World Glaucoma Association

Progression of Glaucoma

Robert N. Weinreb, David F. Garway-Heath, Christopher Leung,
Jonathan G. Crowston, Felipe A. Medeiros

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The 8th Consensus Report of the

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Editors

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PREFACE

Progression of Glaucoma is the topic of the eighth World Glaucoma Association Consensus. There has been considerable attention to the diagnosis of glaucoma during the past twenty years. In fact, this was the topic of the inaugural WGA consensus report in 2003. During the past decade, however, numerous studies have been undertaken to also investigate the progression of glaucoma. With substantial improvement in existing diagnostic technologies and the rapid development of others, one can better determine whether there has been progressive disease. Hence, the results of this report will have broad and significant impact on clinical practice and glaucoma research. The global faculty, consisting of leading authorities on the clinical and scientific aspects of glaucoma progression, met in Paris on June 28, 2011, just prior to the World Glaucoma Congress, to discuss the reports and refine the consensus statements.

As with prior meetings, it was a daunting task to seek and obtain consensus on such a complicated and nuanced subject. It is unclear how each of us decides how we practice, and evidence to guide us often is sparse. Collection of patient data to study progression often takes years. Hence, this consensus, as with the others, is based not only on the published literature, but also on expert opinion. Although consensus does not replace and is not a surrogate for scientific investigation, it does provide considerable value, especially when the desired evidence is lacking. The goal of this consensus is to provide a foundation for identifying progression of glaucoma and how it can be best done in clinical practice. Identification of those areas for which we have little evidence and, therefore, the need for additional research always is a high priority. We hope that this consensus report will serve as a benchmark of our understanding. However, this consensus report, as with each of the others, is intended to be fluid. It is expected that it will be revised and improved with the emergence of new evidence.

Robert N. Weinreb, Chair

Co-Chairs:
Jonathan G. Crowston
David F. Garway-Heath
Christopher Leung
Felipe A. Medeiros
Rohit Varma

Robert N. Weinreb (Consensus Chair)

INTRODUCTION

We mark the eighth consecutive year for the World Glaucoma Association Glaucoma Consensus with Consensus VIII. Our topic is the Progression of Glaucoma.

Global experts were invited and assembled by our international co-Chairs beginning in January 2011, to participate in the Project Forum E-Room, a unique online opportunity to facilitate discussion of each of the consensus meetings. Participants then were engaged in the discussion of five topical areas to reach consensus on key issues that surround and permeate all aspects of the progression of glaucoma. The results of these thoughtful discussions then were summarized by each of the sections with preliminary consensus statements. The Draft of the Consensus Report, including the preliminary consensus statements, was distributed to the Societies and Partners for review and comments prior to the Consensus Meeting that took place in Paris on Tuesday, June 28, 2011.

On this day, relevant stakeholders engaged in a stimulating, educational, and thought-provoking session that highlighted the review and revision of the consensus statements. The Consensus Report then was finalized by Consensus co-Chairs and Editors. Consensus statements were reviewed and finalized by the expert Consensus Panel.

Robert N. Weinreb, Editor

Andy McNaught (section 1 co-author, left), Chris Johnson (section 1 co-Leader, center left), Anders Heijl (section 1 co-Leader, center right) and Kaweh Mansouri (Consensus Secretary)

Anders Heijl (section 1 co-Leader)

David F. Garway-Heath

Andy McNaught

Nomdo Jansonius

Anders Heijl

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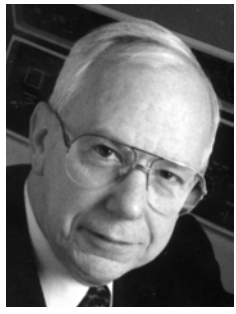

Douglas R. Anderson

William H. Swanson

1. VISUAL FUNCTION PROGRESSION

David F. Garway-Heath, Andy McNaught, Nomdo Jansonius, Anders Heijl, Boel Bengtsson, Douglas R. Anderson, William H. Swanson

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Consensus statements

1. Standard white-on-white automated perimetry (SAP), with a fixed testing matrix covering at least the central 24 degrees, is preferred for measuring progression in eyes with glaucomatous VF loss.
   Comment: more research is needed into the use of alternative measures of visual function (FDP, resolution perimetry, motion perimetry and others) to detect glaucomatous progression, before any of these can be considered alternatives to SAP for measuring progression.
   Comment: It is possible for glaucomatous optic neuropathy to progress structurally in the absence of functional progression and vice-versa.
2. Perform sufficient examinations to detect change.
   Comment: decisions on progression should not be made by comparing only the most recent field with the one before.
   Comment: suspected progression should be confirmed by repeating the field.

Baseline data collection (no previous VFs available) – first two years

3. In clinical practice, at least two reliable VFs is optimal in the first six months.
   Comment: In clinical scenarios, where the lifetime risk of visual disability is high, such as those who already have advanced damage, three baseline VFs may be necessary.
   Comment: A good baseline of reliable VFs is essential to be able to monitor for progression.

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Comment: Unless there are obvious learning effects, high false-positive errors, rim artifacts, or other obvious artifacts, examinations should not be removed from the analyses.

4. At least two further VFs should be performed within the next 18 months.
5. VF testing should be repeated sooner than scheduled if possible progression is identified on the basis of an 'event' analysis.
   Comment: In patients at risk of visual disability, performing six VFs in the first two years enables the clinician to rule out rapid progression (2 dB/year or worse) and establishes an ideal set of baseline data.
   Comment: the identification of possible progression may be on the basis of an 'event' criterion such as the Glaucoma Progression Analysis (in the Humphrey perimeter software) or 'Nonparametric Progression Analysis'.
6. Establish a new baseline after a significant therapeutic intervention (*e.g.*, surgery).
   Comment: the new baseline can be the last fields that defined the previous progression 'event'.

Follow-up data collection (after the initial two years)

7. The frequency of follow-up VFs should be based on the risk of clinically significant progression (based on extent of damage and life expectancy).
8. In low and moderate risk patients, subsequent VF frequency should be one VF per year (unless there is a long follow-up) and, as a rule, repeated sooner if possible. Progression is identified on the basis of an 'event' analysis, or if other clinical observations are suggestive of possible progression or increased risk of progression.
   Comment: relevant clinical observations include structural progression (clinically noted or measured by imaging), a splinter hemorrhage, or inadequate IOP control.
9. In high risk patients, subsequent VF frequency should be two VFs per year and repeated sooner if possible progression is identified on the basis of an 'event' analysis, or if other clinical observations are suggestive of progression or increased risk of progression.
   Comment: following confirmed progression (by an 'event'), the frequency of testing should be based on the estimated rate of progression, risk factors and other clinical indicators of progression, stage of disease and life expectancy.
   Comment: patients who have been stable for a long period, or who are progressing so slowly as to be at little risk for reaching disabling levels of field loss, and other clinical parameters indicate low risk of progression, may have VF testing less frequently than 1 VF per year.

Visual field progression may be analyzed by either 'event-' or 'trend-'based methods

Event analysis: is change from baseline greater than a predefined threshold; the threshold is based on test retest variability (according to level of damage).

Trend analysis: determines the rate of change over time; the significance is determined by the variability of the measurement and the magnitude of change.

10. Both event and trend analyses are needed, largely for different time points in the follow-up during clinical care.
11. In general, event-based methods are used early in the follow-up, when few VFs are available for serial analysis.
    Comment: progression by an event criterion usually requires confirmation on at least two further occasions to be sufficiently sure that progression has truly occurred.
    Comment: confirmation of progression should usually be made on a separate occasion (patients have 'off days').
    Comment: When interpreting VF progression that is confirmed by an 'event' method, the clinician should look at:
    – the baseline fields, to ensure they are reliable and appropriate for the analysis;
    – the estimated rate of progression and the confidence of the estimate;
    – the severity of the visual loss in terms of impending impairment;
    – the risk factors for progression.
12. In general, rate-based analyses are used later in the follow-up, when a greater number of VFs is available over a sufficient period of time to measure the rate of progression.
    Comment: a rate of progression in the first two years is a rough estimate (wide range of possible rates around the central estimate); in most patients it takes longer to obtain a reliable estimate of the rate of progression.
    Comment: trend (regression) analysis provides an estimate of the rate of progression and a measure of the reliability of the estimate; the reliability of the estimate is judged from the confidence limit.
    Comment: clinicians should consider other clinical measures of progression and risk of progression when interpreting this information (these data provide the 'prior probability' for progression).
13. When progression is identified, the clinician should ensure that the progression is consistent with glaucoma and not related to some other cause.

Measure the rate of visual field progression

14. Clinicians should aim to measure the rate of VF progression.
    Comment: Estimating the rate of progression is invaluable for guiding therapeutic decisions and estimating the likelihood of visual impairment during the patient's lifetime.
15. In the absence of significant changes in therapy, the rate of progression of suitable global indices (MD or VFI, but not PSD or LV) is linear in treated glaucoma eyes, except at the most advanced stages.
16. As a linear model for progression is acceptable, trends may be extrapolated to predict future loss if there is no change in therapy, over appropriate intervals.

17. Both local and global metrics are needed for assessment of progression.
    Comment: Rates are most often measured on 'global' parameters, such as mean deviation, mean defect or visual field index. However, focal progression (such as paracentral) may be missed by a global index.
18. Total Deviation based methods are more sensitive to cataract than Pattern Deviation based methods. However, by eliminating or reducing the component of diffuse visual field loss, Pattern Deviation based methods may underestimate progression rates.
19. Use available software support.
    Comment: Subjective judgment of VF print-outs is unreliable and agreement among clinicians is poor. Statistical analysis, either in the perimeter software or stand-alone software, is advantageous to reliably identify and measure progressive VF change.

Pay attention to examination quality

20. Examinations of poor quality will likely lead to an erroneous assessment of progression.
    Comment: The most important factors to reduce test variability are a proper explanation of the test to the patient, appropriate instrument setup and 1:1 monitoring of the patient by a trained technician.
21. Do not rely automatically on the VF reliability indices.
    Comment: The VF reliability indices may be unreliable! The most useful index is the 'False Positive' rate; values greater than 15% likely represent a less reliable performance; values less than 15% do not guarantee reliability. The technician is the best judge to exam quality.
22. If unreliable tests require repeating, the patient should be carefully re-instructed.

Use the same threshold test

23. Clinicians should select their preferred perimetry technology, test pattern, and thresholding strategy for the baseline tests and stick with the same test throughout the follow up.
    Comment: any analysis of progression can only be performed if a compatible threshold algorithm and test pattern is used.
24. In advanced glaucoma, smaller angular size SAP testing grids, *e.g.*, HFA 10-2 may be of value in a minority of patients.
    Comment: Kinetic perimetry and SAP with larger targets (*e.g.*, size V) may also be useful.
    Comment: The advantages of a change in test pattern (*e.g.*, from a 24-2 to a 10-2 grid) should also be weighed against the disadvantages for progression analysis by commercial software.

Clinical trials

25. Event analyses aim to identify a statistically significant difference between study arms and not necessarily a clinically significant difference.

Comment: As glaucoma is a chronic progressive disease and progression is generally linear, small amounts of progression that reach statistical significance become larger, clinically significant amounts of progression if there is no additional therapy.

26. Rate analyses of VF indices are an appropriate statistical approach to identify differences between treatment groups.
    Comment: Rate analysis methods have been used often in trials for other chronic progressive diseases, such as dementia.
27. Difference in the progression 'event' criterion applied in the various clinical trials limits comparison of the incidence of progression determined in those trials.
    Comment: Comparison of groups in different clinical trials is also hampered by mismatch of subjects with regard to stage of glaucoma, quality of visual field exams, and other traits.

Research needs

1. The development of 'event' criteria for progression based on individual patient test-retest variability.
2. There is a need to *compare event-based endpoints* and *rate of progression outcomes* in a data set with data acquired with appropriate frequency and test intervals with respect to clinical trials.
3. Further research is needed into the added value of smaller angular size test grids, and different size stimuli, *e.g.*, size V, in advanced glaucoma.
4. Determine appropriate dynamic ranges of stimulus contrasts for size III, and develop new stimuli with larger dynamic ranges of appropriate stimulus contrasts.
5. Improve the interface between perimetrist and device, and between patient and device.
6. Identify, or develop, stimulus types (*e.g.*, FDT) and test algorithms which provide optimal information content for progression analysis in children and adults who have difficulty performing a reliable SAP test.
7. Develop alternate methods for selecting stimulus locations in order to avoid extensive testing of blind areas and to focus on areas of interest.
8. Further assess the benefits of using prior threshold as a starting point in a follow-up test (or if threshold is < 0 dB previously, confirmation at that point that a 0 dB stimulus is not seen is sufficient).
9. Determine the optimal frequency and timing of tests for individual patients.
10. Use of good mathematical modeling.
11. Develop better approaches to identify learning effects.
12. Identify the appropriate test and frequency of testing for patients with progressive glaucomatous optic neuropathy and SAP within normal limits.

Introduction

The central goal of the management of the patient with glaucoma is preservation of visual function adequate to that individual's needs during his/her lifetime;[1] thus, the identification and quantification progressive vision loss is a fundamental requirement for clinical care. This chapter outlines 1) the technologies available for measuring visual function, providing evidence for their application to monitor for progressive vision loss and guidance for obtaining high quality data; 2) the appropriate frequency and intervals between visual field tests in clinical routine for patients with different levels of risk of visual disability; 3) statistical analysis for serial visual field data and the appropriate choice according to clinical scenario; 4) approaches to visual field testing in clinical trials; and 5) research priorities to improve the visual field assessment tools presently available.

I. Technologies for measurement of the visual field

Andy McNaught

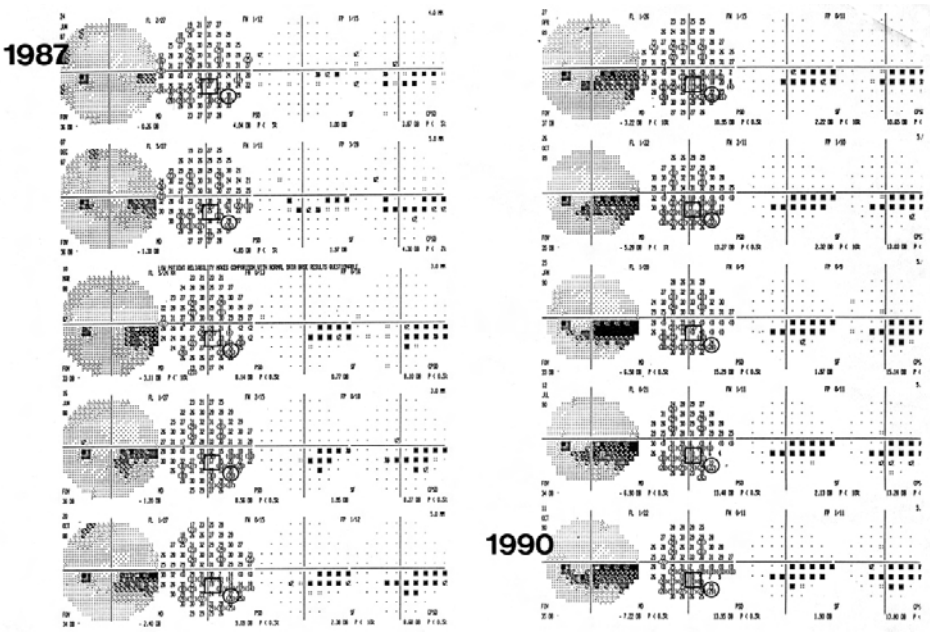

Fig. 1. Series of SAP results showing progressive inferior arcuate VF loss over three years.

Standard 'white-on-white' automated perimetry (SAP)

Standard automated perimetry (SAP) is an extensively researched, and now, well-established technique to quantify the sensitivity of the visual field in glaucoma. The earliest research work which led to the current generation of automated

perimeters began in the mid-1970s.[2,3] The first automated perimeters included the Octopus perimeter and were described in the early 1980s;[4] at this time, there are the first reports of the use of automated perimetry (Fieldmaster) to attempt to detect glaucomatous visual field progression, suggesting improved sensitivity when compared to kinetic perimetry.[5]

The use of probability analysis to separate abnormal visual fields from those from an age-matched population was described by Heijl and Asman in 1989.[6] Further refinements to the Humphrey Automated Perimeter (HFA), including the glaucoma hemifield test (GHT),[7] and testing strategies allowing more rapid threshold estimations 'SITA' were described by the same group in the 1990s.[8]

The HFA is now a prevalent device in ophthalmology units: 99% of UK eye departments use some form of automated perimetry, 78% having the HFA.[9] In a survey of UK community optometrists, the perimeter most frequently used was either one of the Henson range of instruments (39%) or the Humphrey Field Analyser (22%).[10] The HFA is used by both general ophthalmologists, and in research trials, *e.g.*, AGIS, CIGTS, and the EMGT.[11] There has been extensive research confirming the value of SAP, mainly using the HFA, Octopus, or Henson perimeters, in the detection, and monitoring of glaucomatous visual function progression: using both 'event' and 'trend' analysis in the analysis of global indices, as well as point-wise techniques.

Guidance for obtaining reliable SAP test results

To ensure that glaucoma progression is detected at the earliest point possible, it is essential that each SAP test is a high quality measurement of the patient's visual function at that point in time. Research evidence confirms the clinical impression that less variability in each visual function measurement enhances the ability to detect any underlying VF progression over time. Important factors include:

a) It is essential that the suitability of the patient for any visual function testing is carefully appraised before testing begins: poor quality results will result if the patient is physically unable to sit comfortably at the perimeter because of, for example, severe arthritis, especially of the cervical spine. Some patients may not be intellectually competent to undertake the test e.g. those suffering from dementia. Other subjects will have insufficient central visual function to enable adequate fixation during the test, because of extensive macular disease, for example. These patients might be better served with alternative perimetry methods, *e.g.*, Goldmann kinetic perimetry and/or might be better monitored using structural measurements. A patient with a dense cataract will not produce a very valuable perimetry result: it would, where possible, be more sensible to delay perimetry until the cataract is removed.
b) It is essential that the perimetry technician is able to ensure that the subject has appropriate near refractive correction to render the fixation target, and the stimuli, accurately focussed during the test. Defocus will reduce

measured sensitivity. The near correction lenses that are used must be full aperture to ensure that there is no vignetting by the trial frame.

c) Subjects must have a clear idea of the nature of the perimetry test i.e. they must understand that the test will take several minutes to complete, that there might be quite long periods during the test when they do not perceive any stimuli at all (even if their visual field is normal). They need to know that it is not possible to attain '100%', so they must expect that many stimuli will inevitably be too dim to see: they are therefore less intimidated by the test.
d) The perimetry technician must be in close proximity to the patient during the test to ensure they can give advice and encouragement/monitor fixation/allow the patient to rest, if necessary, during the test, *i.e.*, a ratio of subject to technician would ideally be 1:1, but 1:2 might be acceptable, but even if there are fewer technicians, each patient should be supported throughout the test, to ensure the highest quality perimetry test results.
e) The patient's performance is most accurately assessed by the technician who conducts the test, but modern automated perimeters do also undertake automatic measurements which provide some additional information about overall performance. Research suggests that false negative (FN), and short-term fluctuation (SF) measures are less useful than false positives (FP). This is because the former are strongly correlated with the extent of the glaucomatous visual field damage (rather than the patient's fundamental performance);[12] the measures increase with increasing size and number of scotomata, certainly until the field is moderately damaged, *i.e.*, a mean deviation (MD) in excess of approximately -15dB. VF damage more severe than this level is often associated with reducing levels of variability, again, mostly unrelated to the patients fundamental performance, but mainly because of the limited (remaining) dynamic range of the perimeter. Excessive FP responses, however, always indicate an intrinsically poor performance as the patient is indicating a stimulus is seen when none has been presented. For detection of progressive field loss, when a series of fields is available, the Glaucoma Progression Analysis (GPA) of the Humphrey perimeter automatically excludes VFs with ≥ 15% FP responses from the baseline or follow-up series. Notwithstanding the automated removal of fields with excessive FPs, the clinician can also judge the reliability of a visual field and, if it is clearly unreliable, consider removing it from an analysis series, weighing the disadvantage of losing data against the advantage of having only more reliable data.

Short-wavelength perimetry (SWAP)

This perimetry technique features a blue stimulus on yellow background with a higher background bowl luminance than during conventional SAP. The theoretical advantage underpinning this mode of visual function testing is the relatively

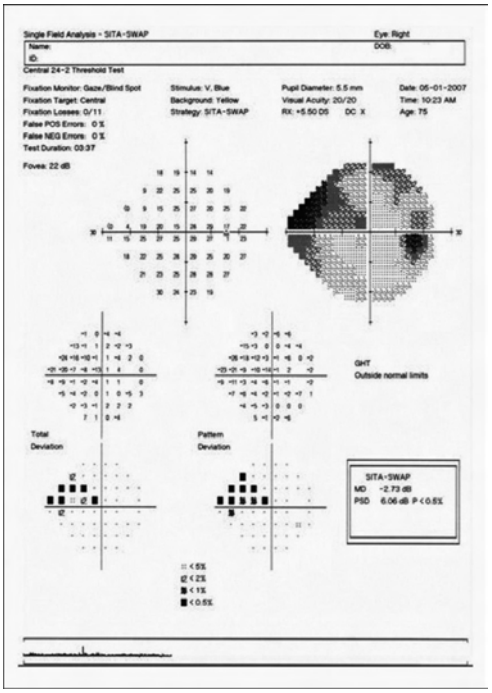

Fig. 2. Result of SITA SWAP test showing a superior arcuate/nasal step defect.

less dense matrix of blue cones serving the central visual field: this 'reduced redundancy' may lead to earlier glaucomatous losses being detectable using shorter wavelength stimuli. The SWAP test has a longer test duration than SAP, although a SITA version of SWAP has been developed which shortens the test duration. Research work by several groups has highlighted higher long-term fluctuation than SAP, and probably more a marked confounding effect of cataract. The higher long-term fluctuation characteristic of SWAP theoretically reduces the appeal of SWAP in the detection of VF progression.

There have been published reports which suggested that SWAP is able to detect glaucomatous progression prior to SAP. More recent work by Van de Schoot *et al*. has not supported this:[13] in a study of 416 ocular hypertensive subjects, 24 eyes of 21 subjects showed conversion using SAP. Of these eyes, 22 did not show earlier conversion in SWAP than in SAP. SAP even demonstrated earlier conversion than SWAP in 15 cases. In only two eyes did SWAP show earlier conversion by up to 18 months. SAP appears to be at least as sensitive to functional conversion to glaucoma as SWAP in a large majority of eyes.

SWAP is now considered less valuable for the detection, and monitoring, of glaucomatous progression.

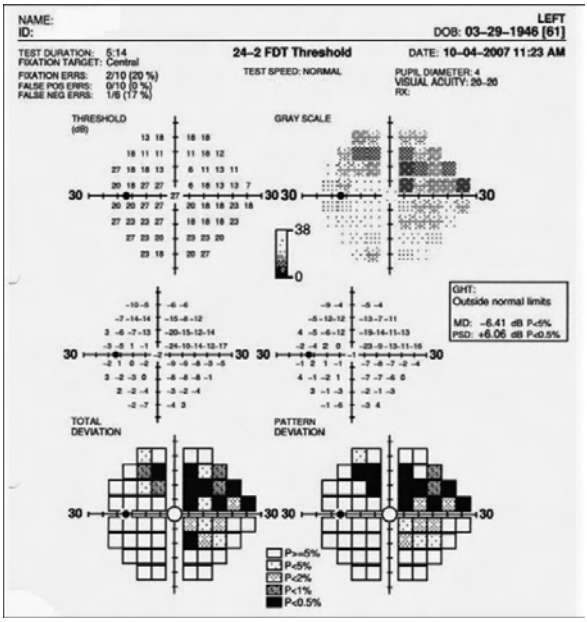

Fig. 3. FDT MATRIX test result from a patient with a superior hemifield defect.

Frequency doubling technology (FDT) perimetry

This rapid visual function test exploits the frequency doubling illusion. Early work has demonstrated a sensitivity of 85%, and a specificity of 90% for the detection of 'early glaucoma' using the HFA as gold standard.[14]

There has been limited work to ascertain if FDT is suitable for detecting progression. A recent study by Xin *et al.* enrolled 33 glaucoma patients (55 eyes).[15] The following tests were performed at two baseline and follow-up exams: Matrix FDT, 24-2 HVF, mf VEP, OCT and stereo-photographs. There was 21.1 (± 1.8 months) follow-up. For HVF there were significant changes in MD in eight (14.5%) eyes. For FDT, there were significant changes in MD in 13 (23.6%) eyes. Only five eyes showed changes in MD for both HVF and FDT. Each test showed progression in some eyes, but agreement among tests on which eyes showed progression was poor. In a further study by Fan *et al.*,[16] in eyes with SAP within normal limits of patients with OAG, FDT detected visual field loss in almost two of every three of these eyes and also predicted to some extent future visual field loss on SAP. However, a study has not yet been performed looking at the predictive value of SAP in eyes with normal FDT. Studies comparing FDT against SAP, in eyes with glaucoma defined by structural damage to the optic disc, find that the diagnostic precision of FDT is similar to,[17] or slightly better than,[18] SAP.

A further study,[19] compared the prevalence of functional progression using SAP compared with FDT (C-20/N-30 programmes) in sixty-five patients who were followed for a median of 3.5 years (median number of examinations, 9).

32 (49%) patients were found to have progressing visual fields with FDT, and 32 (49%) patients with SAP. Only 16 (25%) patients showed progression with both methods.

There is only limited evidence, to date, guiding the use of FDT in the monitoring of glaucomatous progression: the data suggest that there is little or no difference in the facility of the SAP and FDT perimeter to measure progression.

High pass resolution perimetry: HPRP

High pass resolution perimetry (HPRP) is a functional test which involves ring-shaped stimuli on a monitor with background luminance of 20 cd/m^2. The measured threshold is the smallest ring resolved by the subject at 50 retinal locations in central 30 degrees. It is thought that the HPRP response correlates directly with ganglion cell density.[20] The test is fast, five minutes/eye, and acceptable to patients.[21] There is only very limited evidence supporting the use of HPRP to detect glaucomatous visual function progression.

In a study reported by Chauhan *et al*.,[22] POAG patients were observed for a median of 4.5 years. Fifty-seven patients (50.4%) did not show progression with either technique. Twenty-four patients (21.2%) showed progression with HPRP alone, whereas 6 (5.3%) showed progression with SAP alone. The remaining 26 patients (23.0%) showed progression with both techniques.

There is currently insufficient evidence to support the use of HPRP to monitor glaucomatous functional progression.

Motion sensitivity

Motion sensitivity measures the sensitivity of the patient to a moving stimulus within the central visual field. Tests of motion, lacking any resolution component, constitute a 'hyperacuity' test,[23] and are more robust to the effects of cataract and blur.[24] An early version of the test, which tested a single visual field location, did show some potential value in the early detection of functional motion defects which preceded SAP defects with a sensitivity of 75%, and a specificity of 84%.[25] More recent work has described further development of a multi-location motion sensitivity test,[26] but there is no published work, as yet, describing use in the monitoring of glaucoma progression.

There is currently insufficient evidence to recommend the use of motion sensitivity in monitoring visual field progression.

Advanced disease: SAP stimulus size and 10-2

Advanced glaucomatous visual field loss presents additional challenges to the monitoring of ongoing functional loss. Use of the standard HFA 24-2, or 30-2,

testing patterns will inevitably result in large areas of the tested field showing zero sensitivity, and correspondingly low 'resolution' to detect ongoing VF loss in the remaining few central points that do demonstrate measurable sensitivity. Clearly, many of these patients with MD worse than, perhaps, -20dB, will already have severe functional defects, so may already have experienced maximal intra-ocular pressure (IOP) lowering treatment, *e.g.*, surgery. Nonetheless, in some patients it will be desirable to continue to monitor even a very small (< 10 degrees) central remaining visual field for ongoing visual field loss. Options include using a larger angular size stimulus, *i.e.*, size V, instead of the standard size III, and/or a more densely populated testing grid, *e.g.*, HFA 10-2. However, at this time, the evidence supporting either of these strategies is neither extensive nor conclusive:

SAP size V versus size III

Size III may overestimate loss in advanced disease (and may underestimate loss in early disease), but is currently used as the perimetric standard because it is probably a reasonable compromise. Gilpin *et al*. tested ten healthy subjects on the Humphrey Field Analyzer using Goldmann stimulus sizes I-V to determine the effect of varying the area of the stimulus upon threshold:[27] an increased total fluctuation was observed for Goldmann stimulus sizes I (3.69 dB) and II (3.17 dB) and a similar fluctuation for stimulus sizes IV (2.64 dB) and V (2.51 dB) as compared to stimulus size III (2.52 dB). The study suggested no advantage results in reduced threshold fluctuation by changing the Goldmann stimulus from a size III when testing *normal* individuals on the HFA. Wall *et al*. reported research findings comparing ten patients with glaucoma and five age-matched control volunteers who were tested with the HFA which was used to measure frequency-of-seeing curves.[28] At two visual field locations on 24-2, stimuli were presented in 2-dB intervals to at least 10 dB on either side of the estimated program threshold. This protocol was performed for each of three stimulus sizes (Goldmann sizes I, III, and V). For the patients with glaucoma, one test location was chosen in an area of normal visual field sensitivity, the other in an area of 10 to 20 dB loss. Variability was lowest at the abnormal sensitivity test location in glaucoma using a size V stimulus. Differences between the V to III and V to I stimuli were statistically significant (size V = 2.9 dB, III = 10.1 dB, I = 10.1 dB). The conclusion was that the use of size V stimuli in SAP reduces variability in tests of moderately damaged and normal sensitivity test locations in subjects with glaucoma.

Value of HFA 10-2 testing pattern

There is, perhaps surprisingly, little research into the value of 10-2 in advanced glaucoma cases. Much *et al*. reported on 84 eyes of 64 patients who satisfied inclusion criteria with an average follow-up of 8.3 ± 3.1 years.[29] During the study period, 14 eyes lost more than three lines of visual acuity. Of these 14, 8 eyes progressed to a visual acuity of 20/200

or worse. Seven eyes lost 3 dB or more from the MD that could be reproduced over two visual fields**.** They concluded that most treated patients with end-stage glaucoma, whilst quite commonly losing lines of BCVA, did not demonstrate a progressive loss of the central visual field during long-term follow-up. Fujishiro *et al*. reported on 27 eyes of 27 OAG patients with a best-corrected visual acuity (BCVA) of ≥ 40/200 and a mean total deviation of test locations of the 10-2 program of the Humphrey VF analyzer of ≤-20 dB preoperatively.[30] Intraocular pressure (IOP), VF parameters of the 10-2 program, and BCVA were examined for 12 months after trabeculectomy. IOP decreased from 19.7 ± 5.8 to 9.7 ± 2.6 mmHg ($P < 0.001$) over one year postoperatively. The slopes of all VF parameters did not significantly differ from zero ($P > 0.33$), and none of the presumed factors significantly correlated with the slopes of those parameters ($P > 0.14$). There were two eyes (7%) and one eye (4%) with ≥ 2 lines of deterioration in BCVA at one and 12 months, after surgery with no apparent causes. The group concluded that trabeculectomy resulted in little change in the central 10-degree VF, but significant decrease in BCVA without apparent causes might occur approximately 5% of the cases.

In conclusion, there is not very much evidence available supporting the adoption of a size V target in testing advanced glaucoma cases; there is, however, a clear need for more research into this topic, since this may ultimately prove to be a useful option in some patients. The research that is available does suggest that loss of BCVA is not uncommon in advanced glaucoma, but does not necessarily correspond with measured loss on HFA 10-2 pattern testing. As neither 'size V' nor '10-2' VFs can be analyzed within an existing series of 24-2, or 30-2, HFAs to identify progression, the clinician needs to weigh the benefit of the additional information gained from a change in VF strategy against the loss of facility to determine progression from prior data.

II. Data acquisition in a clinical setting

Nomdo Jansonius, David F. Garway-Heath

Summary

Following the collection of baseline data, low- and moderate-risk glaucoma patients can be monitored with perimetry at a fairly low frequency of typically one test per year provided (1) the baseline fields have been collected over a shorter period and (2) the frequency of testing is increased as soon as progression is suspected to have occurred. High-risk patients should be tested more frequently; patients who have been stable for some time can be monitored at lower rates.

Background information

Introduction

This chapter comprises the 'acquisition in clinical practice' section of the functional progression detection consensus. Since most glaucoma patients are taken care of by general ophthalmologists in many health care systems, the rules given here are aimed to be simple, robust and safe, and are presented in a limited number of easy-to-digest statements. These statements are summarized in the consensus statements presented elsewhere. Below some rationale and evidence for the proposed advice will be given.

About evidence

Consensus statements should be embedded as much as possible in evidence. The evidence hierarchy in medicine is often given to start with systematic reviews and meta-analyses of RCTs, followed by the individual RCTs themselves. In perimetry, these types of evidence are rare and, in fact, may not be able to answer many of the important questions. In perimetric progression detection, mathematical modeling is a commonly-used and valuable tool. This can be accepted as being evidence, as long as several requirements have been fulfilled. First, the inevitable assumptions must be clearly stated and reasonable, and adequately discussed. Second, estimates of model parameters must be based on sound experimental data or reasonable assumptions (see first requirement). Third, the effects of small perturbations or larger deviations from the original parameter values on the final conclusions must be clear (sensitivity analysis), that is, measurement variability must be addressed rather than that only averages of parameter values are used.

Studies versus clinical experience

The costs of perimetry are minor compared to total costs in clinical/research studies. Hence, high perimetric rates are used in order to maximize information yield. In clinical settings, with limited resources and elderly patients that have to travel, and so on, it is worthwhile to look for cost-effective perimetric rates. Moreover, it is important to realize that too frequent perimetry may result in the number of falsely-identified progression cases (false-positives) exceeding the true positive cases of progression, and thus may reduce quality of care; test frequencies appropriate to good clinical care are needed.

Another important difference is that a clinician uses additional clinical information to estimate the prior probability of progression (the likelihood that any given patient may be progressing, before the test result is known) and thus to make decisions and to weigh the need of frequent perimetry. Examples are IOP, disc hemorrhages, disease stage and patient age. In a research study, these additional features are covariates in a multivariate analysis, and, to prevent bias,

they should not be part of the outcome measure (progression status) nor should they influence the decision of a treatment change. Studies reveal the risk factors; clinicians use them to optimize care.

For these two reasons perimetric schemes are different in research studies and clinical practice: clinicians have a different job to do.

Acquisition and interpretation influence each other

This chapter is about acquisition. It should be realized that data acquisition and interpretation/analysis mutually influence each other, and treating them independently is to some extent artificial (for example, the number of fields needed for a certain decision depends on the analysis algorithm used; the other way round, the false-positive frequency resulting from the analysis algorithm dictates a minimum required prior probability of change (likelihood of stability), and hence, a minimum follow-up duration (because the prior probability increases with time).

To derive some rules for visual field acquisition in clinical practice, it is assumed that analysis will at least comprise (1) the detection of events; (2) the estimation of a rate (velocity) of progression (ROP); and (3) the timely detection of fast progressors. Most event detection algorithms require two baseline fields and three follow-up fields. These should be collected before clinically important change has occurred in fast progressors. The uncertainty (confidence limits) in a ROP measurement should be much smaller than the range of ROPs found in glaucoma patients (otherwise the measurement does not add any information). This often requires a follow-up of more than five years,[31] but depends somewhat on the actual ROP and the frequency and spacing of the visual fields. In a shorter period, a measurement of the ROP may be used to *identify* rapidly progressing patients,[32] but the estimate of the true ROP is poor. However, the major factor contributing to precise estimates of ROP is duration of follow-up, so that it is difficult to obtain a precise ROP estimate in a period as short as two years. When the ROP is calculated, the precision (confidence intervals for the velocity of change) is also calculated, so the clinician can judge the reliability of the slope (progression velocity) estimate.

Visual field testing in the initial period should be designed to catch rapid progression and provide data for subsequent measurement of ROP over longer periods.

Data acquisition in a clinical setting

New patients/baseline data collection

In patients in whom lifetime risk of visual disability is low, at least two reliable fields should be collected in the first six months; high risk patients may require three fields in the first six months. The reason for this advice is that most event

detection algorithms require two baseline fields (EMGT criterion/GPA-I;[33] NPA;[34,35] GCP[36]). In perimetrically naive subjects, learning may occur during the initial field;[37] a further baseline field should be made in the case of obvious learning. In the Humphrey 'glaucoma progression analysis' (GPA) software, significant learning effects are identified automatically (if all fields are from compatible strategies) and the software warns the user to seek an alternative baseline. In GPA2, the first field is removed automatically if a learning effect is identified. As always, the clinician should judge the fields for reliability and especially fields with high false-positive errors or rim artifacts should be discarded.

Note: Because of this initial learning and of residual learning (small further improvement after the first field), 'progression' within the baseline should alert the clinician to the possibility of rapid progression. A monotonic decrease of the mean deviation (MD) within the baseline may denote this. Here, the clinician should continue frequent visual field testing rather than slowing down to lower frequencies.

Note: The specificity of one of the event detection algorithms, the 'non-parametric progression analysis' (NPA;[34] see below) can be improved (false-positive identification reduced) by taking three baseline fields. A good baseline is no waste of resources – you can never go back to make a better one!

Follow-up visual-field test frequency: adaptive testing

For decades, clinicians were used to performing one visual field per year, almost irrespective of individual risks and test results. Several studies have shown that higher perimetric frequencies were better for an optimal information yield.[32,38,39] These studies assumed the tests to be equally spaced in time. However, clustering of tests may be more efficient ('wait and see')[40] and higher frequencies of testing are not needed in stable patients, due to the fact that, according to Bayesian mathematics, only fields with suspected progression need confirmation/falsification. This is the essence of 'adaptive testing.'[41] Adaptive testing implies that most patients can be monitored with perimetry at a fairly low frequency as long as (1) a baseline has been made over a short period; and (2) the frequency is increased as soon as progression is suspected to occur. A further field should be performed soon after suspected progression is identified to confirm/refute the progression; a single field with no statistical difference from baseline is sufficient to refute progression. A more detailed analysis[42] revealed that adaptive testing combines the information yield (ability to identify progression) of four equally-spaced fields per year ('optimal')[39] with the costs (number of fields and false positive identification) of two fields per year. Figure 4 shows the effects of wait and see and adaptive testing on the timing of visual field tests.

What follows is a *general rule* for frequency of testing, which needs to be *adapted* in the context of the patient by considering the severity of visual field loss and the presence of (other) risk factors or signs for progression (see elsewhere in consensus document), and life expectancy.[43] The timing of visual field tests is determined using the rules of adaptive testing. In adaptive testing, the

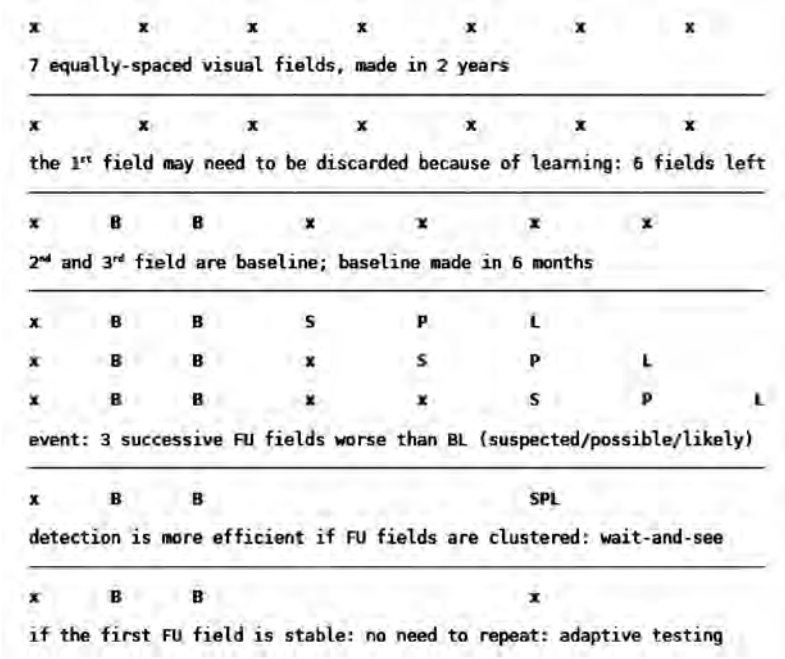

Fig. 4. Effects of wait and see and adaptive testing on the timing of visual field tests.

next scheduled visual field is performed sooner if progression is suspected on the basis of an 'event' analysis. Here, an event is defined as the occurrence of a measurable change from a predefined baseline.

After the baseline, and in the absence of a suspicion of progression within the baseline (see above: new patients/baseline data collection section), the perimetric frequency can be reduced to typically one test per year in low and medium risk patients. As long as a field made during follow-up is considered to be stable according to the event-detection algorithm used (see below), the frequency can be kept low. When progression is suspected according to the event-detection algorithm used, the field should be repeated within a shorter period. To minimize false-positive 'flagging' of progression, progression can only be diagnosed if confirmed. Failure to confirm progression is sufficient to consider perimetry stable.

Note: A single field suggesting progression is called 'suspected progression'. If confirmed once, it is called 'possible progression' and if confirmed twice 'likely progression' (three successive fields worse than baseline). Reducing the interval before the next field may be initiated after either suspected or possible progression, depending – amongst other things – on the 'possible progression' algorithm used (see below). For GPA, reducing the test interval after 'suspected progression' is advisable because of the very low specificity of GPA 'likely progression'. In that case, a single confirmation is sufficient to reach likely progression. For NPA, accelerating may be initiated already after 'suspected

progression', but in that case two confirmations are needed to reach likely progression. The specificity of NPA 'likely progression' is 90% with two baseline fields and 95% with three baseline fields (see above); hence, three baseline fields are needed to ensure a specificity comparable to that of GPA.[11, 44] This is an example where acquisition and interpretation influence each other. All this is indicative as there is currently insufficient evidence to provide a definite threshold for repeating a test to confirm progression.

Note: The base rate in adaptive testing is one test per year and is intended for low- and intermediate-risk patients. High-risk patients should be tested more frequently. Although several risk factors for progression have been established (see chapter 4 on Risk Factors, page 101), it is not possible to establish individual progression risks reliably. However, fine-tuning becomes possible with time. In patients without an event in five years, monitoring may be performed at lower rates (for example, by doubling the interval used in the initial five years).

Note: The base rate in adaptive testing of one test per year is not arbitrary, but follows from Bayesian mathematics, specificity data regarding event-detection algorithms, and observational data regarding the incidence of events. The prevalence/prior probability of what you want to observe should be higher than 100-specificity. A measurable event (confirmed progression) occurs, with current event-detection algorithms, in about 10% of the patients per year (treated arm of Early Manifest Glaucoma Trial (GPA);[45] Groningen Longitudinal Glaucoma Study (NPA)[35]). This suggests a prior probability of 10%, but even the likely progression used in these studies does not guarantee a very high positive predictive value,[34] and thus some (about half) of the 10% with a measurable event may still be false positives. Thus, if we assume a specificity of 95%, testing frequencies higher than yearly will result in too many false-positive findings. In *advanced disease* and *poor control*, the prior probability of progression is higher and the consequence of progression is more important; in adaptive testing this has been implemented by a shortening of the base interval for testing (from one year to, *e.g.*, six months). Similarly, the base interval can (and should) be extended to up to two years in early and well-controlled glaucoma that has been stable for some time.

Note: Only fields with suspected or possible progression need confirmation/falsification. This is because of the low prior probability of progression (typically 10% per year or less). A single test suggesting stability reduces the probability of progression to a few percent (probability of stability almost 100%). No need for further testing! This conclusion is largely independent of the assumed sensitivity and specificity – because of the low prior probability. A single test suggesting progression increases the probability of progression to, for example, 20%. This is obviously not sufficient to make a management decision, and a repeat test is needed. Experimental data showed that approximately 40% of patients returned to a stable field after an initial confirmation,[35,46] indicating that two confirmations are needed. If we would confirm/refute progression with the next field taken at the base frequency of one test per year, instead of testing sooner, a delay to decision-making would result. This is the basis of adaptive testing:

if stable, perform the next test according to the base frequency; if suspected progression, reduce the test interval to confirm or refute progression. In this way, the information yield is optimized for a given number of tests.

Note: When progression is flagged by an 'event' algorithm, consider the time between baseline and the event. A short interval indicates that progression is likely to be rapid; a long interval indicates that progression may be very slow and may not require intervention. Moreover, false-positive 'flagging' of progression can occur and this becomes more likely the longer a patient is followed. It is, therefore, important to consider all other clinical factors (such as intraocular pressure control, imaging results, presence or absence of disc hemorrhages) when interpreting a statistical flagging of progression.

Note: If no event occurs within five years, MD progression is likely to be slower than 0.5 dB/year. During the initial follow-up period (which may be several years), estimates of the true *rate* of progression are usually imprecise; a patient may be *identified* as progressing, because the velocity of progression is statistically significant, but the true velocity of progression may be faster or slower. Some perimeters (*e.g.*, the Humphrey perimeter) provide the estimated velocity of progression and the 95% range of possible progression velocities; clinicians should interpret this range of possible velocities in the context of all clinical data.

Event-detection algorithms

Table 1 below shows the characteristics of some event-detection algorithms. Table 2 gives the definitions of suspected, possible and likely progression for GPA, GCP and NPA.

Table 1. Characteristics of commonly used event detection algorithms

Algorithm	Total deviation (TD) or pattern deviation (PD) based	MD range where the algorithm can be used	Pros and cons
GPA	PD	0 to -15 dB	Specificity depends on variability of individual patient; on average, relatively high specificity; HFA only; not for advanced disease
GCP	TD	Entire range	Specificity depends on variability of individual patient; HFA only; not available for SITA
NPA if applied to MD	TD	Entire range	Specificity equal for all patients and disease stages; specificity relatively low: consider making a third baseline field; applicable to all perimeters

Note: In the Humphrey GPA software, if the baseline MD is ≤ 15 dB or > 5 dB, the software adds a disclaimer that the baseline MD is out of range. For a

given point, if the sensitivity is ≤ 15 dB or > 5 dB, then the 'change' for that point is set to 'No information' (X) for follow-up examinations.

Note: Algorithms based on total-deviation analysis are prone to confounding by media opacities (see next section).

Note: NPA can also be applied to the VFI and, in early glaucoma, up to an MD of approximately -10 dB, also to the pattern standard deviation (PSD) global index.

Note: GPA and GCP are perimeter-specific. In the Octopus, no event-detection algorithms in the restricted sense exist; here, linear regression on the MD is performed right from the beginning and a slope significant at the $P < 0.05$ level is considered an event (with a specificity of 95% for each time the analysis is performed). NPA can be used on all perimeters that provide a global monotonic measure of glaucomatous damage (like mean deviation, mean defect or VFI).

Table 2. Criteria for suspected, possible and likely progression

	Suspected progression	Possible progression	Likely progression
GPA/GCP	≥ 3 open triangles	≥ 3 half-open triangles	≥ 3 black triangles
NPA	1 field with MD < lowest MD of baseline fields	2 consecutive fields with MD < lowest MD of baseline fields	3 consecutive fields with MD < lowest MD of baseline fields

Note: ≥ 3 open triangles is quite common by chance and thus hardly indicative for progression; therefore 'possible progression' requires confirmation in a shorter interval with GPA/GCP (see above).

After diagnosing progression

After an event has been diagnosed, two questions remain. First: is it glaucoma that caused the change? Second: what should be done?

Cause of progression?

The major confounding factor in clinical practice is the development of cataract or posterior capsule opacification. This occurs especially if total deviation analysis is used. Factors that make an optical explanation of the observed progression less likely are:

1. Equal damage in total and pattern deviation plot
2. Individual test locations with normal sensitivity
3. Increase in PSD
4. Absence of media opacities

And factors that make an optical explanation of the observed progression more likely:

1. No increase in PSD in the case of an MD better than -10 dB

Neither these rules, nor the application of pattern deviation analysis, facilitate the identification of localized subcapsular posterior cataracts, retinal lesions or disturbances of the higher visual pathways. Slit lamp, ophthalmoscope, and alertness for homonymous and bi-temporal patterns remain indispensable.

Especially in the case of doubt, the prior probability of progression should be taken into account. Factors that influence the prior probability of progression are IOP, glaucoma stage, age, and *e.g.* the occurrence of splinter hemorrhages. However, these factors are at least partially already discounted in the base interval of adaptive testing because they contribute to the classification of a patient in high, intermediate or low risk.

What should be done?

After confirmed progression has been identified, **a treatment change** may be considered. Factors that may contribute to the decision to change treatment are the glaucoma stage, the rate of progression (or time to event), the location of the scotoma(ta) and its progression, the patient's life expectancy,[43] the patients preference (some may prefer 'to be on the safe side' or to refrain from treatment as much as possible) and the potential impact (such as safety or tolerability) of the next therapeutic step. Following a significant change in treatment (such as surgery), **a new baseline** must be defined. For the new baseline, the last two fields can be used (*i.e.*, the two fields confirming progression); no need to record additional fields for this! If the event occurred beyond five years after the initial diagnosis or the previous treatment change, the rate of progression can be determined.

Some final remarks

Adaptive testing and fast progressors

With the aforementioned recommendations, six fields (five if the first, learning, field needs to be excluded) will be present already after 1.5 years of follow-up in fast progressors: the baseline fields, one field performed a year after finalizing the baseline and two confirmations a short interval following the observed deterioration. If the test interval is shortened after 'possible progression', as is advocated for GPA, confirmation will take 1.5 to 2.5 years (depending on whether the patient's first visual field can be used). These time periods are in line with existing recommendations and should allow for a timely detection of fast progressors.[32] Hence, the approach presented here seems to be an acceptable trade-off, since testing more frequently than this would lead to more false-positive 'flagging' of progression.

Within the first five years of follow-up, the estimation of the ROP is usually imprecise, however, in patients with an event within two years, or more than one event in five years, clinicians should be aware of rapid progression. If no event occurs within five years, progression is typically slow (below the median progression rate). Nevertheless, an event will occur sooner or later when there is little or no true progression because the specificity of event-detection algorithms decreases with increasing length of follow-up (every time a new field during follow-up is analyzed for progression, there is an opportunity for a false-positive identification of progression). Following an event, and with a sufficient number of tests and duration of follow-up (typically five years), a ROP, with corresponding confidence limits, can be determined and the management of the patient can be based on this rate and confidence limits, rather than solely on the occurrence of the event itself.

Finally

Although this chapter is about data acquisition rather than analysis, acquisition and analysis are interdependent and from the text above it is clear that the major future research question is a better event-detection algorithm. An ideal algorithm has a high specificity (without compromising sensitivity), a specificity that is based on patient-specific variability rather than variability based on a population, and can be used over the entire disease severity range and with all perimeters.

III. How to measure/detect functional change; statistical approaches

Anders Heijl, Boel Bengtsson

Introduction

The aim of this section is to discuss different methods to assess functional glaucoma progression, to present consensus statements, and to find support from the literature and possible evidence for the usefulness of the different methods.

Trend vs event analyses

Trend analysis is used to measure/quantify progression, and is typically performed by linear regression analysis of a summary visual field index, where the coefficient of the slope denotes ‘the rate of progression’. Trend analyses can also be performed at individual test points or parts in the field. Event analysis is designed to detect progression, and is typically performed by comparing follow-

up fields with baseline fields. To flag progression, confirmed deterioration is required in consecutive tests. Focal or regional metrics show the location of the progression, while summary/global metrics show the overall progression over time. This is a simple and comprehensive way to evaluate progression, but it is not particularly sensitive to small local changes.

Local trend analyses for detection of progression have lower sensitivity, but better specificity than event analysis.[47-49] Likewise global trend analyses detect progression later than event analyses,[50] however, the intension with trend analyses is not to detect but to measure progression.

All methods available today, both event and trend analyses, for perimetric progression are insufficient at advanced stages of field loss because of truncation (flooring) effects.

Both trend and event analyses have been available in perimeters since the late eighties.

Linear vs non-linear fits in trend analysis

Several papers suggest that linear regression slopes best describe glaucoma progression in treated patients when regressing mean sensitivity, mean deviation, mean defect or the visual field index over time.[51-54] A recently published paper by Caprioli and co-workers suggest that an exponential fit should be more appropriate than a linear fit,[55] which is true at locations or in fields reaching the floor. Thus, this effect is probably caused by truncation. Other global indices describing dispersion of sensitivity values in the field, e.g., pattern standard deviation and loss variance, are similar in normal and in perimetrically blind eyes with a course best described by a second-degree polynomial curve. These two indices, therefore, cannot be used for estimating rate of progression.

Pointwise vs summary parameters

Pointwise and summary parameters are both needed, but for different purposes. Pointwise parameters show the location of the progression. Progression at paracentral points is considerably more clinically important, and also more reliable, than progression at peripheral points. Summary parameters are excellent for measuring general rate of progression, and are used/plotted in easily comprehensible tools to identify patients progressing at rates that threaten quality of life.

Pattern deviation vs total deviation (vs hybrid Visual Field Index)

Total deviation is the deviation from the age corrected normal threshold value, while pattern deviation in addition is corrected for general reduction of sensitivity. The purpose of introducing the pattern deviation concept was to reduce effects on visual field interpretation caused by media opacities.[56] Entirely diffuse sensitivity loss is rare in glaucoma,[57] but at least at the stage of moderate glaucomatous field loss a diffuse component is added to the localized loss. This

means that basing progression on numerical pattern deviation values only will underestimate sensitivity loss caused by glaucoma.[58,59] The visual field index identifies glaucomatous loss in pattern deviation probability maps, but calculates defect depth using numerical total deviation values. A study comparing rate of progression calculated by mean deviation values (mean deviation is a weighted mean of all numerical total deviation values) and by the visual field index, showed similar rates in pseudophakic glaucoma eyes, while rate of progression was smaller with the visual field index than with mean deviation in eyes with increasing cataract.[60]

Clinical routine vs clinical trials

Simplicity is important for clinical routine. Interpretation of trend analyses of a summary index over time is rather intuitive, or can at least be easily taught/learned.

Commercially available progression analyses should be recommended for clinical management.

Validated techniques (event analyses) for detection of progression are suitable for clinical trials (event analysis generally detect progression earlier than trend analysis). The techniques applied in clinical trials are not always suitable for clinical routine, because of differences in testing frequencies, because trial endpoints may be complicated and/or include difficult calculations, or because trials may have been designed for particular stages of glaucoma, et cetera.

Estimating criterion specificity

How can we assess specificity for methods detecting or measuring functional progression? Random test-retest variability may be determined in glaucomatous people at different stages of disease by re-testing patients with intervals short enough that no measurable progression may have occurred. This was done when developing glaucoma change probability maps. The short time interval used, *e.g.*, about one month, may have resulted in smaller variations than would be typical with much longer test intervals.

In the change probability maps each test point has a risk of 5% to falsely be flagged as significantly deteriorated. Considering the relatively large number of test points, 52 in the 24-2 pattern, or 74 in 30-2 pattern, one should expect to have several test point falsely flagged as significantly deteriorated by chance alone. By requiring a certain number of test points to be flagged repeatedly as significantly deteriorated in consecutive tests, specificity increases considerably.

In trend analyses a significant negative slope is often regarded as a sign of progression, but an almost flat slope with just a minimal negative gradient can be statistically significant, and not clinically significant, if the scatter across the regression line is minimal. One should, therefore, consider the gradient of the slope when assessing possible regression.

Finding a valid reference standard when studying specificity of different progression criteria is problematic. Computer simulations have been used[47] and also consensus by expert observers,[11] but such agreement among observers have been reported to be not particular good.[49,61]

Evidence

Progression trend of global indices tends to be fairly linear in treated patients, except in those developing very advanced loss where the effect of truncation change the course of the slope.

Specificity is difficult to determine because of lack of reliable reference standards. Randomizing test sequence is one possible approach to assure that true progression is not falsely classified as non-progression.

IV. Use of visual field testing in clinical trials

Douglas R. Anderson

Introduction: Clinical Research

The traditional 'clinical trial' is a comparison of two groups with two different managements; the principles are the same whenever two groups are compared over a period of time. Some principles apply even when there is only one group, for example to document the range of rates by which glaucoma progresses in a specific group of people.

Measurements of changes in structure or of visual function (or electrophysiologic function) may be appropriate outcome measures of whether the condition is progressing. Other research may aim to determine outcome in terms of the deterioration of the ability to perform tasks, or to enjoy life. Although very important, these impairment or disability outcomes are not included in the scope of the present discussion.

The basis for visual fields as an indicator of progression

Visual field testing is used to measure how function changes (presumably for the worse) over time.

Event analysis and rate analysis

Visual fields are important in *diagnosis* and in determining the *impairment* of the individual; but here we focus on progression, that is use of a *change in visual field measurement* as a means of *determining change (worsening) of the glaucomatous damage*. This analysis of functional changes (usually worsening) over time may be done by tabulating '**Events**' or by calculating '**Rates of Change**' over time.

Analysis by 'events'

An 'event' represents the point in time when a presumably continuous subclinical deterioration of visual function crosses a threshold amount of change compared to some baseline and that there is a certain statistical likelihood that the apparent change in genuine.

To be meaningful, an event (a change from baseline) must be statistically significant. In clinical care of individuals, the event must also be of a magnitude to be consequential to the patient's present or future lifestyle. However, for many clinical studies, the event may not have to be of a consequential magnitude as long as it is statistically significant and is specific (consistently different from the baseline). For example, in the untreated arm of some recent studies, small changes must be detected for ethical reasons, but also specificity must be maintained (in order to avoid false positive determinations of progression events).

Comparing studies

In an effort to satisfy requirements of particular studies, the definition of an 'event' varies among studies. Because the definitions of progression differ, the incidence of progression events cannot be compared between studies. Additionally, the studies involve different populations, perhaps with meaningful differences in the type of glaucoma or the stages of disease in the cohorts.

Therefore, the outcome of treatment for a group in one study cannot be compared to the outcome of another treatment in a group in a different study (different event criteria, different makeup of cohorts studies).

When different criteria that constitute an 'event' are applied to the same data, they may yield similar or yield different incidence-frequencies of progression or developing glaucoma. Even when the incidence frequency is the same, two different criteria often do not identify the same individuals as progressing.

Specific example:[59] In OHTS, the criterion used for visual fields was 'conversion' from a normal field to an abnormal one. When an event analysis criterion for 'progression' is applied instead, the treated and untreated groups are still demonstrably different, but the two criteria do not identify the same individuals as having developed glaucoma. The presumed explanation is that some individuals started barely within normal limits, and changed slightly to become abnormal ('converted'), without meeting event criteria for progression, while perhaps others were highly normal at baseline, could be shown to have progressed, but didn't 'convert' to having diagnosable glaucoma, being still in the normal range. Hence, Venn diagrams show poor agreement between the two criteria with regard to which individuals are identified, even though the two different criteria yield the same relative incidence of endpoint events.

When visual field tests are performed regularly to probe whether progression has occurred, the specificity of the criterion becomes important. As an increasing number of tests are performed (either on one patient by virtue of long follow up, or as a consequence of having large cohorts and hence more examinations),

it becomes increasingly likely that a statistically significant event will occur falsely.[42] To overcome this problem, confirmation of some sort is required. It would make sense that as the number of follow-up tests increases, the number of confirmations required to be increased to maintain specificity (or that other signs of progression are required to accompany the visual field event). Another solution is to require lower p-values as additional tests are performed. The fear of losing sensitivity might be mitigated by the fact that, if it takes a long time for a statistically significant event to occur and, therefore, is in need multiple confirmations, it is likely that the progression is slow and time expended in confirmations is of little consequence.

Event analysis is developed from all the re-test values found on re-testing at locations with a given baseline value on the first test (or averaged baseline tests). Because the cohort includes individuals who are highly variable, significant deviation from the baseline includes the highly variable individuals, which helps ensure that progression is not flagged because of deviant values in a highly variable individual, improving the overall specificity. However, were it possible to know that a particular individual has low variability, it is theoretically possible to detect a smaller change with higher statistical certainty. The mean of duplicate or triplicate baseline tests gives a somewhat more credible starting value, but gives a poor estimate of the individual's variability. This is the basis for 'non-parametric progression analysis' (NPA).[34] However, individual variability of testing is not estimated accurately from baseline tests, and population test-retest variance is used. In contrast, when the rate of decline of a variable (to be discussed below) is determined, the repeatability of an individual patient is automatically taken into account; more test results are required to achieve significance of the trend when reproducibility is poor than when reproducibility is good.

Ageing changes

Visual deterioration with age is a confounder. It is undoubtedly due to a change in the anatomy and physiology of the eye and nervous system (the optical pathway from cornea to retina, and the neural pathway from the photoreceptors, through the visual cortex, to the region of cognition). Changes with age can be considered to tissue deteriorations of various sorts, but they are not the disease under study, that is, glaucoma. Usually an age-related normative data set is used to overcome the average age-related deterioration, and abnormality is expressed as a 'deviation' from the mean value of the measurement among people of that age. Further correction can be made for any diffuse loss due to diseases of age (like cataract) that may be more pronounced in some individuals, for example by making use of the 'pattern deviation' values. However, this correction for uniform diffuse loss from most age-related disease also removes any uniform general dysfunction caused by glaucoma. Thus, only information from those regions that deteriorate to a greater degree than any general deterioration will contribute to a recognizable 'event' of progression due to glaucoma. Without

these corrections for age, for general visual deterioration, or both, 'events' defined as a fixed amount of decline at more than a defined number of points will occur without ongoing progressive increase of glaucomatous damage. For the most part, however, with the corrections presently developed and used widely, changes due to age or disease such as cataract do not interfere with evaluation glaucomatous progression. They do not correct for diseases that produce local visual deficiencies, examples of which are macular degeneration, chorioretinal scars, retinal branch vascular occlusion, and lesions along the neural pathway.

In light of their deficiencies, why do we use event criteria? Defining 'events' does have the advantage of permitting a well-established statistical method to be used, that is, the 'life table' (Kaplan-Meier) analysis with enhancements for multivariate analysis. In this way, comparison of two groups possible in a manner familiar and easily understood.

Insufficient data are available to judge whether statistical analyses comparing study outcomes by 'event' analysis are more or less powerful for showing statistical significance of a difference between two groups than a comparison of rates of decline of a variable.

Rate (or trend) analysis

There are two rates. *Incidence rate* (or cumulative frequency) of events is the number who convert to glaucoma or reach some other threshold criterion (expressed as events per time, or percent per year). In contrast, *Rate of change* in some quantity may be expressed as the number of dB lost per unit time (ΔdB/year). In the previous section we dealt with events, including incidence 'rates'. Now we deal with a fundamentally different 'rate', a trend for change over time.

Trend analysis may take several forms, but is an attempt to estimate a rate of change of some *measurement* (visual threshold, thickness of retinal nerve fiber layer, and so on) that is presumed to have a *direct relationship to the underlying damage* or disease mechanisms (death of axons, failure of axons to transmit impulse, changes in astroglia physiology, loss of support from lamina cribrosa, and other unknown injuries). However, confounders, such as cataract development, should be considered.

Studying the trend of the visual threshold measurement is useful. Global summary measures are not the only clinically relevant parameter for visual impairment, but also bilaterally, diffuse versus local loss, location of loss, etc. Rates (rather than artificial 'events') have an inherent interest as a clinically relevant parameter, because for clinical purposes the rate, combined with location of the worsening defects, life expectancy, and so on, can be combined to decide whether more assertive therapy is needed. In the context of research studies, there may be room for theoretical and empirical work to find ways to use rates more effectively in clinical studies.

The visual field variable usually studied is one of the global indices, a number derived from all the tested locations. However, trend analysis is also used on individual locations, or on anatomically logical groups of tested locations.

Most statisticians seem to feel that in a regression analysis, an estimate of the slope with decent confidence requires six or more data points, which coincides with empirical experience.[32] Greater power (confidence in the slope esitmate) is obtained if three tests are performed at baseline and another trio at the end of the follow-up (say, two or three years), rather than six tests evenly distributed through the time.[40]

In addition to the number of tests, the time between tests in relation to the rapidity of the decline is important. Six tests one day apart will likely not give a meaningful estimate. The range of time over which the slope is meaningfully estimated for an individual will depend on the test-retest variance and the actual slope of the change in the variable being analyzed.

In principle, if two groups are being compared, it may not be necessary that the rates of each individual be quantified accurately if a difference between the average rate in the two groups can be shown.[62] Development of such a method would be equivalent to signal averaging, in which noisy variation is removed to reveal the average trend.

It does not seem well established whether loss of axons in untreated glaucoma is loss of a fixed number of axons per year or a fixed percentage of the remaining axons (or neither). Empirical data suggest that at least one summary statistic of visual fields (MD) has a linear decline in progressive individuals under treatment for glaucoma, but further work on these issues (linear or non-linear degree of damage over time, and linear or non-linear relationship between amount of damage and measured variables) is needed.

At some time-point a rate of decline becomes statistically significant. One strategy for analysis might be to consider reaching statistical significance is an ‘event’, and to use statistics designed for event analysis. Another strategy might be to deal directly with rates, or statistical significance of a difference in rates between two cohorts being compared.

If there is a change in management, the next visual field test could be the beginning of another series to be evaluated with a trend analysis from that time onward, as new tests are obtained, which requires patience to obtain a sufficient number of tests over a sufficient passage of time to show a change in the rate of deterioration. Alternatively, there are statistical procedures that will determine more objectively whether there is a change is the downward slope at a particular time, and an effort might be made to relate this tipping point in time to a change in glaucoma management, to a change in the patient’s general health, or some other cause. If the field test results are variable, it may be difficult to decide whether two periods of time have different slopes, or alternatively that the decline is simply non-linear.

An advantage of trend analysis is that, in highly invariant individuals, the slope may be estimated reliably in a shorter time. Reliable measurements are thus of advantage when estimating the deterioration of an individual. For those individuals with high variability, reaching an endpoint may be delayed until there is enough decline to overcome the variance (while they would be at risk of a false positive progression event if event analysis is used; such individuals

would be subject to false designations of progression if the population average variance was assumed, as is the case for most event analysis techniques). It has recently been proposed that rate of deterioration might be discerned in noisy data by assigning the average population test-retest variance,[63] but scientific evaluation of this approach is just beginning.

In many traditional applications, statistical analysis determines whether the slope is statistically different from zero, and the time when the slope became statistically different from zero is counted as a progression event. However, in the present context of comparing two groups, as in a clinical trial, the standard error of the average slopes of the two groups might be used to determine whether the average slopes are different. If most individuals in a cohort have slow deterioration, or none, they may dominate the averages and make distinction between the groups difficult to discern. In such instances, it may be advantageous to study 'events' and use Kaplan Meier life table analysis.

Bullet points

- In the context of a clinical study comparing two groups, the statistical task is to compare average rates between two groups, that is, to determine that the rates between the groups are different, not to determine the rate of each group. Use of the average deterioration in each group may overcome interference from variances that prevent estimates of the deterioration rate of particular individuals.
- Comparison of rates may be a comparison between two periods of time (before and after an intervention, for example) rather than a comparison of two cohorts.
- A potential advantage of rate analysis of an individual is that individual differences in variances is automatically taken into account when determining statistical significance of the slope (that is, whether the slope differs from zero or not).
- A potential disadvantage when comparing two groups is that the average slope may be dominated by many who have little or no progression.
- Development and empirical testing of statistical methods that utilize slopes is needed to determine whether they have advantage over Kaplan Meier event analysis for comparing two groups and the optimal method for doing so.

Reference cohorts in research

Determination of progression and comparison of two or more cohorts requires statistical analysis, which ultimately requires control or knowledge of variances. These include population variance, as well as measurement variances, including repeatability and reproducibility. In some settings, variances are reduced by including only subjects with low FP or FL rates, for example. This may permit

closer determination of relationships of structure and function, or may more cleanly determine that two groups differ.

In other contexts, exclusion of individuals with high retest variance will mean that the scientific results may not be applicable individuals who do not provide reproducible fields. In this way, the results cannot be generalized to the broader population. If a large proportion of otherwise eligible subjects is excluded, the results may not apply with certainty to the broader population.

It is easy to overlook that studies performed on selected patients may well not apply to those who would not have been eligible for the study. At the same time, complete understanding of the results may require that instances in which the apparent progression was not due to glaucoma.

Bullet points

- In performing clinical studies, it is important to consider the clinical context in which the results will likely be applied, and not to exclude patients to whom the study results might be applied by clinicians not conversant with the eligibility requirements used for the study.
- There may be times when the scientific question permits selection of subjects in order to reduce the unwanted impact of variable and unreliable field tests, or the effects of age and non-glaucomatous disease. However, for other scientific studies, such selection of subjects for study may limit the applicability of the findings to the general population, particularly if a large proportion of volunteers are considered ineligible to participate.
- Even in studies meant to have results that can be generalized, it is wise to identify individuals in whom visual decline is not caused by glaucoma, but by cataract, macular degeneration, diabetes, other vascular disease, intracranial disease, or other causes.

V. Research priorities for functional assessment of progression

William H. Swanson

Bullet points

- Determine appropriate ranges of stimulus contrasts for size III, and develop new stimuli with larger ranges of appropriate stimulus contrasts.
- Improve the interface between perimetrist and device, and between patient and device.
- Develop alternate methods for selecting stimulus locations in order to avoid extensive testing of blind areas and to focus on areas of interest.

A century and a half of clinical perimetry has produced a powerful tool that nothing else can match: we treat patients with glaucoma with the goal of preventing loss of vision, and nothing else can assess visual loss from glaucoma as well as perimetry does. Yet there are several research areas that could allow us to make this good tool even better. In the latter part of the twentieth century there were efforts to detect perimetric defects earlier than conventional perimetry ('pre-perimetric' glaucoma), but over the past decade it has become clear that conventional perimetry is already good enough,[64] and that in many patients perimetric defects are found before glaucomatous optic neuropathy is detected.[65,66] What we need is improved ability to detect progression of glaucomatous defects, because test-retest variability is quite high in scotomata.[67,68]

The first century of perimetry involved the doctor testing the patient, and with Goldmann's standardization[69] it became possible for trained perimetrists to provide reliable and repeatable findings that trained doctors could assess. However, it could take months to train a new perimetrist to give repeatable and reliable results, and two perimetrists could obtain significantly different results on the same patient.[70] Automated perimetry had the goal that different perimetrists would obtain similar results from the same patient, yet as it has moved towards this goal it has seen declines in the repeatability within scotomata. What could make a good tool better, for assessing progression, would be to reduce test-retest variability in defects while retaining perimetry's good ability to detect visual loss. This will involve improved selection of stimuli and test locations, better training of perimetrists, better selection and training of patients, and improved interfaces between the patient, perimetrist, and perimeter.

Conventional automated perimetry uses stimuli that Goldmann based on the methods and laws of psychophysics of the first half of the twentieth century, and with modern display systems we have the opportunity to use new stimuli to reduce variability by utilizing the knowledge of contemporary spatial vision and neurophysiology. Perimetric testing in patients with glaucoma emphasizes technology, but we need to improve the interface between the technician and perimeter, and between the patient and the perimeter.

Automated perimetry was standardized at a time when computing power was limited, and, for a given patient, the doctor had to choose one of several available sets of test locations. Regular grids of locations (30-2, 10-2, 24-2, 60-4) made it possible to compute an interpolated grayscale map of the measured sensitivities, providing clinicians with a visual portrayal that could be compared to the isopters measured with kinetic perimetry. The success of these comparisons lead to widespread adoption of automated perimetry, and emphasis shifted from the interpolated grayscale map to regular grids of probability maps. Statistical analyses have tended to focus on how many adjoining locations show losses, without reference to nerve fiber layer maps. However, glaucomatous scotomata are more likely to follow nerve fiber patterns than locations on a regular grid, so we need a new assessment of choice of stimulus locations.

Stimuli

What is conventional today was new in its time. Perimetry began in the mid-nineteenth century with a physical test object moved to determine the 'perimeter' of the visual field, and was useful for characterizing hemianopsias, ring scotoma, an enlarged blind spot and concentric constriction. By the start of the twentieth century, smaller test objects were being used to measure more subtle defects in the central visual field, allowing detection of arcuate defects. By the mid-twentieth century physical stimuli had been replaced by increments of light produced by an optical system, allowing standardization by using the psychophysical standards of the time.

Basic spatial vision research today uses display systems instead of optical systems, and emphasizes low contrasts. The automation of perimetry left us with a single Goldmann stimulus (size III) and another log unit of contrasts.[71] The utility of these high contrasts is not clear. and adds to test-retest variability in defects. In the 21st century we can use the tools and knowledge of basic psychophysics to develop improved perimetric stimuli.

Goldmann focused on differential light sensitivity for describing thresholds, while contemporary psychophysics focuses on stimulus contrast for describing thresholds. Basic vision science has found that the human visual system has the greatest sensitivity to stimuli that are patches of sinusoidal gratings,[72] and with appropriate choice of parameters these can be detected at contrasts near 3% throughout the central visual field.[73] By comparison, for size III stimulus the contrast required for detection in normal eyes ranges from 10% contrast ('35 dB') to 100% contrast ('25 dB'). In scotomata, very high contrasts are used, such 1000% ('15 dB') and 10,000% ('5 dB').

The use of high contrasts may be a primary cause of high test-retest variability.[74] Psychophysical algorithms assume near-threshold linearity: near threshold, the internal responses mediating detection increase linearly with contrast. This is appropriate for low contrasts, where retinal ganglion cell responses increase linearly with stimulus contrast. However, at high contrasts the responses of ganglion cells become nonlinear, increasing more and more slowly to increase in contrast.[75] A ganglion cell response may increase by a factor of 3 when stimulus contrast increases from 10% ('35 dB') to 30% ('30 dB'), but only by a factor 1.5 when contrast increases from 100% ('25 dB') to 3000% ('20 dB') and may show no increase at all from 10,000% ('15 dB') to 30,000% ('10 dB').[76]

When stimulus contrast is kept below 100%, test-retest variability remains low.[77] By using perimetric stimuli for which mean normal contrast threshold is near 3%, we could more easily avoid high contrasts. In damaged areas, where contrast sensitivity is low, it may be more useful to increase stimulus size rather than use high stimulus contrasts. When evaluating new stimuli, we want to assess effects of lens opacity, pupillary miosis, stray light, and refractive error, as well as normal between-subject variability and test-retest variability in defects. For the size III stimulus, we need to determine appropriate ranges of stimulus contrasts, and assess use of an increase in size in order to avoid high contrasts

(0 to 15 dB). We also need to develop new indices that are related to ganglion cell loss or functional impairment rather than stimulus contrasts, and can be compared across stimuli. Assessment of external validity is important – multiple sites should evaluate the same test.

Interface

In clinical perimetry today it is not unusual for a technician to leave the room while a patient is being tested, or to supervise several patients simultaneously. We need more research to determine the components of technician activity which impact the test outcome. We also need research on identifying which patients who need perimetry are likely to perform the task well, and which may require more diligent monitoring than others.

Some perimeters have gaze tracking, but do not use this to adjust the position of the stimulus or to reject a stimulus presentation where an eye movement or lid closure may have affected performance. We need better use of gaze tracking.

False positive and false negative rates have traditionally been used in psychophysics to assess subject performance, but in perimetry today neither index is very reliable. High false negative rates in patients may simply be due to shallow frequency-of-seeing (FOS) curves, so stimulus development that resulted in steeper FOS curves could allow estimation of false negative rates. False positive rates can be estimated by 'catch trials' in which no stimulus is shown, but in order to have accurate estimates large numbers of catch trials are needed and this increases test duration. Response times are used in some instruments to assess false positive rates, but problems have been found with this approach as well.[78] Research is needed to improve assessment of false positive rates.

The first century of perimetry began with measuring just an outer isopter, the perimeter of the visual field, using a large bright test object. When use of smaller and dimmer stimuli added detection of scotomata in the central visual field, the measurement of isopters by trained perimetrists ensured that much of the time patients were seeing and responding to stimuli. When perimetry was automated, the use of fixed grids of test locations lead to the unfortunate result that automated perimetry takes longer in patients with extensive loss, and that these patients spend much of the test not seeing most stimuli while patients free of field loss would see about half of the stimuli. A patient with a superior hemifield defect would need to be tested with the 24-2 to assess progression in the inferior hemifield, yet a 10-2 field would help assess progression in the superior field near fixation. We need a new assessment of choice of visual field locations.

Test locations

We need to develop alternate methods for selecting stimulus locations in order to avoid extensive testing of blind areas and to focus on areas of interest. If the test locations were adapted to the individual patient, then for a patient with

a superior hemifield defect many locations would be in the inferior hemifield, and a number would be in the macula, and a few large bright stimuli would be used to check that the blind superior hemifield was still non-seeing. Choice of locations could be based on an outer isopter measured on the first visit, data from prior visits, or suprathreshold perimetry. However, the standard for automated perimetry today is to use a fixed grid of test locations and assess how sensitivity at these locations changes over time. In order to adapt location selection to individual patients, we need new methods for assessing change over time. New methods for selecting locations should also allow the clinician to identify non-glaucomatous causes of field loss (*e.g.*, pituitary adenoma).

Today, the standard grids test only the central visual field, a decision that was justified in terms of sensitivity and specificity – it was estimated that peripheral perimetry would cause only modest increases in sensitivity but would decrease specificity due to the wide variability in normal values for peripheral perimetry. However, for patients with severe field loss, some data outside the central visual field could help assess functional impairment.[79] For instance, in a patient with advanced disease, the presence of a residual temporal island can enhance mobility, so it would be useful for clinicians know whether a temporal island exists and whether disease progression is affecting it.

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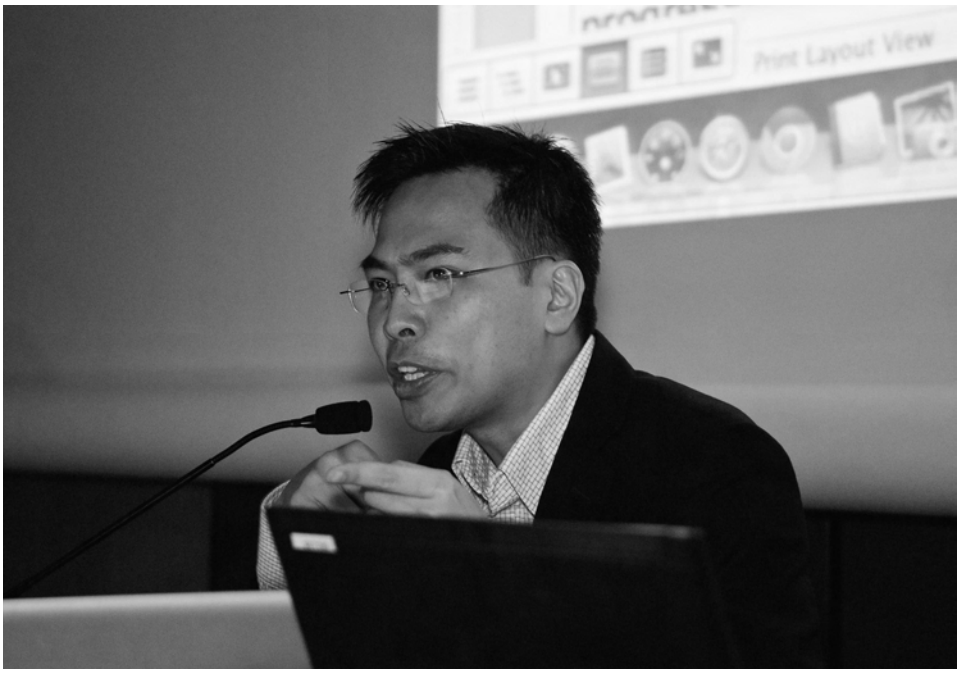

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2. STRUCTURE

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2.1 Technologies for measurement of optic disc and retinal nerve fiber layer (RNFL) parameters

Linda Zangwill, Chris Bowd, Claude Burgoyne, Tae-Woo Kim, Harsha Rao

Consensus statements

1. Serial optic disc stereo-photography and RNFL photography are valuable and enduring methods for monitoring structural progression.
   Comment: Stereoscopic clinical examination of optic disc and RNFL may be useful to detect change in comparison with a baseline photograph.
   Comment: Subjective estimates of cup/disc ratio only detect large changes in cupping and are insufficient for monitoring structural changes.
2. Color fundus photography is the preferred imaging modality to identify disc hemorrhages and parapapillary atrophy.
   Comment: Disc hemorrhages and beta-zone PPA are known risk factors for glaucoma progression.
3. Changes in beta-zone parapapillary atrophy can signal glaucoma progression.
   Comment: Methods for evaluating changes in PPA require further validation and include fundus photography, CLSO, and SDOCT.

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4. Several imaging instruments, including confocal scanning laser ophthalmoscopy, scanning laser polarimetry, and optical coherence tomography objectively provide reproducible measurements and quantitative assessment of the optic disc and RNFL change.
   Comment: The detection of glaucoma progression by comparing sketches or descriptions of cup disc ratio in the clinical chart is generally not suitable for an early detection of progression and may be replaced by imaging techniques and/or optic disc photography.
   Comment: Imaging instruments provide progression detection analyses that can determine whether change is greater than the measurement variability of an individual eye.
5. There are several structural components of longitudinal change detection that likely contribute to the variability of measurements.
   Comment: These include variation in clinical disc margin visibility, intersession variation and accuracy of segmentation algorithms, variation in vascular blood volume and reference plane anatomy, and longitudinal image registration.
6. Image quality can influence our ability to detect structural change.
   Comment: Automated quality indices vary by instrument and are often proprietary with little information available about how they are constructed.
   Comment: Poor quality images can lead to either false positive or false negative results.
   Comment: For patient management decisions, clinicians should review the quality of images included in glaucomatous progression assessment.
7. More than one good quality baseline image facilitates progression analysis.
   Comment: Some instruments automatically acquire several baseline images during one imaging session.

2.1.1 Optic disc stereophotography / Red-free RNFL photography (Tae-Woo Kim)

Background

Optic disc stereophotography and red-free RNFL photography have been used as a standard examination to diagnose and monitor the structural damage in glaucoma.

It is generally considered that early optic disc and RNFL changes can be detected before the first sign of glaucomatous visual field changes.

Notching and narrowing of the neuroretinal rim, and enlargement of cupping are the findings seen in the disc stereo photography in glaucomatous eyes. Disc hemorrhage is also an early sign of glaucomatous damage and it is acknowledged that disc hemorrhage is associated with glaucoma progression.

On the RNFL photographs, glaucomatous damage is observed in the form of localized defects, diffuse loss, or in combination. RNFL examination may provide

more information about minor loss of axons than evaluation of the optic disc where axons are densely packed and serial nerve fiber layer examination is more sensitive than disc evaluation in the detection of progressive glaucoma damage.

Image quality and what influences it

Media clarity and patient cooperation is essential to obtain good quality image for both disc stereo photography and red-free RNFL photography. It is more difficult to obtain good quality image for red-free RNFL photography, as it is highly vulnerable to the effects of media opacity, and scanty fundus pigmentation (fundus pigmentation forms background contrast).

Detecting change

Detection of change can be accomplished by comparison of the serial photographs. Detecting change may be facilitated by comparing the trajectory of the blood vessels on the optic disc between disc stereo photographs. Subjective estimates of cup/disc ratio only detect large changes in cupping and are insufficient for monitoring structural changes.

Color fundus photography is the preferred imaging modality to identify disc hemorrhages, PPA and the changes in PPA.When disc hemorrhage is observed, it can be considered that the eye is at an increased risk of progression. Presence of beta-zone PPA and enlargement of beta-zone PPA also have been shown to be associated with glaucoma progression.

On the red-free photographs, the change may be observed as expansion or deepening of the existing defects or emergence of new defects.

Strengths and limitations

Using photography, it is possible to detect and record the disc hemorrhage. For the red-free RNFL photography, defining progression is straightforward when expansion of the existing defect or a new localized defects is found especially in eyes with localized defect.

However, assessment for progressive change is largely subjective for optic disc and RNFL photography. Intraobserver and interobserver agreement in the detection of glaucomatous progression of the optic disc on disc stereo photographs among the glaucoma specialists are only slight to fair. For the red-free RNFL photography, deepening of the existing defect and progressive change in diffuse loss is often difficult to detect. Serial comparison of red-free photography may be hampered by increasing media opacity such as cataract in elderly patients.

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2.1.2 Confocal scanning laser ophthalmoscopy (Chris Bowd)

Background

Recent developments in HRT technology include the Glaucoma Probability Score (GPS), which is based on a contour line-independent modeling of the optic nerve head based on horizontal and vertical curvature, cup area, cup depth and cup steepness.[1] The HRT software uses a Bayesian machine learning classifier to compare the modeled optic nerve head to those from healthy and glaucoma eyes and provides a probability of class membership in the form of a likelihood of damage score. Evidence suggests that the GPS can discriminate between healthy and glaucomatous eyes about as well as the Moorfields Regression Analysis (MRA), without the need for a subjectively placed contour line (which results in less than perfect inter and intraobserver placement agreement[2]). However, similar to the MRA, the false-positive rate is high for large discs and the sensitivity is low for smaller discs.[3,4] A method to correct this effect by using quantile

in place of linear regression has been described.[5] Evidence also suggests that the GPS can serve as a predictor of conversion to glaucomatous visual field defects or progression based on stereophotograph assessment in suspect eyes, with hazard ratios similar to those of stereophotograph assessment.[6] However, a very recent study suggests that GPS cannot discriminate between baseline measurements from stable eyes and eyes that eventually progress based on SAP GPA or stereophotograph assessment[7] (see also ref. 8). Change in GPS over time (linear regression) is in moderate agreement with change in rim area and change in visual sensitivity.[9] It is not clear if change in GPS over time is in agreement with glaucomatous progression detected using standard techniques (*e.g.*, SAP GPA, masked assessment of serial stereophotographs).

- GPS can discriminate between healthy and glaucoma eyes as well as MRA, although both are currently hampered by the effect of disc size on the diagnostic accuracy.
- GPS likely is predictive of future conversion to visual field defects in suspect eyes and may be predictive of progressive glaucomatous optic neuropathy in suspect eyes.
- Change over time in GPS is associated with change over time in other HRT parameters and change in visual sensitivity.

Image quality and what influences it

HRT image quality is described objectively using mean pixel height standard deviation (MPHSD). There is no consensus in the literature regarding a suggested acceptable/unacceptable MPHSD cut-off. However, the instrument manufacturer suggests that an acceptable cut-off for good/poor image quality is 40 μm. Mean pixel height standard deviation increases test-retest variability.[10,11] In addition, there is evidence suggesting that increased MPHSH results in smaller rim area and deeper cup area measurements.[12] The latter study also suggests that increased age, high myopia, increased visual impairment, blindness and cataract are associated with increased MPHSD (*i.e.*, decreased image quality) (see also ref. 13).

- Mean pixel height standard deviation (MPHSD) provides an objective measurement of HRT image quality.
- There is no consensus in the literature regarding an acceptable MPHSD. The instrument manufacturer suggests a cut-off of 40 μm.
- Increased age and visual impairment likely increase MPHSD.
- Higher MPHSD, indicating worse quality images, increases test-retest variability and may result in inaccurate measurements for some optic disc structures.

Detecting change

HRT change detection is accomplished by assessing change over time of normalized parameters provided by the clinical print-out or by using the Topographic Change Analysis (TCA).[14] TCA compares the variability within a baseline examination to that between baseline and follow-up examinations. By using a nested three-way ANOVA model that accounts for the effects of topograph scan variability, scan time (*i.e.*, baseline or follow-up), and location of topograph height measurements as model factors, TCA describes significant, repeatable change on the superpixel (4 X 4 pixels) level. Super-pixel change is defined as change greater than the variability within baseline exams in three consecutive, or three of four consecutive scans etc. (depending on the number of available scans). Studies show that TCA can detect change detectable by standard techniques, although the agreement is far from perfect (*e.g.*, refs. 15-18). This could be related to the fact that a specific definition of progression based on TCA has not been established, although several studies have suggested cut-offs (*e.g.*, refs. 14, 16, 17, 19). It has also been suggested that cut-off should vary based on disease severity at baseline. HRT progression by TCA also is predictive of VF change.[20] Other techniques are under development/investigation, but are not commercially available.[21-23]

Strengths and limitations

HRT TCA is the most well developed and tested progression detection analysis available for optical imaging techniques. Limitations of TCA are the lack of a clinically usable (*i.e.*, well tested and available) cut-off to define progression and also the inability to interpret areas of improvement (*i.e.*, local increases in retinal height that may be associated with adjacent decreases in height).

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2.1.3 Scanning laser polarimetry (Chris Bowd)

Background

Since the last optical imaging-related consensus meeting, GDx with variable corneal compensation (GDx VCC) has been in widespread clinical use and within the past five or so years, GDx with enhanced corneal compensation (GDx ECC) has been introduced. GDx VCC provided a relatively large number of artifact-laden images, called atypical scans. Atypical scans are scans with an atypical birefringence (*i.e.*, retardance) pattern (ABP) that is not representative of RNFL thickness patterns found histologically (*i.e.*, increased birefringence superiorly and inferiorly, indicating thicker RNFL compared to decreased birefringence temporally and nasally, indicating thinner RNFL). Rather, in addition to high birefringence superiorly and inferiorly, scans with ABP display increased birefringence in the temporal and nasal quadrants in radial patterns centered on and surrounding the entire optic disc (*e.g.*, refs. 1, 2). With GDx ECC software, the corneal polarization compensator is automatically adjusted (biased) so that the combined retardation magnitude from the cornea and the compensating retarder is approximately 55 nm with a vertical slow axis of polarization. This adjustment bias serves to boost the signal to overcome low sensitivity that can make retardation measurements susceptible to optical and electronic noise. After image acquisition, the bias is subtracted to yield the RNFL retardation values.[3,4] Studies have shown that cross-sectional measurement variability is lower using ECC[5], discrimination between healthy and glaucoma eyes is better using ECC[6] or when considering the presence of ABPs,[7,8] and ECC increases the strength of association with OCT-measured RNFL thickness[9] and visual sensitivity (measured using standard automated perimetry).[10] Typical Scan Scores (TSS, representing evidence of atypical scans) are more stable over time using ECC compared to VCC (although this likely is related to a restricted range of TSS using ECC), suggesting that GDx ECC might be better than GDx VCC for detecting true glaucomatous progression because variable TSS result in variable RNF thickness measurements.[11]

- GDx VCC has become the SLP standard over the past years.
- GDx VCC results in a significant percentage of eyes with atypical birefringence (retardation) patterns (ABP).
- GDx ECC was developed to reduce ABP.
- GDx ECC performs better than GDx VCC cross-sectionally (better discrimination between healthy and glaucoma eyes, stronger association with results from other RNFL measurement techniques and SAP).

Image quality and what influences it

The primary image quality issue is the presence of ABPs and this issue seems to have been largely solved by GDx ECC. However, evidence suggests that the removal of cataract or posterior capsule opacification (or LASIK procedures[12]) can change GDx measured RNFL thickness[13-15] (and can also change TSS score[14,15]) indicating a need for a new post-procedure baseline when investigating progression in these situations. In addition, presence of parapapillary atrophy within the scanned region can lead to incorrect RNFL thickness measurement,[16,17] and changes in measurement reproducibility.[18]

- The presence of cataract or posterior capsule opacification can result in incorrect GDx-measured RNFL thickness. After removal, a post-proceudre baseline likely is required for progression analyses.
- LASIK can affect GDx-measured RNFL thickness unless corneal compensation measurements are repeated.
- The presence of parapapillary atrophy within the scanned region can result in incorrect GDx-measured RNFL thickness. Imaging areas of PPA should be avoided by using larger scan circles.

Detecting change

Guided Progression Analysis (GPA) is available for progression detection in GDx. GPA can be run in two different modes depending on the number of images obtained: Fast Mode and Extended Mode. Fast Mode requires acquisition of a single image at baseline and at each follow-up visit, and Extended Mode requires acquisition of three images for each visit. In Fast Mode, progression is defined as a change in baseline outside of the limits of variability derived from a sample population and included in the GDx normative database. In Extended Mode, progression is defined as variability that exceeds the within-subject variability calculated from the three baseline images (similar to HRT Topographic Change Analysis). Using Fast Mode GPA, one study reported 0.50 sensitivity (17 of 34 eyes, +LR = 12.5) for detecting known progression defined using standard techniques (SAP GPA or masked serial stereophotograph assessment). Specificity in 434 stable (by SAP GPA or photo assessment) suspect eyes was 0.96 and specificity in 22 healthy eyes was 1.0.[19] Another study used the Fast Mode GPA to detect change using GDx VCC and GDx ECC and showed significant change in six eyes (8.8%) and eight eyes (11.8%), respectively. Agreement between techniques was moderate (kappa ranged between 0.41 and 0.57).[20] Finally, evidence suggests that the rate of GDx VCC-measured RNFL loss is greater in progressing eyes than in stable eyes (by SAP GPA or photo assessment). Although in both cases, RNFL thinning was observed over a median follow up of approximately four years.[21]

- GDx GPA can detect progression defined as population-based or within-subject variability.
- Sensitivity and specificity using GDx GPA are acceptable.
- Eyes with known progression by SAP GPA or masked stereophotograph assessment show a greater rate of RNFL loss than apparently stable eyes.

Strengths and limitations

The fact that GDx (VCC and ECC) can detect progression in eyes that show known progression is a strength. In addition, it seems that the low variability in measurements allows the detection of age-related change (or alternately, disease-related change in suspect eyes apparently stable by current methods). Also, the availability of Fast Mode and Enhanced Mode GPA allows the application of change detection to archival data, no matter the number of images obtained at each visit. However, there are limitations. First, VCC and ECC measurements are not compatible (see Section I above), so when switching instruments, a new baseline is required for GPA analyses. Also, when using GDx VCC in particular, ABPs can have a significant effect on detection of progressive RNFL loss. Eyes with chronic atypical birefringence patterns, fluctuations of these patterns over time, or both may show changes in measurements that can appear falsely as glaucomatous progression or can mask true changes.[22] It is possible that this issue has been remedied by ECC. Finally, it is likely that the progression detection techniques using GDx are not optimized because the cut-offs to define progression may not be ideal (are somewhat arbitrary).

- Using GDx GPA or tracking change over time allows detection of glaucomatous progression in eyes with known progression using standard techniques.
- RNFL thickness over time is observable in eyes that are apparently stable by standard techniques, possibly suggesting early change detection.
- Presence and fluctuation of typical scan patterns in GDx VCC images can confound progression detection.

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2.1.4 Optical coherence tomography (time-domain /spectral-domain) (Harsha Rao)

Background

Though the spectral domain OCT (SDOCT) has gained popularity during the last couple of years, time domain OCT (TDOCT, Stratus OCT) remains a useful device for detection of progression. Major limitations of TDOCT include slow acquisition times and interpolation of data. Some of these limitations have been largely addressed by the SDOCT technology now. Advantages of SDOCT over TDOCT are shorter image acquisition times that lead to reduced eye-motion artifacts, acquisition of more data points to allow three dimensional imaging and scan registration from session to session, and higher resolution with precise segmentation of retinal layers.[1-3] OCT technology is evolving rapidly and it is likely that numerous software and hardware advancements will be made in the near future.

Both TDOCT and SDOCT devices have been shown to provide reproducible measurements in normal and glaucomatous eyes.[4-20] A few of the above studies also evaluated the inter-test variability of SDOCT measurements and were found to be excellent.[14,18,20] For the RNFL measurements, average RNFL measurement showed the best reproducibility while the nasal RNFL measurement was the least reproducible.[5,8-10,12]

Reproducibility estimates have been reported to be better with SDOCT compared to TDOCT devices.[21]

Reproducibility was better in normal eyes compared to glaucomatous eyes.[5,12] No relationship was found between the severity of glaucoma and variability of OCT RNFL measurements,[14-15,22-23] while the variability of ONH parameters were found to be affected by the severity of glaucomatous damage.[23]

Image quality and what influences it

Some of the important attributes of image quality are signal strength, centration errors and segmentation errors. Low signal strength affects the measurements with both TDOCT[24-26] and SDOCT devices.[27] Scans with lower signal strengths are also reported to have significantly greater artifacts compared to scans with good signal strengths.[28] SDOCT has been reported to provide better scan quality compared to TDOCT.[29]

Detecting change

While comparing the progression rates by Stratus OCT and perimetry over a median follow-up of 4.7 years, Wollstein *et al*. found that 22% eyes progressed on OCT (defined as a reproducible mean RNFL thinning of > 20 μm) while

only 9% of eyes progressed on visual fields (defined as a reproducible drop in visual field mean deviation of at least 2 dB).[30]

Currently, Stratus OCT has a progression detection algorithm called Guided Progression Analysis (GPA) which evaluates and compares scans acquired longitudinally and reports a summary analysis after considering the expected test-retest variability. The corresponding rate of change and a p value are provided. Evaluating GPA, Medeiros *et al.*[31] found that Stratus OCT RNFL parameters discriminated between eyes progressing by visual fields or optic disc photographs and eyes that remained stable by these methods and performed significantly better than ONH and macular thickness parameters in detecting change over time. Leung *et al.* also demonstrated the utility of GPA in determining progression and found that the RNFL thickness decline with time did not agree very well with the decline of visual field index on perimetry.[32] Leung *et al.* also showed that the fast RNFL scans were preferable in following up glaucoma patients for detection of progression.[33]

Strengths and limitations

Strengths of OCT technology are their ability to measure structural parameters without the need for a reference plane or magnification correction, and their ability to image all three scanning areas namely, RNFL, ONH and macula. Limitations are the influence of signal strength on the measurements and the non-compatibility of current SDOCT technology with the earlier OCT technologies.

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2.1.5 Limitations of imaging technologies to detect progression (Claude Burgoyne)

Several structural components of longitudinal change detection that likely contribute to the variability of measurements have not been formally assessed. These include variation in clinical disc margin visibility and disagreement as to what the clinician sees as the disc margin by clinical examination, within clinical disc photographs and within SDOCT B-Scans.[1-5] Intersession variation and accuracy of segmentation algorithms[6-14] and reference plane anatomy[15-17] are beginning to be studied but their effect on progression detection have not been formally assessed. At the present time strategies for longitudinal image registration vary between manufacturers and the effects of these strategies on the sensitivity and specificity of longitudinal change detection have not been assessed.

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2.1.6 Influence of image quality on structural measurements (Linda Zangwill)

Background

Automated image quality scores and / or indices are now provided on all imaging instruments. The quality scores are usually visible during image acquisi-

tion so that operators and technicians know whether the images acquired meet manufacturer's quality criteria. The quality scores are also included on standard printouts for change detection analysis so that clinicians can determine whether the image is of sufficient quality to include in clinical management decisions.

The calculations used to construct the quality scores vary by instrument and are often proprietary in nature with little specific information available about how they are constructed. In general, the quality scores incorporate measures of both the signal strength and noise. However, each instrument calculates the summary measures of the image signal and noise differently. For example, one SDOCT instrument uses the maximum signal strength in an OCT scan relative to the maximum strength of the background noise. Other SDOCT instruments use various measures of signal and noise to calculate their quality score.

It is important to note that not all image quality concerns can be identified objectively or represented in a summary quality score. For example, floaters and software segmentation failures in optical coherence tomography images are often not identified by the automated quality scores. It is therefore important that clinicians do not solely rely on the automated quality score for assessment of image quality. Rather, clinicians should subjectively review images in conjunction with the image quality score to determine whether the image is of sufficient quality to be used for detection of glaucoma management decisions.

The proportion of images obtained that are of poor quality will vary by the operator, patient characteristics (lens opacity, eye movement, etc.) and instrument. Since the proportion of images that were excluded from studies due to poor quality is reported in only a limited number of publications,[1-4] it is difficult to estimate the frequency of obtaining poor quality images in both research and clinical settings.

1. Automated quality assessment scores, now available on most imaging instruments, provide important information on whether a scan is of sufficient quality to be used in clinical management decisions.
2. Image quality can influence RNFL and optic nerve head measurements.
   Comment: There is consistent evidence that image quality can influence RNFL and optic nerve head measurements. Specifically, HRT stereometric parameters are significantly affected by mean pixel height standard deviation – a measure of quality,[5] Stratus OCT RNFL and optic nerve head measurements are influenced by image signal strength.[6-9] Evidence of signal strength influencing RNFL thickness with SDOCT is less consistent; some studies suggest a limited effect if scans are 'good quality'[10] while other evidence suggests that signal strength can influence SDOCT RNFL thickness measurements even in the 'good quality' range.[11] In addition, a recent SDOCT study (using RTVue FD-OCT) reported that optic nerve head parameters were significantly affected by the scan quality (RTVue signal strength) and scans with low signal strength are likely to be falsely classified as glaucomatous.[3] Moreover, 'Scan quality within the range recommended as acceptable by the manufacturer of each imaging device does not affect the glaucoma

discriminating ability of GDx or HRT but does affect Stratus OCT glaucoma discrimination.'[12] This may at least in part be due to consistent evidence that Stratus OCT scans with higher signal strengths are associated with greater RNFL thickness measurements[13-17] and macular thickness measurements.

Estimates of the proportion of scans with segmentation algorithm failures are few, but suggest that the problem is not small.[18-20] Specifically, evidence from Stratus OCT suggests that automated segmentation algorithms may fail, particularly in eyes with pathology.[18-20] In addition, there is evidence to suggest that algorithm failures in delineating retinal thickness are more frequent in Stratus OCT (detected in 69.2% of scans) than Cirrus OCT examinations (detected in 25% of scans), but remain a problem with both technologies.[19] It is likely that as software algorithms improve, the frequency of segmentation algorithm failures will decrease.

3. Poor quality images can lead to either over-detection (false positive) or under-detection (false negative) of structural change.
   Comment: Inconsistency in segmentation algorithm over time can result in inaccurate assessment of structural progression. In addition, changes in the existence and location of artifacts (floaters, atypical scan pattern, etc.) over time can lead to erroneous detection of change or false negative results. For example, changes in GDx atypical scan pattern over time can result in inaccurate assessment - both over and under-detection of change.[21] For this reason, it has been suggested to include only scans with a typical scan score of 80 or higher in change analysis.[21,22] Floaters, particularly when occurring within the optic disc for optic nerve head measurements, and along RNFL measurement circles can also reduce the accuracy of the optic nerve head and RNFL measurements.

   Scan placement can also influence the accuracy of measurements and ability to detect change over time. Evidence suggests that scan placement can affect Stratus OCT regional RNFL thickness measurements, while the global RNFL thickness measurements remain relatively robust.[16]
4. For patient management decisions, clinicians should review the automated quality scores as well as subjectively assess the quality of images included in glaucomatous progression assessment.

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2.2 Reproducibility of digital imaging instruments

Chris Girkin, Tanuj Dada, Antonio Martinez Garcia, Michael Kook

Consensus statements

1. Measurement variability influences the ability of any device to detect progression.
   Comment: There is a wide range of reproducibility estimates in the literature for SLP, CSLO, and OCT. Although studies of comparisons of instruments within the same patient populations are limited, these techniques likely provide data of similar reproducibility.
   Comment: Overall, SDOCT has better reproducibility than TDOCT.
2. There is a lack of consensus in the literature as to whether reproducibility changes across disease severity and this may vary across measured anatomic structures and techniques.

2.2.1 Overview (Chris Girkin)

What are the relative reproducibility of the imaging devices?

The HRT III, TDOCT and GDx-VCC all have similar levels of measurement variability when compared within the some study population (Table 1).

Does SDOCT provide better reproducibility?

Spectral Domain OCT compares favorably across multiple studies compared to TDOCT. (Average ICC (SDOCT = 0.97), average ICC (SDOCT = 0.81) (Table 2).)

Table 1. Comparision of reproducibility of HRT, GDx, and TDOCT in the same study population

	RC	ICC	Sensitivity to Change
HRT 3 Global Rim Area	0.22mm^2	0.97	10.2
GDx-vcc NFI	4.7 μm	0.98	11.3
TD OCT RNFL	11.7 μm	0.97	9.3

(From: Leung CK, Cheung CY, Lin D, *et al.* Longitudinal variability of optic disc and retinal nerve fiber layer measurements. Invest Ophthalmol Vis Sci 2008; 49: 4886.)

Table 2. Reproducibility/variability characteristics of publications with SD and TD OCT

Study	Measurements	Subjects	OCT	ICC	CV (%)	IV(μm)
Schuman *et al.*[1]	Average RNFLT	Glaucoma	TD	0.56	NA	NA
Blumenthal *et al.*[2]	Average RNFLT	Glaucoma	TD	NA	13.0	5.8
Carpineto P *et al.*[3]	Average RNFLT	Glaucoma	TD	0.52	NA	NA
Gurses-Ozden *et al.*[4]	Average RNFLT	Healthy	TD	NA	6.9	NA
Budenz *et al.*[5]	Average RNFLT	Glaucoma	TD	0.98	3.7	5.2
Pueyo *et al.*[6]	Average RNFLT	Glaucoma	TD	NA	9.6	NA
Budenz *et al.*[7]	Average RNFLT	Glaucoma	TD	0.96	5.2	6.6
Menke M *et al.*[8]	Average RNFLT	Healthy	SD	0.95	2.9	NA
Cettomai D *et al.*[9]	Average RNFLT	MS	TD	0.91	NA	NA
González-García A *et al.*[10]	Average RNFLT	Glaucoma	SD	0.97	1.9	4.6
Vizzeri G *et al.*[11]	Average RNFLT	Glaucoma	SD	0.98	1.6	NA
Antón A *et al.*[12]	Average RNFLT	Glaucoma	TD	0.94	4.4	NA
Leung CK *et al.*[13]	Average RNFLT	Glaucoma	TD	0.87	3.6	11.1
Leung CK *et al.*[13]	Average RNFLT	Glaucoma	SD	0.96	1.8	4.86
Garas A *et al.*[14]	Average RNFLT	Glaucoma	SD	0.99	2.2	3.7
Lee S *et al.*[14]	Average RNFLT	Glaucoma	SD	0.99	2.0	3.8
Mwanza JC *et al.*[15]	Average RNFLT	Glaucoma	SD	0.99	1.9	3.9
Li JP *et al.*[16]	Average RNFLT	Healthy	SD	0.95	3.9	8.3
Wu H *et al.*[17]	Average RNFLT	Glaucoma	SD	0.95	1.7	2.3
Cremasco F *et al.*[18]	Average RNFLT	Glaucoma	SD	0.99	3.7	NA
Mansoori T *et al.*[19]	Average RNFLT	Glaucoma	SD	0.99	4.0	NA
Langenegger SJ[20]	Average RNFLT	Glaucoma	SD	0.99	2.7	NA

Abbreviations: OCT= optical coherence tomography; ICC= Intraclass correlation coefficient; CV= coefficient of variations; IV= Intratest variability; TD= time domain; SD= spectral domain; MS= Multiple sclerosis.

Is there an effect of disease severity on reproducibility?

Numerous publications have examined the reproducibility of instrument across disease severity with conflicting results. Some studies show no change in reproducibility of rim area (HRT) and RNFL thickness (GDx and TDOCT) while others show an increase in variability with disease severity.

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2.2.2 Confocal scanning laser ophthalmoscopy (Michael Kook)

For the HRT 1, the ICC ranged between 0.79 and 0.99 for intraobserver intraimage evaluation and between 0.56 and 1 for intraobserver interimage evaluation. The ICC ranged between 0.54 and 0.99 for interobserver intraimage and between 0.65 and 0.97 for the interobserver interimage evaluation. Interimage evaluation showed a higher variability than intraimage evaluation in both of interobserver ($p = 0.012$) and intraobserver evaluation ($p = 0.028$ and $P = 0.031$ for the two observers).[1]

For the factors that influenced the HRT variability, the regional variability of topographic measurements correlated with the steepness of the corresponding region and is highest at the edge of the optic disc cup and along vessels.[2] The quality and variability of the images was associated with pupil size[3] and density of nuclear and posterior subcapsular cataracts.[4,5] In addition, HRT measurements were influenced by changes in intraocular pressure[6,7] and cardiac cycle.[8] Intervisit variability was generally higher than intravisit variability.[1]

With the HRT 2, the variability in healthy subjects was reportedly less than 12% in all but three parameters, with rim area being the least variable parameter.[9] The mean standard deviation for one pixel of the total image is about 30 microns in glaucoma patients and 25 microns in healthy subjects.[10,11]

Intervisit variability data over a clinically relevant time period with multiple measurements would be more important and useful to use in determining the true 'biological' change or progression over time in a given device. For the HRT 3, in terms of longitudinal variability, the coefficient of variation and ICC for global rim area were 0.22 mm^2 (95% CI:0.19-0.24 mm^2), and 0.97(95% CI:0.95-0.98) respectively including both normal and glaucoma subjects. For normal subjects only, the coefficient of variation was 0.13 (95% CI:0.11-0.15) while that of glaucomatous patients was 0.28 (95% CI:0,24-0.32).[12]

For the glaucoma probability Score (GPS) of HRT 3, there was heteroskedasticity. The variance of repeat tests is not equal across the range of the variable. There seemed to be high reproducibility (tight distribution around the mean difference) at low and high GPS scores and poor reproducibility (wide distribution around the mean difference) in between. Reproducibility of GPS was better at its extremes(-0.01 ± 0.20 for GPS 0-0.30, and 0.02 ± 0.09 for GPS 0.78-1.00) than in its mid range (0.07 ± 0.54 for GPS 0.30-0.78).[13]

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2.2.3 Scanning laser polarimetry (Tanuj Dada)

Variability of corneal polarization axis and magnitude

Mai *et al.*[1] investigated the longitudinal corneal birefringence (corneal polarization axis [CPA] and corneal polarization magnitude [CPM]) variability in scanning laser polarimetry with variable corneal compensation and its effect on retinal nerve fiber layer measurements with polarimetry images obtained every six months for 3.2 years in 16 healthy eyes, 38 eyes with ocular hypertension, and 53 eyes with glaucoma in 107 white participants. The CPA and CPM measurement variability showed no trend with time and did not differ between diagnostic groups. It did not appear to be affected by age. With more than 90% of the CPA and CPM measurement variability within the range of ± 5 degrees or ± 5 nm, no significant effect on the retinal nerve fiber layer measurements was observed. The CPA and CPM measurement variability did not differ be-

tween groups, showed no trend over time, was independent of subject age, and did not seem to systematically affect retinal nerve fiber layer reproducibility.

Intersession reproducibility of GDxVCC

Iacono *et al.*[2] assessed the intersession reproducibility of retinal nerve fiber layer (RNFL) thickness measurements on scanning laser polarimetry with variable corneal compensation (GDx-VCC) in a sample of 29 healthy subjects and 29 glaucoma patients at one week interval. GDx-VCC parameters considered were TSNIT average and standard deviation (SD), superior and inferior average (SA, IA), Nerve Fiber Indicator. Coefficient of variation was <6% for TSNIT average, SA and IA in both groups. Corresponding values for TSNIT SD in healthy subjects and in glaucoma patients were 13.7 and 11.4%, respectively, whereas for Nerve Fiber Indicator they were 82.9 and 13.3%. Intraclass correlation coefficient ranged from 0.794 to 0.907 in healthy subjects and from 0.924 to 0.972 in glaucoma patients. In healthy subjects, TSNIT average, SA and IA intersession difference was 5% or less in 55-69% of eyes, whereas the value for TSNIT SD was 34.5%. Corresponding values in glaucomatous eyes ranged from 69 to 79.3% for TSNIT average, SA and IA and was 37.9% for TSNIT SD. Intersession reproducibility of RNFL thickness measurements on GDx-VCC is high, both in healthy and in glaucomatous eyes. In a few cases, however, intersession variation may be larger than 10%. Caution is necessary while interpreting these changes during follow up, in order to separate physiological variability from real RNFL thickness variations.

RNFL measurement repeatability of GDxECC

Mai *et al.*[3] investigated the measurement repeatability of the various standard retinal nerve fiber layer (RNFL) parameters in scanning laser polarimetry (SLP) with enhanced corneal compensation (ECC) in 16 healthy eyes, 32 eyes with ocular hypertension (OHT), and 35 glaucomatous eyes. SLP ECC imaging was performed three times on the same day. Intraeye within-subject standard deviation (Sw), repeatability coefficient, and the two-way mixed intraclass correlation coefficient for various standard RNFL parameters in SLP ECC were evaluated. In glaucomatous eyes, the Sw and repeatability coefficient for the nerve fiber indicator and temporal-superior-nasal-inferior-temporal average were statistically significantly higher than in healthy eyes and eyes with OHT. The Sw values for various parameters were generally considerably less than 9% of the measurement spectrum. RNFL measurements by SLP ECC had, in general, a good measurement repeatability, although some parameters seemed to be less stable in glaucomatous eyes than in healthy eyes and eyes with OHT. SLP ECC may therefore probably be employed for the detection of glaucomatous progression.

Longitudinal Variability of RNFL measurements with GDxVCC

Leung *et al*.[4] evaluated the longitudinal variability of optic disc and retinal nerve fiber layer (RNFL) measurements obtained from Stratus OCT, GDxVCC and HRT 3. Forty-five normal and 43 glaucomatous eyes of 88 subjects were analyzed in this longitudinal study. Three separate measurements taken over an average period of 8.8 ± 1.2 months were used to evaluate measurement variability. Reproducibility coefficient, coefficient of variation, intraclass correlation coefficient (ICC), and sensitivity to change [(97.5 percentile value – 2.5 percentile value)/2 x within-subject standard deviation (Sw)] of the global measures were calculated. Low variability was found for RNFL measurements. The reproducibility coefficient, ICC, and sensitivity to change for OCT average RNFL thickness, GDx VCC TSNIT average, and HRT global rim area were 11.7 microm (95% confidence interval [CI]: 10.5-12.9 microm), 0.97 (0.96-0.98), 10.2 (9.2-11.4); 4.7 microm (4.2-5.1 microm), 0.98 (0.97-0.99), 11.3 (10.2-12.6); and 0.22 mm^2 (0.19-0.24 mm^2), 0.97 (0.95-0.98), 9.3 (8.4-10.4), respectively. Longitudinal RNFL and neuroretinal rim measurements obtained with OCT, SLP, and CSLO have low variability. As the measurement variability does not change with the severity of glaucoma, these parameters are useful for assessment of glaucoma progression.

Longitudinal Retardance Pattern Variability

Grewal *et al*.[5] evaluated the impact of retardance pattern variability on retinal nerve fiber layer (RNFL) measurements over time using scanning laser polarimetry with variable (GDxVCC) versus enhanced corneal compensation (GDxECC) in 51 glaucoma suspect and 35 glaucomatous eyes with four years of follow-up participating in Advanced Imaging in Glaucoma Study. Typical scan score (TSS) values were extracted as a measure of retardance image quality; atypical retardation pattern (ARP) was defined as TSS < 80. TSS fluctuation over time was measured using three parameters: change in TSS from baseline, absolute difference (maximum – minimum TSS value), and TSS variance. Linear mixed-effects models that accommodated the association between the two eyes were constructed to evaluate the relationship between change in TSS and RNFL thickness over time. There was significantly greater fluctuation in TSS values over time using GDxVCC compared with GDxECC as measured using the absolute difference (18.40 ± 15.35 vs 2.50 ± 4.69 units, $p < 0.001$), TSS variance (59.63 ± 87.27 vs 3.82 ± 9.63 units, $p < 0.001$), and change in TSS from baseline (-0.83 ± 11.2 vs 0.25 ± 2.9, $p = 0.01$). The change in TSS over time significantly ($p = 0.006$) influenced the TSNIT average RNFL thickness using GDxVCC but not GDxECC. The authors concluded that longitudinal images obtained with GDxECC have significantly less variability in TSS values and retardance patterns, and reduced bias produced by ARP on RNFL progression assessment.

Effect of severity of glaucoma on intrasession variability

Garas *et al*.[6] evaluated the influence of pupil dilation on repeatability of scanning laser polarimetry with variable (GDx-VCC) and enhanced (GDx-ECC) corneal compensation, in different stages of glaucoma. One eye of each of 37 Caucasian participants [14 healthy and ocular hypertensive subjects with mean deviation (MD) < 2 dB, 11 glaucoma patients with MD 6 to 12 dB, and 12 glaucoma patients with MD > 15 dB] was imaged five times with both GDx-VCC and GDx-ECC, before and after pupil dilation. No statistically significant alteration was found for any parameter or most coefficients of variation in any group, or in the total study population, due to pupil dilation. Intrasession variability was below 6 μm for all parameters and all groups irrespective of corneal compensation and pupil dilation. By using GDx-ECC, a statistically significant trend for higher coefficient of variation values in more severe stages of glaucoma was found,irrespective of pupil dilation (Jonckheere-Terpstra test, $P < 0.026$, for all parameters). With GDx-VCC, this trend was not seen for two of the three parameters before pupil dilation, but did appear for all parameters in mydriasis ($P < 0.002$). The authors concluded that repeatability of GDx-VCC and GDx-ECC is similar, and is satisfactory for clinical purposes; it is only minimally influenced by pharmacological mydriasis. However, repeatability of the measurement decreases with increasing severity of glaucoma. This characteristic is better detectable with GDx-ECC than with GDx-VCC.

GDX vs OCT repeatability

Garas *et al*.[7] compared repeatability of measurements of peripapillary retinal nerve fiber layer thickness (RNFLT) made using the RTVue-100 Fourier-domain optical coherence tomograph against repeatability of those made using scanning laser polarimetry with variable corneal compensation or enhanced corneal compensation (GDx-VCC and GDx-ECC, respectively) in one eye of each of 37 participants (14 normal and ocular hypertensive subjects, 11 patients with moderate, and 12 with severe glaucoma; groups 1, 2, and 3, respectively) was imaged using the RTVue Optic Nerve Head Map scan,GDx-VCC, and GDx-ECC, each five times on the same day. The coefficient of variation (CV) were compared. The average RNFLT CV was significantly lower with RTVue (2.11%) than with GDx-ECC (3.22%, $P = 0.004$), for all participants. For temporal quadrant RNFLT in all participants, and group 1, CV with RTVue (4.88% and 3.30%) was significantly lower than with GDx-ECC (7.40% and 5.88%; $P = 0.004$), and tended to be lower than with GDx-VCC (6.81% and 5.80%; $P = 0.011$ and 0.016, respectively). For all participants, CV for inferior quadrant RNFLT was significantly lower with RTVue (3.49%) than with GDx-VCC (5.20%, $P = 0.002$). For average peripapillary RNFLT and temporal quadrant RNFLT, repeatability of RTVue was better than that of GDx-ECC, and tended to be better than that of GDx-VCC.

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2.2.4 Optical coherence tomography (Antonio Martinez Garcia)

Reproducibility of optical coherence tomography

Optical coherence tomography (OCT) is a high-resolution imaging technique that allows *in-vivo* measurements of the retinal nerve fiber layer (RNFL) in cross section. However, for the instrument to measure the presence of glaucoma or its progression accurately, it first must be shown to be reproducible.

The NFL thickness measurements of normal and glaucomatous eyes using OCT have proved to provide adequate reproducibility. Schuman *et al.*[1] used an OCT technique that performed circular scans around the center of the optic disc using a 2.9-, 3.4-, and 4.5-mm circle diameter and reported that reproducibility, as measured by intraclass correlation coefficients, ranged from 0.42 to 0.57 in normal and glaucoma patients, respectively. Blumenthal *et al.*[2] reported a coefficient of variation (CV) of 13.0%. Nevertheless, this found that the CV was significantly smaller in the normal eyes (7%, $p = 0.02$) than in glaucomatous eyes. Additionally, this study found that the coefficient of variation was larger in the temporal and nasal quadrants than in the superior and inferior quadrants. Carpineto *et al.*[3] in 2003 found similar results to those found by Schuman *et al.*[1] Gürses-Ozden *et al.*,[4] using a OCT-3 (software version A1.1, Carl Zeiss Meditec, Inc., Dublin, CA), reported, in patients with glaucoma, a CV for mean total RNFL thickness measurements that ranged from 6.9 +/- 6.4%

to 8.0 +/- 3.5% for operators 1 and 2 in fast and regular RNFL protocols. The CV, with the OCT-3, for mean total RNFL thickness measurements ranged from the 2.9% observed by Menke *et al*.[8] to the 9.6% reported by Pueyo *et al*.[6] On the other hand, reproducibility with the OCT-3, for mean total RNFL thickness measurements, as measured by Intraclass correlation coefficients, ranged from 0.91 reported by Cettomai *et al*.[9] to 0.98 found by Budenz *et al*.[5]

The average retinal nerve fiber layer thickness measurement showed the best reproducibility figures.[5-7,9] However, different studies referred the nasal quadrant as the least reproducible.[2,5-7] Superior quadrant was found to be the least reproducible in a study with patients affected by multiple sclerosis.[9] Reproducibility with the Spectral domain OCT, for mean total RNFL thickness measurements, as measured by Intraclass correlation coefficients, ranged from 0.95 reported by Menke *et al*.[8] to 0.99 found by different authors.[13-15,18-20]

Additionally, the CV for the mean total RNFL measurements ranged from 1.6%[11] to 4.0%.[19] Different studies have shown that time domain OCT (TD OCT) intrasession variability is low,[5-7,9,12] with the tendency for the measurements in glaucomatous eyes to be more variable.[5,7]

Nevertheless, it seems that the new spectral domain OCT (SD OCT) technology provides better reproducibility/variability figures in both healthy[8,10,16] and glaucomatous eyes.[10,11,13-15,17-21]

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2.3 How to detect and measure structural change?

Christopher Leung, Jost Jonas Ki-Ho Park, Kyung Rim Sung, Remo Susanna

Consensus statements

1. Event and trend based analyses are both useful for change detection.
   Comment: These analyses do not always concur.

2. It is important to estimate the rate of structural progression for clinical management decisions.
   Comment: The rates of change obtained from measurements from optic disc, RNFL and macular parameters may vary from each other.
3. Quantitative assessment of optic disc and retinal nerve fibre layer (RNFL) with imaging instruments is useful and complementary for change detection.
   Comment: Data are limited on whether macular measurements may be useful for change detection.
4. Differences in technologies and scan protocols could influence the detection of progression even when the same structure is measured.
5. There is no clear consensus on which instruments or parameters are optimal to detect structural progression. As technologies evolve, new instruments and parameters which are clinically useful will emerge.

2.3.1 Trend versus event analyses (Kyung Rim Sung)

Event analysis (EA)

EA defines progression as a change that exceeds a certain predefined threshold compared with the baseline value. The threshold is generally determined by the measurement reproducibility, or the reproducibility coefficient. A number of factors may influence the measurement reproducibility of the optic disc and the retinal nerve fiber layer (RNFL). These include reliability of optic disc margin determination, accuracy of segmentation, location of reference plane, and precision of longitudinal image registration. There is a wide range of reproducibility estimates in the literature for scanning laser polarimetry (SLP), confocal scanning laser ophthalmoscopy (CSLO), and optical coherence tomography (OCT). Generally, measurement reproducibility employed in EA is determined by group data. However, some imaging devices estimate individual reproducibility coefficient for EA.

Since EA aims to detect ‘change from baseline’, more than one good quality baseline image facilitates progression analysis. Some instruments automatically acquire several baseline images during one imaging session.

Trend Analysis (TA)

TA examines change over a designated time period using regression analysis. TA generally requires more examinations to obtain a reliable regression slope. Compared with EA, TA has the advantage of computing the rate of change and thereby provides an assessment of disease prognosis (*i.e.*, how fast glaucoma is progressing) for individual eyes. It is important to estimate the rate of structural progression for clinical management decisions.

Theoretically, the rate of change of disease progression exceeds the rate of age-related change. Thus, knowledge of age-related change in healthy individuals

is important to evaluate disease progression. Such age-related change preferably comes from actual longitudinal data and not extrapolation from cross-sectional data. However, longitudinal analysis estimating age-related change has not been available.

There are very few studies comparing EA and TA for detection of glaucoma progression although it is generally believed that EA and TA are both useful for change detection. However, clinicians should be aware that these analyses do not always concur.

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2.3.2 Optic disc versus RNFL versus macular parameters (Jost Jonas, Remo Susana)

- If the diagnosis of glaucoma has been made, the most important remaining question is whether the disease is stable and the therapy and the compliance of the patient is sufficient, or whether the disease is progressive and the therapy, in relation to the life expectancy, has to be intensified. The earlier a progression of glaucoma is detected, the earlier the therapy can be adjusted.
- The progression of glaucomatous optic neuropathy is associated with changes in morphological and functional parameters. Which of these parameters are the most reliable ones for the detection of glaucoma progression may differ between open-angle glaucoma and angle-closure glaucoma, and also between different types of open-angle glaucoma and the different stages of the disease.
- The detection of glaucoma progression is facilitated by taking into account potential risk factors for it. These may include a high intraocular pressure, an advanced stage of glaucoma (including small neuroretinal rim, high c/d ratios, advanced visual field loss), type of glaucoma (angle-closure glaucoma versus open-angle glaucoma; pseudoexfoliative secondary chronic open-angle glaucoma versus primary open-angle glaucoma; high myopic open-angle glaucoma versus non-highly myopic open-angle glaucoma), a low compliance of the patient (including a low socioeconomic background and medical co-morbidities), a large beta zone of parapapillary atrophy, potentially a thin cornea, disc hemorrhage and others.
- The morphologic parameters for the detection of glaucoma progression can be divided into quantitative ones, which have to be measured by imaging devices, and qualitative ones, which can be assessed by ophthalmoscopy.
- The most important qualitative parameter indicating glaucoma progression may be an optic disc hemorrhage.
- The most important quantitative parameters indicating glaucoma progression are a loss in neuroretinal rim (as indicated by comparing confocal laser scanning tomograms of the optic nerve head), changes in the thickness and profile of the retinal nerve fiber layer (as measured by (spectral-domain) optical coherence tomography) or scanning laser ophthalmoscopy (GDx), changes in the contour of the optic nerve (measured by confocal laser scanning tomograms of the optic nerve head or optical coherence tomography),

and an enlargement of beta zone of parapapillary atrophy (as indicated by comparing optic disc photographs or manually comparing HRT print-outs).
- Potential additional parameters indicate glaucoma progression may be OCT-measurements of macula thickness.
- The detection of glaucoma progression by comparing sketches in the clinical chart is generally not suitable for an early detection of progression and may be replaced by imaging techniques.
- An algorithm combining the parameters for glaucoma progression may further increase the diagnostic precision.

2.3.3 Agreement of progression detection among structural measures (Christopher Leung)

There are only a handful of clinical studies directly comparing optic disc, retinal nerve fiber layer (RNFL), and macular parameters for evaluation of glaucoma progression. In a longitudinal study following 390 glaucoma and glaucoma suspect patients, RNFL thickness measured by scanning laser polarimetry (SLP) was found to have a higher performance to discriminate eyes with progressing glaucoma by standard automated perimetry (SAP) and/or optic disc stereophotographs from stable eyes than rim area (RA) measured by CSLO.[1] In another study measuring optic disc, RNFL and macular parameters with the time-domain OCT in 253 glaucoma and glaucoma suspect patients, RNFL parameters (rates of change of RNFL thicknesses) performed significantly better than ONH and macular thickness measurements (rates of change of ONH and macular parameters) in discriminating progressing from nonprogressing eyes.[2] In a prospective study following 70 glaucoma patients for more than three years, the agreement of progression detection between RNFL (obtained with a time-domain OCT) and neuroretinal rim (obtained with a CSLO) measurements was poor.[3] The rates of RNFL and neuroretinal rim progression vary considerably within and between glaucoma patients.

The discordance in the rate of change and progression detection among various structural parameters could be related to the differences in tissue composition of optic disc, RNFL and macular measurements. While the RNFL is largely composed of the axons of retinal ganglion cells, the neuroretinal rim also contains non-neural structures. Measurement of macular thickness with OCT comprises the inner and outer retina (longitudinal study on measurement of inner macular thickness has not been available). The inclusion of the outer retina in macular measurement may weaken the sensitivity to detect change. With major differences in structural composition, the longitudinal profiles of neuroretinal rim, RNFL and macula measurements are likely to be different.

Differences in technologies could affect the detection of progression even when the same structure is measured. GDx ECC performed significantly better than VCC for detection of change and their agreement was moderate.[4-5] Spectral-domain OCT outperformed time-domain OCT in detecting more eyes

with RNFL progression.[6] With reduced measurement variability, it is expected that spectral-domain OCT can detect RNFL progression earlier than time-domain OCT. Differences in scan protocols from the same technology could also result in discordance in progression analysis. It has been shown that the agreement between the fast (256 A-scans) and the regular (512 A-scans) circumpapillary scans obtained with the time-domain OCT for detection of RNFL progression was only fair to moderate.[7] The rate of average RNFL thickness progression was also different between the scan protocols (-1.01 μm/year for the fast RNFL scan and -0.77 μm/year for the regular scan).

To summarize, (1) the agreement for progression detection among optic disc, RNFL and macular parameters is poor; (2) the rates of change of optic disc, RNFL and macular parameters vary considerably within- and between- glaucoma patients; and (3) differences in technologies and scan protocols could influence the detection of progression even when the same structure is measured.

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2.3.4 Commercially available methods: HRT TCA, GDx GPA, OCT GPA (Ki-Ho Park)

There are a number of commercially available methods to detect structural glaucoma progression by imaging instruments. One is topographic change analysis (TCA) of confocal scanning laser tomograph (Heidelberg Retina Tomograph, HRT; Heidelberg Engineering, Heidelberg, Germany) to detect progression in optic disc damage. TCA compares the topographic height variability at super-

pixels (4x4 pixels) in a baseline examination with the height change between baseline and follow-up examinations.

The other methods are trend based guided progression analysis (GPA) of optical coherence tomograph (OCT; Carl Zeiss Meditec, Dublin, CA) and scanning laser polarimetry (GDxVCC or GDxECC, Carl Zeiss Meditec. Dublin, CA) to detect retinal nerve fiber layer (RNFL) progression.

Longitudinal studies have reported acceptable performance of these methods to detect progression in glaucoma. However, there still remains an issue on how to set a reference standard of structural progression to evaluate these new methods because it has been well recognized that the agreement between progression by visual field and progression by structure is poor.

- TCA parameters of confocal scaning laser ophthalmoscope (HRT) can discriminate between progressing glaucomatous eyes and longitudinally observed stable healthy eyes, when the glaucomatous progression was defined by optic disc stereophotograph and/or standard automated perimetry guided progression analysis.
- GPA of scanning laser polarimetry (GDx) offers an approach to augment detection of glaucomatous RNFL structural progression. There was poor agreement between structural progression by GPA of GDx and functional progression by the slope of the visual field index.
- GPA of optical coherence tomography offers an approach to augment detection of glaucomatous RNFL structural progression.
- Because of reduced measurement variability, the SD-OCT detects more eyes with RNFL progression than the TD-OCT by trend based analysis.
- There is a possibility that early structural progression can be detected by the trend based analysis of imaging instruments before functional progression to be detected.

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2.4. How to define clinically significant structural change? (Bal Chauhan)

Consensus statements

1. Interpretation of statistically significant change should take into account test-retest variability and knowledge on the magnitude of age-related change in healthy individuals.
2. Knowledge of age-related change in healthy individuals should preferably come from actual longitudinal data and not extrapolation from cross-sectional data.
3. A statistically significant change in a structural parameter such as rim area or nerve fiber layer thickness is a relevant change, however, it may not be clinically meaningful. The latter also should take into account the age and stage of the disease as well as an assessment of risk factors present.
   Comment: Currently, we have the tools to measure statistically significant change, however, to date we do not know how to fully assess the clinical importance of this change.

What do we mean by a clinically structural clinical change?

From the outset we are at a disadvantage here. Is there a direct real world consequence of a structural change? A patient is not likely to say 'Doctor, I feel my cup-disc ratio has increased,' but is more likely to indicate the functional consequence of a progressing scotoma close to fixation. There have now been some reports on the 'predictive' ability of a structural change for a functional (SAP) change. While there is evidence now that patients with structural change are more likely to encounter subsequent functional change than those that do not have structural change (in both ocular hypertension and manifest glaucoma), we would suggest that previous functional change is more predictive of subsequent functional change (and the same for structural change).

Structural changes at different stages of the disease process almost certainly have different real world consequences. We are only beginning to scratch the surface of this problem, but certainly defining a clinically meaningful structural change is more difficult than defining a clinically meaningful functional change (which is also not easy!).

What is the rate of age-related structural change and how do we differentiate aging from glaucomatous pathology?

We would like to propose from the outset that we define 'age-related' change appropriately. Most studies in this area have come from cross-sectional data with the assumption that this somehow is representative of how single individuals age. We and others have shown that this is certainly not the case and since the average magnitude of change we are talking about is really small, extrapolation of longitudinal change from cross-sectional data can lead to significant errors.

The key issue is that using longitudinal data, normals do vary tremendously as they age. Finally, most longitudinal studies on aging have perhaps at most 10 years of data (at least with frequent testing), so we must acknowledge that we are only getting a small window of information on aging.

We also need to be very specific about what we mean by 'structure' (and 'function', but that is for the other group). Segregating age-related RNFL change from pathological glaucomatous change may be a different task than separating the age-related changes from the glaucomatous ones in the nerve head. There is no question that rates and topographical variations in the RNFL and nerve head have to be characterised in aging.

In the final analysis we can characterise changes with age and define in individuals or groups what deviates significantly from aging. However, in the final analysis we are left with powerful statistical evidence (though it may not be biologically significant) that something has changed. This is quite far away removed from what is a clinically meaningful change.

2.5 Issues in clinical practice

Makoto Araie, Andreas Boehm, Gadi Wollstein, Kyung Rim Sung, Christopher Leung

Consensus statements

1. The optimal frequency of imaging tests is unknown.
   Comment: It depends on the severity of the disease and on the expected speed of progression.
2. In longitudinal studies investigating optic disc and RNFL progression in glaucoma, imaging tests have been performed once a year to three times a year.
3. The same structural measures (e.g. RNFL thickness) obtained with different instruments from the same manufacturer or the same technology from different instrument manufacturers (*i.e.*, spectral domain OCT) are not necessarily interchangeable for progression assessment.
4. Structural assessment of change is a valid method for detection of glaucomatous progression in a clinical trial.
   Comment: structural change has been shown to be predictive of future functional loss in glaucoma.

2.5.1 How often should an imaging test be performed? (Makoto Araie, Kyung Rim Sung)

There has been no study reporting on the optimal frequency of imaging test in following glaucoma progression. Theoretically, increased frequency of testing may improve the sensitivity to detect change. However, a higher frequency of

testing often requires additional resources. Thus, the optimal frequency of imaging test should be determined by considering the clinical profiles of individual patients. For example, patients with advanced glaucoma may require more frequent testing as treatment reinforcement may be needed to prevent irreversible loss of vision if progression is identified and confirmed. Likewise, patients who showed a rapid rate of change would need more frequent monitoring to evaluate treatment response. Most published studies investigating glaucoma progression had imaging test(s) performed in intervals ranging from every four months to once a year. Further studies are needed to investigate the optimal frequency of imaging tests.

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2.5.2 Should treatment be initiated or reinforced when structural progression is detected? (Andreas Boehm)

The decision of initiation or reinforcement of treatment depends on the likelihood of developing significant functional impairment during the patient's life time.

Glaucoma is a chronic progressive optic neuropathy. The disease is characterized by irreversible loss of neuroretinal tissue. In the course of the disease, visual field defects develop and may progress to blindness. If structural progression is detected, it needs to be verified, whether the progression is true (or an artifact) and whether the progression is typical for glaucoma (progressive rim thinning, excavation, notching, nerve fiber layer defects or disc hemorrhages). Ideally one should measure the rate of structural progression and estimate whether the rate of progression will lead to functional impairment of the patient during life time. However, it must be noted that agreement between visual field progression and progression detected by various imaging techniques is generally poor.[1-8]

The goal of the treatment is to preserve the patient's visual function during his life time. The earlier the treatment the less likely the development of functional impairment. For the decision to treat or not to treat at the time interval in which the progression occurred, the stage of the disease (How far is the structural damage progressed? Is already a functional damage present? If yes, how far advanced is the functional damage?), and the patient's age (How long is his natural life expectancy?) need to be considered. If, for example, the structural progression developed over a long period of time, the glaucomatous damage is in an early stage, and the patient does not have many years of life expectancy to develop functional impairment, it may be suitable to wait without an initiation or intensification of the therapy. However, if the structural progression occurred over a short period of time, the patient is young or the disease is advanced and in all cases of doubt a detection of structural glaucomatous progression should lead to an initiation or reinforcement of treatment.

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2.5.3 Adapting to the continuing rapid evolution of imaging technology (Gadi Wollstein)

Imaging of the optic nerve head and macula regions are routinely used clinically for diagnosing and monitoring the structural damage in glaucoma. Because glaucoma is a chronic, slowly progressing disease it is mandatory for imaging devices to provide accurate and reproducible measurements of the tissue of interest to allow precise detection of changes over time. Measurements obtained over time with different iterations of the imaging device need to be treated as a continiuum and the device must show fixed bias and/or comparable imprecision across iterations. Glaucoma imaging devices are currently going through a phase of rapid evolution of their hardware and software, leading to improved resolution, increased scanning speed and innovative software to enhance diagnostic ability.

When considering the comparability between measurements acquired with different iterations of the same technology one should take into account factors such as:

– Scan pattern
– Sampling density
– Reference plane

– Definition of boundaries location
– Measurement reproducibility

Any of these factors can affect the reliability of the acquired data and the ability to compare measurements over time. It is desirable for measurements obtained over time with different iterations of the same imaging device to be treated as a continuum. In order to accomplish this, the measurements need to show fixed bias and comparable imprecision across iterations. Without accounting for these sources of variability, minute changes might be undetected or stable structural measurements might be classified as exhibiting change.

Transition between iterations that can be regarded as a continuum has been mostly accomplished with the switch from HRT1 and 2 toward HRT3. However, GDx measurements are not interchangeable with GDx-VCC, GDx-ECC or GDx PRO and similarly time-domain OCT measurements are not interchangeable with spectral-domain OCT measurements.

A conversion scale needs to be established to allow comparisons between measurements obtained with devices showing fixed bias and/or comparable imprecision across iterations. In all other situations, new baseline measurements need to be established with the new iteration of the device.

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2.5.4 Structural endpoints in clinical trials (Christopher Leung)

The need of new endpoints for evaluating glaucoma therapies in clinical trial has been extensively discussed in major ophthalmology and visual sciences conferences including the World Glaucoma Association Consensus meeting 2010 (Medical Therapy: Unmet needs) and the National Eye Institute / Food and Drug Administration Glaucoma Clinical Trial Design and Endpoints Symposium 2010. It is widely recognized that there is an eminent need to investigate if structural parameters measured by digital imaging technologies could be used reliably as endpoints in clinical drug trials. Regulatory agencies consider structural change to be an outcome measure in clinical trials for evaluating and approving neuroprotective treatment for glaucoma only when there is evidence supporting that the new outcome measure is predictive of functional change that is clinically relevant to a patient.[1] In order to qualify as a valid endpoint, it is crucial to demonstrate that progressive structural change is predictive for development of visual field progression.

Two recent studies have shown that optic disc progression examined by stereophotography [2] and confocal scanning laser ophthalmoscopy (CSLO)[3] was predictive of development of subsequent visual field loss. In the longitudinal study by Medeiros *et al*., they showed that optic disc changes identified by stereophotographs was a strong predictor with a hazard ratio of 25.8 (95% confidence interval: 16.0-14.7) for development of visual field defects in glaucoma suspects.[2] In the study by Chuahan *et al.* following patients with open-angle glaucoma, eyes with visual field progression were three times more likely to have prior optic disc progression defined by Topographic Change Analysis.[3] These results provide evidence supporting that optic disc progression is predictive of subsequent visual function loss. Structural assessment of change can be regarded as a valid method for detection of glaucoma progression in a clinical trial.

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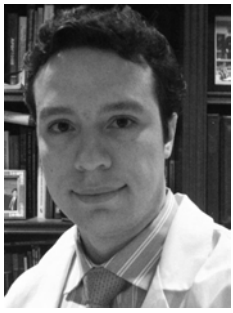
Jian Ge (left) and Robert N. Weinreb.

Felipe A. Medeiros, Kaweh Mansouri, Chris Bowd (left to right).

Felipe A. Medeiros (at podium) with Robert N. Weinreb (center) and Jeffrey M. Liebmann.

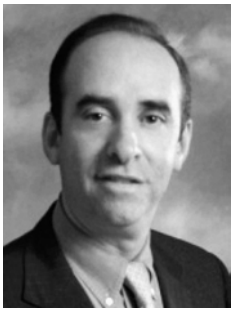
Felipe A. Medeiros



Gustavo de Moraes

Balwantray Chauhan

Remo Susanna



Jeffrey M. Liebmann

3. STRUCTURE AND FUNCTION

Felipe A. Medeiros, Gustavo de Moraes, Balwantray Chauhan,
Remo Susanna and Jeffrey M. Liebmann

Section leader: Felipe A. Medeiros
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Remo Susanna

Consensus statements

1. Both optic nerve structure and function should be evaluated for detection of glaucomatous progression.
2. Currently, no specific test can be regarded as the perfect reference standard for detection of glaucomatous structural and/or functional progression.
3. Progression detected by functional means will not always be corroborated using structural tests, and vice-versa.
   Comment: This is due to the imperfect nature of testing analysis, individual variability, and the structure-function relationship.
4. The use of standard automated perimetry as the sole method for detection of change may result in failure to detect or underestimate progression in eyes with early glaucomatous damage.
   Comment: In glaucoma suspect or ocular hypertensive eyes with initially normal achromatic perimetry, a change in optic nerve structure (*e.g.*, optic topography, retinal nerve fiber layer, optic disc hemorrhage, or parapapillary atrophy) may occur before perimetric change.
5. In general, detection of progression is more difficult in eyes with advanced disease.
   Comment: In eyes with advanced visual field damage, alternative perimetric strategies (*i.e.*, larger stimulus, macular strategies, kinetic perimetry, etc.) may need to be employed.
6. A statistically significant change in structure and/or function (which takes age and variability into account) is not always clinically relevant.
   Comment: Its clinical relevance for patient management must take into account other risk factors and lifetime risk of visual disability.

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Edited by Robert N. Weinreb, David F. Garway-Heath, Christopher Leung, Jonathan G. Crowston, and Felipe A. Medeiros

7. Progressive structural changes are often but not always predictive of future development or progression of functional deficits in glaucoma.
   Comment: The predictive strength depends on the method used to assess structural/functional change.
8. Corroboration of glaucomatous progression through the use of more than one test may provide more effective and more rapid detection of glaucomatous progression than repeated confirmation of change using a single modality.
   Comment: Examples of corroborative change include structure-function (*e.g.*, a structural change of the optic nerve and a spatially consistent functional change).
9. In order to increase the likelihood of detecting progression, test results should be of sufficient quality and appropriate quantity to provide meaningful information.
   Comment: While adjunctive testing can help clinical decision making, the use of multiple modalities of testing, at the expense of quality and appropriate frequency and quantity, should be avoided.
10. Life expectancy should be considered when evaluating the clinical relevance of a structural and/or functional change in glaucoma.
11. Structural and/or functional testing should be conducted throughout the duration of the disease.

Introduction

Glaucoma is a progressive optic neuropathy characterized by intraocular pressure (IOP)-dependent and IOP-independent mechanisms that contribute to disease onset and progression. Damage to the optic nerve may be followed by characteristic patterns of visual function loss, which is most commonly measured with achromatic perimetry. Although a variety of genotypes and phenotypes exist, reduction of intraocular pressure (IOP) has been demonstrated to delay or prevent further injury across the glaucoma spectrum and remains the only modifiable risk factor for which proven treatment is currently available. Since the main goal of treatment is to either halt or slow disease progression, clinicians must be able to identify patients at increased risk of progression and, most importantly, be able to detect and objectively measure progression when it occurs. Conceptually, all glaucoma patients progress, albeit at different rates, and their rate of change is the most objective measure to guide treatment decisions and interventions.

The structure-function relationship in glaucoma and its implication for detection of change over time

The optic neuropathy in glaucoma is characterized by progressive neuroretinal rim thinning, excavation and loss of the retinal nerve fiber layer.[1] These structural changes are usually accompanied by functional losses, which may ultimately

result in significant decrease in vision-related quality of life. Although there is an unquestionable relationship between structural and functional damage in glaucoma, their precise association and the evolution of this association over time are still unclear.[2-5]

The vast majority of studies investigating the structure and function relationship in glaucoma have used only cross-sectional data in an attempt to extrapolate what would be the true longitudinal course of changes in individual patients.[6-17] In these studies, quantitative structural measures derived from different imaging technologies, such as confocal scanning laser ophthalmoscopy (CSLO), optical coherence tomography (OCT) and scanning laser polarimetry (SLP), have shown different degrees of correlation to psychophysical tests such as standard automated perimetry (SAP). There is still uncertainty regarding which mathematical model better describes the relationship between structural and functional loss in glaucoma.[3-5,13,18-22] However, most studies have identified a curvilinear relationship between structure and function, when these measures are expressed in their original scales. It should be noted that visual field indexes are usually expressed in a logarithmic scale (dB). Scaling of data in clinical perimetry is necessary because the ranges of stimulus intensities cover several orders of magnitude. Scaling of perimetric stimulus intensities has been incorporated into standard clinical testing, where the stimulus intensities are scaled by a logarithmic transformation to decibel (dB) units of attenuation for both the intensity staircase procedure for threshold measurements as well as for the report of the final threshold intensity. Several investigators have suggested that such scaling may introduce an artifactual relationship between structural and functional measurements in glaucoma.[13,23-25] The logarithmic scale would accentuate sensitivity changes in the visual field at low decibel values and minimize changes at high decibel levels. Therefore, visual function changes would be less apparent in the early stages of structural damage giving the impression that structural losses occur first. For example, considering a linear rate of retinal ganglion cell (RGC) loss in glaucoma, a 10% loss of RGCs from 100% (normal) to 90% (early damage) would correspond to approximately 0.5 dB loss ($10*\log_{10}1 - 10*\log_{10}0.9$) in sensitivity measured on a logarithmic scale. Considering a field region with age-expected sensitivity of 30 dB, such change would represent only 1.67% loss (0.5/30) in sensitivity. In a more advanced stage of disease, a change from 50% to 40% in the amount of surviving RGCs would correspond to the same 10% loss in RGCs, however, it would represent approximately 1 dB loss ($10*\log_{10}0.5 - 10*\log_{10}0.4$) in sensitivity measured in logarithmic scale and 3.3% loss (1/30) in a percent scale. Thus, the same rate of structural loss would translate into greater rates of visual function loss in later compared to earlier stages of the disease. The small percent changes in visual function in early progressive disease would also be more difficult to detect in individual eyes due to variability and, therefore, subjects with early disease would show less progression with visual fields and more progression with structural tests. This is suggested by several studies looking at structural and functional progression in glaucoma.

The scaling differences may help explain disagreements when different structural and functional tests are used to assess progression. Due to the nature of the structure-function relationship when assessed using current clinically available methods, such disagreements will be unavoidable and should not necessarily be interpreted as lack of accuracy of one of the methods. However, although disagreements between detection of glaucoma progression with structural and functional tests may be expected, it is important to demonstrate that changes in these tests carry significant prognostic information for patients. The clinical importance of a deteriorating visual field seems unquestionable and there is evidence that even early changes in standard automated perimetry may already affect vision-related quality of life.[26] Recent studies have also shown that structural tests are predictive of visual function loss in glaucoma, as detailed below.

Predicting functional loss from structural changes in glaucoma

Previous investigations have shown that cross-sectional baseline structural measurements, either by expert assessment of stereophotographs or objective imaging methods, are predictive of future development of visual field loss in glaucoma suspects, suggesting a potential role for these measurements in early detection of disease.[27-33] However, measures of predictive ability reported in these studies have generally indicated a low accuracy of cross-sectional structural measures for predicting individual functional outcomes. This is likely due to the wide variation in the appearance of the optic nerve, which makes it difficult to identify early signs of disease at a single point in time. Detection of progressive optic disc change over time is likely to be a more specific indicator of the presence of structural damage from glaucoma and to correlate better with functional outcomes.

A recent study by Medeiros *et al.*[34] showed that optic disc progression was highly predictive of development of functional loss in glaucoma. The authors followed 639 eyes of 407 glaucoma suspect patients for an average of eight years. Patients suspected of having glaucoma at baseline and who had progressive optic disc change on stereophotographs had almost 26 times higher chance of developing a visual field defect (HR = hazard ratio [HR]: 25.8; 95% CI: 16.0 – 41.7) during follow up. Presence of optic disc progression was the most important predictive factor for conversion, with an R^2 of 79%, well above that of any other known risk factor for development of glaucoma, such as IOP and corneal thickness. This is not surprising if we consider that progressive structural deterioration is indicative of the disease itself, rather than a risk factor.

Another study Chauhan *et al.*[35] evaluated whether progressive optic disc changes measured by the Topographic Change Analysis (TCA) software of the Heidelberg Retina Tomograph (Heidelberg Engineering GmbH, Dossenheim, Germany) were predictive of functional loss in a cohort of 81 patients with glaucoma. Among the many different criteria for TCA progression evaluated by the authors, a conservative one was able to significantly predict future functional deterioration with a positive likelihood ratio of 3.02.

Although IOP has traditionally been used as an endpoint in glaucoma clinical trials, it is an imperfect surrogate for the clinical outcomes of the disease. Many patients can progress despite low IOP levels and others remain stable despite having IOP measurements considered consistently high.[36-38] Further, IOP is not a suitable endpoint for clinical trials investigating certain treatment modalities for glaucoma, such as neuroprotective therapies. The use of visual fields as the sole endpoint in glaucoma trials is potentially limited by the need for large samples, long-term follow-up, variability of results and inconsistency in the available methods to define visual field progression.[39] Being a valid surrogate for development of functional loss, progressive optic disc damage could be used as an endpoint in glaucoma clinical trials with a number of advantages, including faster acquisition of a sufficient number of endpoints with reduction in sample size requirements, enabling shorter and less expensive trials. It is important to note that in both of Medeiros *et al*. and Chauhan *et al*. studies, many patients developed visual field progression despite undetectable changes in the optic disc. Therefore, it is important to use both structural and functional endpoints in studies of glaucoma progression.

Combining structural and functional measures of glaucoma progression

The disagreement between structural and functional methods for detecting progression could be related to the different algorithms employed to assess change, to the variability of measurements over time, or to the different scales used to assess structure and function.[40-50] Whatever the reason might be, it is likely that a combination of structural and functional measurements would improve detection of clinically significant disease progression compared to either method used alone.

An ideal method for detection of glaucomatous progression should not only give an indication of whether the eye or the patient is likely showing progression, but also needs to give an estimate of the rate of deterioration. Although most glaucoma patients will show some evidence of progression if followed long enough, the rate of deterioration can be highly variable among them.[51-55] While most patients progress relatively slowly, others have aggressive disease with fast deterioration which can eventually result in blindness or substantial impairment unless appropriate interventions take place. The elucidation of the longitudinal relationship between structural and functional tests and their rates of change over time is essential in order to determine the relative utility of these tests in monitoring the disease.

Several approaches could be potentially used to combine structural and functional information for detection of progression. Medeiros *et al*.[56] proposed the use of joint modeling of longitudinal changes using Bayesian statistics to combine structural and functional tests. The joint modeling approach enables a better characterization of the true underlying relationship between structural and functional tests, as it decreases the impact of measurement error by incorporating

it in a simultaneous model of the two longitudinal outcomes. By joint modeling the two outcomes, information derived from one test is allowed to influence the inferences obtained from the other test. For example, a visual field change that would otherwise be declared non-statistically significant by analysis of visual field data alone may be declared significant after taking into consideration the structural changes occurring in the same eye. Using this approach, Medeiros *et al*.[56] found a significant improvement in detection of glaucoma progression and estimation of rates of change in a group of 434 eyes of 257 participants followed for an average of four years using SAP and scanning laser polarimetry.

Other studies have attempted to quantify the discordance between structural and functional measurements and better characterization of their relationship. In a recent study, Zhu and colleagues[57] proposed a methodology to predict functional damage from structural losses measured by retinal nerve fiber layer assessment with scanning laser polarimetry. The method generated clinically useful relationships that related topographical maps of RNFL measurement to visual field locations and allowed the visual field sensitivity to be predicted from structural measurements. It may also enable evaluation of structural and functional measures in the same domain which could potentially be advantageous for combining them into a test to detect glaucomatous progression.

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4. RISK FACTORS

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Consensus statements

1. Risk factors for glaucoma progression should be ascertained in all patients with glaucoma or suspected of being at increased risk of glaucoma.
2. Clinical risk factor assessment in glaucoma serves two roles. It provides (a) prognostic information; and (b) a basis for disease management.
   Comment: While proof of causality is desirable, the pragmatic nature of clinical medicine allows the use of risk factors of varying evidence quality and even clinical signs to be used in clinical management.
3. The use of risk factors in clinical management should take into account: (a) the strength of the risk factor for disease progression; and (b) the practicality and potential harm of reducing that risk factor.
4. Ocular hypertension is itself a strong risk factor for glaucoma, with rates of progression depending on the presence or absence of other risk factors.
   Comment: Accounting for these risk factors is critical to clinical decision making in the management of OHT patients.
   Comment: Risk factor assessment in OHT helps determine an individual's need for IOP lowering medication and also informs on the frequency of follow up.
5. Risk calculators provide a means for quantifying risk of glaucoma progression in appropriate individuals with similar baseline characteristics to those present in the study.

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Comment: The utility of these risk calculators in clinical practice still needs to be determined.

6. Higher mean IOP is a strong risk factor for glaucoma progression.
   Comment: More studies are needed to evaluate the role of other IOP parameters as risk factors for glaucoma progression.
7. A thinner central cornea is a risk factor for progression in patients with higher baseline IOP.
8. The presence of pseudo-exfoliation syndrome is an independent risk factor for progression.
9. The presence of a disc haemorrhage, older age, and lower ocular perfusion pressure are risk factors for progression.
   Comment: The relationship between low blood pressure and risk of progression is complex.
10. While estimates of risk of progression for individual patients based on completed large clinical trials are available, the use of such estimates varies considerably in clinical practice.
11. There is greater information available regarding the importance of risk factors for progression from early to moderate disease than from moderate to severe disease.
    Comment: Few adequately powered studies have prospectively assessed the risk factors for blindness from glaucomatous disease.
12. The relative importance of risk factors for progression may vary depending upon the stage of glaucomatous disease.
    Comment: Some risk factors that do not appear to be important predictors of progression from early to moderate glaucoma may be relatively more important in predicting progression from moderate to severe disease and vice versa.
13. Studies that longitudinally assess risk factors for functional vision loss and blindness from glaucomatous disease are needed.

Future directions:

- Useful information regarding the importance of various risk factors for glaucoma progression and functional vision loss may be obtained via the use of Electronic Health Records in the future.
- Longitudinal studies that determine risk factors for glaucoma progression in angle-closure patients are required.

1. Definitions

Risk factor (for progression) definition: ‘A factor associated with an increased rate of progression of a disease, not completely explained by a co-related factor (confounder) or an inappropriate comparison (bias).’

When a risk factor is proven to lead directly to disease progression it is known as a causal risk factor.

Proof of a causal risk factor necessitates:

1. Ruling out (as best as possible) of biases and confounders (usually when a number of high quality, well-conducted, independent studies show similar risk associations.)
2. Identifying a plausible biological link between the risk factor and the disease (usually by understanding the cellular mechanism of disease).
3. Showing a reduction in disease progression in a people not exposed to the risk factor (usually by an randomized controlled interventional trial or an epidemiological cohort study).

A risk factor that is not causal may be a surrogate for a true causal risk factor or an epiphenomenon on the causal pathway. While these risk factors may still be useful in assessing risk of progression, their direct reduction does not lead to a reduction in disease progression.

Attributable risk

The impact of a causal risk factor (and thus the impact of eliminating that risk factor) is called its attributable risk. There are two types of attributable risk: the attributable risk among exposed which measures the impact on individuals exposed to a risk factor and population attributable risk which measure the impact on society.

Attributable risk among exposed (ARE) definition: 'The proportion of disease progression in the group exposed to a risk factor attributable to that risk factor.'

Population attributable risk (PAR) definition: 'The proportion of progression in the total population attributable to a particular risk factor.'

Risk factors can be rated by three criteria:

1. The strength of evidence for it being a risk factor;
2. The strength of the risk factor itself in terms of glaucoma progression;
3. The capability of changing that risk factor and the impact of changing it on the disease.

2. Risk factors for the development of glaucoma in normal eyes and ocular hypertensive eyes

Global risk factor assessment plays a key role in guiding the clinician toward making a therapeutic decision in individuals who have elevated risk of developing glaucoma. Data covering risk factors for incident glaucoma in normal eyes has been derived largely from longitudinal population studies; notably the Rotterdam Eye Study[1] (RES, largely European decent), The Barbados Incidence Study of Eye Disease[2] (BISED, largely African decent) and the Melbourne Visual Impairment Study[3] (MVIP, largely European decent). In contrast, data on

risk factors for conversion of ocular hypertension to glaucoma are derived in the most part from two large prospective randomized intervention studies, the Ocular Hypertension Treatment Study[4] and the European Glaucoma Prevention Study.[5] These are covered in an excellent review by Coleman and Miglior (Surv Ophthalmol 2008).[6]

Hazard ratios (the risk of a new event occurring within a specific time) generated from these studies have informed the creation of algorithms or risk calculators that can help determine an overall risk of a particular patient progressing. The most recent iteration has combined data from OHTS And EGPS and is available online.[7] The utility of these in clinical practice, however, remains to be determined. (http://ohts.wustl.edu/risk/calculator.html).

Table 1. Combined OHTS/EGPS model for establishing five-year risk of developing OAG in OHT patients.*

	Hazards Ratio (95% CI)
Age (per decade)	1.26 (1.06-1.50)
Baseline IOP	1.09 (1.03-1.17)
CCT (per 40 micron thinner)	2.04 (1.70-2.45)
Vertical C:D ratio (per 0.1 larger)	1.19 (1.09-1.31)
Pattern Standard Deviation (per 0.2dB greater)	1.13 (1.04-1.24)

*These data apply to individuals who fulfilled the inclusion criteria of the two studies and may not be extrapolated to individuals who do not. (Modified from Coleman *et al*.[6])

Risk Factors for progression in normal eyes

As detailed above, evidence for risk factors predisposing to incident glaucoma in previously healthy, non ocular hypertensive eyes have been derived from longitudinal population studies. Older age and higher IOP at baseline are consistently strong risk factors for incident open-angle glaucoma across studies. The incidence of definite OAG increased from 0% of participants aged 40 to 49 years to 4.1% of participants aged 80 years and older.[3] In the RES incident bilateral open angle glaucoma was five times more common in the over 75's compared to those under 75 years of age.[1] In MVIP, RES and BISED a 1mmHg or great increase in IOP above average was associated with a 10 to 14% increased risk of POAG.[6]

A number of other risk factors were positively associated with incident POAG in some, but not all population studies. These included positive family history, thinner central corneal thickness and reduced ocular perfusion pressure (BISED), pseudoexfoliation and use of alpha-agonists (MVIP) and calcium channel blockers for systemic hypertension (RES). Differences among studies may reflect the relatively small numbers of incident cases in these studies.

Table 2. Relative risk of glaucoma in population-based longitudinal studies. (From: Coleman *et al.*[6])

Risk Factors (Relative Risk with 95% Confidence Intervals) for Development of Open-angle Glaucoma in Population-based Longitudinal Studies			
	BISED (9 yrs incidence)	RES (6.5 yrs incidence)	VIP (5 yrs incidence) of "probable OAG"
Age (per order year)	1.04 (1.03–1.05)	1.06 (1.02–1.09)	-
Age at baseline 50–59	-	-	n.s. – multivariate 2.0 (0.21–19.5)
Age at beaseline 60–69	-	-	8.4 (1.1–66.6)
Age at beaseline 70–79	-	-	12.2 (1.5–103)
Age at beaseline ≥ 80	-	-	n.s. – multivariate 8.6 (0.63–116)
OAG family history	2.4 (1.3–4.6)	-	n.s. – multivariate 1.1 (0.29–4.0)
IOP (per mm Hg)	1.12 (1.08–1.16)	1.14 (1.08–1.21)	1.10 (1.04–1.20)
CCT (per 40 mm thinner)	1.41 (1.01–1.96)	-	-
Ocular MPP (< 40 mm Hg)	2.6 (1.4–4.6)	-	-
SBP (per 10 mm Hg)	0.91 (0.84–1.0)	-	-
Diabetes	n.s. – age adjusted 1.2 (0.7–1.8)	n.s. – multivariate 0.65 (0.25–1.64)	n.s. RR not reported
Ca Channel antagonists	-	1.9 (1.1–3.3)	-
A-blocker	-	-	4.8 (2.0–63.3)
C/d ratio > 0.7	-	-	11.0 (4.6–26.8)
PEX	-	-	11.2 (2.0–63.3)

BISED = Barbados Incidence Study of Eye Diseases; RES = Rotterdam Eye Study; VIP = Visual Impairment Project; OAG = open-angle glaucoma; IOP = intraocular pressure; CCT = central cornea thickness; MPP = mean ocular perfusion pressure; SBP = systolic blood pressure; PEX = pseudoesfoliation syndrome.

Risk factors for progression of OHT patients to OAG

'Progression of ocular hypertension' refers to conversion of eyes with IOPs above 2 SD of the population mean without structural or functional signs of glaucomatous damage into eyes with structural and or functional evidence of glaucoma damage. Although IOP lowering significantly lowers progression rates in OHT the majority of OHT patients do not progress over an initial five-year period (OHTS, EGPS). Decisions as to which OHT subjects to treat, are therefore based largely on risk factor analysis, which aim to treat individuals most at risk of going on to suffer vision loss from glaucoma.

In the Ocular Hypertension Treatment Study, elevated IOP, advancing age and disc hemorrhages were significant risk factors for progression to glaucoma.[4] In the European Glaucoma Prevention Study (EGP) elevated IOP, age and pseudoexfoliarion syndrome were significant risk factors for progression of OHT to glaucoma.[5] Additional predictive factors that were not significant at baseline but

became apparent during the follow up included disc haemorrhage, smaller IOP reduction (in the treatment arm) as well as a higher mean IOP during follow up.

The role of IOP variation is not clear. Long-term IOP variation (quantified as the standard deviation of average IOP over the entire follow-up period) was not associated with POAG in OHTS or EGPS. In a further study from Sweden, short-term variation (IOP variation over the circadian period) was also not associated with progression from OHT to glaucoma.[8] The DIGS cohort from San Diego has also investigated risk factors for progression in this clinic-based cohort. Similar risk factors for conversion were seen here as per OHTS. In addition Medeiros and colleagues did not find a positive association between long-term circadian (24-hour) IOP variation and conversion to POAG.[9]

Although eyes with thin central corneas are more likely to progress, it is not absolutely clear what impact corneal thickness has on applanation tonometry. As such, the role of corneal thickness as an independent risk factor for progression of ocular hypertension to glaucoma is not fully established. Recent findings demonstrate that adjusting IOP measurement for corneal thickness does not improve our ability to predict progression (Brandt in press) as the predictive accuracy of the OHTS/EGPS prediction model for the development of POAG was not improved by correcting IOP for CCT using formulae published by Ehlers, Whitacre, Orssengo and Pye, Doughty, and Kohlhaas (Brandt *et al*., in press).

Although there is wider evidence indicating that a positive family history increases the risk of an individual having glaucoma (the RES reported a ten-fold higher risk of glaucoma in 80 year-old individuals with a positive family history compared to controls). The evidence supporting family history as a risk factor for incident glaucoma is weak, with neither OHTS or EGPS finding a significant association. Family history in these studies was self-reported. This likely underestimated the true rates of familial glaucoma.[10] Despite the lack of compelling evidence for family history being associated with progression to glaucoma in OHT subjects, there was broad consensus among the panel that a positive family history should be considered as an important risk factor for incident glaucoma in ocular hypertensive patients.

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3. Progression of POAG

Glaucoma is a progressive disease. In EMGT 76% and 59% progressed in the untreated and treated cohorts respectively over the eight-year follow-up period.

Early in the course of disease management, progression rates for an individual patient are usually not known. Management at this stage is therefore often based on risk factors for progression and markers that determine the stage of the disease. (Garway-Heath)

Progression rates are highly variable across populations, Risk factor analysis may only accounts for a small part of this variability for any individual patients. (Heijl)

- Although we cannot tell which patients will progress, risk-profiling does help us decide:

– which patients to watch most closely
– in which patients to concentrate our limited resources

Therefore for any given set of risk factors, more aggressive intervention (IOP lowering) and closer observation may be required for cases with advanced disease who are at greater risk of functional vision loss.

In EMGT the average progression rates was 0.9dB/yr. Only 10% of the cohort progressed at rates exceeding 1.5dB/year

Rates of blindness in POAG are low, with only 9% and 27% blind by WHO criteria in both eyes or one eye respectively, at 20 years (Olmstead County). POAG – 27% in one eye; 9% OU (N = 295).

OHT – 14% in one eye; 4% OU (N = 114).

Risk factors for progression of OAG

In the last years, several studies have been published addressing risk factors for open-angle glaucoma.[1] Some of them have focused on risk factors for progression.[2]

Risk factors for progression of OAG have been analyzed in five multicentered large randomized trials: Early Manifest Glaucoma Treatment Study (EMGTS), Advanced Glaucoma Intervention Study (AGIS), Collaborative Normal Tension Glaucoma Study (CNTGS), CIGTS and Canadian Glaucoma Study (CGS).[3-12] Each of these trials evaluated different factors in OAG in different stages of the disease. The specifics of design, methods and results can be found in the respective publications. Based on these large trials, as well as in other studies, risk factors, divided into ocular and systemic, are depicted below.

Table 3. Risk factors for glaucoma progression.

Category	Risk Factor	Supporting studies / Comments
Ocular		
IOP	Higher IOP at baseline	EMGTS[3,4]
	Higher mean IOP	EMGTS, AGIS, CGS[3-10]
	Greater IOP variation	AGIS (in patients with low mean IOP)[5-7] Not in EMGTS[3,4,10,11]
Central Corneal Thickness	Thinner corneas	EMGTS (in patients with higher baseline IOP)[11]
Exfoliation syndrome	Presence of exfoliation syndrome	EMGTS[3,4,11]
Bilateralness	Presence of bilateral disease	EMGTS[3,4,11]
Disc	Disc hemorrhage	CNTGS12, EMGTS[3,4,11]
Disc	Smaller neuroretinal rim	Erlangen Glaucoma Registry[13]
Disc	Larger parapapillary beta zone	Erlangen Glaucoma Registry[13]
Disc	Progression of optic nerve damage: predictor of visual field loss	Erlangen Glaucoma Registry[13]
Visual field	Advanced perimetric damage	Erlangen Glaucoma Registry[13]
Visual field	Initial damage to both hemifields at diagnosis	Retrospective study[14]
Systemic:		
Age	Older age	EMGTS, AGIS, CGS[3-9]
Gender	Females	RF in CGS, not in EMGTS[3,4,8,9] Women with migraine more likely to progress in CNTGS[12]

Table 3. Continued.

Category	Risk Factor	Supporting studies / Comments
Gender	Males	Suggestion of increased risk in AGIS[5]
Genetics	Myocillin or Optineurin associated with more severe course and more likely to progress	Reference 15
Ethnicity	African-derived persons	CNTGS[12]
Blood perfusion pressure	Lower ocular systolic perfusion pressure	EMGTS[11]
Blood perfusion pressure	Lower diastolic blood pressure in patients with lower baseline IOP	EMGTS[11]
Blood hypertension on hypotensive medications	Systemic hypertension treated with hypotensive medications may be a risk factor for increased progression of optic nerve parameters in glaucoma suspects compared with age -matched normotensive subjects	Reference 16
Cardiovascular status	Cardiovascular disease history in patients with higher baseline IOP	EMGTS[11]
Diabetes	Self-reported diabetes	Associated with progression in AGIS[5,7] Not in CNTGTS and EMGTS[11,12]
Anticardiolipins	Abnormal baseline anticardiolipins	CGS8
Family History	Higher risk in first-degree relatives	Rotterdam study[17]

IOP as a risk factor for progression

Mean IOP

Different multi-center, randomized clinical trials support the role of mean IOP as a risk factor for progression. The Early Manifest Glaucoma Trial (EMGT) evaluated the role of IOP reduction on progression of glaucoma in subjects with early disease.[3,4] The study included patients with early glaucomatous damage evidenced by reproducible visual field defects at baseline, who were randomized to treatment versus no treatment. Patients in the treatment group were treated with laser trabeculoplasty and betaxolol, and achieved a 25% reduction of baseline IOP. After six years follow-up, 62% of patients in the control group progressed versus 45% in the treated group ($p = 0.003$). Each 1 mmHg of mean IOP was associated with a 13% higher risk of progression. Each 1 mmHg higher baseline IOP increased 5% the risk of progression.

The Advanced Glaucoma Intervention Study (AGIS) evaluated two different surgical therapeutic sequence strategies in glaucoma patients with moderate

disease who were uncontrolled on medical therapy.[5] One of its reports evaluated the results according to the percentage of visits that the eyes had IOP less than 18 mmHg during follow-up.[6] Eyes were allocated to one of the following four groups: Group A had 100% of visits with IOP less than 18 mmHg; Group B had 75% to less than 100%; Group C had 50% to less than 75%; and Group D had less than 50% of visits with IOP less than 18 mmHg. Mean IOP during the six years follow-up was: 12.3 mmHg, 14.7 mmHg, 16.9 mmHg and 20.2 mmHg; respectively for groups A, B, C and D. Visual field deterioration (measured by a specific score), was almost none in eyes belonging to group A. Eyes in groups B, C and D had more visual field progression compared to group A.

The Canadian Glaucoma Study (CGS) is a multicenter interventional study, whose primary objective was to determine which baseline demographic and systemic risk factors were associated with progression of visual field damage in patients with open-angle glaucoma. This study used an established protocol for IOP control. After a median follow-up of 5.3 years, the study identified higher mean follow-up IOP as one of the factors associated with visual field progression (HR per 1 mmHg, 1.19; 95% CI: 1.05-1.36).

IOP variation

Long-term IOP variability as a risk factor for glaucoma progression was addressed by two multicenter, randomized, prospective studies that yielded opposite results. Long-term IOP variation was considered a risk factor for glaucomatous visual field progression in the AGIS study, after a post-hoc analysis.[7] Long-term IOP variation was obtained as the standard deviation of all IOP readings. Eyes with an IOP standard deviation < 3 mmHg remained stable, while those with an IOP standard deviation > 3 mmHg progressed.

Long-term IOP variation, also measured as standard deviation of IOP readings over follow-up time, was not considered to be a risk factor for progression in the EMGT.[10] A significant difference between studies that may explain this discrepancy, is the fact that the AGIS included IOP readings obtained after progression occurred, while in the EMGT, readings were obtained up to the point of progression.[18] Distinct study designs and populations may also explain the difference. A latter publication reported that IOP variation is a prognostic factor for subjects who underwent only one surgical intervention and had low mean IOP (were in the lowest tertile of mean IOP).[19]

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4. Risk factors for development and progression of primary angle closure and primary angle-closure glaucoma

According to a conceptual model of natural history, angle closure diseases are classified into three board categories, primary angle-closure suspect (PACS), primary angle closure (PAC) and primary angle-closure glaucoma (PACG).[1] Demographic characteristics, ocular anatomy, genetic, systemic and some external factors are all identified as risk factors for angle closure. However, the majority of risk factors identified are from either cross-sectional studies or clinical ob-

servations. Lack of systematic longitudinal data hinders a better understanding of the natural history of the diseases and a correct identification of risk factors.

Incidence data are useful to estimate the onset and development of angle closure in the population. Based on retrospective case identification from medical records, the incidence of acute PAC was reported to be 3.8 per 100,000 per year in Finland,[2] 4.2 in Israel[3] and 8.3 in Minnesota.[4] Based on the one-year prospective data, this rate was identified as 15.5 per 100,000 per year (95%CI: 13.3-17.7) in Singapore Chinese population[5] compared to 7.0 previously reported in Thailand and 11.4 in Japan after age and sex standardization. In the prospective island-wide incidence study in Singapore, risk factors identified were female (Relative risk, RR, 2.4), Chinese ethnicity (RR 2.8) and 60+ years (RR 9.1). A relationship between the number of acute attacks per day and mean number of sunspots and mean solar radio flux was also identified. Risk factors identified were similar in other incidence studies.

Longitudinal data from population-based studies suggest that the rate of progression from narrow angle to established angle closure (including any forms of angle closure) is around 16% in ten years in Eskimos,[6] 22% in five years in Indians[7] and 19% in a mean of 2.7 years in Caucasians.[8] A study in Mongolia found that 20% of people with normal angles develop occludable angles in six years.[9] Each of these studies also had limitations, so the true rate of angle closure development is not certain. Female gender was identified as having greater risk, but ocular anatomy, such as anterior chamber depth, lens thickness and axial length, were not identified as the statistically significant risk factors for the progression. The fact that these studies had relatively small number of subjects may compromise the power to detect the true risk factors.

The risk factors for progression can be inferred from cross-sectional studies. Studies consistently suggested that a narrow drainage angle is the primary anatomical risk factor for the angle closure. Anterior chamber depth (ACD) increases between seven and fifteen years and then decreases with increasing age. The decrease in ACD in older individuals is likely mainly due to the thickening and anterior movement of lens.[10] Female gender is a major predisposing factor for ACG development. The prevalence of all categories of angle closure is two to five times higher in women than men. This increased prevalence is likely due to more shallow anterior chambers in women.

Ethnical difference has been well recognized for angle closure. Both prevalence and incidence data demonstrate that the angle closure affects East Asian people more frequently than European-derived persons.[11] This ethnic difference may be attributed to the differences in anterior chamber and angle anatomy. The majority of evidence suggests an inverse association between ACD and the rate of angle closure in various ethnic groups: shallower ACDs are normally found in populations with higher rate of angle closure.

A positive family history has long been recognized as predisposing to angle closure.[12] The similarity of ocular biometry in first degree relatives of patients indicates that angle closure related anatomical characteristics are heritable. The risk of developing angle-closure glaucoma was reported to be 3.5 times higher

in first degree relatives of affected Inuit patients.[13] An investigation of Chinese twins confirms that the heritability of anterior chamber depth and drainage angle width could be as high as 70~90%.[14]

Given PAC development is very uncommon even in high-risk populations, it remains challenging to predict or identify people who will develop PAC. It is poorly understood what causes eyes with narrow angles develop PAC given the natural history data is largely not available. The fellow eye of individuals who have a one-eyed acute attack are at highest risk of developing an AAC attack. Early studies of such persons indicate that nearly half will develop an acute attack within approximately five years.[15,16] In fact, 10% of all attacks are bilateral. Fellow eyes should therefore undergo prophylactic laser iridotomy as soon as possible. Similarly, people with milder episodes (based on history and clinical signs of previous angle closure) are also considered as high risk, especially if there is evidence of a transient elevation in IOP, and they require iridotomy as well.

Appositional closure is commonly used as an indication for increased risk of developing angle closure damage and therefore requires a prophylactic treatment, although this is opinion rather than evidence-based. Anterior segment imaging systems, such as UBM or ASOCT, are able to identify contact between the iris and the trabecular meshwork, but might not able to confirm whether it is appositional or synechial contact. Dynamic factors of the iris may also contribute to the development of angle closure[17] and it was also confirmed by iris histologic study.[18] This finding has yet to be replicated, however, and the difficulties of measuring iris dynamics pose additional challenges when considering using this as a predictor.

Some investigators have used provocative tests to identify at-risk individuals. These tests simulate the physiological conditions under which angle closure may develop. Nearly ten types of provocative tests have been proposed but the most common one is the dark room prone provocative test. A UBM dark room provocative test may have greater sensitivity to identify high risk eyes.[19] However, none of these provocative tests has been shown to be truly predictive of developing PAC. In fact, Lowe and Wilensky have both asserted that provocative tests are probably poor predictors of future risk based on their research.[8,20] Given the effort and potential risk when performing the tests and the lack of proven benefit, most practitioners in the West do not perform this as part of the clinical evaluation. More evidence from longitudinal data are needed to determine if they confer additional benefit in clinical practice.

Evidence documenting the progression from PAC to PACG or progression among PACG mainly come from clinical studies. One has to be cautious that almost all the studies on ACG progression are based on observations on the participants that under treatment, because it is simply not ethical to remain patients untreated, and therefore natural history data among people with established angle closure damage are simply not available. Interestingly, one population-based study in India reported that seven patients, among 19 PAC patients who refused laser PI, developed PACG in five years.[21] Again, in part due to the small num-

ber of subjects, this study did not identify significant biometric parameters to differentiate those progressing or not. More data on treatment reluctant patients will provide more insights into the natural history.

Management of the early stages of angle closure focuses on the modification of the anterior configuration, hopefully before irreversible trabecular damage and GON develops. When GON has developed, the aim of the treatment is to lower the IOP in order to prevent the progression. Laser, surgery and medical treatment are recognized options for modifying the anterior drainage angle configuration. Laser iridotomy and iridoplasty are two laser treatments for opening a narrow angle. Surgical iridectomy or lens extraction are surgical procedures with similar purposes. Filtering surgery aims to lower IOP in those with established GON damage. Progression (or prognosis) data among the patients under treatment largely come from clinical case series instead of randomized trials.

Laser PI eradicates relative pupil block and equalizes the pressures between anterior and posterior chamber. The progression among people with patent PI depends on the underlying mechanism and the stage of disease. Greater extent of PAS, higher presenting IOP and a large cup disc ratio are all predictors for poor pressure controls and progression following iridotomy.[22] After an acute episode of angle closure, satisfactory IOP control can be achieved in at least half of cases with PI alone,[23] however, once GON damage is established, virtually all cases will require further treatment to control IOP.[24]

Residual angle closure following patent PI may be a risk factor for progression. A study on Asian people suggests that 51 of 111 patients had residual angle closure even with patent PI.

Trabeculectomy in general has much lower success rate in acute PAC cases,[25] but reasonably good outcome in chronic angle closure in comparison with POAG eyes,[26] particularly when in combination with cataract extraction surgery.[27] It will be interesting to investigate the factors conferring risk of progression despite with IOP lower surgery.

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5. Challenges and future opportunities: How do we put risk factor analysis into clinical practice and what else do we need to know?

The lack of adequate information regarding the relative importance of various risk factors for glaucoma progression continues to pose a challenge to the ophthlmic practitioner and the clinician-scientist. In particular, the paucity of information regarding the role of individual risk factors in predicting functional vision loss and glaucoma blindness is noteworthy. Relatively greater prospective risk factor information is available for the development of glaucoma in patients with ocular hypertension and for the progression from mild to moderate glaucomatous diseasitional risk factors to be that require further evaluation include: the compliance of the patient, the socioeconomic background of the society in which the patient lives , and the socioeconomic background of the single patient. Further work is required prior to also considering the potential role of the trans-lamina cribrosa pressure difference with the IOP and the orbital CSF pressure as the measurable determinants.

Establishing a clear role for using risk factors in clinical practice

Provided that we can create a solid list of risk factors, all backed by solid evidence, do we know how to translate this accumulated data to treatment recommendations for individual patients? In this respect, it is reasonable that patient A with a far worse 'risk factor profile' than patient B might:

1. Receive more frequent follow-up visits.
2. Receive more frequent diagnostic tests (visual fields, imaging, IOP measurements (be it office visits or continuous/home tonometry).
3. Be subjected to more aggressive therapies (be it a lower target pressure, earlier surgery).

In the future, increasing use of electronic health records may make it possible to assess risk factor importance retrospectively. Prospective risk factor assessment in large clinical trials is time consuming and expensive. Standardization of such electronic health records will be necessary for such an approach to be useful.

Making data sets from large prospective studies, which have evaluated structural and functional progression available to the ophthalmic community may aid in risk factor assessment. Such data may be used for meta-analyses that can assess risk factors for progression.

Norbert Pfeiffer (left) and Thierry Zeyen.

Jonathan G. Crowston (co-Chair and section 4 Leader), Esther Hoffman and Norbert Pfeiffer (left to right).

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5. GLAUCOMA AND ITS IMPACT ON PATIENT FUNCTION

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Consensus statements

1. Standard measures for assessing glaucoma include measures of optic nerve structure and function including cup/disc ratios, thickness of the retinal nerve fiber layer and ganglion cell layer, white on white visual fields, blue on yellow visual fields, and intraocular pressure. While these measures provide an assessment of the eye, they are surrogates for how the patient is functioning. Both patient reported outcomes (PROs) and functional performance assessment tests provide important information in addition to standard tests on the impact of glaucoma on the patient.
2. It was previously believed that only advanced glaucoma damage has an impact on the patient ability to function. However, more recent cross-sectional clinic-based and population-based studies have demonstrated that early glaucomatous visual field loss has an impact on the patients' ability to function as assessed by patient reported outcome measures and functional performance tests.
3. Future studies are needed to explore the relationship between PROs and functional performance measures and glaucoma progression.
4. Numerous instruments and tests have been used for assessing PROs and functional performance measures in research settings. However, there is no consensus on a single PRO or functional performance measure (or set of PROs or functional performance measures) for clinical practice. There is a need to create simpler PROs and functional performance tests which can easily be reproduced in a wide variety of settings.

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Introduction

Glaucoma is a leading cause of visual impairment and blindness. It is a chronic disease that requires lifelong observation and treatment. The impact of glaucoma includes activity limitation (e.g. driving, household tasks, and reading) due to impaired vision but also effects general health, lifestyle and emotions and therefore a person's quality of life.

Objective endpoints of vision loss such as the measurement of visual acuity and visual field may fall short in capturing the real impact of glaucoma on the patient's daily life. The patient's perspective and their objective performance on tasks is therefore important in order to fully understand the impact of glaucoma on their functioning and well-being, and should be more integrated in clinical practice and research evaluations because some effects are only known by the patients or can be detectable only using specific task based tests and are not detectable or interpretable by using the standard battery of clinical tests.

A large number of instruments exist for assessing the patients' perspective and performance. However, it may be challenging for clinicians or researchers to evaluate which instruments are most appropriate for their intended clinical evaluation or research project. Hence, they may benefit from guidance on how specific outcomes are best assessed based on published evidence. The assessment will cover two types of instruments – patient reported outcomes and functional performance tests assessing specific tasks. This chapter is divided into four sections: (1) How do we measure the impact of Glaucoma? (instruments, validity, reproducibility, estimate of clinically meaningful difference, limitations); (2) What is the relationship between patient reported outcomes, functional performance and glaucomatous damage in cross sectional studies?; (3) What is the relationship between measures of patient reported outcomes, functional performance and progressive glaucomatous damage?; and (4) Consensus statement on PROs and measures of functional performance in Glaucoma, including measures to use in research and clinical practice.

How do we measure the impact of glaucoma? (instruments, validity, reproducibility, estimate of clinically meaningful difference, limitations)

Patient Reported Outcomes

The US Food and Drug Administration (FDA) recently recommended the term 'Patient Reported Outcomes (PRO's)' as an umbrella term covering a broad range of health data reported by the patient. Aspects that are covered include patients' physical (ability to carry out activities of daily living, such as self-care and walking), psychological (emotional and mental well-being) and social functioning (relationships with others and participation in social activities); perception of health status; personal construct (spirituality and stigma) and satisfaction with life or care.

A large number of PRO self-report questionnaires have been developed to assess several aspects of the patients' health status, yet the selection of an instrument largely depends on the objectives and the targeted population. While generic PRO instruments capture a broad range of health status aspects, allowing comparisons among different diseases, they do not capture the patient's perception on specific aspects of a disease or health problem, such as glaucoma. Disease specific instruments are more sensitive to capture small changes in the condition specific health status, and may help to interpret and capture clinical outcomes of glaucoma or its treatment comprehensively, if well developed and validated. PRO's are therefore a unique indicator of the disease's impact on a patient's life and are essential for evaluating treatment efficacy or side effects. Hence, instruments measuring PRO's may provide essential disease and treatment information and their results can be considered as a key-element in treatment decision making and research.

The impact of glaucomatous visual field loss (VFL) on an individual's perceived well-being and function has been investigated using a variety of generic (*e.g.,* SF-36[1,2]), vision-specific (*e.g.*, NEI-VFQ,[3,4] IVI[5]), and glaucoma-specific instruments (*e.g.*, GQL-15[6]), which have been reviewed previously.[7-9] Vision specific instruments are designed to measure the impact of chronic eye disease or symptoms on perceived health, which may include areas such as emotional well-being, social functioning, and ability to complete daily vision-related tasks. Glaucoma-specific instruments typically focus on questions related to visual ability, tasks that are impacted by decreased visual ability, and the importance of the loss of visual ability or ability to form the vision-related task to the individual.[7]

In this chapter, we attempt to establish the relationship between glaucomatous damage and the impact on daily life. Therefore, we did not include PROs for assessing side effects and symptoms. To determine if previously published PRO-instruments are well developed and validated they should be evaluated according to existing guidelines, such as the United States Food and Drug Administration (FDA)-guidelines and/or the framework outlined by Pesudovs *et al*. (2007). These quality criteria emphasize the importance of both the developmental history and the psychometric characteristics of PRO's. According to these guidelines the following criteria are important indicators of an instruments' quality: (1) Were the purpose of the instrument and its target population well defined?; (2) Were adequate steps taken in defining the content of the instrument, the rating scale and the scoring system?; and (3) is the instrument performing well in view of validity and reliability? There are several existing guidelines and published standards for evaluating and judging psychometric properties (*i.e.*, validity and reliability) of PRO-instruments, but ideally good PRO-instruments require scientific evidence concerning: construct-, criterion-validity, responsiveness and reliability. According to the FDA-guidelines validity, reliability and responsiveness testing should be repeated when a PRO instrument is modified: (a) to measure another concept; (b) to be used in a different population or condition, (c) changing the item content or instrument format, or (d) in terms of mode of administration, culture or language application. Of the existing instruments

to assess PROs particularly activities, limitations, social well-being, and daily performance the following instruments were consider to have established validity: GQL-15, IMQ, GSE, Glau-QOL-36, NEI-VFQ-25, and the IVI.

Functional performance impact

Functional performance impact is defined as the 'objective task based assessment of a person's ability/inability to perform certain tasks'. One method for objectively measuring the impact of glaucoma is through monitoring of adverse events. Several different adverse events have been screened for in glaucoma, including motor vehicle crashes, falls, and fractures. Database searching is required if these adverse events are to be measured objectively. For example, previous work has assessed government records to evaluate if falls or motor vehicle crashes were more common in glaucoma patients.[10-12] The strength of this work is that its impact is easily interpretable. For instance, we can all understand the meaning and impact of a motor vehicle crash or an injurious fall. A significant limitation to this approach is that the accuracy and validity of the work is difficult to assess, as there is no gold standard for knowing whether the event actually occurred or not. As such, the accuracy and validity publications using this approach needs to be assessed on a case-by-case basis, and depends on our interpretation of whether the database utilized can pick up the adverse events consistently and without bias. Another shortcoming of this approach is that results can only be gathered for individuals covered by the databases used, limiting the generalizability of the work. Developing nations, for example, typically do not have such databases.

Adverse events can also be picked up through patient report, and therefore this section straddles the two sections defined for this consensus report. Work in the field of motor vehicle crashes has suggested that objective measurement of adverse events may be more accurate than self-report of adverse events, though this may not necessarily be true for other outcomes. Additionally, individuals with eye disease may be more likely to report some adverse events (*i.e.*, falls) due to awareness of their disease and its possible consequences, and less likely to report other events (*i.e.*, motor vehicle crashes) due to fear of the consequences of reporting the event (*i.e.*, loss of driving privileges). However, some adverse events (all falls, discontinuation of driving) can only really be measured through patient report, leaving no other suitable option available (at present).

A second method for objectively measuring the impact of glaucoma is through monitoring of individuals in their normal routine. For example, accelerometers have been validated as a tool for measuring real-world mobility and physical activity done as part of one's daily routine.[13,14] Tracking technology is also now available which can determine where people move, drive or travel, and video systems have been created to observe how they drive, and could certainly be expanded to assess how they perform other activities of daily living.[15-17] The strength of this approach is that it gives us insight into what is actually happening in a person's life and normal routine. Limitations to this work are par-

tially attributable to the technologies used to monitor the patient. For example, accelerometers may not properly classify the physical activity associated with all activities (*i.e.*, swimming), GPS tracking devices may fail to track people when they are in indoor locations, while car cameras may not pick up happenings outside the view of the camera. As such, the accuracy and validity of these studies needs to be evaluated on a case-by-case basis by individuals with knowledge of the technological shortcomings of the monitoring systems used. Some of these monitoring techniques also require participation by the subject in terms of wearing a device, which can lead to inaccurate results if compliance is an issue. Additionally, people may live in very different home environments, making it difficult to discern if measured difficulty is due to their disease or to their environment. Finally, direct observation of patients' lives is by necessity intrusive, and generates a greater burden on the patient.

A final method for objectively measuring glaucoma's impact on function is to directly observe individuals' ability to perform a standardized task or set of tasks. Studies using this approach have either focused on a single task, or aggregated a set of tasks into a composite measure.[18] Studies evaluating performance using at single tasks have generally focused on functional domains identified as having the greatest value to glaucoma patients: mobility and reading.[19,20] For example, previous work has examined how quickly individuals read, how well they drive through a standardized route, and how well they navigate a mobility course.[21-23]

The concept of validity is difficult to apply to tests which involve performing a single task, as measuring how a single task is performed is very unlikely to fully reflect a complex construct such as mobility, driving or reading. The question to be asked of single-task measures is how central is this task to the construct being examined. For example, balance is relevant to mobility in that it may result in falls and/or lead to restriction of physical activity, but is certainly not as reflective of mobility as direct measurement of fall rates or daily physical activity levels. Likewise, a driving simulator performance is relevant with respect to the construct of driving, but certainly less relevant than direct observation of how someone drives on the road or if they actually get into an accident. Additionally, each test should be evaluated to determine if it was conducted in a method to minimize error and bias.

Composite measures have the benefit of capturing and summarizing performance disability experienced in a variety of functional domains. Several composite measures of functional performance ability have also been created,[18] though only one has been used to describe the impact of glaucoma.[24] The Assessment of Disability Related to Vision (ADREV) involves nine tasks of varying difficulty each graded on a 0-7 scale. ADREV scores have been shown to be uni-dimensional and strongly correlated with numerous measures of vision loss.[25]

Identifying a clinically meaningful difference in composite measures can be difficult. Firstly, summary measures which generate a summary score are hard to evaluate, as the composite measure reflects multiple items which are being assessed together. Secondly, it is easier to understand what a meaningful difference is for measures graded on an intuitive scale. For example, it is easy

for us to understand the clinical significance of reading 20% slower, as we can imagine how this would impact our own lives. It is more difficult to assess the meaning of a 20% reduction in the composite ADREV score. Finally, it is easier to understand what difference is clinically meaningful when we can compare the effect of glaucoma to other diseases or conditions. For example, changes in performance may be equivalent to ten years of aging or the presence of a second comorbid illness. These data are available in many publications which take care to measure important covariates and present the results of multivariable models, though these findings are rarely highlighted.

What is the relationship between patient reported outcomes, functional performance loss and glaucomatous damage in cross-sectional studies?

Patient reported outcomes

Glaucoma patients have scored significantly worse on vision-specific quality of life (QOL) instruments than control participants without glaucoma. Gutierrez *et al*.[26] found visual field loss among glaucoma patients was associated with worse NEI-VFQ and SF-36 scores than individuals without glaucomatous visual field loss. They further described a steady, linear decline between visual field loss and HRQOL in glaucoma patients (N = 147) using the National Eye Institute Visual Functioning Questionnaire (NEI-VFQ).[26] These data support the finding that vision-specific QOL begins to decline with mild VFL and continues to decline with increasing severity of VFL. The magnitude of the association may vary however, as other investigators have found only modest associations between VFL in glaucoma patients and vision-specific or general measures of HRQOL.[27,28] A concern when interpreting all clinic based samples is that patient knowledge of their glaucoma and treatment status may influence perception and reporting of HRQOL.

Glaucomatous visual field loss also has been associated with worse NEI-VFQ-25 and SF-12 scores in population-based samples.[29,30] In the Los Angeles Latino Eye Study (LALES), a monotonic trend was observed between visual field loss and most NEI-VFQ-25 subscale scores, such that glaucoma cases with severe visual field loss had lower QOL scores than participants with no VFL.[29] In the same study, lower SF-12 Physical Component Summary (PCS) scores were found among glaucoma participants compared to participants with no visual field loss. This pattern was present when using monocular (better or worse seeing eyes) or calculated binocular data. An important aspect of this study was the fact that over 75% of participants with glaucoma did not know they had the disease and were not being treated for glaucoma. Thus, the relationship between QOL scores and visual field loss was not biased by either knowledge of the disease nor by treatment of glaucoma. In a population-based study of African-origin participants from Barbados, West Indies, investigators

found glaucoma was associated with significantly lower NEI-VFQ-25 scores, including distance activities, mental health, peripheral vision, and color.[30] The association of decreased scores with mild visual field loss in glaucoma patients also was reported by Nelson *et al.* when using the Glaucoma Quality of Life (GQL-15) instrument.[6] The results from these studies suggest that adults with glaucoma experience measurable loss in HRQOL early in the disease process and that prevention of small or early changes in VFL may have important HRQOL benefits for adults with glaucoma.

Parrish *et al*.[6] found only moderate correlations between binocular visual field loss using the Esterman binocular visual field testing score and the NEI-VFQ and Noe *et al*.[6] found no association between Esterman binocular VF testing scores and HRQOL using the Impact of Vision Impairment Questionnaire. In LALES, correlation coefficients between NEI-VFQ scores and visual field were similar for monocular and binocular measures.[29] Measures of binocular VFL are assumed to be more representative of true vision than monocular, however work by Jampel *et al*. indicates that correlations between all visual field test scores (*e.g.*, monocular better seeing eye, monocular worse seeing eye, or Esterman binocular) and vision specific HRQOL are modest overall.[31] Mills *et al*. found weak correlations between the Visual Activities Questionnaire and VFL of glaucoma cases at enrollment into the Collaborative Initial Glaucoma Treatment Study.[32] A recent study of Greek glaucoma patients found visual field loss (as measured by mean deviation and pattern standard deviation) were strongly associated with quality of life scores from the Vision-specific quality-of-life (VS-QOL) questionnaire.[33] A study of African-American and White glaucoma patients found similar NEI-VFQ and Glaucoma Symptoms Scale scores for both races and found worse scores for most NEI-VFQ-25 subscales associated with worse visual field defect scores.[34] Sherwood *et al*.[35] and Wilson *et al*.[36] using general health measures of HRQOL found glaucoma cases had lower SF-20 or SF-36 scores than controls.[35,36]

Self-reported falls were twice as likely for individuals using a glaucoma medication compared to those that did not in the Blue Mountains Eye Study,[37] and were four times as likely for individuals with glaucoma in the Singapore Malay Eye Study.[38] A four-fold higher risk for falling was also reported for glaucoma patients in a clinic- based study by Haymes *et al.*[39] All these studies measured falls retrospectively by simply asking subjects whether they had a fall in the previous 12 months, and previous work has demonstrated significant limitations for this method of falls assessment.[40] Research from health care databases has also suggested that sequelae of falls, *i.e.*, fractures, may be more common in glaucoma. Glaucoma patients cared for by the United States Medicare system had slightly higher rates (odds ratio = 1.6) of falls and femur fractures if they were also coded to be visually impaired.[10] Analyses of Medicare data also found that men with glaucoma may be more likely to sustain a hip fracture and require skilled nursing care.[11] One consequence of falling or fear of falling may be a restriction of physical activity. Recent work suggests that the amount

of daily walking decreases significantly with worsening VF loss, with a 5-dB decrement in better-eye VF loss associated with a 10% decrease in the number of daily steps.[41]

Motor Vehicular accidents appear to be more common in individuals with glaucoma. McGwin *et al*. found that individuals with glaucoma had a three-fold increased risk of having an accident documented by State records,[42] and even higher relative rates (OR = 6.6) were measured in a clinic-based study from Canada.[39] A case-control study of individuals seen in an eye clinic further suggested that accident rates increase as visual field loss worsens.[43] Some studies, however, have not document increased crash rates in individuals with glaucoma. Hu found that crash rates were less than twofold higher in men but not higher in women with glaucoma,[44] while another report noted fewer (OR = 0.67) state-recorded accidents for individuals with glaucoma.[12]

Many individuals with glaucoma limit or stop driving, possibly due to fear of driving, or pressure because of government licensing restrictions or the recommendations of a physician or family members. Individuals with bilateral glaucoma in the Salisbury Eye Evaluation were nearly three times as likely to have stopped driving and a lesser effect was suggested for subjects with glaucoma manifesting in only one eye.[45] Driving cessation was also more common (OR=2.2) in glaucoma subjects participating in the Blue Mountains Eye Study,[46] though the likelihood of driving cessation was not assessed for varying levels of VF loss. Several other studies have noted that individuals with glaucoma report restriction of driving to certain locations, or avoid certain weather conditions, though this has never been assessed objectively, and has not been confirmed in all studies.[45]

Location of glaucomatous visual field loss also has been found to influence QOL scores. In a review by Evans *et al.*, investigators found that both peripheral and central vision loss had a negative impact on general and vision-specific measures of QOL, however the specific domains most impacted varied by location of visual field loss.[47] In LALES, glaucoma participants with any central VFL had lower mean scores for all NEI-VFQ subscales than participants with no VFL or unilateral peripheral VFL.[29] The lower HRQOL scores for glaucoma participants with any central VFL fits with the disease course progressing from peripheral VFL in early stages of the disease to central and peripheral VFL in more advanced stages of the disease.

Functional performance

Functional performance has mostly been studied for specific tasks, with most tasks falling within the broad categories of reading, ambulation, and driving. These studies have generally been performed in developed nations, and may not reflect the most important activities impacted by glaucoma in people of developing nations.

Reading: "Out loud" reading speed was directly measured as part of the Salisbury Eye Evaluation (SEE).[23] In this study, only individuals with very advanced bilateral glaucoma had significantly decreased "Out loud" reading speeds. A worse visual field score did not lead to slower "Out loud" reading rates when visual acuity was accounted for. Recent work presented at ARVO 2011, however, suggests that silent reading speed is nearly 15% slower in individuals with bilateral glaucomatous visual field loss, and is significantly worse in individuals with greater VF loss in their better-seeing eye (8% slower reading per 5 dB worsening in the better-eye VF). Additionally, reading speed is more likely to decrease when glaucoma patients perform sustained reading, suggesting that they may fatigue during this process.[48] Furthermore, individuals with glaucoma also read low-contrast materials more slowly than individuals without glaucoma.[49]

Walking, Balance and Falls: Several aspects of ambulation in glaucoma have been studied in cross-sectional studies. Mobility course data has demonstrated that individuals with glaucoma walk roughly 15% slower, and that walking speeds are slowest in glaucoma patients with the most visual field damage.[21,50] Additionally, individuals with glaucoma are nearly twice as likely to bump into objects placed in the mobility course when compared to individuals without glaucoma.[21]

Glaucoma has also been associated with poor balance. Individuals with glaucoma have more trouble performing balance tasks[21] and have greater postural sway than individuals with normal vision with their eyes open, but not with their eyes closed. Postural sway has also been noted to be greater in glaucoma patients with greater visual field loss. Balance limitations may also explain the increase risk of falls in glaucoma.

Driving: Driving is a critical function in developed nations, and is often necessary for independent living.[51] As such, there is a need to balance the independence and quality of life of the individual with glaucoma with their safety and the safety of society. Indeed, many individuals with advanced VF loss continue driving, making it important to set evidence based standards for whether they should or should not be allowed to drive.[45] In driving simulators, individuals with glaucoma had been noted to have more accidents.[52] Glaucoma has been associated with lower likelihood of seeing pedestrians on the side of the road during on-road driving evaluations.[22] Additionally, individuals with glaucoma were 6 times as likely to require a critical intervention by the professional driving instructor evaluating them.[22] Using a tracking device, Hochberg and colleagues demonstrated that glaucoma subjects made 25% fewer excursions away from home, and were significantly more likely to not leave their home on a given day.[53]

Relatively few studies have examined function in glaucoma outside the domains of mobility and reading. Kotecha and colleagues demonstrated slower, more tentative reaching for objects, suggesting that many activities of daily living may be affected by glaucoma.[54] The ADREV test also evaluated many

tasks outside of reading and mobility, including recognition of facial expressions and street signs, detection of motion, location of objects, placement of pegs into holes, matching socks and use of a telephone. All functions were significantly correlated with both visual field measures and contrast sensitivity, with the greatest correlations observed for motion detection, sock matching, and finding objects.[24]

What is the relationship between measures of patient reported outcomes, functional loss and progressive glaucomatous damage?

In LALES, change in PRO as measured by the NEI-VFQ-25 in relation to visual field loss due to any reason was investigated.[55] Increasing losses and gains in visual field were associated with increasing losses and gains in the NEI-VFQ composite score and 10 of its 11 subscales (all *P*-trends < .05). Baseline visual field, baseline visual acuity and change in visual acuity modified the effect of change in visual field on vision-specific HRQOL. Specifically, visual field loss was associated with greater loss in HRQOL scores in the presence of pre-existing loss of visual acuity compared to no impairment. Clearly, this is an important future area of study.

To date, no functional performance measures have been studied relative to progressive glaucomatous damage in the same individual.

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Linda Zangwill, David F. Garway-Heath and Tanuj Dada (left to right).

SUMMARY CONSENSUS POINTS

Section 1 – Visual function progression

1. Standard white-on-white automated perimetry (SAP), with a fixed testing matrix covering at least the central 24 degrees, is preferred for measuring progression in eyes with glaucomatous VF loss.
   Comment: more research is needed into the use of alternative measures of visual function (FDP, resolution perimetry, motion perimetry and others) to detect glaucomatous progression, before any of these can be considered alternatives to SAP for measuring progression.
   Comment: It is possible for glaucomatous optic neuropathy to progress structurally in the absence of functional progression and vice-versa.
2. Perform sufficient examinations to detect change.
   Comment: decisions on progression should not be made by comparing only the most recent field with the one before.
   Comment: suspected progression should be confirmed by repeating the field.

Baseline data collection (no previous VFs available) – first two years

3. In clinical practice, at least two reliable VFs is optimal in the first six months.
   Comment: In clinical scenarios, where the lifetime risk of visual disability is high, such as those who already have advanced damage, three baseline VFs may be necessary.
   Comment: A good baseline of reliable VFs is essential to be able to monitor for progression.
   Comment: Unless there are obvious learning effects, high false-positive errors, rim artifacts, or other obvious artifacts, examinations should not be removed from the analyses.
4. At least two further VFs should be performed within the next 18 months.
5. VF testing should be repeated sooner than scheduled if possible progression is identified on the basis of an ‘event’ analysis.
   Comment: In patients at risk of visual disability, performing six VFs in the first two years enables the clinician to rule out rapid progression (2 dB/year or worse) and establishes an ideal set of baseline data.
   Comment: the identification of possible progression may be on the basis of an ‘event’ criterion such as the Glaucoma Progression Analysis (in the Humphrey perimeter software) or ‘Nonparametric Progression Analysis’.
6. Establish a new baseline after a significant therapeutic intervention (*e.g.*, surgery).
   Comment: the new baseline can be the last fields that defined the previous progression ‘event’.

Follow-up data collection (after the initial two years)

7. The frequency of follow-up VFs should be based on the risk of clinically significant progression (based on extent of damage and life expectancy).
8. In low and moderate risk patients, subsequent VF frequency should be one VF per year (unless there is a long follow-up) and, as a rule, repeated sooner if possible. Progression is identified on the basis of an 'event' analysis, or if other clinical observations are suggestive of possible progression or increased risk of progression.
   Comment: relevant clinical observations include structural progression (clinically noted or measured by imaging), a splinter hemorrhage, or inadequate IOP control.
9. In high risk patients, subsequent VF frequency should be two VFs per year and repeated sooner if possible progression is identified on the basis of an 'event' analysis, or if other clinical observations are suggestive of progression or increased risk of progression.
   Comment: following confirmed progression (by an 'event'), the frequency of testing should be based on the estimated rate of progression, risk factors and other clinical indicators of progression, stage of disease and life expectancy.
   Comment: patients who have been stable for a long period, or who are progressing so slowly as to be at little risk for reaching disabling levels of field loss, and other clinical parameters indicate low risk of progression, may have VF testing less frequently than 1 VF per year.

Visual field progression may be analyzed by either 'event-' or 'trend-'based methods

Event analysis: is change from baseline greater than a predefined threshold; the threshold is based on test retest variability (according to level of damage).

Trend analysis: determines the rate of change over time; the significance is determined by the variability of the measurement and the magnitude of change.

10. Both event and trend analyses are needed, largely for different time points in the follow-up during clinical care.
11. In general, event-based methods are used early in the follow-up, when few VFs are available for serial analysis.
    Comment: progression by an event criterion usually requires confirmation on at least two further occasions to be sufficiently sure that progression has truly occurred.
    Comment: confirmation of progression should usually be made on a separate occasion (patients have 'off days').
    Comment: When interpreting VF progression that is confirmed by an 'event' method, the clinician should look at:
    – the baseline fields, to ensure they are reliable and appropriate for the analysis;

– the estimated rate of progression and the confidence of the estimate;
– the severity of the visual loss in terms of impending impairment;
– the risk factors for progression.

12. In general, rate-based analyses are used later in the follow-up, when a greater number of VFs is available over a sufficient period of time to measure the rate of progression.
Comment: a rate of progression in the first two years is a rough estimate (wide range of possible rates around the central estimate); in most patients it takes longer to obtain a reliable estimate of the rate of progression.
Comment: trend (regression) analysis provides an estimate of the rate of progression and a measure of the reliability of the estimate; the reliability of the estimate is judged from the confidence limit.
Comment: clinicians should consider other clinical measures of progression and risk of progression when interpreting this information (these data provide the 'prior probability' for progression).
13. When progression is identified, the clinician should ensure that the progression is consistent with glaucoma and not related to some other cause.

Measure the rate of visual field progression

14. Clinicians should aim to measure the rate of VF progression.
Comment: Estimating the rate of progression is invaluable for guiding therapeutic decisions and estimating the likelihood of visual impairment during the patient's lifetime.
15. In the absence of significant changes in therapy, the rate of progression of suitable global indices (MD or VFI, but not PSD or LV) is linear in treated glaucoma eyes, except at the most advanced stages.
16. As a linear model for progression is acceptable, trends may be extrapolated to predict future loss if there is no change in therapy, over appropriate intervals.
17. Both local and global metrics are needed for assessment of progression.
Comment: Rates are most often measured on 'global' parameters, such as mean deviation, mean defect or visual field index. However, focal progression (such as paracentral) may be missed by a global index.
18. Total Deviation based methods are more sensitive to cataract than Pattern Deviation based methods. However, by eliminating or reducing the component of diffuse visual field loss, Pattern Deviation based methods may underestimate progression rates.
19. Use available software support.
Comment: Subjective judgment of VF print-outs is unreliable and agreement among clinicians is poor. Statistical analysis, either in the perimeter software or stand-alone software, is advantageous to reliably identify and measure progressive VF change.

Pay attention to examination quality

20. Examinations of poor quality will likely lead to an erroneous assessment of progression.
    Comment: The most important factors to reduce test variability are a proper explanation of the test to the patient, appropriate instrument setup and 1:1 monitoring of the patient by a trained technician.
21. Do not rely automatically on the VF reliability indices.
    Comment: The VF reliability indices may be unreliable! The most useful index is the 'False Positive' rate; values greater than 15% likely represent a less reliable performance; values less than 15% do not guarantee reliability. The technician is the best judge to exam quality.
22. If unreliable tests require repeating, the patient should be carefully re-instructed.

Use the same threshold test

23. Clinicians should select their preferred perimetry technology, test pattern, and thresholding strategy for the baseline tests and stick with the same test throughout the follow up.
    Comment: any analysis of progression can only be performed if a compatible threshold algorithm and test pattern is used.
24. In advanced glaucoma, smaller angular size SAP testing grids, *e.g.*, HFA 10-2 may be of value in a minority of patients.
    Comment: Kinetic perimetry and SAP with larger targets (*e.g.*, size V) may also be useful.
    Comment: The advantages of a change in test pattern (*e.g.*, from a 24-2 to a 10-2 grid) should also be weighed against the disadvantages for progression analysis by commercial software.

Clinical trials

25. Event analyses aim to identify a statistically significant difference between study arms and not necessarily a clinically significant difference.
    Comment: As glaucoma is a chronic progressive disease and progression is generally linear, small amounts of progression that reach statistical significance become larger, clinically significant amounts of progression if there is no additional therapy.
26. Rate analyses of VF indices are an appropriate statistical approach to identify differences between treatment groups.
    Comment: Rate analysis methods have been used often in trials for other chronic progressive diseases, such as dementia.
27. Difference in the progression 'event' criterion applied in the various clinical trials limits comparison of the incidence of progression determined in those trials.

Comment: Comparison of groups in different clinical trials is also hampered by mismatch of subjects with regard to stage of glaucoma, quality of visual field exams, and other traits.

Research needs

1. The development of 'event' criteria for progression based on individual patient test-retest variability.
2. There is a need to *compare event-based endpoints* and *rate of progression outcomes* in a data set with data acquired with appropriate frequency and test intervals with respect to clinical trials.
3. Further research is needed into the added value of smaller angular size test grids, and different size stimuli, *e.g.*, size V, in advanced glaucoma.
4. Determine appropriate dynamic ranges of stimulus contrasts for size III, and develop new stimuli with larger dynamic ranges of appropriate stimulus contrasts.
5. Improve the interface between perimetrist and device, and between patient and device.
6. Identify, or develop, stimulus types (*e.g.*, FDT) and test algorithms which provide optimal information content for progression analysis in children and adults who have difficulty performing a reliable SAP test.
7. Develop alternate methods for selecting stimulus locations in order to avoid extensive testing of blind areas and to focus on areas of interest.
8. Further assess the benefits of using prior threshold as a starting point in a follow-up test (or if threshold is < 0 dB previously, confirmation at that point that a 0 dB stimulus is not seen is sufficient).
9. Determine the optimal frequency and timing of tests for individual patients.
10. Use of good mathematical modeling.
11. Develop better approaches to identify learning effects.
12. Identify the appropriate test and frequency of testing for patients with progressive glaucomatous optic neuropathy and SAP within normal limits.

Section 2 – Structure

2.1 Technologies for measurement of optic disc and retinal nerve fiber layer (RNFL) parameters

1. Serial optic disc stereo-photography and RNFL photography are valuable and enduring methods for monitoring structural progression.
   Comment: Stereoscopic clinical examination of optic disc and RNFL may be useful to detect change in comparison with a baseline photograph.
   Comment: Subjective estimates of cup/disc ratio only detect large changes in cupping and are insufficient for monitoring structural changes.
2. Color fundus photography is the preferred imaging modality to identify disc hemorrhages and parapapillary atrophy.

Comment: Disc hemorrhages and beta-zone PPA are known risk factors for glaucoma progression.

3. Changes in beta-zone parapapillary atrophy can signal glaucoma progression.
   Comment: Methods for evaluating changes in PPA require further validation and include fundus photography, CLSO, and SDOCT.
4. Several imaging instruments, including confocal scanning laser ophthalmoscopy, scanning laser polarimetry, and optical coherence tomography objectively provide reproducible measurements and quantitative assessment of the optic disc and RNFL change.
   Comment: The detection of glaucoma progression by comparing sketches or descriptions of cup disc ratio in the clinical chart is generally not suitable for an early detection of progression and may be replaced by imaging techniques and/or optic disc photography.
   Comment: Imaging instruments provide progression detection analyses that can determine whether change is greater than the measurement variability of an individual eye.
5. There are several structural components of longitudinal change detection that likely contribute to the variability of measurements.
   Comment: These include variation in clinical disc margin visibility, intersession variation and accuracy of segmentation algorithms, variation in vascular blood volume and reference plane anatomy, and longitudinal image registration.
6. Image quality can influence our ability to detect structural change.
   Comment: Automated quality indices vary by instrument and are often proprietary with little information available about how they are constructed.
   Comment: Poor quality images can lead to either false positive or false negative results.
   Comment: For patient management decisions, clinicians should review the quality of images included in glaucomatous progression assessment.
7. More than one good quality baseline image facilitates progression analysis.
   Comment: Some instruments automatically acquire several baseline images during one imaging session.

2.2 Reproducibility of digital imaging instruments

1. Measurement variability influences the ability of any device to detect progression.
   Comment: There is a wide range of reproducibility estimates in the literature for SLP, CSLO, and OCT. Although studies of comparisons of instruments within the same patient populations are limited, these techniques likely provide data of similar reproducibility.
   Comment: Overall, SDOCT has better reproducibility than TDOCT.

2. There is a lack of consensus in the literature as to whether reproducibility changes across disease severity and this may vary across measured anatomic structures and techniques.

2.3 How to detect and measure structural change?

1. Event and trend based analyses are both useful for change detection.
   Comment: These analyses do not always concur.
2. It is important to estimate the rate of structural progression for clinical management decisions.
   Comment: The rates of change obtained from measurements from optic disc, RNFL and macular parameters may vary from each other.
3. Quantitative assessment of optic disc and retinal nerve fibre layer (RNFL) with imaging instruments is useful and complementary for change detection.
   Comment: Data are limited on whether macular measurements may be useful for change detection.
4. Differences in technologies and scan protocols could influence the detection of progression even when the same structure is measured.
5. There is no clear consensus on which instruments or parameters are optimal to detect structural progression. As technologies evolve, new instruments and parameters which are clinically useful will emerge.

2.4. How to define clinically significant structural change?

1. Interpretation of statistically significant change should take into account test-retest variability and knowledge on the magnitude of age-related change in healthy individuals.
2. Knowledge of age-related change in healthy individuals should preferably come from actual longitudinal data and not extrapolation from cross-sectional data.
3. A statistically significant change in a structural parameter such as rim area or nerve fiber layer thickness is a relevant change, however, it may not be clinically meaningful. The latter also should take into account the age and stage of the disease as well as an assessment of risk factors present.
   Comment: Currently, we have the tools to measure statistically significant change, however, to date we do not know how to fully assess the clinical importance of this change.

2.5 Issues in clinical practice

1. The optimal frequency of imaging tests is unknown.
   Comment: It depends on the severity of the disease and on the expected speed of progression.

2. In longitudinal studies investigating optic disc and RNFL progression in glaucoma, imaging tests have been performed once a year to three times a year.
3. The same structural measures (e.g. RNFL thickness) obtained with different instruments from the same manufacturer or the same technology from different instrument manufacturers (*i.e.*, spectral domain OCT) are not necessarily interchangeable for progression assessment.
4. Structural assessment of change is a valid method for detection of glaucomatous progression in a clinical trial.
   Comment: structural change has been shown to be predictive of future functional loss in glaucoma.

Section 3 – Structure and function

1. Both optic nerve structure and function should be evaluated for detection of glaucomatous progression.
2. Currently, no specific test can be regarded as the perfect reference standard for detection of glaucomatous structural and/or functional progression.
3. Progression detected by functional means will not always be corroborated using structural tests, and vice-versa.
   Comment: This is due to the imperfect nature of testing analysis, individual variability, and the structure-function relationship.
4. The use of standard automated perimetry as the sole method for detection of change may result in failure to detect or underestimate progression in eyes with early glaucomatous damage.
   Comment: In glaucoma suspect or ocular hypertensive eyes with initially normal achromatic perimetry, a change in optic nerve structure (*e.g.*, optic topography, retinal nerve fiber layer, optic disc hemorrhage, or parapapillary atrophy) may occur before perimetric change.
5. In general, detection of progression is more difficult in eyes with advanced disease.
   Comment: In eyes with advanced visual field damage, alternative perimetric strategies (*i.e.*, larger stimulus, macular strategies, kinetic perimetry, etc.) may need to be employed.
6. A statistically significant change in structure and/or function (which takes age and variability into account) is not always clinically relevant.
   Comment: Its clinical relevance for patient management must take into account other risk factors and lifetime risk of visual disability.
7. Progressive structural changes are often but not always predictive of future development or progression of functional deficits in glaucoma.
   Comment: The predictive strength depends on the method used to assess structural/functional change.

8. Corroboration of glaucomatous progression through the use of more than one test may provide more effective and more rapid detection of glaucomatous progression than repeated confirmation of change using a single modality.
   Comment: Examples of corroborative change include structure-function (*e.g.*, a structural change of the optic nerve and a spatially consistent functional change).
9. In order to increase the likelihood of detecting progression, test results should be of sufficient quality and appropriate quantity to provide meaningful information.
   Comment: While adjunctive testing can help clinical decision making, the use of multiple modalities of testing, at the expense of quality and appropriate frequency and quantity, should be avoided.
10. Life expectancy should be considered when evaluating the clinical relevance of a structural and/or functional change in glaucoma.
11. Structural and/or functional testing should be conducted throughout the duration of the disease.

Section 4 – Risk factors

1. Risk factors for glaucoma progression should be ascertained in all patients with glaucoma or suspected of being at increased risk of glaucoma.
2. Clinical risk factor assessment in glaucoma serves two roles. It provides (a) prognostic information; and (b) a basis for disease management.
   Comment: While proof of causality is desirable, the pragmatic nature of clinical medicine allows the use of risk factors of varying evidence quality and even clinical signs to be used in clinical management.
3. The use of risk factors in clinical management should take into account: (a) the strength of the risk factor for disease progression; and (b) the practicality and potential harm of reducing that risk factor.
4. Ocular hypertension is itself a strong risk factor for glaucoma, with rates of progression depending on the presence or absence of other risk factors.
   Comment: Accounting for these risk factors is critical to clinical decision making in the management of OHT patients.
   Comment: Risk factor assessment in OHT helps determine an individual's need for IOP lowering medication and also informs on the frequency of follow up.
5. Risk calculators provide a means for quantifying risk of glaucoma progression in appropriate individuals with similar baseline characteristics to those present in the study.
   Comment: The utility of these risk calculators in clinical practice still needs to be determined.

6. Higher mean IOP is a strong risk factor for glaucoma progression.
   Comment: More studies are needed to evaluate the role of other IOP parameters as risk factors for glaucoma progression.
7. A thinner central cornea is a risk factor for progression in patients with higher baseline IOP.
8. The presence of pseudo-exfoliation syndrome is an independent risk factor for progression.
9. The presence of a disc haemorrhage, older age, and lower ocular perfusion pressure are risk factors for progression.
   Comment: The relationship between low blood pressure and risk of progression is complex.
10. While estimates of risk of progression for individual patients based on completed large clinical trials are available, the use of such estimates varies considerably in clinical practice.
11. There is greater information available regarding the importance of risk factors for progression from early to moderate disease than from moderate to severe disease.
    Comment: Few adequately powered studies have prospectively assessed the risk factors for blindness from glaucomatous disease.
12. The relative importance of risk factors for progression may vary depending upon the stage of glaucomatous disease.
    Comment: Some risk factors that do not appear to be important predictors of progression from early to moderate glaucoma may be relatively more important in predicting progression from moderate to severe disease and vice versa.
13. Studies that longitudinally assess risk factors for functional vision loss and blindness from glaucomatous disease are needed.

Section 5 – Glaucoma and its impact on patient function

1. Standard measures for assessing glaucoma include measures of optic nerve structure and function including cup/disc ratios, thickness of the retinal nerve fiber layer and ganglion cell layer, white on white visual fields, blue on yellow visual fields, and intraocular pressure. While these measures provide an assessment of the eye, they are surrogates for how the patient is functioning. Both PROs and functional tests provide important information in addition to standard tests on the impact of glaucoma on the patient.
2. It was previously believed that only advanced glaucoma damage has an impact on the patient ability to function. However, more recent cross-sectional clinic-based and population-based studies have demonstrated that early glaucomatous visual field loss has an impact on the patients' ability to function as assessed by patient reported outcome measures and functional tests.

3. Future studies are needed to explore the relationship between PROs and functional measures and glaucoma progression.
4. Numerous instruments and tests have been used for assessing PROs and functional measures in research settings. However, there is no consensus on a single PRO or functional measure (or set of PROs or functional measures) for clinical practice. There is a need to create simpler PROs and functional tests which can easily be reproduced in a wide variety of settings.

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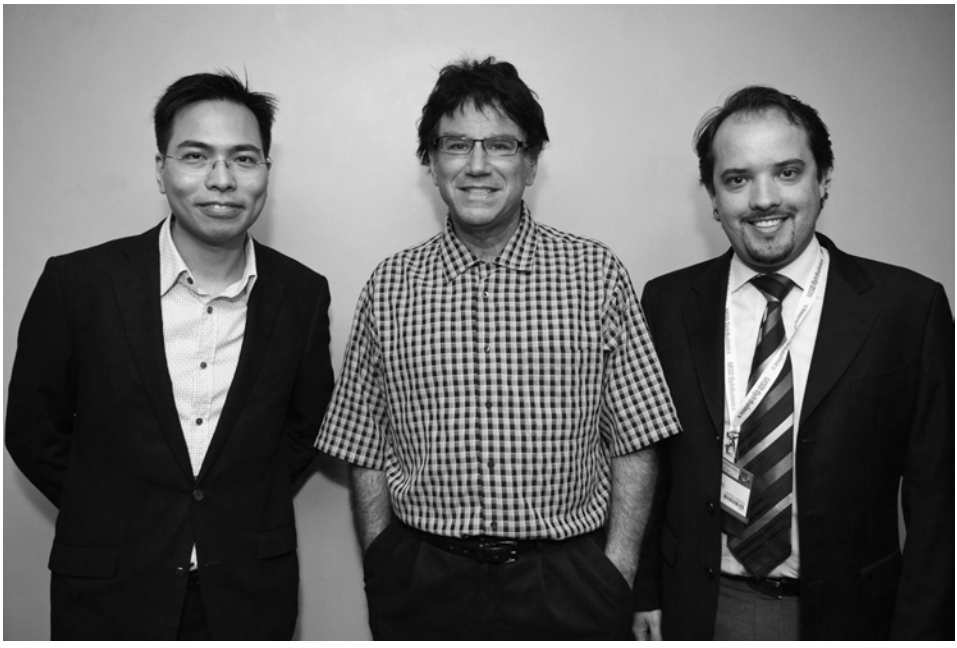

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N (No Commercial Relationship) Indicates there is no commercial relationship relevant to the related to the Consensus on Progression of Glaucoma.

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Name	Y/N	F	I	E	C		R
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Aung, Tin	Y	Alcon, Allergan, Aquesys, Carl Zeiss Meditec, Clarity, Ellex			Alcon, Merck, Pfizer		Alcon, Allergan, Carl Zeiss Meditec, Clarity, Ellex, Merck, Pfizer, Santen
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Burr, Jennifer	Y						
Caprioli, Joseph	Failed to disclose						
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Name	Y/N	F	I	E	C		R
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Kook, Michael	N						
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Turpin, Andrew	Y	Heidelberg Engineering					
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