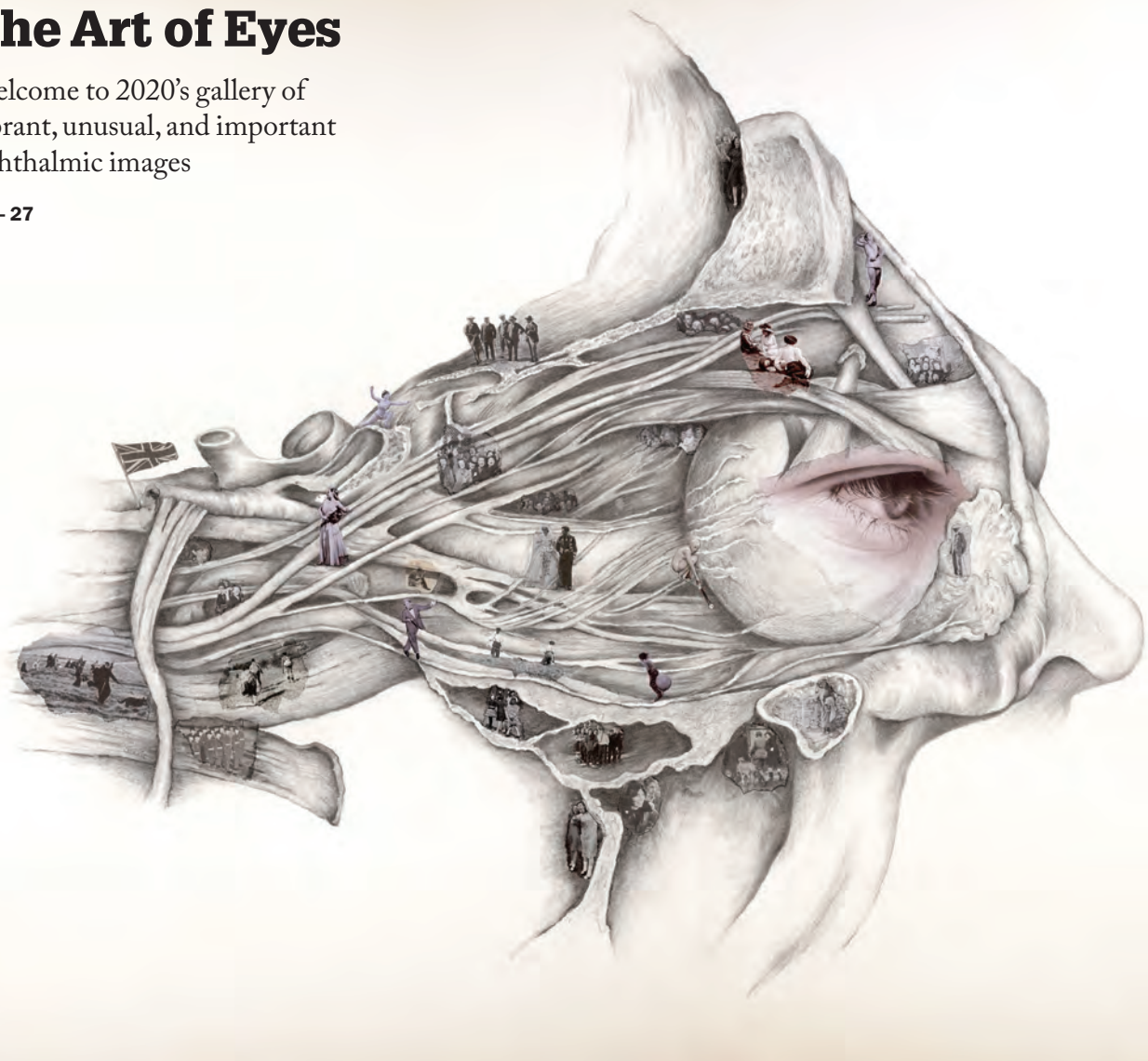
JULY/AUGUST 2020 # 46

the Ophthalmologist™

The Art of Eyes

Welcome to 2020's gallery of vibrant, unusual, and important ophthalmic images



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The global impact of pandemic mitigation measures on has been immense – and vision science is no exception. Social distancing and lockdowns have led to delays in most research and clinical trials (as our contributor, Sean Ianchulev, mentions on page 46), with researchers unable to either take their work home or carry it out in their usual settings. In the US, institutions have had to put limits on trials and studies without the prospect of direct benefit during the COVID-19 pandemic (1).

Some practicing clinician-researchers were redeployed to take care of patients affected by COVID-19. Many others have devoted their attention to COVID-19's impact on eye care, with record numbers of papers produced and published on the topic – the trend is understandable, but to the detriment of other crucial vision-related research. In some settings, lab equipment has been repurposed to ramp up the number of available diagnostic tests for COVID-19. Importantly, with childcare settings and schools closed, researchers with caring responsibilities cannot always balance both duties – a challenge that disproportionately impacts women, resulting in fewer grant applications and paper submissions from female researchers (2).

But these obstacles aren't new. COVID-19 is merely exacerbating challenges the scientific world has faced for a long time. Could the pandemic be our chance to improve the situation – not just temporarily, but as a permanent fix for some of scientific publishing's most pressing issues?

Researchers and journal publishers are now pulling together to lessen the impact of the pandemic on their output. Papers are being published rapidly, with over 50 leading publishers opting to make all COVID-19-related content accessible to all (3). Meanwhile, authors are publishing their work on preprint servers or through open-access platforms ahead of peer review (4). Collaboration on local and international levels is rising as researchers explore new ways of remote networking and disseminating information. An open letter listing ways in which funding bodies can alleviate the impact of caring responsibilities on researchers' productivity has been signed by hundreds of leading scientists worldwide (5). Is there an opportunity in this crisis to change scientific research for the better – forever?

Aleksandra Jones
Editor

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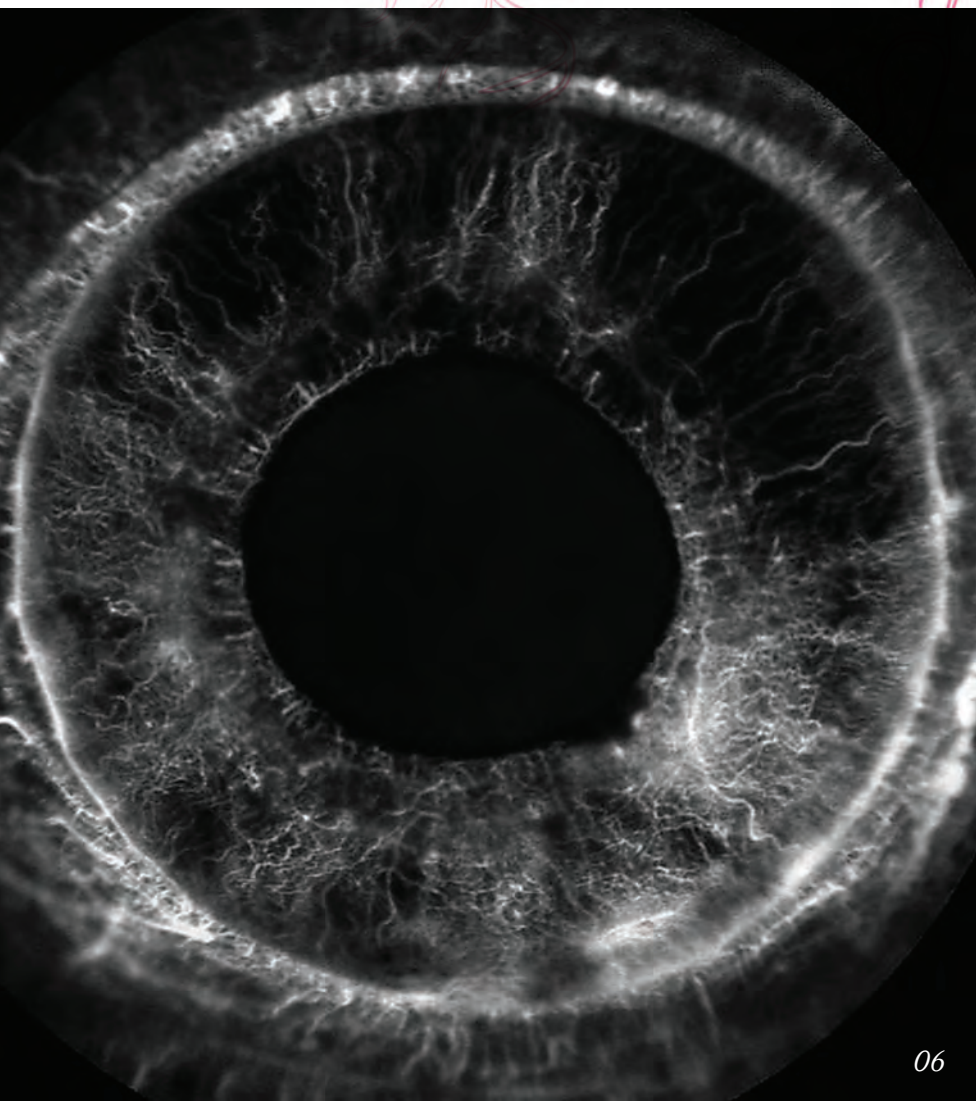

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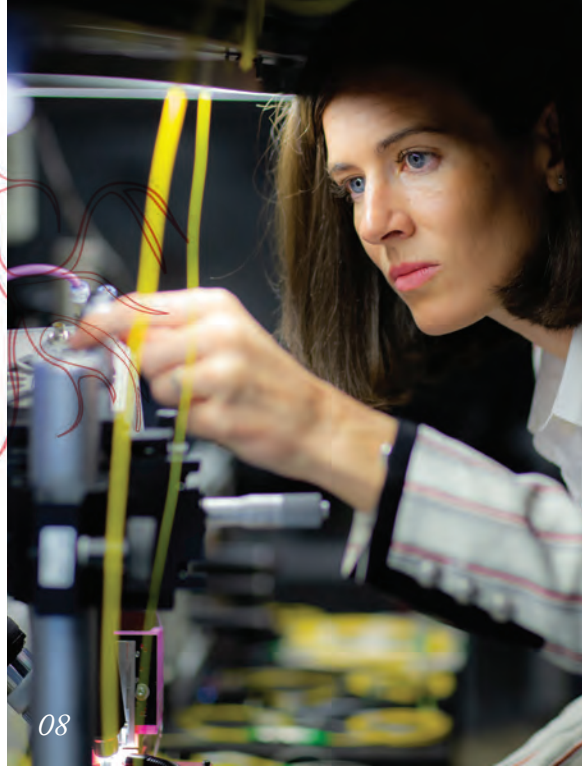

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On The Cover

The Seat of the Soul, an artwork by Jennie Jewitt-Harris

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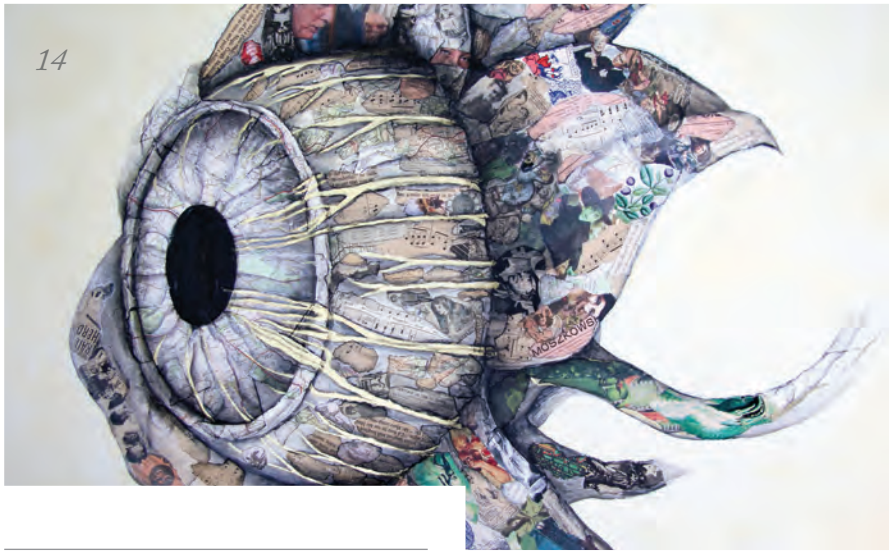
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In Practice

NextGen

Sitting Down With...

the Ophthalmologist

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The Living Image

The app offering a non-invasive alternative to traditional blood tests

Researchers at Purdue University have found a way to assess blood hemoglobin (Hgb) levels from a simple smartphone photo. The software uses super-resolution spectroscopy (SSR) to compute exact blood Hgb content from a photo of the patient's inner eyelid. The team chose the site as its easy accessibility and relatively uniform vasculature are unaffected by confounding factors of skin pigmentation, negating the need for personalized calibration. Young Kim, Associate Professor at the Weldon School of Biomedical Engineering at the University explains how SSR works. "Super-resolution means high-resolution reconstruction of digital images acquired with low-resolution systems – in this case, a smartphone. We successfully extended this concept to the detailed color domain (wavelength) for spectroscopy. SSR allows us to mathematically reconstruct a spectrum from a regular photo that has three color information: red, blue and green, allowing us to transform the phone's built-in camera into a spectrometer without the need for any hardware modifications or accessories."

So how did it perform? In a clinical study of 153 patients, prediction errors for the smartphone technique were promisingly within 5 to 10 percent of those measured with clinical laboratory blood. "This is a good example that a data-driven technology can minimize hardware complexity" says Kim. "Computation is fast, with super-resolution and Hgb spectroscopic analysis taking 0.0003 and 0.0004 seconds, respectively, using cloud computing (MATLAB Mobile) on a low-end smartphone (Samsung Galaxy J3)." The team say the results support the feasibility of SSR in noninvasive blood Hgb measurements, with the possibility of extending the algorithm to different models of smartphones in the future. Blood tests are used to assess a range of hematologic disorders, as well as transfusion initiation, hemorrhage detection after traumatic injury and acute kidney injury. The researchers hope the approach will improve care in low- and middle-income countries where access to testing laboratories is limited.

INFOGRAPHIC

Lockdown Worries

Recommendations for people with sight loss among concerns that visual impairment (VI) will get worse due to the pandemic

4 out of **10**

people in the UK fear their vision will deteriorate further due to COVID-19 lockdown, while

73%

admitted their access to treatment got worse due to canceled surgeries and anti-VEGF injections

Online support groups on social networking platforms, as well as **web-based meditation** or **mindfulness programs** should be set up, and existing resources need to be well publicized

BUSINESS IN BRIEF

The latest industry news – in 50 words or less

- Samsung Bioepis Co. has initiated its first randomized, double-masked Phase 3 clinical trial for SB15, the company's proposed biosimilar of Eylea (aflibercept). The multicenter study will compare efficacy, safety, pharmacokinetics, and immunogenicity between SB15 and Eylea in 446 patients with neovascular AMD.
- A study part-funded by Fight for Sight has pioneered a gene therapy approach to reverse retinitis pigmentosa. Researchers used a viral vector to carry a replacement RP2 gene to malfunctioning cells in lab-grown mini-retina models of the disease, after which the cells began to produce the essential protein associated with the gene.
- Epipole has secured £1.5 million in funding to prepare to enter the US market. The retinal imaging specialist also announced the appointment of Ian Stevens as Chairman. Stevens previously spent nine years at Optos, first as CFO and then as General Manager of its North American business.
- Implandata Ophthalmic Products GmbH has announced the launch of its web-based IOP tracking service for remote glaucoma monitoring and management. "The EYEMATE system is backed by 10 years of clinical data, which means the safety and utility are proven," said CEO Max Ostermeier in a statement.
- Harris Williams has advised The Retina Group of Washington, a leading provider of retinal and macular eye care in the greater Washington, DC, Maryland, and Virginia region, on its transaction with PRISM Vision Group. The group will be responsible for building a vertically integrated eye care network in the region.
- Wasatch Photonics has expanded its Cobra OCT spectrometer product line to include a 1,600 nm OCT spectrometer for deep-tissue SD-OCT imaging. The Cobra 1600 builds on the company's existing line of off-the-shelf spectrometer models, offering greater depth penetration with high contrast for highly scattering tissues and materials.

References can be found online

Gut Feeling

Twin study investigates how gut organisms influence the immune system

A partnership between Fight for Sight and the Royal College of Ophthalmologists hopes to shed new light on the link between the gut microbiome and AMD. Their method is simple – study twins. Stool samples from twin siblings are undergoing advanced genetic analysis to identify the microorganisms more common in healthy individuals versus those with AMD, while OCT scans look for macular changes. Zakariya Jarrar from King's College in London, UK, was awarded the Fight for Sight John Lee Primer Fellowship to lead the research. "Studying twins is helpful in understanding what genetic and environmental components contribute to age-related macular degeneration," said Jarrar (1). "This is because twins share their genes and therefore the influence of the environment can be explored, particularly when one twin develops the disease and the other does not."

Reference

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EXERCISE PROGRAMS or **ACTIVITY ADVICE** should be customized for people with **VI** and available regularly on **RADIO, TV OR PODCASTS**

2 in 5 SURVEY RESPONDENTS

with severe sight loss found it difficult to follow social distancing rules

Retailers are asked to offer **priority** online shopping slots to **partially-sighted people**

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Scattered Light

An eye test to diagnose Alzheimer's disease?

A team at Duke University has developed a light-scattering technique to screen for Alzheimer's disease. The technique – angle-resolved low coherence interferometry (a/LCI) – combines imaging modalities to measure both the thickness and the texture of various layers of the retina. "a/LCI looks at the angular scattering pattern from tissue to determine the scattering structures while using the depth resolution from LCI. This lets you see structures that can't be easily visualized in OCT," explains Adam Wax, Professor of Biomedical Engineering and Physics at Duke and the technique's creator. Studies have shown that Alzheimer's disease can cause structural changes to the retina. Notably, thinning of the inner retinal layers can indicate a decrease in the amount of neural tissue, suggesting Alzheimer's is present. However, other diseases – namely, glaucoma and Parkinson's – can cause similar thinning. Nevertheless, Wax hopes this new measurement could be a more easily accessible biomarker for Alzheimer's.

The team are now incorporating the technology into a low-cost clinical OCT scanner (currently awaiting FDA clearance). Built with 3D-printed parts, the scanner is portable and lightweight at just four pounds. "Our next research goal is to test this in humans with Alzheimer's disease," says Wax. Although diagnoses are currently only made after a patient begins to show symptoms of cognitive decline, Wax and his colleagues hope the machine could be used to screen patients in their 40s or 50s at routine checkups. "As our ability to detect Alzheimer's disease improves, it opens the door for greater preventative measures. With a diagnostic test that is easy to use, there is a chance to monitor disease progression much as we might check blood pressure or cholesterol."

Reference

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(Ultra)short and Sweet

Could a new incarnation of the soliton laser find its way into eye surgery

A completely new way of applying laser light could be used for biomedical applications, including corneal surgery. Researchers at the Institute of Photonics and Optical Science at the University of Sydney, Australia, have developed the "pure-quartic soliton laser," which can deliver large amounts of energy in ultrashort bursts. And it could aid in removal of material from the eye without causing damage to the surface. The laser uses soliton waves that can maintain their shape, but previously could not be produced at sufficiently high energies. The newly-developed laser is capable of delivering pulses as short as a picosecond (one trillionth of a second), with high amounts of energy. Eventually even shorter bursts could be achieved, and the scientists hope to see the laser deliver hundreds of kilowatts of peak power.

Reference

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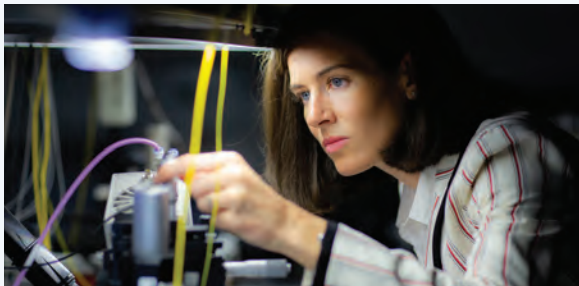
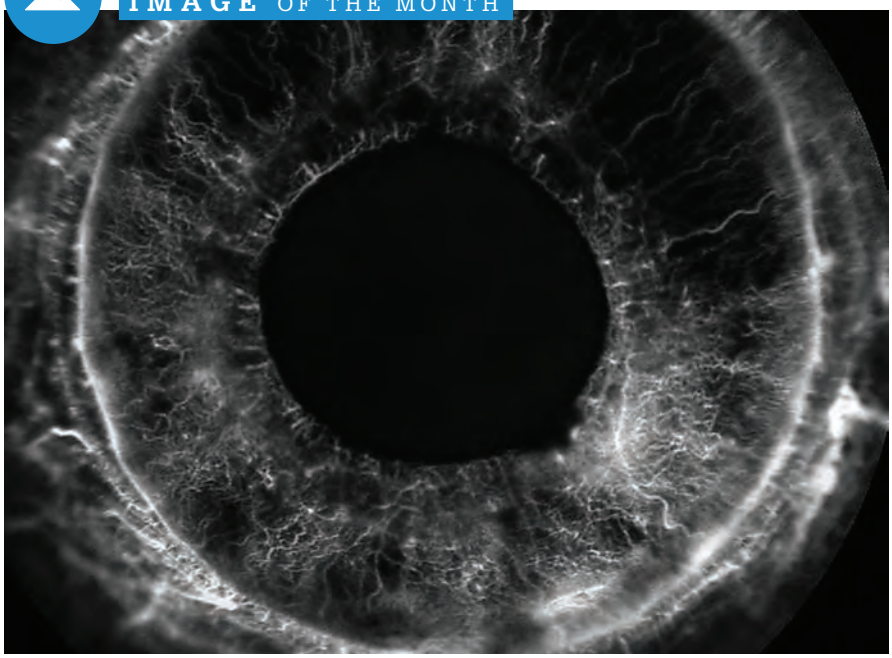


Image: Andrea Redondo-Blanco in a lab in the Sydney Nanoscience Hub. Photo University of Sydney.

IMAGE OF THE MONTH



Black Hole Sun

This month's image shows iris angiography of ocular ischemia secondary to stenosis of the left carotid artery.

Credit: Julien Bouleau, CHU Lille, Clinique d'Ophtalmologie, Lille, France.

Would you like your photo featured in Image of the Month? Send it to edit@theophthalmologist.com

QUOTE OF THE MONTH

"It is estimated that the global number of people affected by blindness will triple by 2050. As ophthalmologists, we cannot triple all our efforts in the next 30 years, but we can easily ramp up and triple our digital activities – we could scale them up by a factor of 100!"

Daniel E. Neely, pediatric ophthalmologist at the Midwest Eye Institute and Professor of Ophthalmology at Indiana University School of Medicine, Indianapolis, Indiana, USA

In Safe Hands

Regular use of alcohol-based hand sanitizers can cause ocular surface disease

Clinicians in India are reporting that 60 percent of their virtual consultations during the COVID-19 pandemic have been for red eye; a quarter of cases were diagnosed as infective, but the rest were non-specific. Patients have admitted to using hand sanitizer sprays frequently (5–30 times a day), and so the authors of a study published in the Indian Journal of Ophthalmology (1) are now drawing attention to sanitizer aerosol-driven ocular surface disease (SADOSD). Symptoms of SADOSD include precorneal tear film changes and ocular surface discomfort. The researchers go on to list ocular risks associated with alcohol-based hand rubs and provide a list of measures for responsible use of hand sanitizers, while pointing out that the use of soap and running water should be encouraged.

Reference

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In My View

Experts from across the world share a single strongly held opinion or key idea.

Preparing for a New Landscape

How we will deal with the pandemic of neglected chronic eye disease following the COVID-19 lockdown

By Livia Faes, Research Fellow, Dawn A. Sim, Pearse A. Keane and Konstantinos Balaskas, Consultant Ophthalmologists at Moorfields Eye Hospital, London, and Lucas M. Bachmann, Founder, Medignition Inc., Zurich, Switzerland

Hindsight is a cruel judge. When reflecting on the COVID-19 pandemic, a singular emphasis on infection and associated death rates provides an incomplete picture of the health, well-being and socio-economic impact this disease will have on populations globally. Inevitably, severe cutbacks in everyday medical care have led to disruption in provision for diseases that are the most frequent causes of morbidity and mortality outside a pandemic. Undersupply of care is also observed for many chronic diseases that do not lead directly to death, but to increased complications, more severe courses, a reduction in quality of life, and more complex and risky treatments.

In ophthalmology, the undersupply is particularly visible. During the pandemic, within only three months, we observed a 79 percent reduction in ophthalmic appointments in the UK – the most of any medical specialty (1). Disruptions in care for common chronic conditions, such as AMD or diabetic retinopathy (DR) that – if left untreated – can lead to irreversible vision loss and blindness, are particularly severe given that this patient population is at a high risk of serious illness from SARS-CoV-2.

Care structures are poorly prepared for the unprecedented challenges of a pandemic. In many places, new health delivery models have been launched under great time pressure and difficult conditions to offer at least minimal care. The focus of these initiatives was always on bringing medical care to the patient (and not, as usually the case, bringing the patient to the care center).

Although a large number of concepts were proposed and, in some cases, already implemented before the pandemic, digital health approaches, such as telemedicine, virtual clinics and home monitoring, are still a shadowy existence in the care landscape. These approaches have great potential to improve access to medical care and efficiency of care pathways even outside of pandemics.

Several organizational and political steps are necessary to effectively introduce these innovations into care. At the center of these activities is the involvement of non-medical specialists, such as opticians, optometrists, and medical-technical practice assistants, who can provide delegated services. Consequently, there is a need for more interdisciplinary and transdisciplinary collaboration. Robust evidence from implementation science will be essential to demonstrate the safety, efficiency and sustainability of such care pathway transformations. High-quality evidence generation is a time-consuming process, so such initiatives have to be launched quickly. The pressing need for minimizing vision loss during the pandemic justifies the rapid deployment of innovative care pathways on a pilot basis, providing preliminary evidence of their potential.

Shifting the provision of care for chronic eye diseases, such as AMD, DR and glaucoma, to non-medical practitioners requires training and direct access to professional input from hospital-based medical experts (2). Evidence already exists that shared care by hospital-based optometrists and specialist eye nurses to monitor chronic eye disease may be equivalent to ophthalmic care in certain circumstances (3). Telemedicine allows patients to be triaged remotely, reducing unnecessary and costly hospital visits, and optimizing access to medical care. It also enables referrals to be made by remote verification of the imaging performed close to the patient (for example, at the local optician or optometrist) by hospital-based experts. The technical requirements for this type of care already exist and have been implemented on a small scale in pilot projects (4, 5, 6, 7). Evidence from robust prospective validation research will guide meaningful implementation of such pathways at scale, and a small number of such initiatives are already underway (8).

Not unlike the search for a vaccine

"Thanks to both technological innovations and miniaturization of examination equipment, completely new forms of ophthalmic care are now possible."

against SARS-CoV-2, further investment and prioritization of research in digitally-enabled eye care by national funders is needed to quickly and successfully redesign our services for the post-pandemic reality. In a further step, the time-consuming image evaluation by clinical experts can be partially replaced by AI-supported decision aids for the triage of referrals. Studies in this context have shown that automated classification of OCT scans and fundus images with new algorithms is equivalent to expert assessment for AMD and DR screening, but further validation and system-level transformation analysis of pathways will be needed to embed these tools in real-life care pathways (8, 9, 10, 11).

In the aftermath of the pandemic, collaborative care between community optometry and hospital-based eye services will be crucial when it comes to absorbing the expected capacity pressures – and telemedicine technologies can enable this link. During a pandemic, home monitoring of vision could provide the only remaining option for surveilling vision of vulnerable patients with AMD and DR who are self-isolating or cannot access hospital and community-based eye care. Two FDA-approved applications (mVT of Genentec and Alleye of Oculocare medical) are currently on the market to home-monitor visual functions of patients remotely, and recently, Notal Vision announced a home-monitoring OCT device (12, 13, 14).

Thanks to both technological innovations and miniaturization of examination equipment, completely new forms of ophthalmic care are now possible. The well-planned interplay of telemedicine, decentralized diagnostics, algorithmic processing of image data, and the automated triage of the patient group that requires prompt consultation and treatment makes it possible to transform eye care provision. This possibility, however, meets regulatory or organizational hurdles in many places, and often lacks robust evidence from validation and implementation science.

An important lesson we can learn from the SARS-CoV-2 pandemic is this: it is worth being prepared. The consequences of late intervention lead to suffering and patient harm that could be avoided with good planning. Now is the time to act – both by piloting new care pathways to minimize the impact of the pandemic on preventable vision loss; and by prioritizing research that will provide the evidence on efficiency and sustainability of an entirely new eye care landscape – probably bearing little resemblance to everything we knew as "standard care" just a few months ago.

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When a Doctor Becomes a Patient

How I switched operating table positions three times in my life

By Nikica Gabrić, Founder of the Svjetlost group of eye clinics. He is based in Zagreb, Croatia

Like many of my fellow ophthalmologists, I have performed surgery – including LASIK and refractive lens exchange – on many high-profile figures. However, my most exciting patients are not the famous ones, but other doctors. Being able to share amazing, innovative technologies with "one of my own" is a great feeling!

I have worked as an ophthalmologist for over 35 years and have "become the patient" three times so far. The first was when I was 46 years old. I had LASIK to treat oblique astigmatism – an easy decision I made within minutes after seeing the new Wavelight machine operated by refractive surgeon Matthias Maus in Köln, Germany.

The second surgery took place around Christmas 2017. I was 56 and – because I suffer from diabetes – the vision in my right eye started to deteriorate due to an early cataract. Because my vision was so poor (about 20/100), my second decision to have surgery was as easy as the first. I considered a few different IOL platforms but, after surgical successes with TECNIS Symfony, opted for that. We did a classic post-LASIK calculation and made an adjustment for a slight myopic shift to make reading easier. I was amazed by the results and returned to work less than 24 hours later. My left eye was still fine, with an uncorrected visual acuity of 20/25.

When talking to my patients about surgical procedures, I've been able to use my own example to convey my trust in the technology. In my experience, doctors tend to talk to patients about halo and glare using a scientific, model-based approach, rather than from personal experience. I can tell you: these dysphotopsic phenomena are not nearly as bad as we tend to show them in our presentations. At traffic lights, the red light makes larger, more noticeable halos; the yellow halo is less pronounced; the green is almost nonexistent.

After my second surgery, time went on and I was a 20/happy patient. Then, in 2019, I was shown a new lens: the TECNIS Synergy. At first, I was skeptical, but I tried a batch of 50 IOLs and found that they enabled us to perform successful refractive lens exchange on plano-presbyopia patients – a group we had previously avoided because post-surgery complaints were so frequent. Now, eight months on, we have implanted over 900 Synergy IOLs, 20 percent of them for plano-presbyopia treatment.

My left eye had uncorrected vision of 20/30. With my other eye just slightly myopic, I could read J1–2. I had good vision, with no issues when reading or performing my day-to-day activities. Nonetheless, I couldn't get the idea of another surgery out of my head.

It took me six months to find the time – but when the COVID-19 pandemic completely cleared my schedule, I decided to go through with it. I consulted Warren Hill to make sure that the calculations for my third surgery were spot-on. I knew in my heart that I was making the right choice, but involving multiple people in the calculations and predictions helped me to make sure my decision was rational. I've always been a person driven by emotions, quick to act and prone to risk-taking, but I didn't want to be reckless with my vision. In the end, the procedure was uneventful.

"I had good vision with no issues when reading or performing my day-to-day activities. Nonetheless, I couldn't get the idea of another surgery out of my head."

I have a rule of never offering or performing a procedure on your patient that I would not perform on my own family. Now, having had LASIK and refractive lens exchange, I can upgrade the mantra to, "I perform surgical procedures that I've had myself!" I feel that this is the ultimate test of trust in the technology I use on my patients. Can you, too, say that the procedures you offer are ones you would undergo yourself?

Opening the Door

What has living in lockdown meant for Charles Bonnet Syndrome sufferers?

By Judith Potts, Founder of Esme's Umbrella, a UK-based campaign group raising awareness of Charles Bonnet Syndrome

As we slowly emerge from the past 12 weeks of the COVID-19 crisis, it is time to reflect on how the lockdown – though essential to quash the virus – has impacted on those who live with Charles Bonnet Syndrome (CBS). We were already aware that stress, isolation, and fever cause an upsurge of CBS episodes – and lockdown has confirmed this beyond any doubt. The number of calls to my Helpline (answered on behalf of Esme's Umbrella by the Eye Health Team at the RNIB) have doubled – in stark contrast to the fall in general eye health calls. And my inbox and social media channels have also been twice as busy.

Louise Gow, Specialist Lead for Eye Health at the RNIB, also confirmed a change that I had detected. She told me, "There are a greater number of people reporting hallucinations that are more frightening and realistic. They are having a difficult time working out that the hallucinations are not real."

Not only is this causing great distress to the person living in a world of vivid, silent, visual hallucinations, but for relatives – unable to visit – it is particularly troubling. Perceived images of people in the house, gushing water or fire have caused many to call the emergency services and isolation rules have had to be broken by anxious relatives or friends. As we journeyed through lockdown, I received calls from people who confided their suicidal thoughts. Directing these calls to experienced helplines like Samaritans and The Silver Line, I discovered that I needed, first, to explain CBS. Another successful route I took was to refer people to The Macular Society's group's telephone counseling service, which was specifically set up for people living with CBS.

For many years, it was considered that CBS only developed in the elderly but, again, lockdown has confirmed what we already knew: children and young people are not exempt. Describing the change in his CBS, one young person told me, "My hallucinations have gone berserk."

"There are still far too many people who are not confiding in anyone about their hallucinations."

I suspect part of this new development is due to being confined in the house, with none of the usual stimuli available, but I wonder if the CBS episodes, which have shifted from annoying or upsetting to terrifying, will retreat back once the stress and isolation is lifted. Will those people who developed CBS during lockdown retain the condition? No one knows; it is yet another factor in the unravelling of this complex condition.

There are still far too many people who are not confiding in anyone about their hallucinations, and far too few GPs, hospital doctors, ophthalmologists, and optometrists who know about CBS. All my calls to patients' GPs during lockdown to explain the condition were met with astonishment – but gratitude, too. Dominic ffytche of King's College London, my medical advisor, estimates that there are at least 1 million people in the UK living with CBS. With the anxiety felt about visiting hospitals or clinics caused by COVID-19, the number of undetected and late-diagnosed eye conditions will add to this figure.

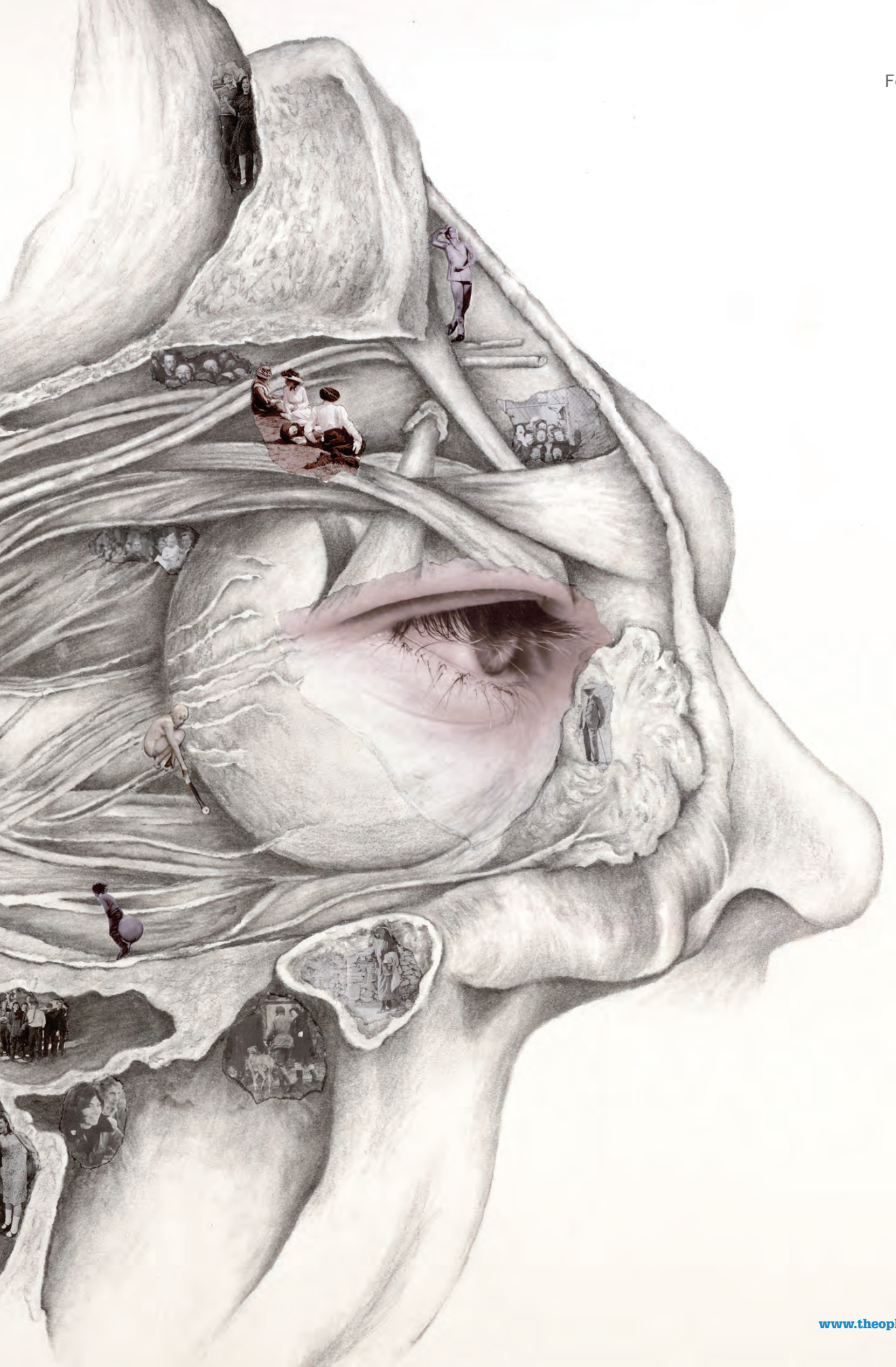
Sometimes, all someone needs is the reassurance that CBS is a recognized side effect of sight loss and not the beginning of a mental health condition. "It is like watching a beautiful gardening documentary," one person told me. For others, disturbing images require much more support. My website (www.charlesbonnetsyndrome.uk) carries coping strategies and a printable explanation of CBS, which can be shown to the relevant healthcare professional. With great creativity, local low vision charities have morphed their Esme Room Support Group gatherings into "Esme's Friends," allowing people to chat together via video or audio calling.

The work of Esme's Umbrella has resulted in a growing interest in CBS amongst the research community in the UK and Ireland. Delayed by COVID-19, these studies and research projects will be announced soon. The door on CBS research is wide open.

CBS is not "fanciful" nor caused by an "overactive imagination." And it is not possible to "ignore it, until it goes away." For the sake of everyone living with sight loss and those who will develop it, I would urge all healthcare professionals to educate themselves about Charles Bonnet Syndrome.

The ART of EYES 2020

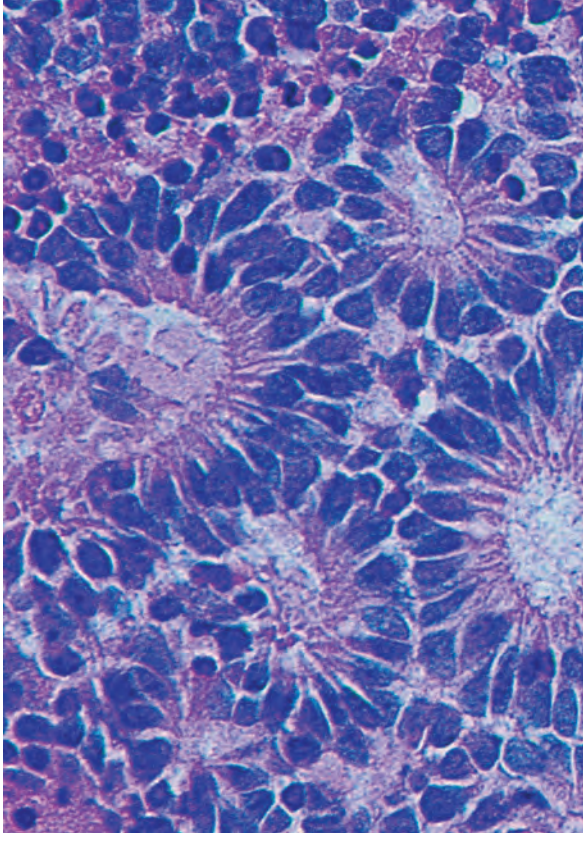
Eyesight, arguably the most precious of our senses, is naturally associated with perceiving beauty, and many artists are preoccupied with capturing the intriguing organs we use to view the world. We present this year's best ophthalmic images, through the eyes of ophthalmic and documentary photographers, watercolor artists, pathology technicians, veterinary ophthalmologists and interdisciplinary artists. The result: a real feast for the eyes.



FLOWERS *and* WAVES

Hillary Stiefel is an Assistant Professor at the Casey Eye Institute, Oregon Health & Science University in Portland, OR, USA, where she practices comprehensive ophthalmology and ocular pathology. She takes many photographs as part of her work, "aiming to capture images of the eye that include visually striking details that appeal to the imagination of all viewers," as she explains. "Much of my work incorporates unique patterns and colors reminiscent of abstract art." Stiefel has previously displayed her photography at Casey Eye Institute for the appreciation of patients, colleagues, and community members.

Clockwise from top left:

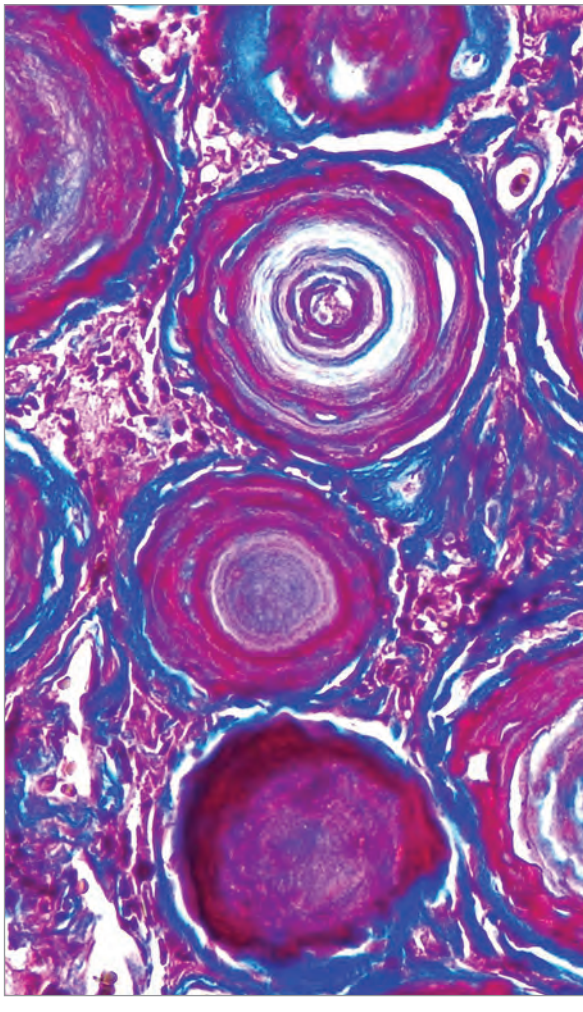


ROSETTES

This photograph displays Homer Wright and Flexner-Wintersteiner rosettes, the striking arrangements of tumor cells in a case of retinoblastoma. *H&E stain, 40X.*

RETINAL WAVE

This is a photograph of the human retina. In this case, the retina is detached from the underlying tissue, giving it a wave-like quality. *H&E stain, with adjusted tint and contrast, 10X.*



VIEW FROM WITHIN

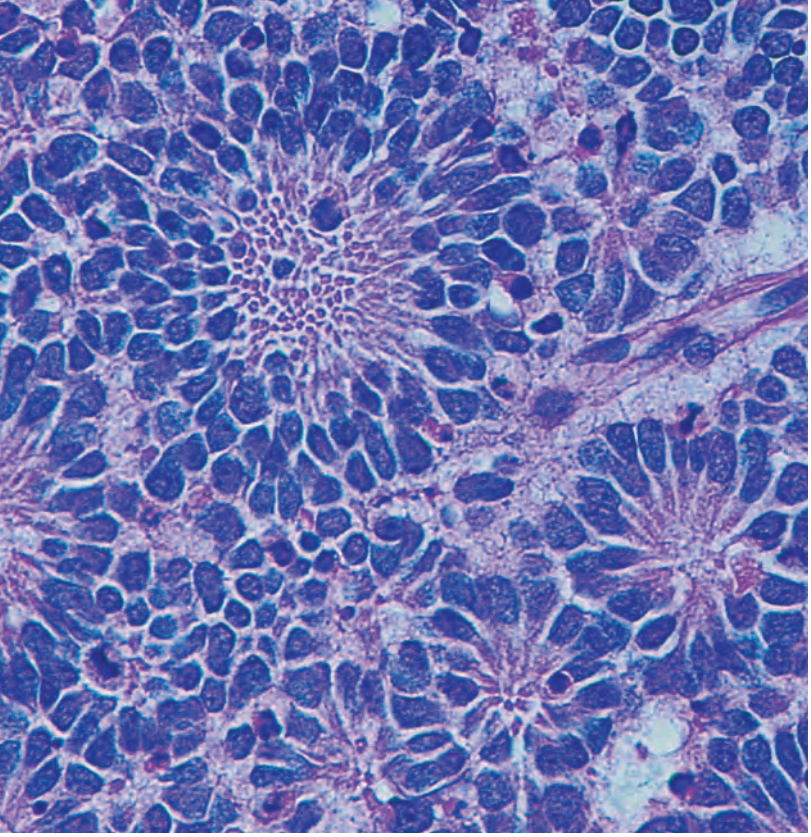
This photograph showcases the wall of a blood vessel, with numerous layers creating the visual impression of a vortex. The black stain highlights elastin fibers, while a collection of red blood cells can be seen within the center of the vessel. *VVG stain, 20X.*

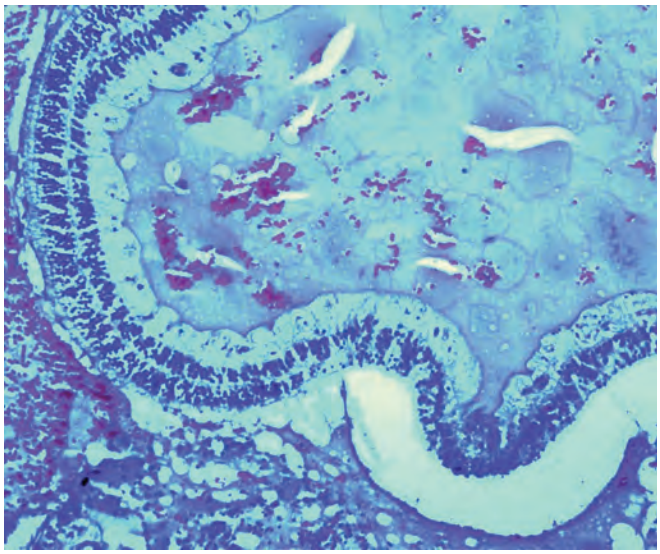
VISUAL REALITY

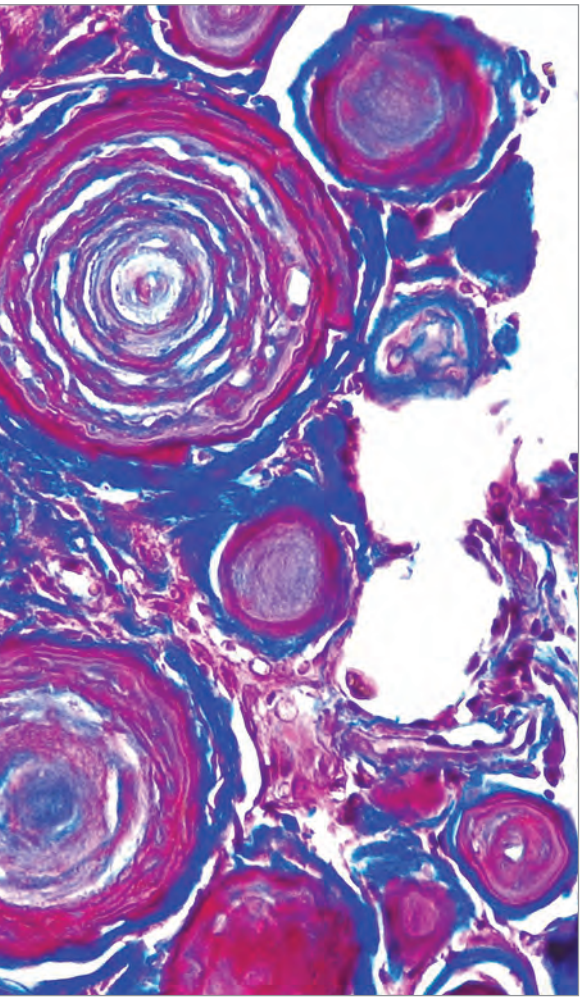
This photograph displays the beauty of the human retina, with many of the unique retinal layers involved in the complex process of sight visible. From top to bottom: retinal ganglion cell layer, inner plexiform layer, inner nuclear layer, outer plexiform layer, outer nuclear layer, outer segments of photoreceptors (rods and cones), retinal pigment epithelium, Bruch's membrane, and choriocapillaris. *H&E stain, 40X.*

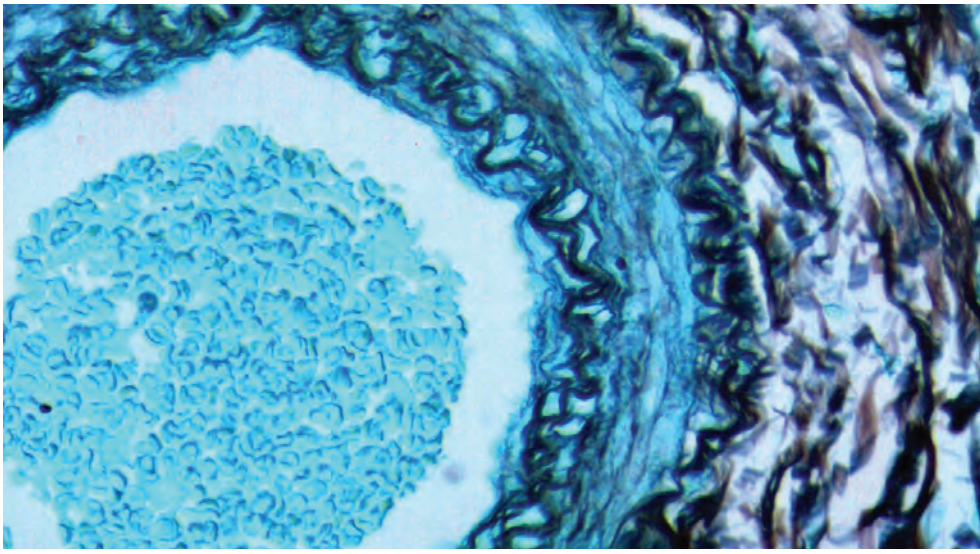
WHIRLS

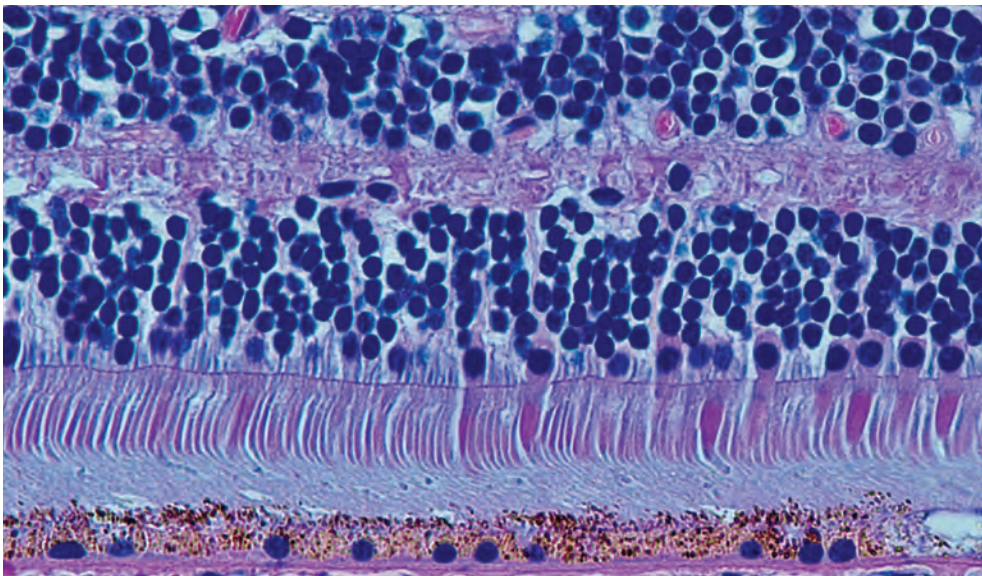
This photograph demonstrates the striking features of an optic nerve sheath meningioma. The whirl-like proliferation of meningothelial cells and calcified psammoma bodies is reminiscent of concentric circular shapes found in the natural world, such as tree rings or geodes. *Masson Trichrome stain, 20X.*











COMMUNITY *Eye Care in* INDIA

Renowned photojournalist and frequent contributor to The Ophthalmologist Terry Cooper visited Aravind in southern India, just before the country was closed to visitors because of the COVID-19 pandemic. He accompanied nurses and a manager at an retinopathy of prematurity (ROP) outreach clinic at a hospital near Madurai.

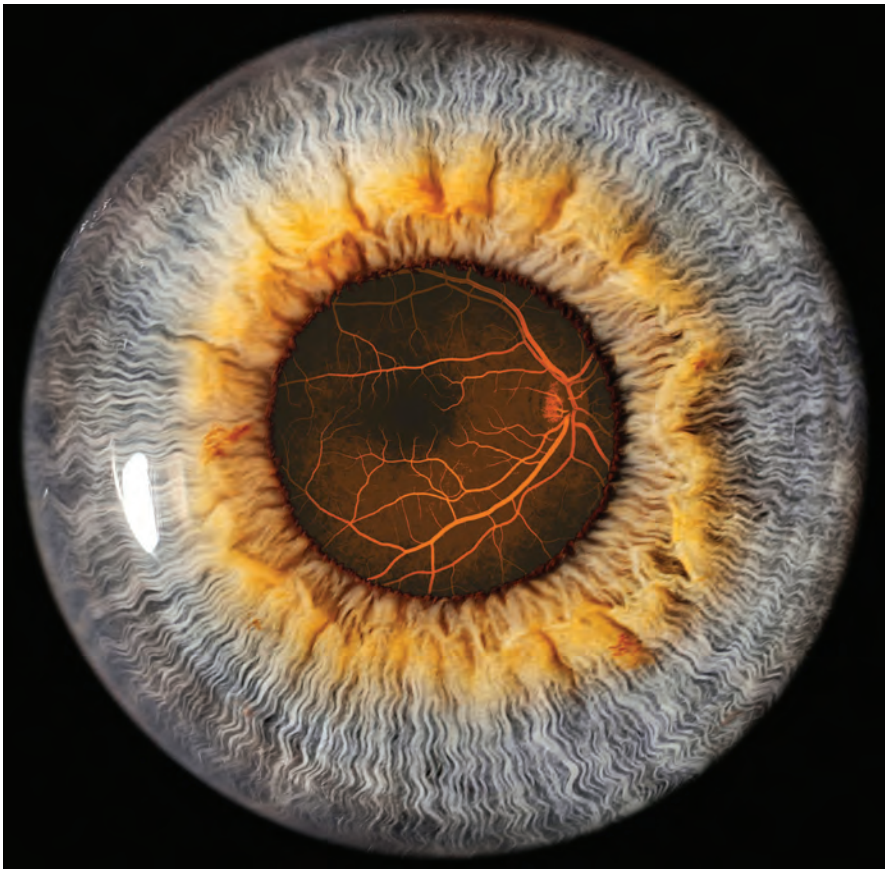
The IRIS KALEIDOSCOPE

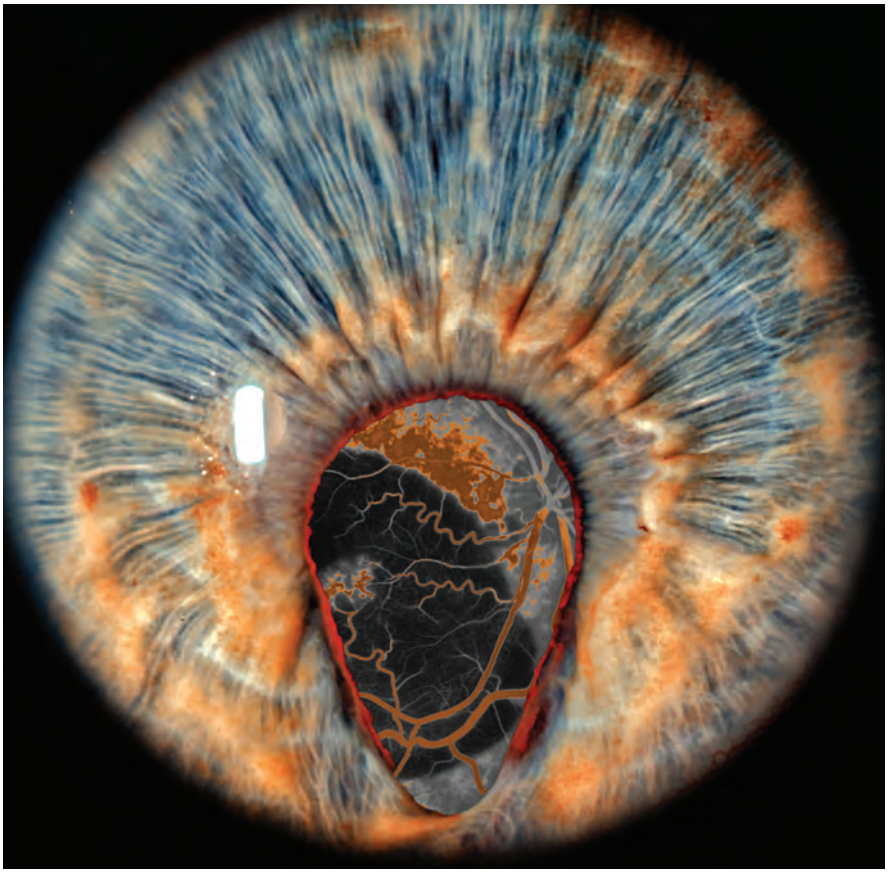
Monika Majchrowicz has been practicing ophthalmology in Bielsko-Biała, Poland, for over 20 years.

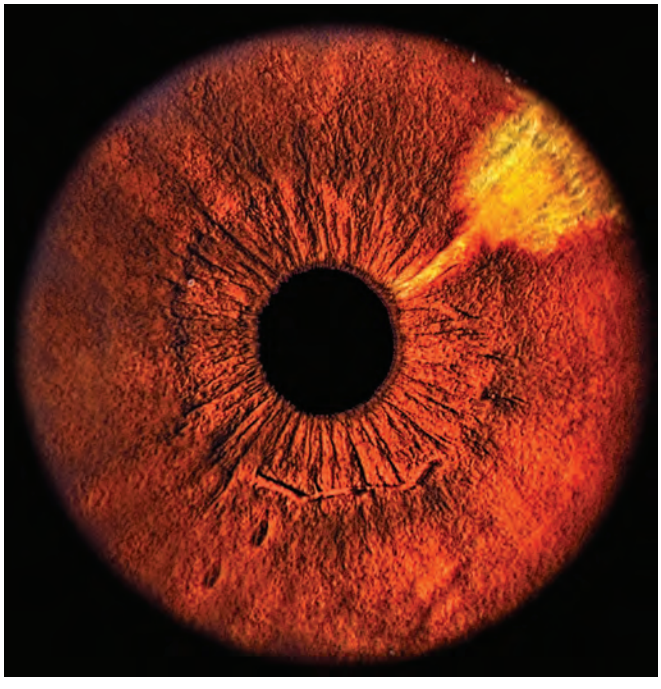
She comments: "I think that the iris is one of the most fascinating tissues found in our body. Its patterns are quite unique and very intricate, with many furrows, crypts, and rings, so it is possible to use our eyes for identification that is even more accurate than fingerprints. Not even identical twins have the same iris patterns. This tissue is exceptional for one more reason: you cannot guess its age. Irises of older people are as beautiful as the young ones.

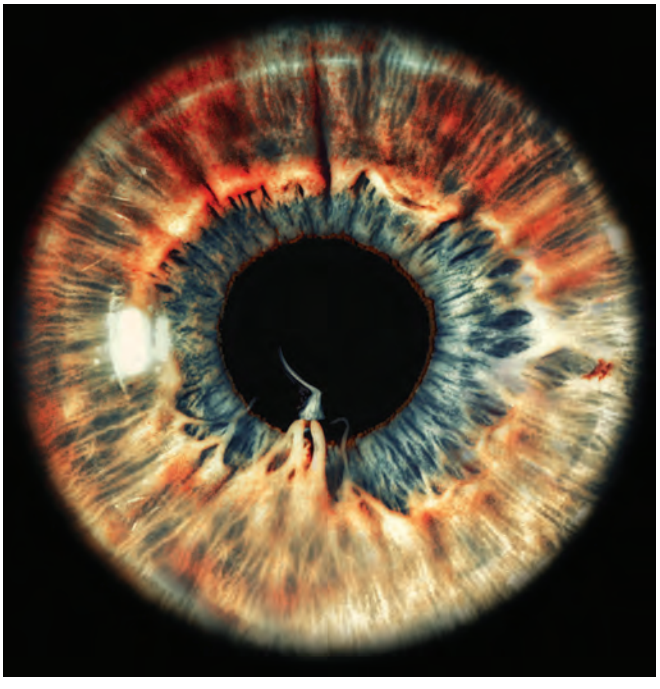
I appreciate the chance to watch this world hidden from the naked eye through the magnification of a slit lamp, and I have started to take photographs of these stunning kaleidoscopic views. In my photos the iris is sometimes isolated from its surroundings and shown within a very plain, minimalistic black frame. Occasionally, I like to play around with a picture and make it seem less realistic. I also like to combine iris images with photos from the fundus camera. Sometimes, it is all about the pattern – I have even used an iris prosthesis in one of my pictures.

My inspiration is Suren Manvelyan, an Armenian photographer who created a gripping animal eye close-up series of images. In these extreme close-ups, it is possible to see details such as the irises' color gradients, textures, patterns, and even tiny blood vessels, causing these eyes to look like alien landscapes."









EXPLORATION *of* EYESCAPES

Ronald Dykes, Managing Partner at Diamatrix, The Woodlands, Texas, USA, received his Bachelor of Fine Arts degree from the University of Connecticut in 1976. He started working in ophthalmology in 1980, following training at Georgetown University in Washington DC. In 2001, he opened Art of the Eye Studio in The Woodlands, in Texas.

Dykes says: "Art of the Eye is a combination of two disciplines I have been involved in: art and ophthalmology. Using this combination, I am creating contemporary images, some of which are abstract, and others representational, but all have one unique voice."

You can see more of his artwork at *www.artoftheeye.com*.

Eyescape: Deepwater Horizon

Red Thread

Psyche

Red Connection

Eye on Stone

The SEAT *of the* SOUL

Jennie Hewitt-Harris has a PhD in Fine Art Practice for her research into the reasons why many people refuse to donate their corneas after death.

Find out more about the project on pages 24-27.

ANYTHING *but the* EYES

AN ART-BASED INVESTIGATION INTO WHY PEOPLE WON'T DONATE THEIR CORNEAS AFTER DEATH

By Jennie Jewitt-Harris, CEO of the Transplant Links charity

Support for organ donation is widespread and the benefits of corneal donation are well-known. There remains, however, a consistent – and significant – proportion of potential donors who refuse corneal donation despite their willingness to donate all other organs (1). In 2019, one in 10 registered donors restricted the organs they would donate. Of these, 68 percent excluded the donation of corneas (2) – four times the number of the next-highest restriction (the heart, which 17 percent preferred not to donate). For some people, the concern over corneal donation is so great that even social and moral pressure to donate cannot overcome it.

This hesitance is often wrongly attributed to religious beliefs or squeamishness, but the real reasons behind it are poorly understood (3). Surveys of potential donors in western countries have revealed some factors that make corneal donation refusal more likely, but a significant number of people are unable to explain why they say no (4).

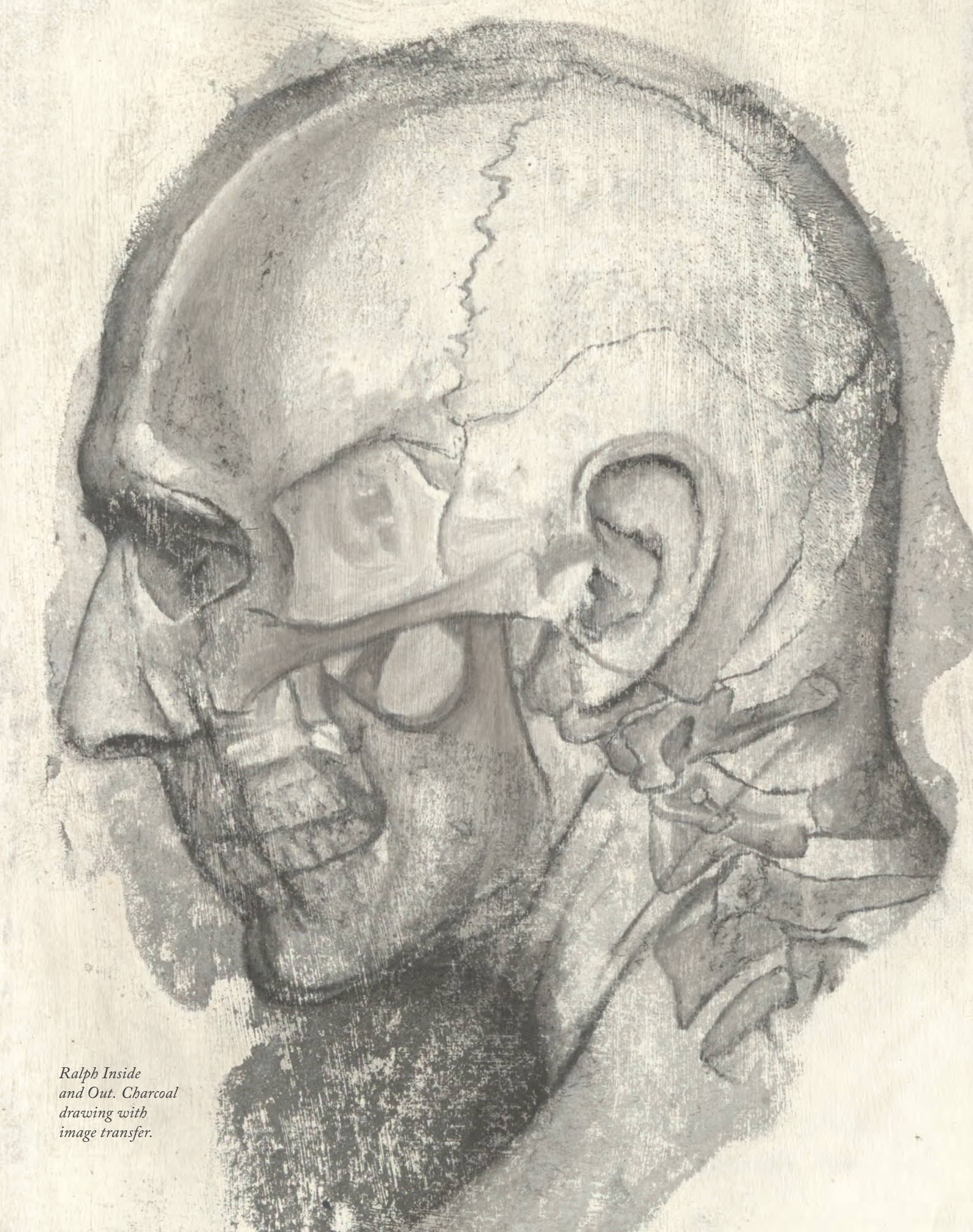
METHOD MEETS ART

A qualitative, grounded-theory approach can play a valuable role in understanding areas that cannot be accessed quantitatively. Art-based research can open up new avenues of inquiry in medicine and interpret phenomena like corneal donation refusal in terms of the meanings people assign to them (5).

The goal of my research into the issue of corneal donation refusal was to understand the concerns that underpin people's unique relationship with the eyes and to provide a new perspective on this internationally recognized phenomenon.

Eye Flower. Collage, charcoal and paint on canvas.


DOGS · TEAS · ICE CREAM
OH, GOLLY!
MOSZKOWSKI



Ralph Inside and Out. Charcoal drawing with image transfer.

I recruited people who have specifically refused to donate their corneas, but are willing to donate all other organs. A semi-structured interview elicited beliefs and metaphors that underpinned concerns. I also used discourse analysis tools, which revealed common themes that were explored using creative artistic practice. I used art as a medium to connect with and embody the feelings of participants – an alternative language for communicating their concerns. Finally, I held follow-up interviews with participants to discuss the emerging artworks and develop them further to connect with people's fears and concerns.

The following themes were revealed across all interviewees: that the physicality of the eyes could not be separated from self and identity; that the eyes were perceived as a personal black-box recorder of a person's life that cannot and must not be shared; that some people equated donating the eyes with the erasure of identity; that the eyes were equivalent to the self and this association continues after death regardless of what happens to the physical body (burial or cremation); that a deep interconnection exists between anatomy and the individual lived experience; and that the eyes carry the past of their owner. These findings refute the "rational" Cartesian model of mind and body separation on which transplantation relies (6). The findings fit more with the phenomenological position of Merleau-Ponty (7), who rejected the Cartesian view to incorporate a more realistic perspective on social and individual reality and regarded perception as the very foundation of human existence.

DISSEMINATING THE FINDINGS

The artworks I created were publicly exhibited and will be further exhibited in 2021. The exhibitions have been an important catalyst for conversation, encouraging people to consider and discuss their desire to donate corneas and to understand the views of those who decline. There is often a clear lack of respect for non-gift-of-life views and donation refusal; it is considered superstitious, selfish, or ignorant to withhold organs. The research participants and many exhibition visitors, on the other hand, expressed feelings of embarrassment and guilt and often kept quiet about their concerns for fear of negative reactions. The debate about donation must acknowledge that non-religious spiritual beliefs need to be respected. These concerns are deeply held and difficult to explain. The desire to push through them by introducing an opt-out system for donation is understandable, but I believe we must understand, uphold, and respect alternative beliefs and wishes. Some people need a more flexible system in which they can opt out of donating certain organs, without having to opt out of donation entirely, to protect their eyes.

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NO PLACE LIKE HOME

The ForeseeHome® AMD Monitoring Program provides a safety net for intermediate AMD patients from the comfort of home, especially if routine eye exams are canceled or postponed

Wet age-related macular degeneration (AMD) is often diagnosed late – unsurprising given that less than a third of patients are able to detect early symptoms themselves (1), but problematic because studies have shown that early detection of wet AMD is critical to maintaining functional vision (≥20/40). Though patients with poor visual acuity at diagnosis regain more letters with anti-VEGF treatment, the majority do not return to that level of vision (2). Patients being treated for wet AMD in one eye are at a higher risk of conversion in the fellow eye (3) and must be frequently monitored– a significant burden when office visits are required.

At the same time, the COVID-19 pandemic has meant that many patients have been reluctant to leave their homes, and routine exams have been canceled or postponed. The upshot? Patients at risk of developing wet AMD have not been receiving the same level of routine care. And with many practices accommodating longer intervals between treatment during the pandemic, conversion in fellow eyes is more likely to go undetected for a longer period. The pandemic has forever changed the way opthalmologists practice, and home-based remote diagnostic solutions that allow them to remotely monitor their patients' disease are becoming invaluable tools for many practices.

One such solution for AMD sufferers and their physicians is the ForeseeHome® AMD Monitoring Program. Designed by Notal Vision, the monitoring device can be prescribed to intermediate AMD patients as part of a remote diagnostic service provided by the Notal Vision Diagnostic Clinic, extending patient management from the clinician's office to patients' homes. In brief, by using automated AI-based alert generation, ForeseeHome helps detect wet AMD at an earlier stage, so treatment can be initiated quicker, minimizing the risk of irreversible visual acuity loss. Put simply, it is a safety net for intermediate AMD sufferers.

The AREDS2-HOME study, sponsored by the National Eye Institute (NEI), demonstrated that 94 percent of patients whose wet AMD was detected using ForeseeHome retained better

NANCY HOLEKAMP, RETINA SPECIALIST FROM PEPOSE VISION INSTITUTE IN CHESTERFIELD, MO, USA, PRESENTS A CASE STUDY OF A PATIENT WHOSE WET AMD WAS DETECTED DURING THE COVID-19 PANDEMIC

One of my patients has been using the ForeseeHome device for several years, and I happened to receive an alert during the COVID-19 pandemic. Although she was asymptomatic, vision had fallen from 20/20 at baseline to 20/25 between March 2013 and April 2020. Despite our general reluctance to subject patients to unnecessary appointments at this difficult time, we knew she had to be seen right away. The OCT showed no definite cystoid macular edema or subretinal fluid, but there was elevation of the RPE inferotemporal to the foveal avascular zone, as well as intraretinal hyper-reflective foci in that area. Although we are currently trying to keep testing to a minimum, I felt a fluorescein angiogram was essential. Sure enough, IVFA showed a very early area of CNV inferotemporal to the fovea. The patient was treated that day with an anti-VEGF injection.

The ForeseeHome program has clear advantages in "normal" times – but right now, amidst the pandemic, it is ideal. We can keep our patients safely monitored at home, but know we can bring them into the office when there is a hint of a problem."

than 20/40 vision, as opposed to 62 percent of patients whose clinicians were only using standard care detection methods, such as the Amsler grid (4). In fact, ForeseeHome usage was deemed so efficacious – patients using the device in the study lost significantly fewer letters at incident neovascularization than with standard care alone – the independent Data Safety and Monitoring Committee decided to stop the trial ahead of schedule.

Preferential hyperacuity perimetry (PHP) lies at the core of ForeseeHome technology, which assesses the central 14 degrees (or approximately 4.2 mm) of the macula (4). Invented by three ophthalmologists (Barak Azmon, Yair Alster, and Omer Rafaeli), PHP is able to detect tiny changes in the central visual field, including metamorphopsia and scotomas.

Once prescribed, patients are instructed to test their eye (or eyes) daily – patient compliance is monitored remotely by the Notal Vision Diagnostic Clinic, an independent diagnostic testing facility and medical service provider of ForeseeHome – and the results are automatically transmitted at the end of each test to the Clinic. In the background, an AI-based classifier identifies changes in visual distortions that may indicate a conversion to wet AMD by continuously comparing test data with a normative database threshold and the patient's own baseline; when a statistically significant change of test patterns is detected, the testing facility alerts the practice, so that they can determine the best course of action. Patient testing data can be accessed by the physician through a secure portal at any time.

The ForeseeHome AMD Monitoring Program is covered by Medicare and billed by Notal Vision Diagnostic Clinic as the healthcare provider. The clinic provides all the necessary disease education, device setup and support, patient engagement, and compliance monitoring needed by practices that refer their patients for ForeseeHome.

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Extended Presence

What role has Orbis' flagship telemedicine platform Cybersight played in the COVID-19 pandemic?

By Daniel E. Neely

What has the COVID-19 pandemic been like for you and your patients?

In the US, during the worst outbreak of COVID-19, we were only seeing emergency patients – at most 10 percent of our usual schedules – and we suspended all surgical procedures. It later picked up to around 50 percent of our usual workload. During those strict lockdown weeks, we tried to conduct as many virtual appointments as we could. At Orbis, we are used to regularly employing innovative ways of communication, but this has been quite a new experience for us.

In your experience, how widespread was telemedicine in eye care before the pandemic?

Some settings offered this option, but it wasn't common – more of a fringe service. During the pandemic, physicians in many places around the world were forced to conduct direct telemedicine consults. Just as children and university students got used to remote learning, doctors and patients have grown accustomed to remote care. In terms of telemedicine use, I can't see us ever going back to where we were at the beginning of 2020. Telehealth and remote education now have a completely different acceptance level.

When I first started doing virtual appointments, we tried to replicate an office visit, going through the same processes and getting the same information we would in person – but we quickly found that this approach was not practical. The value of a virtual visit is the conversation you have with the patient, answering their questions, reassuring them. Most of the time, you can arrive at a diagnosis without a physical examination.

Orbis has used telemedicine for a long time; what did that look like?

We have been successfully applying telemedicine solutions since 1998, but not between the patient and the physician. Rather, they were between two physicians, one (based in an industrialized country) acting as a mentor, the other (in a developing country) as a mentee. Sustainability of eye care is crucial to Orbis. When we use our Flying Eye Hospital, we don't just go to a location and perform a lot of surgical procedures. The goal is to pick cases that we can work on with local doctors and that they can perform on other patients once we are gone. Cybersight, the telemedicine platform we use, is just an extension of that. Its creator, Eugene Helveston, one of Orbis' first volunteer faculty members, described it as "extended presence." It

Rebecca Cronin, Chief Executive of Orbis UK, on the impact the COVID-19 pandemic has had on projects worldwide

The pandemic has inevitably had an impact on our programs around the world and we are working closely with our in-country partners and local leaders to carefully monitor the COVID-19 situation as it evolves. Of course, the health and safety of staff, volunteers, partners, and the people we train and treat remains our highest priority. Our programs are following the direction of the WHO and continuing to provide essential and emergency eye care wherever possible.

We've made the difficult decision to ground the Orbis Flying Eye Hospital for the remainder of 2020. Despite this setback, we're finding ways to work effectively with the local eye health professionals we support, equipping them with the resources they need to save and restore vision in their communities. Our incredible partners and volunteers are committed to Orbis' sight-saving mission, and that means providing care in urgent cases – even in the midst of a pandemic.

One way we can aid the safe, socially responsible diagnosis and treatment of eye conditions is through Cybersight. It is proving to be a powerful tool and a lifeline for our hospital partners in low- and middle-income countries.

Much will need to be done to address the backlogs – both of people requiring sight-saving treatments and of those in need of screening to identify their existing eye conditions. Healthcare workers around the world are working tirelessly to fight this pandemic. This includes our incredible expert medical staff and volunteers, many of whom are now working on the frontline within the NHS in the UK. We are proud of, and inspired by, the dedication our local partners, volunteers, and staff show to their work and their patients, and we are unwavering in our support of them.

allows us to meet at the same time, no matter where we are in the world.

What has changed for Cybersight since March this year?

Since the pandemic began, we have experienced record growth. Before March, we had between 600 and 700 new users a month. In March, when lockdowns started affecting various countries, this number doubled – and in April, the number of new registered users was around 3,400. Overall, Cybersight has had over 28,000 users from all over the world.

Our webinars before March attracted anywhere from 50 to 200 participants. Fast forward to May and, for each of the last three webinars we did, we had well over 1,000 participants. My last webinar attracted around 1,200 participants from 105 countries. Our webinars are usually in the form of hour-long lectures. After that hour, I offered to take questions; two hours later, I was still answering hundreds of questions from people around the world. This tells me how much such a service is needed, and it shows us that this really is a big moment for telemedicine. It's like a switch has suddenly been flipped.

How long have you been using the platform yourself and how has it changed in that time?

I trained under Gene Helveston. I was his fellow in postgraduate training in 1998, when he first developed Cybersight after his trip to Cuba, and I have been using it ever since.

To give you a frame of reference on the state of technology back then, I received my first email only a year earlier, in 1997. I really wasn't convinced that this was the future – I wasn't sure why I needed an email account. As it turned out, the initial Cybersight consults

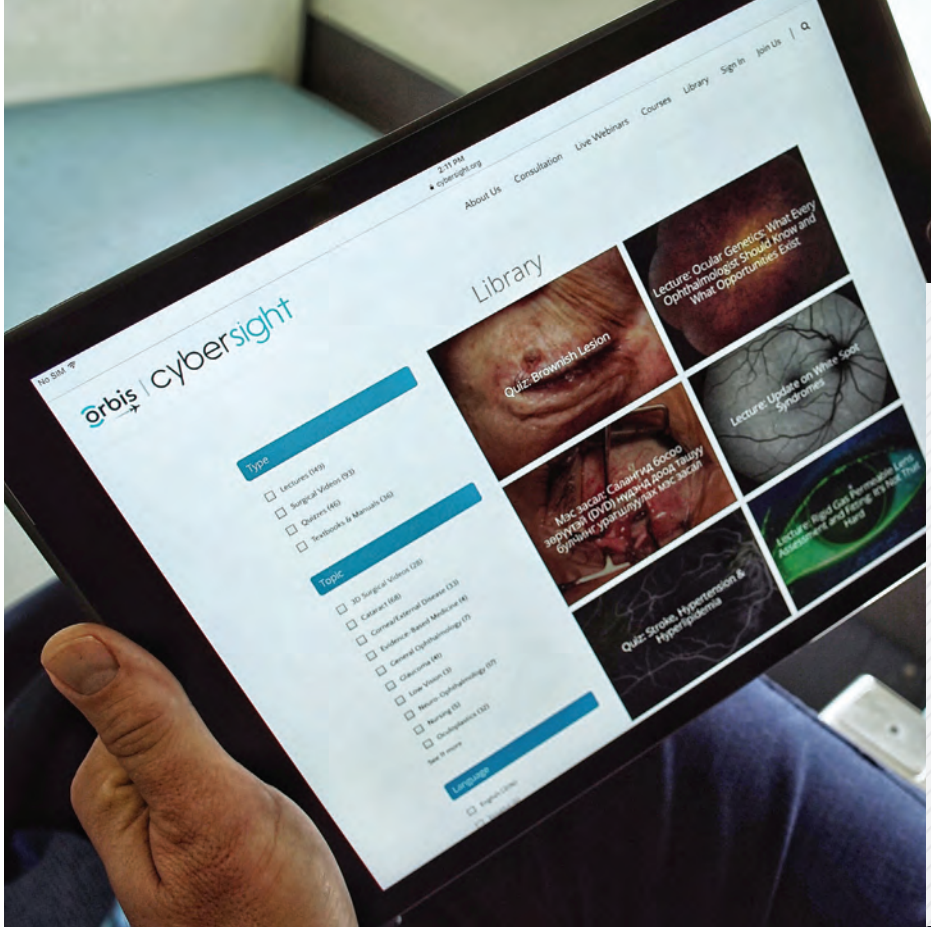
were simply text emails! Eventually, Helveston was able to raise money for basic programming to create a web-based platform, which became the first phase of Cybersight that was donated to Orbis. For the next decade, it stayed in the format of three or four text boxes with some notifications. Afterwards, we got more financial support to get the platform to its current state: a consult service that looks a bit like an electronic medical record. The big changes have been the features we have incorporated into the platform.

Which features do you see as the most useful and innovative?

There is now an artificial intelligence feature, which can assess fundus photographs for signs of diabetic retinopathy, detect optic nerve anomalies, or estimate the cup-to-disc ratio. For the last few months, Cybersight has been employing a full-time AI programmer. Right now, AI is still in its infancy and it's more of a novelty than it is a game changer, but eventually it will be everywhere in eye care. We need to be ready for when it really takes off – that is why we keep developing these solutions now.

We're also working on incorporating AI into our digital resource library – hopefully directing doctors submitting a consult to all our existing resources on a particular topic or to similar cases that have already been assessed. The Cybersight library also has all the surgical videos that we record on the Flying Eye Hospital, narrated by the surgeon, with subtitles in different languages, and featuring answered questions from viewers.

As I mentioned before, we have a catalog of webinars given by international experts streamed simultaneously in all ocular subspecialties. These webinars come with subtitles, and we have had attendees from every country in the



Orbis and Cybersight

Orbis, the global charity fighting for avoidable blindness, aims to train local teams to deliver eye care to their communities. Cybersight is used by Orbis as the online training and mentorship service, linking eye health professionals worldwide, and helping ophthalmologists in developing countries with access to specialist courses, webinars, and resources.

cybersight.org

world. If we identify any gaps in this webinar catalog, we recruit a new member of faculty to give a lecture on that topic.

What are the pros and cons of learning remotely?

Remote education is a double-edged sword. Faculty don't have to travel, so they are more likely to participate. For us, this opens up a much larger potential pool of available lecturers. However, participants don't get to experience the special connection they would if they spent time together in person. Often, if you travel to a different location and work with other doctors, you become friends for life. This connection is important, especially when people are receiving advice about performing surgical procedures or dealing with patients. Mentees have to be able to trust you and get a sense of who you are – not just a talking head on a laptop.

On the other hand, participant anonymity can be an advantage for remote learning settings. If I gave a lecture in person, very few people would raise their hands and ask questions. A remote environment gives them the courage to ask the questions they want. After my last webinar, I had 296 questions – that would never happen in a lecture theater!

What features would you like to see the platform acquire in the future?

As I mentioned earlier, AI will become ubiquitous, and so will live surgical teaching, which we've only done a handful of times. We need an efficient system to do that from anywhere in the world. We also face some language barriers; we have faculty that speak various languages, but whereas we have thousands of users in India, we may only have hundreds of users in China because the language barrier is too intense. That is why we need improved, simultaneous, automated language translation. I would also like to see a regional component to the system, where mentors give advice to mentees from the same country or region, using our infrastructure, with no language barriers. This would open our service to many physicians who do not currently benefit from it.

It is estimated that the global number of people affected by blindness will triple by 2050 (1). As ophthalmologists, we cannot triple all our efforts in the next 30 years, but we can easily ramp up and triple our digital activities – we could scale them up by a factor of 100! The doctors to whom we give consultations are responsible for their patients and we can give them the tools to make the right decisions.

Daniel E. Neely is a pediatric ophthalmologist at the Midwest Eye Institute and Professor of Ophthalmology at Indiana University School of Medicine, Indianapolis, Indiana, USA.

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Channeling Your Creativity

A stepwise approach to getting your innovation off the ground

By Salman Waqar

Every innovation should be preceded by a need. As with most surgeons, I always contemplate the wants and needs of my patients: how can their safety be enhanced? How can we make them more comfortable? Can their surgery be performed more efficiently or effectively? Such questions have motivated me to embark upon journeys of creativity, invention, and – to overcome inevitable hurdles – learning opportunities. Ultimately (or hopefully!), no matter how rocky the road, the destination is an innovation that fulfils the original need.

I've had the good fortune to be involved in the development of two innovations: the Waqar suture removal forceps and the intravitreal (IVT) injection guide (Malosa single use instruments, BVI). And I've also had the good fortune to be in a supportive workplace and to have a framework around me that has enabled me to divert my time and energy. But this isn't the case for everyone; constraints or a lack of encouragement can stop many in their tracks. Here, I hope to encourage would-be innovators to bring their ideas to life by providing my own personal guide to getting an innovation off the ground.

The journey from idea to market

Step 1: The birth of an idea

First, put your idea down on paper; sketch out the skeleton, including the main concepts and features. Sign and date it; this will act as proof of originality if issues of patents or intellectual property (IP) arise further down the line.

Step 2: Understand who holds the IP rights

As I am an employee of the National Health Service (NHS) in the UK, my employer holds the IP rights to any idea relating to my routine work. So, in establishing IP ownership, your hospital must be your first point of contact. This process may vary in different countries, so it is useful to know what the unique arrangements are in your place of work. Developing good working relationships helps greatly at this stage.

Step 3: Keep it to yourself

Don't disclose your idea or you may affect subsequent patent applications.

Step 4: Call in the help!

If your workplace permits, get in contact with the local innovation team – which may include someone with an engineering or IP background – as well as the research and development (R&D) team, to gain their insight. For me, this is the NHS innovation panel and pathway team, and a regional pathway, which is run independently as a collaboration between local R&D departments. This framework was able to provide much needed expertise in all areas ranging from computer-aided designs (CAD), 3D printing and IP, to negotiating contracts with commercial companies.

Step 5: Be patient

Patience is key during the planning and modeling phase; our in-house experts made several different models of the IVT injection guide before achieving the final version.

Step 6: Find a commercial partner

It is essential to find a supportive commercial partner to manufacture, market, and distribute your product – for me, that was BVI. The right commercial team will fully understand the nuances of every stage of the development process, as well the legal aspects, such as non-disclosure agreements and IP, and they will propose how your product can be cost-effectively manufactured to scale.

"I hope to encourage would-be innovators to bring their ideas to life by providing my own personal guide to getting an innovation off the ground."

"I can't emphasize enough the importance of having a supportive and informative team around to guide you."

Bringing ideas to life

The Waqar suture removal forceps (see Figure 1) were created to ease the removal of corneal sutures and to improve patient safety. Instead of the traditional two-step technique – using a long 23- or 25-gauge needle with separate forceps, which can pose safety issues in the hands of inexperienced surgeons or nurse practitioners – the new instrument eliminates the sharp, long needle, making suture removal a one-step process.

Patient safety and comfort were also at the forefront of my thinking in designing the IVT injection guide (in collaboration with Plymouth and Torbay NHS innovation panels; see Figure 2). The guide was created to facilitate the fast, safe, and precise delivery of an IVT injection.

With the prevalence of retinal disease continuously increasing, the growing volume of IVT injections is placing substantial pressure on medical retina departments. In short, the quicker IVT injections and other services can be delivered without compromising safety or quality, the better. The traditional way to deliver an IVT injection involves applying a lid speculum (which can be quite uncomfortable), and a surgical drape across the patient's face (which can feel claustrophobic). Finally, a caliper is used to measure the site of the injection. The idea was to create an instrument that would combine these three steps, while controlling position, depth, and the angle of injection to improve efficiency and increase surgical throughput.

The guide consists of a curved, triangular base plate, which follows the natural contour of the eye, and three studs at each corner, which ensure stabilization. The cylindrical chamber adjacent to the lash guard allows the injection to be delivered at the precise location and depth of the eye, avoiding the risk of retinal damage. All these features were given a great deal of consideration along the developmental pathway, but getting them finalized did not come without challenges...

Not plain sailing

For any clinician, taking an idea further can be daunting and difficult. The key is to know what resources to use. As I mentioned earlier, I can't emphasize enough the importance of having a supportive and informative team around to guide you; it will make any difficulties that arise easier to overcome.

One big challenge for me was simply finding time. As a clinician, time is already in short supply; work, family life, and other commitments leave little room for innovation. You really need to rely on your drive and passion.

You must also prepare to face skepticism. During the development of both the Waqar suture removal forceps and the IVT injection guide, many clinicians were skeptical about their effectiveness. To date, we have published

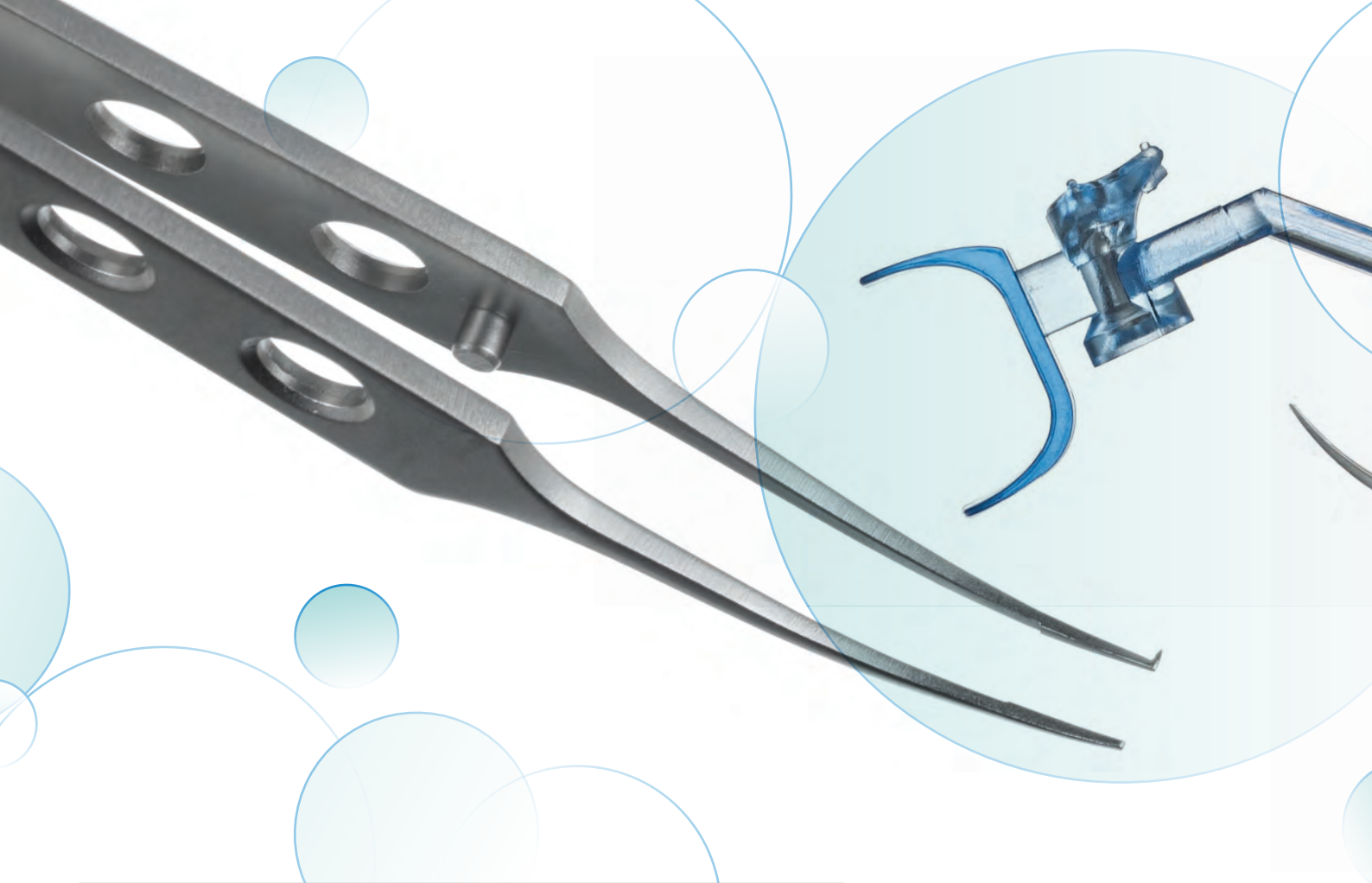

Figure 1. Waqar suture removal forceps. The bespoke tip at the end of the forceps allows the suture to be released and cut in one swift motion, facilitating efficient removal (patent pending).

Figure 2. Intravitreal injection guide, consisting of a polycarbonate lash guard with stainless-steel swage guide tube, triangular base plate with three stabilizing studs, 39 mm, 45 degree-angled wishbone handle.

evidence that demonstrates the safety and efficacy of the IVT injection guide (1). In this paper, we presented results from two sites (the first comparing outcomes in 50 patients, 25 of whom received an IVT injection with the guide and 25 without; the second focused on retrospective notes evaluation of 60 patients injected with the device). No adverse events were noted, and the device appears to be well tolerated by patients. Use of the guide did not result in a statistically significant increase in pain (p value >0.05), but the mean score (on a unidimensional numerical rating scale) was noted to be slightly better. All patients gave very positive, informal feedback.

We also have anecdotal evidence of efficiency benefits from nurse practitioners in Plymouth, UK, where they report a higher throughput of patients when using the guide to deliver an injection compared with the traditional method of delivery. We are now doing a time and motion study to objectively quantify this and expect more evidence in the next year or so.

The surgeon knows best

To conclude, I'd like to say how important I think it is for innovations to be driven by surgeons. Clinical experience is key; it is only the surgeon who knows what works, what doesn't, and what is most likely to improve the lives of their patients.

"Clinical experience is key; it is only the surgeon who knows what works, what doesn't, and what is most likely to improve the lives of their patients."

The short version for budding innovators: be motivated from the start and maintain the momentum. Set aside time and be realistic about the amount of time required. Don't cut corners; go through each step of the development process to improve your chances of developing a valid end product. And don't forget to have fun!

Salman Waqar is a consultant ophthalmic surgeon at the Royal Eye Infirmary in Plymouth, UK.
He has consulted with BVI on instrument development and worked with Glaukos on educational activities.

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The Future of OSD?

The technologies and treatments set to revolutionize the way we approach ocular surface disease

By Preeya Gupta

Ocular surface disease (OSD) is more widespread than many clinicians once thought. Recent studies have shown that the majority of patients presenting for cataract surgery have ocular signs of dry eye or Meibomian gland dysfunction (MGD), regardless of whether they report symptoms (1, 2). My colleagues and I have demonstrated that signs of MGD, once thought to be a condition limited to postmenopausal women, are common even in children (3). Although we are fortunate to have a wide array of treatments for OSD, including artificial lubricants, topical anti-inflammatory drops, thermal pulsation, and punctal occlusion, many patients get insufficient relief from these approaches. There are a number of new and pipeline treatments designed to address the gaps in treatment.

New cyclosporine formulation

In recent years, we have seen the development of several new higher-concentration formulations of cyclosporine. The only FDA-approved therapy so far is Cequa (Sun Pharma), which has nearly double the concentration of cyclosporine (0.09%) compared with the established drug, Restasis (cyclosporine 0.05% Allergan). To me, what is even more important than the concentration is Cequa's novel nanomicellar formulation, which likely aids absorption and tissue penetration by improving the drug's bioavailability. As a result, improvements in Schirmer scores and corneal staining were seen as early as one to three months in Phase III clinical trials (4), which is more rapid than we have come to expect from topical cyclosporine.

Safer steroids

We can also expect to see a new topical loteprednol formulation on the market soon. Positive results were reported from the Phase III STRIDE-3 trial of KPI-121 (loteprednol 0.25%, Eysuvis, Kala Pharmaceuticals) and the company has just submitted a new drug application for this drug with the FDA. Patients treated with the low-dose steroid had improvements in ocular discomfort severity and conjunctival

"In recent years, we have seen the development of several new higher concentration formulations of cyclosporine."

hyperemia. Here again, the formulation – a mucous-penetrating particle drug delivery technology meant to enhance delivery – may play an important role. I would expect to use this new drug to treat patients with episodic flares of dry eye, for whom we don't currently have good options. I'm reluctant to give these patients a 15-ml bottle of prednisolone due to the potential for misuse, whereas loteprednol has an excellent safety profile.

Autologous serum made easy

Cornea specialists have long relied on autologous serum eye drops (ASEDs) for highly symptomatic dry eye patients and those with significant staining or poor epithelial healing. Like natural tears, serum contains many replenishing growth factors that are not available in any other dry eye treatment modality (See Table 1) (5). However, the rate-limiting factor preventing wider adoption of ASEDs has been the difficulty of obtaining them, especially for anyone outside of a major city or research university. Patients had to get their blood drawn, then work with the physician to deliver the blood to a compounding pharmacy able to produce the serum.

In recent years, a company called Vital Tears has greatly simplified the process for both doctors and patients, with faster turnaround and lower cost. Vital Tears collaborates with a large network of labs across the country and centralizes preparation and shipping of

"Although we are fortunate to have a wide array of treatments for OSD, many patients get insufficient relief from these approaches."

	Tears	Serum
pH	7.4	7.4
Osmolality	298 ± 10	296
Growth factors		
Epidermal growth factor (ng/ml)	0.2 – 3.0	0.5
Transforming growth factor β (ng/ml)	2-10	6-33
Vitamins and antibodies		
Surface immunoglobulin (µg /ml)	1190 ± 904	2
Vitamin A (mg/ml)	0.02	46
Proteins and enzymes		
Fibronectin (µg/ml)	21	205
Lysozyme (mg/ml)	1.4 ± 0.2	6

Table 1. Human tears and serum share similar properties. Source: Based on Geerling et al. (5).

the drops. Patients can now get their blood drawn in their home town (or sometimes even in their own home) and then Vital Tears takes care of the rest. This makes it much easier to prescribe ASEDs for our patients with moderate to severe dry eye. I've also found them to be invaluable for patients with multiple sensitivities and allergies who can't tolerate preservatives or other components in commercial drops.

Nasal neurostimulation

Stimulation of the trigeminal nerve through the nose is a novel treatment pathway that was first introduced by Allergan, with its TrueTear device. The device is placed in the intranasal cavity to deliver a mild electric current that stimulates the trigeminal nerve (CN V), which is responsible for innervation of the lacrimal functional unit. In addition to triggering lacrimation through the efferent pathway, it also stimulates the Meibomian glands and goblet cells to produce complete, physiological tears (6, 7). However, accurate insertion and positioning can be challenging, limiting effective use of the device. That barrier may be overcome by a nasal spray technology currently in the pipeline (OC-01, Oyster Point). This preservative-free spray contains a nicotinic acetylcholine receptor (nAChR) agonist to stimulate the trigeminal nerve parasympathetic pathway (Figure 1). It was just announced that primary and secondary endpoints were successfully met in the drug's Phase III clinical trial, ONSET 2, so we can expect to see a new drug application submitted later this year. The novel mechanism of action and

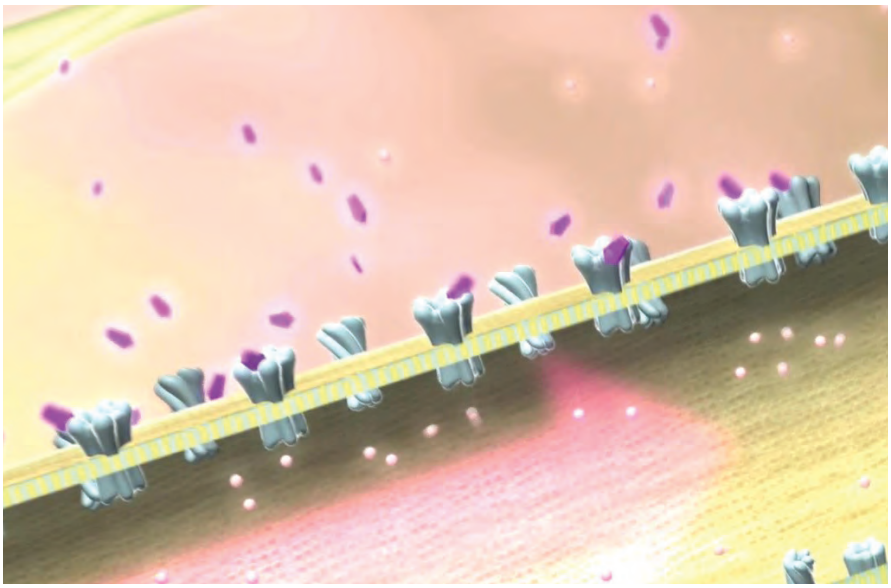

Figure 1. The active drug in the OC-01 nasal spray binds to nicotinic acetylcholine receptors (nAChR) to activate the trigeminal parasympathetic pathway and stimulate natural tear film production.

rapid onset could make OC-01 a nice complement to existing drug options.

Demodex blepharitis

A common cause of blepharitis is the Demodex folliculorum mite, which has proved challenging to treat. Tarsus Pharmaceutical is developing a preserved, multi-dose topical drop with a new molecule (TP-03) that – when used twice daily for six weeks – results in the paralysis and death of the Demodex mites. A Phase II study revealed positive results in decreasing both the mite load and the collarettes or cylindrical dandruff that are pathognomic for Demodex blepharitis. A Phase III trial is launching soon and Phase II trials for MGD and rosacea are underway.

Treatments for corneal pain

Further out in the pipeline, but certainly on my wish list, are treatments for corneal pain. There are a number of new molecules under investigation for pain caused by severe dry eye or neuropathic conditions masquerading as dry eye. For example, Neuroptika, a company spun off by Senju Pharmacuetical, has a new small-molecule topical drug, NRO-1.

It releases glial cell-derived neurotrophic factor (GDNF) to protect and regenerate corneal nerves. Researchers hope it will improve corneal sensitivity, lacrimation, and corneal epithelial health in patients with dry eye and other conditions. It has shown some promising results in animal studies and is currently in Phase II human clinical trials. At the University of Illinois at Chicago, researchers are studying an enzyme-based treatment for severe dry eye. In this approach, drops containing recombinant deoxyribonuclease (DNase) are used to break up pro-inflammatory DNA material on the ocular surface. A Phase I/II study showed the treatment to be effective in improving corneal damage and reducing corneal pain in patients with Sjögren's syndrome or graft-vs-host disease (8).

It's exciting to see so many new avenues opening up in dry eye treatment, from unique formulations of older drugs to innovations in drug delivery and logistics – even new mechanisms of action altogether.

Preeya Gupta is an Associate Professor of Ophthalmology at Duke University School of Medicine, Cornea and Refractive Surgery Division, and Clinical Director at the Duke Eye Center of Page Road in Durham, NC, USA. She is a consultant to Allergan, Johnson & Johnson Vision, Kala, and Oyster Point.

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The Epidemic Behind the Pandemic

Tackling rapid acceleration of progressive childhood myopia following a period of increased screen use and reduced outdoor activity

By Sean Ianchulev

In recent conversations on the impact of COVID-19 on our patients' lives, one interesting aspect keeps arising. In the middle of the pandemic, there's an undercurrent of an epidemic of progressive myopia, made worse by the necessary implementation of lockdown measures to curb the spread of COVID-19.

There are two well-established reasons why progressive myopia has turned into a worldwide epidemic over the last two or three decades: one, children spend much less time outdoors than they used to, and two, they spend a lot of time looking at the near point on devices such as smartphones and tablets (1, 2).

During the pandemic, especially in the weeks and months of strict lockdown measures, remote learning has been the reality for many children and young adults – a situation that may continue for a long time. As a result, young people spend even longer hours indoors, in front of computer and tablet screens, sacrificing both outdoor time and time spent looking at far points such as a blackboard or whiteboard in a classroom. Meanwhile, studies show that a single hour of outdoor activity significantly reduces the risk of progressive myopia by as much as 45 percent (1, 3, 4). Children who use electronic devices for longer than six hours a day and have less than three hours of outdoor activity per week have twice the risk of developing myopia (2). All this means that when we return to normal – or the "new normal" – we may see a dramatic acceleration of myopia.

Can technology help?

Innovative technologies are partly responsible for the growing incidence of progressive myopia, but can they also help prevent the progression? The impetus behind dealing with progressive myopia has been steadily growing.

Significant myopia can result in complications such as retinal detachment, which can lead to sight loss, so it is crucial to address it early and in the right way.

In 2017, the American Academy of Ophthalmology confirmed that level one evidence supports the use of atropine in small doses for preventing myopic progression (5). Evidence shows that what is needed to halt progression of the disease is precise delivery of small doses of atropine to the ocular surface, getting into the eye before the patient can blink. Both children and adults have problems with accurate delivery of eye drops and, in the case of atropine, it is important to minimize unnecessary exposure to larger quantities of the drug than needed. Eyenovia's microdosing technology – micro-array print – not only delivers a precise dose of atropine, but also features compliance monitoring built into the electronic device, which communicates with a smartphone. This means that the patient, their family, and the physician can accurately monitor the amount of atropine that has been applied.

"The impetus behind dealing with progressive myopia has been steadily growing."

Giving evidence

Following large, collaborative studies on the therapeutic impact of atropine, such as ATOM 1 and ATOM 2 (6, 7) and LAMP (8), we initiated a Phase III randomized, double-masked clinical trial called CHAPERONE in 2019. The trial was set to enroll over 400 children aged between three and 12;

unfortunately, the pandemic has delayed our progress, but we hope to get it back on track as soon as possible. In the meantime, we are following up with our clinical partners virtually.

So far, our research has focused on the age group between three and 12 years old. Progressive myopia continues until the 20s, when the growth of the eyeball stops and the condition stabilizes (so we may yet conduct additional studies in different age groups), but we should aim to catch the progression as early as possible, and ideally before the age of 12-13.

In the CHAPERONE trial, we will follow children's results with atropine for a number of years, until their eyes stabilize and they are no longer in the risk zone. Ahead of approval, the FDA will require a long duration of observation, so the primary endpoint for this study is three years from the last patient we enroll (plus an additional year of follow-up and observation), which makes it one of the longer follow-ups in the field.

"Over the next few years, we will see a huge change in therapeutic approaches to progressive myopia, and the post-COVID-19 epidemic may well contribute to this."

The FDA needs solid data but, outside the US, atropine is becoming the standard of care for progressive myopia. In some Asian countries, such as China or Thailand, around 80 percent of children now report having progressive myopia – and, in some areas, an equal percentage regularly apply eye drops (a habit similar to brushing their teeth every night). The FDA is well aware of that and has been very helpful, allowing us to use collaborative group trials such as ATOM and LAMP in lieu of one of our registration studies, based on data available so far. This means that we are only doing one registration trial.

Myopia status quo needs to change

All evidence shows that progressive childhood myopia is a huge unmet need. Parents are not waiting for official approvals – they are taking charge now, based on their physicians' experience of using therapeutics and on available clinical trial data. A lot of clinicians are using compounded atropine drops from pharmacies, although they don't know whether the drug gives their patients a 20 or 50 percent improvement because it is not monitored. Other solutions include using orthokeratology or products such as the recently approved MiSight 1 day contact lens from CooperVision.

I think that, over the next few years, we will see a huge change in therapeutic approaches to progressive myopia, and the post-COVID-19 epidemic may well contribute to this. I can see many pharmacologic and non-pharmacologic options available on the market in the near future that will work synergistically to tackle this problem.

Sean Ianchulev is Professor of Ophthalmology at the New York Eye and Ear Infirmary of Mount Sinai, New York, USA, and President and CEO of Eyenovia, Inc.

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A Lifelong Fascination

Sitting Down With… Antonia Joussen,
Professor and Chair, Department of Ophthalmology, Charité Universitätsmedizin Berlin, Germany

If you weren't an ophthalmologist, what would you do?

I would have loved to study music – I played the organ and the piano when I was young. If I were to choose another medical specialty, it would have been oncology. When I had my final year rotations in an oncology ward in the 1990s, I was very excited to see how stem cell transplantations were implemented into clinical practice. I actually learned a lot for my basic research, which still looks at macrophages and microglia cells.

So why did you choose ophthalmology?

I was introduced to the specialty very early; my father was an ophthalmologist! He was training with Gerd Meyer-Schwickerath in Essen, Germany, when I was born. Later, he set up a private practice, and we visited him almost every day. Consequently, I spent many hours in an ophthalmic practice as a child, so ophthalmology became a natural thing to me.

During medical school, I saw the first phacoemulsification procedures performed by Hans-Reinhard Koch in Bad Godesberg. It was thrilling to observe such a fast and efficient way to restore a patient's vision – and improve their quality of life. Later, I was fascinated with vitreoretinal surgery when working with Bernd Kirchhof in Cologne. I have never regretted following in his footsteps. Ophthalmology is my life-long fascination, as is vascular research. I'd like to encourage my colleagues at the start of their careers to "lean in" – keep their focus on what excites them the most, and stick to it.

Who would you list as your most important mentors?

In Heidelberg, I started my PhD thesis with Friedrich Kruse, a corneal specialist, who had just returned from a fellowship at Bascom Palmer in Florida, USA. We worked on corneal neovascularization. When I did my own fellowship in Boston, I had the pleasure of working with Anthony P. Adamis in Judah Folkman's lab at the Boston Children's Hospital. It was the most productive time in my life.

"I'd like to encourage my colleagues at the start of their careers to 'lean in' – keep their focus on what excites them the most, and stick to it."

What made you choose retina and ocular oncology as your sub-specialties?

I already mentioned the impact of Bernd Kirchhof at the University of Cologne on my interests in vitreoretinal surgery. Later, I was fortunate to receive Norbert Bornfeld's (Essen University Hospital) friendship and guidance in ocular oncology. When I came to Berlin, my focus was vitreoretinal surgery. I was given the task of merging two ophthalmology departments, one belonging to the former Freie University, and the other to Humboldt University. Under my predecessor, the department of Freie University had become one of the two specialist ocular oncology departments in Germany.

I have big hopes for our field of expertise. My ultimate dream for this field is the discovery of a more specific molecular approach for treating choroidal melanoma. Right now, my team is working on systemic medicine approaches to metabolic eye disease (diabetic retinopathy) to gain knowledge from combining molecular, functional, and structural measures.

Why has research been such an important part of your career?

Without basic research there would never be any improvement in the understanding of diseases. The knowledge that we gained in the first rodent experiments with anti-VEGF or angiopoietins is now helping millions of patients with vascular diseases of the retina or age-related macular degeneration.

What is your proudest achievement?

It has to be the combined successes of my former and current team members – in Berlin and formerly in the lab in Cologne, and the Department of Ophthalmology in Düsseldorf. Ten of my coworkers have already finished their Habilitation – a comprehensive thesis required to become a faculty member – while others have gained good independent positions elsewhere. It is fun working with them in all the diverse areas of ophthalmology.

What about your own clinical practice?

In ocular oncology you always remember patients with the most difficult manifestations of the disease, such as tumor endoresections, when we can maintain eye-sight and even in some patients maintain some visual acuity. One of my particular interests is in retinal vascular disease, so I treat a lot of children with Coats' disease and familial exudative vitreoretinopathy (FEVR); it is a great pleasure to observe their development over many years.

"In ocular oncology you always remember patients with the most difficult manifestations of the disease."

Do you appreciate working as part of a diverse team?

I had the chance to do a four-month elective internship at Moorfields Eye Hospital in London, UK, during my last year of medical school, and I enjoyed the international feel of that working environment, as did I later on in Boston. Our team in Berlin is also very diverse, with members from many European countries and abroad. We also try to maintain equal gender proportions, which so far has worked out well on all levels.

And do you still play the piano?

I actually picked it up again after almost 30 years! Interestingly, there are several good pianists in ophthalmology… I would like the opportunity to play a four hands duet with Tara McCannel – an ocular oncology expert from UCLA.

How has your life changed during the COVID-19 pandemic?

We have been able to do about 80 percent of our normal surgical load, and outpatient clinics see similar patient numbers. We maintain hygiene and distance rules, and use masks and other protective equipment for patients and personnel. I believe we will have to stick to the relatively strict hygiene rules for a rather long time...

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4 CONTRAINDICATIONS
Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients in the formulation *[see Adverse Reactions (6.2)]*.

6 ADVERSE REACTIONS
The following serious adverse reactions are described elsewhere in the labeling:

- Hypersensitivity *[see Contraindications (4)]*

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In five clinical studies of DED conducted with lifitegrast ophthalmic solution, 1401 patients received at least one dose of lifitegrast (1287 of which received lifitegrast 5%). The majority of patients (84%) had ≤ 3 months of treatment exposure. One hundred-seventy patients were exposed to lifitegrast for approximately 12 months. The majority of the treated patients were female (77%). The most common adverse reactions reported in 5%-25% of patients were instillation-site irritation, dysgeusia, and reduced visual acuity.

Other adverse reactions reported in 1%-5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus, and sinusitis.

6.2 Postmarketing Experience
The following adverse reactions have been identified during post-approval use of Xiidra. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Rare cases of hypersensitivity, including anaphylactic reaction, bronchospasm, respiratory distress, pharyngeal edema, swollen tongue, and urticaria have been reported. Eye swelling and rash have been reported *[see Contraindications (4)]*.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
There are no available data on Xiidra use in pregnant women to inform any drug-associated risks. Intravenous (IV) administration of lifitegrast to pregnant rats, from pre-mating through gestation Day 17, did not produce teratogenicity at clinically relevant systemic exposures. Intravenous administration of lifitegrast to pregnant rabbits during organogenesis produced an increased incidence of omphalocele at the lowest dose tested, 3 mg/kg/day (400-fold the human plasma exposure at the recommended human ophthalmic dose [RHOD], based on the area under the curve [AUC] level). Since human systemic exposure to lifitegrast following ocular administration of Xiidra at the RHOD is low, the applicability of animal findings to the risk of Xiidra use in humans during pregnancy is unclear *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

Data
Animal Data
Lifitegrast administered daily by IV injection to rats, from pre-mating through gestation Day 17, caused an increase in mean pre-implantation loss and an increased incidence of several minor skeletal anomalies at 30 mg/kg/day, representing five, 400-fold the human plasma exposure at the RHOD of Xiidra, based on AUC. No teratogenicity was observed in the rat at 10 mg/kg/day (460-fold the human plasma exposure at the RHOD, based on AUC). In the rabbit, an increased incidence of omphalocele was observed at the lowest dose tested, 3 mg/kg/day (400-fold the human plasma exposure at the RHOD, based on AUC), when administered by IV injection daily from gestation Days 7 through 19. A fetal no observed adverse effect level (NOAEL) was not identified in the rabbit.

8.2 Lactation
Risk Summary
There are no data on the presence of lifitegrast in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to lifitegrast from ocular administration is low *[see Clinical Pharmacology (12.3) in the full prescribing information]*. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for Xiidra and any potential adverse effects on the breastfed child from Xiidra.

8.4 Pediatric Use
Safety and efficacy in pediatric patients below the age of 17 years have not been established.

8.5 Geriatric Use
No overall differences in safety or effectiveness have been observed between elderly and younger adult patients.

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*In some patients with continued daily use. One drop in each eye, twice daily (approximately 12 hours apart).

†Xiidra is an LFA-1 antagonist for the treatment of dry eye disease. Pivotal trial data: The safety and efficacy of Xiidra were assessed in four 12-week, randomized, multicenter, double-masked, vehicle-controlled studies (N=2133). Patients were dosed twice daily. Use of artificial tears was not allowed during the studies. The study endpoints included assessment of signs (based on Inferior fluorescein Corneal Staining Score [ICSS] on a scale of 0 to 4) and symptoms (based on patient-reported Eye Dryness Score [EDS] on a visual analogue scale of 0 to 100).[3]

A larger reduction in EDS favoring Xiidra was observed in all studies at day 42 and day 84. Xiidra reduced symptoms of eye dryness at 2 weeks (based on EDS) compared to vehicle in 2 out of 4 clinical trials. Effects on signs of dry eye disease ICSS (on a scale from 0-4; 0=no staining; 4=coalescent) was recorded at each study visit. At day 84, a larger reduction in inferior corneal staining favoring Xiidra was observed in 3 of the 4 studies.[3]

Indication

Xiidra® (lifitegrast ophthalmic solution) 5% is indicated for the treatment of signs and symptoms of dry eye disease (DED).

Important Safety Information

- Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients.
- In clinical trials, the most common adverse reactions reported in 5-25% of patients were instillation site irritation, dysgeusia and reduced visual acuity. Other adverse reactions reported in 1% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.
- To avoid the potential for eye injury or contamination of the solution, patients should not touch the tip of the single-use container to their eye or to any surface.
- Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration.
- Safety and efficacy in pediatric patients below the age of 17 years have not been established.

Please see Brief Summary of Prescribing Information on adjacent page.

References: 1. U.S. Food and Drug Administration. Code of Federal Regulations, Title 21, Volume 5 (21CFR349). https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=349&showFR=1. Accessed April 17, 2020. **2.** Jones L, Downie LE, Korb D, et al. TFOS DEWS II Management and Therapy Report. *Ocul Surf.* 2017;15(3):575-628. **3.** Xiidra [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; November 2019.

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