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What rates of glaucoma progression are clinically significant?

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Summary

Clinically important rates of glaucoma progression (worsening) are ones that put a patient at risk of future functional impairment or reduction of vision-related quality of life. Rates of progression can be evaluated through measuring structural or functional changes of the optic nerve. Most treated eyes do not progress at rates that will lead to future visual impairment, but there are a significant proportion (3-17%) of eyes, that are at risk of impairment even under clinical care. While very fast rates of progression (e.g. MD progression of -1.5 dB/year) are generally problematic, much slower rates also may be deleterious for young patients, particularly those diagnosed with late disease. As a result, it is important to consider life expectancy, disease severity and vision-related quality of life based treatment targets to estimate future prognosis when evaluating whether a rate of glaucoma progression can be clinically relevant.

Keywords

Glaucoma; quality of life; progression rates; standard automated perimetry; spectral domain optical coherence tomography; confocal scanning laser ophthalmoscopy; life expectancy

Glaucoma is a chronic progressive disease and a leading cause of blindness, affecting more than 70 million people worldwide [1]. The main goal of glaucoma treatment is to not only prevent blindness but to prevent progression of the disease from reaching a stage that adversely affects the patient's vision-related quality of life (VRQoL). Progression (worsening) in glaucoma patients is typically measured using a combination of structural and functional methods. Methods of glaucoma progression detection can further be divided between event and trend analysis approaches. Event analyses compare baseline measurements to future follow-up measurements to define whether that measurement is significantly worse, while trend analyses use serial measurements to determine rate of progression. Although event analysis methods are useful in determining whether patients are getting worse, they do not provide information about the velocity of vision loss or whether there is significant risk that these rates of loss will affect their vision-related quality of life. For this reason, this review focuses on rates of glaucomatous progression measured using trend analysis. We define a clinically significant rate of progression as a rate that can lead to permanent visual disability or loss of VRQoL. In evaluating whether a rate of loss is

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Declaration of Interest

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clinically important, three factors require consideration: 1) the current stage (or severity) of disease; 2) the life expectancy of the patient; and 3) the severity/stage of disease at which VRQoL would be affected.

There are several structural and functional methods that can be used to measure rates of glaucoma progression. Despite being patient-dependent and subject to considerable test-retest variability [2-5], visual field (VF) testing using standard automated perimetry remains a gold standard for measuring glaucoma progression. However, increasingly sophisticated imaging technologies, such as spectral domain and swept-source optical coherence tomography (OCT), are being utilized to qualitatively and quantitatively assess the rate of structural change [6-14].

Rates of visual field loss

Measuring rates of VF progression provides a direct measure of optic nerve function and how it is changing over time. Trend analyses using VFs often involve linear regression of summary statistics such as Mean Deviation (MD) and, more recently, the Visual Field Index (VFI). Despite the fact that rates of VF worsening are not necessarily constant over time in reality (e.g. treatment intensity and adherence could change for instance), rates of VF loss are typically expressed as linear rates of change of dB/year in practice. Interestingly, past studies investigating rates of linear loss using these summary statistics in patients with glaucoma tend to show apparently slow progression rates. For instance, the of the Early Manifest Glaucoma Trial found that the median rate of MD loss in untreated eyes of 118 glaucoma patients was -0.4 dB/year [15]. However, median rates of loss of glaucoma patients in treated clinical practice vary widely among studies, ranging from -0.05dB/year to -0.62dB/year [16-19]. Others have reported average rates of VFI loss in glaucoma patients to be between -1.1 and -1.5%/year [20-22]. Placing this in perspective, rates of VF sensitivity decline due to aging have been estimated to be -0.06dB/year [23]. Moreover, rates for the most pessimistic study suggest it would take 20 years for the “average” patient with a mean constant VF progression rate of -0.6dB/year to progress from 0dB to -12dB, which is commonly defined as severe VF loss [24], and a further 17 years to reach -22dB, a standard for statutory blindness[25], so it is unlikely for the average patient to suffer glaucoma-related impairment during their lifetime, particularly as glaucoma tends to affect older individuals [26-29].

However, there is large variability in rates of VF loss among patients. Distributions of rates of loss in various studies suggest that though most do not progress very quickly, a sizeable proportion of eyes do, as reflected by the fact that the mean rates of VF loss in studies are systematically more pessimistic than medians [15-17]. The reported proportion of glaucomatous eyes progressing at faster than -1.5 dB/year have varied from 3 to 17% in some previous studies [16, 17, 19, 20, 30-35], while others found that 15-20% of eyes seem to progress at rates of VFI loss greater than 5% per year [21, 36]. Such rates of loss would lead to perimetric blindness in 20 years assuming rates of loss remain constant. These numbers echo those of a number of older studies estimating the number of patients going blind from glaucoma that range between 6 to 13% [37-39]. Hence, glaucoma management, then, should be directed at differentiating patients who are in danger of progressing to stages

of visual impairment and/or blindness from those that are not. One diagnostic paradigm that has been proposed to achieve this is frequent early testing [40].

However, this raises an important question: how should “fast progression” be defined? Some definitions of fast progression have been fairly arbitrary with round numbers such as a VF MD rate of -1.5 dB/year [30, 33] or -2 dB/year [18, 40], commonly chosen. Without doubt, these rates would almost always have a deleterious impact on a patient’s visual health. However, an irreversible impact on a patient’s VRQoL could occur even at a much slower rate than this depending on their life expectancy and severity of disease.

Rates of structural loss

Neuroretinal rim area measured using confocal scanning laser ophthalmoscopy and retinal nerve fiber layer (RNFL) measurements measured with Optical Coherence Tomography (OCT) have tended to be the most commonly used metrics to measure structural change. As with VF-based measurements, progression is often expressed linearly in the form of change per year, despite the fact that the relationship between clinically utilised functional and structural measurements is not linear [41], so they cannot both progress at a constant over time simultaneously. Although, the true relationship between structure and function may well actually be linear, the fact that commonly-used measurements are not (due to the fact VF sensitivity measurements are log-transformed) is still an important consideration when thinking about structure-function correspondence [41]. In glaucoma patients, the rates of global neuroretinal rim area loss measured using confocal scanning laser ophthalmoscopy (CSLO) have been found to range between -0.018 and -0.0072 mm²/year [7, 11, 12, 22, 42-44] while average rates of global SD-OCT based RNFL thinning have been estimated to range between -0.76 and 1.5 μm/year [8-11, 45-47]. Faster rates of rim area using CSLO and RNFL loss have been reported in ocular hypertensive or suspect eyes developing glaucoma (rim area loss: -0.01 mm²/yr, RNFL loss: -2.02 μm/year) compared to those that did not (-rim area loss: 0.003 mm²/yr, RNFL loss: -0.93 μm/year) [10, 12, 48]. Typically rates of rim area loss have been found to be between 3.7 and 4.6 times faster in eyes progressing compared to those not [12, 44, 46]. Moreover, faster rates of CSLO measured rim area loss and OCT-based RNFL thinning are associated with an increased risk of developing VF damage [10, 48]. One relatively new OCT measure suggested for monitoring structural change is the Bruch’s membrane opening minimum rim width. Some early studies have suggested that this may be a more sensitive method of detecting structural change independent of aging [11] with greater correlation to RNFL thickness and MD than rim area measurements measured using CSLO [49]. Few studies have been conducted using this approach, but average rates of change have been recorded to be -2.18 μm/year in glaucoma patients [11]. However, there is some evidence that minimum rim width may not be as sensitive to monitoring progression as change in RNFL thickness [50]. Estimating the loss in retinal ganglion cells has also been suggested, with studies suggesting losses of 10,000-11,000 ganglion cells per year on average in glaucoma patients and suspects [13, 51]. In glaucoma suspects, these rates are noticeably faster in eyes showing VF progression during follow-up (-18,987 cells per year) than those that not (-8,808 cells per year) [51].

However, there are challenges in evaluating whether rates of structural progression are clinically significant for a particular patient. Most importantly, it is difficult to differentiate between deterioration as a result of aging and that caused by glaucoma as there is little longitudinal information on how the structure of the retina changes in normal subjects over time. Without this context, the clinical implications of any measured structural change are unclear. Estimates of significant mean RNFL rates of loss in healthy eyes of between $-0.33 \mu\text{m}/\text{year}$ (cross-sectional analysis) and $-0.52 \mu\text{m}/\text{year}$ (longitudinal analysis) have been reported [8]. However, RNFL thickness in healthy eyes can vary widely; RNFL thicknesses have been measured between 114.6 to 182.2 μm in the inferior hemifield of the optic disc and 83.4 to 166.1 μm in the superior hemifield [41]. To put these numbers into context, mean rates of superior and inferior loss in healthy eyes were reported as -1.35 and $-1.25 \mu\text{m}/\text{year}$ respectively [8].

Another difficulty in evaluating the significance of rates in structural measurements is that patients tend to have vision well beyond the dynamic range of many structural measurements; this measurement “floor effect” for structural measurements typically occurs earlier than for corresponding VF measurements [41, 52] (although the usefulness of VF thresholds beyond the range of structural measurements has been disputed[53]). The importance of the dynamic range lies in the fact that it represents how well a measurement reflects the severity of the disease of the patient through the full range of disease. “Floor effects” lead to measurements becoming uninformative at a stage of disease while patients still have measurable vision remaining worth evaluating. As a result, poor dynamic range resulting from “floor effects” mean that rates of vision loss cannot be accurately measured in late disease.

It is further difficult to reconcile measures of structural loss to what a patient can see as research in this area is scarce. Notably, it has been found that RNFL loss is associated with longitudinal reduction in quality of life, even after adjustment for progressive visual field loss [54]. RNFL loss is also related to real world metrics of functional impairment such as reaction time in driving [55]. However, it is not yet possible to come up with some universal standard for what rates of progression are clinically important and more research of how structural changes relate to changes in VRQoL is needed.

What stage of vision loss affects vision-related quality of life?

Whether progression is “fast” or not needs to be considered in the context of a patient’s VRQoL, yet research of this has been sparse on the matter of considering what levels of VF or structural loss are associated with a substantial reduction in VRQoL [56]. However, the effect of glaucoma on quality of life is difficult to measure quantitatively, especially as patients use two eyes; loss of vision in one eye will inevitably not affect quality of life as much as when both eyes are affected. Further, patterns of VF loss in each eye tend to vary from patient to patient suggesting that patients with pairs of eyes with similar MDs may have very different experiences of vision loss.

One obvious milestone to prevent glaucoma patients from reaching is statutory blindness as defined by the US Social Security Administration (US SSA). The US SSA generally defines

statutory blindness in terms of acuity; however, if the widest diameter of the visual field is found to subtend at an angle less than 20 degrees then this can also qualify as a measure for statutory blindness[25]. An MD of -22 dB in the better eye is said to correspond to this definition of blindness and has been used in other studies [19, 57], so this is a significant landmark. However, other visual activities are likely affected well before this stage of disease, with evidence that quality-of-life differs between patients with the disease and without the disease even at early stages of visual field loss [58]. Furthermore, more severe disease has also been linked with increased reduction in both general health and VRQoL evaluated using questionnaire responses [59-62]. Unfortunately, there is little evidence demonstrating what disease stages are associated with impairment of various day-to-day activities.

Three of the most important vision related tasks are mobility, reading and driving [63-65], so treatment targets related to these activities make sense. Reading tends to be most affected by damage to the central-most part of the VF [66, 67]; this part of the VF tends to be preserved until the end-stage of the disease [68], but studies have shown that the central field can also be damaged in early disease too [69]. Determining the severity of VF loss that inhibits driving safety has proven difficult due to the complexity of the task with many studies even struggling to find evidence that individuals with glaucoma are unsafe to drive [70-72]. Driving simulations have perhaps generated some of the most interesting insights into aspects of vision used when driving and provide promise for identifying more robust means of evaluating fitness to drive based on the VF in the future [55, 73-78]. Mobility is the area that has been most tested with Assessment of Disability Related to Vision testing showing some weak correlation to VF measurements [79]. Loss of balance [80, 81] and risk of falls [82] have also been shown to be associated with VF health.

Overall, it is important to know the severity of disease that needs to be prevented in order to define what rates of loss are rapid enough to risk future visual impairment and more work needs to be done to achieve this aim. Most current treatment targets are either based on intraocular pressure measurements or arbitrary functional or structural measurements not based on clinical evidence, which means that rates of loss thresholds defined as “fast” or even “catastrophic” in many studies are arbitrary.

Predicting future patient status according to their life expectancy and baseline measurements

In evaluating what rates of progression put patients at risk of reduced VRQoL, it is also essential to consider how much VF loss the patient has already experienced and how long they are likely to progress at their current rate of loss. For instance, a patient that already has substantial VF loss does not have to lose vision that quickly to become blind. This is especially important given links between disease severity at diagnosis and future visual impairment [19, 83, 84].

In addition, the life expectancy of the patient is also important to consider, as older patients will usually have less time to lose their vision than younger patients with the same level of disease severity [85]. For example, assuming for simplicity that VF loss remains constant

over time, a patient losing 0.5dB of VF MD per year will lose 10dB if they live an additional 20 years and 20dB if they live another 40 years. In spite of the importance of this issue, few studies have actively attempted to incorporate what is known about the life expectancy of the patient into risk of VF progression [19, 85]. One of the main challenges is that predicting life expectancy of a given patient is even more difficult than predicting future rates of glaucoma progression. Previous studies have suggested that medical worker predictions can lack accuracy in estimating remaining life expectancy, with a bias towards underestimating the years a patient has to live left [86-89]. As a result, clinicians need to be conservative and make clinical management decisions as if their patients will exceed their expected life expectancy.

We have provided a schematic, again assuming a constant rate of change in VF loss over time, to help illustrate whether a specific progression rate is fast for an individual patient. For instance, the Figure A illustrates that for an individual patient with a starting VF MD of -7dB (commonly defined as moderate VF loss) would need an MD of -1dB/year to reach a severe VF loss of -12dB if the patient lives for five years, but this lowers to just -0.1dB/year if the patient lives fifty years. Similarly, the Figure B shows that a patient already blind in one eye who will likely live another 15 years requires a rate of loss of -1.4dB/year to reach statutory blindness if diagnosed early (MD = -1 dB), but this rate goes down to -0.7 dB/year if this patient already has severe disease (MD = -12dB).

It is worth bearing in mind that, in practice, it is unrealistic to expect rates of loss to remain constant over time. For a start, changes in treatment intensity and its adherence, as well as risk factors for progression may change over time, which would in turn affect rates of both structural and VF change. There is further evidence that natural progression of the disease can be better fitted using exponential or other non-linear models [90-93], which is supported by studies that suggest that rates of progression become faster with age [15]. However, given the complexity of the task of modelling rate of VF progression over long periods of time, there is not unanimous evidence that non-linear models are substantially more useful in practice than assuming rates of change are constant [94]. For these reasons, an argument can be made for repeatedly evaluating rate-of-change over shorter trends (say using the last 8 tests or evaluations in the last 10 years) [95] as a practical approach for estimating rates of change for clinical management decisions. This is particularly important in the context of changing treatment during follow-up; one study has shown, for instance, that the rate of MD loss is reduced by 56% after trabeculectomy [96]. Failing to account for events such as surgery and change in medication risks over-estimating an eye's current progression rate.

Given the difficulty in evaluating rates of progression, it is useful to use concurrent risk factors when evaluating patient risk of progression rate of patients; for instance, it is known that higher intraocular pressure is a major risk factor for faster disease [33, 97], so a patient with less controlled pressure is more likely to progress quickly in the future. Rates of change alongside considering other risk factors such as intraocular pressure, race and family history of glaucoma, and change in treatment and surgery should therefore be used in deciding whether progression could lead to decline in VRQoL.

Expert Commentary

Addressing the question of what rates of progression in glaucoma are clinically relevant is highly nuanced. At first glance, rates of -1.5 or -2 dB visual field MD change per year or equivalently around 5 to 10% of VFI per year are fast and should always be avoided, if possible. However, far slower rates of loss may be significant for other patients. What rates of loss are clinically important depends on the life expectancy of the patient, the severity of disease, risk factors, and what daily activities need to be preserved. This means that a catastrophic rate of loss for one patient (e.g. a newly-diagnosed 60 year-old female progressing at a rate of -1dB/year from a baseline MD of -10 dB) may not be clinically important for another (e.g. a newly-diagnosed 90 year-old male progressing at a rate of -1dB/year from a baseline of -2dB). These examples clearly show that it is not only important to determine whether a glaucoma patient is progressing, but it is also critical to estimate the rate of progression to determine how aggressively to treat the patient. To do this, regular monitoring of patients is essential in glaucoma management.

Five Year View

The future of clinical treatment in glaucoma could one day be based on individualised progression rate-based treatment targets to prevent functional impairment and blindness based on the age/life expectancy, risk factors and severity of disease of each patient. As more is known about how new structural changes in the retina impact on what patients can actually see, one would expect structural measurements to play an increasing role in glaucoma management; not only in the context of detecting progression, but evaluating future prognosis for the patient. New technology such as OCT-angiography may further elucidate the disease process and allow better links to be made between how the eye is changing and how it functions [98-100]. Further, changes in test algorithms [101, 102], stimulus size [103, 104] and location [105-107] as well as analysis methods [108-112] of visual field measurements may help deal with the noise that currently obfuscates interpretation of visual function measurements. For example, an analytical method called ANSWERS has showed particular promise in this regard, allowing increased test-retest variability with disease severity to be taken into consideration when measuring rates of progression [110, 111]. Further, new objective technologies such as pupil-based perimetry [113-115] or electrophysiological testing [116, 117] may reduce variability caused by human error that currently plights perimetry [116, 117].

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Key Issues

- A clinically significant rate of progression in glaucoma is one that could lead to a high risk of future visual impairment for the patient.
- Only trend-based analyses can be used to evaluate rates of change.
- Most eyes do not suffer disease progression at rates that may lead to future visual impairment.
- However, between 3 and 17% of eyes progress at rates of loss that could lead to perimetric blindness within 20 years.
- A key challenge in glaucoma management is differentiating between patients that are at risk of blindness and those that are not.
- It is important, but difficult, to consider age-related changes in structural measurements (e.g. neuroretinal rim area and retinal nerve fiber layer thickness) when evaluating glaucoma progression.
- Regular testing of patients is required to accurately evaluate rate of disease progression.
- What rates of loss are clinically important depends on the life expectancy of the patient, the severity of disease and what daily activities need to be preserved.
- Risk factors should also be utilised, alongside direct measurements of rates of loss, to evaluate risk of future patient progression to visual impairment.

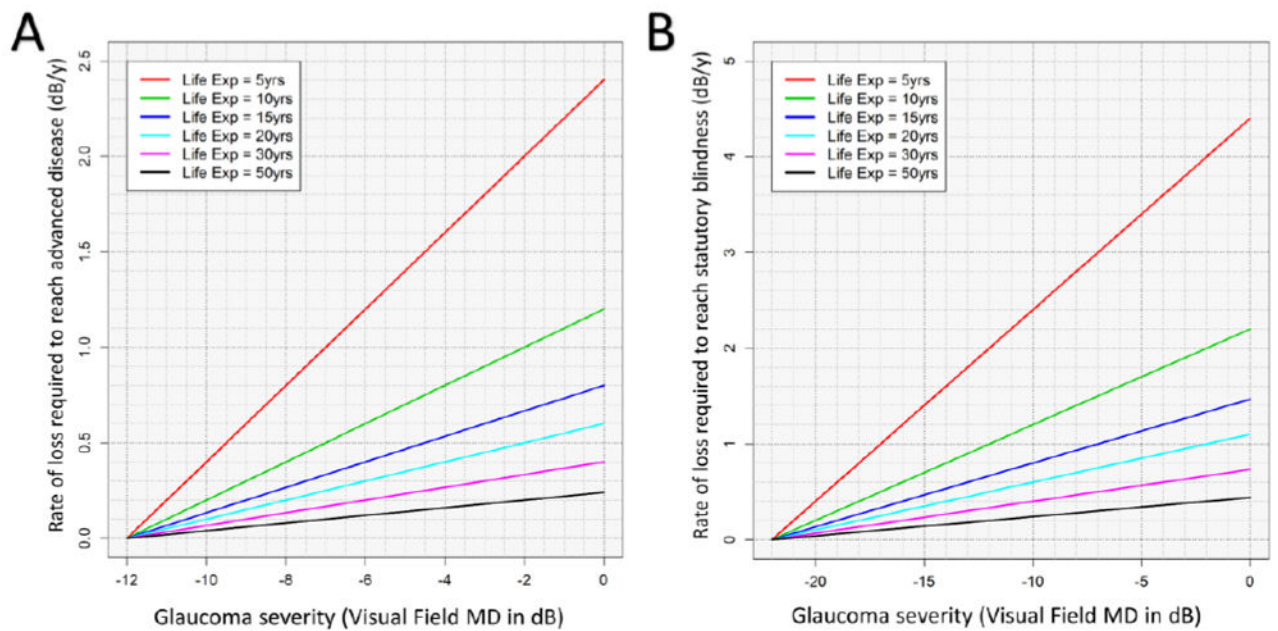


Figure 1.

Incorporating severity of disease and life expectancy to identify clinically important rates of progression for an individual patient. The baseline visual field mean deviation (MD) is on the x-axis. The y-axis represents the linear rate of visual field loss that will result in advanced disease (Figure A) and blindness (Figure B). Advanced disease is defined as MD -12dB in Figure A, while Figure B uses an MD -22dB to represent statutory blindness. By estimating the patients remaining life expectancy, a critical rate of visual field loss to avoid can be defined. Each colored line corresponds to a different life expectancy (Life Exp) remaining.