MAY 2017 # 09

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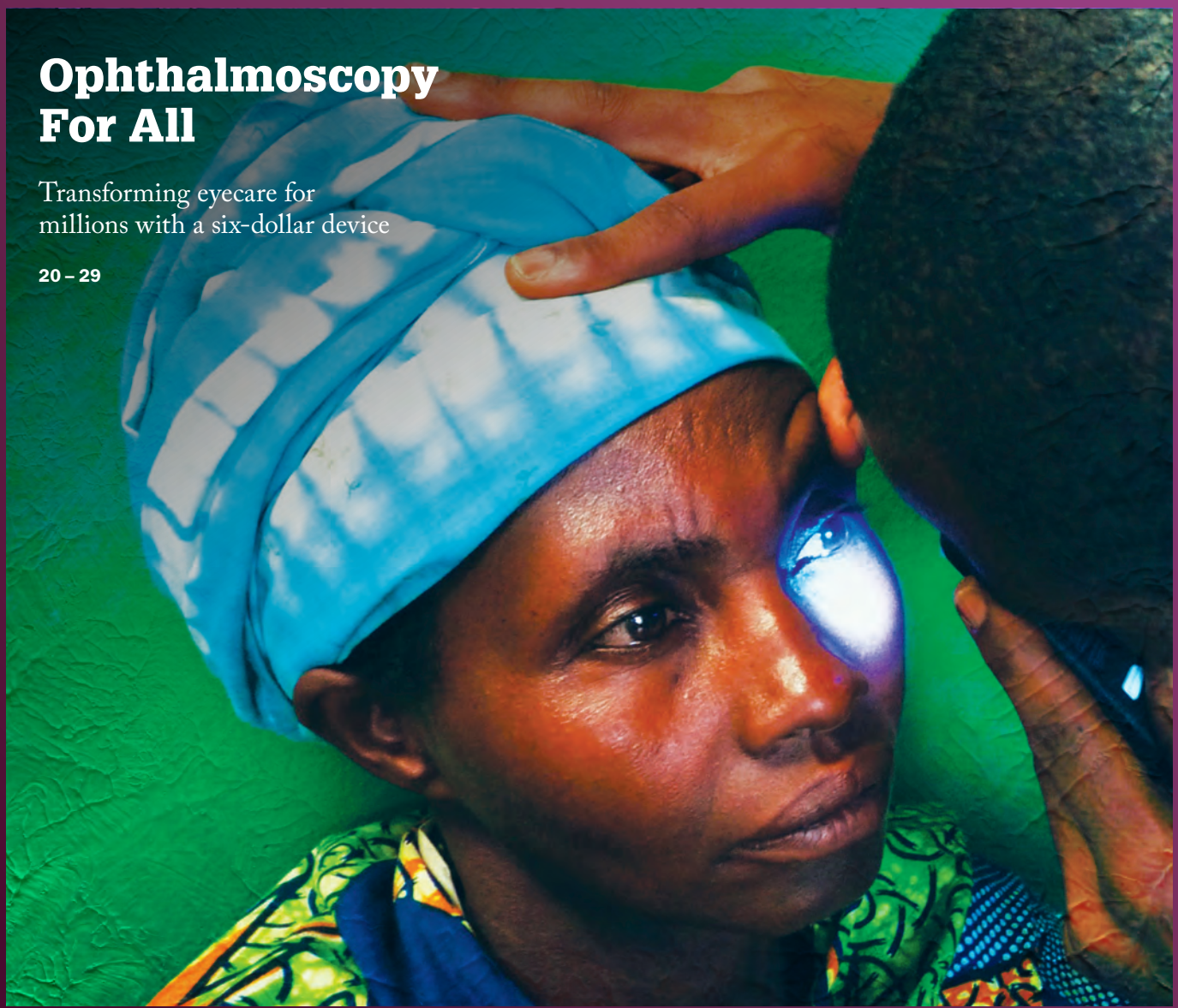

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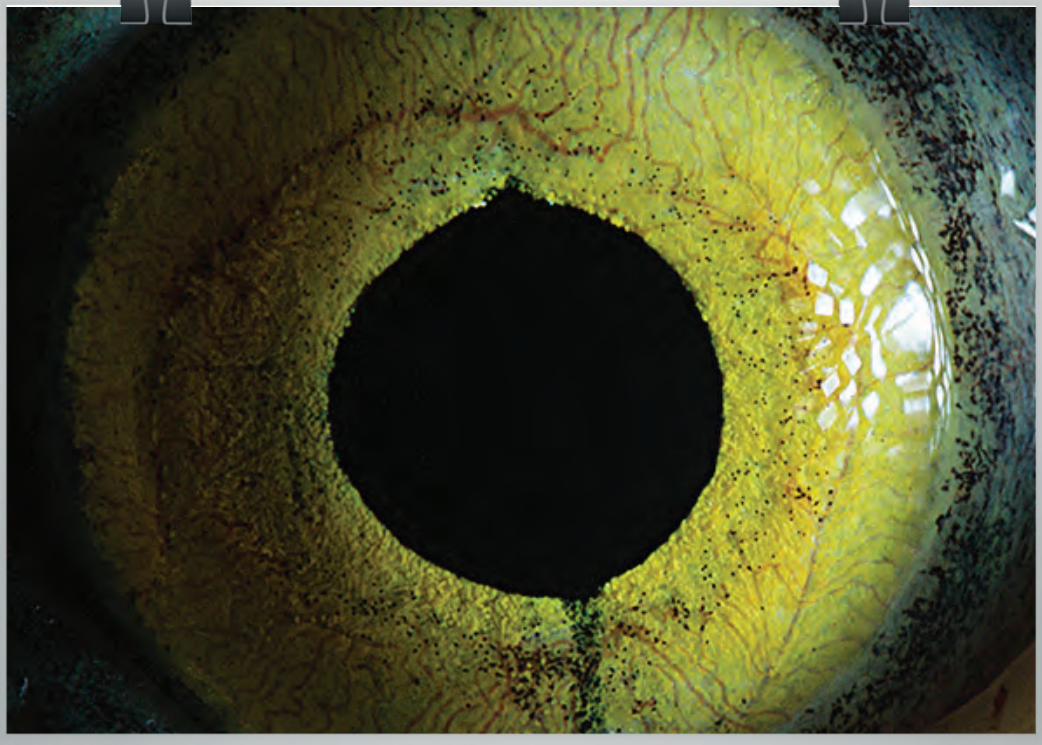
Image of the Month



Lizard Eye

Suren Manvelyan is a professional photographer with a wide range of photographic interests. This image is a close-up of a Basiliscus lizard's eye and is part of one of his latest popular series which features close-ups of human and animal eyes. Suren says "It is much more difficult to photograph animal eyes – you can't tell them to stay calm! I also need to be very close to the animal, which is why I have fewer eye photos from dangerous animals!" As well as photography, Suren also teaches physics, mathematics, projective geometry and astronomy, and can play five musical instruments.

Image courtesy of Suren Manvelyan, http://www.facebook.com/SurenManvelyan

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

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A health worker using the Arclight on a patient in Rwanda. Credit: Clare Morton.

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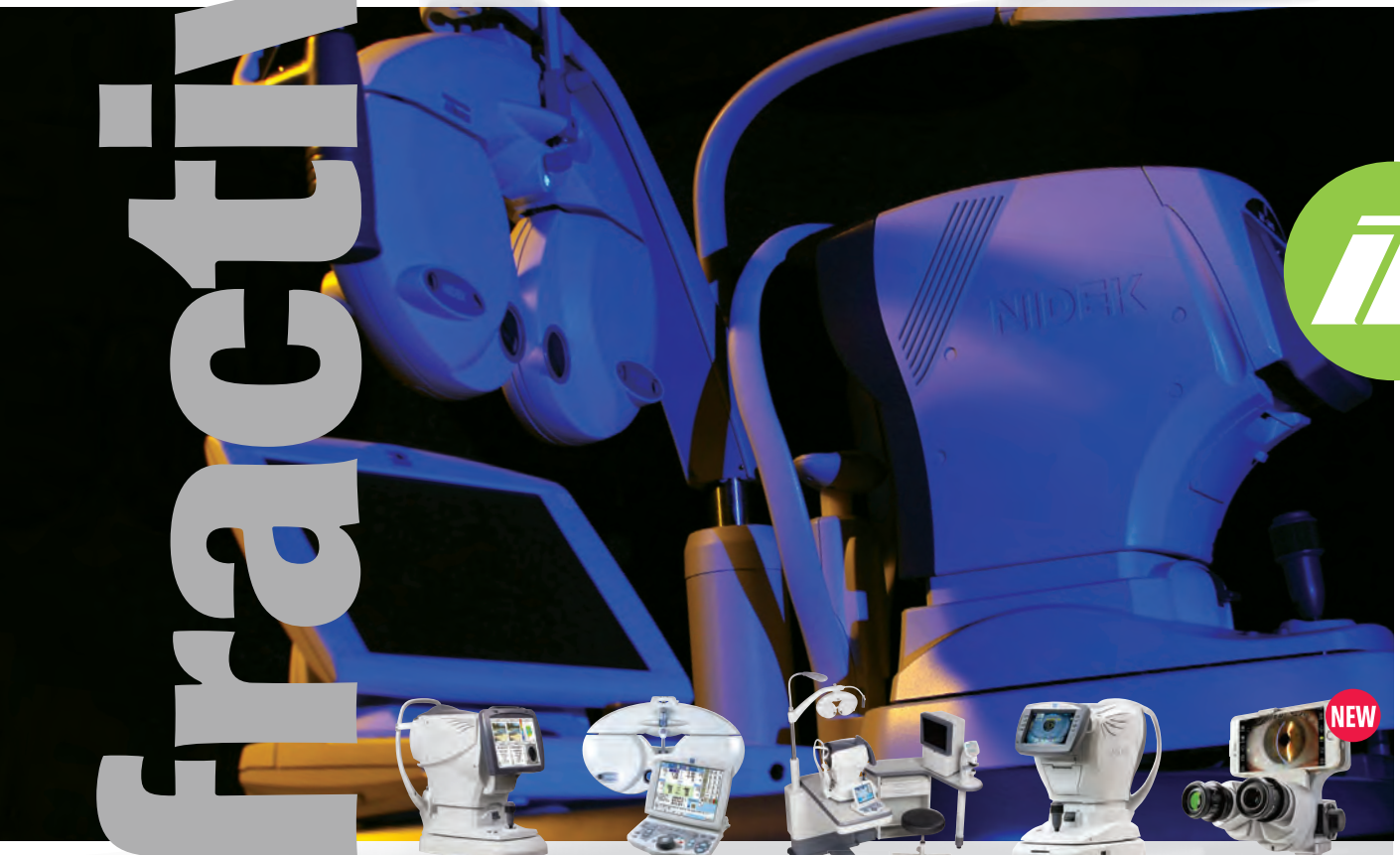

OPD-Scan III Wavefront

TRS Total Refraction Automation

EPIC Refraction Workstation

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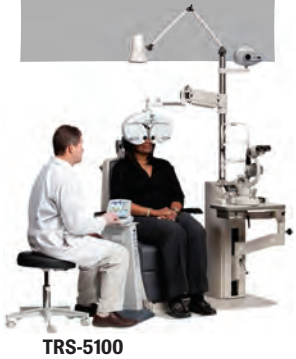
SOLUTIONS



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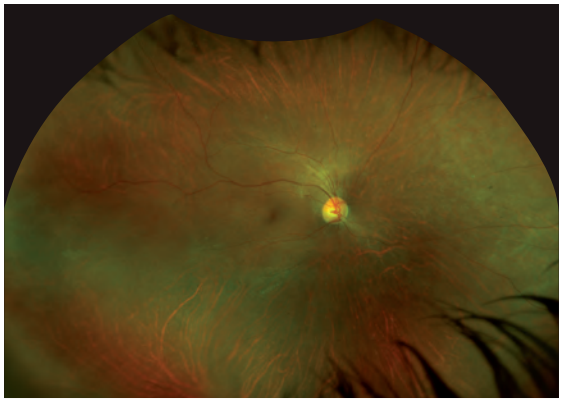
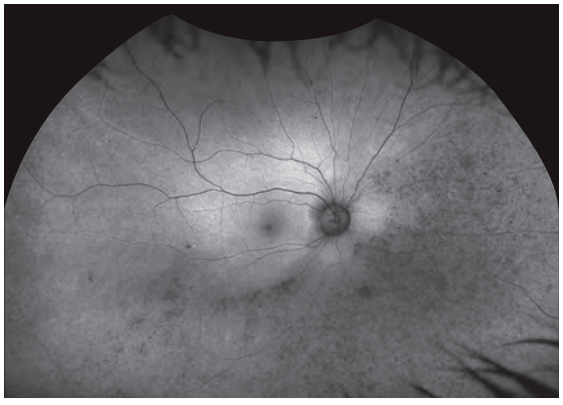


optomap ***plus*** Courtesy of SriniVas Sadda, MD



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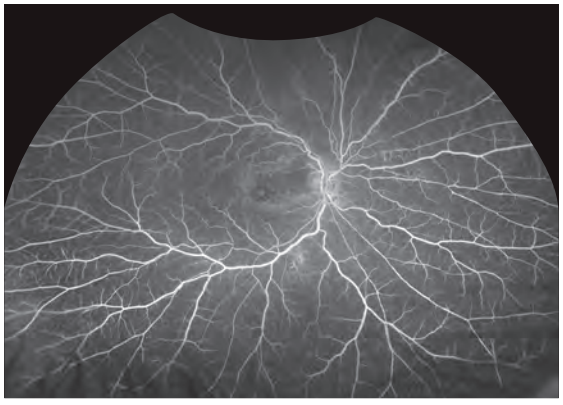
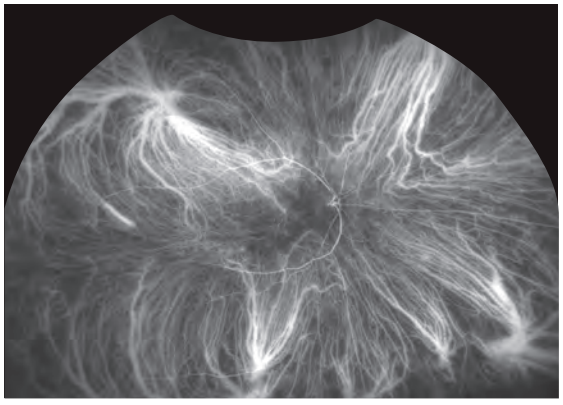


optomap ***fa*** Courtesy of Paulo Stanga, MD



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*"Seeing more of the retina provides greater insight, improves diagnosis and management. Without seeing, we cannot treat. Ultra-widefield **opto**map imaging has set the standard of care, it is difficult to imagine going back to standard fundus photography".*

Prof Paulo E. Stanga, Manchester Royal Eye Hospital, UK

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It's in Our Nature

Altruism in ophthalmology: it's never just "you scratch my back, I'll scratch yours."

The Maasai herders of the Serengeti plain in eastern Africa have a tradition called "osotua". It translates as "umbilical cord" and is a central component of their society – essentially, it is true altruism. Life is hard there; if disease, drought or even marauding bandits render a Maasai without livestock, they ask for help and know that their brother Maasai will support them – usually by offering livestock of their own. Crucially, nobody expects the gift to be repaid – there's no underlying agenda of "you scratch my back, and I'll scratch yours."

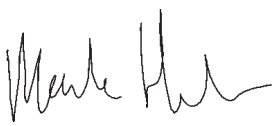
This month's issue features the stories of two highly altruistic endeavors – the story of the ultra-low cost solar-powered ophthalmoscope, Arclight, and Kevin Waltz's efforts to move away from simply performing cataract surgery in Honduras to building infrastructure to support the future. In both cases, ophthalmologists, scientists and engineers have been incredibly generous with their time and money – for people they've never met before – and it has life-transforming results. It represents altruism that's almost as pure as the Maasai.

Clearly, the development and manufacture of an ophthalmoscope with LEDs, small solar panels, rechargeable batteries and a USB charging port has to be paid for at some point – the cause might be charitable, but the company making the device won't be. In Kevin's case, even if the equipment shipped to Honduras is donated free-of-charge, transport is not. And the clinics that benefit from them require local staff who have rent to pay and families to feed. Such assistance cannot be achieved through the gift of a goat: it requires money. Thank goodness, then, for not only the doctors and technicians, but also all the companies and international societies that support this work with grants.

There can still be an element of quid pro quo – on-site surgeons clearly gain valuable experience, but I think there's more to it than that. Kevin talks of negotiating with a local ophthalmic equipment supplier to help support a piece of kit he's brought into the country in return for his team promising to buy certain consumables from them. But that's the reality: in this situation, you have to be practical, pragmatic, creative and ready to compromise to get things done. It's no easy task. So it may not be the same kind of sacrifice as the Maasai: giving away some of the livestock that sustains you and your family, but it can be just as big: your time, effort, resource and headspace.

I don't know about you, but that humbles me. To those of you involved in such endeavors: thank you.

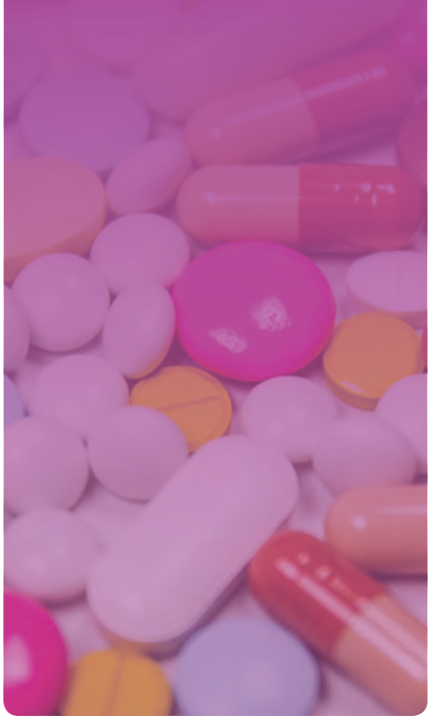
Mark Hillen
Editor



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



Turning the Tables

FDA outpaces the EMA on regulatory review and approvals

For some years, there has been a general (mis)perception that product approval is faster through the European Medicines Agency (EMA) than through the US Food and Drug Administration (FDA). But now, conclusive proof comes from a recently published study that compares the two agencies between 2011 and 2015: the FDA has outpaced the EMA in terms of review times and approvals of new therapeutic agents (1).

Here, we present some key results:

- The FDA approved 170 new therapeutic agents compared with 144 approved by the EMA.
- Median total review time for the FDA was significantly shorter than the EMA for all regulatory reviews (306 versus 383 days, $p<0.001$), as well as for the 142 therapeutic agents approved by both agencies (303 days versus 369 days, $p<0.001$).
- On average, FDA review times were 60 days shorter than the EMA's.
- The FDA approved a higher percentage of orphan drugs than the EMA (43.5 percent of all approvals versus 25 percent of all approvals, $p<0.001$).

The authors were driven to perform the analysis by the imminent expiry (October 2017) of the Prescription Drug User Fee Act (PDUFA) – a regulation that oversees the speed of the regulatory review process; Congress need to consider its reauthorization. Given that the findings are similar to those from analyses of the period 2001–2010 (2), the authors assert that their analysis "provides reassurance that the FDA continues to complete regulatory reviews more quickly than the EMA, and has the potential to inform discussions regarding the reauthorization of the PDUFA." *RS*

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Near, Not Far

Little has been done to discover how near vision impairment progresses in a population... Until now

Presbyopia correction is one of the largest untapped elective ophthalmic surgery markets. Given the fact that near vision impairment (NVI) – the most common early presentation of presbyopia – is estimated to affect 517 million people worldwide (1), you may be surprised that very little work has been done to characterize it over the years. NVI and presbyopia have a prevalence of 60 percent or higher in those aged 35 years or older – rising to 90 percent in those aged 70 years or older (2) – and are associated with worsening quality of life in both developed and developing countries (3). One country that particularly stands to benefit from characterization of NVI is China, where it is estimated that the number of people aged 65 or older will double in the next 20–30 years. To that end, Xiaotong Han and colleagues set out to characterize NVI incidence and progression in an adult Chinese population (4). Figure 1 shows what they did, and what they found. *MH*

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Who?
Adults aged ≥35 years at baseline

What?
Population-based prospective cohort study

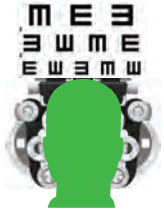
Where?
Yuexiu District of Guangzhou, China

When?
2008–2014

Why?
To estimate the progression of near vision loss in an urban Chinese cohort

Examinations

Noncycloplegic autorefraction



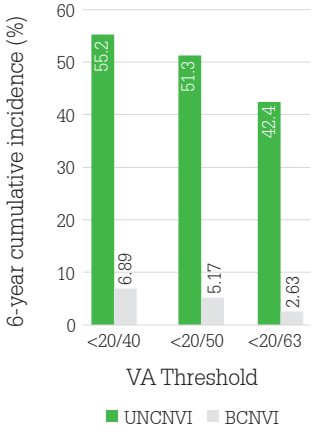
Binocular NVA ± near vision correction at 40 cm*

Outcome measures:

Year	n=	n/N (%)
2008	1817	100%
2010	1595	87.8%
2014	1427	78.6%

-1.5 lines (±1.74 lines)

Change in UCNVA from baseline to 2014 follow-up exam



6-year cumulative incidence of vision impairment at: ≤20/40, ≤20/50 and ≤20/63 thresholds.

Figure 1. Near vision impairment progression in a Chinese adult population over a six-year period.
*Those with uncorrected binocular NVA (UCNVA) ≤20/40 underwent subjective refraction to obtain best-corrected NVA (BCNVA).

"A" is for Anxiety

Research uncovers hidden sufferings in patients with neovascular AMD

Anti-VEGF agents have revolutionized the treatment of neovascular age-related macular degeneration (AMD). But recently published research has suggested that it is not always enough to treat the visual problem – many patients also suffer anxiety and depression that persist despite improvements in vision (1). Increased awareness of these "hidden" symptoms could help identify patients at risk – as could better communication between clinicians and patients.

Tariq Aslam is a consultant ophthalmologist at Manchester Royal Eye Hospital in the UK and lead author on the corresponding paper; when asked about the origins of the work, he recalls, "I was previously investigating a potential cutting-edge technology and was delighted to see that it helped maintain excellent vision for a patient. It was only during extensive discussions as part of the detailed trial protocol that I realized that this normally smiling and joking patient was actually suffering deep depression and psychological stress. We had helped her sight but had not appreciated her state of mind that possibly negated any ophthalmological benefits." Realizing that there was a lack of information in this area, Aslam and his team decided to investigate.

Enrolling 300 patients with neovascular AMD who had received at least one prior injection of an anti-VEGF agent, the group used surveys to collect data on patients' experiences and performed a variety of psychological assessments using validated questionnaires. They discovered that over half of the patients reported experiencing anxiety related to their treatment (Figure 1), the most common reasons being the fear of going blind and fear of treatment failure. Of the patients with clinical levels of anxiety and depression, a high proportion (~90 percent) were not receiving any appropriate psychological or psychiatric help. Aslam says, "The numbers of patients with undiagnosed and untreated depression and anxiety was of concern. I felt personally disappointed that I had not appreciated this before." Highlighting the lack of research into how patients with neovascular AMD experience treatment, he adds "stem cells, bionics and genetics can often be judged as more 'attractive', irrespective of demonstrating definitive benefits to patients or significant advancements to the field. Clinical research outside these areas must not be left behind and should be equally appreciated as it has the potential to deliver a strong and immediate impact to patients."

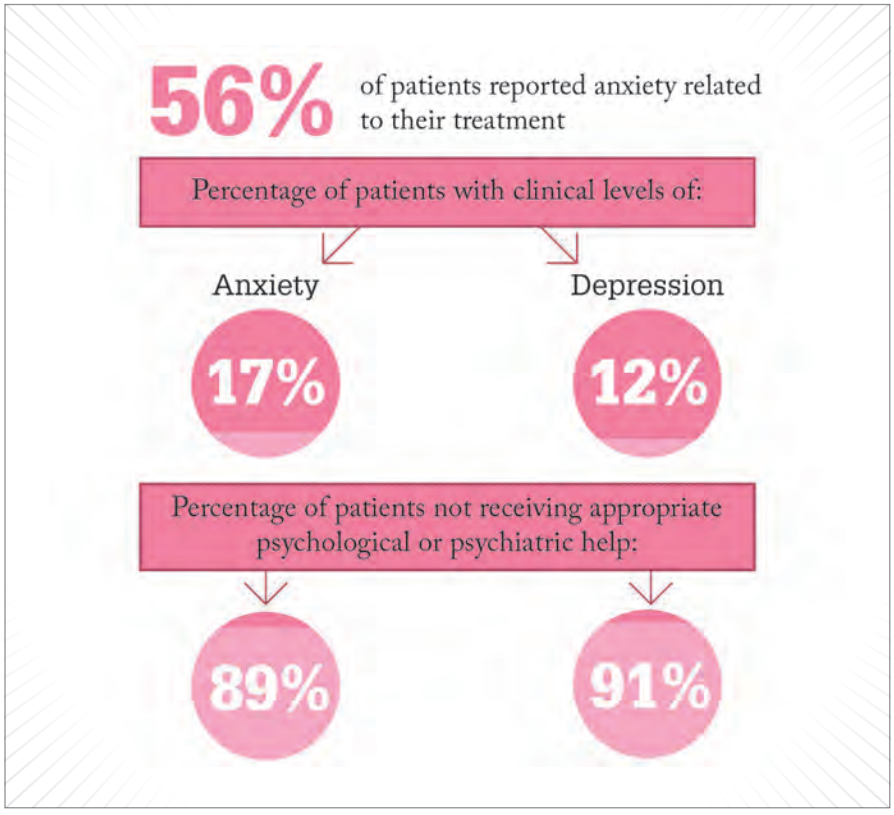


Figure 1. Key results from the study (1).

The group now plans to develop strategies to diagnose and manage anxiety and depression in patients, and then demonstrate their validity and utility in the clinic. In the meantime, he offers some practical advice: "Communication is important at all points in a patient's journey through treatment cycles. Anxiety is not necessarily inevitable and some of the causes could be simply resolved. Severe depression and anxiety can occur and limit a patient's quality of life irrespective of the vision improvements provided, so it is important that we work out ways to counter this within the constraints and pressures of busy practices." *RS*

Reference

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Body Clock Control

How a subset of retinal ganglion cells might be the answer to jet lag

Modern life comes with modern perils... International travel and night shifts both disrupt the circadian rhythm, which can lead to more serious health issues, such as depression and even cancer (1,2) in the longer-term. Circadian rhythm control stems from the suprachiasmatic nucleus (SCN) in the hypothalamus, which releases various hormones and neuropeptides to set the pace. But fine-tuning comes from the retina – specifically from intrinsically photosensitive retinal ganglion cells (RGCs) that convey light information directly to the SCN where the neurotransmitter glutamate is released (3). But it turns out that this isn't the whole story...

Now, a team of researchers has discovered another subpopulation of RGCs in rats that communicate directly with the SCN, signaling with the neuropeptide hormone vasopressin (4) – and are aptly named vasopressin-expressing RGCs (VP-RGCs). After showing that these cells project directly into the SCN, the team demonstrated that expression of Fos, a transcription factor implicated in the regulation of vasopressin synthesis, was significantly higher in VP-RGCs following light stimulation and that, in turn, light-evoked vasopressin release enhanced both the responses of SCN neurons to light, and the expression of *c-fos* in the SCN. The team reports, "Vasopressin, well known to be an important output of the SCN, is also a time-dependent mediator of light information from the retina to the SCN."

But what about jet lag? With previous studies supporting a link between vasopressin and circadian rhythm misalignment (5), the new findings further support the potential of vasopressin as a therapeutic target. Lead author Mike Ludwig says, "Our exciting results show a potentially pharmacological route to manipulate our internal biological clock. Studies in the future which alter vasopressin signaling through the eye could lead to developing eye drops to get rid of jet lag, but we are still a long way off from this." *RS*

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Looking at Listening

If you want to know if someone is empathizing with your tale, watch their pupils…

How can you tell if someone is really listening to you? Apparently, their pupils can reveal a lot of information – the most moving parts of your story or whether you are properly connecting with the listener, for example. Researchers Thalia Wheatley and Olivia Kang from Dartmouth College, New Hampshire, recorded videos of students telling an emotional personal story and used eye tracking to monitor pupillary dilation (1). The stories and speakers were then independently ranked in terms of engagement using only audio. Next, participants – also monitored with eye-tracking – watched the videos; Wheatley and Kang then compared listener pupillary response with the storytellers to determine periods of shared attention. They also investigated how listener pupillary response varied between highly expressive and less expressive speakers.

Highly empathic and less empathic listeners, as assessed by the Interpersonal Reactivity Index, all paid attention to the climax of stories, but the 'empaths' followed the story more closely. Notably, those speakers ranked as highly expressive were more likely to achieve pupillary synchrony with listeners. The findings add to previous work from the same duo, which found that pupil dilation patterns can show when someone is paying conscious attention to something (2). Together, the findings suggest that pupil synchrony can track shared attention between people.

"'The eyes are the window to the soul' is an ancient saying supported by many scientific studies linking pupil dilation and eye gaze to mental states, such as attention and intention. Here, we show that the eyes not only reveal the inner workings of one mind, but reveal when two minds connect," says Wheatley. *RM*

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Business in Brief

Acquisitions, approvals, agreements and a potential Alcon spin-off

- Beaver-Visitec International are to acquire the single-use ophthalmic instrument manufacturer, Malosa Medical.
- According to Bloomberg, Novartis are rumored to have hired Bank of America for an Alcon business review – and may pursue a spinoff, with Novartis' CEO Joe Jimenez quoted saying that the business is worth "$25–35 billion."
- Novartis have also licensed ECF843, a recombinant human lubricin, from Lubris LLC. Lubricin deficiency is observed in many patients with dry eye.
- Heidelberg Engineering (HE) acquired UK-based electronic medical records firm, Medisoft Limited, adding to its ophthalmic IT offerings. Medisoft will retain their UK headquarters, and HE's Arianna Schoess and Kfir Azoulay have joined Medisoft's board of directors.
- Allergan and Argentum have reached an agreement to settle a patent dispute over Restasis. The agreement gives Argentum the right to sell a generic version of Restasis before Allergan's patents on the drug expire.
- FDA approves ranibizumab for all forms of diabetic retinopathy, based on the results of the DRCR.net's Protocol S study, which compared ranibizumab injections with panretinal laser treatments for patients with diabetic retinopathy, some with DME, and some without.
- Imprimis licenses the Richard Lindstrom-developed chondroitin sulfate-containing topical dry eye treatment, Klarity eye drops, and signed a three-year exclusive sales agreement with Precision Lens, who will deploy a dedicated sales team to introduce Imprimis' ophthalmic portfolio into select geographies, principally 13 states in the US Midwest.

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 team at edit@theophthalmologist.com

Good Things Come to Those Who Wait

When performing pars plana vitrectomy to remove retained lens fragments, what's the rush?

By Caroline Baumal, Retina Specialist,New England Eye Center; Associate Professor, Tufts University School of Medicine, Boston, Massachusetts, USA.

Deciding on the timing of pars plana vitrectomy (PPV) to remove retained lens material following cataract surgery can be a balancing act. On one hand, the cataract surgeon and the patient may be expecting immediate results. On the other, we need to plan the removal of the retained lens fragments in a way that avoids potential complications. So how do you choose your timing?

In my experience, it is usually not necessary to perform same-day vitrectomy, and it may be preferable to delay the procedure – but this can mean different things for different patients. The evidence supports performing the procedure at a time that is individualized, taking into account patient, surgical and ocular factors, which allows us to optimize visual outcomes and reduce complications. Usually, this means waiting for the corneal edema to clear, which can be anytime from four or five days after cataract surgery to the next week or two. The good news is that the timing of PPV to remove retained lens fragments is not critical – and this has been shown in the literature.

The largest retrospective case series study published to date (1) evaluated 569 eyes: 117 had same-day PPV, and the rest were delayed. The results showed that both groups had similar outcomes with regards to visual acuity and complication rates. A meta-analysis (2), performed by my colleague Michael Stewart, evaluated 23 papers that compared same-day versus delayed PPV; they found no association between clinical outcome and the timing of PPV. There are a whole host of studies that reach the conclusion that timing is not critical (3–7). Problems reported with same-day and immediate PPV include increased rates of surgical complications, such as choroidal hemorrhage, and corneal decompensation, which may affect visualization of lens pieces. In addition, there are practical issues, such as informed consent, transport to another OR (or another facility), and the possibility that a retinal physician won't be available when you need them.

> *"There are a whole host of studies that reach the conclusion that timing is not critical."*

There are some mixed results in the literature, but this is because many studies are retrospective, non-randomized, and have variations in the procedure and the surgeon performing it. There's often limited information available about any complications that occurred during the initial cataract surgery, which might ultimately be

the cause of the final visual outcome.

It is critical to refer the patient promptly to a retinal surgeon, either on the day of the event or the following day; the retinal surgeon is best placed to assess whether there are any posterior complications that need to be addressed immediately – or if the PPV can wait. As for my advice to the retinal surgeon? I would suggest that they anticipate a rise in IOP, corneal edema, inflammation/cystoid macular edema, and wound and lens instability, and prophylactically treat for high IOP and inflammation. Do a controlled assessment of complications, optimize your visualization, and obtain informed consent. By tailoring the timing to the patient, you have the best chances of achieving a good outcome.

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Timing Is Everything

The timing of vitrectomy for retained lens material is important – but not in the way you might expect...

By Michael W. Stewart, Professor and Chairman of Ophthalmology, Mayo School of Medicine, Jacksonville, Florida, USA.

The optimal timing for the removal of retained crystalline lens fragments from the vitreous following complicated cataract surgery is still controversial. Some retinal surgeons believe that removing the fragments on the day of cataract surgery is the best approach, while others believe it is unnecessary to operate this quickly. Same day vitrectomy can interfere with the surgeon's ability to obtain informed consent from the patient and could increase the rate of complications, and in cases where a retinal surgeon is not immediately available, same day removal is not possible.

"In my opinion, the timing of retained lens fragment removal is time sensitive."

In my opinion, the timing of retained lens fragment removal is time sensitive – just not in the way most physicians might think. Outcomes following retained lens fragment removal first appeared in the literature as the adoption of phacoemulsification became more widespread (1). Results from the initial reports were somewhat disappointing but visual acuity (VA) results improved slowly over time (2). Some reports suggested that immediate vitrectomy appeared to reduce the risk of secondary glaucoma and retinal detachment (3), but superior VA improvements were inconsistent (4), and the discovery that medical management was possible in small, carefully selected groups of eyes only further complicated matters (5). Finally, the largest retrospective non-randomized cohort showed only a minimal trend to better vision following vitrectomy within the first week (6).

Faced with hundreds of studies that produced inconsistent and conflicting data, we decided to dig deeper for answers regarding the timing of vitrectomy by posing the following research question: what does the entirety of the literature actually tell us? To answer this we performed a systematic review of the literature followed by a three-step statistical evaluation that included two meta-analyses. The first meta-analysis sought to determine the effects of delayed vitrectomy, and we found that early vitrectomy performed within three

to 14 days after complicated cataract surgery decreased the risk of developing visual and anatomic complications (7). Mathematical modeling showed that the likelihood of patients remaining complication-free decreased with time to vitrectomy. But surprisingly, the review also suggested that performing a vitrectomy from days zero (same day as cataract surgery) to two resulted in worse vision – something that conflicted with our own institutional experience.

We then analyzed our own 10-year data and found the opposite result – immediate vitrectomy resulted in improved long-term vision and less glaucoma progression (8) when compared to delayed vitrectomy.

Finally, we performed a second meta-analysis that compared immediate vitrectomy with delayed vitrectomy, and determined that immediate vitrectomy is comparable to a three- to 14-day delay, but superior to a zero (but non-immediate) to two-day delay, and a 14+ day delay (9).

Our work, therefore, suggests that the optimal timing of vitrectomy for retained lens material is actually bimodal – the best times are either immediately, or between days three and 14. So if immediate vitrectomy isn't a viable option, all is not lost as there is still time to achieve an optimal outcome.

The author reports no relevant financial disclosures.

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Rehab for Third Party Addiction

You may not believe this yet, but you do have options to regain control and enjoyment of your practice while remaining financially solvent

By Jane Lindell Hughes, ophthalmologist and ophthalmic surgeon at Jane Lindell Hughes M.D., F.A.C.S, San Antonio, Texas, USA.

On November 1, 2015, I divested myself from all commercial insurance and became an "out-of-network" physician. The reasons were many, but the final deciding factor was the threat of financial harm to my patients with a "punitive brand name drug charge" versus the "appropriate brand name drug charge" unless I sent a form attesting that I had tried two generics that then failed in my covered glaucoma patients. This insurance company was using payment for services as a means of controlling my professional behavior without any of the risk or responsibility for the patient's outcome!

I will address Medicare strategies later, but first commercial insurance – and understanding how we got here. With employer purchase of insurance, bundles of patients are handed over to the lowest insurance bidder for any fiscal year: I served two terms as a Trustee for a large school district and saw first-hand this yearly churning of insurance policies. The insurance companies' provider contracts demand at least 20 percent discounts to the physician's usual fees by threatening loss of access to "X" number of potential patients. Comparing the discounted fees with Medicare, many signed "on the dotted line" for the commercial contract. But these contracts self-renew unless you give notice, meaning that over time little attention has been paid to the slowly increasing intrusions of the third party payers. It is therefore crucial to educate yourself on the time and resources you and your employees spend processing

requests for generic substitutions, pre-authorizations, proof of insurance and deductibles, as well as requests that make you uneasy. Do this for a week and log daily results. Have your office manager pull 20 frequent procedures and office visits to compare Medicare payment rates with all of your commercial payers. You may be surprised to find that many commercial payers are paying less than Medicare for some of your codes, but it is difficult to detect; payments come in bulk, deductibles are different, and previous payment rates for the same service are not readily apparent. Your results should motivate you to become an out-of-network physician rather than subsidize insurance companies.

"The CMS itself said 49 percent of doctors will be financially hurt with MIPS payment system – choose not to be one of them."

How best to achieve this? Pre-planning is crucial – and getting your employees on board will ensure as smooth a transition as possible. Any change is stressful, and although one need not take the leap with all insurance at the same time, I found it eliminated a "gray area" because all of my patients were charged the same fee regardless of their insurance. I posted my fee schedule on my website, included it in letters to my patients to notify them two months ahead of the change, and scripted how I wanted our new policies to be presented on the phone and in person.

We reassured our patients that we would continue to file for them (no increase in overhead as I was already electronically filing), and that they could expect a 50–60 percent reimbursement. Interestingly, many people found that it cost little more to pay me compared with using their insurance because of the high deductibles and co-pays. The most difficult job is to devise your own fee schedule. I looked at Medicare payments, commercial payment averages, and the Wasserman Physician's Fee Reference that lists the 50th, 75th and 90th percentile fees for all codes across the country. I then used this information to decide what I felt was an honest and fair fee based on resources utilized, complexity and average cost.

So, how did this work out? There was a definite temporary drop in my schedule volume, which took about six months to rebound as we filled it in with new patients who understood our practice model and agreed with my rationale for changing. There was not a month where I did not make a profit – and that was without adding new procedures or aesthetics – and the number of fax requests has dropped to almost zero, even when I write branded prescriptions. It has taken cheerleading of the team along the way to reassure them that we are building a better practice, but I stressed that our model would withstand almost anything the political environment threw at us, because it is ideal for high deductibles, cash pay and health savings accounts.

On to Medicare. I believe that every physician in the US should become a non-par provider, which means the patient pays you at the time of the visit, you file, and they get reimbursed, usually within 21 days. You have the option of accepting assignments as needed on a case-by-case basis, which does several things. Over-utilization drops significantly, and patients (and you!) become better stewards of Medicare dollars as the discussions turn from whether or not insurance pays for it to rather how much it costs and why is it needed. Finally, you get paid 9.25 percent more than the participating provider – CMS.gov will show you the figures. This extra 9.25 percent allows you to implement the final step towards returning joy to your practice – ignoring MACRA and all of the impossible mandates like electronic medical records and the Physician Reporting Quality System for the potential "reward" of a 9 percent bonus or 9 percent punishment under the ridiculous Merit-Based Incentive Payment System (MIPS). Be proud of your zero rating! The CMS itself said 49 percent of doctors will be financially hurt with the MIPS payment system – choose not to be one of them. A Cornell-Weill Medical College study estimates the cost of compliance per physician per year to be $40,000 (1). In other words, you would need approximately $450,000 Medicare baseline revenue to recover your $40,000 investment with the 9 percent reward.

In closing, we are at a time in American medicine with a great opportunity for constructive change to the distortions to our healthcare system. By divorcing yourself from third party contracts and becoming a non-par Medicare provider, you will optimally position your practice for the future and rediscover the enjoyment of your practice.

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OPHTHALMOSCOPY For All

How one team is on a mission to transform eyecare with simple yet clever engineering – and a focus on low cost

By Ruth Steer

In a bid to provide affordable technology to resource-poor countries, the humble ophthalmoscope has had a makeover – or rather a 'makeunder.' With a simplified design, a patented LED light source and a solar panel, the Arclight is a pocket instrument the size of a marker pen and lighter than an AA battery. The device is significantly lower in cost than the traditional ophthalmoscope – and its potential to serve those who need it most was quickly recognized by global health leaders. More than 8,000 devices have been distributed across the world – with the International Agency for the Prevention of Blindness (IAPB) based in London, UK, helping with marketing and sales to many countries including Malawi, Ethiopia, Fiji and Indonesia.

But the device isn't just for eyecare. It also features an otoscope and a magnifying loupe, making it a valuable multi-tool for general physicians across specialties – as well as a handy teaching instrument for medical students. The ultimate goal? To make ophthalmoscopy more accessible to all, and to transform care in low and middle-income countries. John Sandford-Smith, Andrew Blaikie and William J Williams share the story behind the Arclight…

Making a Difference Globally

"The story has not yet fully been told."

By John Sandford-Smith

I've always been interested in the challenges of developing country ophthalmology and avoidable world blindness. Before becoming a consultant ophthalmologist at Leicester Hospital in the UK, I'd had a rather unusual career spending nine years overseas in Pakistan and Nigeria. I'd seen first-hand the totally different disease spectrum in the developing world; vitamin A deficiency, post-measles keratitis, onchocerciasis, trachoma and fungal keratitis (to name a few of the worst) were all extremely common in some areas and you just wouldn't see them in many developed countries. The burden of preventable and treatable eye disease was also huge. Reflecting on this, I realized that there was no available resources for working and teaching in developing countries, which stimulated me to write two textbooks ("Eye Diseases in Hot Climates" and "Eye Surgery in Hot Climates"). Over the years, I ended up spending three to four weeks each year in different countries, so I kept my focus on the problems in the developing world. In 1997, I was working in a hospital in Gondar (Ethiopia) and, as far as I could discover, there was only one ophthalmoscope in the entire teaching hospital – one that served around 10 million patients! Outside of the teaching hospital, there wasn't any quality eyecare at all. "Something needs to be done about this," I thought.

> "There was only one ophthalmoscope in the entire teaching hospital – one that served around 10 million patients!"

A good friend of mine, the late Alexander (Sandy) Holt-Wilson, had also spent time in Gondar and realized there was a desperate need for a basic low-cost ophthalmoscope, so together we started to hunt for one. Guided by an article by Roger Armour on the manufacture and use of homemade ophthalmoscopes in the Christmas edition of the BMJ (1), we had discovered a person who was making homemade

Introducing the Arclight

- The device measures 4.3 × 1.0 × 0.35" (110 × 26 × 9 mm) and weighs 0.63 oz (18 g).
- Features: solar panel, LEDs (warm-white, daylight white, blue/violet), ×4 magnification loupe, lenses and filters, near VA chart, specula (4.5 mm and 2.5 mm), USB port.
- The device is available to low-income countries from ~$6/£5 per unit through the IAPB. It is also available in the UK and Europe from the University of St Andrews online shop.

"Providing simple, robust, easy-to-use medical equipment to those who really need it is where the biggest changes must occur."

Arclights charging in the sun.

ophthalmoscopes with cardboard rolls and mirrors. Following some encouragement from us, he secured some funding to develop a lower cost device, but unfortunately the end result was still too expensive at around £65 (~$80).

We continued our hunt and finally met William J Williams, a bright young optometrist with an interest in electronics and design. He'd patented the idea of using LEDs rather than filament bulbs in ophthalmoscopes and had the idea of using solar panel charging. Listening to advice from several of us, William further developed his ideas and the Arclight was born (See Box "Introducing the Arclight").

Sandy was good friends with Richard Le Mesurier, Medical Director of the Fred Hollows Foundation, and he too became very interested in the device. The Foundation gave William £100,000 (~$125,000) to develop his prototypes. They wanted 5,000 devices and, much to their surprise, William developed everything and produced them. Andrew Blaikie (one of my juniors in Leicester) became intrigued by the device; and his clinical studies have shown that many find the Arclight just as good as the much more complex conventional direct ophthalmoscope

So far, the device has had the biggest impact in the developing world. When we submitted our recent article to the BMJ (2), we received a mix of referee comments, but one of the positive reviewers had themselves visited an eye department in Nigeria and seen that doctors were queuing up to use the one – and only – ophthalmoscope. She realized the potential impact of handing Arclight devices to everybody... Providing simple, robust, easy-to-use medical equipment to those who really need it is where the biggest changes must occur. I also hope that the device will have an impact on medical students. Throughout 2015 and 2016 there was an ongoing debate published in Eye about whether ophthalmoscopy should even be taught to students. More than a handful of people thought it shouldn't; the direct ophthalmoscope has rather gone out of favor as other technologies have 'superseded' it. They argued that patients with eye problems should be referred rather than examined, which I thought was a rather defeatist attitude. If we boost training so that medical students are more confident in performing ophthalmoscopy and diagnosing basic problems in the eye, I believe it would be a very positive step forwards for medical school training – as well as the health service.

The Arclight is an interesting story, but the story has not yet been fully told. Right now, we have various ideas in the pipeline; William wants to make some improvements to the device and we're planning to include in-built memory with educational content. Given that there is such a need for training people at a grassroots level in Africa, I've been working with another group here in Leicester to produce a multimedia training program about how to manage eye disease. It's currently available on DVD and online, but loading it onto the Arclight will give people a mini textbook guide – all in this little device that fits in their shirt pocket.

I am excited that I have been a small piece in the jigsaw. The key player is William; he has done everything himself – designing, prototyping, developing, sorting out the patents and CE marking, and visiting manufacturers in Hong Kong and China. He's done so much – he's really interested in making a difference globally.

John Sandford-Smith is an emeritus Consultant Ophthalmologist at Leicester Royal Infirmary. He is a widely-respected expert on eye diseases and has been extensively involved in teaching, training and voluntary work, both during his career and since his retirement in 2000. In 2007, he received an MBE for services to blind people in developing countries.

Richard Le Mesurier holds the IAPB Western Pacific Chair, and is the Fred Hollows Foundation Medical Director. He has huge worldwide experience – from Africa to the Pacific – with an interest in trachoma, cataract surgical training, and medical innovation.

The late Alexander (Sandy) Holt-Wilson was a Consultant Ophthalmologist, and founder and chairman of the charity: Gondar (Ethiopia) Eye Surgery (GEES). GEES supported Gondar University and also the emerging Optometry school. He was pivotal in linking people and groups together.

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Getting the Idea Out There

"I am a consultant pediatric ophthalmologist and it's my 'go-to' ophthalmoscope – I always have one in my pocket in the clinic!"

By Andrew Blaikie

I was mentored in my first ophthalmology job in Leicester, UK, by John Sandford-Smith, a much-respected ophthalmologist in the international and low-income setting. I always kept in touch with John, even after he retired, and several years later, he introduced me to William J Williams who'd had an idea for a low-cost ophthalmoscope using LEDs instead of filament bulbs. We chatted and I forwarded on different bits of old equipment he could take apart and play with.

Because William likes to keep his head down and out of the "limelight," John and I have been supporting him over the past few years in developing, evaluating and promoting the device along with several other key people. Contact with the Fred Hollows Foundation, in particular with Richard Le Mesurier, brought seed development money to move to a production version. Through my position in the University of St Andrews Global Health Team, I've been well placed to evaluate the device, and present and publish work related to the device. This has led to greater awareness and interest in the Arclight.

International and educational outreach

So far, I've supervised a number of different studies evaluating the device in both Malawi and in the UK, and the results so far have been very positive (1–4). The Arclight is at least as good as traditional devices, and better in some ways. It's now listed as one of the IAPB's recommended devices for use in low and middle income settings. One of the major ongoing projects is a large screening exercise of children aged 0–3 years in Uganda and Kenya, which is being driven by the charitable group Sense International. In this, nurses who are on immunization screening programs use the Arclight to screen for media opacities. The program runs until 2019, and will assess the impact of early intervention in infants with vision impairment from cataract and retinoblastoma (5). Similar work is on-going in Tanzania through the International Centre for Eye Health based in London. The Fred Hollows foundation is also currently using the device to screen for trachoma in Ethiopia.

Although improving eyecare in low income and rural settings was the main aim, the device is useful for nearly all physicians. I am a consultant pediatric ophthalmologist and it is my "go-to"

"It's exciting to be involved in the development, evaluation, and promotion of a revolutionary and groundbreaking device."

The device can be worn around the neck or carried in a pocket.

ophthalmoscope – I always have one in my pocket in the clinic! I've found the magnifying loupe and bright white light extremely useful for examining the anterior segment of babies or small children as you get a very clear view up close. ENT specialists find the device handy in their day-to-day care, and dermatologists like the blue light because it helps highlight certain skin lesions. In the future the aim is to add polarizing filters to the blue light to improve its skin lesion diagnostic capabilities. We have a dermatology colleague trialing a prototype in the field at the moment in Ethiopia.

The device is also useful for teaching – it's an excellent tool to get medical students interested in ophthalmology and fundoscopy (6). Textbooks might feature nice high-resolution, wide-field images of the back of the eye, but in reality ophthalmoscopy is a tricky technique. The field can be small, there are aberrations, and the view can "jump around" and shift in and out of focus. Many medical students have no idea what the back of the eye really looks like through an ophthalmoscope, but attaching the device to a smartphone allows them to see what direct ophthalmoscopy should look like. I've been really impressed with the impact of this approach – because students can understand what they are trying to see, they are much more confident at performing ophthalmoscopy. The small size of the device also makes ophthalmoscopy more accessible; physicians carrying the device around their necks or in their pockets might be more likely to perform regular examinations – in turn increasing their confidence and accuracy. It's important for physicians to be looking at the back of the eye, and if our device can help more doctors do this routinely, I would hope implicitly that this would lead to better healthcare.

The next generation

Right now, as well as being available to low-income countries through the IAPB website, the Arclight is on sale in the UK and Europe via the University of St Andrews online shop. With only seven percent of that revenue going to overheads, 93 percent of the cost goes directly back into distribution, promotion and development of the device in low and middle income countries – Malawi in particular. The School of Medicine in St Andrews and the College of Medicine in Blantyre (Malawi) as well as the eye department in Fife (UK) and the eye department in Lilongwe (Malawi) are twinned, and combined with the historical relationship between Scotland and Malawi, we hope the social business developing around the device will be an important part of the Arclight story. We are also hoping to make the device available to physicians in North America very soon.

The next iteration of the device should become available later this year, and will feature a programmable switch for greater control over the light settings. It will also include an internal memory chip loaded with teaching and educational material explaining the use of the device, clinical signs to look out for, and suggested treatments and referral pathways for ophthalmic and ENT conditions. We see this as an important tool for rural or field settings as the information can be accessed anytime offline using a micro USB cable and a basic smartphone.

Looking further ahead, there are more tools in development that will be also be ultra-low cost, compact and solar powered. There will also be a number of software developments to maximize the diagnostic potential of the devices, and we are actively working with the computer science department here in St Andrews on a few fascinating eye-related projects…

It is gratifying to see the impact that the device has had so far. It's exciting to be involved in the development, evaluation, and promotion of a revolutionary and groundbreaking device. I hope it will continue to have a big impact on blindness and deafness prevention in countries where the access to diagnostic tools is least and the burden greatest.

Andrew Blaikie is a Consultant Pediatric Ophthalmologist in NHS Fife, and senior lecturer in the School of Medicine of the University of St Andrews, Scotland, UK.

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Bringing the Idea to Life

"With a popsicle stick, an LED and some willing volunteers – including a cat – I was onto something."

By William J Williams

I've always been amazed by 'pound shops' – how can things be manufactured, packaged and shipped around the world with middlemen and mark-ups and still be so cheap? Combining a knowledge of optics and electronics, I figured I could create something low cost too. With zero thoughts about business plans or world blindness – it was just a fun weekend challenge to simplify the ophthalmoscope, making it lighter, cheaper, and maybe even better.

The laws of direct ophthalmoscopy optics don't change, so my first approach was to strip out almost every feature on scopes that are designed to last a career, so that all it could 'do' was ophthalmoscopy and nothing else. LEDs are bright and very small, and can be mounted directly below the sight hole facing the patient; removing the mirror and optics allows the device to have a slim profile, letting users hold it close to both their own and the patient's eye for a clear dust-free view (Figure 1). The first prototype – which took 10 minutes to make – was a plastic popsicle stick with a hole and an LED. I tested it on a young cat, then a dog, a child, a middle-aged person, then a pensioner – in order of ascending eye and pupil viewing difficulty. A wooden size and shape mock-up followed. With the basics sound, better prototypes came, adding in solar power and USB charging (Figure 2). Later, I fitted a loupe lens, realizing that with a bit of adjustment, it made a highly maneuverable otoscope.

"Simple, low-cost, easy-to-use scopes let users make quick on-the-spot common pathology diagnoses."

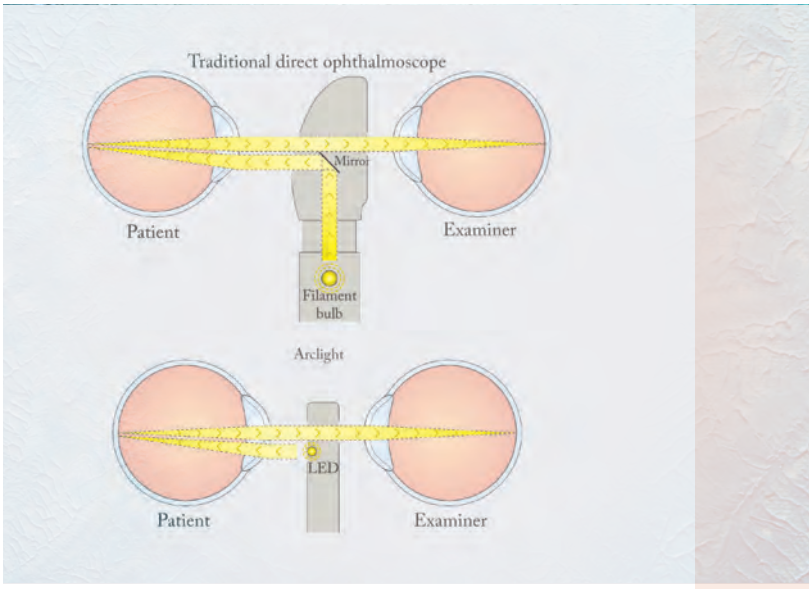

Figure 1. Light path of a traditional direct ophthalmoscope and the simplified light path of the Arclight. Credit: William J Williams.

Throughout the process, I've had to be a bit of a "jack of all trades" – learning computer-aided design, injection molding, ultrasonic welding, as well as web and graphic design. With no committees, I could be nimble – and use a common sense "keep it simple" mantra with engineering. The decision to move from prototype to product came from listening to the wisdom of ophthalmologists, such as John Sandford-Smith and Richard Le Mesurier who have huge global experience and were convinced that there was a crying need for this device, especially in Africa. I was also fortunate to be linked early on with the IAPB who also saw its potential.

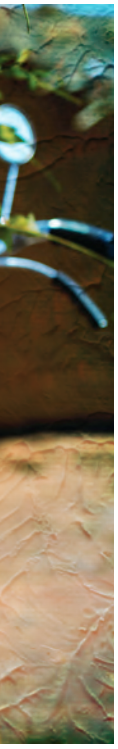

Figure 2. a. Wooden mock-up version of the Arclight. b. Prototypes of the device with additional features. The prototype at the top is the original prototype created from a popsicle stick.

The device is already having a positive impact – and that's great – but we've only scratched the surface. Health workers need a package with education posters and vital hands on instruction, model eyes to practice on, as well as ongoing mentorship. Implementation in developing countries is the "nut to crack" – easy to say and hard to do. Here in the UK, I use the device every day. It is particularly useful with children, as it is less "scary" and medical looking than the traditional ophthalmoscope.

The basic format of the device has leant itself nicely to new add-ons: a smartphone clip (that costs pennies) for images and videos, a polarized dermascope attachment, and a "lenser" beam concentrator for hands-free ENT inspection with a simple headband.

Our view is that simple, low-cost, easy-to-use scopes let users make quick on-the-spot common pathology diagnoses – ideal for patients and the wider community in remote areas, and also the health worker's own confidence and knowledge. Telemedicine imaging has its place, and can be part of the mix for teaching and opinions on rarer cases.

You won't be surprised to learn that I'm now applying the same design concepts to more eye and ear devices...

William J Williams designed the Arclight, and is Director of Arclight Medical. He is an Honorary Research Fellow at St Andrews University, and an optometrist based in Liverpool, UK.

John Sandford-Smith reports no conflicts of interest relevant to the content of this article. Andrew Blaikie reports that he is seconded to the University of St Andrews from NHS Fife. The University owns a social enterprise subsidiary company, for which Blaikie acts as an unpaid adviser, which sells the Arclight to users in the UK & Europe with profits being used to fund distribution and education exercises of the device in low income countries via the Global Health Implementation team at the University of St Andrews. William J Williams is Director of Arclight Medical.

Credit for Arclight images: Andrew Blaikie, William J Williams and Clare Morton.

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With fast visual recovery and grafts that can be harvested from almost any age group, PDEK's a compelling keratoplasty option. Here's how to do it.

By Amar Agarwal

For the last few years, when it comes to treating corneal endothelial disorders with endothelial keratoplasty (EK), the debate has mostly been about whether to perform Descemet stripping endothelial keratoplasty (DSEK) or Descemet membrane endothelial keratoplasty (DMEK) (or their automated counterparts, DMAEK and DSAEK). The consensus is that DMEK is the more technically challenging of the procedures – but it does provide better visual outcomes. Rather than replacing the diseased DM-endothelium complex with posterior stroma (as with DSEK), you're replacing it with healthy donor DM-endothelium (1,2). However, the DMEK graft from young donors is more elastic, flexible, and difficult to harvest – and it tends to curl up slightly, making it difficult to unfold and position once inside the recipient's eye. This along with the fact that it has a greater corneal curvature, means that most surgeons prefer to use donor corneas from those aged 40 years or older.

In 2013, Harminder Dua was the first to describe a pre-Descemet's layer (PDL) of collagen, present between the corneal stroma and DM (3), and we have used this knowledge to produce a new EK variant: pre-Descemet membrane endothelial keratoplasty (PDEK). PDEK involves the separation of the PDL and the DM-endothelium complex from the residual donor stroma by the formation of a Type 1 big bubble (bb; 3,4) – see Figure 1. The presence of the PDL makes the injection and bubble creation essentially as easy to perform as regular DMEK and should help avoid accidentally creating a Type 2 bb (5). PDEK has a number of advantages over previous EK methods: not only does it permit the use of younger tissue (dramatically increasing the potential donor pool), it also yields tissue that typically has a far greater endothelial cell density than typical DMEK grafts. The result should be a faster resolution of post-procedural corneal edema and improved graft longevity relative to DMEK-prepared grafts (4,5). So how is it performed?

At a Glance

- *Worldwide, there's a donor cornea shortage – but technical and handling reasons mean most surgeons won't use a DMEK donor cornea younger than 40 years*
- *PDEK is a DMEK-like procedure that offers DMEK-like outcomes – but can use younger corneas – even those of infants*
- *It exploits the presence of the pre-Descemet ("Dua's") layer and uses a Type 1 big bubble to separate the PDL and the DM-endothelium complex from the residual donor stroma*
- *The younger tissue used in PDEK also has the advantage of increased endothelial cell density – meaning longer graft survival times*

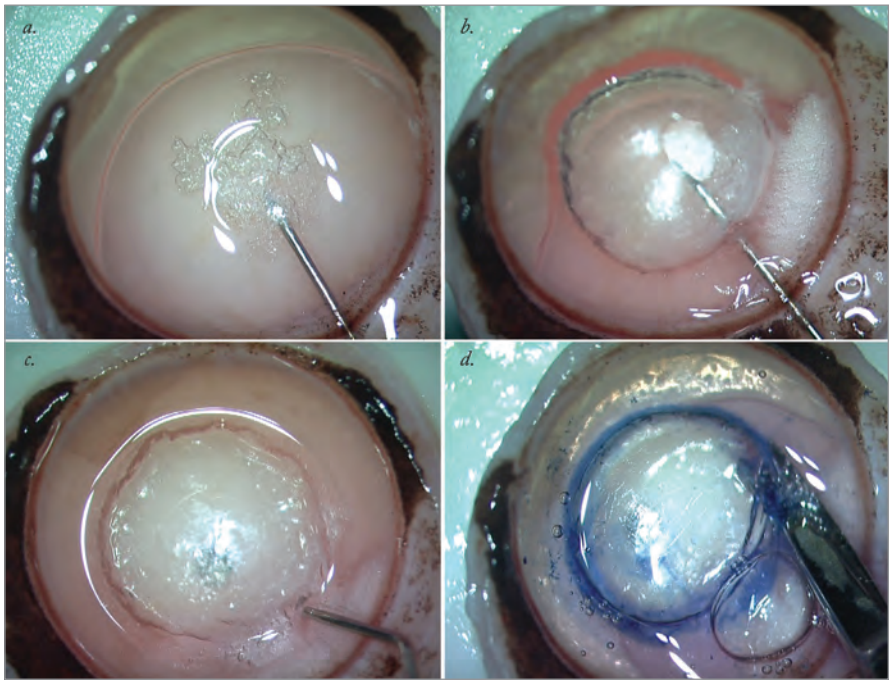

Figure 1. Graphical display of creation of Type-1 bubble (bb).
a. The image demonstrates all the layers of cornea with graft placed with endothelial side up; b. An air filled 30 G needle is introduced from the periphery beneath the pre-Descemet's layer (PDL). The PDL-Descemet membrane (DM)-endothelium complex is seen lying above the bevel of the needle; c. Further injection of air lifts the entire PDL-DM-endothelium complex that comprises of PDEK graft above the residual stroma; d. Fully formed Type-1 bb.

"PDEK has a number of advantages over previous EK methods."

Donor graft preparation

The most important part of the PDEK procedure is preparation of the donor graft – and it's essential to get it exactly right. The formation of Type 1 bb is essential for success (Figure 1) and separates the PDL from the DM-endothelium complex. This is in contrast with DMEK, which involves the formation of Type 2 bb via the passage of air in between the PDL and the DM-endothelial complex, leading to only the DM-endothelial layer being harvested, with the PDL being left behind in the remains of the donor graft.

A mixed Type 1 and Type 2 bb can often be created during the air dissection procedure – in which case, the surgeon needs to be very careful to avoid any rupture of the bubble, while ensuring that the bb is passed along the correct plane. Harvesting a Type 2 graft would necessitate abandonment of PDEK graft preparation and the conversion of the graft preparation and surgical procedure to a DMEK procedure instead.

Next, the donor graft (with corneo-scleral rim) is held endothelial side up. A 30 G needle attached to an air-filled 5 mL syringe is introduced from the periphery of the graft, into the center, and air is injected. A Type 1 bubble is formed that should spread from the center to periphery and should be around 8 mm in diameter. The edge of the bb is entered with a side port blade and Trypan Blue is injected inside to stain the graft. The graft is then cut with the corneo-scleral scissors all around the periphery of the bubble and it is then placed in the storage media.

Mastering PDEK in 15 steps

- Step 1 – Fix the trocar anterior chamber (AC) maintainer (T-ACM). A routine anterior chamber maintainer can also be fixed if the surgeon is not well versed with the use of a T-ACM. Preparing an infusion set-up allows the surgeon to easily switch over between an air/fluid infusion as and when required during the surgical procedure.
- Step 2 – Connect T-ACM to an air pump. This facilitates continuous air infusion into the eye; it helps to perform the procedure with an AC that is always well formed.
- Step 3 – Two side port incisions are made at superotemporal and superonasal positions, to allow these sites to be utilized later in the procedure for further intraocular manipulation.
- Step 4 – The Descemetorhexis is performed with a reverse Sinskey hook – this step is essentially the same as in a DMEK procedure.
- Step 5 – A 2.8 mm clear corneal incision is made and the scored DM-endothelium complex is removed. This allows the introduction of the graft in to the eye.
- Step 6 – Inferior iridectomy is

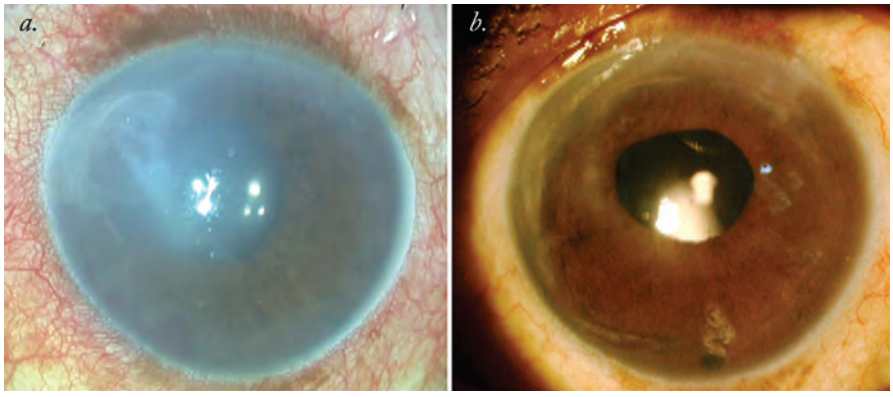

Figure 2. PDEK: Pre- and post-op. a. Preoperative image of the patient; b. Three months postoperative image shows clearance of the corneal haze.

performed with a vitrector, and helps to prevent pupillary blockage from occurring.

- Step 7 – Load the PDEK graft in the cartridge of the foldable IOL applicator (with the injector spring removed), as originally described by Francis Price.
- Step 8 – Switch OFF the air pump. This step is performed before the graft is injected so that the force of the air does not displace the graft. It also ensures that there is enough room for the graft to enter and be properly placed in to the AC.
- Step 9 – Inject the PDEK graft in the AC. If the AC is shallow, then the assistant can inject some fluid in to AC from a side port incision.
- Step 10 – Suture the clear corneal incision; this ensures there is no wound leakage and that the graft is placed in a well-formed AC.
- Step 11 – The correct orientation of the graft is checked; an endo-illuminator can be used to facilitate this.
- Step 12 – Unroll the graft and inject a little air beneath it.
- Step 13 – Switch ON the air pump connected to the T-ACM. This pushes the graft and helps it adhere to the corneal surface.
- Step 14 – Unroll the graft fully using the reverse Sinskey hook and center it properly. Corneal massage is performed to adjust the centered position of the donor graft and to eliminate residual fluid at the donor graft–recipient interface. Residual interface fluid can also be drained through corneal venting incisions.
- Step 15 – Suture the wounds and remove the T-ACM.

After completion of the surgical procedure, the patient is made to lie in the supine position for around two hours and is allowed only minimal movements for the next 24 hours. A postoperative regimen comprised of antibiotics and steroid drops is prescribed, and these are slowly tapered off over a period of three months, when corneal haze should have cleared (Figure 2).

Treating more with the same resources

The upper age limit for donor tissue usage is generally considered to be around 75 years – but there is still no clear consensus on the lower age limit of donor tissue. Most centers accept tissue from pediatric donors aged over 6 months – but we know that infant donor tissue has not been used because of fears associated with the technical challenges of preparing the graft and implanting such immature tissue.

"There is still no clear consensus on the lower age limit of donor tissue."

Indeed, when it comes to DMEK, it's rare that anyone uses tissue from donors younger than 40 years of age partly due to the fear of tearing the DM during donor tissue harvesting, due to the strong adhesion between the DM and stroma. PDEK obviates this risk and, in a world where many countries face a shortage of donors, it enables a far greater pool of tissue to be used to treat corneal endothelial disorders with DMEK-quality outcomes.

Amar Agarwal is Chairman, Dr. Agarwal's Group of Eye Hospitals, Chennai, and a pioneer of many techniques and procedures used routinely today in corneal and cataract surgery.

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Window of Opportunity

OCT can – and should – be used to support treatment decisions in glaucoma

By Felipe Medeiros

The introduction of imaging with optical coherence tomography (OCT) has allowed clinicians to acquire quantitative information about the eye structures affected by glaucoma with unprecedented detail. Despite this fact, clinicians are often confused about how to use OCT information in clinical practice. Should we make treatment decisions based only on OCT? I am asked this question very often and so below I provide some evidence of why I believe OCT should be used in clinical decision-making – even in the absence of concomitant visual field loss.

I will use three main points to justify my position:

At a Glance

- *SAP is considered to be the gold standard technique for identifying visual field loss in patients with glaucoma*
- *However, there is debate over whether changes seen on OCT alone can be used to support treatment decisions in glaucoma*
- *I believe that OCT can – and should – be used, because it provides a window of opportunity into early management of the disease*
- *Presenting supporting evidence, I justify my position and explain how basing clinical decisions on OCT (even in the absence of a concomitant visual field defect) can improve outcomes for patients*

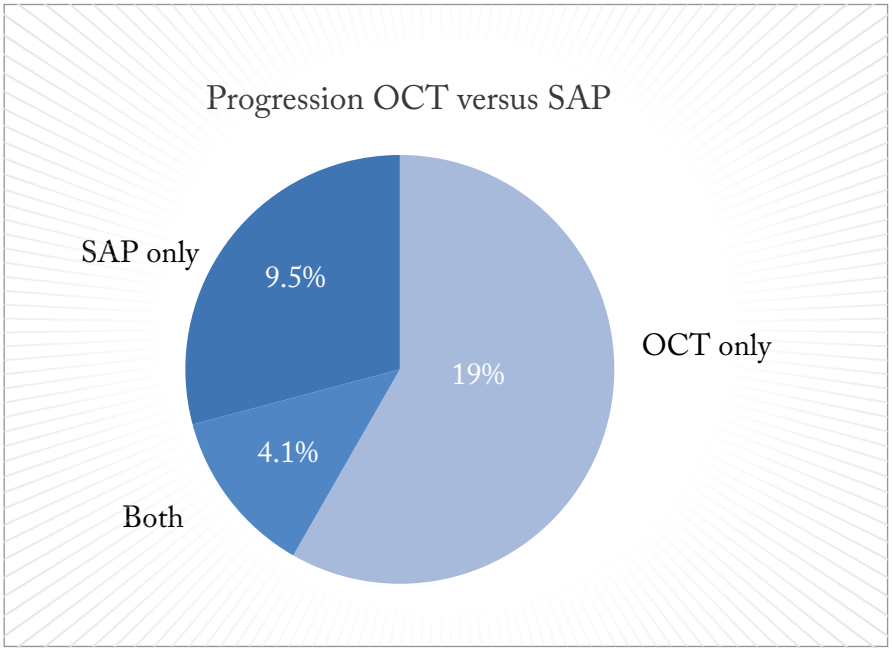
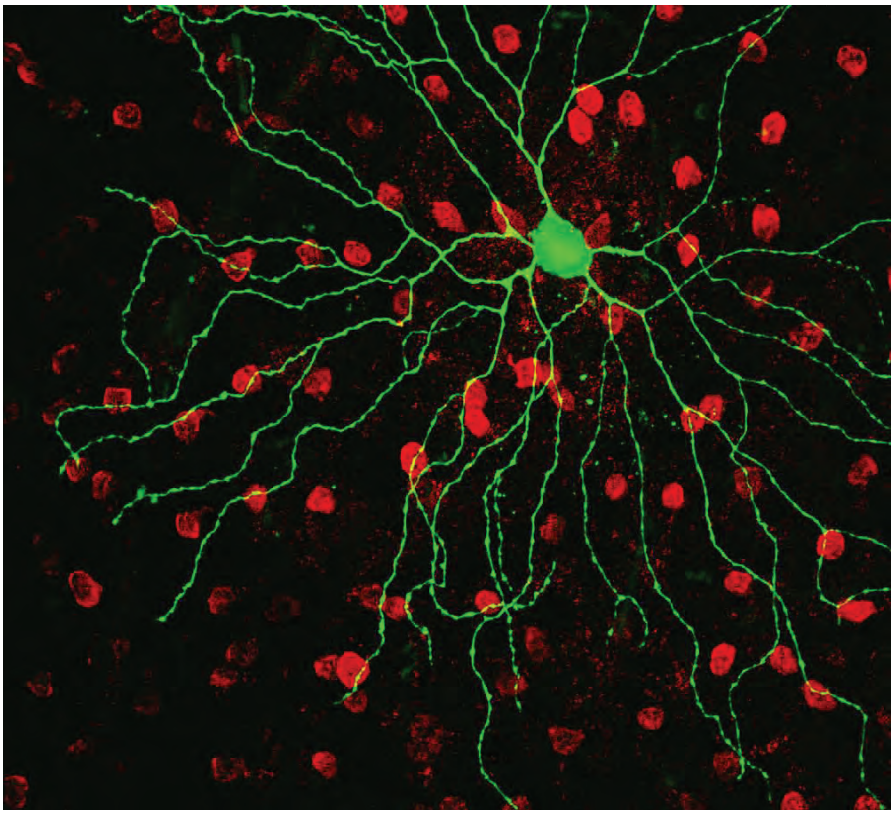


Figure 1. Percentage of patients in whom progression was identified by SAP only, OCT only, or both SAP and OCT. The tests were matched by specificity through determining the cut-offs for rate of change that were faster than the 95th percentile established from healthy eyes (1). OCT, optical coherence tomography; SAP, standard automated perimetry.

1. A diagnostic test should only be used if its results have a reasonable chance of impacting decisions about treatment.
2. Contrary to some prevailing thoughts, the value of OCT for monitoring glaucoma over time is predominantly based on the fact that the test actually disagrees substantially with standard automated perimetry (SAP).
3. OCT provides a window of opportunity into the management of glaucoma.

The first point above hardly needs any additional justification – it should be obvious as a standalone statement. Nevertheless, for those who may have any doubts, let me repeat: any ancillary diagnostic test – including OCT – should only be acquired if its results can impact decisions about diagnosis, treatment or overall management; otherwise, acquiring the test is just a waste of resources. For example, if I am only willing to consider a change in treatment if I see progressive visual field loss over time, then there is no justification for acquiring another ancillary test that can be costly and time consuming for patients.

However, I should note that the above does not necessarily imply that changes seen on OCT will always lead to modifications in treatment. Clearly, all treatment decisions need to be based on many factors, including the severity of disease and risk of functional impairment, as well as the patient's age, life expectancy, and risks and potential side effects of therapy. Changes seen on OCT may also lead to modifications in management, for example, by indicating a need for more frequent follow-up visits. However, the main point to drive home is that unless a clinician is willing to make changes in management based on progressive changes that are seen only on OCT and in the absence of concomitant loss of visual



function, OCT will hardly have any value as an ancillary test.

My second point should also be quite obvious. If OCT results agreed with visual field assessment in most patients, there would be little justification to acquire another test besides the traditional gold standard, which is SAP – in other words, one would suffice. However, the evidence is very clear that agreements between OCT and SAP in detecting change over time are the exception rather than the rule. Recently, my colleagues and I followed 462 glaucomatous eyes from 305 patients, with spectral-domain OCT and SAP performed at approximately every 3–6 months over a mean period of 3.6 years, to investigate the relative odds of detecting progression by one test versus the other (1). We found that OCT and SAP agreed on progression in only 4.1 percent of the eyes, whereas 19.0 percent of glaucomatous eyes showed progression only on OCT and 9.5 percent showed progression only on SAP (Figure 1).

The need to act – based on progression seen concomitantly by OCT and SAP or by SAP alone – is generally not under debate, as long as the changes are considered repeatable. However, almost 20 percent of patients with glaucoma exhibited changes in OCT that were faster than age-related change (95th percentile established from healthy eyes) and were seen in the absence of concomitant SAP changes. Once again, if we are not willing to make decisions based on OCT only, are we to ignore progression seen in this large proportion of patients?

We – and others – have previously published on the reasons for the frequent disagreements between OCT and SAP. Such disagreements become easy to understand once one considers the properties of the tests, such as different scaling and issues related to variability. Importantly, the changes seen on OCT, such as slopes of retinal nerve fiber layer thickness loss over time, have been shown to predict future development of visual field loss (2,3) and be associated with a decline in patient-reported quality of life in glaucoma (4). At this point, it is worth asking: "Can't I just wait until I see a change in the visual field to start or modify treatment?" In other words, do I need to bother with early treatment? Such questions bring us to the third point, which is the window of opportunity that OCT provides.

Because of the nonlinear relationship between visual field loss measured by SAP and retinal ganglion cell (RGC) number, it can take a substantial loss of RGCs for an initial visual field defect to become clearly apparent. OCT can frequently detect progression before that. However, once such a defect is apparent on SAP, it actually takes a smaller amount of RGC loss for the defect to progress to significant functional impairment (Figure 2). In other words, once a visual field defect is present, less change can be tolerated, meaning that more aggressive treatment will likely be needed to slow down the disease to avoid progression to functional impairment. On the other hand, if treatment is initiated earlier – within the window of opportunity offered by OCT – there will be a greater tolerance in the allowed rates of change that can prevent future functional impairment, meaning that treatment can potentially be less aggressive.

In conclusion, we know as clinicians that treatment decisions should never be based on a single test; candidly, that's common sense and is not the point of this discussion. However, there is evidence to suggest that changes seen only on OCT in the absence of functional loss have important prognostic significance for patients with glaucoma or those suspected of disease. Ignoring these changes based on claims of lack of agreement between OCT and SAP reflects a misunderstanding of the

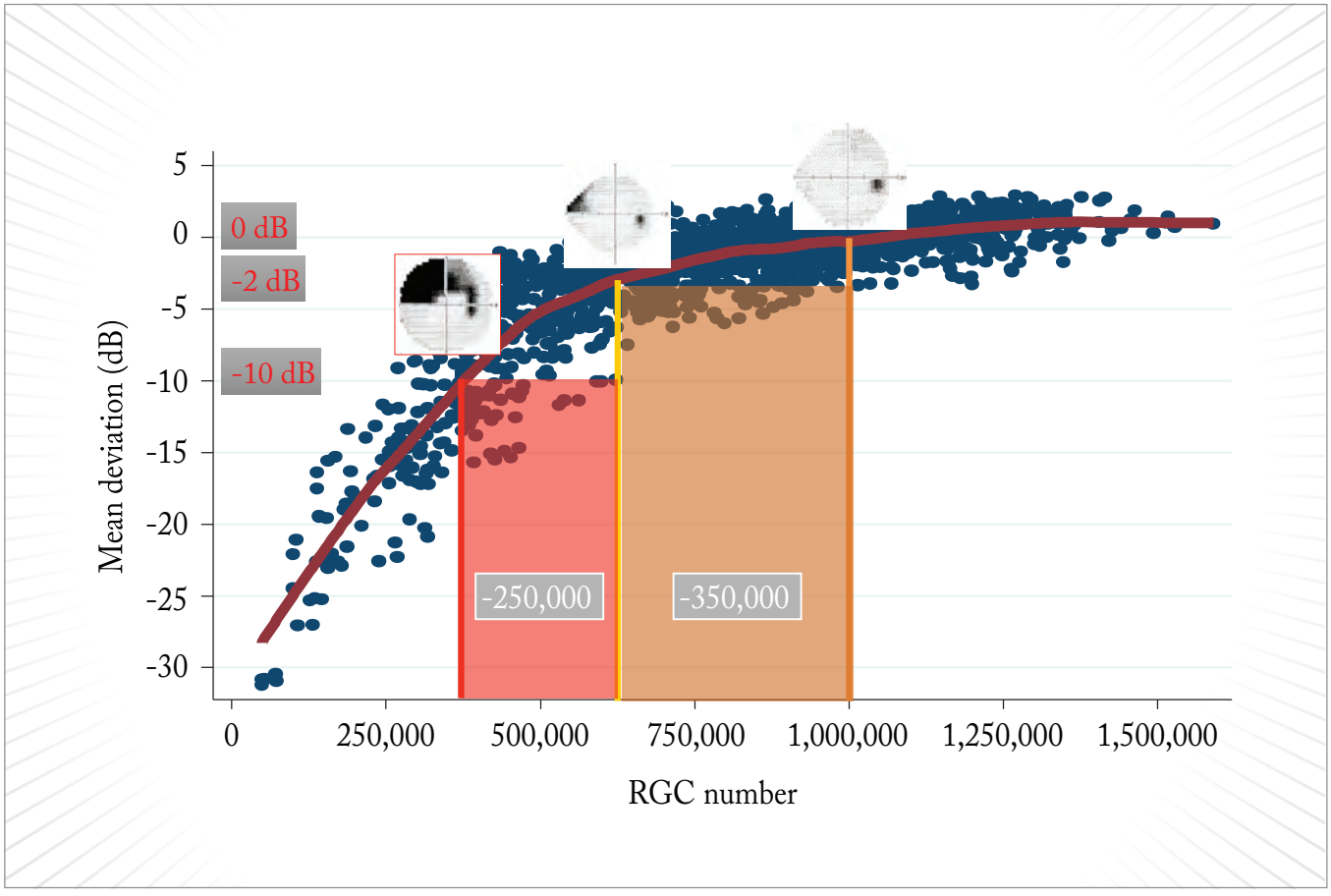


Figure 2. Relationship between visual field loss and RGC numbers. A normal visual field in a healthy individual has approximately 1 million RGCs. At a mean deviation of -2 dB, which equates to an early field defect, RGC number has decreased by around 350,000 cells. At -10 dB, a field defect that can result in functional impairment and quality of life decline, RGC number has decreased by a further 250,000 cells from the RGC number at -2 dB. Adapted from (5, 6). RGC, retinal ganglion cell.

structure-function relationship in the disease. If the structural changes seen on OCT are real, repeatable and faster than age-related loss, we should consider them in making treatment decisions. If we fail to do so, we could be missing a window of opportunity to improve outcomes for our patients.

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NextGen

Research advances
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Small(er) Sequence, Big(ger) Promise

Efficient CRISPR gene editing with a newly characterized CjCas9 orthologue might bring the approach one step closer to the clinic

Ruth Steer interviews Seokjoong Kim and Sung Wook Park

There is little doubt that the future of medicine is gene editing. But right now, the focus is on figuring out how to get there as safely and effectively as possible. An approach at the forefront of our gene-editing endeavors is CRISPR (clustered regularly interspaced short palindromic repeats)/Cas – and since its debut in 2013 (1–3), research has been booming.

Although CRISPR/Cas9 shows much promise therapeutically, improvements and tailored modifications are needed before it hits the clinic. For example, the Cas9 endonuclease – which binds and cuts DNA at specific locations as dictated by a short guiding RNA (sgRNA) sequence (Figure 1) – could benefit from optimization; the most commonly used orthologue (derived from *Streptococcus pyogenes* – SpCas9) weighs in at a mighty 4.10 kbp and 1,368 amino acids, and is too big to be packaged into a single adeno-associated virus (AAV) vector along with its sgRNA sequence. It can be split over more than one AAV vector, but this can come at the cost of reduced endonuclease activity (4). One alternative is Cas9 from *Staphylococcus aureus* (SaCas9); it's around 1 kbp smaller than SpCas9 and can be packaged into a single AAV vector. Unfortunately, the number of targetable genes is predicted to be limited by a much less frequently occurring protospacer-adjacent motif (PAM) – a 2–6 base pair DNA sequence that acts an essential targeting component of the system.

Given the apparent lack of a "good" choice, a team in South Korea decided to seek alternative Cas9 orthologues – with promising results. In their recently published study (5) they characterized Cas9 from *Campylobacter jejuni* (CjCas9),

At a Glance

- *CRISPR/Cas9 gene editing shows much promise therapeutically, and since its debut, there's been lots of research into developing and using the technique*
- *But although SpCas9 and SaCas9 are currently the most commonly used Cas9 orthologues for CRISPR/Cas9 gene editing, each has limitations for gene therapy approaches*
- *According to recently published research, a team from South Korea might have found a promising alternative – CjCas9*
- *SeeokJong Kim and Sung Wook Park, co-authors on the paper, tell us about their work and what's next*

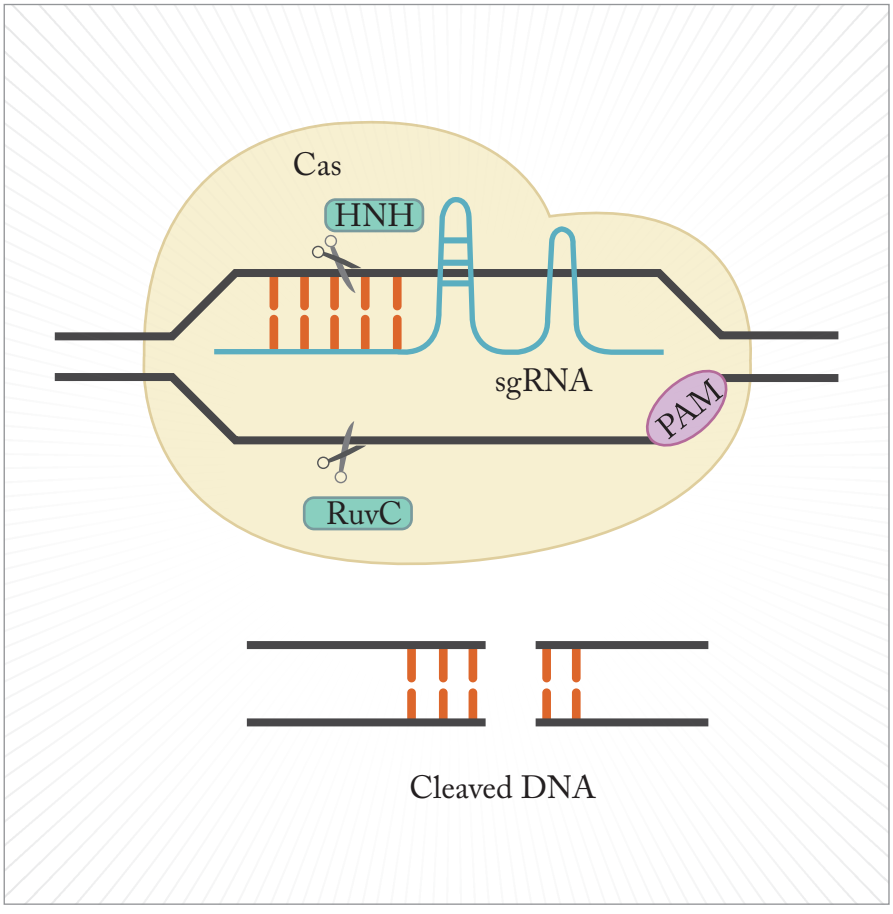

Figure 1. CRISPR gene editing. Cas9 binds to DNA guided by the sgRNA sequence, and the HNH and RuvC nuclease domains of Cas9 cleave the DNA. For Cas9 to bind and cut the DNA, a PAM sequence must be present immediately downstream of the target sequence recognized by the sgRNA. Adapted from (6).

demonstrated its use for in vitro and in vivo gene editing, and showed that CjCas9 targeted to *Vegfa* or *Hif1a* could reduce choroidal neovascularization (CNV) in a mouse model of age-related macular degeneration (AMD; See Box – Summary of Key Results and Figure 2). Seokjoong Kim, Research Director of Toolgen, and Sung Wook Park, one of the lead authors on the paper, tell us more.

What inspired your study?

Seokjoong Kim: I'm a molecular biologist, and over the last 10 years I've been working to develop gene editing tools such as transcription activator-like effector nucleases (TALENs) and CRISPR. When we were ready to move into the clinical translation of CRISPR technology, I found AAV very attractive because it has been clinically proven to deliver genes very efficiently and safely. I wanted to combine a CRISPR/Cas9 system with AAV, but I quickly found out that the typical Cas9 system from *Streptococcus pyogenes* is simply too big. We started to use Cas9 systems from different species, but decided to focus on CjCas9 because it was the smallest we could find in the literature and databases. In collaboration with The Institute for Basic Science in Seoul, we

Summary of Key Results

- At 2.95 kbp and 984 amino acid residues, CjCas9 is around 30 percent smaller than SpCas9
- Cleaving of human genomic DNA in vitro by CjCas9 was found to be more specific than SaCas9 with no reduction in efficiency
- In vivo, CjCas9 was shown to induce targeted mutations in three genes:
    - In mouse myotubes, CjCas9 induced targeted mutations at the *Rosa26* locus
    - In mouse retina, targeted mutations were induced in *Rosa26*, *Vegfa* and *Hif1a* in retinal pigment epithelium (RPE) cells
- In a laser induced CNV mouse model, the team found that targeting *Vegfa* and *Hif1a* each reduced the relative CNV area by over 20 percent (see Figure 2). *Hif1a* encodes hypoxia-inducible factor alpha (HIF-1α), a transcription factor that activates the transcription of VEGF-A.
- To investigate the potential side effects of the partial knockouts of *Vegfa* and *Hif1a* in RPE cells, cone function was measured by full-field electroretinography. Photopic and flicker response were not significantly decreased, but the size of the opsin-positive area was reduced when *Vegfa* was targeted.

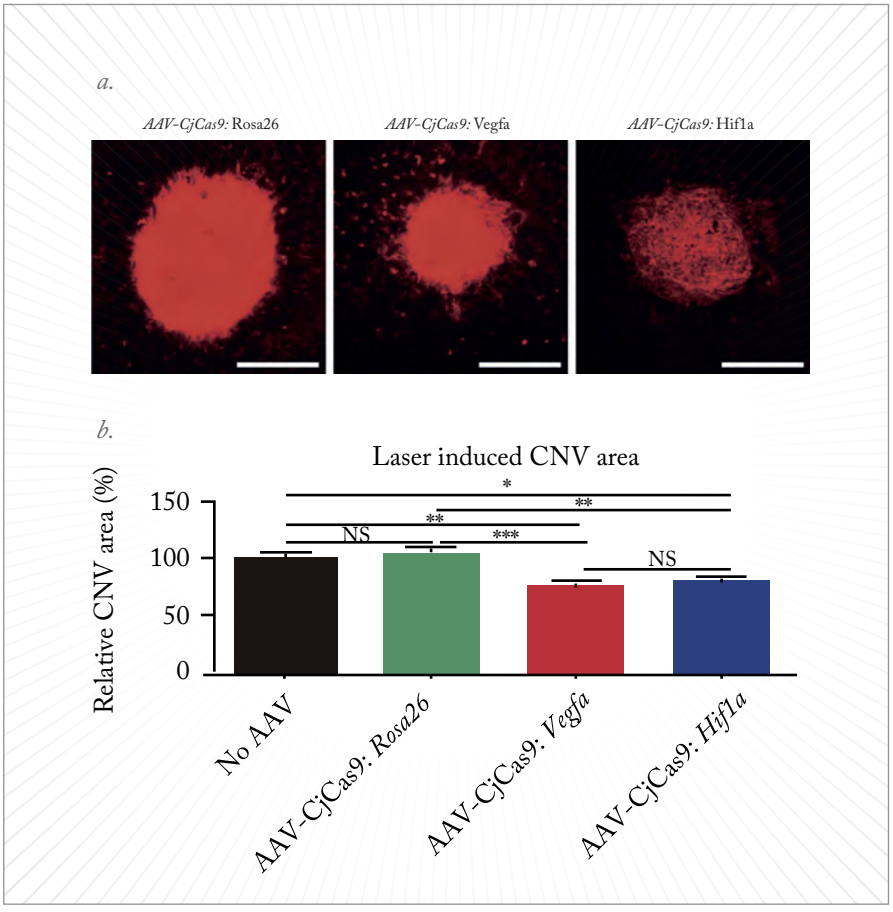

Figure 2. Mice injected with AAV-CjCas9 targeted to *Rosa26*, *Vegfa* or *Hif1a* were treated at day 42 post-injection to induce CNV; they were analyzed one week later. a. Representative images showing the area of laser-induced CNV (stained with isolectin B4). Scale bar, 200 mm. b. Graph showing the relative CNV area. Error bars indicate SEM. (n=17–18). One-way ANOVA and Tukey's post hoc tests, *P<0.05; **P<0.01; ***P<0.001; NS, not significant; SEM, standard error of the mean. Adapted from (5).

then performed a full characterization of CjCas9, including its PAM sequence and the optimal size of the sgRNA. We showed that we were able to support efficient gene editing in vitro and in vivo with CjCas9. Our initial trial was in muscle, but we later focused on gene editing in the eye to establish a therapeutic effect. We chose the eye because it is an isolated organ and easy to access, and this resulted in our collaboration with Jeong Hun Kim and Sung Wook Park, and the focus on AMD and diabetic retinopathy (DR).

Sung Wook Park: We'd been looking for an efficient tool for genome editing in the eye. Because Cas9 is too large to package into AAV vectors without "splitting up," we were trying to find different ways to pack it into AAV vectors. Biotech company Toolgen had already begun developing CjCas9, so we got involved.

What are your most important findings?

SK: We are pleased that we have been able to develop the *Campylobacter jejuni* CRISPR-Cas9 system and show that AAV-mediated delivery can support very efficient gene editing in the eye – we saw editing efficiencies of 30–60 percent. Fortunately, the dose efficiency of gene editing was enough to show some phenotypic changes, and we were happy to see that targeting *Vegfa* and *Hif1a* in the eye with CRISPR gene editing could change the phenotype in a mouse model of laser-induced CNV.

"There is no limit to the genes you can edit with the CRISPR-Cas9 system."

SWP: The delivery method is really quite different. Most gene therapy relies on AAV2, which is typically delivered through subretinal injection, which inevitably causes damage to the retinal layer. We already had experience in using AAV9 for targeting RPE cells, and we delivered the CjCas9 AAV9 viral vectors via intravitreal injection. We believe intravitreal injection is a much better delivery method because we limit damage to the retinal neurons. Also, simply injecting the viral vector into the vitreal cavity can increase efficiency because more cells in the retina or RPE can be transduced and edited.

Any surprises or challenges along the way?

SK: When I initially chose the study, I thought that the production of AAV would be well established because there had been so many trials – so I was surprised at how inefficient and expensive it is, even at the research level! With the ongoing work on AAV-mediated gene therapy in the US and Europe, I hope

that in the near future we will have more established and optimized protocols and processes for AAV production.

SWP: It isn't proven in well-established studies, but there is some evidence that targeting the *Vegfa* gene can cause problems, so we needed to check the side effects. There was some local opsin decrease but there were no constant functional decreases in photoreceptor response. So at the present time, we believe that targeting *Vegfa* is still a viable option.

When do you expect to move into human trials?

SK: It's hard to say! We believe we can perform some large animal studies within this year – and we hope that we'll be able to prepare enough data to file an investigational new drug (IND) application in 2018. One thing for us to consider is the fact that we are currently targeting *Vegfa* and *Hif1a* –but these are not actually defective genes in AMD and DR. We do believe that targeting these genes – and others that we are working on – could be a viable option for long-term AMD or DR therapy, but we're not sure if regulatory bodies will be comfortable with targeting non-defective genes with CRISPR. Therefore, we are also interested in targeting other genetic diseases in the eye that might be more easily accepted by regulatory bodies and society.

SWP: We also have to consider the hurdles to overcome before getting to trials. As well as the necessary larger animal and safety trials, we need to find an effective human sequence and prove that it can be edited with the CRISPR-CjCas9 system. *Hif1a* is quite conserved between the mouse and human genomes, so we are thinking of targeting this in clinical trials. Additionally, because anti-VEGF therapy is a well-established treatment regimen for AMD and DR, we'll need to demonstrate how effective CRISPR is compared with existing therapies. These diseases usually wax and wane over time, so multiple repeat injections of anti-VEGF agents are needed; we hope that our genome editing approach might be able to downregulate VEGF and other factors to below the threshold level that causes disease.

Where do you hope your work will take you?

SWP: Using the advantage of the small size of CjCas9, we might be able to think about combinational therapy approaches where we target dual genes with a single AAV system. We haven't tried this yet, but we are looking into the possibility of different approaches.

SK: There is no limit to the genes you can edit with the CRISPR-Cas9 system. VEGF is a key target for modulating vascularization, firstly because it is one of the very important factors in the process, but also because it can be inhibited extracellularly by current therapy models like monoclonal antibodies. We're also looking at genes for intracellular or nuclear proteins that cannot be easily modulated by antibodies or small molecules. Looking forward, we want our technology to bring new hope to patients who are losing sight.

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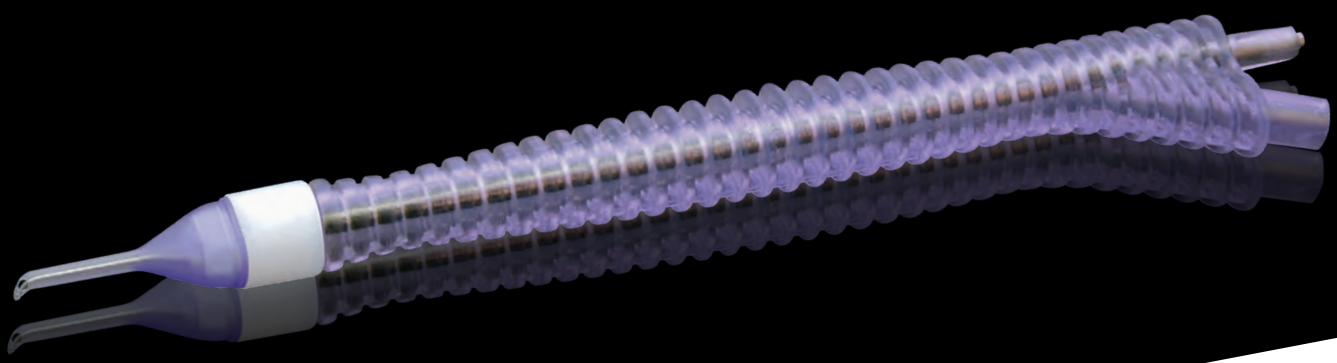

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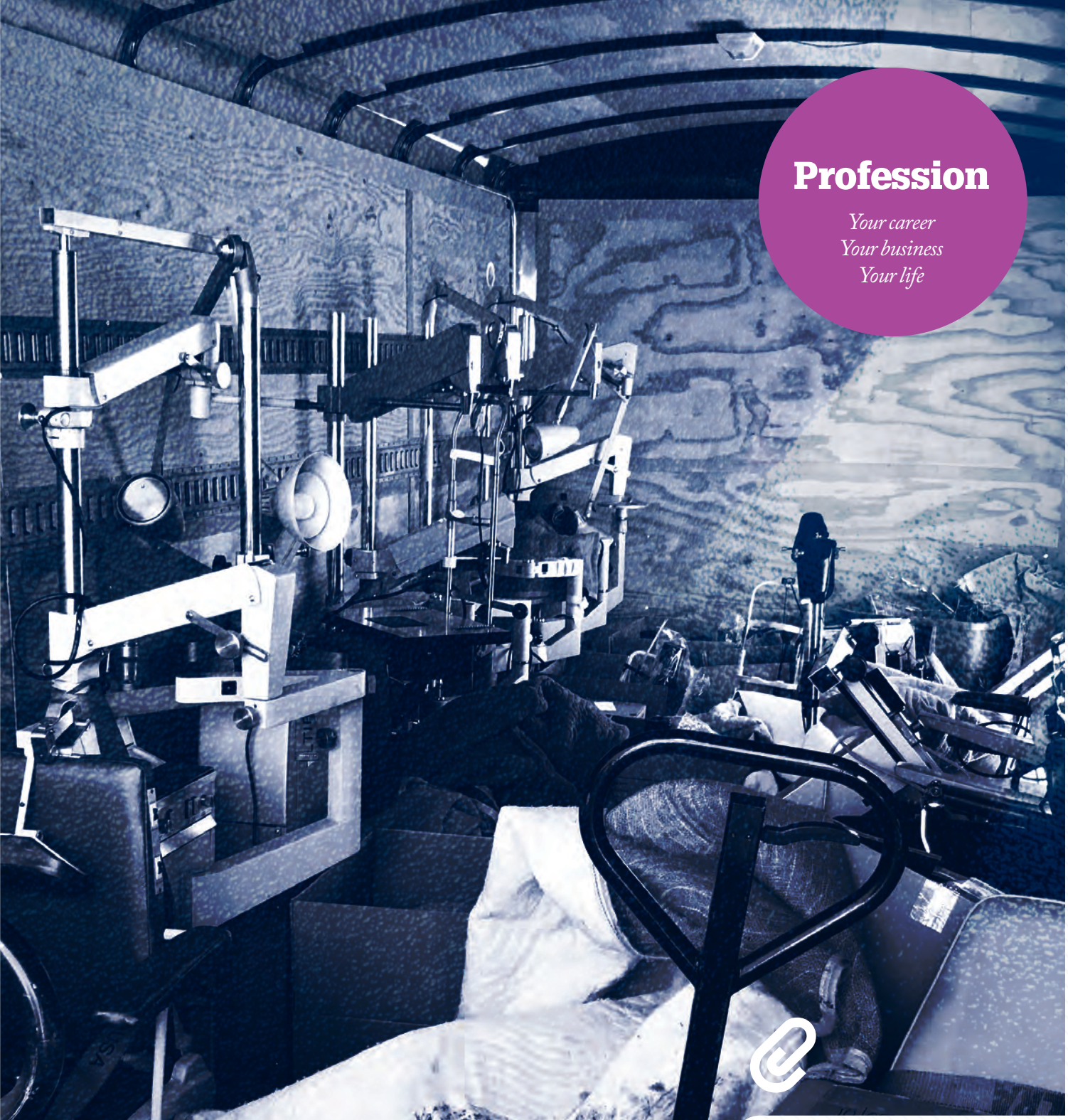


There's Doing Good, Then There's Doing *Good*

How to be a more responsible "medical tourist" in seven lessons

By Kevin Waltz

I thought I was doing some good in Honduras – offering free cataract surgery on my own dime, importing equipment, making a difference. But about five years in, a 37-year-old patient walked into my clinic with posterior subcapsular cataracts. And this conversation followed:
"Yes, we'll do your surgery."

At a Glance

- *You might think that flying to a developing country and performing surgery for free is a worthy endeavor. And it is – but there are better and worse ways to go about it*
- *The people on the ground have to earn a living, and importing expensive equipment can distort the local market – not respecting that can be detrimental to the charitable cause*
- *Taking an organic approach ultimately will have the greatest payoff: equip the facilities and help train up staff to build a legacy and help more people than a single surgeon ever could accomplish*
- *Your intervention can change the fabric of society – for the better. Going about it in the right way can consolidate – and propagate – the good you're doing*

"I've been reading on the Internet. Are you going to be doing phaco?"

"No, we're not going to do phaco."

"I read that's the best way of doing it, why aren't you doing it the best way?"

"I don't have phaco here – but if I could, I would."

"I'm going to think about how badly I need this surgery..."

Even back in the year 2000, the patients who received charity care in Central America were, thanks to the Internet, quite savvy – and they wanted the best. I realized that I'd either have to quit – or give them the best. And that's when I started importing more sophisticated equipment and working with local doctors to start building an infrastructure to provide a better service. The process taught me an awful lot, and I've gone from being a medical tourist, albeit on the provider side (I'd go down for about a week, do a bit of surgery, feel good about myself, then go home), to something more than that.

Lesson #1: Ask nicely

There's a difference between asking nicely and doing so in a productive way, and begging and being a jerk – they are at very different ends of the spectrum. If you ask somebody nicely and with a pure heart, more often than not, they will say yes. Once I'd learned that, I was amazed by the number of people who came out and worked with us.

For example, I work with one of the best phaco machine repairers in the world. He's based in the US and works for Johnson & Johnson Vision. He volunteers his time and expertise to support our efforts in Honduras in his free time – tuning up the equipment before we send it down, and then he comes out to Honduras to set it all up. In Honduras, we have two biomedical engineers who are part of another organization that we made friends with. We've already trained one of those engineers in the US, which is all part of building up that essential infrastructure. And it all started by asking for help nicely.

"Respecting partners goes a long way to achieving your goals."

Lesson #2: Respect that people need to make a living

Don't spend all of your money on supplies and transportation – some local people who want to help still have to feed their families; consider salaries.

Equipment manufacturers also want to help, but importing equipment and giving it away for free while totally ignoring the local situation can have a negative impact on their local partners. If something is likely to affect a local distributor's business, talk to them about it. Some charities ignore the local reality in the ground; they burst onto the scene as a totally self-contained unit, perform lots of cataract procedures, then fly back home – and ruin local people's livelihoods in the process. Remember that a single donation can completely change the market, and it can take years for the local system to recover. If, however, you involve everyone in the process, the local distributors can get involved in helping the very people who need it most.

It's not that we won't import a vital piece of equipment because of the impact on their business – but we can mitigate the impact in the process. For instance, I imported an expensive photo slit lamp from the US that I couldn't get locally. But before I did that, I

bartered with the local distributors. I said, "Look guys: I can't get this locally, so I want to import it – will you repair it once it's here? If you do, I'll buy this other equipment from you." Here, we both get something out of the process. Respecting partners goes a long way to achieving your goals.

Lesson #3: Respect your patients, their time, and the danger they put themselves through to reach you

I get up at about 3.30 am in Indianapolis, board a plane, travel by car from the airport, and arrive at the clinic at about 4.00 pm local time. It takes a while! But it can take even longer for some patients to get from their house to the clinic – and involve greater levels of danger. My patients are blind; they can perhaps tell the difference between light and dark, but that's it. So even though the surgery is free, they still have a journey to make; possibly needing to hold someone's hand while they walk to the local bus stop, taking one or two buses (at not insignificant cost) to get to my clinic in Honduras. Then it's another hour's walk up a very steep hill to get to my clinic from the bus stop. Suddenly, my journey doesn't seem too bad – and I don't have to worry about tripping up or walking into traffic.

Lesson #4: Your intervention changes the fabric of society

I got really excited about working in Central America when I realized that restoring the vision of grandparents actually changed the social fabric of the family. In the US and other developed countries, middle-aged people are somewhat oppressed – they've often got kids and aging parents to juggle. But that's nothing when compared with a Central American family that has to cope with blind grandparents. When I operate on a grandmother, she contributes to the family again. The mom is suddenly free to look after – and read with – the kids. The upshot is that the next generation has a better chance in life. It reminds me of a TED talk by a very interesting Swedish epidemiologist, Hans Rosling, who noted that the fundamental event that changed society in Sweden was the washing machine. Suddenly, grandma didn't have to spend all of her time doing the wash; she could help do the dishes, she could help cook – and Mom could read with the kids. He recognized how much better off the next generation was after the washing machine was introduced.

In a small way, I think we're helping to do the same in Central America.

Lesson #5: Bad clinics can get closed... by drug dealers

Hugo Chávez was famous for using Venezuela's oil wealth to fund doctors for the poor – he would send tens of thousands of barrels of oil to Cuba each day. Part of what he got in return was tens of thousands of Cuban doctors and teachers who worked in its barrio slums. Things are different now – oil prices have dropped – but, at the time, the Honduran government did the same as Chávez. The problem was that when it came to cataract surgery, many Cuban doctors did a bad job – and people simply wouldn't go back and risk having their second eye operated on by them. I know this story well because I ended up doing many of the second eye surgeries myself...

Being a part of this world exposed me to one leveling effect of the drug trade. The barrios where the Cuban doctors worked are areas where drug dealing is rife. Quite naturally, the parents of drug dealers get cataracts. They go to the local Cuban-run clinics, it doesn't go well, and their parents are blinded. The drug dealers know how to deal with that... And the clinics close. It's an unusual case of where drug dealing was actually beneficial to society!

The US government has been in a constant struggle with Venezuela under Chávez and his successors for many years – and competing philosophies on how to help those in need is one of those areas of conflict.

Explore online

See the videos online at top.txp.to/issues/0517/701

Donated instrument preparation and screening

Capsulotomy training – on chocolates

Spanish language phaco technician training

The Hospital San Felipe OR

It is ironic that US volunteers were providing a very strong counterpoint to the efforts of the Venezuelan government by providing a superior service to the needy people of Honduras.

Lesson #6: Interventions on a small scale can be more effective than big ones

Every healthcare system has its problems – Central America is by no means unique in that respect. But they also get many aspects right. The systems in Central America are shockingly efficient – they have to be because they have so few resources to work with. If you feed them resources in the right way, they are incredibly effective at using them. Consider Mississippi – it is the poorest state in the US by far with a median household income under $40,000. In Honduras, which shares a coast on the Gulf and has a similar population, the median income is under $4,000. So on a tenth of the income, they take pretty good care of themselves.

When it comes to charitable donation, I've observed something important: it's bad to give large injections of cash; large amounts of money end up just disappearing. But small boluses of money – properly managed – can be incredibly powerful at helping people. I'm finding that the local doctors are really great at spending that money effectively and efficiently in the local supply system. As noted above, they are used to be being careful with their cash.

Lesson #7: If you build it, they will come

Ophthalmic equipment companies often take back 'old' equipment as 'trade-ins' – but these are still valuable in developing countries. Despite being previous generation technology, the equipment is still great – it was cutting-edge in the developed world five years ago. We put it to work for the local population, and it becomes cutting edge (more or less) for Central America.

Part of charity care is logistics. An eye surgery room needs heavy equipment to operate at the highest level. Our logistics partner is the Orville, OH-based non-governmental organization (NGO), Central American Medical Outreach (CAMO). CAMO has supported healthcare in western Honduras for the last twenty plus years and has done – and continues to do – a remarkable job at it. The Central America Eye Clinics has partnered with CAMO to improve eye care in Honduras and El Salvador.

Our professional colleagues are stepping up to help. We are supporting the national residency program of Honduras. The American-European Congress of Ophthalmic Surgery (AECOS) has begun recruiting ophthalmologists to participate in mission trips to Honduras to perform surgery and to participate in training local ophthalmologists. They have also established AECOS Global Charities as a separate 501(c)(3) non-profit organization to solicit donations that will support organizations such as the Central American Eye Clinics and others dedicated to improving the standard of ophthalmic care in underserved populations of the world. For example, Johnson & Johnson Vision has been a very strong supporter of AECOS Global Charities for the last two years, and with this kind of support, we hope to strongly support the transfer of technology and training of local doctors and staff.

And so, in February of 2015, in Tegucigalpa, the capital of Honduras, we installed "new" (used) equipment and changed the technology used to train the residents. We donated three microscopes, four phaco machines, 10 sets of hand instruments, and the technology transfer required to use them. Patricia Sierra, Sheri Rowen, and I spent a week training the residents and faculty in phaco. And we're starting to support, in person, their ongoing training – our society's members will cycle through to help maintain the process. We've already made a scouting trip to the

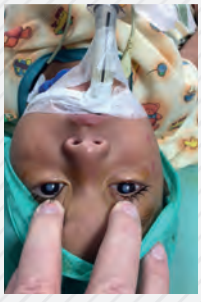
Yester's story

Yester, a four-year-old boy, had been blinded by cataract for the last two years. He was in particular danger because his family lived on a very steep hillside; to keep him indoors – and safe, they kept him in chains. The local hospitals didn't have the capabilities to perform pediatric cataract surgery – and that's where I stepped in.

The local hospital agreed to pick him and his family up and also to provide the operating room. I agreed to provide the equipment and the expertise. I performed the surgery and implanted a Tecnis multifocal lens, to help him see at both distance and near – it was not realistic to expect Yester would be able to obtain glasses postop.

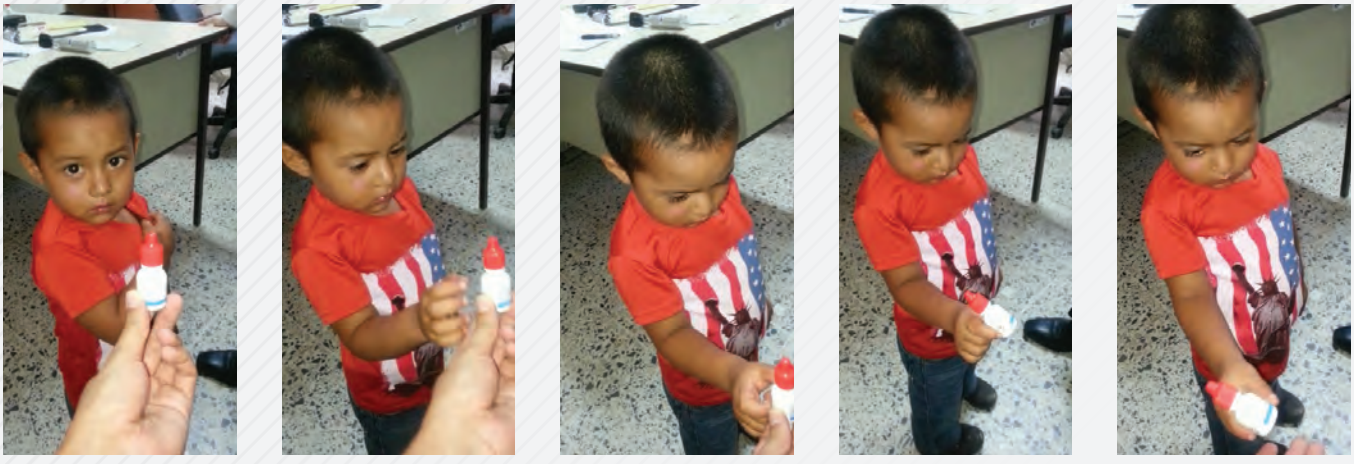
Two months later:
Can he see perfectly? No. But he can interact with his world – and that means he can have a life.

See the videos online at top.txp.to/issues/0517/701



Pre-op

Immediately post-op:



Can he see perfectly? No. But he can interact with his world – and that means he can have a life.

national residency program in San Salvador, El Salvador. We hope, in the near future, to do the same there.

We believe that if we give people the opportunity and bring the equipment needed to make a difference to the next generation of ophthalmologists in Central America, they will come. The result will be stronger and more capable local ophthalmologists. We're taking a kind of organic view of charity. We're providing good seeds, planting and watering them. And in doing so, we are building a legacy – one where far more patients can be seen and far more good can be done than one surgeon could ever do alone.

Kevin Waltz is President of Ophthalmic Research Consultants, and Chief Medical Officer for Central American Eye Clinics. He is a consultant for Johnson & Johnson Vision, AcuFocus, Hoya Surgical Optics. Omega Ophthalmics and a Consultant and Medical Monitor for Mynosys Cellular Devices.

Finding My Place in a Translational World

Sitting Down With... Alex Huang, Assistant Professor, Doheny and Stein Eye Institutes, Department of Ophthalmology, David Geffen School of Medicine, UCLA, California, USA.

Number one on the "Rising Stars" 2017 Power List. How does it feel?

It's a real honor – especially for all of us young clinicians and scientists on the list. These are the kinds of things that help us gain traction in our careers. It really feels like a blessing to be recognized.

How did you end up as a glaucoma clinician–scientist?

My training started at Hopkins with Sol Snyder. As an MD PhD, from the beginning, I was always thinking about how to find my place in a translational world. I chose ophthalmology because you can wear both medical and surgical hats at the same time; I felt it would give me a comprehensive overview of everything that I could then draw scientific questions from. Then it was: glaucoma versus not glaucoma? The issue is that glaucoma never makes good grand rounds – there's no diagnostic mystery, right? What does almost every patient who walks into a glaucoma clinic have? Glaucoma. Instead, you're faced with a multitude of ways to handle it and it's about customizing the treatment to that patient in terms of what they have, what they need and where they are at that moment in time. In my case, putting together the gestalt of the treatment plan was more exciting and also offered more research potential than if I was more concentrated on the diagnosis of different ophthalmic disorders.

In 10 years, how is glaucoma going to be treated differently?

There has been a big push by the NIH to focus on personalized medicine. Big data is very important because it helps us understand fundamental principles – but not everyone is the same. The combination of the NIH's mission of customizing each individual's treatment with glaucoma care has resulted in early surgery with more minimal techniques taking hold – and this approach will likely play an even greater role in the future. As an example of my research, aqueous angiography is a technique that might help you customize glaucoma surgical treatment to individual eyes as it tells you where the aqueous humor is flowing. One of my mentors, James Tan, taught me about a patient who came to him and said, "Doctor, I didn't actually feel like I had glaucoma until I started eye drops." It was the irritation from the drops that made him say this and while most ophthalmologists start with drops first – that might change. As James was alluding to, if we can get more effective, smaller surgeries to the forefront, then maybe people can use fewer drops, and in a way, not feel like they have a disease.

"Glaucoma never makes good grand rounds."

Who else do you consider a mentor?

After my graduate training with Sol, Robert Weinreb greatly influenced me and my thinking. My glaucoma fellowship at UCSD with Robert was a major turning point for me in terms of my career. First, he gave me a lot of freedom; most fellows who are trying to push down the clinician–scientist road feel a lot of pressure to carry out any productive research – no matter how small – to demonstrate scientific achievement and momentum. Robert emphasized this too, but he also gave me some flexibility and freedom too – he really encouraged me to spend time reading the field and simply writing about research topics that interested me. There were times that I was writing with no audience that I'd be able to submit to. He just wanted me to write to organize my thoughts into a research program. As a result, we threw out all sorts of little grants here and there during my fellowship, and the truth is, every single one failed! But that one year gave me a vetting experience. Through that process, I internalized and seriously weighed every remark, suggestion, and criticism so that when I came out as faculty and started applying for broader research support, it looked like I had my ducks in a row right away – but that was never true! Robert gave me the opportunity and time to explore and most importantly to fail so that then I could be set up for success.

What are the best pieces of advice you've received so far?

From Sol Snyder, it was: work on something that's important to you, because then you'll have the energy and the desire to move forward no matter how hard it gets. Robert Weinreb told me to always value the people, irrespective of the brand. The key there is to identify a person that you can develop a trustworthy working relationship with – that's probably one of the best pieces of advice he's given me. Srinivas Sadda said, "When you're young, just go for everything. Good things will come, and take it from there." At an early stage, none of us are smart enough to know if any endeavor will pay off – or what won't.

If you could go back in time a decade, what advice would you offer yourself?

Mentoring is more important than you think, so have as many mentors as possible – especially ones at different stages of their career and ones you can actually go to and ask questions. Don't be afraid, there's no ego here – there's only one goal and the goal is to succeed. You can only succeed if you get help and learn from people who've been there in the past.

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