Redefining clinical outcomes and endpoints in glaucoma

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Summary

Introduction: Increasing life expectancy and ageing populations across the world are causing the number of glaucoma patients to rise dramatically. With longer lifespans also comes the need to improve the timeframe and accuracy with which we can diagnose, monitor and treat patients, ensuring longevity of vision contributes to a meaningful quality of life. Current markers used in glaucoma practice are in many cases suboptimal in their ability to accurately identify glaucomatous damage in time to prevent irreversible optic neuropathy. **Areas covered:** This review summarises the important properties of successful biomarkers and surrogates, and relates this to how intraocular pressure, visual field testing, and imaging have been refined to improve early diagnosis and progression analysis of glaucoma patients. Secondly, we discuss newer concepts in imaging, genetics, and objective measures which may provide biomarkers and surrogate endpoints with which to develop novel treatments in the future. **Expert Commentary:** We summarise the key relevant points in glaucoma research, and the current techniques being trialled that are most likely to lead to valuable biomarkers for the future.

Keywords

Glaucoma; biomarkers; endpoints; surrogate marker; neurodegeneration.

1. Introduction

1.1 Tackling the burden of disease

Glaucoma is one of the leading worldwide causes of irreversible blindness [72]. It was estimated that in 2010 there were 60.5 million sufferers worldwide, with this figure projected to rise to 111.8 million by 2040 [216]. However, the Ocular Hypertension Treatment Study (OHTS) demonstrated that only 9.5% of those with untreated ocular hypertension develop glaucoma [114]. Considering this, we must aim to develop diagnostic tools with high specificity to identify patients who will not progress to glaucoma in their lifetime. Conversely, it is crucial we develop new tests with high sensitivity in order to manage and monitor treatment early, for those at risk of blindness. Finding new ways to detect ocular neurodegeneration will also help to uncover the underlying pathological processes and identify novel treatments.

The need to improve glaucoma diagnosis and monitoring is especially pertinent in the developing world where the number of eye-care professionals is struggling to match the targets set by Vision 2020 [168]. Moreover, these patients are often at higher risk of glaucoma and more likely to develop severe disease and blindness [125], whilst potentially vulnerable to widening health inequalities if not able to access new technologies. Hence, novel techniques must simplify the acquisition process, avoiding reliance on operator skills or patient ability in order to achieve the most reliable, universally accessible and transferrable data. New ways of monitoring stable and low risk glaucoma patients such as virtual clinics have been developed to meet the capacity of national healthcare systems [48].

This review aims to highlight the characteristics of valuable surrogate markers and endpoints, and discuss how those currently used in research and clinical practice have been improved and extended. Secondly, we will explore exciting novel endpoints and biomarkers that have potential to change the way we monitor glaucomatous degeneration, testing new treatments and hopefully identify early disease.

1.2 Defining terminology: biomarkers, clinical endpoints and surrogate endpoints

A *biomarker* is shortened form for a biological marker, with the most widely quoted definition by the National Institutes of Health Biomarkers Definitions Working Group [28] as:

> *"A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention"*

A *clinical outcome* or *clinical endpoint* is seen from the patient's point of view, and defined as [55]:

> *"A characteristic or variable that reflects how a patient feels, functions, or survives"*

A *surrogate marker* is used as a predictor of a clinical outcome. These are often regarded as more readily accessible and faster measures of treatment response or disease activity [171]. In addition to correlating with, and predicting the clinical outcome, a surrogate marker must comprehensively 'capture' the effect of treatment on the clinically relevant endpoint. Prentice

suggested four criteria for surrogate markers; (1) the surrogate endpoint has a significant impact on the true end point, (2) treatment has a significant impact on the surrogate endpoint, (3) treatment has a significant impact on the true endpoint, (4) the full effect of treatment on the true endpoint can be captured by the surrogate [176]. However, these have not been without controversy. Berger discusses the complexities of assumptions using surrogate markers, pointing out that if a surrogate endpoint is validated using one treatment, how is it possible to progress to using this endpoint to trial a different treatment as one would have to already know that the new treatment has a significant impact on the true endpoint to satisfy the criteria [27]. This also serves as a reminder of the risks and benefits to be weighed up before using a surrogate marker, to avoid harm [73].

1.3 Using biomarkers and clinical outcomes in glaucoma research and clinical practice

In chronic conditions such as glaucoma where patients can progress slowly and are followed up over long periods of time, it is important to obtain reliable indices to benchmark progression and gauge effectiveness of treatments on outcomes that are clinically relevant. Ideally, we would be able to take into account visual disability when making treatment decisions, however quantification of such a qualitative parameter is challenging.

In glaucoma, the 'gold standard' test for estimating a patient's visual impairment from field loss is standard automated perimetry (SAP). However, visual field defects can take many years to develop, during which the process of irreversible Retinal Ganglion Cells (RGCs) damage occurs [150]. For this reason, surrogate endpoints are under investigation aiming to reduce the cost and duration of clinical trials and expedite the release of new treatments [235]. A surrogate endpoint that is used in both clinical and trial settings can provide prognostic information and evidence-based treatment decisions. Aside from Prentice's criteria, more practical properties

of a good marker include ease with which it can be recorded, interpreted, and its cost-effectiveness. As we recognise glaucoma as a heterogeneous group of conditions with multifactorial pathogeneses, we will need to be specific about which biomarker is most appropriate to fully capture the characteristics relevant to each patient's individual disease pathology [139].

2. Current markers and endpoints

2.1 Intraocular pressure

Intraocular pressure (IOP) is the only modifiable risk factor in preventing the onset and progression of glaucoma. The 'gold-standard' technique for estimating IOP is Goldmann applanation tonometry quoted as having reasonable repeatability (R_{95}=2.0 mmHg, CV 4.9%) and reproducibility (95% limits of agreement = -2.0 to 3.4 ± 2.7mmHg) under test conditions [209]. Whether it is the peaks or fluctuations in intraocular pressure that is most harmful, getting an accurate assessment of either measure from sporadic clinic visits is challenging [15]. Furthermore, different factors can affect readings including corneal thickness [200], IOP diurnal variation [15, 52, 79, 198], widening or narrowing of the palpebral fissure [103, 156], the Mueller or Valsalva manoeuvres [140, 187, 227], recent exercise [130, 148, 186], and positioning [213]. Diurnal variation alone has been shown to be up to 6.4 ± 1.4 mmHg in healthy subjects and 10.3 ± 2.0 mmHg in glaucomatous subjects. The majority of peak values occur in the morning around 7-9am before patients are typically seen in clinic [198]. IOP "phasing" throughout the day, is used to evaluate IOP fluctuation, however this is time consuming and possibly lacks reproducibility in itself [205].

The OHTS has demonstrated that lowering IOP reduces the rate of conversion to glaucoma in ocular hypertensive patients (NNT (number needed to treat) = 20) [90, 100, 114]. Given the

rapid response to treatment, and the fact that it is the target of all currently available therapies, IOP has been the biomarker of choice in glaucoma trials. However, it has been shown 4.4% of patients with adequately treated IOP will still progress to glaucoma [114]. This indicates that IOP is an imperfect surrogate marker for glaucoma progression. The Collaborative Normal-Tension Glaucoma Study (CNTGS) has shown that reducing IOP also prevents disease progression in 'normal-tension' glaucoma (NTG) [63, 220]. One study by Krupin et al. questions whether this is a purely pressure-dependent effect as they found a significantly lower rate of visual field progression with brimonidine (9.1%) when compared to timolol (39.2%, P=.001) despite comparable IOPs [122], suggesting a potential neuroprotective effect of brimonidine, with some provisos [46].

The use of IOP fluctuation as an independent risk factor and possible biomarker in glaucoma has been debated, with varying results [15, 25, 152]. To further characterise IOP variation and the biomechanical properties of the eye, several continuous IOP monitoring systems have been devised [60]. Over a few seconds, dynamic contour tonometry (DCT) has been used to show IOP fluctuations within the cardiac cycle (ocular pulse amplitude, OPA) [174, 178]. IOP monitoring over longer periods has been achieved with a contact-lens based system [146], or implantable devices inserted into the ciliary sulcus or orbital wall [61, 121]. This latter system was explored in non-human primate glaucoma models and concluded that IOP variation did not predict any change in retinal nerve fibre layer thickness [77]. However, it did highlight how changes in body positioning significantly influenced IOP, with supine and lateral decubitus (dependent eye) positioning causing a rise in IOP [224].

2.2 Structural biomarkers

Understanding the structure-function relationship between the optic nerve head (ONH), retinal nerve fibre layer (RNFL) and visual field defects is crucial to being able to identify biomarkers

that predict which patients will go on to develop visual loss. Often, progressive RNFL thinning and loss of neuroretinal rim (NRR) with characteristic cupping of the disc occurs prior to the development of visual field defects [3, 252]. In 'pre-perimetric glaucoma' patients[183], this lead-time has been estimated to be around 2 years on average, stretching to as long as 8 years in up to 19% of cases [123, 249]. It is during this gap that detection of structural changes ideally should be made in order to initiate treatment before functional damage occurs. However, in patients with advanced disease, a 'floor effect' of neuroretinal rim thickness has been reported. This is suspected to consist of glial cells and blood vessels beyond which accurate segmentation of layers on OCT images cannot occur [29, 181], indicating the need for alternative biomarkers to monitor these patients.

In order to image the earliest structural changes, the exact site of cellular injury to the RGC needs to be considered. Most recent experimental evidence supports axonal injury as the culprit leading to retrograde cell death [10, 184]. It has been proposed that damage to the RGCs may occur at the level of the lamina cribrosa by impedance of axonal transport flow as the trigger for eventual apoptosis at the cell body [62]. Considering the increasing sensitivity and specificity of retinal imaging devices, the National Eye Institute (NEI) and Food and Drug Administration (FDA) Center for Drug Evaluation and Research have recommended that the use of structural biomarkers as a surrogate for visual outcomes in glaucoma could be used, as long as they can be proven to predict clinically relevant functional change [235].

Ophthalmoscopic estimation of cup-disc-ratio is unreliably subjective [112, 214] and has been superseded by advances in imaging technology. Structural characteristics of the optic nerve can be objectified using imaging modalities such as stereoscopic photography [18], confocal scanning laser ophthalmoscopy (cSLO) [39], scanning laser polarimetry (SLP) [236], and optical coherence tomography (OCT) [196]. Of these, the most widely used in current clinical practice is OCT, which has been quoted as having a sensitivity and specificity of 83% and 88%

respectively for detecting significant RNFL abnormalities [35], in addition to good repeatability [58] [212]. Furthermore, images are quick to acquire and the acquisition process is well tolerated by patients, with optical media opacities being the major limiting factor for this technology [99, 127].

Current spectral-domain OCT (SD-OCT) scanning protocols in glaucoma aim to assess either the optic disc where RNFL thickness, minimum rim width, neuroretinal rim (NRR) area and cup volume can be measured, and the macula region where the thickness of the ganglion cell complex (GCC) can be mapped out. Baseline structural parameters as predictors of progression have been investigated to assess the implications of imaging on initial consultation. RNFL thickness (Area Under Receiver Operating Characteristic curve = 0.839, 95% CI 0.757 - 0.921) and Bruch's membrane opening-minimum rim width (BMO-MRW) (AUROC curve = 0.821, 95% CI 0.731 - 0.921) [81] have good ability to distinguish pre-perimetric patients from healthy controls at baseline. GCC focal loss volume (AUROC curve = 0.753, 95% CI 0.683 - 0.814), and nerve fibre layer (NFL) focal loss volume (AUROC curve = 0.655, 95% CI 0.583 - 0.728) [255] were also found predictive of future progression amongst glaucoma suspects and pre-perimetric glaucoma patients to varying degrees. Incorporating baseline structural parameters into composite markers with corneal thickness, age and visual field indices has been shown to marginally improve accuracy in certain studies [254, 255].

Progression analysis of structural markers as a potential surrogate marker might be a more useful concept. When imaging the same patient longitudinally, all the variables present in the instruments' normative database are mitigated [191]. Longitudinal studies [40, 135, 149, 153, 154], have shown the predictive value of structural progression having hazard ratios quoted up to 8.44 (95% CI 3.30-21.61) when using trend-based progression analysis of serial RNFL thickness maps [249]. As to whether structural parameters measured by OCT are a true

surrogate marker for visual field progression is yet to be fully answered. Using cSLO, a previously widespread method for detecting structural progression in glaucoma, NRR area measurements were shown to satisfy Prentice's criteria for surrogacy, with 65% of IOP-lowering treatment effect 'captured' by this marker [151], possibly indicating similar potential for other imaging modalities.

Swept-source OCT (SS-OCT) technology uses a longer wavelength (1050nm) than spectral domain OCT (SD-OCT) (840nm) enabling it to image more of the deeper ocular structures such as the posterior lamina cribrosa surface and the choroid [145], whilst providing similar diagnostic accuracy to SD-OCT [247]. Greater tissue penetration could allow for further studies on the biomechanics of the lamina and its effect on axonal transport and cellular damage [62]. The features of the lamina associated with glaucoma include the depth of the anterior surface and insertion [74] [169] [128], shape [223], thickness [164], and focal defects [211, 248]. Lamina cribrosa depth has also been shown to be significantly different between high-tension and normal-tension glaucoma subtypes [131] implicating intraocular pressure in these observations. With regards to monitoring progression and disease activity, the rate of change of posterior lamina displacement has been shown to predict the progression of visual field defects [245]. However, with both anterior and posterior depth displacement in glaucoma having been reported, this biomarker is yet to be fully characterised [246]. The significance of choroidal thickness (CT) measurements using SS-OCT in glaucoma is more controversial with the literature presenting conflicting results [204, 229, 253, 256].

OCT angiography is a new technology which uses the extreme speed of second generation SD- and SS- OCT to evaluate retinal and choroidal microvasculature. In glaucoma, it has been used to assess the optic nerve and peripapillary regions [94, 106]. Initial studies have shown significant reductions in peripapillary blood flow and vessel density [136, 231], which strongly

correlated with RNFL thickness (Pearson R range: 0.652 to 0.771, P ≤ 0.0046) [94]. Further studies have demonstrated a strong correlation between reduction in retinal blood flow in the temporal peripapillary zone and the presence of paracentral visual field defects in glaucoma patients [95]. Furthermore, a recent proof-of-concept study has shown the possibility of capturing treatment effect using this technique; in a young cohort of newly diagnosed glaucoma patients treated aggressively with IOP lowering medications, an increase in peripapillary capillary blood flow was inversely correlated with the IOP values [93]. Further work in a larger number of patients is needed to prove the significance of these initial findings in OCT angiography, as a potentially useful surrogate marker in investigating and treating the possible vascular component of glaucoma [41, 69, 198].

Adaptive optics (AO) is a technology that can improve the real-time resolution of optical systems by using a deformable mirror to reduce optical aberrations [132]. Previously incorporated into fundus cameras and cSLO, AO in OCT combines the superior axial resolution of OCT with the ability of AO technology to improve lateral resolution, increasing three-dimensional resolution of optic nerve head and retinal imaging to a theoretical 3 μm^3 / voxel [59]. In glaucoma this can enable visualisation of RNFL axon bundles [118], with initial studies demonstrating double the light reflectivity from these fibres when compared to surrounding tissue [117]. This brings the potential for a new biomarker to monitor progression in the specific cell type of interest in glaucoma, and with good reproducibility [117]. There is also some evidence to suggest reflectivity may reduce prior to RNFL thinning, allowing for earlier diagnosis [98]. As with SS-OCT, AO-OCT has been shown to image the lamina cribrosa including its posterior surface [202]. The addition of AO technology to SS-OCT in the future is likely to provide an excellent combination of depth penetration and resolution [107], and therefore further characterise the lamina changes in glaucoma that may become future

surrogate markers.

2.3 Visual Fields

Visual field testing (perimetry) is currently the gold standard method to monitor visual loss in glaucoma. Automated Humphrey (Carl Zeiss Meditech, Dublin, CA) or Octopus (Haag-Streit) static visual field analysers are the most widely used as they are quick and less operator-dependant than kinetic perimeters, with the latest threshold algorithms able to assess one eye in less than 4 minutes [24, 172]. The number of points corresponding to the area of retina being tested depends on the schedule chosen, with 30-2, 24-2 and 10-2 settings indicating points 30, 24, and 10 degrees from the central point of fixation respectively at which light sensitivity is measured. A reliable test requires a patient to fixate on a point and maintain concentration. Furthermore, an obvious learning effect has been documented, suggesting more than one and preferably at least three baseline visual fields should be used to assess glaucoma severity [76, 172]. For the significant number of patients with multiple comorbidities including those causing fatigue, musculoskeletal disease or dementia, it can be challenging to maintain the physical posture or the mental concentration to produce acceptable reliability indices such as low fixation losses, low false positives and low false negatives.

There are several factors that limit the performance of standard automated perimetry (SAP) in both clinical and research settings. During the lag time between onset of glaucomatous optic neuropathy and clinically detectable visual field defects ('pre-perimetric glaucoma') [165], it has been estimated that between 20-30% of RGCs are lost [150, 182]. Progression is also typically slow in POAG with only 5.6% of patients reported to be progressing faster than -2.5dB per year [89]. This could foreseeably affect the prompt initiation of treatment, or the choice of SAP as the primary outcome in clinical trials. One study has estimated that four-monthly testing would be required to reliably identify a mean deviation (MD) change of 4 dB

over the space of 2 years, a target that is difficult to meet in a public-funded clinical setting [36]. The first prospective placebo-controlled study to demonstrate the efficacy of a single drug using visual fields (24-2) was the United Kingdom Glaucoma Treatment Study (UKGTS). This showed latanoprost treatment in newly diagnosed POAG patients reduced the rate of visual field progression over a 24-month period [78]. The authors reported that their comparatively short duration was enabled by using altered event-based criteria from the Early Manifest Glaucoma Trial (EMGT), frequent visual field testing, and a large sample size (n=516). Previously, large trials monitoring visual field progression had 3 to 9 year follow-up [11, 90, 157]. This contrasts with the original latanoprost studies using IOP reduction only as the end point, over 6 to 12-month periods [32, 33, 233].

Progression of visual field defects is an important endpoint representing glaucomatous disease activity, as it has been shown that short term linear progression analysis is able to predict future progression [26]. Commonly, this is gauged in a subjective manner in the clinical context of the patient, but relies on observer experience. Objective progression analysis can be conducted in a trend-based, event-based or cluster-based manner. Trend-based analysis examines the variation in sensitivity within a complete series of visual field tests. Often change in mean deviation (MD) or visual field index (VFI) is analysed, however, global indices may be less specific for progression as certain points are affected more than others in glaucoma [23, 26, 226]. Pointwise linear regression (PLR) is the most commonly used trend-based analysis, using a linear regression model to test the significance of change of sensitivity for each point in the field, such as PROGRESSOR software [241]. Developing from this, permutation analyses of pointwise linear regression (PoPLR) has since been shown to be able to provide an overall statistical significance value of an individual patient's visual field deterioration by comparing the observed series to many different order permutations [162]. In combining PLR with a binomial test, it has been proposed the results can also be improved in consistency [113]. Most

recently, analysis with non-stationary Weibull error regression and spatial enhancement (ANSWERS) has been developed to take into account increasing variability in sensitivity as the differential light sensitivity reduces, as well as spatial correlation between test locations, providing increased sensitivity for visual field progression when compared to PoPLR [257]. Event-based analysis examines change from the baseline test and therefore requires fewer consecutive examinations. When change in sensitivity is outside that which would be physiologically expected, a point is registered as progressing. This approach has been used in the Glaucoma Progression Analysis (GPA) software which indicates pointwise levels of change in sensitivity [13] in addition to suggesting "possible" or "likely" progression according to the quantity of progressing points in a number of consecutive visits. When trend-based and event-based analyses are compared head to head, event-based GPA shows earlier and more sensitive detection of progression, with only moderate agreement with VFI [34]. Cluster-based analysis is a further variant used to detect progression in sensitivity of point clusters [37, 158]. This is to try to improve upon global indices which may provide inadequate sensitivity, and individual test point analysis susceptible to between-point dispersion and background noise [144, 161], and has been shown to correlate with the location of optic disc changes [30].

10-2 field tests are becoming increasingly recognised as a useful endpoint to detect paracentral visual field defects, often the most detrimental to quality of life [1]. This is due to the finding of significant paracentral visual field defects even in early glaucoma [64] [194, 221]. The superior sensitivity for parafoveal defects of 10-2 testing over 24-2 testing is achieved by having 68 points in the central ±10 degrees of visual field, in contrast to only 4 points in the central ± 8 degrees in 24-2, representing approximately 30% of retinal ganglion cells [49]. Significantly, up to 39.5% of glaucoma suspect eyes and 61.5% of glaucomatous eyes were found to contain central visual field abnormalities on 10-2 that were not detected with the 24-

2 protocol [56]. This indicates that 10-2 visual fields may be a vastly underused endpoint in glaucoma. Pointwise linear progression analysis has also shown to have superior sensitivity using this protocol in patients with parafoveal scotomas [170] [57]. Furthermore, In advanced glaucoma, testing the remnants of the central papillo-macular bundle with a higher density of points is thought to be more valuable, compared to the standard 24-2 protocol [189, 234].

Frequency-doubling perimetry (FDP) uses high-frequency flickering (greater than 15Hz) that doubles the apparent spatial frequency of a grated target presented to the patient [9]. This method was originally thought to selectively test the function of large-diameter M_y cells of the magnocellular ganglion cell pathway [143], however further work has cast doubt on this theory [237, 251]. Regardless of its exact mechanism, first- and second- generation FDP has shown promise both in screening and detection of early visual field defects. Whilst being more portable than a Humphrey field analyser enabling its use by mobile optometrists, the large targets also mean it is less affected by refractive error (up to 6 dioptres). Patients may also wear their own spectacles, with each eye only taking 30 seconds to 2 minutes to test (depending on visual field defects) compared to that of 4 to 7 minutes on Swedish Interactive Threshold Algorithm (SITA) 24-2 fast and standard protocols, respectively. In addition to these favourable practicalities, baseline characteristics have been shown to match and in some cases be superior to SAP, including improved reproducibility especially in areas of reduced sensitivity [38, 173, 208]. FDP testing locations have been adjusted to match the Humphrey 24-2 perimetry grid (*Humphrey Matrix FDT perimeter*, Carl Zeiss Meditec, Dublin, California, USA) allowing for head-to-head comparisons; significant diagnostic correlation was shown (p<0.001 for MD and PSD) [12, 129]. Again, FDP technology was able to match and even modestly improve the sensitivity in detecting early glaucomatous damage, [97, 110, 129, 137] however no improvement in monitoring progression of established glaucoma was found [96].

Microperimetry is a technique useful for testing retinal sensitivity in the context of poor fixation. Tracking fundus landmarks allows compensation for any eye movements during testing. Historically mainly used by macula specialists, this technique can also help in glaucoma patients with co-existent macular pathology or advanced centre-involving visual field defects. The *Compass* microperimeter (CenterVue, Padova, Italy) has been designed especially for this use, evaluating the central 30° of retina [193]. In glaucoma, the remit of microperimetry has largely been in research to accurately monitor macular sensitivity in combination with ganglion cell complex imaging to better understand structure-function relationships [91]. Clinically, it has been shown to have better sensitivity than SAP for early field defects where corresponding OCT changes are found [134, 190].

Home monitoring of visual fields has become a possibility, given the increasing ownership of affordable computerised devices with high quality screens (in terms of viewing angles and resolution) [14, 210]. By using these planar screens as a 'tangent' perimeter, the increased frequency of testing could expedite the 'learning curve' that patients undergo with such tests [76]. These could also serve to increase accessibility for housebound patients with home optometrist visits, and self-assessment. Examples which both demonstrate good correlation with SAP include the *Melbourne Rapid Fields* application [119] and the *Visual Fields Easy* app (George Kong Software) [111]. With integrated user-facing cameras in most mobile devices, there is also the potential for head and eye movement tracking to be incorporated into the testing procedure [111]. With regards to progression analysis, a computer model simulation has proposed that weekly home monitoring can increase the sensitivity with which we detect significant progression in mean deviation [8]. This may be made possible by improving retest variability with increased test frequency. The results suggested a sensitivity of 80% for detecting rapid field loss could be achieved in 0.9 years with weekly home monitoring (63%

home monitoring compliance) compared to 2.5 years with traditional 6-monthly clinic visits. This would provide a potentially significant lead-time in which to treat patients.

3. Defining future biomarkers and outcomes

3.1 Detection of apoptosing retinal cells

Glaucoma is a neurodegenerative disease similar to Alzheimer's, Parkinson's, and motor neuron diseases [51, 80]. In glaucoma, visual loss is a result of apoptosis and death of retinal ganglion cells [75, 179, 185] associated with progressive axonal loss and atrophy of the visual pathways [85, 250].

DARC (Detection of Apoptosing Retinal Cells) [44] is a novel technique which holds potential as a surrogate marker for glaucoma [47]. This technique uses fluorescently labelled Annexin 5 (ANX776) to visualise and quantify individual retinal cells undergoing apoptosis as a marker of disease activity. Whilst radiolabelled annexin has been used to quantify apoptosis in other tissue types such as in the myocardial infarct, brain and tumours [92, 126, 218], the resolution with which this can be detected in more opaque tissue types is uniquely surpassed in the eye due to its clear optical media, enabling single-cell resolution imaging. This might offer the opportunity to investigate the effect of apoptosis modulators, and the possibility of finding a reversibility window in the apoptosis and stress process during which to rescue cells marked for destruction [45].

ANX776, has so far been shown to be safe for human use and proven to demonstrate significantly higher DARC counts (total number of unique ANX776-labelled spots) in glaucoma patients compared to healthy controls (2.37-fold DARC count, 95% confidence interval: 1.4–4.03, P = 0.003) [47]. As a possible endpoint, it potentially holds advantages over current gold-standard techniques in several respects; for 'pre-perimetric' patients, the potential for earlier diagnosis before irreversible field defects occur is suggested by post-hoc analysis

demonstrating a significant relationship between DARC count and rate of progression [47]. In terms of its lack of susceptibility to patient-factors, DARC may be able to quantify the disease activity in those who are not able to complete a visual field test due to lack of comprehension or concentration ability. Patients with unusual disc morphologies such as in myopia, along with extremes of central corneal thickness and corneal pathology may also stand to benefit, however it is likely that significant corneal opacities would also prevent an accurate DARC count, although due to the fluorophore being in the NIR spectrum, its penetration is superior to 488 dyes.

DARC has been shown to possess the potential to trial new treatments, successfully demonstrating the effect of the known neuroprotective antioxidant, coenzyme Q10, in an experimental model. It was able to demonstrate a pressure-independent neuroprotective effect in rats, in keeping with post-mortem Brn3a histological assessment of whole retinal mounts [53]. Another study has used DARC in a rotenone-induced rodent model of Parkinson's disease, demonstrating the protective effect of rosiglitazone on neurodegeneration [160].

3.2 Molecular biomarkers

The role of genetic and molecular biomarkers in glaucoma has expanded with the increasing sophistication of laboratory techniques, high powered computer-aided analysis and statistical methods. In POAG, approximately 16-20% of disease risk has been attributed to genetic factors, with first and second degree relatives shown to be at increased risk [230, 243]. Through genome-wide association studies (GWAS), large numbers of genomes have been studied to compare single nucleotide polymorphisms (SNPs) in individuals with and without a disease phenotype [31, 159]. These studies have highlighted many susceptibility loci for POAG [19, 68, 138, 238] such as *TXNRD2* involved in mitochondrial function, *ATXN2* which is implicated

in other neurodegenerative disorders [66, 177], and *FOXC1* important in anterior segment development (Axenfeld-Rieger syndrome). However, the number of specific gene biomarkers has so far been limited, with less than 10% of cases predicted to be due to specific mutation inheritance.

Examples of individual genes which have been associated with significant glaucoma risk include the myocilin (*MYOC*), optineurin (*OPTN*) and TANK-binding kinase 1 (*TBK1)* genes. *MYOC* mutations have been associated with up to 36% of juvenile-onset open-angle glaucoma [86, 201, 232] compared to only 3 to 5% of all POAG cases [71]. It is expressed in most ocular tissues and has been proposed to be the culprit of a gain-of-function mutation causing abnormal protein aggregation and restriction of trabecular meshwork aqueous outflow [4, 101, 115, 240]. Furthermore, the autosomal dominant inheritance pattern has been shown to correlate to juvenile-onset cases, enabling earlier monitoring and prompt treatment when detected [206, 207]. Significantly, detection of *MYOC*-related glaucoma patients has also led to the possibility of trialling gene therapy to treat this condition [102]. Animal models of *MYOC* mutations have shown contradictory results [82, 199]. The *OPTN* and *TBK1* mutations are also autosomal dominantly inherited and have been found to be associated with 1-2% of NTG cases [5, 17, 192]. *TBK1* genes represents a kinase protein that phosphorylates the autophagy receptor optineurin [155, 239] which is also implicated in amyotrophic lateral sclerosis, another neurodegenerative condition [147].

In contrast to this aforementioned minority, most of the inheritability of POAG is likely to be complex in nature, with certain polymorphisms associated with particular characteristics of the disease. For example, variants in cyclin-dependent kinase inhibitor 2B (*CDKN2B-AS1)* as well as the sineoculis homeobox homolog 1 and 6 genes (*SIX1* and *SIX6*) are associated with

variation in cup-to-disc ratio [188]. Variants of the atonal homolog 7 region (ATOH7) are associated with optic disc size [142], and the transmembrane and coiled-coil domains 1 (*TMCO1*) and growth arrest-specific 7 (*GAS7*) are associated with variation in IOP [225]. Most crucially, *TGFBR3-CDC7* has been associated with visual field progression (HR 6.71 p=0.003) [222] which in the future could serve as a useful biomarker in risk analysis with the increasing availability of genetic testing. As more genes are identified, these biomarkers can be implemented in animal models to test genotype-specific treatments [258] that may form a large part of the personalised medicine of the future. However, genetic testing must also be weighed up against the risk of over-diagnosis and over-treatment of patients with suspect genotype, but no evidence of disease [42].

In the case of pseudoexfoliative (PXF) glaucoma, the *LOXL1* polymorphisms have been associated with disease [2, 219] [116] [65] . Given PXF glaucoma is often more aggressive [83, 88], this could potentially be useful in diagnosis and early treatment. However, PXF can also be detected on clinical examination therefore the clinical advantages of using genetic tests are yet to be validated. Furthermore, the difference in PXF prevalence in different populations is not explained by a corresponding difference in *LOXL1* allele frequency, suggesting the regulatory genes controlling transcription of *LOXL1* may be the real subject of interest [67]. Studies have shown changes in the rates of *LOXL1* gene transcription and resultant protein formation in different stages of pseudoexfoliative glaucoma [195] indicating that measuring gene expression or lysyl oxidase concentrations could provide a future clinical surrogate marker of disease activity or even a treatment target.

Protein markers are used to monitor diseases in other areas of the body such as prostate cancer [133]. Proteins that are found to be upregulated in glaucomatous eyes are currently being used in research as targets for investigating pathogenesis and novel neuroprotective treatments.

Those that have been associated with POAG are many, including apolipoprotein B and E [43], myotrophin and heat shock proteins including crystallins [215, 217]. One example is growth differentiation factor 15 (GDF15) which has been shown to increase in levels in the aqueous following RGC axonal injury, as well as being associated with worse visual fields [20]. Taking crystallins as another example, these are molecules expressed in the lens and retina and upregulated during retinal damage such as trauma, ischaemia and macular degeneration. Therefore they are thought to play an important role in retinal repair and axon regeneration [141, 217]. In rat ocular hypertension models it has been shown that intravitreal crystallin injections have neuroprotective properties for retinal ganglion cells in terms of cell loss and nerve fibre layer thinning [6, 7].

Autoimmunity is thought to play an important role in the pathogenesis of neurological conditions such as multiple sclerosis [120] and Alzheimer's disease [50]. Therefore it is not surprising that many specific immune profiles and pro-inflammatory cytokines have been found to be present in glaucoma patients, in both blood and aqueous humour samples [84, 108, 109]. Specific IgG antibody patterns have been found in POAG, NTG and healthy individuals [108] indicating the potential role for immune screening and immune specific therapies in glaucoma [22, 197] .

3.3 Quality of life indicators

The ultimate aim in preserving vision is to maintain quality of life (QoL) for patients. However using QoL as a surrogate marker in research or clinical practice is challenging as it is subjective, multifactorial, and can alter according to unpredictable timeframes [180]. In an effort to standardise QoL, questionnaires have been created relating to physical, emotional, psychological and social wellbeing, closely in line with the World Health Organisation's

(WHO) definition of health: 'A state of complete physical, mental, and social well-being not merely the absence of disease' [166]. These include general quality of life questionnaires such as the WHO's WHOQOL [175, 203], and SF-36 [124, 242]. Vision-specific quality of life is assessed in more detail in patient-reported outcome measures such as the NEI-VFQ [167], independent mobility questionnaire [70], and the glaucoma-specific glaucoma symptom identifier [228] covering topics such as eye discomfort, drop side effects, and a variety of visual activities . It follows that we must take into account the effect of diagnosis and treatment on all aspects of physical, mental and social well-being when declaring treatment, a success in individual patients.

Correlation between QoL and visual field defects seems to be present in the majority of studies, especially those using vision-specific questionnaires [87, 167, 180]. However, those studies not involving patients in the advanced stages of disease showed little correlation with QoL scores, suggesting their limited ability to detect progression in the majority of patients [163]. Defects found to be most detrimental to quality of life were those developing in the second eye, causing difficulty in recognising faces, or affecting central inferior vision used for reading [1, 87]. It follows that similar-sized defects in different locations and in different patients may reduce QoL scores to varying extents, implying poor ability to act as a surrogate marker. Alternatively, patients may adapt to their field defects, with less detriment to a QoL score over time, as well as being subject to fluctuant mood disturbance which has also been found to correlate with patients' own perception of their visual function [104].

Although QoL scores are unlikely to prove useful in detecting glaucoma progression, they have been incorporated into large glaucoma trials such as the OHTS, CIGTS and AGIS, and can help us examine the effect of a diagnosis or treatment on a patient. Firstly, it appears that even the suspicion of glaucoma is associated with a possible deleterious effect on a patient's quality

of life [242]. Once treatment is initiated, the effect of use of drops and their side-effects on quality of life can be quantified by specific patient-reported outcome measures (Comparison of Ophthalmic Medications for Tolerability – COMTOL [21] and the Treatment Satisfaction Survey-Intraocular Pressure PROM - TSS-IOP [16]). If patient satisfaction with the treatment is improved, the compliance is then also likely to be higher [54]. In the surgery vs. medical therapy conundrum, the CIGTS used a 'Symptom and Health Problem Checklist' with the Visual Activities Questionnaire (VAQ) [244] to show that quality of life was very comparable between those on medical therapy and those with initial surgical management [105]. In a clinical setting, quality of life scores may be useful in visual rehabilitation at an individual patient level to help practitioners support patients with their individual needs [167].

Glaucoma research is now evolving into a multidisciplinary field, drawing together imaging, molecular medicine, neurodegeneration and informatics specialists. Further understanding of intraocular pressure control and progression analysis of visual field defects have been gained in the past few years, with imaging techniques becoming part of the routine standard of care. However, few new treatment strategies have come to light.

The confirmation that intraocular pressure is a poor surrogate marker has been key to highlight the need for new research into finding better biomarkers for glaucoma with which to trial novel therapies. Although there is good evidence supporting the role of intraocular pressure reduction in slowing glaucoma progression, we have little to suggest it is anything more than a modifiable risk factor as demonstrated in patients that progress despite optimum IOP lowering treatment, and in normal-tension glaucoma. In a shift away from investigating fluctuation in IOP as an important biomarker, future work may focus on the effect cardiovascular and endocrine diseases and pharmacological treatments have on the regulation and supply of perfusion to the optic nerve head. This in turn will bring together specialists in both the research and clinical settings to decipher to what extent the search for evermore effective treatments has on other, seemingly distant organ systems.

Imaging developments are likely to play a large role in the future development of glaucoma management. The most significant advance in biomarkers in the past few years has been the universal adoption of OCT technology which is now imaging deeper and at higher resolutions than ever before. As these boundaries expand, deeper and smaller structures are being characterised, which brings with it a steady stream of possible new biomarkers. Current examples of interest include characteristics of the choroid and lamina cribrosa. The ability to image blood flow in the retina, choroid and optic nerve without the use of contrast has begun

to revolutionise medical retina practice, and may assume an important role in glaucoma with further uptake and developments of the technique.

Although visual field technology and progression analysis have come a long way since inception, the ceiling of their abilities has ultimately been limited by patient ability to carry out the test. In stark contrast, the possibility of objectively quantifying apoptosis in real-time using the DARC technique offers the exciting opportunity of capturing glaucomatous degeneration upstream, directly at the site of injury. By potentially compressing years of progression analysis into a single image, we can aim to prevent visual field defects from occurring as opposed to waiting for them to develop. This in turn will hopefully provide more people with certainty of diagnosis and better disasease management. With new investigations relying less on patient compliance or practitioner experience, we will simultaneously increase our capacity for rapidly expanding patient numbers, and potentially explore other neurodegenerative conditions through the eyes. The hope is that further studies validating this technique will enable its use in more accurately assessing the neuroprotective effect of novel therapies.

It is becoming clear that glaucoma is a heterogeneous group of diseases with a final common pathway leading to retinal ganglion cell death. The key to unlocking new treatments for glaucoma will be active collaboration between scientists and clinicians with varying specialist knowledge and skillsets. With the incorporation of artificial intelligence such as *Deep Learning* into medicine, we will soon be handling information with complexity above the level of human understanding. It is only by using a tight co-operative approach that we will have the chance of harnessing technology to provide new biomarkers and treatments. Whilst human life expectancy continues to increase, we must aim to sustain vision in order to complement longevity with *quality* of life.

Key issues

- The number of glaucoma sufferers worldwide is increasing rapidly and expected to reach 111.8 million by 2040.

- The gold-standard for monitoring progression of disease is visual field testing which provides a good representation of visual impairment. However, irreversible defects can progress slowly and be complex to monitor. Furthermore, VF technology can be unreliable in a significant proportion of patients prompting new developments to improve its sensitivity and reproducibility.

- Intraocular pressure remains the only modifiable risk factor in glaucoma. Despite all currently available treatments having been proven using this biomarker, it remains an imperfect surrogate for glaucoma progression.

- The number of potential imaging biomarkers is increasing rapidly with the development of swept-source OCT and adaptive optics, able to image the posterior surface of the lamina cribrosa and the choroid, with increased resolution.

- Widespread ownership of electronic devices with high quality screens and cameras is opening up opportunities for home monitoring and virtual clinics.

- Glaucoma is increasingly being recognised as a neurodegenerative condition, and we now have a technique (DARC, Detection of Apoptosing Retinal Cells) that has the potential to directly measure disease activity by visualisation of retinal ganglion cell apoptosis.

- Genome wide association studies and advances in molecular biology have unearthed many gene loci, proteins and antibodies inferring glaucoma risk and pathogenesis. However, as yet few of these findings have provided a viable screening tool.

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Financial Disclosures