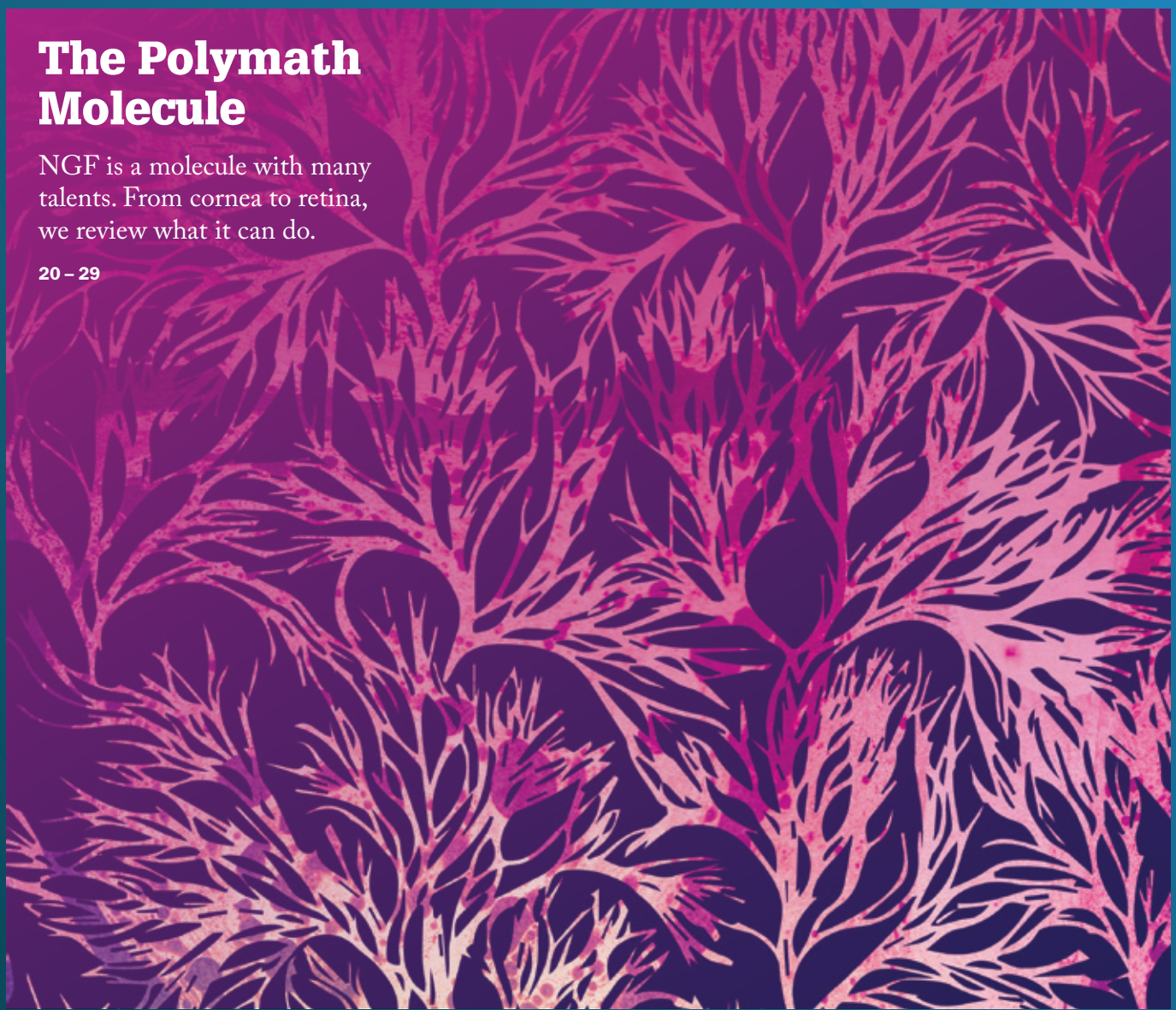
MARCH 2016 # 28

the Ophthalmologist



The Polymath Molecule

NGF is a molecule with many talents. From cornea to retina, we review what it can do.

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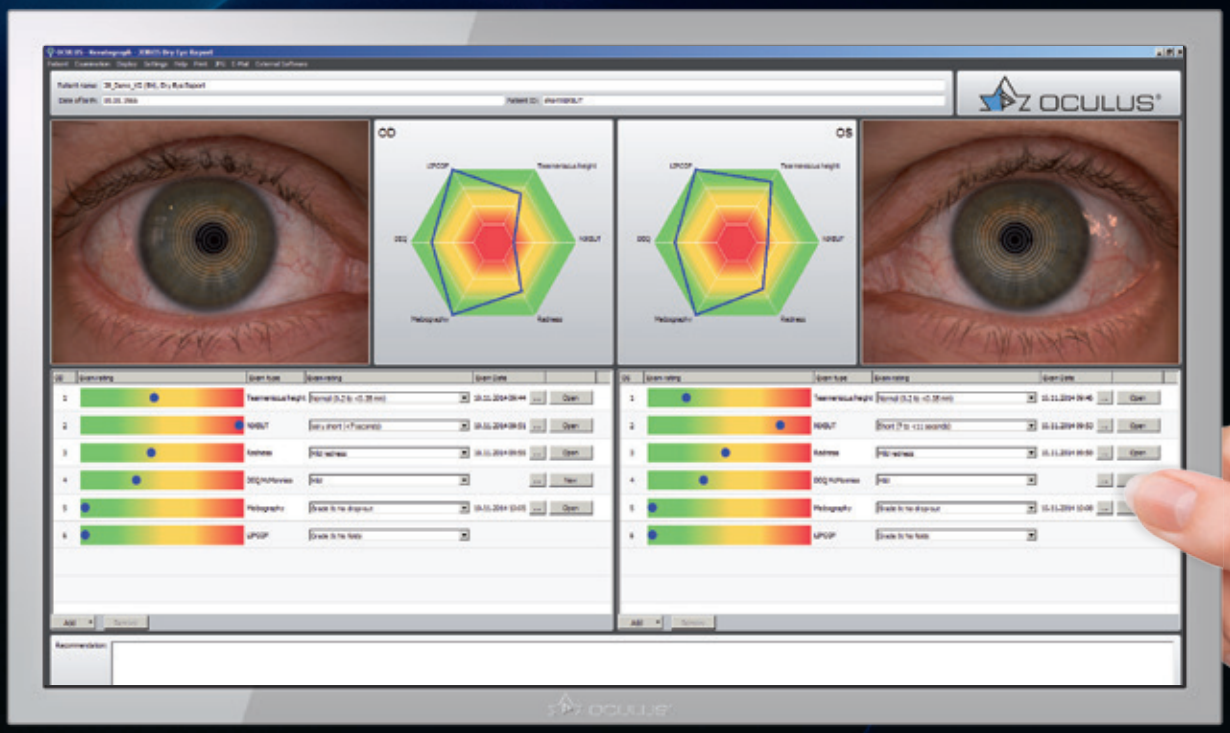

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Image of the Month

Annette Terebuh is a glaucoma specialist and gardening enthusiast based in Ohio. She created her ophthalmology-inspired painting for a local art project. "My painting, 'In the Eye of the Beholder' shows three fundi as flowers, each showing different types of pathology. Perhaps when I retire from ophthalmology I will work more seriously on my artistic skills and embark on a new career!" she says.

Do you have an image you'd like to see featured in The Ophthalmologist? Contact mark.hillen@texerepublishing.com

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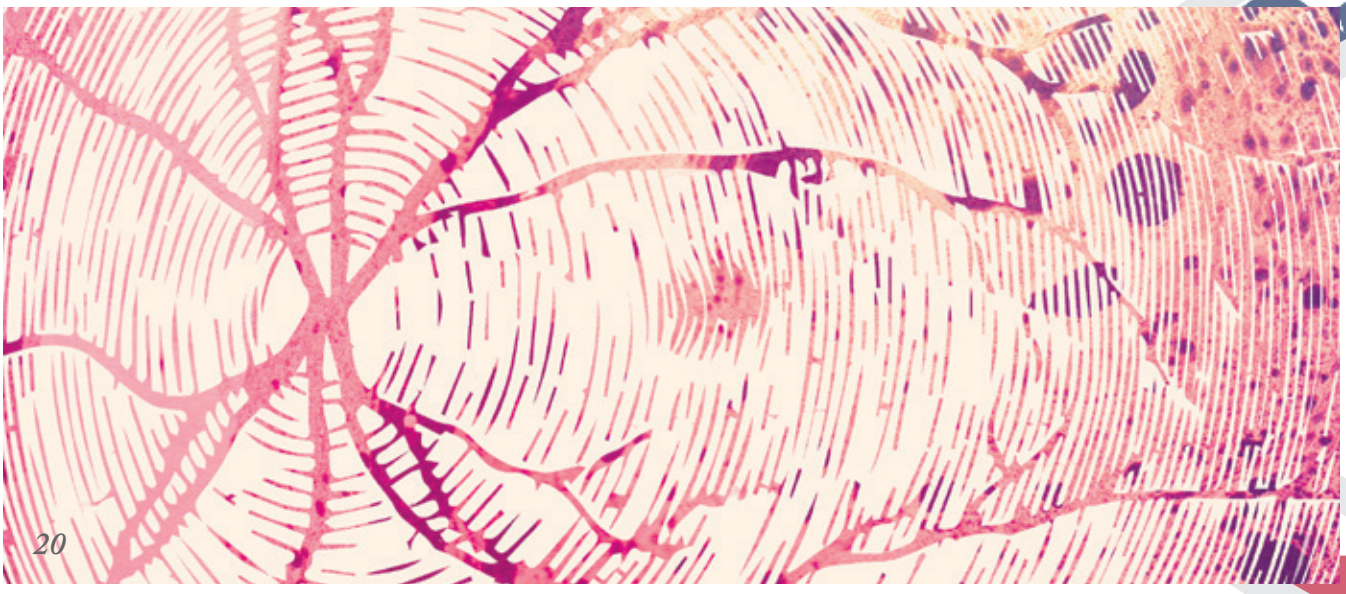
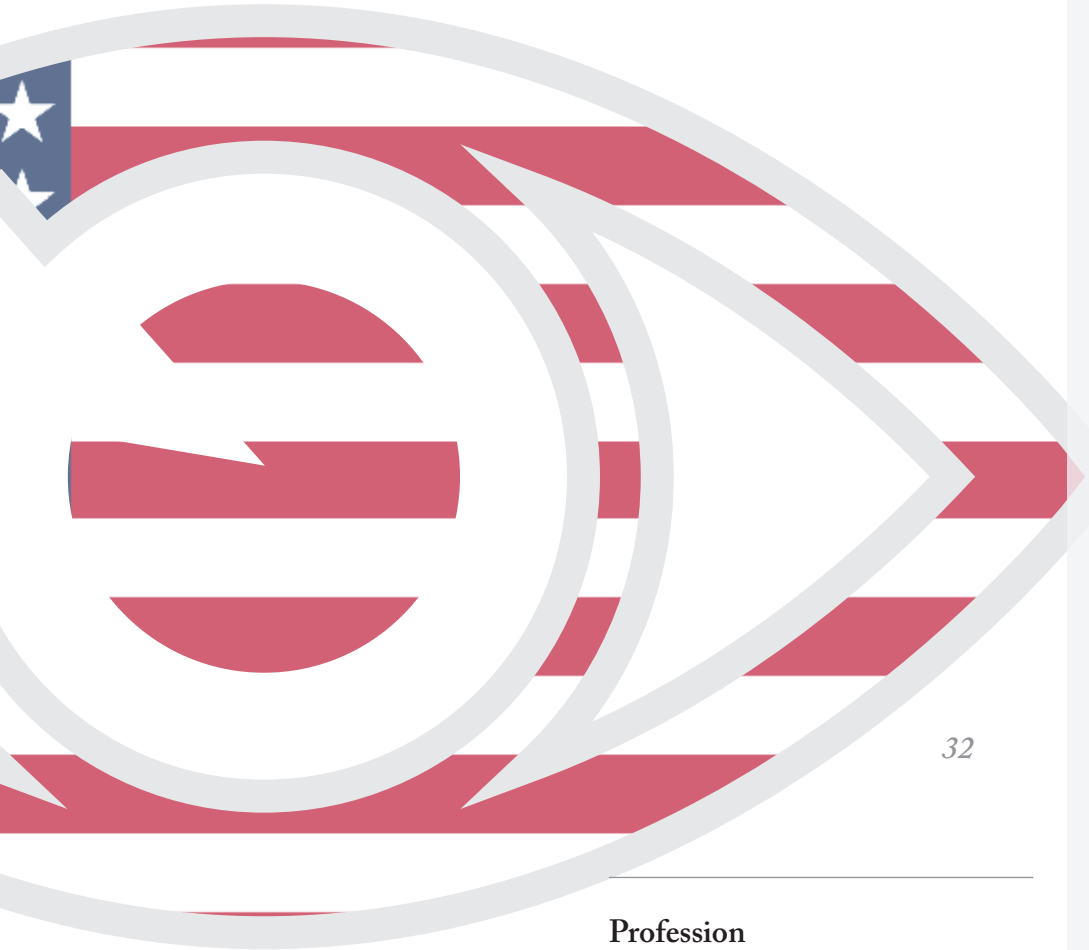


On The Cover

An artistic interpretation of the corneal nerves – just one of the tissues that this 21st Century polymath, NGF, acts on.

Upfront

Feature



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Sitting Down With

the Ophthalmologist

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tracey.nicholls@texerepublishing.com
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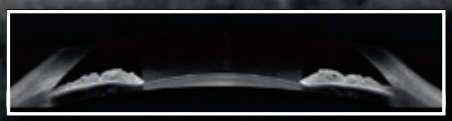

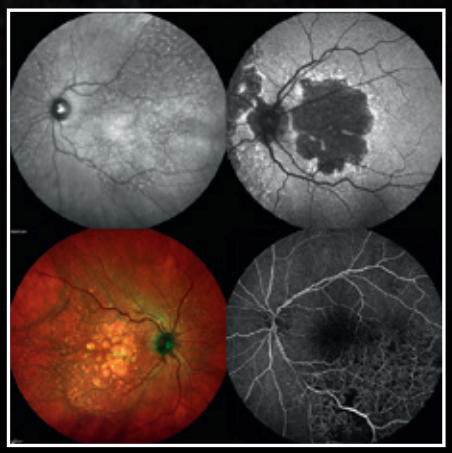

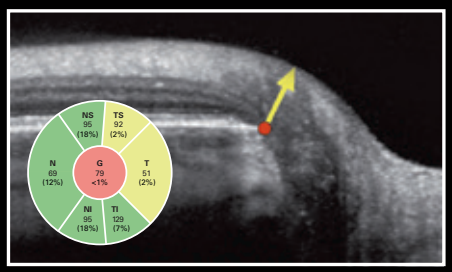

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The Impact of The List

The Power List is a celebration of excellence – and the impact it's had on those it highlights has been impressive

This is the third year that The Ophthalmologist has run the Power List. In 2014, we asked you to nominate the names of the people in ophthalmology who you believe make the biggest impact to our field – your "key opinion leaders." Those nominated didn't have to be ophthalmologists; research scientists, industry executives and even venture capitalists were all welcome, and some from every category made the list. Last year, we asked for your "rising stars" of ophthalmology in our Top 40 Under 40 Power List – celebrating those that are doing the work today that will change the face of ophthalmology tomorrow.

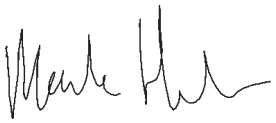
What's interesting is the impact it's had on the careers of those on the lists. I've managed to bump in to many Power List alumni since 2014, and it's humbling to see what being on that list has done for them. Some – particularly the Top 40 Under 40 – have received job offers that I'm told have been purely on the basis of the list. Others have felt that it's made the difference between research grant applications being approved and declined (although unless the grant reviewers have told them this I don't know how they'd know). A few have said that it had made them the go-to media contact in ophthalmology in their region – and I think a lot of power a person has is reflected in (and derived from) their media profile.

Despite the rise of the bloggers and the purported decline of traditional media formats, the Fourth Estate still wields considerable influence over society. There are many media outlets in medicine in general, and ophthalmology in particular – from the most learned of journals to the sparkliest of iPhone apps – and I think it's the interface where the lay press and the trade press meet where some of that power is generated. The Power List concept is something that gets picked up by the "normal" media. It's an idea that a lay readership can easily understand and get behind, it has a great narrative, and if a journalist or news researcher is making inquiries into something eye-related, the Power List pops up at the top of their search results. This means that not only are the Power Listees having their achievements celebrated by ophthalmologists, but often the public too.

If we were trying to market a new product or a service provider with some deliberate clickbait gimmick, the pageviews and column inches provided by the Power List would probably be worth a fortune in marketing terms. It wasn't deliberate, but that's what's happened. I think that exposure has helped those worthy recipients of a place on the list. Perhaps in 2016, that exposure could help you too.

To have a chance of being on the Power List, you first have to be nominated – which can be done here: http://top.txp.to/powerlist-2016.

Mark Hillen
Editor



David Chang

A past president of ASCRS and current chair of the AAO Cataract Preferred Practice Pattern Committee, David is the cataract/refractive surgeon who wrote what many consider to be the definitive textbook on the subject. He has been teaching cataract surgery to ophthalmology residents-in-training for more than a quarter of a century, and is also an Adjunct Clinical Professor of Ophthalmology at the Chinese University in Hong Kong.

On page 32, David tells us why he feels he can't justify the expense and workflow implications resulting from introducing a femtosecond laser into his practice.

Mitch Jackson

Mitch wanted to be an ophthalmologist from the age of eight. His father was blinded in one eye by bacterial meningitis that involved the optic nerve, and this drove the young Mitchell to study hard to find new cures. Mitch has been involved with many clinical trials over the years across multiple indications: laser vision correction surgery, dry eye disease and keratoconus. Mitch runs his own private practice, Jacksoneye in Chicago, Illinois.

On page 32, Mitch explains why he believes that EUREQUO fails to provide the true story on the superiority of FLACS versus manual cataract surgery.

Greg Parkhurst

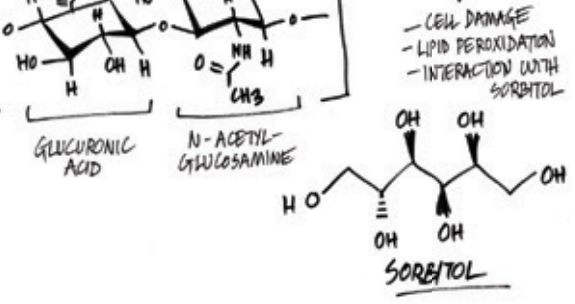
Greg is the founder and CEO of Parkhurst NuVision, Texas, and the President-Elect of the Refractive Surgery Alliance, he's also a former Chief of Ophthalmology and Refractive Eye Surgery in the US military at the world's largest military base. A principal investigator for several FDA clinical trials, and a faculty instructor for the AAO, ASCRS and ESCRS, Greg ranked #8 on our Top 40 Under 40 Power List in 2015.

On page 47, Greg describes his research into ophthalmologists' attitudes about LASIK – how many would recommend it to friends and family?

Anat Loewenstein

The Professor of Ophthalmology and Vice Dean of the Sackler Faculty of Medicine, Tel Aviv University, and Director of Ophthalmology, Tel Aviv Medical Center, Israel, Anat has contributed to numerous peer-reviewed journals and written chapters for several ophthalmology textbooks. Her research focuses on AMD, retinal vein occlusion and drug toxicity in the retina, and she has also worked to develop new technologies for the early detection of AMD.

We Sit Down with Anat on page 50 and talk about her career, being an educator, and the challenges she has faced climbing the career ladder.



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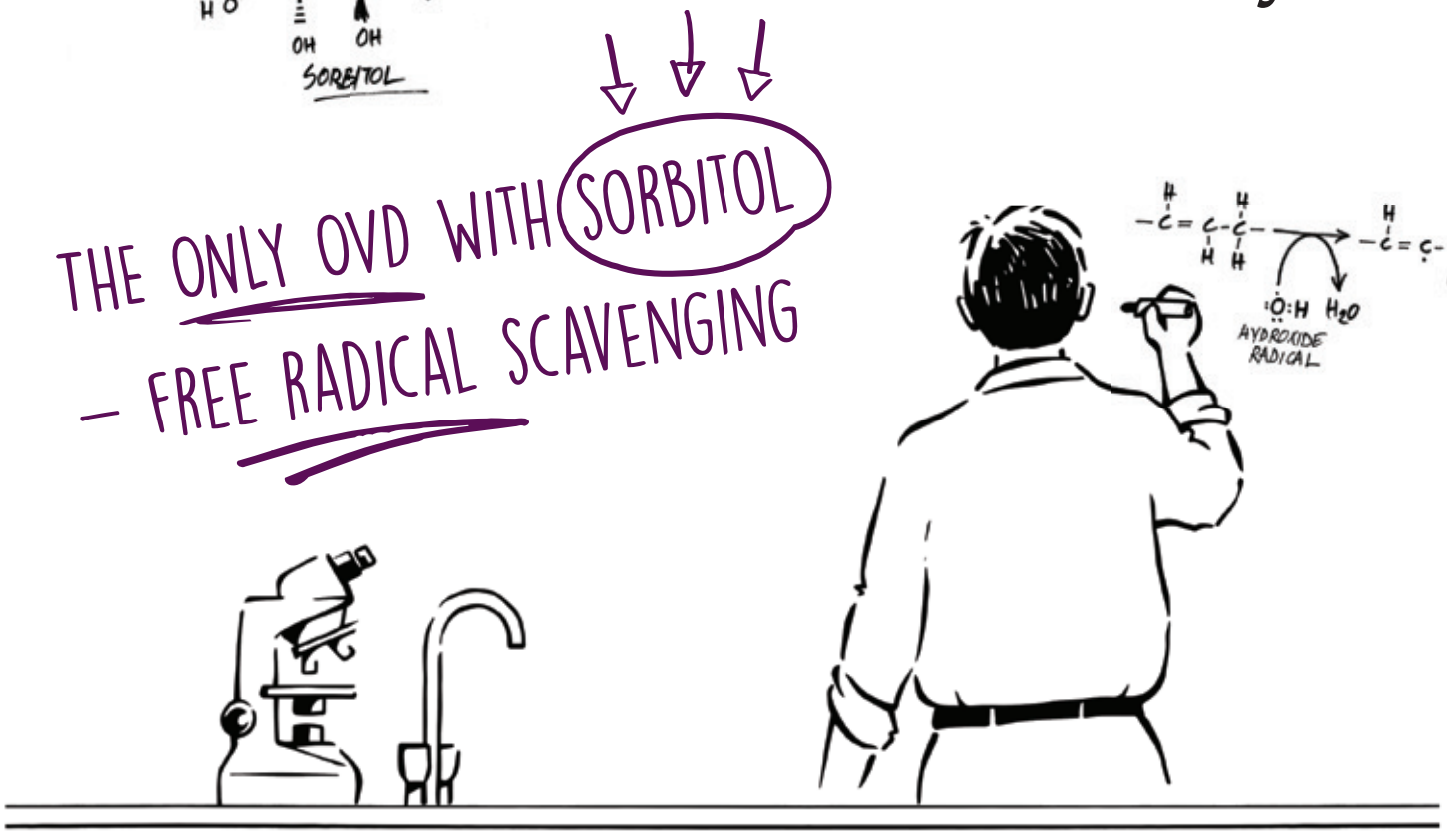

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Upfront

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

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

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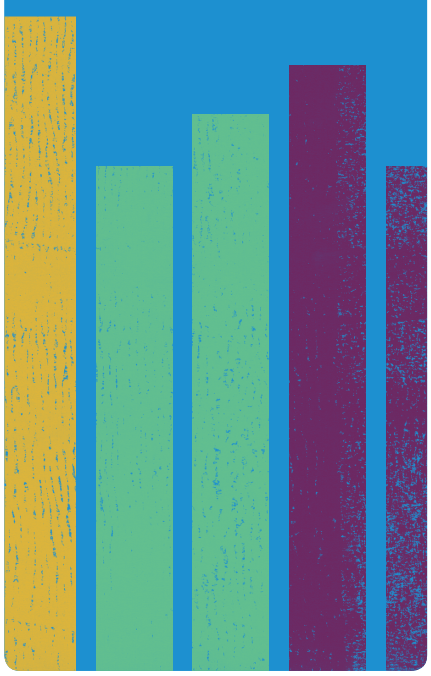

Protocol T: Two Years On

Benefits achieved in the first year maintained; VA performance gap in patients with low baseline vision narrows

Last year saw the publication of the one-year Protocol T trial results (1). Six hundred and sixty patients with diabetic macular edema (DME) were randomized to receive intravitreal aflibercept, bevacizumab or ranibizumab (see Figure 1). All drugs performed well, but aflibercept did best of all – its use was associated with significantly greater improvement in best-corrected visual acuity letter scores from baseline levels than either of the other two drugs – but that didn't tell the full story. For eyes with relatively good vision at baseline (78 to 69 letters; Snellen equivalent, 20/32–20/40), aflibercept-receiving patients did as well as patients receiving either ranibizumab or bevacizumab. But in patients with worse baseline vision (<69 letters; Snellen equivalent, 20/50 or worse), aflibercept use gave patients significantly greater VA improvements (from baseline levels) than patients who received bevacizumab or ranibizumab (see Figure 2a).

Although Protocol T's primary outcome measure was assessed at 52 weeks (on the logic that if a difference was going to be seen in the relative efficacies of these drugs for the treatment of DME, it would be apparent by one year), the trial included follow-up through to the end of the second year of treatment. So when the results were presented at the 2016 Macula Society meeting (and published in Ophthalmology (2) almost immediately afterwards) there was considerable interest in whether or not these results held for the second year.

In essence, it was a similar story after two years, but aflibercept lost its superiority over ranibizumab in the low-vision group (see Figure 2b) – and all three drugs continued to yield similar gains in vision from baseline. In patients treated with aflibercept, mean VA improved by 12.8 letters; in those who received bevacizumab, the improvement from baseline was 10 letters, and those in the ranibizumab group experienced an improvement of 12.8 letters. In those with a baseline VA of <69 letters (Snellen 20/50 or worse), mean VA improved by 18.3, 13.3 and 16.1 letters in the aflibercept, bevacizumab and ranibizumab groups, respectively. In patients with baseline VA of 78 to 69 letters (Snellen 20/32 to 20/40), mean VA improved by 7.8, 6.8 and 8.6 letters, respectively.

Notably, focal/grid laser coagulation was given to 41 percent of patients in the aflibercept group, whereas 64 percent of patients in the bevacizumab group and 52 percent of patients in the ranibizumab group received it.

All of this came with fewer injections in the second year (Figure 3) – almost half as many were administered to patients in the second year of the study as compared with the first.

On assessing adverse events, risk of heart attack, stroke, or death from a cardiovascular condition or an unknown cause by end of the trial was found to be higher among participants in the ranibizumab group. Twelve percent of ranibizumab participants had at least one event, compared with five percent of participants in the aflibercept group and eight percent in the bevacizumab group. Interestingly, this difference in cardiovascular event rates has not been seen across other studies, and therefore may be due to chance. Certainly, serious cardiovascular events are a known potential consequence of diabetes, but continued assessment of their association with these drugs looks like it's going to be important in future studies. The occurrence of eye complications, such as eye infections and inflammation, was similar for all three drugs.

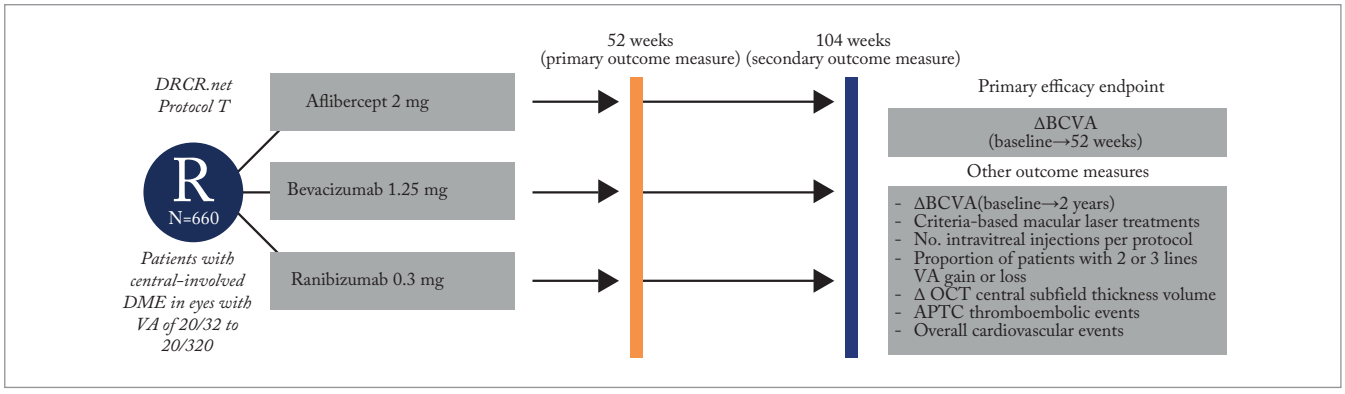

Figure 1. Protocol T trial design. Most patients received monthly injections during the first six months; thereafter, participants received additional injections of assigned study drug until DME resolved or stabilized with no further vision improvement. Subsequently, injections were resumed if DME worsened. Laser treatment was given if DME persisted without continual improvement after six months of injections. APTC, Anti-Platelet Trialists' Collaboration; VA, visual acuity.

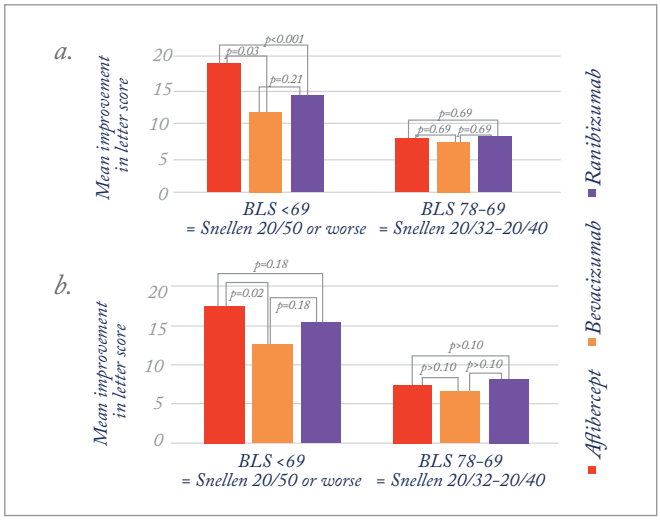

Figure 2. Protocol T: mean letter score BCVA improvements from baseline at year 1 (a), and year 2 (b). BLS, baseline letter score.

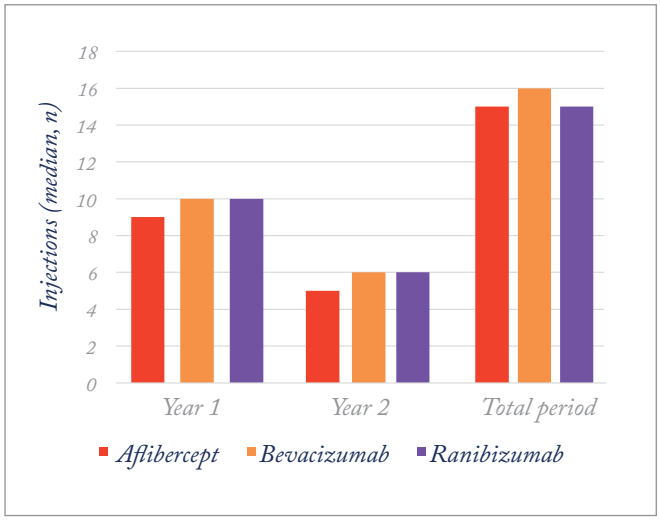

Figure 3. Median number of injections in years 1, 2 and for the total two-year follow-up period of the Protocol T trial.

The lead author of the Protocol T study, John Wells noted, "The results of the DRCR Network's comparison of Eylea, Avastin, and Lucentis will help doctors and their patients with diabetic macular edema choose the most appropriate therapy," adding, "The study suggests there is little advantage of choosing Eylea or Lucentis over Avastin when a patient's loss of visual acuity from macular edema is mild, meaning a visual acuity of 20/40 or better. However, patients with 20/50 or worse vision loss may benefit from Eylea, which over the course of the two-year study outperformed Lucentis and Avastin."

These results need to be placed in the context of the trial's location (the US) and the sponsors – the NEI (essentially the US federal government). Based on Medicare allowable charges, the per-injection costs of each drug (at the doses used in the study) were about $1,850 for aflibercept, about $60 for bevacizumab, and about $1,200 for ranibizumab. It'll be interesting to see what difference the two-year results from Protocol T will make on anti-VEGF agent prescribing patterns in DME in the US going forward. *MH*

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1. *JA Wells et al. "Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema", N Engl J Med, 372, 1193–1203 (2015). PMID: 25692915.*
2. *JA Wells et al. "Aflibercept, Bevacizumab, or ranibizumab for diabetic macular edema. Two-year results from a comparative effectiveness randomized clinical trial", Ophthalmology (2016). Article in press.*

Credit: University of Waterloo/Martin Schwalbe

A study participant about to undergo transcranial direct current stimulation.

Beyond the "Critical Period"

Could transcranial direct current stimulation treat amblyopia in adults?

It's now more than half a century since David Hubel and Torsten Wiesel discovered that sewing a newborn kitten's eye shut for the first three months of its life led to two things: full vision only developing in the open eye, and that this monocular deprivation leads to permanent electrophysiological and anatomical changes in the cat's brain. Crucially, these changes were not seen if the eye was sewn shut closed after three months of age, so the immediate postnatal three months was named the "critical period" (or "sensitive period") for vision development.

In humans too, the greatest effects of vision deprivation on the brain are immediately after birth – although at 24 months long, their critical period is considerably longer than in cats. The conventional wisdom was that it was essential that ocular abnormalities are identified and resolved during the first two years of life. Plasticity in the visual system progressively diminishes thereafter and appears to be almost gone by the age of eight – and therefore if diseases like amblyopia are not treated before eight years of age then the opportunity to save sight is completely lost.

Today, we know that not to be the whole story – for example, children born blind with congenital cataract (and who were blind throughout the critical period, with cataract surgery occurring afterwards) can still experience significant improvements in vision (2). If you're an adult with amblyopia, though, there's new hope: transcranial direct current stimulation (tDCS) .

In the visual cortex, the structures that deal with inputs from both eyes are called ocular dominance columns (another Hubel and Wiesel discovery). The input from an amblyopic eye is subject to suppression from input from the fellow eye. This means that the amblyopic eye generates weaker visual evoked potentials (VEPs) than the fellow eye, and this is what leads to the characteristic visual deficits of the amblyopic eye, such as decreased visual acuity and impaired contrast sensitivity. It turns out that stronger suppression is associated with greater deficits in amblyopic eye contrast sensitivity and visual acuity.

An international team of researchers based in Guangzhou in China, Waterloo and Montreal in Canada, Hong Kong, and Auckland, New Zealand decided to test whether noninvasive tDCS of the visual cortex would modulate VEP amplitude and therefore contrast sensitivity in adults with amblyopia (3). tDCS is an interesting approach – it can transiently alter cortical excitability and may even reduce suppressive neural interactions – such as from the dominant eye in people with amblyopia. Indeed, tDCS can be tuned – it appears to act in a polarity-specific manner; it has been

shown previously that anodal (a-)tDCS of the occipital poles transiently decreases TMS phosphene thresholds, whereas the opposite effect is observed when cathodal (c)-tDCS is applied (4,5).

The research team assembled 48 participants – 21 had amblyopia and 27 were present as controls. They received separate sessions of a-, c- and sham (s-) visual cortex tDCS. What they found was a-tDCS transiently and significantly increased VEP amplitudes in all eyes – amblyopic, fellow and control – and also contrast sensitivity for amblyopic and control eyes. c-tDCS decreased VEP amplitude and contrast sensitivity and s-tDCS had no effect.

So what is behind these transient changes? Clearly, further work is needed to elucidate these mechanisms (and whether these changes can be made to stick), but the prime candidate for a-tDCS' mechanism of action is reducing the amount of the inhibitory neurotransmitter, GABA, in the visual cortex, thereby reducing the chronic suppression of inputs from the amblyopic eye. a-tDCS also has excitatory effects, so the authors hypothesize that this "may lead to a transient enhancement of the cortical response to amblyopic eye inputs in the form of an increased VEP amplitude and improved contrast sensitivity."

Study co-author, Benjamin Thompson explained that these initial results demonstrate the proof-of-concept that will allow him and his research group to take the next step toward clinical trials, and that their "ultimate goal is to develop an evidence-based treatment that patients can receive right in their ophthalmologist's office," noting that, "We expect there are other primary visual cortex problems that we may be able to address with this method" – such as visual impairment secondary to stroke. *MH*

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1. *T Wiesel, D Hubel, "Effects of visual deprivation on morphology and physiology of cells in the cats lateral geniculate body", J Neurophysiol, 26, 978–993 (1963).*
2. *A Kalia et al., "Development of pattern vision following early and extended blindness", Proc Natl Acad Sci U S A, 111, 2035–2039 (201 PMID:24449865.*
3. *Z Ding et al., "The effect of transcranial direct current stimulation on contrast sensitivity and visual evoked potential amplitude in adults with amblyopia", Sci Rep, 14,6, 19280 (2016). PMID: 26763954.*
4. *A Antal et al., "Manipulation of phosphene thresholds by transcranial direct current stimulation in man", Exp Brain Res, 150, 375–378 (2003). PMID: 12698316.*
5. *N Lang et al., "Bidirectional modulation of primary visual cortex excitability: a combined tDCS and rTMS study", Invest Ophthalmol Vis Sci, 48, 5782–5787 (2007). PMID: 18055832.*

Spending and Trending

OpenPrescribing.net shows some interesting trends in ophthalmic therapy prescription and spend over the last five years

In December 2015, after several years of development, the website OpenPrescribing.net was launched online. The brainchild of doctor and author Ben Goldacre and computer programmer Anna Powell-Smith, the website (which is still in beta) is the first of its kind in the UK, and offers free, comprehensive access to anonymized data concerning National Health Service (NHS) prescribing patterns and healthcare spending in England.

"If we want to improve standards in healthcare we need good data that can be accessed and interpreted quickly," insists Goldacre. "With a very small amount of funding we've taken prescribing data from the NHS and made it open to everyone and free to access. Doctors and others in the NHS can get useful simple feedback on prescribing behaviors that are potentially wasteful, or even harmful. Crucially this service is fully open: that means everyone can see the data and use it, whether they are a practice manager, a patient, a journalist, a member of the public, a doctor, or a researcher," he adds.

So what do prescribing patterns for ophthalmic conditions reveal? The charts (Figures 1–8) show some very interesting patterns, perhaps unsurprisingly, the seasonal variation in prescription of certain drugs (antibacterials, corticosteroids) and perhaps more surprisingly, the rising spend on anti-infectives over the past 12 months alone.

With the caveat that the site is still under development (currently, the data on anti-VEGF agents is… sparse), it offers a new and engaging way of analyzing prescription patterns in England and will no doubt continue to reveal some interesting trends. *RM*

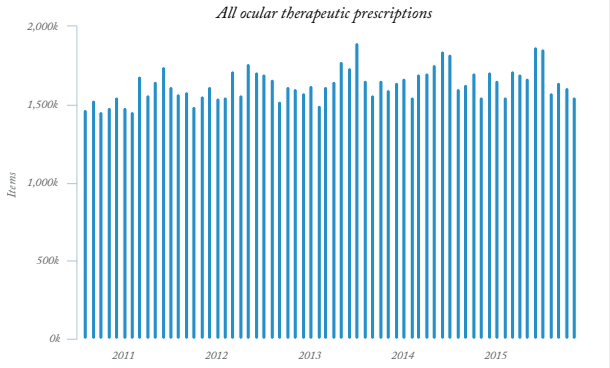

Figure 1. Total prescribing of ocular therapeutics across all practices in England.

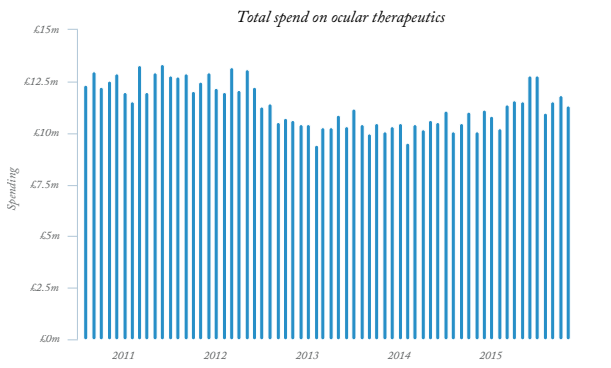

Figure 2. Total spending on ocular therapeutics across all practices in England.

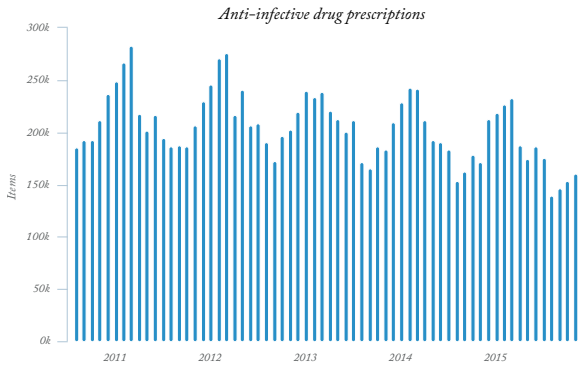

Figure 3. Total prescribing of anti-infective drugs across all practices in England.

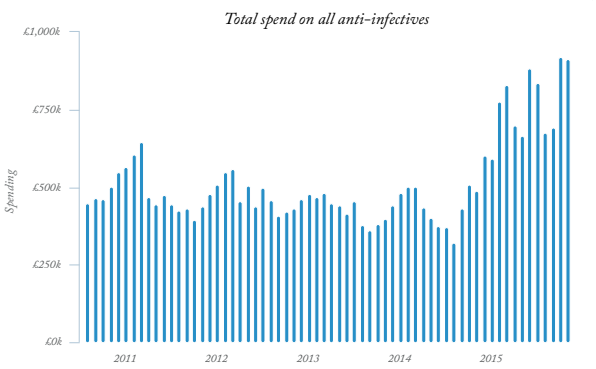

Figure 4. Spending on anti-infective drugs across all practices in England.

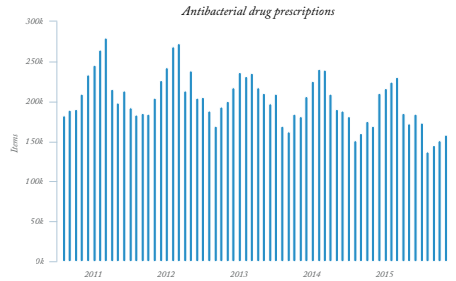

Figure 5. Total prescribing of antibacterial agents across all practices in England.

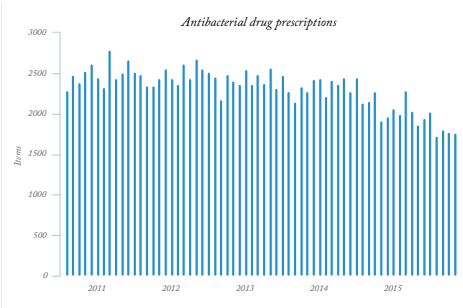

Figure 6. Total prescribing of antiviral drugs across all practices in England.

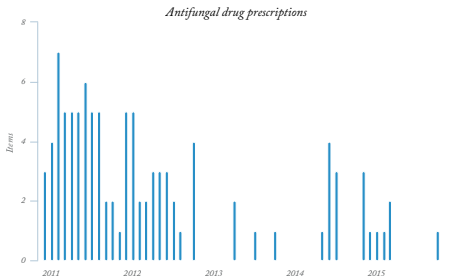

Figure 7. Total prescribing of antifungal agents across all practices in England.

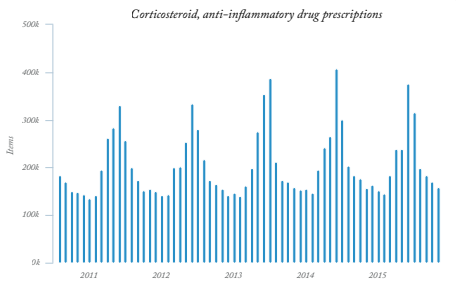

Figure 8. Total prescribing of corticosteroids and other anti-inflammatory drugs across all practices in England.

Common Keratoconus Causes Uncovered

Racial background modifies risk; diabetes protects, but asthma and sleep apnea predisposes

The US healthcare administration is one of the best developers of comprehensive patient databases. And those databases are a goldmine for healthcare research; they permit large-scale retrospective longitudinal cohort studies to be performed, and can help reveal nuggets like never-before-noticed associations between one disease and another.

To this end, Woodward et al. (1) mined the Clinformatics DataMart database (OptimumInsight), which contains detailed records on all insured patients (nearly 16 million) in a large, nationwide, US managed care network over a 12-year period spanning from January 1st 2001 to December 31, 2012. The purpose? They wanted to establish if a link exists between common systemic diseases, sociodemographic factors, and keratoconus. In there, they identified 16,053 patients who had been diagnosed with keratoconus on two or more separate occasions, and a further 16,053 matched controls, from which they could begin to identify sociodemographic factors and common systemic diseases that were associated with the development of keratoconus. The sheer size of their dataset was a considerable advantage over many previous studies on the same topic, which had sample sizes ranging from just 25 to 1,529 patients.

What they found confirmed some previously-found associations, but contradicted others (Figure 1). For example, the odds of a person being diagnosed with keratoconus varied by race – relative to White people, Black and Latino people had higher odds of developing keratoconus (by 57 percent and 43 percent, respectively), whereas Asian American people were less likely to develop the disease (by 49 percent). Considering the impact of systemic disease, those with diabetes mellitus and collagen vascular disease were less likely to have keratoconus (see Figure 1), whereas people with asthma, sleep apnea, and Down syndrome were considerably more likely to receive a diagnosis. Education status and income level had no significant effect, however people living in large, rural communities had a 20 percent lower odds of having the disease.

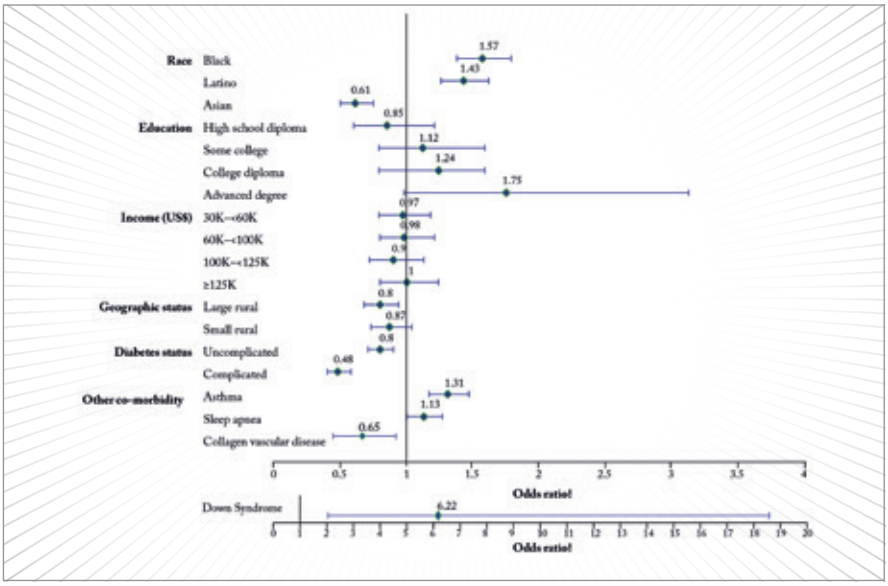

Figure 1. Conditional logistic regression model estimating associations of various covariates with keratoconus – adapted from (1).

So what do the study's authors think is going on? The observation of a decreased risk of keratoconus in American patients of Asian ethnicity contradicts previous findings (from smaller studies) that suggest that Asian people are at a greater risk of developing the disease. The fact that patients from rural areas were 20 percent less likely to be diagnosed with keratoconus might arise from the fact that fewer corneal specialists are present in rural areas, and this might mean that patients with mild or form fruste disease go undetected. With diabetes, it's possible that elevated levels of (the highly reactive ketone) glucose can lead to glycosylation and cross-linking of the cornea, thereby strengthening it – and if a patient has diabetes complicated by end-organ damage, this is suggestive of even poorer glucose control (and even greater circulating levels).

While the authors do not propose potential causative reasons for the association between asthma and sleep apnea with a keratoconus diagnosis, they do note that it's probably appropriate to ask patients with keratoconus if they are experiencing breathing difficulties, as this might reveal cases of undiagnosed asthma. Similarly, screening for sleep apnea, initially with the Berlin questionnaire, should be considered. *MH*

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The App That Cuts Clinic Queues

Could patient self-testing help to free up eye clinics, and spot macular degeneration earlier than traditional testing methods?

The sheer volume of patients who need treatment for age-related macular degeneration (AMD) can result in long waiting times – and for patients who need assessment of their disease progression to determine if another anti-VEGF injection may be required, too much of a wait could lead to an irreversible loss of visual function. Can the consumer healthcare revolution help solve the problem? Developers of a visual assessment app that offers patients the option to test their visual function at home, and send the results to their eye clinic for analysis, certainly think so.

MultiBit is an iPhone and iPad app that displays sets of test digits that are built up by varying numbers of pixels – the fewer the pixels, the greater the difficulty. The test task is for users to speak aloud what digits are displayed; when the test is completed, recorded answers are played back to allow self-scoring of results, which are automatically transferred to the patient's caregiver. What's the value of the app and other similar apps that are in development? Advocates of this approach hope that they will detect changes in visual function in a manner that can detect macular degeneration well before traditional visual acuity tests will spot it.

"Our studies show that the apps are better than traditional examinations conducted in the clinic. It opens the possibility for apps to replace many patient visits and in this way, free up healthcare resources and reduce wait times," claims the researcher behind Multibit, Christina Winther (1).

That's a big claim, but if proven correct, this self-monitoring revolution would certainly have a huge impact on ophthalmology practice management and patient quality of life. *RM*

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Five Years in A&E

Many patients visit the emergency room with ocular problems that might be better treated elsewhere – why? And what's the solution?

What does it take for a patient to present to their local hospital's emergency department with an eye injury? The answer is worth knowing – an understanding of the epidemiology of eye-related emergency department visits allows policymakers to make the most appropriate allocation of resources based on some solid evidence.

The US Nationwide Emergency Department Sample holds records on 11.9 million emergency department visits across the nation, including eye-related visits, and interrogating the data over a period spanning from 2006 to 2011 has yielded some useful information.

It turns out that 44.3 percent of all eye-related visits were for conditions unlikely to require urgent care – such as conjunctivitis or external hordeolum, and if people did present with these non-emergent conditions, they tended to be from lower income groups, and have either public insurance (Medicare/Medicaid) or none at all – precisely the patients who are less likely to have access to a primary care physician (something that's associated with fewer non-emergent visits), and are more likely to visit the emergency department for non-urgent health issues in general (1).

The solution? Improving access to eyecare professionals, and information outreach. Making sure patients are aware of specialized urgent care centers where they exist (and directing them there) should cut costs – it's estimated that visiting the emergency department for an issue that could have been treated

elsewhere costs as much as two to three times more (2). And since many locations in the US (and many other countries too), won't necessarily have an ophthalmologist or other trained eyecare professional to hand in the emergency department, it could result in improved care for patients. *RM*

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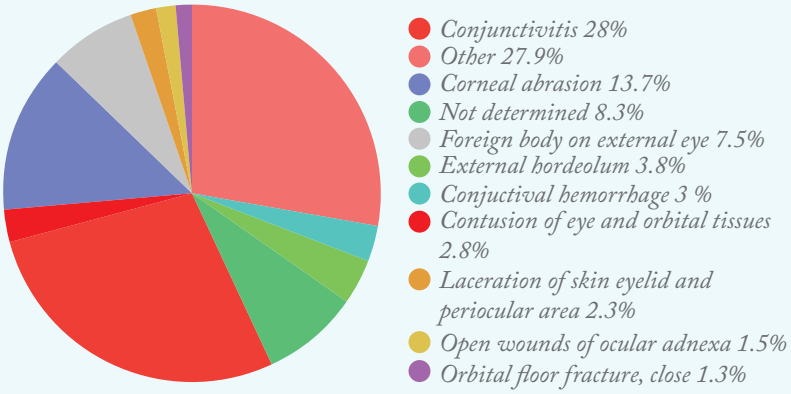
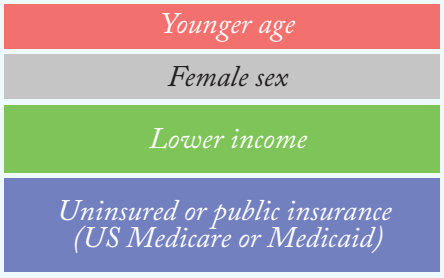
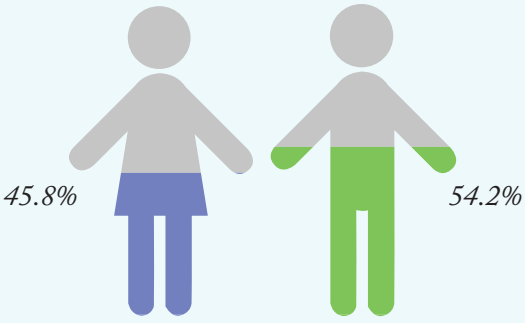
Most common ophthalmic problems encountered at the emergency department



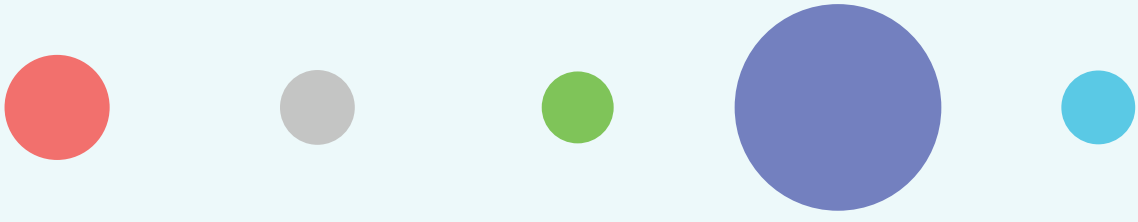
Characteristics associated with emergency department visits for non-emergent conditions



Eye-related emergency department visits: men vs. women



Eye-related emergency department visits: patient age



0–5 years	6–12 years	13–18 years	19–64 years	≥65 years
15.8%	8%	7.4%	61.1%	7.8%

The Polymath Molecule

From cornea to retina, NGF's regenerative and neuroprotective potential seems immense. What does the future hold for this versatile little neurotrophin?

By Mark Hillen

Rita Levi-Montalcini led an interesting life. Born in Turin on April 22nd 1909, she wanted to become a writer in her teenage years. Instead, she went to the University of Turin's medical school, graduating with an MD in 1936, and worked in the laboratory of the noted neurobiologist, Giuseppe Levi. Political events conspired to take that position away from Levi-Montalcini – Hitler's growing influence over Benito Mussolini meant that in 1938, Il Duce introduced the Manifesto of Race, which banned Jews from positions in government, banking and education, robbing Rita of her job. But Rita continued her work – in her bedroom in her Turin home, examining the growth of nerve fibers in chicken embryos, then after the Germans invaded Italy in 1943, from a corner of the shared living space in a building in Florence, where she and her family had fled. In 1947, Rita took a position in Viktor Hamburger's laboratory at St. Louis' Washington University, and it was there that she and the biochemist Stanley Cohen made the discovery that would, over three decades later, win them the 1986 Nobel Prize in Physiology or Medicine. Levi-Montalcini had observed that when tumors from mice

Rita Levi-Montalcini Facts:

- First ever Nobel laurate to reach 100 years of age
- The tenth woman to be elected to the US National Academy of Sciences
- One of three Nobel laureates who were tutored by Giuseppe Levi
- Founder and first president of the Europe an Brain Research Institute
- Despite being a professed atheist, became a member of the Pontifical Academy of Sciences in 1974
- Made a Senatore a vita (Senator-for-life) in the Italian Senate in 2001

were transplanted to chick embryos, they induced potent growth of the chick embryo nervous system – specifically sensory and sympathetic nerves, even when there was no direct contact between chick embryo and tumor. Rita's conclusion was simple: the tumor releases a "nerve growth-promoting factor" that had a selective action on certain types of nerves. Stanley Cohen's contribution was to use his skills as a biochemist to help the Hamburger lab identify and purify what was then called simply "nerve growth factor", or NGF – and he went on to discover a very useful, enriched source of NGF, the mouse salivary gland, and later, to uncover another trophic factor: epidermal growth factor (EGF).

Since then, NGF's role in the developing (and mature) body has been widely characterized, as has its part in a wide array of disease states – not just the growth, maintenance and survival of neurons. It also appears to have therapeutic applications in conditions ranging from acromegaly to Wegener's granulomatosis, and from melanoma to… myopia correction. And it doesn't stop there. It seems that this small-but-mighty molecule could have a number of therapeutic applications, both in the anterior and posterior segment – and if only a small portion of the theories become reality, NGF could turn out to be a game-changer for ophthalmology.

NGF and the anterior segment

If we start with the front of the eye, topical NGF therapy is currently being investigated for the treatment of three disorders: ocular surface disease, ocular surface/ corneal sensation issues after laser refractive surgery (PRK and LASIK), and neurotropic keratitis (NK).

Neurotropic keratitis

To better understand NGF's role in NK it's important to understand how NK develops. When corneal sensory nerves are damaged, the cornea suffers. It's an avascular tissue, so the cornea relies heavily on its innervation for trophic support. When those nerves are damaged, it compromises the ability of the cornea to heal, and kickstarts a vicious circle: patients start to lose reflex tear secretion, leading to reduced protection of the eye. But if there is damage to the eye, patients aren't going to feel it, notice, or seek treatment. So a lesion of the corneal epithelium can easily progress to corneal melting, and then on to corneal perforation. As NGF acts to stimulate not just nerve proliferation, but also epithelial cell proliferation, this means

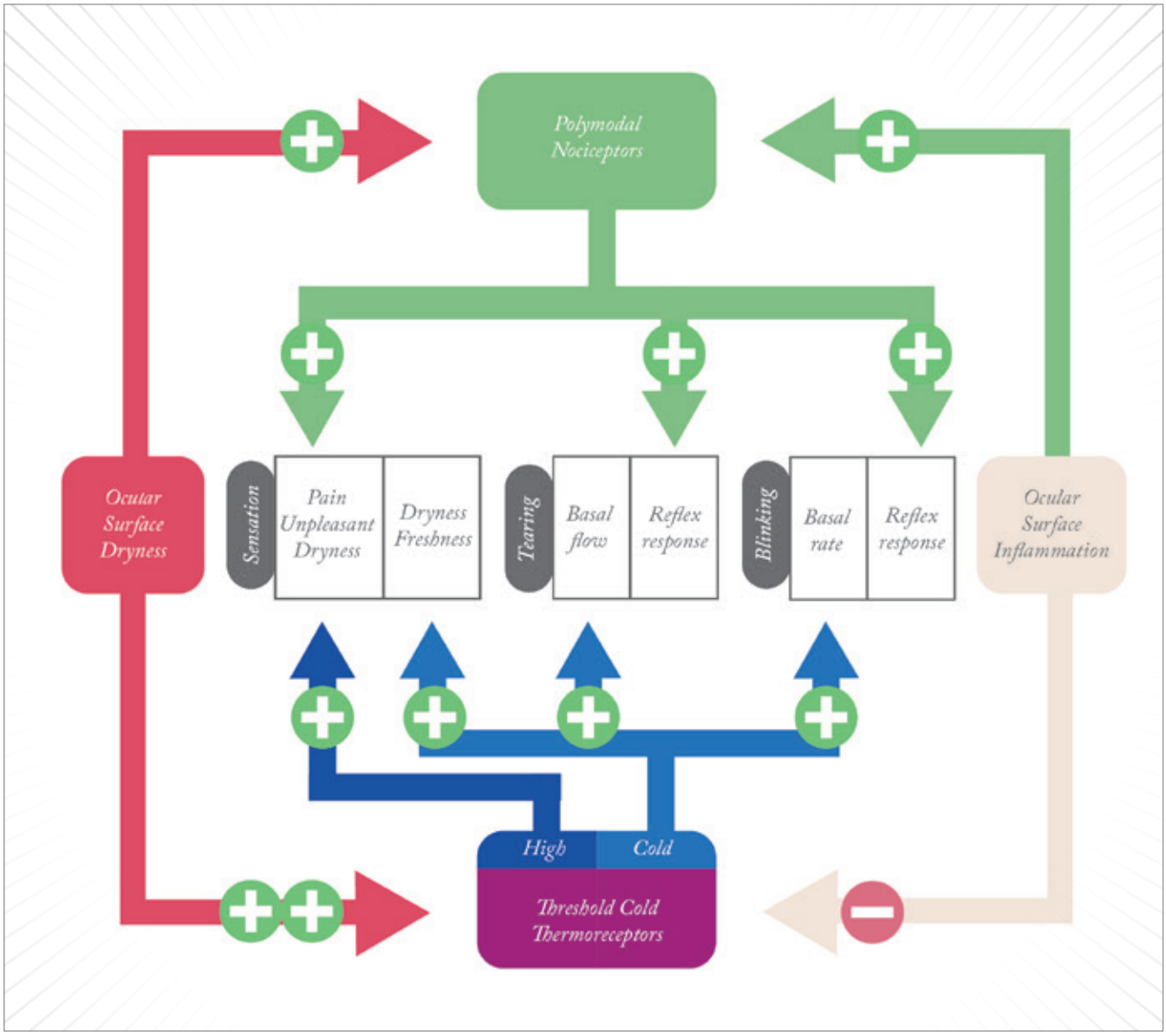
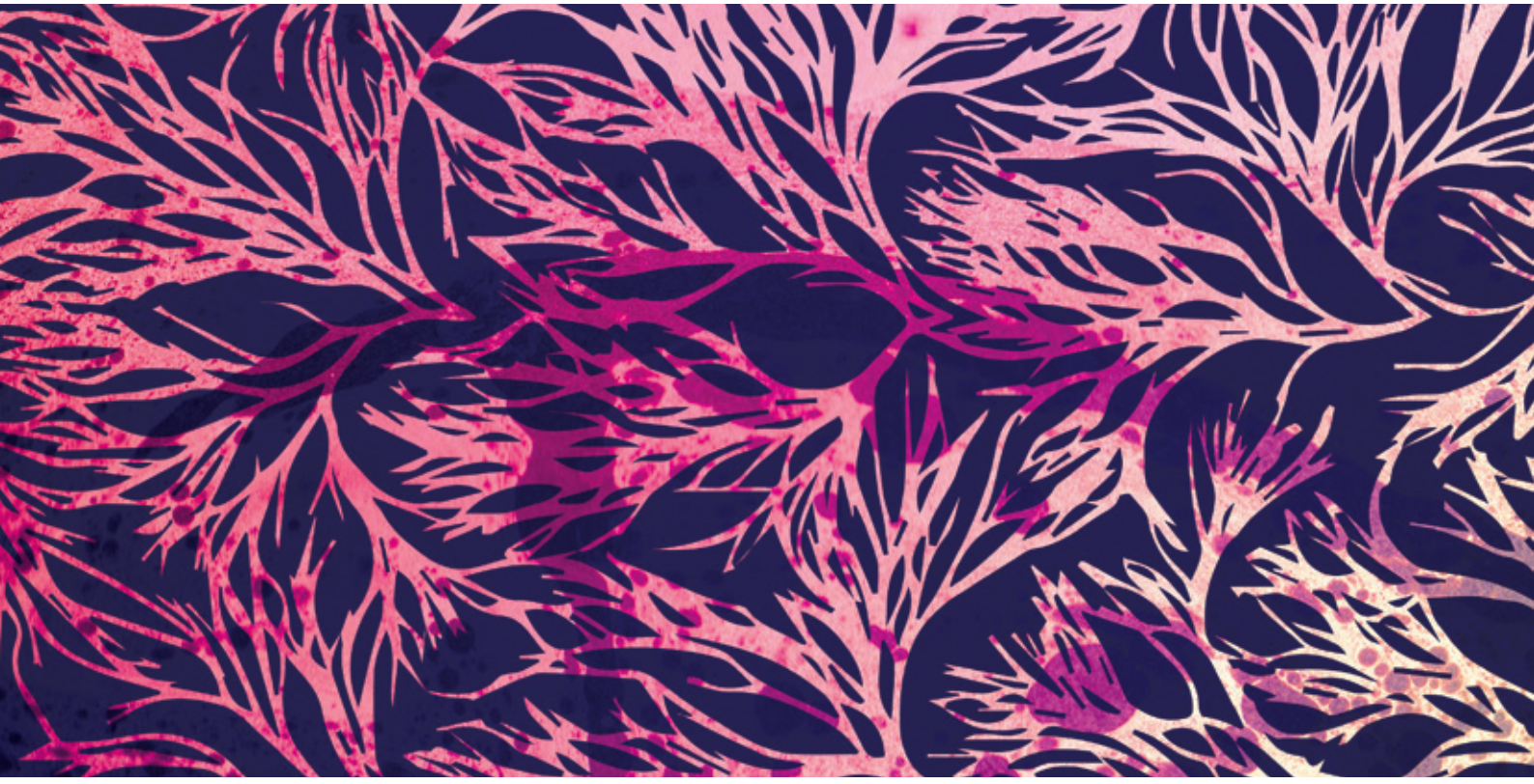


Figure 1. Dysfunction in corneal sensory receptors – in particular, cold thermoreceptors, and polymodal nociceptors –drives ocular surface dryness.

that in theory, it can tackle both pathologies.

Paolo Rama, Chief of the Cornea and Ocular Surface Unit, at the Ospedale San Raffaele di Milano-IRCCS, Milan, tells of how NGF was first used to treat a patient with NK.

It was back in Venice in 1996, and we had one patient in our clinic who had only one eye. She had presented with a painless white corneal infiltrate that was caused by a Candida infection – we couldn't understand how she got infected with Candida in a healthy eye! After the resolution of the infection a deep corneal ulcer remained and on inspection, we discovered that she had a congenital aplasia of the trigeminal nerve that had resulted in corneal anesthesia, and as she was unaware of the pain, she had developed a very deep neurotrophic ulcer. Together with Alessandro Lambiase we decided to try NGF under compassionate use. We received murine NGF from Levi-Montalcini's lab, and we treated her topically with it. After 10 days, the ulcer was completely healed, and after 6 months, the girl could see 10/10 through that eye – perfect vision. And so we started treating some other neurotrophic



ulcers, and again, we saw that it worked. We presented the data to the New England Journal of Medicine, and it was accepted. Everything started from there (1).

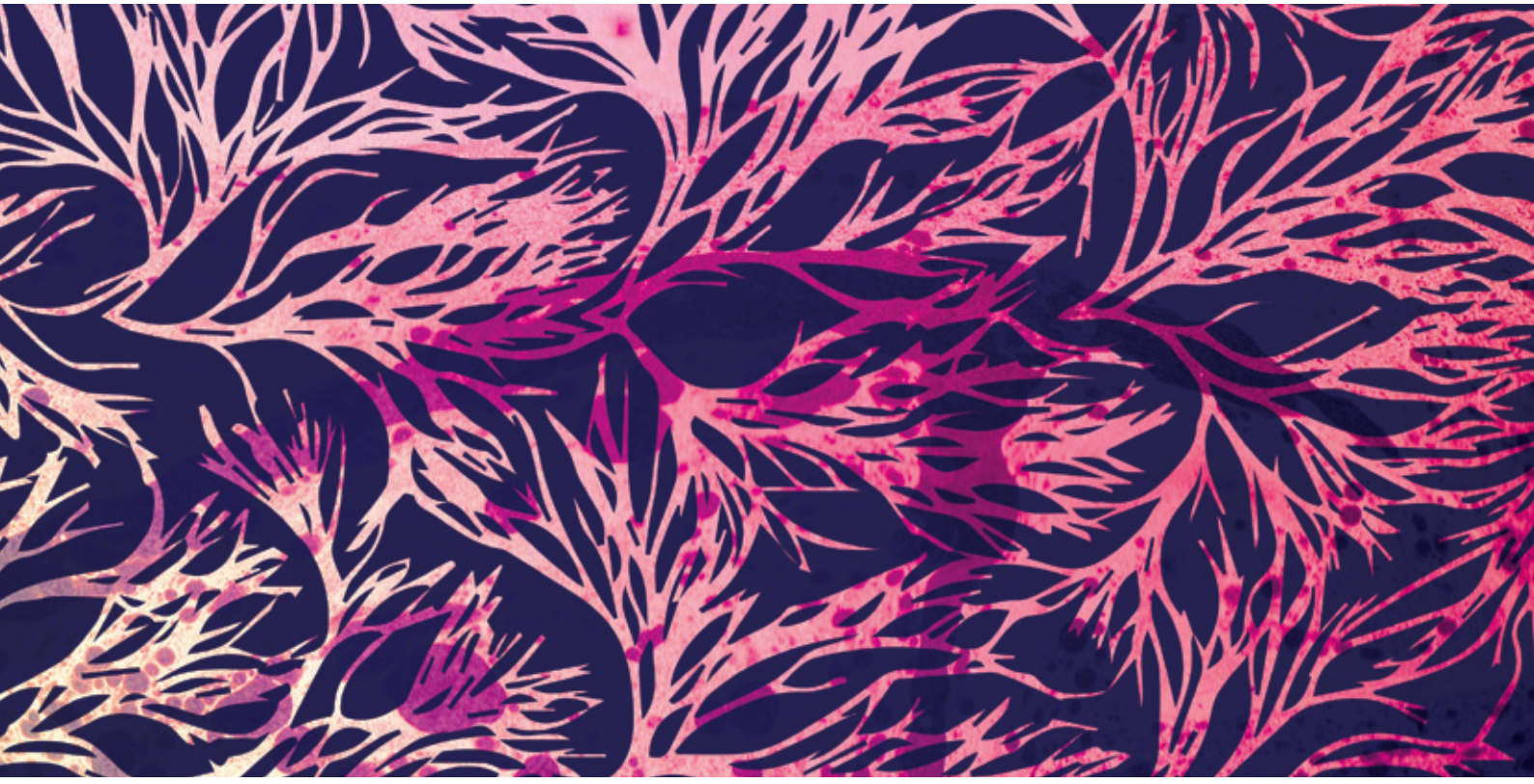
The study Rama describes involved 12 patients (and 14 eyes), and topical murine NGF (mNGF) use resulted in a rapid healing of all of the ulcers, improved corneal sensitivity in most of them and improved visual acuity (1). Similar results were seen in a later study where mNGF was used to treat NK that was non-responsive to conventional treatments (2). Complete healing of the corneal defect was achieved in all patients between 12 days and 6 weeks after mNGF treatment was initiated. Side effects were also described: hyperemia and moderate pain in the eye and periocular area, but these were well tolerated and were expressed only during the period where mNGF treatment was necessary for corneal keratitis remission.

A later study of 11 patients with NK (3) showed similar efficacy (complete ulcer healing in 9–43 days) and investigated mNGF's adverse event profile in more detail, revealing that ocular discomfort was associated with eyedrop instillation, but this lasted for less than one hour and such painful sensations disappeared after the corneal ulcers healed – even when NGF continued to be applied. One concern with NGF use is the possibility that patients' immune systems would begin to recognize mNGF as non-self, but this study found no trace of anti-mNGF antibodies during the period in which therapy was administered, nor during the follow-up period of up to 72 months.

Today, recombinant human NGF (rhNGF) is available (see Box: Making rhNGF), and a multinational, multicenter Phase I/II clinical trial of topical rhNGF eye drops for the treatment of NK has recently been completed (NCT01756456), and a similar trial in the US is underway (NCT02227147).

Dry eye disease

The etiology of dry eye disease (DED) is massively multifactorial, but it's clear that corneal nerve dysfunction plays a role – and an increasingly important one as the disease progresses (4). There are four main types of sensory receptors in the cornea – low threshold mechanoreceptors, high threshold mechanoreceptors, polymodal nociceptors, and cold thermoreceptors (CTRs). The mechano- and polymodal nociceptors signal pain. CTRs are rather interesting (Figure 1). They fire spontaneously at normal corneal temperatures

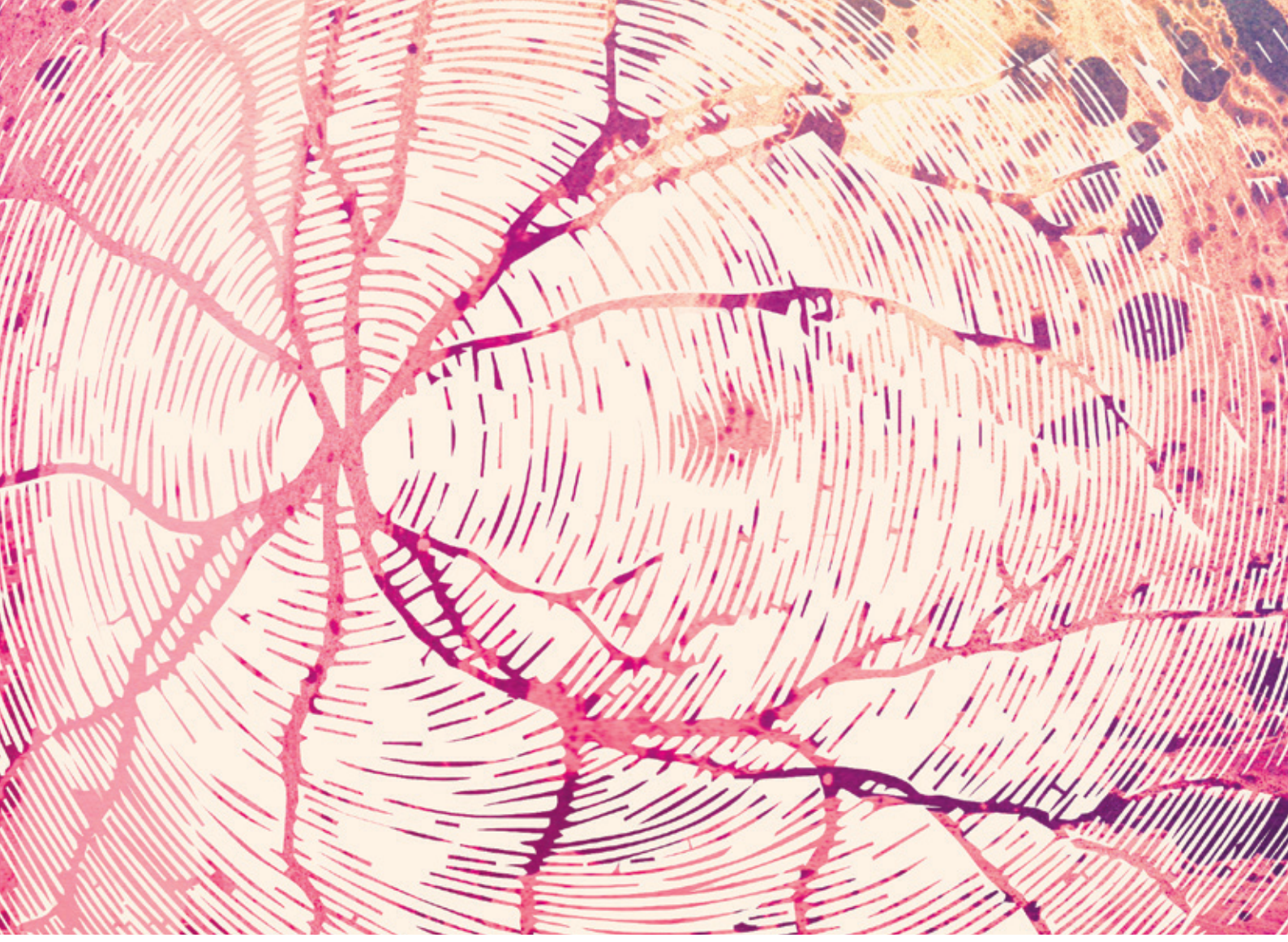


(34–35˚C), and under experimental conditions, human CTRs are exquisitely sensitive to transient temperature variations – being able to detect temperature changes of less than half a degree Celsius. The thing is, there's no evidence that ocular CTRs play any role in environmental temperature assessment in humans or animals. So what are they there for?

The answer appears to be detecting the wetness of the eye. When you blink, your ocular surface temperature is ~34˚C. That blinking distributes the tear film across the eye, which then evaporates during the interblink period. As evaporation is an endothermic process, this means the temperature of the cornea drops by approximately 0.3˚C per second – and it appears that this drop in temperature increases the CTR firing rate and acts as a tonic stimulus for basal tear fluid secretion – likely activating the parasympathetic secretory drive to the lacrimal glands and goblet cells at the superior salivary nucleus. It's hypothesized that CTR activation acts in the same manner as skin thermoreceptors – they fire at a basal rate, and their input remains subconscious, but when a sufficient number of ocular cold sensory fibers (with CTRs firing at high frequencies) are recruited, people begin to experience conscious sensations of dry eye. It's therefore easy to see how tear film instability, like in the case of meibomian gland dysfunction, can lead to that unpleasant sensation of dry eye.

But that's not the only issue. Elevated tear osmolarity – another common sequelae of dry eye – also activates CTRs, augmenting their firing rate, and making the sensation of dry eye that bit more unpleasant (4). Worse, as DED progresses, the polymodal nociceptors – which confer the stinging and burning sensations – start to get involved as the cornea starts to become increasingly desiccated and inflammatory processes take hold. Of course, LASIK and PRK both involve transecting corneal nerves, and this might underpin cases of post-photorefractive surgery dry eye: the brain interprets this aberrant activity of these nerves as ocular surface dryness – at least until the corneal nerves regrow after 3–6 months. Imagine if topical NGF could speed that process…

And think about this too: people with DED are contraindicated from receiving laser refractive surgery, and are only able to receive it if their DED has been successfully treated. If topical NGF turns out to be an effective dry eye therapy, then this could open the door for far more people to undergo laser vision correction procedures.



NGF and the Posterior Segment

Let's turn our attention to the back of the eye. As proteins go, NGF is relatively small at 13 kDa – but, given the right formulation, that's small enough to reach pharmacologically relevant concentrations in the retina after topical administration. Surely, a molecule that promotes the survival and even growth of mature neurons, might be able to play a neuroprotective role in the retina? It appears so.

Retinitis pigmentosa

Back in 1996, a paper was published by Lambiase et al., which showed that intraocular/retro-ocular mNGF injection partially rescues the photoreceptor loss phenotype of C3H mice – animal models that exhibit photoreceptor degeneration resembling human retinitis pigmentosa (RP) (5). This year, 20 years on from that paper, comes the publication of the first manuscript to describe short-term (10 days) topical mNGF administration in patients with RP (6). Of the eight patients included in the study, three reported "subjective feeling of improved visual performance" that was associated with a temporary enlargement of the visual field in all three patients, and an improved focal ERGs in two of them.

Glaucoma

In glaucoma, irrespective of intraocular pressure (IOP), the hallmarks of the disease include retinal ganglion cell (RGC) loss and degeneration of the axons which (along with glial cells) form the optic nerve. Ophthalmologists have a variety of approaches for reducing IOP (which remains the only modifiable causative factor in glaucoma) – but can do nothing to address the RGC loss and optic nerve damage that occurs. Can NGF help here?

The basic research looks promising. Experimentally-induced glaucoma in in rats (via episcleral vein injections of hypotonic saline) leads to progressive RGC degeneration that's associated with the downregulation of NGF, TrkA and TrkB – and topical NGF administration has been found to significantly attenuate

this deficit (7), promoting RGC survival.

As NGF has already been shown to help prevent neuronal degeneration in animal models of other neurodegenerative diseases (8,9), it seems reasonable to assess its use as a neuroprotective strategy for the medical treatment of glaucoma.

In 2009, a study was published that described the evaluation of topical mNGF therapy over a period of three months in three patients with advanced glaucoma who were at an "imminent risk of loss of visual function" despite adequate IOP control (10). Electrophysiological and visual acuity tests were performed immediately after the treatment period, and at a three-month follow-up visit. VA was significantly improved after the treatment period (and remained unchanged three months later), and the electrophysiological tests showed that the improvement in post-retinal conduction found at the end of the treatment period was also maintained after three months.

Age-related macular degeneration

The preclinical evidence to support the use of NGF in the treatment of AMD is sparse: the first publication of which was a case report back in 2009 (11). A 94-year-old patient with bilateral wet AMD was given topical mNGF over a period of six years in her right eye, but not her left, and visual and electrophysiological assessments were made quarterly. Topical mNGF therapy improved BCVA (both near and distance) and focal ERG amplitude in right eye after only three months of treatment, whereas no improvements in either parameter were observed in the left, untreated, eye.

It was actually two years later in 2011, that a paper that investigated the molecular mechanisms involved was published (12). The experiment was as follows: cultured human RPE cells, exposed to hydrogen peroxide undergo apoptosis, something that the addition of NGF protected against. NGF also induced RPE cell migration, which is essential to regenerating damaged parts of the retina. Some insight into the intracellular signaling pathways was also given – the addition of the PI3K/Akt inhibitor LY 294002, or the mTOR inhibitor, rapamycin, blocked the NGF-induced cell survival and migration effects in hydrogen peroxide-treated cells.

Given this promising avenue of research, it's not surprising that NGF isn't the only neurotrophin under investigation for the treatment of the retinal disease – brain-derived neurotrophic factor (BDNF), fibroblast growth factors (FGFs), transforming growth factor beta (TGF-β), vascular endothelial growth factor (VEGF) and neuropeptide-Y (NPY) are all being investigated – but each of these molecules appear to be expressed in greater amounts when NGF is applied to the retinae of RCS rats (7,13). NGF use is not without adverse effects, though; the most common in the case reports and small trials published so far being a transient, tolerable local corneal irritation.

But ultimately, NGF is a molecule that was discovered in the early 1950s, was first successfully used in the clinic in a small number of patients in the mid 1990s, 2000s and 2010s. Now rhNGF can be

NGF's role in anterior segment pathophysiology

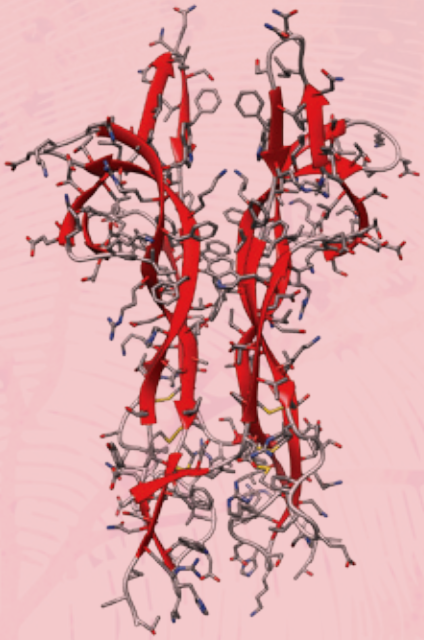
- Mutant mice lacking the high-affinity NGF receptor, TrkA (*NTRK1*$^{-/-}$) exhibit reduced corneal sensation, sensitivity and are more prone to corneal lesions
- NGF increases corneal sensitivity in an animal model of refractive surgery
- NGF treatment reverses Capsaicin-induced corneal sensory denervation and healing impairment

NGF's effect on corneal epithelial cells

- NGF promotes epithelial cell proliferation and differentiation in vitro
- NGF promotes keratocyte differentiation, migration and contraction
- NGF stimulates epithelium healing in vivo

NGF's neuroprotective role in the posterior segment

- NGF inhibits apoptosis and upregulates other neurotrophic factors, increasing RGC survival and axonal sprouting
- NGF promotes photoreceptor survival in animal models of retinitis pigmentosa and has shown promise in initial evaluations in patients
- Case reports show promise for NGF treatment in wet AMD



Making rhNGF

Mature human NGF isn't a very big protein – just 118 amino acids – but the fact that it includes three interlaced disulfide bridges means that comes in a complicated package. Often, the production of large quantities of a given protein is relatively simple: clone the gene that encodes the protein into *E. Coli,* let it express the protein, grow it on an industrial scale, and harvest your protein of interest from the broth. Unfortunately, when human NGF is expressed in *E. Coli*, it accumulates in the bacteria's inclusion bodies. The rhNGF can be extracted from the inclusion bodies and folded – but this process is both inefficient and very slow – less than ideal when you require large volumes for pharmaceutical development work, or if wider clinical use is planned.

The Italian pharmaceutical company, Dompé, in collaboration with German protein engineering company, Scil Proteins, have developed a considerably more efficient way of producing appropriately folded rhNGF in *E. coli* cells – resulting in a NGF molecule that's identical in sequence and structure to the human form.

produced on an industrial scale and is finally undergoing formal clinical trial evaluation for ophthalmic disease. What might NGF in the 2020s bring to the field of ophthalmology? Will it make it to the market? Will it serve only the small number of people with NK? Will those that undergo laser vision correction surgery receive it as part of their postoperative care? Might it delay the progression of glaucoma, or help treat AMD? It's easy to see how this could be a game-changer, and we have Levi-Montalcini, Cohen and everyone who's worked on the molecule since to thank for it.

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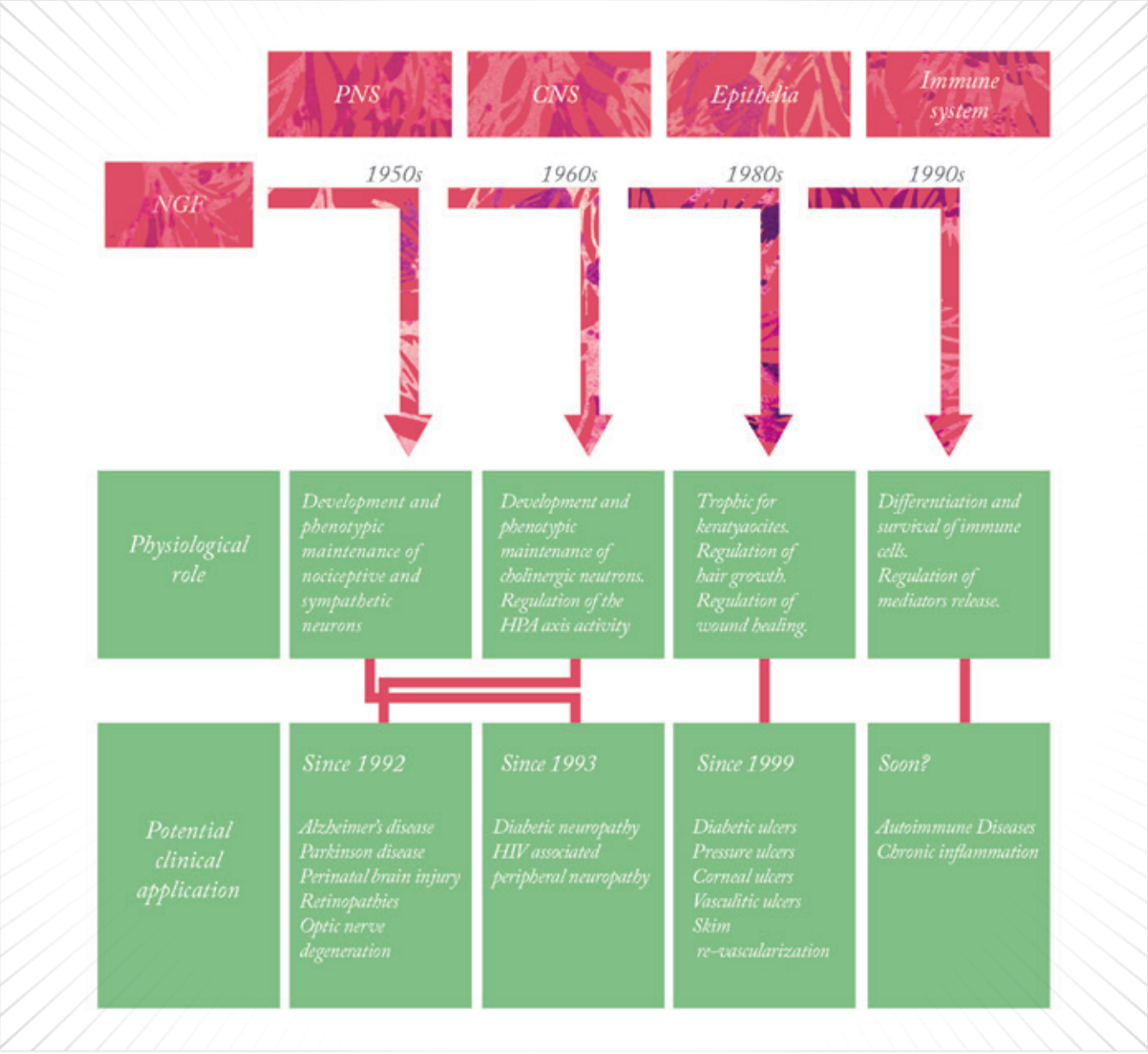
13. *L Aloe et al., "Nerve growth factor: from the early discoveries to the potential clinical use", J Transl Med, 10:239 (2012). PMID: 23190582.*

NGF from Research to Clinic



The huge amount of research data produced since its discovery in the 1950s, first characterized the physiological role of the neurotrophin NGF in the regulation of development and phenotypic maintenance of peripheral nervous system (PNS). A similar role for central cholinergic neurons was described starting from the 1980s, while more recently NGF has been characterized as a survival, differentiative and trophic factor also for cells belonging to the immune system and the epithelial lineage. Basic and translational research based on such described NGF activities have since explored the possibility of developing NGF-based pharmacotherapies for peripheral neuropathies, brain degenerative and traumatic diseases, several kinds of epithelial derangements. A possible, yet unexplored field is based on its activity as immune-regulator, possibly involved in autoimmune and chronic inflammatory pathologies. Adapted from (13).

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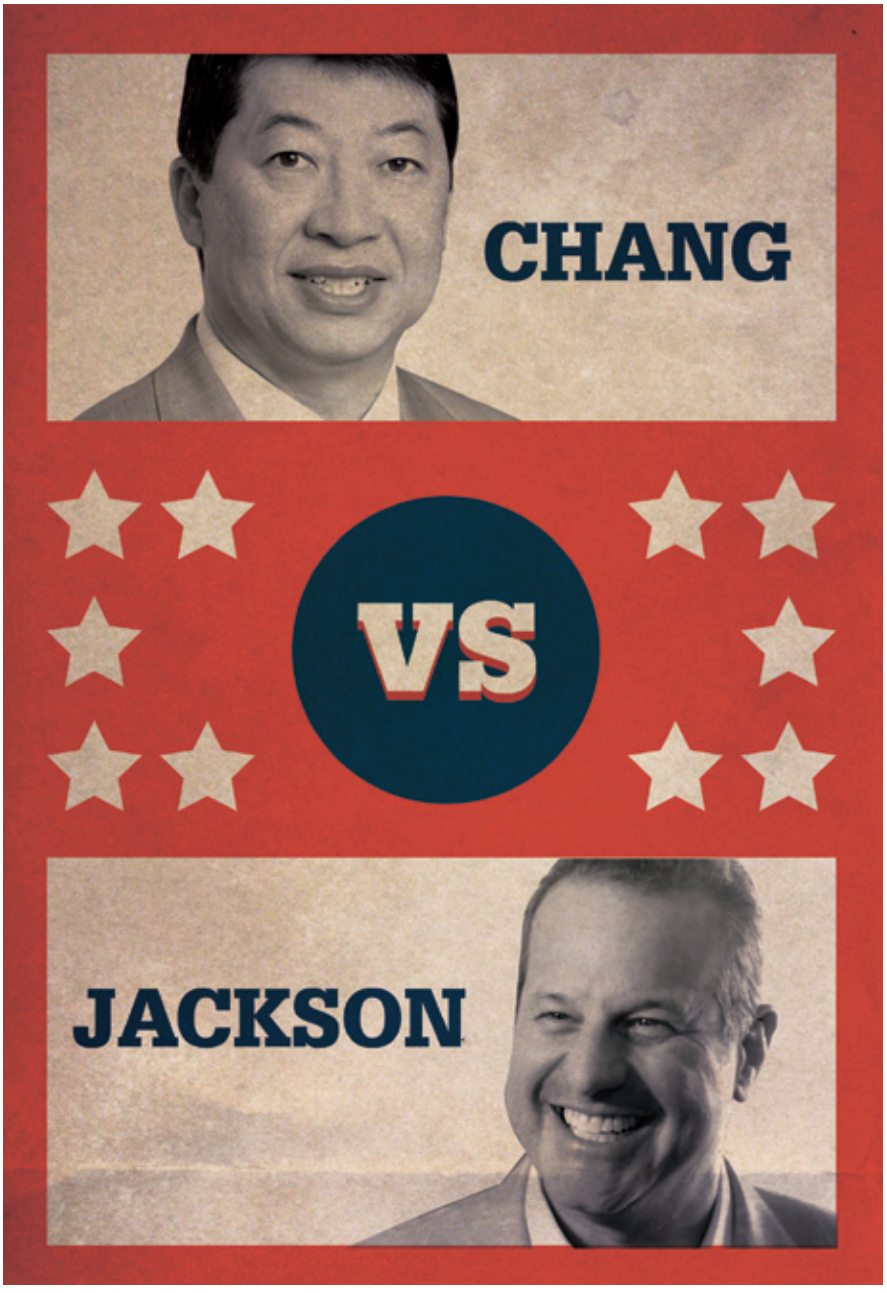
The US View on EUREQUO

Last month, Peter Barry reviewed the EUREQUO registry. This month, we get the transatlantic perspective

By Roisin McGuigan

In the February issue of The Ophthalmologist, we interviewed Peter Barry, past president and current board member of the ESCRS, about the European Registry of Quality Outcomes in Cataract and Refractive Surgery (EUREQUO) database (1). Established in 2006, EUREQUO allowed clinics all over Europe to enter their cataract and refractive surgery data into a registry, anonymously, so that they could compare their surgical outcomes with those of their national and European peers. During his presidency, Peter decided to use the EUREQUO dataset to compare the outcomes of patients who received femtosecond laser-assisted cataract surgery (FLACS) with the outcomes of patients who underwent traditional manual capsulorhexis and phacoemulsification. What did his search find? There was no real difference in surgical outcomes between the two methods.



But EUREQUO is very much a European registry – do the findings translate to other countries that have seen substantial uptake of the femtosecond laser, like the US? We asked two expert cataract surgeons from across the pond, David Chang and Mitchell Jackson, to share their thoughts.

At a Glance

- *EUREQUO is a database, maintained by the ESCRS, that contains information on ~1.5 million cataract surgeries*
- *It was recently mined for a precisely-matched case-control study of FLACS vs. manual capsulorhexis and standard phacoemulsification – and neither method came out on top*
- *But what do US surgeons think? In spite of considerable uptake of FLACS stateside, surgeons' views on the technique are conflicted*
- *We asked David Chang and Mitchell Jackson to share their thoughts on the EUREQUO results, and the "man vs. laser" debate.*

Can you describe a typical day in your practice?
David Chang: I perform 200 cataract surgeries per month. Alternating between two rooms, I'll perform 30–32 cases per day. I schedule the most time-consuming and complicated cases at the end of the day.
Mitchell Jackson: I perform 100-125 cataract surgeries per month. I schedule the most difficult cases at the end of the day, or on a separate day of just a few complex cases only.

"This study is registry-based and lacks prospective randomization, and in my opinion, is not a valid enough study to make a claim that FLACS is inferior or riskier than manual phaco alone."

What's your standard procedure for cataract removal/ IOL placement?
DC: I perform manual phaco exclusively. We have never had a femtosecond laser at our surgery center because we wanted to first be convinced that the benefits would justify the substantial costs that would need to be passed on to our patients.
MJ: I perform 100–125 cases per month, the vast majority of which (89–92 percent) are FLACS, and are all done in same room with femto in the OR. This maximizes our efficiency, and we average 25–30 cases/day. We also use the intraoperative aberrometer in the same room in up to around 56–63 percent of cases.

What particular advantages do your methods convey?
DC: I am very comfortable with manual continuous curvilinear capsulorhexes and with phaco chop, regardless of the case complexity. In the US, we are not allowed to charge Medicare patients out of pocket for any technology or instrumentation used to perform cataract surgery. We are allowed to charge Medicare patients for astigmatic keratotomy and for the OCT imaging component of

"It clearly dispels marketing claims by some American surgeons that laser cataract surgery is a major advance or superior to the non-laser methods."

the technology, "if the surgeon believes that this imaging will improve the refractive outcome." I use Alcon's ORA intraoperative wavefront aberrometry for refractive cataract cases, which includes toric and multifocal IOLs, LRIs, and post-LASIK eyes. I use the Zeiss Callisto eye system to mark the astigmatic axis intraoperatively. Although they add time, these two complementary technologies improve my refractive outcomes for these cases. However, I do not believe that femtosecond laser imaging or capsulotomy would have any further refractive benefit. I cannot justify using and charging my patients for this as a means of improving refractive outcomes.

MJ: CMS rulings allow for charging Medicare patients for the astigmatism management and OCT digital imaging component of FLACS. But the real benefits from FLACS come from precise capsulotomy, which has been proven and published to yield more accurate effective lens position (ELP) postoperatively, and customized capsulotomies based on pupil or optical axis (the latter being my preference when using multifocal IOL implants). Further, Burkhard Dick has many publications showing that using femtosecond laser to pre-fragment the nucleus significantly reduces effective phaco time. My own data (presented at ASCRS 2015 and at ACES SEE 2016) shows significant reductions in EPT FLACS with LENSAR and Stellaris phaco microburst technology combined. I find ORA intraoperative aberrometry system useful for aphakic IOL power determination, especially in post laser vision correction patients (LASIK, PRK) and for pseudophakic axis placement in toric IOL cases.

Are there any situations where you feel femtosecond lasers might be a better choice for capsulotomy, or is your preference for manual tools universal?

DC: I understand the preferences of some surgeons to use the femtosecond laser with certain complicated eyes, such as white cataracts. However, these cases are uncommon and we are not able to legally pass the substantial per-case charges on to our American Medicare patients. In addition, the infrequency of these cases would not justify the significant economic and workflow costs of having and maintaining a femtosecond laser.

What are your views on the EUREQUO study design and results?

DC: The advantage of this study is that it compares very large numbers of patients over an extended postoperative period. There was no industry sponsorship and no reporting bias, because the results were going to be presented regardless of what was found.

An acknowledged weakness of any registry-based study is the lack of prospective randomization. Because of this, the investigators made a diligent effort to match the two study populations – including age, preoperative acuity, and co-morbidities. It was certainly notable that the femtosecond laser patient population had statistically higher postoperative complication rates. Because of the study design limitations, this doesn't conclusively prove that femto is inferior or riskier than phaco. However, it clearly dispels marketing claims by some American surgeons that laser cataract surgery is a major advance or superior to the non-laser methods. Such public advertising has unjustifiably left many non-femto cataract patients feeling short-changed. The EUREQUO study provides some of the strongest evidence to date that such broad claims of superiority are misleading and wrong.

If you look at the FLACS surgeon group in the EUREQUO study, you'll see that they are all top cataract surgeons within their respective countries. It is the European femto surgeon "all-star" team! I would have expected this elite group of experienced surgeons to have superior collective outcomes compared against the broad universe of community ophthalmologists from the registry. I was impressed that even when armed with this cutting edge technology, the top femto surgeons in Europe and Australia did no better – and by some parameters worse – than the registry surgeons using manual phaco. To me, this was a striking finding.

MJ: This study is registry-based and lacks prospective randomization, and in my opinion is not a valid enough study to make a claim that FLACS is inferior or riskier than manual phaco alone. In my hands, in over 1,000 FLACS cases, EPT was statistically reduced, astigmatism was managed with excellent visual outcomes of up to 1.5 D cylinder preoperatively, using iris registration on the Cassini topography linked via Streamline to LENSAR. Corneal edema was less on postoperative day one (enhancing a patient's "wow" factor and likelihood to refer more patients), and I did not

have as high a postoperative complication rate as the EUROQUO study claims. I believe a true comparative prospective study needs to be performed matching age, technology used, and co-morbidities in a large series in the United States.

What do you say to patients who specifically request the femtosecond laser?

DC: I explain that the preponderance of studies has been unable to show any benefit. Otherwise, we would have it and would let our patients decide if they wanted to pay the extra costs.

MJ: Basically, I would agree with them. Luckily, I would not need any extra chair time preoperatively to convince the patient of the need for FLACS.

What improvements would you like to see made to femtosecond laser technology?

DC: There are several exciting technologies such as CAPSULaser and Zepto that automate the capsulotomy step without click fees. I am a consultant and investigator for Mynosys on their Zepto device, which is a disposable instrument that uses nanopulse technology to achieve a perfect capsulotomy without cautery. Zepto would be used in the normal surgical sequence and may be able to automate creation of a precise diameter capsulotomy without the high costs and workflow inefficiency of the femtosecond laser – making it available to most cataract patients.

MJ: I want to downplay the misconception by most non FLACS surgeons that there are workflow inefficiencies using femtosecond laser technology. Sure, it could be faster, but having the LENSAR in the OR, we are able to perform 25–30 cases per day without any real workflow issues after the one-day learning curve that was needed to incorporate femtosecond technology into our practice. With the use of Streamline iris registration for astigmatic management, there is no need for marking (which saves time), and with the lens fragmentation, EPT is reduced (which saves time). And in more complex cases, such as prior trauma, dense nuclear cataracts, and pseudoexfoliation cases, fragmentation makes phaco less risky in terms of EPT and vitreous loss (which saves more time). In reality, femtosecond laser technology has made my surgery days more workflow efficient.

Reference

1. *M Schubert, "A EUREQUO Moment", The Ophthalmologist, 27, 44–48 (2016). Available at: top.txp.to/issues/0216/601*

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[1] Lallemand F et al. J Drug Deliv 2012: 604204 [2] SANSIKA study, Santen Data on File 0001
[3] SANSIKA study, Santen Data on File 0002

Date of preparation: September 2015 **Job code:** STN 0717 IKV 00019(eu)

NextGen

Research advances
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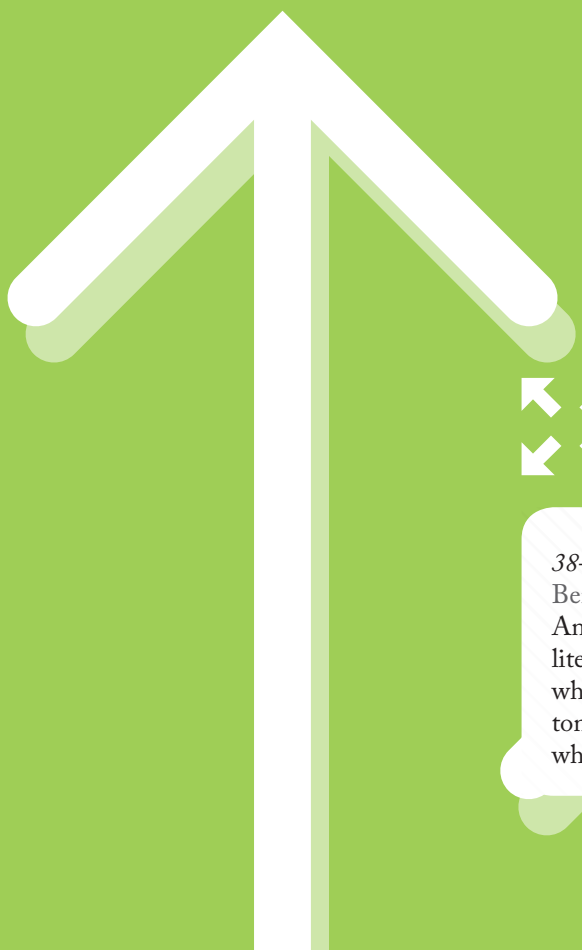


Benchmarking Corneal OCT

What does analysis of the last five years of literature on corneal optical coherence tomography tell us about the priorities of the field, and the contributors to it?

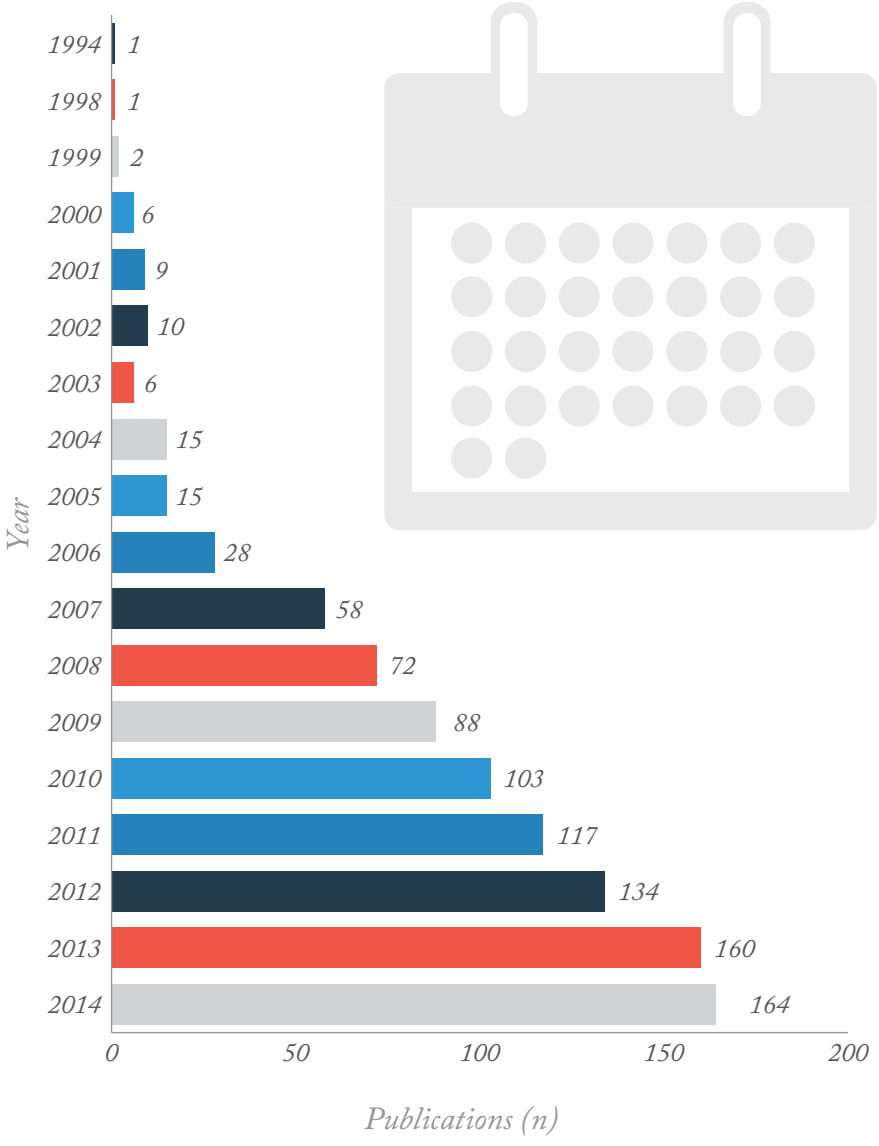
By Roisin McGuigan

Optical coherence tomography (OCT) revolutionized retinal imaging, and is now being increasingly used to image the anterior chamber, in particular, the cornea. So where is this technology heading? To answer this question, we decided to benchmark the PubMed-listed literature on the topic, asking:

- What are the major topics for the field?
- Which journals have the greatest impact?
- How is the knowledge available online?
- What type of articles are being published?
- Who are the most prolific authors?

PubMed was searched for "optical coherence tomography" AND "cornea" (for a focus on the anterior of the eye), in humans (for a clinical focus). The data were analyzed in Microsoft Excel 2013.

Publications per Year

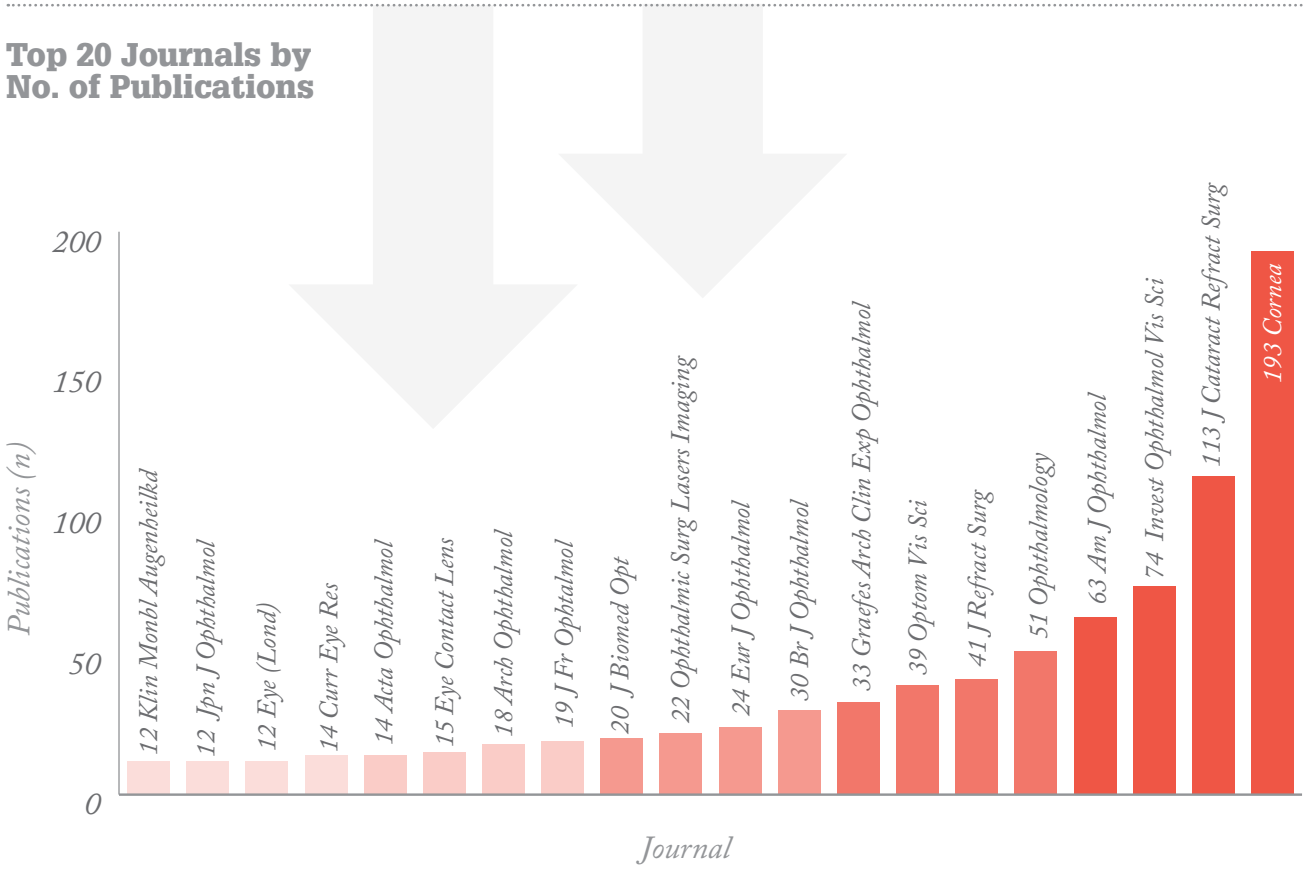


Fee or Free?

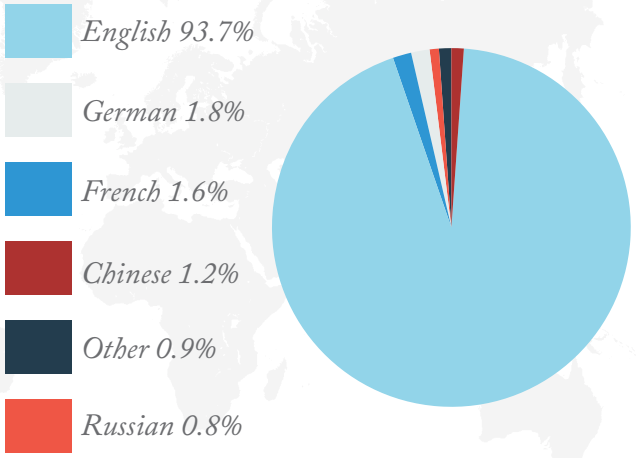
Proportion of articles by availability online.

Full Text Upon Payment/Subscription 77.2% *Free Full Text 18.2%* *Unavailable Online 4.6%*

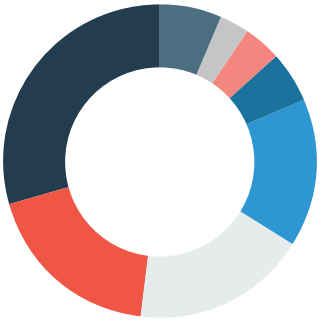
Top 20 Journals by No. of Publications

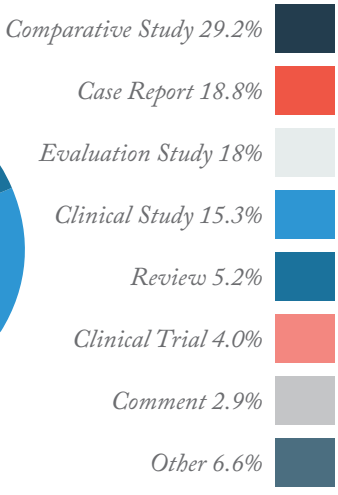


Languages



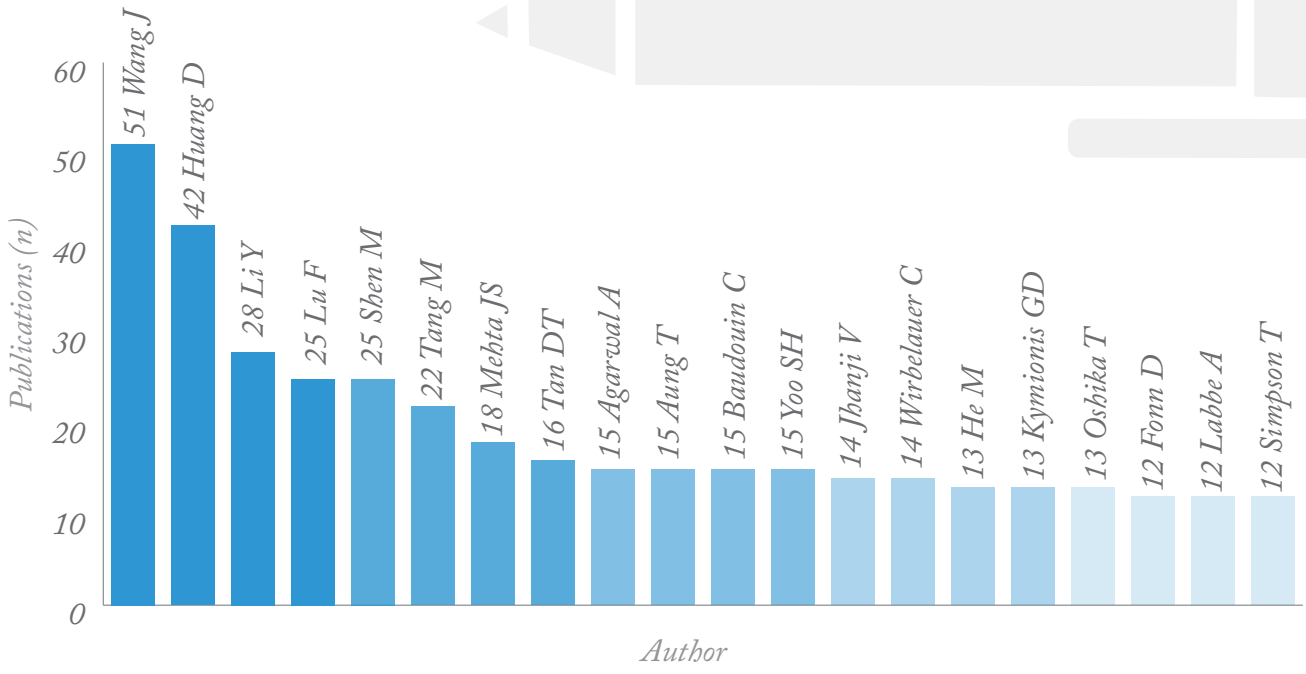
Article Categories



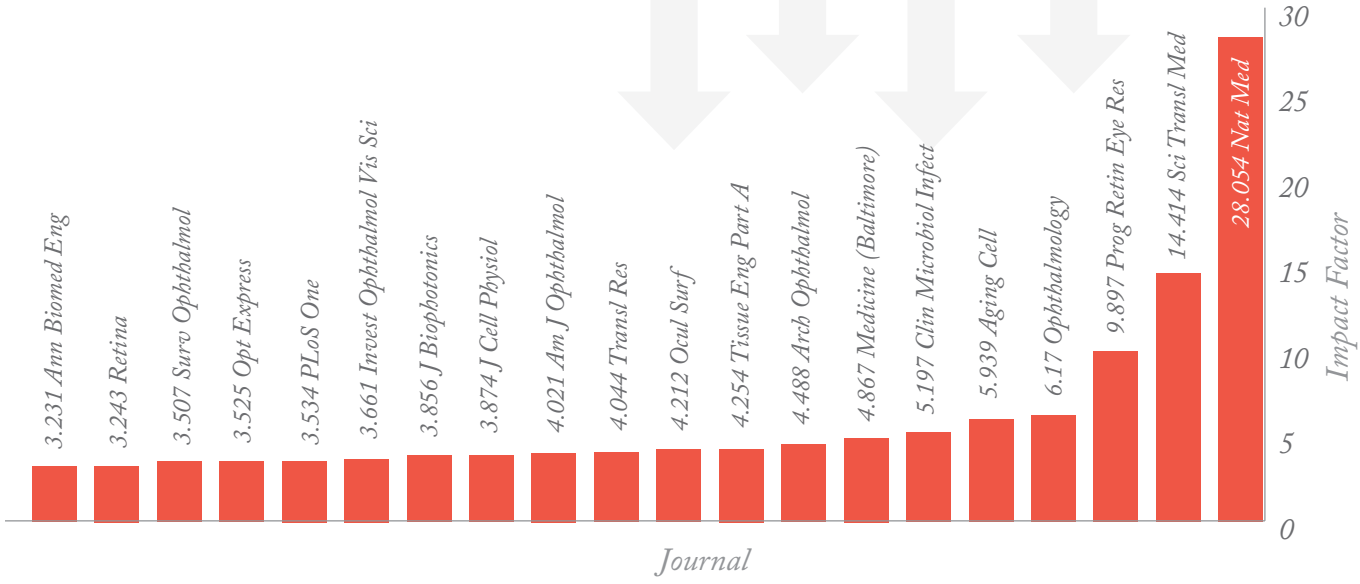


Articles are categorized according to PubMed criteria.

Top 20 Authors by No. of Publications



Top 20 Journals by Impact Factor

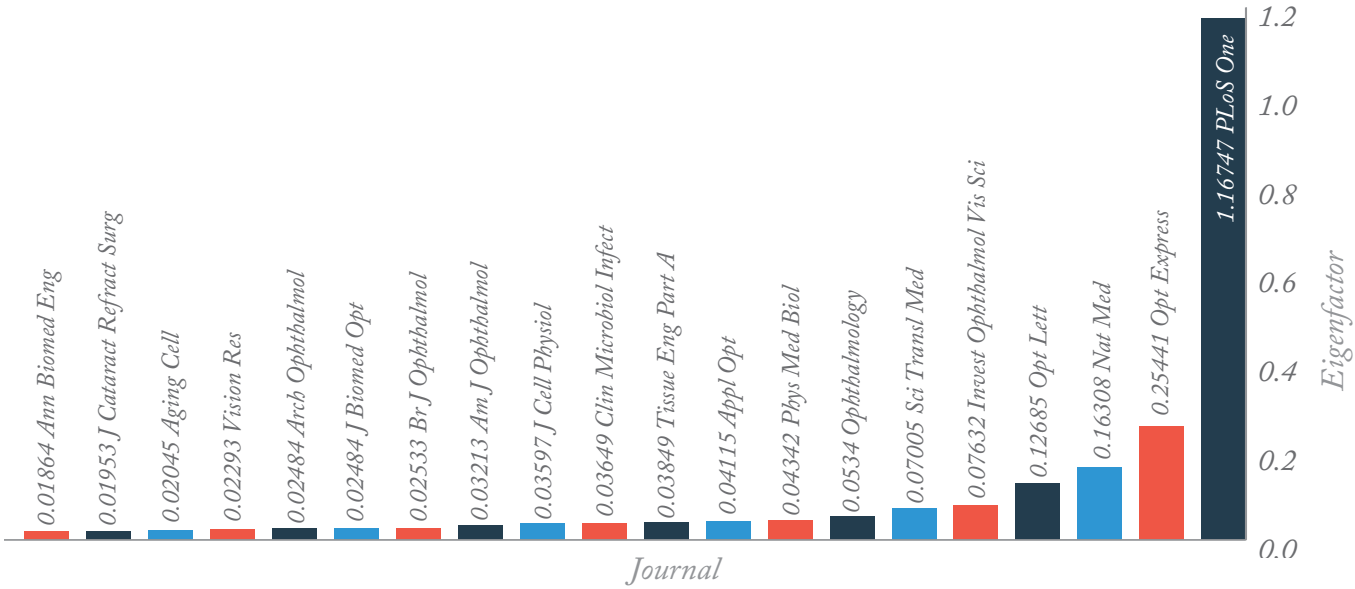


Important Words

1.Coherence	11.Scheimpflug
2.OCT	12.CCT
3.Pachymetry	13. Intralase
4. Iris	14. Pachymetric
5.CXL	15. Orbscan
6. Descemet	16. Microns
7. Meditec	17. Oculus
8. Corneal	18. Keratoplasty
9. Optical	19. Keratoconic
10. Cornea	20. Microincision

Here are the top 20 important words found in the literature. Important words have more frequent occurrences in the result subset than in the MEDLINE as a whole; therefore they distinguish the result subset from the rest of MEDLINE.

Top 20 Journals by Eigenfactor



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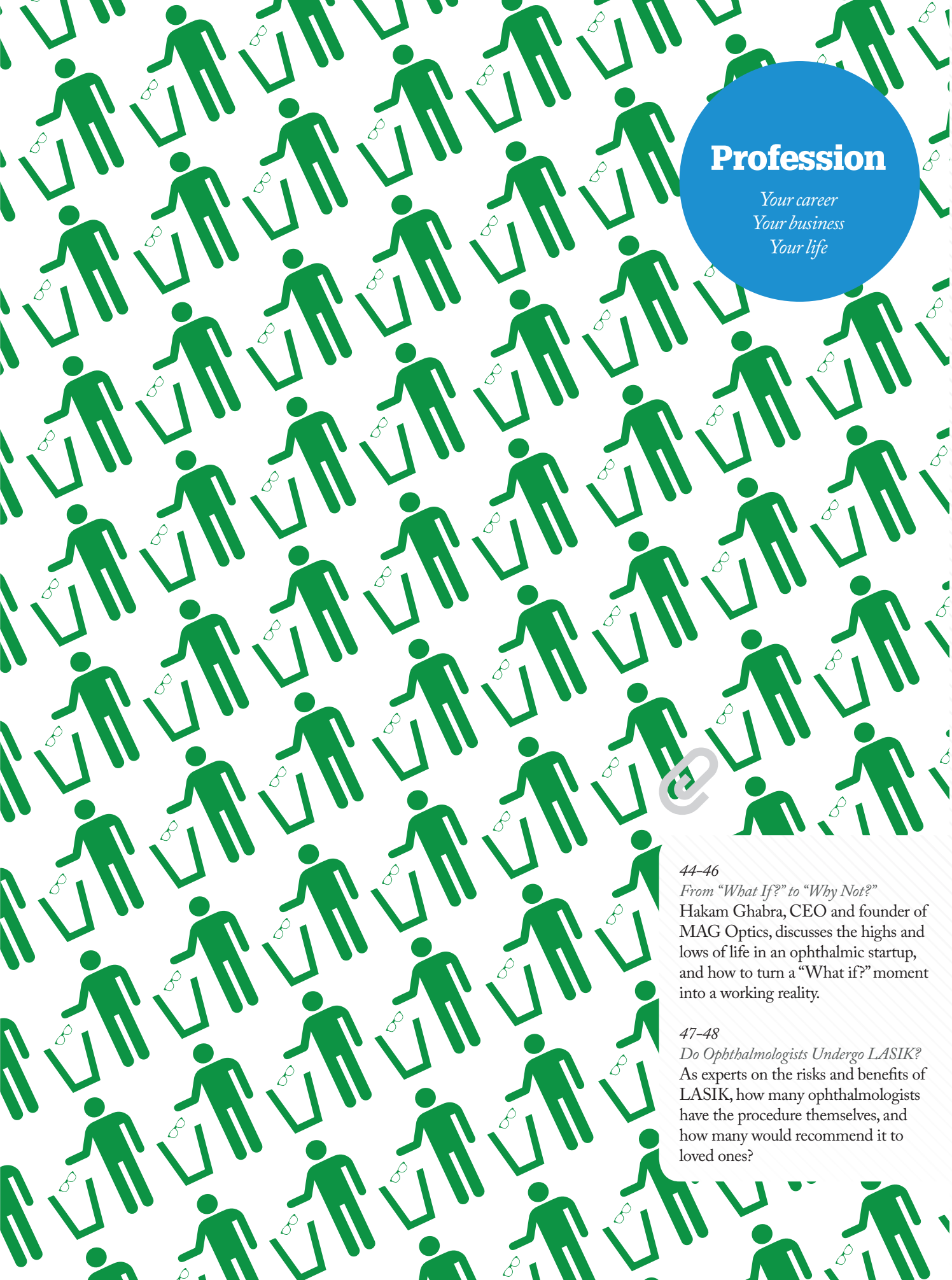

Profession

Your career
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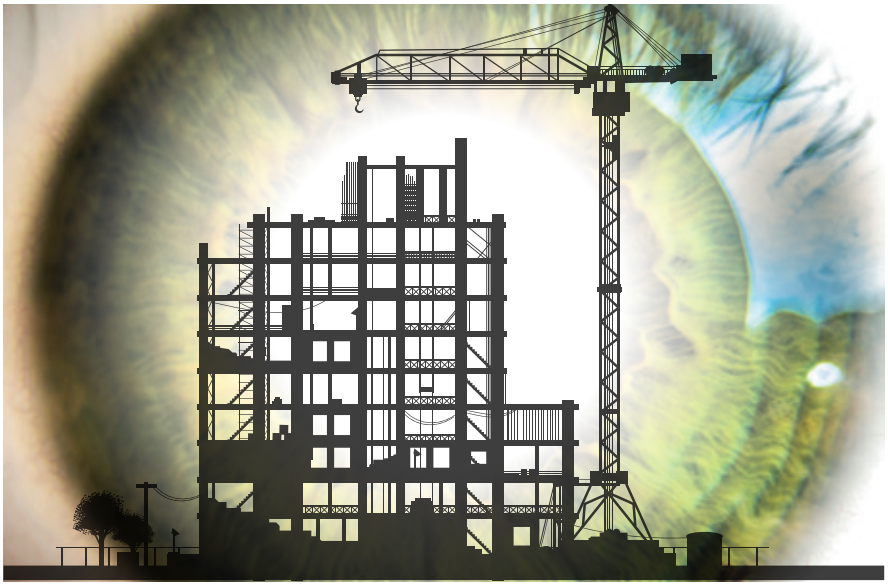
From "What If?" to "Why Not?"

Taking an ophthalmic startup from concept to reality

By Hakam Ghabra



On the battlefield, necessity is the mother of invention – and my father, Marwan Ghabra, can attest to this. Between 1998 and 2012, he was based in Syria, setting up two specialist eye hospitals. During this time, the second Iraq war broke out – and at one point, 60 percent of the workload in both eye hospitals were casualties of war, and conflict-related injuries are some of the most challenging cases there can be. The practice of ophthalmology under these circumstances is a rapid incubator of two skills: on-the-spot improvisation and the ability to innovate your way out of a situation. He tells many stories that stretch belief of how he's "MacGyvered" his way out of some incredible surgical situations – were it not for his surgical video library, nobody would believe him.

Today, my father practices ophthalmology in the UK as a consultant ophthalmic surgeon at London's Whipps Cross University Hospital – but even amongst the terraced houses of the North London suburb of Leyton, he still requires the same skills that served him so well in the arena of war, and the last 30 years of clinical practice of ophthalmology.

I am also a surgeon and, I suppose, as CEO of MAG optics (which my father and I founded), this makes me a "doctorpreneur" too. For the last few years, my father and I have been developing and refining designs for two novel ophthalmic devices – one, a presbyopic accommodating IOL, the other, a novel corneal inlay design for the treatment of a wide array of refractive errors. Both are almost at the proof-of-concept phase. So how did we get there?

At a Glance

- *MAG Optics, our early-stage ophthalmic device company, are in the process of bringing two such devices to the market*
- *One is a fresh take on an accommodative IOL design, that features dual optics, and the other is a novel approach to corneal implants*
- *We've learned that to get by, you need to be nimble, ready to receive feedback from the experts, and work with the right people*
- *Each setback has helped us improve and we now have our end goal – our products in the clinic – fully in view.*

Discussions over dinner

If you gather a group of surgeons together at a dinner party, inevitably, the discussion will turn to work – the triumphs, disasters, hopes and frustrations are all voiced as the evening progresses, with anecdote after anecdote piling as high as the plates that need washing up later.

When my father and I sat down for dinner, we would tackle the meatier "What if?" questions: What if we could produce a truly accommodative IOL? How might you correct the cornea with something that incorporates design elements that account for differences in individual curvature and thickness? Given the highly complex nature of the eye's anatomy, what could we do that is unique? Once the ideas were formed, the next question was always, "What would it take to..?" Dad was always bristling with new ideas and designs, because quite frankly, at heart, he is an inventor – and someone who is rarely content with available technology.

These discussions over dinner inevitably led to doodles on napkins. In our family, the next step after that is to mock up prototypes using whatever's to hand – like spare contact lenses and superglue. It might sound cliché, but that's really how we got started. If we think we have something that shows promise, the next question is: why not?

The "Why Not?" is the meatiest question of all – ideas and prototypes built on the kitchen table can easily be dismissed as food for thought, but there comes a point where, if you believe in your concept, you have to take the next step. It was this, borne of our insatiable curiosity and an

overarching desire to improve the lives of patients that has led us on a rollercoaster journey from the ideas for both devices, to their initial designs, and far beyond. Now we find ourselves not asking "Why not?" but we are building a company to develop what we believe are game-changing technologies for the treatment of cataracts, presbyopia, and broad refractive errors.

When the day job informs the development

My father's 'day job' sees him give out substantial amounts of advice – not just on the planning of complex surgical procedures, but also in the training of junior doctors. It's his 30 years of experience in bridging the gap between theory and practice that gives him the authority to do that – and it's this experience that's been invaluable in the development of our IOL and corneal inlays.

If we focus on the development of the IOL for the moment, it's quite a challenge to come up with a solution for the cataract surgery-induced loss of one of the most complex natural biological processes: lens accommodation. At this point, we should acknowledge the excellent work of Daniel Goldberg, whose computer animated models of accommodation and the theory of reciprocal zonular action has been invaluable, as it supports the unique mechanical aspects of our two part, dual optic, accommodating IOL. He's enthusiastic about our design, noting that it "holds the promise of achieving a lasting solution to correcting both near and far vision with an intraocular lens."

It's this combination of experience and maintaining a scholarly interest in the latest developments that's given us the confidence to take our ideas and run with them.

Keeping an eye on the anatomy

What we've learned on this journey is that the lens needs to be designed to address the inevitable failure of the anatomy, and this lens needs to be unhindered by capsular fibrosis. The second lesson was that as every patient's needs and eyes are different, the lens needs to be customizable – so our IOL design has an adjustable component of the lens that can be modified by the internal diameters of the eye. Finally, the lens must be designed in a way to prevent posterior capsule opacification and we've done that by developing a new approach that utilizes aqueous flow.

"We have managed to have these designs vetted by external engineering teams and some of the biggest-name IOL experts in ophthalmology."

The IOL currently requires a degree of intraoperative positioning, which does mean that a small amount of initial surgeon training will be required, and the positioning may prolong the procedure by a few minutes – but this is not unlike any other new technology. One of the challenges we found was ensuring that the rest of the surgery aligns with industry standards – like keeping incision sizes down to 2.8 mm. Helpfully, we managed to achieve that relatively early in the development process, and we have managed to have these designs vetted by external engineering teams and some of the biggest-name IOL experts in ophthalmology – and have received some very positive and encouraging feedback.

Cadaver eyes and corneal topographers

Moving onto the work that we have done to develop the corneal implants for use in patients with refractive error, presbyopia or keratoconus, we've gone through the same journey – from several design iterations to cadaver implant work. We had two objectives. First, we wanted to preserve the sanctity of the central optical zone. Second, it should be customized to adapt to patient's corneal thickness and curvature allowing for superior patient outcomes.

We've managed to achieve good results early on using the implants to treat astigmatism in cadaver eyes. One example was a cadaver eye with 2.25 D of regular astigmatism. When the implants were implanted on the steep meridian, the degree of astigmatism was increased by 3 D. However, topography revealed that there was a coupling effect on the cornea, in a 1:1 manner (Figure 1). Within the coupling effect, we noticed that when the two implants were placed at 90° to the steep meridian, this results in a reduction of 3 D in the steep meridian, and the overall result of placing these implants in the cornea was a reduction of 3 D in the steep meridian to 0.5 D of astigmatism.

Partnering with the appropriate professionals

Organizing and securing finance has also been a challenge. This is where the third co-founder of MAG Optics comes in – Chicago-based Geeta Singh. Geeta has over 25 years of business management and boardroom expertise, the kind of non-technical – but absolutely essential – business management and strategy planning skills that we needed. She has truly been the driving force behind the transformation of an idea into a viable business proposition. She's also the person that has dealt with that two-ton elephant in the room: capital. So far, MAG optics is bootstrapped, milestone-driven, and extremely cash-conscious, but we're seeking seed capital to advance

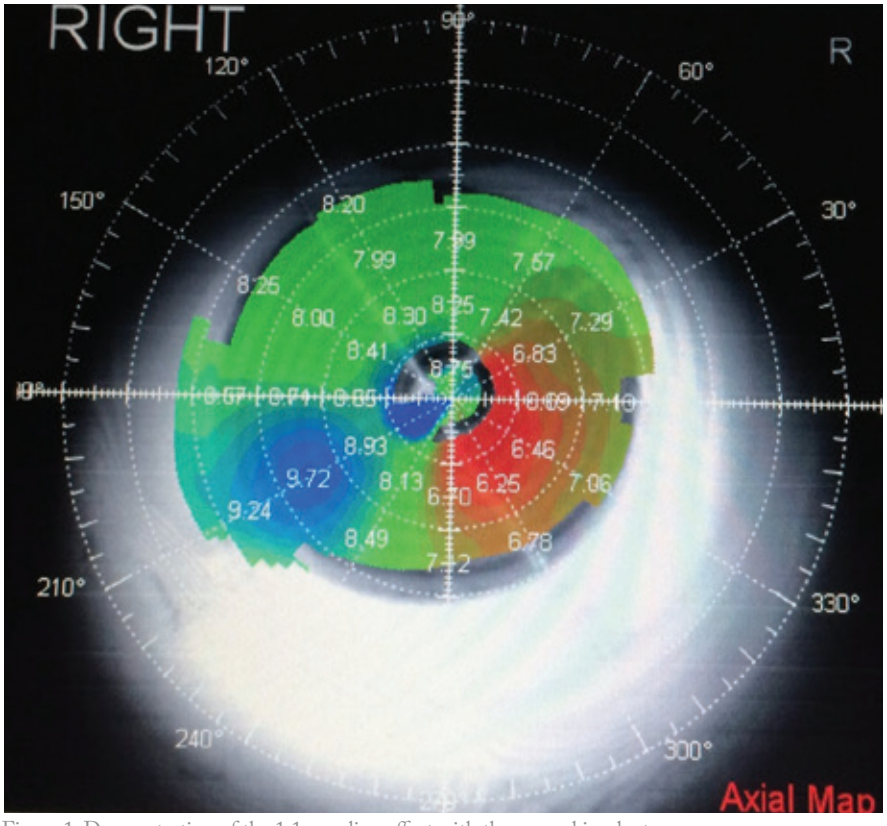


Figure 1. Demonstration of the 1:1 coupling effect with the corneal implants.

the development of the prototypes, to test them, and to implant them.

In addition to Geeta, there were two important skills that we needed to turn to other professionals for. First: engineering. We're working with the University of Liverpool's Professor of Biomaterial Mechanics, Ahmed Elsheikh, to perform finite element analyses (FEA) that will allow us to place the implants in the most optimal position, and we're now on our third prototype. FEA has also let us identify and pre-test design elements for the IOL, helping us streamline the iterative design process for the lens. As of today, we have a working prototype, and we're expecting to have initial results within the next few months. The use of FEA, simulation data and analytics has been crucial in refining our design prototypes.

Second: manufacturing. When it came to selecting clinical-grade materials, the appropriate engineering methods, manufacturing tools and processes, and ensuring adherence to regulatory standards, we've had to turn to other small-to-medium enterprises (SMEs) to help us out.

We are pleased to be working with Contamac in the UK, one of the leading IOL and contact lens material experts, on developing our material for this lens, and our manufacturing partners include specialist companies in France and Spain, both with extensive expertise in IOL and corneal device engineering and prototyping. We are also working with the David J. Apple Laboratory in Heidelberg – which has world-renowned IOL testing capabilities – to provide independent efficacy results.

Dealing with setbacks

When you're a very early stage company, you'll find many, many challenges – particularly when you're working with complex technology, in a close-knit community, and trying to perform iterative designs without the infrastructure that large companies have… it can be quite a challenge.

The way we've dealt with those setbacks is through aggressive research and outreach – we've gained valuable insight from top key opinion leaders (KOLs), and worked with some of the most agile and effective materials and prototyping SMEs out there. Rapid problem solving requires rapid design iterations, and with our partners, that's what we've been able to achieve – for example, we've gone through four, rapid, as Geeta would put it, "innovation cycles" on the IOL, based on input from KOLs and the manufacturing experts.

You can't navel gaze in this game

This might sound cliché, but you really do have to view each setback you come across along the way as an opportunity, and each setback we've come across has led us to improve our game – quickly. Frankly, if we didn't, and weren't as nimble as we are, we wouldn't be where we are today. But when you're trying to build something that could be as game-changing as a truly accommodative IOL, you can't navel gaze – you can only work as hard as possible to move forwards.

We've dealt with setbacks through focused research, outreach, grit and determination. We've gained valuable insight though collaboration, and we're fortunate that our KOLs and partners share our excitement and help continue our momentum to the market. Stay tuned.

Hakam Ghabra is CEO and founder of MAG Optics Ltd. He is a cross-specialty practicing surgeon at University College London, UK.

Do Ophthalmologists Undergo LASIK?

Refractive surgeons know the pros and cons of LASIK better than anyone – but how many would recommend it to their family, or undergo it themselves?

By Greg Parkhurst

As ophthalmologists, we've been performing laser refractive surgery for a very long time. The first excimer laser gained FDA approval for photorefractive keratotomy in 1995, and since then these technologies and procedures have come a long way – by comparison, just think about what cars and mobile phones looked like in the early 1990s compared with what they're like today. LASIK has essentially been around since the Berlin Wall fell, and the last days of Ronald Reagan's presidency! Laser vision correction (LVC) has more than proven itself as having effectively passed the test of time, and has been proven extremely safe and accurate in countless peer reviewed publications, when performed on appropriate candidates. And patients agree – a meta-analysis of the literature shows that an average of 95.4 percent of patients are satisfied with the results of LASIK surgery (1).

"Two years ago, I had the privilege of performing LASIK for my mother, and just last year, I performed femto cataract surgery with multifocal IOLs for my dad!"

But would you, as an ophthalmologist, undergo this procedure yourself? Would you recommend it for your partner, your children or your parents? As someone with a personal and professional interest in the subject, my co-authors and I decided to find out more about LVC amongst my peers…

Game-changing surgery

As refractive surgeons, we've had the honor of providing people with vision correction from almost every background and profession. We've helped teachers, firefighters, quadriplegics, musicians, attorneys, accountants, engineers, nurses, pilots, astronauts, divers, mountain climbers, radiologists, professional athletes – the list goes on and on. The results can be a serious game-changer for our patients – according to Mark Cuban, owner of the Dallas Maverick's NBA basketball franchise, having LASIK is not much different than taking performance enhancing drugs to gain an advantage on the court!

I think the Dublin-based Arthur Cummings of the Refractive Surgery Alliance put it the right way: "You keep on seeing great, life-changing result after great, life-changing result and eventually you want it for yourself too. And your nearest and dearest."

Leading by example

I remember vividly what a life of myopia was like before my own LVC procedure back in 2003. Going water skiing meant worrying about the potential of my glasses sinking to the bottom of the lake. Playing basketball often meant a contact lens popping out on the court. I really hated having to wear glasses, and I recognized how much money I was wasting on contacts and back-up glasses, so I planned to have my vision corrected as soon as I could. Now, when I travel for humanitarian cataract missions, I don't have to worry about the risks of wearing contacts in environments where the water may not be clean. It helps me as a surgeon to see as best as I can and not have to worry about glasses getting dirty, sweaty, broken, or simply in the way.

LVC has changed my life and my patients' lives in a transformative way. It's one of the best things I've ever done for myself and my family. Two years ago, I had the privilege of performing LASIK for my mother, and just last year, I performed femto cataract surgery with multifocal IOLs for my dad. My wife has had Visian ICLs for over 5 years now. These procedures have good safety

At a Glance

- *Laser refractive surgery has been around for over two decades and (like any other technology) it has become safer and more predictable over this period*
- *Refractive surgeons recommend this surgery to their patients all the time, and some surgeons (including myself) undergo it themselves, but would they recommend it to close family and friends?*
- *A recent survey found that over half of refractive surgeons had already had a procedure on their own eyes, and over 90 percent would recommend it to friends and family*
- *The fact that so many refractive surgeons use and recommend it goes to show how far it has come.*

A young Greg Parkhurst, before he underwent laser vision correction and retired his glasses.

and performance, and have improved the lifestyles of my entire family.

By now, I've almost started to take my great vision for granted. It wasn't that way initially. I remember waking up in the morning and reaching for the nightstand to put my glasses on, only to realize with utter amazement that what I was reaching for wasn't needed anymore!

Asking the experts

My own experiences made me wonder about what the wider acceptance of LASIK was in my field – we've all heard anecdotes about refractive surgeons healing themselves through LASIK. But there's conflicting information on how ophthalmologists truly feel about the subject. There has been some misinformation reported in the lay media that "LASIK is one procedure ophthalmologists won't have themselves", but no study had documented the incidence of our profession undergoing the procedure in a formal, scientific way. As the experts who know all about the risks, and benefits, of these procedures, are we willing to undergo them, and are we willing to recommend them to our own flesh and blood?

We decided to look more closely – last year, my colleagues and I published a study in the Journal of Cataract and Refractive Surgery. We used a 22 question survey to assess the attitudes of ophthalmologists who have performed LVC in the last ten years, to see how many had undergone LVC themselves, and how many would be willing to recommend it to immediate family members (2).

The results were very interesting – 62.5 percent of refractive surgeons with refractive error amenable to treatment have already had laser vision correction, and 95 percent are completely, or at least mostly, satisfied with their outcomes. This level of acceptance is around five times the prevalence of refractive surgery in the general population, far surpassing any other profession with the possible exception of the military. We also found that the vast majority (over 90 percent) of the refractive surgeons we surveyed have performed or recommended LVC to one or more of their parents, spouses, siblings, and/or children.

Our results are based on a prospective, protocol driven study that randomly sampled 250 known refractive surgeons using an online questionnaire, with a high level of participation, (249/250 ophthalmologists, [99.6 percent] participated). In my opinion this high response rate makes the study extremely reliable, in part because the study population was defined before questions were presented, effectively eliminating response bias.

Time to rethink self-LASIK?

So for patients, doctors, or ophthalmologists in any other ophthalmic subspecialty wondering whether it is time to close the book on any safety concerns they have about committing to refractive surgery, either for themselves, their families, or their friends, I can think of no stronger endorsement than the results we found. Our study puts the myth that ophthalmologists don't trust LASIK to rest, finding that they undergo the procedure much more frequently than nearly any other profession! And surely there is nothing more reassuring than getting LVC from an ophthalmologist who was so confident in the safety and success of the procedure, that he underwent it himself?

Greg Parkhurst is the founder and CEO of Parkhurst NuVision in San Antonio, Texas, USA.

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Following Destiny's Path

Sitting Down With...
Anat Loewenstein, Chair of the Department of Ophthalmology, Tel Aviv Medical Centre, Professor of Ophthalmology and Vice Dean, Tel Aviv University, Israel.

What drew you to ophthalmology?

My parents were physicians, as was my grandfather, so medicine was a natural choice for me. I knew that I wanted to do something that would allow me to achieve career excellence, climb the ladder, and help people at the same time. But as an intern rotating through different departments, I realized that in many areas of medicine, you basically have a lot of debates, but have little power to actually help the patient in a timely manner. Ophthalmology offers the possibility of helping patients achieve better vision, relatively quickly – and that's even truer today than it was when I started out.

"Being a woman who has a family is a little bit challenging in ophthalmology, especially if you want to advance to the senior positions."

You hold a lofty position in Tel Aviv University. How did you get there?

I pursued an academic career and simply worked my way up – from lecturer, to associate professor, to full professor, then becoming incumbent of a chair, and from there to the vice dean. What drove me was a passion for educating students, so I could pass on to them the knowledge and skills they need. This is what brought me to the university, and it's what keeps me there.

What kind of manager are you?

I learned my management style as a vitreoretinal fellow at the Wilmer Eye Institute at Johns Hopkins in Baltimore. As opposed to how my own country did things at the time, in the US it was all about sharing responsibility. Instead of having a chair who dictates how things are done, people were given responsibility over different areas. In my institute I have a person in charge of the outpatient clinic, another in charge of the OR, another in charge of the inpatient clinic and so on – and these people are experts in that particular area. This allows me to oversee all of the units, and perform quality control.

How did you become interested in retinal toxicity?

It started with a girl who came to our hospital after being injected with a long-acting steroid. The drug got into one of her eyes and she lost vision, even though the morphological trauma was not very severe. We realized that the drug was toxic, and from there we conducted research on this particular drug, demonstrating that the vehicle of the drug was extremely toxic.

Later, I was fortunate enough to play a part in the advent of anti-VEGF agents – bevacizumab was originally used without toxicity studies, so I volunteered to conduct one. Within a month I already had results that showed the drug wasn't toxic to the retina, and I think my work helped to influence the face of modern retinal therapy.

If you could give yourself from 20 years ago advice, what would you say?

I've been very fortunate because I would tell myself to take the same path that I did. I think it's really important to concentrate on one field and try to be as good as you can in that field, this way you can become a leader with a lot of knowledge. What I would tell myself is that we always need to put patients first, and remember that we are here to treat them, to improve their vision and quality of life.

Do you feel that you had to work harder than your male counterparts to climb the ladder?

I think being a woman who has a family is a little bit challenging in ophthalmology, especially if you want to advance to the senior positions. I think that women are of course, just as capable as men, but they have a challenge as society sometimes expects them to focus solely on home and childcare. And I think this needs to change. Until it changes, the people in senior positions need to give women opportunities, perhaps with more flexible hours or in different areas, to allow them to show that they have comparable skills to men. Not to do less work, just perhaps to do it at different times of the day.

What do you expect your practice will look like in 2030?

Well, I think my practice will still be crowded, because we will have more and more diseases that we are able to treat! But hopefully patients will be able to visit us less often, as the development of longer acting-drugs, slow release devices and topical therapies reduce the need for frequent appointments. I think vitrectomy will become faster and more accurate, too, as technology continues to develop.

What do you enjoy most about your job?

I enjoy the diversity. My week is divided between surgery, research, university work and administrative tasks. I travel to interesting meetings, where I meet new people to brainstorm and share ideas – and these are people who are very senior and knowledgeable, so I can learn a lot from them. I sit on advisory boards, and I also get to take part in developing new technologies. I have the best job in the world!

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