MARCH 2015 # 17

the Ophthalmologist

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Online this Month

The Power List 2015 – Top 40 under 40

Last year, we ranked the Top 100 most influential ophthalmologists in our inaugural Power List. This year, we shift the focus to the up-and-coming ladies and gentlemen who are already making waves. We want to profile 40 ophthalmologists aged 40 years or younger to shine a light on those surgeons, specialists, researchers and industry leaders who are shaping a bright and innovation-rich future.

Once again, we invite you to nominate the men and women who you believe have what it takes to be the trailblazers of tomorrow. Your suggestions will be considered by our panel of judges who will select the Power List.

To nominate your chosen candidate(s), either fill out the short online form at top.txp.to/PowerList2015 or email the editor (mark.hillen@texerepublishing.com) with your with your nominee(s) name, affiliation, reason for nomination, and your connection to the nominee.
The deadline for nominations is Thursday 12 March 2015, so nominate your candidate now!

The Ophthalmologist on Twitter

What got you tweeting this month? Here are some of our most popular tweets…

The 2015 Power List
The Ophthalmologist @OphthoMag
This year, we want to profile today's top 40 influencers who are under the age of 40. Send us your nominations now! http://ow.ly/JuzqQ
11:10 AM - 25 Feb 2015

First EU approval for a stem-cell based medicinal product
The Ophthalmologist @OphthoMag
Holoclar approved by the EU. Autologous #stemcells for the repair of severe corneal damage. #chiesi http://bit.ly/1Expwzl
4:34 PM - 20 Feb 2015

An ITV casting call
Optomen Television @OptomenITVDoc
@OphthoMag Optomen TV are making a new ITV documentary series and want to speak to the UK's top ophthalmologists! http://tinyurl.com/ldwndwg
11:40 AM - 18 Feb 2015

Virtual reality in medicine
The Ophthalmologist @OphthoMag
More medical applications for VR headsets http://bit.ly/1zP4urr (In The Ophthalmologist: http://bit.ly/1vFIMLf)
11:36 AM - 17 Feb 2015

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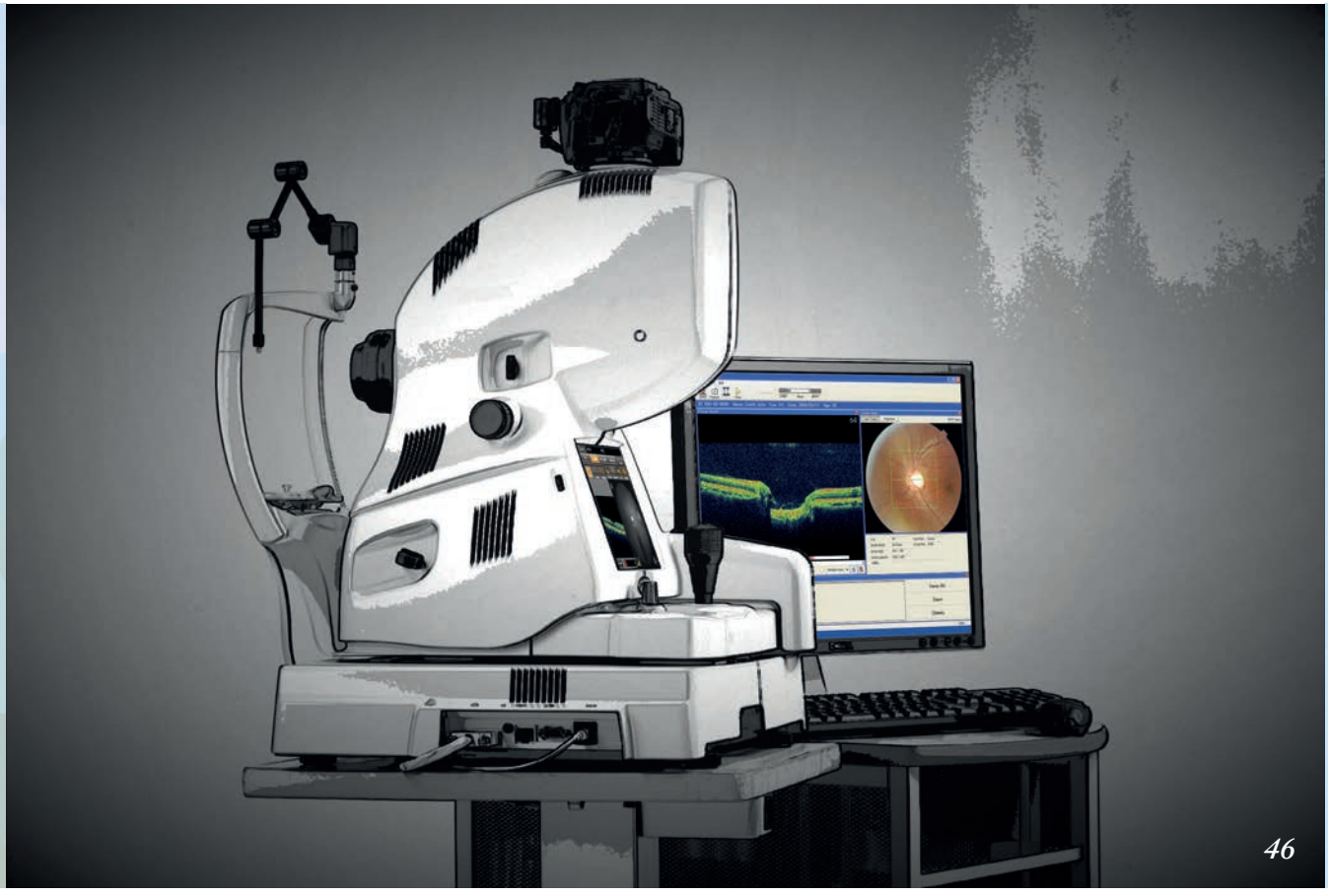


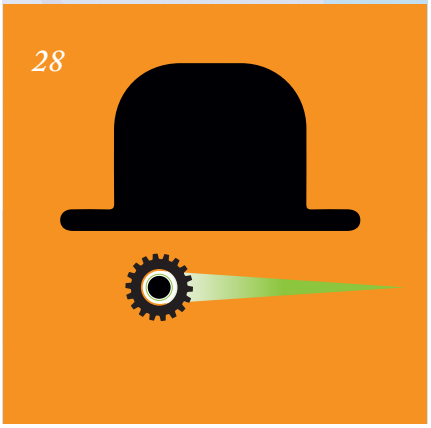
On The Cover

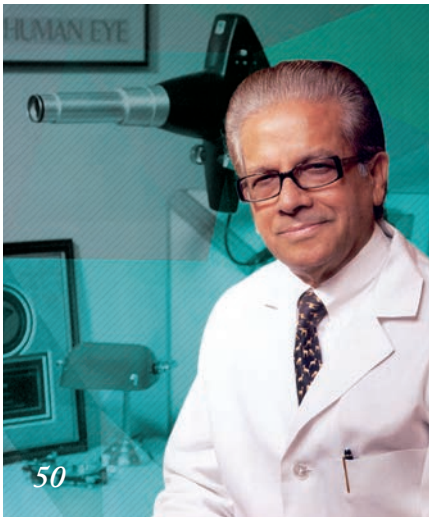
Entrepreneurs in the limelight (and other assorted colors).

Upfront

Feature

In Practice





Next Gen

Profession

Sitting Down With

the Ophthalmologist

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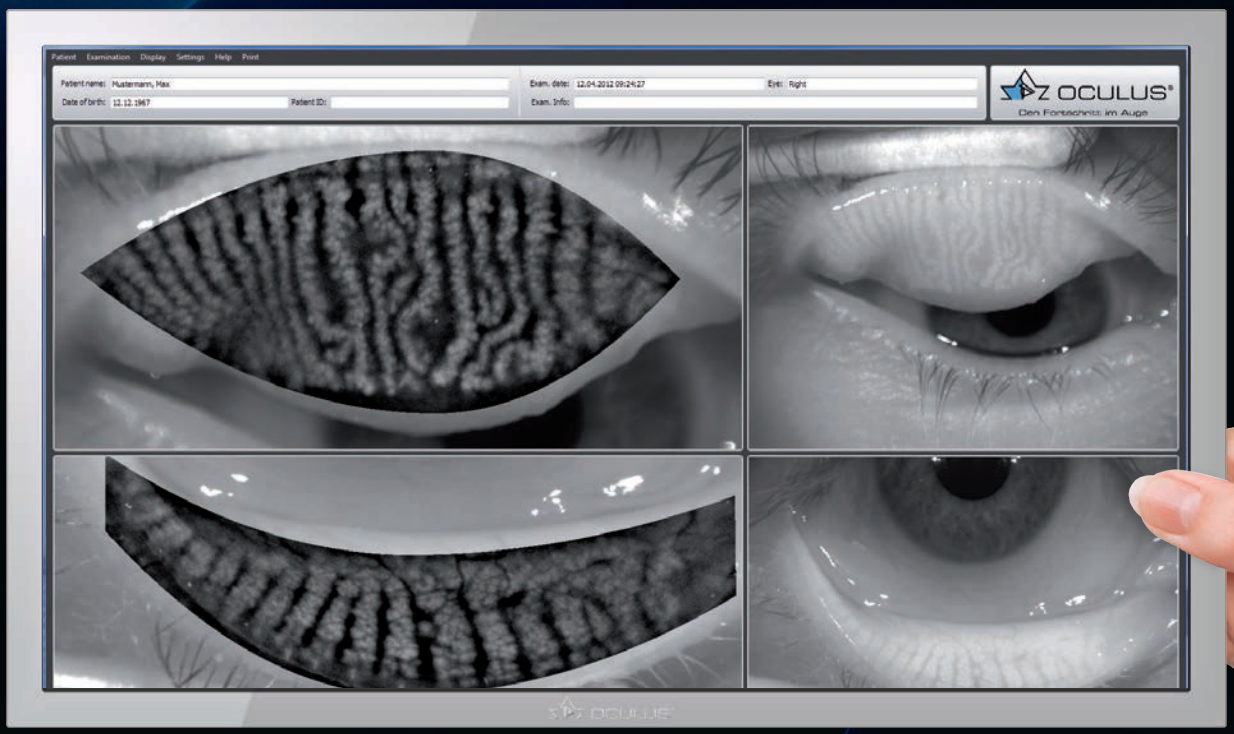

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Eye to the Telescope

This time around, The Ophthalmologist Power List seeks ophthalmology's rising stars.

Hopefully, you are now all well aware that our next issue will be devoted to the "Top 40 Under 40" Power List, featuring the younger generation of personalities and pioneers that will lead our field down a bright and forward-thinking path. (Don't worry, the Top 100 Power List will return in 2016!)

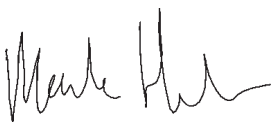
It was clear from last year's Power List that it's not just ophthalmologists that drive our field – in other words, you don't have to have a MD to make a difference. Research scientists, epidemiologists, pharma executives, venture capitalists all found a place on the list because of the huge contributions they have made to ophthalmology over the years.

Why not run another Top 100 list again this year? Instead of focusing on the past, we want to try to imagine the world of ophthalmology to come. What will our field look like in 10, 20 or 30 years? Just consider how much it has changed in the past 30. Consider the world today: the simple equation of 'aging baby boomers' + 'age-related eye disease' = 'incredible number of patients in need'. Will that number go down? Unlikely. In fact, I suspect there'll be far more in need of help in just a decade's time... It should come as no surprise that there is huge interest in the future – getting it right is incredibly important. The level of anticipation/trepidation is demonstrated by the popularity of events like the Ophthalmology Futures Forum and the Ophthalmology Innovations Summit; many big names (a fair few from the 2014 Power List) attend to present or listen – typically both.

We feel that it's extremely important to cheer the work of the young ophthalmologists, researchers and businesspeople who will fully shoulder the responsibilities of tomorrow. After all, these are the people who are already stepping up to the task – the people who are already researching, innovating, and forging a route through the growing challenges being stacked in front of them.

If you have already submitted a nomination for the "Top 40 Under 40" Power List, many thanks! If not, there's still time: please visit top.txp.to/PowerList2015 to thank the younger generation for all the hard work they've done so far, while pausing to consider all that they will face in the coming decades.

Mark Hillen
Editor



Frederik Raiskup

Frederik Raiskup is a senior consultant at the Universitätsklinikum Dresden's Department of Ophthalmology. He is a Fellow of the European Board of Ophthalmology and was awarded his *pro venia legendi* in the subject in 2014 by the Technische Universität Dresden. His interests include corneal, ocular surface and refractive surgery, with an emphasis on the study of corneal collagen cross-linking (CXL).

On page 28, Frederik shares his insight into corneal collagen cross-linking, and whether epi-on CXL is yet able to match epi-off CXL for the treatment of keratoconus.

Arthur Cummings

"I started my career in South Africa as a retinal surgeon, and developed a special interest in the anterior segment," says Arthur Cummings. Today based at the Wellington Eye Clinic in Dublin, Cummings is an internationally renowned expert on customized laser treatments having performed upwards of 25,000 LASIK procedures and 5,000 cataract and other IOL procedures. His research interests include refractive surgery, cataract surgery and corneal surgery for keratoconus.

Arthur shares his experience of running the Wellington Eye Clinic and developing and evaluating innovations that might shape the future of ophthalmology on page 22.

Bobby Qureshi

Bobby Qureshi a hugely experienced ophthalmic surgeon who likes to be at the leading edge of eye surgery, utilizing the latest techniques and equipment at the London Eye Hospital, where he serves as its Medical Director. He was one of the first surgeons in the world to perform partial-thickness corneal endothelial transplantation, and the first ophthalmic surgeon in the UK to receive a femtosecond laser.

To read Bobby's story of building the London Eye Hospital, and his self-financed development of the iolAMD implant, turn to page 24.

Farhad & Nikki Hafezi

Instrumental in building IROC in Zürich, and the 2014 recipient of the Carl Camras award, today Farhad Hafezi is building a new eyecare and research facility: the ELZA institute. His clinical focus is on corneal and refractive laser surgery including irregular astigmatism, and on enhancing and extending the use of CXL.

Nikki Hafezi is the Managing Director and CEO of GroupAdvance Consulting and EMAGine SA, which provide business development and fundraising advice to companies in the medical technology field, and develops, manufactures and markets medical products to address unmet ophthalmic needs. Nikki is also in charge of the ELZA institute's business strategy and development.

Read Nikki and Farhad's story of how they approached building the ELZA institute on page 20.

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Upfront

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

We welcome suggestions on anything that's impactful on ophthalmology; please email

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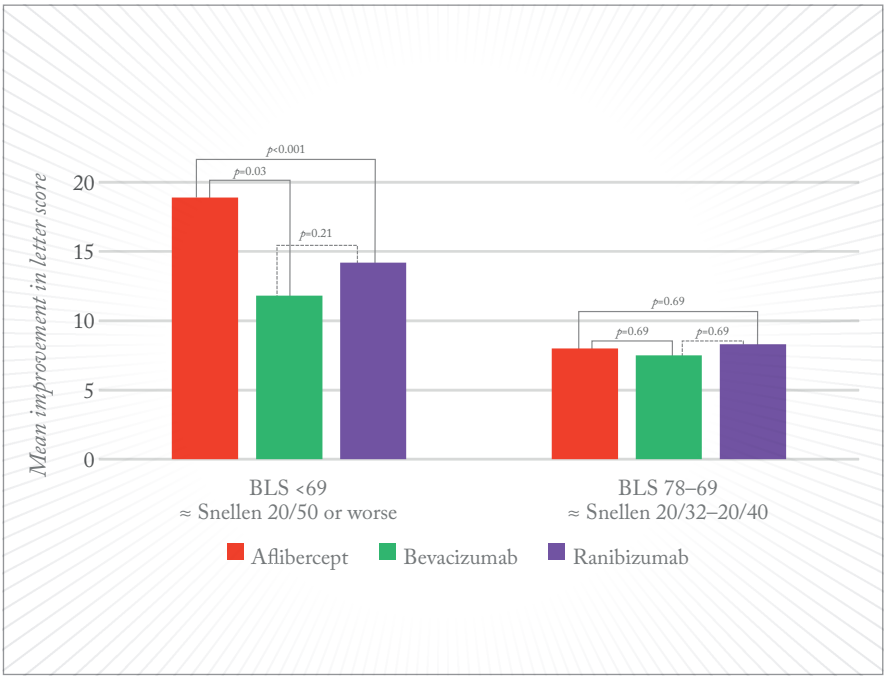

Figure 1. Visual acuity outcomes in the Protocol T trial after one year. BLS, baseline letter score.

Let's Settle This Argument Once and For All...

Which anti-VEGF agent works best in patients with DME? The US government sponsored the DRCR.net's Protocol T trial to find out.

Aflibercept is currently the new kid on the block when it comes to marketed anti-VEGF agents. Like ranibizumab, bevacizumab (and pegaptanib) before it, it has a number of potential therapeutic uses in age-related ocular disease: wet age-related macular degeneration (AMD), myopic choroidal neovascularization, retinal vein occlusion, and diabetic macular edema (DME). The questions is: which one is best for which disease?

Establishing that is easier said than done. Understandably, given the costs involved, there's a fair amount of reticence among pharmaceutical companies to run head to head trials of their drugs versus the competition. This is where the US government has stepped in. As with the CATT trial (which compared ranibizumab with bevacizumab in patients with neovascular AMD, [1]), the National Eye Institute (NEI) has funded the DRCR.net's Protocol T trial, which compared aflibercept, bevacizumab and ranibizumab for the treatment of DME (2).

The study's chairperson, Jack Wells explains, "The relative effectiveness and safety of the three drugs was unknown. We compared them by randomly assigning 660 patients with center-involved DME and vision loss from 20/32 to 20/320 to receive intravitreous

injections of either aflibercept, bevacizumab, or ranibizumab at a maximum of every four weeks for one year. The primary outcome of the study was the mean change in vision at one year in each group."

Was there a clear winner? "The results are reassuring: all drugs have been shown to be effective in improving vision and are equally safe, so doctors can confidently use them," says Wells. "In eyes with mild vision loss at baseline (20/32 to 20/40), the average gain in vision was eight letters with all three, but in eyes with baseline vision of 20/50 or worse, aflibercept-treated eyes gained significantly more vision – about one line on a Snellen chart – than eyes treated with the other two drugs" (Figure 1).

What might be the explanation? According to Wells, there are differences in the structure and relative VEGF binding affinities of the drugs, with aflibercept having the highest binding affinity. A pre-specified hypothesis of the study was that eyes with worse vision would have worse DME and greater macular thickness on OCT – due to higher retinal VEGF levels – and there might be differences in the drugs' efficacy related to their VEGF binding affinities. "That is why the interaction with baseline vision is compelling: it was pre-specified in the study's statistical analysis plan," Wells explains. *RM*

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Italy vs. Big Pharma

Italy reimburses off-label bevacizumab use in ophthalmology – pharma complains to the European Commission.

Eight months ago, the Italian medicines authority, the Agenzia Italiana del Farmaco (AIFA) made a decision: to reimburse patients with wet age-related macular degeneration (AMD) who were treated with bevacizumab. There's no doubt that the drug works in wet AMD, with the CATT trial broadly describing its safety and efficacy profile relative to ranibizumab (1). There is a slight problem: the drug is being used off-label: bevacizumab's approved indications are entirely oncological and not ophthalmological (2). You can see the attraction to AIFA – it is less expensive than the EMA-approved alternatives, and austerity-hit Italy needs to save money.

Understandably, representatives of the pharmaceutical industry are unimpressed. Healthcare payers are increasing pressure on pharma companies to reduce the cost of medicines, and AIFA's move might herald copycat moves by other EU states. In fact, in the UK, the co-chair of the NHS Clinical Commissioners group, Amanda Doyle, is campaigning for the UK Government's Department of Health and NHS England to "remove the current barriers" to off-label use of bevacizumab for the treatment of wet AMD (3).

Three trade federations – the European Confederation of Pharmaceutical Entrepreneurs, the European Federation of Pharmaceutical Industries and Associations, and the European Association for Bioindustries – have filed a complaint against Italy with the European Commission (4). They claim that the AIFA's decision infringes on European law and could potentially compromise patient safety.

Italy certainly appears to up for the fight. In February 2014, the Italian competition authority, the Autorità Garante della Concorrenza e del Mercato (AGCM), accused Roche and Novartis (who hold the EU marketing authorizations for bevacizumab and ranibizumab, respectively) of contriving to restrict competition in favor of the more expensive treatment.

Novartis has issued a statement that it "fully supports the complaint… which highlights the discrepancy between Italian rules on off-label use of medicines and the EU's pharmaceutical legislation" (5). *RM*

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5. *The Wall Street Journal. "Pharma files complaint against Italy for reimbursing off-label prescribing", (2015). Available at: http://on.wsj.com/17dPgFU. Accessed March 01, 2015.*

Chinese Myopia Mystery

The prevalence of myopia in Chinese children in middle-income areas far outstrips that of low-income areas – even after accounting for all known risk factors.

East Asia has a myopia crisis – and many environmental factors have been associated with its development: inadequate outdoor light exposure, underutilization of peripheral vision, close reading, mobile phone or tablet use, and genetic factors have also been found to play a role (1). Most myopia data in China comes from the country's richer and middle-income areas, but there were some suggestions that the rates of myopia were far lower in poorer areas. A team of researchers decided to investigate, and see if anything could be learned about the potential treatment or prevention of myopia along the way.

They measured myopia using the same machines, protocols and personnel in two nearby areas: Gansu, the second poorest of all China's provinces, and Shaanxi, which has a mean income that is right in the middle for China. One of the researchers, Nathan Congdon, explains: "We measured all of the major risk factors that are generally agreed upon as being important for myopia – including time spent on 'near focused' activities, time outdoors, wealth, academic performance, use of blackboards versus textbooks, parental education, population density, and more. We expected that when we took account of these, we would be able to explain the differences."

Instead, the results baffled the team. Even after taking account for all of these factors, Shaanxi kids had 70 percent more myopia, a finding that they couldn't explain – these two populations don't have major genetic, geographic, climate or environmental differences. "We expected to find an explanation – the fact that we didn't suggests to me that there are factors controlling myopia that we still haven't figured out," says Congdon.

So what might these other factors be? "That is the $64,000 question! We looked at lack of healthy sleep and nutrition in other populations, and didn't find much effect. There has been some emphasis in Chinese research on reading posture, but it's not clear to me how that would work biologically," explains Congdon. "What is changing as China gets richer that is leading to so much myopia?" he asks. "It's still an open question, but one we need to answer; we need to learn what behaviors in the poorer children are keeping myopia levels low." *RM*

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Wink to Zoom

Scleral contact lens plus smart spectacles equals 2.8 × magnification with a wink.

Currently, patients with dry age-related macular degeneration (AMD) don't really have a lot of options once they start to lose their vision: their magnifying glass starts to become their closest companion as the disease progresses. But, a team of Swiss and US-based researchers have developed a telescopic contact lens that could help (1).

How? The lens itself contains a very thin reflective telescope encapsulated within a breathable scleral contact lens. The telescope magnifies vision by about 2.8 times, and has an annular structure with gaps between the mirrors and a clear central aperture. The regions that don't contain mirrors have the ability to pass unmagnified light to the eye, and the result is a contact lens that creates two images.

Eric Tremblay, of the École polytechnique fédérale de Lausanne (EPFL) and one of the researchers explains: "We can switch between normal and magnified views with polarizing films that are placed on the contact lens, combined with liquid crystal glasses that align the polarization of light to one aperture of the contact lens or the other. This effectively acts as an electric shutter – changing the polarization of the liquid crystals switches the contact lens' zoom." The glasses also have another trick up their sleeve: a small light source detector that recognizes winks (and ignores blinks) – so winking is all that's required to switch the glasses' polarization and therefore the lens' magnification. *RM*

Reference

1. *E Tremblay, "Smart glasses and telescopic contact lenses for macular degeneration", Presentation at the 2015 AAAS Annual Meeting, San Jose, CA, USA; February 13, 2015.*

Optic Ultrasound Predicts Stroke Outcomes

After a stroke, the brain swells... and for every millimeter that the optic nerve sheath diameter swells, the risk of death increases by 4–6 times.

Imaging the retina to understand systemic disease is not a new concept – you're able to noninvasively image not only the retinal vasculature, but with optic nerve and the retinal nerve fiber layer, neural tissue too. This is beginning to be exploited to map the progression of both vascular and neurological diseases (1,2). It's also starting to be useful in predicting outcomes after patients have experienced a stroke (3).

Severe strokes tend to result in sharp increases in intracranial pressure (ICP) – and makes for a poor prognosis for the patient. ICP can be measured by lumbar puncture, but this is invasive, and can easily be confounded by other aspects of the patient's medical management, such as acute sedative use. It turns out that measuring the optic nerve sheath diameter (ONSD) with optic ultrasonography (OUS) is a promising method of assessing ICP.

How was this established? Researchers at the Gainesville campus at the University of Florida performed OUS on patients (n=86) who presented with stroke on both the day of admission and one day later, measuring ONSD – transversely and laterally – in both eyes (3). Regression analysis was then used to assess the relationship between ONSD and patient outcomes.

The researchers found that there was a significant difference in mean ONSD between patients who died within the first six months and those who survived: for every extra millimeter, the risk of death was four times higher in patients with ischemic stroke, and six times higher in patients with intracerebral hemorrhage (Figure 1a). Larger ONSD was also associated with a greater probability of death after six months (Figure 1b), poorer functional outcomes, and more severe disability.

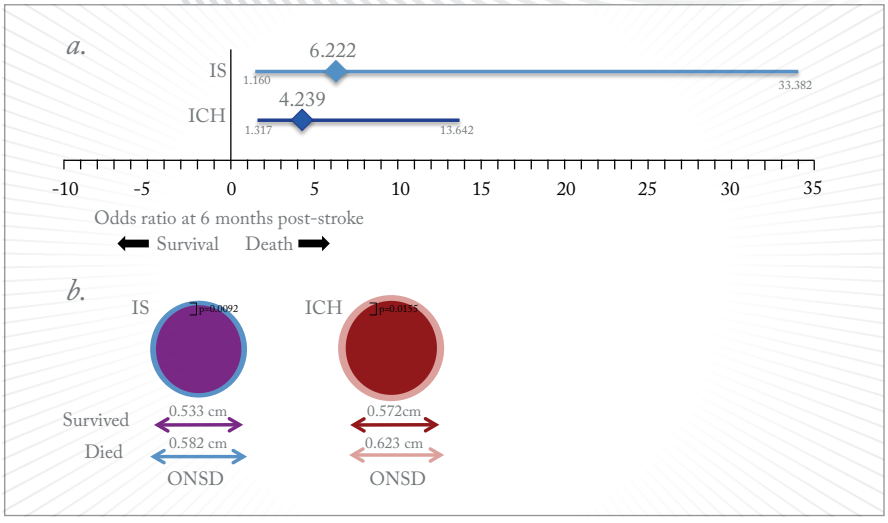

Figure 1. a. Odds ratio of mortality 6 months after stroke; b. Mean in-hospital ONSD was smaller in patients who had survived at 6 months post-stroke, compared with those who died within that period. ONSD, optic nerve sheath diameter; ICH, intracerebral hemorrhage; IS, ischemic stroke.

The authors are hopeful that OUS could offer an attractive screening alternative for ICP, as it is a routine bedside test that is performed using gel and a device placed on closed eyelids, potentially allowing doctors to reliably and noninvasively detect elevated ICP and initiate ICP-lowering treatment earlier. *MH*

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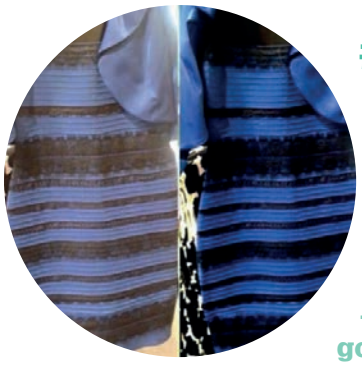

#TheDress That Impressed

One Tumblr post "broke the internet" – but what's really going on in the visual pathway?

By now, you've all heard about The Dress: a piece of clothing with fabric that seems to shift from blue and black to white and gold depending on who's looking at it. With over half a million notes on Tumblr and nearly 40 million BuzzFeed views, everyone is talking about it – even ophthalmologists. Shortly after the photograph of the dress went viral, ophthalmologists took to the media in droves to explain the phenomenon. According to Julia Haller, Ophthalmologist in Chief at Wills Eye Hospital, Philadelphia, PA, USA, there are two main theories for the dress' mysterious power – it's either in the eye or in the brain.

One possibility is that the image hits the "sweet spot" – the wavelength where rod and cone photoreceptors share duty. There's also a tiny level of variability in photoreceptor function between individuals, so those who perceive the dress as blue and black may have cones that function slightly differently to those people who see it as white and gold, or they may just be relying more heavily on their rod cells. It's likely not just the photoreceptors themselves that are responsible for the effect, though – ophthalmologists at the 38th Annual Macula Society meeting in Scottsdale, AZ, USA, think that contextual processing in the brain might also play a part. The picture was taken under some pretty serendipitous lighting conditions – some brains perceive it as overexposed, and therefore color-correct to "see" blue and black – whereas others, thanks to the Purkinje effect, perceive it as a white and gold dress in dim light. Contextual processing can be manipulated – try changing the brightness on your monitor, or exposing your eyes to bright or dim light before looking at the picture, and you may even see the colors "change."

The dress was actually blue and black, but the facts aren't nearly as interesting as the spotlight The Dress is shining on visual processing. *MS*

Plastic and Fantastic

Damage to the primary visual cortex strengthens neuronal connectivity between the retina and pulvinar nucleus of the thalamus – and might explain a few phenomena.

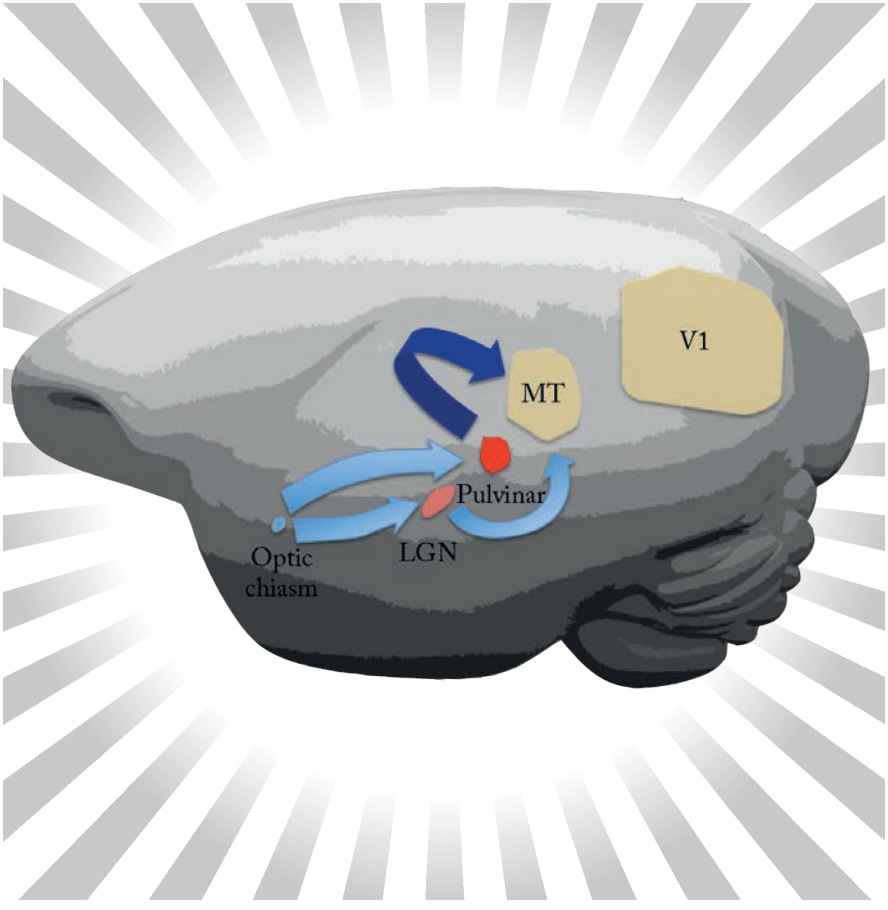

Figure 1. The retina-pulvinar-MT pathway supports the preservation of vision following a lesion of the primary visual cortex (V1) in early life (1). LGN, lateral geniculate nucleus, MT, middle temporal region of the cortex.

A recent study (1) has shed new light on how the brain can reroute visual information to bypass damaged areas and preserve vision. As vision is the most complex of our senses, over half of the cerebral cortex is devoted to facilitating it. Typically, signals travel from the retina via the lateral geniculate nucleus (LGN) in the thalamus and on to the primary visual cortex (V1). From there, it is distributed to other areas of the visual cortex. The middle temporal (MT) area of the visual cortex also receives input from the LGN. If this pathway is damaged, it can often result in cortical blindness. However, children with lesions in the V1 area can often retain vision, while adults with identical injuries go blind.

The study involved removing sections of V1 in neonatal and adult marmoset monkeys, then using neural tract tracing, diffusion magnetic resonance imaging and immunohistochemistry to measure brain and visual activity. In the neonatal monkeys, damage or removal of V1 resulted in greater connectivity between the retina and the pulvinar nucleus of the thalamus, and degeneration of retinal input to the LGN, when compared with both controls and adults with V1 lesions – indicating the potential importance of the pulvinar in preserving vision.

To date, research has mainly focused on the role of the retina–LGN–MT pathway in the absence of the primary visual cortex, but the study authors argue that the retina–pulvinar–MT pathway, and its ability to restructure itself in childhood, has not been accounted for. "Decades of research have focused on one pathway in the brain thought to be responsible for conscious vision. We knew the brain has the capacity to rewire itself following injury or trauma but the idea that there is a second pathway providing visual information to the brain is a relatively new phenomenon," said James Bourne, a professor at Monash University, Australia, who led the study. "Our research proves a second pathway exists (Figure 1), but significantly it also shows the brain is much more plastic than originally believed."

"The next step is to undertake more work to better understand the complex circuitry of the visual brain and how pathways are established in early life and removed at a later stage," added co-author Claire Warner, stating "We're a long way off but this opens up a whole new line of inquiry to see if we can develop regenerative techniques to restore vision loss." *RM.*

Reference

1. *CE Warner at al., "Preservation of vision by the pulvinar following early-life primary visual cortex lesions" Curr Biol, 25, 424–434 (2015). PMID: 25601551.*

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Enterprising Ophthalmology

Four people, three stories, one topic: entrepreneurship

By Mark Hillen, Roisin McGuigan and Michael Schubert

Ophthalmology and entrepreneurship go together well. An aging population means that there's a growing market, margins are good, and new drugs and technologies are continually being introduced that are transforming the way ocular disease is diagnosed and managed. Simply put, a lot of people want improved vision. If you can provide it better than the competition, there's money to be made.

Building a success story isn't easy, and there's no one right way to do it. We interviewed four people who have experienced considerable success within ophthalmology to hear their stories of building an eye institute (Nikki and Farhad Hafezi), running a successful and resilient clinic (Arthur Cummings), and making the leap from the NHS to starting an eye hospital, and designing, developing and marketing a new IOL design (Bobby Qureshi).

Nikki and Farhad Hafezi are a husband-and-wife team who have taken on the challenge of building a new eye hospital and research center in Zürich: the ELZA institute.

Nikki is in charge of ELZA's business strategy and development, and is also the Managing Director and Chief Executive Officer of GroupAdvance (fundraising and business development service provider) and EMAGine (developer and manufacturer of ophthalmic medical products).

Farhad serves as ELZA's Chief Scientific and Chief Medical Officer. He's also Professor of Ophthalmology at the University of Geneva, Clinical Professor of Ophthalmology at the Keck School of Medicine, at the University of Southern California, Los Angeles, USA, and was instrumental in building IROC, the Institute for Refractive and Ophthalmic Surgery with Michael Mrochen and Theo Seiler. Farhad is also one of the pioneers of corneal collagen cross-linking, being a great proponent of its use for the treatment of corneal ulcers.

Arthur Cummings is the Medical Director of the Wellington Eye Clinic, Sandyford, Dublin. A well-known congress speaker who has been involved in the development and clinical evaluation of many of ophthalmology's recent innovations, he shares his experience of not only building a highly successful cataract and refractive practice in Ireland, but of also surviving the storm of recent Irish austerity measures.

Bobby Qureshi was just finishing his training and about to start a Consultant position within the UK's National Health Service, when he founded the London Eye Hospital (LEH) in 2004, followed by London Eye Hospital Pharma in 2011.

In 2014, LEH Pharma launched iolAMD – a micro-incision, injectable telescopic implant that solved the big problems that held back earlier telescopic implants from a more widespread adoption. It could be the most successful new implant in history. He's also independently wealthy, and has never had to court or answer to investors.

Planning for Success

Nikki and Farhad Hafezi on….

How they decided to build a new ophthalmology institute, ELZA

Nikki Hafezi: There has been a paradigm shift in the mentality of young ophthalmologists in recent years. When Farhad was a young resident, he aspired to climb the traditional academic ladder. He obtained his MD/PhD, garnered fellowships, became a really good clinician and, with time, he was appointed chairman of a university clinic. Any ophthalmologist of his age group would agree that Farhad has achieved what many hope to in their professional careers.

Nowadays, his students and residents have different aspirations. There's more focus on work-life balance and on quality of life. While dreams of climbing the ladder are still present, the "new" generation have other criteria in their career development plans: innovation, economics and entrepreneurship. We know that income influences almost everyone's life, but it's not necessarily the most important factor anymore; people want a blend of quality of life, entrepreneurship, creativity, research, and clinics. They want it all, basically. Providing that will form the foundation of the ELZA Institute, which is on course to open in April.

The planning process

NH: We wanted to treat the future institute not as a private practice relying on a specific doctor, but as a business venture. The first consideration when building ELZA was its location in Zürich. Instead of having a private practice in the middle of the city center, we chose to go where patient demand would be the greatest. The northwest region of Zürich has a relatively low ratio of ophthalmologists to patients, and considering the building and expansion plans of the region, the population and industry are booming, that is where we decided to set up our first site.

Farhad Hafezi: Our second consideration was that we needed to focus on our social media and Internet presence. We know our patients are really plugged in. They read, research, talk to each other – and all of that communication is on the Internet. So we put a lot of effort and investment into our online presence to attract patients and build our referral network.

NH: We also needed to reserve time for good and valuable research. Why? We have a term, 4P, which stands for "podium power and peer-reviewed publications." We believe that 4P is just as important for sales as sponsorship or direct marketing efforts, especially in the medical field. Farhad, for instance, publishes good data; people read about him; he's onstage at congresses speaking about his research and clinical experience. So he's an opinion

maker, and at the same time, he's building research collaborations, increasing his referral network, and becoming more appealing to industry, which could be fruitful in terms of funding and collaborations. 4P relates to ELZA in that it will support research collaborations with other opinion makers in the field, indirectly support a referral network, and provide opportunities with industry, like directed research projects.

The most important element of the business plan is human resources. Identifying, recruiting and retaining the "right" employees are the most challenging tasks for any company. So what is ELZA's unique selling point to potential employees or collaborators? How can we attract the best and the brightest people? With much thought, we decided we want to offer the work-life balance that younger generations say they want – flexibility, competitive income, academic opportunities, creativity and a career future. This increases our chances of recruiting and retaining ambitious young ophthalmologists. And because these ophthalmologists want to balance the benefits of a private setting with the advantages of academia, we will provide lab space and research opportunities. In a nutshell, ELZA will offer them a clear career future so that they can better envision staying with us on a long-term basis.

Attracting patients to ELZA – ultimately, the referrer needs to keep their patients

FH: It's absolutely essential for private practitioners to have a referral network. The idea of "if you build it, they will come" is too risky in Zürich. While we hope that the location of the building will draw patients, we can't rely on it happening. So, we asked: why would a colleague refer a patient to us? What is our unique selling point?

One thing we will offer is the assurance that referrers will keep their patients. For example, a general ophthalmologist might have a long-term patient who develops keratoconus – but it may be intimidating to refer the patient to a subspecialist in case the patient does not return. This fear is one of the obstacles specialists need to address to build their patient referral network. Another important aspect is that specialists should provide good, prompt feedback. A referral network goes beyond just medical colleagues; opticians and optometrists often also spot ophthalmic disease, refer their patients to a specialist, and rarely get structured feedback. Therefore, I think the referred specialist should treat anyone who refers a patient with enough respect to provide feedback, regardless of whether the referring individual is an optometrist or a fellow ophthalmologist.

Minimizing the risks involved in building a new institute

NH: One of the most common pitfalls when building a company is to involve emotion when making decisions. From the start, we had to eliminate the emotion and ego aspects. We opted not to play the "famous professor" card; we didn't want to assume we'd immediately have patients if we just installed ourselves in the city center. We knew that the competition was much higher in the city than in the periphery due to the supply of specialists, not to mention the much higher running costs. We acted as if Farhad were a young ophthalmologist just leaving academia, and simply chose a location where the competition for attracting patients was much lower.

The possible obstacles in our business plan were: how can we obtain patients fastest? How can we reduce the obstacles for referring medical professionals to send their patients outside the city center? Where can we reduce our costs the most? If you had asked Farhad 10 years ago, he would probably not have considered setting up a private institute outside the city center, but now we know that we need to think outside the box to maximize the potential of the institute.

Funding the enterprise

FH: ELZA is 100 percent self-financed. At this time, no investors or shareholders are involved, for all of the good and bad that it entails.

NH: To pick low-hanging fruit, we're making ELZA as complete as possible. So we're starting with fully equipped anterior and posterior segment practices. We've hired a seasoned medical retina specialist who helped develop the current benchmark OCT technology. While Farhad's subspecialty is irregular astigmatism, ELZA will be more than happy to operate on patients with simple refractive errors. Farhad is a trained fellow in medical and aesthetic lid surgery, so ELZA will also offer these procedures. Ultimately, our institute will aim to be as comprehensive as possible, even offering pediatric ophthalmology services, to improve its chances of success.

Regarding equipment and infrastructure, it's important to us that we're equipped with a state-of-the-art excimer (Schwind AMARIS) which will be fully available for use from the opening of the clinic in April. In terms of cataract surgery, discussions are underway to decide on the best option for both the patients and the institute.

The lasers aren't the only expensive items, though – ELZA has purchased the full spectrum of anterior and posterior segment OCT technology, Scheimpflug and Placido-based corneal topographers, and instruments for fundus photography and visual field examination. Good practice management software isn't cheap, either, but it's worth it to create a network that will allow future growth. The renovation and construction costs for ELZA's brand new building were high, but we believe our decisions will make ELZA an institute that's built to last.

Juggling projects and finding time to relax

NH: On a more personal note, the daily grind can be exhausting. Farhad and I are also active parents of two young daughters, so we try to keep a balance between work and family. Anyone who knows us probably knows our daughters because they have frequented many meetings in the past. Some people think we're crazy to work together and involve the kids, but honestly, we wouldn't have it any other way.

Focusing On Fundamentals

Arthur Cummings on…

Building a successful practice…

There are no shortcuts. If you want to build a successful clinic, you've got to do it right. You need to start with a good, solid foundation laid by good clinical decisions in the best interest of the patient – you can't focus on generating income. I have a clinic manager who takes care of the business; he makes sure we stay afloat, especially in tough times. But all of the clinical decisions are mine. I have no problem seeing 10 patients a day and referring nine away because they aren't good candidates. I make my decisions based on the patient's suitability, and it's not an issue if we don't treat everyone we see. I've not got anyone looking over my shoulder saying, "Hey! We didn't get enough patients today!" Why don't we have a high-pressure selling environment? Because we operate on word of mouth. It's the most valuable thing a practice can have. But there is only word of mouth if the patient's experience is consistently good.

As for the last few years of austerity, I suppose our biggest feat is surviving. It's been tough in Ireland, no question about it. But we've got through it well and things are definitely turning around. One thing we learned from the recession was that we needed to diversify more. We were doing an awful lot of LASIK and less intraocular work, but I think now the balance is about half and half.

We also put emphasis on following outcomes. When our general manager, Ed Toland, joined us he asked me what our conversion rate was and I asked, "What's that?" What you don't measure, you simply don't know. Now, we let the numbers talk. We have a very good idea of how we drive nomograms for LASIK, or of what's working in our clinic and what isn't. When we try a new procedure, I'm not the judge; the patients are. If enough of them are satisfied, we keep doing it, and if they aren't, we stop. It's not rocket science, just good clinical practice.

We treat people individually – we don't have a protocol to work through. We sit down and listen, then give them the best advice we can. If someone isn't a good candidate for LASIK and there's an alternative, we offer that too. It's always good to have different solutions available. Also, I think something that's quite unique for a big surgery like ours is that I see all of our patients preoperatively, perform the surgery, and follow up with them postoperatively too. I don't just do the surgery and let someone else do the rest; I stay heavily involved. So we actually work in a small, country practice style, just on a bigger scale.

My advice is, to be successful, focus on your patients and their experience in your clinic. Do that properly, and the rest will follow.

… and promoting it

We've tried traditional marketing, advertisements and so forth, but we didn't like the way it worked. We got some people who would come in because they'd seen our advertisements, but they weren't really interested. For me, it's all about word of mouth. If you make decisions based on your patients, eventually you'll build a base of patients who would use you again and recommend you to others. About 30,000 patients have had LASIK in our clinic, and the vast majority are good word of mouth proponents because they've had a good experience. That's how we build our reputation.

Alternatively, if your patients are unhappy, word of mouth can turn against you – negative comments spread farther and faster than positive ones. In terms of online restaurant reviews, one critical comment can negate 11 good reviews. If you don't do things right, word will spread quickly, and you will not be successful.

Investing wisely in new technology

We're always on the lookout for new innovations that could benefit our patients. Our mission statement says that patient satisfaction is our top priority. When something new comes on the market, I ask, is it interesting, and is the science behind it reliable? If the answer is yes, I'll usually speak to the company's CEO or CTO, and find out how it works and who's used it before. It's important to get as complete a picture as you can before you invest your time and money. Even then, you need to be careful not to make promises to patients that just aren't true and have not yet been validated. We'll only make a final decision to try something if we have a need for it – if it will benefit our patients or our practice, rather than just buying it as a toy.

We're not always the first to adopt new ideas. Often, we'll note new technologies early on and keep an eye on their development. I was very slow to come on board with femtosecond lasers, for example. At first, all they were doing was making flaps, and I couldn't see the value. But they developed into a fantastic cutting tool. When femto started doing things like channels for rings, pockets for corneal inlays, and penetrating and lamellar keratoplasties, it became a much more interesting option. I got my first femto in 2010, about a decade after they entered the market.

If you want to try new things, they've got to make economic sense too. So when I want to try something new, I run it past my clinic manager and say, I'm thinking about this new technology and here is the cost, and because he understands the field, he won't just look at the monetary return. He'll look at what it could do for the clinic, and for the patients. Technology may be expensive, but it might also offer your patients more options and add to their perception that your clinic always does its best.

The next (potential) purchases

Cassini is a very nice tool that I've enjoyed getting to know over the past year, and I'm thinking seriously about getting SMILE; I've been hearing a lot of good things about it, and I think it's going to be part of the future. But some of the things I'm most excited about at the moment are actually homegrown projects. Our clinic has a very strong academic link, despite being private. Someone who's had a big influence on my interest in science is Michael Mrochen. He'll say, "Hey, look at this cool new idea; what do you think?" and we'll go through it from a clinical perspective.

Some things we're working on now include an ocular biometer that combines a Purkinje imaging method with an OCT device to measure many aspects of the eye, including things like posterior cornea and the geometry of the anterior and posterior crystalline lens, which gives us really precise predictions of IOL power. So this device has the potential to make it much easier to choose a lens, even with difficult eyes. Michael presented some of the preliminary results at Winter ESCRS recently.

Another example is a device capable of mimicking any optical solution – any through-focus curve. It can therefore allow the patient to preview any trifocal, bifocal or extended depth of focus IOL, as well as other presbyopia solutions. So in theory the patient arrives in the clinic and puts this helmet on, and it gives them a live view – not a simulation – of what it would be like to look through any optic before they make a decision; it gives the patient a better idea of what to expect. It's all about managing expectations, as any refractive surgeon would be well aware.

Keeping things interesting

Back in South Africa before I relocated to Ireland, I had a senior colleague say to me, "You know, your enthusiasm is fine, but you've only been in practice three years. Wait until you've been doing this 10 years – you'll be as bored as anything." And I thought to myself, it's taken me a long time to get here; I don't want to get bored!

I've discovered that the best way to stay engaged and excited is to always be involved in the search for the next solution, the next leap forward. The entrepreneurial, start-up side of my work has kept the day-to-day much more fun. If you go in every day and think of your work as just a job, then maybe you'll get bored. But if you're continuously looking at new things, evaluating them, considering them, discussing them, it keeps things interesting. So I love the research side of my work – it's fabulous. It breaks up your time in the clinic so that when you do see patients, you're fresh and enthusiastic. It's so important to enjoy what you do.

What You Can Achieve... When You Believe in Yourself

Bobby Qureshi on…

His beginnings

I've always been a geek. I grew up watching Star Trek, playing video games, learning how to code computer programs, and building my own telescopes. I went to medical school at the University of St. Andrews, then Guys and St. Thomas' Hospitals. My father wanted me to become a cardiologist, but I had such a good time during my ophthalmology elective that I knew it was for me – I'd do ophthalmology or I would leave medicine. I did my PhD in Liverpool and my training at Moorfields Eye Hospital. From there, it's been natural for me to combine my two passions – technology and ophthalmology.

I've always gone my own way and I've never given in to criticism. I am happy to listen – but I find that everybody just wants to look backward and find reasons why things can't be done, rather than look forward and find ways to make them happen. There's no such thing as "impossible!" I think underlying it all is the fact that I believe I can do this, and this confidence allows me to take calculated risks beyond other people's comfort zones.

Setting up the London Eye Hospital

During my time at Moorfields, I conceived the idea of forming my own hospital. I feel like too many people just get through the day, do their job and go home – they're not giving the best they can, and putting their heart into their work. I can't believe I spent 25 years with the UK National Health Service (NHS), I really felt it drained me of my energy and enthusiasm; I left for good in 2011. It is a great organization with so many brilliant people but they aren't always appreciated and sometimes treated badly by the people who run it.

I wanted to show people how it could be done, when all you had to do was what's best for the patient based on your experience – without having to consider cost, internal politics, mainstream practice. That's what I believe I've created with the London Eye Hospital (LEH) – the best technology, the best doctors, and the best service possible.

This may sound odd, but when I first set up LEH, I didn't have a business plan, or even a strategy for breaking even. My main goal was to have the best technology and facilities I needed, and I did whatever it took to create my ideal practice. I simply wanted to create the best eye hospital in the world. For years, it cost me huge amounts of money, but I kept funding it because I believed in what

I was doing. Now the tide has turned – I own a very profitable organization that is still based on my original principles. Our patients appreciate that we don't compromise on anything; we just offer the best treatment available anywhere in the world for their individual case using state-of-the-art equipment and facilities and the most experienced surgeons.

Innovation

I want to keep pushing boundaries, trying anything that is innovative and could benefit my patients. A lot of people bring new ideas to me now because I have a reputation for trying them – though I choose carefully; I have to believe in their potential. Some people may think we're out on a limb, and I've drawn criticism from my colleagues, but time has already shown us that with some of the technologies we try, others follow. I remember purchasing my first first femtosecond cataract laser – the first one in the UK. I believed they were the future – and this year will see the first NHS hospital get one – so many of the things we do are just ahead of our time. We have things in our pipeline that sound like science fiction – but they are the future, and I believe the whole world will follow.

Ultimately, I think our dedication to innovation and trying the latest techniques and technologies means we can offer our patients a bespoke service – you need to try everything out there to find the best treatment. So that's what we do – the best that can be done. We aim to provide every option there is, from the cheapest to the most expensive. And we aim to know our patients – their hobbies, their sports, how big their computer screens are, how close they sit to the television, how often they drive. We don't consider value for money; we just offer the best possible treatment for that patient.

Developing iolAMD

I first had the idea for iolAMD in 2007. I've implanted a lot of different lenses at LEH, including telescopic ones for AMD. I was one of the first to implant the IOL-VIP, I believe I implanted the first IOL Revolution, and I've implanted hundreds of each – but both had issues. They were huge lenses, requiring a 7 or 8 mm capsulorhexis (which isn't easy, even with a femtosecond laser), and the surgery took a long time. You have to put several things into the eye, then fix them together like Lego – it's a nightmare. I felt that it was fundamentally flawed, and it was never going to take off. I can't have been the only person in the world who thought there must be a better way to do this.

Dry AMD is the biggest untreated ophthalmic need in the world right now, and we had no suitable treatment options. Until stem cell therapy and other therapeutics arrive, our only options are optics and vitamin supplements. Therefore, creating the iolAMD was the greatest opportunity I could see – a lens based on a simple Galilean principle, updated for the 21st century. It's foldable and can be inserted through a small incision. The total procedure, including cataract extraction, takes less than 10 minutes, and I believe it provides high-quality vision for patients with AMD.

I couldn't believe no one else had done it yet – the market is huge, it's phenomenal. I knew that creating something that can be done at the same time as a routine phaco procedure, without additional risk, that conveys extra benefits to patients with AMD would be huge. In potential revenue and sales, it's billions of dollars.

Assembling a great team

I know a lot about optics, so I could model the lens myself, but I needed other people to fine-tune it for me and work on other aspects of developing it. I had learned from my experiences with the LEH and wanted to find the best people I could. I already knew Pablo Artal from our work with Calhoun Vision's Light Adjustable Lens – and at first, he said it couldn't be done. But I wouldn't let it go because I knew it could, and eventually he gave in.

I met Rob Hill, who was a partner in the company that introduced the IOL-VIP to the UK and had a lot of knowledge about telescopic lenses. I knew I wanted him to work with me on iolAMD. So I built a great team, including scientists, managers and lawyers, but I wouldn't take any investors. I didn't want to lose control of what I was doing. The last thing I wanted was someone telling me what to do because they gave me the money to do it.

A £500,000 training exercise

Next, I needed to learn about the regulatory process, which is where the vitamins LEH Pharma sells come in – I wanted to make the best-quality evidence-based product in the world. Not only do they add to the AMD products available, but also they were a relatively cheap way to learn. To take a drug through regulatory processes can cost you tens of millions, but taking a vitamin through the regulatory and commercial processes costs maybe half a million, which is why I chose it. I learned so much with that half a million.

That's why I set up LEH Pharma, opening with iolAMD and with a lot more ideas in the pipeline – although I can't talk about them just yet! I plan to continue to develop my pharmaceutical business on a timeline that introduces new products every few years.

Believing in yourself

To anyone looking to bring their own innovation to market, I'd say: don't listen to anybody. People will either pull it to bits, or tell you it's amazing when it actually can't be done. So many times, I've said I'm going to do something – like launch a range of vitamins, or build my hospital, or create a lens for AMD – and people simply didn't believe me. Now that I've done it, people have to believe me. I think if you have an idea and you really believe in it, go for it, no matter what anyone says. Worst case scenario, it won't work out, but you'll learn so much in the process. And next time, you'll do even better.

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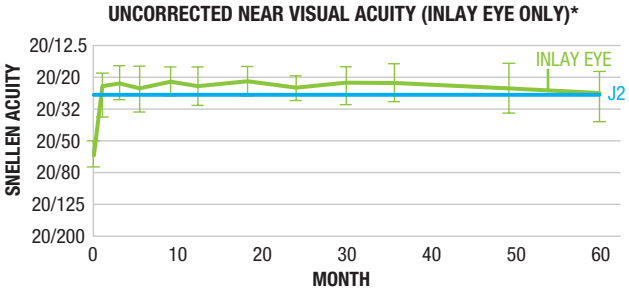

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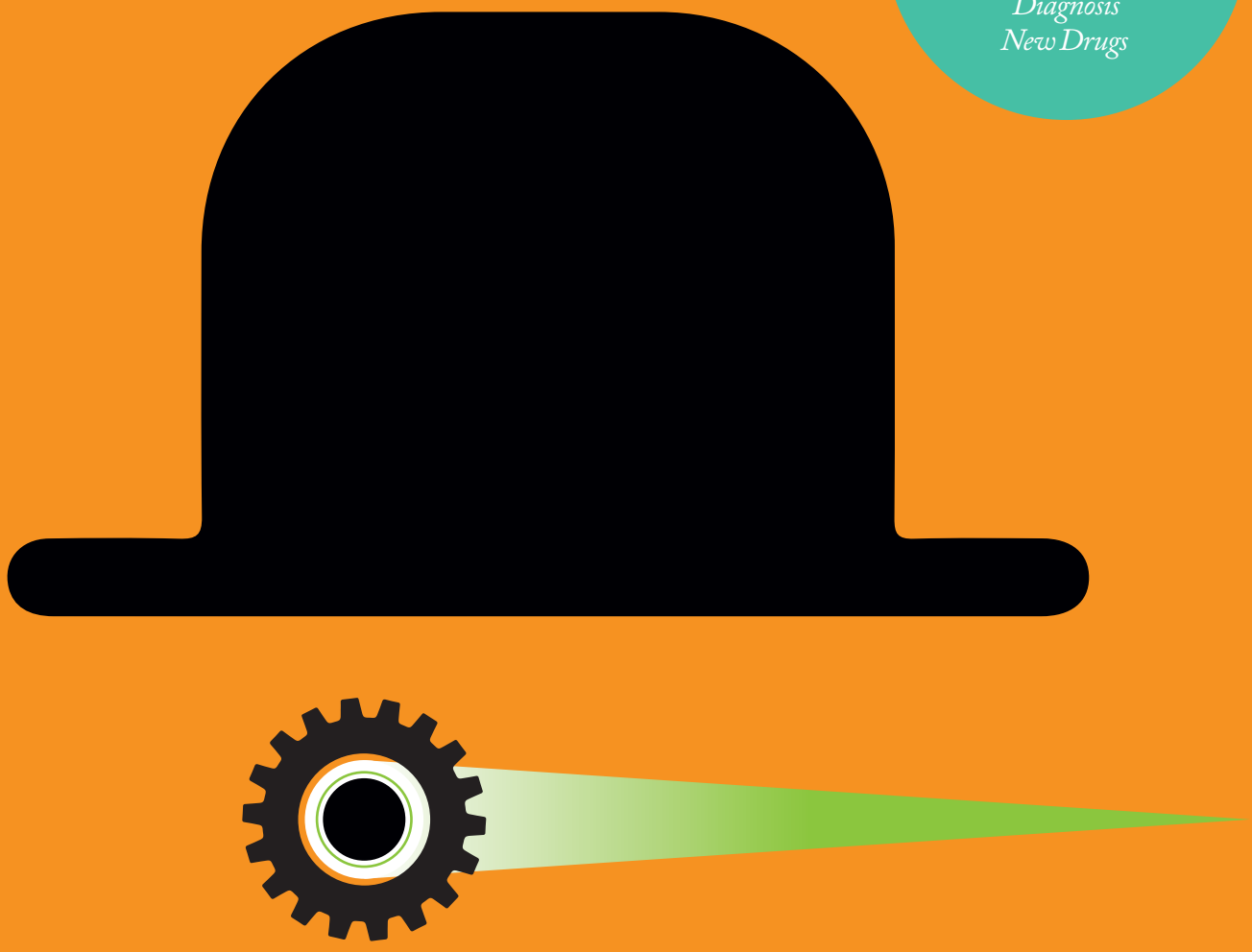


Epi-On or Epi-Off?

Corneal cross-linking can halt the progression of keratoconus, but what is the best approach to treatment?

By Frederik Raiskup

Keratoconus is a common corneal disorder, affecting around 1 in 1,500 of the general population, where the central or paracentral cornea undergoes progressive thinning and steepening to generate the classic cone-shaped cornea (Figure 1). As keratoconus progresses, it results in irregular astigmatism, and scarring begins to occur on the exposed high points of the cornea. This leads to a slow but clear decrease in best-corrected visual acuity (BCVA), with low-contrast visual acuity (VA) deteriorating more rapidly than high-contrast (1,2). It's not just VA that is progressively lost with keratoconus, though; it's also quality of life. The disease typically has a young age of onset, and this has two main implications: significantly impaired vision-related quality of life, and the lifetime economic burden of its treatment (3). For context, in 2011, the average annual cost of routine vision care for someone in the US with myopia was estimated to be US$200, whereas the estimated annual price tag for keratoconus was US$653; the lifetime cost of the disease for a single patient, including clinic visits, fitting fees, contact lenses, surgical procedures, and potential complications, was estimated to be US$25,168 (3). It's a significant, lifelong public health burden. In patients with mild-to-moderate keratoconus, VA is typically corrected with spectacles or contact lenses (and, in some cases, intracorneal ring segment implantation). Advanced disease typically requires corneal surgery, including deep lamellar keratoplasty or penetrating keratoplasty. But if you want an intervention that's able to slow – and even halt – the progression of keratoconus, you need to look to corneal collagen cross-linking (CXL; Figure 2).

CXL involves a photochemical reaction. Ultraviolet (UV)-A illumination activates riboflavin, which leads to oxidative cross-linking of collagen in the corneal stroma, strengthening the cornea in the process (4) – which is why keratoconus progressions is one of the principal indications for CXL. The procedure is indicated in several circumstances, particularly when keratoconus progression (measured by changes in K values, astigmatism, pachymetry, corneal hysteresis or VA) is evident. Children with keratoconus are at a particularly high risk of progression, which is often rapid, so diagnosis in patients, particularly boys aged under 18 years, is a prompt indication for CXL (5,6).

At a Glance

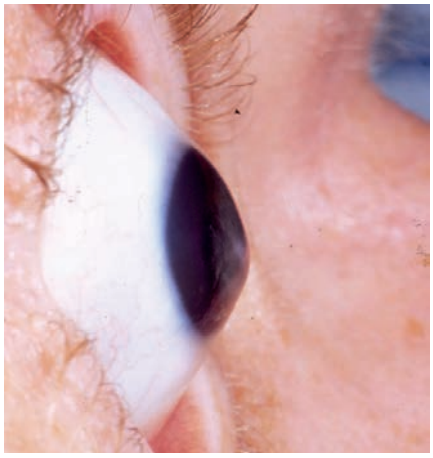
- *There are a number of treatment options for keratoconus, but only corneal cross-linking (CXL) appears to halt the progression of the disease*
- *To guarantee effective cross-linking, CXL treatment involves removal of the corneal epithelium prior to riboflavin application and ultraviolet light illumination – "epi-off" CXL*
- *Several methods of "epi-on" (transepithelial) CXL have been proposed, as keeping the corneal epithelium intact should be less painful and help avoid other CXL-associated adverse events*
- *The evidence so far is that epi-off CXL remains the most effective but transepithelial methods are gaining ground*

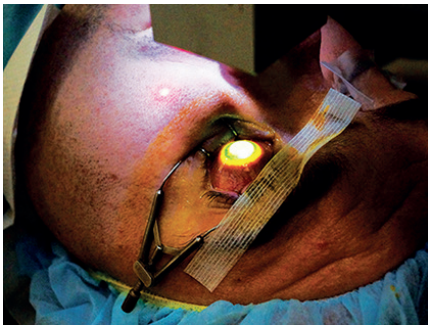
The history lesson

In clinical use since 1999, the original CXL procedure is known as the 'Dresden protocol' (7), and is an "epi-off" procedure (Figure 3). After anesthetizing the eye, the central 8 mm of the corneal epithelium is removed to expose the collagen-rich stroma, and riboflavin solution (0.1% riboflavin-5-phosphate and 20% dextran T-500) is applied to the surface of the cornea both 30 minutes before irradiation and at 5 minute intervals during the course of a 30 minute exposure to 370 nm UVA with a fluence of 3 mW/cm^2. After treatment, antibiotic drops are applied and some patients also receive a bandage contact lens. All patients use antibiotics, steroid drops and lubricants postoperatively until re-epithelialization is complete.

The evidence is that epi-off CXL works – and that its effect lasts for at least 10 years (8), as recently demonstrated by the results of a retrospective interventional case series study I performed with my colleagues. Our study enrolled 24 patients whose eyes (n=34) were treated with the classic Dresden protocol for progressive keratoconus between the years of 2000 and 2004. Patients' mean age (standard deviation) at the time of the procedure was 28.4 (±7.3) years, and the mean follow-up period was 10.9 (±1.7) years. We found that on average, compared with baseline values, the maximum keratometry (K), minimum K, and apical K (at the peak of the cone) values were significantly lower 10 years after CXL was first performed – and mean astigmatism was also reduced (Figure 4).

Having said that, a recent systematic review and meta-analysis (9) – which was published before our 10-year study paper (8) was available – did register some concerns, not about the technique per se, but about the quality of the available evidence. Their analysis incorporated 49 studies that involved patients receiving epi-off CXL, of which 39 were graded as "very low quality evidence." A number of reasons were given, including study design, lack of a comparator arm, high loss to follow-up, and incomplete reporting. The investigators also stated that "uncertainty





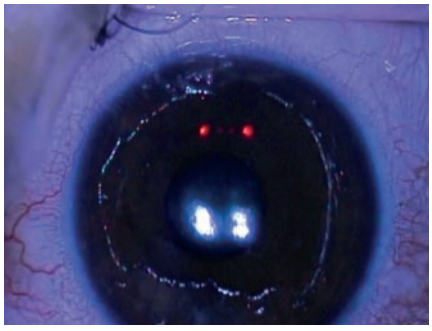


Image credit: GD Kymionis, bit.ly/epioff

From left: Figure 1. The classic conical cornea morphology observed in patients with keratoconus. Figure 2. A patient undergoing the corneal cross-linking procedure. Figure 3. Epi-off: removed corneal epithelium, prior to riboflavin application.

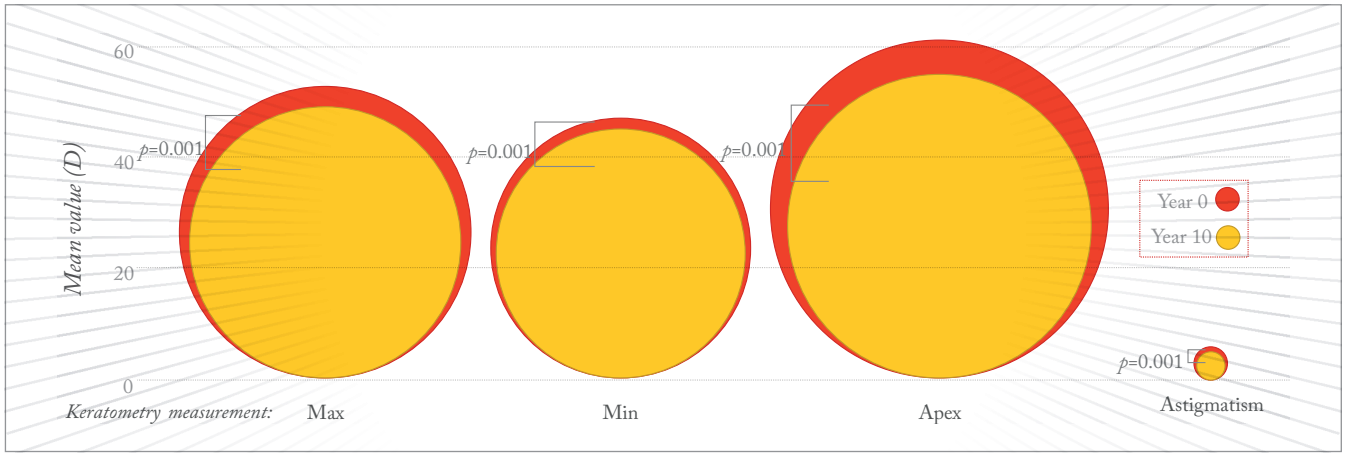


Figure 4. Mean K values before and 10 years after CXL. Apex, the apex of the keratoconus; max, maximum; min, minimum.

remains about duration of benefit." However, they did recognize that "delaying or preventing the need for corneal transplant and improving the fitting of contact lenses could be benefits that are highly valued by people with keratoconus." Importantly, the most common side effects were pain, corneal edema, and corneal haze, which are usually associated with wound response, but usually resolve within a few days of the procedure. Epi-off CXL also carries a small risk of viral reactivation, haze, melting, infectious ulceration and the development of permanent stromal scars (10). However, most of these adverse events are avoidable or manageable with topical antibiotics, steroids and appropriate peri- and postoperative analgesia. However, it would be nice for patients not to experience these issues.

The transepithelial approach

There is another approach: transepithelial (TE) or "epi-on" CXL. Leaving the corneal epithelium intact should eliminate wound-related complications and pain associated with epi-off CXL, the latter being of particular importance in very young patients or those with Down Syndrome (where one in 67 develop keratoconus), and should also lead to a shorter interruption of contact lens wear.

Can it work? The reason the Dresden protocol involved epithelial cell removal was the fact that riboflavin is a large hydrophilic molecule that cannot penetrate an intact epithelium; it also doesn't help that the epithelium blocks about 20 percent of the UV illumination administered. Accordingly, a number of approaches have been taken to try and get the riboflavin to the stroma, including pharmacological cleavage of epithelial tight junctions, intrastromal application of riboflavin through injections or femtosecond laser-created pockets, and iontophoresis.

Does it work? A preclinical study (11) performed in rabbits has shown that pharmacological disruption of the epithelial tight junctions with the

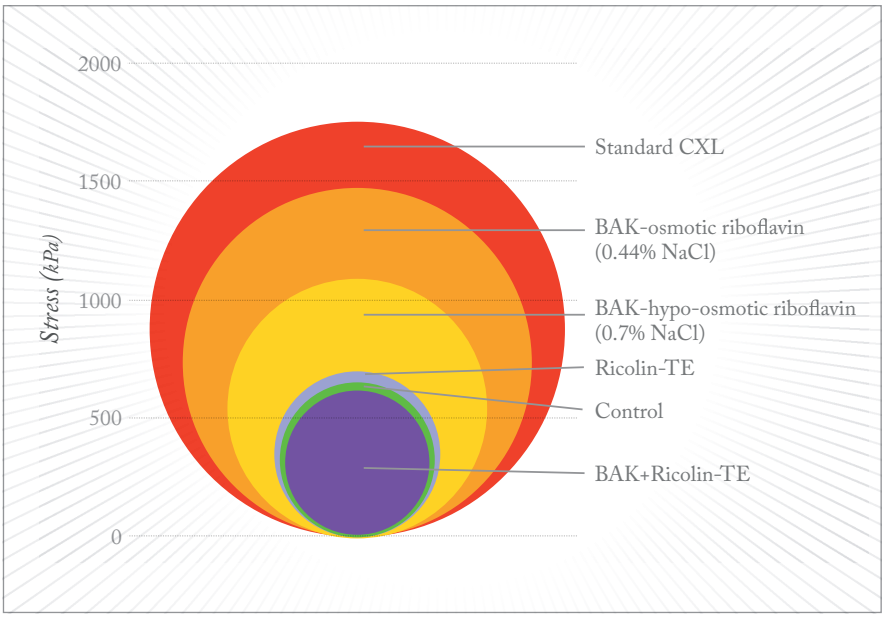


Figure 5. Stiffening effect of standard (epi-off) CXL and a range of transepithelial riboflavin preparations in rabbit corneas (12).

surfactant benzalkonium chloride (BAK) 0.005% (prior to the regular Dresden illumination and riboflavin application protocol) does increase corneal stiffness – but only by approximately one-fifth of what regular, epi-off CXL achieves. Brillouin microscopy of CXL-treated porcine eyes that had received either an epi-off or TE (with 0.02% BAK and 0.44% NaCl as the penetration enhancers) protocol showed that TE-CXL was 70 percent less effective in terms of biomechanically strengthening the cornea than standard epi-off CXL (12).

When evaluated clinically (10), this protocol managed to improve corrected distance VA and corneal topography parameters (including Kmax) on Placido disc topography (EyeSys) remained stable, although the Kmax on Scheimpflug imaging (Oculus Pentacam) and I-S value on Placido topography deteriorated. Treatment failure rates were 7 percent (similar to epi-off CXL failure rates in the literature), and no haze or other complications were noted in the 18-month follow-up period reported. Another study that used different penetration enhancers both for a 30-minute pretreatment soak and throughout the 30 minute illumination period (riboflavin 0.1%, dextran T500, trometamol and EDTA; Ricrolin TE) appeared to halt keratoconus progression with a statistically significant improvement in VA and topographic parameters – according to Placido topography (Optikon Keratron Scout 2000). Another study, using Ricrolin TE for TE-CXL resulted in keratoconus instability, particularly in patients aged 18 years and younger. The study reported that "50 percent of pediatric patients were retreated with epi-off CXL due to significant deterioration of all parameters after 12 months of follow-up" (13). A number of riboflavin solutions have now been, and their transepithelial corneal stiffening effect has been compared relative to standard epi-off CXL in rabbits (Figure 5), with epi-off CXL having the greatest effect (14).

A summary of recent clinical studies of epi-on CXL is presented in Table 1, but please let me draw your attention to the last one in the list (15): the protocol involved instilling gentamicin, BAK and EDTA for three hours, followed by oxybuprocaine for 30 minutes. Riboflavin 0.1% in 20% dextran T500 and oxybuprocaine were then instilled for 30 minutes, finally being followed by 30 minutes of UV-A irradiation to the central 7.5 mm of the cornea while riboflavin was instilled every 5 minutes. I would argue that there would be few epithelial cells left after that process and question its nomenclature as an "epi-on" procedure.

Femtosecond laser pockets

What about using a femtosecond laser to create a localized corneal pocket for riboflavin infusion? Pig eye studies have shown that "the biomechanical effect of CXL using the femtosecond laser pocket technique is about 50 percent less pronounced than that after standard CXL" (16), and it has been tried in the clinic too. John Kanellopoulos performed a small trial, taking ten eyes with early keratoconus, using the femtosecond laser to make an incision 100 µm in depth, and irradiating the eyes with UV-A illumination with a fluence of 7 mw/cm^2 for 15 minutes (17). Initial outcomes were good in terms of mean uncorrected and best spectacle-corrected VA, and no ectasia progression (as determined by keratometry) was noted during the mean 26 month follow-up period. It shows promise, but the data aren't there yet.

Iontophoresis

Another method under active investigation is the iontophoretic delivery of riboflavin into the corneal stroma (Figure 6). Riboflavin is water-soluble, negatively charged at physiological pH, and has a low molecular weight – all of which means that the application of a low-intensity electrical current flowing between a negatively charged delivery electrode placed on the cornea and a counter electrode (placed on the patient's forehead) should be able to

Reference	*Paper title*	*Conclusion*	*Study type*
M Filippello et al., J Cataract Refract Surg (2012)	Transepithelial corneal collagen-cross-linking: bilateral study.	"…appeared to halt keratoconus progression, with a statistically significant improvement in VA and topographic parameters"	Cohort study
C Koppen et al., J Cataract Refract Surg (2012)	Refractive and topographic results of benzalkonium chloride-assisted transepithelial cross-linking.	"Transepithelial CXL is […] less effective than standard CXL"	Cohort study
A Caporossi et al., J Cataract Refract Surg (2013)	Transepithelial corneal collagen-cross-linking for progressive keratoconus: 24-month clinical results.	"Functional results after TE-CXL showed keratoconus instability, in particular in pediatric patients"	Prospective case series
I Kocak et al., J Fr Ophthalmo (2014)	Comparison of transepithelial corneal collagen-cross-linking with epithelium-off cross-linking in progressive keratoconus.	"TE-CXL does not effectively halt the progression of keratoconus"	Retrospective case review
D Touboul et al., J Refract Surg. (2012)	Corneal confocal microscopy following conventional, transepithelial, and accelerated corneal collagen cross-linking procedures for keratoconus.	"In vivo corneal confocal microscopy […] TE-CXL did not appear to alter corneal morphology"	Prospective case series
A Caporossi et al., Eur J Ophthalmol. (2012)	Transepithelial corneal collagen-cross-linking for keratoconus: qualitative investigation by in vivo HRT II confocal analysis.	"TE-CXL showed a limited apoptotic effect […] about one-third of classic epi-off"	Prospective case series
L. Mastropasqua et al., Cornea (2013)	Morphological modification of the cornea after standard and transepithelial corneal cross-linking as imaged by anterior segment optical coherence tomography and laser scanning in vivo confocal microscopy.	"Marked corneal modification […] which was poorly evident in the TE-CXL…"	Prospective case series
A Leccisotti, T Islam, J Refract Surg (2010)	Transepithelial corneal collagen cross-linking in keratoconus.	"A limited but favorable effect" "The effect appears to be less pronounced than …CXL with de-epithelialization"	Prospective, consecutive study

Table 1. Summary of key transepithelial CXL publications.

Reference	*Paper title*	*Conclusion*	*Study type*
N. Bouheraoua et al., Invest Ophthalmol Vis Sci (2014)	Optical coherence tomography and confocal microscopy following three different protocols of corneal collagen cross-linking in keratoconus.	"The demarcation line was present in less than 50% of cases and was more superficial than with the traditional procedure"	Prospective, consecutive, non-randomized study
S. Bonnel et al., J Refract Surg (2015)	Demarcation line evaluation of iontophoresis-assisted transepithelial corneal collagen cross-linking for keratoconus.	I-CXL "creates a demarcation line […] which seems less easily distinguishable and shallower than in conventional CXL.	Cohort study

Table 2. Summary of recent clinical iontophoretic, transepithelial CXL publications.

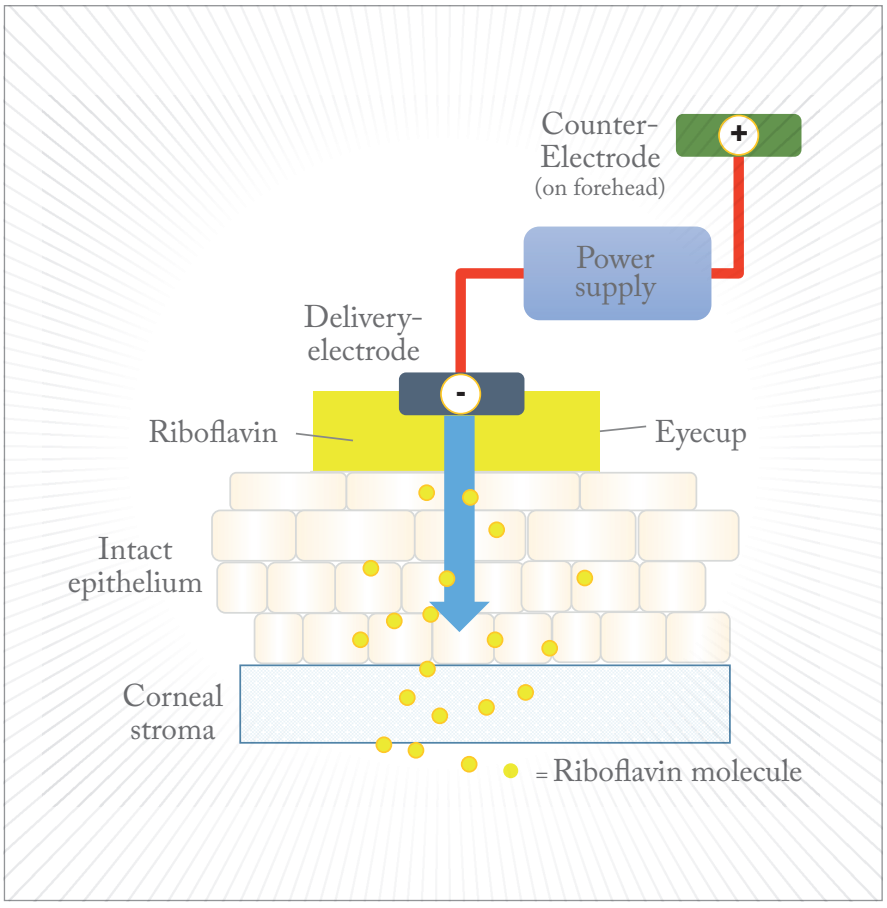


Figure 6. Iontophoretic delivery of riboflavin into the corneal stroma.

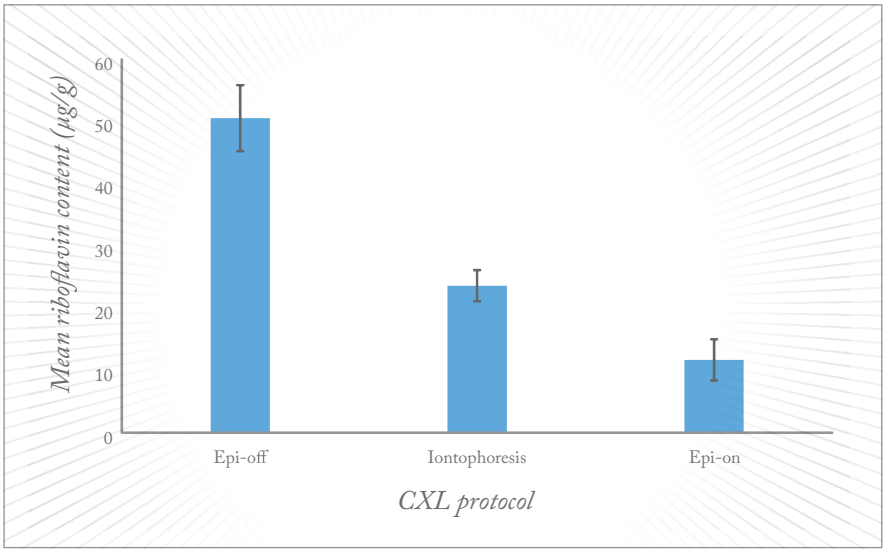


Figure 7. Mean riboflavin content in the anterior 150 mm of human cadaver corneas following Epi-off, Iontophoretic-and Epi-on-CXL (16).

drive riboflavin across the intact epithelium and into the corneal stroma.

As it turns out, the composition of the solution in which the riboflavin is prepared matters a great deal. It was established early on (in rat corneas) that the standard Dresden protocol riboflavin preparation (0.1% riboflavin, 20% dextran T500) failed to penetrate the corneal epithelium into the stroma in any significant amounts with iontophoresis, but that the far more soluble 0.1 % riboflavin-5'-phosphate did (18).

A comparison of epi-off versus iontophoretic TE-CXL (I-CXL) was performed in rabbit eyes using a different riboflavin solution, Ricrolin+ (0.1% riboflavin, EDTA and trometadol), 1 mA for 5 minutes. That study showed that I-CXL was associated with a 45 percent lower corneal riboflavin concentration than corneas soaked using the traditional epi-off method. However, when these corneas were subjected to stress-strain assessments and challenged with collagenase digestion, both the epi-off and I-CXL-treated corneas exhibited similar median stress at 10 percent strain and similar collagenase resistance (19).

Mastropasqua et al. (20) compared the concentration of riboflavin in human cadaver corneas as introduced by epi-off, TE and iontophoresis, finding that the mean riboflavin content in the superficial slice in the epi-off group was about two-fold greater than that of the iontophoresis group (50.5 ± 5.3 µg/g and 23.6 ± 2.5 µg/g, respectively) and four-fold greater than that of the TE group (11.7 ± 3.3 µg/g) (Figure 7). Clinical experience with I-CXL is beginning to be reported (Table 2), too, and it appears to tell a similar story: the cross-linking effect appears to be better than regular TE-CXL, but not as great as epi-off CXL.

One study that reported one-year results of I-CXL on 20 eyes from 20 patients with progressive keratoconus has provided some initial, encouraging results: significant improvements in corrected distance

	Experiment	*Clinical*	*Safety*	*Effect*
Epi-off	Yes	Yes	Yes	Yes
Epi-on	Yes	Not yet	???	???
Iontophoresis	Yes	???	???	???

Table 3. State of evidence supporting the use of epi-off, epi-on TE and I-CXL.

VA, with no progression noted over that period and non-significant trends toward topographic improvement (21). The study authors speculated that I-CXL "has the potential to become a valid alternative for halting the progression of keratoconus while reducing postoperative patient pain, risk of infection, and treatment time in select patients," but noted that "the relative efficacy of this technique compared to standard epithelium-off techniques remains to be determined."

The availability of evidence

Ultimately, it comes down to this: the evidence for epi-off CXL is a known quantity; it works and its effects persist for at least a decade (Table 3). Removing the corneal epithelium might be uncomfortable for the patient – yes, it's a lengthier and more painful procedure than TE or I-CXL, and yes, it does carry a small increase in risk of corneal infection or other adverse events like haze. But these risks can easily be mitigated, and the pain and hazing can be managed. TE CXL – either with or without iontophoresis – would be a great option for patients with keratoconus, if it could work as effectively as epi-off CXL, but there's just not enough proof at the moment that either epi-on technique can. Until there's good evidence that a TE-CXL protocol can come close to the efficacy of epi-off CXL with the Dresden protocol, it's going to remain that way.

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The Burden of Dry Eye Disease

With many causes, great prevalence, and substantial underdiagnosis, dry eye disease poses a great burden on patients and your practice

Dry eye disease (DED) is burdensome for both doctor and patient for three main reasons: high prevalence, many causes, and – especially in the case of severe DED – little in the way of effective treatment options. Up to 100 million people globally are thought to be affected by DED to some extent, and for many reasons, it has been both underdiagnosed and undertreated. Milder forms are rarely vision-threatening, and a lot of people with DED will go to their pharmacist, buy an over-the-counter lubricant, self-treat and make do. It can therefore take years before these people navigate through the path of pharmacist, general practitioner, optometrist, general ophthalmologist, until finally getting to see a cornea specialist. Furthermore, some patients show the signs, but not the symptoms of DED, further delaying their presentation to an ophthalmology clinic.

Nevertheless, a substantial volume of patients still present to ophthalmology clinics with DED. Indeed, it has been estimated that up to 60 percent of patients under the care of an ophthalmologist have some form of DED. Such patients are present in every subspecialty and in every clinic – even posterior segment specialists will talk of patients with fluctuating vision that leads to a DED diagnosis. Given that eye clinics are already busy enough dealing with aging baby-boomers with age-related ocular disorders, this is far from ideal.

It's also far from ideal if you're a patient with DED. Symptoms include red, tired, irritated, itchy eyes, gritty or burning sensations, light sensitivity, fluctuating vision. Everyday tasks like driving a car, working with a PC, or even being in a room with a fan heater can all be painful undertakings.

It's not just the impact on quality of life that warrants concern; this is

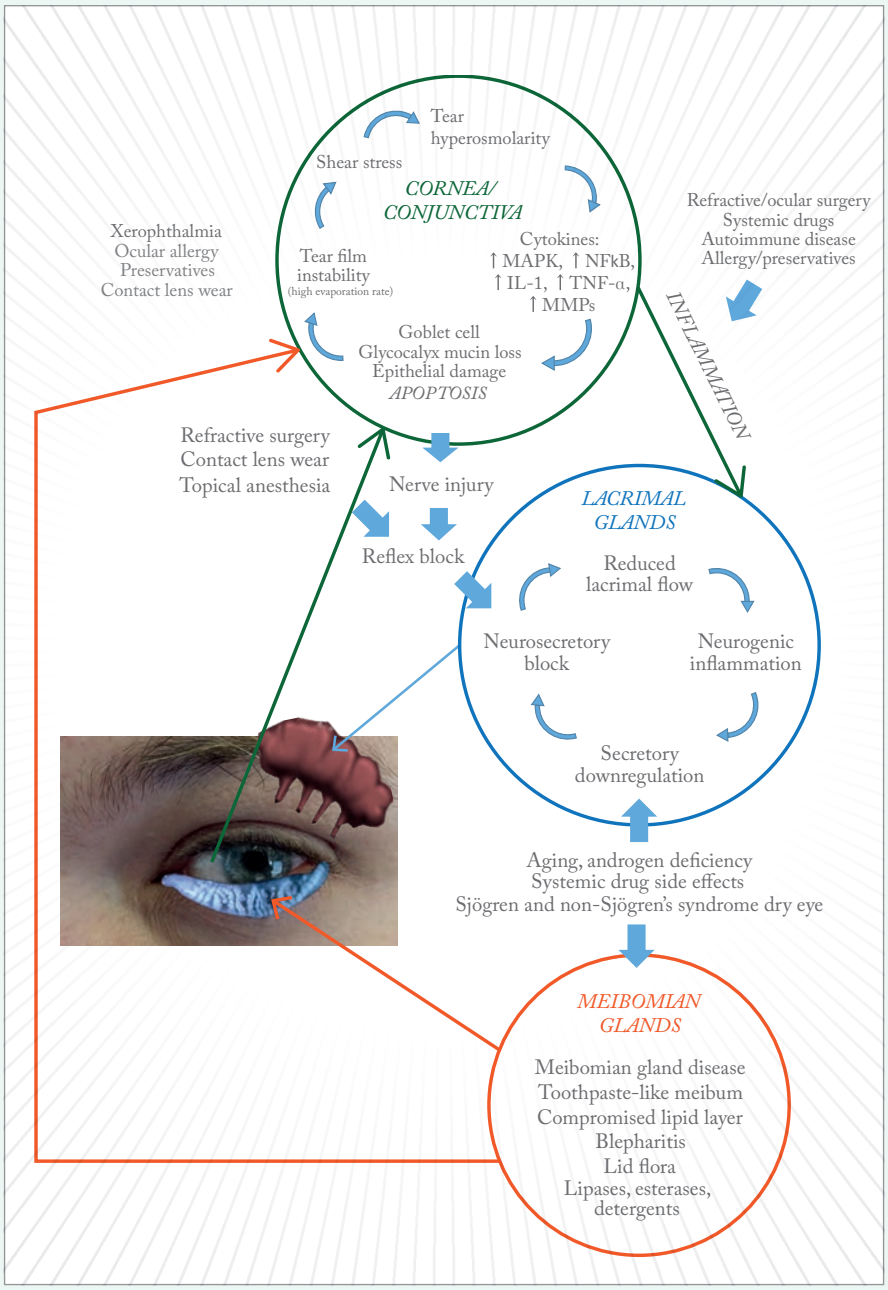


Figure 1. The many origins of dry eye disease (DED). Many systemic and external factors can result in dysfunction of one of the three main constituents of the lacrimal functional unit – the cornea, lacrimal glands, and meibomian glands. Impairment of any one of these then prolongs and drives the progression of DED by inflammatory, hyperosmolar and stress conditions that damage the other components of the ocular surface.

a disease that actively harms the eye, causing inflammatory damage to cells on the ocular surface. Then there's the fact that it's a disease with many causes: aging, air conditioning, air travel, autoimmune disease, androgen deficiency – these are just some that begin with the letter "A." There really is no standard natural history of DED and there are many points where a patient can enter its vicious cycle (see Figure 1), and few places where patients can exit it – certain contributing factors (if present) like blepharitis or meibomianitis can be treated, which should help, but too often it isn't enough to exit the cycle. As DED can involve not just the cornea and conjunctiva, but also the lacrimal and meibomian glands too, there's a complex interplay between the pathologies that develop in each site (Figure 1) that can all drive inflammatory pathways, accelerating ocular surface damage.

"It's not just the impact on quality of life that warrants concern; this is a disease that actively harms the eye"

As we'll explore in future issues of The Ophthalmologist, diagnosis is also a real challenge, but the big picture is that patients with DED are not happy. Gallup, the multinational management consulting company, conducted a poll in 2008 and found that:

- 72 percent of patients were recommended artificial tears for their dry eye problem by physicians,
- 82 percent of patients agreed that they wish there was something more effective to treat their dry eye, and
- 97 percent of patients reported that their dry eye condition is frustrating.

An effective treatment would certainly improve this situation. The problem is that, for patients with severe DED, the treatments currently available – mostly artificial tears and lubricants – just aren't that effective; they are essentially symptomatic treatments and do nothing to dampen inflammation or interfere with the disease processes. It's therefore frustrating for not just the patient, but also the ophthalmologist, that nothing more – short of surgical or experimental interventions – can be done.

Next month

Dry Eye Disease's Big Diagnostic Challenge

Diagnosing DED is challenging, mainly because of the discordance between signs and symptoms: patients can have severe symptoms, yet show no sign of ocular surface damage; others have advanced damage to the ocular surface, yet report no symptoms, as their ocular surface is so damaged, they can no longer feel anything.

Historically, there has been a lack of correlation between patients' irritative ocular symptoms (e.g., as determined by questionnaires) and the results of commonly performed tests such as corneal fluorescein staining (CFS, Figure 1) or the tear film break up time (TFBUT). We will explore why, and learn how this is changing for the better.

Figure 1. Application of fluorescein to a patient's cornea.

NextGen

Research advances
Experimental treatments
Drug/device pipelines

Benchmarking AMD

What does analysis of the last five years of the AMD literature tell us about the priorities of the field and the major contributors to it?

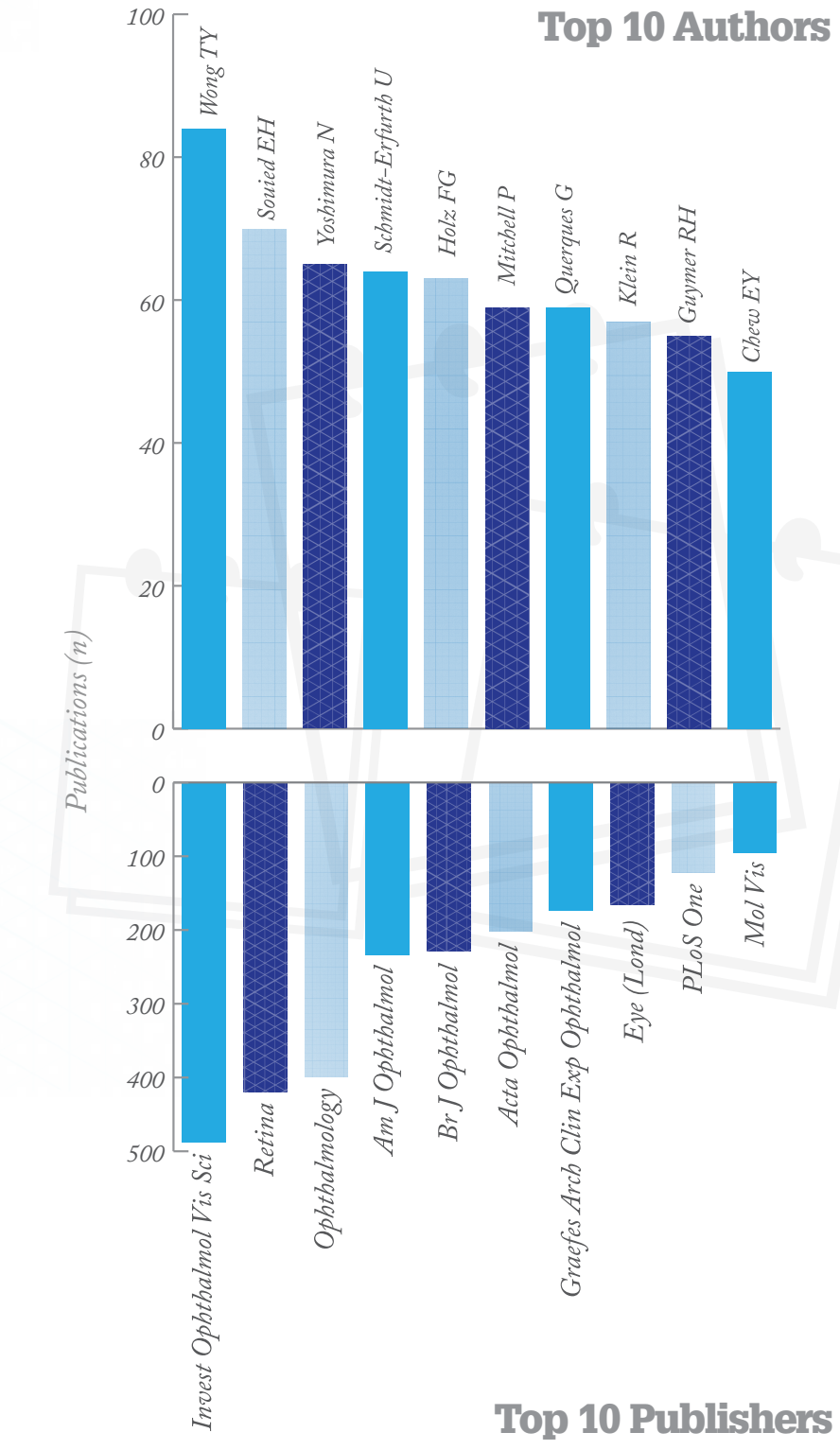
By Mark Hillen

Over 100 PubMed abstracts state in their first sentence that age-related macular degeneration (AMD) is the main cause of visual impairment and blindness in people aged over 65 years in developed countries. Lifelong nutrition appears to play a role in AMD's pathogenesis; it can occur in "dry" or "wet" forms, with the latter having one notable treatment option: intravitreal anti-VEGF inhibitors. Furthermore, optical coherence tomography (OCT) imaging has revolutionized the diagnosis and assessment of AMD, and is essential for the clinical management of wet AMD, permitting the pro re nata and treat-and-extend regimens used in many patients today.

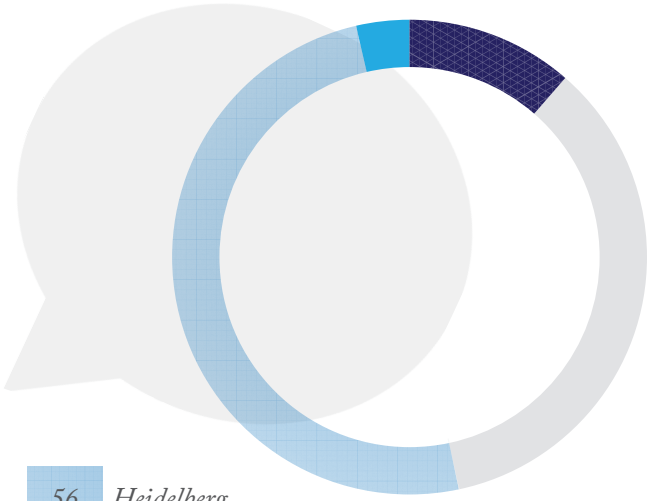
To provide insight into the past and predictions for the future of the field, a series of metrics were applied to the last five years of published literature. We asked:

- What are the major topics for the field?
- Who are the most prolific authors?
- Which anti-VEGF agents are mentioned most often?
- How central is OCT imaging to AMD research?

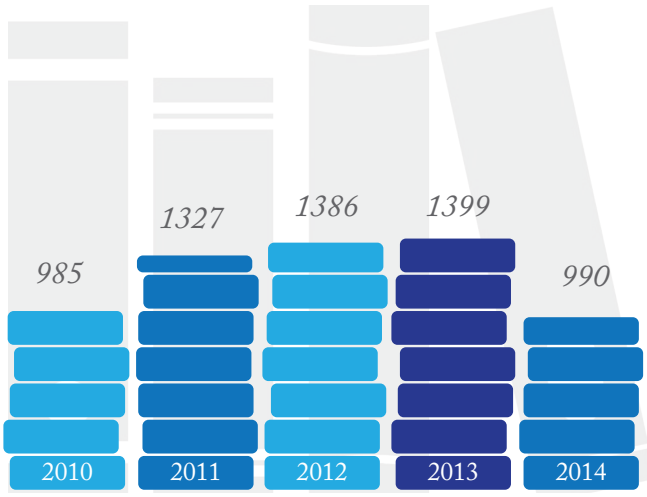
PubMed was searched for "age-related macular degeneration", with results limited to the last five years in humans (for a clinical focus). The data were analyzed in Microsoft Excel 2013. "Mentions" were determined by searching the title and abstract text for all imported abstracts, followed by a manual inspection and verification, e.g. searching for "Heidelberg" would identify both the instrument manufacturer and the city, and Heidelberg Engineering produce more than just OCT instruments; inappropriate records were de-flagged.



Mentions of OCT manufacturer



56	Heidelberg
40	Zeiss
13	Topcon
4	Optovue



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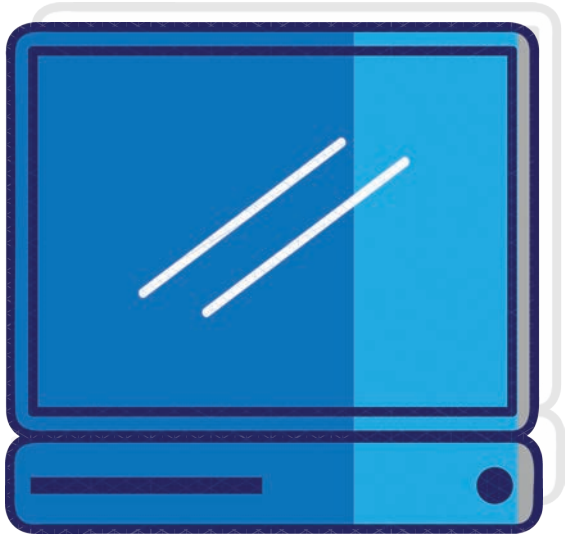

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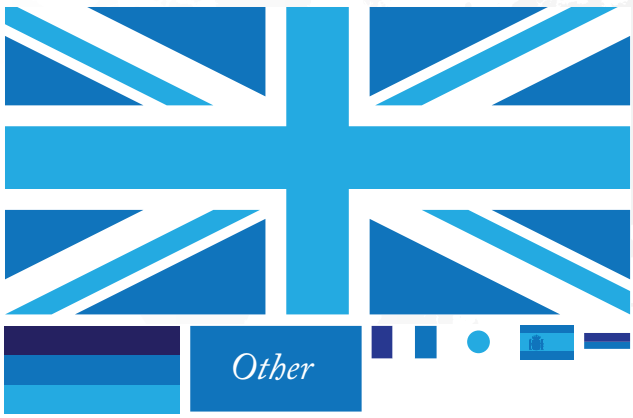

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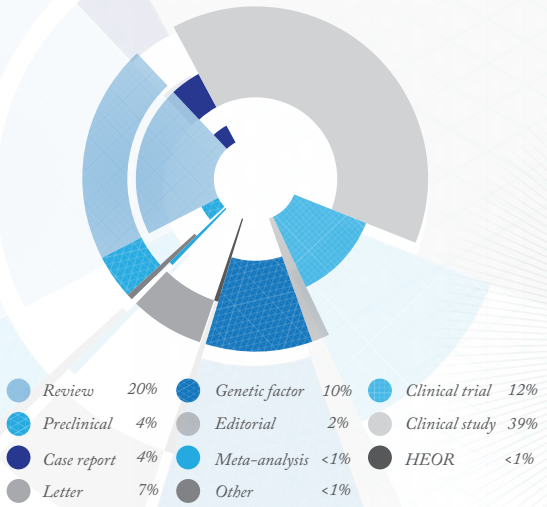
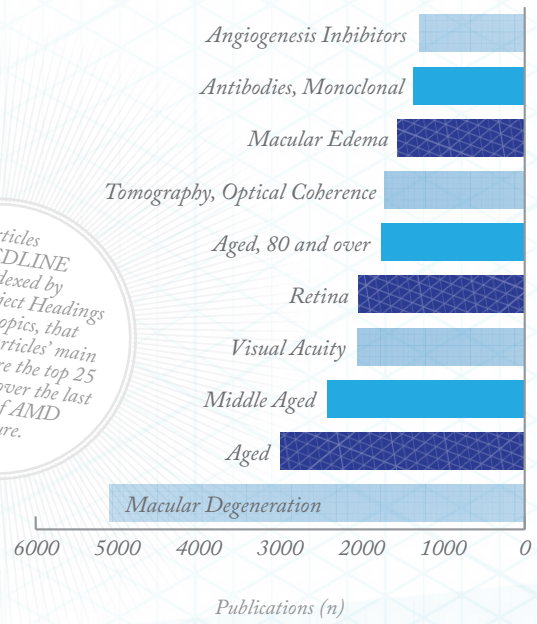


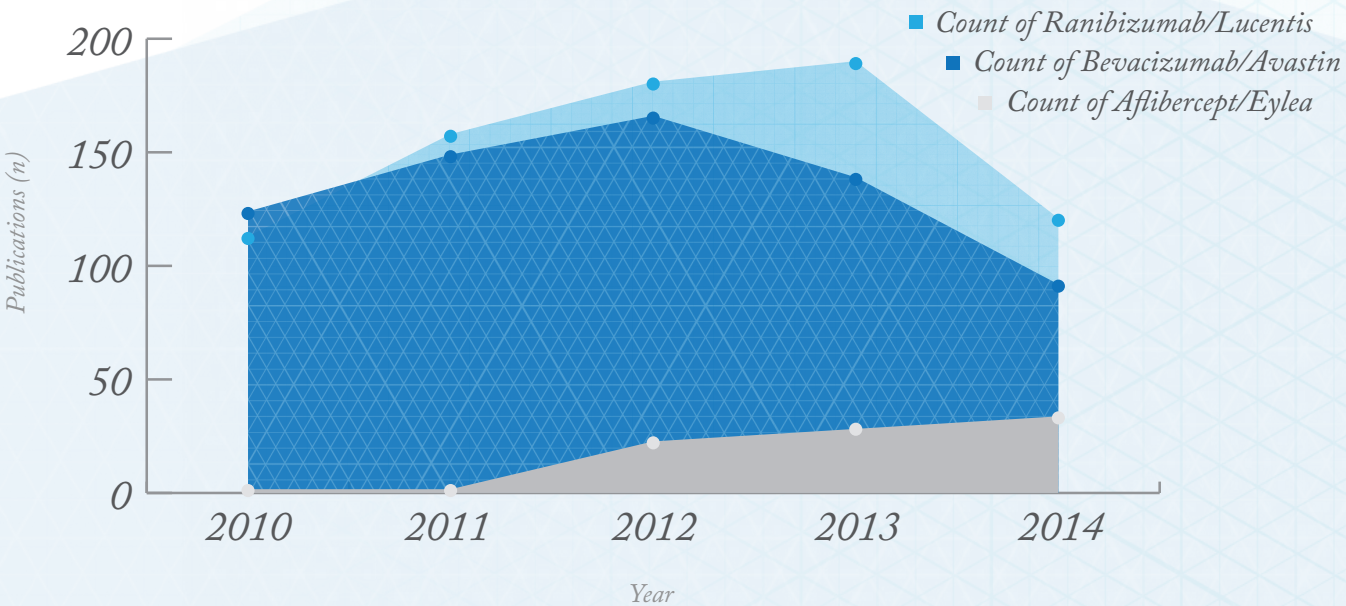
Articles are categorized according to PubMed criteria. Clinical study represents a clinical evaluation of a drug, device or technique that was not a clinical trial.

Most frequent topics on PubMed

Articles in MEDLINE are indexed by Medical Subject Headings (MeSH) topics, that describe the articles' main topics. Here are the top 25 MeSH terms over the last five years of AMD literature.



Mentions of the top three anti-VEGF agents



Why Vision Research?

We ask the next generation of ophthalmology researchers why they do what they do – and where they want to be 10 years from now.

By Michael Schubert and Mark Hillen

There's likely a very good reason why you're reading an article in a magazine called The Ophthalmologist. At some point in your medical, academic or business career, you made a decision to work in a field that improves people's eye health; an understandable move – restoring any amount of vision to an individual can profoundly improve their quality of life, not to mention the pharmacoeconomic and societal benefits. But not everyone reading will have decided to pursue a career path that involves vision research. We wanted to know what drives young, up-and-coming physicians and scientists at the cutting-edge.

Here, four members of Farhad Hafezi's research group at the University of Geneva share their motivations and aspirations.

At a Glance

- *We asked: what motivates young scientists and physicians to undertake a career that involves vision research?*
- *We interviewed four researchers in Farhad Hafezi's research group at the University of Geneva*
- *They speak about the importance of their research (into corneal collagen crosslinking), and what impact it has on the clinic*
- *The researchers voice their career ambitions, telling us where they want to be in a decade's time*

Why did you choose ophthalmology over any other field?

Sabine Kling: I've always been interested in both physics and medicine. In ophthalmology, I found a very interesting combination of these two fields. Physics is integral as the eye forms a natural optical system, but biomechanical properties determine the geometry of these optical components, especially the cornea and the crystalline lens. Physical systems are also required to correct refractive problems (for instance by laser ablation) and to facilitate the diagnosis of other ocular pathologies (for instance with the use of topographers and tonometers).

Basile Salmon: What attracted me most to ophthalmology was the fact that it is one of very few specialties that combine very precise and delicate surgery with a wide array of research fields. As my initial training was in engineering, research is still a part of my nature and I consider it vital that I work in a field where I can put this inclination to use.

Raphaël Wuarin: The eye has always fascinated me. It's truly amazing what this small organ is capable of. We Swiss like our watches, and the more complicated they are, the better. As far as bodily organs go, the eye is definitely "haute horlogerie." Its complexity is astonishing, and its role is very precious.

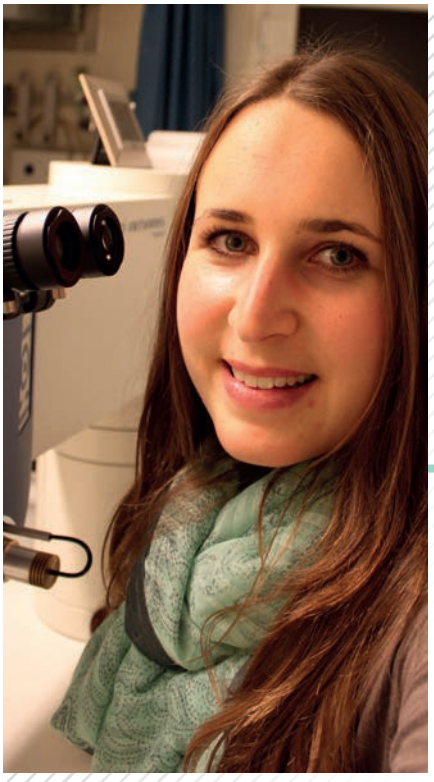
David Tabibian: More than any other specialty, ophthalmology touches many different aspects of the medical field, and that makes it a complete and very interesting specialty from my point of view. Physicians have daily contact with patients, which helps develop their social skills, improving not only patient comfort, but also treatment adhesion and clinical outcomes. It's also a highly specialized field with different subspecialties. I like the fact that, although you have to learn highly specific pathologies, you also regularly have to refer to other fields in medicine to take care of patients with systemic or complex diseases. Ophthalmology is a very active specialty in fundamental and clinical research – I'm very enthusiastic about ophthalmology research, especially as I'll certainly witness new discoveries in the coming years that will change and improve patient care and modify my daily practice.

"The eye is definitely 'haute horlogerie.' Its complexity is astonishing, and its role is very precious."

Why did you choose corneal cross-linking (CXL) research?

SK: Because it's an ideal method of increasing the stiffness of the corneal tissue without damaging it. CXL helps to develop realistic new techniques for the *in vivo* measurement of biomechanical properties, which are essential for evaluating the corneal response to refractive surgery or the progression of certain pathologies (such as keratoconus). I'm also interested in understanding the working principle behind CXL to improve treatment efficacy.

BS: I was mainly attracted to the technical aspects of CXL. I see it as the perfect intersection of engineering and medicine, which is exactly where I find myself today.

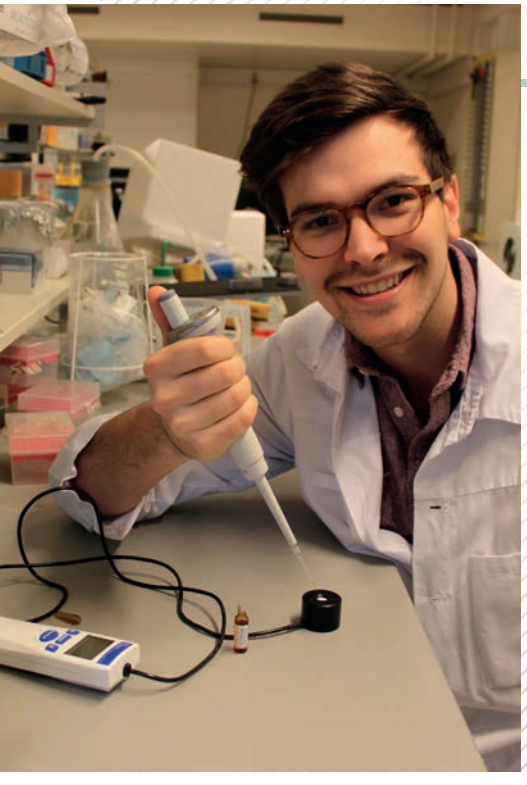


The Postdoc

Sabine Kling

The Medical Students

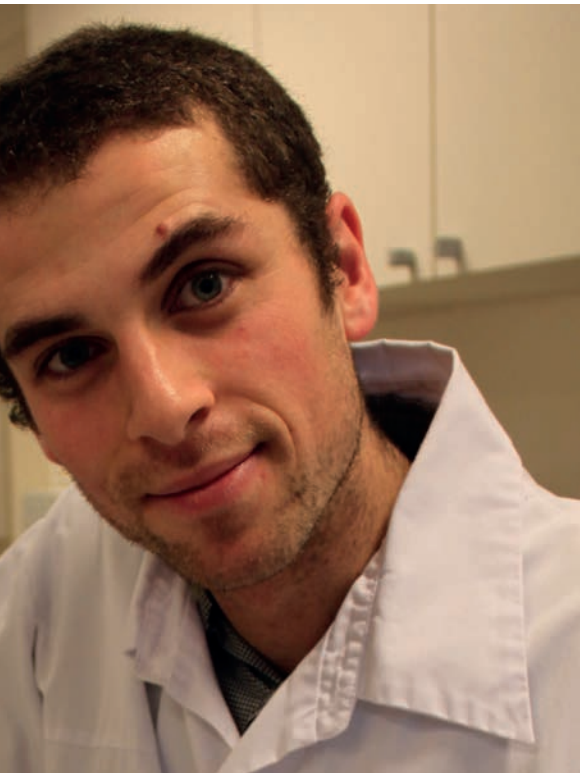
Basile Salmon



Raphaël Wuarin

The Resident

David Tabibian



RW: As a student, I feel lucky to be working in CXL research. It is a cutting-edge medical treatment with direct clinical impact. I'm amazed to see what research has done to push CXL's potential forward – it started off as a treatment for keratoconus, and we are now discovering the many other clinical applications it holds.

DT: At the beginning of my training, Farhad Hafezi introduced me to the technique. After a few weeks, we were already discussing the potential improvements our team could bring to the field, as well as the new applications of CXL to treat other diseases like corneal infections. I soon decided to start some clinical and fundamental research on the subject. Initially, I was working on it after my clinical duties – but later on I decided to devote a whole year to our CXL projects.

How does your research relate to clinical ophthalmology?

SK: My research aims at developing systems to measure corneal biomechanical properties *in vivo*, improving CXL efficacy to reduce the current treatment duration, making CXL applicable to a wider range of patients, and performing simulations to predict patients' individual responses to refractive surgery or CXL treatment.

BS: The process I was involved in aims to bring CXL treatments outside operating theatres, giving more people the access to PACK-CXL. It truly is delivering a game-changing treatment for keratitis in regions of the world where sterile environments are not widely available.

RW: My research has focused on better defining PACK-CXL protocols in human and animal corneas. Veterinary ophthalmologists want to know how to adapt the protocols to their patient populations, and researchers are interested in knowing whether results obtained with animal corneal models also apply to the human cornea.

DT: I'm currently working on PACK-CXL. We use CXL technology not to treat corneal ectatic disorders, such as keratoconus, but to heal corneal infections by killing bacteria and fungi. We see in our clinics that the research we're currently doing directly benefits our patients – and that's a very motivating outcome.

Where do you see yourself in 10 years?

SK: I aim to be a professor and principal investigator with a small, high-quality research group and international collaborations.

"The research we're currently doing directly benefits our patients – and we see that in our clinics."

BS: In 10 years, I hope to have evolved in combining my research and technical abilities with my passion for the medical profession. I want to continue in the field of ophthalmology, and to be in the operating room helping patients recover their vision using methods to which I have contributed through research.

RW: That's a tough question to answer, as I'm still in my medical studies. Both the clinic and the research draw me towards ophthalmology – so ideally, I would love to combine the two.

DT: I am currently in the fourth year of my residency, so I will have to work for a few more years to become a fully trained ophthalmologist. In 10 years, I hope to be working in a university hospital facility, with a position that allows me to see patients as well as to continue doing clinical and fundamental research in ophthalmology.

Sabine Kling is a postdoctoral fellow at the University of Geneva, Geneva, Switzerland.

Basile Salmon and Raphaël Wuarin are both medical students at University of Geneva.

David Tabibian is a resident physician in the Ophthalmology Department of the University Hospital of Geneva.

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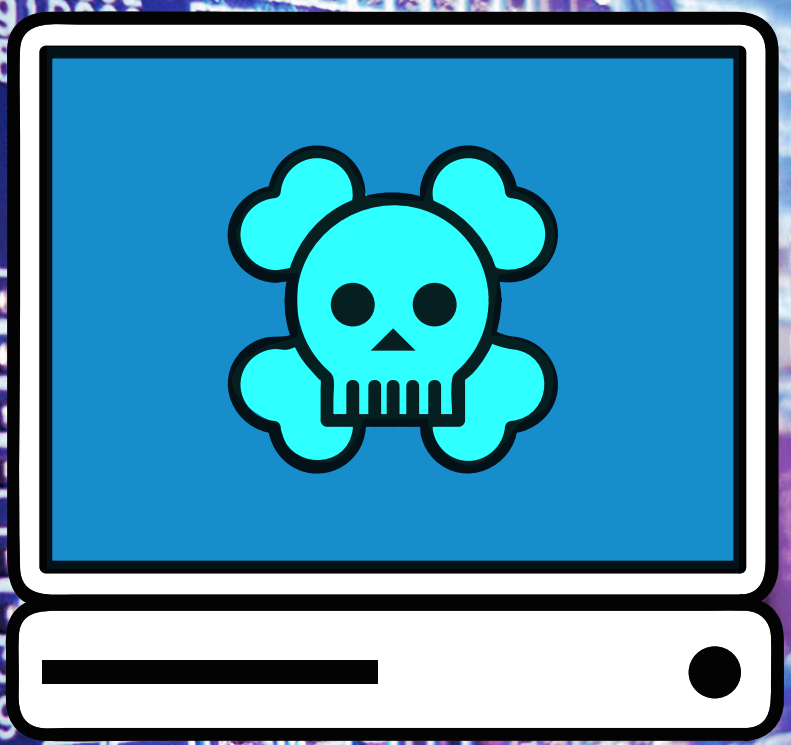

46-48

The risks you take with a dead OS

Healthcare is a hacker's honeypot – the data is very valuable to certain criminals. Windows XP – which many hospital PCs and instruments is dead. No support, no security patches, nothing. What risks do you run if you still have PCs or devices that still run it?

The Risks You Take With a Dead OS

Windows XP is dead. No support, no security patches, nothing. You might have PCs or instruments in your office that still need XP to function – so what are the risks that you run?

By Mark Hillen and Pete Williams

August 24, 2001 saw the launch of Windows XP. Almost 13 years later, on April 8, 2014, Microsoft ended its "Extended Support" phase for the operating system. Given that on that date, roughly a third of all PCs had Windows XP as their operating system, that was an awful lot of people to cut loose – no more security patches, no support information, nothing. Microsoft, however, is continuing to patch security vulnerabilities in Windows XP, though, but not for individuals. If you're a big corporate customer, however, you can purchase "Custom Support", for a cost of ~US$200 per PC per year. For example, the UK Government paid Microsoft £5.5 million last April for a year's worth of Custom Support for national and local government, education and the National Health Service – but won't renew the contract again this April. It will be interesting to see what happens next.

At a Glance

- *Microsoft no longer supports or updates Windows XP with security patches*
- *Many PCs across the world still run it – including ones used in the clinic*
- *Unpatched XP on PCs represents huge (and easy) pickings for hackers*
- *We explore what this means for you if you still have PCs and instruments that run XP*

Figure 1. An OCT instrument that requires a PC running Windows XP for image acquisition.

You can be certain that all devices that run software have the potential to be exploited – even the microcontrollers of your camera's SD card is at risk (bit.ly/CCCSD). The latest versions of Windows and Mac OS X will have security holes that hackers will find and exploit. Both Microsoft and Apple will close these holes as soon as they can after they discover them; it's a cat-and-mouse game between them and the hackers. The problem with Windows XP, is that Microsoft has essentially given up on their part of the game, even though hundreds of millions of people still use it – and many of those work in healthcare.

Windows XP was the de facto PC operating system for just over eight years, from early 2001 until Windows 7 was launched in late 2008 (Windows Vista, when launched in 2006, just didn't sell well). This meant that there was the best part of a decade where medical instruments were being built, and bespoke applications written, to work on Windows XP (Figure 1).

Most medical instruments have a non-trivial cost attached to them – so if they continue to work, or it's cheaper to fix, for example, a corneal topographer that cost €100,000 than it is to replace it, then in these austere times, they're

"It's a cat-and-mouse game between them and the hackers."

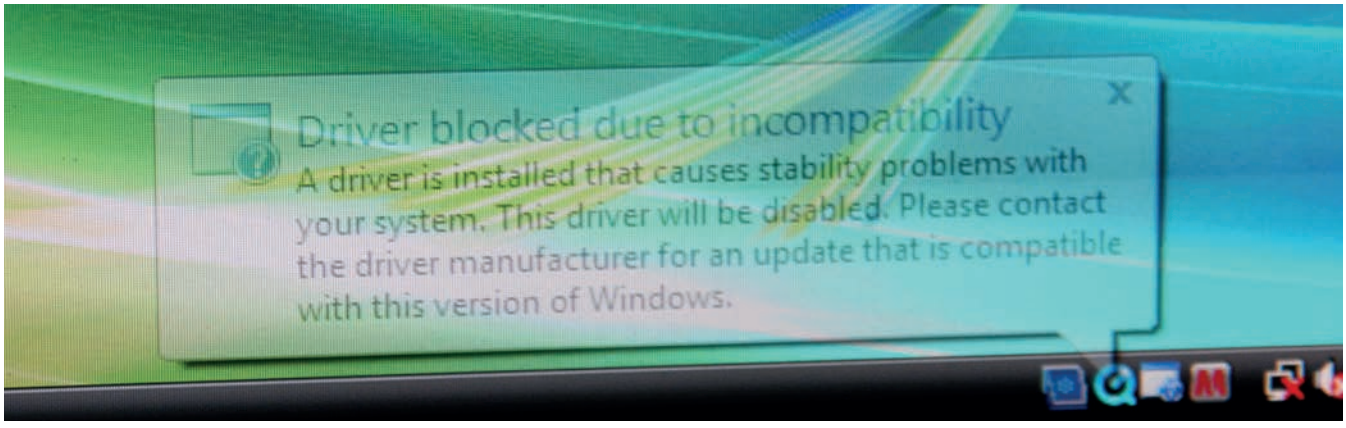

Figure 2. Later versions of Windows can break the functionality of the device drivers you need for your instrument to work – meaning that you cannot upgrade.

likely to continue to be used until they absolutely have to be replaced.

What do hackers want?

The bad guys want control of your PC for a number of reasons. If it's on the internet, it can participate in a botnet, and be told to do any number of nefarious tasks, like denial of service attacks, where your PC, in concert with many others, bombards servers with so many requests for information, it can't function (just like what happens organically to ticket websites the moment after tickets for a popular event goes on sale). They could use your PC to mine Bitcoins – earning a virtual currency for them, at the expense of your electricity bill. Or they could use it to infect other computers – botnets can be rented out and can represent a good hacker revenue stream. Media like CDs, DVDs, USB flash or external hard drives are another method of malware propagation. The most prominent example is Stuxnet – a worm (self-replicating and propagating computer virus) that targeted the systems controlling Iranian nuclear centrifuges (and ruined a fifth of them). It was introduced into their nuclear facility on a USB flash drive, reportedly by an Iranian double agent working for the Israeli secret service, and once Stuxnet was on their internal network, it could propagate and update itself profusely (bit.ly/thestuxnet).

Hackers also love hacking healthcare. It's viewed as insecure and easy to hack (see below; bit.ly/easytohack) and there's two strands of data to mine: financial and personal. The second-biggest health insurer in the US, Anthem, was hacked last month, reportedly by Chinese state-sponsored hackers. The information taken reportedly included names, birthdays, social security numbers, street addresses, email addresses and employment information, including income data (bit.ly/anthemG) – certainly enough to commit fraud. Irrespective of location, though, health records are a rich database of proclivities, health concerns, prescription (or illegal) drug use and in some cases, some seriously private information that could be used to smear or blackmail people. And it's quite possible your instrument or PC running Windows XP is on the same network as computers that health records are accessed from… Network security is already important, and with hackers increasingly focusing on healthcare as a target, its importance is only going to increase.

"It's almost a form of superstition… the installation engineer hands it over to you to use, with the warning: it works now, don't change anything!"

Can't you just upgrade Windows?

That's not as simple as it sounds – sometimes you have no choice in the matter. Many medical device and instrument manufacturers prohibit the installation of antivirus software on their products, let alone upgrading Windows XP. Either they fear that something might break in the process, or they have concerns (particularly in the USA) that revising the software might mean that the entire system needs to be recertified to stringent regulatory standards. The fact is that most medical device instrument manufacturers aren't massive corporations with a large

number of programmers that can update – or even test – device drivers (the interface between the operating system and the added bit of hardware) for older instruments whenever a new version of Windows comes out (Figure 2), let alone a service pack or security update. It's almost a form of superstition – during the commissioning of the instrument, the installation engineer hands it over to you to use, with the warning: it works now, don't change anything! In an ideal world, manufacturers should build in security updates into the costs of the instrument, but in the real world, this doesn't always happen.

Tinkerers rejoice: this doesn't mean that the user can't try upgrading their version of Windows at their own risk – but in many cases, risking downtime with a practice-critical instrument or device would be pretty irresponsible. Ironically, given its unpopularity, Windows Vista would have been the safest bet – its device driver model is similar to Windows XP's (Windows 7 added additional layers of security – device signing – that can cause problems). Sadly Vista doesn't have long to live: Microsoft's "Extended Support" period expires on 4 November, 2017.

Windows 7 does have one trick up its sleeve: Windows XP mode (actually, Windows 8 and 8.1 can do this too if you know how: bit.ly/XPmode8). It enables you to run a copy of Windows XP in a virtual machine (bit.ly/XPmodeVM). It's not likely to help with medical devices, but it could help you get a new PC to run software that won't run on later versions of Windows. Internet Explorer 8 is one such example – launched in 2008, even today one PC in five runs this version of the web browser. The reason why: many bespoke web applications – from appointment booking to electronic healthcare record systems – are broken by changes made in Internet Explorer 9.

Figure 3. Windows XP came with a rudimentary firewall as a security feature, which was originally switched off by default, but was later activated by subsequent security updates.

Can you survive with XP?

Possibly. Windows XP does have some safety features like a firewall (Figure 3) that can block incoming traffic from the internet (but not internal networks – people like to be able to see their servers and printers), and antivirus products are still made for the operating system (although whether you're allowed to install them is another matter). The problem is that Windows XP's firewall isn't perfect, and there are any number of other ways for malware to be installed on a PC; visiting a compromised website, opening a nefarious email attachment – even infected PCs or laptops can spread viruses to vulnerable computers on internal networks.

You can maximize the chances of keeping your Windows XP-based PC secure by curtailing its connectivity: keeping it off the internet, potentially even the intranet, and as the Stuxnet case has shown, prohibiting the use of removable media. Unfortunately, that's not very useful – in most cases, people will want to move data on and off these PCs, be it images, patient records, or datasets for analysis. The reality is that they will be used, they will be vulnerable, and they are likely to be infected with computer viruses or malware, hence headlines like "Computer Viruses Are 'Rampant' on Medical Devices in Hospitals" (bit.ly/rampantviri). Whether or not that interferes with the function of the PC is another matter, and clearly using an infected PC is not an ideal situation particularly if patient safety is at stake – but some will have the philosophy that if it works, it works, and if antivirus software can't be installed… how will people know if there's malware on the computer in the first place? The PC is slow? It's old!

PCs from the Windows XP era are starting to get old – parts fail, and even eventually the computers will be scrapped. However, when that PC is fundamentally required to run an expensive instrument, and you can almost certainly get the parts you need inexpensively from eBay… it's more likely that if the instrument still does the job it needs to do, then the PC will be repaired rather than the whole system (PC and instrument) being replaced. PCs running Windows XP are a security worry with a long tail – just be aware of the risks associated with using them.

Pete Williams is an independent IT security consultant based in Cheshire, England, UK.

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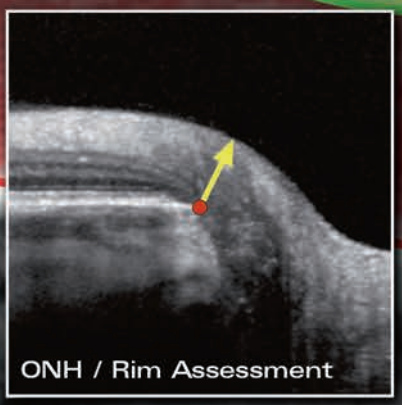

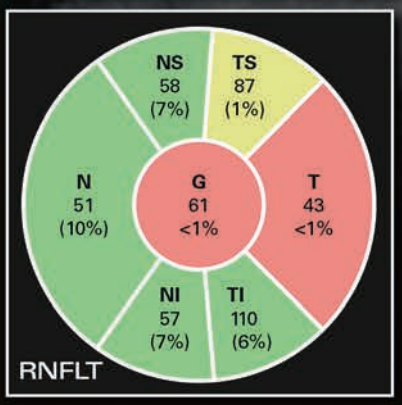

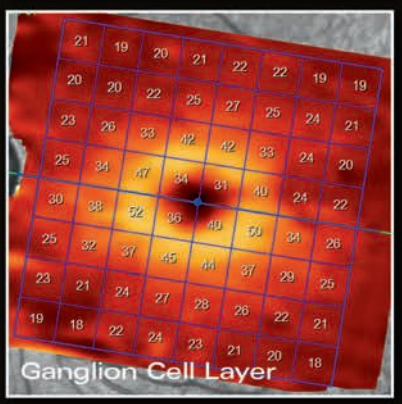

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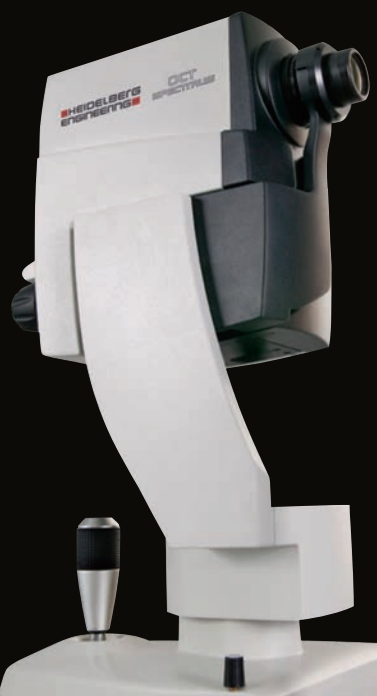

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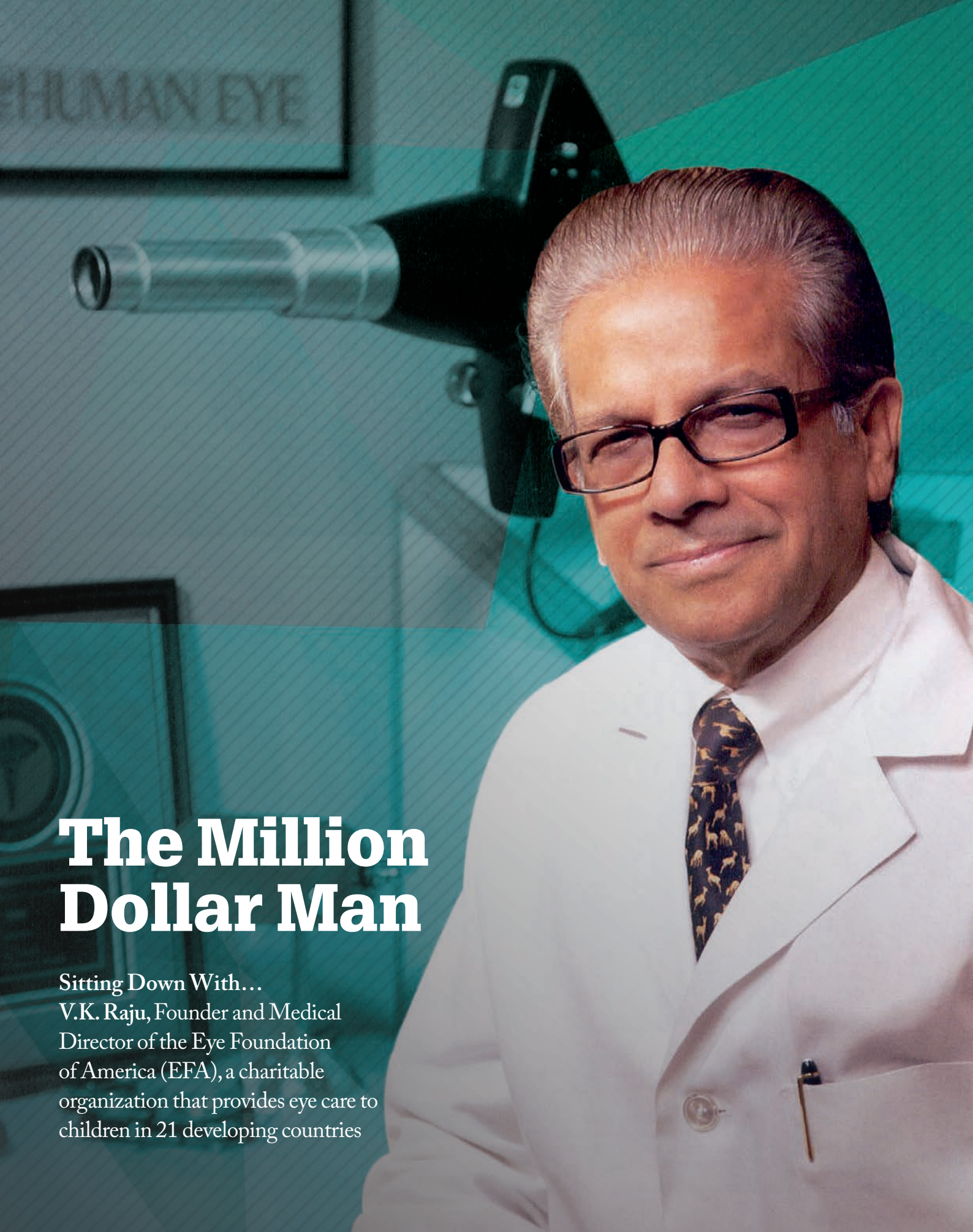

The Million Dollar Man

Sitting Down With…
V.K. Raju, Founder and Medical Director of the Eye Foundation of America (EFA), a charitable organization that provides eye care to children in 21 developing countries

India is a rapidly developing country, but there's a massive rural population with unmet eye care needs. How can they be helped?

India is a highly developed country in some respects – if I began my ophthalmology training now, the education in India is so good that I could have done it there. But in other respects, it still has the problems of a developing country. We can send a mission to Mars, but rural areas still have a lot basic health problems. While living in the United States, I went to India on holiday and a farmer came to show me his eyes. I didn't have any instruments with me, so I was like a fish out of water; that's what prompted me to start my first "eye care camp" in 1977.

The World Bank once said that the most cost-effective intervention in the world is combating childhood blindness; children's vision is a passion of mine, so as the eye camps expanded, we concentrated on children. We established a continuous vision screening program in schools – we train teachers to screen students so that we can catch refractive errors in time. Otherwise, people think that children aren't paying attention – but what's really happening is that they can't see the blackboard, so they don't understand the lessons.

The future of our world relies on us taking care of children. There are so many conditions that cause blindness in childhood; we can deal with them now that we have technology that wasn't there 30 or 40 years ago. We recently bought a retinal imager that allows us to identify the easily treatable condition, retinopathy of prematurity. The most satisfying aspect of what we do is giving children back their vision thanks to early diagnosis and treatment.

What made you form the Eye Foundation of America?

I formed the Eye Foundation of America (EFA) in 1982 to get funding and to send instruments to India. Border control was so rigid in the late 1970s that I was having a tough time getting surgical instruments out there. We couldn't perform cataract surgery on children using the same methods we would use on an adult, so we aspirated the cataracts through a small needle. We could do it without a large incision, but we also needed to remove a little of the vitreous to avoid problems after surgery – so I needed vitrectomy instruments. I was told it would be easier to bring them into India if I started a foundation for charitable work. That's how the EFA began, I'd never considered fundraising, but my daughter started that 20 years later! Meanwhile, I'd spent over US$1 million of my own money on the foundation. Things are very different today; a lot of patients and friends now help us financially.

"I'd spent over US$1 million of my own money on the foundation…"

It's interesting. Here in America, patients pay me for LASIK surgery in order to get rid of their glasses – and that money goes to the EFA. One procedure means that 30 to 40 children elsewhere in the world get glasses! One big issue in India is that many people don't know that children can be born with cataracts. In many places in rural India, there are some non-ophthalmologist doctors who think, "We mustn't operate on such a small baby," not realizing the consequence is that the untreated child will soon lose their vision forever. It's a matter of education. That's why educating doctors, policy makers, and the public with outreach programs is so important. My mentor in London used to say, "Raj, there are three solutions to every problem. The first is education, the second is education and the third is education."

Do you see parallels between the underserved areas of the US and India?

The expectations of people in the United States are very different from those in India and other countries. They don't want to wait in line; they want the best treatment straight away. But I don't think it is right, when the United States is one of the richest countries in the world, that anyone should be without insurance. Nobody should ever be denied healthcare. Many of the inexpensive instruments and techniques developed for eye care screening and surgery in developing countries could be used in the United States as well, but I fear that can't happen until the legal system is… more balanced.

Nevertheless, there are physician exchange programs between the United States and India, where doctors from America can observe how things are done in developing areas and learn to provide eye care – and health care in general – in a less expensive way. So many doctors in underserved areas are very innovative, and learning those methods is good for both sides. In the last 35 years, there've been more than 40 major medical breakthroughs, but the technological advancements can be expensive – so I think education, prevention and early diagnosis will help to keep costs down. But ultimately, developing countries' outreach programs are the answer to combat childhood avoidable blindness.

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