, and certain patterns of disc cupping and visual field loss, may be more common in NTG than in HT-POAG. But none is pathognomonic for either entity, so rather than thinking of them as separate diseases, it might be more productive to consider NTG to be a subset of POAG, and to acknowledge that POAG exists across the entire spectrum of IOP (3).

Clearly, though elevated IOP is a risk factor for glaucoma, it is neither necessary nor sufficient to explain the presence of glaucoma. For people who develop OAG and yet have IOP in the normal range, other as-yet unidentified pathophysiologic processes must be at play, such as vascular dysregulation.

Approach to treatment

My next comment may sound obvious, but the first step in preventing visual dysfunction caused by NTG is to screen for it. I recommend that every patient receives a careful screening evaluation of the optic nerve, the nerve fiber layer, and the peripapillary region, regardless of his or her IOP (Box 2: Screening for NTG in the Clinic).

Evidence from major clinical trials, including the Early Manifest Glaucoma Trial, the Advanced Glaucoma Intervention Study, and the Collaborative Normal-Tension Glaucoma Study (CNTGS), have confirmed that medical and surgical interventions geared toward lowering IOP can delay or prevent the progression of glaucoma, including NTG (6–8).

The CNTGS, which randomized patients with NTG to receive treatment or no treatment, showed that patients in the treatment arm (medications, laser or surgery) fared much better than those randomized to the no-treatment arm, achieving a nearly threefold reduction in progression over five years (35 percent in the treatment arm versus 12 percent in the no-treatment arm) (8). However, among untreated patients with normal IOP but abnormal looking optic nerves, two-thirds (65 percent) did not progress during five or more years of follow up (8).

When we see typical glaucomatous optic nerve and visual field changes in an eye with elevated IOP, it is logical and usually correct to attribute the damage to the IOP and thus to POAG. In eyes with optic nerve and visual field damage but normal IOP, we must first rule out non-glaucomatous causes of nerve damage

At a Glance

- *Clinicians frequently fail to detect normal tension glaucoma (NTG) – until it reaches an advanced stage*
- *The reason? Failing to suspect NTG in patients whose IOP is within the normal range*
- *Given time and resource constraints, the clinician might not perform a careful optic nerve exam, thereby missing the early signs of glaucomatous optic neuropathy*
- *This article reviews how to identify those who need treatment – and when and how to treat them*

(Box 3: Differential Diagnosis of NTG). In addition to the entities in Box 3, we should also consider the possibility that our patient may simply have odd-looking but otherwise healthy optic nerves, or may have had prior optic nerve insults that are now historical and non-progressive – for instance, a remote history of systemic steroid use with damage that occurred years or decades in the past and is now static.

In light of these considerations (including the numbers of NTG patients in the CNTGS that did not progress), once I've diagnosed a patient with NTG, the initial clinical challenge becomes deciding whether treatment is indicated. A compelling case can be made for deferring or delaying treatment in a "watchful waiting" approach to many patients with NTG. Those who don't progress over a several-year period of observation, or who progress very little in such a time frame, may be at low risk for developing visual dysfunction from glaucoma in their remaining lifetimes.

So, who should receive treatment – and when? What are the clinical criteria for initiating treatment in patients with glaucoma and normal IOP? Immediate treatment is generally indicated for patients who present with the following:

- Sight-threatening visual field loss at initial diagnosis
- A clear history of visual field loss and/or progression of optic nerve damage at their current pressure
- Blindness in one eye, regardless of the disease stage in the other eye
- A strong family history of vision loss related to glaucoma.

Clinical management strategies in NTG

The CNTGS defined the gold standard for treatment (whether medical or surgical) as a 30 percent reduction in IOP from baseline (8). In other words, my treatment target for a patient with glaucoma at an IOP level of 16 mmHg might be 11 mmHg. Fortunately, advances in topical drug therapy and/or selective laser trabeculoplasty (SLT) enable us to achieve this goal in the majority of patients with NTG without having to resort to incisional surgery.

Currently, five classes of IOP-lowering agents, which work by mechanisms affecting aqueous production and outflow, are available. These include: prostaglandin analogs (PGAs), beta-blockers, carbonic anhydrase inhibitors (CAIs), adrenergic agonists, and miotics (9).

Despite the advantages of PGAs and availability of multiple drug options, there is information that suggests that a significant proportion of glaucoma patients do not reach target IOP with a single-agent regimen (10). In addition, even if IOP is maintained within target levels, some patients may continue to develop progressive glaucoma damage and field loss (6). These treatment challenges highlight a continued need for additional therapies. A number of glaucoma patients, including some with NTG, require greater IOP reduction than others. Effective IOP reduction may require pressures close to 10 mmHg or even lower around the clock, and it may be difficult to reduce pressures to such levels with either a single agent or multiple agents. Even with multiple medications – which can adversely impact adherence (11) – pressures in this range can be difficult to attain in most patients.

My standard approach to treating glaucoma is to start with either a PGA or SLT, whichever the patient prefers. Subsequently, if first-line therapy fails, I will step up to second-line therapy with whichever intervention the patient did not choose initially. Third-line options involve a combination approach in which either a CAI, a β-blocker, or an α_2 adrenergic agonist is added to a PGA. Of these three agents, numerous studies support the addition of the CAI to a PGA regimen to produce the most robust IOP reduction (12–14). However, when aiming to achieve aggressive IOP reduction, I might also choose to maximize adjunctive therapy by going straight to a fixed-dose combination product added to PGA therapy. The bottom line: we can now add any combination of these three adjunctive therapies to a PGA in a fixed-dose combination.

In the event that pharmacologic therapy and SLT fail to control the patient's NTG, incisional surgery is another option (9).

NTG take home

The treatment goal for glaucoma across the spectrum of IOP, including NTG, is to achieve an impactful IOP reduction by whatever means necessary (whether pharmacologic, SLT, or incisional surgery) to halt or delay further optic nerve damage. We have studies to support specific IOP reductions by stage of disease – for instance, a 22.5 percent reduction in ocular hypertension (15), an approximate 25 percent IOP reduction in early POAG (7), and a 30 percent reduction in NTG (8).

I use these studies as guidelines rather than absolutes. In fact, the American

Box 1. Risk Factors for Glaucoma

- High IOP
- African or Hispanic heritage
- Thin central cornea
- Family history
- Age >40 years
- Farsightedness or nearsightedness
- Diabetes, migraine, poor blood circulation/vascular dysregulation, or other systemic problems (17).

Box 2. Screening for NTG in the Clinic

1. Take a proactive role in screening for NTG. In one study, approximately 20 percent of patients diagnosed with glaucoma had seen an ophthalmologist or optometrist within the prior 24 months (18).
2. Carefully examine the optic nerve. Focus on the size, shape, and contour of the cup to see if it appears healthy and intact; look for focal thinning or notching of the rim; examine the peripapillary region for other signs of glaucoma damage such as disc hemorrhages, nerve fiber layer bundle defects, or peripapillary atrophy; and, if possible, take photographs to objectively document changes over time.
3. Rule out CNS disease (i.e., tumors, strokes, lesions, empty sella syndrome) by ordering a brain MRI if the clinical picture is inconsistent with glaucoma.
4. Note that findings in NTG are similar to those in HT-POAG, therefore, every patient, regardless of his or her IOP, should receive a comprehensive optic nerve exam.

Box 3. Differential Diagnosis of NTG

- Undetected POAG (diurnal IOP fluctuation)
- Intermittent IOP elevation (e.g., intermittent angle closure)
- Glaucomatocyclitic crisis/uveitic glaucoma
- "Burned-out" pigmentary glaucoma
- Corticosteroid-induced glaucoma
- Nonglaucomatous optic nerve
- Congenital disc anomalies/cupping
- Myopia with peripapillary atrophy
- Optic nerve coloboma/pit
- Vascular etiology
- Temporal arteritis (AION)
- Carotid and ophthalmic artery occlusion
- Central retinal artery occlusion
- Neurological etiology
- Meningioma
- Pituitary adenoma
- Empty sella syndrome
- Leber's optic atrophy
- Syphilis
- Tonometric error/thin cornea (19)

Academy of Ophthalmology has created evidence-based guidelines for initial POAG treatment (16). In these guidelines, an initial 25 percent IOP reduction is recommended for all forms of POAG, including NTG, with the caveat that individual risk profiles may support a more or less aggressive approach on a patient-by-patient basis.

Today the prognosis for patients with POAG across the spectrum of IOP is better than ever. Our therapeutic options continue to expand, but there is also a continued need for additional pharmacologic therapies for those patients who do not achieve their target IOP.

Our challenge as eyecare professionals is to recognize the disease in its early stages by performing a thorough ophthalmic exam on every patient who walks through the door, regardless of his or her IOP. Only with early detection can our patients with NTG benefit from the full spectrum of management options.

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Here Come the Waterworks!

Working up patients with excessive tearing

By Elizabeth Shen and Jeremiah Tao

Epiphora, or excessive tearing, is a common complaint seen in any eye practice. Excess tears can be bothersome, embarrassing, and even impair vision. Tearing patients are often assumed to have one of two broad problems: dry eye or a nasolacrimal obstruction. Artificial tears are often prescribed for presumed dry eye disease, but these can make matters worse if a lacrimal drainage obstruction is present. On the other hand, many physicians recommend tear drain surgery if their patients' excess tears are attributed to increased tear secretion. Epiphora can be caused by a wide variety of problems and difficult to diagnose, so a systematic approach is necessary for teary-eyed patients.

At a Glance

- *Many patients present with epiphora; excessive tearing – which is unpleasant for the patient and can cause issues with vision*
- *The condition has many underlying pathologies, but can be broadly grouped into two main causes: overproduction or under-drainage of tears*
- *Overproduction of tears can result from conditions such as dry eye disease or eyelid abnormalities, whereas under-drainage can result from obstructions in the lacrimal system*
- *We provide guidance on the different causes of epiphora, advise on diagnostic techniques and summarize the treatment options.*

Tear physiology

The lacrimal and accessory lacrimal glands produce tears at a basal rate of around 1.2 µL/minute, but reflex tearing can increase this rate by 100-fold. Each blink spreads the tear film evenly over the ocular surface, and evaporation eliminates 10–20 percent of the tears volume. Contraction of the orbicularis muscle pumps most of the tears into the upper and lower puncta where they eventually enter the nose through the nasolacrimal duct (Figure 1a). A tear capacity of 8 µL rests on a delicate balance between production, evaporation, and drainage. Any disruption of this balance leads to tear overflow. Hence, it is helpful to think of epiphora in terms of overproduction or under-drainage (Figure 1b).

Overproduction

Ocular surface disease

Dry eye disease is ubiquitous and perhaps the most common cause of tear overproduction. Surface dryness or irritation stimulates reflex tearing that can exceed lacrimal drainage. Blepharitis, keratoconjunctivitis sicca, trichiasis, lagophthalmos and exposure keratopathy, allergic conjunctivitis, and medicamentosa can all also lead to over-secretion of tears.

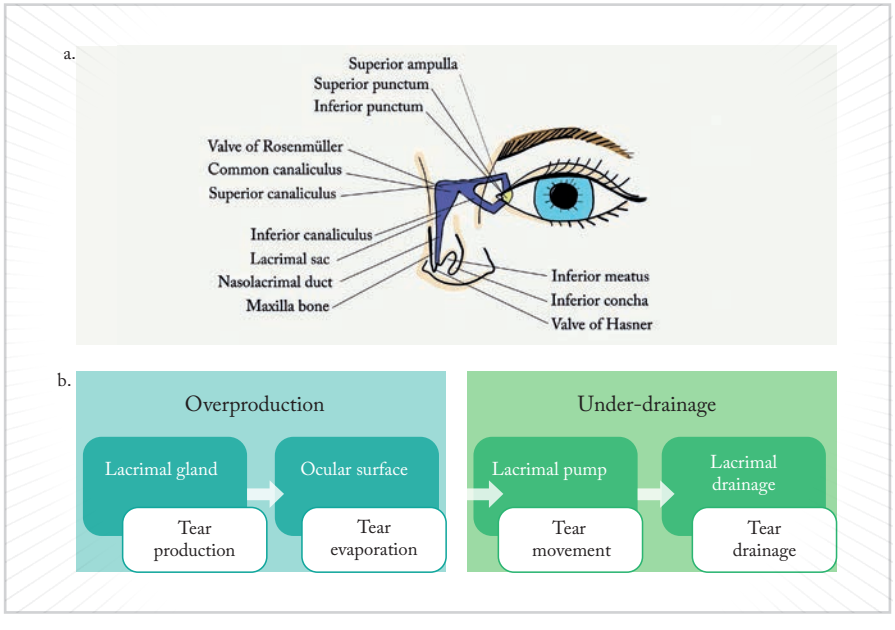

Figure 1. Anatomy of the lacrimal drainage system (a) and pathology of epiphora (b)

Level of lacrimal drainage obstruction	*Type of obstruction*	*Treatment*
Punctum	*Occlusion*	Dilation, punctoplasty
Canaliculus	*Stenosis*	Silicone intubation or stenting
	Complete occlusion	Reconstruction (excise occluded segments, anastomose remainder)
	Severe obstruction	Conjunctivodacryocystorhinostomy
Common canaliculus	*Obstruction*	Canalicuolocryocystorhinostomy
Nasolacrimal duct	*Stenosis*	Usually dacryocystorhinostomy but sometimes silicone intubation
	Complete obstruction	Dacryocystorhinostomy

Table 1. Recommended surgical corrections for epiphora based on extent of obstruction

Identifying the correct underlying etiology is necessary to properly treat the surface.

What to look for:

- Increased tear lake height
- Decreased tear breakup time (TBUT) <10 seconds
- Devitalized corneal epithelium using topical rose bengal or lissamine green
- Epithelial defects or erosions on fluorescein staining
- Misdirected eyelashes
- Poor eyelid closure.

Eyelid abnormalities

Eyelid abnormalities can contribute to ocular surface exposure or irritation.

What to look for:

- Eyelid malpositioning (for example, entropion, ectropion, floppy eyelids, trichiasis, retraction [Figure 2], lagophthalmos)
- Facial asymmetry
- Weak eyelid closure, abnormal blink reflex, or decreased blink rate
- Eyelid laxity.

Many of these eyelid conditions also compromise the integrity of each blink and thus impair movement of tears and outflow. Poor blink function can result from loss of eyelid connective tissue tone from old age or a facial nerve palsy. More rarely, scarring can cause eyelid deformity, resulting in a "stiff" eyelid that cannot pump or distribute tears normally. One common condition is Parkinson's disease, which is associated with a decreased blink rate; this both increases evaporation and decreases tear movement.

Under drainage

Obstructive lacrimal drainage disorders

A soft rule of thumb is that if excess tears flow down the cheek, as opposed to just making the eye "watery," a tear outflow problem may be present. Problems in the "plumbing" can occur anywhere from the punctum, canaliculus, nasolacrimal duct, to the nose. Punctal eversion, or ectropion, is usually easily identified. Punctal plugs commonly used to improve dry eye can migrate within the canaliculi, becoming a source of obstruction. Less frequently seen, punctal and canalicular stenosis can result from inflammation (for example, Stevens-Johnsons syndrome, ocular pemphigoid), infection (for example, herpes), chronic bacterial inflammation (for example, caused by Actinomyces israelii), medication (for example, pilocarpine, epinephrine), or trauma. A general rule for assessing stenosis is that the normal lumen should be the same size (or bigger) than the end of a paperclip. (But do not actually poke the eyelid with a paperclip!)

The most common cause of tear outflow obstruction is acquired nasolacrimal duct obstruction (NLDO) or stenosis. Other possible causes are dacryoliths, dacryocystitis, chronic sinus disease or prior sinus surgery, trauma, and rarely, sino-nasal or lacrimal sac malignancy.

What to look for:

- Lacrimal obstruction (see "lacrimal drainage system irrigation" below)
- Fullness over the lacrimal sac on palpation, indicating dacryocystititis
- Nodular fullness over lacrimal sac, which could indicate neoplasm
- History of eyelid trauma
- History of sinus disease
- History of punctal plug use
- History of bloody tears, suggestive of malignancy.

Probing for a diagnosis

A thorough inspection of the eyelids and ocular surface is the first step in determining the cause of epiphora. Three essential diagnostic tests can further guide your diagnosis:

1. *Dye disappearance test (± Jones I and II test)*
   A drop of fluorescein is instilled into the conjunctival fornix of each eye. Instruct the patient to not wipe or touch their eye. After five minutes, the dye should clear spontaneously if there is no obstruction. Persistent or asymmetric clearance suggests possible obstruction, especially if dye is seen flowing down the eyelids

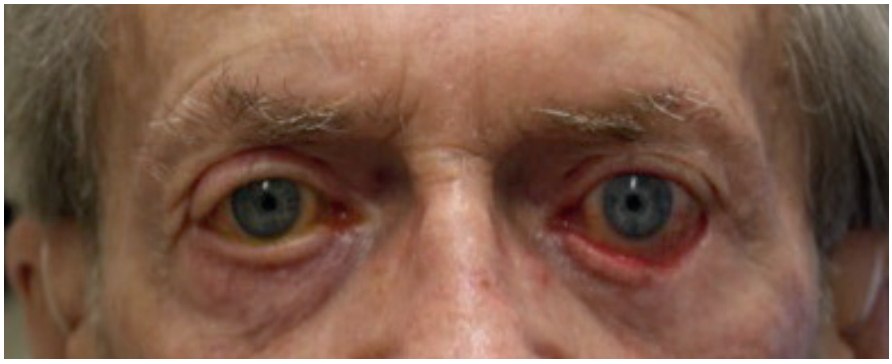

Figure 2. Abnormal eyelid retraction in a patient.

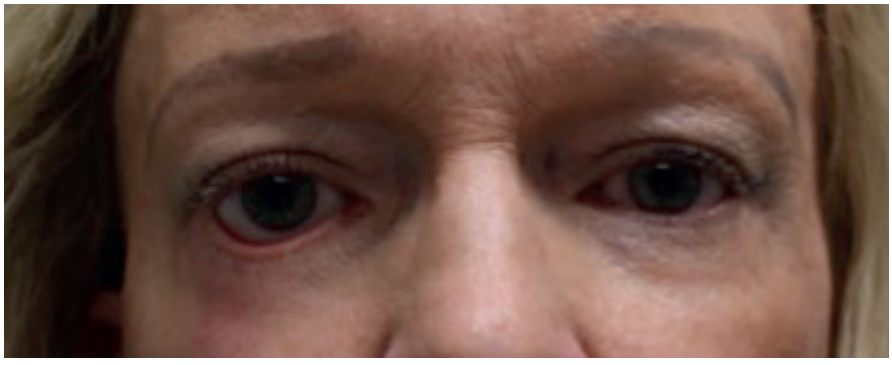

Figure 3. Poor right lower eyelid position after an eyelid snap test.

and cheeks. The Jones I and II tests attempt to recover fluorescein in the nose. Since nasal swabbing can be uncomfortable and misleading, many skip Jones testing and proceed with lacrimal syringing.

2. *Snap and distraction test*
   This exam technique assesses eyelid laxity. The lid is pulled down or away from the globe. Stretching the lid >8 mm indicates excessive laxity. After releasing the lid, it should take <8 seconds for the lid to "snap back" to its normal position. Poor appositional return also suggests laxity (Figure 3).
3. *Lacrimal drainage system irrigation*
   After applying topical anesthesia, a blunt lacrimal cannula on a syringe with normal saline or water is inserted into the punctum with some lateral traction on the lower eyelid. The cannula is gently advanced. When no obstruction is present, the cannula moves easily. Next the syringe is depressed. If tear drainage is normal, saline or water should pass freely into the nose or throat without reflux. The patient may cough, swallow, or otherwise grimace with the sensation of fluid in their nasopharyngeal area. Difficulty advancing or fluid reflux indicates some level of obstruction. When the fluid refluxes from the same punctum (or one cannot irrigate at all), a canalicular obstruction is likely. Reflux occurring through the opposite punctum points to a blockage at or distal to the common canaliculus. Pus or mucous reflux points to a dacryocystitis.

Treatment

Once again, correcting the underlying cause is key to treatment. A large percentage of patients will have ocular surface disease requiring only medical management. Trichiasis can be temporarily managed with epilation or ablation, but more severe eyelash misdirection may need excision, eyelid reconstruction, or mucous membrane grafting. Patients with either an outflow or a plumbing problem will more likely need surgical correction, for which the specific treatment is based on the level of obstruction (Table 1).

Eyelid laxity and involutional ectropion are often corrected with eyelid tightening procedures, such as a lateral tarsal strip or lateral canthopexy. Punctal or canalicular stenosis may respond to silicone intubation or stenting. For a NLDO, a dacryocystorhinostomy (DCR) is the treatment of choice. The goal of this procedure is to bypass the NLDO. This is accomplished by creating an anastomosis from the lacrimal sac through the adjacent bone to the nasal cavity. If the blockage is at the common canaliculus, a DCR may work, but a conjunctivodacryocystorhinostomy (CDCR) with a Jones tube that bypasses the entire native tear outflow system may be indicated.

DCR is one of the most common tear outflow procedures. A stent is usually placed temporarily across the new tear passageway during the healing process. Some common complications include persistent tearing, infection, bleeding, early loss of the stent leading to occlusion, and sinusitis. However, prognosis is excellent, with success rates of greater than 90–95 percent (1).

In summary

Causes of epiphora can be multi-factorial, and unless there is an obvious complete drainage obstruction, treatment should begin with noninvasive options. Helping your patients understand the basic physiology of tears and partnering with them to find the best treatment is the first step to ending those waterworks.

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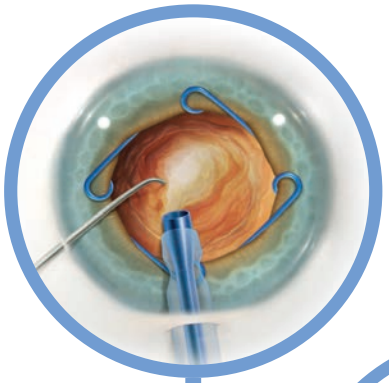

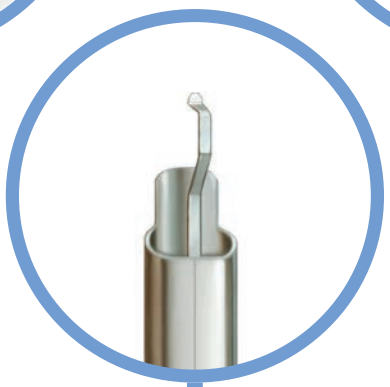

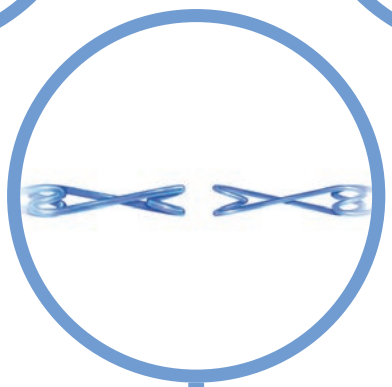

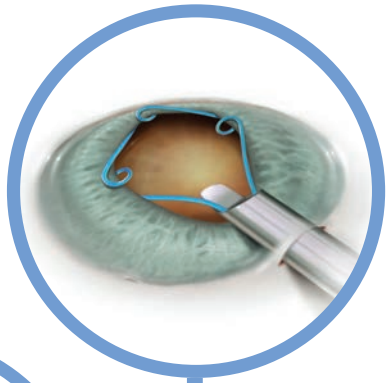

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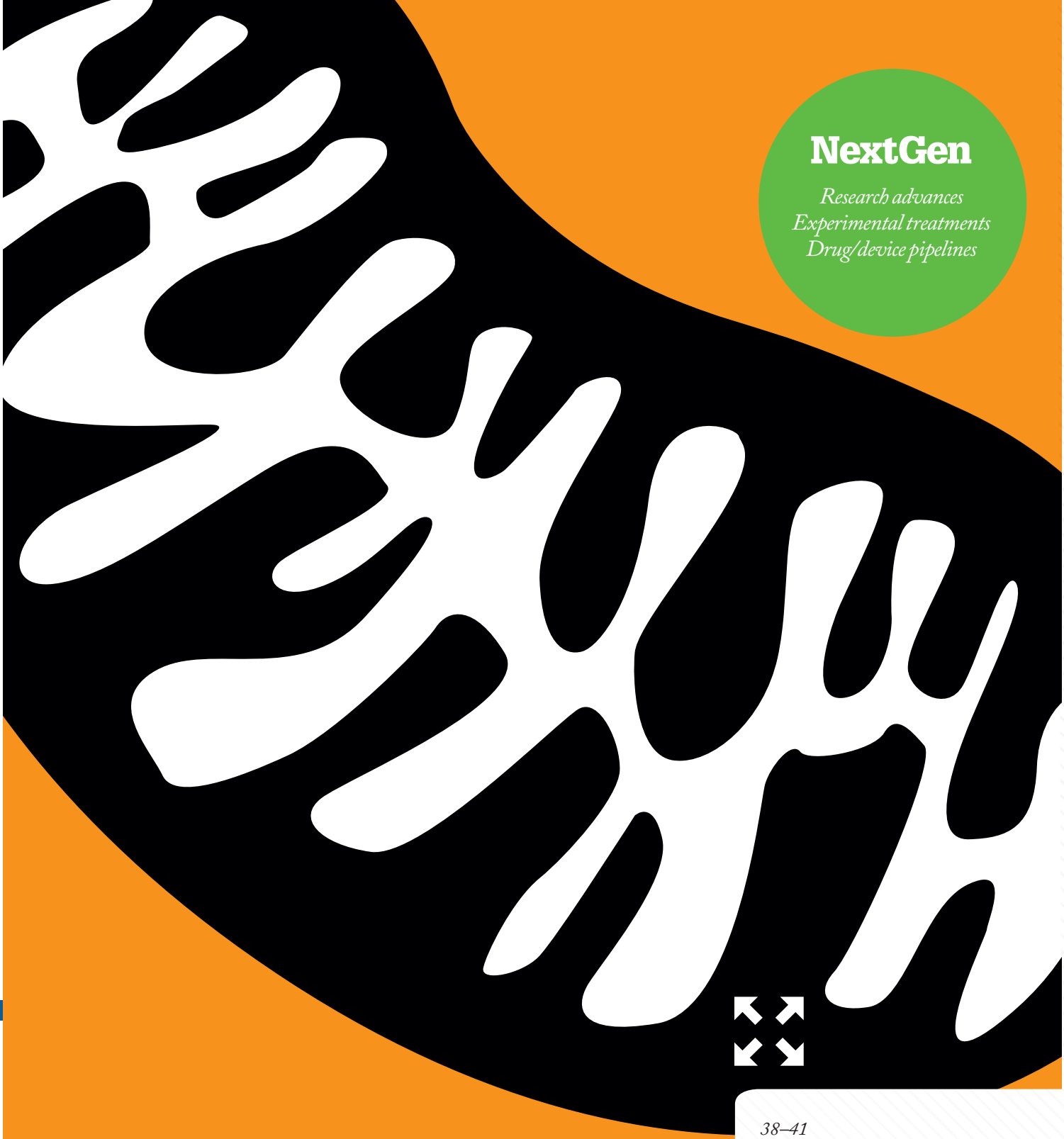
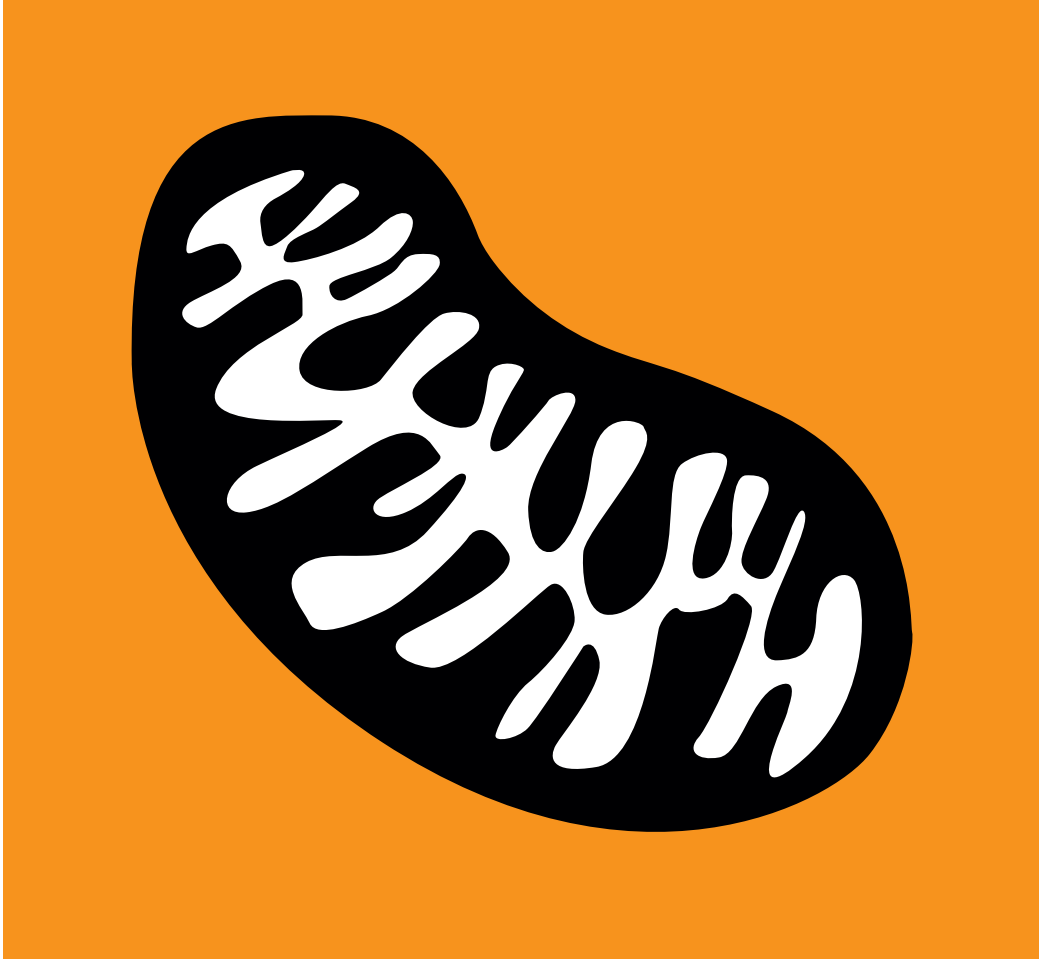


NextGen

Research advances
Experimental treatments
Drug/device pipelines



Metabolism, Melanin and Multiple Modalities

How new imaging approaches are broadening our understanding of retinal biological function in health and disease

By Hao F. Zhang

Back in 2009, we were given a challenge – to optically measure the oxygen rate of the retina. It was a problem – at the time, gross retinal blood flow could be measured using laser Doppler velocimetry (and more recently, and with greater granularity, using OCT angiography). Retinal blood oxygenation saturation (sO_2) can be determined using live-time fluorescence imaging or camera-based oximetry – and this approach has shown that blood flow and sO_2 is altered in several pathologies, such as diabetic retinopathy and glaucoma. But there are limitations to our current knowledge regarding the retinal metabolic rate in health and disease. Why? Mainly because there is no technology that can measure both blood flow and oxygenation at the same time. To gain a more comprehensive profile of biological function and disease status, we set out to find a way to measure both.

At a Glance

- *Understanding of retinal metabolic activities and retinal melanin decay are limited, primarily because the technology has not existed to measure and study these parameters*
- *We set out to improve understanding by developing new imaging modalities*
- *Specifically, we are working with photoacoustic imaging and vis-OCT*
- *These new understandings will likely inform how we diagnose, stage and treat retinal disease.*

Combining optics

Our first thought was to combine OCT with photoacoustic microscopy in the same device. As OCT angiography allows the precise determination of retinal blood flow, and photoacoustic imaging has been shown to quantify sO_2 in several tissues (1), we believed that the approach would allow us to quantify everything from a single scan.

I am sure there is no need to explain how OCT works to an audience of ophthalmologists, but I will offer a little more insight on photoacoustic microscopy. Principally, it is a hybrid imaging technique that detects laser-induced ultrasound (see Box – Photoacoustic Imaging Explained [1]). To make the technique suitable for retinal imaging, photoacoustic microscopy had to be modified, resulting in photoacoustic ophthalmoscopy (PAOM), an optical scanning photoacoustic microscopy system that can image retinal blood vessels and retinal pigment epithelium (RPE; 2). In 2014, we used an integrated photoacoustic ophthalmoscopy and SD-OCT system, and demonstrated that we could non-invasively measure both retinal blood flow and sO_2, and quantify the retinal metabolic rate ($rMRO_2$), in rats (3, 4).

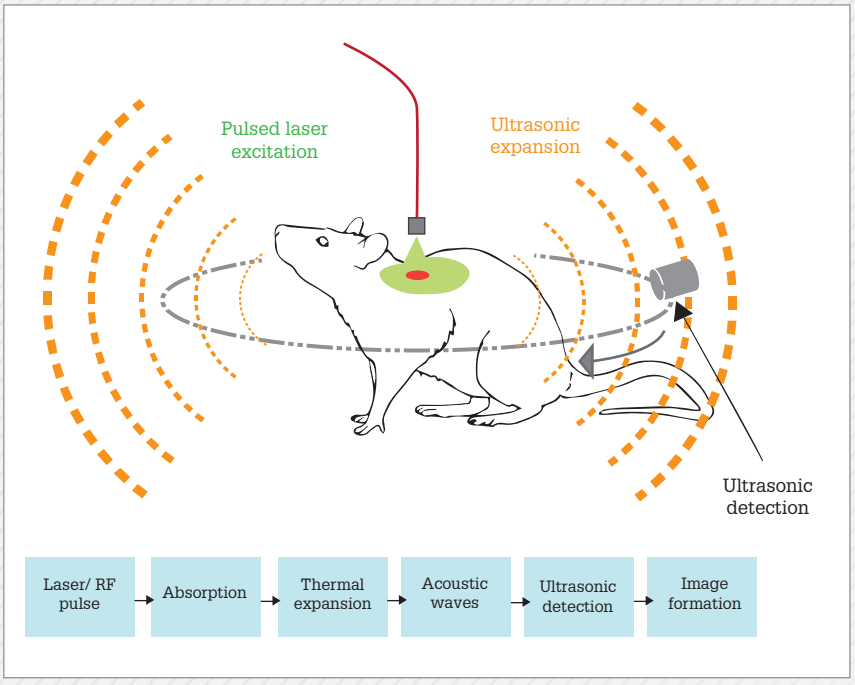
A better detector

Unfortunately, there is a major challenge with photoacoustic imaging: detection. Photoacoustic imaging was first developed for skin cancer; later on, people pushed for it to be used in brain imaging and endoscopy, but it had never been successfully used in eye imaging, primarily because a high quality detector did not exist. And we faced the same challenge: ultrasonic detection needs contact with tissue (or a coupling agent). In the early stages of our work, we used a very tiny piezoelectric transducer attached at the

side of the eyelid. But everything had to be aligned too perfectly, even in mice and rats, so we realized that it was not the best way to image humans. Furthermore, many commonly used piezoelectric detectors are constrained in terms of axial resolution. To solve the ultrasonic challenge, I worked with Cheng Sun here at Northwestern University and we developed a better detector for photoacoustic imaging: the microring resonator (5).

The microring resonator is a soft (or compressible) waveguide, nanofabricated on a transparent substrate, i.e. a piece of quartz (Figure 1). The waveguide has a square shape and forms a circle. It is tiny at only 60 μm in diameter and 1 μm in height, yet it is so sensitive it can detect ultrasonic pressure as low as 10 Pa, which is more than 10 times more sensitive than state-of-the-art piezoelectric detectors. It also offers an enlarged detection bandwidth that improves the axial resolution of photoacoustic microscopy (6). The combination of its small size and optical transparency means that we can detect ultrasound reflected back from the retina at a higher resolution than existing methods. For us, it seems a natural step to insert the detector into a contact lens, so that it is in contact with the eye, and we want to make it customizable so that the microring will be inserted while the contact lens is being 3D-printed. Our projection for the future is that the combined system will be used in humans; the contact lens containing the microring resonator will be placed on the patient's eye, and together with OCT, retinal biological activities can be measured.

As we are working on developing better and cheaper microring detectors, we have discovered that we're not just limited to ophthalmic fabrications. Replacing the coverslip in traditional microscopic studies with a microring resonator-containing piece of glass means that scanning laser microscopes can become photoacoustic microscopes. This means that researchers wouldn't have to buy a system from scratch, but can rather modify their existing system with minimal effort. We've also been approached by investigators to develop endoscopes, so esophagus or colon can be viewed using optical transparent detectors combined with their existing optical imaging setups. We were also recently approached by a geologist who wanted to measure seismic waves at the core of the earth!



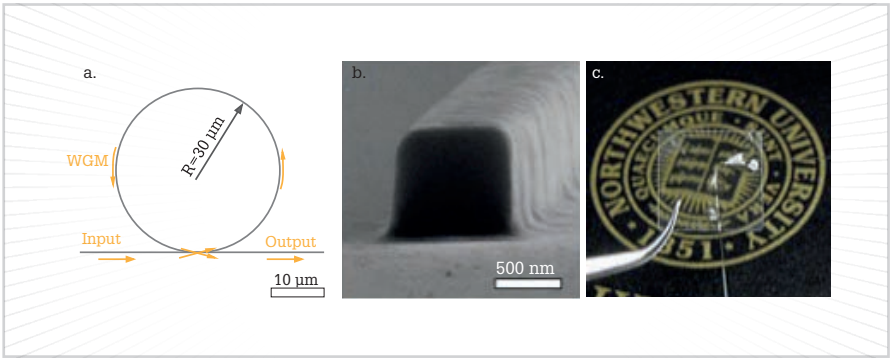
Credit: Bme591wikiproject

Photoacoustic Imaging Explained

Photoacoustic imaging relies on optical absorption contrast. For biomedical imaging, optical absorption can be closely associated with physiological properties such as oxygen saturation, molecules such as hemoglobin or melanin, or from exogenous contrast agents. In photoacoustic imaging, a short-pulsed laser beam is directed into tissues; this laser energy becomes absorbed, leading to thermoelastic expansion and emission of ultrasonic – or photoacoustic – waves. An ultrasound detector detects the waves, the amplitude of which is proportional to the concentration of local optical absorbers. Axial resolution is determined by the bandwidth of the ultrasonic detector. The photoacoustic waves are then analyzed to produce reconstructed anatomical images.

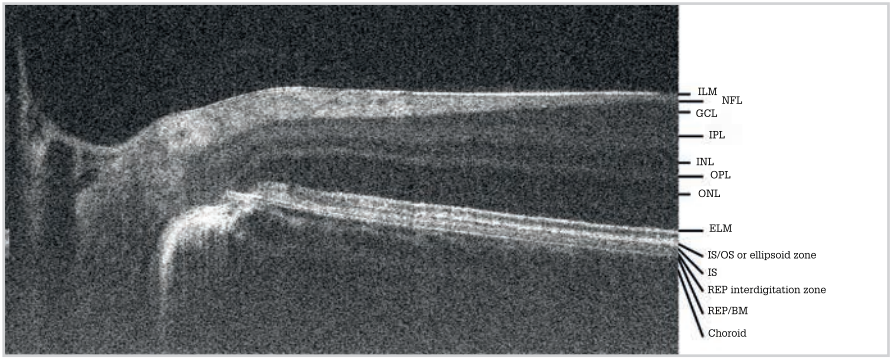
From metabolism to melanin

Measuring retinal metabolic rate might have been the major reason to begin our studies, but our other aim was to quantify melanin RPE concentration. Why? Melanin is one of the key pigments comprising the RPE, where it helps protect against photodamage and oxidative stress.



Credit: (5) and Northwestern University.

Figure 1. The micro-ring resonator. a. Scanning electron micrograph of the micro-ring resonator showing dimensions. b. High-magnification view shows the square-shaped cross section of the waveguide with a side length of 800 nm. c. A photograph of the microring resonator. WGM, whisper gallery mode.



Credit: IOVS (17).

Figure 2. Vis-OCT scan showing 13 layers of the human retina.
BM, Bruch's membrane; ELM, external limiting membrane; GCL, ganglion cell layer; ILM, Inner limiting membrane; INL, inner nuclear layer; IPL, inner plexiform layer; IS, inner segment; ONL, outer nuclear layer; OPL, outer plexiform layer; OS, outer segment; RPE, retinal pigment epithelium.

But melanin concentration in the RPE decreases with aging, leaving the eye more susceptible to damage and degeneration (7, 8). Reduced concentrations of melanin in the RPE are considered to be a key indicator of the presence of age-related macular degeneration (AMD), especially in the later stages of disease, and many researchers now believe that if melanin dysfunction could be measured in the early stages of disease it could represent an early risk factor of the presence of disease. Accurately measuring RPE melanin concentration would give us more insights into both the natural history of how melanin concentration changes with age, and how this is changed as retinal diseases, such as AMD, progress.

Right now, fundus autofluorescence imaging is used to measure retinal melanin concentration, typically with infrared or blue light sources. The main downside of these fundus-based imaging techniques is that they have poor axial resolution, and rely on diffused reflective photons from the retina to accumulate all the information from multiple layers, from the ganglion to photoreceptors to the RPE, and even choroid. They all mix together, and although it is not impossible to dissect information from this mixed signal, it is highly challenging. But if we could have a technology that can provide an axial resolution, say at the level of 10 µm, then we wouldn't need to perform all these dissections, and we could image multiple layers separately. Photoacoustics is the perfect way to provide this axial resolution, and using our microring resonator on an inverted microscope system, we have for the first time, quantified the melanin concentration in both the RPE and the choroid at an axial resolution of 15 µm in samples of RPE-choroid complexes from human and porcine eyes (9, 10). In the future, we would like to explore how to quantify the melanin concentration at different stages of AMD. To do this, we are trying to monitor the melanin decay time course at different stages in a transgenic mouse model of geographic atrophy.

A better way

Although photoacoustics is very sensitive, the downside is the requirement for a contact measurement. So we have developed a better technology for metabolic rate imaging – visible OCT or vis-OCT – which we now use instead of photoacoustic imaging. How does it work? Vis-OCT is much the same as traditional OCT – the key difference is that it uses light across the visible spectrum (center wavelengths: 570 nm). Most commercial OCT systems use near-infrared light (center wavelengths: 830 nm or 1,330 nm) because it is more comfortable and "patient friendly" than visible light. But to measure both blood flow and oxygenation, we had to shift the wavelength from infrared to visible light; sO_2 can only be measured by OCT when in the visible spectrum (11).

We've previously shown in rat eyes that with a single vis-OCT scan, we can obtain high quality retinal anatomical imaging (close to 2 µm; Figure 2), as well as accurate measurements of $rMRO_2$ (12). Back in 2015, we demonstrated that vis-OCT was safe for human imaging (13) and here at Northwestern, we have now imaged over 100 patients with a range of diseases (including diabetic retinopathy, drusen formation, wet AMD and vein

occlusion) referred to us by physicians. We've recently published results demonstrating that vis-OCT could be used to quantify sO_2 in humans: in four healthy volunteers, we observed a 20 percent difference in sO_2 between retinal arteries and veins (14). We've also used vis-OCT to show that inner retinal oxygen metabolic rate is increased in diabetic mice (15).

"Benefits with vis-OCT include a complete profiling of the metabolic signatures at the back of the eye using a single scan."

Of course, the downside of vis-OCT is that the use of visible light makes it more uncomfortable for the patient, and because visible light is blocked by the RPE, we cannot image the anatomical structures beyond this, such as the choroid, so choroidal circulation can't be assessed. Furthermore, as the models used to calculate sO_2 are based on continuous blood flow, they cannot quantify sO_2 in capillaries correctly (16). Despite these limitations, the benefits with vis-OCT are a much higher axial resolution compared with any state of the art OCT, as well as a complete profiling of the metabolic signatures at the back of the eye using a single scan.

Looking ahead

In terms of photoacoustics, we want to better understand melanin decay before we begin studying it in humans. Melanin decay has not been studied historically – likely because of a lack of technology. We're hoping to establish an approach using photoacoustic imaging based on microarray to provide an extremely sensitive way to measure melanin, and we're currently at the laboratory validation stage. With regards to vis-OCT, we want to expand our clinical sites to collect enough patient data to submit an application to the FDA. We're currently working with leading ophthalmologists from Northwestern University Memorial Hospital and the New York University Medical Center, but we're also looking for more collaborators! We'd also like to develop metabolic profiles of patients with different stages of disease. It's fair to say that we're at the beginning of a long but exciting journey.

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Disclosures: Zhang reports that he is co-founder and shareholder of Opticent Health.

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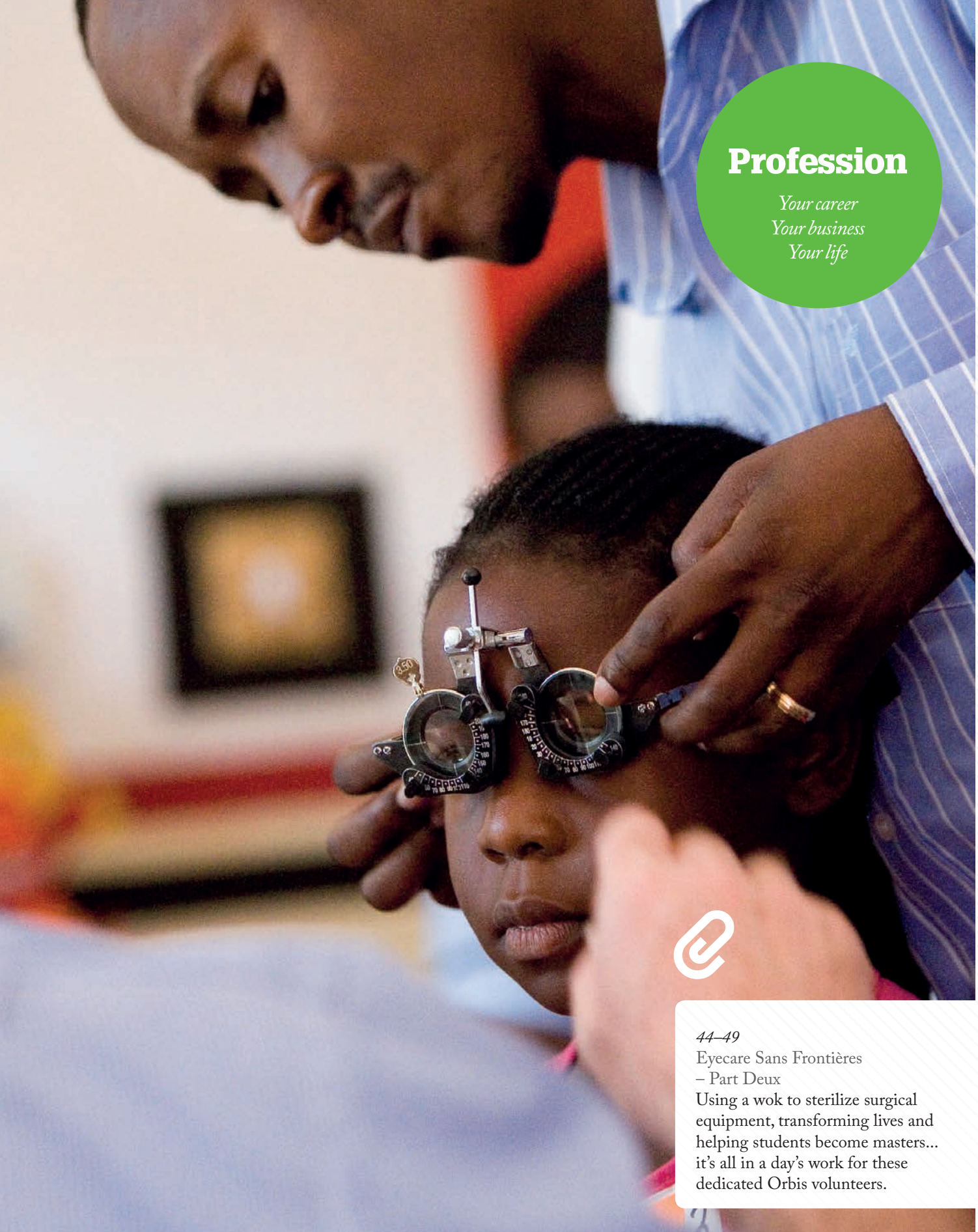

Profession

Your career
Your business
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Eyecare Sans Frontières – Part Deux

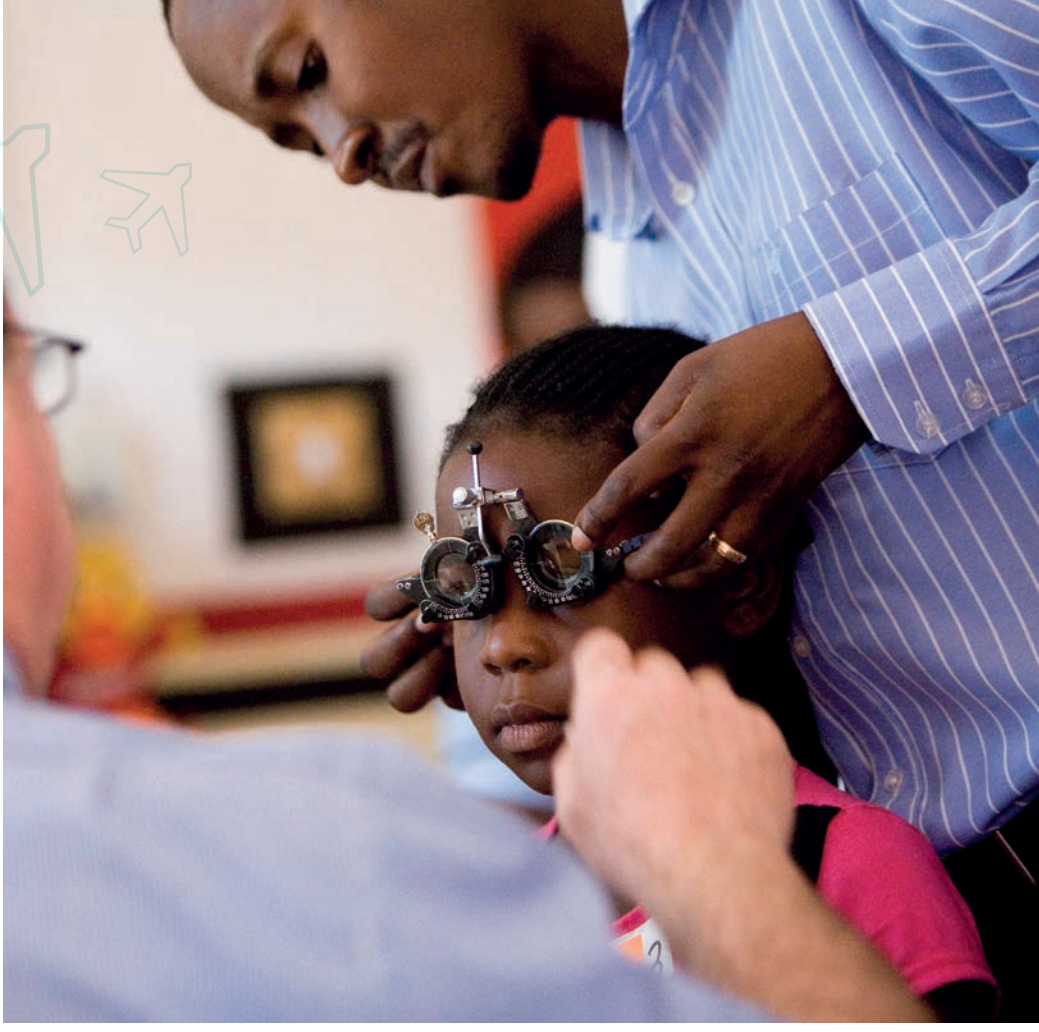
Meeting the volunteers who take to the skies to bring eyecare and education to those on the ground

By Ruth Steer and Roisin McGuigan

In last month's issue, we took a tour of Orbis' new Flying Eye Hospital, and learned about the history of the organization. This month, we feature the stories of just a few of the dedicated volunteers who devote their lives to preventing and treating avoidable blindness and visual impairment across the world. Meet Rob Walters, volunteer surgeon, Ann-Marie Ablett, volunteer nurse and Orbis ambassador, as well as anesthetist trainee and trainer duo Luu Tong and Andrew Choyce. Read about a typical working day with the organization and delve into the unusual practices sometimes required to "get the job done" – like boiling surgical equipment in a wok…

At a Glance

- *In part two of our Orbis feature, we meet four volunteers from the organization*
- *Rob Walters, volunteer surgeon, discusses the focus and priorities of the organization*
- *Volunteer nurse and global ambassador, Ann-Marie Ablett, shares and reflects on a typical day in a mission, including the need for some fast thinking and a sense of humor*
- *Luu Tong, a pediatric anesthetist, and her trainer, Andrew Choyce, talk about their journeys and how health education provides many with the ability to train others.*



Flying Through Fear

"I realized after day one that I had simply changed location – I was surrounded by different staff and friends I hadn't met yet"

Ann-Marie Ablett, Senior Ophthalmic Nurse at the University Hospital of Wales, Cardiff, Wales, and Volunteer Nurse and Brand Ambassador for Orbis

Ann-Marie Ablett

Take us through a typical day with Orbis…
We arrive at the aircraft at 7:30 am and change into our "theater blues" and prepare the operating theater – just as we would do at home. Then the surgery begins; we're allocated different areas by the Lead Nurse and we five nurses take turns overseeing particular programs. We probably perform about five or six surgeries a day depending on the level and skill of the local doctors; our focus is on training, not numbers. We're there to exchange knowledge and skills so that when we leave the country, the staff will have the necessary skills. After surgery, we hand over care to the recovery nurses, and the patients are then discharged back to the local hospital. After that we have to 'turn everything round'; we're nurses by day, but cleaners by night. Sometimes we work until well after 9 pm at night, but

"I just asked if they wanted help, and they had a huge willingness to learn."

that's part of the charm – no two days are the same. It's all about the opportunity to transfer and exchange skills.

What kind of skills do you teach?
Orbis is incredibly supportive. Before we travel to a country, we'll be given all the information on the population, culture and beliefs of our colleagues, and also what the specialties will be for that particular program, so that we can prepare. We share best practice on topics such as hand washing as there is a proper way to do it (I remember meeting nurses who had been scrubbing with wooden brushes with hard bristles to ensure they prevented any infection!) We also teach the staff skills such as gowning and gloving, safety and sterility practices (including how to hand the surgeon equipment to avoid needlestick injuries), and how best to advise patients in terms of the expected surgery and possible complications. We cannot guarantee 100 percent – no one can! And also, the importance of hand washing and compliance. In Zambia, the nurses asked what they could do to preserve eyesight. I had never been asked that before, so we spoke about the obvious way to protect your vision and for homework that evening I put a presentation together - luckily I am flexible and have a sense of humor! I prepared a presentation on simple things: best practice with eyedrop medication, safety and protective equipment, getting screened if there is glaucoma in the family, and eating enough greens. All things that we tend to take for granted. I actually learned a lot myself, because I hadn't thought about how I can protect my own sight – and that makes it a real exchange.

How did you get involved?
I worked with Rob Walters at the University Hospital of Wales in Cardiff, and, when I heard him talking about Orbis, I asked if I could join! I flew to Chittagong in Bangladesh for my first mission 15 years ago. I didn't know what

to expect. I knew it was hot, but it was hotter than I imagined – and that was just the start of the unexpected! At the hospital, I realized after day one that I had simply changed location – I was surrounded by different staff and friends I hadn't met yet. I put myself in their shoes, and thought how I'd feel with unfamiliar people coming in and telling me what I'd been doing wrong. But that's not why we were there; we were there to exchange knowledge and information and we learnt as much as they did. I just asked if they wanted help, and they had a huge willingness to learn. We were readily accepted into the team. And I felt that I was home.

Any notable memories?

There are so many I wouldn't know where to start. I remember a young Zambian girl – Mercy – who had slow-to-develop congenital cataracts, and managed to present herself to the doctors when we were in town. She had successful cataract surgery and when we removed the dressings the first thing she did was pick up a book, and she had a huge smile. I only play a small part, but to be lucky enough to be involved in Mercy's treatment – and her future – is so special; you simply can't describe it.

Many times, we had to think on our feet. In Ethiopia, we needed some tubing to use in a dacryocystorhinostomy but, as is typical in developing countries, equipment was limited. We looked in every room and ended up finding some tubing from an old vitrector. We cut a length and boiled it in a saucepan to sterilize it, then used it to keep the tear duct open during surgery. The procedure was a success. In China, I have seen tubing being sterilized in a wok because the sterilizers stopped working! It's fair to say that you have to be adaptable and flexible. But, above all, you have to have a sense of humor. I recall one notable surgery where I spent the entire time underneath the operating table holding the plug for the cautery in the socket to stop bleeding! You have to laugh. Who'd have thought that they would be sterilizing tubing in a wok or needing to hold a plug under a table? Nevertheless, those are some of my contributions to care – you don't know what you're going to find, but you know you'll find a way to work around it!

Where to next?

Volunteering for Orbis turned out to be one of my better decisions. It has changed my life in ways I never imagined it would, and I'd love to continue working with Orbis for as long as possible. My experiences have been magical. And the old DC-10 aircraft – there was just something healing about it. Some Orbis fairy dust!

In 1970, I set out to care for patients – and if I could have the 47 years back, I would do it all again. I absolutely love my job.

Do you think you'll ever go to Arizona to visit the DC-10?

Maybe if I am near the West Coast, but it is certainly not on my bucket list because I hate flying! I pray for weeks before we go, feel sick and do not speak to anyone until I land in the country, except to ask for tea! Orbis and my family are the only reasons I'll get on a plane – the amazing feeling at the end of the trip is worth it – on the way back it's back to not talking until I land back at Heathrow, knowing I'll do it all again… Just waiting for the e-mail…

On a Mission

"The work that Orbis does is not about the ophthalmologists alone – it's about the whole team."

Robert Walters, retired Consultant Ophthalmologist from the University Hospital of Wales, Cardiff, and Volunteer, Trustee and former Chairman of Orbis International

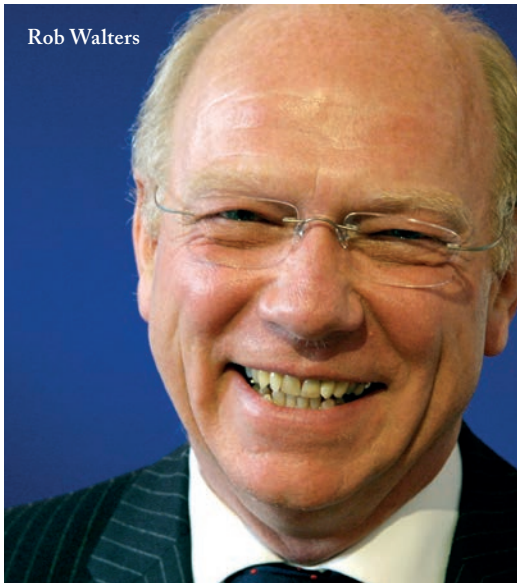
Take us back to the beginning…
I have been with Orbis since 1994 – my first mission was to Khartoum, Sudan. I was just an ordinary ophthalmologist who had an interest in overseas ophthalmology, particularly in developing countries. One of the reasons I was interested in Orbis was because I learned to fly when I was very young and Orbis is where you get interdigitation of aircraft and ophthalmology!

My first visit to Khartoum was a revelation to me; we regard ourselves as being well-trained ophthalmologists but when I got there I realized we hadn't really scratched the surface. It was familiar… yet so very different. You'd see cataracts, but they weren't the same as what I was used to; the response to surgery could be entirely different; for example, the patient could have a much greater inflammatory response. The burden of disease is absolutely huge – you just don't realize how gargantuan the work is and how very little there is available with which to do it. There were patients who had walked for days to bring their child to see you in the hope that you could deliver a miracle for them. Sometimes you could, but sometimes you couldn't.

How does Orbis approach missions?
We are a capacity-building organization rather than a volume-based organization. We're invited to countries by ophthalmologists who are working there and who'd like us to share our expertise. Then we select the volunteers. One very important point is that the work Orbis does is not about the ophthalmologists alone – it is about the whole team. On my own, I am completely useless. But surrounded by my colleagues – nurses, orthoptists, and the biomechanical engineers who mend and service the equipment – we can help and make a real difference.

Tell us a bit about the new aircraft…
The Flying Eye Hospital is a very important icon for us. It is a state-of-the-art hospital that is internationally registered and recognized, and it can deliver top quality ophthalmic treatment anywhere in the world. It is a very significant investment, and has come almost entirely from donations; the aircraft itself was donated by FedEx. All of this has given us the opportunity to bring on board cutting-edge ophthalmic equipment. We have surgical simulators which are very important as they allow visiting ophthalmologists in the early stages of training to learn the basics of hand-eye coordination and ophthalmic surgery without needing to practice on people. There are many other technical aspects regarding the aircraft; payload, fuel consumption and where it can land – all of which are also much improved. Although its payload is still quite significant, it is a much lighter aircraft than our previous one, which means we can go to more places as we can land and take off on shorter runways. We try to keep it on the road – or rather in the air – as much as possible; there is no base, but there are periods of downtime when the airplane needs to be serviced for which we'll go wherever we're offered the best quality and best value maintenance.

The Flying Eye Hospital is only a very small proportion of what we do. The majority of our work is providing country-based programs, and we currently have 15 offices across the world, and we will continue to do so until those countries no longer need us.


Rob Walters

What is your current role in Orbis?
Though I still operate in the UK, I no longer perform surgery on missions. I took a decision when I became Chairman of Orbis that I would cease volunteering medically. I am still volunteering, but I am doing different work now; I'm part of the committee that oversees programs to ensure we are achieving what we set out to, I'm involved in medical strategy and what our clinical foci should be, and I check that we're spending our money appropriately. In 2017, Orbis will be providing eye care treatments for hundreds of thousands of people around the world and treating over six million people at risk of blinding trachoma, so it is a very big organization with a very small number of staff – around 220 worldwide.

What are the main missions of Orbis?
If you look at where we spend most of our money, the three main areas would be in teaching cataract surgery, treating trachoma and pediatric ophthalmology.

No-one can ignore cataract – it represents around 50 percent of the world's blind people, and I think it is where we can reach out to the most people. Trachoma is a very important part of what we do, and

one of our clinical interests is to eliminate it, which I think it is completely possible – just like smallpox was eradicated. We are incredibly grateful to Pfizer who donate azithromycin to us for the treatment of trachoma. They ship it to the country where we need it and through our in country partners, we distribute it for them. Our pediatric ophthalmology work covers a whole panoply of diseases, and with millions of blind and visually impaired children in the world, needless to say, there is a great deal to be done. We also perform many oculoplastic surgeries, as well as treat eye movement disorders.

Any notable memories?

I do remember being absolutely devastated by the tumor ward in Khartoum. Adults and children had basically been given up on; there were children with huge retinoblastomas and there was no hope for them. We couldn't help those specific patients, but what we could do was put in place a system that would allow these conditions to be diagnosed earlier so that they were treatable, and teach the healthworkers how to administer treatment. Seeing this ward really drove it home to me: the need for what we can provide and teach was absolutely huge because these people had been sidelined. They had been condemned simply because there wasn't a system in place to deal with them. It was a very shocking moment for me.

Can you share any highlights?

There are so many wonderful highlights. My first mission in Khartoum was during the civil war between North and South Sudan, and we were visiting a huge refugee camp to find patients who might need us. We came across a 23-year-old woman who was completely blind in both eyes because of cataract and was being led around by a young relative. She had nothing – and she was never going to be able to marry, work, be educated, or contribute to her community in any way. We took her back to the Flying Eye Hospital and performed cataract surgery. I will never forget the day that the bandage was removed from her right eye – her life had changed. She could now do what all of us do; a life we take for granted. And it just struck me so powerfully that if we hadn't seen her, she would have never seen again. So what Orbis can do is give individuals and communities hope, where hope didn't exist before. And that is a wonderful thing.

Luu Tong and Andrew Choyce

I have so many similar stories and experiences, but one that particularly sticks in my mind was a woman in Bangladesh who had a divergent squint. Culturally, this meant that no one would marry her, even though she was incredibly beautiful. I performed surgery to correct her squint, and after the surgery, she wrote to me and said: "I wanted to thank you and I thought you'd like to know that I have had three offers of marriage – but I have decided to think about it." What a wise woman she was!

How are priorities shifting?

Diabetic retinopathy is becoming very important, because diabetes mellitus is an increasingly prevalent disease where ophthalmologists become involved when medicine and the system has failed patients. My own view about diabetic retinopathy is that, of course, we need to treat it, but we also need to work with the physicians to ensure that the majority of these patients never reach the stage where they need ophthalmological treatment. So we are starting to do a little bit more work on diabetic retinopathy in terms of diagnosis, prevention and treatment.

We also recognize that refractive error is extremely important – and is becoming even more so. Recent research has shown that refractive error, particularly myopia, can be induced by 'close work.' So whilst we may not have a direct clinical focus on refractive correction, it is very important we focus on it, and we do this through working with other partners. We work 'hand in glove' with partners all round, and although we may, in theory, compete for funds, in practice we collaborate all the time because the power of partnership is how we succeed.

From Trainee to Teacher

"Now I can work to help others in my position"

Luu Tong, pediatric anesthetist at Da Nang Eye Hospital, Vietnam, and member of the Orbis volunteer faculty

What drew you to medicine?
There was a tradition in Vietnamese families for one member to become a doctor to take care of everyone else. My parents wanted me to be a doctor, and even though it wasn't necessarily what I thought of doing, I'm glad it chose me. As for anesthesia, when I applied to work at the newly opened hospital in Da Nang, they asked if wanted to be an anesthetist because they needed one. So I went to Ho Chi Min City to study anesthetics.

How many pediatric anesthetists are at your hospital?
It's just me! I work with seven anesthetic nurses who help me to organize the drugs and prepare the patients, but when I first started there was only me to deal with patients and very small babies. I was scared because I was alone, so I only worked on patients five years old or above. When Orbis visited our hospital in 2006, I had a great opportunity to learn from their volunteers. The Flying Eye Hospital has visited us four times now, and volunteers and Orbis staff such as Andrew have visited on their own. Thanks to these visits, I now have the confidence to help much younger patients, from one month of age. It has been so helpful and I have learned so much; what I can now do for patients is all thanks to Orbis. Before I could anesthetize younger children, they had to travel to Ho Chi Min City or Hanoi, which was not ideal because some parents didn't have enough money, or the child's condition was too complicated. Some parents couldn't go with their child, which was sad. But now, we can care for younger children in the center of Vietnam and the highlands.

How does it feel to now volunteer for Orbis?
When Orbis call and need me, I say "I'm ready!" I have worked with many other organizations, but I am so impressed with Orbis. They are the only organization I have worked with that focuses on training doctors and nurses, which is so important because the help for patients continues when the volunteers leave. They have made me strong and confident, and now I can work with them to help others in my position.

I am so proud to be an Orbis volunteer – it is a dream come true. Since joining, I have volunteered in Vietnam and worked on two international programs in China and the Philippines. I could have never imagined that one day I would also be with Orbis; they are my family, my hospital is my family – we are all joined together.

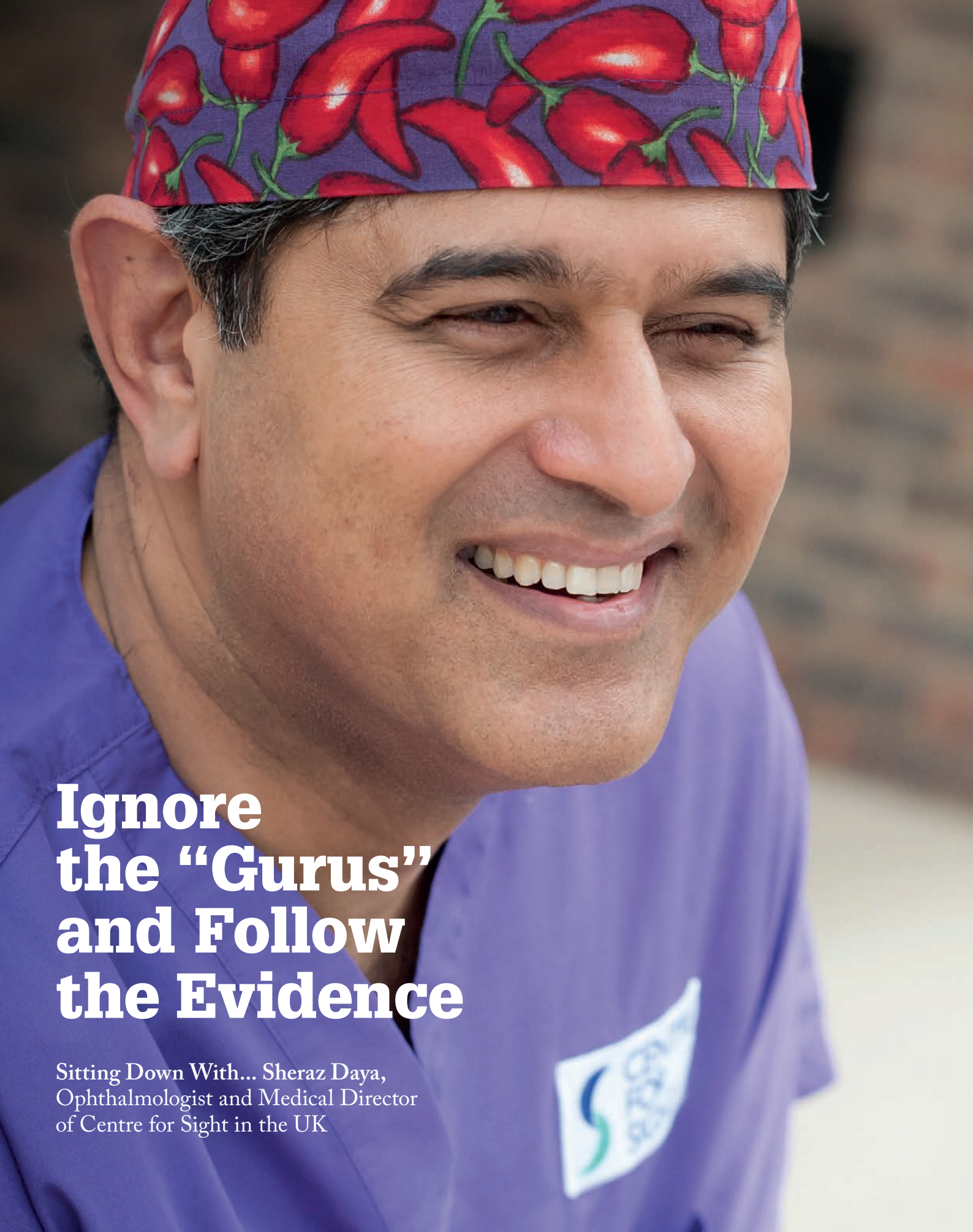
Andrew Choyce, staff anesthetist at King's College Hospital, London, UK, and Orbis staff anesthetist

What led you to your involvement with Orbis?
I have always had an interest in working in lower- and middle-income countries. Within 18 months of finishing University, I took myself off to New Zealand and found a position in the South Pacific. I loved it, and once I started in anesthesia, I never lost the love for the work and challenging myself in more difficult environments. I started volunteering for Orbis in 2005, but I then gained the opportunity to be more involved, and I have actually worked part time for Orbis since 2010. It is to their benefit that I continue my job in the UK so that I can maintain a broader set of skills, and I think it is important as a working clinical doctor that I maintain my proficiencies within my own country. I probably travel for around 12–14 weeks of the year and can respond at short notice if they need someone.

How has it been to see Luu progress?
I have worked with Luu many times over the past 11 years in various capacities; sometimes as a hands-on trainee and more recently as a volunteer. She's also been invaluable as a colleague and as a translator! It has been a real pleasure to see her skills develop to the point that she has joined us as a volunteer; before she started to receive training she wouldn't anesthetize anyone below the age of five. Orbis recognized Luu's potential and invested in her training, providing opportunities to work with British and American volunteers and receive fellowships both in Ho Chi Min City and at Stanford University. She is very dedicated to her work, and she has really concentrated on improving her skills as well as giving a lot of time to improving the safety of surgery at her hospital – as well as doing a lot to improve things on a national level in Vietnam, through in-country volunteering. We have always kept in touch via email, and we regularly exchange ideas, information and advice.

What do you consider one of the most valuable aspects of Orbis?
We often take for granted how hospitals are often close by. But in some countries, patients may have to forego their livelihood for a week to travel, receive their treatment and follow-up, and then travel home. In places like Vietnam, where income is often dependent on farming activity, this can be very difficult for patients. I remember a parent of a patient who was in tears at the end of a screening day because she had realized that not only was the surgery going to be free of charge, but that accommodation would be provided for them. The relief of that parent had such an impact on me; it brought home to me how people's economic status truly affects everything. It is something that Orbis takes seriously, and they advocate for high-quality eyecare and promoting services that are affordable. We help build the capacity of our partners, helping to improve safety and identifying people, such as Luu, who can invest in the good of their hospital and their partners. By identifying Luu as a doctor dedicated to Da Nang Eye Hospital, we have invested in the long term success of the hospital, even after the end of a 5-year partnership between Orbis and Da Nang.

Orbis fights avoidable blindness around the world. Find out more at orbis.org.uk



Ignore the "Gurus" and Follow the Evidence

Sitting Down With... Sheraz Daya,
Ophthalmologist and Medical Director of Centre for Sight in the UK

What gets you going in terms of research?

It's really curiosity that motivates me – asking a question or encountering a problem, and then going out there to find the solution. I have a considerable dislike for dogmatic thinking and process and confess that when I find flaws, I do challenge them using fundamentals as a basis. The use of trifocal diffractive lenses in post corneal laser surgery patients is one example; it is something that some "gurus" say should not be done as the corneal and lens optics are not compatible with each other. But we perform this in carefully selected cases – with phenomenal outcomes.

What's wrong with ophthalmology today? What's right?

I am an optimist! I do not believe there is anything terribly wrong with ophthalmology today, with the exception of things like refractive surgery being hijacked and treated as a widget by high-volume providers. There, the care provided, with its lack of continuity and pure algorithmic process, forgets the patient and focuses on volumes, targets and profits. This is a sure recipe for trouble and sadly taints the reputation of refractive surgery which despite this, is excellent and better than it ever has been. Otherwise, I believe the specialty of ophthalmology is wonderful and often leads the way in medicine.

LASIK is 25 years old now, and you pioneered its use in Europe. Did you think you'd still be using it 25 years later?

The predecessor of LASIK was automated lamellar keratectomy, which used a manual microkeratome to resect a 130 or 160 µm free flap, followed by a refractive cut using the same device. I had performed this on two myopic patients (one, -8.00 D, the other -12.00 D) in New York and was amazed at the outcomes. Using a laser to perform the refractive cut was far more elegant and much more accurate. I just knew that LASIK was here to stay when I saw the outcomes of my first patients.

Back then, what we were doing was rather elementary and we had a lot to learn about optics. Today, we have a far better understanding, and technological advances mean that modern day lasers provide patients with very predictable and accurate outcomes. The advent of femtosecond laser flaps has also made a huge difference. The terror of having a problematic flap and having to pacify a distressed patient has gone, which was the major motivator for us taking the plunge in 2004 and acquiring UK's first IntraLase laser. Again, I knew that for reasons of safety alone this would become the gold standard.

What do you think refractive surgery will look like in 10 years' time?

Ten years is a relatively short time and much of what might be available in 10 years is probably at the late stages of development now. LASIK will still be here, and perhaps it will be performed more commonly once we develop a better understanding of dry eye and nerve re-innervation. SMILE is in its infancy and like so many innovations, this will go through a period of evolution and further development. Reversibility of surgery is very attractive, and for this reason, I believe that phakic IOLs will grow in prevalence. Allograft or synthetic collagen corneal inlays also follow the theme of reversibility and may well become more prevalent too.

For those in the older age group, lens exchange will remain the dominant procedure – what will change is the type of lenses being offered. The Holy Grail is a reliable accommodative lens, but moving parts within the eye have been an issue so far and I expect there will be something very simple in terms of innovation that will come from in from left field that will provide a solution.

In 2030, given the advances in stem cell biology, will corneal transplants be the exception, rather than the rule?

Corneal transplantation has changed considerably over the last 15 years and many of those changes are thanks to technology derived from refractive surgery! Microkeratomes enabled Descemet's stripping endothelial keratoplasty (DSAEK), which ended up evolving into Descemet's membrane endothelial keratoplasty (DMEK). I expect both procedures will be replaced by therapeutic modalities, such as corneal cell therapies with Rho Kinase inhibitors.

Stromal substitutes are already in development and I expect synthetic corneas will become more commonplace. Stem cell treatments will have a role, so long as the correct concoction of cytokines and growth factors can be found to get stem cells recruited from the bone marrow and provide the necessary repairs required. So yes, transplants will reduce in number, but will still be performed in many cases for many years to come, particularly in cases of trauma and where initial reconstruction of the front of the eye is required.

Can stem cell treatments scale – or will cost considerations keep them a niche offering?

At the moment, we are at the stage of stem cell treatment being conducted by some sort of procurement, tissue engineering ex-vivo and then transplantation. In 20 years' time, this will seem quite medieval, once there is a better understanding of wound repair and the role of cytokines in recruiting or stimulating host stem cell recruitment and production.

If you had to describe your career in a single sentence, what would it be?

I find it hard to describe my career but would rather put a sentence together about a realization that has been of great benefit and for which I am very thankful. Anything one does requires good foundations and it is thus important to start with fundamentals and first principles and at the same time continue with good intent to strive for absolute excellence and so-called good luck follows!

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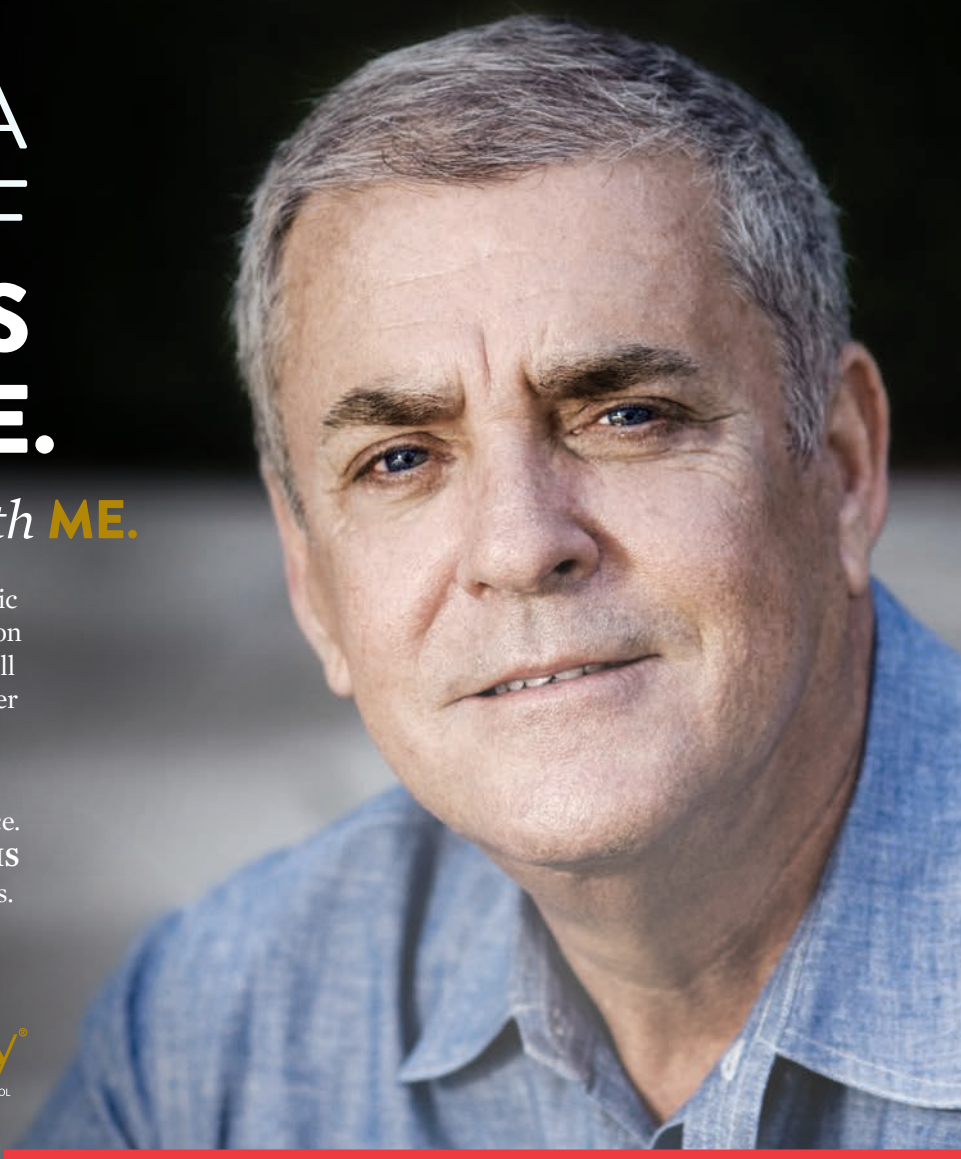

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