AUGUST 2019 # 36

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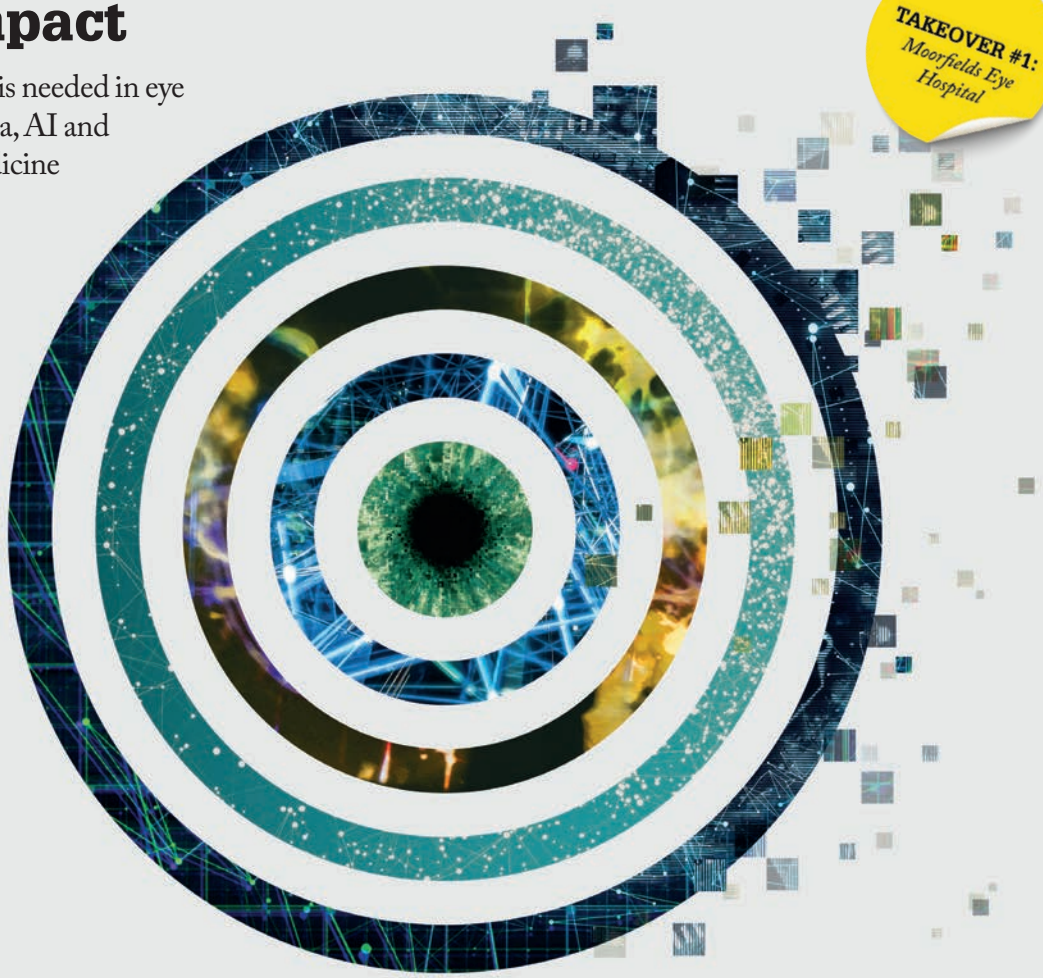

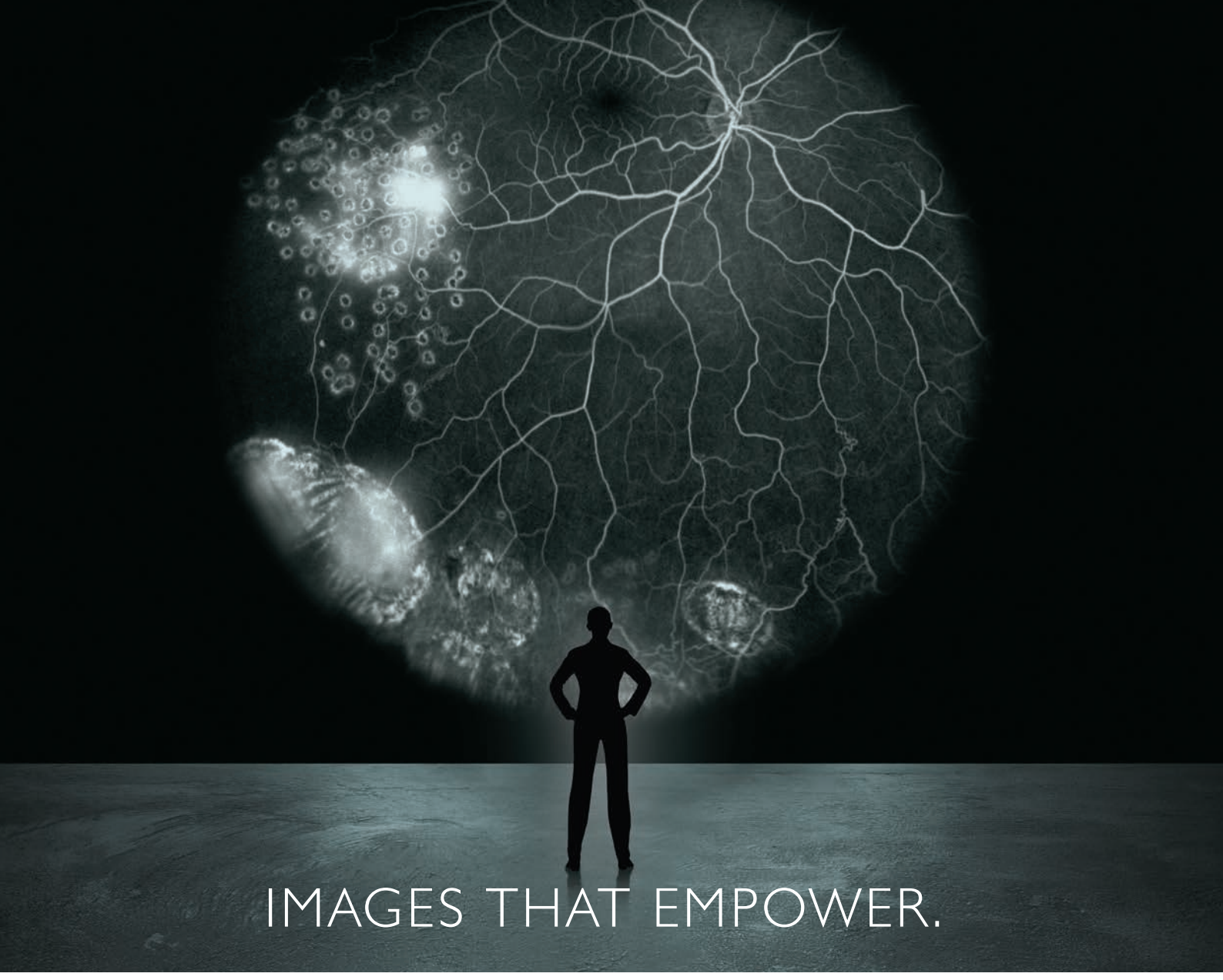

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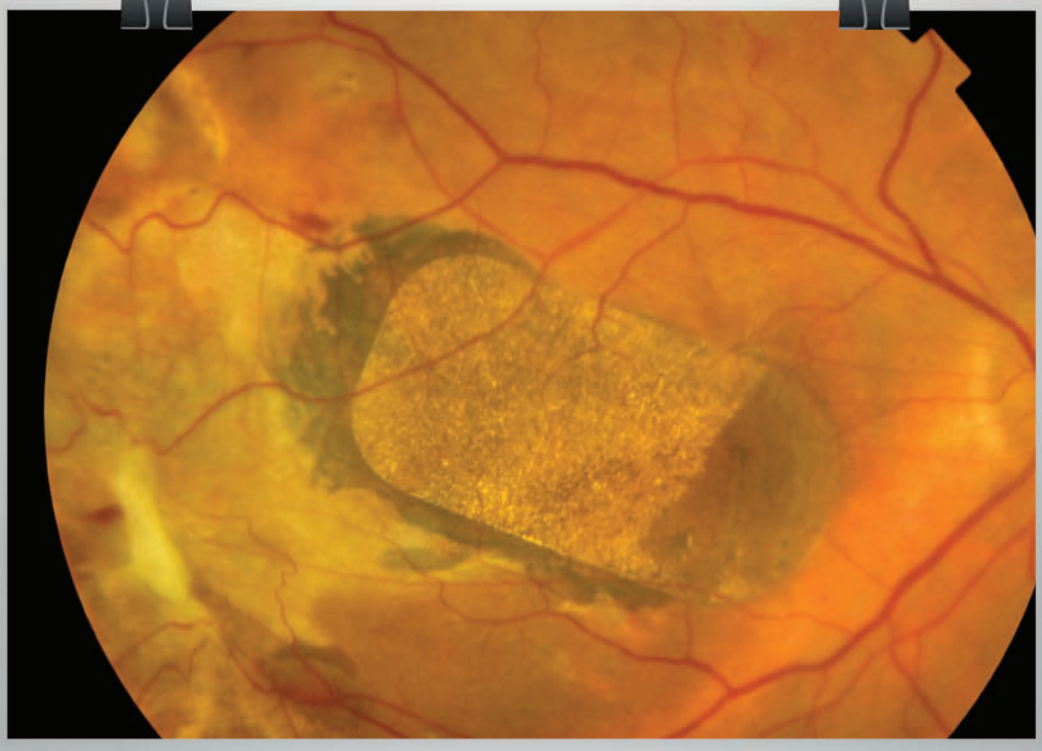

Patched Up

This month's image shows a retinal pigment epithelium patch, developed from human embryonic stem cells, which has been transplanted under the retina. This procedure is the first of its kind performed on a patient.

Credit: Lyndon da Cruz, NIHR Biomedical Research Centre, Moorfields Eye Hospital and University College London.

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

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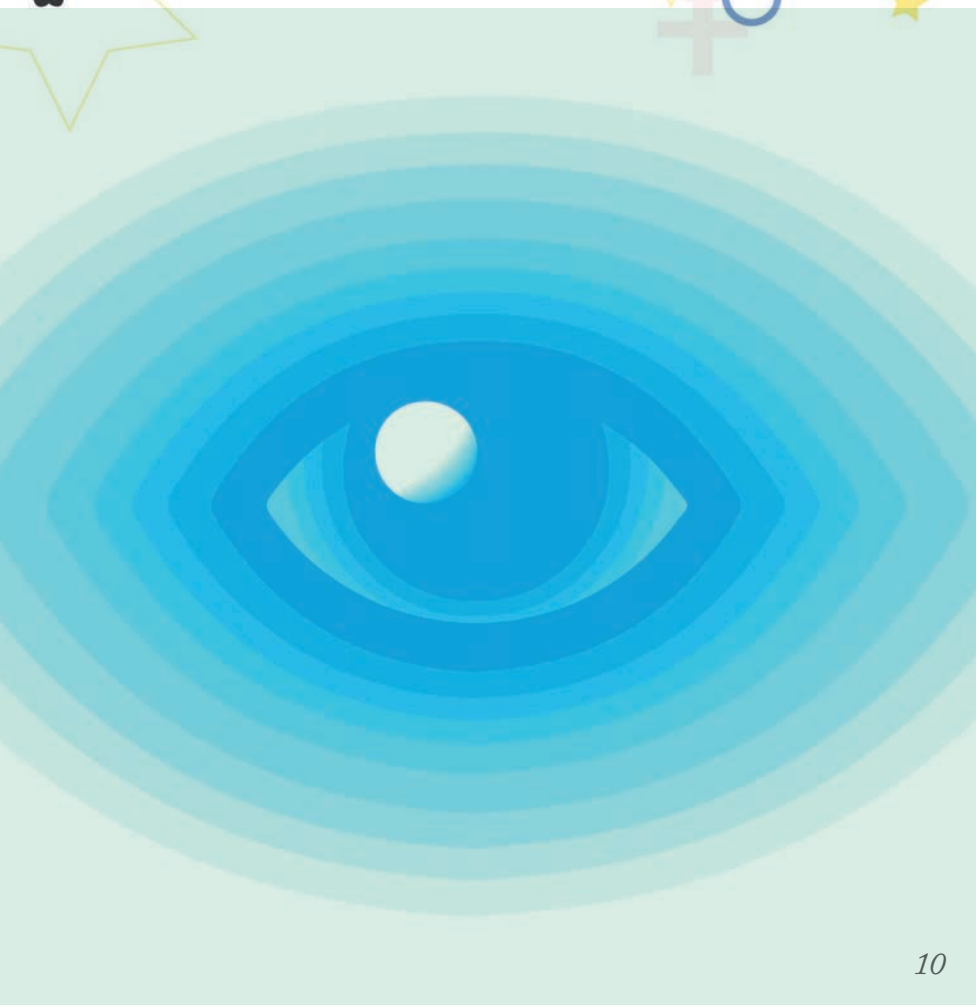

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Fighting Spirit

After 200 years of providing world-class eye care, Moorfields Eye Hospital is still leading the field

For over two centuries, Moorfields Eye Hospital NHS Foundation Trust has been at the forefront of the delivery of ophthalmic care, research and education. The establishment of this single specialty eye hospital was a visionary move by a group of dedicated surgeon oculists – as was the development of ophthalmic subspecialization, which took place at Moorfields during the latter half of the 20th century. The spirit of innovation has remained a core facet of Moorfields' life and has enabled us to not only survive, but also to flourish. We are now entering perhaps the most exciting phase of our history, with our proposed move into a purpose-built, integrated clinical, research and education facility.

Much of our ground-breaking work, undertaken at the National Institute of Health Research (NIHR) Biomedical Research Centre alongside our research partner, the UCL Institute of Ophthalmology, will be familiar to the readership of The Ophthalmologist – and many of our staff members have featured prominently in the Power Lists. This Moorfields "takeover" issue is a wonderful opportunity for us to demonstrate how research breakthroughs can help shape the future of ophthalmology, and allows us to showcase the broad range of our work, which is made possible thanks to NIHR funding; with such strong support for major research initiatives, we're able to fast track projects that benefit patients.

But we must acknowledge that new developments in therapeutics and diagnostics will not be enough to meet the looming crisis of increasing demand and diminishing resources. Just as the blight of "military ophthalmoplegia" was the catalyst that led to the founding of Moorfields, the aging demographic and economic downturn are forcing all involved in eye care to deliver services in increasingly innovative ways. Moorfields is active in meeting this challenge – through the upskilling of the ancillary workforce and through more effective, efficient and widespread use of existing technologies, such as virtual clinics and tele-ophthalmology.

Moorfields does not exist in a vacuum and we could not deliver the best care, research and education without collaboration, partnership and dialogue with other providers, universities and commercial entities. Moorfields is now very much an external-facing entity, keen to reflect on and adopt best practices developed elsewhere, as well as encouraging our staff to discover, develop and deliver great advances in their own right. It is my great honor to serve as Moorfields' Medical Director and to act as guest editor for this issue. I hope the following articles will interest, educate and inspire you.

Nick Strouthidis
Medical Director,
Moorfields Eye Hospital

Upfront

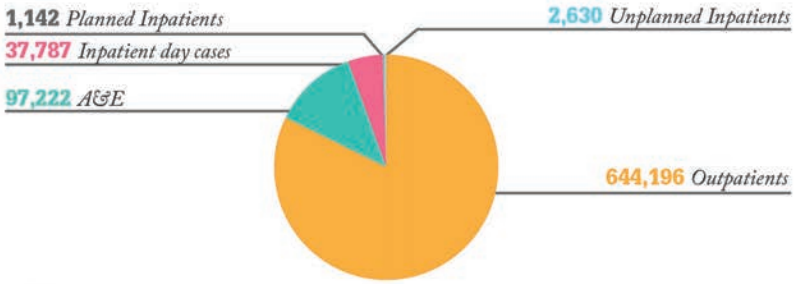
Reporting on the innovations in medicine and surgery, the research policies and personalities that shape the practice of ophthalmology.

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

Moorfields in Numbers

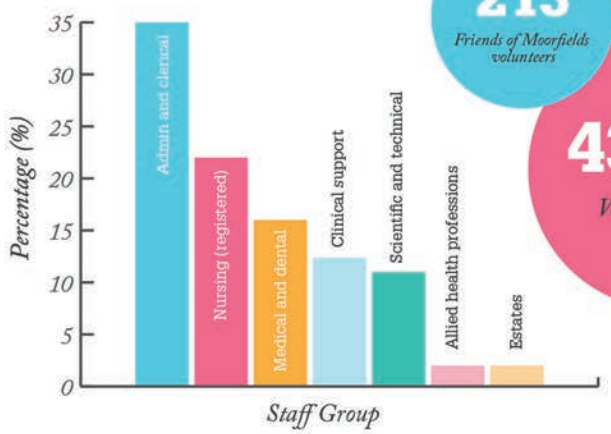
Moorfields is one of the world's largest eye institutions, with over 30 sites in London, the south-east and the United Arab Emirates. Here's what you need to know.

Patient visits



Finances

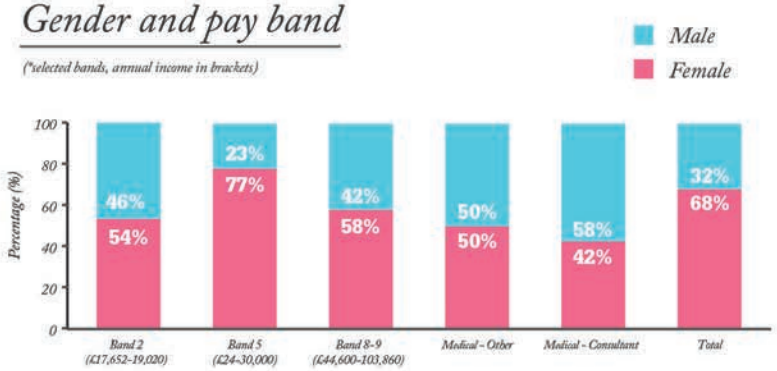
Workforce



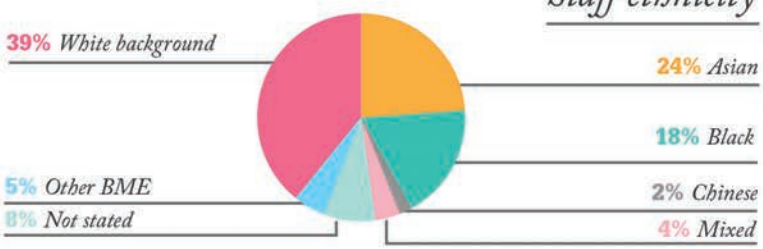
Volunteers

Gender and pay band

(*selected bands, annual income in brackets)

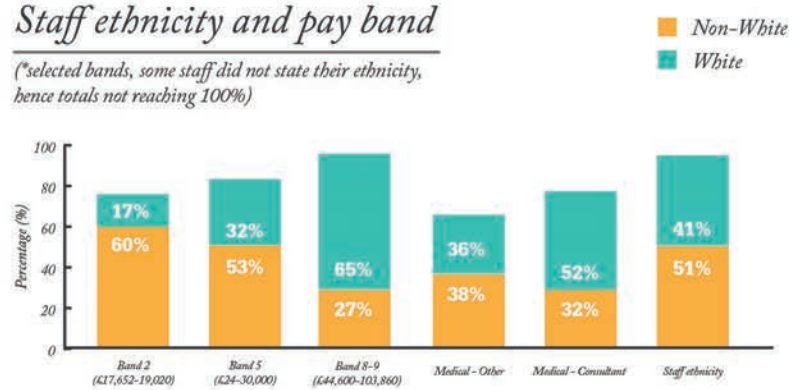


Staff ethnicity



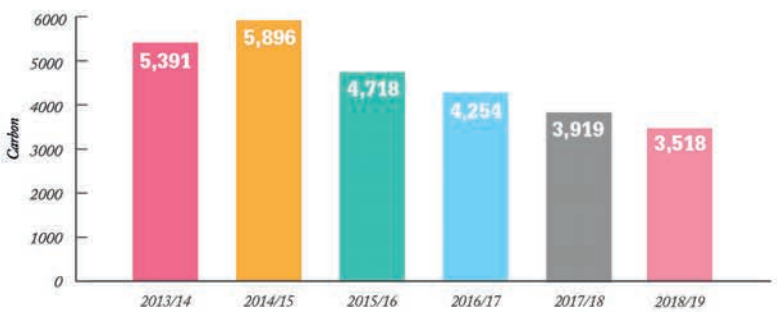
Staff ethnicity and pay band

(*selected bands, some staff did not state their ethnicity, hence totals not reaching 100%)



Carbon footprint

(energy supplies where Moorfields is responsible for procurement)



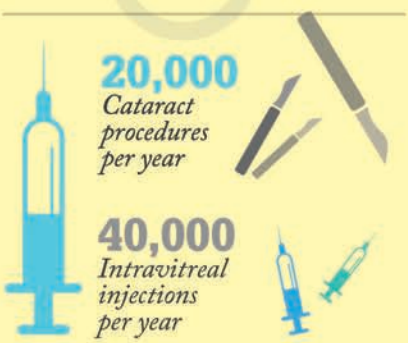
2,120
Full and Part-time Staff

87
Fellows

782,977
Patient visits per year

68% *Female staff*

32% *Male staff*



20,000
Cataract procedures per year

40,000
Intravitreal injections per year

Data taken from the Moorfields Annual Review 2017/2018 and the Focus on Inclusion 2018 document, prepared by Moorfields Eye Hospital NHS Foundation Trust.

Investigating the Inner Layer

Research Fellow Alice Davidson explains how discoveries in the genetics of corneal dystrophies are leading to new therapeutic avenues

How and why did you get into the genetics of Fuchs' dystrophy?

Fuchs' endothelial corneal dystrophy (FECD) is the most common corneal dystrophy, affecting up to 4.5 percent of individuals over 50 years of age. It is an inherited, age-related, degenerative condition that primarily affects the innermost layer of the cornea and it is the most frequent indication for corneal transplantation in the developed world. Corneal transplantation is currently the only treatment option available for patients experiencing visual loss. However, these are invasive procedures that rely upon specialist facilities and healthy donor corneas, of which there is currently a global shortage. With life expectancy rapidly increasing, age-related conditions such as FECD are placing an increasing burden on healthcare systems, so we are looking for innovative (donor tissue independent) and preventative therapies to address this global healthcare need.

In 2013, I was working on a group of conditions associated with corneal endothelial disease with Alison Hardcastle and Steve Tuft, and the discovery that FECD was associated with a triplet repeat expansion within a gene called TCF4 gave me the impetus to develop my own independent research program. In 2015, I was awarded a Fight for Sight fellowship to work on the genetics of primary corneal endothelial disease, and decided to initially focus my efforts on developing endothelial cell culture methods to study the pathophysiology of TCF4 triplet expansion-mediated FECDs. I subsequently partnered with ProQR Therapeutics to explore the therapeutic potential of antisense oligonucleotides (ASO) therapy to treat this repeat expansion-induced pathology (1).

What is the current focus of your research program?

Our program aims to identify genetic causes of corneal endothelial disease, investigate how and why different disease-associated mutations cause endothelial cell dysfunction, and use this knowledge to develop new preventative therapies. To identify the genetic origins of disease, my lab analyzes patient DNA samples using a broad range of DNA sequencing methodologies. In parallel, using donated tissue removed during planned corneal transplant surgery, we use specialist techniques to grow and maintain the corneal endothelial cells, enabling us to study how and why particular mutations cause cellular dysfunction and disease. We aim to harness this knowledge to design preventative gene-directed treatment strategies and diagnostic tests (1, 2).

What are the key findings of your work?

My lab has demonstrated that 80 percent of patients affected by FECD in the UK have the same genetic cause of disease; the aforementioned triplet repeat expansion within the TCF4 gene (1). We have also made significant progress with respect to understanding rarer genetic subtypes of corneal endothelial disease (3, 4, 5, 6, 7). Furthermore, we have developed an in vitro patient cell-derived model to learn about mutation-induced pathology and develop ASO therapies to treat the most common genetic cause of the disease. Our proof-of-concept data suggest that this approach could be an effective preventive therapy for this common sight-threatening disease in the future (1). Most recently, we have developed an innovative method to sequence the disease-associated TCF4 repeat expansion. The method, termed "No Amp Targeted Sequencing," provides a robust and accurate method for genotyping clinically-relevant samples and overcomes the limitations of alternative approaches. Furthermore, work has revealed that the TCF4 mutation behaves in a dynamic way, providing novel insights into the cellular mechanism responsible for the disease (2).

What are your plans and expectations for the future?

I am actively collaborating with ProQR Therapeutics to develop a preventative ASO therapeutic approach to treat the most common genetic causes of FECD. As a scientific community, our understanding of genetics and how an individual's genome predisposes them to disease has advanced immeasurably over the past decade. However, we are only starting to realize the clinical and translational potential of this knowledge. In the next decade I anticipate – and hope – we will see many exciting advances in the field of personalized genomic medicine that will have a positive impact on people's health.

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1. *C Zarouchlioti et al., Am J Hum Genet, 102, 528 (2018). PMID: 29526280.*
2. *NJ Hafford-Tear et al., Genet Med, [Epub ahead of print] (2019). PMID: 30733599.*
3. *P Liskova et al., Am J Hum Genet, 102, 447 (2018). PMID: 29499165.*
4. *AE Davidson et al., Am J Hum Genet, 98, 75 (2016). PMID: 26749309.*
5. *P Liskova et al., Eur J Hum Genet, 24, 985 (2016). PMID: 26508574.*
6. *AE Davidson et al., Eur J Hum Genet, [Epub ahead of print] (2019). PMID: 31201376.*
7. *L Dudakova et al., Exp Eye Res, 182, 160 (2019). PMID: 30851240.*

Master of Ceremonies

Matias Iglicki has been awarded a $50,000 research grant by the ICO-Allergan program

Pictured at the presentation, Peter Wiedemann (ICO President), Matias Iglicki, Emilio Torres-Netto, Berthold Seitz (ICO Director of Fellowships), Montu Sumra and Neeru Gupta (ICO Vice President)

The ICO-Allergan Advanced Research Fellowship is fast becoming ophthalmology's most coveted grant for young clinician researchers. Now in its second year, this $50,000 award supports a researcher as they continue their work at an institute of their choice for 12 months. A panel of expert judges met at ARVO in Vancouver, Canada, to select a winner. The decision was unanimous: Matias Iglicki – a retinal surgeon and researcher from the University of Buenos Aires, Argentina. Iglicki received his award at a celebratory reception at the European Society of Ophthalmology (SOE) Congress in Nice, France, in June 2019.

Berthold Seitz opened the ceremony – attended by the ICO committee, members of Allergan and a host of renowned ophthalmologists – with a succinct introduction: "It has been an honor to hold the position of Chairman of ICO Fellowships for the past three years. I have had the pleasure of reviewing all the applications for the fellowship – both this year's and last's – and I am delighted to formally award our newest recipient, Matias Iglicki."

Iglicki came forward to collect his prize and was congratulated by the ICO committee. "First of all, I would like to thank the ICO and Allergan for choosing our project," he said. "This funding will allow us to create a modified algorithm for detecting early evidence of diabetic retinopathy – and help countless people in the process. Telemedicine projects like ours have huge potential in rural areas, where many people have little or no access to an ophthalmologist. Our algorithm acts as a first-line screening tool: it works by assessing basic fundus photos – taken in the city hall when a patient goes to apply for a driving license – for evidence of diabetic retinopathy. If any are found, the patient is flagged for an appointment with the ophthalmologist," explained Iglicki. "Hopefully in a year's time we will be able to show you how many patients our project has saved from diabetic retinopathy. So again, thank you so much."

Last year's winner, Emilio Torres-Netto, followed Iglicki to share his own experiences of the grant. "The Fellowship has allowed us to investigate past contraindications, and extend our reach in terms of both scope and geography," said Torres-Netto. "We now know that keratoconus is not a rare disease and slowly others are beginning to realize that, too. Thank you, ICO, and thank you, Allergan, for helping us to change perceptions; it has been an amazing journey."

Montu Sumra, Executive Medical Director, International Head of Medical Affairs at Allergan, ended the ceremony with a few words for the recipients. "I'd like to offer my congratulations to both Emilio Torres-Netto and Matias Iglicki," said Sumra. "The work these young ophthalmologists are doing is making an immense contribution to our collective understanding of the conditions which affect the eye, and how best to treat them. The Fellowship is truly an essential research award, which is why I'm pleased to announce that we will be extending the partnership for a third year. We look forward to the next batch of innovation."

A combined ICO-Allergan committee present Matias Iglicki with his award: a $50,000 research grant

To apply – and for more information – visit *www.icoph.org/refocusing_education/fellowships.html*

In My View

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

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

Contact the team at edit@theophthalmologist.com

Time to Transform the Glaucoma Treatment Paradigm

SLT is an effective intervention for newly-diagnosed patients – and now we can prove it

By Gus Gazzard, Consultant Ophthalmic Surgeon and Glaucoma Service Director at Moorfields Eye Hospital

In April this year, we published the results of our six-year NIHR-funded trial assessing primary treatment for newly-diagnosed glaucoma (1). We compared two interventions; selective laser trabeculoplasty – a well-known, but less widely adopted first-line treatment – and the current standard of care, eye drops. A total of 718 patients were randomly allocated to a group and monitored to establish which intervention was more effective in lowering intraocular pressure (IOP). We managed to retain over 90 percent of those patients, which is not only a feat in itself, but a major metric of a successful study. The results were surprising – even to us.

SLT was found to be as effective, if not more effective, than eye drops at controlling IOP – giving drop-free control to three quarters of the patients in the laser group for at least 36 months. They also required fewer surgeries – there were no trabeculectomies needed in the SLT group, compared with 11 in the medication-first group – and fewer cataract extractions, a common side effect of habitual drop use. SLT was also significantly more cost effective than eye drops. We worked out that using SLT as a first-line treatment resulted in savings of £451 per patient in specialist ophthalmology costs. To put that in perspective, SLT could save the NHS £1.5 million a year in treatment for newly-diagnosed patients, with the potential to save a further £250 million a year if SLT proves to be as effective in previously-diagnosed patients.

Our final test came down to quality of life outcomes, which was assessed using the EQ-5D questionnaire – a generic tool eliciting utility values in multiple settings. Promisingly, we found no clinically-significant difference between the two groups. This, paired with our findings on disease progression, achievement of target intraocular pressure and cost, suggest that we should shift our treatment paradigm to primary SLT – something that seems to be happening around the world already. I've had conversations with senior colleagues in Australia, America and Europe who are all now using SLT as a first-line treatment on the basis of our study.

The recent standard of care for newly diagnosed patients has been eye drops – more and more – and still more – until they need surgery. If surgery doesn't work, they go back on eye drops. But now we know there is an alternative. SLT has proved itself to be adept at controlling and preventing the deterioration of glaucoma. Our research is already having a positive and profound impact on patients with newly diagnosed glaucoma outside of the UK – isn't it time it starts having an impact here, too?

Reference

1. *G Gazzard et al., "Selective laser trabeculoplasty versus eye drops for first-line treatment of ocular hypertension and glaucoma (LiGHT): a multicentre randomised controlled trial", Lancet, 393, 1505 (2019). PMID: 30862377.*

Unlocked Potential

The evolving treatment options for patients with stem cell deficiency

By Sajjad Ahmad, Consultant Ophthalmologist at Moorfields Eye Hospital

Stem cells are essential to the maintenance of a healthy corneal epithelium. Without a continuous supply; for example, in limbal stem cell deficiency (LSCD), the ocular surface becomes unstable, leading to ocular pain, corneal erosions and decreased vision from stromal scarring or epithelial irregularity. Stem cells are typically damaged in one of two ways: through trauma, such as chemical assault or burn, or as a result of genetic disease. Rare congenital conditions, such as aniridia or ectodermal dysplasia, Stevens Johnson's syndrome and mucous membrane pemphigoid can all cause significant damage to the surface of the eye. But with the advent of new therapies, there is hope for patients with LSCD. We can now take cells from a patient's healthy eye and grow them in the lab, amplifying the cells until there are enough to transplant into the deficient eye. In my practice, we outsource our cells to an Italian lab with EMA-approval and NHS England-authorization. In cases where both patient's eyes are diseased, we rely on external sources. For this, we take stem cells from donor eye tissue and immune suppress the patient to reduce risk of rejection. We recently published the world's first randomized control trial for allogeneic stem cell treatment and the results were extremely promising (1). Interestingly, treatment options are no longer dependent on the availability of donor tissue. If there are no ocular stem cells available, we can take cells from non-ocular sources, such as the mouth – a process known as cultivated oral mucosal epithelial transplantation, or COMET. In cases where the clinician cannot – or does not want to – immune suppress the patient, COMET is an option; however, the results are not as good as those derived from corneal stem cells.

Practical challenges also stand in the way of stem cell therapy development. I have worked in the field for 15 years, which is roughly how much time it takes for a treatment to reach patients. Not only is the process long – it is also expensive; many clinicians who enjoy success in early clinical trials are unable to continue their work because they don't have commercial funding from a pharmaceutical partner.

We have been awarded £2.8 million (over $3.5 million) from the Medical Research Council to conduct the first human trial for aniridia-related keratopathy, a rare form of stem cell deficiency. Hopefully, we will know how effective that treatment is within the next five years. Unfortunately, for other deficiencies, the future isn't quite so certain; there is no currently available funding for patients with disease in both eyes. And though there are therapies in the research setting, none that have traversed into the commercial environment. And the most promising option may still need further clinical trials...

"Society must address a growing and disturbing root cause of stem cell deficiency: chemical attacks."

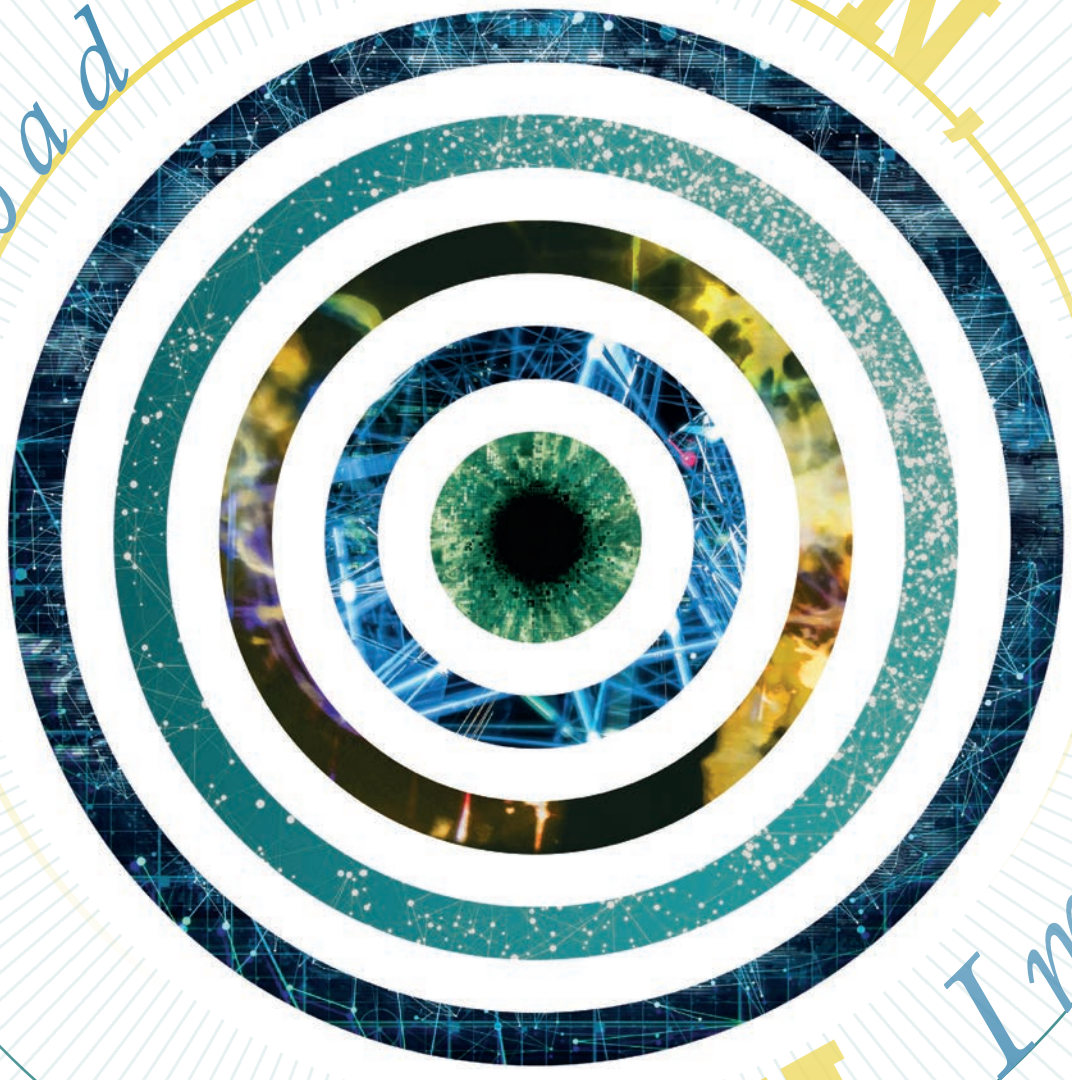
One of the big challenges for our community is finding a treatment that is commercially available on the NHS. There are still unanswered questions surrounding the long-term outcomes of donated stem cells. Studies have found that transplanted donor cells seem to disappear after around a year, causing the surface of the eye to normalize. So far, no one knows why. The industry is also looking to molecular therapies as potential treatment options, which will hopefully come to fruition in the next five to 10 years.

In the meantime, society must address a growing and disturbing root cause of stem cell deficiency: chemical attacks. I see patients on a weekly basis – mostly young men – suffering from corneal burns. The issue may be underreported in the media, but it is ever present in the clinic. Though we, as ophthalmologists, can help victims of chemical assaults, more work needs to be done to prevent these attacks from happening in the first place.

Reference

1. *JDM Campbell et al., "Allogeneic ex vivo expanded corneal epithelial stem cell transplantation: a randomized controlled clinical trial", Stem Cells Transl Med, 8, 323 (2019). PMID: 30688407.*

Broad VISION, HIGH Impact



Sir Peng Khaw (page 49) knows that big data and AI have the power to radically change healthcare. By tapping into experience and knowledge generated over thousands of lifetimes, patients across the globe can be given the same gift: the best possible diagnosis, prognosis and treatment – all contained in an algorithm.

On the following pages, Moorfields experts share their vision of big data, AI and personalized medicine in current and future ophthalmic practice – and argue that these technologies are not optional; rather, they represent the only way the profession will be able to cope with the enormous demand for eye care that is both inevitable and imminent.

In This *Day* and *Age*

Challenges of delivering high-quality eye care to an aging population

By Paul Foster

The world has seen dramatic improvements in health and life expectancy over the last century. People are now living healthier and longer lives, particularly in industrialized countries – a result of improvements in environmental and public health, as well as in nutrition and physical safety. However, as life expectancy has increased, so too has the number of people living with age-related degenerative diseases. Foremost among these in the news are the projected rise in dementia and the forecasted tsunami of health problems related to higher rates of diabetes. Less prominently in the news, but probably as important in terms of the numbers of people affected, are the degenerative eye diseases of later life, comprising cataract, AMD, glaucoma, and diabetic retinopathy.

In the UK, rates of visual impairment are 20 percent in people age 75 and older, and 50 percent in those aged 90 and over. Two thirds of these are women, and people from black and minority ethnic communities are at significantly greater risk of losing sight. Currently, there are over 2 million people in the UK who have daily problems with their sight. By 2050, projections double this number to over 4 million. A report from Deloitte Access Economics estimated that the cost of sight loss in the adult population of the UK totalled £28.1 billion (~$35.14 billion) in 2013. This figure comprises both direct and indirect costs – and the costs associated with reduced health and well-being. The figure has increased dramatically from £22 billion (~$27.5 billion) reported in 2008.

For healthcare providers, the problem is particularly problematic through increasing numbers of patients presenting for care. In 2015–2016, 16.3 million people underwent NHS sight tests with an optician. A further 8.2 million people attended hospital eye service appointments. Around 396,000 cataract operations were performed and 2.9 million people with diabetes underwent retinopathy photographic screening. There are currently 5.8 million people with sight threatening conditions in the UK. These figures put ophthalmology second only to orthopaedics and trauma as the busiest sector of the NHS in the UK.

AMD is by far the most common cause of registered visual loss in the UK. Although the numbers of those affected are increasing in absolute terms, the age-specific rates of disease are now clearly dropping in western European countries – thanks to improvements in public health, and more effective interventions, such as anti-VEGF treatments. Smoking is well known to be a strong modifiable risk factor for AMD. The public places smoking ban introduced in the UK in 2007 will almost certainly reap enormous benefits in the future: in the same way that traumatic eye injuries almost disappeared from ophthalmology departments following the seatbelt legislation introduced in 1983, the smoking ban will have a lasting, significant, beneficial impact on rates of AMD. Sadly, a similar, pragmatic and effective public health intervention for diabetes is proving elusive. Rising rates of obesity need changes in dietary habits and exercise, which are not easy to achieve. The smoking ban will also help drive down the rate of cataract development. However, once again, this benefit will probably be counter-balanced by rising rates of diabetes. Cataract surgery is one of the most effective interventions ever developed by modern healthcare and at least in this regard patients can look forward to a relatively straightforward and low risk way of improving their vision.

Probably the greatest scientific challenges presented by the four common diseases of later life relate to glaucoma. Though we have now confirmed and quantified the role of intraocular pressure, and clearly documented the benefits of lowering IOP, our understanding of the etiology of this condition has not changed in a meaningful way in the last hundred years. IOP remains the sole, proven, modifiable risk factor. The disease is now well known to be a polygenic abnormality, probably influenced by mutations in around 200 locations in human DNA. However, effective interventions based on genetic risks have proven elusive. The drive towards risk stratification using elevated intraocular pressure have not given any benefits – screening for glaucoma is not viable. In fact, the introduction of guidelines for England and Wales for

referral of all those people found to have IOP >21 mmHg only served to generate a three-fold increase in referrals, without any increase in detection of sight threatening glaucoma. Two things are now desperately needed: firstly, other modifiable risk factors need to be identified for this condition. Secondly, and most importantly, we need better ways of identifying the small number of patients who will progress to develop significant sight loss within their lifetime.

Rising to these challenges in the "age of austerity" is no easy feat. However, solutions are at hand, as my Moorfields colleagues outline in the pages of this issue of The Ophthalmologist. Conceptually, these fall into three broad categories: People, Processes, and Technology. Training the global workforce to deliver the highest standards of medical care regardless of where they work makes education a core part of our agenda. Developing newer ways of working, to deliver more efficient models of care is a subject of great interest to many. Virtual clinics and telemedicine allow us to monitor the enormous number of patients who need ophthalmic surveillance, but are currently stable and do not need procedures or changes in medication. Finally, in the "post-human genome project" era, where big data and AI are all the rage, technological advances look set to truly revolutionize the way ophthalmology is practiced.

Paul Foster is a Professor of Ophthalmic Epidemiology and Glaucoma Studies, UCL Institute of Ophthalmology and Honorary Consultant, Moorfields Eye Hospital.

Genomics *and* Glaucoma

Advances in genotyping offer great potential in the prediction of ocular disease and treatment outcomes – but also present ethical challenges

By Anthony Khawaja

Personalized medicine, precision medicine, individualized or stratified care… All these phrases essentially mean the same thing – that we treat each patient as an individual with the most beneficial approach rather than applying the same standards of care to the whole population.

In the move towards personalized medicine, genomics is going to be a significant driver. Our genetic code can help predict the risks of bad outcomes, as well as potential risks of side effects from certain treatments, and chances of responding positively to others (including varying doses). Genetic code screening for specific variants is inexpensive (~$60), and will most likely become the standard in predicting and diagnosing many diseases, as long as we know exactly what we should look for. Glaucoma is a very complex condition, with hundreds of risk factors working together, and various thresholds within each factor; nevertheless, it is also vitally important to detect disease at an early stage, to prevent irreversible vision loss. And so, huge sample sizes are needed to develop a deeper understanding of the genetics of this disorder.

In the past year or so, we have made real advances towards developing a comprehensive view of the genetics of glaucoma, using big studies, such as the UK Biobank (see page 22). We are now in the process of figuring out how useful the genetic information really is – and which aspects of it are important. We have found, for example, that if you take the strongest genetic variants for glaucoma and eye pressure, and you add it to the OHTS study risk calculator (1), it strongly improves prediction ability, more so than other variables, such as age or cup-to-disc ratio. My paper, published last year, identified over 130 genetic variants that predict higher IOP, and which can determine glaucoma risk (2). What does that mean? Right now, using genetic markers measured at birth, and taking a person's sex into consideration, we can predict the likelihood of developing glaucoma with 76 percent accuracy. In turn, this information can help us decide which parts of the population are at a higher risk and, therefore, may benefit from a personalized screening program. Population-wide screening for glaucoma is not recommended, as there the false positive rate is too high; personalized screening for high-risk individuals would be a big step towards preventing sight loss as a result of disease progression.

As genotyping is now affordable, I can see a future where every person who comes into contact with a healthcare system will go through this process. One challenge associated with genomics is the need to ensure that any system ultimately developed should be accessible and useful for ophthalmologists and centers around the world. To date, most genomic research has been conducted on people from European backgrounds, so any benefits derived from available data – and potentially the most appropriate treatments – will be applicable only to people from those backgrounds. A pertinent ethical question arises: should we develop a potentially more successful way of practicing medicine even though it can only be offered to people from one ethnic background at first? It seems clear that more work needs to be done to replicate prior research for other ethnic groups – and to develop a framework that leaves no group of patients disadvantaged.

Anthony Khawaja is Consultant Ophthalmologist at Moorfields Eye Hospital, Chair of Royal College of Ophthalmologists Informatics Committee and Director of European Leadership Development Programme.

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Getting *Eye Care* Down to a Science

Using digital technologies to streamline care for patients with common retinal conditions

By Konstantinos Balaskas

There is a very timely need in the retina subspecialty to transition to new, digitally-enabled models of care, and then implement them into real-life practice. To get there, we need to use the capabilities of digital health technologies, including telemedicine and AI decision-support systems – tools that can help professionals make diagnostic and management decisions for patients with common retinal conditions and at the same time improve the patient experience of care. Such tools require a number of validation processes, as well as evidence gathered through what is known as "implementation science," so that we can better understand their place in clinical practice.

There are three main steps in the development and introduction of AI decision-support systems and other digital technologies. The first one is a proof-of-concept step: developing the algorithm, which can then be tested against professional experts on retrospectively collected data sets – this should show performance as good as that of retinal experts in making the correct diagnosis. The second step requires gathering evidence from prospective research in real-life settings – introducing the developed and tested algorithm into a hospital setting, as well as community optometry practices (high street opticians), and gathering evidence of how it performs in real-life environments and in the general population. The third step involves "implementation science" – exploring how patients and practitioners interact with new digital technologies, and how offering and receiving care changes as a result of the algorithm implementation. This final step can include any changes to the workflow, any enablers or barriers to successful adoption, perceptions of these technologies, and economic aspects (the impact on the healthcare system's finances, and on various professions involved).

The FENETRE study is one of the implementation science projects that I'm leading. It is a multi-site, clinical trial, based in 16 hospital-based departments in England, and around 40 community optometry practices – and it's just about to begin. FENETRE is funded by the National Institute for Health Research in the UK, and is looking at an alternative model of care for AMD patients, who could receive their care in community optician practices rather than in hospital settings. This model is facilitated by digital technologies, and looks at creating a link between community optometry and specialized hospital-based services used to deliver second opinions, as needed, to ensure safety, and to provide training and quality assurance for the community partners.

The exploratory part of this project will analyze all the data collected in the study to check that management decisions made in the community and hospital settings match the decisions recommended by an AI decision-support system, assessing its performance. We have also developed a way to evaluate the economic impact of this model – investigating how finances might be affected if decisions were made by AI instead of human experts. We hope that the project will help determine the best pathways for management of patients with AMD.

One interesting point that makes this study even more timely, is the fact that community optometry practices are increasingly equipped with advanced imaging technologies (such as OCT). If they are capable of undertaking more primary and high-volume routine care for patients with common retinal conditions, such as AMD and diabetic retinopathy– with easy access to secondary care as a safety net, it would provide a convenient alternative pathway to patients; these community settings are often easier to access and more patient-friendly. And it would release some of the significant burden of care and treatment on the healthcare system, allowing better and faster access to hospital-based care for patients that require treatment.

Konstantinos Balaskas is a Consultant Ophthalmologist and Head of Moorfields Reading Centre at Moorfields Eye Hospital, readingcentre.org.

Thoroughly Modern *Medicine*

Retinal imaging in the era of personalized medicine

By Michel Michaelides

We are lucky to have unprecedented multimodal abilities to non-invasively image the retina these days. Understandably, this has transformed the practice of many retinal physicians and vision scientists. And yet, though our capabilities may be the envy of most other subspecialties, personalized medicine introduces a number of challenges for applications of retinal imaging in ophthalmology.

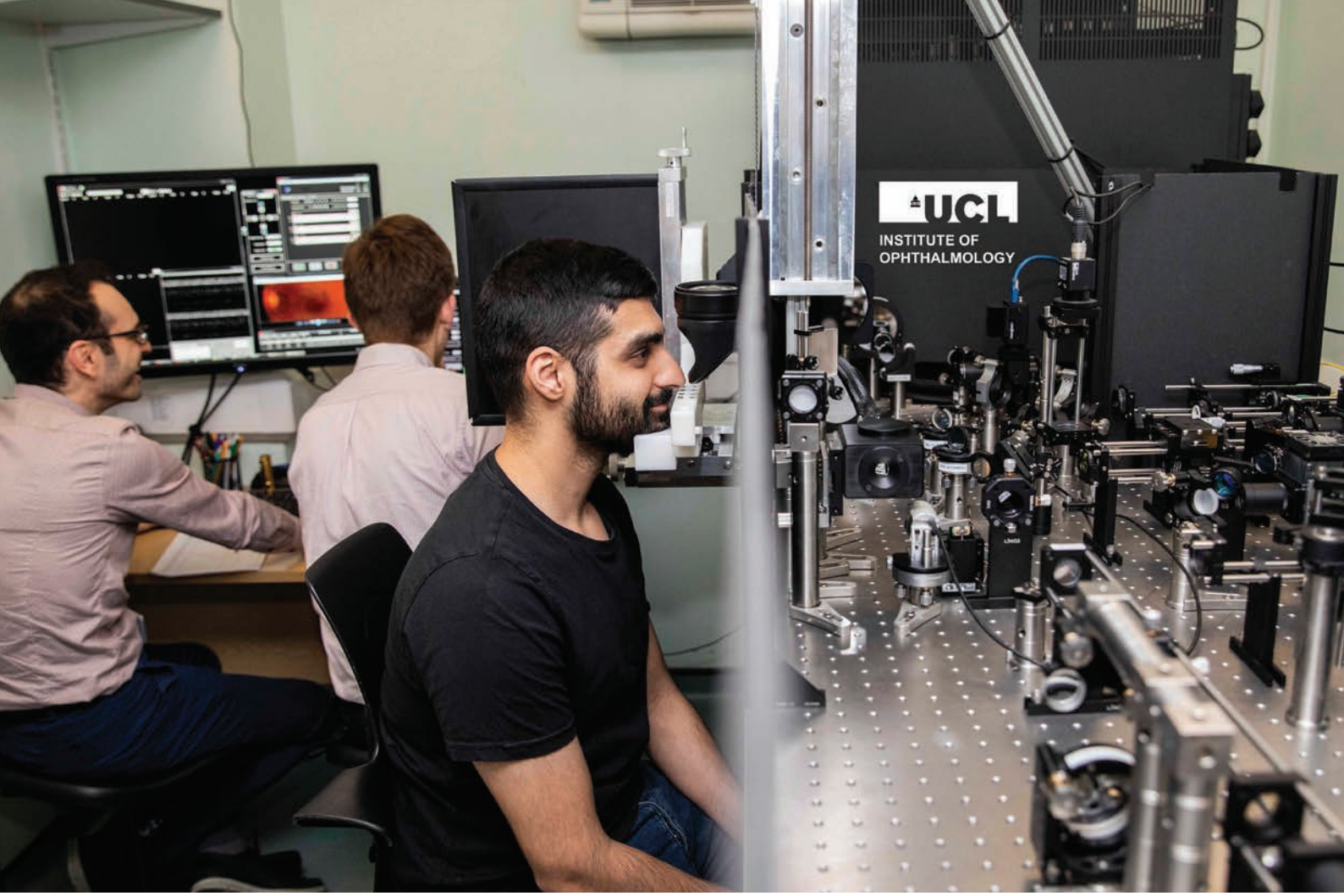
A major issue is that imaging is still not routine in unaffected or "normal" individuals. This knowledge gap is problematic; to understand whether a feature in a given image represents pathology or just a normal variant demands the availability of patient-specific normative databases. By this we mean that the demographics of the reference or normative database needs to match that of the patient – one cannot necessarily compare image features from a 68-year-old black man to normative data comprised of white women aged 19-23 years of age. The field remains surprisingly naïve with respect to the need for stratifying normative data by age, gender and race. There may well be certain features in retinal images that clearly signify active disease (such as intraretinal fluid viewed on optical coherence tomography), but the utility of images to detect subtle and early changes associated with pathology is limited by the quality of the image and the robustness of the reference database.

A second important challenge is that the information contained within images is currently extracted in either a qualitative fashion (by "expert" grading) or quantitatively through the use of segmentation or analysis algorithms. Why is that problematic? Because imaging technology continues to evolve exponentially, meaning that clinicians and researchers are constantly re-inventing the wheel when it comes to analysis and interpretation of images. What works for one imaging modality won't necessarily work for another one (compare segmenting lesions on color fundus images versus segmenting lesions on en face OCT images). Even within a single modality, analysis and interpretation of images can be variable. Logically, an OCT image of the same retina from six different commercial devices contains the same information – but whether a grader or algorithm extracts the same information is variable. What happens when patients switch providers or when a clinic changes devices? We risk potentially compromising the ability to make confident longitudinal assessments on a given patient.

In addition, related to longitudinal imaging, there is a lack of prospective protocol-driven natural history data for the vast majority of retinal conditions. Such datasets are invaluable in the development of image-based biomarkers that could be used to predict progression or even detect the disease. Besides applying natural history studies to more conditions, such studies should be comprehensive in the imaging modalities used. Moreover, most of these studies only deal with monitoring progression after diagnosis. It is exceptionally rare to have data that exists prior to and after diagnosis. However, this is exactly the type of data that could fuel powerful AI approaches.

AI is being increasingly applied to a growing number of retinal imaging studies, seeking to identify features within an image or to classify images by disease type. But the holy grail of personalized medicine is the ability to identify, for example, whether changes in a given individual represent normal aging changes or whether they are likely to progress to age-related macular degeneration. Though there are environmental and genetic "risk factors," ultimately, it stands to reason that the answer for an individual patient rests within their retinal imaging. The challenge for researchers and AI algorithms is to extract this information in a reliable, sensitive and robust way.

Michel Michaelides is Professor of Ophthalmology and Consultant Ophthalmic Surgeon, UCL Institute of Ophthalmology and Moorfields Eye Hospital.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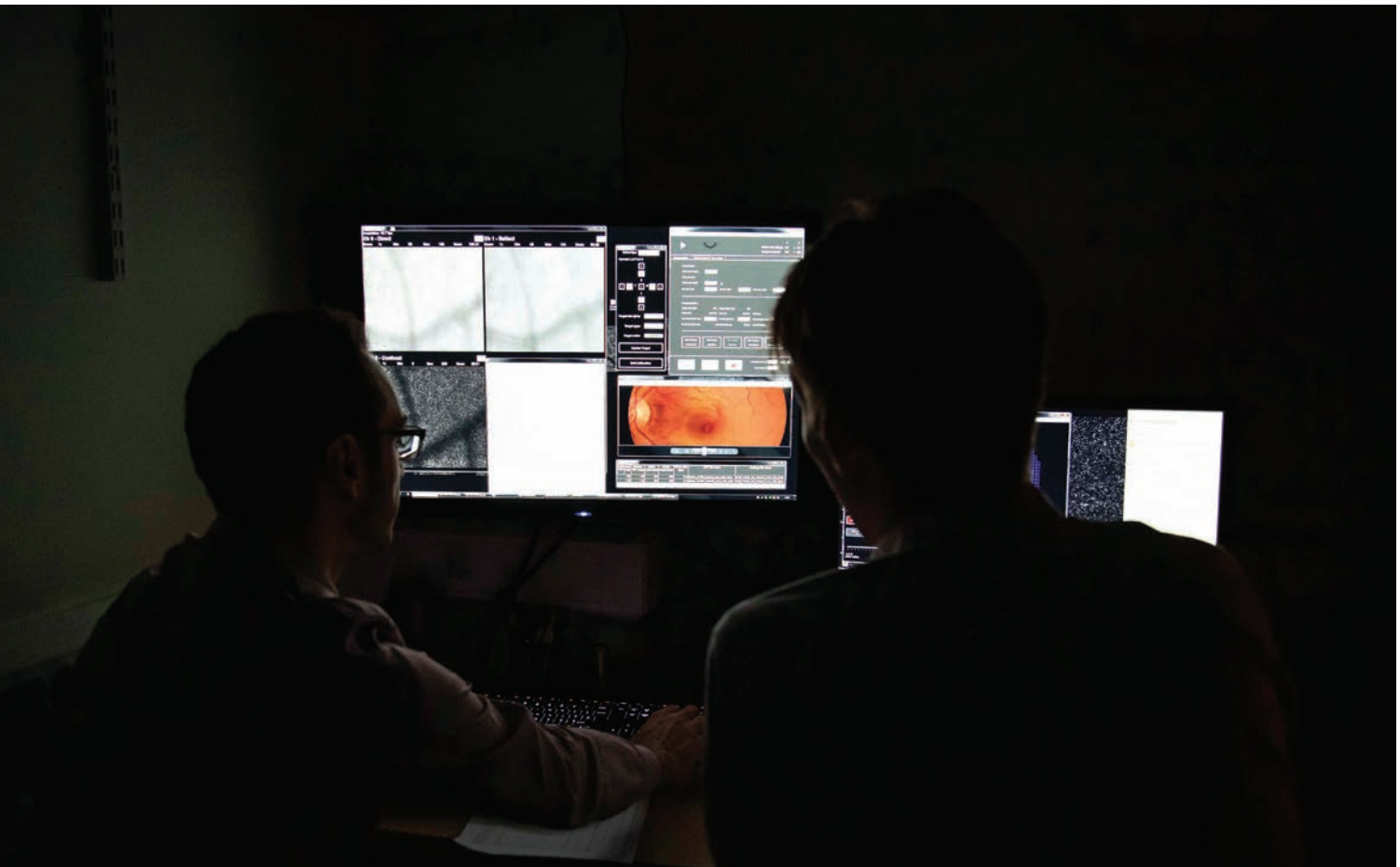

Glimpses of the *Future:* Virtual Clinics at Moorfields

In the UK, just 1,500 ophthalmologists manage nine million outpatient appointments each year. This imbalance in supply and demand is untenable – and begs for the efficiencies promised by digital technology

By Dawn Sim

Ophthalmologists rely on – and are trapped by – devices and instruments that run on incompatible software systems. Ophthalmic services would benefit enormously from IT solutions that enable communication between these systems. The development of an integrated IT platform accessible for all – GPs, optometrists, ophthalmologists – could save time, reduce service fragmentation and eliminate sources of error (loss of information, scan mix-ups). For example, improved IT connectivity would assist optometrist-led referrals into secondary care – without the need to go via a GP – which would speed up referrals and relieve GPs of some of the ophthalmology referral burden. At Moorfields, we are making this vision a reality. Fortunately, we are not alone in understanding the importance of communication technology; the recent NHS "Fit for the Future" plan stipulates a 10-year "digital-first" objective (1). But this revolution will require organizational change; a key requirement is an overhaul of our archaic patient pathways. At present (see Figure 1), these comprise multiple stages separated by periods of waiting. The NHS "digital-first" strategy aims to streamline and compress this pathway via technician-mediated teleophthalmology clinics, followed by location-independent assessment of eye-scan data by graders or ophthalmologists.

But, as noted in the Topol Review – an independent report commissioned by the UK government (2), digital transformation of healthcare systems will depend on appropriate workforce development. Accordingly, the NHS is funding 20 fellowships nationally, across all specialties, in fields relevant to our digital future. Moorfields has won two such fellowships. One involves assessment of Alleye, an approved system that uses a mobile phone app to detect and characterize metamorphosia in patients with retinal conditions. The object is to reduce hospital visits while improving communication and patient care. The second fellowship aims to assess "Big Picture" – a cloud-based, machine-learning system that uses the "smart clinical history" web app, in combination with Optomed Aurora (a non-mydriatic automated retinal camera). The idea is to perform opportunistic diabetic eye screening at home or in GP surgeries, with asynchronous transfer of retinal images to Moorfields for grading. This initiative hopes to address non-attendance at diabetic eye screening clinics and eliminate the current two-week waiting time for test results.

Moorfields is also expanding its teleophthalmology capabilities in other areas. Our virtual medical retina clinics, introduced in 2016, have been shown to optimize resource use without compromising patient safety or clinical quality (3). Briefly, of 728 patients who were on their second "virtual clinic" appointment were assessed, 497 (70 percent) proceeded to virtual follow-up; 108 (15 percent) were referred to a face-to-face clinic; 107 were discharged; and 17 were referred for urgent treatment. Overall, 542 patients (82 percent) were diagnosed with diabetic retinopathy, and only eight patients were unsuitable for virtual follow-up. Similarly, an earlier study (4) concluded that Moorfields' virtual medical retinal clinics improve the efficiency of resource allocation by directing care to those who require treatment, thereby helping medical retinal services meet growing demand. Finally, a retrospective cohort study indicated that a Moorfields cloud-based referral platform – designed to improve communication between optometrists and ophthalmologists – reduces referrals to hospital eye services by over 50 percent (5). Specifically, our system found that 54 of 103 patients who were initially placed into the referral pathway did not need a specialist referral, while 14 were classified as needing urgent treatment. This Moorfields digital-first platform therefore enables rapid-access eye care via referrals from community optometrists, and facilitates essential communication between healthcare providers.

These results confirm our belief that the role of communication technology in eye clinics can only grow. We expect that digital patient portals will increasingly use artificial intelligence-based chatbots to enhance the patient experience and ultimately streamline the patient journey: for example, by reminding patients to take drugs, renew prescriptions, make or keep appointments and manage their self-care. This artificial intelligence assistance may also triage patients by digitally administering questionnaires, and by combining demographic and clinical information with current symptoms. The overall effect will be to speed up processes for both patient and provider. At the same time, home monitoring will become the norm, we believe; its benefits will include better access for patients to healthcare systems, lower costs and higher efficiency for the NHS as a whole . Similarly, capture of patient-reported outcome measures (PROMS) via the patients' own mobile devices will allow functional measures to be continually assessed, which will in turn help improve ophthalmic services,

support health-related quality of life measurements and cost-effectiveness calculations, and allow those in secondary care to provide timely feedback.

In sum, these developments will push screening and monitoring services into the community, thereby permitting NHS hospitals to focus on treatment of patients. Cloud-based home monitoring, artificial intelligence and workforce evolution – such that ophthalmic nurses, optometrists and technicians operate in extended roles – will allow specialist consultants to attend to those patients who most need their expertise. The end result will be a national health service that provides better care, more efficiently and more conveniently. This 'digital-first' transformation is inevitable, and we at Moorfields are directly involved in its development and implementation, not least in the form of virtual medical retina clinics. Realization of the opportunities that technology provides in the eye healthcare sector will take time – but we are playing a long game in the name of safety, inclusiveness, and quality.

Dawn Sim is Director of Telemedicine and Consultant Ophthalmologist in Medical Retina and Cataract Surgery at Moorfields Eye Hospital.

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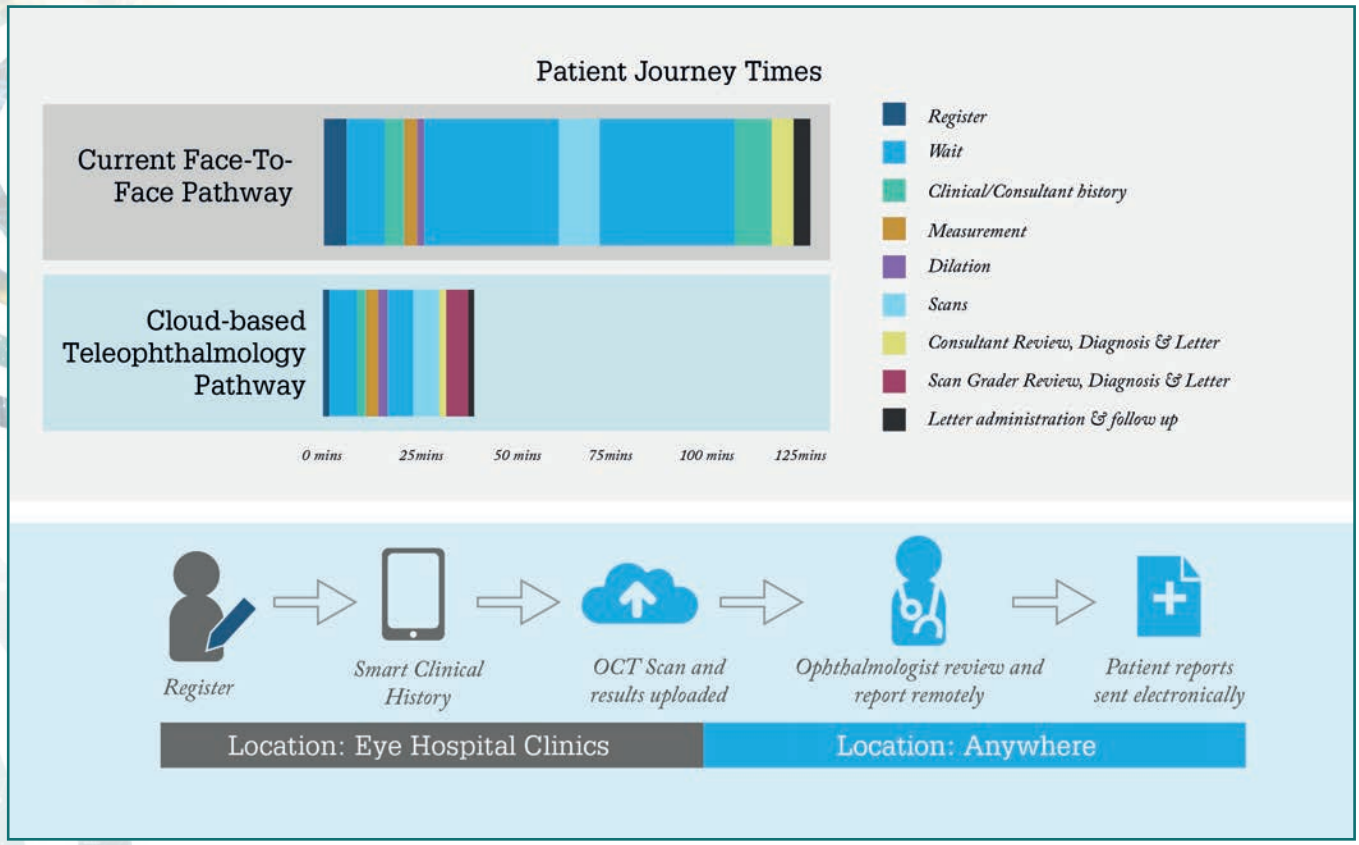

Figure 1. Current pathways (top of figure) involve several waiting periods (blue fields). Teleophthalmology initiatives will remove these delays through a technician-mediated initial phase and a location-independent expert assessment phase.

Banking on *Data*

Research groups around the UK are investigating over 100,000 clinical eye images and other data gathered by the UK Biobank to revolutionize ophthalmology

By Paul Foster

UK Biobank (UKBB) is a major national health platform in the UK (and a registered charity in its own right), which aims to improve the prevention, diagnosis and treatment of a wide range of serious and life-threatening illnesses. The original scope of the study was broadened from an initial focus on cardiovascular disease, stroke, cancer and diabetes to include more detailed examination of participants, including assessment of physical fitness, brain and cardiac imaging, as well as an examination of eyes and vision. Through their NIHR Biomedical Research Centre, Moorfields and the UCL Institute of Ophthalmology fought hard to include the eye and vision module, and then formed a UK wide consortium to develop and analyze data.

Eye data available within UKBB include visual acuity, auto-refraction and intraocular pressure data on more than 117,000 people. In addition, simultaneous digital fundus photography (single-field 45° centered on the macula), as well as macular optical coherence tomography was carried out on 67,321 people. During the data collection phase of UKBB, the Image Reading Centre at Moorfields provided a rapid turnaround quality assurance service for the macular photos and OCT images, finding them to be of high quality, compared with other studies using similar methodology. Links to other data available in UKBB, together with the longitudinal design of the study, make this possibly the most valuable research resource for ophthalmology in the UK (1).

Eye and vision researchers around the UK have formed a consortium, which meets in February each year for a day-long program of planning, discussion, and debate at the Wellcome Trust Conference Centre in London. And it has led to the formation of groups working on various aspects of data, including visual acuity, refractive error, intraocular pressure, retinal vascular characteristics, genetics and outcomes adjudication and monitoring.

Activity within the Consortium can be grouped according to the type of data or image that forms the primary focus of the research effort. Groups with shared interests have joined forces to use different data sources, some of which relate solely to eye and vision data, while others (such as genetics and record linkage) draw on resources with broader application. Four eye examinations were conducted in the latter stages of the UK Biobank baseline examination, and have been continued in the follow-ups (see Box: UK Biobank baseline eye examinations).

A Quick Research Tour

The following study groups have been formed by eye and vision researchers in the UK:

Nutrition and Eye: to investigate the association between diet and AMD, diabetic retinopathy and glaucoma, explore how these relationships relate or are modified by systemic factors identified by the blood biochemistry results, such as markers of inflammation or redox balance, and explore the existence of gene-environment interactions between dietary and lifestyle factors in AMD, diabetic retinopathy and glaucoma.

Cataract: to identify novel risk factors and examine diseases associated with cataracts, and to find common pathways and potential new preventive strategies, comparing the full dataset of 500,000 people and their environmental, lifestyle, biometric and genetic characteristics of people following cataract surgery, with those who haven't been through it.

Crowdsourcing: to use large numbers of people to analyze over 100,000 clinical eye images. The group developed an interactive online training module and webpage, and plans to promote public participation to assist in the classification of ophthalmic medical images.

Genetics: to determine how an individual's genetic make-up, lifestyle and environment all interact to increase or decrease risk of disease.

Giant Cell Arteritis (GCA) and Polymyalgia Rheumatica

"Links to other data available in UKBB, together with the longitudinal design of the study, make this possibly the most valuable research resource in the UK."

UK Biobank baseline eye examinations

- Visual acuity
- Refraction and keratometry (Tomey RC 5000)
- Intraocular pressure (IOP) and corneal biomechanics (Reichert ORA)
- Images of the retina and the optic nerve - A Topcon 3DOCT-1000 Mk 2 was used to capture a single-field 45° colour digital photograph centred on the macula including the optic nerve in the photographic field, together with 3D OCT images of the macula, 6.0 x 6.0mm, at a resolution of 512 x 128 pixels. The retinal images produced are sufficiently high resolution to distinguish separate cellular layers in the retina.

(PMR): to highlight potential associations of GCA and PMR that could stimulate further research into pathogenesis. This group intends to perform a cross-sectional study to investigate associations of GCA and PMR within UKBB. Additionally, it aims to determine whether ocular imaging, including OCT and retinal vascular caliber measurements, reveals particular features of GCA/PMR.

Intraocular pressure: to explore the factors that determine eye pressure, in order to help identify new interventions that can be used to control glaucoma in the UK and around the world (2).

Refractive Error: to investigate the complex relationships between myopia and visual function, and a diverse range of risk factors. The group aims to identify risk factors that can be modified, or biological processes and pathways that would merit further research (3).

Retina and Cognition: to explore the relationship between retinal anatomy, cognitive function, and other measures of neurological decline using OCT images included in UKBB. This might offer new methods of detecting and monitoring neurodegenerative conditions such as Alzheimer's disease, and potentially new insights into its etiology (4).

Retinal Detachment: this group has demonstrated that several gene pathways influence the risk of developing retinal detachment. Using single nucleotide polymorphisms (markers of genetic variation), the aim is to extend the assembled genetic database and perform a larger, case-control genome-wide association study on retinal detachment cases and population-matched controls. This research has the potential to identify new pathways in the disease process, and new therapeutic targets aimed at the prevention or treatment of this condition.

Retinal Image Grading: to study AMD, diabetic retinopathy (DR) and glaucoma in order to classify all retinal photographs in the UKBB dataset as normal, showing signs of disease or being un-gradable, assess the frequency and characteristics of DR in known diabetics, assess the frequency and describe the characteristics of AMD, measure the cup to disc ratio as a marker for glaucoma, to record the presence of any congenital or acquired abnormalities of retina or optic nerve, and to explore how AMD, DR and glaucoma characteristics are associated with socio-economic factors, lifestyle and environmental exposures of participants.

Retinal Vascular Morphometry: two groups within the consortium are actively developing new methods of examining the characteristics of retinal blood vessels to assess risk of disease.

Optical Coherence Tomography: in collaboration with the manufacturers of the OCT device used in UKBB (Topcon) this group was able to perform rapid, fully-automated retinal sublayer analysis on the OCT images.

Outcomes Adjudication and Record Linkage: to develop methods for the long-term follow up of the cohort, through centrally managed processes for ascertainment, confirmation, and sub-classification of both prevalent and incident outcomes of interest.

Visual Acuity: to learn more about the distribution of visual function and the frequency of different levels of sight impairment, to identify the biological, social and lifestyle factors that might influence the development of visual dysfunction, and to find out more about the general and mental health, social circumstances and ethnic diversity of adults with impaired sight in the UK today.

Paul Foster is a Professor of Ophthalmic Epidemiology and Glaucoma Studies, UCL Institute of Ophthalmology and Honorary Consultant, Moorfields Eye Hospital.

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Pressure to *Change*

How a cross-sectional study raised the glaucoma referral threshold by 3 mmHg – and reduced referrals by 67 percent

By Michelle Chan

Until very recently, community optometrists followed the 2010 guidance issued by the Royal College of Ophthalmologists: refer any patient with ocular hypertension – meaning IOP over 21 mmHg – to a glaucoma clinic, even if no other risk factors are present. Unfortunately, this advice resulted in a ~35 percent increase in referrals without increasing glaucoma diagnoses. A high proportion of these "glaucoma suspects" required monitoring for five years; so it is unsurprising that, by 2015, glaucoma and suspected glaucoma together accounted for the sixth largest share of NHS outpatient attendances.

IOP under pressure

It's easy to understand why we relied on IOP for screening: it's the major known, modifiable risk factor for POAG, its measurement is straightforward, and it is presented in the form of a number that requires no expert interpretation. The warning signals regarding over-reliance on IOP, however, have been evident for decades; around half of those presenting with POAG have IOP below 21 mmHg, and many of those with IOP over 21 mmHg never develop glaucoma. But changing an established screening system for an important, sight-threatening disease cannot happen overnight – it requires a lot of hard data.

We set about collecting this data in the EPIC Norfolk Eye Study, a community cross-sectional study where nearly 9000 participants were recruited in Norfolk and underwent detailed eye examination between 2004-2011. (see box: What does high IOP really mean?) Historically, the figure 21 mmHg was derived from a 1966 study, and corresponds to two standard deviations above a population's mean IOP (1). Our aims, in brief, were to re-examine the 21 mmHg IOP referral threshold by measuring the distribution of IOP in this UK population. We also wanted to assess the potential consequences of changing the referral threshold: how might such changes affect referral numbers and diagnosis rates?

Over-pressure underperformance

Our study (2) confirmed the views of many who work in the field: there is no IOP cut-off value that is sufficiently sensitive and specific to distinguish between those who have optic nerve damage and those who do not.

In fact, in our study population, 76 percent of patients newly found to have glaucoma had IOP below 21 mmHg, and therefore would have been missed by the standard screen. Furthermore, 10 percent of those without glaucoma had IOP in excess of 21 mmHg, suggesting the potential for over-diagnosis and unnecessary

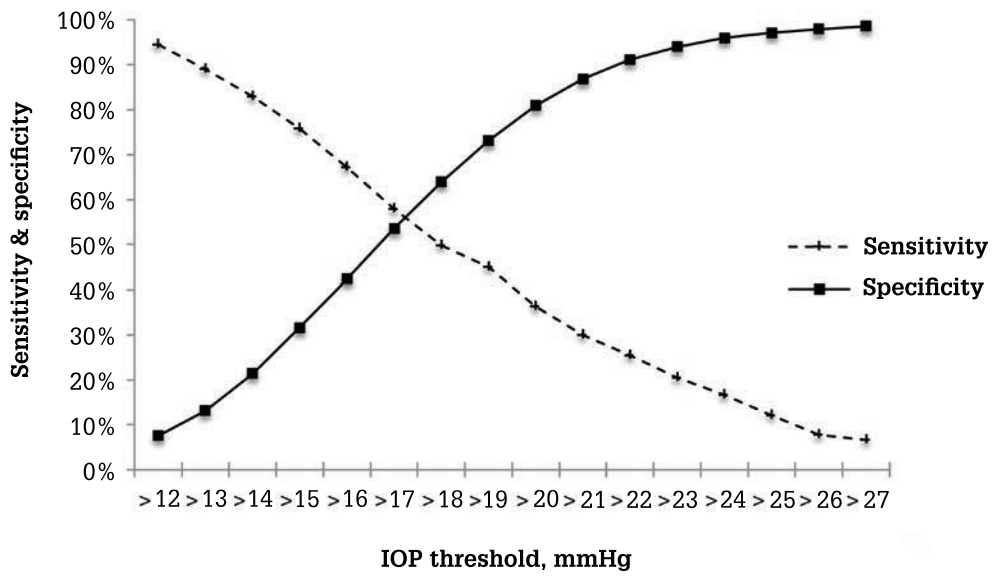

Figure 1. Sensitivity and specifity for all cause glaucoma detection in the EPIC-Norfolk cohort

treatment. Overall, many normal eyes have pressures over 21 mmHg, and many glaucomatous eyes had pressures below 21 mmHg (Figure 1).

Taking the pressure off the NHS

Using these data, we modeled the impact of different IOP thresholds on potential referral numbers, and showed that even modest increases – from 21 to 22 or 23 mmHg – could lead to referral reductions of up to 31 and 52 percent, respectively, while raising the threshold to 24 mmHg could cut referrals by up to a massive 67 percent. The great majority of these reductions represent false positives, because the specificity of glaucoma case-finding improves with higher IOP thresholds. Therefore, increasing the threshold will have only a relatively small negative impact in terms of missed diagnoses. Further, we found that the risk of undiagnosed glaucoma correlated with a lower optic cup/disc ratio, such that optic disc changes appear less severe. Our recommendation therefore was that careful optic disc screening should be a key part of glaucoma screening, and should be emphasized in the training of all eye care professionals. Attention in this area should decrease the frequency of missed diagnoses.

Pressing on

Our overall conclusion was that relying on IOP alone for glaucoma screening was not a viable strategy. This finding transformed glaucoma care in the UK: in November 2017, the National Institute for Health and Care Excellence (NICE) raised the glaucoma referral threshold from 21 to 24 mmHg. There is little doubt that this new guidance will reduce false referrals and save NHS resources.

Looking ahead, one of our other findings – that lower corneal hysteresis and higher corneal-compensated IOP (IOPcc) is more closely correlated with POAG than is higher Goldmann-corrected IOP (IOPg) – suggests new metrics to include in future glaucoma screening programs. Other factors to take into account could include demographic information (glaucoma is more common in older people and in those of African ethnicity) and family history (having a first degree relative with glaucoma is a significant risk factor). This comprehensive approach would mitigate against any increased risk of undiagnosed cases resulting from increasing the IOP referral threshold.

In summary, careful analysis of large datasets and sensible adoption of the resulting recommendations can bring about radical cost-savings and improvements to care.

Michelle Chan is a Consultant Ophthalmologist specializing in Glaucoma at Moorfields Eye Hospital.

What does high IOP really mean?

The EPIC-Norfolk Eye Study looked at the link between IOP and glaucoma in nearly 9,000 patients over 7 years (2004–2011).

- Design: Community-based, cross-sectional observational study
- Population: 8,623 subjects, aged 48-92, 99.4 percent white, 55 percent female
- Aims: assess IOP and glaucoma prevalence by age and sex
- Methods: Subjects underwent ocular examination to measure IOP and identify glaucoma:
  - IOP measured with Reichert Ocular Response Analyzer (ORA) non-contact tonometer for most, and a small subset with Reichert AT555 non-contact tonometer
  - Glaucoma status determined by a systematic ocular exam to detect characteristic structural optic disc and visual field changes
- Results: IOP measured in 8,401 participants, 243 of whom used ocular hypotensive eyedrops:
  - 10 percent had ocular hypertension (IOP>21 mmHg)
  - 4 percent had glaucoma; of these, 87 percent had POAG and 67 percent had already been diagnosed with glaucoma
  - 76 percent of patients with newly diagnosed POAG (83/107) had IOP below 21 mmHg
  - No single IOP threshold provided adequately high sensitivity and specificity for the diagnosis of glaucoma (see graph)
  - The upper limit of IOP distribution (mean +2 standard deviations) for participants without glaucoma is 24 mmHg
- Conclusions: IOP alone is a poor screening tool for glaucoma.

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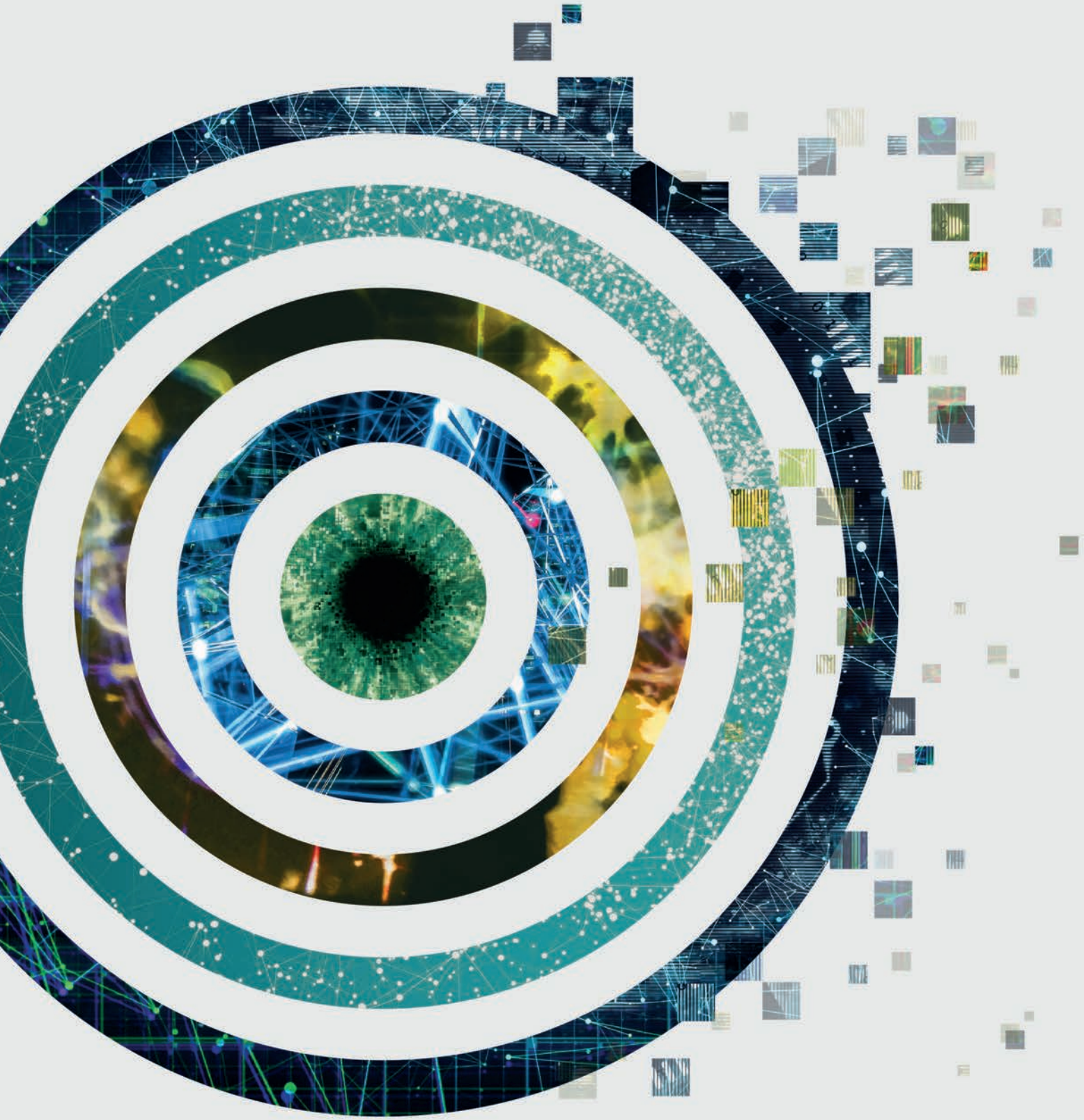

From the *Eye* to the *Brain*

Are stratification studies the key to identifying patients at risk of dementia?

By Siegfried Wagner and Pearse Keane

Estimates suggest that 50 million people were living with dementia in 2017. With the progressive aging of the population, the number is predicted to reach 75 million by 2030. Yet it has been noted that 50 to 80 percent of cases remain undiagnosed in high income-countries. Why? Part of the issue lies with the logistics of making a diagnosis. The gold standard for the most common form of dementia, Alzheimer's disease, has classically been neuropathological confirmation, post-mortem. Research into newer techniques, such as amyloid positron emission tomography (PET) scanning and cerebrospinal fluid analysis, has supported their utility as potential biomarkers; however, these tests are invasive, expensive, and not pragmatic on a large scale. Could assessment of the neurosensory retina – derived embryologically from the same tissue – be the answer?

The impact of Alzheimer's disease on ocular anatomy was first convincingly demonstrated in 1986 when widespread axonal degeneration was found in the optic nerve of eight recently deceased patients with the disease. Though subsequent work showed some evidence of an association between retinal venous diameter and Alzheimer's disease, true relationships only began to emerge when cross sectional measurement of the retinal nerve fiber layer became possible. In particular, the introduction of OCT and the establishment of large prospective cohort studies that incorporate ocular imaging have demonstrated that people with dementia show thinning of the retinal nerve fiber (RNFL) and ganglion cell-inner plexiform layers. However, thinning of the inner retina is not just a feature of prevalent dementia; rather, it may be predictive of its development. Last September, two large prospective studies – UK Biobank and the Rotterdam Study – revealed that participants with thinner RNFL were significantly more likely to develop cognitive decline and dementia.

However, as noted by the Rotterdam Study team, prediction modeling to identify those individuals at risk of developing dementia has not yet been feasible because of the small number of cases in prospective cohorts, which generally recruit healthy middle-aged volunteers. Moreover, it remains unclear whether these relationships are generalizable to the non-Caucasian population. To address these observations and more, we designed AlzEye: a large-scale record linkage dataset combining all forms of retinal imaging captured over the last ten years at Moorfields – the largest ophthalmic center in Europe and North America – with the national Hospital Episode Statistics (HES) database. HES is a centralized data warehouse, overseen by the UK's National Health Service (NHS) Digital arm, which contains details of all hospital admissions, emergency attendances and outpatient appointments in England. In the AlzEye Study, we have linked approximately 2.3 million images of more than 250,000 patients across a diverse population of varying ethnicity and socioeconomic status with diagnostic codes – including dementia. The approach will provide an estimated 5,000 cases of incident dementia. Not only will AlzEye allow the development and validation of traditional statistical models, it will also provide an opportunity to employ cutting-edge artificial intelligence techniques for the potential for prediction. Leveraging the expertise at the Centre for Medical Image Computing of University College London, AlzEye aims to provide a much-needed risk stratification tool to identify people at risk of dementia.

Siegfried Wagner is NIHR Academic Clinical Fellow at Moorfields Eye Hospital.

Pearse Keane is a Consultant Ophthalmologist at Moorfields Eye Hospital, London, and NIHR Clinician Scientist at the Institute of Ophthalmology, University College London.

"Not only will AlzEye allow the development and validation of traditional statistical models, it will also provide an opportunity to employ cutting-edge AI techniques for the potential for prediction."

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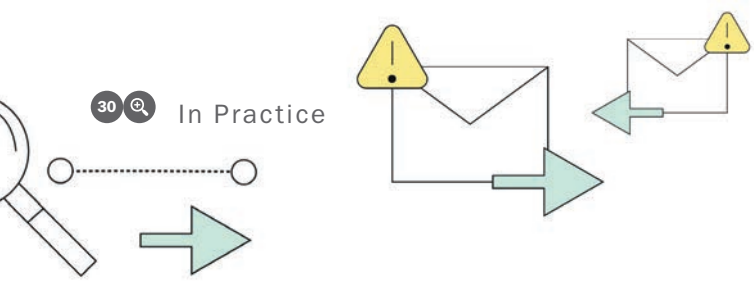


Setting the Standard

Unmet expectations, inconsistent patient information – enter the unstandardized world of elective surgery

By Bruce Allan

Refractive surgery is functional. It reduces dependence on spectacles and contact lenses, and allows patients to engage in a more active lifestyle, with clearly documented gains in quality of life. However, like cosmetic surgery, refractive surgery is elective – and, as such, self-funded – for most patients. As a result, the provision of routine refractive surgery is dominated by a competitive marketplace and an independent healthcare sector.

At a Glance

- *Over 100,000 refractive surgery procedures are undertaken in the UK every year*
- *Though results are generally good, concerns have been raised regarding the quality of care and information that patients receive*
- *To address this, a group of surgeons and ophthalmologists have come together to form the Refractive Surgery Standards Working Group (RSSWG), to work on updating existing standards and to increase engagement*
- *The group has developed new patient information leaflets and professional standards for refractive surgeons to improve patient safety and quality of care.*

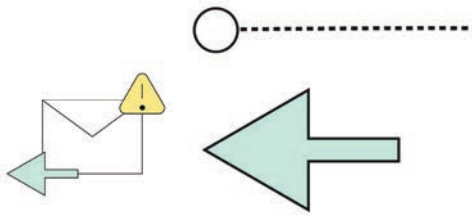
New standards

The need for better regulation was first highlighted by the 2013 Keogh Report in the wake of the Poly Implant Prosthèse (PIP) breast implant scandal. Keogh condemned irresponsible advertising and inconsistent care standards, calling for improvements in three key areas: patient information, quality of care and support when things go wrong. By 2015, public and professional perceptions of refractive surgery had been damaged by the imbalanced press coverage and suboptimal delivery of care of previous years. Refractive surgery was under-represented in training curricula, treated with suspicion by many eye care professionals and presented to the public with little consideration of the balance of risks with contact lens wear – the main alternate choice for patients seeking an active lifestyle.

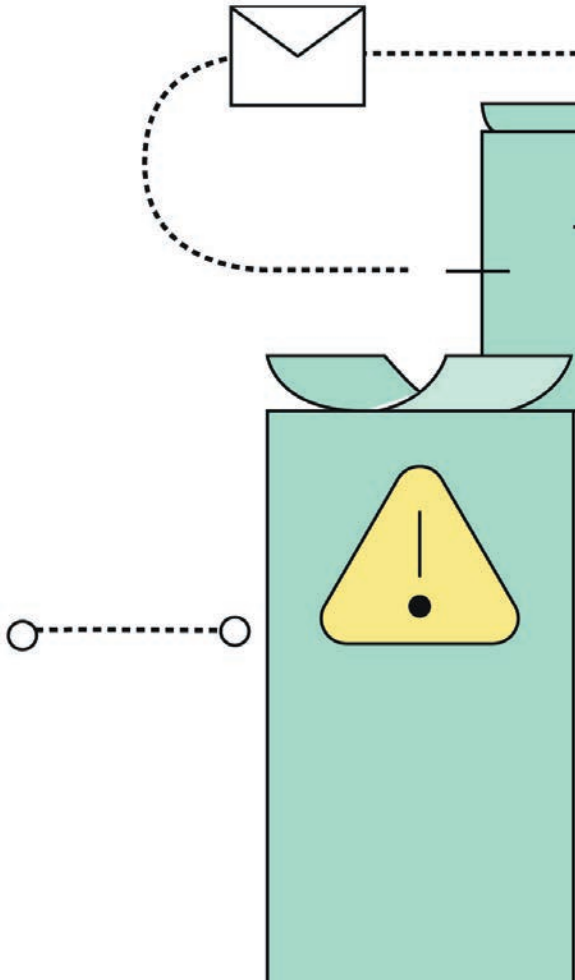
In response, the Royal College of Ophthalmologists formed the Refractive Surgery Standards Working Group (RSSWG), on which I serve as chairman. The group was intended to build on the foundations laid by the GMC and the Royal College of Surgeons, downstream of the Keogh report. Beyond simply updating existing standards, we aimed to increase engagement with the wider ophthalmic community, promote a more balanced discourse, and restore public and professional confidence in refractive surgery. Understandably, there were challenges along the way.

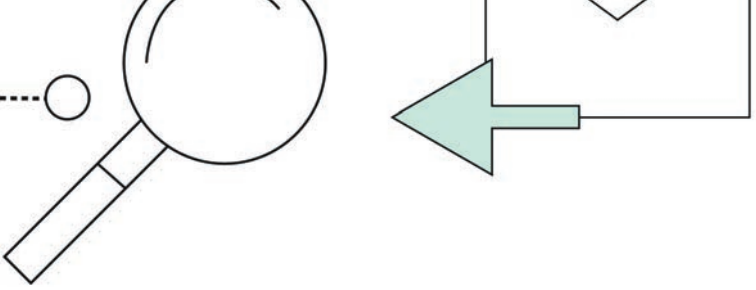
A matter of form

The RSSWG was faced with a small – but highly vocal – campaign against refractive surgery on one side (propagated through social media and the press) and, on the other, aggressive, litigious major providers. Steering change was no easy task. It required commitment and hard work from the panel of stakeholders – including optometric, scientific and lay input, layers of professional and public



"Beyond simply updating existing standards, we aimed to increase engagement with the wider ophthalmic community and restore public and professional confidence in refractive surgery."





consultation – and strong support from the administrative team at the Royal College.

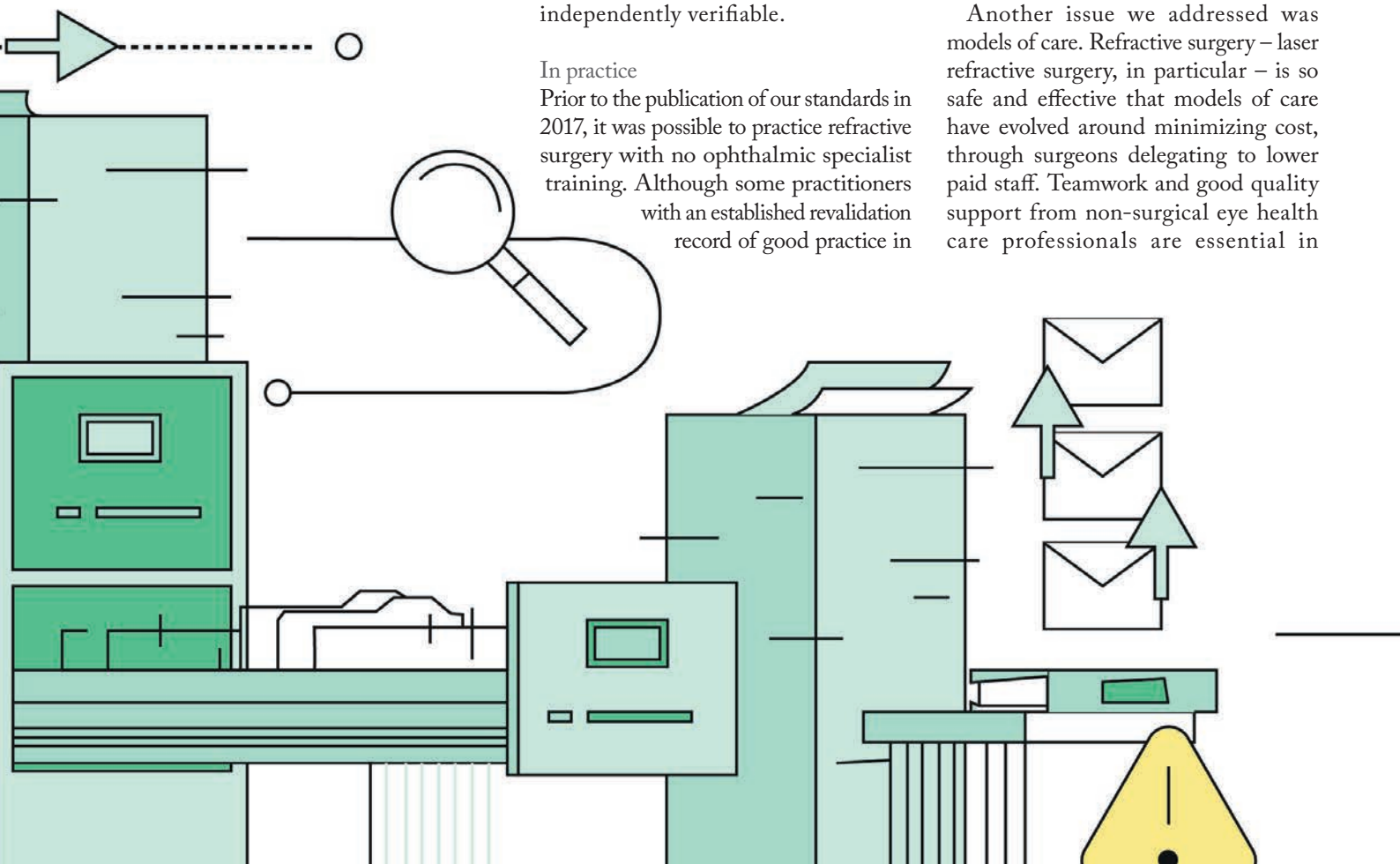
Keogh's first call was for an informed and empowered public, centered on advertising and consent. We were keen to get away from the current situation, whereby patients were pulled in by glossy marketing, then disquieted on the day of surgery by a consent form reading like a disclaimer. The GMC is clear that consent is a process. Any information given to patients must be consistent from first contact to discharge. Not only that, the tone and content of marketing information should be consistent with other patient information documents. Written consent forms should simply comprise procedure information – which should be available to the patient throughout – and a short consent statement.

We developed standardized documents for each of the main refractive modalities: laser vision correction, phakic intraocular lens implant and refractive lens exchange. Each document was based on a framework developed by the Royal College of Surgeons to identify the points that mattered most to patients. Our aim was to produce evidence-based material in simple language. A particular learning point for me in this was how much a first draft can be improved by lay input. Without this feedback, it is easy to include impenetrable jargon or technical terms that are meaningless to a non-expert reader. The standardized information documents we produced are available on the Royal College website (www.rcophth.ac.uk) and can be customized with individual provider branding and information, provided it does not contradict our guidelines. Any claims for superior results should be independently verifiable.

In practice

Prior to the publication of our standards in 2017, it was possible to practice refractive surgery with no ophthalmic specialist training. Although some practitioners with an established revalidation record of good practice in refractive surgery were grandfathered in, there was no real debate about the need to ensure that refractive surgeons were both Cert LRS-qualified and on the specialist register. Making the Cert LRS examination a requirement called into question the blurred boundary between refractive lens exchange and cataract surgery. When does a cataract surgeon become a refractive surgeon and, therefore, need to sit the exam? Should you have to sit the exam to use toric and multifocal lenses? Is it logical to restrict treatment of astigmatism during cataract surgery to refractive surgeons? Clearly there is some crossover, and the form of words we settled on in the end reflects this: our guidance (and the need to sit the Cert LRS exam) applies wherever "the primary purpose of surgery is to reduce reliance on spectacles and contact lenses and the patient has a normal cornea and a normal lens in both eyes."

Another issue we addressed was models of care. Refractive surgery – laser refractive surgery, in particular – is so safe and effective that models of care have evolved around minimizing cost, through surgeons delegating to lower paid staff. Teamwork and good quality support from non-surgical eye health care professionals are essential in



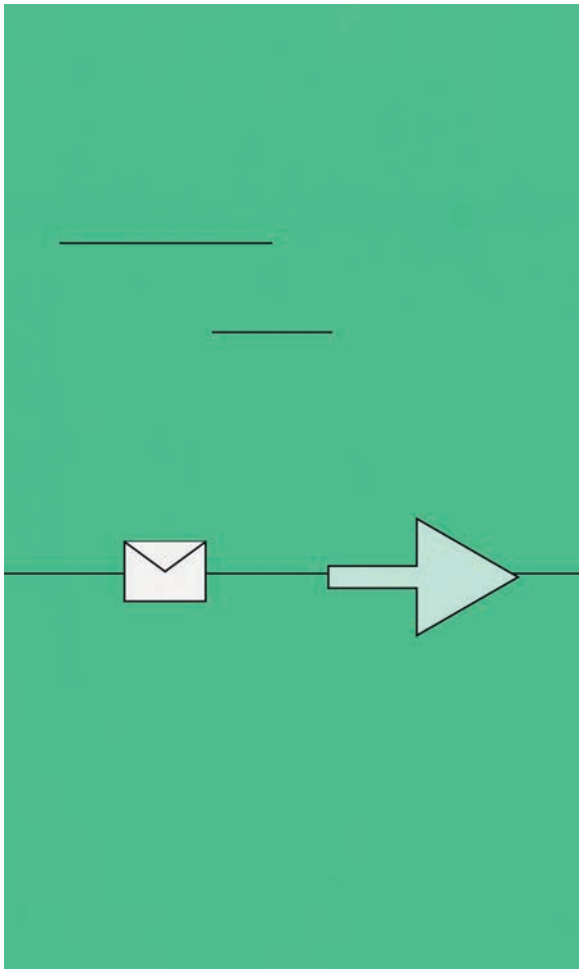
refractive surgery and our outputs emphasise this, but the operating surgeon remains responsible for patient care throughout. Models in which the surgeon only meets the patient on the day of surgery are problematic, both from the point of view of procedure choice and consent before surgery, and timely interception of problems afterwards. The clash between traditional models of private surgical care, in which the operating surgeon takes charge of every consultation, and the high-street approach in which the surgeon is treated as a technician, appearing on the day of surgery only, was one of the hardest fought areas in developing updated Professional Standards. The eventual compromise was that the operating surgeon would have to be present to advise on procedure choices at the pre-operative consultation, but postoperative care could be delegated, provided that clear lines of communication with the operating surgeon remain in place. The operating surgeon or a suitably qualified colleague should also remain available to perform revision interventions when required. Note that the Professional Standards are minimum standards, and that end-to-end continuity of care, in which the surgeon, backed up by a strong clinical team, sees the patient at every visit, remains the gold standard for refractive surgical care.

The main determinant of practice volume in refractive surgery hinges on reaching patients effectively. Traditional channels include word of mouth referrals, research publications, teaching and clear patient information. But direct marketing now dominates and one of our key objectives was to steer this away from damaging and unethical practice. Sheraz Daya led on this and did a great job pulling together what are now our Advertising and Marketing Standards. Key recommendations include ensuring that any incentive to refer is transparent to patients, keeping cost information clear, avoiding time-limited deals and inducements, and keeping marketing and consent information consistent.

No matter how successful a surgeon becomes, there will always be problem cases. Although most can be resolved satisfactorily through good continuity of care, patients who lose confidence in their surgical provider in the self-pay sector may feel that they are left staring down the barrel of an open-ended financial commitment in seeking revision care elsewhere. Keogh highlighted this and called for better mechanisms of redress.

Great expectations

Specialist refractive surgical revision care is available free of charge in some NHS centres, including Moorfields, but the real cause of unhappiness is often simply a breakdown in communication or an unrealistic set of expectations. This, in part, is why it is so important that surgeons themselves should take charge of the pre-operative consultation and, where possible, postoperative consultations, too. Even with the best practice, problems in communication can arise, and "alternative dispute resolution" (ADR) mediation services are currently being explored as an effective alternative to litigation when in-house complaint resolution does not bring closure. ADR provision for refractive surgery remains a work in progress but has high success rates in other sectors, such



"Key recommendations include keeping cost information clear, avoiding time-limited deals and inducements, and keeping marketing and consent forms consistent."

as optometry and dentistry.

Other work downstream of the Professional Standards is centered on the development of a National data registry. The emergence of electronic healthcare record systems offers some really exciting possibilities for automatic data extraction and pooling, artificial intelligence guidance for nomogram development and procedure choices, and data mining to answer important research questions. The National Ophthalmology Database in Cataract Surgery has already demonstrated the potential for this approach in the UK. Seeking to emulate this, a new working group was convened to agree the Clinical Dataset for Refractive Surgery, published in 2018. This is a common set of outcome measures and timepoints that should be easy to implement in routine clinical practice, and will form the basis for the data fields to be extracted from EHR systems and pooled for analysis.

My hope is that the outputs from the Refractive Surgery Standards Working Group will, in time, impact positively on public confidence in refractive surgery procedures, which must surely be amongst the most effective healthcare interventions available. Whilst the Royal College can set standards and has called for legislative back-up, enforcement is currently a matter for the regulators: the General Medical Council, the Care Quality Commission, the Advertising Standards Agency and equivalent bodies in devolved areas of the UK. However, it is in all of our interests to practise to a high standard and to strive constantly to chip away at the small percentage of patients whose outcome from refractive surgery does not match or exceed expectations. So, don't wait for the regulator to call. Re-read the Standards and try to ensure that your own practice stays ahead of them.

Bruce Allan is a Consultant Ophthalmic Surgeon at Moorfields Eye Hospital.

The Big See

Good management of ocular malignancies, in both children and adults, depends on careful attention to diagnostic features revealed by modern imaging systems

By Mandeep Sagoo

The eye can develop a range of primary or secondary tumors: some are more common in adults, while others are more typical of children. We therefore adopt somewhat different investigational approaches for the pediatric and adult populations; in both groups of patients, taking a detailed medical and ophthalmic history, performing a thorough examination and using imaging are key to correct diagnosis and management. These patients are best managed as part of a multi-disciplinary team of professionals.

At a Glance

- *Approaches for diagnosing and treating pediatric and adult intraocular and ocular surface tumors differ, but advanced techniques are increasingly being used for both patient groups*
- *Treatment approaches include brachytherapy, proton beam radiotherapy, photodynamic therapy (PDT), and chemotherapy depending on the type, size and location of the tumor*
- *For pediatric retinoblastoma, local cryotherapy or laser treatment and brachytherapy plaques can be used for smaller tumors; chemotherapy approaches are used for more advanced cases, given systemically, into the ophthalmic artery or vitreous cavity.*
- *Application of virtual clinics and artificial intelligence has the potential to pick up suspicious lesions at an earlier stage – and to make the referral process much more streamlined.*

Grown-up work-up

In adults, we deal with diverse tumor types, from benign choroidal nevi to malignant melanoma; vascular tumors in the fundus that can be part of a syndrome; lymphoma; and secondary deposits in the eye. We also see conjunctival tumours such as melanoma and its precursor, primary acquired melanosis. When investigating adult melanoma suspects, a large part of our diagnostic work-up comprises procedures aimed at distinguishing benign from malignant or pre-malignant tumors. The need for this differentiation is a consequence of the high incidence of benign lesions – up to 10 percent of the Caucasian population has a choroidal nevus. Furthermore, as imaging procedures become more sophisticated, increasing numbers of nevi are detected by optometrists and referred to ophthalmologists. How should we manage this burgeoning workload? At Moorfields, we think the answer includes the application of virtual clinics and artificial intelligence; our experience is that these tools help to efficiently differentiate benign nevi from melanoma in a large proportion of cases. The virtual approach makes assessment far less labor-intensive, and as it is still based on the Wills Eye Hospital clinical factors scheme (see sidebar "Know Your Nevi"), it should be no less rigorous as a screening method than the standard approach. Indeed, the prospective studies we have so far completed indicate that remote assessment of patients' images – ultrasound scan, OCT scan and photograph – at a reading center gives results highly concordant with the gold standard (assessment by an ophthalmologist). These results are sufficiently encouraging for us to actively contemplate pushing this system back into the community. For example, by giving optometrists a scoring system so they have a better idea of what they should refer on to us, we could release

Know Your Nevi

Researchers at the Wills Eye Hospital have a long history in the refinement of systems for predicting the transformation risk of choroidal nevi. A 1995 study (2) identified five factors predictive of transformation into malignant melanoma:

- thickness greater than 2 mm on ultrasound scan
- fluid beneath the retina
- symptoms
- orange pigment
- margin of tumor

These could be recalled with the assistance of the mnemonic "To Find Small Ocular Melanoma," and the presence of three or more of these risk factors indicated a >50 percent chance of transformation.

The TFSOM algorithm has been of great practical assistance to clinicians, and has been updated at various points over the years, culminating most recently in the incorporation of risk factors as visualized with multimodal imaging (3). This new scheme can be remembered with the mnemonic "To Find Small Ocular Melanoma Doing IMaging," and comprises the following:

- thickness >2 mm by ultrasound
- fluid in subretinal space by OCT
- symptoms of vision loss
- orange pigment by autofluorescence
- melanoma hollowness by ultrasound
- DIaMeter >5 mm by photography.

specialists from the burden of assessing large numbers of nevi, which in the majority are harmless; remember, the risk of a nevus developing into malignant melanoma is only ~1 in 8,000.

But for those lesions that do turn out to be malignant melanoma, what kind of management strategy should we apply? Again, clinical decisions rely heavily on imaging modalities because, unlike other sites in the body, we rarely take diagnostic biopsies from ocular tumors. Ultrasound technology is improving, but for key information we increasingly rely on OCT and auto-fluorescence. At Moorfields we also heavily employ ultrasound color flow mapping, which helps categorize the tumor; pattern recognition is a very important component of this technology.

Once we understand the tumor, the multidisciplinary team – comprising an oncologist, specialist nurses and several consultants – ratifies a management plan, with the patient at the center of the decision. Quite often, this includes a brachytherapy technique pioneered here at Moorfields and St Bartholomew's Hospital in the 1920s and 30s: briefly, a small radioactive disk is sutured onto the eye so that the intraocular tumor is locally irradiated. Some tumors, however, are not suitable for brachytherapy – the tumor may awkwardly located or too big, for example. In those cases, we might administer proton beam radiotherapy. We've also been looking at the potential of photodynamic therapy (PDT) in the treatment of small melanomas – this approach may be able to eradicate the tumor with less vision loss than is associated with radiotherapy. I think we'll see more of PDT type treatments in the future, as there are some interesting new drugs in development.

Some patients, however, have tumors that have progressed too far for radiotherapy to be of any use; in those cases, we must remove the eye. Fortunately, we have access to orbital implants, which can be attached to the orbital muscles, so that the false eye moves quite realistically. Even so, at Moorfields we continue to look for better ways of doing things, and currently we are investigating new technologies for rehabilitating the socket. Technology does not stand still!

In all cases, given the small risk of local (ocular) and larger risk of systemic relapse, melanoma patients need to be followed over the long term by an ocular oncologist and a medical oncologist. We know that certain melanoma genotypes are associated with a higher systemic relapse risk, so we offer appropriate genetic tests as necessary. In this context, we're assessing next-generation sequencing; in particular, we are participating in a collaboration intended to sequence our ocular tumor tissue archives and identify correlations between genotype and patient survival.

Other adult tumors that we see include squamous cell tumors, lymphoid tumors, lymphoma, and benign reactive lymphoid hyperplasia. A new development in the management of these malignancies is the use of immunotherapy eye drops, such as interferon alpha, particularly in squamous

Reflect on the White Reflex

The white reflex – in which incident light causes a white reflection from the retina – is a classic signal of retinoblastoma. However, we should remember that the symptom does not correlate exactly with this condition; not all children with retinoblastoma have the white reflex, and not all children with a white reflex have retinoblastoma. Other conditions linked with this signal include the following:

- Normal finding – if the image captures the optic nerve
- Cataracts
- Congenital malformations, such as coloboma
- Retinal detachment
- Vascular diseases, such as retinopathy of prematurity, Coats' disease or persistent fetal vasculature
- Non-retinoblastoma tumors, including medulloepithelioma or astrocytoma
- Inflammation; for example, as a consequence of ocular toxocariasis
- Vitreous hemorrhage following trauma

Observation of the white reflex in children therefore requires the ophthalmologist to rigorously apply differential diagnostics to distinguish between a range of serious conditions. That said, many of these conditions are very rare; one study suggests that among children with white reflex, the symptom is caused by cataracts in about 75 percent and retinoblastoma in about 20 percent of patients, while all other reported conditions occurred at frequencies <1 percent (4).

cell tumors, such as ocular surface squamous neoplasia (OSSN). Equally, chemotherapy eye drops can be very useful; in fact, we recently carried out a study on the efficacy of 1 percent flurouracil eye-drops after surgical removal of OSSN. This work – which we carried out in Africa, where OSSN is relatively common – showed that a one-month course of these drops reduced OSSN recurrence threefold (1). It was particularly gratifying to be involved in this trial, because Africa has a higher prevalence of OSSN than the UK, but doesn't have similar access to systems for reducing recurrence, such as devices to surgically freeze the edges of the resection margin or to give adjuvant radiotherapy. In resource-limited countries, a cheap chemotherapy eye drop can make a big difference to OSSN patients, so I like to think that Moorfields is making a global difference to eye cancer through this kind of work.

Kids' stuff

Among pediatric patients, we see a number of retinoblastoma cases. This tumor is quite rare – only about 50 cases per year in the UK – and its identification requires a careful approach to differential diagnosis, which again relies heavily on imaging techniques (see sidebar "Reflect on the White Reflex").

Where retinoblastoma is diagnosed, we can select from a range of treatments. For smaller tumors, we may opt for local cryotherapy or local laser treatment; brachytherapy discs also can be used for smaller retinoblastomas, but external beam radiotherapy, in which most or all of the eye is irradiated, is no longer used in retinoblastoma. For larger lesions, we may choose the systemic chemotherapy approaches developed in London about 30 years ago. However, a newer approach, developed in Japan and the USA, involves pulsing chemotherapy directly to the eye via a delivery catheter inserted at the groin and sent up through the neck to the ophthalmic artery. Many eyes that would otherwise be removed have been salvaged by this technique. A major source of failure in retinoblastoma treatment was vitreous seeding. Chemotherapy can also be applied locally in this situation, by intravitreal injection, but this approach was prohibited until recently due to concerns of seeding tumours outside the eye – a potentially life-threatening event. Recently, however, workers in Sweden and Switzerland developed a safety-enhanced technique for intravitreal chemotherapy, which avoids the release of tumor cells into the vitreous. The method involves reducing the IOP, administering the injection and freezing the needle track as the needle is withdrawn. Finally, for retinoblastomas that are too far advanced or that are resistant to treatment, enucleation may be the only choice. We are harnessing our archive of DNA from these patients to examine molecular signatures by next-generation sequencing, which may direct the choice of optimal treatment – hopefully entering the era of personalized medicine for eye tumours.

Mandeep Sagoo is Professor of Ophthalmology and Ocular Oncology at UCL Institute of Ophthalmology and Consultant Ophthalmic Surgeon at Moorfields Eye Hospital and at Barts Health NHS Trust, London, UK. Currently he is Visiting Professor at Byers Eye Institute, Stanford University, USA.

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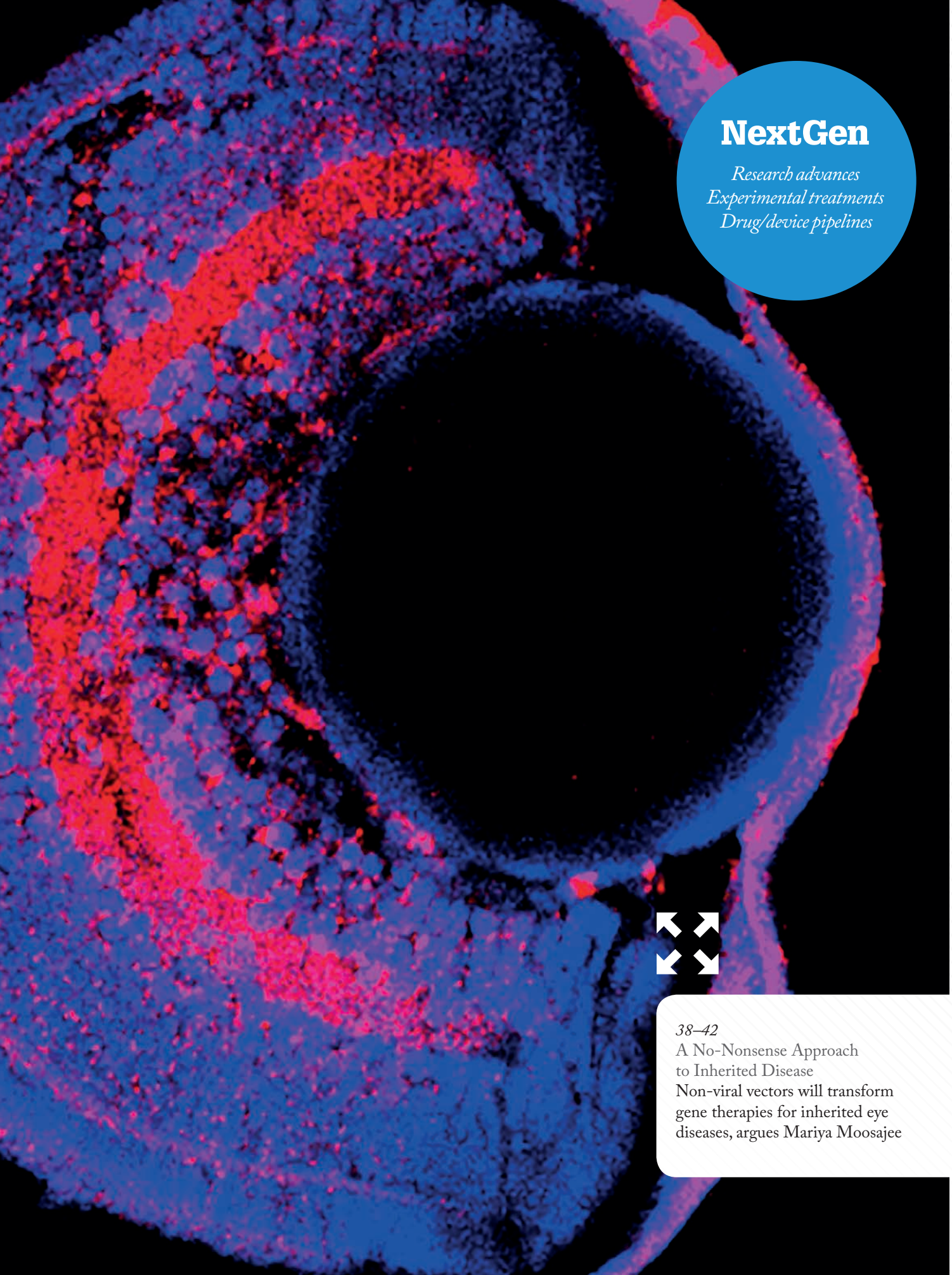

NextGen

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A No-Nonsense Approach to Inherited Disease

A new generation of non-viral vectors can help treat more genetic disorders while making gene therapy easier and safer – and new treatment modalities promise to entirely change the management of inherited eye disease

By Mariya Moosajee

Anyone who doubts that we have entered the era of genomic medicine should consider the 100,000 Genome Project launched by the Department of Health in 2012. The task of this initiative was to sequence the entire genome of thousands of NHS cancer and rare disease patients; the aim was that whole genome sequencing will give these patients the genetic diagnoses that current tests cannot. Accurate diagnoses in turn will guide treatment and support the development of new therapies – not least, gene therapies. These developments give hope to patients with inherited disease.

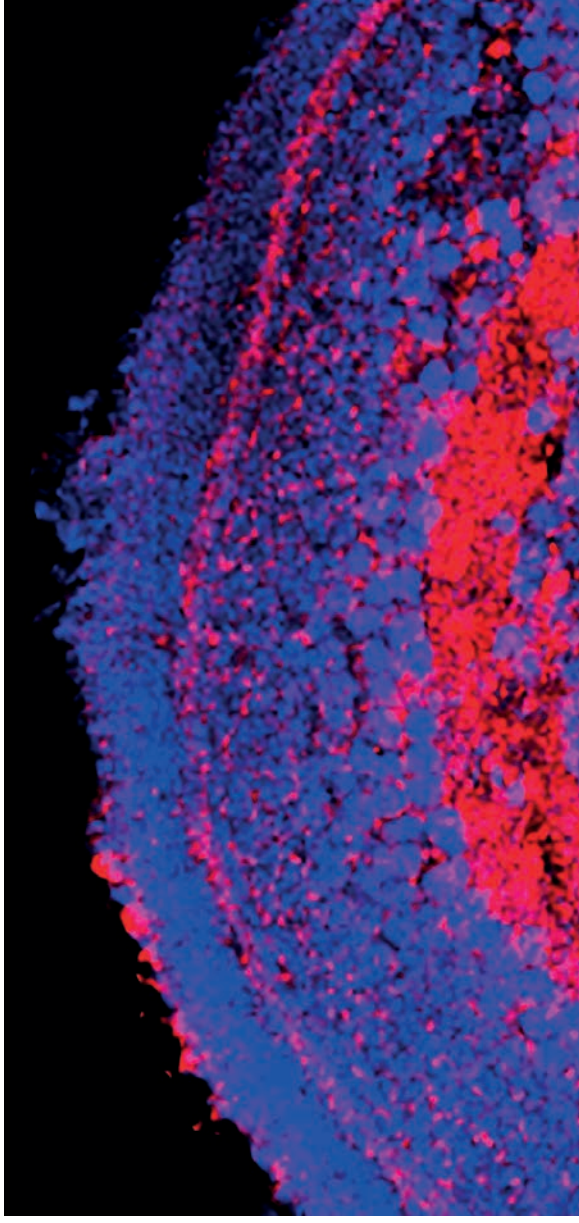
At a Glance

- *Gene therapy for inherited eye diseases of the eye is conceptually attractive, but has drawbacks relating to vector characteristics and health economics*
- *Now, innovative vectors both circumvent the transgene silencing issue associated with legacy non-viral vectors and avoid the capacity limitations, immunogenicity and insertional mutagenesis potential of viral vectors*
- *At the same time, new classes of therapeutics – including nonsense suppressors – promise the ability to ameliorate multiple inherited diseases with a single drug*
- *Together, these advances are likely to provide patients with new and effective options and to transform both the management of genetic disease and the economics of the gene therapy sector.*

Questions

But is such hope well-founded? Certainly, gene therapy for genetic eye conditions has advanced in recent years; however, it remains imperfect. Consider the vector – that element of the gene therapy which encapsulates the therapeutic DNA, transports it into the target cell and enables its expression. Most vectors are based on modified viruses; but these have a number of problems. First, their carrying capacity is rather limited – about 5 kilobases (kb) in the case of adeno-associated viral (AAV) vectors used in most current trials. And for those seeking treatments for genetic diseases of the eye, this is a problem, because many inherited retinal diseases are caused by mutations in much larger genes. For example, Type 2 Usher Syndrome – the commonest cause of deaf blindness worldwide – is associated with mutations in USH2A, whose transcript is about 19 kb in length. Viral vectors can't handle genes of that size, so Usher syndrome patients have no prospect of a gene therapy based on conventional vectors. Similarly, ABCA4 (just over 7 kb) and EYS (10 kb)– the genes behind Stargardt's Disease and one of the autosomal recessive forms of retinitis pigmentosa, respectively – are too large for standard vectors.

But if the viral vector can accommodate the therapeutic sequence, would all our vector problems be solved? Well, no. Remember, these vectors are based on particles which our immune system is adept at rejecting; any viral proteins associated with the vector may cause inflammation and specific immune responses. And that has consequences; inflammation requires modulation with steroids before, during and after surgery, while the risk of unpredictable consequences from an anamnestic immune response to the vector may preclude repeat administrations. If the first dose of a viral vector-mediated gene therapy is insufficiently effective, bad luck; a second dose is currently not allowed. Luxturna is an example of a gene therapy that is limited to a single administration for this reason. And the problems associated with this vector class don't end there; some viral vectors, such as lentiviruses, insert DNA into the host genome, which carries the risk of insertional mutagenesis, i.e. the disruption of host genes by integration events.



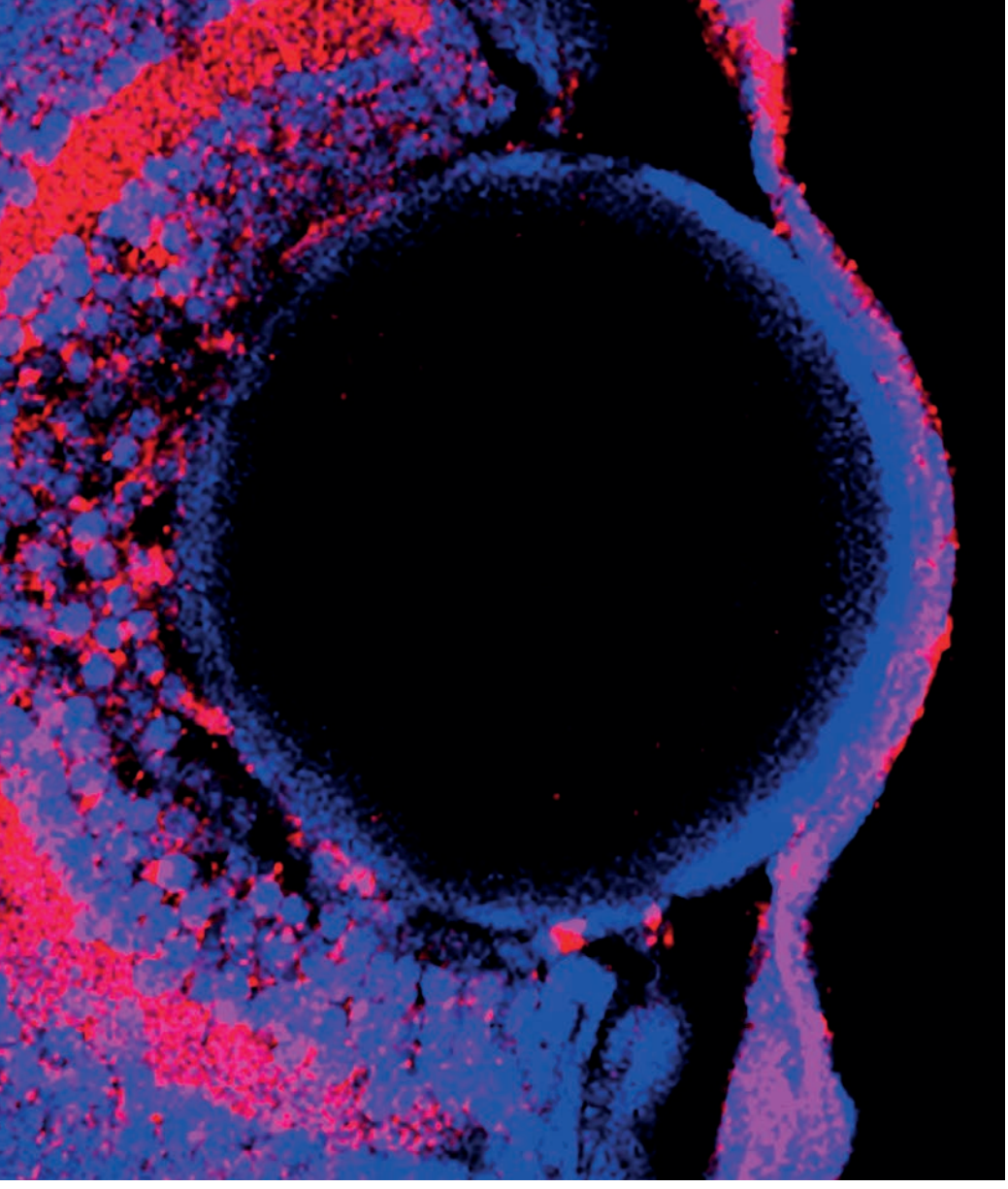


Figure 1. The transfection of non-viral S/MAR vectors across the zebrafish retina following injection at the single cell stage.

But if we overcame all of these technical considerations, would gene therapy take off? Not necessarily. The field has a fundamental economic problem which must be resolved if the modality is ever to be broadly applied. In brief, the huge cost of developing a gene therapy – tens of millions of pounds – is a commercial investment that must be recouped. As many inherited diseases are very rare, the development costs are spread over smaller numbers of patients – which translates into very high therapy prices. For example, Luxturna costs $850,000 per administration. Multiply this figure by 250 or more – the number of genes that are known to cause inherited retinal disease – and you start to wonder about the financial impact of gene therapies on over-burdened health care systems.

But regardless of these problems, there are patients out there with inherited diseases of the eye, hoping and asking for effective treatments. What can we say to them?

Answer #1: SMARt vectors

I consider that at least part of the future of gene therapy lies with non-viral vectors. These vectors traditionally were thought to be less effective than viral vectors because they tend to be silenced by cellular machinery – they can get genes into the cell, and the genes would be expressed at first, but after a couple of weeks they would be switched off. That problem, however, has been fixed by the discovery of scaffold or matrix attachment regions (S/MARs). These are naturally-occurring DNA sequences that support the structural configuration of chromatin. By incorporating S/MARs downstream of the DNA cargo of non-viral vectors we can get the therapeutic transgene to sit alongside the host DNA – and one effect of this is that the therapeutic DNA is not silenced by the host cell. Furthermore, S/MAR-containing vector sequences are heritable in that host cell division (mitosis) results in replication of both transgene and host DNA; thus, daughter cells also express the transgene. Importantly, this permanent fix is achieved without integration into the host genome; therefore the risk of insertional mutagenesis is greatly reduced as compared with many viral vectors. Other advantages of non-viral vectors include an unlimited cloning capacity – these systems can easily accommodate large genes, and therefore could make gene therapy accessible to a cohort of patients for whom viral vectors can never provide a treatment. Also, as these vectors don't have viral components, they have less risk of provoking an immune response after injection. In short, they are intrinsically safer.

"The field has a fundamental economic problem which must be resolved if the modality is ever to be broadly applied."

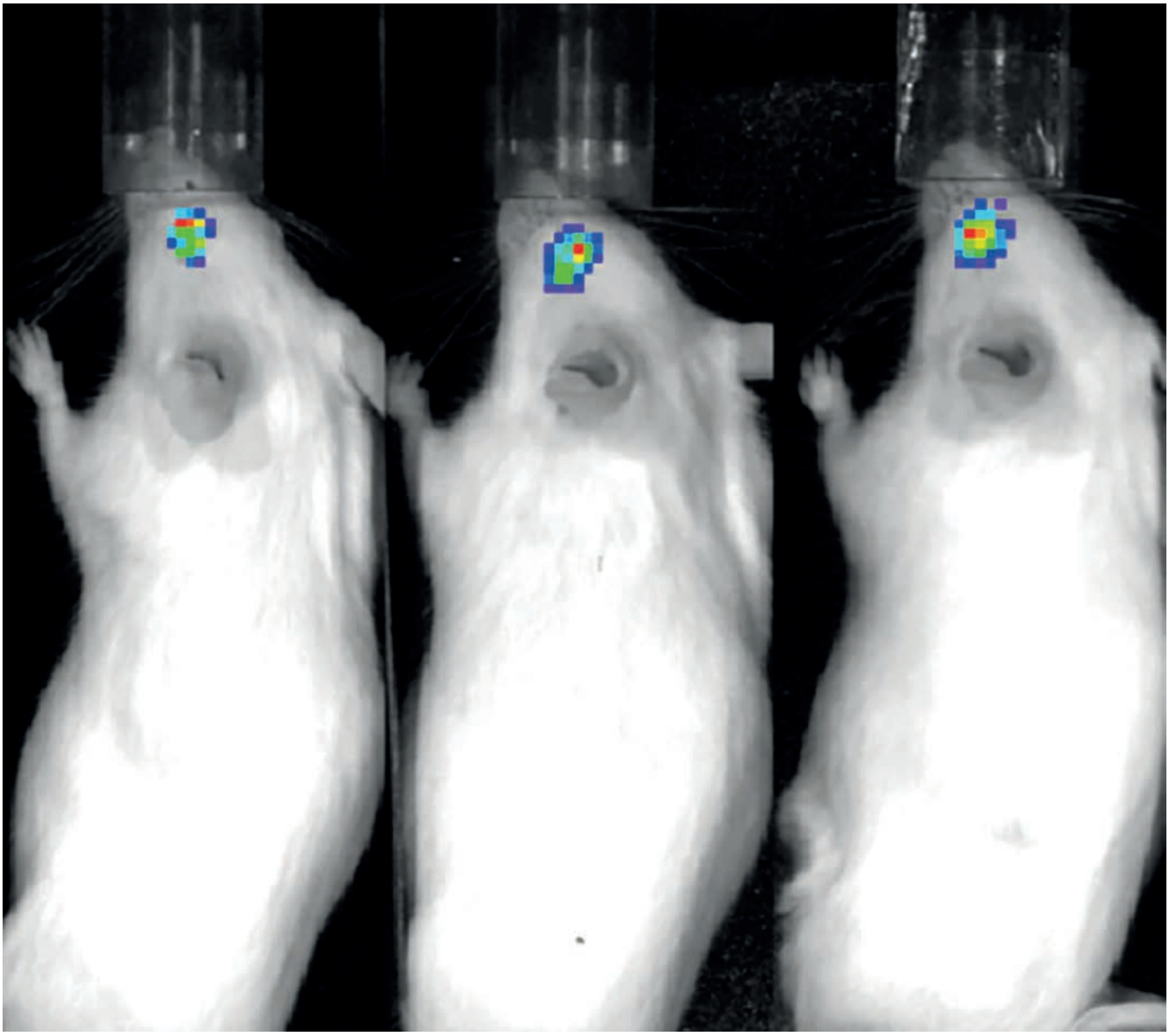


Figure 2. Expression up until one year, following single sub retinal injection into the mouse eye with non-viral S/MAR vectors.

For all these reasons, I believe that our non-viral, S/MAR-containing vectors should be safer, more effective and more broadly applicable than historical gene therapy vectors. We are actively developing this system with our collaborator Richard Harbottle from the German Cancer Research Centre, Heidelberg; our first target is Type 2 Usher syndrome, which is unsuitable for gene therapy with standard vectors. There's a lot of work to do, however, as we are still at the stage of in vitro and animal model studies. Nevertheless, given that our vectors provide expression levels equivalent to those associated with viral vectors – up to a year in mouse retina – it seems likely that our technology will soon reach the clinic.

Answer #2: Stop that nonsense

But even non-viral vectors can't address the intractable problem associated with gene therapy: the huge cost of treatment, which is largely a consequence of the need to develop a unique therapy for each of many very small patient populations. Is there an answer to this problem? I believe so: development of agnostic treatments

able to address elements of molecular pathology that are common to many different inherited diseases. We are taking an approach based on the phenomenon of nonsense suppression. This concept was first discovered when investigating the bactericidal effect of aminoglycoside antibiotics, which weaken the specificity of the bacterial ribosomes so that they read the messenger (m) RNA incorrectly and produce jumbled non-functional proteins, the accumulation of which kills the prokaryotes. Aminoglycoside antibiotics and related compounds have a similar but much weaker effect on human eukaryotic ribosomes – and this can be turned to therapeutic advantage.

Briefly, much genetic disease is associated with single nucleotide mutations that have the effect of introducing a premature stop codon into mRNA, thus truncating translation. These are known as nonsense mutations. When a ribosome finds a nonsense mutation in mRNA, it pauses to sample the correct code and then inserts a release factor, thus terminating translation. Under normal circumstances, in less than 1 percent cases the correct amino acid can be inserted instead of a release factor, leading to correction and continued production of full-length protein. The effect of nonsense suppression compounds, such as the aminoglycosides, however, is to modulate the ribosome such that the correction rate is greatly increased. Indeed, in the presence of some compounds, around 25 percent of protein expressed from a mutant gene is normal. Thus, by remarkable good fortune, nonsense suppressors weaken ribosomal specificity in eukaryotes just enough to override the nonsense mutations during a ribosomal pause, but not enough to interfere with the normal protein sequence during regular transcription or effect natural termination codons (which have a readthrough frequency of <0.1 percent). Perfect for addressing genetic disease!

Clearly then, nonsense suppressor compounds could form the basis of drugs that ameliorate the effect of any genetic disease caused by the presence of premature stop codons. The potential is enormous; up to 70 percent of human genetic disease and about a third of inherited retinal disease is associated with nonsense mutations. Indeed, in some diseases – for example, aniridia – 40 percent of patients exhibit premature stop codons in the causative gene. Nonsense suppression therefore may enable us to address a broad range of genetic disease with a single therapy.

"Aminoglycoside antibiotics and related compounds have a similar but much weaker effect on human eukaryotic ribosomes – and this can be turned to therapeutic advantage."

Unfortunately, it is not as simple as just giving aminoglycoside antibiotics to patients with inherited disease; in particular, aminoglycoside antibiotics are associated with hearing loss and kidney damage when used over protracted periods, so must be modified to eliminate these side effects. In fact, a medicinal chemist Timor Baasov from Technion, Israel, has reported removal of toxicity-associated domains of the antibiotic while retaining domains associated with nonsense suppression. These designer aminoglycosides are now coming through to clinical trials. Another problem with the nonsense suppression approach is that our cells have a natural surveillance mechanism – nonsense-mediated decay (NMD)– that corrects nonsense mutations at the mRNA level to prevent the build-up of harmful mutant proteins. This raises a problem for nonsense suppressor drugs – they can't facilitate the production of corrected protein from mutant mRNA if the mutant mRNA is being destroyed by NMD.

Our nonsense suppression approach, however, addresses both of the above problems. Firstly, we are working with a nonsense suppressor drug candidate that has been used to treat mouth ulcers and asthma for the last 50 years. The non-toxic nature of the compound is therefore well-established, and by 'repurposing' an approved drug for indications in genetic disease, we will benefit from a much cheaper and faster development route – the compound has already gone through safety trials, and only requires proof of concept. We've already conducted extensive pre-clinical work with this compound, looking at its application for inherited retinal diseases in particular, with excellent results (1). Furthermore, we recently found a possible fix for the issue of nonsense-mediated decay. We've shown that every patient has a different level of mutant mRNA – in fact, patients with exactly the same mutation have a 40 percent variation in mRNA levels (2). Checking a patient's baseline mRNA levels will therefore guide treatment: we can use mRNA levels to predict nonsense suppressor outcomes, and apply drugs, such as caffeine, to boost mRNA levels prior to nonsense suppressor treatment. We are very encouraged by these results and currently investigating the potential of nonsense suppression in conditions including microphthalmia, aniridia, inherited retinal disorders and other genetic eye diseases. Our aim is to

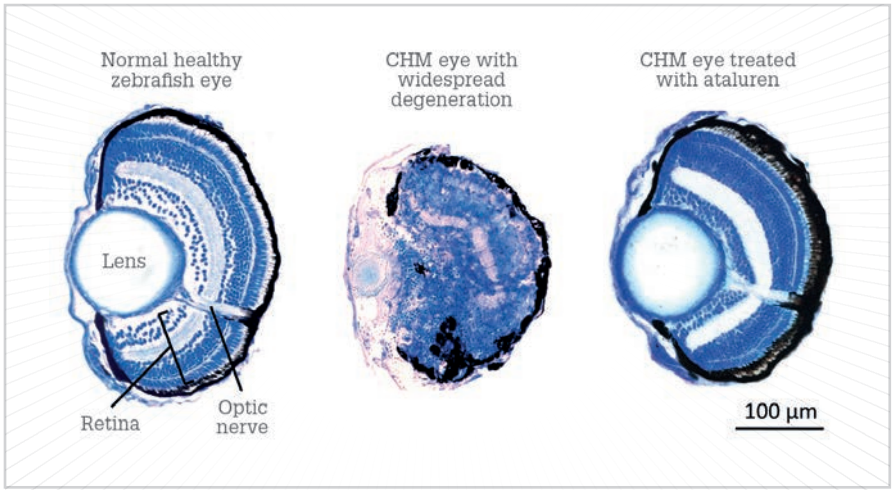


Figure 3. A panel of 6-day-old zebrafish retinal sections from wild type, untreated choroideremia (CHM) and treated CHM with ataluren highlighting significant rescue in phenotype with nonsense suppression drugs.

design clinical trials that assess our drug not just in one condition, but in perhaps three different inherited retinal diseases associated with nonsense mutations – a more cost-effective approach than running a separate trial for each disease.

In brief, the great promise of nonsense suppression is that it works in a disease- and gene-independent manner, and hence is likely to be highly cost-effective. Furthermore, it could suggest new treatment strategies: for example, children who have started to develop night blindness, but who do not want to immediately opt for invasive gene therapy surgery, could choose nonsense suppression to non-surgically maintain normal protein production and slow retinal degeneration until such time as they are ready for the gene therapy option. It will also potentially help patients with syndromic disease as these drugs can be given orally and therefore improve any systemic dysfunction.

Overcoming economic hurdles

The ideal situation is that every patient with a genetic eye disease receives a genetic diagnosis. But that's certainly not happening at present; our own research (3) suggests that a patient with genetic eye disease has a 25 percent chance of getting a genetic diagnosis under the current genetic testing regime. The rate rises to about 60 percent for the inherited retinal diseases subset – but what about the other 40 percent? My hope is that increased availability of whole genome sequencing will significantly improve rates of genetic diagnosis for all patients – and turn many of them into candidates for genetic therapy. With regard to implementation of gene therapy approaches, the biggest obstacle remains the economic challenge. The cost of gene therapy development is huge, and given that in some diseases there may be only 100 patients worldwide, it's hard to see how those costs would be recouped under current circumstances.

Nevertheless, circumstances are changing, and I am confident that the next two to five years will see many more gene therapies entering later stage clinical trials. Most of these will be based on viral vectors. Within five years, however, I expect to also see clinical studies of therapies based on non-viral vectors. Some of these, I hope, will be approved, which will demonstrate the utility of this modality and offer hope to all patients with inherited disorders – not just those whose diseases are compatible with the limitations of viral vectors. Importantly, an increase in the number of approved treatments – not just more gene therapies, but also nonsense suppressors and other therapies – will drive down treatment costs through competition. The advent of therapeutic systems that target common disease pathways, such as those involved in metabolism or cell death, could at least slow down disease progression in patients with inherited retinal disease and prevent further deterioration. One possibility is suggested by Jose Alain-Sahel's work on rod-derived cone viability factor (RdCVF). This neuroprotectant facilitates glucose uptake in cones, thereby helping them maintain the high metabolic rate necessary for their function. Treating the retina with RdCVF therefore may preserve cones and maintain the central vision of patients at risk of cone loss.

In conclusion, I expect that the combination of existing gene therapy approaches, new vectors and novel modalities, such as nonsense suppressors and metabolic support agents, will provide the basis of an armory that will give patients a new and broad range of effective options. Isn't that far better than expecting them to rely on one option that does not work in all patients, or which must be discontinued after a small number of administrations, or which is unacceptable to the patient? Being able to offer a significant number of effective alternatives to patients with inherited retinal disease – that's my dream.

Mariya Moosajee is a Consultant Ophthalmologist at Moorfields Eye Hospital and Great Ormond Street Hospital for Children, and Associate Professor and Wellcome Trust Beit Prize Clinical Research Career Development Fellow at UCL Institute of Ophthalmology.

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Profession

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Teaching – and Learning – Reimagined

Increasing demand for healthcare services and a changing technological landscape are demanding a rethink of ophthalmic training. We, as educators, must react now to meet the needs of tomorrow

By Nora Colton

We are extremely fortunate to live in a time where there is so much information and research available to address ophthalmic health challenges – both now and in the future. However, with all this information comes pressure to continuously re-evaluate what we do and why. We, in education, must ensure that outdated education training does not slow the needs of patients or breakthroughs in research. Various transformations are impacting our lives, including demographic change and globalization – and these drivers are being accelerated by big data, genomics and artificial intelligence. As educators, we have a duty to be more than just responders; we need to reshape our approach to ophthalmic education to ensure we do not leave our students, staff and patients behind.

At a Glance

- *The Royal College of Ophthalmologists reports that 75 percent of UK eye clinics are struggling to provide the service required by their local population*
- *Ophthalmic training needs to meet increased demand, and reflect shifts in technology and patient demographics*
- *Educators need to prepare the workforce for uncertainty that comes with AI – while also instil within them the flexibility required to harness technological innovation*
- *Continual assessment of our curricula is essential. And by letting educationalists drive how technology is used in the education setting, rather than the other way around, we can – and will – meet today's healthcare needs.*

The challenge

In 2010, the International Council of Ophthalmology surveyed 213 global ophthalmic societies and found 204,909 ophthalmologists practicing across 193 countries, with a significant shortfall in developing countries. Despite the number of practitioners increasing in developed countries, the population of over-60s was growing at twice the rate of ophthalmologists going into practice (1). This trend is not unique to Western countries – people are living longer all over the world. Demographic shifts mean aging populations with longer life expectancies and more comorbidities (2) will become a challenge for clinicians everywhere. In 2016, the Royal College of Ophthalmologists reported that 75 percent of hospital eye clinics in the UK are struggling to provide the service required by their local population, 50 percent of the units have unfilled consultant roles and over 90 percent are undertaking waiting list initiatives for ophthalmic surgery and clinics (3). Another study by the Royal College of Ophthalmologists forecast that demand for cataract treatment in the next 10 years is set to increase by 25 percent, while demand for medical retina and glaucoma services are expected to increase by 30 percent and 22 percent, respectively. The UK alone needs at least 326 more ophthalmologists to meet demand. Problematically, almost a quarter of ophthalmologists are over the age of 55 and so approaching retirement (4). We also see disparities of demand worldwide due to the rapid trend towards urbanization. Already, 4.2 billion of the world's 7.5 billion people live in urban areas – a figure that will grow to 68 percent by 2050, according to the UN (5). This phenomenon causes services to be biased toward cities, leaving large regions with poor or non-existent ophthalmic

services. With this move comes shifts in socio-economic power and disparities in education. These phenomena are creating particular increases in secondary causes of eye disease, including diabetes and hypertension.

Rising healthcare costs are the subject of widespread concern, particularly for specialties such as vision and eye health. There is not an election in the world today where candidates do not speak on health care access and cost containment. Economists refer to this phenomenon as the "cost disease." They explain that the disproportionate rise in health care expenses is correlated to the fact that, while other sectors of the economy have adapted to labor savings and substitution through mechanization, health care has not (6). However, with rising demand and diminishing budgets, governments can no longer sustain a high level of health and ophthalmic care, which, in turn, puts hospital executives and clinical professionals under increasing pressure to do more with less.

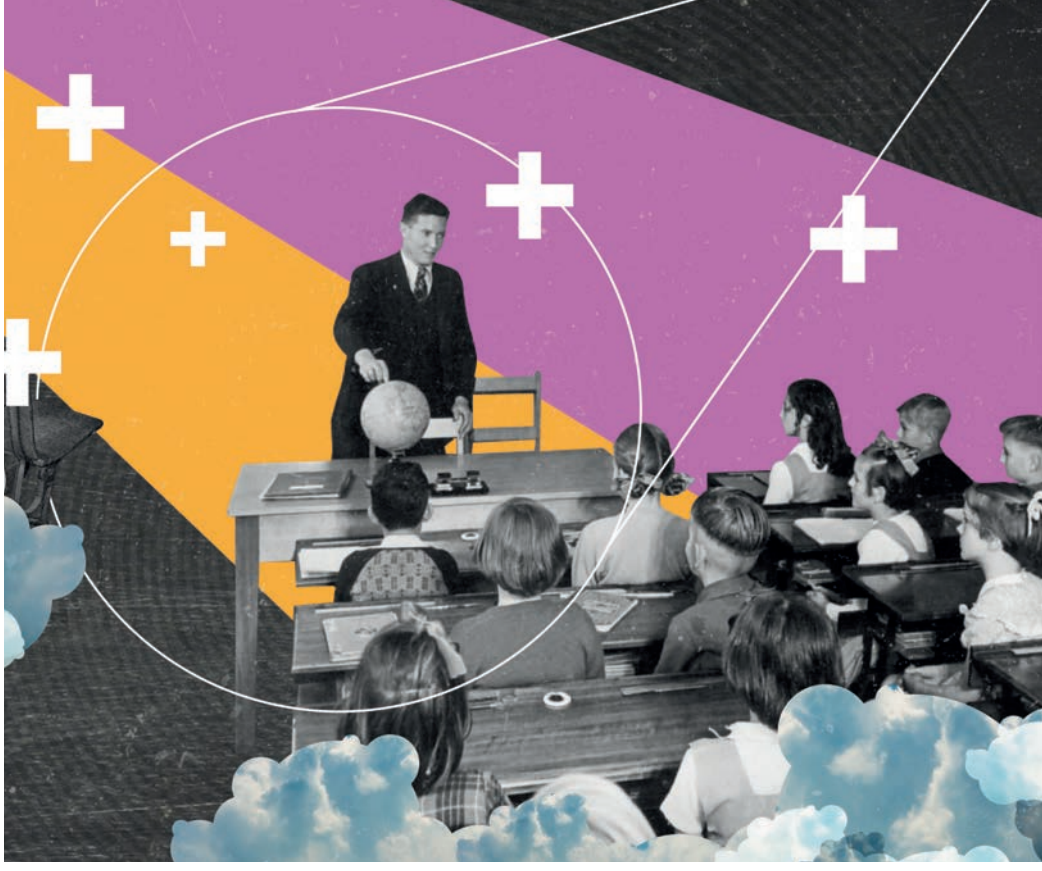
If we look to other professional groups, such as optometrists, orthoptists and pharmacists, we see that they are also caught in a place of uncertainty. A workforce survey by the General Optical Council found there were 12,099 full-time optometrists in the UK; however, their distribution across the country was uneven, proving it is not just the supply of workers, but the distribution, that favours urban settings (7). Nursing is also an area of uncertainty, as ophthalmic nurses, like ophthalmologists, come through a general training process before specializing. A study by the King's Fund found the number of nurses entering the profession in the UK did not keep pace with population growth (8). It is fair to say we have a supply and demand imbalance.

We need to prepare our workforce, patients and students for the impact artificial intelligence will have on workplaces, homes and educational spaces. We also need to prepare them for uncertainty, promoting flexibility while embracing change. It may mean encouraging less specialization or creating new roles, as well as understanding the role that technological innovation will provide. It requires training and retraining throughout our careers, as well as continually redesigning our curricula for education and training. It is about creating problem solvers, because problem-solving will always be relevant – even as the world changes.

Reimagining the future

Machine learning is slowly but surely replacing human jobs, freeing up time for individuals to take on other necessary tasks. A recent Price Waterhouse Cooper report looked at how AI, machine learning and robotics will impact the international workforce over the next few decades. They found that health has one of the lowest risks of automation between 2020 and 2035, with most jobs at risk of replacement in transport and similar industries (9). It seems the future of ophthalmic services is not in downsizing our workforce, but supporting it with technological innovation – using AI to help our professionals meet accelerating demand. The future of our profession and our workforce depends on how we decide to use technology to serve our patients better. What unfolds will not just be about technology, but about our health care system and how we can address the growing needs of society.

But the decisions do not stop there. Changes in population demographics and life expectancies are changing the skills we must build to sustain our eye hospitals. These changes, amongst others, come at a time where hospital executives are already wrestling with unprecedented disruptions, so how do we use technology and research to educate and train for the



future? The answer is clear: we must nurture innovation and re-skilling as AI supports our practices. We should be creating life-long learners who are at higher levels of thinking, regardless of their role. We must encourage and support our students to become problem solvers who embrace change. Research undertaken by the Royal College of Ophthalmologists explored the confidence of UK ophthalmic trainees' in different clinical and nonclinical aspects of ophthalmology. It was interesting to note that they reported being less confident in nonclinical skills, such as preparing a business case, while aiming to specialize in surgical sub-specialities (10). In the future, we will need ophthalmologists who are change agents, innovators and discoverers, and so we must ensure that they are skilled in areas outside their clinical specialization.

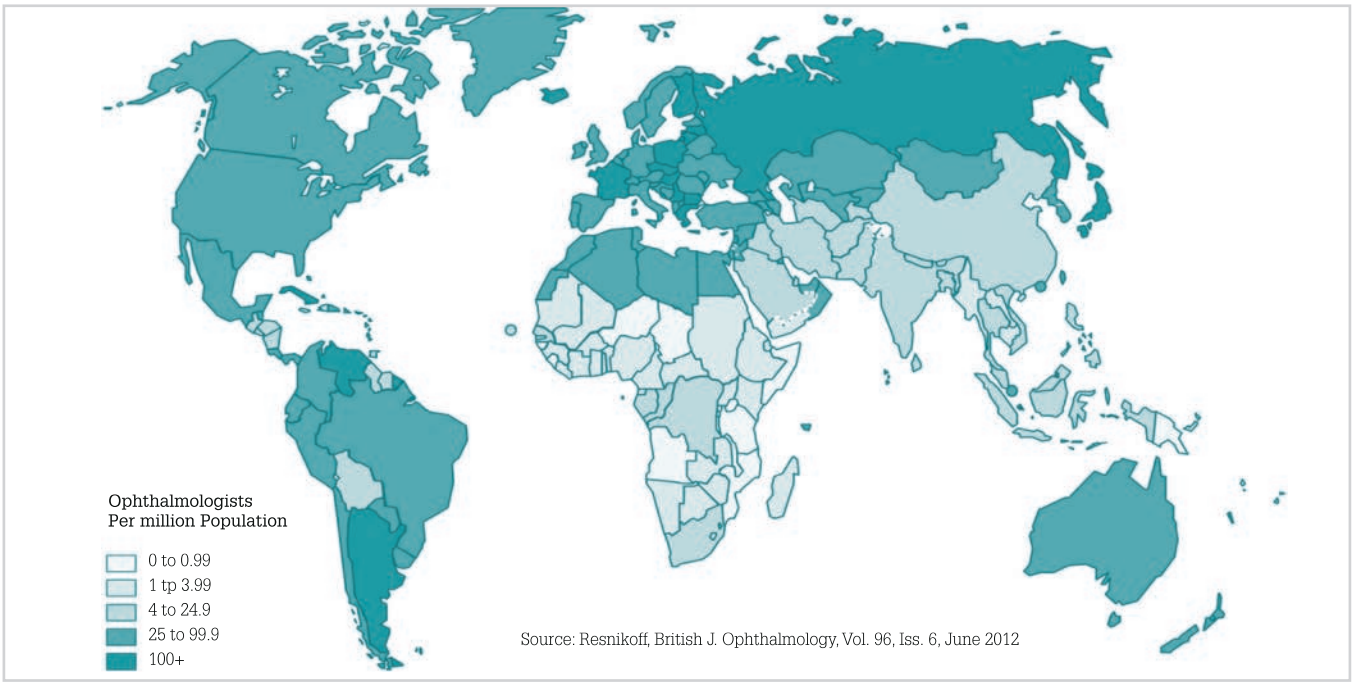
There are a number of changes that will define our classrooms, both in terms of the students we teach and the approaches we take – AI is one of them. AI will continue to advance to the point where computer-based clinical algorithms are not just being used for diagnosing, detecting and following disease in tertiary clinics, but throughout our entire health system. We will also see more computer-assisted clinical decision making. At the same time, demands on health care systems will continue to change. It is our job to make sure professionals are prepared for these changes. The Netherlands undertook two significant studies assessing major drivers for a paradigm shift in perception, learning and action about health care education (11). They found that consumer eHealth is rising with professional eHealth. In other words, more patients are better informed about their health and want to self-manage their illness with the help of technology. This more informed patient will lead to new personalized professional roles.

Reframing ophthalmic education

Truthfully, there is no single solution. Meaningful change requires a multifaceted approach. We can start by setting aside our professional divides and focusing on the challenges ahead; then we can decide, as a sector, what competencies our students, staff and patients need to address those challenges. But that is not all. Changes in ophthalmic education are not keeping pace with higher education or clinical breakthroughs. We take too long to decide how we teach, what we teach and who we teach. Some of us are too conservative and risk averse – often rightly – so we cling to historical methods of training and long-established learning practices. Not only does this mean our curricula content and delivery lags, but also that the message we send our students is in opposition to what they need to thrive in this era of digitalization and increased demand for services.

The future demands that we, as educators, are piloting, prototyping and publishing our approaches for meeting the 21st century needs of ophthalmic education. We have to allow our students to learn independently and work collectively as integrated teams. We are also going to have to infuse entrepreneurship into the curriculum because, with inevitable disruption, many of us are going to have to transform – or be transformed – to match job roles that may not exist today. Outcome-based education and backward design thinking have never been more important.

Fortunately, the silos that exist in our eye hospitals and clinics are breaking down, allowing us to deliver better patient care. We must support this change by moving towards an approach that embraces expanded roles through cross training – something that is particularly important for allied health professionals. We must also make sure that we do not deliver curricula that dates quickly. Instead, we should instil a real understanding of translational education through scientific inquiry and clinical practice. There is much that we can do with our allied health professionals and non-medical professionals to assist in supporting the gap in ophthalmic services. This approach is something we have keenly embraced at Moorfields and UCL Institute of Ophthalmology. We are developing new, innovative degree programs



that align with the thinking of other institutions, including the Royal College of Ophthalmologists, Royal College of Nursing, The College of Optometrists, British and Irish Orthoptic Society and the Association of Health Professions in Ophthalmology, with the launch of the new Ophthalmic Common Clinical Competency Framework (OCCCF).

However, increasing capacity through the better use of trained allied health and non-medical professionals is still in its early stages. Though change is being embraced in the UK, it is far from universally implemented. We need to work together as a community to imagine better learning management systems – ones in keeping with technological advances. And that means online resources offering 24-hour access to virtual tutors for students around the world; learning materials that know no language barriers; simulation exercises; even gamification of case studies. While we will always need clinical and surgical skill training, better use and preparation of our virtual spaces can facilitate student learning. Just as we speak about personalized ophthalmic care for our patients, the virtual space affords us an opportunity for personalized student journeys, where learning can be adjusted to the level and needs of each student. There is no reason that ophthalmic education cannot be developed to the pace and skills of our students as long as they achieve and demonstrate the key outcomes.

By collaborating in this way, letting educationalists drive what technology is used for in the education setting, rather than the other way around – with core learning across our professions in addition to specific skills – we can and will meet today's healthcare needs. For every challenge we face, there is an equally exciting solution that we can use to drive our education agendas for students, staff and patients.

Nora Ann Colton is Professor of Global Vision and Eye Health Education and Director of Education at UCL Institute of Ophthalmology and Moorfields Eye Hospital.

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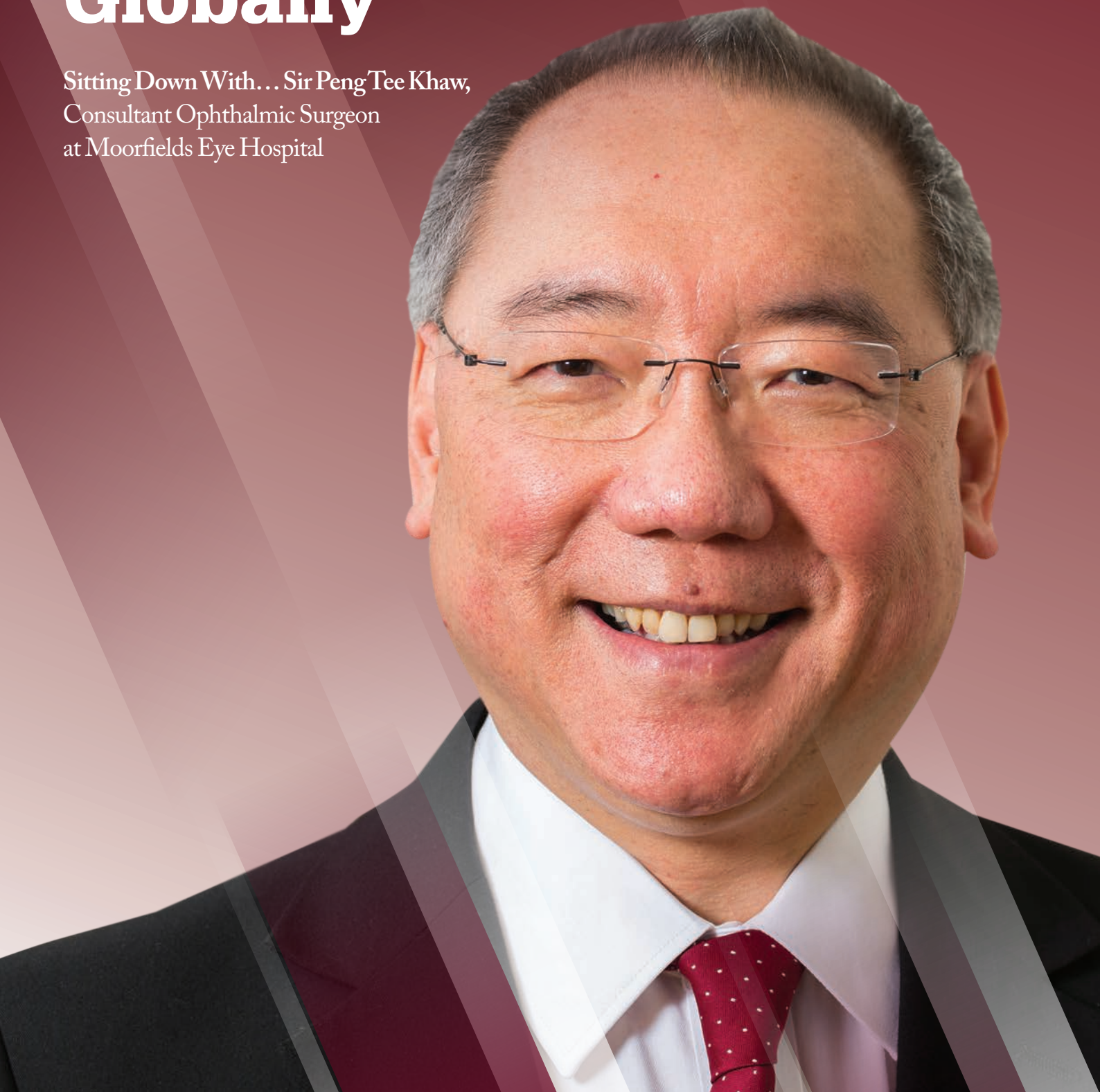
Thinking Globally

Sitting Down With… Sir Peng Tee Khaw,
Consultant Ophthalmic Surgeon
at Moorfields Eye Hospital



Why ophthalmology?

In medical school, I found it very hard to make a choice between general medicine and ophthalmology. One of my mentors, Andrew Elkington, suggested I do general medicine training first, and try ophthalmology afterwards. It was a great piece of advice: by practicing general medicine, I learned so much about general disease and looking after patients, talking to them. I worked under a neurosurgeon, John Garfield, who taught me how to assess and make a diagnosis just by taking a history, without even touching the patient – a lesson I have used throughout my career. However, when I turned to ophthalmology, I enjoyed it enormously, and I knew that it was what I wanted to do. I love operating, developing and using novel techniques and technology, but also dealing with patients. Preserving and restoring people's sight is incredibly rewarding, and the intricacies of the eye and vision discovered through research are fascinating. As a complete profession, ophthalmology is unbeatable.

And why glaucoma specifically?

My mentors, Andrew Elkington and Roger Hitchings, were great authorities on glaucoma. When I came to Moorfields, I was in a very privileged position, as every week, Roger Hitchings and I would sit for an hour and he would go through everything to do with glaucoma with me: pathogenesis, treatments, the use of modern technologies. It is such a common and complex disease, which causes so much blindness, and yet it was strangely misunderstood. It made me want to understand it better. The research that has been done over the years has helped us with this enormously. We now have potentially realistic solutions to deal with glaucoma globally.

How do you find the right balance between research and clinical practice?

Conducting research at the same time as practicing medicine and surgery is not easy, but, if you get it right, it is one of the most satisfying and rewarding things you can do. Discovering new findings that can change the lives of your patients is an unbelievable privilege. Having great mentors and being awarded a Wellcome Trust Fellowship enabled me to learn about science and lab work for three or four years. This changed my life, and taught me to always look for answers. These days, there are perhaps more support systems for young clinicians wanting to pursue careers in research, for example the National Institute for Health Research, which has revolutionized clinical research in the UK. On the other hand, there is now more focus on completing physician training rather than conducting research, and so, clinicians may be disincentivized from taking the research path. I believe this could be to the detriment of ophthalmology. The population is ageing rapidly, and incidence of eye-related disease is rising so quickly that current models of eye care will not be able to cope with future demands. The only way to cope is with new methods of diagnosing and treating people with eye disease. That is why research is not just an option – it is the only way forward – it is an absolute necessity, if we are to cope with the demand for eye care in the future.

Which qualities have helped you become a leader in your field?

I've always been very curious. All my life I've had the need to find out how things work, and how I can make them better. To improve things and make a real difference, you need knowledge and experience – and the willingness to learn new things. When I was President of ARVO in 2013, I had the task of setting the theme of the meeting, and had to figure out what the 15,000 members had in common. The answer? Making a difference to people's lives. And that's how the "Life Changing Research" theme came to be. Leaders need the desire to make things better. We also have to think globally. At Moorfields and the UCL Institute of Ophthalmology, we aim to change lives in London, in Britain, and in the world – this is our job and our responsibility. The way I see it, there is no point in building a new hospital site in London, if it's not going to be used to improve lives in the whole country, and all around the world. Global thinking is important in every aspect of our lives, from climate change to ophthalmology.

What's your proudest achievement?

My proudest moment stems from one of the worst. Many years ago, I treated a child with glaucoma, who was completely losing vision in one eye despite multiple operations. I operated using mitomycin C – a new technique at the time. The operation worked and the child was well for three or four years after that. But then she came back with endophthalmitis, and subsequently developed severe scarring on the retina. The retina shredded during vitreoretinal surgery and my young patient lost her vision. I knew that I could not deal with this scenario of bleb-related endophthalmitis throughout my career, so I went back to the lab and redesigned trabeculetomy, introducing a much safer way of applying antimetabolites, which I called the Moorfields Safer Surgery system. The work changed the safety profile of the operation – markedly reducing the incidence of blebitis and endophthalmitis, and reducing hypotony. It was a change in technique, based on research, and it has been popularized around the world. This was helped hugely by Paul Palmberg's advocacy of the technique; he also persuaded the developers of the Innfocus implant to use mitomycin with our technique, which has been critical in its clinical success. I am proud that I was able to help make glaucoma surgery safer for patients everywhere.

Has your Knighthood made any difference to your career?

It has certainly made fundraising easier – and it has brought me into contact with a much wider selection of very interesting people. I am very proud of the children's eye hospital that I helped raise money for, and of the Biomedical Research Centre – the only one in Britain specializing in ophthalmology, for which I led the funding application, and that I am now privileged to head up. But the most important thing about the title is the recognition of the importance of ophthalmology. To the best of my knowledge, there have only been two knighthoods for services to Ophthalmology in the last hundred years, the first one being Sir Harold Ridley for the first intraocular lens, though there have been a few other knighthoods for ophthalmologists for services to Royalty. I feel that medicine in general does not get enough recognition for changing peoples' lives so dramatically. I hope many more of my colleagues will be recognized in this and other ways. For me, it is an acknowledgement of how important research is – and for that I am very grateful.

What do you consider your most important collaboration – now or in the past?

My most successful collaboration has been with my wife – without her I would not have achieved any of the things I have done. And, of course, the collaboration with my mentors including Roger Hitchings, Noel Rice, Ian Grierson and Gregory Schultz, and also the collaboration and support of my colleagues at Moorfields and UCL Institute of Ophthalmology, and our colleagues around the UK and the world without whom our center would not be the success that it is.

What keeps you motivated?

Thinking about how an organization can encourage people to make a difference. Developing our future building is another huge driving force – but it is going to be more than just a building. If we were just using bricks and mortar, it would be a waste of time and resources. We are developing a structure to equip us to move into the future, from artificial intelligence and advanced informatics – imaging, genomics, through to rapid diagnostics and therapeutic devices and therapies, using research and all our clinical strengths together to improve lives around the world.

Is there anything you do not enjoy about ophthalmology?

There is a lot of regulation, which makes our work harder and harder. The number of regulatory hurdles to go through when bringing something new to the field these days is phenomenal. Sometimes it doesn't feel like the system works in our favor. The bigger the organizations, the more systems have to be built around them, which slows down important work.

Do you have time to pursue any interests outside of ophthalmology?

It is difficult to find spare time, but I used to be a keen drummer. I have played with some very interesting people – Greg Lake from Emerson, Lake and Palmer, for one! I also like mending things, so I make improvements around the house; if something mechanical is broken, I can usually fix it myself; in my early days, I played a lot with Lego and Meccano, which must have helped.

How do you think glaucoma care may change in the coming years?

My vision of the future is being able to get a portable non-invasive test of a patient's visual function including fields and dynamic contrast sensitivity (a greatly neglected but critical functional defect in glaucoma) and structure. This includes having a detailed background function of the cellular components of the optic nerve (missing in current imaging) including bioenergetics, genetics, and assessment of their risk of developing the disease; then inputting the anonymized data into a standard communal database that can be accessed around the world and that will determine the risk of vision impairment over a period of time. We spend a lot of time trying to absolutely define glaucoma, but as our cellular and molecular understanding of the disease and its natural history progresses, we will be able to define this group of diseases as much more cellular and molecular defined entities.

Based on the data of millions of patients, and the individual's data, we would be able to offer unprecedented accuracy diagnosis and prognosis, and choose the most appropriate treatment with the minimum follow up necessary. Importantly, we would not have to follow patients unnecessarily, as the ones who do not need frequent visits could be followed up remotely. With the advances of AI and information , this is something that could be achieved in the future.

I would also love to see a glaucoma surgical treatment that lowers pressure very significantly, and for a long time, according to the 10-10-10 target I set the glaucoma community: maintaining eye pressure of 10 mmHg (a level considered safe enough to prevent glaucoma progression in over 95 percent of patients) lasting 10 years – and achieved safely in 10 minutes. There are so many glaucoma patients in the world, and the number is increasing with the ageing population. Unless we have a safe, quick and easily reproducible treatment that will last for a long time, we won't be able to cope with the demand. This probably requires a microdevice that is easily inserted, coupled with anti-scarring therapy that can be easily delivered during surgery and can be titrated according to the anticipated healing response. Lasers may also help this, and the recent LiGHT trial (see page 12) is showing the potential of maintaining pressure for several years without medicines.

One final wish: to turn the clock back, and give my patients some of the vision they have already lost. Gene and stem cell therapy for glaucoma now has the real prospect of turning the clock back at least by a couple of years for patients with end-stage glaucoma. I am privileged to be involved in the discovery of the Moorfields-Institute of Ophthalmology Muller cell, which now has a real prospect of optic nerve therapy.

All of these dreams are incredibly ambitious, but the most amazing thing about them is that they are achievable; they are based on research done over the years. I often think back to the child who lost her vision – and I realize how much progress our specialty has made thanks to research advances.

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

Be ambitious, be inspired. You never know what you might achieve if you don't try – and it makes the future very exciting.

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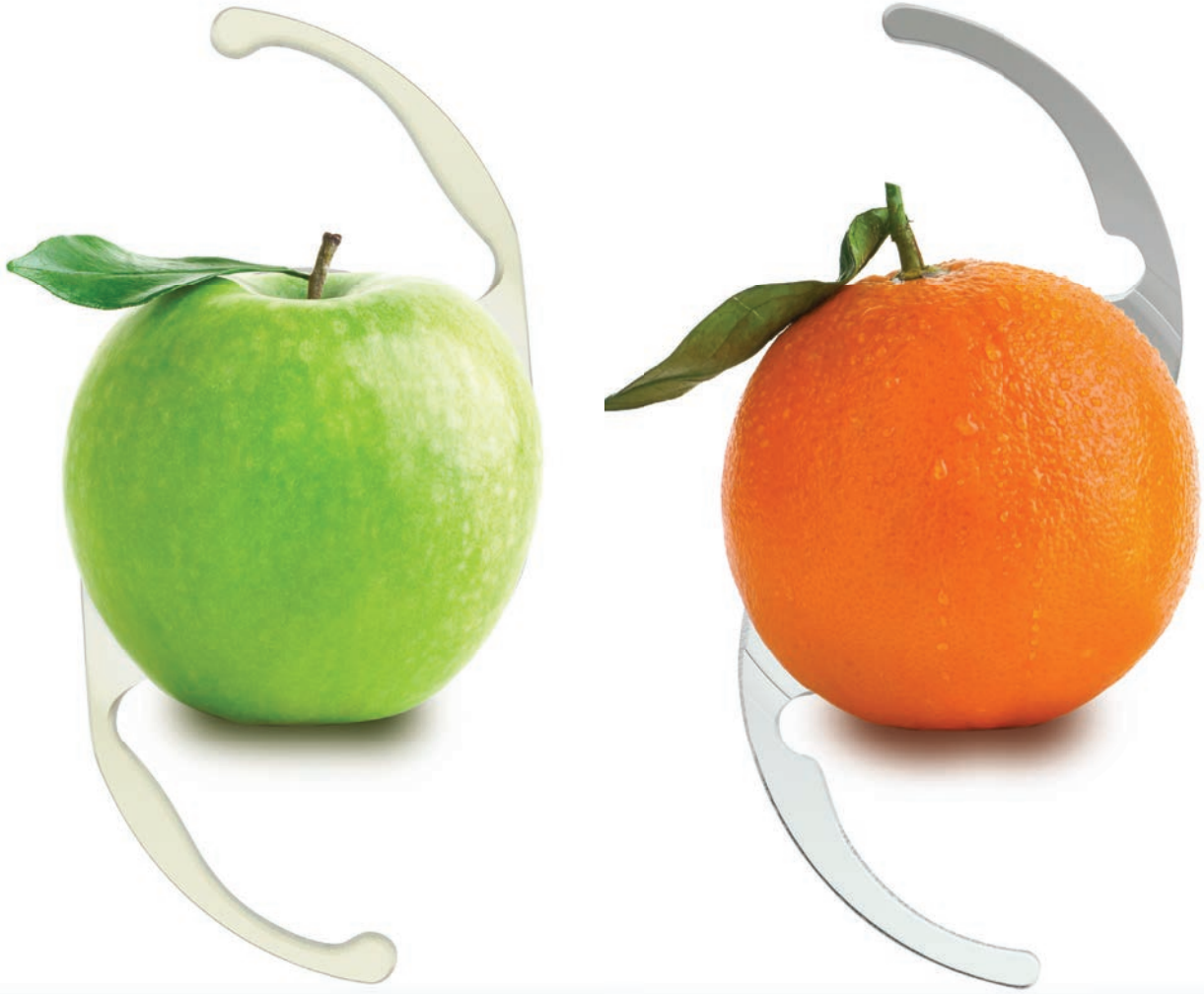

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