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Image of the Month

The Hills Are Alive…

Keith Salmon is a professional artist who has been visually impaired for the last 25 years. Trained in fine arts and sculpture, Salmon worked to adapt his techniques as his eyesight deteriorated due to diabetic retinopathy. This image is of Glen Rosa on the Isle of Arran, Scotland. "Although I am primarily a painter, I have been experimenting with the idea of incorporating sound with some of my larger artworks. In late 2015 I was invited to join a small research team working at Microsoft in Seattle, who had developed the idea of using their Kinect technology to create an audio interpretive tool to help visually impaired folk better interpret two-dimensional images. This evolved into a large installation piece called The Oregon Project, which is now to be exhibited at the Tent Gallery in Edinburgh University in April this year." *Image courtesy of Keith Salmon, www.keithsalmon.org*

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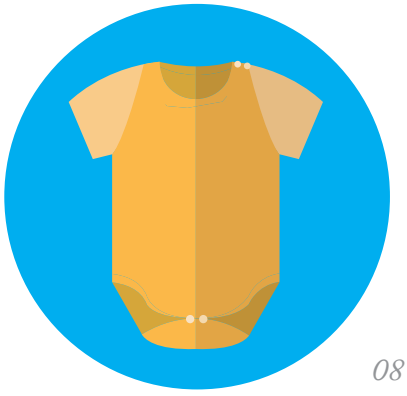

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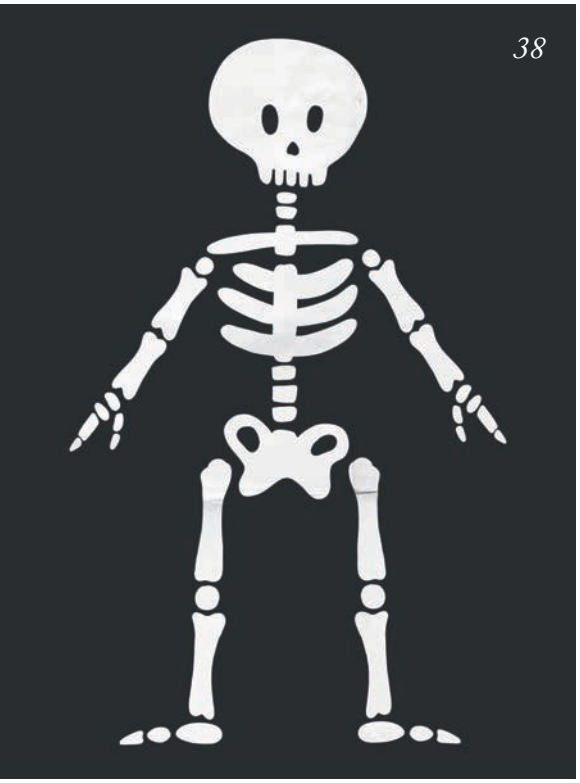

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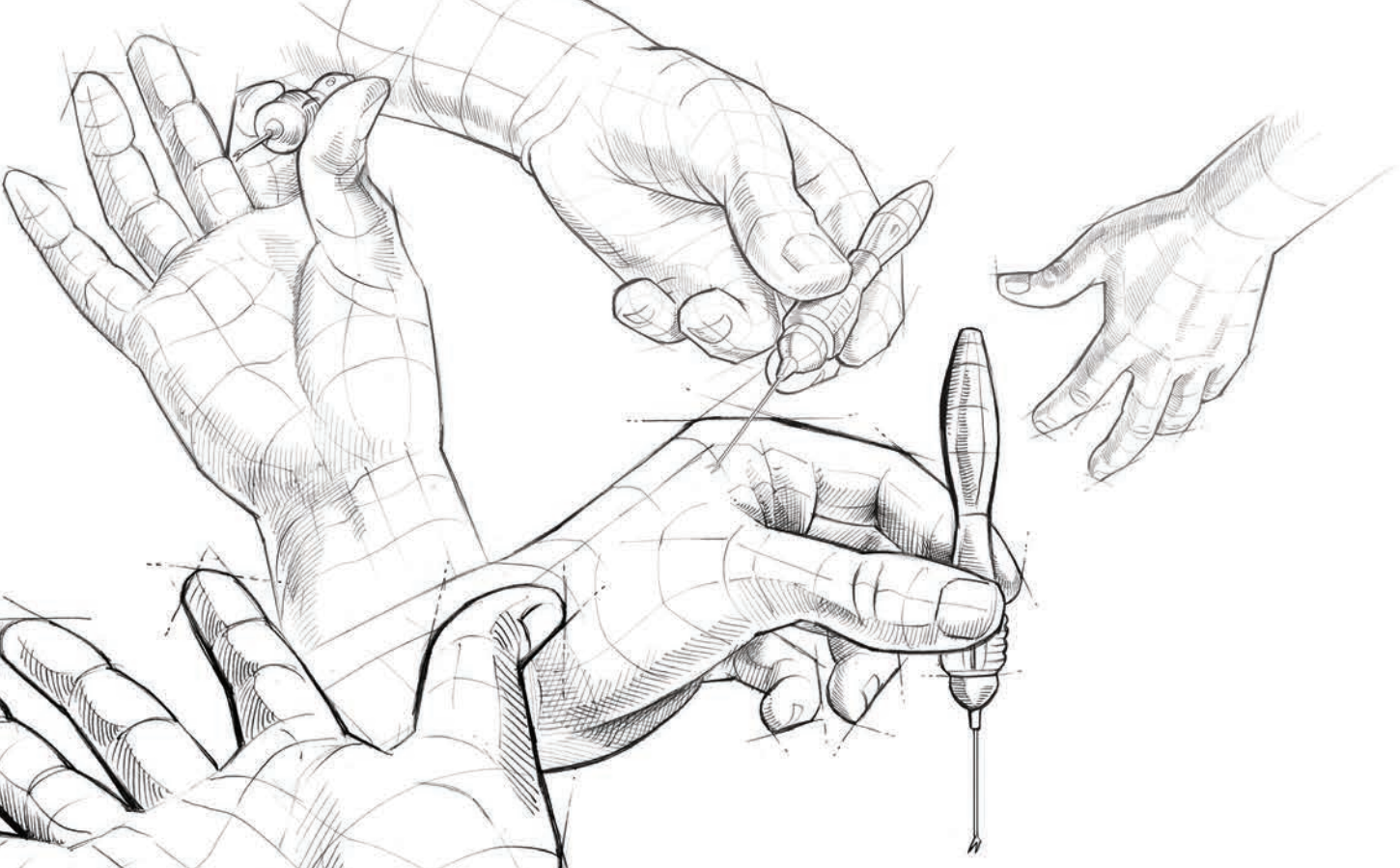

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An Issue of Inequity

Poorer people suffer poorer outcomes across all of medicine. Can eyecare buck the trend?

When people ask me where I'm from, I usually answer, "Glasgow, Scotland." (I'm actually from Coatbridge, two miles east of the city's border, but few people outside of Scotland have heard of the place, so Glasgow is close enough.) True to my roots, I'd like to highlight the work of a Glasgow-based academic called Watt – not James, but Graham.

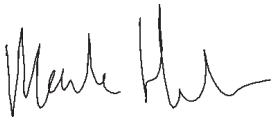
Graham Watt is a Professor of General Practice at Glasgow University, and is also a founder of "General Practitioners at the Deep End," which works with the GPs serving patients from the most deprived areas of the city. The project has revealed Glasgow to be a stark example of the Inverse Care Law (1), which suggests that the availability of good medical care tends to vary inversely with its need in the population it serves. One finding was spectacular, especially in a country with universal social medicine: the life expectancies of men and women in the lowest socioeconomic groups were 57 and 61 years – compared with 76 and 78 years for the richest (2).

I recently read that there's not only a difference of seven years in life expectancy between the poorest and richest members of society in the UK, but also a difference of 17 years in "disability free life" (3). There are many interrelated socio- and health-economic reasons at play here, but the reality is that being poor begets poorer outcomes.

And eyecare is not immune. Many vision problems are detected by eye tests in the community, usually by an optician or optometrist. In relatively affluent areas, people usually present regularly for tests, have any vision problems identified, and start down a suitable treatment path. But in deprived areas, far fewer people present (4). Why? Because they are scared of the perceived cost of spectacles. And so ocular disease gets caught later – with predictable consequences on outcomes.

What can be done? There are many societal issues that need to be addressed, but community engagement and a concerted investment in campaigns to drive awareness of ocular disease is one proposed route (5). Unfortunately, when it comes to healthcare funding in many countries, these are uncertain times. The battle to improve medical outcomes across the socioeconomic spectrum will cost precious time and resources. But surely it is a battle we should fight hard to win.

Mark Hillen
Editor



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Upfront

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

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

Ctrl + Shift + IOL

Controlling for myopic shift following cataract surgery in infants: too many variables?

Pediatric cataract surgery poses its own special challenges – the eye is still growing, with the cornea and crystalline lens flattening at the same time as axial elongation occurs. So when you operate to remove a cataract and implant an IOL, the long term results can be difficult to predict. It can be especially difficult in younger children – the eye undergoes 3–4 mm of axial elongation before a child is one year old, meaning young infants require a very different approach to older children. Calculating IOL power is tricky, as the amount of myopic shift can vary significantly as the eye grows, and there is currently no agreement on just how much doctors should undercorrect vision by when implanting IOLs in infants.

The Infant Aphakia Treatment Study Group sought to better understand the best approach by studying myopic shift in a group of infants with unilateral congenital cataract, who were treated with primary IOL implantation or contact lenses. The team studied 43 eyes of infants who underwent unilateral IOL implantation at one to six months, and followed them from the time of cataract surgery to the age of five. They found that myopic shift followed a piecewise, linear relationship; the most rapid shift occurred in the first year and a half of life (mean of 0.35 D/month) before slowing after this age (mean of 0.08 D/month) (1).

None of the characteristics the group measured – including age at cataract surgery, IOL power, and axial length – affected the rate of the shift. However, only a small percentage of eyes showed the myopic shift the researchers predicted, and only ~25 percent were

within a diopter of the expected change, demonstrating that accurate prediction is extremely difficult.

So what can be done to offset this effect? For their study, the authors had a goal of emmetropia at five years – so postoperatively, they used hypermetropic targets of +8 D in children aged four to six weeks, and +6 D for children aged seven weeks to six months. When the children studied reached five years old, the mean refractive error was calculated at -2.5 D – suggesting that to have a better chance of achieving emmetropia, an additional 2.5 D of postoperative hypermetropia may help to more accurately compensate for myopic shift. But they also offer a word of caution: there are many factors to be considered, such as refractive error in the fellow eye, and other conditions such as glaucoma. They conclude that although targeting an extra 2.5 D might be a beneficial approach, "the variability in myopic shift among patients will continue to result in unanticipated anisometropia at later ages." *RM*

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It's Good to Talk

What patients report versus what physicians record can be substantially different – with far-reaching implications for EMR-based research

How well are you communicating with your patients? A recent study by researchers from the University of Michigan Kellogg Eye Center found significant differences between self-reported eye symptoms experienced by patients and the entries on their electronic medical records (EMRs). To discover the extent of the disparity, the team carried out an observational study, in which patients filled out an eye symptom questionnaire before their appointment with an ophthalmologist.

The investigators compared the presence or absence of blurry vision, glare, pain/discomfort, redness, burning/stinging, itching, gritty sensation, and sensitivity to light. And of the 162 patients studied, only 38 (23.5 percent) had an "exact agreement" between their medical records and the pre-appointment questionnaire (Figure 1).

And though it might seem like a worrying statistic, it isn't necessarily surprising, according to Paula Anne Newman-Casey, co-author of the associated paper (1). "Issues with doctor-patient communication are age-old and some issues will continue regardless of whether notes are taken on paper or electronically. In the era of paper charts, the purpose of a medical record was to allow the physician to document the history of the illness and diagnosis plan for each patient, not to be a compendium of information to facilitate the measurement of the quality of care delivered," says Newman-Casey. "Any unrecorded symptoms are not necessarily missed ones – when speaking to their doctor, patients may focus on some symptoms more if a particular thing is bothering them. But because EMRs allow researchers and others to extract information in a way that has never been previously possible, the implications of capturing patient data in the most accurate way becomes much more imperative."

Newman-Casey suggests that pre-appointment questionnaires could actually be the way forward – patients could offer information on their symptoms on a tablet in the waiting room, which could be monitored over time to see what effect any treatment was having. The information could also be used on a wider scale to improve healthcare overall by better capturing both symptoms and patient-centered outcome measures. "The data captured in the electronic health record, if it is highly accurate, can be used to improve the quality of care that we deliver in a way that data captured on disparate paper charts never made possible," adds Newsman-Casey. *RM*

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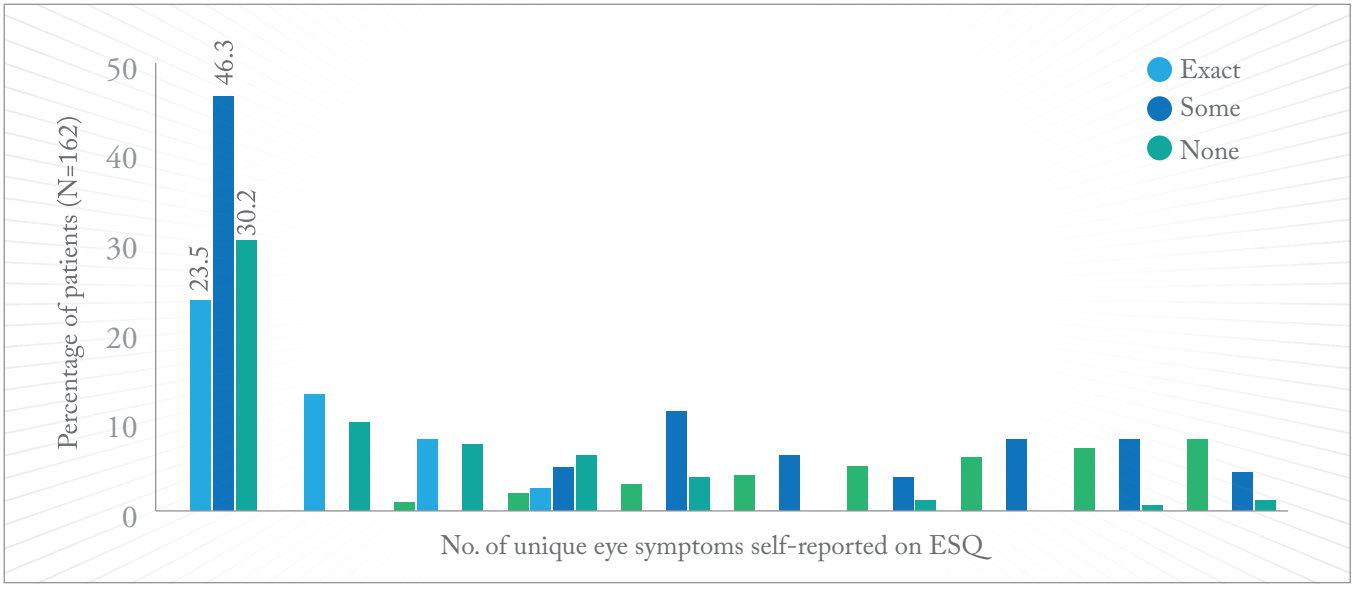

Figure 1. Agreement levels (exact, some, none) between symptoms reported through the eye symptom questionnaire and electronic medical records. Adapted from (1).

ON Delayed Gratification

Could a newly identified retinal ganglion cell type unlock the mystery of myopia?

Myopia is increasingly prevalent worldwide (1), but the mechanisms by which it develops are still unknown. Researchers from Northwestern University, Chicago, might have uncovered a clue: a new type of retinal ganglion cell (RGC) in mice, dubbed an ON delayed RGC. Highly sensitive to light and image focus, they hypothesize that the newly discovered cell could be involved in the control of emmetropization. Gregory Schwartz, who led the associated study (2), talks about the work behind the theory.

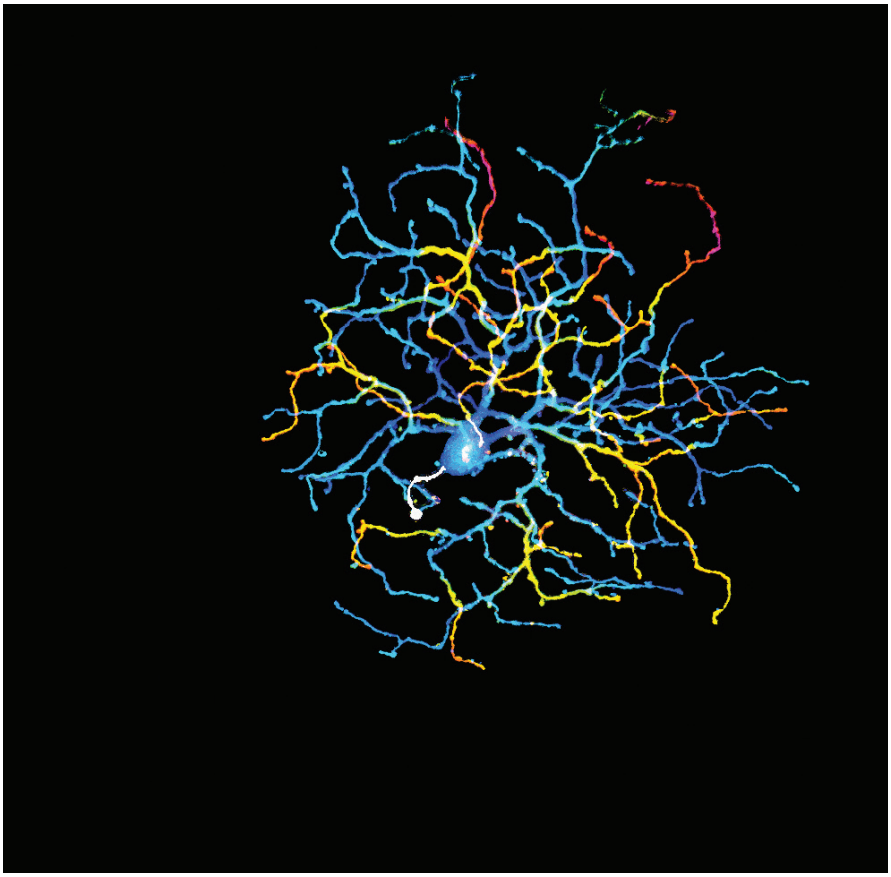

Figure 1. An ON delayed retinal ganglion cell colored by its depth in the retina. Credit: Gregory Schwartz and Adam Mani, Feinberg School of Medicine, Northwestern University, Chicago.

What inspired your study?

My lab measures the light responses, morphology, and genetic signature of individual RGCs. This study was part of a large effort to characterize all the RGC types in the mouse – of which there are around 50 – and several lines of evidence suggest we are nearing completion in our effort.

What did you find?

We found an RGC with a very unusual receptive field, which we named "ON delayed RGC," because it has a very long response delay. Studying the circuit mechanisms responsible for this delay and the cell's other unique receptive field properties revealed several new functional roles of inhibition in the retina. We also found that the ON delayed RGCs are more sensitive to the global focus of an image than any other RGC we measured – this observation led us to speculate about its role in myopia.

What were the surprises along the way?

This project has been full of surprises! Perhaps the biggest one was the apparent paradox that a cell with an unusually large receptive field and no surround suppression was actually the most sensitive RGC to the fine spatial scales that change with image focus. Several elements of this RGC's circuit mechanisms were also surprising, including its activation well beyond its dendrites. The dendritic field of a RGC has always been viewed as a good approximation of the size of its receptive field; that relationship is broken in ON delayed RGCs.

And the challenges?

The source of activation beyond the cell's dendrites stumped us for a while. Carefully measuring the voltage-dependence of the current responsible for this activation revealed it was disinhibitory and carried by K^+ – a very unusual kind of synaptic current to find in a RGC. Also, we went through many ideas about the functional role of ON delayed RGCs before landing on the hypothesis about a global focus signal involved in emmetropization and accommodation.

What impact could your findings have?

The connection with emmetropization is currently speculative but, if proven, it opens a completely new target for clinical interventions in the prevention of childhood myopia. Knowing the cellular substrate of the global focus signal would be a landmark that has

eluded the field for decades. The unique disinhibitory current may even offer a clue into a specific pharmacological target to manipulate ON delayed RGCs in vivo. This current relies on $GABA_B$ receptors, which have minimal roles in other retinal circuits.

What are your next steps?

We are pursuing two main lines of research. The first is using retrograde viral tracing to see if ON delayed RGCs project to areas in the brain known to control pupil dilation to establish a role in accommodation via the pupillary near reflex. The second is using single cell RNA-sequencing to identify genes specific to ON delayed RGCs. With such genes, we will be able to use modern genetic tools to manipulate this cell during development and measure possible changes in eye growth. *RS*

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Business in Brief

CMS will fund educational initiative for small and rural practices, new chief medical officer joins Glaukos, and Shire gets the ball rolling for Canadian approval of lifitegrast

- EyeGate has entered into a licensing agreement with Valeant to allow one of Valeant's subsidiaries worldwide commercial and manufacturing rights to the candidate EGP-437 combination product for post-operative pain and inflammation in ocular surgery patients.
- The Centers for Medicare and Medicaid Services (CMS) has announced that it will be providing up to $100 million of funding to improve education about the Quality Payment Program. The money will be awarded over the next five years to community-based organizations to provide training and educational resources on the program to small and rural practices across the USA.
- According to a press release from Ocular Therapeutix, the FDA has accepted a new drug application resubmission for its dexamethasone insert, Dextenza.
- L. Jay Katz, Director of the Glaucoma Service at Wills Eye Hospital and Professor of Ophthalmology at Thomas Jefferson University, has been appointed chief medical officer of Glaukos.
- Regenxbio has announced that the investigational new drug (IND) application for a Phase I trial of its wet AMD drug RCX-314, is now active. Patient enrolment in the multicenter, open-label, multiple cohort dose escalation trial is expected to begin in Q2/Q3 of this year.
- Shire has revealed revenue of $54 million from their dry eye drug, Xiidra (lifitegrast), which launched in the USA in August 2016. Shire also announced that it has filed a New Drug Submission (NDS) with Health Canada for the marketing authorization of lifitegrast for the treatment of dry eye in adults.

Peptide Power

Could a small biomimetic peptide be a promising alternative to anti-VEGF treatment?

Like all treatments, anti-VEGFs have their pros and cons. Whilst effective for many patients with age-related macular degeneration (AMD) or macular edema (ME), frequent injections are needed and some patients can experience suboptimal outcomes. That's exactly why the hunt is on for new and improved anti-angiogenic agents.

Joining the search are a group of researchers based at Johns Hopkins University School of Medicine, Baltimore, USA, who might be onto something with their biomimetic peptide derived from collagen IV. "Using bioinformatics, we identified shared sequences of proteins that have anti-angiogenic activity, and selected a series of peptides to test and optimize using cultured cells from blood vessels. The AXT107 peptide showed the most promise so we decided to investigate if it has the potential to treat disease," says Peter Campochiaro, corresponding author on the paper (1). Comparing AXT107 treatment with aflibercept (and scrambled controls) in different animal models of retinal disease, the investigators saw promising results following injection of the peptide (Figure 1). "AXT107 suppressed abnormal blood vessel growth and leakage in several mouse models relevant to wet AMD and diabetic retinopathy, and showed similar efficacy to aflibercept," says Campochiaro, adding "the combination of AXT107 and aflibercept was better than either alone."

The team also encountered a surprising finding: following injection into the vitreous of rabbit eyes, the peptide formed a gel-like depot that could still be observed in the same location 30 days later. "The depot disassembled slowly, providing sustained delivery," comments Campochiaro. "AXT107 suppressed abnormal vascular leakage for two months while aflibercept suppressed leakage for one month" (Figure 1b).

With the belief that their findings will improve the treatment of patients with wet AMD, diabetic retinopathy, and retinal vein occlusion, Campochiaro indicates "These studies suggest that AXT107 may provide benefit for patients who are having suboptimal outcomes with current treatments, and may also reduce the frequency of intraocular injections that are needed." Confirming that the team have had a pre-Investigational New Drug (IND) meeting, Campochiaro reveals that the team are currently performing the extensive toxicity studies that are needed before human trials can begin, which they anticipate will start before the end of the year. *RS*

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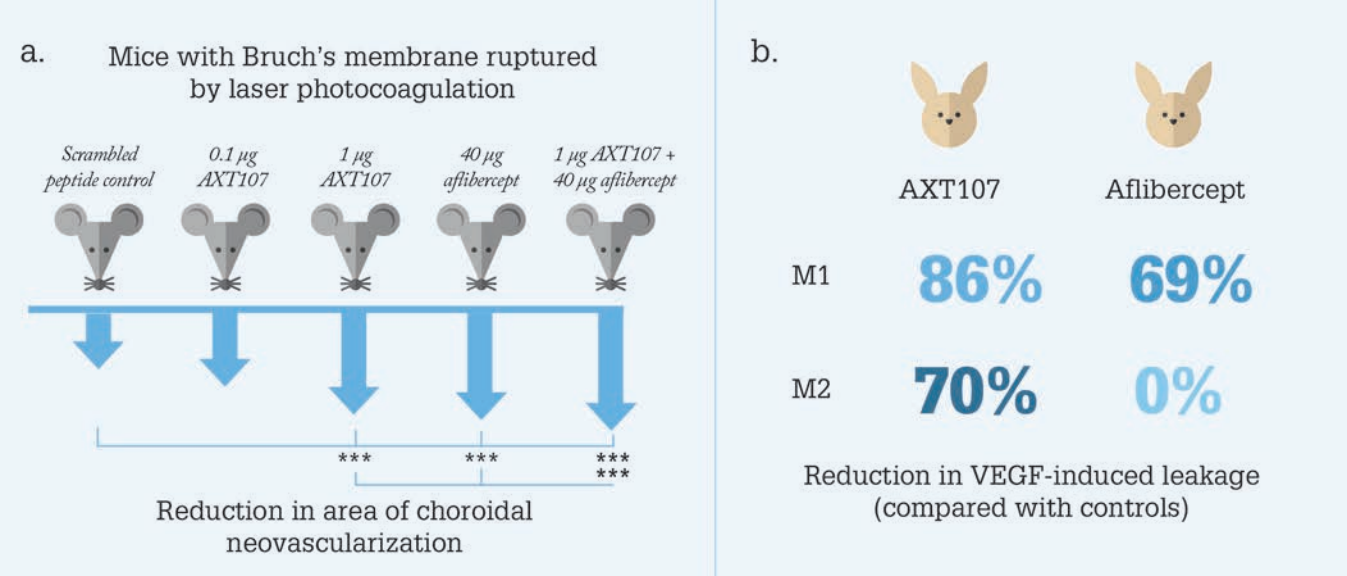

Figure 1. a. Area of choroidal neovascularization was significantly reduced following injection of 1 µg AXT107, aflibercept, and 1 µg AXT107 and aflibercept ($p<0.001$ versus control). b. VFP results showing reduction in fluorescein leakage (induced by 10 µg VEGF) in rabbit eyes following injection of 50 µg AXT107 or 500 µg aflibercept. AXT107, $p<0.001$ at months 1 and 2 versus control. Aflibercept, $p<0.01$ at month 1 versus control. VFP, vitreous fluorophotometry.

Rupture Risk

Mounting evidence suggests intravitreal injections increase the risk of posterior capsule rupture during cataract surgery, but why?

Posterior capsule rupture (PCR) occurs in around 2 percent of patients undergoing cataract surgery (1). But who is most at risk? Multiple indicators have already been identified, but new research is providing further evidence that previous intravitreal injections might need adding to the list (Figure 1).

A team from Moorfields Eye Hospital recently published the research online – and the study's findings came as a surprise to Zaid Shalchi, lead author of the corresponding paper (2). "I was adamant that there is no reason why injected eyes should have a higher risk of PCR and wanted to prove myself right. How wrong I was!" says Shalchi.

Using the Moorfields Patient Administrative System and OpenEyes electronic databases, the team retrospectively analyzed all cataract surgeries between January 1, 2012 and August 31, 2015 for incidence of PCR – a total of 62,994 procedures. They found that prior intravitreal injections were associated with a higher risk of PCR (odds ratio, 1.66; p=0.037), in accordance with previously published studies (3, 4). However, the team did not identify any risk factors in the prior injection cohort, unlike Lee et al., (3) who identified that risk increased with the number of previous injections. The team write that their findings "may indicate that a single intravitreal injection is sufficient to disrupt lens capsule/vitreous anatomy sufficiently to increase the risk of subsequent PCR."

Shalchi comments, "The research has led to a lot of questions and debate as to the reason why these eyes have higher risk of PCR." The team's next steps are to try to reach some conclusions. "We'll be presenting results from our follow-up study at ARVO this year, which has studied when PCR happens in injected eyes and how this compares with non-injected eyes," adds Shalchi. *RS*

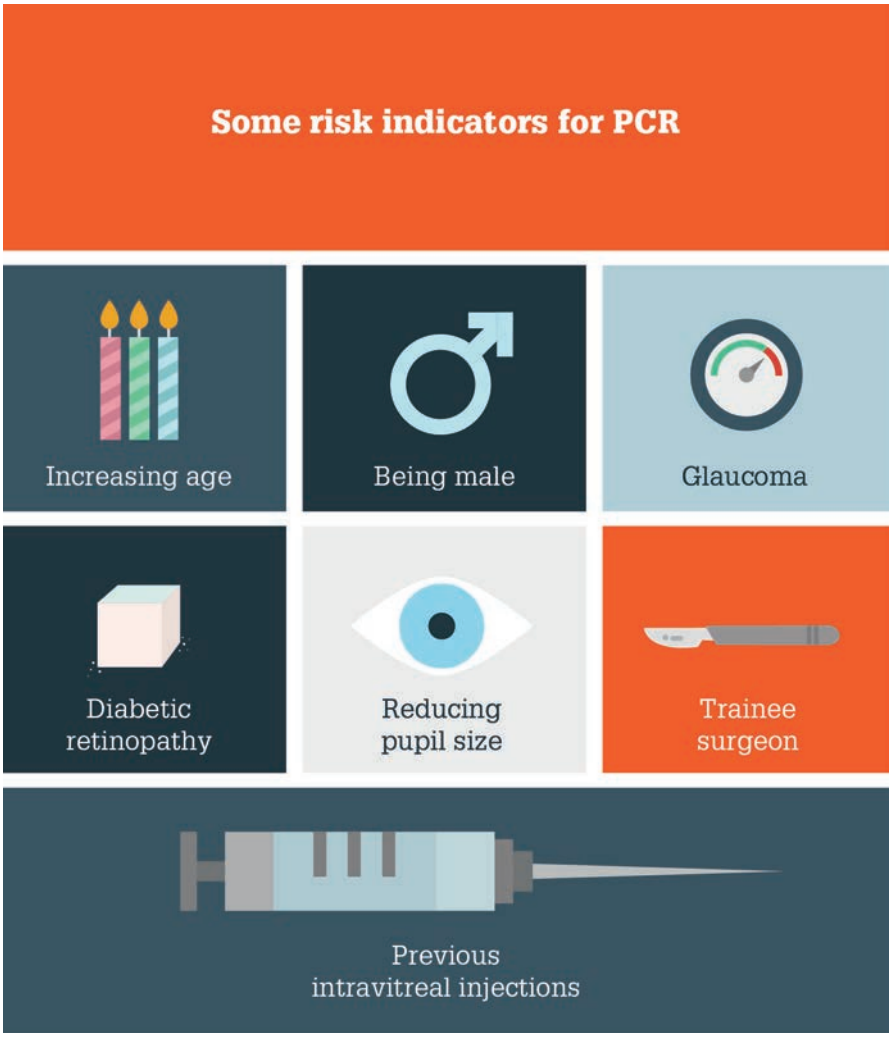

Figure 1. Some risk indicators for PCR during cataract surgery. Created from (1, 2). PCR, posterior capsule rupture.

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In My View

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

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

Contact the team at edit@theophthalmologist.com

How Good a Doctor Are You?

Your income may depend on it... but we have no real way to measure what actually matters to patients

By Harry Quigley, A. Edward Maumenee Professor of Ophthalmology, Wilmer Eye Institute, Johns Hopkins University

Every physician strives to do their best for patients, but are we doing enough? Currently, there is no way to truly know how our outcomes compare with others, which also makes it impossible to know if we are "up to standard." Implementation has begun on systems that measure individual physician outcomes and then base reimbursement upon them; such systems are a desirable replacement for fee-for-service because they could reduce unneeded care and improve the care that is delivered – but the devil is in the details…

Current methods do not truly assess our success as doctors. Detailed case-by-case oversight only occurs when there is an accusation of malpractice or negligence, and although devastating complications are sometimes reviewed at morbidity and mortality conferences, these do not measure routine care. Infrequent board exams might test a minimum standard of knowledge, but they cannot measure its application in daily practice. And although self-described Centers of Excellence may publish case series with success and complication rates, reports of general results in the wider community are rare.

The overall upshot? When selecting a surgeon for ourselves or a family member, it's very difficult to objectively determine who is best – or even who is adequate. Online voting polls and magazines listing "Top" doctors receive much attention (mostly in advertisements for those voted highest), but are based on subjective responses from unknown respondents. One popular assumption is that a doctor who frequently performs a certain procedure or frequently treats a specific condition must be better than one who seldom does – and there is considerable evidence that this is correct. (1). However, the fact that surgery rates for a procedure vary dramatically by region of the country suggests that more surgery may not be better for patients (2). More research would be helpful to study the need for surgery and its quality, including its effect on patient quality of life (QoL).

There are many reasons why doctors and patients should favor standardized, publically available data on medical outcomes. For physicians, such data can improve the overall quality of care because it could help identify the methods that are most successful. For patients, it could provide reassurance that their medical team is competent.

The challenge is to develop outcome criteria that represent objective, quantifiable, and valid measures of the results of care. With the advent of electronic medical records (EMR) and national databases generated for billing purposes, some initial attempts have been made to do this. Unfortunately, the big databases that are available are not designed to assess outcomes, but rather to mimic paper charts and to record details for billing purposes. From them, one can determine how often tests, exams, or procedures were performed – but not whether they were appropriate, interpreted correctly, or had a reasonable outcome. The outcomes reported so far have been "process measures" – how many have you done? These data have

been compared with Preferred Practice Patterns of national organizations, which are generated by consensus, but rarely validated by prospective studies. As big database studies can derive provocative findings – for example, the recent report that fewer elderly hospitalized patients die under the care of female internists than male internists (3) – prospective validation is vital for such work.

To use a specific example, consider how to assess the quality of care provided to a glaucoma patient. It is fashionable to propose that the best measure of outcome is the patient's perspective, because patient-oriented outcomes are not routinely captured in clinical measures (acuity, visual field tests etc.). However, although QoL questionnaires theoretically measure the patient's viewpoint, individual expectations and mental state can affect the correlation between clinical measures and reported QoL: the more depressed a person is, the worse they rate their visual function – even when it is normal. Furthermore, because diseases such as glaucoma have minimal disease-related symptomatology until late in their course, the inevitable side effects of standard eyedrop treatment – even when performed perfectly in accord with recommended practice – might lead patients to conclude (legitimately) that their quality of vision or life is either no better or even worse after treatment. How many of us can think forward 10 years to what would have occurred had such treatment not been given?

Currently, well-validated QoL questionnaires are not included in commercial EMRs. Medicare may have implemented post-visit questions for patients, but these deal in the "experience" during a visit ("how quickly were you seen?" or "did the staff treat you well?"). And though these may maximize service quality, they do not assess medical outcome. For instance, a 2012 Archives of Internal Medicine report demonstrated that respondents in the highest patient satisfaction quartile had a higher likelihood of hospital admission, greater expenditures, and higher mortality (4). And there may be other negative consequences – one possible contributing factor (among many) for the current opioid epidemic could be Joint Accreditation reviews that emphasized patient reports of inadequate pain relief (5).

"The healthcare system has never really stressed the things that are important to patients."

Instead of QoL questionnaires, what standard clinical measures would be good benchmarks? Visual acuity after cataract surgery? Visual field progression rate for glaucoma? These exist in EMRs, but they may conflict with the patient's view of their desired outcome. Patients who want uncorrected distance vision and need glasses after IOL implants are unhappy with uncorrected 20/20, just as few glaucoma patients appreciate that the dramatic slowing of field worsening with successful therapy is "better" than their natural course. To select a field criterion for glaucoma patients we need to know the rate of slowing that is compatible with best present outcome. It may not be "no" worsening, but an "acceptable" rate, adjusted by the distribution of case severity and patient demographics. If knowledge of physicians' ranking is effective, it could produce a shift toward better overall outcomes, as in the cardiac surgery example mentioned above.

There has been a rush to produce outcome measures that are "practical" – data easily gleaned from the EMR. One such "quality measure" recently suggested was a particular IOP lowering after laser angle treatment for glaucoma… Compared with recently published data, the particular success criterion selected (from one 20-year-old clinical trial) is far too strict. Rather than picking immediate standards that later must be amended, studies are needed to estimate reasonable outcomes based on data from a variety of practice settings.

In my view, the healthcare system has never really stressed the things that are important to patients, and we need to develop methods to accurately benchmark if we are doing a good job for our patients. It is past the time when we can act as if someone else will make this transition meaningful – we all need to be productively involved.

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A-peeling Approach?

I currently perform ILM peeling for macular holes, but recent research suggests peeling in all cases is not necessary – or without risk

By Dante Pieramici, Co-Director of the California Retina Research Foundation, partner at California Retina Consultants, and Assistant Clinical Professor of Ophthalmology, Doheny Eye Center, California, USA

Filippo Pacini, the Italian anatomist who discovered the internal limiting membrane (ILM) around 170 years ago, would probably be surprised by the amount of time we spend talking about this tissue. One frequently raised question is: does the ILM need to be removed, in all cases of macular holes? The short answer is, no. For the longer answer, we should ask three questions: is ILM peeling in all cases necessary? If it's not necessary, does it improve the odds of success? And finally, is it safe?

First, the issue of necessity: the most important pathologic tractional force in most macular holes is vitreomacular traction. We know this because in the era prior to ILM peeling, we were able to close 60 to 90 percent of holes with just the removal of the posterior hyaloid. We can also use pharmacologic agents like ocriplasmin to close holes – in the MVI-TRUST study, this was effective in about 40 percent of cases (1). We can also get a successful closure using other methods that separate the macular posterior hyaloid and spare the ILM, such as placing an intraocular gas bubble in the office without vitrectomy. With today's modern OCT imaging technology, I believe we can now preoperatively or intraoperatively identify those cases that may only require posterior hyaloid removal, potentially sparring additional retinal dissection.

Second, I will concede that ILM peeling does improve the chance of closure (and lessen the chance of reopening) and now using ILM removal we are guaranteed closure in nearly 100 percent of cases. But this benefit comes at the price of potential risks; when we remove the ILM, we not only remove the footplates of Müller cells, but also nerve fibers and glial cells. Most studies find little difference in visual outcomes when comparing peeling versus no peeling, but the majority of these studies used non-standardized visual acuity measurements, and had limited follow-up. Additionally, vision is only one measure of central visual function. One microperimetry study found microscotomas and decreased sensitivities in patients who had undergone ILM peeling, but not in non-ILM peeled patients (2). Visual field defects are also more common with ILM peeling versus no ILM peeling for macular holes (3). And we've seen that ILM-peeled patients display a decreased b-wave response in multifocal electroretinograms (4).

Additionally, most surgeons (in the United States at least) use indocyanine green (ICG) for intravitreal staining of the ILM, which has demonstrated retinal toxicity (5). In meta-analysis, it has also been associated with lower post-surgical improvements in visual function than patients who underwent an ILM peel without ICG being used (6).

In summary, ILM peeling is not necessary in all cases, but does improve

"We were able to close 60 to 90 percent of holes with just the removal of the posterior hyaloid."

chances of closure – with the tradeoff of exposing your patient to all of the risks inherent to the ILM removal procedure. With today's technology, we're better placed than ever before to identify patients who may only need the posterior hyaloid removed. In my practice today, I still remove the ILM – but it is becoming clear that in some cases, less may be more.

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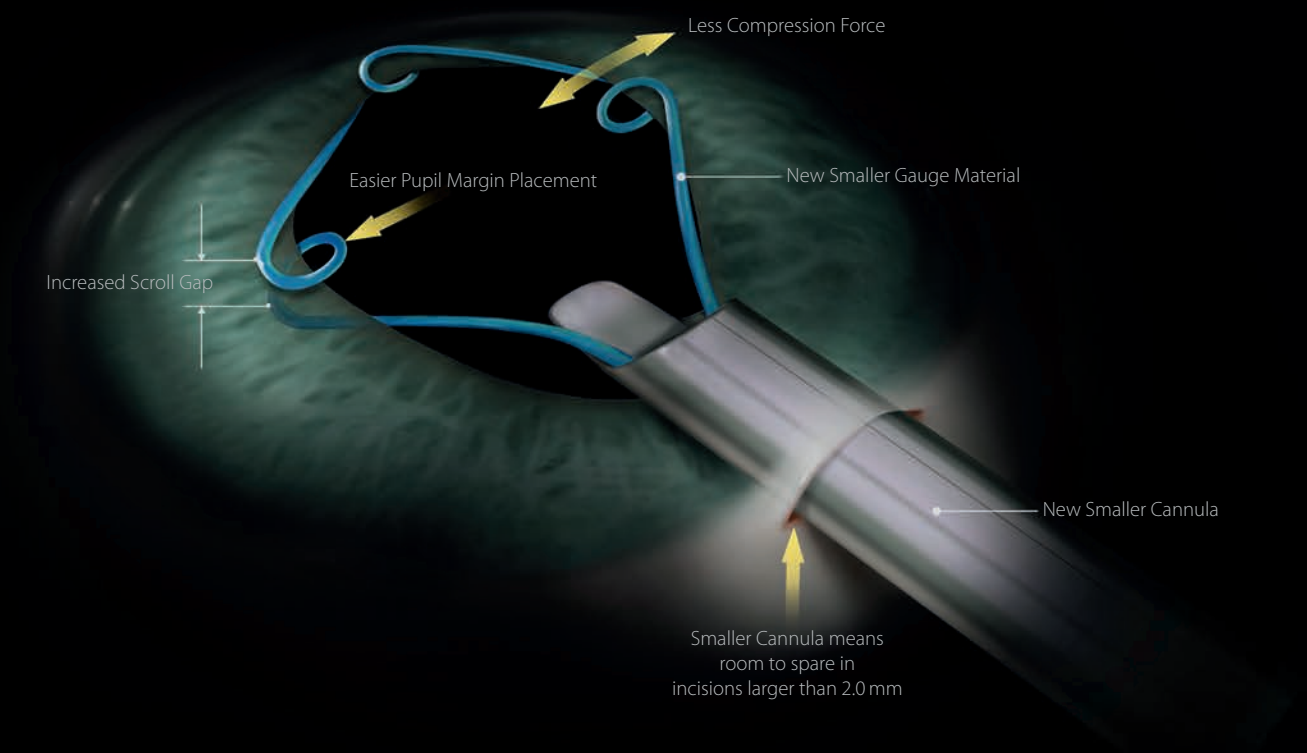

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REFRACTIVE SURGERY'S HOLY GRAIL...

Eyedrops for presbyopia

By Shafi Balal, Raquel Gil-Cazorla, Shehzad A. Naroo, Anant Sharma, Sunil Shah

Twenty-five years old is a good age to be. Any older and your hearing starts to decline; the loss may be barely detectable at that stage – but it's only going in one direction. By the start of your fourth decade, your bone and skeletal muscle mass starts to decline, and by your mid-forties, a number of ocular diseases start to manifest: incipient cataract, slight drusen deposits, a small raise in IOP... and presbyopia. Some people experience it in their forties, others in their fifties. It's most definitely age-related, and for now, almost certainly inescapable.

The progressive loss of accommodation (Table 1) is the big issue with presbyopia because it brings with it the inability to focus on near visual tasks (1). In developed countries, that's easily dealt with: you wear spectacles. But having to wear them for near tasks can be a pain, and we all know that there's a great appetite for being "spectacle-free" – it's what drove the LASIK boom of the early 2000s. Glasses cost money, prescriptions change, they can get broken and lost, they need to be cleaned and cared for, and you might not like how you look wearing them – all valid complaints. But if you are in a developing country, presbyopia is more of a problem. If your livelihood or survival requires the use of near vision and you don't have access to spectacles, you're in trouble. Clearly, solving the presbyopia problem has the potential to transform many lives, which is why presbyopia correction is often referred to as the "Holy Grail of refractive surgery" (2).

Over the years, many surgical strategies have been developed in an attempt to correct presbyopia, but none have truly solved the problem, with each having risks and limitations, and all resulting in some compromise in visual function. But what about a pharmacological approach to reduce the impact of presbyopia?

Appreciating the anatomy

To understand how drugs might be used to treat presbyopia, it's worthwhile considering the main anatomical units involved in accommodation: the ciliary muscle, lens and zonular fibers.

The ciliary muscle is predominantly under parasympathetic control, with sympathetic innervation playing a minor role in relaxation only (by inhibiting accommodation). The contraction of the ciliary muscle alters the shape and position of the lens, thereby invoking the accommodative capacity. Notably, the ciliary muscle also contains muscarinic-3 acetylcholine receptors (M_3).

It's important to note that the iris is also under heavy influence of the parasympathetic system – cholinergic stimulation of the M_3 receptors on the iris sphincter muscle causes miosis. Conversely, the iris dilator muscle is sympathetically innervated and contains α-adrenergic receptors. If these receptors are antagonized, it allows the parasympathetically innervated pupillary sphincter to predominate (as it is unopposed), resulting in miosis.

Depth of focus: the pinhole effect

Most pharmacological approaches for the treatment of presbyopia are based on reducing the aperture of the pupil. Small aperture optics have long been known to increase near visual acuity (VA) by increasing the depth of focus. Peripheral light waves are most distorted by refractive error: by blocking these and allowing only the most central rays of light to reach the retina, this results in not only clearer vision, but also an increase in the depth of field of clear vision. It's this principle that underpins the surgical approaches of AcuFocus' small aperture corneal inlays and intraocular lenses (IOLs). Their Kamra corneal inlay features a central 1.6 mm aperture (a size AcuFocus claim achieves an expanded depth of focus without significant visual degradation) and their IC-8 IOL contains a 1.36 mm central aperture and is implanted in the non-dominant eye – and has shown promising early results. Clearly, for a pharmacological option to be successful it must create a similar and long-lasting effect on pupil size (3).

However, manipulating pupil size is not without undesired consequences. A constricted pupil (understandably) decreases vision at night – less light enters the eye, and diffraction at very small pupil sizes can degrade overall vision quality. For elderly patients in particular, decreasing the amount of light falling on the retina worsens vision.

Understanding accommodation

To appreciate why some pharmacological formulations may or may not work in presbyopia, it is essential to understand accommodation. Accommodation isn't a completely settled topic: there are a number of competing theories that seek to explain the mechanism(s), with Hermann von Helmholtz's 166 year-old theory being the most widely accepted.

Von Helmholtz suggested that when the eye is at rest and focused for distance, the ciliary muscle is relaxed (Figure 1). To focus on a near object, the ciliary muscle contracts, causing the ciliary body to move forward and towards the axis of the eye. Simultaneously, the tension of the zonular fibers around the lens equator relaxes, which allows a soft lens to be molded by the elastic capsule into a more spherical and accommodative form. A larger, stiffer lens – such as one that arises from ageing – will not change shape as much, thereby compromising accommodation.

Ronald Schachar proposed an alternative theory: that only the equatorial zonules are under tension during accommodation (Figure 1). When the ciliary muscle contracts, equatorial zonular tension is increased, causing the central surfaces of the crystalline lens to steepen, the central thickness of the lens to increase, and the peripheral surfaces of the lens to flatten. The increased equatorial zonular tension keeps the lens stable and flattens the peripheral lens surface during accommodation. In this scenario, presbyopia occurs because the equatorial diameter increases with age. However, this theory is opposed by the well-documented occurrence of lens stiffening and failure of scleral surgical approaches (which are based on Schachar's theory) to correct presbyopia. Furthermore, studies have shown that it is axial thickness that is increased and not equatorial diameter.

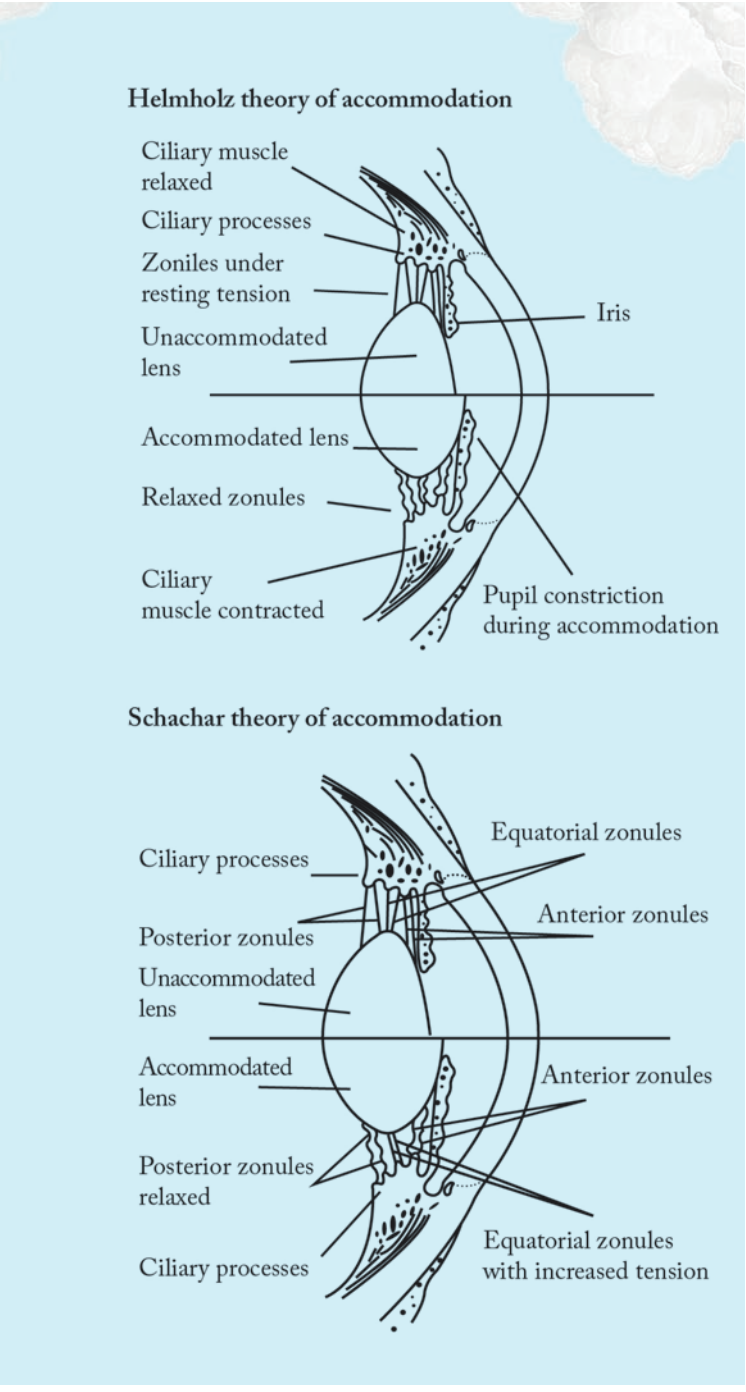

Figure 1. In the Helmholz theory of accommodation (top), ciliary muscle contraction leads to a relaxation of the zonular fibers; the reduced zonular tension lets the elastic lens capsule contract, increasing anterior and posterior lens curvature. In the Schachar theory (bottom), the equatorial zonules are under tension only during accommodation, and the anterior and posterior zonular fibers offer only passive support structures for the lens.

The most important aspect to remember is that true accommodation results in a dioptric change in the power of the eye. Most interventions achieve pseudoaccommodation: functional near vision from non-accommodative factors like small pupils, against-the-rule astigmatism and spherical aberration. Indeed, most pharmacological treatments attempt to exploit pseudoaccommodation from a small pupil.

"Accommodation isn't a completely settled topic: there are a number of competing theories that seek to explain the mechanism(s)."

Pharmacological potential

1. Muscarinic agonists with non-steroidal anti-inflammatory (NSAID) agents

Many groups have investigated this combination over the years (Table 2), the rationale being that a muscarinic agonist causes the ciliary muscle to contract (with a corresponding increase in lens thickness). However, this may only be achievable in younger presbyopes, as stiffer lenses are less easily induced into accommodation. Muscarinic agonists also cause miosis with resulting increase in depth of focus and pseudoaccommodation.

What about the NSAIDs? Jorge Benozzi's group has advocated the use of diclofenac for the inhibition of inflammation in the anterior uveal tract, claiming that it decreases spasmodic ciliary contraction, pigment dispersion and posterior synechia formation secondary to parasympathomimetic drugs (9). However, it must be noted that our group was unable to find any evidence to substantiate that NSAIDs achieve this, and pilocarpine is not known to cause pigment dispersion or posterior synechiae in normal eyes.

Similarly, Patel et al. (10) have claimed that including NSAIDs with muscarinic agents prolongs the effects of the parasympathomimetic agent through the inhibition of prostaglandin synthesis in the anterior uvea. This seems counterintuitive – NSAIDs are used in cataract surgery to help prevent miosis – but nevertheless, Patel and Salamun believe

Unit	*Change with age*	*Effect*
Lens	Less elasticity Greater size	Less ability to deform under accommodation
Lens capsule	Decreased elasticity	Inability to deform lens Other investigations indicate mechanical properties may remain the same with age
Zonules	Reduced number Increased fragility More anterior insertion	Surprisingly no effect on zonular tension with age
Ciliary muscle	Decreased strength	Reduced muscle movement
Bruch's membrane capsule	Less elastic	Restriction of ciliary muscle mobility
Vitreous	Liquefaction	Reduced peripheral compression of lens

Table 1. Possible contributing factors in etiology of presbyopia. Adapted from (4–6).

it shows promise and have patented the approach along with Claes Feinbaum. They are currently attempting to minimize any adverse effects by using an intravitreal micro-insert to slowly release low concentrations of the insert's ingredients. The micro-insert should have a number of advantages over repeated drop instillation: topical administration is associated with drug loss through the eye's natural drainage channels, and this permits lower drug concentrations to be used. To date, no study data has been published on this device (10).

Juan-Carlos Abad (13) has attempted to exploit the pharmacology of NSAIDs one step further. NSAIDs inhibit the cyclooxygenase (COX) enzyme family, which are responsible for prostaglandin and thromboxane synthesis. Humans have two functional COX isoforms, COX-1 and COX-2, with COX-2 typically being expressed in inflamed tissue. Abad's patent identifies using COX-2 specific inhibitors in combination with a cholinergic or muscarinic agent in an attempt to target COX-2 specific pro-inflammatory mediator production, but sparing COX-1's "housekeeping" prostanoid production. Whether there is an advantage in this targeted approach over non-specific NSAIDS remains to be seen.

A slightly different drug combination approach was taken by Humberto Carrera, who combined pilocarpine with the NSAID, bromfenac. His rationale was that bromfenac's duration of action can be as long as 24 hours, and this should allow for a once-daily topical application – unlike diclofenac, which has an ocular half-life of under two hours. However, once again, no published studies are available on this formulation to date (14).

We must note here that presbyopia is a benign condition, so it is essential not to advocate potentially iatrogenic therapies. NSAID drops such as diclofenac have been associated with devastating adverse effects, such as corneal melt, epithelial defect and sterile infiltrates, so extensive patient evaluation is required before long-term treatment initiation is warranted.

2. Muscarinic agonist with sympathetic agonist

Carbachol is a parasympathomimetic agent and, unlike pilocarpine, is a full agonist that also promotes release of acetylcholine from parasympathetic nerve endings. Additionally, its carbamate structure means it may also inhibit cholinesterase enzymes (15). In terms of inducing miosis, the most commonly used strength of carbachol is 2.25% (which is equivalent in effect to about 3% pilocarpine; 16). Brimonidine is an α_2-receptor agonist, licensed in glaucoma, exhibits pupillary action, and can produce significant miosis, typically in low light conditions.

Kaufman (18,19) presented a study (summarized in Table 3) of the combination of both classes of drugs. Kaufman states "each combination was tested in each patient" but it is unclear if this was a true cross-over study or why uncorrected near visual acuity (UNVA) rather than best distance corrected near visual acuity (BDCNVA) was used. The near and distance visual acuities were measured 1, 2, 4, and 8 hours after instillation of the drugs. The results demonstrate the preparation is effective – but that adverse effects remain an issue.

In what appears to be an extension of Kaufman's work, Abdelkader (20) looked at carbachol 2.25% in combination with brimonidine 0.2%. The drops resulted in statistically significant UNVA improvements, and all patients stated they would continue to use the drops if available (whereas none were prepared to continue using the placebo drops). It's well known from pilocarpine use in glaucoma that patients experience a dull headache on initiation with pilocarpine therapy, but that this should improve with time. The group have recently published another clinical trial (23), which compares the 3% carbachol formulation with brimonidine 0.2% in only 10 patients – but again, statistically significant results were shown. Given that they recruited almost five times as many patients for the 2.25% formulation (20), one can infer the formulation they likely favor. Interestingly, the trial was registered on November 11, 2016 but received by the journal in July 2016. Retrospective trial registration has been discouraged for some time by the ICJME (24).

Allergic reactions to ophthalmic agents for the treatment of presbyopia have not been extensively studied. However, brimonidine (when used for the treatment of glaucoma), has. Blondeau (25) found that that up to 25.7 percent of patients with glaucoma experienced such a reaction in his study.

Another combination of a muscarinic agonist with a sympathetic agent (pilocarpine and phenylephrine) has also

How much accommodation do we need to restore?

A 45 year-old will have around 4 D of accommodative power but only uses around 2 D of this comfortably (Figure 2). The usual reading distance is around 40 cm and this requires 2.5 D of accommodation. Therefore a recovery of only 1–2 D would be sufficient to treat most presbyopic patients.

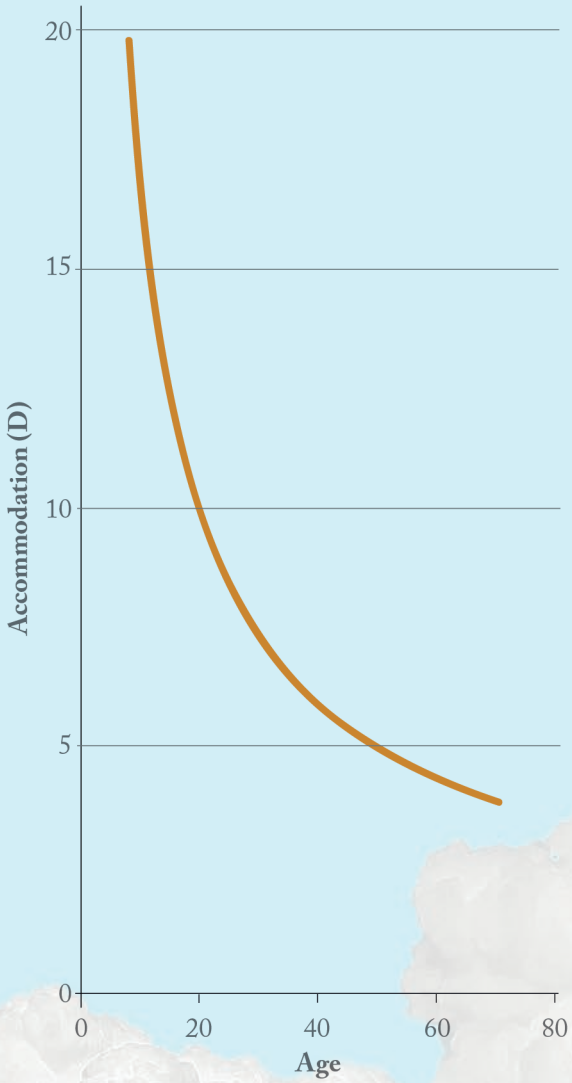

Figure 2. Mean Accommodation versus age. Adapted from (7).

been evaluated as a presbyopia therapy (21). Phenylephrine is a α_1-adrenergic agent – but has shown little to no effect on the ciliary muscle or the centrally stimulated accommodative response. In the past, this combination was used as the Mapstone test, which consists of phenylephrine 10% and pilocarpine 2%, as provocation of closed-angle glaucoma. The proponent of this combination, Vejarano (22), has anecdotally stated that he has used the drops on himself for over five years with no change to his distant UCVA and a 2 line improvement in UNVA.

Vejarano has not reported any adverse effects (such as brow ache or headache), but if pilocarpine does cause ciliary spasm leading to these adverse effects, they may remain unresolved by the addition of phenylephrine. It is also unclear how well patients tolerate the worsening of distance vision in the first hour of instillation, which has implications on, for example, operating heavy machinery and driving. The worsening may be caused by a delay in maximal pilocarpine action, resulting in an initial unopposed phenylephrine-induced mydriasis – the iris' melanin acts as a pilocarpine reservoir, delaying it from working on the ciliary muscle immediately (26).

"If pilocarpine does cause ciliary spasm leading to adverse effects, they may remain unresolved by the addition of phenylephrine."

3. Muscarinic agonist with muscarinic antagonist

The combination of a muscarinic agonist with a muscarinic antagonist is found in PRX-100, a proprietary preparation developed by 'Presbyopia Therapies', which contains aceclidine and tropicamide. Aceclidine is a muscarinic agonist that is less potent than pilocarpine and carbachol; tropicamide is an anti-muscarinic agent. The combination is reported to effectively cause miosis without stimulating accommodation and, according to Presbyopia Therapies' internal data, 1.6–1.9 mm is the optimum pupil diameter. Results reported in an article by Steven Dell are summarized in Table 4. Dell attributes the beneficial effects of PRX-100 under scotopic conditions to the reduction in light that's received by retina, which is thanks to the smaller pupil

Active agents	*Patients*	*Outcomes*	*Adverse effects*	*Authors/Patent*
Pilocarpine 1%, Diclofenac 0.1% 6 hourly	100 patients of both sexes, aged 45–50 with no ocular or systemic disease	All study patients had a near vision of Jaeger 1 (J1). Distance vision remained 20/20	1 discontinued due to ocular discomfort and burning, 4 discontinued due to preference for spectacles	Benozzi (8,9)
'Presbyeye drops' (unknown exact active ingredients; authors state combination of parasympathomimetic and NSAID)	15 eyes recruited in Sweden	Pupil size reduced from 4.1 mm to 2.7 mm ($p<0.001$). Statistically significant improvements in UCVA for near and distance; improved depth of focus reported	Transient nausea and ocular discomfort	Patel, Salamun (10)
Diclofenac 0.006% to 0.12%, Pilocarpine 0.2% to 0.4% and Sodium hyaluronate 0.1% to 0.9% intravitreal insert	N/A	N/A	N/A	Feinbaum, Patel, Salamun (11)
'PresbiDrops' (unknown exact active ingredients; authors state combination of parasympathomimetic and NSAID)	81 patients; 10 pseudophakic, 4 with cataracts, 10 post LASIK; 57 eyes without opacity	1 mm reduction in pupil size associated with a 0.9 D increase in depth of field. Effects lasted up to 14 hours. Near and distant VA also 'significantly improve.' Post LASIK patients maintained 20/20 distant UCVA	25% patients with 4 cases each of nausea, headache, dryness or burning, stinging, blurry vision. All these dissipated within 5 minutes	Feinbaum, FEPASAET group (12)
Muscarinic agonist and α-agonist or a COX-2 selective NSAID	N/A	N/A	N/A; adverse effect sparing effect of the COX-1 enzyme remains to be elucidated	Abad (13)
Pilocarpine 1%, Bromfenac 0.0018%	N/A	N/A	N/A	Carrera (14)

Table 2. Summary of results for muscarinic agonists and NSAID combinations. NSAID, non-steroidal anti-inflammatory; UCVA, mean uncorrected visual acuity.

diameter being offset by an improvement in contrast sensitivity and the elimination of stray light (27). However, this effect remains poorly understood: the amount of light entering is decreased, so presumably retinal adaptation is also occurring. This latter formulation perhaps has shown the most promise for patients given that it has progressed through various stages of regulatory approval. Indeed, a Phase II US clinical trial has been completed but (at the time of writing this article) is still unpublished (28).

The mydriatic, tropicamide, has the opposite effect of aceclidine. Its use can appear counterintuitive, but a closer look at its pharmacology reveals why it may have been chosen. A study by German et al., (26) found that tropicamide displays a much higher affinity for iris M_3 receptors (as opposed to ciliary M_3 receptors) compared with other anti-muscarinic agents. What this allows is pupil dilation with minimal influence upon accommodation. This predilection for the iris may reduce the sphincter pupillae spasm with the minimal undesired antagonism of ciliary contraction, which is required for accommodation. In addition, its small effect on the ciliary muscle may explain why no brow or headache has been reported. The effect is well recognized and is exploited in the use of cyclopentolate, another muscarinic antagonist, to reduce aching pain caused by ciliary and iris spasm in corneal abrasion.

4. AGN-199201 and AGN-190584

AGN-199201 (presumed to be oxymetazoline, an α-sympathomimetic agent [29]) and AGN-190584 (a currently unknown agent) are two compounds, used together, currently under investigation by Allergan. The first of two Phase II clinical trials has been completed – and some results have been published (30). A second has been registered but, at the time of writing, patient recruitment has yet to begin (31). Oxymetazoline's α-adrenergic action causes vasoconstriction, which is exploited for its use as a nasal decongestant and ocular anti-hyperemia agent. Its use is often restricted to several days due to rebound nasal congestion – an effect seen even with ocular use.

However, α-receptor agonism in the eye acts on the iris dilator muscles to produce mydriasis – which is undesirable when you're trying to treat presbyopia, as it decreases the depth of focus. It may be that AGN-199201 is only being included to attenuate an adverse effect caused by AGN-190584, such as hyperemia, or to allow AGN-190584 to remain in the eye longer and slow systemic absorption; it may even induce synergy.

Allergan recruited 65 participants in a trial with the above mentioned agents (30), the results of which are summarized in Table 4. Combining AGN-190584 with oxymetazoline did not appear to negate the formers' adverse effects. But the

Active agents	*Patients*	*Outcomes*	*Adverse effects*	*Authors/Patent*
Carbachol 2.25%/3% and brimonidine 0.2%	Masked placebo study of 12 patients using non-dominant eye only	Carbachol 2.25% and 3% alone group mean improvement was 6.3J; 3% had longer duration of action. Brimonidine 0.2% with carbachol (strength not stated) mean improvement 6.3J but had the longest duration of effect (up to 8 hours)	Ocular discomfort was seen in 10 to 30% of all patients, including in the placebo group; 90% of patients stated they would use the drops if available	Kaufman (17–19)
Pilocarpine 1% and brimonidine 0.2%	Masked placebo study of 12 patients using non-dominant eye only	In pilocarpine 1% alone mean UNVA improved by 2.3J lines. Pilocarpine 1% with brimonidine 0.2% resulted in a mean improvement of 3J lines	As above	Kaufman (17–19)
Carbachol 2.25% and brimonidine 0.2%	Double blind placebo trial on non-dominant 48 emmetropic and presbyopic eyes. All had 20/20 UDVA and no ocular pathology	Acuity tested at various time points for distance and near vision. Significant improvement in UNVA ($p<0.0001$). No loss of effect was observed over a three month period. The control group received only placebo drops	Dull headache in 10% of patients and one person reported difficulty seeing in dim light for the first couple of weeks. Mild ocular burning was reported in all groups but most frequently in the carbachol group	Abdelkader (20)
Pilocarpine and phenylephrine (PE) (unknown strengths) 'PresbV drops'	20 patients, 9 emmetropes and 11 prior LASIK. Observed for 30 days	UNVA improved by about 2 to 3 mean Jaeger lines in each eye and binocularly by 2J. Mean distant UCVA worse for the first hour and then improved by average of 1 line in each eye	No adverse effects reported. Tear film quality/quantity, endothelial cell count, intraocular pressure (IOP) and contrast sensitivity unaffected	Vejarano (21, 22)

Table 3. Summary of results for muscarinic agonists with sympathetic agonists. UCVA, mean uncorrected visual acuity.

combination from Allergan has clearly shown some promise and are pursuing it in a second Phase II study.

5. Sympathetic antagonist with muscarinic agonist

It is possible that a muscarinic agonist and an α-sympathetic antagonist agent could act synergistically to allow miosis; not only would that assist in increasing pseudoaccommodation but would also reduce ciliary body spasm (because of a reduced muscarinic dose and possible opposing effects of the drugs at the ciliary muscle) and its putatively associated adverse effects, such as brow ache. The decrease in pupil size is the mechanism to increase the depth of focus and hence improve UNVA. It is a combination of drug classes that has been proposed by Anant Sharma in two formulations: pilocarpine with dapiprazole and pilocarpine with thymoxamine (33).

Thymoxamine is a competitive post-junctional α_1-antagonist that has been investigated for the discernment between angle-closure and open-angle glaucoma, and to reverse phenylephrine-induced pupil dilation. As sympathetic innervation has very little influence on the ciliary muscle (although opposite to muscarinic agonism), thymoxamine allows the size of the pupil to be affected without significantly affecting the ciliary muscle. The half-life is about 10 hours which is much longer than that of pilocarpine, which is about 1 hour (34). Susan Small and her colleagues showed back in 1976 that after 90 minutes, mean reduction in pupil size with thymoxamine was 1.6 mm with a 1 D increase in accommodation (35).

The other proposed sympathetic antagonist, dapiprazole, has been studied for reversal of pharmacologically induced mydriasis and shares thymoxamine's mechanism of action. When Wilcox (36) used dapiprazole 0.5%, the greatest increase in accommodation was gained with two drops as opposed to one drop. Notably, brown eyes were slower in their reversal of mydriasis.

β-blockers, such as timolol, are another class of sympathetic

Active agents	*Patients*	*Outcomes*	*Adverse effects*	*Authors/Patent*
PRX-100 (aceclidine and tropicamide)	Castillejos et al. (27,28) study in Mexico. Recruited 9 subjects, mean age of 51.3 years	Investigated at undisclosed concentrations. Drops achieve rapid pupillary constriction to a stable diameter of 1.6 mm, lasting approximately 8 hours in a majority of participants. UNVA was in the range of Jaeger 1 to Jaeger 1+. Distance acuity improved without glare or halos, as did vision at night	Participants did not report brow ache or reduction in distance acuity. The only adverse effects reported were conjunctival injection and stinging	Horn, Nordan Presbyopia Therapies (32)
AGN-199201 (presumed to be oxymetazoline) with AGN-190584	65 participants. Mean age of patients was 49.2 years	Percentage of participants with at least a 2 line improvement from baseline UNVA 70.6% (AGN-190584 alone), 68.8% when both agents were used in both eyes and only 46.7% in AGN-199201 alone group	No serious adverse. Eyelid retraction in 26% oxymetazoline alone users, none in the combined group. AGN-190584 group had 1 case each of blurred vision, hyperemia, increased lacrimation and eye irritation	Abad (13)

Table 4. Summary of results for PRX-100 and AGN-199201 with AGN-190584.

agents that could be used. The iris and, to a lesser extent, the ciliary muscle also have β-adrenergic receptors, which when antagonized cause contraction, miosis and an increase in accommodation. However, timolol's use may be limited as it can cause significant systemic adverse effects. Despite the drawbacks, Neufeld patented a preparation consisting of a β-blockers only (37), but no trials evaluating its effect on presbyopia have been performed.

Direct lens manipulation: softening

As noted earlier, perhaps the most significant hampering of accommodation occurs due to lens stiffening, which is caused by the crystalline protein's sulfhydryl groups undergoing oxidation to disulfides as the human lens ages (38).

Topically administered ester derivatives of lipoic acid have been investigated as lens softening agents. In fact, the choline ester of lipoid acid (LACE) was patented (as EV06) by Encore Vision for this purpose (39). LACE is a prodrug; it penetrates the cornea where it is quickly metabolized into choline and lipoic acid. Enzymes within the lens fiber cells chemically reduce the lipoic acid to dihydrolipoic acid, which is thought to reduce the disulfide bonds in the lens, restoring the lens' "softness" – and, hopefully, natural accommodation.

Encore Vision announced some (as yet) unpublished results from their Phase I/II randomized, double-masked, multicenter study, which examines the safety and efficacy of EV06/LACE 1.5% (compared with placebo) in 75 patients aged 45–55 years, over a 90 day period for the treatment of presbyopia and the primary endpoint of BDCNVA. In the EV06 group, mean change from baseline was a 0.191 LogMAR improvement and 0.095 LogMAR with placebo. The drops were "well tolerated and not associated with any significant adverse effects" (40). The group still needs to ascertain dosing frequency in a Phase III study. Initial results are encouraging and perhaps underline that lens stiffening plays a prominent part in the etiology of presbyopia – and this may explain Novartis' announcement at the end of 2016 that they are to acquire Encore Vision (41).

"There are only two approaches: generating a small pupil size, and lens softening."

Are we nearly there yet?

Pharmacological presbyopia therapy continues to evolve – but it hasn't matured to a point where widespread adoption is on the horizon. Although there are data available on the

various formulations mentioned in this article, they are often from unpublished studies and/or only available through news articles. The lack of peer-reviewed information – and a general absence of large-scale studies with robust data – makes appraisal of this approach to presbyopia therapy frustrating.

It appears that there are only two approaches to the pharmacological treatment of presbyopia: generating a small pupil size, and lens softening. Any intervention that takes the first approach has to tick a number of boxes to be successful: it must be long-acting, produce significant miosis, have minimal or no myopic shift and be relatively side-effect free. To achieve this, it seems that the active ingredients must not only act synergistically but also allay any shortcomings (or side effects) of their counterparts; the combination of a muscarinic agonist and sympathetic antagonist appears to best create this synergy.

We all know that we can increase the depth of focus by reducing aperture. Even monocular pharmacologic treatment with a single miotic agent has been shown to result in acceptable reading vision for many presbyopes, even in older recipients. And this same increase in the depth of defocus may improve distance vision in low hyperopes. It is also important to consider whether there would be an effect from other potential variables; for example, different colored irides and different ethnicities.

Perhaps the most exciting formulations remain the lens softeners, which address presbyopia at a fundamental (and potentially longer-lasting) level. Although this is a much newer approach than the pharmacological induction of small aperture optics, safe and effective lens softening holds immense promise as a presbyopia intervention. Even if the accommodative outcomes and implications are currently difficult to predict, it's still exciting times for topical 'presbyopic' treatments.

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Declaration

Shafi Balal declares no conflict of interest. Shehzad Naroo has been awarded a research grant to investigate lens softening using femtosecond laser and a research grant to investigate scleral surgery to help presbyopia and grants to investigate intraocular lenses for presbyopic patients. Anant Sharma is an intellectual property (IP) holder of related technologies and products. Sunil Shah is a shareholder in company holding IP for presbyopia related technologies and products.

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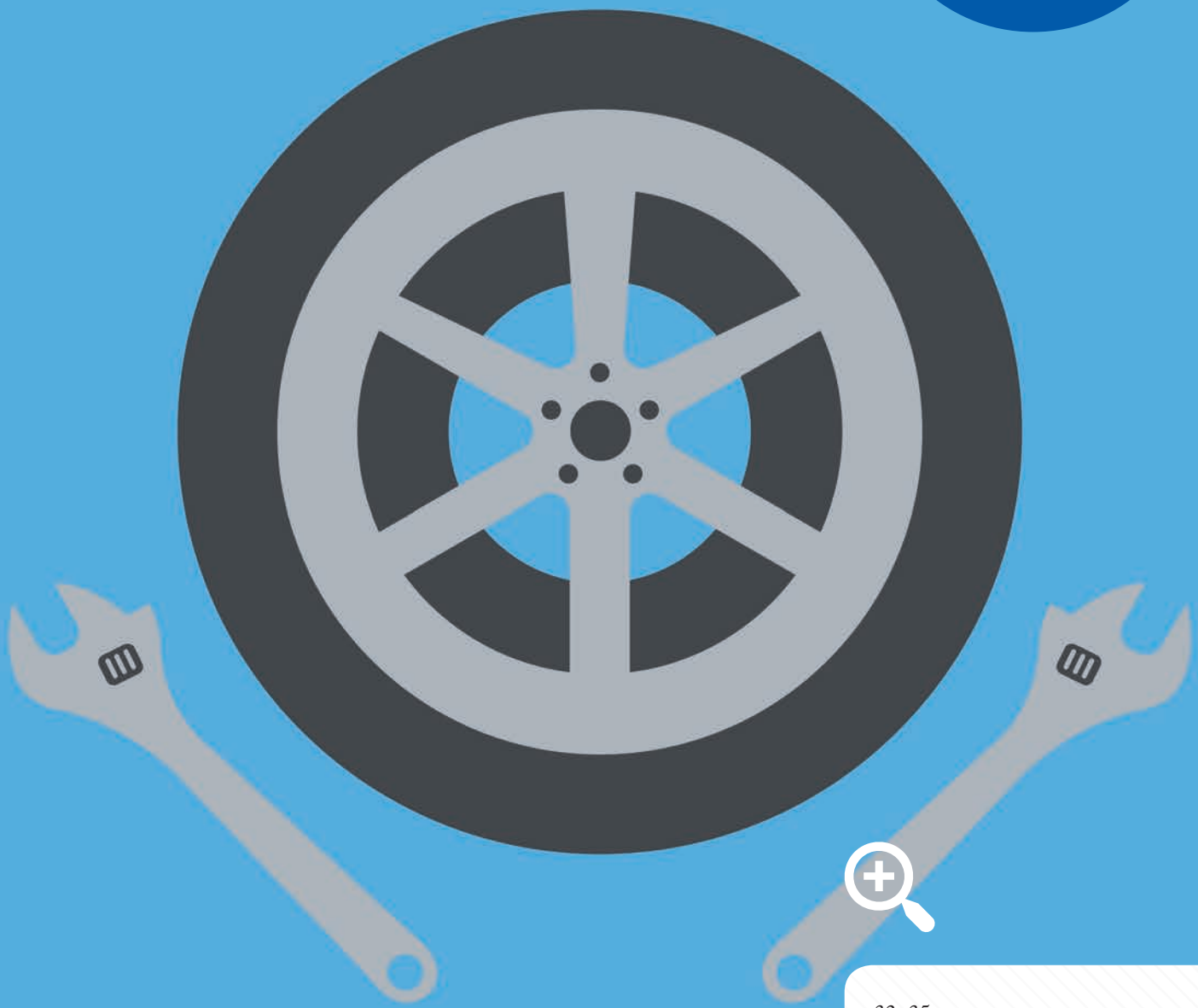


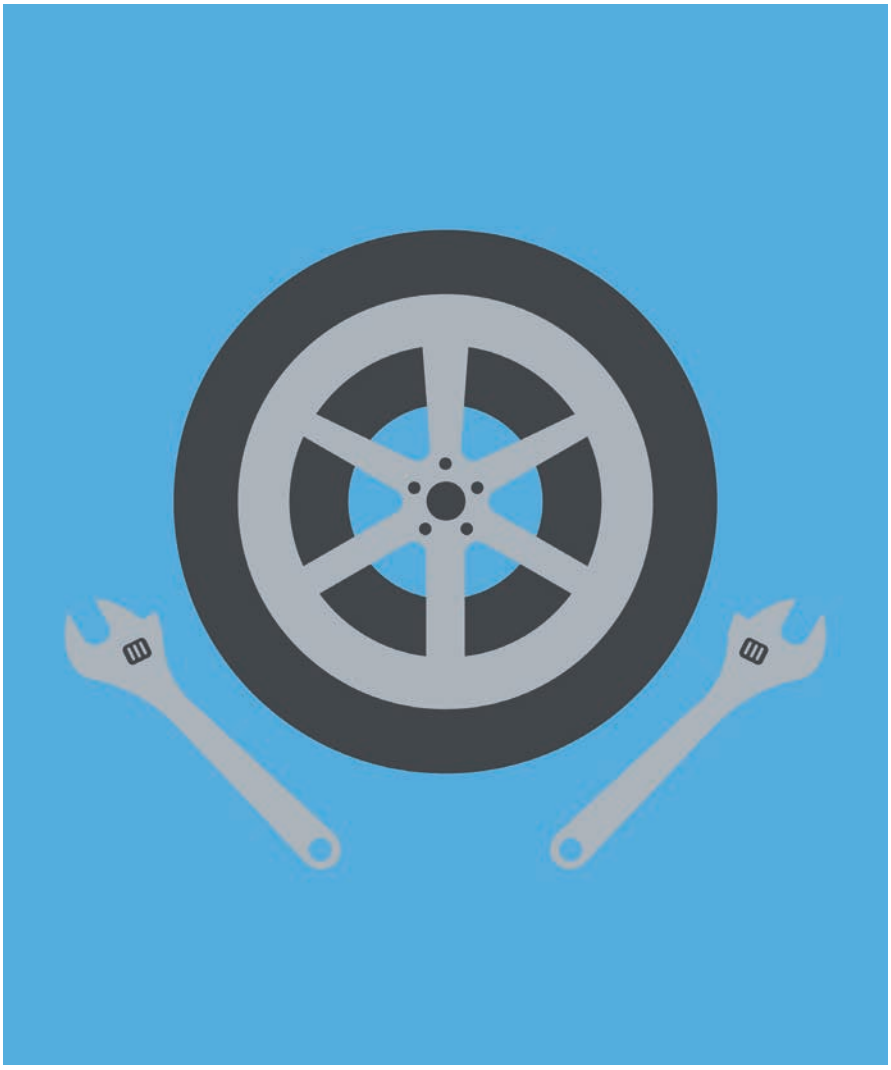
32–35
Bowman + Bulk = Better Results
Mid-stromal lamellar keratoplasty (MSLK) offers a new approach to the management of advanced keratoconus that can bypass some of the problems other techniques present.

Bowman + Bulk = Better Results

Mid-stromal lamellar keratoplasty (MSLK) is a new surgical technique for the management of advanced keratoconus

By Mohammad Khan, Jonathan Martin, Priscilla Mathewson and Sunil Shah

There are several ways to treat keratoconus today, but none are perfect – each approach comes with drawbacks or limitations. Take corneal collagen cross-linking, which has revolutionized the field because of its ability to strengthen the cornea and slow progression (1) – and even flatten it slightly (2). But it's never going to restore the corneal architecture, so your patients' often highly debilitating visual symptoms remain.



At a Glance

- *Advanced keratoconus can be managed and treated with many methods – but all have drawbacks: the challenge is to minimize them*
- *Keratoplasty is an option of last resort – but PK and DALK sacrifice much of the host cornea*
- *Bowman's layer transplantation (BLT) and placement into a mid-stromal pocket is a potentially tissue-sparing approach. It might restore some corneal architecture – but it doesn't address the primary problem of apical stromal thinning*
- *We describe a mid-stromal lamellar keratoplasty technique (MSLK) that both increases central corneal bulk and thickness, and flattens the cornea more than BLT, and describe the first clinical application of MSLK*

You do have a number of strategies available to improve your patients' visual acuity (VA), starting with spectacle correction and moving onto rigid gas permeable contact lenses (RGPCL), intra-corneal ring (ICR) segments and phakic toric intraocular lenses (IOLs) (2). But again, there are drawbacks: people can become RGPCL-intolerant, ICR segments flatten the mid-periphery and have a variable effect (especially if the ectasia is primarily central), and phakic IOLs only correct regular astigmatism.

In more advanced disease (or in cases of RGPCL intolerance), you then have to consider penetrating keratoplasty (PK) or deep anterior lamellar keratoplasty (DALK) – but this approach sacrifices the majority of the host cornea. Other older keratoplasty techniques have fallen out of favor – but keratoplasty for the treatment of corneal ectatic disorders, such as keratoconus, is an area of intense research. For example, Gerrit Melles' team has recently described Bowman's layer transplantation (3), which involves the isolation and detachment of Bowman's layer from the anterior stroma of a donor cornea and transplantation into a manually created mid-stromal

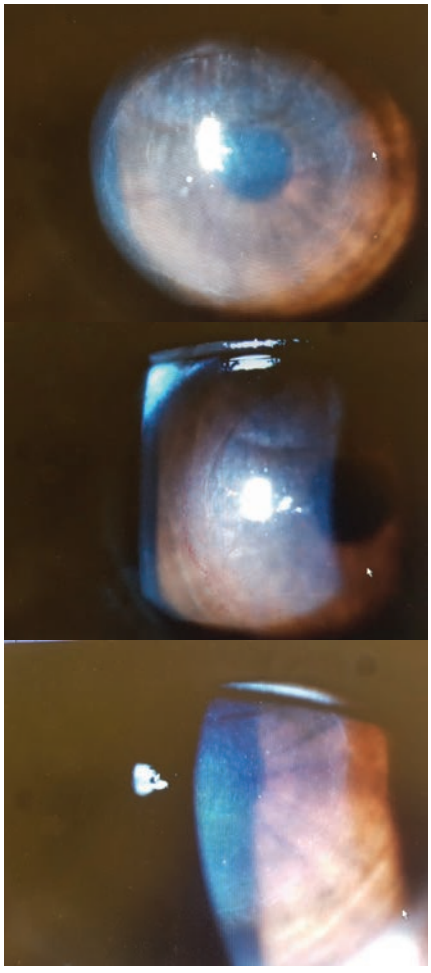


Figure 1. Post-operative week 1: anterior segment photographs reveal a well-positioned and central intrastromal lamellar graft.

	Pre-op	Day 1 post-op	1 week post-op	2 weeks post-op	4 weeks post-op
UCVA	6/60	CF	6/76+1	2/60	6/75
BCVA	6/7.5	CF	6/60+1	6/36	6/15
Refraction	-3.00/-3.00×130	-	-2.00/-5.50×5	-2.00/-5.50×40	-3.00/-3.50 ×10
K1	47.5 D	-	49.0 D	49.1 D	48.8 D
K2	52.7 D	-	50.5 D	51.2 D	51.0 D
Astigmatism	5.2 D	-	1.5 D	2.1 D	2.2 D
CCT	425 µm	1062 µm	733 µm	596 µm	521 µm
IOP (GAT) mmHg	07	10	10	10	11
IOP (iCare) mmHg	06	09	08	09	07

Table 1. Key corneal parameter assessments, pre- and post-operatively (up to four weeks' follow-up). UCVA; uncorrected visual acuity. BCVA; best corrected visual acuity. CCT; central corneal thickness. IOP; intra-ocular pressure. GAT; Goldmann applanation tonometry.

pocket. Why? Histopathological studies have indicated that Bowman's layer fragmentation contributes to the progression and visual debilitation of keratoconus (4), so its replacement is a logical therapeutic approach.

However, the fragmentation of Bowman's layer is a late and secondary phenomenon in keratoconus, and there's little or no established correlation between its fragmentation and reductions in VA (5). Replacement tissue will restore some of the original shape of the cornea, but it does not address the primary problem of apical stromal thinning – one of the biggest contributors to the corneal protrusion and irregular astigmatism present in keratoconus. Histopathological studies have shown that this stromal thinning is caused by a significant increase in the diameter of the collagen fibrils in the stroma and their interfibrillary distance (6), alongside a reduction in their number (7).

In theory, a procedure involving an intrastromal lamellar graft would, therefore, be expected to not only increase the central corneal bulk and thickness but also flatten the corneal architecture to a greater extent than Bowman's layer transplantation – thereby reducing the need for more conventional grafts such as DALK or PK.

We report the first case of a novel surgical approach in the form of a mid-stromal lamellar graft assisted by collagen cross-linking for the management of advanced keratoconus. Whilst small incision lenticule extraction with cross-linking has been used for the treatment of keratoconus (8) this is the first report, to our knowledge, of an intrastromal lenticule being implanted to restore the stromal architecture in a keratoconic cornea.

Methods

Our patient was a 28 year old with advanced keratoconus and RGPCL intolerance. Following informed consent, a number of preoperative measurements were obtained including pachymetry, topography, anterior segment OCT (AS-OCT), and intraocular pressure measurements with Goldmann applanation tonometry and iCare tonometry.

The lamellar graft/lenticule was prepared with a Gebauer SLc Expert microkeratome system. This keratome, plus the use of a pre-shaped base, allowed precise cuts of defined thickness and a pre-defined shape to be made. This permitted the definition of two separate parameters: for this patient, a thickness of 100 µm with a 7 mm diameter, and a planar rather than concave or convex shape was chosen.

An anterior chamber paracentesis was created at 9 o'clock and air was injected following aqueous aspiration. A 7 mm superior limbal incision was fashioned to a depth of 250 µm and a mid-stromal pocket was then created manually using the dissection technique previously described for DALK (9), encompassing a

"Given the delicate nature of Bowman's layer, it is not surprising that tearing of the graft is a significant problem during preparation."

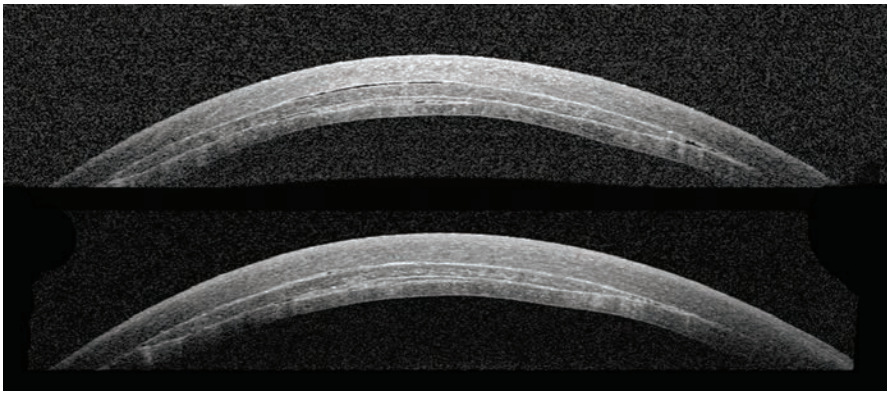


Figure 2. Anterior segment OCT four weeks post-operatively.

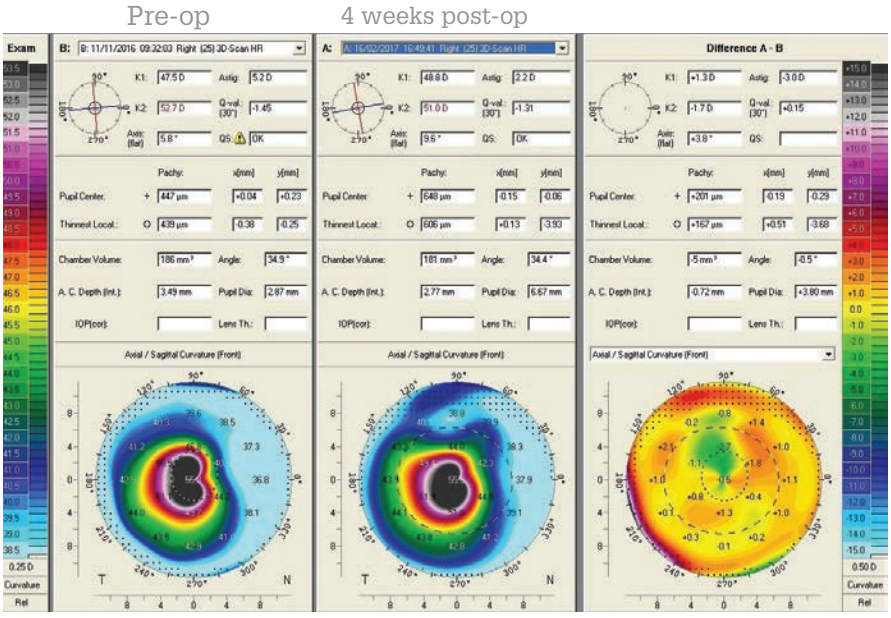


Figure 3. Topography: Pre-operatively, and four weeks post-operatively.

diameter of 8 mm. The lamellar graft was guided into the stromal pocket with an anterior chamber IOL surgical glide and positioned with a Rycroft anterior chamber cannula. Cross-linking was performed by immersing the intrastromal pocket (and graft) in riboflavin for 10 minutes followed by ultraviolet light exposure (9 mW) over a 9 minute period.

Post-operative anterior segment photographs, AS-OCT images, and topography are highlighted in Figures 1–3.

Results

Post-operatively, there was a significant reduction in topographic cylinder over four weeks and an increase in central corneal thickness of about 100 µm. The AS-OCT images show a well-positioned, mid-stromal lamellar graft (Figure 1). There is evidence of interface fluid, which would be expected to resolve with time and thereby improve contact and regularity between the graft and host surfaces, and this should aid further visual recovery. Table 1 details the patient's pre- and post-operative results up to four weeks of follow-up.

Discussion

Our technique theoretically confers a number of advantages over Bowman's layer transplantation. First, the 100 µm planar lamellar button resting intrastromally would be expected to provide more strength, bulk and flattening of the corneal architecture than Bowman's layer alone (which is approximately 17 µm thick (10)). In Bowman's layer transplantation, the preparation of the graft involves manual dissection of Bowman's layer with a 30-gauge needle and a custom-made stripping device as well as McPherson's forceps. Given the delicate nature of Bowman's layer, it is not surprising that tearing of the graft is a significant problem during preparation – this affects almost 30 percent of all grafts harvested (11). Due to its elasticity, Bowman's layer also tends to roll up and needs to be unfolded manually within the stromal pocket, putting the graft at further risk of damage (11). The lenticule used in our technique is much thicker (100 µm) and is prepared using an automated microkeratome. It also includes Bowman's layer within the lenticule, so it may have the benefits of

Bowman's layer transplantation, plus added bulk. In theory, this should make it less likely to be damaged during harvest.

Our mid-stromal lamellar keratoplasty (MSLK) procedure has the advantage of being less technically challenging than Bowman's layer transplantation and therefore is likely to have a more favorable learning curve – for example, it uses a microkeratome system to dissect the donor tissue, and only the host corneal pocket is created manually. There's another potential advantage to using a microkeratome when performing the graft dissection – in DSEK, VA recovery is reported to be faster than when manual graft dissection is performed (12), likely secondary to a more irregular interface between the host and graft that's created in manual dissection (13). The procedure may be improved further by femtosecond laser creation of the pocket.

"MSLK, it is hoped, offers an exciting way forward for the management of keratoconus."

The relative absence of sutures (when compared with other techniques such as DALK and PK) means that MSLK is relatively less time-consuming: this first case took 45 minutes to complete.

There are a number of potential limitations of this technique, like intraoperative perforation of Descemet's membrane, as has been reported with Bowman's layer transplantation (3). It is likely that patients with a very thin cornea could be ineligible for MSLK as the risk of perforation may be high. However, the procedure could still be attempted and converted to a different form of keratoplasty if a perforation occurred, as in DALK. In addition, the procedure could be completed even in the presence of a perforation. A DALK or PK is likely to be advantageous in cases of significant corneal scarring involving the visual axis.

Conclusion

There are many methods by which keratoconus can be treated – but all have drawbacks associated with their use. Recent years have seen some innovative keratoplasty approaches that aim to minimize these drawbacks, and MSLK, it is hoped, offers an exciting way forward for the management of keratoconus, with fewer drawbacks and compromises than the Bowman's layer transplantation approach – and might offer a viable alternative to DALK or PK.

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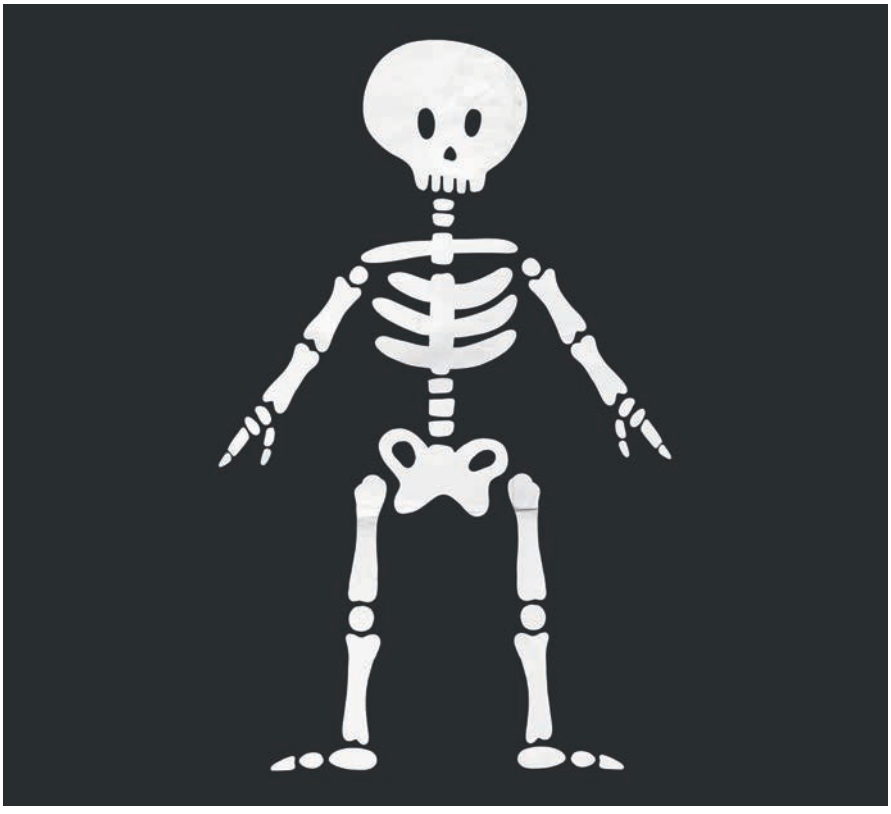
We attempted to understand the field of dry AMD research by performing a benchmarking analysis of the last 5 years of PubMed-listed publications.

It's in Their Bones

Bone marrow stem cells for the treatment of retinal disease? They're closer to the clinic than you might think

By Elad Moisseiev and Susanna Park



We are in the middle of a demographic time-bomb. Post-war baby-boomers are now getting to the age where they're beginning to experience vision loss from age-related eye diseases: principally cataract and retinal disorders like age-related macular degeneration (AMD), diabetic retinopathy and retinal vein occlusions. Cataract is relatively easily resolved. Retinal diseases, on the other hand, aren't. Our current approach to the treatment of many retinal diseases is limited – and most retinal diseases are not only age-related but also result in irreversible vision loss.

But we are lucky in some respects. Retinal diseases like neovascular AMD, diabetic macular edema (DME), and the sequelae secondary to retinal vein occlusions are treatable with anti-VEGF agents, steroids, or laser therapy – unfortunately, these are not permanent solutions and disease progresses. Even if the drug treatment regimen is adhered to completely (which is essential), these agents can become less effective over time. Moreover, some vision loss is not recovered with any of the available treatments. In other words, there's a clear unmet need for an intervention that could limit – or even better reverse – the vision loss that's associated with these extremely (and increasingly) common retinal disorders.

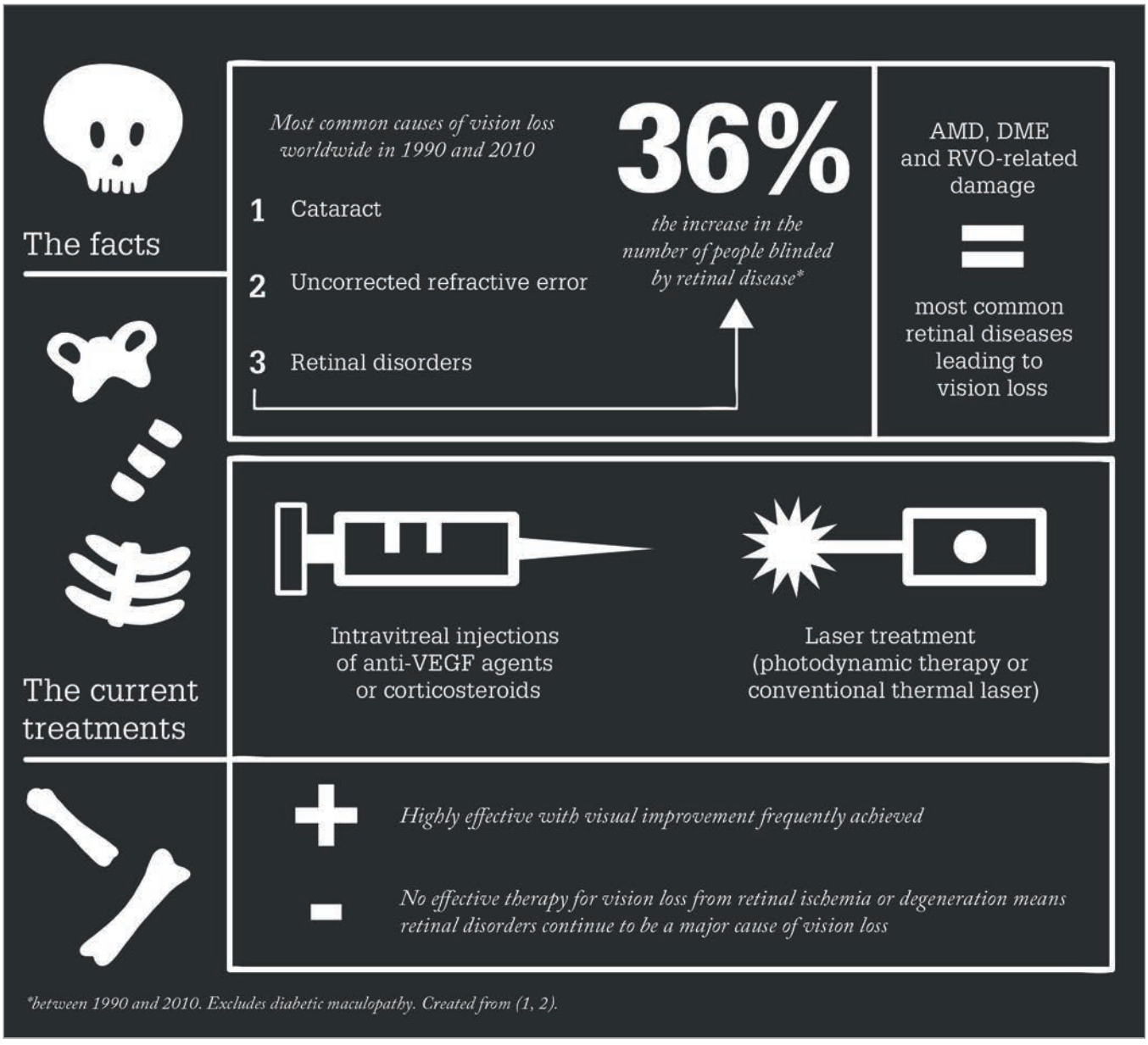
Cell therapy to the rescue?

Might stem cell therapy be the answer? In theory, it has many advantages over current treatment approaches. Cell-based therapy should be able to influence more pathways and induce a broader and more physiologic effect in target tissues than conventional pharmacological interventions. They might differentiate into the cells of the target tissue, integrate and function – the hope is that this eventual tissue replacement will have a long-lasting and regenerative effect in the retina.

Research has progressed to such an extent that a number of early phase clinical trials are underway, and some have already reported results on their use for retinal diseases such as advanced AMD or Stargardt's disease. It's worth noting that these studies have involved the surgical subretinal transplantation of retinal pigment epithelial cells derived from embryonic pluripotent stem cells (3–5). Initial results have been encouraging: the procedure appeared to be tolerated in most eyes and some patients experienced

At a Glance

- *Adult bone marrow stem cells – including mesenchymal stem cells (MSCs) and CD34+/ hematopoietic stem cells (HSCs) – may have beneficial paracrine trophic effects on the ischemic or degenerating retina*
- *Bone marrow MSCs are easily harvested and expanded in culture and allogeneic transplantation may be possible – but there are safety concerns when administered by intravitreal injection*
- *CD34+/HSCs home into the retina after intravitreal injection and may have regenerative effects in ischemic or degenerating retina*
- *Early clinical studies show autologous intravitreal administration of CD34+ cells from human bone marrow is possible in eyes with retinal disorders without major safety issues*



improved visual function afterwards. But subretinal cell delivery is not without danger. Every manipulation of the retina risks damage, and the intervention needs to be more curative than the manipulation is damaging. There is also a big safety issue; because these cells are allogeneic, prolonged systemic immunosuppression is required to avoid rejection of the transplanted cells. The problem is that systemic immunosuppression was not tolerated in all subjects in these studies. Having said all of this, there may be an alternative source of allogeneic stem cells for treatment that can sidestep this issue.

Bone marrow as a stem cell source

Adult bone marrow is a source of therapeutic stem cells, and it's one that's actively being explored for the treatment of a number of diseases, including those affecting the retina. Figure 1 shows the two principal bone marrow stem cell types that are currently under investigation: mesenchymal stem cells (MSCs) and hematopoietic stem cells (HSCs). HSCs in humans express the CD34+ cell surface protein, making them easy to identify by immunohistochemistry (6), but MSCs are more easily harvested and expanded by bone marrow cell culture – and have already been evaluated in animal models as stem cell therapy for retinal diseases. There is debate over whether MSCs differentiate into cells beyond mesodermal origin – but what they can definitely do is produce factors that induce a paracrine protective effect on surrounding tissues (6–14). Another appealing advantage of MSCs is that they can be autologous or allogeneic without immunosuppression' without immunosuppression. By contrast, HSCs do not readily expand in culture and must be harvested from the bone marrow mononuclear cell fractions by positive selection based on cell surface

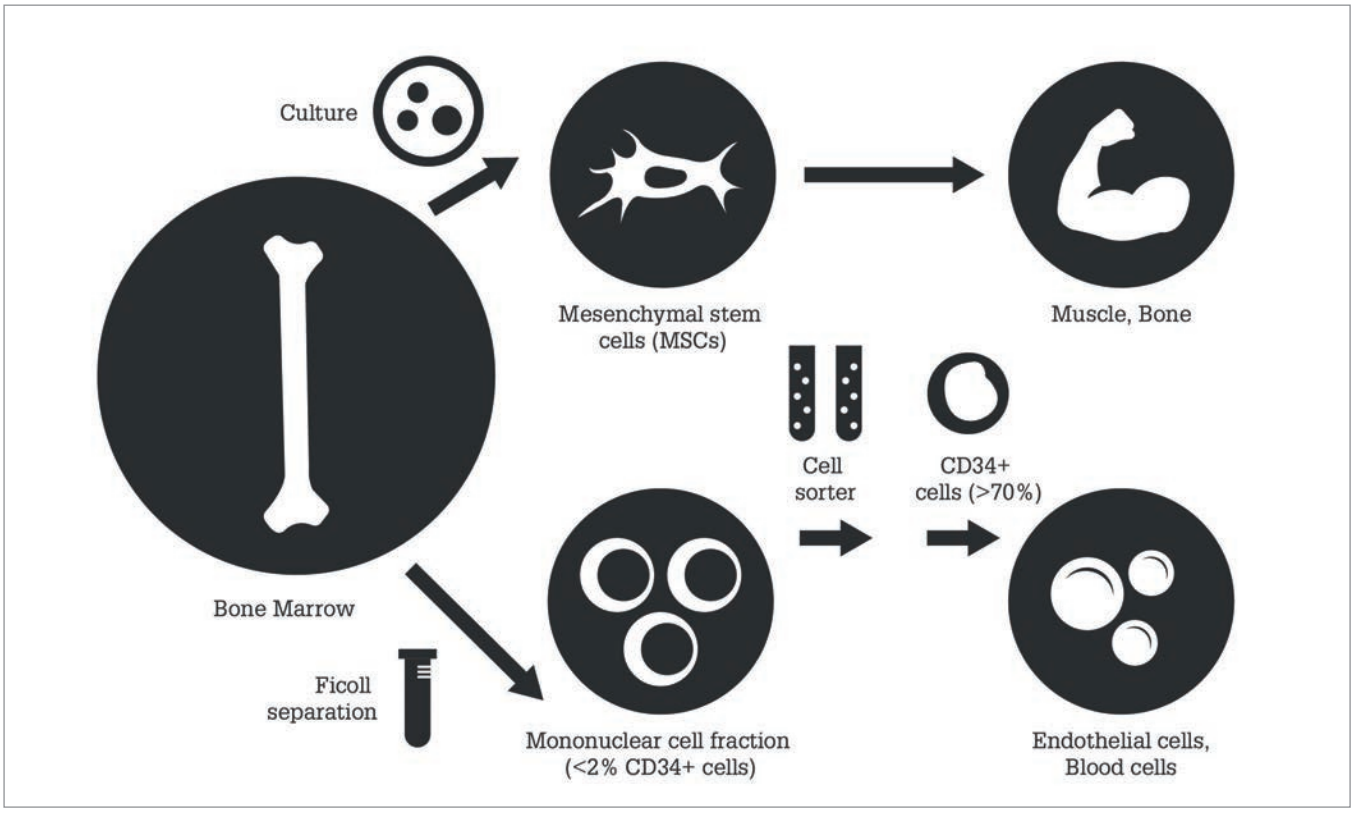


Figure 1. Types of stem cells isolated from bone marrow. Mesenchymal stem cells are easily cultured and expanded from bone marrow aspirate. Human hematopoietic stem cells can isolated by the cell surface marker, CD34. Human hematopoietic stem cells can isolated by the cell surface marker, CD34.

markers (which, in humans, is principally CD34) (14).

Both the intravitreal and subretinal MSC administration routes have been explored in animal models of retinal degeneration, with both displaying a neuroprotective effect on the degenerating retina with minimal engraftment. Studies also show subretinal MSC administration may be the more effective route of administration for the treatment of retinal degeneration (13,14). However, intravitreal MSC injection would be the simpler and easier way of administering cell therapy; unfortunately, this approach can result in the cells clumping in the vitreous cavity. In vivo retinal imaging has shown fibrovascular proliferation that results in significant complications like tractional retinal detachment (14), raising safety concerns about this route of administration. To date, there are no published clinical data using MSCs for the treatment of retinal disease, although multiple Phase 1 and 2 clinical trials have been conducted for non-ocular conditions without safety concerns (14).

Human bone marrow CD34+ cells contain mostly HSCs. These cells can differentiate into various cells of various blood cell lineages, and may also have paracrine regenerative effects (6,14). The CD34+ cells include endothelial progenitor cells (EPCs) that are mobilized into the peripheral circulation in response to tissue ischemia and are thought to play an important role in tissue revascularization (6). In mouse models of ischemic retinal vasculopathy, CD34+ cells have been shown to home in on the damaged retina and retinal vessels and secrete factors that promote tissue repair and regeneration (15,16). The CD34+ HSCs may play an important role in patients with retinal disease. For example, CD34+ HSC levels are elevated in the systemic circulation of patients with exudative AMD, and it is possible these cells play a role in the physiologic repair response to the disease state (17). By contrast, defects in the homing capability of CD34+ cells in peripheral blood of diabetic subjects have been observed, and it's thought that this plays a role in the pathogenesis of a number of diabetic complications, including retinopathy (18–20).

Our work

We have shown that intravitreal administration of human CD34+ cells from bone marrow into the eyes of NOD-SCID mice with acute retinal ischemia-

reperfusion retinal injury results in not only long-term incorporation of the human cells in the retinal vasculature but also the apparent normalization of the retinal vasculature (21). Why NOD-SCID mice? We chose them as their innate immunodeficiency makes them incapable of rejecting the human CD34+ cells. The safety profile observed in the NOD-SCID mice was excellent, with no ocular or systemic adverse effects being associated with the administered CD34+ cells injected into the vitreous; the CD34+ cells themselves remained viable and detectable within the retinal vasculature for over six months. The fact that this study demonstrated a favorable long-term safety profile with this route of cell therapy lead to the FDA issuing Investigational New Drug Application (IND) clearance to explore this cell therapy in a clinical trial.

"CD34+ HSCs may play an important role in patients with retinal disease."

We've also used a systemically immunocompromised mouse model of retinal degeneration to investigate the effect of intravitreally-administered human bone marrow-derived CD34+ stem cells on inherited retinal degeneration (22). In this study, *Pde6*$^{brd1/rd1}$ mice were used, as they display a rapidly progressive severe retinal degeneration with loss of electroretinographic (ERG) signals by four weeks of age. The mice were immunosuppressed pharmacologically with tacrolimus and rapamycin, which were delivered continuously using an implanted ALZET pump. Following immune suppression, we administered either GFP (green fluorescent protein)-labeled CD34+ cells harvested from human bone marrow, or saline by intravitreal injection. The mice underwent in vivo retinal imaging to visualize the cells in the eye. Simultaneous scanning laser ophthalmoscopy and optical coherence tomography were used. Then, the mice were euthanized at either one or four weeks after the injection of stem cells for histological and microarray analysis of the retina.

As with the previous study, the safety profile was excellent and no ocular or systemic adverse effects were observed. The GFP-labeled CD34+ cells appeared to home in rapidly into the retinal surface and seemed viable over the entire study duration of the four-week period after injection. Microarray analysis of the gene expression changes in the retinae of these mice after CD34+ cell injection demonstrated altered expression of more than 300 genes – predominantly those regulating photoreceptor function and maintenance as well as apoptosis. These findings support the concept that the CD34+ cell therapy can affect the degenerating retina at multiple levels via multiple pathways, similar to the effects of MSCs described above (22–24). We proposed that the observations were best explained by a paracrine effect of the CD34+ cells as we observed no direct incorporation of human cells into the degenerating photoreceptor layer in these mice.

Clinical promise

Our group also initiated a Phase I clinical trial investigating intravitreal autologous CD34+ cell therapy for retinal disease under an IND cleared by the FDA. The CD34+ cells were isolated from bone marrow of patients with ischemic or degenerative retinal disorders and administered autologously (NCT01736059). The bone marrow aspiration and intravitreal cell injection were performed in-office under local anesthesia on the same day, no systemic immunosuppression was used, and the CD34+ cells were isolated from the mononuclear cell fraction of the bone marrow aspirate under Good Manufacturing Practice conditions. The first six patients included two patients with Stargardt's disease, two patients with AMD, one patient with retinitis pigmentosa and one patient with a combined central retinal artery and vein occlusion (CRAO/CRVO). As this is a Phase 1 clinical trial, all subjects had advanced permanent vision loss in the study eye at enrollment. After six months, four of the six eyes showed visual acuity improvements of two or more lines during the study follow-up period (25). The most dramatic improvement in vision was achieved in the patient with CRAO/CRVO, where that pathogenesis of vision loss is more acute and ischemic rather than progressive and degenerative. No ocular or systemic complications were recorded in any of the study subjects.

The results of the Phase I clinical trial showed the promise that CD34+ cells have for retinal regeneration and further investigation is planned. The advantages of this approach to cell therapy are obvious: CD34+ cells are relatively simple to obtain from bone marrow and can be used autologously without the need for systemic immunosuppression. Intravitreal cell delivery is technically simple and may be an effective route of cell delivery for the treatment of retinal disorders based on preclinical studies (13). The paracrine effects of these cells on damaged retina may allow this cell therapy to have a broad clinical application that may be therapeutic for both degenerative and ischemic retinal diseases – think of the potential it might have to treat the baby-boomer generation with age-related retinal disease. The safety profile of this cell therapy has been excellent thus far but, clearly, larger clinical trials are needed to further characterize the safety and efficacy of this cell therapy. Given that some serious ocular adverse effects have been reported in individuals receiving unregulated cell therapies for vision loss, it's critical for patient safety that the proper characterization and

isolation of cells in bone marrow is performed before intraocular administration (14).

The ultimate goal of this area of research is to develop a therapeutic treatment for patients with vision loss from retinal disorders that are currently untreatable without compromising patient safety. If this can be achieved, the consequences for patients, medicine, and society could be profound.

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Benchmarking Dry AMD

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

By Roisin McGuigan

Age-related macular degeneration (AMD) is the leading cause of blindness in developed countries and the third-leading cause in developing countries. Dry AMD, unlike the neovascular, wet form, has no effective therapies available today – bad news, especially as it comprises about 85–90 percent of all AMD cases. Then again, a number of potentially disease-modifying therapies are currently under clinical evaluation, so this situation may change in the future.

In 2015, we benchmarked the PubMed-listed AMD literature as a whole (1), and we've also reviewed the entirety of the AMD trial data that's available on clinicaltrials.gov (2). This month, we set out to specifically assess the dry AMD literature.

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

We asked:

- Who has published the most?
- Who has had the greatest impact?
- What are the big topics being discussed?
- Is this knowledge available online (for free or for a fee)?

PubMed was searched for dry AND "macular degeneration", with results limited to the last five years, and the data were analyzed in Microsoft Excel 2013.

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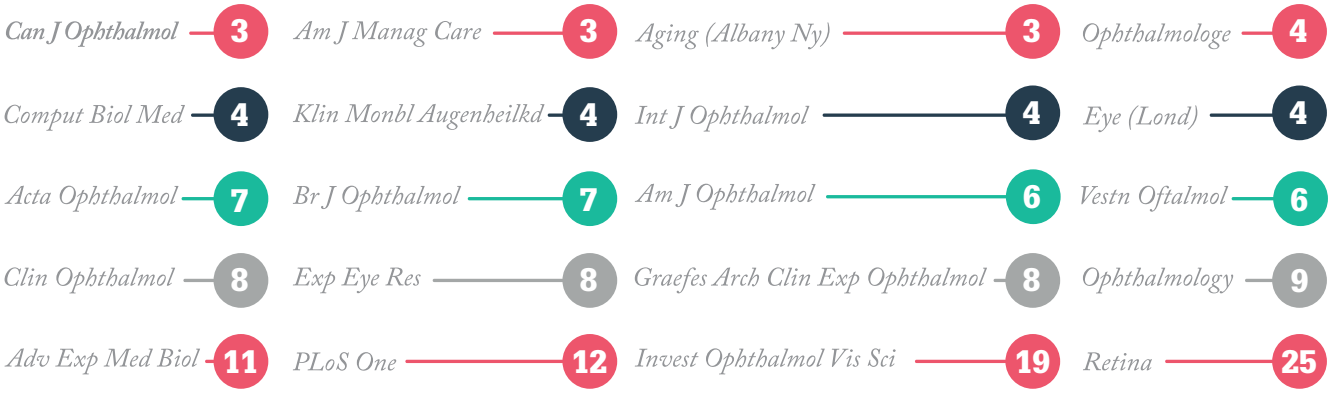
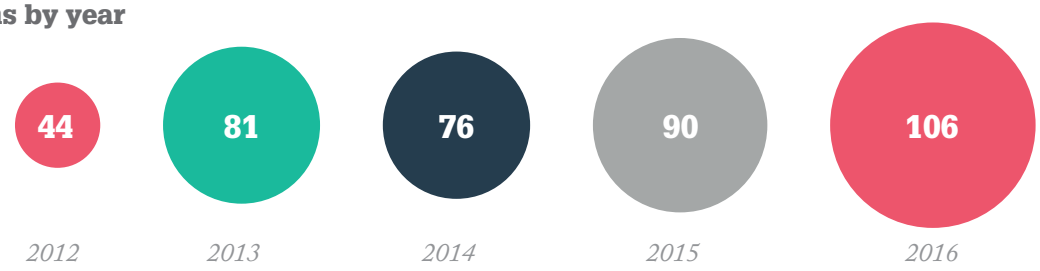
Top 20 Journals by number of publications



Publications by year



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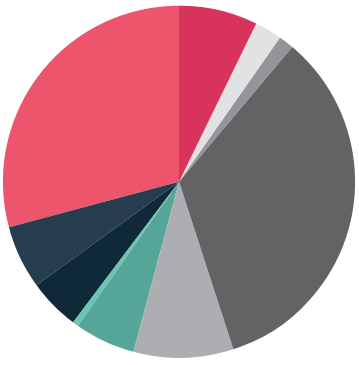

- 34% Clinical study
- 9% Clinical trial
- 6% Comparative study
- 5% In vitro study
- 1% Cross-sectional study
- 29% Review
- 7% Animal study
- 6% Other
- 2% Case report
- 1% Case-control study

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Top 15 Topics

- Macular Degeneration 245
- Retina 105
- Aged, 80 and over 87
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- Tomography, Optical Coherence 60
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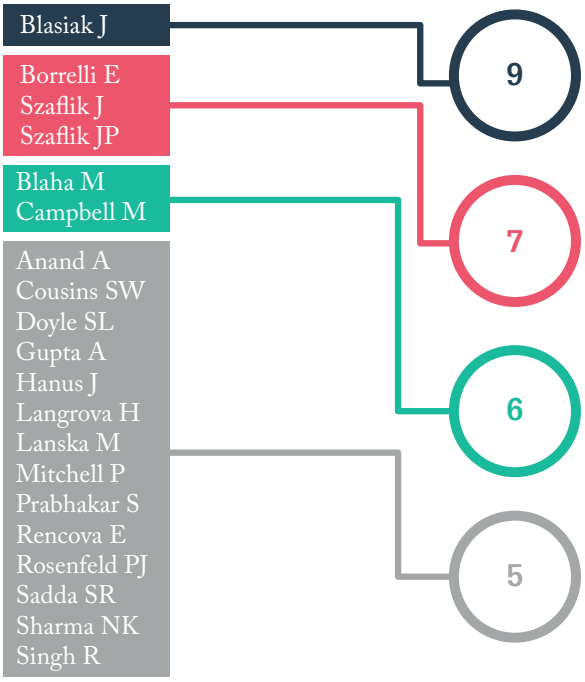
- Retinal Pigment Epithelium 50
- Case-Control Studies 44
- Risk Factors 42
- Wet Macular Degeneration 39
- Prospective Studies 32
- Oxidative Stress 30
- Fluorescein Angiography 29
- Vascular Endothelial Growth Factor A 29
- Disease Progression 25

Top 20 authors by number of publications



Country

35% USA	17% Other	6% Germany	5% Japan
5% UK	5% Poland	4% China	4% Italy
3% Turkey	3% Republic of Korea	3% Australia	3% France
3% Spain	2% Singapore	2% India	2% Russia

Profession

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46–49
From Obamacare to Trumpcare
Trump's presidency has thrown US healthcare into a state of flux - but what might the coming changes mean for ophthalmology?

From Obamacare to Trumpcare

For now, the future of healthcare remains uncertain – but what are the potential outcomes for ophthalmology?

By Alan Reider and Allison Shuren

Ever since the results of the US election became international news on November 9, speculation on the changes Trump might make to the healthcare system have been rife. His promise was to repeal and replace Obamacare, but the big questions remain: what form will this take, and what will it mean for healthcare – including ophthalmology? It's still too early to predict (with any degree of precision) how the US healthcare delivery systems will change under the Trump administration and a Republican-controlled Congress, but two changes appear more likely than others:

At a Glance

- *President Trump has promised to "repeal and replace" Obamacare – but what does this mean for ophthalmology?*
- *With more individuals likely to be driven to join commercial healthcare plans, more physicians are likely to seek to partner and network with other physicians and organizations*
- *There are a number of alternative practice strategies physicians could embrace – but ultimately, it is too early to tell which will prove the most successful*
- *Ophthalmology has endured changes before, and many practices continue to thrive – so it's also entirely possible that the expected levels of disruption may never materialize*

dismantling the core of the Accountable Care Act related to state exchanges and eliminating mandatory health insurance.

Safety in numbers

Most of the Republican proposals will drive more individuals, including Medicare and Medicaid beneficiaries, into commercial health plans. As a result, the trends among commercial payers to i) pay for services-based value and quality-based purchasing, ii) narrow physician networks, and iii) increase reliance on risk sharing contracts will continue to encourage physicians to seek alternative practice arrangements that offer greater integration of care and more providers with whom to share risk. It is likely that physicians will be considering a number of options, such as joining Accountable Care Organizations or patient-centered medical homes, seeking to grow the number of physicians and physician extenders in their practices, or exploring the potential of leveraging the services of professional management services organizations (MSOs). Physicians may also consider partnering with new owners or investors. Ultimately, one thing is predictable: the US health care delivery

"The increasing administrative burden required to participate in federal healthcare programs is making the cost of operating small practices prohibitive."

Talking From Experience

Lessons learned from completing a large private equity transaction

By Candy Simerson

Independent physician practices that decide to go down the path of mergers or acquisitions will find that these activities involve a substantial amount of due diligence, and more scrutiny than a privately held business has experienced in the past. Although it's a great learning experience, it is also a time-consuming and arduous process. As physician owners consider exploring merger and acquisition options, taking the time to review and improve business operations in advance is a worthwhile investment. The due diligence process for any transaction involves meticulous examination of many elements, a few of which are discussed below.

Financial performance, including growth, monitoring of key metrics and operational efficiency trends are of vital importance for any potential buyer. It is important to ensure the accuracy of calculating and reporting exact net revenue on financial statements, and the accrual accounting method is preferred over cash basis accounting. Key performance metrics will typically include strong management of accounts receivable, reports on patient volumes, specific services provided and related volumes, physician productivity, payer mix and growth trends.

The ability to produce all material contracts, such as all shareholder agreements, employment agreements, property lease agreements, equipment lease, major vendor contracts and others is also important. A study of antitrust and regulatory matters should include a review of coding and reimbursement compliance, conflicts of interest and other related party transactions to evaluate any potential future risks or liability.

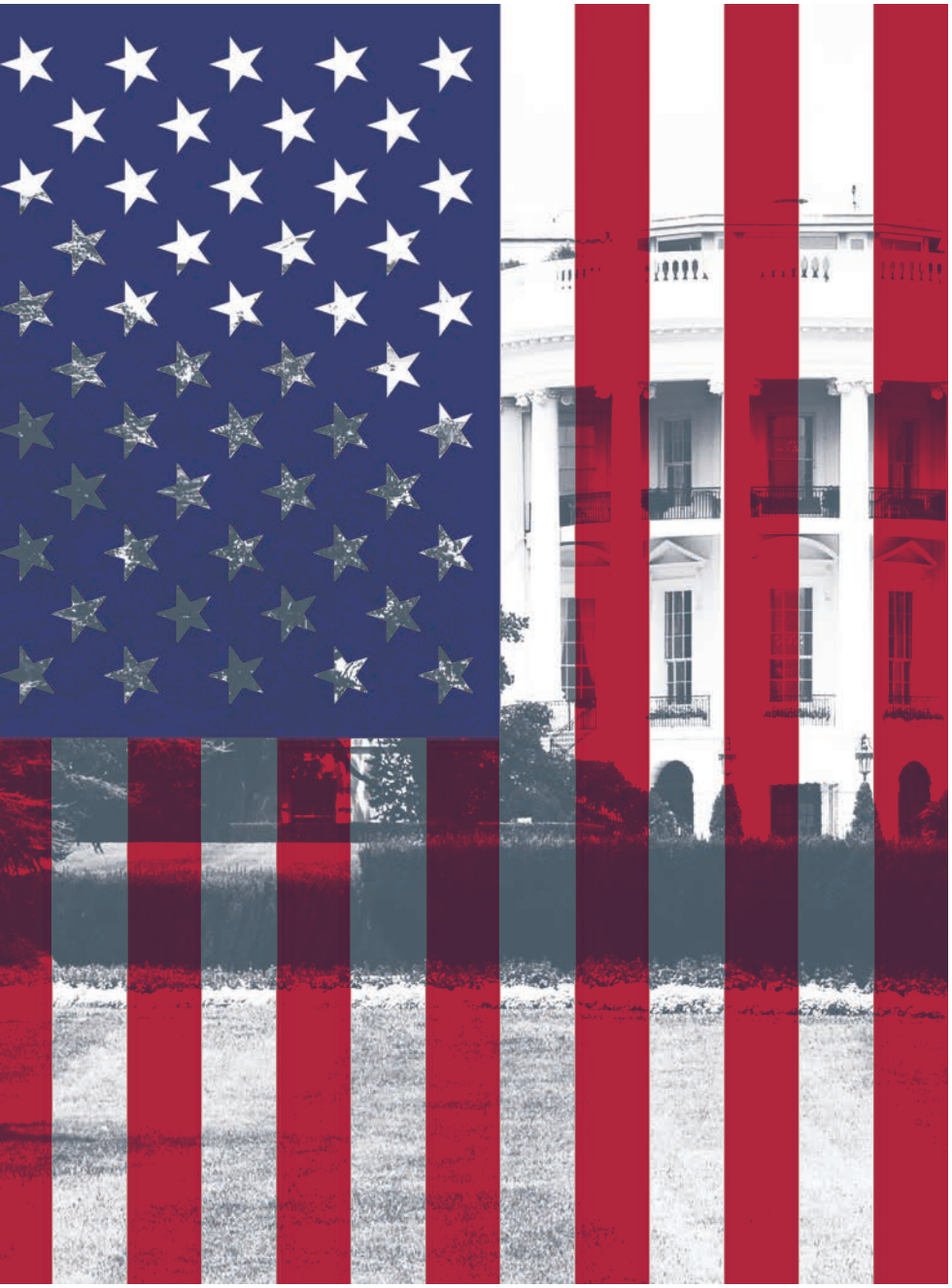
A review of organizational structure and management of human resources, compensation and benefits, personnel policies and compliance with reporting requirements should also be carried out. After completing a due diligence process, it should be clear to all parties whether the relationship is a good fit – and if it makes sense to move forward.

Candy Simerson is Director of Business Development for Precision Eye Services, Bloomington, Minnesota.

system will be in flux and some turmoil for years to come.

Weathering uncertainty

Many ophthalmologists are concerned about the uncertainty as we transition from Obamacare to Trumpcare, and are wondering what this transition means for their practices. However, as a result of forces in the marketplace over the past several years, some ophthalmologists have already begun to address this new frontier – often by taking steps toward consolidation. In my opinion, this transition will continue regardless of the direction of healthcare policy from Washington.



There are several factors that appear to be driving this transition. First, for some time we have seen a gradual movement away from traditional fee-for-service Medicare and Medicaid in favor of managed care plans. These plans often restrict the number of physicians who can participate on their panels, and consolidation is seen as a defense mechanism, as participation with a larger enterprise should enhance the ability to participate with payers to assure access to patients. Second, the downward pressure on reimbursement makes it difficult for any but the most highly efficient practices to thrive. Consolidation allows physicians to operate more efficiently by sharing overhead – at least in theory. Similarly, the increasing administrative burden required to participate in federal healthcare programs is making the cost of operating small practices prohibitive.

Practice strategy pros and cons

Regardless of the direction of healthcare policy in the future, physicians are likely to be driven to a number of new practice strategies. And although it's currently too early to tell which approaches will succeed and which will fail, the risks and benefits of some of the more common options are discussed below.

1. Engage with private equity

Those who have been in ophthalmology for many years will recall the frenzy in the development of the Physician Practice Management Companies (PPMC) in the 1990s, where ophthalmologists across the country engaged with venture capital in an attempt to monetize the value of their practices and consolidate for the future. And although the concept of consolidation to realize efficiencies of scale has merit, these ventures all failed. Now, 25 years later, we are seeing the re-emergence of this model through private equity funding.

Despite its previous failures, the model should offer some significant benefits. It provides a practice the opportunity to participate in a network with multiple practices, making it attractive to payers seeking to contract with a single entity to provide a broad range of specialty services to its subscribers. It also offers the benefit of sophisticated management to address complex business, regulatory, and competitive issues. The private equity model also provides access to capital, which is critical for growth and access to new technology. And it provides some ophthalmologists with the opportunity to cash out at an attractive multiple of

earnings with the possibility of further financial benefit if the investment is eventually taken to the public market.

But as proven in the past, the model also has its limitations. First, there is no assurance that other practices will join a particular venture – and the model is unlikely to succeed with only one or two participants. Second, there is the question of whether management will really be effective. Some believe that the failure of the PPMCs in the 1990s was based, in part, on an inability to properly manage all of participating practices. Third, ophthalmologists must give up a great deal of autonomy and decision-making, which may seem simple in theory but is challenging in practice. The fundamental question that still needs to be addressed is: why will this model work today when a similar model failed 25 years ago?

"It's currently too early to tell which approaches will succeed and which will fail."

2. Cooperative MSOs

In response to the need for more efficient practice management, some practices have established an MSO, designed to consolidate administrative overhead for multiple practices. The MSO contracts with each practice individually to provide management services, presumably at a cost below what each practice would incur independently. And unlike some of the other models, the MSO enables practices to maintain a greater degree of autonomy in overall decision-making.

But there are drawbacks. The MSO model requires a commitment of time and resources to implement – it is not a project where the administrator of a practice can develop it in his or her spare time. Once again, there is no guarantee of finding other practices that are willing to participate – and even if you do, there is always the potential for disputes concerning personnel, technology, or other decisions by management that will affect each of the contracted practices. Finally, the MSO model only addresses the cost aspect. It doesn't address the key concern of ophthalmologists: how to protect their patient base and continue to participate on payer panels. Without significantly more integration, the MSO model seems unlikely to address that concern.

3. Merge with other practices

In a clear pursuit of "bigger is better," ophthalmology practices are merging to cover all subspecialties and expand their geographic reach. Not only do these practices hope to achieve some cost efficiency, they also hope to be more attractive to payers; after all, such 'mega-practices' can meet all health plan subscribers' vision care needs. A true merger also may offer some operational efficiencies as all overhead costs are shared.

But merging with other practices is not a panacea. Physicians must surrender a great deal of autonomy; a big challenge for the physician will be to find potential merger candidates with compatible values and culture. Further, there are some real operational problems with practice mergers: administrative issues, such as consolidating employee benefit plans, salary structures, and simply retaining staff, can all present significant legal hurdles. A merger requires total integration from both the financial and clinical perspective – failure to do so raises potential antitrust risks.

4. Develop an integrated network

The development of an integrated network may be viewed as the complement to the development of the MSO. An integrated network establishes a panel of providers to contract with health plans for the provision of vision care services for health plan subscribers. The network model allows practices to maintain their autonomy in structure and operation, while providing access to patients.

However, there are limitations here as well. The cost of developing a network in both time and resources is not insignificant, and depending on the payment methodology for the services provided (for example, fee for service or capitation), there may be a significant degree of financial and/or clinical integration required to avoid antitrust issues. Nevertheless, these networks have been evolving and some have met with significant success.

Déjà vu...

As noted above, there is great uncertainty as to the direction of healthcare delivery in the future. In many ways, however, one can say, "it's like déjà vu – all over again..." It is entirely possible that those who decide not to make any moves at all will be able to continue to operate in the future with little or no disruption. We do seem to have been in this place before and, despite significant changes over time, ophthalmology practices have, for the most part, continued to thrive.

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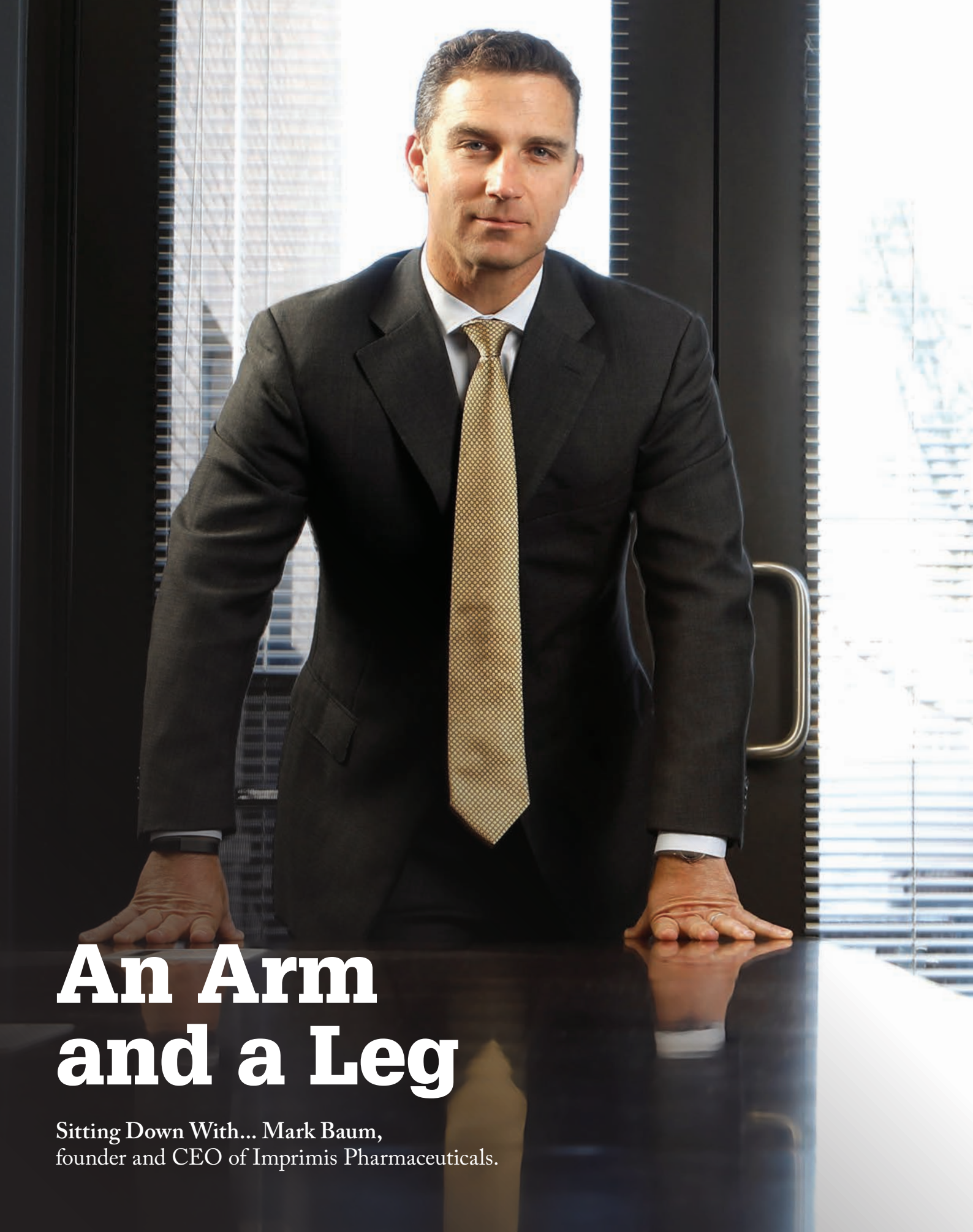

An Arm and a Leg

Sitting Down With... Mark Baum,
founder and CEO of Imprimis Pharmaceuticals.

How serious and widespread is the problem of overpriced drugs?

It's an incredibly complicated and pervasive problem. Our federal policies create and protect monopolies so drug companies can charge whatever they want, even for old off-patent drugs, and in a growing number of cases, for generic drugs. It's statutory, regulatory and it has permeated our drug economy at the cellular level. We have created the opportunity for exploitative behavior like the infamous Martin Shkreli, who increased the price of the toxoplasmosis drug Daraprim from $13.50 a tablet to $750 overnight. Hauled in front of Congress, he plead the Fifth Amendment, and then later tweeted to the world that his Congressional interlocutors were "imbeciles." However, the reality is that those same people angrily questioning Shkreli that day made the very policies that created his opportunity in the first place. And guess what? Nothing has changed.

In a year where there will likely be reform of the Affordable Care Act, we should consider reform of the other areas of the healthcare value chain, including drug pricing. While wages have been stagnant for most Americans for decades, drug companies raise prices every year and sometimes twice a year. Patients are dealing with increasing out of pocket costs and higher deductibles. While we need to reward innovation, we should use market-based principles to rebalance patient exposure to high drug pricing.

How do we make the distinction?

Consider cataract surgery, the most commonly performed elective surgery in the world. It's an incredibly successful and safe procedure, but it can always be improved, right? The problem arises when innovation results in increased costs to patients for only minor improvements in their outcomes. Does using that expensive laser to make a hole in the bag really give much better results than a surgeon doing it by hand? It certainly costs more! Do we want to invest in improvements of products that are marginal or do we want to invest in truly innovative products such as Sovaldi and Harvoni that have the power to cure hepatitis C? As a society, we must encourage and reward transformative innovation and consider the value we are willing to pay for more marginal advancements, while always allowing patients to have the freedom to buy what they wish.

How did you manage to offer a one-dollar alternative to Daraprim?

When drugs are affordable, you don't need discount cards, rebate programs, "patient access" teams, prior authorizations or pharmacies "switching" prescriptions. In that specific case, making a drug where the chemicals used to make it costs less than potting soil was the easy part. These types of drugs should be affordable – but they're not, in large part because our country's policies do a much better job of advancing the interests of large pharmaceutical companies instead of the customers who rely on their products. It would be a good thing if pharmaceutical companies believed their "customer" was a patient-in-need instead of an insurance company or a drug benefit manager. For too many, the opposite is true.

What about the regulatory landscape?

We need reform, including amending the mission of the FDA to overcome our current competition and affordability challenges. There are many opportunities to make effective change. For example, one in five prescriptions in the US is written off-label. It's common and, candidly, necessary. The question is: why, when we have the FDA, is there even such a thing as an off-label drug? That doesn't sound good or safe, does it? The next question is: how do we make it easier to get drugs approved so that we have fewer off-label uses of drugs?

And what does that reform look like?

If something isn't working, we should change – and not persist in failure. A first step is to commit to reform. Second, regulatory barriers need rethinking. Why should orphan drugs be approved with one efficacy trial, not the two or three it usually takes? If a new chemical entity orphan drug can be approved with a less expensive and risky standard of evidence, then why do we require two or three trials for new uses of old off-patent, already approved drugs – or for any drug for that matter? Why should people with orphan diseases be treated any differently than a patient who cannot afford a medication because Martin Shkreli finagled the creation of an artificial monopoly for its product? Reforming these policies and embracing competitive forces in the market would squash the likes of Shkreli and his ilk.

I also say we need a strong FDA to protect the public from unsafe drugs. But how about allowing the market to work more with respect to efficacy? In practice, companies spend millions (if not billions) of dollars to take a drug through multiple risky and expensive efficacy trials, yet insurance companies can decide not to put the drug on formulary and in effect deny access. Patients are beginning to understand that they are ultimately paying for the high cost and risk associated with multiple efficacy trials which limit competition and increase the costs of drug development.

So for new chemical entities, let's treat non-orphan drugs the way we treat orphan drugs. For old off-patent FDA-approved drugs, if it is legal to prescribe an approved drug off-label, why make companies take massive risk to go through multiple efficacy trials to get a new label? Why not eliminate efficacy trials for new uses of already approved drugs, or allow an efficacy submission to be based on the clinical experience of the many off-label uses? The bottom line is that the entire process needs rethinking, but we also need lawmakers to have the gumption to take action.

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