Significant advances in glaucoma detection and management during 2016 included new dietary advice, the use of Optical Coherence Tomography Angiography (OCT-A) for glaucoma diagnosis, an explosion of minimally invasive glaucoma surgery (MIGS) technology, as well as novel and exciting methods of detecting glaucomatous visual dysfunction. These findings will drive our work in 2017 and beyond.

DIETARY ADVICE
One of the more headline grabbing studies conducted during 2016 came from the long running ‘Nurses Health Study’, which suggested a diet rich in nitrates (found in green leafy vegetables), was protective against glaucomatous vision loss. This was especially true for paracentral scotomas, the most functional vision threatening forms of glaucomatous visual field loss. This effect was dose dependent and seemed to confer a 20-30 per cent decrease in primary open angle glaucoma (POAG) risk. Thus it makes sense to advise a diet rich in nitrates and antioxidants for our patients in order to reduce the risk of vision threatening glaucomatous visual field loss.

OPTIC NERVE/RETINAL IMAGING AND GLAUCOMA
OCT-A is a relatively new non-invasive method to measure microcirculation in various retinal layers separately. With wide reaching applications across ocular diagnostics, it has specific application to glaucoma in the evaluation of the peripapillary microvasculature. When normal eyes are compared to glaucomatous eyes, peripapillary microvascular dropout is associated with glaucomatous damage. Specific risk factors for microvascular dropout include choroidal thinning, reduced diastolic blood pressure and lamina cribrosa defects. Localised microvascular dropout is often adjacent to the lamina cribrosa defect. It appears that the degree of vascular dropout is proportional to the severity of glaucomatous visual field loss and may be more closely correlated to visual field loss severity than retinal nerve fibre layer (RNFL) thinning measured by non-angiographic OCT. Eyes diagnosed with ocular hypertension (raised intraocular pressure (IOP) with healthy-appearing optic nerves demonstrate reduced peripapillary microvascular perfusion, indicating OCT-A may detect very early, previously unrecognised glaucomatous damage. Reduced-IOP improved peripapillary microvascular perfusion, indicates a reversible pathological mechanism, at least early in the disease course.

“A new automated method of classifying angle closure glaucoma mechanisms based on anterior-segment OCT was proposed”

In non-angiographic OCT, significant progress was made refining both Fourier-domain and Spectral-domain OCT in structural disc diagnosis in glaucoma, with excellent test-retest repeatability, was reported in Spectral-domain OCT. With increasing resolution of technology, new layers can be more finely discriminated such as the macular RNFL. The macular RNFL thickness appears as good as macular ganglion cell complex (GCC) and circumpapillary RNFL thickness measurements in discriminating between glaucomatous eyes and controls. The ganglion cell layer complex is gaining importance in glaucoma monitoring. Evaluating OCT parameters in high myopes can be challenging, as myopia can cause similar OCT-detected changes as glaucoma. However measuring asymmetry of the GCC difference across the temporal raphe appears to be more useful than other OCT parameters (e.g. peripapillary RNFL thickness) in distinguishing glaucomatous damage in high myopes. OCT progression analysis is limited by floor effects, in that once enough damage has occurred to the nerve, it is difficult to detect further progression due to the overall thinning,
at which point visual field progression becomes much more useful. One study evaluating floor effects in OCT monitoring found that GCC measurements had fewer and later floor effects than the RNFL, indicating a greater utility of GCC than RNFL in moderate to advanced disease. GCC measurements were found to have greater ability to diagnose glaucoma accurately than functional visual tests (microperimetry and standard automated perimetry).17

**NOVEL MEANS OF MEASURING VISUAL FUNCTION IN GLAUCOMA**

Last year a variety of novel ways to measure visual function in glaucoma were described, some of which show promise to complement, or one day, even replace visual field testing. The photopic negative response of the electroretinogram was evaluated as a quantitative metric of optic nerve function. Objective testing like this may have a vital role in future clinical studies evaluating new glaucoma therapies.18 Tablet perimetry recorded using an Apple iPad appears to show great promise, with strong correlation to Humphrey field analysis and good test-retest reliability.19 Such technology may have a role in home perimetry or for remote or regional patients without access to specialized health care resources.

**QUALITY OF LIFE IN GLAUCOMA**

Our understanding of how glaucoma influences the daily quality of life (QoL) continues to grow. One unique study found that clinicians are still poor at discussing QoL implications of the disease with their patients, despite the importance of glaucoma’s influence on patients’ QoL.20 Driving impairment and motor vehicle accidents (MVAs) are a major consequence for patients with glaucoma influencing their independence of living. In a population-based Japanese study, several risk factors for MVAs were assessed in POAG patients; visual acuity in the worse eye was the strongest predictive factor.21 One cross-sectional study found contrast sensitivity, chromatic vision and reading ability to be worse in moderate POAG patients compared to early POAG patients, indicating impairment of a variety of visual functions as the disease progresses.22 A new computerised simulation test to identify the way in which glaucoma limits daily activities has been described, which may bridge the gap in patient understanding of how their visual impairment can influence daily life.23

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**“Micropulse infrared laser shows promise as an alternative to traditional continuous wavelength delivery”**

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**MINIMALLY INVASIVE GLAUCOMA SURGERY**

MIGS, involving tiny microstents inserted into the trabecular meshwork and/or suprachoroidal space, continues to increase in scope and promise. MIGS appears increasingly likely to have a role in mainstream glaucoma therapy. Amid the hype there is confusion and controversy about which device is best and the role the myriad of new MIGS devices will play within current glaucoma therapies. The COMPASS trial, evaluating the supraciliary (Cypass) microstent in glaucoma patients undergoing cataract surgery was evaluated in a randomized control trial (RCT) with two year follow up (n=505).24 Compared with the control group (patients undergoing cataract surgery alone), the Cypass resulted in lower IOP (7.4 v 5.4 mm Hg reduction) and medication use at 12 and 24 months. Some hypotony was reported but no vision-threatening microstent-related adverse events occurred. The Hydrus microstent, inserted ab-interno into Schlemm’s canal, was compared to selective laser trabeculoplasty (SLT) in POAG patients.25 Both reduced IOP, however Hydrus implantation significantly reduced medication dependence whereas SLT did not. The Hydrus however, had a greater complication rate, with some patients having a transient IOP spike or visual acuity reduction.

Several studies evaluated the iStent trabecular bypass stent (both the first generation iStent and second generation iStent inject) combined with cataract surgery. These found a recent decrease to the trabecular bypass in terms of reduction in IOP and number of medications used.26-28 As a stand-alone procedure in pseudophakic eyes, the iStent has a modest IOP reduction but does not alter the number of topical medications, indicating it may be more potent when combined with cataract surgery.29 In newly diagnosed patients with POAG, researchers compared two iStents inserted with topical prostaglandin monotherapy with a similar safety profile, and IOP reduction at three years follow up.30 The iStent inject was compared to the Trabecutome in a contralateral eye comparison study; both resulted in significant IOP lowering with no significant difference between treatment types.31 Several other devices are on the horizon and show great promise. For instance, the Xen subconjunctival implant is inserted trans-sclerally from an ab-interno approach. It is due to be released this year.

**LASERS IN GLAUCOMA**

SLT is increasingly used in the treatment of open angle glaucoma or ocular hypertension as a first line of therapy, in addition to drops, or to delay glaucoma filtration surgery.32 Research conducted last year challenged many of our beliefs about SLT. SLT is pro-inflammatory, and its efficacy is generally believed to be reduced by use of topical anti-inflammatory medication post-laser. However, De Keyser et al found that post-laser medication had no effect on pain, redness, cells in the anterior chamber or final IOP outcomes.33 SLT is typically performed by aiming the treatment directly onto the pigmented trabecular meshwork (TM) using a gonioscopic mirror. Curiously, a study by Geffen et al found that direct application to the limbal area without direct visualisation of the TM produced similar results to conventional treatment.34
SLT is frequently quoted to be less effective on subsequent treatments than primary treatment, yet new evidence from three separate population-based studies suggest repeat 360 degree SLT is as effective as initial 360 degree treatment. SLT appears to be effective even in eyes post-trabeculectomy. Pattern-scanning SLT, formed using the semi-automated Pascal laser, appears to have a similar safety and efficacy profile to the conventional SLT. In a case-controlled study involving 118 patients, SLT had similar efficacy in POAG as in primary angle closure (PAC)/primary angle closure glaucoma (PACG) patients whose angles had been opened by laser iridotomies prior to SLT.

Continuous transcleral cyclodiode laser to the ciliary body is often used for refractory glaucoma. Alternatives to the conventional cyclodiode laser were evaluated last year. Micropulse infrared laser shows promise as an alternative to traditional continuous wavelength delivery, and may display similar efficacy with reduced inflammation and hyptotony. High-intensity focused ultrasound (HIFU) is an alternative ciliary body coagulation modality for IOP lowering and it appears to be safe and effective in two small consecutive studies. Endoscopic cyclophotocoagulation combined with cataract surgery is a good treatment option for patients with plateau iris syndrome.

ANGLE CLOSURE
PAC is a multifactorial disease associated with a combination of pupillary block, peripheral iris thickening, plateau iris and/or phacomorphic (lens-related) vault. Teasing out the various mechanisms that allows application of the correct treatment can be challenging clinically. A new automated method of classifying angle closure glaucoma mechanisms based on anterior-segment OCT was proposed, which may be more efficient and less user-dependent than traditional methods.

The role of clear lens extraction in the management of PAC is as controversial as ever. However, some light has been shed on the issue with the publication of the EAGLE study in the Lancet in 2016. In one of the largest population based RCTs in the field of PAC, clear lens extraction (CLE) was evaluated in patients with PAC/PACG aged >50 years with IOP >30 mm Hg.

CLE showed greater efficacy and was more cost-effective than laser iridotomy, and is recommended by the authors as first line treatment instead of laser iridotomy. However, given the stringent inclusion criteria, the results cannot necessarily be extrapolated to all PAC/PACG patients.

Persistent angle closure following laser peripheral iridotomy is a common problem in clinical practice. Argon laser peripheral iridoplasty (ALPI) has a controversial role in opening the angle further in such patients, potentially allowing safe deferral of cataract surgery. In the IMPACT study the role of ALPI was evaluated in patients with persistent angle closure following iridotomy using swept-source anterior segment OCT. The study found that all angle parameters improved following ALPI, resulting in reduced maximal IOP and diurnal IOP fluctuations. However, ALPI appears to be less effective at IOP control than prostaglandin monotherapy in patients with persistent appositional angle closure following PI.

A new formula was proposed predicting postoperative intraocular pressure after cataract surgery in PACG based on pre-cataract surgery IOP and anterior chamber depth. It shows reasonable predictive power.

MEDICAL THERAPIES FOR GLAUCOMA
Since the advent of prostaglandin therapy for glaucoma in the early 90s, there has been no new class of drug to add to the armoury of glaucoma medications that
is any better than what we currently have. This is despite some initial promise and a lot of scientific work for many potential target medications. Research is continuing on the Rho Kinase inhibitors and latanoprost bunod as potential adjunct therapies. There may be a role for drugs such as trabedenoson, and Adenosine A1 receptor mimetic which seem to demonstrate a dose dependent and prolonged action in recently published Phase II studies.56

We have known for some time that adherence to glaucoma medications is very poor over time. Accordingly, there has been much work recently on depot preparations of IOP lowering agents. The most advanced of these technologies (in terms of progress through clinical trial) is bimatoprost slow release (SR) depot delivered into the eye. This is currently undergoing Phase III trials (ARTEMIS 1 and 2, ATHENA) in centres across Australia. Another biopolymer derived depot platform uses travoprost as the drug of choice and is currently undergoing a Phase II trial. There are a variety of biopolymer and nanoparticle derived technologies under development. While not specifically being developed for glaucoma, these could deliver depot glaucoma medications either inside or adjacent to the eye. Additionally, while collagen implants, punctal plugs and contact lenses impregnated with glaucoma medications have shown a modest effect on IOP, it is relatively early days with this sort of technology. Many of the medical device companies also have plans (but no trials) for drug eluting medical devices that may drain aqueous – in a similar way to a drainage tube or a MIGS device. This may drain aqueous into the treatment of glaucoma may be rapid indeed.

**BASIC SCIENCE OF GLAUCOMA**

With the large multinational genetic consortiums such as NEIGHBOR and GLAUGEN studies as well as access to the genetic information collected as part of the Norfolk based EPIC study and locally based ANZRAG study, our understanding of the complex genetic interactions that form part of the pathogenesis of glaucoma continues to improve. Genome-wide associated studies identified three new genes associated with POAG51 and five with PAC.55 There has been additional work looking at how the genes associated with glaucoma interact with each other.55 This is an emerging field and as we map out the complex molecular pathways affected by glaucoma, we may be able to develop new and better-targeted therapies. There is increasing evidence that vascular dysregulation, impaired metabolism and mitochondrial dysfunction play a role in glaucoma pathogenesis. Hypoxia may induce previously unexpected outcomes such as fibrosis in the trabecular meshwork, impairing aqueous outflow.54 A large genetic study looked at the role of mitochondrial genetic variations and mapped metabolic pathways, especially lipid and carbohydrate metabolism pathways.55 This exciting new field is rapidly opening potential therapeutic targets. Given the array of cardiovascular drugs already approved for use in these areas, the potential clinical translation into the treatment of glaucoma may be rapid indeed.

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**References**


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