NOVEMBER / DECEMBER 2021 # 58

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References
[1]US Patent NO: US8647383. [2]Data on file, BVI, 2019.

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Boldly Going

Scientific advancements are constant – but does science fiction help drive us forward while maintaining ethical standards?

I have always loved science fiction stories, as you'll notice from our cover feature. Whether on a screen or in a (comic) book, the blending of scientific and futuristic concepts with a good plotline always grabs my attention. When consuming sci-fi of generations past, though, I have noticed how strongly the themes are dictated by the society of the time – in both the worries and the aspirations that surround scientific and technological progress.

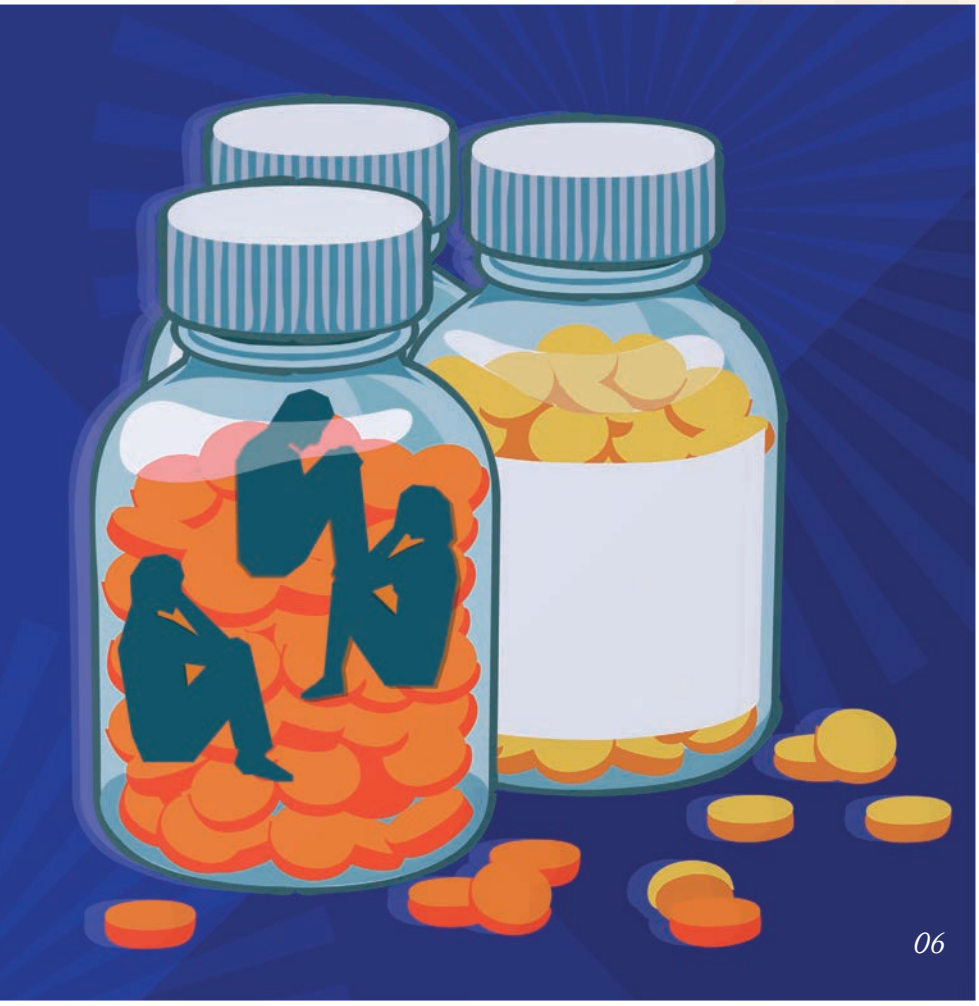
A prime example of this is Mary Shelley's Frankenstein (or, The Modern Prometheus), written at a time when medical science was toying with the idea of bringing life to corpses. Frankenstein is pushing the boundaries of science, but the story itself serves as a warning about how scientific endeavors without a moral and ethical compass can go awry. The "worries and aspirations" theme has continued throughout the years – from Godzilla (born in fiction from the very real and devastating aftermath of the atomic bombs in Japan) to the cosmic exploration of Star Trek and The Fantastic Four (heavily influenced by the space race of the time). Pushing the limits of human achievement but keeping a moral and ethical check on progress is also a focus of most genetic engineering stories; as we learned from Ian Malcolm in Jurassic Park, "… scientists were so preoccupied with whether or not they could, they didn't stop to think if they should."

Bringing this all back to ophthalmology… Many sci-fi stories embrace technology's potential to enhance the eye or give vision to those without; for example, Star Trek's Geordi La Forge wears a VISOR (Visual Instrument and Sensory Organ Replacement), freeing him from his blindness but also enabling sight in different spectra. Double-edged aspirational and ethical warnings come from two Judge Dredd tales of eye replacement – in the comics, he is given bionic replacements after losing his eyes (making an already effective lawman more efficient) but, in the 2012 film, one of the antagonists forces binocular bionic eye replacements on a subordinate to allow him to look through a building's security cameras.

Although ophthalmology is represented in sci-fi, I feel there is room for more – either focusing on our aspirations to cure visual impairment or the ethical quandaries that may stem from enhancing vision beyond our natural ability. Will professions that favor good eyesight one day require bionic upgrades?

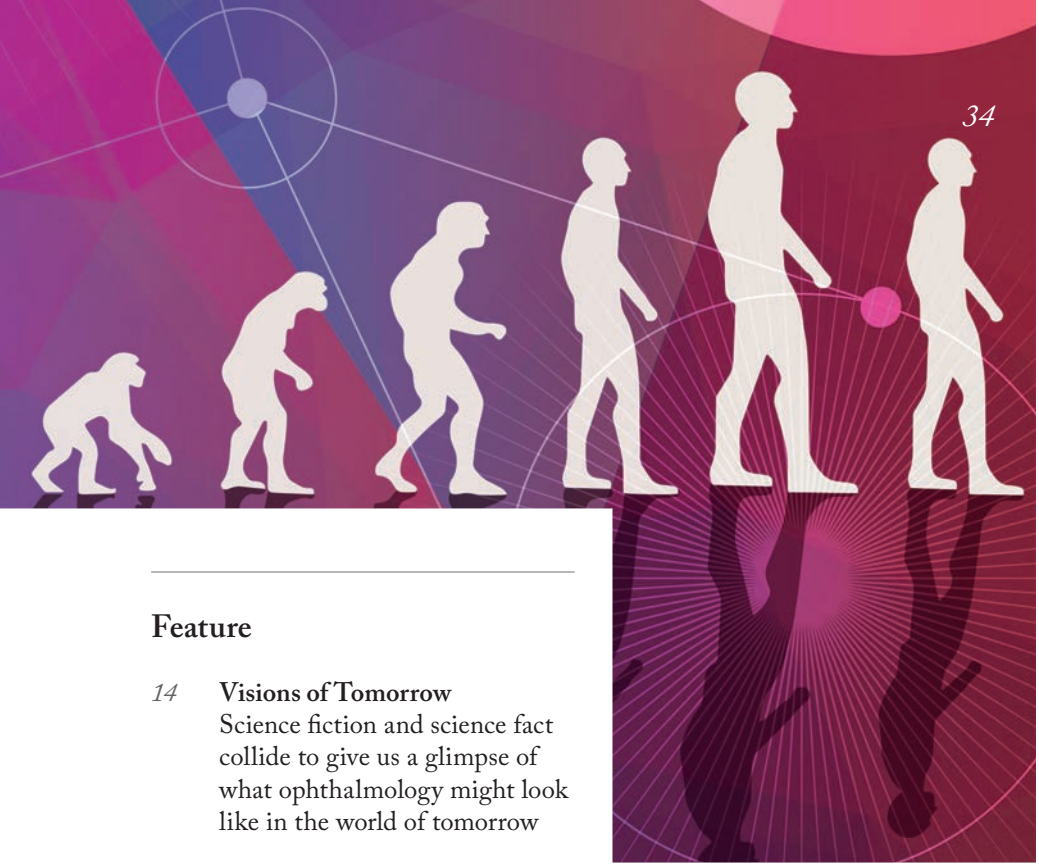
Geoffrey Potjewyd
Associate Editor

Contents



On The Cover

A glimpse into the future of ophthalmology
Images for cover feature sourced from shutterstock and RawPixel.com



Feature

In Practice

NextGen

Profession

Sitting Down With

the Ophthalmologist

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Two Diseases, One Stone

Qi Cui tells us how a diabetes drug may reduce the risk of glaucoma

Type 2 diabetes increases the risk of glaucoma, and with the latter being the leading cause of irreversible blindness worldwide there is a need for novel treatments for both conditions. Researchers from The University of Pennsylvania, USA, have linked the real-world use of an approved diabetes drug class, glucagon-like peptide-1 receptor (GLP-1R) agonists, to a reduced the risk of being diagnosed with glaucoma (1). The publication is authored by Qi Cui, who was kind enough to answer some of our questions about the work.

What led to you looking at real-world data for his drug class for glaucoma use?
In a previous study, we found that a new, long-lasting GLP-1R agonist, NLY01 rescues neurons that make up the optic nerve in a model of glaucoma (2). This was exciting to us since it suggests that GLP-1R agonists, a class of diabetic medication also approved for weight loss treatment, may be beneficial for glaucoma patients. The link between diabetes and glaucoma, and the devastating effect it can have on lives is why our team was eager to discover if these drugs protect against glaucoma development in diabetic patients.

What was your main finding?
Using data from a national insurance provider, we showed that treatment with GLP-1R agonists reduced the chance that diabetic patients in this database will be diagnosed with glaucoma by almost half (44 percent).

How can this help patients and clinicians?
Although our understanding of what causes glaucoma is improving, available treatments largely rely on lowering intraocular pressure (IOP) using medicines, lasers, or surgery. But lowering IOP can be insufficient to prevent disease progression, or impractical due to low baseline IOP. Our findings suggest that GLP-1R agonists do not rely on IOP lowering for neuroprotection, and will be a novel addition to the therapeutic arsenal available to ophthalmologists should they prove beneficial for treating glaucoma.

The study is retrospective, and the first to highlight a potential benefit of GLP-1R agonists in glaucoma prevention. It is preliminary and certainly not definitive, but it does suggest that clinicians might consider preferentially using GLP-1R agonists in diabetic patients with existing glaucoma risk.

See reference online at: top.txp.to/two/diseases

INFOGRAPHIC

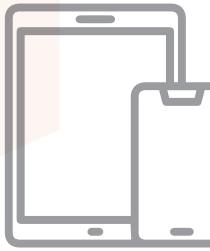
Not So Smart?

Is there a link between the use of digital screen devices and myopia?

A Lancet paper looked at **3,325** articles and included **33** in a review and **11** in a meta-analysis

Studies included children over 3 months old and adults under

33



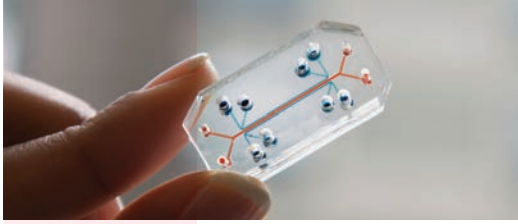
BUSINESS IN BRIEF

From appointments to product launches… What's new in the ophthalmic industry?

- Visus Therapeutics has appointed David Guyer as the chairman of the Board, while Ted Danse has become head of business development (both pictured). Guyer has over 30 years' experience in ophthalmic drug development, including commercialization of the first anti-VEGF drug for AMD. Danse has held key executive roles in multiple life science companies, including Allergan and Neurotech.

Figure. Newly appointed by Visus Therapeutics: David Guyer (left) and Ted Danse (right).

- Erin Parsons has joined the Board of Directors at Alimera Sciences. Parsons brings with her more than 20 years of experience overseeing scientific strategy, communications, advocacy, and educational programs in the ophthalmic industry, including the retina space.
- Rayner Surgical Group has acquired Omeros Corporation's ophthalmology assets, including Omidria, a product used widely for mydriasis maintenance during surgery, protecting the eye from cystoid macular edema, and reducing post-operative pain without the use of opioids. The transfer will be complete by the end of 2021.
- EyePoint Pharmaceuticals and ImprimisRx jointly announced the expansion of a commercial alliance in which ImprimisRx will assume full responsibility for US sales and marketing for DEXYCU (dexamethasone intraocular suspension) 9%, for the treatment of post-operative inflammation following ocular surgery in the US.
- Ophthalmic Sciences has launched IOPerfect, a contactless device that measures IOP and monitors glaucoma using artificial intelligence as part of a VR-like headset. The device uses tele-diagnosis, and allows patients to monitor the IOP at home without the need of recalibration or the use of additional therapeutics.



Credit: Wyss Institute for Biologically Inspired Engineering, Harvard University

Retina on a Chip

How combining stem cells with organ-on-chip technology presents a new translational model for gene therapy research

Biotechnology is ever evolving, with breakthroughs enabling researchers to more efficiently translate data produced in the lab to human need. The advent of the organ-on-chip (OOC) technology represents one such breakthrough – and now researchers at Eberhard Karls University Tübingen, Germany, have combined OOC and human induced pluripotent stem cells (iPSCs) to develop a retina-on-a-chip model to help determine the effectiveness of gene therapy vectors (1).

The group grows human iPSCs into 3D retinal organoids – containing all the cells of the retina in a mini-organ. These are contained within the chambers of a fluidic device (the chip), which allows imaging and feeding of the tissue. The researchers used the model to analyze the function and potency of adeno-associated virus (AAV) vectors – with correlating in vivo data, showing the translational effectiveness of their model. The team hope the retina-on-a-chip model will be used for high-throughput screening.

See reference online at: top.txp.to/retina/chip

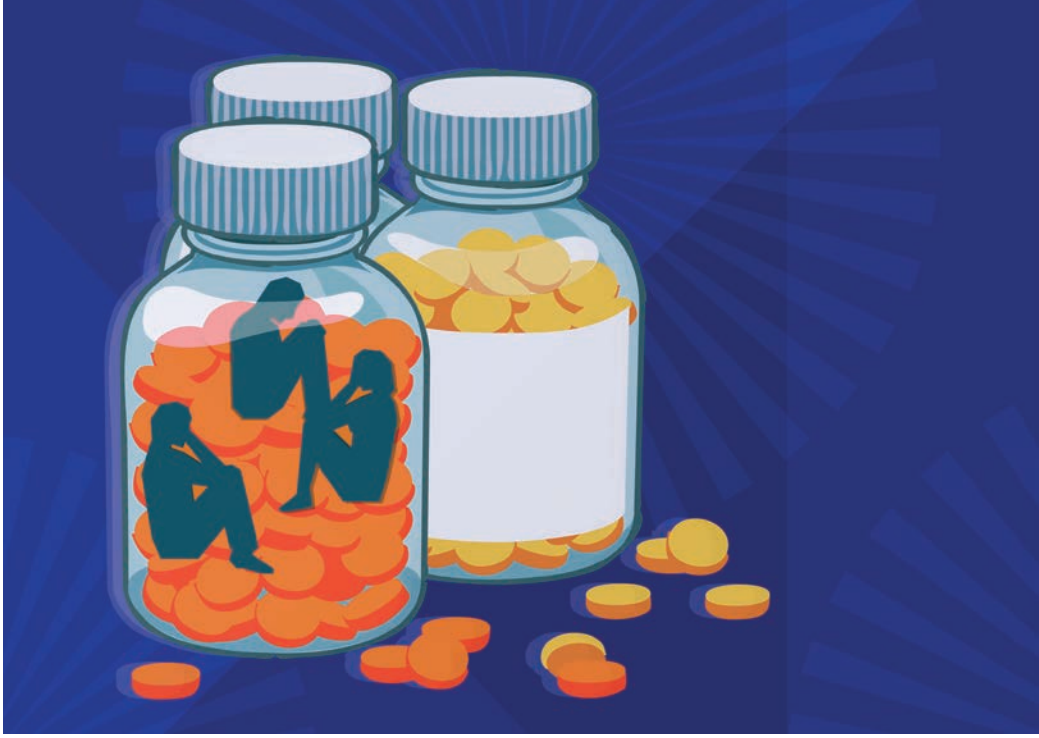
Smart device use alone and in combination with computer use was strongly associated with myopia

HOWEVER, NONE OF THE STUDIES INCLUDED RELIABLE MEASURES OF SCREEN TIME

Myopia-related outcomes were objectively measured only in 79 PERCENT of studies

Reference

1. *J Foreman et a., Lancet Digit Health, 3, e806 (2021). PMID: 34625399.*



A Rough Deal

How common is substance abuse among older adults with vision impairment?

Sight loss and vision impairment is associated with increased risk of reaching for controlled substances and developing substance use disorder (SUD). With societies growing older, increasing numbers of older adults live with visual impairments for longer, it has been assumed that psychoactive substance use has increased; now, a team of researchers from the University of California, San Diego, and the New York University Grossman School of Medicine in New York, USA, have attempted to estimate the prevalence of substance use among middle-aged and older visually impaired patients in the US (1).

Data from almost 44,000 of noninstitutionalized respondents aged 50 or older who reported serious difficulty seeing, even when wearing glasses, recorded by the National Survey on Drug Use and Health between 2015 and 2019, were analyzed for reported misuse of prescription opioids, sedatives, stimulants, and tranquilizers, and use of cannabis and cocaine. Prevalence of alcohol use disorder and nicotine dependence was also measured in this cohort. Women made up the larger part of the sample, at 53.2 percent, and 44.4 percent of the analyzed patients were older than 65 years. Just under 6 percent of the sample of over 50-year-olds were estimated to have a serious impairment impacting their sight.

What did the study find? After accounting for age, sex, ethnicity, marital status, income, and presence of two or more chronic diseases, results shower a clear correlation between visual impairment and higher prevalence of cannabis and alcohol use, opioids and tranquilizer misuse, and nicotine dependence in the previous year.

Sight loss among older adults is associated with an increased risk of isolation (2), which can lead to depression and irregular substance use. There is a risk that visual impairment coupled with intoxication can lead to injuries, as well as exacerbation of existing chronic conditions. Can anything be done to reduce the potential impact of this link? Screening for mental illness and substance use among adults suffering from sight loss could be an important first step in addressing the issue.

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1. *BH Han et al., JAMA Ophthalmol, [Online ahead of print] (2021). PMID: 34762104.*
2. *CE Coyle et al., J Aging Health, 29, 128 (2017). PMID: 26762396.*

An Eye for Detail

On November 20, 1886, an ophthalmologist's first story was accepted for publication… But do you know the protagonist?

Correct. There are few who haven't heard of Sherlock Holmes and Dr Watson, arguably the most famous and formative crime sleuthing duos to inhabit the genre – but did you know that the creator, Sir Arthur Conan Doyle, was an ophthalmologist?

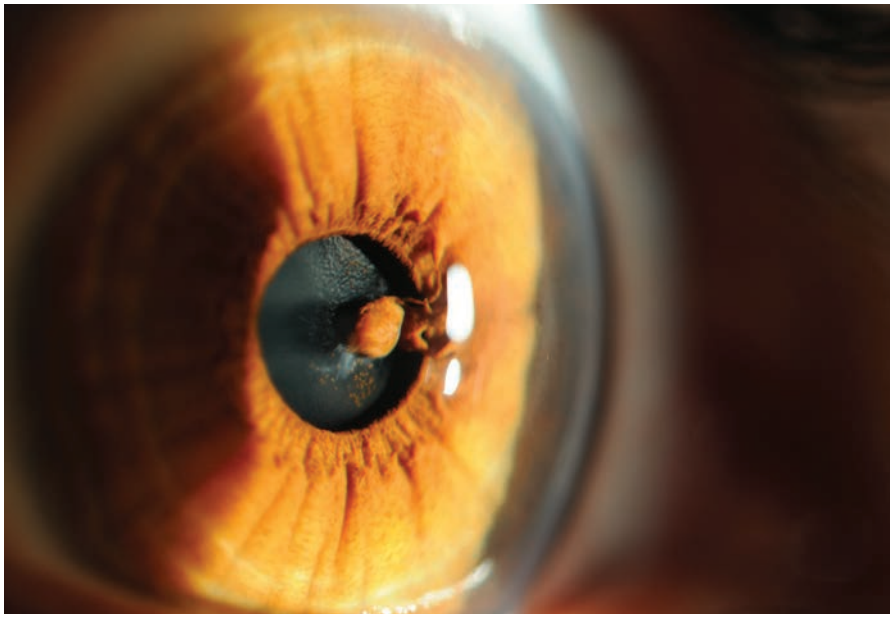
After achieving a Bachelor of Medicine and Master of Surgery in 1880, and an MD degree in 1885, he chose to specialize in ophthalmology in 1890, training in Vienna and Paris before setting up an ophthalmology practice in central London. Eventually, the medical career would subside for his literary pursuits, but the influence of his time as a doctor and ophthalmologist was clear – with ophthalmology bleeding into the pages of one mystery (spoiler warning), where the murder weapon was a cataract surgical knife.

Apart from Watson being a physician, Holmes' methodical reasoning, perceptive deductions, and diagnostic processes (coined as Holmesian) share a great deal with those employed by doctors (albeit with fewer fictitious elements), and were affected greatly by Doyle's medical career (1).

Reference

1. *J Reed, Med Humanit, 27, 76 (2001). PMID: 23670927.*

IMAGE OF THE MONTH



A Frog Jumping into the Pupil

The images have been taken with the SL9900 slit lamp. For OCT images of this case, visit our website.

Credit: Fabrizio Zeri, Department of Materials Science, University of Milano-Bicocca, COMiB Research Centre, Milan, Italy, and College of Health and Life Sciences, Aston University, Birmingham, UK.

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

Drillers Versus Scanners

Which visual tracking approach gains the most information from digital slides?

Diagnosing from medical images has become much easier in the digital age – and whole-slide images can offer gains in both processing and accuracy. But what is the most effective visual technique for evaluating slides in the digital realm – scanning the XY plane or "drilling" by zooming in and out of the Z plane? A group of researchers tracked eye movements to compare how pathologists and radiologists visually assess breast pathology slides – and established that, whereas pathologists gain their critical diagnostic information primarily from scanning, radiologists prefer drilling to interrogate critical features (1). They also found that pathologists' scanning rates correlate with higher diagnostic accuracy, but further work is needed to determine whether there is a causal relationship between scanning rate and accuracy. In the meantime, perhaps it's time to consider – how do you review your slides… and is there a better way?

Reference

1. *T Drew et al., J Vis, 21, 7 (2021). PMID: 34636845.*

In My View

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

A Tale of Two Cities

The dangers of unawareness of the true needs of our patients

By George Spaeth, Esposito Research Professor at Wills Eye Hospital, and Professor of Ophthalmology at Sidney Kimmel Medical School, Thomas Jefferson University, Pennsylvania, USA

The frail, elderly man, who came to my office with his frail, elderly wife, knew he had lost most of his sight due to glaucoma and that his vision was continuing to fade. I wondered whether he could tolerate surgery, and I knew it would be very hard – perhaps insurmountably – for him to return for postoperative visits. He had already had two laser trabeculoplasties performed by the referring ophthalmologist. I advised him to add another drop to his regimen.

When he returned a month later, his intraocular pressure seemed about the same; he had not noted any improvement in vision. He was not using the new drops.

"Why are you not using the new eye drops?" I asked in, I fear, a critical tone.

"Well," he answered softly in a scratchy voice, "It was either buying food or buying drops."

How could I have been so unaware, so totally living in the City of Doctors, unaware of life in the City of Patients? The resident dutifully told me that we needed to lower the IOP further it was above TP and the patient had a thin CCT (speaking in the strange language only heard in the City of Doctors: LMD, OD, OS, c/d, NVG, OCT, CRVO, NVI).

I asked, "What difference does it make that the cornea is thin?" Of course, the compliance of the cornea affects the tonometric measurement of the IOP, but precisely by how much, is not known. A study has shown that a group of people with thin central corneas is more likely to have visual field deterioration than a group with thicker corneas, but there is no knowledge that a particular person with a thin cornea is more likely to become symptomatic than is a person with a thick cornea. How can doctors be unaware of that? Of course, the idea of personalizing the level of eye pressure that might possibly be fine for a patient is an advance over just using the standard distribution curve, but target pressures are just a useful guess – a "guesstimate." How can it be that today doctors are not aware that the best way to establish stability versus deterioration of health is by documenting stability or deterioration of health?

I dread going to medical meetings where I hear about the latest, greatest surgery or medication, where I am titillated by the totally confident surgeon demonstrating their magnificent technique in a video enhanced by Mozart's 23rd piano concerto. I dread being told authoritatively that patients need to have hysteresis and the flow of blood measured with OCT-A.

I watched a truly thoughtful colleague present a promotional talk on "AS-OCT." Afterwards, I asked him privately, "How can you recommend anterior segment OCT when you know it's a poor substitute for gonioscopy?" "But George," he replied, "AS-OCT is better than nothing. You know few doctors gonioscope their patients, and even if they do, they don't know what they're seeing." Of course, he is right. But is the solution to that problem to start using an expensive test that is not as good? Or should doctors learn and perform gonioscopy?

We, eye doctors, carry on, not hearing what needs to be heard, not examining well what needs to be examined, testing what does not need to be tested and not testing what should be tested, not treating what needs treatment or treating what does not need treatment, content with our unawareness, because we soldier on, unaware we are living in our isolated City of Doctors. College students go to medical school because they want to help people; that has been supported by good studies. What causes the transformation from that intention to becoming unaware? By the time these well-intended people start medical practice they have moved from the City of Patients to the City of Doctors. How is it that we become unaware we are following a standard of care inappropriate for most of those living in the City of Patients?

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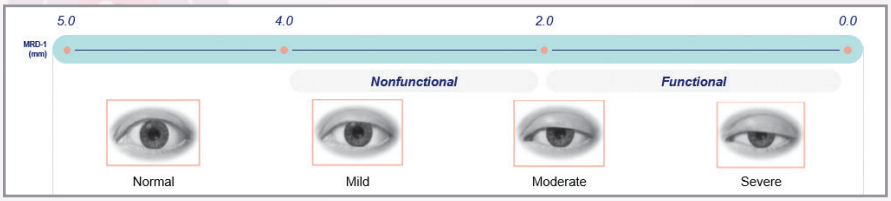
Things Are Looking Up for Acquired Ptosis Treatment



How has the introduction of a non-surgical acquired ptosis treatment changed exam and treatment protocols?

Sponsored content by RVL Pharmaceuticals, Inc.

David A. Goldman, MD - Founder of Goldman Eye, Palm Beach Gardens, Florida, and Ophthalmology Team Lead, Anterior Segment, Modernizing Medicine, USA, talks about his experience with Upneeq® (oxymetazoline hydrochloride ophthalmic solution), 0.1% from RVL Pharmaceuticals – an FDA-approved treatment for acquired ptosis in adults.

My practice consists of two ophthalmologists and one optometrist. We take care of everything covered by comprehensive ophthalmology, including the various forms of ptosis. Acquired ptosis in adults is prevalent in my practice – especially in the elderly patient demographic, which is the majority of our patient population. The condition's prevalence is, however, much better separated into those who medically require surgery and those who seek surgery for cosmetic benefit. There is wide variation in ptosis severity, from minimal to severe (requiring surgery) – but even patients with mild ptosis will often ask about their lid surgery eligibility.

Widening the patient pool

The introduction of Upneeq has completely changed how I treat acquired ptosis across the board. Before, medically indicated ptosis patients would be referred to an oculoplastic specialist for surgery; elective patients with less severe presentation would also be referred, but without the likelihood of insurance coverage for the procedure. Now that Upneeq is available, I can offer treatment to patients with milder acquired ptosis, enabling patients with lesser functional infringements and cosmetic impact to address their condition. And the increased reach doesn't just relate to acquired ptosis severity – one of Upneeq's advantages is that the subset of acquired ptosis patients in whom surgical repair is contraindicated (such as those on blood thinners) may now have the opportunity to improve their field of vision. For some patients, field of vision improvements can potentially lead to noticeable impacts on day-to-day activities such as driving, reading, and sports. However, it's important to keep in mind that Upneeq may not be right for all patients. Since Upneeq may impact blood pressure, physicians should tell patients with cardiovascular disease, orthostatic hypotension, and/or uncontrolled hypertension or hypotension to monitor their condition and call the office if it worsens.

The benefits extend to mild ptosis, in which patients may experience significant self-consciousness over asymmetry between lids or wish to make their eyes look more open. Acquired ptosis patients can now treat the appearance of their eyelids before any social or professional event without the need for surgery. This is especially valuable in mild ptosis patients who aren't quite ready for surgery yet; operating too early can increase the risk of worse ptosis outcomes in older age or scarring following the procedure.

I see patients who have had lid surgery performed by a plastic surgeon (rather than an oculoplastic surgeon) who has removed the skin, but did not address the levator muscle. This will naturally droop over time and either be difficult to rectify with surgery or leave insufficient skin for a successful outcome. The non-surgical therapeutic option offered by Upneeq is appropriate for such patients – and it may be helpful for them.

Changes in practice

As I mentioned, in the past, patients interested in lid surgery were referred to an oculoplastic specialist. Now, the non-surgical option of prescribing Upneeq provides a stepping stone for apprehensive patients. Many of my patients have been so happy with the results from the eye drop that they asked to continue with a prescription in place of surgery.

There has been a significant trend in which our patients who have started using Upneeq are very satisfied with their clinical outcomes. By giving samples to patients and taking before and after pictures (15 minutes apart), my colleagues and I can quickly show patients the visible benefits – we even let appropriate patients test Upneeq on the spot in the office. Our staff educates patients on how to correctly instill eye drops and reminds patients not to touch the tip of the container to their eye or any other surface to avoid contamination. We also discuss potential adverse events which may occur in 1-5 percent of patients, including punctate keratitis, conjunctival hyperemia, dry eye, blurred vision, instillation site pain, eye irritation and headache. Patients are very curious about the product and ask us – "How long has this been available?" and "Why haven't I heard of this before?" I have received comments such as, "I've got to tell my friends about this." Their excitement and willingness to talk to friends about their

satisfying experiences is fantastic advertising – perfect for generating further interest from other patients who may have been ignoring their acquired ptosis.

Unexpected ptosis diagnosis

A common complaint following cataract surgery is that patients feel their eyelids have become droopy. This is often not the case, but patients frequently go from wearing corrective glasses that can cover acquired ptosis to having a clear view of their eyelids. For this reason, we take a picture before cataract surgery so that patients can see for themselves whether there has been a change. Situations like this are often perfect for the prescription of Upneeq® (oxymetazoline hydrochloride ophthalmic solution), 0.1%, because the patient's potential disappointment at that point can be addressed with a noninvasive prescription that avoids another surgery. This is also an example in which quick and early diagnosis of ptosis is extremely useful – diagnosing a patient before surgery is considered a pre-existing condition, whereas diagnosis afterwards can be considered a complication in the patient's mind. It's also important to keep in mind that ptosis may be associated with neurologic or orbital diseases and consideration should be given to these conditions during diagnosis. By managing the patient's expectations and flagging any eye health concerns early, cataract surgery is much more likely to have a great outcome for everyone involved.

Flow and distribution

My practice staff talk to patients about ptosis before I've even seen them. Having the staff give a brief and informal introduction to the condition and the options available is brilliant both for the patients and for me – leading to many appropriate patients keen to try the prescription instead of surgery. We even have one staff member who has become an Upneeq user and is delighted with the effect it has on her unilateral acquired ptosis.

Upneeq's distribution model makes the process easy for me and my patients. Because it works outside of insurance, it's been easy to go through RVL for the prescription. The pricing of the product is appropriate for what it delivers; it won't be affordable for everyone but, given the results that many of my patients see, it's definitely a fair price for the service it performs.

My advice to any ophthalmologists who may want to start using Upneeq in their practice is to give their acquired ptosis patients samples and offer to write them a prescription. This, combined with taking before and after pictures with patients' own cell phones, is typically a good way to ensure a successful launch of Upneeq in any ophthalmic practice.

IMPORTANT SAFETY INFORMATION

INDICATION

UPNEEQ® (oxymetazoline hydrochloride ophthalmic solution), 0.1% is indicated for the treatment of acquired blepharoptosis in adults.

WARNINGS AND PRECAUTIONS

- Ptosis may be associated with neurologic or orbital diseases such as stroke and/or cerebral aneurysm, Horner syndrome, myasthenia gravis, external ophthalmoplegia, orbital infection and orbital masses. Consideration should be given to these conditions in the presence of ptosis with decreased levator muscle function and/or other neurologic signs.
- Alpha-adrenergic agonists as a class may impact blood pressure. Advise UPNEEQ patients with cardiovascular disease, orthostatic hypotension, and/or uncontrolled hypertension or hypotension to seek medical care if their condition worsens.
- Use UPNEEQ with caution in patients with cerebral or coronary insufficiency or Sjögren's syndrome. Advise patients to seek medical care if signs and symptoms of potentiation of vascular insufficiency develop.
- UPNEEQ may increase the risk of angle closure glaucoma in patients with untreated narrow-angle glaucoma. Advise patients to seek immediate medical care if signs and symptoms of acute narrow angle glaucoma develop.
- Patients should not touch the tip of the single patient-use container to their eye or to any surface, in order to avoid eye injury or contamination of the solution.

ADVERSE REACTIONS

Adverse reactions that occurred in 1-5% of subjects treated with UPNEEQ were punctate keratitis, conjunctival hyperemia, dry eye, blurred vision, instillation site pain, eye irritation and headache.

DRUG INTERACTIONS

- Alpha-adrenergic agonists, as a class, may impact blood pressure. Caution in using drugs such as beta-blockers, anti-hypertensives, and/or cardiac glycosides is advised. Caution should also be exercised in patients receiving alpha adrenergic receptor antagonists such as in the treatment of cardiovascular disease, or benign prostatic hypertrophy.
- Caution is advised in patients taking monoamine oxidase inhibitors which can affect the metabolism and uptake of circulating amines.

Dr. David Goldman is a paid consultant of RVL Pharmaceuticals, Inc.

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VISIONS OF TOMORROW

WELCOME TO THE INTERSECTION OF SCIENCE FICTION AND OPHTHALMOLOGY – OR, AS I LIKE TO CALL IT, "EYE-FI"

By Geoffrey Potjewyd

Science is constantly pushing the boundaries of what we know and what is possible, but the catalogue of how we would like technology to help us in the future is constantly being filled by the magic of science fiction. Star Trek gave us visions of tablets, cell phones, and replicators – all of which have been (at least somewhat) realized in modern technology. Robocop, Geordi LaForge, and Judge Dredd are among those who have benefited from bionic eyes – and the real-world research into restoring sight through implants and prostheses is being advanced year on year. Additive manufacturing (3D printing) has gone from a fanciful dream for most to a technology that is a one-click delivery away – and won't (quite) break the bank. Adding to the scene is a plethora of eye-based regenerative medicine that brings the worlds of reality and sci-fi closer than ever (1).

But what role could today's ophthalmology have in a fictional world of tomorrow? What kind of future do we want – and how do these findings potentially take us there? We asked our contributors how their research could be used in future – in either a realistic application or a fanciful extrapolation of current capabilities. Welcome to eye-fi!

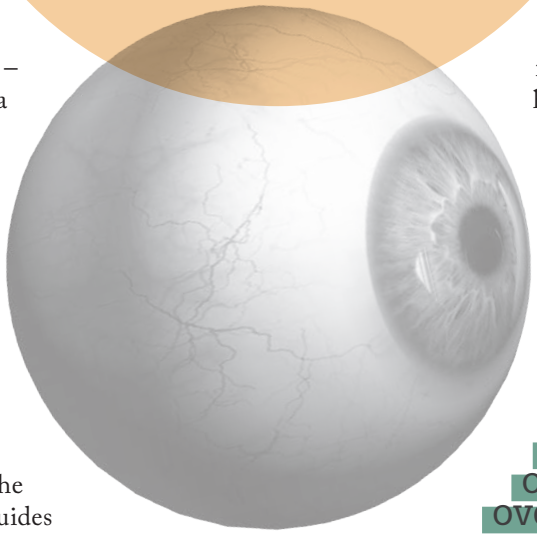
Master of magnetism

In "The Birds Have (Magnetic) Eyes," we outline the amazing finding that migrating songbirds have a retinal protein that is sensitive to magnetic fields, and therefore may be responsible for the uncanny biological "compass" that guides them from opposite ends of the globe (2).

But how could these magnetic eyes be used in the future? Peter Hore, one of the authors of the original study, suggests one realistic application: "We could develop man-made magnetic sensing devices using organic spintronics to mimic natural magnetoreception."

We at The Ophthalmologist wonder if one day this could be applied to survival orientation devices in the harshest environments, maybe using only our handy inbuilt magnetoreceptors? Could we eventually develop a device using these principles to control magnetic fields around us, like a live action Magneto – disabling electronic devices and remotely moving objects? What an X-ceptional idea.

"ARE WE SEEING THE FUTURE OF TELEMEDICINE – WHERE VR HEADSETS CAN PERFORM DIAGNOSTIC TESTING?"



Let there be light

"Of Mice and Men" looks at the discovery of the focea region in the mouse visual cortex, which performs a similar role to the human fovea in enabling enhanced spatial resolution vision (3). The work shows that mouse vision is much closer to our own than previously realized.

Lead researcher Pieter Roelfsma explains how their lab is using the visual cortex to restore vision – taking a sci-fi concept into a near-future reality. "We are now working on a prosthetic device to restore a rudimentary form of vision in blind individuals," he says. "Technologies we aim to use for stimulation of the human visual cortex are currently being tested in mice and monkeys in our lab."

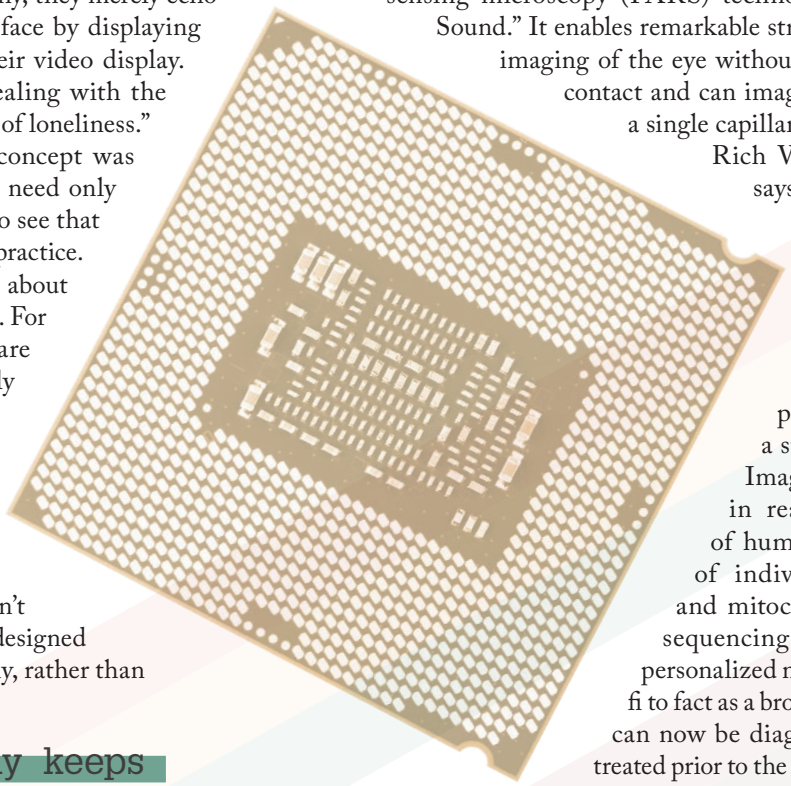
So are we on the cusp of bionic vision to cure blindness? Can we go a couple steps further and enable ourselves to see previously non-visible forms of light? Watch this space.

I, for one, welcome our new robot overlords

David Alais explains the concept of face pareidolia in "Carface" – and his research shows that we emotionally process false faces in the same way as real faces (4). Cars,

clocks, and handbags can all look angry, happy, perplexed, and more.

When asked if this could help robots maintain a semblance of normality during a hypothetical machine uprising, he confirmed my fears. "Yes, it would be sensible to make robots with expressions – we know that there is nothing to prevent an object such as a robot from conveying genuine facial emotion." Moving onto a more realistic perspective of how we design robots for everyday use, he says, "This would clearly be a useful adaptation in our design of robots as we inevitably interact more and more with them. It could even be interactive; the robot could display empathy by using happy and sad templates to determine the emotion of the human they encounter. To display empathy, they merely echo the emotion in the human face by displaying a happy (or sad) face on their video display. This could be helpful in dealing with the mental health consequences of loneliness." And, if you thought that concept was reserved for the future, you need only walk through a parking lot to see that this is already being put into practice. "Designers know intuitively about emotional response to objects. For example, some motor cars are designed to look like friendly or happy faces; they satisfy the face template with their headlights (eyes), grille (mouth), and badge in the center (nose). This applies to the design of many objects; even if they don't all look like faces, many are designed to look soft, round, and fleshy, rather than harsh and angular."



An injection a day keeps blindness away

In "The H Factor," Simon Clark tells us how his research collaboration led to the discovery of increased factor H-related (FHR) proteins in AMD patients' blood, the realization that they cause disease-related damage, and the development of a new mass spectrometry-based technique for the simultaneous identification of all seven factor H family members (5).

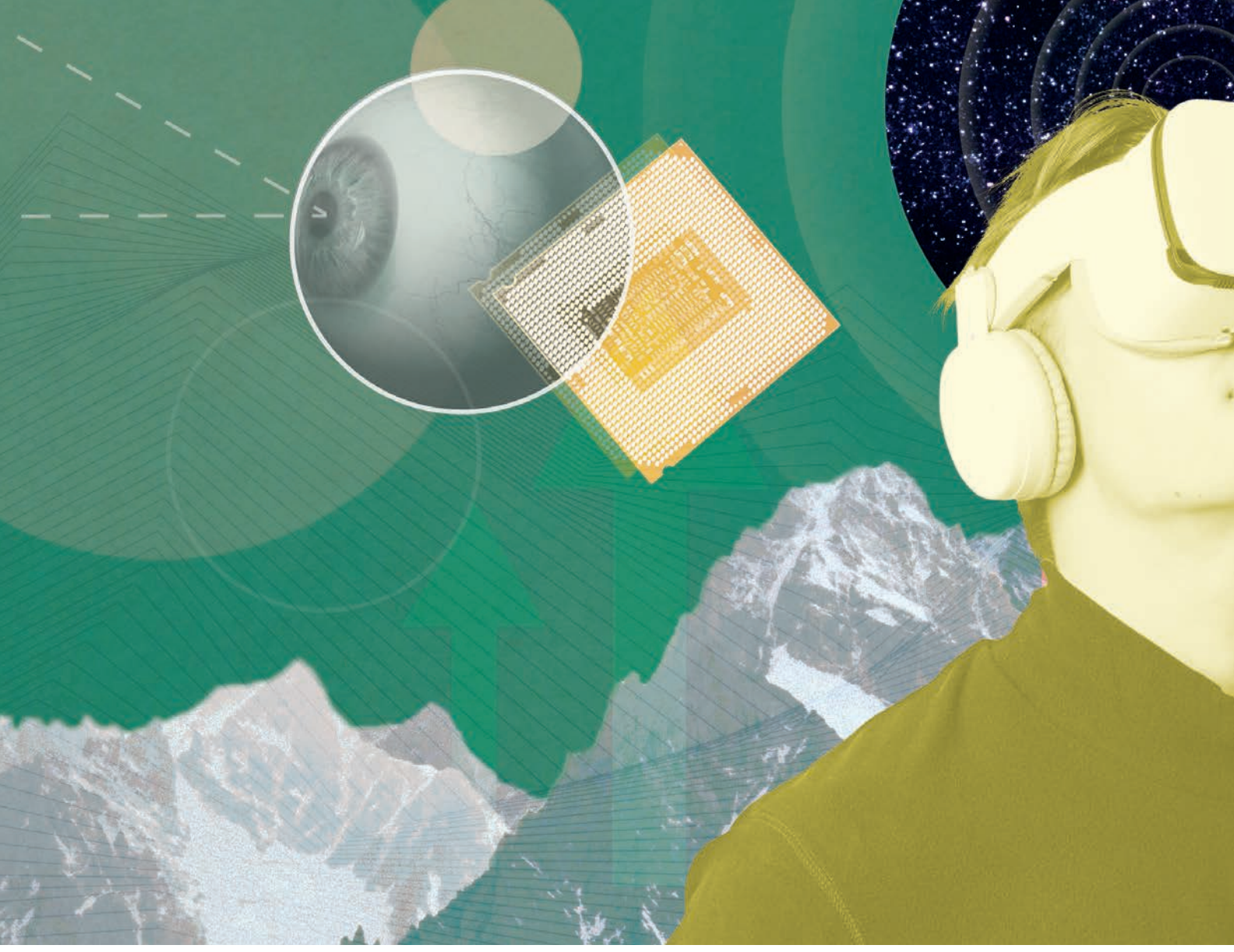
Clark suggests a sci-fi future where their findings may be used to prevent blindness. "FHR proteins that ultimately lead to vision loss are made in the human liver and we already have techniques to lower gene transcription in the liver – so imagine a world where people have a small injection at breakfast to prevent them from going blind. A daily subcutaneous injection delivering gene-silencing drugs to the liver could reduce FHR protein levels and prevent FHR-mediated inflammation in the back of the eyes. A better alternative to monthly intravitreal injections or surgery!" Perhaps one day soon we will be able to add AMD to the spectrum of "unnecessary blindness."

Surround sound

Parsin Haji Reza outlined his amazing photoacoustic remote sensing microscopy (PARS) technology in "Structurally Sound." It enables remarkable structural and functional imaging of the eye without the need for physical contact and can image down to the level of a single capillary or red blood cell (6). Rich Weinstein of EyeStart says, "In the future, PARS technology will be incorporated into a handheld device and used not only by ophthalmologists, but by all health care professionals as part of a standard medical exam. Imagine being able to scan in real time the anatomy of human tissue to the scale of individual cellular DNA and mitochondria. Instant gene sequencing will allow for truly personalized medicine to go from sci-fi to fact as a broad spectrum of diseases can now be diagnosed and potentially treated prior to the onset of first symptoms. Finally, envision a device that can not only image the cell, but also use a unique algorithm of different light wavelengths as a therapeutic tool for cellular repair. The possibilities are infinite." There is plenty of scope for future innovation and application for this technology in our world of tomorrow.

Honey, I shrunk the OCT

Sohaib Rufai, author of A Practical Guide For Aspiring Ophthalmologists, gives advice on how to secure an



ophthalmic specialist training post in "The Aspiring Ophthalmologist's Guide to the Galaxy" (7) – along with some inspiring pictures of him conquering the Rocky steps in Philadelphia.

His take on the pioneering sci-fi future of ophthalmology technology centers on the optimization of optical coherence tomography (OCT), which he uses for his neuro-ophthalmological research at Great Ormond Street Hospital and Leicester Royal Infirmary, UK. "Conventional OCT devices are large and table-mounted, designed mainly for adults and older children – but this technology has since been scaled down and adapted into a futuristic handheld device, enabling gentle non-contact OCT examination in infants." He goes on to predict the potential applications of technology miniaturization. "I believe more ophthalmic technology may be scaled down to smaller devices suitable for patients of all ages, possibly even facilitating home-based ophthalmic monitoring." So expect our eye-fi future to have ophthalmic equipment available in home and travel sizes…

Bionic eye maintenance

Research by Harpreet Kaur, Sarj Athwal, and their team (see "Lifting the Lid on Eye Pressure") shows that lower lid tightening surgery increases intraocular pressure (IOP) (8) – an important consideration for surgeons when planning procedures such as this in patients with glaucoma.

But how does this apply to a hypothetical future society where bionic eyes are commonplace? Imagine that implants and upgrades could be integrated onto the surface of the eye to enhance ocular function… Kaur and Athwal have this to say, "these implants could cause an increase in the IOP due to external compression, as demonstrated in our research. So, despite all these technological advances, ophthalmologists of the future will probably still be relied upon to monitor and manage IOP."

It's great to see ophthalmologists who are so well prepared for a sci-fi future in ophthalmology!

Brain training

In "Seeing is Believing," Yair Yahav talks about technology that can not only improve vision in adults with amblyopia, but also enhance anyone's vision by training the visual cortex (9). The technology combines two Nobel Prize-winning scientific discoveries into a home training program that has helped people to do everything from obtain pilot's licenses to read TV program titles for the first time.

Yahav says, "The technology is already sci-fi – people are skeptical about how we can improve vision through training the brain, but then they learn how exactly the science works to enable us to work on specific neurons in the cortex – and the clinical results speak for themselves."

With this development and its applications firmly rooted in science, it's one for fans of "hard" sci-fi. Could it be used to help super-soldiers improve marksmanship in battle zones – or could it be translated to sporting endeavors, with mandatory vision training to increase athletic performance come game day?

"ANTICIPATE THAT OPHTHALMOLOGISTS IN THIS FUTURE SOCIETY MAY STILL BE BUSY WITH REGULAR IOP CHECKS."

Virtual reality ophthalmologist

In "Equity: Facts and Future," Tina Felfeli and Yvonne Buys outlined the state of play for male and female ophthalmologists and found the figures wanting (10). Maybe we can reach equity in a

non-sci-fi future?

Asked about the future of ophthalmology in relation to sci-fi technology, Buys brought up her involvement in a project that fits the bill. "I am involved in the development of a portable perimeter – which is hard sci-fi, because we have already developed the technology and we're testing it now." The device takes eye testing directly to patients' homes with a virtual reality (VR) headset that hooks up with a smartphone, remote clicker, and control analysis software. "This is something that could significantly change the way we do visual fields," says Buys. Are we seeing the future of telemedicine – where VR headsets can perform diagnostic testing? Or can the technology even be extended to a device that can deliver procedures from the comfort of the patient's favorite armchair?

Medic!

In a soon-to-be-published article, Jongmin Kim and Dong-Woo Cho explain how they are using decellularized eye tissue as a bioink to 3D print retinal tissue for research and potentially implantation.

Although 3D printing of human tissue for these purposes is already well within the realms of sci-fi, Kim has a suggestion for a home comfort application. "Imagine that there is a highly advanced 3D cell printing system containing various types of decellularized ECM bioink – and that people have their own stocks of stem cells, such as induced pluripotent stem cells (iPSCs). An injured person could be treated by replacing their damaged organ with a 3D-printed organ using a bioink of dECM and their own iPSCs." Kim adds, "In a warzone, the army medical officer could carry a hard case with a small 3D cell printing system and bioinks tailored for the soldiers, ready to print replacement tissues when needed. In modern warfare, there are a lot of eye injuries due to shots fired and improvised explosive devices. We hope that our research and future technologies can help soldiers in all military branches who are suffering from eye damage or vision loss."

"IMAGINE THAT THERE IS A HIGHLY ADVANCED 3D CELL PRINTING SYSTEM CONTAINING VARIOUS TYPES OF DECELLULARIZED ECM BIOINK."

Chip-ready vision upgrades

One of our upcoming contributors, Che Connon, will explain his group's amazing work on engineering human cornea tissue both for research and to meet the growing need for cornea replacements.

His work on bionic corneas fully embraces the intersection of sci-fi and ophthalmology. "A professor of microelectronics and I are working together to embed a microchip within the tissue," says Connon. Obviously, the translation to reality isn't quite plug and play. "There are factors we need to consider and overcome – including how to power the chip, how to send and receive signals from a chip embedded in tissue (which has many biomaterial implications in itself), and how to get the chip to integrate in the tissue and avoid rejection issues." Once microchip technology is successfully integrated into the cornea, the number of potential applications is startling. "The interesting question about integrating electronics into a functional cornea is, 'What do you want the electronics to do?' An obvious answer is to monitor IOP for a range of ocular pathologies. But it's more tempting to think about cameras and things like that; with a camera you can look at all sorts of things – internal monitoring of

blood flow, drainage, or anything within the eye; external cameras could be used for vision on a range of wavelengths." So with a bionic cornea on our sci-fi menu, are we headed for a marvel of medical monitoring – or are we about to crest the horizon of technological espionage seen in the wildest Bond films?

Hollywood meets ophthalmology

Another upcoming article features the work of Qi Cui and team, who are investigating the relationship between a diabetes drug and a reduced risk of glaucoma.

Cui mentioned that the 1966 sci-fi classic Fantastic Voyage reminds her of her own research. "The scene where one of the scientists is eaten by a white blood cell is forever ingrained in my brain! It honestly gave me nightmares for weeks. It's strangely appropriate because my current research focuses on curbing reactive microglia and macrophages to save neurons in the eye, and that killer white blood cell is just such a reactive macrophage doing what it's designed to do – to the detriment of poor, villainous Dr. Michaels." If there is ever a remake, perhaps Cui's work will ensure that the biological response to human intruders is not only horrific but realistic!

The final frontier

It's amazing how sci-fi and science can end up interchanging concepts – with sci-fi ideas appearing in labs, and lab research ultimately cameoing in fictional tales. Whether it be revolutionizing eye care from home, repairing eye trauma in a war zone, or using implanted electronics to restore, monitor, or even improve eyesight, it is clear that ophthalmic research is rapidly progressing beyond what we previously would have deemed to be science fiction.

As science and technology progress even further, we will have to keep redefining what we put in the respective spaces of science fiction and science fact.

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IS IT OR ISN'T IT DRY EYE?

How the TearLab® Osmolarity System supports DED diagnosis and therapy management

The TearLab Osmolarity System offers objective laboratory style data that can help you better distinguish dry eye patients from non-dry eye patients. This diagnostic test guides clinicians in gaining immediate insights into ocular surface health disease, including dry eye disease (DED).

Tear film instability and hyperosmolarity are key signs of DED and can impact visual acuity; 70 percent of total refractive power occurs at the tear film surface (1). Ocular Surface Disease (OSD) can affect the clarity and stability of vision, reduce the accuracy of refractive diagnostic tests, and negatively impact on cataract surgery and LASIK results, leading to refractive surprises and dissatisfied patients. With around 80 percent of cataract patients presenting a sign of OSD (2, 3), it is imperative clinicians have access to objective data to confirm DED or rule it out.

How it works

The test requires 50 nl of tear sample – collected at the tear film and transported via microfluidics onto the chip. Osmolarity levels (salt content) is calculated through electrical impedance technology. An osmolarity value is then displayed in mOsm/L and will fall in a range between 290 and 400 mOsm/L (see Figure 1). This value must be interpreted by the clinician, and a diagnosis based on DED severity can be made.

Why test osmolarity?

The TearLab Osmolarity System is the only FDA approved device that measures osmolarity and aids early detection of DED. Elevated (abnormal) osmolarity indicates an unhealthy tear film, which can result in damage to the ocular surface; in fact, elevated osmolarity is the very first biomarker of developing DED (5).

Managing the "Normal" Symptomatic Patient

Osmolarity values, like any laboratory test, has value not only in detecting DED, but also in triggering a further examination if the patient has a normal reading. Put another way, a normal osmolarity reading for a symptomatic patient alerts the clinician that a more detailed investigation needs to be conducted. In 30 percent of cases, symptoms indicative of DED are not caused by dry eye, but by another factor, such as allergies.

TearLab

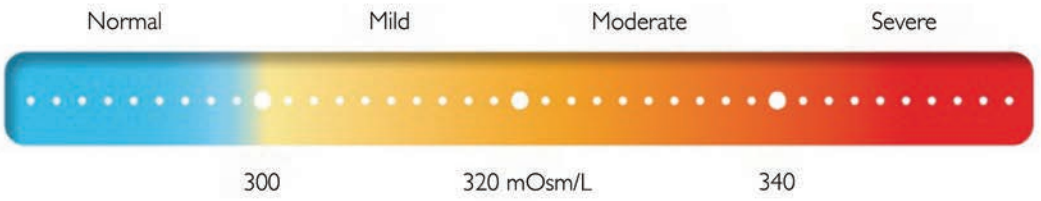

Figure 1. Osmolarity scale.

Ashley Brissette, Assistant Professor of Ophthalmology at Weill Cornell Medicine, New York Presbyterian Hospital, discusses normal osmolarity – and how useful it is in making a DED diagnosis (5)

In 2018, my colleagues and I conducted a prospective observational cohort study to explore the diagnostic utility of normal tear osmolarity in patients with symptoms suggestive of DED (6). Our aim was to evaluate the presence of any alternate diseases causing DED-like symptoms.

We evaluated 100 patients who reported one or more symptoms indicative of potential DED and subsequently underwent tear osmolarity testing (TearLab Osmolarity System). The patients we included had a normal tear osmolarity test (value <308 mOsm/L in each eye, and an inter-eye difference <8 mOsm/L). The main outcome measure was the presence of any alternative diagnosis to explain the patient's symptoms.

Among these patients, the mean tear osmolarity was 293.40 mOsms/L (± 6.82), with a mean absolute difference of 2.85 mOsms/L (± 1.98) between the eyes. A possible alternative diagnosis was established in 89 percent of patients with normal tear osmolarity testing. The most frequent diagnoses included anterior blepharitis (26 percent) and allergic conjunctivitis (21 percent). Our study highlights the diagnostic value of a normal osmolarity with an extremely high proportion of patients exhibiting an alternate OSD diagnosis to account for their symptoms.

Clearly, it is important to find out what the true cause is and treat accordingly – and the TearLab Osmolarity System plays an vital role in detecting patients that otherwise could have been treated for DED.

Conclusion

The TearLab Osmolarity test has been used on 20 million eyes in 50 countries over the past decade – and it is predictive of DED 89 percent of the time (4).

The test guides a clinician by providing objective osmolarity values. This data allows a clinician to have a view on the patient's tear health, even prior to the clinical examination. Finally, the TearLab Osmolarity System is fully reimbursed by Medicare.

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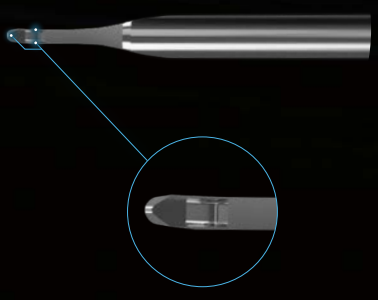
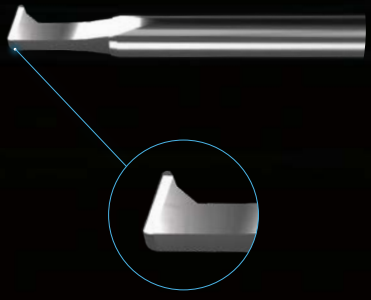
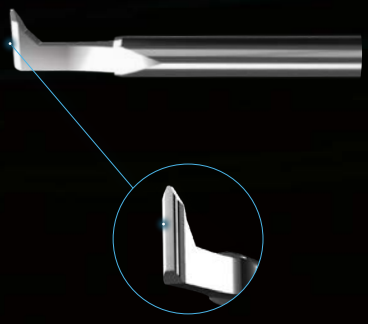


ROUNDED HEEL



TAPERED SIDES & FOOTPLATE



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THE INNOVATORS

AS ONE OF THE MOST INVENTIVE FIELDS IN MEDICINE, OPHTHALMOLOGY IS OFTEN AT THE FOREFRONT OF CUTTING-EDGE TECHNOLOGIES AND TREATMENTS. HERE, SOME OF THE LEADING INNOVATORS FROM THE OPHTHALMIC SPACE PRESENT THEIR LATEST OFFERINGS: FROM IMAGING AND DIAGNOSTICS, TO REFRACTIVE SURGERY AND GLAUCOMA CARE.

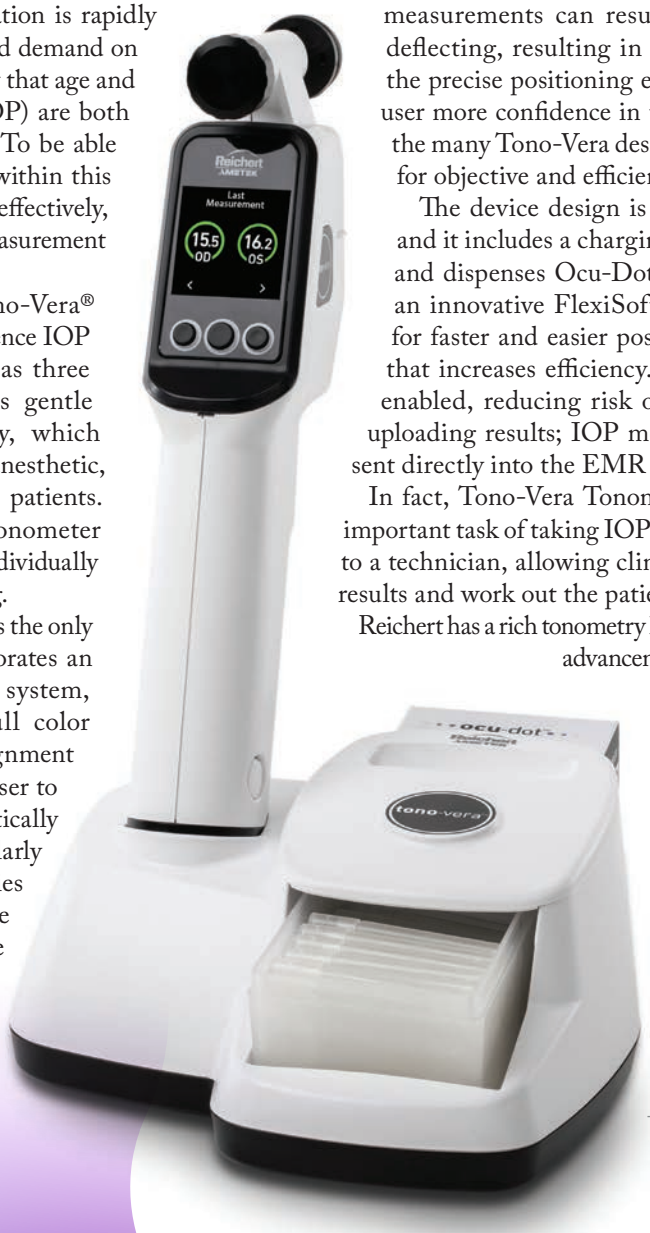
TRUSTED IOP – UNDER PRESSURE

Tono-Vera® Tonometer from Reichert® provides fast, objective, and repeatable results, giving clinicians more confidence in IOP measurements

We all know the world's population is rapidly aging, with a subsequent increased demand on healthcare systems. We also know that age and elevated intraocular pressure (IOP) are both major risk factors for glaucoma. To be able to detect and manage glaucoma within this at-risk population accurately and effectively, ophthalmologists need an IOP measurement they can trust.

The all-new Reichert® Tono-Vera® Tonometer enables a high-confidence IOP result to be obtained in as few as three measurements. The device uses gentle rebound tonometry technology, which eliminates the need for topical anesthetic, making it more comfortable for patients. Tono-Vera uses Ocu-Dot® Tonometer Probes, which are single use and individually packaged for fast and easy loading.

Notably, Tono-Vera Tonometer is the only handheld tonometer that incorporates an interactive camera positioning system, ActiView™, which offers a full color view of the eye with intuitive alignment prompts that quickly guide the user to the apex of the cornea and automatically measures. This feature is particularly important because tissue properties differ from the center to the periphery of the cornea. These property differences impact the accuracy of the measured IOP. In addition, off-center measurements can result in the probe glancing and deflecting, resulting in unreliable measurements. But the precise positioning ensured by this device gives the user more confidence in the IOP readings and is one of the many Tono-Vera design features specifically tailored for objective and efficient measurements.



The device design is compact and calibration-free, and it includes a charging base that conveniently stores and dispenses Ocu-Dot Tonometer Probes, as well as an innovative FlexiSoft™ Forehead Rest that allows for faster and easier positioning – a thoughtful design that increases efficiency. Tono-Vera is also Bluetooth® enabled, reducing risk of errors being recorded when uploading results; IOP measurements can seamlessly be sent directly into the EMR system.

In fact, Tono-Vera Tonometer is so easy to use that the important task of taking IOP measurements can be delegated to a technician, allowing clinicians more time to review the results and work out the patient's treatment plan.

Reichert has a rich tonometry heritage, having driven continuous advancement in tonometry and diagnostics for over 75 years. With the addition of the new Tono-Vera Tonometer, Reichert now offers the most comprehensive line of tonometer options to fit any practice and patient needs.

Tono-Vera is currently pending FDA Clearance; Pending Health Canada Licensing.

ADVANCING AUTOMATED CAPSULOTOMY

Improving precision and efficiency of cataract surgery with ZEPTO® – a convenient and cost-effective capsulotomy platform

Centricity Vision understands that operational efficiency is essential to serving the greatest number of patients without compromising quality of care. In addition, the changing landscape of cataract surgery has increased the demand for precision, in particular for patients receiving advanced technology lenses. When it comes to the key step of cataract surgery – creating the anterior capsulotomy – approaches that were once considered "good enough" are now obsolete, as any lack of precision at each step of a cataract procedure can impact patients' visual outcomes and satisfaction, and – ultimately – the success of surgery. And that's why Centricity Vision – a technology-focused company that is continuously innovating to help surgeons achieve clinical excellence and improve patient outcomes – recently launched its next generation ZEPTO.

Long-term visual benefits of cataract surgery are dependent on the overall stability and position of the intraocular lens implant. ZEPTO's unique microsurgical technology supports more effective positioning of the IOL within the capsular bag using precise, strong, routinely centered and automated capsulotomies that benefit from a 360-degree IOL overlap for long-term stability. The dual benefit of being able to routinely center the IOL on the patient's visual axis and to create an evenly placed 360-degree overlap with the IOL doesn't just deliver the best possible visual outcomes, it also decreases postoperative adverse events.

And it is fast. ZEPTO is able to consistently deliver capsulotomies in just 4 milliseconds.

What's more, it can be easily integrated into the existing surgical workflow; indeed, the patient and the surgeon remain together throughout the process, which improves workflow efficiency.

Imagine all this at a fraction of the cost of a femtosecond laser.

The next generation of ZEPTO includes over 16 newly enhanced features for improved usability and even more consistent capsulotomies for precise surgical outcomes. The company reports that physicians include ZEPTO in their premium IOL or refractive astigmatism-correcting packages. Centricity Vision is committed to introducing additional product enhancements and new products – some of which were first shown at the recent 2021 edition of the AAO meeting in New Orleans, USA.

A QUANTUM LEAP FOR IOLS

Setting a new standard in monofocal IOLs thanks to innovative enhancement using QUANTUM optical technology

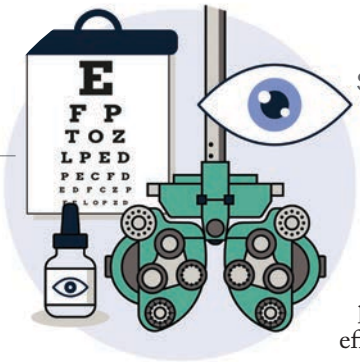
Cataract and refractive surgery patient expectations are at an all-time high, so it is important that doctors have the finest devices available to help patients achieve the best vision possible. An IOL that gives the patient the best and most accurate refractive outcomes, and a better functional vision for intermediate ranges following standard cataract surgery is a game changer in this field – and Teleon Surgical ticks all these boxes with the LENTIS QUANTUM.

The LENTIS QUANTUM enhanced monofocal IOL represents a substantial leap in monofocal IOL technology. How? By mimicking EDoF technology for improved intermediate vision, but also by ensuring a low chance of photic phenomena. This refining innovation represents a new standard in monofocal IOL design and addresses the increasing patient demand for improved outcomes following standard cataract treatment.

The Q-zone optic design is the secret sauce that gives patients improved intermediate vision. In effect, this Q-zone mimics an extended range of focus but, because a progressive surface profile is used, there is no interruption of light focusing on the retina, as there would be with a multifocal or trifocal design. Thanks to this innovative optic concept, surgeons have the opportunity to provide patients with better refractive results and functional vision compared with aspheric monofocal IOLs.

The QUANTUM optic technology will be made available on various IOL platforms, as well as toric models, to address patients requiring astigmatism correction – and will enable Teleon Surgical to continue defining the IOL space in the future. The platform – recently launched at the ESCRS 2021 conference in Amsterdam – is available in a range between 10.0 D and 30.0 D in 0.5 D increments.

Now popular with an increasing number of surgeons globally, the LENTIS QUANTUM IOL addresses increasing patient demands to achieve better outcomes in the standard range of monofocal cataract treatments.



PATIENT ADMINISTRATION WOES? HERE'S A CLEAR SOLUTION

Clearwave is a one-stop shop for digital patient engagement and administration

Patient administration is a job that must be done, but patients, clinicians and other medical staff want to spend as little time as possible dealing with it. Ideally, administration should be a relatively painless, yet reliable process. And that's where Clearwave comes in. Thanks to the platform's enabling of smooth patient scheduling, intake and automatic verification of insurance, clinicians and patients can get on with their appointment without interruption.

Clearwave's Patient Engagement Platform is the only solution on the market to enable automated, real-time insurance eligibility verification, without staff intervention. At the time an appointment is scheduled (and seven times throughout the patient engagement), primary, secondary and tertiary benefits are checked and verified within seconds. In 2021, Clearwave's Eligibility-as-a-Service automated verification and saved hundreds of thousands of hours of work for ophthalmology staffers, and contributed to a better patient experience by enabling patient financial transparency and efficient intake, overall increasing practice revenues by 65 percent.

With over 900 connections to healthcare payers, Clearwave instantly verifies both medical and vision eligibility – which is vital for ophthalmic practices. Clearwave also verifies VSP eligibility and obtains VSP authorizations instantly through its direct connection to Eyefinity, which is verified and displayed in standard format. Ultimately, it means that front desk staff are efficient and empowered, patients are happy, and physicians can focus on care. Clearwave's automated eligibility verification is embedded in Clearwave Connect and Clearwave Scheduling, providing the flexibility and efficiency of a digital tool in a one-stop shop.

All Clearwave's solutions are developed to enhance and strengthen the healthcare industry, lifting the administrative burden from patient visits. The company will continue to develop its products to support specialty practices with an understanding of their patient and performance needs.

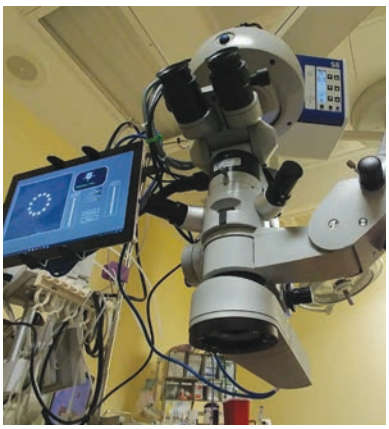
Customers are currently benefiting from Clearwave's Eligibility-as-a-Service in the United States.

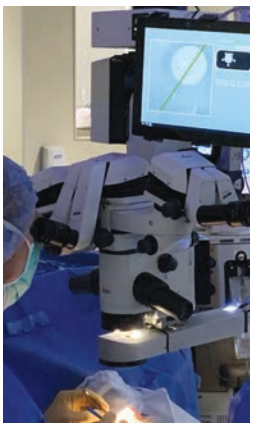
A NEW TOOL FOR TORIC IOL ALIGNMENT

Real-time intraoperative measurement of anterior cornea astigmatism with 1° accuracy during cataract surgery

Currently, only 20 percent of US cataract patients receive toric IOLs to eliminate ocular astigmatism – but 40 percent of people over 60 have astigmatism of 1D or higher, making them candidates for toric IOLs. This low rate of toric IOL adoption is partly due to the lack of simple, accurate, and affordable instruments for toric IOL alignment.

To answer this unmet need, Keen Sight, Inc. has developed a new, highly accurate tool – the Polaris Keratoscope. This novel, microscope-mounted intraoperative diagnostic device is designed to guide cataract surgeons through toric IOL implantation. Employing a patented design, Polaris Keratoscope intraoperatively measures and displays the anterior cornea astigmatism angle in real-time with 1° accuracy, providing precise surgical guidance for toric IOL alignment on touchscreen display. The device provides retro-illumination for optimum visibility of toric marks.





Polaris Keratoscope's high accuracy and ease of use aim to increase the adoption rate of toric IOL technology by cataract surgeons. Keen Sight, Inc. is dedicated to the development of new innovative ophthalmic devices to improve vision and quality of life for millions of people.

This product is currently FDA-listed and available for sale in the US. It is manufactured in California, USA.
keen-sight.com

SAVING SIGHT WITH LIGHT

Noctura 400 from PolyPhotonix offers a revolutionary, home-based non-invasive diabetic retinopathy treatment that reduces oxygen demand in the retina

Diabetic retinopathy (DR) is one of the most common causes of blindness in the world – yet most of this sight loss is preventable, if treatment is given early. Unfortunately, the majority of currently available treatments are prohibitively expensive, highly invasive, and present a significant burden to patients and healthcare systems, leaving many patients untreated.

The retina uses more oxygen per unit mass than any other tissue in the body, thanks to the phenomenally high metabolic rate of photoreceptor cells. The high demand for oxygen becomes even greater at night, rising by around 40 percent, as rod photoreceptors dark-adapt. Under normal circumstances this isn't a problem; additional oxygen demand is met by increased retinal vasculature blood flow. It's no surprise that problems start to occur when the vasculature becomes damaged – a common feature of diseases, such as DR and diabetic macular edema (DME).

Noctura 400 is a home-use, clinician prescribed (and monitored) treatment for both early and later-stages of the condition. It can also be used, in conjunction with good glycemic control, to help prevent early onset. And it seems more relevant now than ever; after all, COVID-19 has shone a new spotlight on the need for effective home-based treatments – especially for high-risk patients, including those with diabetes (the second most common underlying condition among COVID-19 patients who have died from the disease). Worn at night during sleep, Noctura 400 treatment prevents the rods from dark adaptation, which reduces the oxygen demand of the eye at night, thus preventing hypoxia and the consequent compromised blood vessel proliferation that can result in the retina.

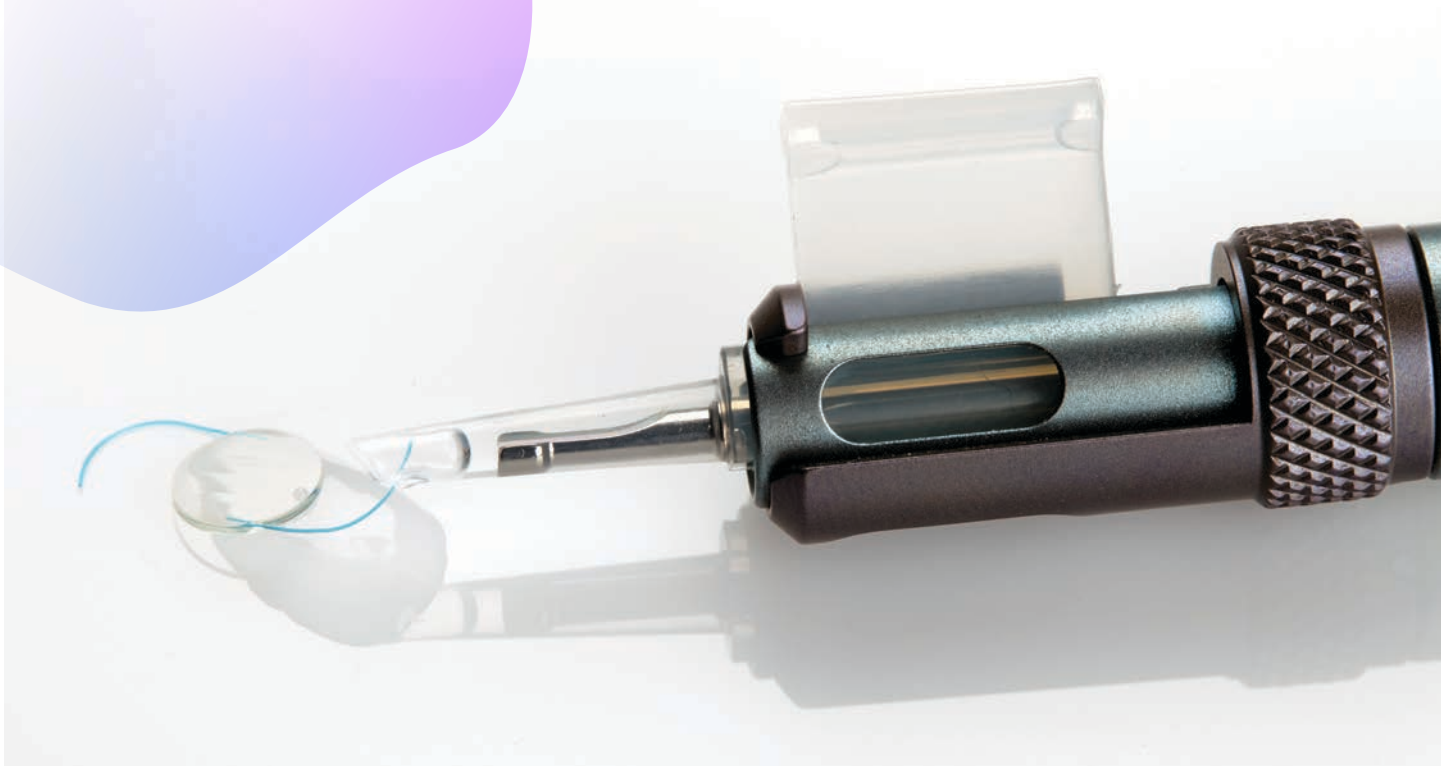
The Noctura 400 mask registers patient usage time and this information is uploaded to a PolyPhotonix-designed software system (PPX Works), which can be accessed by healthcare providers and treatment payers. Monitoring can be done remotely and the collected compliance data shows how regularly the mask has been worn – this data that can be matched with changes in visual acuity and the overall condition of the disease.

Noctura 400 already has CE marking in Europe and regulatory approval for use in a number of countries around the world.

The most recent real-world study on Noctura 400, carried out by the NHS on a group of 26 patients with diabetes displaying DR and DME, showed clinical improvement or stability in 94 percent of the patients who completed the study.

Noctura 400 revolutionizes DR treatment at a very low cost – with the aim of providing affordable treatment to the millions of people affected around the globe.

PolyPhotonix is the manufacturer of Noctura 400.



CUSTOMIZED EYESIGHT

The RxSight Light Adjustable Lens® is flipping the script by matching the IOL to the patient – not the patient to the IOL

Everything in our society, from smartphones and cars to travel experiences, is moving towards consumer customization, so why aren't intraocular lenses tailored to the customer yet? The RxSight Light Adjustable Lens (LAL) is the first and only IOL that can be customized after cataract surgery. The LAL is made of a special photosensitive material that can be adjusted in response to UV light. This optimization is done by the surgeon in the weeks following lens implantation, after the eye has healed, through a series of non-invasive light treatments, lasting only a few minutes each. Each patient has the unique ability to adjust and preview their vision until it meets their personal needs and lifestyle requirements.

Customizing the RxSight LAL is a move away from off-the-shelf lenses based on preoperative prediction – which can increase the potential for residual error. Additionally, patients who select a modern multifocal or trifocal lens cannot trial their vision to determine how they might be impacted by glare or halos.

The LAL has demonstrated the lowest level of residual refractive error seen in any astigmatism correcting IOL (1-3). The refractive corrections are performed by the RxSight Light Delivery Device that is programmed to correct spherical and cylindrical refractive error. Each adjustment is precisely administered in 0.25 D increments, correcting residual astigmatism as low as 0.50 D. By optimizing the spherical refractive target in both eyes, Dr. T. Hunter Newsom showed that out of 86 patients who were bilaterally implanted with the LAL, 80 percent saw at least 20/20 at distance and J1 at near (both uncorrected) at a follow-up visit after all light treatments were complete (4).

The LAL flips the script using postoperative adjustment and is the first ever opportunity for cataract patients to customize and test-drive their vision until they are happy with the results. There may soon be a time when people look back at cataract surgery prior to the LAL the same way we would view optometry prior to customized prescription glasses. RxSight believes this new value proposition – combining the benefits of unsurpassed refractive accuracy and complete customization to deliver the highest quality vision — will drive patient demand in coming years.

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THE ANSWER FOR AGING EYES?

Introducing LSM: a new technology that addresses age-related cross-linking of ocular tissues to tackle presbyopia, some types of glaucoma, and other ocular pathologies

The accommodation mechanism is the core moving "engine" of the eye – responsible for dynamic range of visual focus, as well as hydrodynamic equilibrium and circulatory functions. Doesn't it seem likely that there would be potential ocular health benefits in rejuvenating rigid ocular tissues?

Today, there still is no authentic viable therapeutic to rejuvenate ocular rigidity and restore accommodation biomechanics. While other surgical approaches focus on exchanging the refractive power of the cornea or the lens, LSM presents an opportunity to treat one of the causes of aging eye pathogenesis.

Aging is characterized by the accumulation of protein crosslinks and modifications that participate in tissue stiffening. In the eye, ocular rigidity has been correlated with increasing age, loss of visual accommodation as well as other age-related eye diseases. Clearly, there is an opening for a biomechanical solution to a biomechanical problem.

Introducing Laser Scleral Microporation (LSM) – an innovative therapy for the aging eye that aims to treat the ocular rigidity that occurs with age

In simple terms, LSM uses the VisioLite® Er:Yag laser to create tiny micropores in scleral tissue, in a matrix array uncross-linking collagen fibrils in hardened sclera, allowing the ciliary muscles and other accommodative anatomy beneath this ocular coat to move more freely. The 2.94 µm Er:Yag laser is a new laser wavelength in ophthalmology that is at the peak absorption of water (3.00 µm), which is ideal for vaporization of ocular connective tissue. The aim? Biomechanical restoration of Dynamic Range of Focus (DRoF) of the crystalline lens throughout all ranges of vision.

Notably, LSM does not directly affect any of the optics of the eye and is therefore a therapeutic treatment rather than a refractive correction procedure. However, because of its mode of action on cross-linking, LSM could be considered a core technology that addresses the root cause of presbyopia, certain types of glaucoma, and other age-related diseases of the eye.

Microporation therapeutics is an untapped space in ophthalmology and could expand into ocular drug delivery through scleral tissues for retinal diseases – a paradigm shift from options available today.

Right now, LSM is being evaluated in pilot studies outside of the US with Ace Vision's Gen I Prototype laser; over 180 patients have been treated. The newly developed Gen II clinical laser will be released in 2022, and US FDA clinical studies are planned for the spring of 2022.

The Aging Eye and the pathogenesis of age-related eye diseases, including accommodative biomechanical dysfunction, are poorly understood. Ace Vision's core science and research in ocular rigidity and its impact on ocular health and accommodation biodynamics are currently being packaged into courses at all major ophthalmology meetings, "The Aging Eye: The Final Frontier." The podium goals are directed not only on presenting the results of the LSM procedure, but also on illuminating accommodation biodynamics and hydrodynamics as well as the impact age has on its various functions in the eye. The company is also committed to exploring the VisioLite® technology applications in other disease states through clinical and research investigations.

The LSM procedure is currently being investigated in IRB registered pilot studies outside of the US.

PASCAL SYNTHESIS PHOTOCOAGULATOR

The fourth iteration of Pascal Laser continues to set the standard in pattern-scanning lasers

The Pascal® Laser revolutionized how retina laser treatments were performed when it was launched in 2005. Its speed, precision, and ease of use was a quantum leap in ophthalmic laser technology and was quickly adopted by the retina community – earning Pascal the title of gold standard for the treatment of diabetic retinopathy and solidifying its position as the market leader in pattern-scanning lasers. Pascal has evolved alongside the laser industry; the ergonomic Pascal Synthesis, developed by Topcon, is the technology's fourth iteration and has features specifically requested by doctors and clinical staff.

Now part of the Iridex laser family, the Pascal Synthesis is one of the most clinically efficient and versatile laser systems ever designed. Its reduced power and short pulses make procedures more comfortable for patients (1) – and its patented four-fiber beam delivery system enables even burns over varying elevations and with larger patterns. Multiple laser spots can be delivered with a single footswitch depression and the aiming beam displays the pattern for added precision. In addition, the system's new, intuitive software and high-speed pattern generators make it easy to handle large patient volumes.

Pascal features an array of treatment options – whether it's single spot, patterns, laser indirect, subthreshold retina treatments with Endpoint Management, or Pattern Scanning Laser Trabeculoplasty. The platform's innovative features make Pascal Synthesis an essential tool for retina practices, and continue to set the standard in pattern-scanning lasers.

Learn more at iridexretina.com

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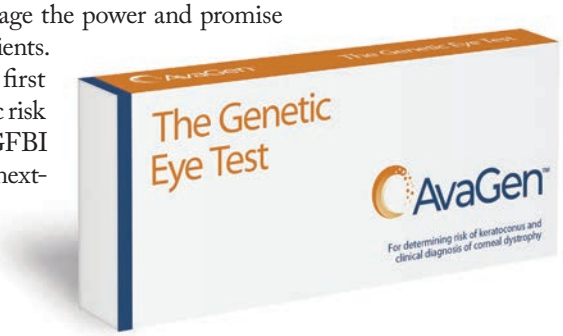
TARGETED GENE TESTING

AvaGen, The Genetic Eye Test, utilizes next-generation sequencing in its user-friendly, easily interpreted test for keratoconus and corneal dystrophies

We are in a golden age of science, with tremendous leaps being made particularly in genomics. And it is now possible for the ophthalmology community to leverage the power and promise of genetic information to benefit patients.

AvaGen™ from Avellino is the first genetic test that quantifies the genetic risk of keratoconus and presence of TGFBI related corneal dystrophies. It uses next-generation sequencing (NGS) to target both the 75 genes and more than 2,000 variants associated with keratoconus, while also targeting 70 variants of the TGFBI gene for stromal corneal dystrophies.



As keratoconus is a debilitating genetic disease that is often misdiagnosed, AvaGen is an important step ophthalmologists can take to diagnose the condition earlier, which can make a significant difference toward preserving vision over a lifetime.

AvaGen empowers more confident patient management by providing a polygenic risk score (PRS) for keratoconus, and a "yes" or "no" indication for corneal dystrophies. The results can help rule patients "in" or "out" for refractive surgery; identify the genetic risk of disease among family members; and help inform patients with suspect topographies or progressive vision changes.

The patient sample is taken via a simple cheek swab and processed in Avellino's CLIA-certified lab. The results are available to the doctor via a HIPAA-compliant portal and complimentary genetic counseling is available.

Avellino expects to expand AvaGen in 2022 to test for additional ocular diseases with a broadened panel, as well as offering a genetic test for Fuchs' dystrophy and glaucoma.

In Practice

Surgical Procedures
Diagnosis
New Drugs

Superior Surface Skills

Our adoption of technological advances should not be at the expense of the ocular surface

By Ivan Mac

As ophthalmologists, we strive to meet outcomes that match the increasingly high expectations of our patients. To do this, we invest in the latest diagnostic equipment, commit to staying at the cutting edge of innovation, and continue to learn and adopt new technologies.

But technological advancements are wasted when we don't factor in the critical role of ocular surface health in the predictability and accuracy of both pre-operative measurements and post-operative outcomes. Our clinical knowledge of ocular surface disease (OSD) must evolve alongside improvements in technology – and we must adapt our protocols for managing dry eye prior to any surgical treatment. Long gone are the days of prescribing artificial tears to all cataract patients – we can now use a much more comprehensive treatment algorithm, factoring in Meibomian gland dysfunction that occurs in up to 86 percent of all OSD cases (1).

For significant OSD, we use aggressive lid hygiene regimens, such as a course of intense-pulse light therapy or thermal lid pulsation, paired with a short course of lower-potency steroids, like fluorometholone acetate ophthalmic suspension (Flarex; Eyevance Pharmaceuticals), or at-home lid hygiene therapy, such as loteprednol (Avenova; NovaBay), in addition to artificial tears. We typically see patients three weeks after treatment – if the ocular surface has improved significantly, we go ahead and proceed with the cataract surgery measurements. We've found this regime rapidly improves the ocular surface for the vast majority of patients. And if it doesn't, we use immunomodulators, like lifitegrast or cyclosporine, and wait a few more weeks before surgery.

With each evolution in our approach, we increase the quality of visual outcomes for all patients, regardless of them opting for a premium lens or not.

"Our clinical knowledge of ocular surface disease must evolve alongside improvements in technology."

Look after the surface

Along with surgical skill, a healthy tear film is one of the most important factors for achieving excellent vision following cataract surgery.

The tear film is the first refractive surface of the eye; when it's unstable, the quality of corneal reflections is affected. This instability adversely impacts accuracy of keratometry measurements (2, 3), leading to changes in the magnitude and axis of astigmatism – then variable K-readings can affect the accuracy of IOL calculations and

result in suboptimal refractive outcomes (2–6). Moreover, it is common for dry eye disease (DED) symptoms to worsen after surgery (7) – or for the procedure itself induce or exacerbate DED (8, 9).

Beyond the accuracy of astigmatism measurements, DED can cause higher order aberrations – the most clinically significant of which are spherical aberration and coma, but these often improve with treatment.

Increases in tear osmolarity have a central role in the pathophysiology of DED, as described by the Dry Eye Workshop (10). Research supports the use of tear osmolarity as a tool for diagnosis, severity grading, and tracking therapeutic response in DED (11-18).

In our protocol, patients with osmolarity scores (measured by TearLab Osmolarity testing) above 315 mOsms/L will not proceed to the cataract workup – instead, those patients see me for further ocular surface examination. Time is a valuable commodity to all involved; the cataract workup takes up to 45 minutes, so I waste as little time as possible by not proceeding to this stage unless no further ocular surface optimization is needed.

In short, we have a golden rule: No patient goes to cataract surgery with OSD. Optimizing the ocular surface allows for a more precise outcome and a smoother postoperative course – and it also allows more patients to qualify for a premium IOL.

Conversation is key

Surgeons may worry about telling patients about delays in their progression to cataract surgery, but ensuring the best outcome must be a priority. As always, good communication goes a long way! I carefully explain that that the surface of their eye is too dry for cataract surgery, and I use this analogy: "If your car windshield isn't clean, you're never going to see well, so if I rush you through the cataract surgery without taking care of the dry eye 'windshield' preoperatively, the outcome will be one that neither of us are proud of."

In my experience, this sentence engenders patients trust – they are often willing to do whatever it takes because they know that I am looking out for their best interests, and want to deliver a superior outcome. It's also important that patients understand that dry eye is a disease, just like high blood pressure or high cholesterol. We don't wait for someone to have a heart attack before we initiate treatment for the latter. And after they've had a heart attack, we don't stop treatment! Dry eye is the same – a lifelong disorder that we can manage, but not eliminate.

An opportunity to upgrade

Through treating the ocular surface, more patients qualify for premium technology. Some surgeons worry that doing any self-pay procedures prior to cataract surgery might discourage patients from paying for advanced IOLs, but I find the reality is the opposite.

When the patient has an optimized ocular surface, they're told they are now a

"It's also important that patients understand that dry eye is a disease, just like high blood pressure or high cholesterol."

good candidate for an advanced refractive lens, and you can feel the buzz of excitement generated from them. Their willingness and enthusiasm to invest in advanced IOL technologies and OSD treatments increases, once they realize the impact that good vision has on their quality of life – especially when they've already made a good step in the right direction. It's like rewarding yourself with better running shoes after you've completed a couch-to-5k program – this prior investment in the process often leads to patients opting for the most advanced technologies available to them, thereby increasing the financial return for my practice. I continually reinforce the idea that living with OSD is a process that requires life-long treatments to both preserve the health of patients' eyes, and achieve their best vision.

In other words, devoting time to optimization of the ocular surface benefits both the patients and our practice – a true win-win!

Ivan Mac is the Founder of Metrolina Eye Associates in North and South Carolina. He is based in Charlotte, North Carolina, USA.

He reports the following financial disclosures: Consultant to Alcon, Tarsus Inc., Eyevance/Santeen Pharmaceuticals, Sun Pharmaceuticals, Ellex Inc., NovaBay, Visionary Ventures Group, TearLab.

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Under Lock and Key

Improving artificial intelligence development using blockchain – where digital health technologies converge

By Wei Yan Ng and Daniel Shu Wei Ting

Artificial intelligence (AI) is one of the key digital technologies that are expected to shape our future healthcare model (1, 2). The ophthalmic fraternity is experiencing rising optimism over the viability of AI being integrated into clinical ophthalmic care following recent successes in AI diabetic retinal photography assessment. The availability of Big Data allows AI models to be effectively trained to perform a variety of roles such as clinical decision support, virtual nursing assistance and automated diagnosis. Naturally, data as well as model architecture remain the key ingredients for the development of a robust AI algorithm. Conversely, these also present challenges that could create a bottleneck, limiting the viability of such systems. These include restrictions arising from data governance as well as trust and explainability concerns pertaining to the black-box architecture. Obstacles to data transparency and transferability not only limit multi-center collaboration but also negatively impacts user confidence.

Blockchain on the other hand is a form of distributed ledger (transaction recording) technology that emphasizes decentralization, transparency, immutability and auditability. Each transaction is recorded in a block which is linked cryptographically to the previous block via the preceding block's hash key. Metadata, such as data provenance, contributes to the derivation of the hash key and is similarly stored. This unique identifier is analogous to the fingerprint as it is both collision-resistant and deterministic. Each block undergoes a consensus process by participating stakeholders, known as nodes, before it can be verified, approved and stored on the chain. This costless verification results in an ever-growing chain of readable but immutable transactions. Popular consensus mechanisms found in most mainstream blockchain platforms include Proof of Work (Bitcoin), Proof of Stakes (Ethereum) and Practical Byzantine Fault Tolerance (Hyperledger). Blockchain platforms are also differentiated based on participation and access-rights. These include public (permissionless), private (permissioned with a single authority) and consortium blockchains (permissioned with multiple governing organizations), of which the latter two are better suited for healthcare implementation.

Blockchain in healthcare

The meteoric rise of cryptocurrency globally has generated significant interest in the utility of blockchain. As acceptance increases, the utility of blockchain has expanded beyond the usual financial remits. The healthcare sector could be poised for disruption if blockchain technology achieves greater traction. This potential was not only aptly highlighted in the 2019 technical report by the International Telecommunication Union – Telecommunication Standardization Sector (3), but has also gained new impetus with the onset of the COVID-19 pandemic. One of the most widely explored indications involves the management and access control of electronic health records. A new paradigm of patient-centric care is achieved through decentralization and cryptography, enabling peer-to-peer transaction via patient-controlled access.

"The healthcare sector could be poised for disruption if blockchain technology achieves greater traction."

This creates a new mode of medical data flow that is both traceable and secure, allowing true democratization of healthcare data. In comparison, traditional healthcare databases with client-server architectures are dependent on a central approving authority. This not only greatly limits efficient data exchange, but also creates a single point of failure that could be exploited by malicious actors.

The challenges brought about by the COVID-19 pandemic have also emphasized the need for verifiable data exchange. The case for blockchain-enabled pandemic management is clearly demonstrated by two unique scenarios – immunity or health certificates (4), and vaccine supply chain management (5). Secure cross-border exchange of data that is immutable, auditable and verifiable is critical to the success of pandemic control. Fraudulent activities such as counterfeit vaccines and forged immunity certificates are deterred in view of the transparency and traceability afforded by blockchain technology. This in return ensures proper movement control monitoring, robust contact tracing and transparent vaccine management.

Decentralized solution

Ubiquitous measures adopted to control the pandemic, such as social distancing and movement control, have also encouraged decentralization of healthcare services. These have primarily employed remote monitoring, teleconsultation as well as the integration of Medical Internet of Things (MIoT) (6). These innovative models of care not only reduced the strain on hospitals by distributing healthcare services into the community, but also deliver a measure of convenience and scalability that was lacking previously. Similarly, clinical research protocols that were previously institution-centric have been compelled to adopt remote monitoring in a bid to negotiate pandemic-induced disruptions. To achieve these, it is necessary to ensure efficient transfer and data integrity between stakeholders. In this sense, blockchain provides a ready decentralized solution by leveraging cryptography and encryption techniques to support peer-to-peer networking and costless verification. This allows medical data to be transacted in a secure purposeful manner both offline and online in spite of the need for physical separation.

The impetus for decentralization experienced in the financial sector can transform the healthcare insurance sector as well (7). In the current state, there is a lack of visibility of a patient's coverage amongst healthcare insurance providers, leading to overlapping coverage that could lead to duplicative claims. Compounding this are fraudulent claims for frivolous or excessive treatments by either patient or healthcare provider which are difficult to detect, resulting in significant losses for insurance providers. Furthermore, there is a lack of a direct communication channel between the hospital, patient and insurance provider. Coordinating between multiple parties often proves to be a long-drawn process, resulting in significant delay before a claim can be approved. Blockchain on the other hand has the potential to bridge this gap. Through peer-to-peer networking, confidential healthcare data and insurance policies can be accessed directly by pre-approved nodes, providing clarity to participating healthcare insurance vendors simultaneously. Separately, the adjudication process for each medical claim could also be expedited using blockchain smart contracts. Typically, each claim undergoes a time-consuming and laborious process involving several rounds of review prior to approval. Removing these steps through smart contract automation would significantly improve the efficiency and turnaround time for the insurance provider, reducing needless anxiety for the policyholders.

"Ubiquitous measures adopted to control the pandemic, such as social distancing and movement control, have also encouraged decentralization of healthcare services."

To read more about AI and blockchain in healthcare, and to check the references, go to top.txp.to/blockchain.

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1% / 0.3%

CME=cystoid macular edema; IFIS=intraoperative floppy iris syndrome; PEDs=pupil expansion devices.

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From Brain Science to Full Vision

Treating amblyopia in adults – and improving vision for all – with a home-based treatment course that bypass the physiology and anatomy of the eye? There's a (admittedly highly sophisticated) web-app for that.

By Yair Yahav

Visual performance is often distilled from the health of the eye – with acuity changes occurring as a direct result of eye conditions, such as amblyopia. But what if you could improve vision without targeting the physiology or anatomy of the eye? My team and I have further developed technology to do just that. By using a web-app based program that trains the visual portion of the brain, we've proven that vision can be improved by an average of 2.5 lines on the visual acuity (VA) scale and contrast sensitivity function (CSF) can improve by 100 percent (post-cataract surgery patients can return to the normal range of CSF – a 150 percent increase). These improvements can be gained at home through a course of 30–40 half-hour sessions over a two to three month period.

In short, our program enhances vision by probing specific neuronal interactions, using a set of patient-specific stimuli that improve neuronal efficiency and induce improvement of Contrast Sensitivity Function (CSF), due to a reduction of surrounding neural noise and an increase in signal detection point. The improved contrast sensitivity results an improvement in visual acuity, and also stereo acuity in amblyopia.

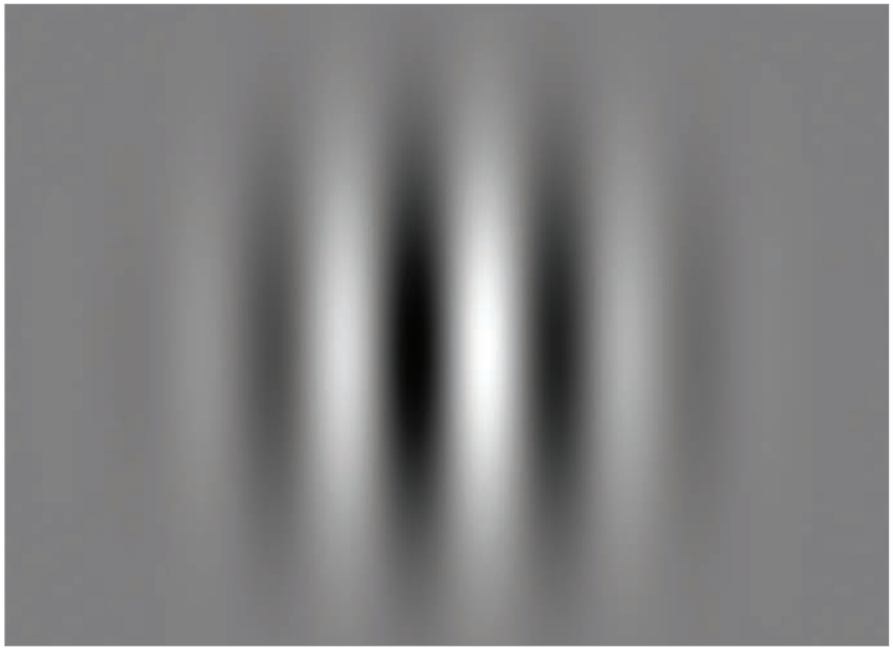

Figure 1. Gabor Patch which is mathematically designed to efficiently describe the shape of neuronal receptive fields in the visual cortex – representing the most effective stimulation.

Standing on the shoulders of giants

The scientific principles at play stem from the work of several Nobel Prize winning scientists. First up is Dennis Gabor, who created the hologram and, importantly for us, the Gabor patch (see Figure 1). The patch image has a mathematical formulation and shape that perfectly matches the receptive field of neurons in the visual cortex – and it induces a high level of stimulation for this area (2). Second, we have David Hubel and Torsten Wiesel's prize-winning discovery that individual neurons respond to visual stimuli of precise location, orientation, and spatial frequency – and also that collective neuronal interactions are responsible for image characterization (3). And that basically means that we can use specific images to target and stimulate specific individual and collective neurons to improve


Credit: Pixabay.com

vision for the patient. The final aspect of scientific background to the technology comes from discoveries made by Uri Polat: who demonstrated how neural respond of specific neurons in the primary visual cortex can be effectively increased through Lateral Masking Technique - placing Gabor patches at specific flanking positions, which masks the central Gabor target. The response to stimuli presented within the receptive field can be facilitated or suppressed by other stimuli falling outside the receptive field which, when presented in isolation, fail to activate the cell (4). In a later controlled randomized study, published in PNAS (5) Uri Polat demonstrated how this technique improves vision in adults with amblyopia beyond the critical period with lasting effect.

All of this knowledge allows us to take advantage of the brain's amazing plasticity – to both diagnose and treat visual issues. Using this Lateral Masking Technique with Gabor patches of a different location spatial arrangement, contrast, orientation, frequency, and exposure duration we can stimulate and train individual and collective neurons to improve vision tailored specifically to the patient's own visual deficits. These discoveries have led to the recent revamping of the technology, into a platform that is friendly to patients and clinicians, and the company as we know it today.

Plastic fantastic

In fact, almost all humans can improve their visual performance by capitalizing on the remnant's neuroplasticity that exist in adults. But those with visual impairments clearly stand more to gain. For example, amblyopia was previously only treatable at a critical period in youth (under nine years of age); our technology is unique in its ability to improve vision in adulthood – and there's perhaps no greater proof than FDA approval to treat amblyopia in patients over the age of nine, with no upper age limit!. Recently, the American Medical Association has approved 2 new unique CPT codes for amblyopia treatment, using RevitalVision software.

Although the technology is designed to treat one condition, by applying it to people without a cortical defect (for example, those with a minor refractive error or physical damage to the eye) we still see improved processing of images in the brain, which compensates for the blurry images being transferred from the retina. In essence, any patient with a low-vision condition can improve their eyesight through visual cortex training.

Yair Yahav is the Founder and Chief Executive Officer of RevitalVision.

Life changing improvements

The exciting thing about this technology is the broad range of people it can help. For example, consider a patient with congenital nystagmus as a consequence of albinism, who hasn't been able to acquire a driver's license; here, a couple of lines gained in VA could be life changing. We have seen people who are amazed at being able to see the subtitles on TV at home for the first time, which allows them to sit at a normal distance away from the screen. I remember an 83-year-old patient with one remaining eye, who had vision loss when she was young and had suffered from dry AMD for the last 20 years; she went from 20/100 to 20/40 vision. We have seen candidates for air force pilot course who pass all their examinations – apart from the vision exam – gain the boost needed to qualify. And we have also seen patients with Stargardt disease who retained their improved VA for at least 12 months.

It's a marathon, not a sprint

In developing the technology, we've faced a few obstacles – not least the need to start from scratch to transform it from an old windows based technology to a modern web-app to make the program and technology platform user friendly. We thought the project would take around six months – three years later, we were getting close to completion. Another burden was financial – why should investors pay into a technology that failed to reach the market after investment of $35 million by the previous owners of the company. Thankfully, by explaining the exact problem and how we were going to overcome it, we were able to gain investors. Due to the company being focused on research and development, and the rehaul that was needed on the old platform to make the treatment user friendly for clinicians and patients, our work has somewhat flown under the radar. Whereas the old platform was used because it was the only option, now that the new technology platform is finished, we're ready to hit the ground running.

Now, the main challenge ahead is the ongoing education of the market – especially when the treatable visual system is more or less perceived to end at the retina or the optic nerve. We will continue to highlight the value of our technology to all potential "customers" – which includes eye care professionals, patients, and payers in the US. Despite the brain being seen as a black hole (and neuro-ophthalmology often being more bench than bench-to-bedside), we believe the visual cortex and visual processing should be brought into modern eye care for one simply fact: it's proven ability to improve vision in line with patient needs.

In our mission, we are trying to reach as many people as possible all over the world. We currently have customers all around the world. Our focus on research and development over the past three years has had us working somewhat under the radar – but now we are very much looking forward to launching our system in the US and working with regulators in other markets.

Seeing is believing

We have a proven way to benefit from the plasticity of the human brain – in a relatively short time frame. And I can see no reason to neglect treating the brain when vision is involved; we have clinically proven that visual performance is not eye deep. I firmly believe that our treatment will become a standard part of care for treating other diseases and visual conditions. To that end, we want to expand the FDA approval to other conditions (currently, it only covers amblyopia for ages nine and above).

If you're reading this and in any way dubious about the technology, I am very keen to point you to our solid base of research and evidence. We find that skeptical ophthalmologists typically change their stance after a short presentation outlining the scientific principles and clinical data, but they often want to check it out for themselves – and we encourage all good doctors to do the same! After all, "seeing is believing."

Yair Yahav is the Founder and Chief Executive Officer of RevitalVision, based in Modi'in-Maccabim-Re'ut, Israel.

See references online at: top.txp.to/brain/science

Picture perfect

How does the technology work?

With a digital camera, the quality of the final image depends on two main factors: image capturing and image processing. Therefore, if you use a digital camera with an imperfect lens but improve the processor, you can access an image with better resolution. Similarly, the quality of the image seen by humans is dependent on how the image is transferred from the retina to the brain and subsequent visual processing. If you can't improve the anatomy of the eye any further, vision can still be improved by working on the processor.

Another analogy is fitness training – but instead of the effects of your hard work wearing off when life gets in the way and you can't train for a while, the neural connections built over the sessions stay. In that way, I suppose it is more comparable with learning to swim or ride a bike – the visual improvement is retained for years when it is improved through the brain.

tyrvaya™
(varenicline solution)
nasal spray 0.03 mg

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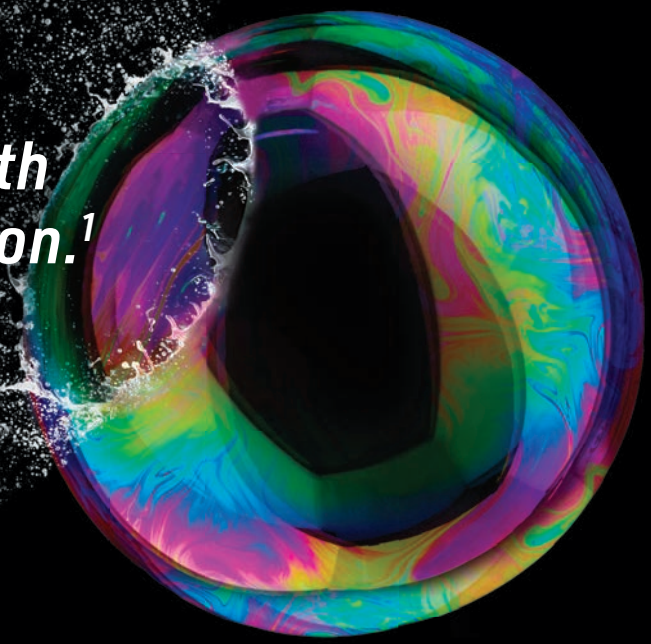

Dry eye starts with tear film disruption.[1]

Treat by activating tear film production.[2]

INTRODUCING A WHOLE NEW WAY TO TREAT DRY EYE DISEASE.[2]

Tyrvaya™, the first and only nasal spray approved to treat the signs and symptoms of dry eye, is believed to activate the trigeminal parasympathetic pathway via the nose, resulting in increased tear film production.[2] The exact mechanism of action is unknown at this time.

Watch Tyrvaya in action at Tyrvaya-pro.com.

INDICATION

Tyrvaya™ (varenicline solution) Nasal Spray is indicated for the treatment of the signs and symptoms of dry eye disease.

Please see Brief Summary of Prescribing Information on the adjacent page and the full Prescribing Information at Tyrvaya-pro.com.

IMPORTANT SAFETY INFORMATION

Adverse Reactions

The most common adverse reaction reported in 82% of patients was sneezing. Events that were reported in 5-16% of patients were cough, throat irritation, and instillation-site (nose) irritation.

References: 1. Craig JP, Nelson JD, Azar DT, et al. *Ocul Surf.* 2017;15(4):802-812. **2.** Tyrvaya. Prescribing Information. Oyster Point Pharma; 2021.

tyrvaya™
(varenicline solution)
nasal spray 0.03 mg

BRIEF SUMMARY: Consult the full Prescribing Information for complete product information available at www.tyrvaya-pro.com.

INDICATIONS AND USAGE

TYRVAYA™ (varenicline solution) nasal spray is a cholinergic agonist indicated for the treatment of the signs and symptoms of dry eye disease.

ADVERSE REACTIONS

Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the 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 three clinical trials of dry eye disease conducted with varenicline solution nasal spray, 349 patients received at least 1 dose of TYRVAYA. The majority of patients had 31 days of treatment exposure, with a maximum exposure of 105 days.

The most common adverse reactions reported in 82% of TYRVAYA treated patients was sneezing. Other common adverse reactions that were reported in >5% of patients include cough (16%), throat irritation (13%), and instillation-site (nose) irritation (8%).

USE IN SPECIFIC POPULATIONS

Pregnancy: Risk Summary: There are no available data on TYRVAYA use in pregnant women to inform any drug associated risks. In animal reproduction studies, varenicline did not produce malformations at clinically relevant doses.

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data: *Animal Data*: Pregnant rats and rabbits received varenicline succinate during organogenesis at oral doses up to 15 and 30 mg/kg/day, respectively. While no fetal structural abnormalities occurred in either species, maternal toxicity, characterized by reduced body weight gain, and reduced fetal weights occurred in rabbits at the highest dose (4864 times the MRHD on a mg/m^2 basis).

In a pre- and postnatal development study, pregnant rats received up to 15 mg/kg/day of oral varenicline succinate from organogenesis through lactation. Maternal toxicity, characterized by a decrease in body weight gain, was observed at 15 mg/kg/day (1216 times the MRHD on a mg/m^2 basis). Decreased fertility and increased auditory startle response occurred in offspring at the highest maternal dose of 15 mg/kg/day.

Lactation: Risk summary: There are no data on the presence of varenicline in human milk, the effects on the breastfed infant, or the effects on milk production. In animal studies varenicline was present in milk of lactating rats. However, due to species-specific differences in lactation physiology, animal data may not reliably predict drug levels in human milk.

The lack of clinical data during lactation precludes a clear determination of the risk of TYRVAYA to an infant during lactation; however, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TYRVAYA and any potential adverse effects on the breastfed child from TYRVAYA.

Pediatric Use: Safety and efficacy of TYRVAYA in pediatric patients have not been established.

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

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Issued: Oct 2021
OP-TYR-000867 10/21

Profession

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Your business
Your life

OCTA Whisperer

Philip Rosenfeld, an inspiration to the world of retina, shares his life story and his views in an interview with Omer Trivizki

Omer Trivizki, Macular Center, Director of Ophthalmology at Tel Aviv Medical Center, Tel Aviv University, Tel Aviv, Israel, and Research Associate in Ophthalmology at the Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami, Florida, USA:

Let's start at the very beginning! Did you always want to be a physician?

Philip Rosenfeld, Professor of Ophthalmology, Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, FL, USA: Yes, I did! My uncertainty was whether I wanted to get formal research training. Nowadays, MD/PhDs are common, but when I was in college, the idea of getting a combined degree was just getting traction. There were always PhDs who went back for an MD, but it was unusual for a clinician to go back and get a PhD. I often ask those people whether they were researchers who wanted the insurance of an MD title or clinicians who wanted to do research. In the past, physicians who wanted to do research would just go into a lab and be a postdoc, and while there are many examples of successful clinician-researchers, I came to realize that laboratory science was getting so complex that the training I would get as a postdoc would be very different to the training I would get as a real PhD student learning how to be a scientist. Nowadays, some MD/PhD programs will grant the PhD after a certain number of years in the lab, but I wanted a real PhD; I wanted a program that threw the PhD student into the lab with no guarantees. I spent five years in the lab, and, in retrospect, it was far more difficult to get the PhD than the MD; moreover, the experience made me a far better researcher than if I had gone back after medical school to be a postdoc. The PhD gave me the basic tools on how to direct my skills and answer any research question. I learned that scientific rigor was most important – not the techniques or learning about the specific scientific area of the PhD research. I see MD/PhD graduates making the same mistake over and over again when they stubbornly stick to the same area of science that they studied as a graduate student. The real value of the MD/PhD training is to follow your medical passion and ask the important research questions in whatever medical field you choose – and then to go ahead and advance medical knowledge and patient care in that specialty.

How did you get into ophthalmology?

I fell in love with ophthalmology as a fourth year medical student after I already matched in OB/GYN to be a reproductive endocrinologist. I got two-thirds of the way through my third year of my four-year OB/GYN residency before I switched to ophthalmology. As an OB/GYN resident, I decided to spend my elective time with Stuart Fine, who was very influential in getting me to fall in love with ophthalmology as a medical student. His fellows at the time were Karl Csaky and Jenny Lim. How lucky could I get?! I was convinced there and then to make the switch into ophthalmology. We all remain good friends and it all goes back to when they were medical retina fellows and I was an OB/GYN resident.

"I often ask myself if I've made any bad decisions in my life, and I'm fortunate to say that I would not change anything."

That's a long story, but it's a great

Philip Rosenfeld

Omer Trivizki

example of a decision being both a mistake and a great turn of events, in many ways. I often ask myself if I've made any bad decisions in my life, and I'm fortunate to say that I would not change anything. By changing one decision, there is no guarantee that I would end up in the same place, and I have the greatest job in the world. My dream would be to do what I do now – but with unlimited funding so that I could explore all the essential but unanswered questions in retina – especially in AMD. And if I won the lottery, I would self-fund all my research and continue on exactly the same path.

What inspired you to become a retina specialist?

Genetics. I was a molecular biologist/geneticist by training and I loved the way inherited retinal diseases could be followed by just examining the eye.

What questions are bothering you today?

I embrace cognitive dissonance. I look at the facts and try to make sense of them, and when the puzzle pieces don't go together, I start thinking of alternative explanations. And that's why favorite saying is "Sacred cows make the best burgers." Also, I'm hypnopompic, which means I get my best thinking done just before I wake up, and that continues into the shower. By focusing on a clinical problem that's really bothering me, I use the morning to devise experiments that will answer the question. For example, the other morning I was torturing myself by trying to understand why extrafoveal GA grows faster than foveal-involving or central GA. I think I understand why the cone-rich/Mueller cell-rich fovea resists atrophy until late in the disease process, but why should the entire GA lesion slow down once the GA is consumed. I think I figured it out – and now we're testing my hypothesis.

If you could to talk to Phil in his first day of residency, what would you tell him?

"Relax, you've got this. Trust your gut, follow your instincts, and ask the important questions; specifically, go where's the unmet need. One of the great advantages of going down a unique untraveled path is that you don't have to read all the research that was done by others. Worry less, and enjoy the journey!"

Philip, you changed the world with Bevacizumab. How did it come about? What in your training or your personality made you capable of making this amazing step?

Well, it goes back to my PhD training and being comfortable with science even though it was outside my area of specialization. As a graduate student, I studied adenovirus DNA replication, protein biochemistry, and viral molecular biology. It was that training that made me comfortable understanding the molecular biology and protein biochemistry of VEGF. I soon realized that Avastin and Lucentis were derived from the same bacterial plasmid construct, they bound VEGF at the same

"One of the great advantages of going down a unique untraveled path is that you don't have to read all the research that was done by others."

position, and the only real difference was size. Avastin was commercially available for colon cancer therapy, so I devised an experiment using intravenous Avastin, which was successful, and that led to intravitreal Avastin. Of course, OCT played an important role in this research; however, it was my PhD training that gave me the confidence to connect the dots and devise the clinical study.

Let's pretend for a moment that I know nothing about your research. What is your research group currently working on?

Our goal is to understand the progression of AMD and help develop a treatment to prevent this progression and preserve vision. OCT imaging has played a pivotal role in this research, and swept source OCT angiography (SS OCTA) has been instrumental in our success.

What is it important for ophthalmologists to know about this technology?

OCT and OCTA are inseparable. It isn't one or the other. OCTA needs the structural information as well as the flow information. You need to let the OCTA teach you about the disease, and to achieve this goal, you have to interact with the scans and learn the importance of segmenting the layers you want to study. The information that OCTA provides about a disease is never ending, you just have to open your mind to the technology. I guess I'm an OCTA whisperer.

Unfortunately, it has been held back due to cost, time, effort, and some clinicians' lack of willingness to learn.

What are your expectations for this research?

I want to image a patient with AMD, characterize their disease primarily by using SS-OCTA, and predict their disease progression without treatment. Then, we can show them what will happen and then start treatment and change their destiny.

With the significant advances in ophthalmic imaging and automated algorithms, do you think there will ever come a time when ophthalmologists are more like radiologists?

These algorithms will free us to ask the next important question. Think of them as liberating, rather than limiting what we will do.

What's changed for you since the start of the pandemic?

My clinic is more efficient. I rely more on OCT imaging. I travel less. And my research has been more productive. I doubt I will ever go back to my road-warrior days. I think the long-term effects of the pandemic on the field of retina will be more imaging, and fewer exams.

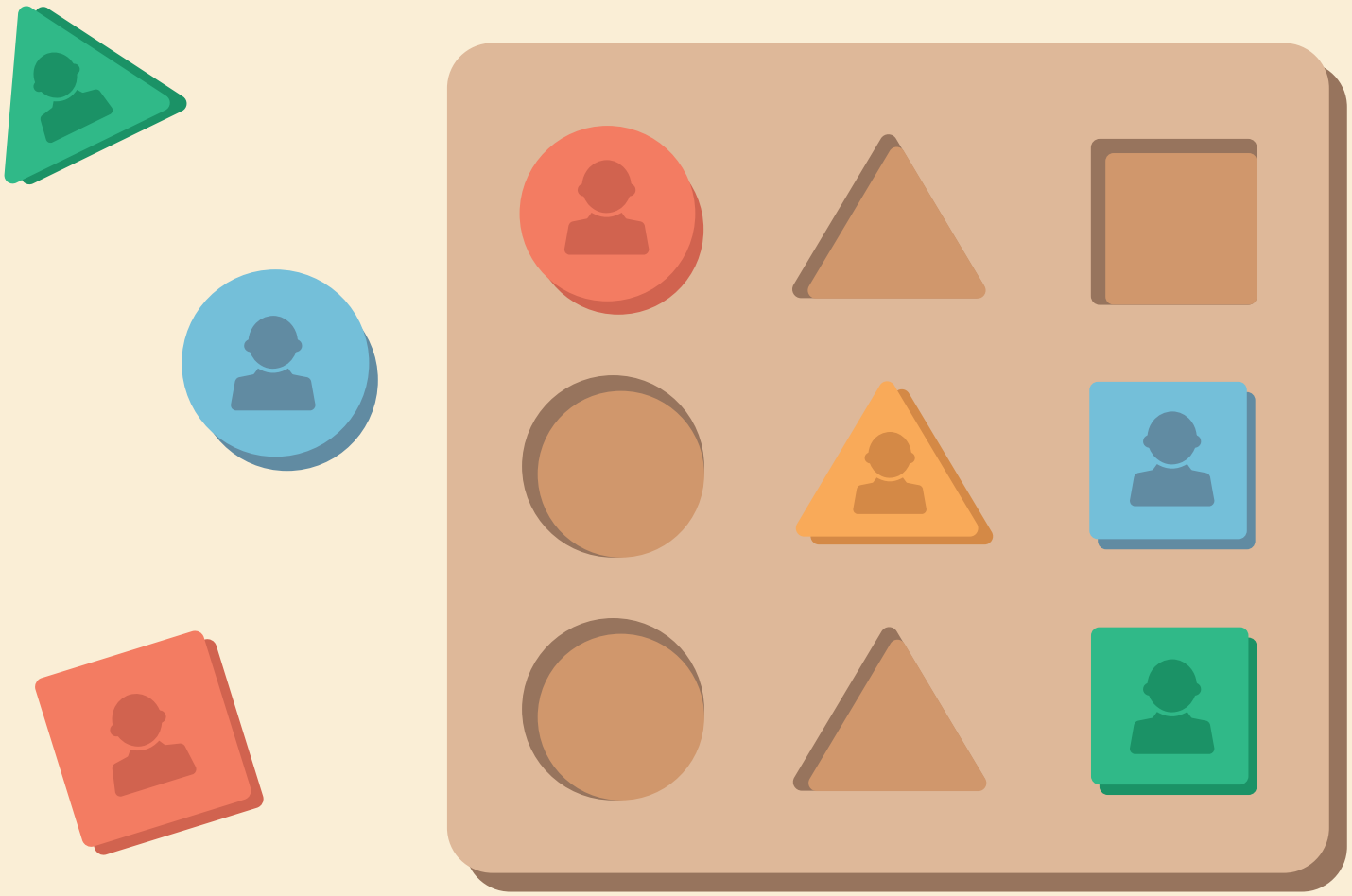
Do you worry about the future of the field?

I have no fears about retina; there are so many unanswered questions and so much vision to save!

When One Size Doesn't Fit All

Improving your ergonomic set up to ensure a long and healthy career in ophthalmology

By Samuel Masket



Even before the pandemic threw a curveball, wellness of physicians was becoming an increasingly prominent subject. "Wellness" – unsurprisingly – is a multifactorial issue, with loss of physician autonomy, bureaucratic snafus, loss of the doctor-patient relationship, and trivialization of medical expertise gained over time, being a snapshot of examples. Many of these forces culminate in physicians working longer hours and having an increased throughput of patients – resulting in both mental and physical fatigue. The latter is closely intertwined with the ergonomics of the workplace and its impact on the physician's body.

As Vince Lombardi (legendary American football coach) once stated, "fatigue makes cowards of us all." Translating that adage to the practice of ophthalmology: a tired physician, or one in chronic pain, will perceive their own function as unsatisfactory, and this will likely lead to underperformance.

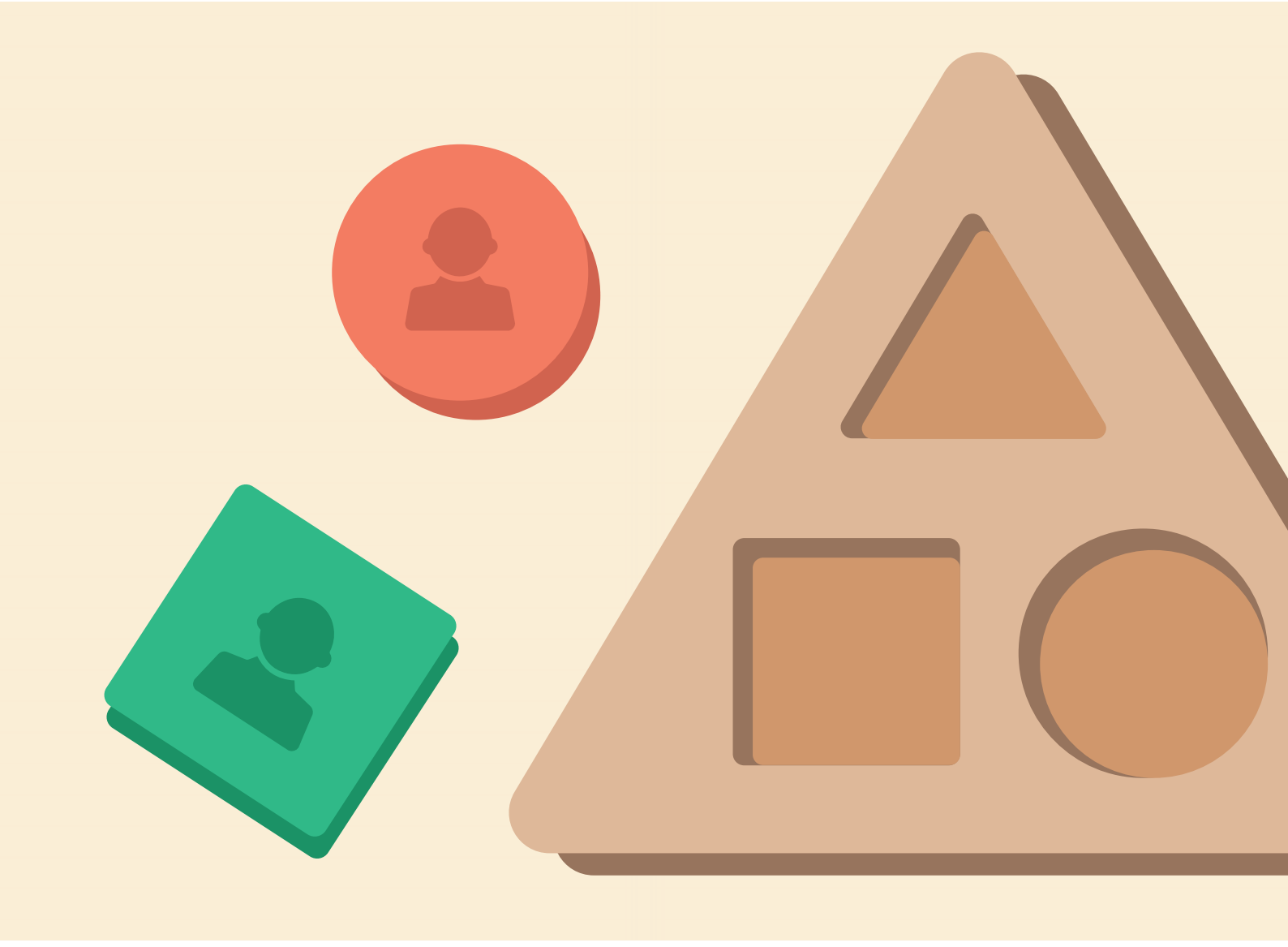
Evidence shows that ophthalmologists are over twice as likely to have neck pain, two and a half times more likely to suffer hand or wrist pain, and three times more likely to experience back pain than family medicine practitioners (1). These musculoskeletal disorders (MSDs) are linked to age, hours of work, numbers of procedures performed, and being female – and, shockingly, they are responsible for premature retirement in 15 percent of ophthalmologists (2).

Whodunnit?

First of all, we must ask, "Where do these problems begin?" Consider the workplace of the office and the operating theater and how physicians position their bodies – factoring in the elements of time and repetition. Slit lamps often require that the examiner pull their head forward, inducing neck hyperextension or increased lordosis. Typically the patient has their head erect, whereas the examiner cranes their neck to see through the oculars – a posture that may lead to permanent structural damage to the neck.

"I have no doubt that the changes in my neck are related to an absence of good ergonomic design and posture planning during my career."

A good example of this is my own neck! It's possible to see the structural changes that have occurred after a long ophthalmology career in my now 74-year-old neck compared with a healthy young adult neck MRI – particularly the increased lordotic curve and the stenotic cervical canal. I have no doubt that the changes in my neck are related



to an absence of good ergonomic design and posture planning during my career. Moreover, indirect ophthalmoscopy with a patient whose neck is in an erect position forces the examiner into contortions that will undoubtedly induce fatigue and, later on, structural damage to the back. During my training program, indirect ophthalmoscope exams were carried out with the patient supine on an examination table, inducing far less stress; however, in daily clinical practice this is impractical.

Another culprit is the operating theater, where the surgical microscope causes surgeons to conform to a standardized set up – making it difficult to properly perform surgery and assure patient comfort for best results. It is uplifting to recognize that a newer approach to surgery incorporates a "heads up" remote view for the surgeon, reducing neck stress.

A final set of burdens to an ophthalmologist's physical wellness are computer monitors and keyboards, which can both add significant stress to necks and wrists when not arranged with occupational health in mind.

Prevention – better than cure

Physical changes that occur in senior surgeons are likely chronic – and remediation is therefore challenging if not impossible. So a major concern to me is that trainees and young practitioners appear to be largely unaware of the looming problems; after all, it is their age group that has the greatest chance of preventing MSDs. It is sobering to learn

"A major concern to me is that trainees and young practitioners appear to be largely unaware of the looming problems."

that many corporations evaluate and advise on the ergonomic set up for new office staff members – unfortunately, ophthalmology residents and fellows get no such investigation and support in their training programs. Adding insult to injury, a recent review of the literature found 41 articles related to ophthalmic operating theater ergonomics, but only nine referenced trainees (3). Early career intervention is key to remove the issue and prevent problems later in one's career – requiring the cooperation and involvement of national and supernational organizations.

Equally important, we need coordination among equipment designers, ergonomic experts, and physical therapists to establish a plan for prevention and treatment of MSDs among ophthalmologists. Akin to professional athletes, ophthalmologists cannot compete without their own good health. With a comprehensive approach, we can improve the longevity and productivity of all eye surgeons' careers.

Samuel Masket is Clinical Professor at the Stein Eye Institute, UCLA, Los Angeles, USA, and Chair - American Academy of Ophthalmology Senior Ophthalmologists Committee.

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Neurotrophic keratitis is a degenerative disease that warrants immediate attention[1]

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Endogenous NGF is a protein involved in the differentiation and maintenance of neurons and is believed to support corneal integrity through three mechanisms (in preclinical models): corneal innervation, tear secretion, and epithelial cell growth.[3-5]

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OXERVATE is a recombinant human nerve growth factor indicated for the treatment of neurotrophic keratitis.

Important Safety Information

WARNINGS AND PRECAUTIONS

Patients should remove contact lenses before applying OXERVATE and wait 15 minutes after instillation of the dose before reinsertion.

ADVERSE REACTIONS

The most common adverse reaction in clinical trials that occurred more frequently with OXERVATE was eye pain (16% of patients). Other adverse reactions included corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation, and increase in tears (1%-10% of patients).

Please see additional Important Safety Information on accompanying page and full Prescribing Information, including patient information, at OXERVATE.com/prescribing-information.

You may report side effects to FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Dompé at 1-833-366-7387 or Usmedinfo@dompe.com.

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*Study NGF0212 (REPARO): 52 patients per group; European patients with NK in one eye; 72% of patients completely healed; key findings were after 8 weeks of treatment; 6 times daily; vehicle response rate 33.3%.[2] Study NGF0214: 24 patients per group; US patients with NK in one or both eyes; 65.2% completely healed; vehicle response rate 16.7%[2,7]

†Complete corneal healing was defined as the absence of staining of the corneal lesion and no persistent staining in the rest of the cornea after 8 weeks of OXERVATE treatment.[2]

References: 1. Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. *Clin Ophthalmol.* 2014;8:571-579. **2.** OXERVATE (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/mL) [US package insert]. Boston, MA: Dompé U.S. Inc.; 2019. **3.** Voelker R. New drug treats rare, debilitating neurotrophic keratitis. *JAMA*. 2018;320:1309. **4.** Mastropasqua L, Massaro-Giordano G, Nubile M, Sacchetti M. Understanding the pathogenesis of neurotrophic keratitis: the role of corneal nerves. *J Cell Physiol*. 2017;232:717-724. **5.** Muzi S, Colafrancesco V, Sornelli F, et al. Nerve growth factor in the developing and adult lacrimal glands of rat with and without inherited retinitis pigmentosa. *Cornea*. 2010;29:1163-1168. **6.** Data on file. Dompé U.S. Inc.; 2021. NGF0212. **7.** Pflugfelder SC, Massaro-Giordano M, Perez VL, Hamrah P, Deng SX, Espandar L, et al. Topical recombinant human nerve growth factor (cenegermin) for neurotrophic keratopathy. *Ophthalmology*. 2020;127:14-26.

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US-OXE-1900180.02 02/21

oxervate®
(cenegermin-bkbj ophthalmic solution) 0.002% (20 mcg/mL)

Brief Summary of Safety

Consult the full Prescribing Information for complete product information.

INDICATIONS AND USAGE

OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% is indicated for the treatment of neurotrophic keratitis.

DOSAGE AND ADMINISTRATION

Contact lenses should be removed before applying OXERVATE and may be reinserted 15 minutes after administration.

If a dose is missed, treatment should be continued as normal, at the next scheduled administration.

If more than one topical ophthalmic product is being used, administer the eye drops at least 15 minutes apart to avoid diluting products. Administer OXERVATE 15 minutes prior to using any eye ointment, gel or other viscous eye drops.

Recommended Dosage and Dose Administration

Instill one drop of OXERVATE in the affected eye(s), 6 times a day at 2-hour intervals for eight weeks.

ADVERSE REACTIONS

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

In two clinical trials of patients with neurotrophic keratitis, a total of 101 patients received cenegermin-bkbj eye drops at 20 mcg/mL at a frequency of 6 times daily in the affected eye(s) for a duration of 8 weeks. The mean age of the population was 61 to 65 years of age (18 to 95). The majority of the treated patients were female (61%). The most common adverse reaction was eye pain following instillation which was reported in approximately 16% of patients. Other adverse reactions occurring in 1-10% of OXERVATE patients and more frequently than in the vehicle-treated patients included corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation and tearing.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary There are no data from the use of OXERVATE in pregnant women to inform any drug associated risks.

Administration of cenegermin-bkbj to pregnant rats or rabbits during the period of organogenesis did not produce adverse fetal effects at clinically relevant doses. In a pre- and postnatal development study, administration of cenegermin-bkbj to pregnant rats throughout gestation and lactation did not produce adverse effects in offspring at clinically relevant doses.

Animal Data

In embryofetal development studies, daily subcutaneous administration of cenegermin-bkbj to pregnant rats and rabbits throughout the period of organogenesis produced a slight increase in post-implantation loss at doses greater than or equal to 42 mcg/kg/day (267 times the MRHOD). A no observed adverse effect level (NOAEL) was not established for post-implantation loss in either species. In rats, hydrocephaly and ureter anomalies were each observed in one fetus at 267 mcg/kg/day (1709 times the MRHOD). In rabbits, cardiovascular malformations, including ventricular and atrial septal defects, enlarged heart and aortic arch dilation were each observed in one fetus at 83 mcg/kg/day (534 times the MRHOD). No fetal malformations were observed in rats and rabbits at doses of 133 mcg/kg/day and 42 mcg/kg/day, respectively. In a pre- and postnatal development study, daily subcutaneous administration of cenegermin-bkbj to pregnant rats during the period of organogenesis and lactation did not affect parturition and was not associated with adverse toxicity in offspring at doses up to 267 mcg/kg/day. In parental rats and rabbits, an immunogenic response to cenegermin-bkbj was observed. Given that cenegermin-bkbj is a heterologous protein in animals, this response may not be relevant to humans.

Lactation

There are no data on the presence of OXERVATE in human milk, the effects on breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for OXERVATE, and any potential adverse effects on the breastfed infant from OXERVATE.

Pediatric Use

The safety and effectiveness of OXERVATE have been established in the pediatric population. Use of OXERVATE in this population is supported by evidence from adequate and well-controlled trials of OXERVATE in adults with additional safety data in pediatric patients from 2 years of age and older [*see Clinical Studies (14)*].

Geriatric Use

Of the total number of subjects in clinical studies of OXERVATE, 43.5 % were 65 years old and over. No overall differences in safety or effectiveness were observed between elderly and younger adult patients.

NONCLINICAL TOXICOLOGY

Carcinogenesis and Mutagenesis Animal studies have not been conducted to determine the carcinogenic and mutagenic potential of cenegermin-bkbj.

Impairment of fertility Daily subcutaneous administration of cenegermin-bkbj to male and female rats for at least 14 days prior to mating, and at least 18 days post-coitum had no effect on fertility parameters in male or female rats at doses up to 267 mcg/kg/day (1709 times the MRHOD). In general toxicology studies, subcutaneous and ocular administration of cenegermin-bkbj in females was associated with ovarian findings including persistent estrus, ovarian follicular cysts, atrophy/reduction of corpora lutea, and changes in ovarian weight at doses greater than or equal to 19 mcg/kg/day (119 times the MRHOD).

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The Pursuit of Perfection

Sitting Down With…
Gerd U. Auffarth, Professor and Chairman of the Department of Ophthalmology, University of Heidelberg; and Director of the International Vision Correction Research Centre, David J Apple International Laboratory for Ocular Pathology, Germany

How did you become an ophthalmologist?

When I was 12 or 13 years old, I came across a book by Albert Schweitzer, a famous German physician, theologian, writer and humanitarian, who built a hospital in Lambaréné, Gabon. Reading about his ethical approach, and about him overcoming difficulties and rebuilding the hospital three times, I was transfixed. So, at the age of 13, I decided I wanted to do what Schweitzer did, and that thought stayed with me. A few years later, I got into medical school. At the time, I was mostly interested in biochemistry and genetics, but before I even got my medical degree, I managed to get to the hospital at Lambaréné! I worked there for a couple of months, practicing pediatrics and tropical medicine, but the person who helped me get there was an ophthalmologist. Wilfried Hunold, professor at the University of Aachen, approached me early on in my medical studies to ask if I was interested in writing a doctoral thesis in ophthalmology. I was really into research, and ophthalmology was the perfect field to pursue those interests. Thanks to Hunold, I started participating in research groups, and I was giving lectures at ARVO in my second and third year of medical school. My thesis was in pediatric ophthalmology. One day, Hunold told me he had a friend who worked in Gabon, and asked whether I'd ever heard about Albert Schweitzer and his hospital! I exclaimed that he needed to call his friend there and then, and ask him if I could join his team.

Tell me more about Hunold and your other mentors…

Thanks to Hunold, I got to do so much interesting work early on in my career. First, I worked with autorefractors for pediatric patients when they were first invented in the 1980s. I also did pharmacological and pharmacokinetic studies on atropine, working with the University of Turku in Finland as they performed blood analysis I needed for my research. When I finished medical school, it was very clear that I would stay with ophthalmology, and my first position was in Hunold's hospital. He introduced me to his good friend, David J. Apple Professor of Ophthalmology and Pathology, Chairman of the Storm Eye Institute at the Medical University of South Carolina, in Charleston, USA, where I then spent two years doing my postdoc. After that, I was in a privileged position, where many German universities were interested in hiring me. I chose Heidelberg and built up my expertise on the clinical side, and then, when Apple died, I moved his laboratory here. Over the years, I went from a resident, faculty member, professor, culminating in the chairman position.

Do you ever wonder where you would be if you made different decisions?

There seem to have been a few very fortunate coincidences in the course of my career, but perhaps I was subconsciously working to make them happen? One thing is certain – when those opportunities arose, I didn't even have to think about them, I was able to say "yes" immediately, grab them, and be on my way. I could've made different decisions – such as staying in the US after the two years I spent in Charleston – but my gut feeling was to come back to Germany, and it has worked out well for me. My wife actually says that whatever I did, I would've ended up in the same position!

When I talk about how my career unfolded, it seems like one opportunity led to another but behind all that, there was a huge amount of hard work.

Could I have succeeded in a different profession? I guess so – I have had an interest in business, seeing how companies work. I have been sitting on boards of directors of a few different companies, which has been really interesting.

How did you become interested in optics?

The late 1980s and early 1990s was a time when so many new optical applications came about. I took part in implanting the very first multifocal lenses at the time, I did a lot of research around new IOLs and their applications – it was a very new and exciting area. My team was the first in Germany to use AcrySof materials in a multicenter trial, and I looked at glistenings. So then, at the Apple lab, it was quite natural for me to focus completely on IOLs. We did a lot of FDA studies on new materials, and a lot of that work was unpublished and confidential, but I learned a lot about IOL pathologies, and I was around innovative ideas in optics. I am quite passionate about finding the perfect material, design and type of optics for an IOL, so that side effects are minimized. It is this pursuit of perfection that has kept me interested in the field!

"When I talk about how my career unfolded, it seems like one opportunity led to another but behind all that, there was a huge amount of hard work."

What motivates you these days?

I find my motivation in family, my academic environment, and seeing how my mentoring and support helps other people develop their potential. I have also found motivation in industry partners understanding how vital it is that they keep finding new ways to develop their optics to reduce side effects such as photic phenomena, and optimize materials. It's heartening to be working in a field where everyone really tries to improve things, and being part of this process.

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References: 1. EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. August 2019. **2.** Data on file. Regeneron Pharmaceuticals, Inc.

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