Title: Seminar: Glaucoma Now and Beyond

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Contributorship Statement: GG, HJ, MK, & DSF all developed the theme of this editorial, contributed to the drafts and revision and approved the final version of the manuscript. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Word Count: 5120

Acknowledgments:

GG is employed by UCL and supported by grants from the National Institute for Health Research (HTA 09/104/40), Moorfields Eye Charity, British Council to Prevent Blindness, Fight For Sight and the International Glaucoma Association. HJ is supported by the Moorfields Eye Charity. GG and HJ are grateful for the support of the National Institute for Health Research Biomedical Research Centre for Ophthalmology at Moorfields Eye Hospital and the UCL Institute of Ophthalmology. DSF receives funding from the National Eye Institute and the Harvard Catalyst. MK is employed by Copenhagen University Hospital and the University of Copenhagen. MK receives funding from the Synoptik Foundation, the Velux Foundation and Fight for Sight, Denmark. The authors are grateful to MD, PhD student Zaynab Ahmad Mouhammad for developing figures. Views expressed in this paper are those of the authors and not necessarily those of any funding body or the UK Department of Health.

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Conflict of Interest: The authors declare that they have no conflicts of interest relating to the material submitted

Abstract:

The glaucomas comprise a heterogenous group of conditions leading to irreversible sight loss characterised by progressive loss of retinal ganglion cells. While often associated with elevated intraocular pressure (IOP), the only currently modifiable risk factor, only X% of variation in prognosis is attributable to IOP. It remains the leading cause of irreversible global blindness, however timely treatment to lower intraocular pressure is effective at preventing the majority of cases of severe vision loss. These currently include laser treatments, topical medications and surgical interventions. Although many recent surgical innovations aim to be less invasive, many have been introduced with minimal supporting evidence from randomised controlled trials. The majority of cases remain undiagnosed until the advanced stages of disease due to the limitations of screening and poor access to opportunistic case finding. Future research aims to generate evidence for IOP-independent neuroprotective treatments, personalised treatment through genetic risk profiling and further exploration of the potential role for advanced cellular and gene therapies.

Search Strategy and Selection Criteria:

We searched the Cochrane Library, MEDLINE, and Embase between January 2000 and July 2022, with the terms: “glaucoma”, “primary open-angle glaucoma”, “secondary open-angle glaucoma”, “angle-closure glaucoma”, “intraocular pressure”, “optical coherence tomography”, “perimetry”, “visual field”, “optic disc”, “optic nerve head”, “optic nerve imaging”, “retinal nerve fibre layer”, “trabecular meshwork”, “glaucoma treatment”, “glaucoma laser”, “glaucoma pathophysiology” and “glaucoma surgery”. We largely selected publications from the past 5 years, but also include highly referenced and highly regarded publications outside of this window. We did not restrict our search by language. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant. Review articles and book chapters are cited to provide readers with further details and more extensive references than permitted within this Seminar.

Introduction

Glaucomas comprise a heterogenous group of conditions leading to irreversible sight loss characterised by progressive loss of retinal ganglion cells (RGCs) and optic nerve injury, often secondary to elevated intraocular pressure.[1,2] Given the slow decline in vision, the frequent asymmetry of disease between the two eyes and neurological mechanisms that 'fill-in' areas of missing vision, patients are often unaware of vision loss until late in the disease course, despite measurable negative impacts on many aspects of visual function.[3-5] Over 90% of glaucoma cases are undiagnosed in developing countries whereas about half are undiagnosed in higher income countries.[6] Although glaucoma is the leading cause of irreversible blindness globally,[7] most patients with glaucoma retain useful vision throughout their lives and treatment is effective at preventing the majority of cases of severe vision loss from glaucoma if initiated in a timely manner. Nearly 95 million people have glaucoma around the world, about 10 million are blind in at least one eye, and many more suffer visual impairment and activity limitation owing to glaucoma.[8] At present, no treatments restore vision lost from glaucoma, so case detection and effective treatment are essential. Glaucoma prevalence globally will rise dramatically in the coming decades[8] as populations age and better detection and care of glaucoma will be needed to avoid unnecessary preventable blindness.

Epidemiology, Risk Factors & Patient Impact

Glaucoma can be divided into several phenotypes. One major distinction of primary glaucomas relates to the anatomy of the anterior chamber angle (Figure 1). The majority have an "open angle", but others have "angle closure", and in general the disease course in angle closure glaucoma (ACG) is more severe. Globally, about 65 million people have open angle glaucoma (OAG) and 30 million have ACG, but about half of global blindness is attributable to ACG. There are numerous other subtypes of glaucoma, including congenital glaucoma and secondary glaucomas.

Elevated intraocular pressure (IOP) is strongly associated with the development of glaucoma, however almost half of all patients with glaucoma have IOP in the "normal" range.[9,10] Secondary glaucoma occurs when an ocular condition causes elevation of IOP, which then leads to optic nerve injury. Common causes of secondary glaucoma include uveitis, anterior segment neovascularisation, typically as a complication of diabetic retinopathy and retinal vascular occlusions, and ocular trauma. Secondary glaucomas often result in severe vision loss, as IOP can be especially high affected eyes.

The single most important risk factor for glaucoma is age with most glaucoma diagnosed in patients over forty years of age.[8] About 10% of people from European ancestry over 75 years of age have OAG, with higher rates among Hispanics and African populations.[8,11] African ancestry is associated with almost four times the risk of OAG, an earlier age of onset and greater disease severity.[12] Similarly, Hispanic populations have substantially higher rates, especially in older age.[13] The relationship between blood pressure and glaucoma is complex with several studies indicating an increased risk for glaucoma in patients with both low and high blood pressures.[14,15] Smoking and alcohol use have not been consistently associated with glaucoma. Those with OAG at low-normal IOP, referred to as Normal Tension Glaucoma, tend to be more likely to suffer from migraine, Raynaud's phenomenon and be female.[16]

Glaucoma is highly heritable (see genetics section below) and a true family history of glaucoma increases the risk in a first-degree relative nearly eight-fold.[17,18]

ACG is more common in Asia, particularly in China, where the highest disease rates are seen in older age and in women. ACG typically presents as a chronic condition without symptoms, but at times can present acutely as an attack. Those suffering an acute angle closure attack have about a 10% chance of severe vision loss and about half suffer damage to the optic nerve.[19] Such acute presentations are typically ocular emergencies.

Congenital glaucoma is an important form of glaucoma with severe lifelong consequences.[20] This is relatively rare affecting 1 per 10-30,000 live births, and early treatment can prevent severe vision loss. The initial treatment for congenital glaucoma is always surgical in contrast to other glaucoma subtypes, where laser or medical treatment is by far the most common first line treatment.

Risk factors for glaucoma can be divided broadly into ocular factors and individual factors. The most important risk factors for glaucoma (both OAG and ACG) are age, IOP and family history in a first-degree relative. As discussed below, a wide range of genetic factors influence the severity and sensitivity to these and other risk factors.

Another major ocular risk factor for OAG is myopia, which in a dose-dependent fashion increases the risk with the degree of myopia. Individuals with more than -3 dioptres of myopia

have a 3.3-fold increased chance of developing glaucoma,[21] while those with more than -6 dioptres of myopia have even higher risk.[22] This has huge implications for the global prevalence of glaucoma as myopia is increasing dramatically in many parts of the world. For example, in Singapore over 70% of youths aged 11-17 and over 90% of university students are myopic, with nearly one in ten having more than -6 dioptres of myopia. Two other associated conditions, with strong genetic components that pose a high risk of OAG, are pseudoexfoliation (PXF) and pigment dispersion syndrome (PDS).[23,24]

The past decade has seen a tremendous growth in our understanding of glaucoma genetics with over 125 genes identified to date that are associated with glaucoma and over a hundred novel single nucleotide polymorphisms linked to the major risk factor IOP alone.[25] Glaucoma is a mostly a complex polygenic disease with rare single mutations responsible for fewer than 5% of all glaucomas, e.g. myocilin (MYOC) is an important affected gene in which mutations can lead to early onset glaucoma and very high IOP. MYOC mutations are present in 2-4% of patients with Primary OAG (POAG), whereas as many as 16-40% of patients with early-age onset (juvenile) glaucoma have the MYOC gene mutations. Patients with normal tension glaucoma (i.e., pressure in the statistically “normal” range) have been shown to have a high incidence of OPTN (optineurin) and TBK1 (TANK binding kinase 1) genes, whereas patients with pseudoexfoliation have a high incidence of the LOXL1 (Lysyl Oxidase Like 1) gene mutation. In patients with congenital glaucoma abnormalities in the CYP1B1 (Cytochrome P450 Family 1 Subfamily B Member 1) gene and LTBP2 (Latent Transforming Growth Factor-Beta-Binding Protein 2) have been identified as well as mutations in the chromosomes 1p36 and 2q212. The risk of converting to glaucoma in patients with increased IOP, but no glaucomatous damage, ocular hypertension (OHT), has been shown to be related to the TMCO1 (Transmembrane and Coiled-Coil Domains 1) gene.[26] Finally, the risk of steroid-induced glaucoma has been related to allelic variations in the TIGR (Trabecular Meshwork Inducible Glucocorticoid Response) gene. In addition to major genetic mutations, recent studies have documented many single nucleotide polymorphisms (SNPs) that are associated with a higher risk for glaucoma.

Researchers are actively developing genetic risk scores for patients which could help for glaucoma screening as well as for prognosis and individualized therapy. Other domains of medicine have used genetic probability risk scores (PRS) to integrate the total genetic risk of an individual based on her collection of minor genes for a disease and shown substantial variation

in risk based on PRS.[27] Similar work is taking place in the study of glaucoma, but the interplay of the very complex genetics of multiply interacting risk factors makes this a complex and challenging task.

Recent publications have emphasised the significant impact that glaucoma has on patients' lives. Several studies have documented the increased risk of car accidents,[28,29] decrease in or cessation of driving,[30] less frequent time spent away from the home, decreases in reading and reading speed, reduced physical activity and higher risk of falls in individuals with glaucoma.[31] These declines in function are seen not only after severe vision loss, but are associated with relatively early visual field loss frequently seen in patients with mild to moderate glaucoma.

Pathophysiology

Elevated Intraocular Pressure

Elevated IOP is the only known modifiable risk factor associated with the development of glaucomatous optic nerve injury.[32,33] Regulation of IOP is the balance between aqueous humour production and outflow (Figure 1). Aqueous outflow is predominantly through the conventional pathway via the trabecular meshwork and Schlemm's canal (to which Schlemm's canal endothelium and trabecular meshwork (TM) extracellular matrix (ECM) comprise significant resistance[34]), and to a lesser extent through the unconventional pathway which includes uveoscleral and uveovortex routes.[35] In addition, the presence of lymphatic channels within the human ciliary body has led to the more recent concept of a uveo-lymphatic pathway also contributing to aqueous outflow.[36]

The homeostasis of outflow resistance is varied by modification of TM cell activity[37] and remodelling of ECM proteins. ECM changes in glaucomatous eyes are thought to alter the biomechanical properties and availability of growth factors both within the conventional and the unconventional outflow pathways.[38] This can lead to loss of the normal homeostatic mechanisms that maintain IOP within normal levels, in part due to loss of TM cellularity or accumulation of ECM.[39] Treatment to lower IOP involves medical, laser and surgical approaches to either reduce aqueous production or enhance aqueous outflow.

Optic Nerve Injury in Glaucoma

Glaucoma is characterized by structural damage to the optic nerve head leading to the progressive loss of retinal ganglion cell (RGC) axons, resulting in loss of neuroretinal tissue referred to as “cupping” of the optic nerve head (Figure 2). This produces characteristic patterns of visual field loss that ultimately lead to visual impairment (Figure 3). As previously described, the role of IOP in the pathophysiology of glaucoma is well established[32,33] and lowering IOP has been shown to reduce the risk of developing glaucomatous optic nerve injury.[40-43] However, patients may still suffer progressive loss of vision from glaucoma despite maximal IOP lowering treatment.

This progressive susceptibility of glaucomatous eyes to further damage may occur because of the cellular and structural mechanisms that occur during the disease process. Although the cellular mechanisms of glaucomatous damage are still poorly understood, it is widely accepted that the primary insult occurs at the ONH, and may involve several mechanisms including obstruction of axoplasmic transport,[44,45] ischaemia,[46] events secondary to the loss of RGC axons[47] as well as events related to the biomechanical stresses upon axons.[48,49] Remodelling of the optic nerve head in glaucoma also involves activation of resident astrocytes.[50] These glial cells within the optic nerve head and retina interact with local metabolic stresses in response to raised IOP and are thought to play a crucial role in limiting disease progression.[51,52]

Studies to determine the mechanisms underlying glaucomatous optic nerve injury are limited, and our current knowledge is therefore derived from the study of experimental glaucoma models. Axonal degeneration induced by chronically raised IOP has been observed in different rodent models of glaucoma, both within the optic nerve head and in afferent axonal bundles and has also been shown to temporally precede loss of the RGC soma.[53-56] Ultimately, the secondary loss of RGCs has been shown to occur through apoptosis, which has been demonstrated in both rodents and primates.[57,58] Gene and microRNA expression studies have identified molecular pathways that may be altered in experimental glaucoma, reflecting the various putative mechanisms involved in glaucomatous optic nerve damage, including ischemia, neuronal degeneration, apoptosis and cellular proliferation.[57,59-62]

Clinical Management

Patient Identification

Glaucoma is a slowly progressive optic neuropathy, is often asymptomatic and even those under care are often unaware of deteriorating visual function. Those who have symptomatic vision loss in glaucoma typically have advanced optic nerve injury (Figure 2E,F and Figure 3D). Early case detection is therefore essential to identify individuals with glaucoma, and this has proven to be challenging. Screening for glaucoma requires visualization of the optic nerve which can be done with fundus cameras, direct examination, or laser scanning devices (that can provide detailed nerve fibre layer assessment) which are all expensive and/or time consuming. Ultimately, most cases are detected during routine optometric eye exams. No national systems currently exist to screen for glaucoma. Screening using IOP alone is inadequate as nearly 50% of people with glaucoma have IOP in the normal range.[63] Potential screening programs have yet to demonstrate that individuals who enter the care process benefit from being identified.[64]

Innovation in screening techniques for glaucoma continues with several groups publishing high sensitivity and specificity using deep learning to detect glaucoma using fundus photographs of the optic nerve.[65,66] Currently, many countries systematically screen for diabetic retinopathy using fundus photography and potentially further development of these algorithms could result in better detection of glaucoma in this population. Other machine learning approaches to glaucoma detection using optical coherence tomography (OCT) images of the posterior segment offer possible candidates for glaucoma screening techniques. Fundus photography is already a widely available technology that could be applied in a wide range of settings including primary care clinics and public locations such as supermarkets and the department of motor vehicles. One can envision a time in the not-too-distant future where worldwide community screening for glaucoma will be widely available.

IOP Lowering Treatment

The only treatment proven to be effective for glaucoma is lowering of IOP. Numerous trials have shown that IOP lowering slows the progression of glaucoma in established disease and reduces the risk of developing glaucoma in patients with OHT.[42,43,67] All current treatments, including medical therapy, laser treatments or surgery are aimed at either reducing the production of aqueous humour, increasing the outflow or both.

Medical Therapy

First-line treatment is traditionally topical medication(s) in the form of eye drops, which either reduce the production of aqueous humour or increase outflow from the eye. Prostaglandin analogues that increase outflow via the unconventional pathway are most frequently used, with beta-blockers that reduce aqueous production as second line due to the risk of side effects from systemic absorption. Carbonic anhydrase inhibitors and alpha-2 agonists are routinely used as 3rd or 4th line therapies.[68] Combination preparations are common in many countries, but access can be limited elsewhere due to regional regulatory constraints.

Two new classes of drug have recently been introduced. Rho Kinase inhibitors, ('ROCK' inhibitors) and latanoprostene bunod. ROCK inhibitors act through direct effects on trabecular meshwork and Schlemm's canal cells (acting on extracellular matrix formation, cell adhesion TM cell contractility), thereby increasing the outflow.[69] They can also reduce reactive oxidative stress induced damage to the trabecular meshwork.[70] They are approved by the FDA and lately the EMA, although not yet launched commercially in Europe. While ROCK inhibitors can lower IOP substantially in some patients they showed a high rate of symptoms in the pivotal FDA trials.[71-73] In this context, 59% reported conjunctival hyperemia among which 5 percent discontinued their treatment. Other significant ocular adverse reactions were corneal verticillata (15%) and conjunctival hemorrhage (11%).

The second recently released drug class 'latanoprostene bunod' is a novel prostaglandin derivative that, via nitrous oxide donation and prostaglandin analogue mechanisms, acts on both the conventional and unconventional outflow pathways to lower IOP, and direct comparisons with prostaglandin drops alone show an average improvement in IOP lowering of about 2mmHg. [74]

Laser Treatments

Recent work studying OAG patients has shown that those randomized to receive selective laser trabeculoplasty (SLT) as initial treatment have better overall clinical outcomes than those randomized to medications, with not only better IOP control, but greater preservation of visual fields.[75] Primary SLT at diagnosis is now recommended as the preferred treatment by NICE (the UK National Institute of Health and Care Excellence), and as an equivalent alternative in the European Glaucoma Society Treatment Guidelines and the American Academy of Ophthalmology Preferred Practice Patterns. Lasers for angle closure are discussed later.

Surgical Interventions

Studies comparing medicines to incisional surgery as initial treatment have not shown such a clear benefit of 'surgery-first' and clinicians rarely start with surgery as primary therapy.[76] However, recent RCT evidence for treating more advanced disease with initial surgery has shown better IOP control at two years with surgery-first, which may lower the threshold for choosing surgery in eyes with significant nerve damage. Further follow up will show whether this translates into better visual field preservation.[77]

One of the major challenges in glaucoma care is adherence.[78] Glaucoma is often asymptomatic until advanced and eye drops often sting on instillation, with prolonged discomfort and sometimes red, irritable eyes. Education to help patients understand their disease, simplification of drug regime and reduction of side effects probably all improve adherence. Drops without preservatives (especially benzalkonium chloride) have several advantages such as less ocular surface irritation, but direct improvements in adherence have not been shown in clinical studies.[78-81] Alternative approaches with injectable slow-release implants (anterior chamber or sub-conjunctival) may also address this issue and, with greater use of SLT and lower thresholds for surgery, achieve more adherence-independent treatment regimes.

Surgery and Laser for Angle Closure Disease

Evidence to guide treatment for angle closure disease (Figure 4) has greatly expanded in the past decade with three definitive RCTs (ZAP, ANA-LIS, EAGLE) leading to changes in some national guidelines.

ZAP[82] and ANA-LIS[83], performed in China and Singapore respectively, studied the use of prophylactic laser iridotomy (LPI) for individuals with contact between iris and trabecular meshwork but no optic neuropathy or raised IOP ('primary angle closure suspects'). Eyes randomized to LPI had slightly lower rates of reaching study endpoints (most of which were interim outcomes and not disease development) than untreated fellow eyes, but the number needed to treat was so high that use of LPI is no longer routinely recommended unless other risk factors are present (such a regular pupil dilation, family history, antidepressant use).

EAGLE, conducted in multiple countries around the world, demonstrated a benefit from early lens extraction (ELE, *not visually significant cataracts*) in more severely affected individuals with ACG or angle closure and high IOP.[84] Individuals in that study randomized to ELE did better

than those randomized to iridotomy followed by medications both in terms of IOP control and self-reported quality of life at three years after intervention.

Surgery for Open Angle Glaucomas

This domain is undergoing rapid change with the introduction and rapid uptake of many new procedures which lower IOP, but with limited supporting evidence. Established techniques of trabeculectomy and drainage tube implants ('shunts') are effective but require intensive post-operative management and carry significant surgical risk. Trabeculectomy routes fluid out of the eye through a surgical opening in the sclera into a blister or 'bleb' beneath the conjunctiva. First described in the 1960s and significantly improved since, it remains a widely used but imperfect surgery due to failure from scarring, unpredictability, and life-long risk of infection. Direct comparison of trabeculectomy with tubes found that tubes work better at controlling IOP in eyes with prior cataract or glaucoma surgery,[85] but less well than trabeculectomy in eyes undergoing a first operation.[86]

Minimally Invasive Glaucoma Surgery or 'MIGS' is a recent term applied to a wide range of implants, devices and techniques that claim simpler, safer, quicker surgery, albeit with less IOP lowering. The term 'Minimally Invasive Bleb-forming Surgery' ('MIBS') has been suggested for the more invasive bleb-forming procedures that still require less tissue manipulation than traditional surgery. 'True' MIGS leave the conjunctiva intact (via ab interno access or ab externo cyclo-destructive procedures) with the option for later bleb forming surgery (e.g. trabeculectomy) if required. In contrast, MIBS techniques shunt fluid from the anterior chamber to subconjunctival space as with traditional surgeries, but with less anatomical disruption than traditional techniques. Nonetheless, disturbance of conjunctiva may limit success rates of any subsequent surgeries, and formation of a bleb still carries a risk of potentially sight-threatening late onset intraocular infection.

Most MIGS are combined with cataract extraction, which itself has modest IOP-lowering effects, and carefully designed randomised controlled trials are needed to define the additional contribution and duration of effect of the extra procedure. Some critics of MIGS have compared the IOP lowering unfavourably to trabeculectomy surgery, but this ignores the greater safety and higher patient acceptance of MIGS over traditional invasive glaucoma surgeries. However, the true comparator for MIGS may be continued drop therapy, rather than incisional surgery.

Deciding what surgery to perform involves consideration of the likelihood of vision loss from glaucoma, the target IOP, and the patient's preferences around different potential outcomes.

MIGS procedures form a heterogeneous group of techniques: they may bypass trabecular meshwork (TM) resistance to aqueous flow with stents into Schlemm's canal (iStent, Hydrus), via drainage into the suprachoroidal space (Cypass, iStent Supra, Miniject) or by excision of TM itself (Trabectome, Kahook Dual Blade); whereas endo-cyclodiode laser uses directly observed ablation of ciliary processes under endoscopic control to reduce aqueous production and ABiC visco-dissects the existing outflow channels. Each of these may present different challenges: supra-choroidal routes have historically failed due to later fibrosis limiting flow; Schlemm's canal routes seem to have a physiological 'floor' of around 16mmHg due to downstream resistance to flow; targeting aqueous production raises concerns about long-term hypotony risks, and it remains unclear what lasting benefit visco-dissection of existing channels will achieve (ABiC). The more invasive sub-conjunctival drainage MIBS techniques (Xen, Preserflo Microshunt) bypass physiological flow routes entirely but are subject to the same risk of failure due to scar formation by tenon's and conjunctival fibroblasts that bedevil traditional ab externo surgery.

Surgeons, at least those in higher income countries, may now choose whether to use a Hydrus microstent, iStent, Miniject, Kahook Dual Blade, endo-cyclophotocoagulation, micro-pulse external diode laser, OMNI device, GATT procedure, high-frequency ultrasound ablation or Trabectome (amongst others). Enthusiastic (often industry-led) adoption of expensive devices has mostly been without robust randomized controlled trial evidence to support their use and there are no independent cost effectiveness analyses. Nonetheless, a recent meta-analysis[87] of evidence concluded that "*based on data synthesized in Cochrane reviews, some MIGS may afford patients with glaucoma greater drop-free disease control than cataract surgery alone. Among the products currently available, randomized clinical trial data associate the Hydrus with greater drop-free glaucoma control and IOP lowering than the iStent; however, these effect sizes were small."* However in lower income countries many of these procedures remain inaccessible to all but a very few.

Patient Monitoring

Given the asymptomatic nature of glaucoma and the often slow decline in visual function, patients must be monitored frequently to assess for worsening of disease. In general, treating physicians set a target IOP for the patient based on eye pressure at presentation, disease severity and associated risk factors. Regular monitoring involves assessment of IOP, automated visual field testing and OCT imaging of the optic nerve (Figure 3). Treatment is intensified if the target IOP is not met, or if disease deterioration occurs despite achieving the target IOP.

Monitoring IOP

The 'true' IOP cannot be known without cannulating the eye - all other methods are estimations. The mean "normal" IOP is around 15 mmHg, with a standard deviation in European populations of around 3mmHg,[88,89] with slightly lower means in Asian populations. IOP is estimated clinically in several ways. Goldmann applanation tonometry (GAT), the approach most used in research and clinical practice, involves indenting a standard area of the cornea until it is flat which allows for translation of this force into mmHg. GAT requires topical anaesthesia and can be challenging to perform depending on the cooperation of the patient and the anatomy of the eye. Experienced clinicians will differ by a clinically meaningful 3mmHg nearly 10% of the time when measuring the same patient at the same time.[90]

The iCare tonometer is available and correlates well with GAT but can over and underestimate GAT IOP. The iCare does not require anaesthesia and a home use version is FDA approved for patients to monitor IOP throughout the day. Although it is available, the use of home monitoring is still not routine, largely owing to cost and logistics. However, more frequent testing at home, analogous to home field assessments, might be more predictive of the risk of future damage than occasional in-clinic measurements, even with lower test precision.

Other devices in widespread use include the Tonopen, which provides a digital readout of the IOP and therefore is easier for lay personnel to use. While correlation in the normal range is good with this device, it can be off by a large amount at high and low IOP. A further device, the Ocular Response Analyser,[91] uses a non-contact air-jet to flatten the cornea and this additionally provides measures of 'corneal hysteresis', which when low is associated with increased risk of developing glaucoma in OHT and of glaucoma worsening in OAG.[92]

Perimetry

Visual field testing documents changes in function. At present almost all visual field testing is done in clinics using custom-designed devices that present dots of light at low luminance to determine the dimmest light that can be seen at a specific location. These responses require focus and attention of the patient and are subject to significant inter-test variability that limits the sensitivity to detect change. Estimates of deviation from age-corrected normative databases facilitate determination of "normality". Longitudinal comparisons that require knowledge about normal variability over time, provide assessments of worsening based on both event- and trend-based analyses. Recent publications point to the potential of machine learning and artificial intelligence to help identify worsening visual fields more rapidly, and this likely will enter practice soon.[65,91,93]

Another novel approach to monitoring visual fields is to test patients outside the office and even in the home. Tablet [94] and virtual reality head-sets[95,96] have both been shown to perform reasonably well, but the need for longitudinal data with these devices limits their clinical use at this time. More frequent testing at home (e.g., weekly rather than once or twice yearly in clinic) may lead to earlier detection of change despite greater test-retest variability.

Optical Coherence Tomography (OCT) Imaging

Optic nerve and retinal imaging using OCT can now detect changes as small as 5 microns in retinal nerve fibre thickness. OCT imaging of the optic nerve is now an integral part of routine glaucoma care: it often detects nerve fibre layer loss before visual field loss is manifest (Figure 3). OCT devices are costly and require sophisticated software to identify change, which in turn require longitudinal databases of those with and without glaucoma which are time consuming and expensive to obtain and so remain relatively few. As a result, detecting the difference between pathological and age-related change can be difficult. The result is that while many devices are available in the market, only those of one or two companies are routinely used for glaucoma monitoring. Innovation in OCT imaging has been less rapid than that for visual field testing, but recent developments suggest that central retinal (macular) assessments with automated identification of intra-retinal layers (retinal ganglion cell layer or complex) may provide even greater sensitivity and earlier detection of both disease and deterioration.[97] The clinical relevance of very small changes in structural measures remains to be demonstrated.

Future Developments

Neuroprotection

The holy grail of glaucoma research is to identify IOP-independent approaches to reduce the risk and extent of glaucomatous optic nerve injury through neuroprotection. A randomized control clinical trial that took almost five years with an estimated cost of over $100 million, failed to show a benefit of oral memantine over placebo[98] and contributed to reluctance to add to the few trials in this area[99] for over a decade. However, refinement of trial design and advances in technology that permit earlier detection of change[67] have reinvigorated this field. This is due to improved understanding of the mechanisms underpinning RGC degeneration and neuroprotection[100,101] as well as advances in basic research to identify putative targets.[102]

High dose oral nicotinamide (Vitamin B3) was shown to have great promise in an initial crossover trial[103] with formal randomized controlled clinical trials scheduled to commence soon.[104] Despite the limited evidence supporting its use clinically, some clinicians are already recommending nicotinamide to patients that progress despite controlled IOP.[103,105] Many other nutritional supplements are widely discussed as putative neuroprotective agents (eg. Gingko biloba), but there is limited robust evidence to support these in clinical practice.[106]

Advanced Cellular and Gene Therapies for Glaucoma

Experimental strategies to address the loss of TM cells in glaucomatous eyes include the regeneration of TM using stem cells. Studies in animal models and *ex-vivo* human organoculture models have demonstrated the ability to restore IOP homeostasis and TM cellularity, thus showing future potential in this approach.[107] This may also be a potential mechanism through which SLT delivers long-term IOP lowering.[108]

A wide range of progenitor cells have been shown to regenerate RGCs in laboratory studies.[109] However, there are numerous challenges in developing a strategy for optic nerve regeneration in mammals, including modulating the molecular microenvironment, coping with the consequences of injury and inflammation, addressing the need to change the intrinsic regulation of cells to regenerate and recreating the complexity of RGC subtypes and directional cues required for them to integrate within appropriate cortical laminae.[110-114]

Mesenchymal stem cell transplantation can also confer a neuroprotective effect in part mediated by Ciliary and Brain Derived Neurotrophic Factor (CNTF, BDNF).[112] An early phase trial is

currently underway studying the safety and efficacy of intravitreal delivery of CNTF-secreting encapsulated cells in patients with glaucoma.[115] Transplantation of human Müller glia with stem cell characteristics improves visual function in experimental models of RGC depletion due to the release of neuroprotective factors. The molecular characterization of exosomes released by Müller glia containing these factors also offers an opportunity for future therapeutic clinical trials.[116]

Gene therapy approaches to promote overexpression of a variety of growth factors have demonstrated a neuroprotective effect in experimental glaucoma models and in some cases have also led to axonal regeneration,[117] however, no gene therapy approaches for the treatment of glaucoma have yet reached human trials.[118]

Further Developments & Future Challenges

We are already seeing a shift away from patient-dependent treatments (daily eye-drops) to compliance-independent therapies (laser, bi-annual drug delivery and earlier surgery). Further refinements to SLT delivery (NIH-funded COAST Trial), novel laser delivery (Belkin Direct SLT), injectable IOP-lowering drugs and more effective and safer minimally invasive glaucoma surgeries will give even more reliable IOP control. Neuroprotection remains unproven but we expect to see accessible therapies within five years, likely guided by more accurate targeting of patients most at risk by genetic risk profiling for vision loss using full genome sequencing. Refinement of trial outcomes,[119,120] and possibly in vivo detection of human RGC death for prediction of disease progression with “DARC”,[121] may speed up developments with shorter trial durations.

Systematic failures of even established market economies to identify up to half of patients with disease and rapidly increasing patient numbers due to demographic shifts remain significant hurdles to preventing glaucoma blindness. Existing inequities in access to diagnosis and treatment risk becoming ever greater with the increasing cost and complexity of care. Robust data from good quality randomised controlled trials, particularly cost-effectiveness or surgical options, become all the more vital despite the challenges of expense and complexity.

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Legends for Figures

Figure 1

Determination of intraocular pressure and the differentiation between Open Angle and Angle Closure Glaucoma. (A) The location within the eye of anatomical structures that determine intraocular pressure. (B) Intraocular pressure (IOP) is determined by the amount of fluid (aqueous humour) produced by the ciliary body (1) and the amount that leaves the eye through the drainage pathways which are located at the iridocorneal angle (2). The black arrow illustrates the direction of aqueous flow within the eye. Open Angle Glaucoma is characterized by an open drainage angle. (C) Angle Closure Glaucoma is characterized by aqueous humour being unable to reach the drainage pathways located at the iridocorneal angle, leading to elevated IOP. This may be due to a combination of mechanisms including the peripheral iris obstructing access to the outflow pathways (3) known as “angle closure” and contact between the iris and pupil obstructing aqueous flow (4) known as “pupil block”.

Figure 2

Anatomical differences between a normal and glaucomatous optic nerve. Glaucoma is characterized by the progressive loss of retinal ganglion cells (RGCs) and their axons, which form the optic nerve connecting the eye to the brain. (A) The optic disc of a healthy eye has a full rim of tissue made up of RGC axons exiting the eye at a right angle forming the optic nerve. (B) Elevated intraocular pressure leads to RGC death and loss of rim tissue resulting in characteristic “cupping” of the optic disc observed in eyes with glaucoma. (C) RGCs form the innermost layer of retina as shown in this cross-sectional diagram of a healthy optic nerve head. This specific retinal layer can be quantified using contemporary imaging techniques. (D) Afferent inputs from retinal neurons including bipolar cells and their associated photoreceptors are received by RGCs (yellow cell bodies). RGC axons (yellow axons) form the optic nerve which enables the cortical processing of visual stimuli following an initial synaptic connection in the lateral geniculate nucleus of the thalamus. (E) The retinal ganglion cell layer of glaucomatous eyes is very thin due to RGC loss as evidenced by optic disc cupping with (F) a corresponding reduction in number and health RGC nuclei and axons (red cells/axons).

Figure 3

The progressive journey from normal vision to blindness in Glaucoma. There is a transition over time from normal visual function to blindness in patients with Glaucoma. There

may frequently be no symptoms until an advanced stage of disease, highlighting the importance of screening and early detection. In addition to the measurement of visual acuity and intraocular pressure, several ancillary tests are commonly performed during the diagnosis and monitoring of patients with glaucoma. (A) Clinical examination or fundus photography can demonstrate and document the progression of optic disc cupping and neuroretinal rim thinning over time, that develops secondary to retinal ganglion cell (RGC) loss. (B) OCT imaging quantifies changes in thickness of the innermost layer of the retina around the optic disc and macula region which comprise retinal ganglion cells and their axons and can compare these to normative databases. This enables detection and monitoring of structural changes at the optic nerve head and macula that may have developed due to glaucomatous injury. Structural changes often precede deficits in visual function and therefore OCT imaging facilitates the detection of glaucoma at an early stage of disease. (C) Visual field testing allows the detection and monitoring of impairment of visual function during the disease course. Early glaucoma is often asymptomatic as there is a threshold of RGC loss below which functional damage may not be present. (D) Even in the presence of significant visual field defects, patients with glaucoma may remain asymptomatic as the brain may “fill in” the perceived picture using saccades and sensory inputs from the fellow eye. This means that patients may feel that their vision is normal until the very late stages of disease.

Figure 4

Treatment for Angle Closure Disease. (A) Aqueous humour outflow occurs in the angle between the iris and cornea at the front of the eye. (B) Angle Closure Disease is characterized by aqueous humour being unable to reach the outflow pathways located at the iridocorneal angle, leading to elevated intraocular pressure (IOP). “Pupil Block” and Angle Closure are often related to an enlarged crystalline lens impeding normal aqueous flow within the eye. (C) Replacement of the crystalline lens with a thinner artificial lens implant (lens extraction or cataract surgery) creates more space within the front of the eye allowing restoration of the normal physiological drainage of aqueous humour. (D) Laser peripheral iridotomy involves the creation of a “hole” in the peripheral iris. This creates an alternative route for fluid to drain to the outflow pathways within the iridocorneal angle and can help to lower the elevated IOP seen in angle closure disease without the need for intraocular surgery.

Table / Panel

Take Home Messages About Glaucoma
● Glaucoma is a group of sight-threatening eye diseases that in most cases become symptomatic only in the late stages of disease.
● Half of glaucoma occurs with a “normal” IOP.
● First degree relatives are at high risk of having glaucoma.
● The risk of developing blindness due to glaucoma is significant if the disease is detected late, but smaller if patients receive timely treatment.
● Treatments are evolving with innovations in medical and surgical treatments to lower intraocular pressure with clinical trials planned to study IOP-independent treatments.
● Inequities in access to treatment remain a significant and increasing challenge with many new therapies unaffordable for large numbers of patients.

Figures

Figure 1

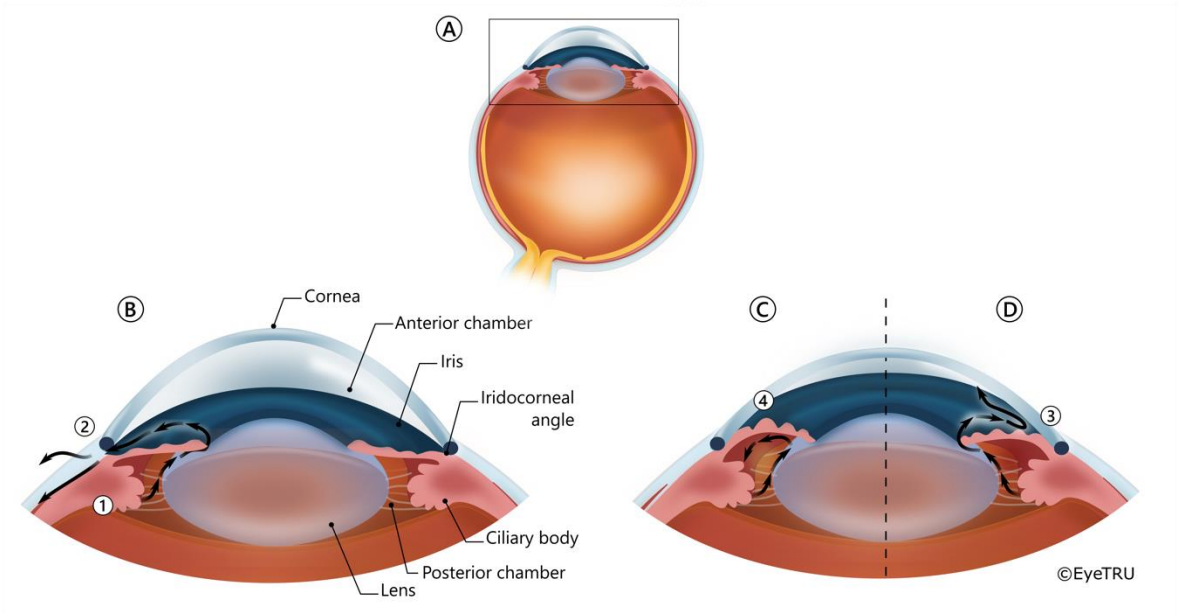

Figure 2

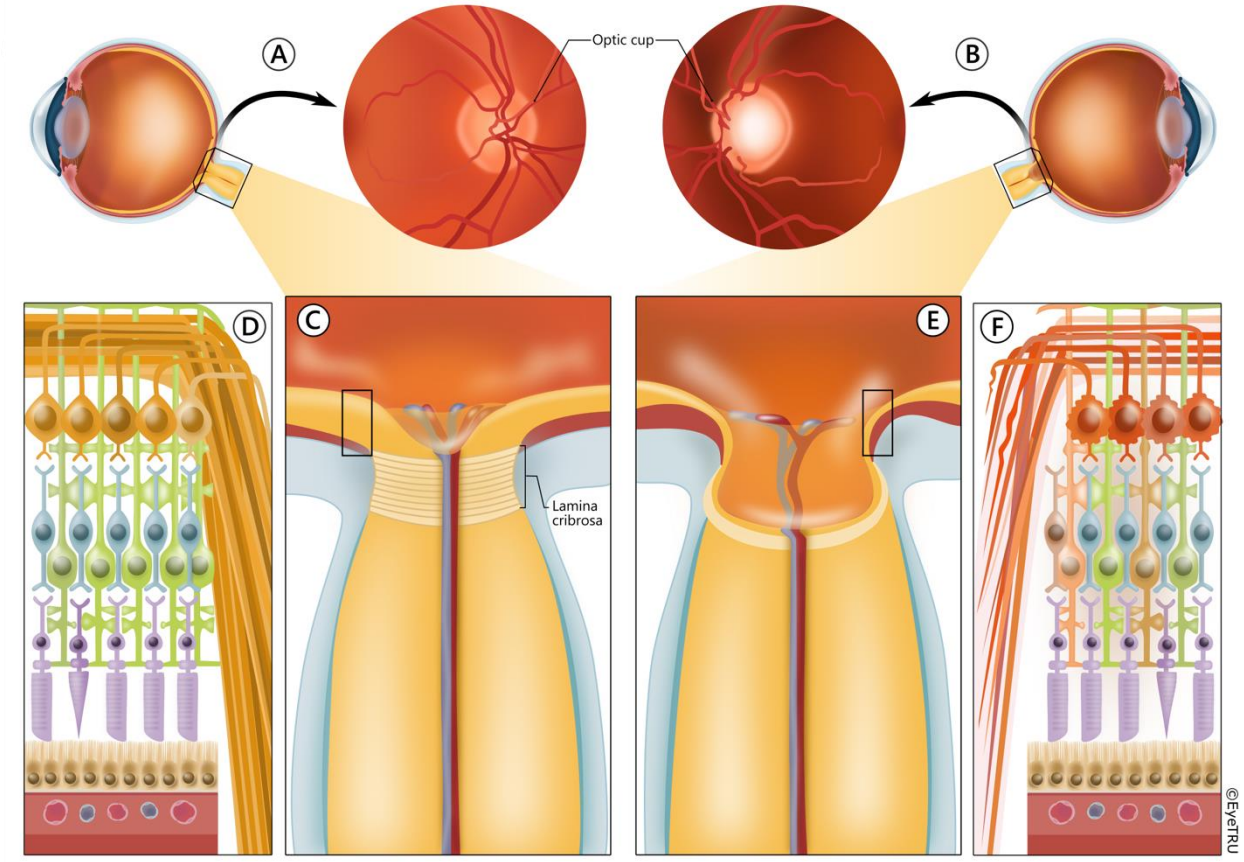

Figure 3

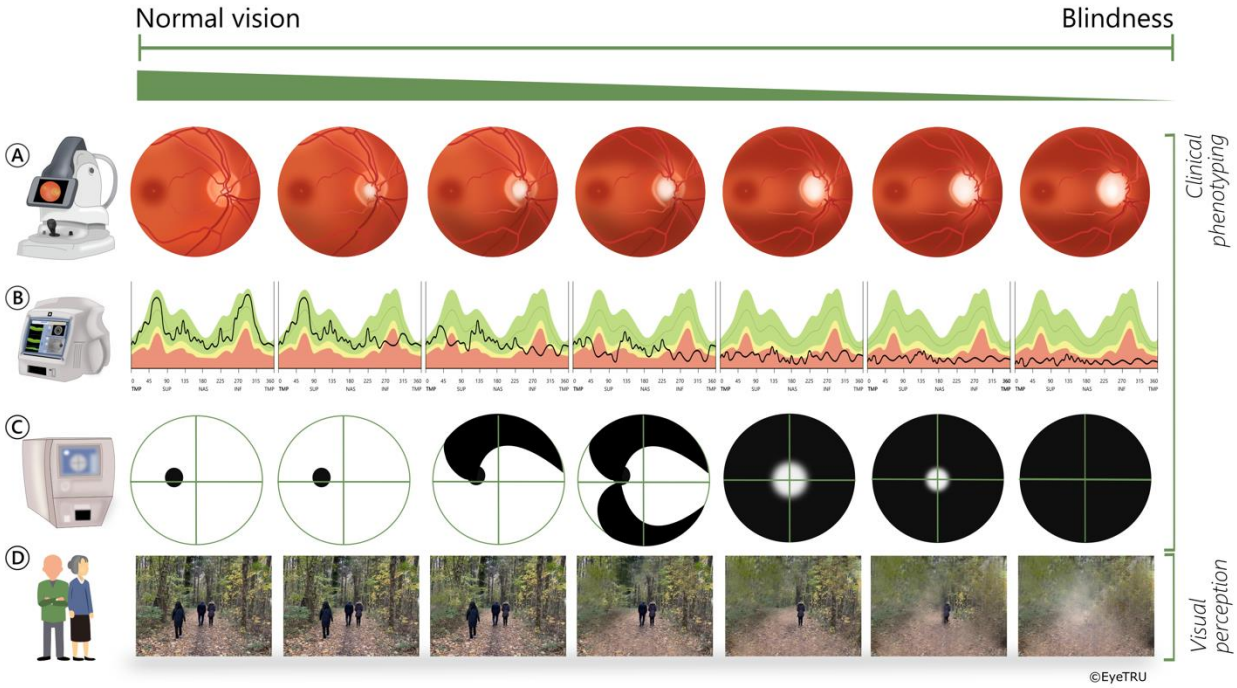
Normal vision
Blindness
A
B
C
D
Clinical phenotyping
Visual perception
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Figure 4