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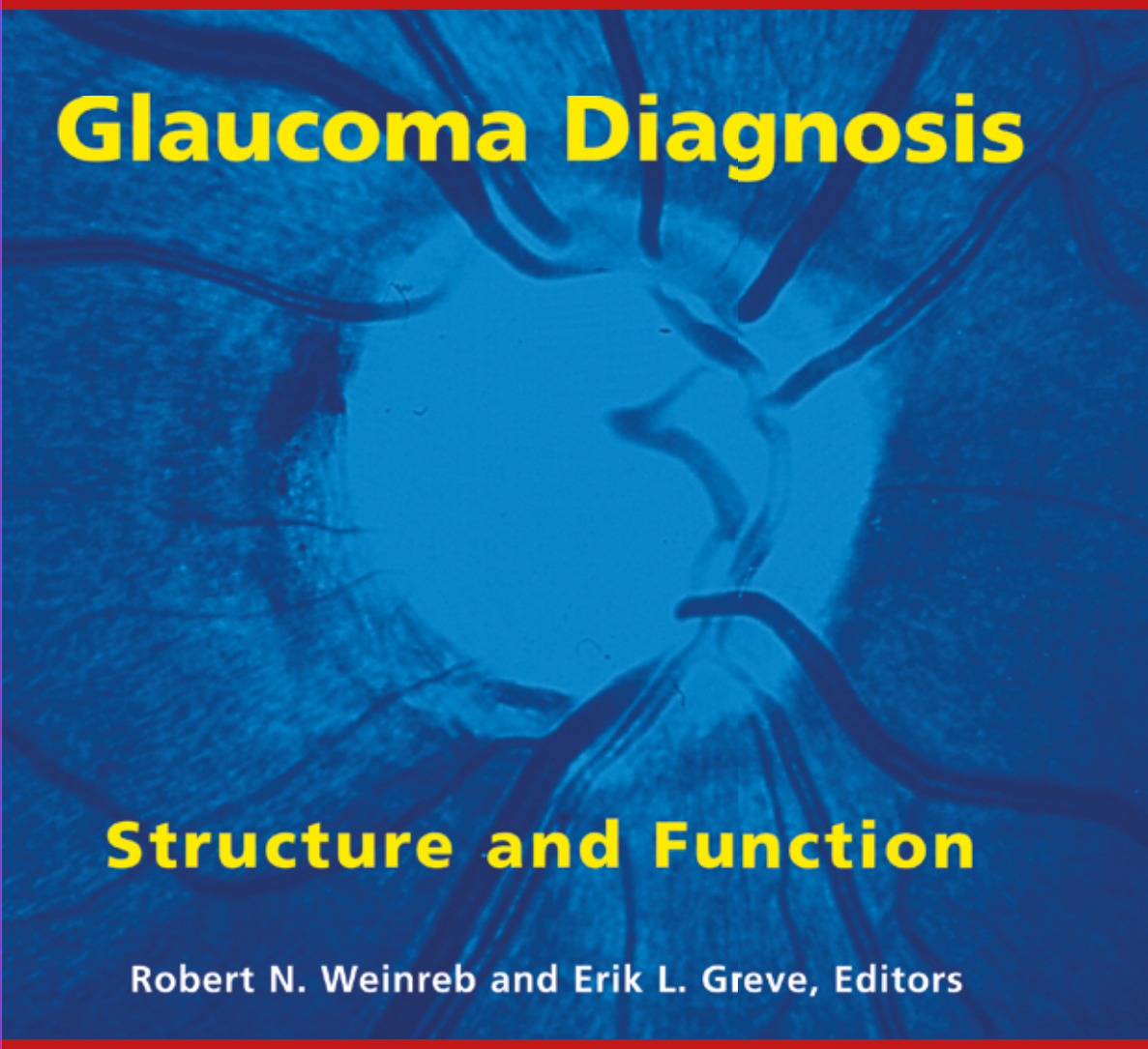

Glaucoma Diagnosis

Structure and Function

Robert N. Weinreb and Erik L. Greve, Editors

Consensus Series - 1

Association of International Glaucoma Societies

GLAUCOMA DIAGNOSIS
STRUCTURE AND FUNCTION

In an autocracy one person has his way;
in an aristocracy a few people have their way;
in a democracy no one has his way.

Celia Green
The decline and fall of science

"Now it is not the end. It is not even the beginning of the end.
But it is, perhaps, the end of the beginning."
Winston Churchill

GLAUCOMA DIAGNOSIS STRUCTURE AND FUNCTION

Reports and Consensus Statements of the 1st Global AIGS Consensus Meeting on 'Structure and Function in the Management of Glaucoma'

Robert N. Weinreb and Erik L. Greve, editors

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This publication is the first of a series on Consensus meetings in Glaucoma initiated by the Assocation of International Glaucoma Societies

ASSOCIATION OF INTERNATIONAL GLAUCOMA SOCIETIES

an independent, impartial, ethical, global organization for glaucoma sicence and care

Vision for Glaucoma

From the Program

To develop an effective world-wide organization to realize common goals and improve standards for glaucoma management and research
To facilitate and co-ordinate communication and collaboration between Glaucoma Societies, Glaucoma Industry, Glaucoma Foundations and Glaucoma Patient Societies and other organizations in the field

The AIGS will create and maintain an environment of integrity and honesty in information exchange on scientific glaucoma data

The AIGS represents the first subspecialty that aims at reaching the above-mentioned goals through global all involving cooperation. This is a unique situation that offers great opportunities.

The Global Glaucoma Network

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AGS	American Glaucoma Society
ANZGC	Australia and New Zealand Glaucoma Club
AOGS	Asian-Oceanic Glaucoma Society
CanGS	Canadian Glaucoma Society
ChinGS	Chinese Glaucoma Society
EGS	European Glaucoma Society
GSI	Glaucoma Society of India
GSICO	Glaucoma Society of the International Congress of Ophthalmology
ISGS	International Society of Glaucoma Society
JGS	Japanese Glaucoma Society
LAGS	Latin America Glaucoma Society
OGS	Optometric Glaucoma Society
PAAGS	Pan Arab African Glaucoma Society
PAGS	Pan American Glaucoma Society
SAGS	South African Glaucoma Society
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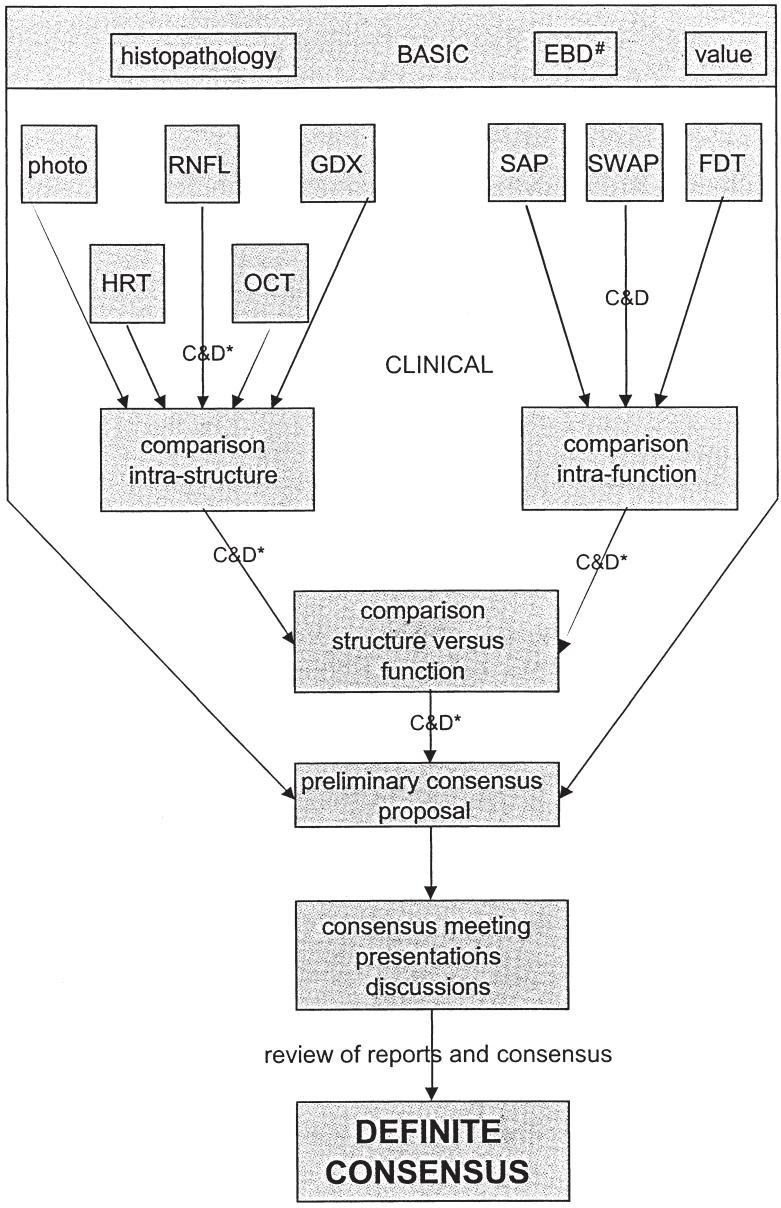
CONTENTS

Organization of the Consensus Meeting



* C&D = comments & discussion in e-Room

EBD = Evidence Based Diagnosis

PREFACE

To the best of our knowledge, the 1st Global AIGS Consensus Meeting on "Structure and Function in the Management of Glaucoma" was also the first global consensus meeting in ophthalmology. The goal was to reach an evidence-based consensus for both clinical practice and research through the use of information obtained from peer-reviewed literature describing functional and structural diagnostic testing in glaucoma.

The faculty and review group consisted of leading global authorities on glaucoma diagnostic testing. The preparation for the Consensus was unique in its format (*see* page xii). Reports on the individual methods of Structure and Function were prepared by an expert group. This was followed by intra-function and intra-structure comparisons and, finally, by a comparison of structure versus function. All the reports were placed in the Consensus e-Room, where they could be commented on by all participants. In addition, basic aspects of this Consensus were considered, as well as the important issue of Evidence-Based Diagnosis. This intense preparation was needed in order to obtain a preliminary Consensus before the meeting. The final Consensus was formulated, based on the preliminary report and adapted following comments from the discussions. It is recognized by all who participated that this is a fluid topic, which will change considerably as further research is conducted and new knowledge is gained.

Robert N. Weinreb
Erik L. Greve
Editors

An important part of the organization of the Consensus Meeting and the composition of the book was in the hands of AIGS director H. Caroline Geijssen.

THE VALUE OF GUIDELINES AND CONSENSUS AND THE REALITY OF CLINICAL PRACTICE

Paul Lee

Paul Lee

- Consensus is important in medical care: 1. to delineate diagnostic criteria and staging severity of disease; and 2. to provide guidance on how best to monitor and treat a disease.
- The quality and nature of consensus will improve over time, moving from expert opinion to evidence-based assessments.
- Several techniques exist to quantitate the degree of consensus that exists.
- Consensus is lacking in glaucoma for both the definition and classification of the severity of the disease, although initial efforts have begun.
- Key steps in providing care for patients are often not done on a regular basis in the USA, particularly gonioscopy, optic nerve assessments, regular follow-up visits, and setting a target pressure range for treatment success.
- Patients with actual glaucoma in the USA may not be treated as aggressively as they should, given the findings of published studies.
- Several techniques can successfully alter physician behavior.
- Technology may offer the potential to greatly assist physicians in improving care delivery, especially when combined with standardized definitions and disease severity staging systems.

Summary

Consensus is agreement among a group of individuals arrived at through a variety of possible means. In health care, consensus is important in two distinct areas, as follows: 1. delineating the diagnostic criteria for a disease and assessing its severity and change over time; 2. providing guidance on how best to treat a condition. Consensus statements are initially arbitrary ('expert opinion'), and are then modified by evidence over time. The value of consensus in the standardization of disease and progression is that the community can move forward much more quickly by means of uniform definitions to allow for comparison and interaction. The value of consensus in treatment is that it both reduces unnecessary variation and will help accelerate the diffusion of knowledge into common practice. However, consensus alone is not enough for this second area.

Glaucoma Diagnosis. Structure and Function, pp. 1-7
edited by Robert N. Weinreb and Erik L. Greve

For glaucoma, there is no general consensus yet on what 'glaucoma' is, how to measure its severity, and how to determine whether it is getting worse. This results in significant difficulties in building upon prior studies and in comparing insights. It also contributes to confusion in assessing how best to treat the condition, since different studies may be assessing somewhat different populations and obtaining different results. By arriving at a consensus for the first area, we will also help to assist ongoing efforts to develop consensus in the treatment area.

Consensus and glaucoma: how and why

What is consensus and how can we achieve it?

Consensus is simply agreement among individuals in a group. In its most informal state, individuals in the group can agree that consensus exists through a mechanism varying from an undefined collective sense to quantitative majority votes (ranging from simple majority to unanimity). At the same time, medicine is moving strongly towards an 'evidence-based' approach which seeks to combine judgment with the best available evidence. In health care, RAND has developed a modified Delphi technique that marries evidence-based assessment with the use of experts to 'fill in the gaps' in the scientific evidence, and that also allows for the expression of disagreement among the experts, and the interchange of ideas in group discussions.[1] The technique has been shown to be valid for determining the appropriateness of various medical services and procedures, but the ratings in areas that do not have a strong evidence base can differ significantly depending on the makeup of the panel, the feedback given to the panel, and the area of investigation.[2-7] Almost as useful, this technique allows panels quantitatively to identify their level of agreement and to identify those areas in which substantial disagreement even among experts exists.[8] In ophthalmology, this process has been found to be valid (in predicting visual acuity outcomes) for cataract surgery.[6,7]

Why do we need consensus, and in what areas?

The presence of consensus does not mean that the group is correct. Indeed, to be useful, consensus need not be correct initially, but it must help to bring about the desired results. In health care, there are two major areas in which consensus can play an important role.

Firstly, there is a need for standardization in the definition of a disease and the metrics used to assess its severity and its progression. Without a common 'language', it is much more difficult to understand or to place different study results in context. For example, the population prevalence of 'glaucoma' can vary significantly by the definition chosen.[9,10] As definitions become more uniform, comparisons and analyses become more compatible and more valid. Indeed, work through Prevent Blindness America, in preparing the 2002 Vision Problems in the USA, was strengthened through the application of standard-

ized criteria across different population-based studies around the world.[11] Such efforts may make it possible for this AIGS or a similar group to provide such a set of working definitions.

There is also a need for standardization in classifying the severity of disease and in identifying when a patient has worsened. In glaucoma, the choice of visual field scoring algorithms can result in a two-fold difference in estimates of disease progression using exactly the same visual fields.[12,13] Furthermore, as noted in the other reports at this AIGS conference, the techniques of measuring disease severity and progression also differ significantly in their classification of patients relative to other techniques. Thus, there is a strong need for standardization in both disease definition and disease classification.

Such consensus early in the process is likely to be more arbitrary, but it is needed to move forward. Indeed, consensus panels may be most appropriate early in the process when evidence is sparse, with quantitative research syntheses being preferable when more studies are available.[14] Thus, as we move forward and determine which characteristics of the optic nerve or visual field are most related to actual progressive disease, we may be able to better refine our definition of who has an active disease needing care and who does not (or at least is at lower risk), moving towards a more evidence-based definition of disease.

The second area in which consensus can be helpful is to enhance the diffusion of knowledge and practice in the treatment of patients. It is now widely acknowledged that even the best randomized controlled trial data are not universally used in clinical care, even many years after the results have been published, and even after NIH Consensus Development Conferences.[15] Furthermore, it is clear that greater variation exists in care where there is no clear, strong evidence to support one particular practice over another, even for specialty society guidelines.[16] Thus, it is the combination of a strong scientific base of evidence together with expert consensus on the meaning of that evidence, as expressed in a consensus statement or guideline, which is most likely to accelerate the acceptance and use of new practice patterns. However, just reaching a consensus and publicizing it is *not* enough to significantly alter the rate of adoption of new care patterns.[15,17] Additional steps are necessary to build upon the educational base generated by consensus statements.

Clinical care today relative to consensus and guidelines

How are we doing today in clinical care relative to consensus guidelines?

In studies conducted around the USA, among both general providers of eye care (comprehensive ophthalmologists and some optometrists) and glaucoma specialists, significant opportunities for improvement of performance were found to exist.[18-20] Using chart review, administrative databases, and other assess-

ment methods, practitioners often do not perform, or at least document, key steps in providing care. Firstly, for many patients seen by non-glaucoma specialists, critical process steps are often not performed on a regular basis, most notably gonioscopy, optic nerve head assessment, and optic nerve head documentation.[18-20] Secondly, critical care decisions are often not made or documented, particularly there is an absence of a stated target pressure range (even among glaucoma specialists).[20,21] Thirdly, patients do not return for follow-up at sufficient intervals, whether for examination or for visual fields or other testing.[22] Fourthly, patients who are being treated are being so without sufficient pressure lowering, given the results of published studies.[20] Thus, ample opportunities exist today for enhancing care patterns. While consensus exists on what a provider should do in the care of patients (in the form of practice guidelines from Europe, America, and the International Council of Ophthalmology), there is no clear consensus on when and how a patient should be treated.

Current practice patterns: data on actual practices (additional details)

History elements routinely obtained on new visit (from a survey of AGS members):

ocular/systemic history	80%
family history of glaucoma	93%
review of pertinent records	57%
ocular surgery	24%
known medication intolerance	57%
time of last use of medications	1%
assessment of vision-related QoL	1%

Examination elements routinely obtained on new visit (Fremont *et al.* and Albrecht *et al.*):

	Community (Fremont *et al.*)	Specialist (Albrecht *et al.*)
visual acuity exam	99%	99%
pupil exam	74%	72%
IOP	96%	99%
gonioscopy	46% *	89%
optic disc/NFL	94% *	96%
fundus evaluation	88% *	91%
visual field test	66% *	88%
target IOP	1%	27% **

*: up to 12 months before, or six months after, initial visit

**: from chart review of 12 glaucoma specialty practices around the USA

Follow-up care:

	Community	Specialist
optic nerve		
within two years	39%	82%
current exam	2%	60%

Follow-up intervals (community):

	Mild	Moderate/Severe
≤ 1 month	15%	24%
1-3 months	21%	21%
3-6 months	40%	38%
6-12 months	20%	14%
> 12 months	5%	3%

Gaps in follow-up care of > 15 months over five years:

None	50%	2	13%
1	17%	3+	20%

Follow-up visual field intervals (community):

	Mild	Moderate/Severe
≤ 3 months	3%	4%
3-6 months	5%	13%
6-12 months	31%	40%
12-24 months	48%	35%
> 24 months	14%	9%

Treatment intensity (community):

Mild damage (up to loss in one hemisphere outside 10 degrees) **	
19 mm or less	48%
20-21 mm	18%
22 mm or higher	34%
Moderate to severe damage (loss in both hemispheres or within 10 degrees) **	
16 mm or less	35%
17-18 mm	17%
19 mm or higher	48%

**: if visual fields were not available, c/d ratio of 0.6 used as threshold in staging

What are the opportunities for enhancing physician behavior?

Evidence now exists as to which methods are effective in changing provider behavior.[23] Firstly, financial incentives can drastically alter service provision. Patients seen under prepaid care systems have a 50% lower cataract surgery rate in the USA,[24] due to delaying surgery until visual acuity rises from a median of 20/50 in fee for service to 20/125 in managed care systems.[25] Secondly, mandatory regulatory schemes will result in changes in physician behavior, when sanctions such as loss of income or eligibility to practice come into play. Thirdly, 'opinion leader' strategies will result in the eventual diffu-

sion and spread of ideas across a cohort of physicians.[26] Indeed, those recommendations that arise from a strong consensus tend to be more readily adopted and used than those with lower levels of consensus.[27] Fourthly, personalized attention, such as 'academic detailing' can influence physician behavior; witness the efforts of the pharmaceutical industry.[23] Fifthly, and related, feedback loops and hands-on interactions are effective means of providing continuing medical education, while classic lecture formats are generally ineffective.[23]

While these traditional methods are effective, the potentially most effective interventions from a larger viewpoint may come from integrating improved systems of care with technological tools.[28-31] The area of patient safety has highlighted the huge potential of automated systems integrated with structured care processes in virtually eliminating medication errors.[31] In addition, neural learning networks and automated systems in ophthalmology already perform at levels similar to providers.[32] Thus, integrating evidence-based guidelines of care with proven technological aids may provide a means of providing high quality care on a regular basis to our patients. **In assessing such systems, our question should not be directed toward perfect performance, but rather to whether such systems improve the care that is being provided today under current conditions**. Thus, the use of standardized definitions of disease, disease severity, and disease progression, together with standardized care recommendations, will enable these new technologies and approaches to grow in assisting providers to care for their patients.

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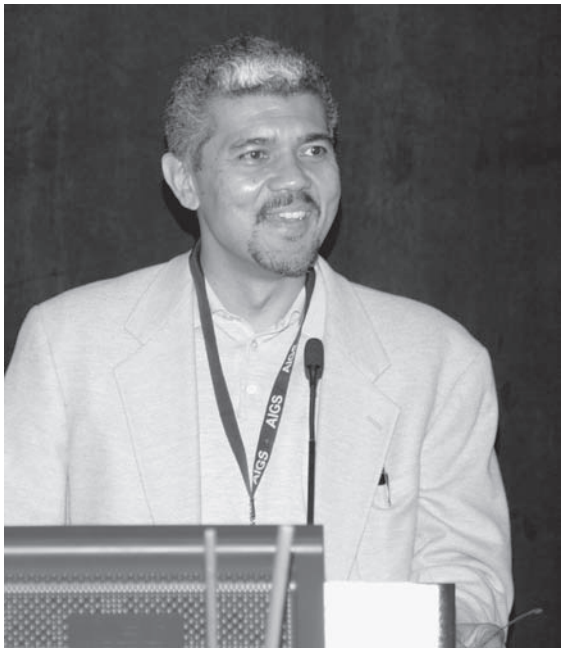

Roy Wilson, Chair of the discussion on Evidence Based Glaucoma

Report authors: Anne Coleman, David Friedman, Kuldev Singh, Anja Tuulonen and Stefano Gandolfi

LEVELS OF EVIDENCE OF DIAGNOSTIC STUDIES

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Stage I

Classifying primary studies according to their quality
(Validity criteria from the EBM working group, JAMA 271:389-391, 1994)

1 = Higher quality / 2 = Acceptable quality

a. Are the results valid?

1 + 2 Risk of false conclusion is small
1 + 2 Alpha of 0.05 and beta of 0.20
1 + 2 Narrow 95% confidence intervals
1 + 2 Population and method suitable for generalizing in the population where guideline will be used.
1 Strong study design appropriate to the question asked (primary *and* secondary criteria fulfilled)
2 Study design appropriate to the question asked

Primary validity criteria
1 Reference standard = progressive structural optic nerve damage
2 A reference standard is defined
1 + 2 Reference standard has been applied to all subjects
1 + 2 Independent, masked evaluation of the diagnostic test and of the reference standard (they are assessed independently of each other)
1 + 2 Appropriate spectrum of patients to whom the diagnostic test will be applied in clinical practice (different stages of glaucomatous optic nerve damage included)
1 Previously unscreened population
2 May not be a previously unscreened population

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Secondary validity criteria

1 + 2 Results of diagnostic test should not influence the decision to perform the reference test (work-up bias)
1 + 2 Complete reporting of the methods so that the test can be replicated

b. What are the results?

1 + 2 Complete reporting of analyses and interpretations
1 + 2 Are likelihood ratios (LRs) presented? Or enough data for calculating LRs?

c. Will the results help me in caring for my patients?

1 + 2 The reproducibility of the test setting is satisfactory for general clinical practice
1 + 2 The spectrum of patients in the manuscript includes patients to whom the clinician would apply the test (generalizable)

3. Lower quality

a. Are the results valid?

- Studies not fulfilling high or acceptable categories

b. What are the results?

- No information on LRs and not enough data for calculating LR are given

c. Will the results help me in caring for my patients?

- The reproducibility of the test setting is not satisfactory for general clinical practice

Stage II

Consensus on the strength of the evidence

To be determined by a group of specialists who have read the relevant manuscripts and who have rated the quality of the manuscripts available on the relevant diagnostic test(s). A possible rating scale for summarizing the strength of the evidence would be:

- Strong research-based evidence (A)
- Moderate evidence (B)
- Limited research-based evidence (C)
- No evidence (D)

Relevance of sensitivity and specificity

Sensitivity and specificity are widely used concepts for presenting the results of a diagnostic test. These summaries are commonly reported for glaucoma assessment techniques, as well as elsewhere in the ophthalmic literature, although they have limitations that are important to understand. Sensitivity is the proportion of subjects with glaucoma in whom the test result is positive, and specificity is the proportion of subjects without glaucoma in whom the test result is negative. In order to calculate sensitivity and specificity, the test results need to be divided into glaucoma versus not glaucoma, with results naturally arrayed in a 2 × 2 table. As we know from other fields of medicine, the results of diagnostic tests are not always unambiguous, and so it can be important to include an 'indeterminate' category. Yet, when sensitivity and specificity are being calculated, the indeterminate results must either be discarded or be included in either the 'disease' or 'no disease' category. This forced decision limits the usefulness of the diagnostic test in clinical practice because you throw away information, and it forces you to choose a cut-point where you classify a test result as positive or negative. Although receiver operator characteristic (ROC) curves may help with the choice in a cut-point, they still rely on dividing the results into 'disease' or 'no disease'.

The value of a diagnostic test depends not only on the sensitivity and specificity, but also the prevalence of the disease in the population. This is particularly relevant concern regarding glaucoma diagnosis. Even diagnostic tests with high sensitivities and specificities are of questionable utility when screening low-risk populations, since a high proportion of cases labeled positive for disease may be false positives, because the prevalence of glaucoma is low in the general population. Another problem with sensitivities and specificities is that the study population in which they are calculated may not be relevant to clinical practice. For example, even a direct ophthalmoscope may have essentially 100% sensitivity and specificity if the study population is comprised of only very severely affected glaucoma patients and unaffected individuals.

A potentially more useful concept than sensitivity or specificity is the likelihood ratio (LR). A likelihood ratio reflects the probability that a person with glaucoma would have a particular test result, divided by the probability that a person without glaucoma would have that test result. LRs from a diagnostic test can be used to update the pretest probability that an individual has glaucoma. LRs of greater than 10 or less than 0.1 generate large, definitive changes in pretest probabilities, while LRs of 1 to 2 and 0.5 to 1 generate more moder-

ate changes in pretest probabilities. (There is symmetry to the interpretation of LRs greater than versus less than 1, the value corresponding to a non-informative test result, with an LR of 10 reflecting the same degree of departure from a non-informative test results as an LR of 0.1, and an LR of 2 reflecting the same departure from a non-informative test result as an LR of 0.5.)

An issue with any diagnostic test result is the choice of the reference standard. In glaucoma research, choosing a reference standard for glaucoma is difficult, because there is currently no widely-accepted 'gold standard' definition of glaucoma. The consensus of our group was that 'progressive structural optic nerve damage' was the best 'gold standard' for glaucoma at this time. Unfortunately, there are only few studies that have been able to follow patients longitudinally for a long enough period to document progressive structural optic nerve damage. Because of test-to-test fluctuations in psychometric tests and their less than perfect concordance with the observation of progressive structural optic nerve damage, we do not recommend psychometric tests as the gold standard at this time.

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HISTOPATHOLOGY UNDERLYING GLAUCOMATOUS DAMAGE – I

Ronald S. Harwerth

Ronald S. Harwerth

Summary

The principles underlying structural measurements are different from the principles for psychophysical measurements of glaucomatous optic neuropathy, and these differences may explain why observable optic disc changes can precede and predict the development of visual field defects.

- Physical measurements of changes in anatomical structures are linear functions.
- Visual thresholds are not determined by linearly summed responses of all the detectors in the total population, but rather by nonlinear interactions (probability summation).
- There is a strong structure-function correlation for standard, white-on-white, clinical perimetry when probability summation and eccentricity factors are included, and similar relationships must hold for alternative forms of perimetry.
- Perimetry stimuli designed to be ganglion cell-specific may be more efficient than white-light stimuli for detecting the initial losses of ganglion cells by reducing the number of detectors in the pool of potential detectors, but these stimuli may not be more effective in following the progression of established visual field defects.

How many and what types of nerve fibers/ganglion cells are lost before structural or functional loss can be detected?

There seems to be convincing evidence for three aspects of this question: 1. structural signs of glaucomatous optic neuropathy can be detected before functional changes;[1-10] 2. functional changes may provide better quantification of progression, especially in the moderate to advanced states;[11-15] and 3. functional measures with ganglion cell specific stimuli provide earlier evidence of glaucoma than standard white-light stimuli.[16-23] A reasonable explanation for these structure-function relationships should lie in differences in the basic principles of the various types of measurements.

On the face of it, measurements of anatomical structure should be more sensitive than psychophysical measurements for the initial neural losses from glaucoma, because changes in the optic nerve head represent changes in wide sectors of the retina rather than local field defects. With a physical measurement, the anatomical loss will be measurable whenever it exceeds the resolu-

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tion of the instrument, and progression will be linear until the residual structure is less than the instrument's resolution. As an example of the measurement of the thickness of the retinal nerve fiber layer (Fig. 1, dot-dash line), if the normal thickness is 100 μm and the measurement resolution 10 μm, then an initial loss should be detectable when it exceeds the 10% pre-nerve fiber loss, and the measurable loss should increase linearly until it exceeds the upper limit of measurable loss of 90% of the initial thickness (a range of about 10 dB).

However, visual thresholds are not determined by linearly summed responses of all the detectors in the total population, but rather by nonlinear interactions, *e.g.*, probability summation among neural detectors. The fundamental principle of probability summation is that an observer will detect a stimulus whenever at least one of the potential detectors in the population detects the stimulus. The general relationship for sensory versus neural substrates derived from probability summation is an exponential function based on the number of detectors and the probability of detection for each of the available mechanisms.[24-29] However, theory aside, the importance with respect to its clinical application for visual field losses from glaucoma is that visual sensitivity as a function of ganglion cell density should be a linear relationship in log-log coordinates. This relationship has been confirmed for experimental glaucoma in monkeys, which showed that the empirical relationship between visual sensitivity, in dB (the threshold value from a given test location for the 24-2 program of the Humphrey Visual Field Analyzer), as a function of ganglion cell density, in dB (ten times the logarithm of the histological count of ganglion cells at the corresponding retinal location), was found to be well-described by linear regression (Harwerth *et al.* IOVS;44:ARVO Abstract 1040). The parameters of the linear regression varied with retinal eccentricity in three important respects: 1. the normal ganglion cell density decreased by 10 dB and normal perimetric visual sensitivity decreased by 5 dB from central to peripheral test locations; 2. the

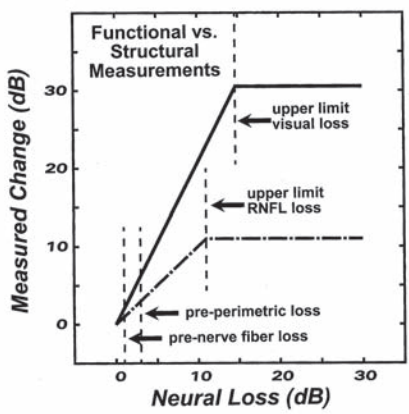

Fig. 1. Diagrammatic relationship between measured changes and neural losses from glaucoma using a functional measurement of visual sensitivity (solid line) or a structural measurement of the retinal nerve fiber layer (dot-dash line).

slope of the function for visual sensitivity versus ganglion cell density increased by about two times from central to peripheral test locations; and 3. the interception of the function decreased with eccentricity by approximately a factor of two. Thus, the number of ganglion cells lost before the confirmation of significant visual field defects will also vary with eccentricity. As an example, with standard clinical perimetry (illustrated in Figure 1 by the solid line) at an eccentricity of 15 x 15°, the relationship for sensitivity loss as a function of neural loss has a slope of approximately 2 dB/dB. At this eccentricity, a preperimetric loss of sensitivity (less than the 95% confidence limits) is about 6 dB, which is correlated to a neural loss of 3 dB, or a 50% neural loss, and the range of measurement extends to an upper limit of measurable visual loss of about 30 dB, or about 97% neural loss. In comparison, for the most central 3 x 3° test locations where the normal cell density is ten times greater, significant visual field defects will occur initially after 40% of the ganglion cells are lost and will increase in depth to a loss of approximately 99% before visual sensitivity becomes unmeasurable.

With respect to structural or functional signs of early glaucomatous optic neuropathy, based on the concepts of the measurement, a structural loss should be detectable very early, with about 1 dB loss of neural thickness, compared to a 3-dB loss of ganglion cells in the mid-peripheral visual field by standard perimetry. But, after visual field defects occur, progression may be detected more easily by perimetry because the functional losses progress at about two times the rate of neural loss, compared to one time for structural loss. In addition, the dynamic range of measurement of functional loss with standard perimetry is larger, especially for central vision, than for measurements of structural loss.

There is very little certainty about the part of the question that asks how many neurons of specific types can be lost before structural or functional loss can be detected. Specifically with respect to structural measurements, although someday it may be possible, there is no current evidence that the imaging methods are sensitive to anatomical or functional sub-classes of ganglion cell axons. In contrast, a very large number of investigations have found that the assessment of functional neural loss by alternative methods provides diagnostic evidence prior to standard clinical perimetry. The custom-stimuli for these studies have been designed to isolate specific neural mechanisms in the anatomically distinct parallel channels of the afferent visual pathway. However, although the evidence that ganglion cell-specific stimuli are more efficient than white-light stimuli in detecting the initial neural loss is substantial, it is controversial whether the efficiency is gained by testing the functions of ganglion cells that are the most susceptible to glaucomatous damage. An alternative explanation, based on the tenets of probability summation as described above, postulates that earlier neural losses are revealed by reducing the number of detectors in the pool of potential detectors. In this way, there is a higher sensitivity for the detection of early functional loss with stimuli that isolate small sub-sets of ganglion cells, because the structure-function relationship is steeper. The studies with experimental glaucoma showed that, with standard clinical

perimetry, the slope of structure-function relationships steepened with increasing retinal eccentricity because the normal density of ganglion cells decreased. Thus, the earliest visual field defects measured with non-specific white-light stimuli occur at peripheral test field locations, and it follows that perimetry with ganglion cell-specific stimuli, which further reduce the number of effective neural detectors, would create even steeper functions. On the other hand, the specific functional characteristics of neurons in each of the parallel pathways only extend the range of sensitivity to specific stimulus features, but do not provide exclusive processing, and it is not clear whether the psycho-physiological links that have been established for normal vision will continue to follow reduced populations of neurons. Therefore, it may be that, after an early deficit related to a ganglion cell-specific response property, such as flicker or motion, progression of neural losses may affect threshold responses equally for all types of stimulus properties.

Are different functional defects caused by different cells?

As stated above, investigations of alternative psychophysical-physiological links for perimetry have resulted in consistent findings that stimuli designed for specific ganglion cell populations improve the early detection of glaucomatous neural loss.[22,23,30-33] The general motivation for alternative test strategies has been to design stimulus properties that match the physiological properties of the neurons that are most affected in the early stages of the disease. However, there does not seem to be a specific class of stimuli that is consistently superior, but rather many alterative forms improve early detection.[34,35] This general finding is consistent with studies of experimental glaucoma which have shown that the slope of the function for sensitivity versus neural loss is dependent upon the normal density of retinal ganglion cells (Harwerth *et al*. IOVS;44:ARVO Abstract 1040). Specifically, the slope of the function is steeper when the initial normal cell density is smaller and, consequently, if a certain stimulus configuration isolates a relatively sparse population, then functional changes will be detected with smaller losses in the overall population of ganglion cells.

On the other hand, once the neuropathy has progressed to the level of clinical significance, there is a high correlation between different perimetry procedures which have been designed to selectively test very different ganglion cell populations, *e.g*., frequency doubling technology, high pass resolution, standard automated perimetry, and contrast sensitivity perimetry with different spatial frequencies.[33,36-39] For example, in an experiment to determine the relative rates of loss in each of the divisions of the retino-geniculo-cortical pathway, increment-threshold spectral sensitivity functions were measured in monkeys with experimental glaucoma.[40] There are three peaks in the increment-threshold spectral sensitivity function that define the components of the parallel pathways; *i.e*., a peak at short wavelengths that identifies the short wavelength mechanisms of the konicellular pathway, an opponent color mechanism at long wavelengths that identifies the parvocellular

pathway, and a non-opponent mechanism in the middle wavelengths that identifies the magnocellular pathway. The results demonstrated non-selective losses for moderate or severe visual field defects with relatively uniform sensitivity losses across all mechanisms. However, with mild defects, the sensitivity losses in either the short wavelength or opponent color mechanisms were larger than with conventional white-light stimuli.

Additional evidence for non-selective neural losses has been presented in recent reports that frequency doubling perimetry, based on the response characteristics of the sparse magnocellular ganglion cells, and high pass resolution perimetry, based on the response characteristics of the most populous parvocellular ganglion cells, are well correlated across various stages of glaucoma.[37-39] Similarly, in experimental glaucoma, the progression of visual field defects measured by standard perimetry and contrast sensitivity perimetry were highly correlated (Harwerth *et al*., unpublished data). There is also a good correlation between the amount of loss of visual sensitivity and the amount of reduction in metabolic activity (*i.e*., cytochrome oxidase reactivity) of neurons in both the parvocellular and magnocellular afferent pathways.[42] Because the cytochrome oxidase levels reflect the combined effects of ganglion cell loss and dysfunction, the results of these histochemical measurements are in agreement with those of previous studies showing correlated results of high-pass resolution perimetry and frequency doubling perimetry. Both sets of data indicated that the early detection of glaucoma with alternative perimetry stimuli is not caused by greater damage to neurons in one of the parallel neural pathways compared to the other.

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HISTOPATHOLOGY UNDERLYING GLAUCOMATOUS DAMAGE – II

Harry Quigley

Harry Quigley

Summary

- Recognition of retinal ganglion cell (RGC) loss by disc or nerve fiber layer examinations could ideally be possible with a loss of 5% of RGC, but under average circumstances, it requires a loss of 30-40% of RGC.
- Functional loss occurs with variable RGC loss, depending upon the method and retinal eccentricity, greater loss being required centrally. Visual field damage by probability values on the Humphrey requires 25-35% loss in a local area. Acuity loss requires 40% RGC death, and an afferent pupil requires a 25% asymmetrical loss.
- In human eyes and animal glaucoma models, the preponderance of evidence suggests that larger RGCs preferentially die earlier, although all RGC types die in glaucoma. In experimental monkeys (but less in human autopsy material), there is a loss of lateral geniculate cells in glaucoma, and even distant effects on the visual cortex.
- The translation of anatomical selectivity into psychophysical testing depends upon the sensitivity with which the loss of RGCs of particular types can be detected by functional testing.

Body of report

1. How many and what types of nerve fibers/ganglion cells are lost before we can detect structural loss (defined as outside statistically normal, and compatible with glaucoma)?

a. Cup/disc ratio or neural rim area has been compared in eyes with measured amounts of retinal ganglion cell (RGC) loss in human and monkey eyes. The loss of fibers depends upon the size of the disc, since the number of fibers is greater in larger discs. Thus, the number of fibers lost with each unit change in cup/disc ratio is dependent upon the original disc size. Rim area is a more accurate measurement of fibers lost and appears to correlate well with fiber number at a ratio of 600,000 fibers per square millimeter of rim. Increase of 0.1 cup/disc ratio unit can mean a loss of as few as 80,000 fibers (5%) for a cup of 0.2 at baseline, while it means a loss of nearly

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480,000 fibers (20%) for an initial cup of 0.6 (see references below). Hence, the amount of loss will depend upon the ability to detect a change of a given amount of rim, combined with the original state of the disc. Many clinicians would probably agree that, with decent photographs at baseline, an increase of 0.1 in cup would be measurably detectable.

Without sequential photographs, the detectable difference from normal in cup is more problematic. We can use the 97.5 percentile for cup/disc ratio in European populations to set the static criterion of cup size abnormality, 0.7 for many populations, and the normal mean is 0.4. Hence, by our calculations, this would involve a loss of 700,000 fibers or 39% of the original total (for 0.4 going to 0.7).

b. Nerve fiber layer examination (clinical/photographs): in another portion of this meeting's analyses, I have included data on the number of RGCs that can be detected as being lost by this evaluation. I presume that others, in presenting their analysis of other instruments, will do so as well. Laser and optical imaging instruments have been used in glaucoma monkeys to indicate the degree of fiber loss indicated by their measures (GDx, OCT, Glaucoma-Scope, Topcon Imagenet). Due to variability in disc size as well as other measures relevant to different instruments (retinal anatomy in the case of OCT), the variation will surely have the same issues as described in cup/disc ratio above.

2. How many and what types of nerve fibers/ganglion cells are lost before we can detect functional loss (defined as outside statistical normal, and compatible with glaucoma)?

a. Visual acuity loss was estimated by Frisen and Quigley to require a more than 40% loss of foveal RGCs in a report that combined glaucoma RGC data and modeling.
b. Visual field (human) was most extensively studied by Kerrigan-Baumrind *et al.* (17 eyes, 13 patients); for eyes that had undergone Humphrey perimetry (HFA 1: standard algorithm): CPSD probability of 0.5% = 36% RGC loss. For individual points, a 5 dB loss was associated with 25% RGC loss. For individual points, abnormal at probability of 0.5%, meant that RGC loss was 29%. Quigley *et al.* (1989) studied three eyes that had automated fields, and concluded that, across all points, a 5 dB loss indicated at least 20% RGC loss, and 10 dB equaled 40% loss. But, in the central 12 degrees, a 5 dB loss indicated 50% RGC loss. Quigley *et al.* (1983) studied one eye by static Tübingen perimetry which had a 72% loss with thresholds that were within 2 dB of normal. Quigley *et al.* (1982) had suggested that about a 40% loss of RGC was needed to achieve the criteria for Goldmann field loss (18 eyes, 12 patients).
c. Visual field (glaucoma monkey): Harwerth *et al.* (1999) studied monkeys, determining that sensitivity losses were not well correlated with ganglion

cell losses of less than 50%. With greater cell loss, the relationship was linear (0.42 dB/percent RGC lost, compared to data from Quigley *et al.* in humans which showed a slope of 0.4 dB/percent RGC lost). Garway-Heath *et al.* (2000) suggest that the relationship might be plotted as a linear function by using 1/Lambert instead of dB compared to RGC lost.

d. Electrophysiology (monkey): using three monkeys, Marx *et al.* (1988) showed that the pattern ERG could be quite sensitive to loss, perhaps even preceding enlargement of the cup (no quantitative RGC data given). Johnson *et al.* (1989) confirmed the ability of pERG to detect unilateral glaucoma damage, but not prior to cell loss. Multifocal and flash scotopic ERGs have also been compared to cell loss, though the latter did not correlate well.

e. Afferent pupil defect was examined in humans by Levin *et al.*, and in experimentally injured monkeys by Kerrison *et al*. These papers found afferent defects when at least 25% of RGCs were estimated to be lost, and in the human cases, even more asymmetry was present.

3. Are different functional defects caused by different cells? Is there a selective loss of certain types of RGCs?

a. Selective effects on RGCs have been studied by six research groups, five of whom have determined that larger RGCs are anatomically more susceptible to injury or death in human or experimental monkey glaucoma.

Two laboratories have studied human RGC bodies. Asai *et al.* (1987) found that RGCs with larger cell body diameter died selectively more often in two human glaucoma eyes. Quigley has reported data on the cell body diameter or axon diameter distribution in 41 human glaucoma eyes (1988, 1989, 2000). In each of these, the predominant evidence was selective loss of larger RGC bodies and larger axons in the optic nerve. Very specific attention was paid to ruling out the possibility that these data resulted from shrinkage of RGCs prior to their death (as suggested editorially by Morgan). The data are completely inconsistent with shrinkage, unless only large RGCs shrink prior to death (see Weber *et al.* below). In this case, early selective shrinkage would simply represent a stage of selective cell death. The selective effect is only seen in mild and moderately damaged eyes, due to the relatively modest number of large RGCs. Areas of the optic nerve that have more large axons show selectively greater damage early in the process, in contrast to ischemic optic neuropathy, which targets smaller RGCs (Levin *et al*., 1983).

In monkeys with chronic laser glaucoma, both RGC body and axon data show a selective loss of larger cells, with no evidence of shrinkage as the explanation (Quigley *et al.*, 1987; Glovinsky *et al*., 1991, 1993). Quantitative studies of axonal transport to the LGN by RGCs show selectively greater decreases in axons terminating in the magnocellular layers, *i.e*., larger RGCs (Dandona, 1991). Vickers *et al.* (1995) labeled RGCs with antibodies to neurofilament protein, which is known to identify more prominently the

large RGCs. They concluded: "NF protein-immunoreactive cells represent a large proportion of the cells that degenerate in the glaucomatous eyes". Morgan *et al.* (2000) obtained usable data from only three monkeys after short durations of IOP elevation (14 weeks), and only a total of 1282 cells could be 'classified'. The difference in RGC loss between parasol and midget types was said to be 'not significant', but no power calculation was given to indicate the difference that could have been determined with these small sample sizes. In rats with experimental IOP elevation, larger RGC axons are also selectively killed earlier (Levkovitch-Verbin *et al*., 2002).

Two groups have studied in detail the possible alteration of dendritic branching among RGCs in experimental glaucoma. Weber *et al.* (1998) studied 14 monkeys with elevated IOP, but seven had a mean IOP greater than 40 mmHg, and three greater than 50 mmHg. Five of the animals were studied after less than four weeks of experimental glaucoma. No RGC loss data were collected (loss was estimated by cup/disc ratio, which is valid only with long-standing monkey damage). They assumed that change in size distribution of the sampled cells was due to 'shrinkage'; however, these data are equally compatible with selective loss of larger cells. Somal size for midget and parasol RGC was actually larger in the 0.4-0.6 cup size group, and only the contribution of the very high, very short duration monkeys leads to size reduction for the overall groups. Dendritic field was not changed in midget RGCs, but was smaller by 50% in parasol RGCs compared to normals, again mostly due to the contribution of high–short pressure animals. Likewise, axon diameter, as measured in retina, was not changed in midget RGCs, but axon diameter of parasol RGCs overall was decreased by 8%, due almost exclusively to the high–short duration animals, whose axons were measured as being 44% thinner. In summary, the effects seen here were more significant for large than for small RGCs, and the result is quite compatible with the loss of larger parasol cells, and not shrinkage. As corroboration of this conclusion, Shou *et al.* (2003) produced experimental RGC damage with short-term IOP elevation in cats. They found size reductions in both larger and smaller RGCs, but selectively greater loss of large RGCs. Hence, the results of both groups show selectively greater injury effects on larger RGCs, and support the greater susceptibility of larger RGCs to experimental IOP elevation.

b. Selective effects in the lateral geniculate and visual cortex
   - Human LGN brain autopsy material from three glaucoma cases and matched controls showed a loss of 20% of LGN cells in the magnocellular layers, but no loss in the parvocellular layers (Chaturvedi *et al*., 1993).
   - Monkey LGN in experimental glaucoma was first studied by Dandona *et al*. (1991), who showed that axonal transport by RGCs to the lateral geniculate was decreased, more in the magnocellular layers than in the parvocellular (five of seven animals, demonstrated quantitatively). Other studies of the LGN and cortex have examined the secondary effects on

further cells along the anterior visual pathway, not on RGCs themselves. It is quite possible that selective effects might be operative on RGCs, but not on the subsequent areas of the visual system. It is equally possible that there may be no selective susceptibility of some RGC functions, yet the partner cells in the CNS would be affected differentially. In summary, a lack of selective effects in the later stages of the visual system does not contradict the findings in RGCs themselves.

Vickers *et al.* (1997) found that labeling for the activity of cytochrome oxidase (CO) was decreased in glaucoma monkeys, with no difference in magnocellular or parvocellular pathways. Crawford *et al.* (2000) corroborated this finding, and noted that the decrease, while being statistically significant, was only 15% below normal CO levels. The power to determine a difference between magno- and parvo- layers was not given in either study.

Weber *et al.* (2000) studied LGN cells by thionine staining, thereby identifying every neuron, and taking into account cell density, cell number, and volume of each LGN layer. They studied 14 monkeys with a distribution of damage from mild to severe. They found a four times greater loss of magnocellular LGN neurons (38%) than that in parvocellular layers (10%). Yücel *et al.* (2000, 2001, 2003) studied LGN neurons, but used immunolabeling with parvalbumin to count them. They found no difference in cell loss between the magno- and parvocellular layers, and even found a loss of 20% or more in the layers corresponding to those in control eyes. It is not clear why two investigators find such disparate results, but their methods are very different. The immunolabeling method of Yücel is possibly affected by alterations in the cell expression of parvalbumin, even if the cells are not dead. Weber's thionine staining would identify all cells, regardless of the expression or presentation of particular antigens. It is interesting to note that, in the most recent publication of Yücel, if one outlier value is removed, six of seven eyes show greater loss in the magnocellular (layer 1) than in the parvocellular (layers 4 and 6) layers, but this one value makes the difference between the pathways insignificant.

In summary, there may or may not be detectable differences in the response of LGN cells in various layers to the effects of glaucoma. Several studies suggest that there is a selective magnocellular susceptibility, while others failed to show a difference. The two studies that counted the number of cells by methods that are not susceptible to metabolic alterations, found that magnocellular loss was greater than parvocellular loss.

4. Functional consequences of selective loss

When initial studies suggested that certain types of RGCs might die earlier in glaucoma, it was logical to exploit these anatomical facts in order, if possible,

to design better tests for glaucoma injury. Magnocellular pathway functions such as temporal contrast sensitivity, scotopic sensitivity, frequency doubling perception, and pattern-evoked ERG testing all showed that initial glaucoma damage could be detected through their modalities.

However, it is not possible to be definitive that a certain test depends upon a certain anatomical substrate. Investigators have written many papers claiming that they have tested humans with 'magnocellular' or 'parvocellular' tests. As pointed out by Johnson, among others, it could be envisioned that some RGCs die first, but that their death may not be as detectable as the death of less susceptible RGCs, due to differences in redundancy in the networks of RGCs to which they belong. Furthermore, the tests that are designed to identify certain 'functions' may differ in their sensitivity, reproducibility, and other features. Each of these are reasons why there might be a quite definite selective anatomical loss of certain RGCs, but psychophysical testing might fail to be able to exploit the difference, or even to detect it with available methods.

The translation of anatomical selectivity into psychophysical testing depends on the sensitivity with which the loss of RGCs of particular types can be detected by functional testing. Some variables that intervene between anatomy and functional testing include: (1) the degree to which anatomical loss of an RGC type affects the function to be tested; (2) the degree to which the function being tested is selective for only one RGC type; (3) how easily deficiency in the functional test can be detected at a given proportionate RGC loss in human subjects (so-called redundancy); (4) the stage of disease being tested; and (5) the heterogeneity of selectivity in damage among glaucoma patients.

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COMMENT ON THE HISTOPATHOLOGY OF GLAUCOMA

James E. Morgan

James E. Morgan

A significant part of Dr. Quigleys report discusses the degree to which they remodel or undergo shrinkage prior to cell death[1]. While the degree of cell shrinkage and remodelling may influence the debate concerning the selectivity of cell death in glaucoma it is of great interest in its own right. Firstly, in experimental glaucoma, observations by Weber[2] and Shou[3] that retinal ganglion cells shrink are consistent with other models of neuronal disease where neurons have a period of sickness and dysfunction prior to the onset of cell death.

Neuronal shrinkage is also seen in the lateral geniculate nucleus following ocular injury[4, 5] or experimental glaucoma[6, 7]. These data strengthen the argument that the pathophysiology of other chronic neurodegenerative diseases[8-10] may help in understanding the pathophysiology of retinal ganglion cell death in glaucoma. Indeed, it might be reasonable to suggest that the absence of retinal ganglion cell shrinkage in glaucoma would be an atypical response to neuronal injury. It is important to note that we do not, as yet, have firm evidence that shrinkage is a widespread phenomenon in human glaucoma though dendritic changes have been reported in end stage disease[11].

Should we be interested in whether cells shrink in glaucoma or remodel prior to cell death? The close relationship between cell structure and function suggests that this should be an important focus for future research. If we knew how retinal ganglion cell structure and function changed prior to the cell death it may be possible to design psychophysical tests to detect this dysfunction, rather than record the absence of cells as is currently done with perimetric analysis. Just as exciting is the possibility that 'sick' cells that have not yet committed to cell death can be recovered and returned to useful function. Recent work in other areas of neuroscience has highlighted the possibility that increasing neurotrophic support can improve neuronal function[12] and harness the innate plasticity that we now know exists in adult (and not just in developing neural tissue). Already, work is underway to evaluate the role of neurotrophin support (such as BDNF) in rescuing retinal ganglion cells in various model of optic nerve damage[13, 14].

Glaucoma Diagnosis. Structure and Function, pp. 31-32
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Dr Quigley's comments highlight the importance of understanding the cellular and morphological changes that occur in the retinal ganglion cell population in glaucoma. The relative paucity of information on the these changes in human disease[15,16] should focus our research efforts in designing experiments to understand, in detail what happens to retinal ganglion cells prior to cell death.

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HISTOPATHOLOGY UNDERLYING GLAUCOMATOUS DAMAGE – III

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Summary

- At least 30-40% retinal ganglion cell (RGC) loss is needed before we can detect diffuse structural loss.
- At least 25-35% RGC loss is needed before we can detect functional loss, as detected by standard perimetry.
- In early glaucoma, evidence suggests that larger RGCs are damaged, and this may be due to their loss and/or shrinkage. Recently described RGC subtypes that are larger than the M RGCs may also be implicated.
- In normal primates, RGC subtypes respond to preferred visual stimuli at the single cell level. However, the loss of input by a subpopulation of RGCs may not always translate into the loss of perception of their preferred stimulus at the single cell level.
- Visual field deficits detected using specific motion or color modalities most likely reflect the dysfunction within an extended neural network from the retina to the visual cortex.

Question 1a. How many nerve fibers/ganglion cells are lost before we can detect structural loss or functional loss?

The proportion of retinal ganglion cell (RGC) loss that can be detected before structural or functional change depends on the ability to detect statistically significant RGC loss by histomorphometry. In post-mortem human and non-human primate tissue, RGC loss is assessed by comparing the number of RGCs in glaucoma to that of controls. The high inter-individual variation in the control group may be a limiting factor in the detection of RGC loss. Indeed, in normal human retinas and optic nerves, RGC counts show a two-fold variability or greater.[1-5] In normal non-human primate retinas and optic nerves, RGC counts show a 1.3-fold variability.[6-8]

This degree of variability suggests that, in order to consider loss of RGCs as being statistically significant, at least 30-40% RGC loss needs to be detected. This may preclude us from exploring the relationship between RGC loss and structural and functional changes in glaucoma at earlier stages.

Glaucoma Diagnosis. Structure and Function, pp. 33-37
edited by Robert N. Weinreb and Erik L. Greve

Further methodological advances are needed to reduce the variance in the observed group. The ability to measure smaller significant RGC losses in glaucoma may improve the assessment of the relationship between RGC loss and structural and functional changes *in vivo*. In addition, studying morphological changes such as shrinkage of the cell body and dendrites may reveal RGC damage and structural changes early in the disease.[9-10]

Question 1b. What types of nerve fibers/ganglion cells are lost before we can detect structural loss?

It is well established that the retinal ganglion cells RGCs are classified into parasol and midget cell types projecting into the magno- (M) and parvocellular (P) layers of the lateral geniculate nucleus (LGN), respectively.[6] Small bistratified RGCs of the koniocellular (K) pathway involved in blue-yellow color processing have also been described.[11] However, recent evidence points to a diversity of RGC types not previously known.[12] Dacey *et al*. demonstrate at least 13 distinct RGC populations projecting into the LGN in primates.[12] Each of the eight newly described RGC types is larger than the large parasol RGCs at corresponding retinal eccentricities (Fig. 1). This evolving information should be considered in our discussions and interpretations of which cell types, based on RGC cell size, are affected in glaucoma.

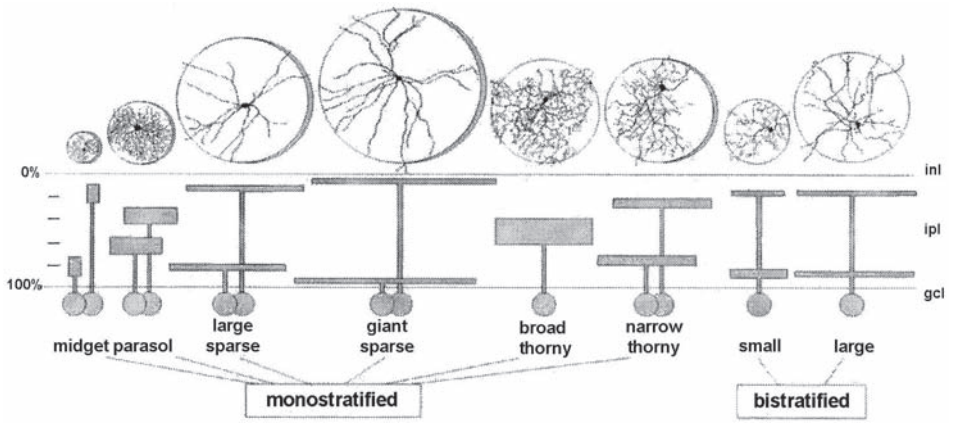

Fig. 1. Schematic summary of 13 RGC types distinguished by mean dendritic field size (top circles) and depth of dendritic stratification in the inner plexiform layer. Each of the recently identified eight RGC types is larger than the previously described midget, parasol, and small bistratified RGCs. (inner nuclear layer (inl), inner plexiform layer (ipl), ganglion cell layer (gcl)). (Reprinted from Dacey DM *et al*. (eds) Neuron, 37, Fireworks in the primate retina: *in vitro* photodynamics reveals diverse LGN-projecting ganglion cell types, 2003 by courtesy of the publisher.)

The assessment of the RGC type(s) lost in glaucoma in post-mortem human and non-human primate tissue, is performed by comparing the morphological features of surviving RGCs in glaucoma to that of controls.

In early studies, the size of the surviving RGCs and optic nerve fibers in glaucoma was compared to controls. In primates, retinal studies showed that, with up to 40% RGC loss, there was a decrease in the number of large retinal ganglion cells (Fig. 5 in Glovinsky *et al.*[13]). Optic nerve studies showed that, with greater than 50% optic nerve fiber loss, a decrease in the number of optic nerve fibers with a diameter greater than 0.44 μm was seen (Fig. 4 in Quigley *et al.*[14]). In humans, although retinal studies are lacking, studies of the optic nerve showed that the number of fibers with a diameter greater than 0.95 μm are decreased.[2] Based on the information available at the time, it was interpreted that there was selective loss of larger RGCs.

More recent studies show significant shrinkage of both surviving larger parasol and smaller midget RGCs.[10] Furthermore, greater shrinkage of larger parasol RGCs compared to smaller midget RGCs has also been shown.[9] Based on this information, the decrease in the number of larger RGCs seen in previous studies may have occurred as a result of shrinkage, rather than of their selective loss.[13] Additional information points to 13 types of RGCs, and many are considered to be 'larger' neurons.[12] Eight of these RGC types are larger than the parasol RGCs involved in the magnocellular pathway. Further studies are now needed to sort out which types of RGCs are affected in early glaucoma, and whether the damage is selective or diffuse in nature.

Question 2: How many and what types of nerve fibers/ganglion cells are lost before we can detect functional loss?

In primate glaucoma with more than 50% RGC loss, functional loss assessed by decreased visual field sensitivity, increased with RGC loss. In cases with less than 50% RGC loss, a decrease in visual field sensitivity of 6-8 dB was consistently observed (Fig. 3 in Harwerth *et al.*[15]). In humans, visual field deficits are associated with at least 25-35% RGC loss.[16] No information regarding the specific types of ganglion cells lost before the detection of functional loss could be found.

Question 3: Are different types of functional defects caused by different (retinal ganglion) cells?

The information we have regarding RGC type functions is based upon single cell recording studies. The measurement of single cell activity in normal primates shows specific RGC types responding to preferred visual stimuli.[17,18] However, there is evidence to suggest that the loss of input by an entire sub-

population of RGCs might not result in the loss of perception of their preferred stimulus at the single cell level.[19] For example, individual M RGCs in primates have much better contrast sensitivity than individual P RGCs.[20] However, the removal of M LGN layers does not result in any discernible deficit in contrast sensitivity, whereas the removal of P LGN layers results in a marked deficit in contrast sensitivity.[21,22] These results suggest that perceptual appreciation of contrast does not relate to the relative sensitivity displayed by individual M and P RGCs, but presumably reflects a pooling of signals from many P RGCs.[23,24]

Surprisingly, the removal of M LGN layers does not affect motion perception,as defined by direction and speed discrimination.[21] It is possible that M pathway lesions disrupt detection of the test stimulus used to assess motion perception.[23,25] However, lesions of the P pathway do cause an apparent complete loss of color perception.[22,23]

In addition, recent experimental evidence suggests that, beyond the primary visual cortex, continuous interactions between different neuronal populations occur.[19,26] Thus, visual field defects detected using specific motion or color stimuli most likely reflect the dysfunction within an extended neural network from the retina to the extrastriate cortex, rather than solely specific RGC types.

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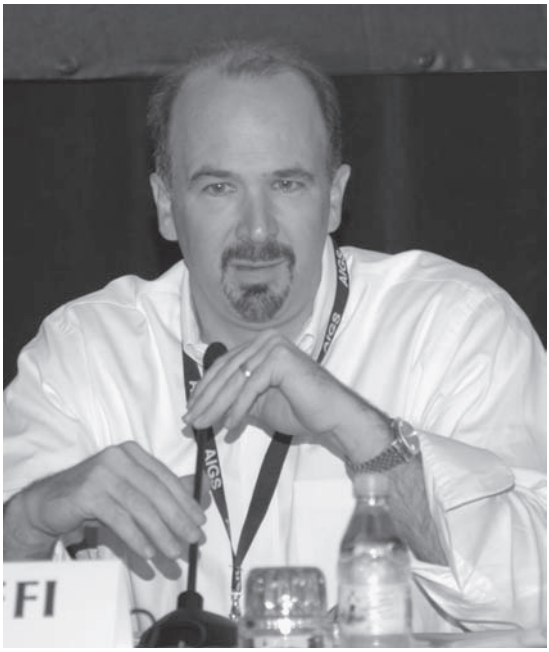

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OPTIC DISC PHOTOGRAPHS

Joseph Caprioli, Jost Jonas and Christiana Vasile

Joseph Caprioli

Summary

- Stereoscopic photographs consist of image pairs obtained simultaneously or sequentially with a spatial shift that provides retinal image disparity.
- Several studies have reported that the reproducibility of stereoscopic information and disc assessment is better with simultaneous compared to sequential stereophotography.
- Previous studies have found that the diagnostic precision of the qualitative evaluation of stereoscopic optic disc photographs by experienced clinicians is superior to any other currently available method of optic disc assessment.
- Glaucomatous visual field abnormalities may be preceded by photographically-documented structural changes of the optic disc.
- In the Ocular Hypertension Treatment Study, 55% of subjects reached the endpoint (primary open angle glaucoma) based on changes of optic disc only, as determined by optic disc photographs.
- Substantial variability exists in the interpretation of optic disc change over time, even with expert observers, with kappa values ranging from 0.50-0.96 for intra-observer agreement and from 0.55-0.81 for inter-observer agreement.
- Standardized methodology in assessing optic disc photographs in addition to adherence to strict protocols of photograph acquisition enhances the agreement amongst observers for assessing optic disc and RNFL, and increases the likelihood of making reasonable comparisons for detecting change over time.

Optic disc assessment is an important tool in the early detection of glaucoma patients. Despite the availability of sophisticated imaging devices, optic disc stereophotographs are widely used in clinical practice and have been shown to be valuable for evaluating change. Glaucoma practice guidelines published by the American Academy of Ophthalmology and the European Glaucoma Society strongly recommend the use of optic disc photos for diagnosing and monitoring glaucoma.

Glaucoma Diagnosis. Structure and Function, pp. 39-46
edited by Robert N. Weinreb and Erik L. Greve

Method

Stereoscopic photographs consist of image pairs obtained simultaneously or sequentially with a spatial shift that provides retinal image disparity. This image disparity allows perception of cup depth and excavation and rim contour. A standard fundus camera can be used to obtain sequential optic nerve images from two different angles by varying the position of the camera itself or by using an Allen Stereo Separator. Photographs taken with this method cannot be used to make quantitative measurements of depth. Simultaneous stereophotographs require a special camera with beam-splitting prisms to image the optic disc. Currently-available cameras place two images in a single frame, resulting in less magnification than the sequential stereo techniques.

Although both methods of stereophotography can provide excellent stereoscopic image pairs cross-sectionally, the sequential method is inferior for the comparison of photographs over time because it requires the introduction of disparity via manual shift of the camera position. Several studies have reported that reproducibility of stereoscopic information and disc assessment is better with simultaneous compared to sequential stereophotography. A stereo-viewer, a light box, and a minimum magnification of 20 degrees are required for assessment of optic disc photos.

The advantages of stereophotography include: permanent recording of the optic disc status especially useful for serial evaluation of the disc, no need for patient cooperation, lack of prolonged patient discomfort, and possibility of more detailed evaluation of the optic disc and peripapillary area. The limitations consist of a need for clear media, dilated pupil, skilled photographer and specialized equipment, an inconsistent degree of stereo-separation in sequential stereo photographs, inconsistent plane of focus, subjective nature, and the delay involved.

Today, relatively few patients (< 5%) have very miotic pupils which cannot be dilated to more than 3 mm (this is still too small for photography!). The technique of sequential stereophotos can be standardized so the left and right stereo photographs are taken just inside the papillary crescent (see Caprioli AOS thesis). This reduces parallax, maximizes the stereo effect, and makes serial comparisons more meaningful.

Intra and inter-observer reproducibility in photograph grading

Few studies have investigated the degree to which masked observers agree in their assessment of photographs. Intra-observer reproducibility (kappa = 0.69-0.96) is consistently higher than inter-observer reproducibility (kappa = 0.20-0.84) in studies evaluating agreement among observers when estimating optic disc parameters and discriminating glaucoma eyes from healthy eyes with stereoscopic photographs. In general, high inter-observer reproducibility values

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are obtained when standardized methods are used. Substantial variability exists in the interpretation of optic disc change, even with expert observers, with kappa values ranging from 0.50-0.96 for intra-observer agreement and from 0.55-0.81 for inter-observer agreement. The inter-observer reproducibility in EGPS ranged between 0.45 and 0.75, while intra-observer reproducibility was 0.79-1.00. A change of imaging parameters, such as focus, stereopsis, quality, magnification, and type of camera used, can influence reproducibility for the detection of progression. Availability of a clear-cut definition for progression and experience of the reader may also affect the results.

Sensitivity and specificity of diagnosis with optic disc photographs

The current literature suggests that glaucomatous field abnormalities may be preceded by structural changes in the optic disc. Previous studies have found that the diagnostic precision of qualitative evaluation of stereoscopic optic disc photographs by experienced clinicians is superior to any other currently available method of optic disc assessment. Qualitative evaluation of stereoscopic color optic disc photographs takes in consideration many features of the optic disc, including cup/disc ratio, neural rim thickness, contour and color, vessel position, presence of disc hemorrhages, and peripapillary atrophy.

In general, sensitivity for the detection of early to moderate glaucoma (with early visual field defects) is good, as is sensitivity to detect progression in *early to moderate* disease. Once the visual field loss becomes more advanced, detection of change with photos is much less satisfactory than with visual fields (see Caprioli AOS thesis).

Monitoring progression with optic disc photographs

Studies that used optic disc and retinal nerve fiber layer (RNFL) photography have shown that an increase in cup area or thinning of the neuroretinal rim, emergence of a focal rim notch or splinter hemorrhage at the disc margin, and thinning of the RNFL, all may precede glaucomatous visual field damage, as tested by achromatic perimetry. Tuulonen and Airaksinen reported that 20 of 23 hypertensive eyes that converted to glaucoma, as defined by the development of glaucomatous visual field loss, demonstrated RNFL defects and disc damage. The rate of progressive rim loss over time with optic disc photography has been estimated to be between 1.7-2.8% in ocular hypertensive eyes and 2.1-3.5% in glaucomatous eyes.

Investigations exploring the relationship between optic disc appearance and visual function measurements, both cross-sectionally and longitudinally, have provided additional evidence that progressive optic disc and RNFL damage can be detected with photographic data. These studies suggest that quantitative changes in visual function likely have predictable qualitative analogues in optic disc photographs. In the Ocular Hypertension Treatment Study, 55% of subjects reached the endpoint (primary open angle glaucoma) based on changes in the optic disc only, as determined by optic disc photographs.

Flicker method

One study reported the use of the flicker method (stereochronoscopy) for longitudinal evaluation of monocular color disc photos (Heijl & Bengston, Diagnosis of early glaucoma with flicker comparisons of serial photographs. Investigative Ophthalmology and Visual Science 1989; 30: 2376-2394). The changes identified by the flicker method were usually visible with conventional evaluation as well, once attention was directed to the altered area. While in this study (by the same group as EMGT) flicker was very sensitive in detecting change, in the EMGT study, only 7% of all 255 patients showed progressive changes in their optic disc during the entire six years of follow-up (compared to progression of visual fields in 53% of patients). Flicker can be a sensitive measure of progression if photographs are taken at a fixed angle during serial visits. A device has been designed for use on a fundus camera which ensures that fixed angle photographs can be taken. In the absence of fixed angle photos, parallax will cause apparent shifts that may be interpreted as change. For similar reasons, the technique of stereochronoscopy was abandoned long ago.

Optic disc photography in glaucoma trials

Two National Eye Institute sponsored clinical trials (OHTS and EMGT) and the Memantine Study by Allergan have used qualitative evaluation of stereo-

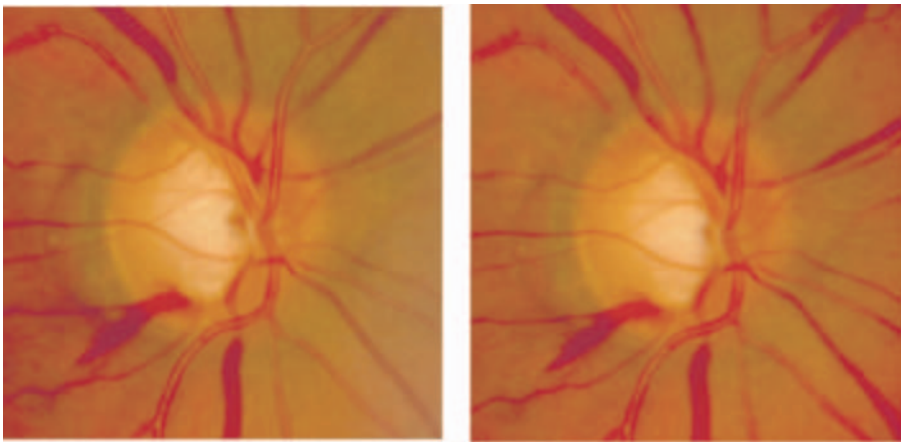

Fig. 1. The left and right stereoscopic pair of disc photographs in a 68 year old patient with primary open-angle glaucoma. The presence of a disc hemorrhage is an important risk factor for progressive damage.

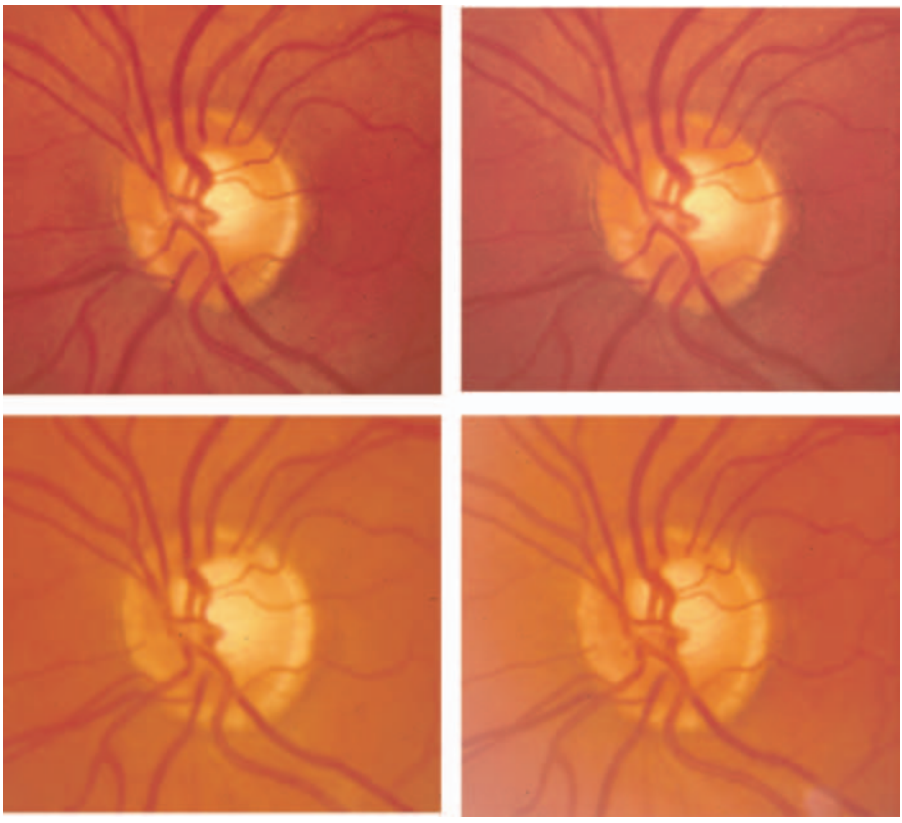

Fig. 2. Top, left and right stereoscopic pair of optic disc photographs in a 68 year-old patient with normal tension glaucoma at baseline. Bottom, the left and right stereo pair at follow-up of the same eye two years later. Note the loss of neural rim at the 1 o'clock position from baseline to follow-up, indicating progressive glaucomatous damage.

scopic optic disc photographs as an outcome measure indicating the acceptance of optic disc photography as a valid tool for the detection and monitoring of glaucoma.

Conclusions

Evaluation of the optic disc and RNFL with stereophotography is the current 'gold standard' for the diagnosis and monitoring of early to moderate glaucoma. Although subjective and dependent upon an experienced observer, this method provides quality cross-sectional information that is reasonably reproducible within and across studies. Furthermore, studies have shown that stereophotograph-derived information from glaucomatous eyes coincides with visual performance, and is predictive of visual field damage. A standardized methodology for assessing optic disc photographs, in addition to adherence to strict protocols of photograph acquisition, enhances the agreement amongst observers for assessing the optic disc and RNFL and increases the likelihood of making reasonable comparisons for detecting change over time.

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RETINAL NERVE FIBER LAYER (RNFL) PHOTOGRAPHY

Harry Quigley, Antoinette Niessen, Anja Tuulonen and Juhani Airaksinen

Harry Quigley

Summary

- The retinal nerve fiber layer (RNFL) can be examined clinically and photographically with a method that shows high reproducibility.
- The method detects loss of RGC axons during the pre-perimetric stage of damage and is one of the few methods that has been proved to predict glaucoma progression in longitudinal cohort studies.
- RNFL examination with photography is not as convenient as laser-imaging systems, it requires high levels of competence by technical personnel, and considerable learning by physician-graders.

How does it work?

Green light reflects from the retinal nerve fiber layer (RNFL), is absorbed by melanin, and recorded well on high resolution black-and-white film using a fundus camera. It was first brought to the attention of ophthalmology by Hoyt.[1] The change detected is from the NFL alone, and changes in retinal thickness in the outer retina are not detected.

What is the reproducibility?

The coefficient of variation was 0.22 for diffuse and 0.11 for local defects (intraobserver).[2] Weighted kappa among observers was as high as 0.818. Using the Niessen system, intra- and inter-observer reliability was 0.9 or greater.[3,4] Using Quigley's system, intra-observer reproducibility = 0.6-0.8 (unweighted kappa), and inter-observer = 0.4-0.731.

Glaucoma Diagnosis. Structure and Function, pp. 47-51
edited by Robert N. Weinreb and Erik L. Greve

What is the minimal damage that can be detected?

In monkeys, local defects that are calculated to involve a loss of only 12,500 axons (1% of normal total) are detectable.[5] Comparison to HRT shows that visible NFL defects measure about 21-47 μm in depth. This confirms that observations in human eyes have a similar sensitivity to that estimated in monkeys.[6]

What is the sensitivity/specificity for detection of early/moderate/advanced damage?

Airaksinen:[2] sensitivity for OH = 56%; OAG sensitivity = 94%, specificity = 83%.
Quigley:[7] sensitivity for OH = 13%; fellow eye of OAG = 28%, mild field loss = 60%, moderate field loss = 100%; specificity = 97% (2/67).
O'Connor:[8] diagnostic precision for separating normal, OH, and OAG = 75%.
Wang:[9] screening in a medical clinic, sensitivity for any OAG was 64%, specificity 84% (must account for abnormal NFL with non-OAG disease).
Paczka:[10] sensitivity for mild/moderate glaucoma = 95%, specificity = 82%.

What is the sensitivity/specificity for measuring progression?

Sommer *et al.*[11] report that 100% of 14 cases developing field loss had NFL defects 1.5 years previously (using old color photographs).

According to Airaksinen,[12] of 25 disc hemorrhage cases, NFL became abnormal and preceded field loss (in eight subjects who developed field loss) by one to two years.

Sommer *et al.*[13] further report that 88% of gradable photographs are abnormal at the time of Goldmann field loss, 60% are abnormal six years prior to field loss. Patients from the same study were studied by Quigley *et al.*[14] in a case/control design, with 37 persons moving from OH to OAG (converters), compared to 37 stable OH. Discs changed in 19% of converters, while NFL changed in 50%. The predictive power for future field loss of baseline disc and NFL photographs are similar. In a risk factor analysis of the same data, Quigley *et al.*[15] found that NFL predicted future initial field defects at a risk ratio of 3.7 (mild defect) to 8 (severe defect). In the same analysis, the cup/disc risk ratio was only 1.5.

In a retrospective review, Caprioli *et al.*[16] suggest that, in 12 persons developing a change in field, disc and NFL were both predictors, with no statistical difference being seen in predictive power (disc numerically slightly better).

Kraus *et al.*[17] studied seven eyes that developed field defect changes, six of which had NFL defects prior to the change (field change in 1/16 with initial normal NFL, and 6/12 with initial NFL defect).

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What studies are available? How do they compare with other methods?

Some authors suggest that there may be a later event than disc hemorrhage in some eyes.[12,18] Other studies report that there are better predictors of damage than cup/disc ratio,[5,13-15,18,19] or that the disc and NFL are similar in predictive power.[8,16] Some methods are correlated to the degree of automated visual field damage,[20-22] including SWAP.[23] Others are correlated to OCT NFL thickness.[22] Another method exceeds the predictive power of the GDx (before corneal correction is introduced).[10]

How strong is the evidence?

Evidence comes from several different clinical groups, in Europe, USA, and Japan, with some of the longest prospective studies ever performed in glaucoma, and with large datasets.

What are the pros and cons?

One strong attribute of NFL examination is its proven predictive power for being able to identify the presence of early glaucoma damage, and for predicting future damage. The technique can be applied to many different variants of the normal appearance of the human disc and posterior retina.

In addition, while it is necessary to learn to read photographs by actual practice, this has been shown to represent only a modest time with programmed

instruction. However, it is recognized (without any formal clinical trial) that reading photographs is more accurate than the clinical examination of the same person.

One weakness is the fact that NFL photographs require a widely dilated pupil and bright flashes for the patient. As a result, readable pictures are obtained in about 80% of typical glaucoma subjects, which is lower than the 90+% image capture of laser devices, which, in addition, do not require dilation.

Further weaknesses are the need to use photographic film that has specific development requirements, and the need for an experienced photographer who must know where to aim and to focus. We cannot know until long after the patient has left whether the pictures have 'come out'. In contrast, laser devices provide a nearly immediate record, and repeat imaging can be performed if the initial attempt is unsatisfactory.

While NFL photography can provide a modest quantification of NFL, especially with the enhanced grading system of Niessen, it cannot be considered to have the numerical detail of newer laser systems.

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SCANNING LASER TOMOGRAPHY (HRT)

Marcelo Nicolela, Alfonso Anton, Somkiat Asawaphureekorn, Claude Burgoyne and Goji Tomita

Marcelo Nicolela

Summary

- The Heidelberg Retina Tomograph (HRT) is a confocal scanning laser device that provides accurate and reproducible topographical information of the optic disc and peripapillary retina.
- HRT examination is well tolerated by the patient, does not require pupil dilation in most cases, and can easily be performed by a technician, particularly using the second generation instrument (HRT II).
- This technique has been shown to discriminate glaucomatous from normal optic discs in a clinical setting at least as well as experts evaluating optic disc photographs.
- There is a paucity of data evaluating HRT as a screening device for glaucoma in an unselected population.
- Longitudinal studies have demonstrated the ability of this device to detect morphological changes of the optic disc in ocular hypertension and in earlier stages of glaucoma.

Methods

The Heidelberg Retina Tomograph (HRT) is a confocal scanning laser ophthalmoscope (CSLO) that uses a 670-nm diode laser to obtain two and three dimensional images of the optic disc and the peripapillary retina. A topographical image is built from a series of 16-64 consecutive optical sections, each consisting of 256 x 256 pixels (first generation instrument, referred to here as HRT I) or 384 x 384 pixels (second generation instrument, referred to here as HRT II) over a 10- (only in HRT I) or 15-degree field of view. When using HRT I, a mean of three topographical images is recommended for analyses. The HRT II automatically captures three consecutive series of scans and generates a mean topographical image. A reference plane is automatically determined at 50 μm posterior to the mean peripapillary retinal height along the contour line at the temporal sector between 350 and 356 degrees, but can be modified. Magnification error is automatically corrected by using patients' keratometry readings, and the power of the correction lens used to acquire the images. The optic disc

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margin needs to be defined by a contour line placed around the inner margin of the peripapillary scleral ring.

As with any imaging device, the quality of the image greatly depends upon the ability of the technician, who requires adequate training. The training period has been significantly shortened with HRT II, an easier machine to use compared to HRT I. Each technician should master and understand the image acquisition, image processing, and placement of contour line, and understand the quality control parameters. However, experienced technicians should be able to acquire good quality images in over 90% of eyes. Advanced cataract, corneal opacities and nistagmus can prevent adequate imaging.

Among the limitations of the technology, we could cite the need to outline the optic disc margin, the need to define a reference plane in order to calculate stereometric parameters, and the lack of a better automated quality control assessment, which would warn the clinician about poor quality examinations or poor alignment of sequential images acquired during follow-up.

Reproducibility of the technique

The mean coefficient of variation obtained with HRT I for stereometric parameters such as cup area or volume was reported to be from 3-5% in glaucoma and normal subjects.[1] With HRT II, the variability in healthy subjects was reported to be less than 12% in all but three parameters, with rim area being the least variable parameter.[2] The mean standard deviation for one pixel of the total image is about 30 μm in glaucoma patients and 25 μm in healthy subjects.[3,4] The regional variability of topographical measurements correlates with the steepness of the corresponding region, and is highest at the edge of the optic disc cup and along vessels.[5] The quality and variability of the images is associated with pupil size[6] and density of nuclear and posterior subcapsular

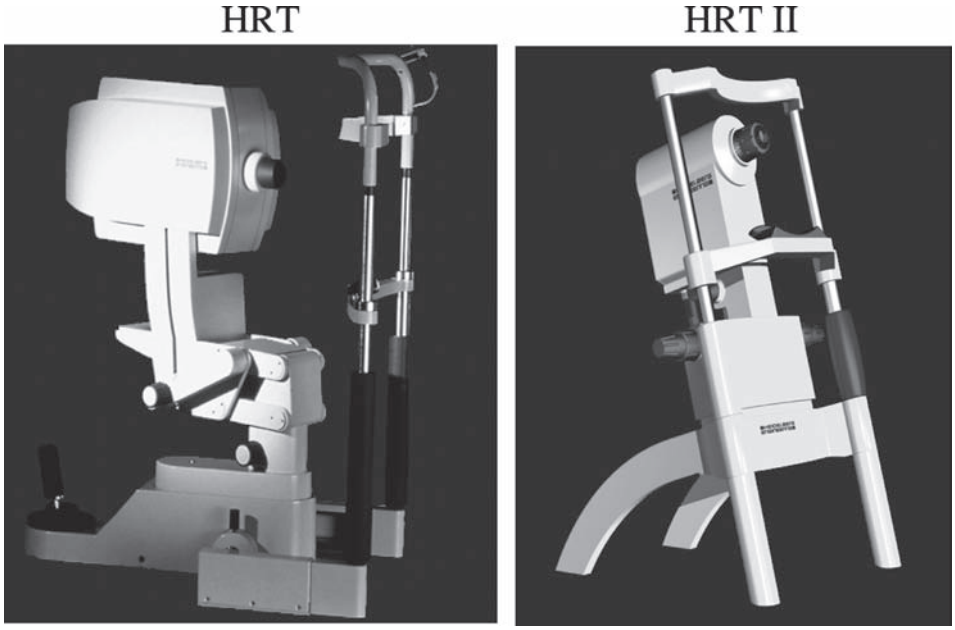

Fig. 1. Picture of HRT 1 (left) and HRT II (right).

cataracts.[7,8] In addition, HRT measurements are influenced by changes in intraocular pressure[9,10] and cardiac cycle.[11]

Sensitivity and specificity of HRT to detect glaucoma damage

HRT has not been tested in a screening situation, in order to evaluate its diagnostic performance in unselected individuals. However, there are a number of studies evaluating its diagnostic performance in detecting glaucoma in patients already diagnosed and attending glaucoma clinics. In general, these studies used one of three methods to discriminate between normal and glaucomatous optic discs: 1. linear discriminant functions;[12,13] 2. comparison of one (or more) stereometric parameters to normative database, which is the approach used in the *Moorfields Regression Analysis*;[14] 3. computer-assisted classifications, such as neural networks.[15,16] In all these studies, the input to discriminate between the two groups was the stereometric parameters (global or sectorial) generated by the HRT software.

The sensitivity/specificity of HRT has been reported to be from 62-87% and from 80-96%, respectively.[12-14, 17-19] However, in most cases, these values were obtained from analysis performed in a similar population used to derive the original discriminating functions. If we apply the discriminating analysis to an independent population, the diagnostic precision is usually worse.[20,21] The diagnostic precision of HRT is influenced by disc size, with larger discs being

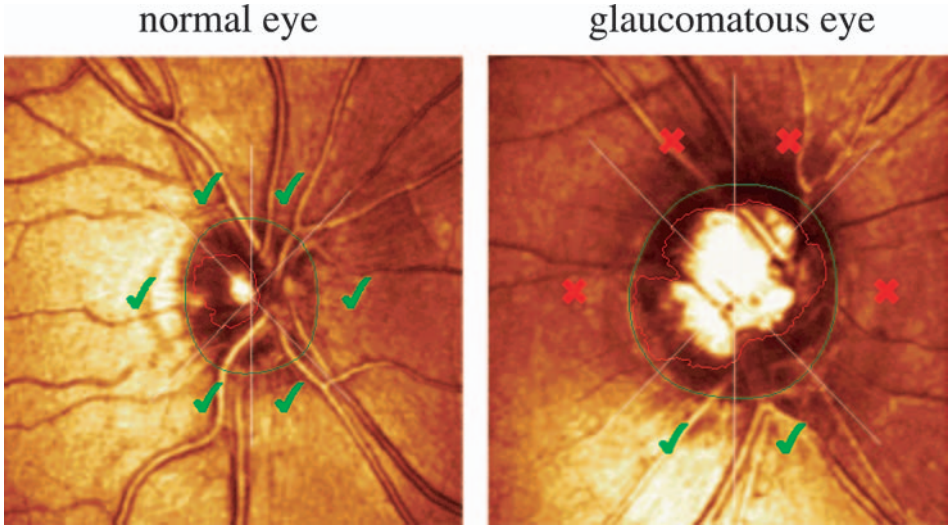

Fig. 2. Examples of a normal and a glaucomatous optic disc, both correctly identified by the Moorfields Regression Analysis.

discriminated with higher sensitivity, but lower specificity and smaller discs with higher specificity but lower sensitivity.[17,21] In a metanalysis of the above published papers, it is also clear that the diagnostic precision of HRT is influenced by the stage of the disease, with better performance in the later stages of glaucoma.

There are some studies that compare the discriminating ability of HRT with the current gold standard in optic disc imaging, *i.e.*, stereo optic disc photography. Wollstein *et al.*[14] found that the *Moorfield Regression Analysis* had a higher sensitivity with equal specificity to detect early glaucoma compared to the majority opinion of five expert observers. However, Greaney *et al.*[22] and Zangwill *et al.*[19] found that qualitative assessment of stereo optic disc photographs by experts functioned as well or better than HRT in discriminating between normal and glaucomatous optic discs.

To date, there is no available animal data on the minimum amount of nerve fiber loss before changes can be detected with HRT, either cross-sectionally (comparing to normal values) or sequentially (comparing to a baseline image).

Due to the very large variability in optic disc size and shape in the normal population, as well as the large variability in patterns of structural optic disc damage found in glaucoma, we believe that the potential usefulness of HRT in a true screening situation for detecting glaucoma in its early stages may be limited, particularly in a situation where we cannot accept a large number of false positive results.

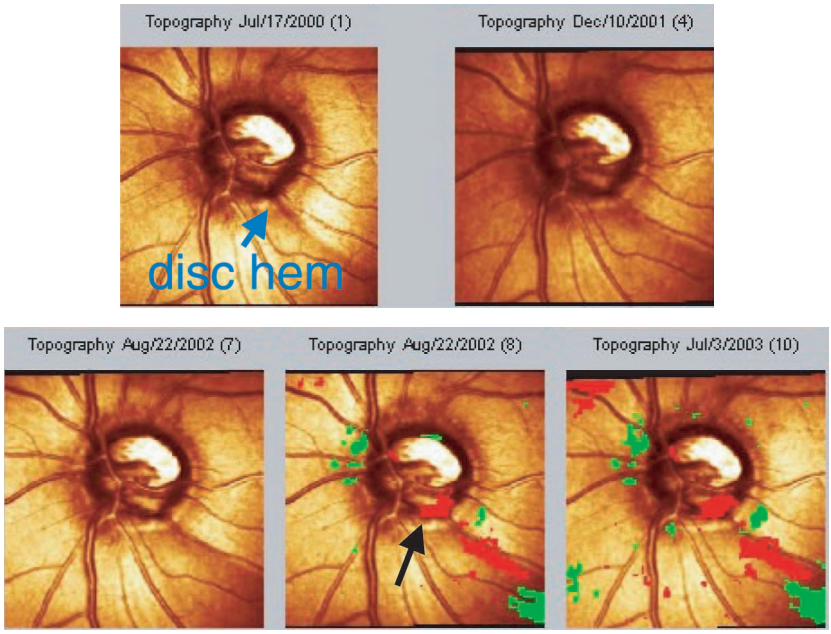

Fig. 3. Infero-temporal optic disc and retinal nerve fiber layer progression detected through the change probability analysis (red super pixels; black arrow) two years after an optic disc hemorrhage occurring in the same location (blue arrow).

Sensitivity and specificity for progression detection

Three strategies for HRT change (progression) detection have been assessed both in 'at risk' and 'normal' human eyes followed longitudinally. Chauhan *et al.*'s[23] super-pixel strategy for optic nerve head (ONH) surface change detection (which has been incorporated into existing HRT software) detected the deterioration of ONH surface change in 31 of 77 (40%) patients with early to moderate glaucoma followed for a median of 5.5 years in eyes with stable visual fields, with a 95% specificity within 37 normal eyes. In addition, in that same study, only 4% of eyes had confirmed visual field progression, with no progression being detected by HRT.[24] Kamal *et al.*[25,26] reported ONH surface change detection using a segmental strategy in 13 of 21 ocular hypertensive visual field converters, 47 of 164 ocular hypertensive visual field non-converters and none of 21 normal eyes. Tan *et al.*[27] analyzed 30-degree sectors of rim area in order to detect change in 17 of 20 ocular hypertensive converters and in one of 20 normal eyes; however, they too needed change to occur in two of three consecutive tests in order to achieve that specificity.

In addition, using a similar CSLO (not HRT) to image monkey eyes, the LSU Experimental Glaucoma Study reported higher sensitivity and specificity for optic disc change detection with CSLO (defined as a significant change in

two of three selected CSLO parameters in two consecutive post-laser imaging sessions) compared to three fellowship-trained glaucoma specialists using stereophoto images of the same eyes.[28,29]

Pros and cons of the technique

Pros

- HRT is a very technician- and patient-friendly technique (particularly HRT II) that generates good quality images in most patients.
- The learning curve for a technician with HRT II is relatively short.
- HRT has excellent reproducibility, which positions it well in terms of being able to detect topographical changes over time.
- HRT is the automated imaging technique with the longest track record and largest number of publications.

Cons

- The internal fixation target can be off-center in some eyes, and ideally we should be able to change the position of the internal fixation target.
- The algorithm that aligns images over time can fail in a small number of eyes, leading to false results.
- Some information provided in the printout has limited clinical value.

Future studies

Future studies are required as follows:

- to evaluate HRT screening performance in a population-based study;
- to develop independent screening and progression strategies for contour lines and reference planes;
- to develop techniques to reduce the number of confirmatory tests required for specific progression detection;
- to evaluate a field conversion rate following change with HRT;
- to better definite the role of HRT in clinical practice;
- to obtain animal data to evaluate the minimum amount of nerve fiber loss needed before progression can be detected with HRT.

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SCANNING LASER POLARIMETRY (SLP)

Hans G. Lemij, Eytan Blumenthal, Robert Fechtner, David Greenfield and Michael Kook

Hans G. Lemij

Summary

- Scanning laser polarimetry provides objective imaging of the retinal nerve fiber layer, based on retardation of polarized light.
- Retardation in the cornea and lens have recently been compensated for (for the sake of brevity and simplicity, referred to here as corneal compensation, CC).
- Custom CC narrows the band of normative data, and improves detection.
- Custom CC improves correlation with other structural measurements.
- Older studies from the literature with fixed CC do not reflect the capabilities of the present version.

Working principle

Scanning laser polarimetry (SLP) is based on the retardation of polarized light. The microtubules in the axons of the retinal nerve fiber layer (RNFL) are believed to show form birefringence, which provides the signal for RNFL measurement.[1] Due to their arrangement in parallel bundles, this form birefringence results in a net change in the retardation of passing light. Therefore, the amount of retardation is proportional to the amount of axonal tissue. In the commercially available scanning laser polarimeter, GDx (Laser Diagnostic Technologies, San Diego, CA), a polarized laser beam scans the back of the eye. The backscattered light that double passes the RNFL is captured and analyzed. The amount of retardation is calculated per pixel and displayed in a retardation map of the scanned area. Areas of higher retardation are thought to represent more axons, and therefore a thicker RNFL.[2-4] Because the cornea and, to a lesser extent, the lens also show form birefringence, their retardation needs to be compensated (neutralized) in order to assess RNFL retardation.[5-14] Previously, a uniform, fixed compensation was used, of which both axis and magnitude reflected the median values of the general population. Only recently has the fixed anterior segment compensator been replaced by a custom (individualized) anterior segment birefringence compensation (for the sake of brev-

Glaucoma Diagnosis. Structure and Function, pp. 61-70
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ity, referred to here as custom corneal compensation, CC). The commercially available instrument provided with CC is known as the GDx-VCC (in which the V stands for variable). It is based on retardation measurements obtained in the macula, based on the form birefringence of Henle's fiber layer.[6,7,53]

Validation

Histological validation of SLP was initially performed in two monkey eyes, the cornea and lens of which had been removed.[3] The factor that transforms degrees of retardation into microns of RNFL thickness was derived from these experiments. Subsequently, one monkey eye scanned by SLP was later subjected to histological RNFL thickness analysis.[15] Qualitative comparisons between SLP images and a small series of red-free fundus photographs of eyes with localized RNFL defects suggest that SLP images obtained with proper CC closely reflect the true architecture of the RNFL.[13] With the outdated, fixed CC, the agreement with red-free fundus photographs is considerably worse.[13] Histological validation in human eyes still needs to be performed. The variable CC has been demonstrated to generate accurate estimates of corneal polarization axis and magnitude, in both healthy eyes and those with maculopathy.[6,14]

Evolution

Custom CC became available as recently as 2002. The GDx-VCC represents the fifth generation of commercially available SLP instruments. The first gen-

Fig. 1. The GDx VCC.

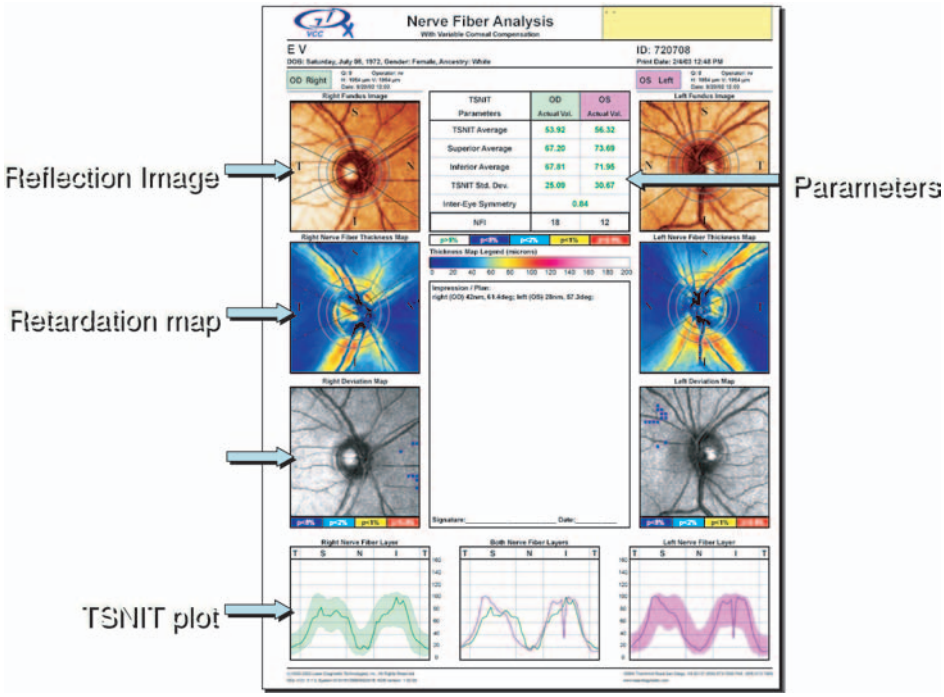

Fig. 2. Example of a GDx VCC print-out of a healthy subject. The two uppermost panels on the sides display reflectance images of the disc and peripapillary area. The two panels below show the color-coded retardation maps, in which bright, warm colors relate to higher retardation and dimmer, colder colors to lower retardation. The next two panels reflect the so-called probability maps, in which color coded super pixels may flag areas of low retardation at specific probability levels. The bottom panels show the so-called TSNIT plots, that reflect a cross sectional retardation along the peripapillary band displayed in the higher panels. Normative ranges have been added to these graphs. For easier comparison between the two eyes, the TSNIT plots have been presented together in the middle lowermost panel. Several parameters, including the Nerve Fiber Indicator (NFI) are presented in the middle uppermost panel. Abnormal parameters may be color-flagged.

eration was known as the nerve fiber analyzer (NFA). With later generations, both hard- and software changes were made, the latter including a normative database and a neural network discriminating algorithm. The third generation was marketed as the GDx and the fourth as the GDx Access. Most literature on SLP relates to instruments mounted with a fixed CC, and should therefore be viewed with caution, because eyes with incomplete compensation were included. Similarly, the normative database of the devices with fixed CC included eyes not well compensated. A new normative database has been collected with the GDx-VCC. Sensitivity and specificity with variable CC (and ROC curves) demonstrate a clear improvement over measurements with fixed CC.[7] Accuracy and reproducibility have not yet been reported.

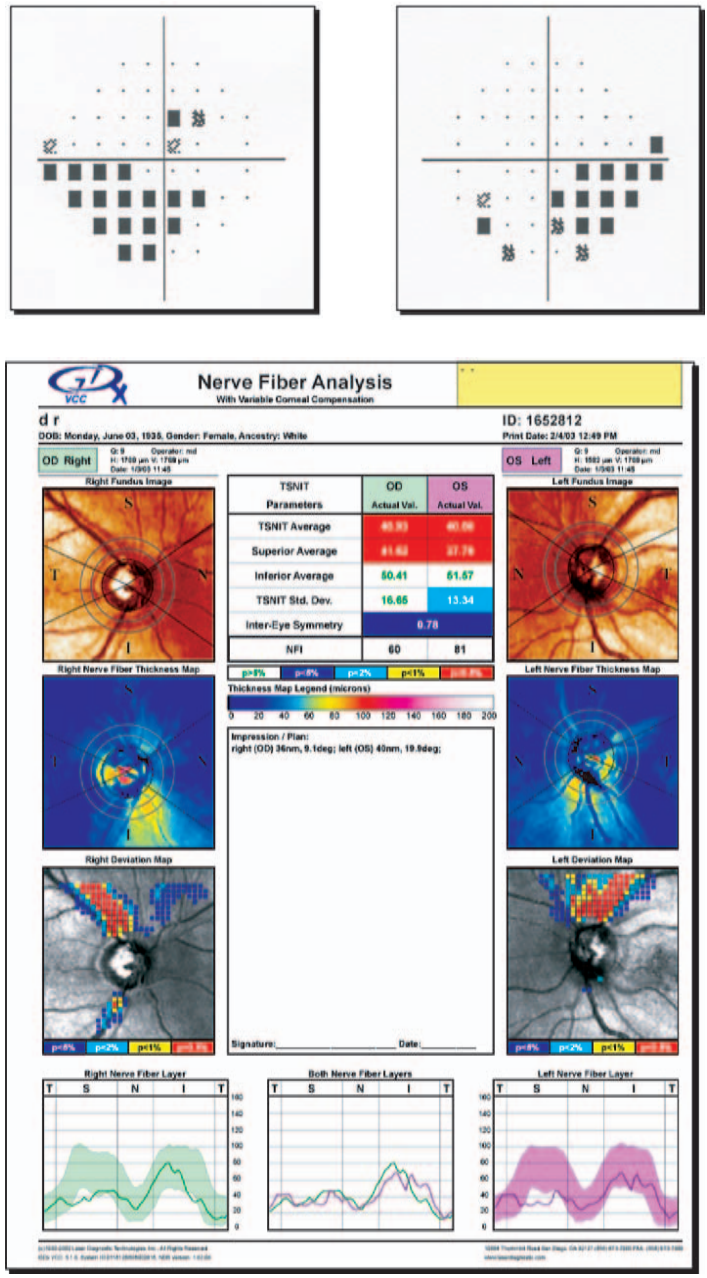

Fig. 3. Example of a typically glaucomatous GDx VCC print-out. In this particular case, there is markedly reduced retardation superiorly in both eyes and also inferotemporally in the right eye, which can be seen in the retardation maps, but also in the clearly flagged probability maps. Note the flagged parameters and the abnormally attenuated TSNIT plots, notably superiorly. The visual field pattern deviation probability plots have been added.

Instrumentation

The current GDx-VCC is a user-friendly and compact device. The subject rests his head in a facemask and looks at an internal fixation light. Two imaging trials per eye are run successively, the first to determine CC, the second to image the area of interest with adjusted compensation. Image acquisition takes approximately 0.7 seconds per trial. Because of the laser wavelength (820 nm), mild to moderate cataract does not degrade the images.[16,17] The printout of the images includes a 20 x 20-degree reflectance image of the disc and peripapillary area, a color coded retardation map, a probability map (in which areas of retardation are compared to those of a normative database and abnormally low retardation areas are color flagged at various probability levels), several graphs and parameters.

Limitations and pitfalls

Images cannot be obtained in eyes with nystagmus. In addition, eyes with large peripapillary atrophy cannot be imaged reliably. Corneal refractive surgery variably affects measurements with fixed CC.[18-20] Variable CC is effective in eyes following corneal refractive surgery.[21] Macular disease probably only slightly affects the calculations of adequate compensation.[14] Images can be reliably obtained within a refractive range of approximately -10 to +5 D spherical equivalent, although the effect of ametropia on each individual's retardation values in both healthy and glaucomatous eyes has not been reported. Some eyes show atypical retardation patterns.

Available studies

Most studies relate to the previous GDx unit with fixed CC. Published reports on studies performed with the GDx-VCC are still limited, due to the relatively recent availability of the instrument. Recent studies have demonstrated that custom CC narrows the band of normative data,[8-10] improves the discriminating power for glaucoma detection,[9,10] improves the relationship with visual function (SAP-SITA),[11] increases the correlation with structural assessments obtained with optical coherence tomography,[12] and improves the correlation with red-free fundus photographs.[13] The relative contributions of CC to these improvements for either or both axis and magnitude have not yet been clearly ascertained.

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Reproducibility

The reproducibility of measurements of SLP with fixed CC is reportedly excellent.[22-30,36,38,52] Reproducibility of measurements, across operators and across instruments, with the GDx-VCC has not yet been reported.

Sensitivity/specificity

Early reports on the sensitivity and specificity of GDx measurements all relate to the previous GDx model with fixed CC. Most of these published data relate to Caucasian populations, showing moderate to excellent discriminating power between healthy and glaucomatous eyes.[25,31-35,37,39-49] Sensitivity and specificity with variable CC (and ROC curves) demonstrate a clear improvement over measurements with fixed CC.[7]

Progression

Very few studies have addressed monitoring progression in glaucoma or other optic neurodegenerative diseases.[40,51] Again, the previous GDx unit with fixed CC was used, which may have limited the ability of this technology to monitor progression. No consensus has been reached on how best to measure glaucomatous structural progression by means of SLP.

Conclusions

SLP with custom CC appears to accurately reflect RNFL structure with high resolution and reproducibility of measurements, although histological validation in human eyes is not yet available. Most of the literature on SLP relates to images taken with fixed CC and should therefore be viewed with caution. Important clinical studies with the new device with custom CC are still limited, and need to be conducted. These include studies on the accuracy of CC and effects of any inadequate CC, reproducibility of measurements, diagnostic accuracy for detection and follow-up, and histological validation. Since SLP primarily images RNFL thickness, the two major applications in glaucoma will probably be glaucoma detection, both in a screening setting and in the office, as well as monitoring progression. It is not yet clear whether SLP will be an equally sensitive and specific monitor throughout the entire spectrum (*i.e.,* from early to end-stage) of the disease. This still needs to be investigated.

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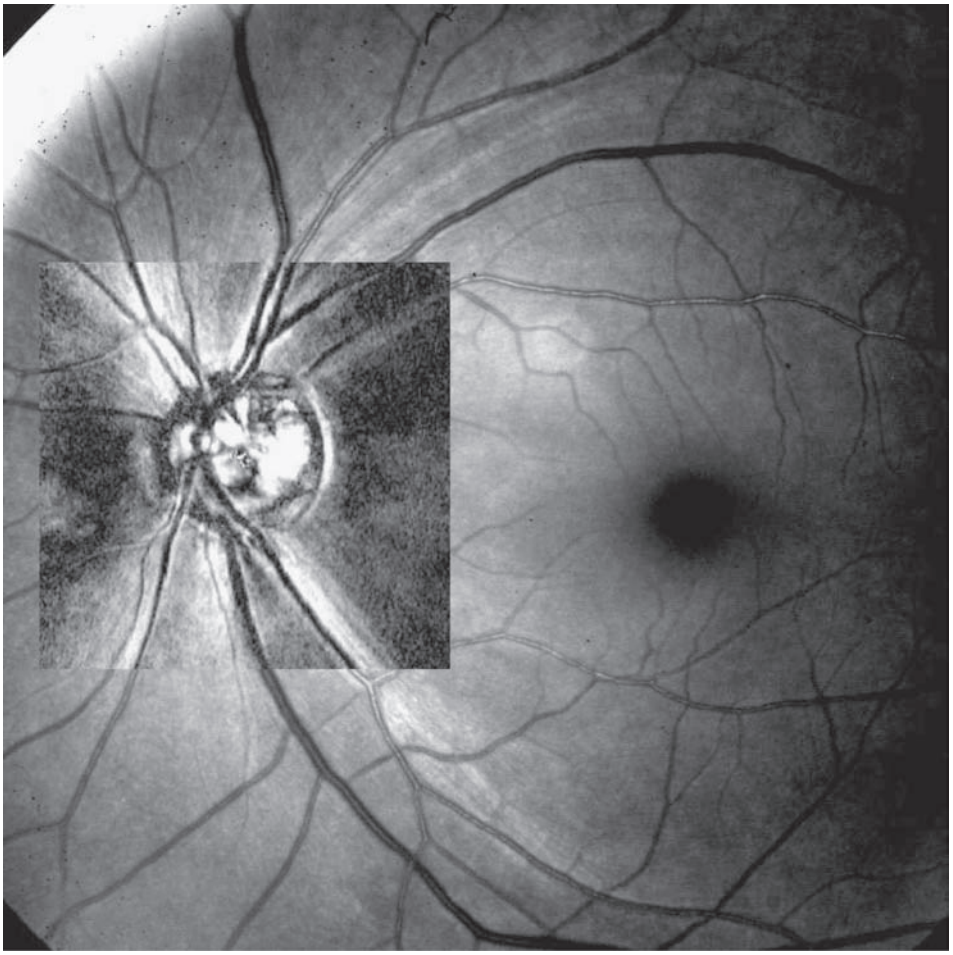

Red-free fundus photograph of a glaucomatous eye with localised wedge-shaped RNFL defects. An image taken of the same eye with the GDx with variable cornea compensation has been fitted to the photograph. For clarity, the GDx image is displayed in black and white. Note how well the wedge-shaped defects, as well as the thinner RNFL striations, in the two images match. This strongly suggests that GDx images taken with variable cornea compensation accurately reflect the true morphology of the RNFL (courtesy of N.J. Reus and H.G. Lemij).

OPTICAL COHERENCE TOMOGRAPHY (OCT)

Jeffrey Liebmann, Christopher Bowd, Felipe A. Medeiros* and Joel Schuman

Jeffrey Liebmann

Summary

- Optical coherence tomography (OCT) is an optical imaging technique capable of providing high resolution, cross-sectional, *in vivo* imaging of the human retina in a fashion analogous to B-scan ultrasonography.
- OCT assessment of peripapillary retinal nerve fiber layer thickness has been reported to differentiate normal from glaucomatous eyes.
- Macular thickness assessment may offer an alternative method of assessing retinal ganglion cell injury in glaucoma.
- The available longitudinal data are insufficient to come to any conclusions about the ability of OCT to detect change over time.
- There is no evidence at the present time to suggest that OCT can be used as a screening tool for glaucoma.

Introduction

Optical coherence tomography (OCT) is an optical imaging technique capable of providing high resolution, cross-sectional, *in vivo* imaging of the human retina in a fashion analogous to B-scan ultrasonography. OCT utilizes light echoes from the scanned tissue to discriminate retinal layers, due to the differences in time delay of echoes from various components of the retina.

Mechanism/how does it work?

OCT uses optical technology that is analogous to ultrasound B-mode imaging, but utilizes light instead of sound to acquire high resolution images of ocular structures, using the principles of low coherence interferometry.[1] In brief, interferometry uses information from interference fringes precisely to determine

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small distances or the thicknesses of structures. In OCT, a low coherence near infrared (840 nm) light beam is directed onto a partially reflective mirror (beam splitter), which creates two light beams: a reference and a measurement beam. The measurement beam is directed onto the subject's eye, and is reflected from intraocular microstructures and tissues, according to their distance, thickness, and different reflectivity. The reference beam is reflected from the reference mirror at a known, variable position. Both beams travel back to the partially reflective mirror, recombine, and are transmitted to a photosensitive detector. The use of low coherence light allows only the reflections from a narrow region of the retina to interfere with the reference beam, giving the high resolution of the instrument. The pattern of interference is used to provide information with regard to distance and the thickness of retinal structures. Bi-dimensional images are created by successive longitudinal scanning in a transverse direction.

OCT image resolution depends on several factors. Resolution can be considered in the axial (z-axis) or transverse (x-y) axis. Earlier OCT models (OCT 2000, Carl Zeiss Meditec, Inc., Dublin, CA) had axial resolution at 12-15 μm, whereas the currently available Stratus OCT (Carl Zeiss Meditec, Inc., Dublin, CA) has a theoretical resolution of 8-10 μm, although this has not yet been demonstrated in practice. The Stratus OCT model can generate 128-512 scan points in the transverse axis, whereas the OCT 2000 is limited to 100 scan points.

Clinical application

OCT is capable of scanning the peripapillary retina, optic nerve head (ONH), and macular region. The peripapillary scan is a continuous circular scan centered on the ONH with a default diameter of 3.4 mm. The final image provided by the OCT appears in a color-coded map that is artificially produced by the OCT software. Dark colors (black and blue) represent regions of minimal optical reflectivity, whereas bright colors (red and white) represent regions of high reflectivity. In order to obtain thickness measurements, OCT first determines the retinal boundaries, constituted by the vitreoretinal interface and the retinal pigment epithelium (RPE), which defines the inner and outer retinal boundaries, respectively. The retinal nerve fiber layer (RNFL) corresponds to the high reflective layer (red) underneath the inner retinal boundary. The posterior boundary of the RNFL is determined by evaluating each scan for a threshold value chosen to be 15 dB greater than the filtered maximum reflectivity of the adjacent neurosensory retina. **G**ood correlation has been reported between the RNFL measured by OCT *in vivo* with histomorphometric measurements in monkeys with experimental glaucoma.[3]

Macular and ONH scans are composed of six radial scans in a spoke-like pattern centered on the ONH or the fovea at 30-degree intervals. Interpolation is used to fill the gaps between the scans. For macular scans, the vitreoretinal interface and the retinal pigment epithelium are utilized to define the inner and outer retinal boundaries, respectively. For ONH scans, disc margin is defined as the end of the RPE/choriocapillaris layer. A straight line connects the edges of the RPE/choriocapillaris, and a parallel line is constructed 150 μm anteriorly. Structures below this line are defined as the disc cup, and above this line as the neuroretinal rim. Additional OCT details can be found in the references cited.[2,4-6]

Available summary information and analyses

Retinal nerve fiber layer scan

A printout of the Stratus OCT RNFL thickness analysis of a glaucoma patient is shown in Figure 1. The curve of the distribution of RNFL thickness values around the optic disc is shown as a black line. The green shaded area indicates the 95% confidence limits of normality, whereas the red shaded area indicates values below 99% of the normal population. Borderline values are indicated by the yellow shaded area. The probability of abnormality is calculated based on an aged-matched normal group.

The printout also provides RNFL thickness values in clock hours and in quadrants. The same color code indicates the probability of abnormality for each sector/quadrant. Summary parameters are also provided, including aver-

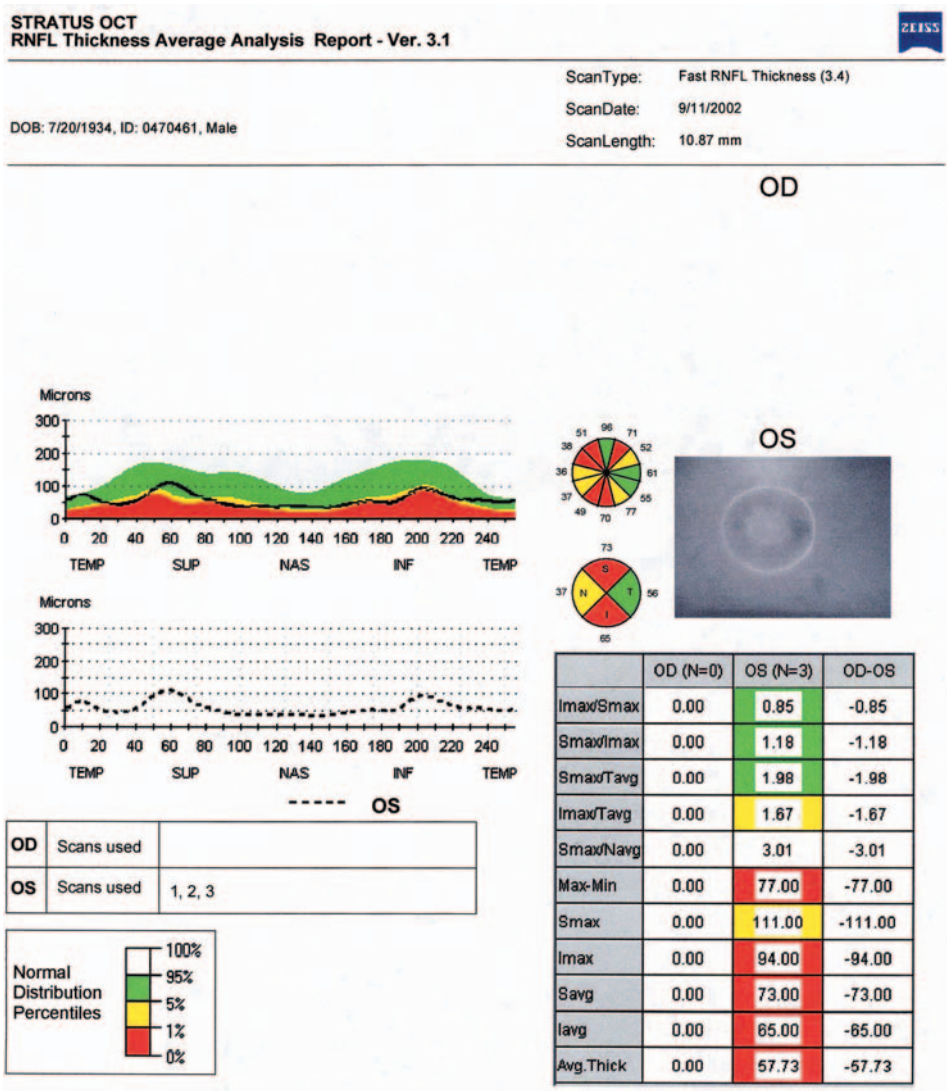
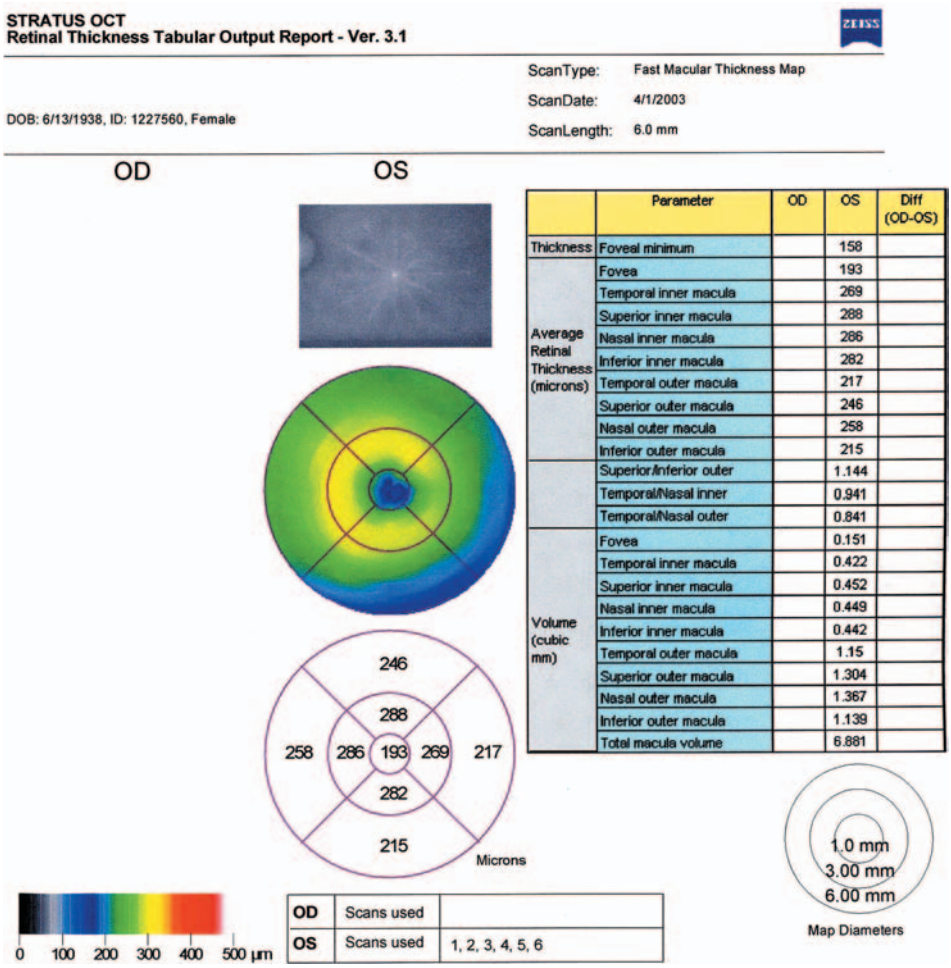


Fig. 1. Printout of the Stratus OCT retinal nerve fiber layer (RNFL) scan of the left eye of a glaucomatous patient. The printout shows the curve of distribution of RNFL thickness measurements around the optic disc, the RNFL thickness measurements in clock-hours and sectors, and several summary parameters. The probability of abnormality is indicated by a color code.

age thickness, ratios, and maximum RNFL thickness values in the superior and inferior quadrants.

Macula scan

The macula scan displays two maps, centered on the macula, showing retinal thickness and volume (Figure 2). Three concentric circles divide each map into



	Parameter	OD	OS	Diff (OD-OS)
Thickness	Foveal minimum		158	
Average Retinal Thickness (microns)	Fovea		193	
	Temporal inner macula		269	
	Superior inner macula		288	
	Nasal inner macula		286	
	Inferior inner macula		282	
	Temporal outer macula		217	
	Superior outer macula		246	
	Nasal outer macula		258	
	Inferior outer macula		215	
	Superior/Inferior outer		1.144	
	Temporal/Nasal inner		0.941	
	Temporal/Nasal outer		0.841	
Volume (cubic mm)	Fovea		0.151	
	Temporal inner macula		0.422	
	Superior inner macula		0.452	
	Nasal inner macula		0.449	
	Inferior inner macula		0.442	
	Temporal outer macula		1.15	
	Superior outer macula		1.304	
	Nasal outer macula		1.367	
	Inferior outer macula		1.139	
	Total macula volume		6.881	

Fig. 2. Example of a Stratus OCT macula scan printout. The macular map is divided in 9 regions by two concentric circles and two diagonal lines. A color-coded map is shown corresponding to the macular thickness measurements in each region. The table also shows the values of thickness and volume for the different regions.

three zones: fovea, and inner and outer macula. The inner and outer zones are further divided into four quadrants by two diagonal lines. Thus, a total of nine areas (fovea, superior outer, superior inner, inferior outer, inferior inner, temporal outer, temporal inner, nasal outer, and nasal inner) are available for analysis. In one map, a color code represents the retinal thickness (or volume) in each area, while in the other map, the actual values of thickness (or volume) are given for each area. The user can select the diameters of the three concentric circles and change the area to be analyzed. Two options are available. One with concentric circles of 1, 3 and 6 mm; the other with concentric circles of 1, 2.22 and 3.45 mm.

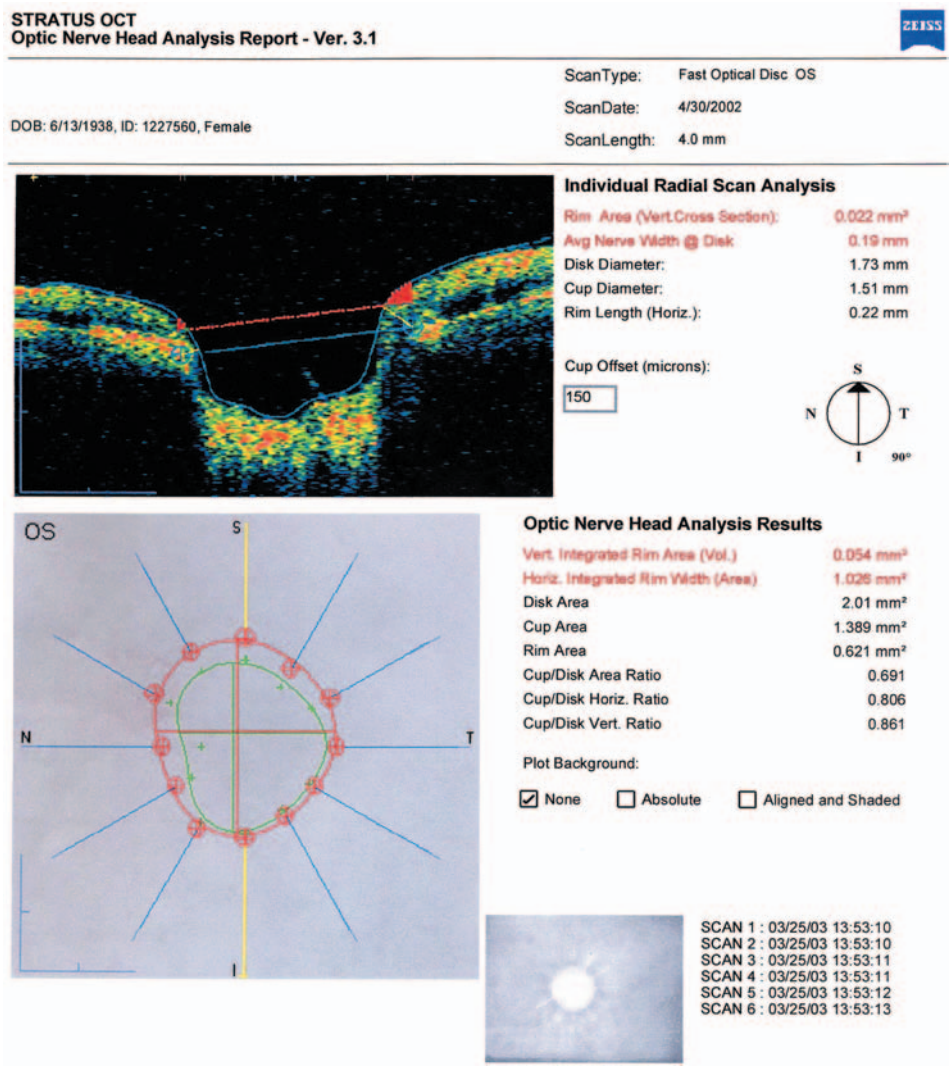


Fig. 3. Printout of the Stratus OCT optic nerve head scan of the left eye of a glaucomatous patient. The graph in the lower left corner shows the final result of the interpolation analysis obtained from the six radial scans centered on the optic disc. The optic disc margin is shown in red and the cup border in green. Several topographic parameters of the optic disc are automatically calculated.

Optic nerve head scan

An ONH scan obtained with Stratus OCT is shown in Figure 3. Several topographic optic disc parameters are automatically calculated including disc area, rim area, cup/disc area ratio, cup/disc horizontal ratio, cup/disc vertical ratio, vertical integrated rim area (rim volume) and horizontal integrated rim width.

Table 1. Ability to detect glaucoma using optical coherence tomography: selected recently-published studies

Reference	*Healthy eyes (n)*	*Glaucoma eyes (n)*	*VF MD in glaucoma eyes (db)*	*Best parameter**	*Area under ROC curve*	*Sensitivity/ specitivity (%)*
17	38	42	-4.0 ± 4.2	inferior thickness	0.91	88/71 79/92
11	39	50	-3.9 ± 2.13	discriminating function	0.88	82/84 67/90
10	33	35	-3.01 ± 2.88	global average	0.94	n/a
37	160	237	-3.13 ± 1.77	inferior temporal	0.87	67/90 81/80
35	50	39	-5.04 ± 3.32	evaluation of standard printout	n/a	76-79/68-81
20	25	42	-4.3 ± 3.3	global average RNFL thickness	0.87	n/a
21	50	41	-5.14	inferior temporal	0.87	76/86 71/94 68/96

Studies available

Glaucoma detection

RNFL measurements

Several studies have indicated that OCT can discriminate between healthy and glaucomatous eyes, although a considerable amount of overlap exists.[7-20] The areas under the receiver operating characteristic (ROC) curves have been reported to range from 0.79-0.94, depending on the parameter and characteristics of the population evaluated (Table 1).[10-12,16,17,21] In studies evaluating the diagnostic ability of several OCT parameters, RNFL thickness in the inferior region often had the best performance for discriminating healthy eyes from eyes with early to moderate glaucoma, with sensitivities of between 67 and 79% for specificities ≥ 90%.[16,17,21] In another approach, a discriminating analysis function combining RNFL thickness measurements obtained from four different 30-degree sectors around the optic disc had a sensitivity of 67% for specificity set at 90%.[11] In some of these studies, the gold standard used for glaucoma diagnosis was the presence of repeatable abnormal standard automated perimetry (SAP) results, a standard independent of the diagnostic test being evaluated. In addition, OCT results did not influence the decision to perform SAP. Both these criteria are required to acceptably demonstrate the validity of a diagnostic test, according to the Evidence-Based Medicine Working Group.[22]

There is some indirect evidence in the literature indicating that OCT RNFL measurements are able to detect glaucomatous damage before functional deficits can be detected by SAP visual field testing.[23,24] Differences between RNFL measurements in ocular hypertensive eyes and normal eyes have been demonstrated, although a large overlap exists between the two groups. An average

decrease in RNFL thickness of about 15% in OHT eyes compared with normal eyes has been reported.[24] Currently, no longitudinal studies are available that directly investigate whether OCT RNFL measurements are predictive of the future development of glaucomatous visual field loss.

Macular thickness

Several studies have recently been reported evaluating the role of OCT macular thickness measurements for the diagnosis of glaucoma. Loss of retinal ganglion cells in glaucoma is also known to occur in the posterior pole, where these cells may constitute 30-35% of the retinal thickness in the macular region.[25] The mean macular thickness of glaucomatous eyes has been shown to be significantly lower than that of normal control eyes.[10,26,27] Also, a significant correlation was found between OCT macular thickness and visual field mean defect in glaucomatous eyes.[26] In one study, the ability of macular measurements to discriminate glaucomatous from normal eyes was inferior to that of RNFL peripapillary measurements.[10] A maximum ROC curve area of 0.77 for macular thickness parameters was obtained for discrimination between early glaucoma and normal subjects, whereas RNFL thickness parameters had maximum ROC curve area of 0.94 in the same situation.[10] It is also important to emphasize that macular thickness measurements have limited use for monitoring or evaluating glaucoma in patients with macular comorbidity.

Optic nerve head topographical measurements

A recent study compared ONH measurements obtained by OCT and confocal scanning laser ophthalmoscopy (HRT, Heidelberg Retina Tomograph, Heildelberg Engineering) in glaucoma patients, glaucoma suspects, and normal individuals. A fair to moderate correlation was found between the results obtained with the two instruments for disc area, cup/disc area ratio, cup area, cup volume and rim volume, with R^2 ranging from 12-72%.[28] In the same study, Stratus OCT ONH parameters were able to discriminate between patients with glaucomatous visual field defects and healthy eyes with ROC curve areas ranging from 0.54-0.76.[28] The areas under the ROC curves were comparable to those obtained with the HRT parameters.[28]

The utility of the topographical evaluation of the ONH with OCT for glaucoma diagnosis and monitoring still needs to be evaluated further. As the automatic algorithm for detection of the disc margin is based on the determination of the end of the RPE/choriocapillaris layer, it is possible that disc margin evaluation will be influenced by changes in these layers, since it may occur in progressive peripapillary atrophy in glaucoma.[29] Although the Stratus OCT also provides a manual option for disc margin determination, the influence of progressive optic disc changes on disc margin and reference plane determination with OCT still needs to be addressed.

Detection of longitudinal change

Currently, there is little published evidence that OCT is able to detect changes in RNFL thickness over time, although studies describing the reproducibility/variability of OCT measurements in healthy eyes (see below) suggest that change detection may prove acceptable. Longitudinal changes in OCT RNFL measurements were reported in a case of traumatic optic neuropathy,[30] and also following IOP reduction after trabeculectomy.[31]

Reproducibility

OCT RNFL measurements show good reproducibility with intraclass coefficients of approximately 0.55, and coefficients of variation of approximately 10%.[32-34] Fair to moderate agreement (kappa = 0.51-0.73) was found between expert observers for classifying OCT clinical printouts as healthy or glaucomatous with fair sensitivities (76-79%) and specificities (68-81%).[35]

Stratus OCT reproducibility data have not yet been reported. As mentioned above, the Stratus OCT is able to obtain a larger number of RNFL measurements around the optic nerve than previous versions of the OCT, and therefore may have better reproducibility.

Effect of IOP change, media and refraction

OCT RNFL thickness measurements increase after trabeculectomy-induced IOP reduction in glaucomatous eyes. A significant increase in overall mean RNFL thickness after trabeculectomy, related to the magnitude of IOP reduction, was demonstrated in glaucoma patients.[31] OCT RNFL measurements are not affected by refraction changes within ± 5.0 D.

Environment for use

OCT is usable in clinical practices without geographical restrictions, although in some markets, instrument price is likely to be restrictive. The technique requires a competent, experienced operator.

Pitfalls and limitations

There is evidence that the current OCT algorithm to detect the boundaries of RNFL is still imperfect. Previous work has demonstrated that the current algorithm tends to determine RNFL borders falsely in some situations, especially when RNFL reflectivity is low, as may occur in glaucomatous patients.[36] A new algorithm has been proposed, based on the search for and evaluation of

peaks of reflectivity of the OCT image, which provided a better detection of RNFL borders than the currently employed algorithm.[36]

In the presence of substantial media or lenticular opacities, scanning with OCT is challenging. Although it has been suggested that no pupillary dilation is required for imaging with the Stratus OCT in patients with pupil diameter >2 mm, there are no studies available reporting on the percentage of patients (with or without media opacities) who require pupillary dilation for good image acquisition.

Currently the Stratus OCT does not provide real-time feedback on image quality. Good quality images should have a focused fundus image and centered optic disc. The signal-to-noise ratio also should be acceptable. There are no reports on the proportion of patients with usable scans.

Percentage of glaucoma patients in whom satisfactory results can be obtained

There are no data in the literature as to the percentage of glaucoma patients in whom satisfactory results can be obtained. At the current time, there is no evidence to support the use of this instrument for glaucoma screening, and there are insufficient data on its ability to detect damage in glaucoma suspects or to differentiate early, moderate, and severe glaucomatous visual field loss.

Conclusions

OCT is a high-resolution imaging device with good reproducibility of the measured data and may be a useful tool to help distinguish between normal and glaucomatous eyes. The available longitudinal data are insufficient to come to any conclusions about the ability of OCT to detect change over time.

Unanswered questions

- Can OCT detect glaucomatous RNFL damage before SAP and/or ganglion cell specific function tests?
- Is OCT useful for glaucoma follow-up (including the requirement of long-term reproducibility)?
- What is the predictive value of OCT measurements in ocular hypertensives and glaucoma suspects?
- How do OCT RNFL measurements correlate with histologically determined RNFL thickness in human eyes?

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STANDARD AUTOMATED PERIMETRY (SAP)

Anders Heijl, Boel Bengtsson, Mike Patella and John Wild

Anders Heijl

Summary

- Standard automated perimetry (SAP) is our oldest and best documented, computerized, subjective visual function test, and measures differential sensitivity to white light.
- SAP is widely available and can be used in the vast majority of patients with manifest or suspect glaucoma.
- Clinicians can use SAP results to understand patients' subjective visual symptoms and problems.
- There are several different sets of criteria that define early glaucomatous defects, but they are all similar and use clustered points with reduced sensitivity or sensitivity differences between the superior and inferior hemifields.
- Many tools for computer-assisted analyses of single fields or series of fields are available for SAP. Such tools are based on large databases of normal subjects and glaucoma patients, and include probability maps, change probability maps, tools to reduce effects of media opacities (the pattern deviation concept) and perimetric learning, hemifield tests and regression analyses.
- There are several different sets of criteria for judging the progression by SAP that have been used in large randomized trials. Newer approaches seem to be more sensitive than older ones. It is likely that such methods will improve further, and that we will see this sooner with SAP than with other functional tests, due to the huge amount of knowledge on SAP.
- Due to variability, repeated testing is necessary for early detection and progression; this is true for SAP and for other diagnostic methods as well, both for other visual function tests and for methods based on photographic or digital images.
- Not all visual field testing modalities reveal early changes at the same time, but the order between test modalities (SAP, SWAP, FDT) seems to differ between patients. Available published studies indicate that SWAP, on average, can detect field loss prior to SAP, but there is no such evidence for FDT.
- More studies are needed to determine the performance of different types of field tests in early glaucoma, but such studies are difficult, time-consuming, and need meticulous attention to design and to the comparability of interpretation criteria.
- SAP sensitivity to detect early defects was smaller than that of stereo photographs in OHTS, but its sensitivity to detect progression was much higher than that of disc analysis in EMGT.

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What is standard automated perimetry?

Standard automated perimetry (SAP) is automated static perimetry performed under specific standardized testing conditions in the central 30 degrees of the visual field. Goldmann Size III (0.43 degrees) white light stimuli are presented against a 10 Cd/m^2 white background. In the most widely accepted version, stimulus duration is usually fixed at 100 or 200 msec. SAP is performed using defined testing strategies. Threshold tests are commonly used for both detection and the follow-up of glaucoma patients. Screening tests are meant for detection only, and are normally used in non-glaucoma clinical settings, and mostly in clinical settings lacking ophthalmologists.

How does SAP work?

Threshold SAP measures local contrast sensitivities at multiple locations in the peripheral visual field. Patients are required to press a response button whenever a stimulus is seen, and stimulus strength is increased or decreased on the basis of patient responses, in order to determine the minimum brightness that can be seen at pre-defined test-point locations. Sensitivity is usually measured at 50 to 80 test point locations in the area within 30 degrees of fixation. Results are compared with age-corrected ranges of normal sensitivity specific to the strategy used.

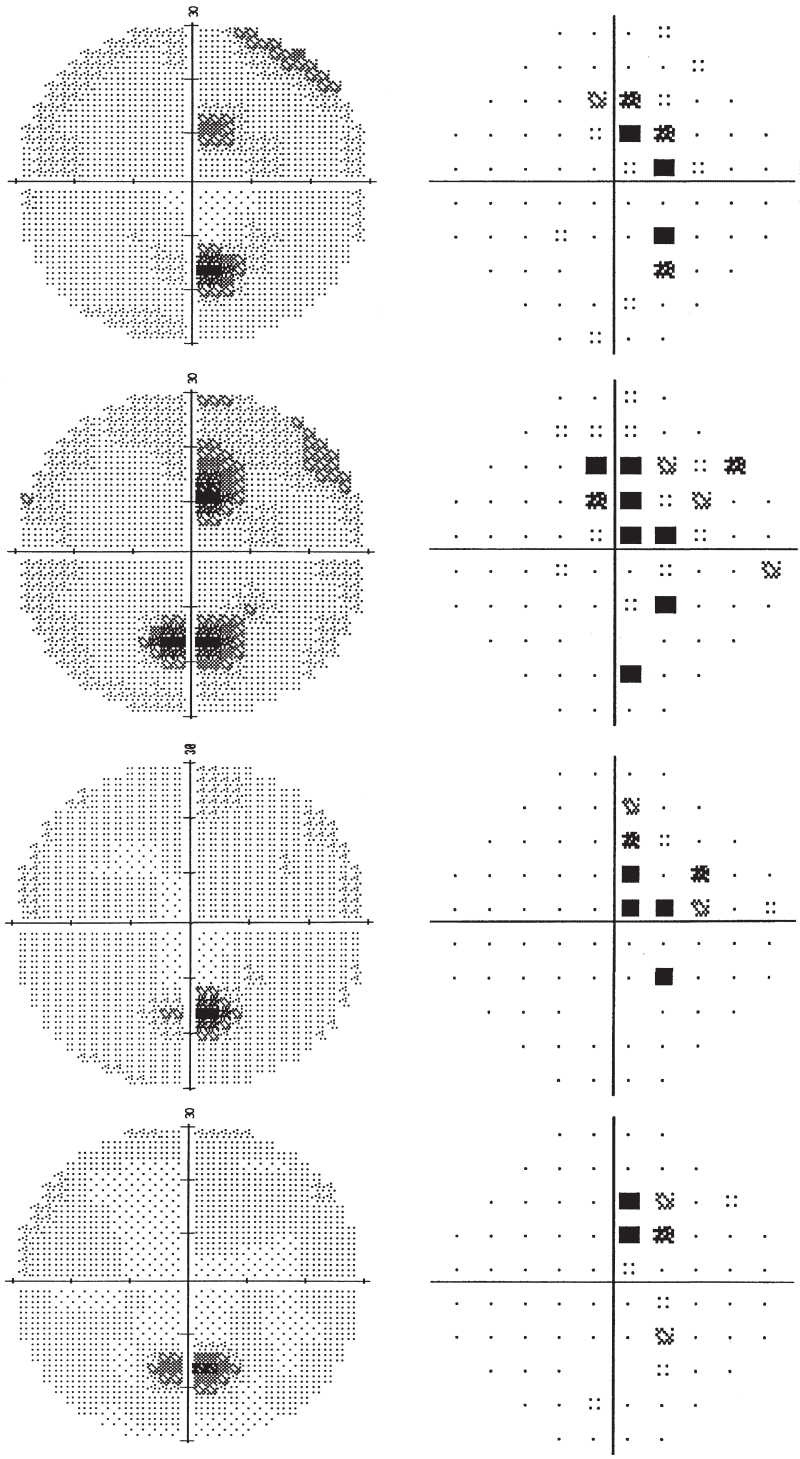

Fig. 1. There are many tools available for computer-assisted interpretation of SAP fields. Here is one example, where probability maps clearly indicate beginning glaucomatous visual field loss earlier than conventional grey-scale representations.

What is the reproducibility of SAP?

The reproducibility of threshold SAP has been studied extensively. The effects of eccentricity, general field status and test location status upon reproducibility are complex, but have all been defined, and cannot be described in simple tables.[1] Reproducibility is generally best in the paracentral field, best in fields that, overall, are closer to normality than abnormal ones, and best in test points that are nearly normal versus points that are highly damaged. Reproducibility also improves with increasing stimulus size, although the overall diagnostic performance of larger stimuli has not been documented. Reproducibility also depends upon the specific testing algorithm used, and significance limits for clinically significant change have been documented for the most commonly used algorithms.

Variability of SAP

The fact that most field defects in OHTS could not been confirmed on re-testing does not mean that most pathological fields need confirmation. OHTS tested and re-tested a large cohort which was preselected because fields and disc findings were initially normal. Less than 5% of the whole population developed any signs of glaucoma damage during five years of follow-up. Thus, the incidence of field loss was approximately 1/2% per eye per year, or in other words, a true incidence of any glaucoma damage of 1/4% per test. In such a situation, it is not surprising that the specificity of initial field loss becomes low, and that most fields judged to be pathological by the reading center were not verified on re-testing. It would have taken a specificity of over 99% for that not to happen, and few, if any, tests offer such specificity even with conservative interpretation criteria. The situation is very different for clinical glaucoma care where most patients often already have very well-established damage at their first visit, but also in the group of 402 newly diagnosed patients, of 33,000 screened for EMGT we found that the average damage of previously undetected glaucoma represented very manifest disease (median MD = -8.0 dB, -11.5 dB in patients with bilateral glaucoma).[2] Several clinical trials have determined that early recognition of progression must be based on repeated testing, and suitable interpretation criteria have been developed for those studies (*cf.* below).

What is the minimal damage that can be detected?

Measurements of ganglion cell counts in human glaucomatous eye-bank eyes for which SAP fields were available showed highly significant localized scotomas ($p < 0.5\%$) to be associated with local ganglion cell losses of the order of

29%. Overall ganglion cell loss for the entire retina in these eyes averaged 10.2%,[3] a value much lower than the 50% ganglion cell losses value associated with earlier evaluations in glaucomatous eyes that had undergone manual perimetric testing.[4]

SAP testing in rhesus monkeys has found that there is no proportional relationship between visual sensitivity and ganglion cell loss in either SAP or monochromatic perimetry.[5] Comparisons of SAP with pattern electro-retinogram and optic nerve topography found a continuous structure-function relationship, suggesting that the impression of a functional reserve results from logarithmic (dB) scaling of the visual field.[6] One possible implication of these findings is that the minimal damage that can be detected may simply be a function of the range of normality associated with current versions of SAP. Therefore, it is possible, but not at all certain, that testing algorithms which further reduce the range of normality may well provide further improvement of sensitivity to damage. Also, testing/analysis methods that more precisely compare baseline with follow-up may hold promise for very early detection.

There are several reports indicating that SWAP can detect glaucomatous visual field loss before SAP, but more studies are needed in this area. Results of comparisons with FDT are variable; thus, there are publications to support that FDT could be an earlier detector, but also results pointing in the opposite direction.

What is the sensitivity/specificity of current versions of SAP for the detection of early/moderate/advanced damage?

Assessment of threshold SAP sensitivity for the detection of early, moderate and advanced damage clearly depends upon disease definition, and is complicated by the fact that SAP is commonly incorporated into the definition of the disease. The previously cited histological studies[3] might be interpreted to suggest rather encouraging sensitivity to early glaucoma – in which localized losses of 29% of ganglion cells were correlated with localized visual field defects, which were highly significant relative to normative limits ($p < 0.5\%$).

The numbers for sensitivity and specificity at various stages depend on the definition of the stages, but also on the interpretation criteria. Very high sensitivity can be combined with high specificity at moderate stages of glaucoma; at advanced stages, very high sensitivity can be combined with very high specificity. At the earliest stage of glaucoma (disc hemorrhages only), all functional methods may give negative results, and often also, all structural methods will be negative.

What is the sensitivity/specificity for measuring progression?

Increased test-retest threshold variability at test points located in areas with depressed sensitivity[1] complicate the measurements of progression. Different methods for measuring progression have been suggested which take variability into account, such as trend analysis using pointwise linear regression and event analysis defining progression as changes larger than expected random variability of baseline pairs of fields. By applying well-specified criteria[7,8] for such analyses, progression can be measured with both high sensitivity and high specificity. In EMGT, SAP progression occurred much earlier than disc progression,[9] and was sustainable in the vast majority of eyes.

Sensitivity of SAP

It is likely that, on average, early glaucoma may be detected somewhat earlier using good stereo photographs from an expert reading center – in a group of glaucoma suspects with initially perfect field and discs – as in OHTS.[10] However, we must also agree that not all disc outcomes may be true, and that after longer follow-up sustainability should be reported and compared for both disc and field findings. Imaging is commonly and erroneously often thought of as being free from variability. Funk *et al.* recently published a very interesting comparison between SAP and HRT in glaucoma follow-up.[11] Their conclusion was simple, but carries a strong message: "The long-term variability of HRT parameters is in the same range as the long-term variability of visual field parameters. Since it is now widely accepted that visual field changes over time should be reproduced at least once or twice before clinical consequences can be drawn, the same should be postulated for HRT changes over time."

The sensitivity of OHTS disc analysis is based on comparisons with baseline photographs. We compared flicker chronoscopy and SAP in high risk ocular hypertension defined as elevated intraocular pressure (IOP), but with normal fields (but where some eyes already had suspect discs at baseline). In that study, field defects and changes in disc topography were usually noted at about the same time, and only one of 131 eyes developed field defects without concomitant alteration of disc anatomy, and on the other side, disc change without field change occurred in just two of 131 eyes.[12] In a more clinical situation and without baseline data, the results of subjective disc analysis are not always impressive. Thus, we found an average sensitivity of 76% in eyes with established and reproducible field loss on SAP, and only 58% in eyes that were in the lowest quartile of disc size.[13]

There is no perfect agreement on progression criteria, and such criteria can and need to be developed further. There is plenty of experience in defining perimetric endpoints using numeric, non-subjective criteria from, for example, the AGIS, CNTGS, CIGTS and EMGT studies. The criteria used in those stud-

ies have similarities and yield quite specific results. It seems clear that change probability maps may offer somewhat higher sensitivity than approaches based on dB changes or scoring in ordinary probability maps. Of course, there is also the possibility that criteria could be tailored to the needs of individual patients/doctors. For such criteria to be useful for practicing ophthalmologists, they should be offered with perimeters.

Studies available

SAP has been studied more extensively than any other commonly-used glaucoma diagnostic tool. To date, several thousand papers cited on Medline address this testing method.

How strong is the evidence?

Sensitivity and specificity depend on the criteria used for analysis, and on the populations studied. Thus, such figures cannot be directly compared to results obtained with other methods in other study populations. There is strong evidence that SAP is more sensitive to glaucomatous damage than manual perimetry. There is also strong evidence that sensitivity and specificity differ between test algorithms.

Quality of life and SAP

Patients' quality of life seems to be affected more by the fear of the consequences of glaucoma than by the disease itself.[14] Thus, a diagnosis of glaucoma should not be made on vague grounds, and quality of life is in jeopardy if we use more and more equipment with low specificity or if we use the indications of only one test (when others are negative) to establish a diagnosis of glaucoma. There are few patients who will truly benefit from a very early diagnosis, and we should not accept false positive diagnoses in patients other than those who need a very early diagnosis.[15] However, we can use a negative SAP field in a way that will not jeopardize quality of life – to be able tell patients that they do not have manifest glaucoma, which patients may find comforting.

More frequent field testing (during the two first years of established glaucoma in order to assess rate of progression) may also be good for quality of life, since we may then avoid initial over-treatment, while at the same time being able to assure the patient that we will find early progression, so that we can intensify treatment down the line if needed. Frequent SAP testing can identify progression early – less than 2 dB worsening in EMGT.[8] Conversely, when a

patient has been found to be stable or almost stable on SAP over long-term follow-up, there is no further need for frequent field tests unless IOP changes considerably. It is likely that SAP should be administered by one test every one to two years after ten years of follow-up, but by three tests per year during the first two years or so.

Pros and cons

Pros

- SAP is widely available worldwide
- it is standardized
- it has been extensively and well studied, with much longer experience than most other technologies
- it is generally accepted and reasonably well understood by practitioners; field defects resulting from causes other than glaucoma can often be separated by the ophthalmologist, based on defect shape and location
- it uses extensive and widely accepted interpretation tools
- it has a short examination time
- it is applicable in the vast majority of glaucoma patients, *i.e.*, also in eyes with concomitant cataract.
- the percentage of patients producing clinically useless or misleading results, or who cannot be tested, is low
- SAP can be administered by personnel with only limited training
- it is non-invasive and there is no need for dilatation; there are no safety issues
- the results are very useful in the assessment of visual handicaps and glaucoma blindness

Cons

- SAP be relatively time-consuming if applied using out-of-date testing strategies
- it often does not pick up the earliest signs of glaucoma, and SWAP is often an earlier detector
- results from patients who have not been properly instructed or monitored can be useless or misleading

Practical implications

SAP is certainly the preferable technique if there is only one type of functional test available, since it can be used for the diagnosis of glaucoma, for follow-up, as well as for the assessment of visual handicaps. SAP is probably the only functional test that has been studied so frequently with regard to follow-up that

general recommendations for its interpretation and use can be issued based on published data.

Potential for screening

The potential for screening is very good if the goal is to detect early to moderate damage, rather than the very earliest changes. Currently, many screening programs originally designed for clinical use are threshold-related. Screening levels are then often elected by threshold determination at a few initial test points or by the age-corrected normal reference field. Simpler approaches would be preferable for population screening, possibly exploiting age-corrected normal limits. A very rapid test with a low number of points might be preferable.

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COMMENT ON STANDARD AUTOMATED PERIMETRY – I

Douglas R. Anderson

Douglas R. Anderson

Standard automated perimetry (SAP) is, in fact, standard. Nearly every glaucoma patient or suspect undergoes a test to determine the threshold visibility of a stationary white stimulus against a white background, with computer assistance, which also produces a report of raw and statistically analyzed results. Newer diagnostic methods may ultimately prove better for some or many clinical purposes, but SAP has the longest track record. It is also available and familiar to all clinicians, who recognize its common artifacts and pitfalls. Mathematical analyses that assist the clinical decisions are more fully validated than for alternative methods. Information is easily exchanged in a familiar format between physicians when patients have several physicians involved in their care.

Relative standardization resulted when only a few automated perimeters remained popular. Their printouts are similar and qualitatively comparable, even if quantitatively these are not exactly the same. As each company makes improvements, even comparisons of fields done with the same machine, but with different testing algorithms, must be done with care.

There are two distinct uses for SAP. One is diagnostic and depends on documenting the range of normal variation. Diagnosis depends not only on the machine, but also on the criteria applied to the test results. If a quantified value or characteristic is infrequent among the non-diseased population, it is taken to represent disease. A better approach includes determining the proportion of those with the particular finding who have glaucoma, but agreeing on cases of mild or emerging glaucoma to be included in the reference population is an unresolved challenge. When glaucomatous damage is just beginning, it is unavoidably difficult to distinguish an eye with early disease from an outlier among the normal population.

The second use for SAP is for monitoring the eye for progression. For this, the range of normal values is irrelevant. What matters is the retest consistency of the traits or quantities being evaluated. With repeated follow-up testing, nearly any amount of change can occur by chance, as an unrecognized testing

Glaucoma Diagnosis. Structure and Function, pp. 93-94
edited by Robert N. Weinreb and Erik L. Greve

error or artifact. Therefore, confirmation by a repeat test or corroborating clinical findings is required.

For SAP and other techniques, manifestations of glaucoma vary. One patient may show one feature as glaucoma develops or progresses, and another may show a different feature as the earliest or main characteristic. In order to document abnormality or change in all patients, several tests and criteria may have to be explored to find the one that shows a definitive finding.

Finally, because the goal of diagnostic tests is to detect and highlight subtle abnormalities or minimal progression, the test result may not relate well to visual symptoms or to the impact on daily activities. In particular, 0 dB threshold sensitivity may or may not be a totally blind location. Large regions may be completely black on a gray-scale display, but be a region in which fingers are easily counted. In such cases, the patient may be able to detect peripheral objects in the environment, not running into objects or people as they walk. In contrast, a small defect, not necessarily deep, located just below fixation may be quite disturbing when reading.

COMMENT ON STANDARD AUTOMATED PERIMETRY – II

Balwantray C. Chauhan

Balwantray C. Chauhan

Conventional standard automated perimetry (SAP) is the most widely used technique for measuring the visual field in glaucoma and many other ocular diseases. It was developed after decades of experience with kinetic perimetry and manual static perimetric techniques using the Goldmann, Tübingen, and other perimeters. Modern methods for estimating thresholds have dramatically reduced test time, a major impediment for SAP and indeed for other perimetric techniques.

Clinical and scientific evidence has shown a discordance between structural changes in the optic disc and/or retinal nerve fiber layer (RNFL) and findings with SAP, in both the detection of the disease and its progression. The question arising from these observations was whether SAP was efficient in detecting the earliest functional changes in the disease. There are several problems in comparing changes between the visual field and the optic disc and/or RNFL in scientific studies (see article by Chauhan in this issue), however, it may be more feasible to compare different visual field techniques for detecting the presence of the earliest glaucomatous visual field defects and their progression.

To date, there are a limited number of longitudinal studies that compare SAP to other tests. The latter include short-wavelength automated perimetry (SWAP), high-pass resolution perimetry (HRP), and pattern discrimination perimetry (PDP). While these prospective studies have several limitations, there is evidence from two independent centers that SWAP detects visual field damage,[1,2] and its progression[3] earlier than SAP. Similarly, it has been shown that HRP detects progression earlier than SAP;[4] however, PDP detected progression later than SAP.[5] Interestingly, in another study, while changes with scanning laser tomography (SLT) were more than twice as frequent as SAP, SLT did not detect progression earlier than SAP.[6] These findings represent the difficulty in relating progressive events in one technique versus another. This problem is more apparent when a comparison is made between structural and functional tests.

Glaucoma Diagnosis. Structure and Function, pp. 95-96
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Studies have to demonstrate that a clinical intervention made on the basis of findings from a non-conventional perimetric technique, following detection of functional glaucomatous damage or its progression by means other than SAP, leads to a favorable outcome for the patient. The lack of evidence does not suggest that further characterization of the performance of these new tests for the detection of glaucoma or its progression is not useful. Indeed, the evidence to date for some of the techniques is convincing and demonstrates that SAP is likely to be insensitive to the earliest functional losses in glaucoma. While SAP will continue to be used in clinical practice for the foreseeable future, effort should be directed towards finding novel means to analyze data, not only from SAP, but also from other techniques.

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COMMENTARY ON STANDARD AUTOMATED PERIMETRY – III

Stefano Miglior

Stefano Miglior

Visual fields changes, based on standard automated perimetry (SAP) has become the reference examination to establish the presence of primary open angle glaucoma (POAG). Today, more than 20 years after the introduction of the first Octopus perimeter, the role of SAP in the diagnosis and follow up of POAG is still necessary.

The reasons for this rely on the fact that SAP: (1) is universally accepted in the ophthalmological community; (2) enables understanding of the loss of visual function in POAG patients; (3) is reasonably reproducible (once the patient is well trained); (4) enables follow-up of POAG with a high level of sensitivity and specificity. In addition, a visual field change detected by SAP represents the gold standard for assessing the clinical ability of other diagnostic tools which have recently been introduced to help in diagnosing and following up POAG patients.

Despite the experience and overall satisfaction of glaucoma specialists in evaluating SAP visual fields, it should be recognized that SAP does have some limitations, particularly when it is used for early diagnosis. Several robust observations have clearly indicated a lack of sensitivity in identifying early retinal nerve fiber layer (RNFL) loss, as well as early optic disc changes. Moreover, the sensitivity of SAP is lower than that of short wavelength perimetry (SWAP) in identifying early glaucoma-related functional changes. SAP does not perform well when its use is not appropriate, and the interpretation of visual field results is not accurate. In fact, some of its limiting factors are often underestimated: learning effect; reliability; long-term fluctuation; reproducibility of progressive changes.

Recent studies indicate that the sensitivity of Frequency Doubling Technology (FDT) is also higher than that for SAP. The limitation of SAP in the early diagnosis of POAG has a relevant clinical implication, as the results of both the OHTS and the EMGT indicate that the early diagnosis of POAG may have a favorable impact on the long-term prevention/treatment of the disease. In addition to its limited sensitivity for early glaucoma diagnosis, another rel-

Glaucoma Diagnosis. Structure and Function, pp. 97-98
edited by Robert N. Weinreb and Erik L. Greve

evant limitation is the lack of agreement in the definition(s) of visual field abnormalities which can be attributed to early POAG. Unfortunately, since POAG is often defined on the basis of SAP abnormalities, this may limit the real appreciation of its own clinical validity, as well as that of other newer technologies (imaging and function analyses). Despite these limitations for early diagnosis, SAP remains necessary for follow-up, and its clinical importance increases in the more advanced stages of glaucoma.

Therefore, SAP is still the reference examination for POAG-related change in visual function. It has a limited usefulness for early diagnosis, but still is needed to monitor POAG patients over time.

SHORT WAVELENGTH AUTOMATED PERIMETRY (SWAP)

Shaban Demirel, John Flanagan and Pamela Sample

Shaban Demirel

Summary

- Short wavelength automated perimetry (SWAP) is relatively more affected by pre-retinal factors, is more variable (both within a subject and within a population) and, as currently implemented, takes longer to perform than standard automated perimetry (SAP).
- Notwithstanding these limitations, there is still acceptable evidence and consensus of agreement that SWAP is able to detect glaucoma at an earlier stage than SAP.
- There is some evidence that not having a SWAP defect has a good negative predictive value for glaucoma.
- As currently configured, SWAP is not likely to be used in a primary setting, but it may be more clinically attractive with a rapid (SITA SWAP) threshold algorithm.
- Longitudinal studies are still needed to examine the ability of SWAP to follow glaucoma patients into moderate/advanced stages of glaucoma, as are studies to examine the use of SWAP in a screening setting.

Method

Short wavelength automated perimetry (SWAP) is performed as a 'yes-no' detection task. In most respects, SWAP is administered in a manner similar to standard automated perimetry (SAP). Most investigations have implemented SWAP using a full-threshold or FASTPAC thresholding algorithm,[1] but it has also been implemented as a screening test.[2] A rapid thresholding algorithm (SITA SWAP) has recently been described,[3] and should be released relatively soon.

Mechanism/how does it work?

SWAP assesses functioning of the short-wavelength sensitive (SWS) pathway comprised of the s-cones, the s-cone bipolars, the blue-yellow retinal ganglion cells, and its upstream cortical processing. This is accomplished by measuring the detection threshold for a relatively large (Goldmann size V) narrow-band

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short wavelength stimulus (centered on 440 nm) presented upon a bright, broadband yellow background (100 cd/m^2).[4] The background desensitizes the rod photoreceptors, middle-wavelength sensitive cones and long-wavelength sensitive cones, thus facilitating detection of the stimulus by the s-cones (see Fig. 1). It is still not known why testing the SWS pathway generates earlier detection of glaucomatous functional damage, as it appears that SWAP monitors the

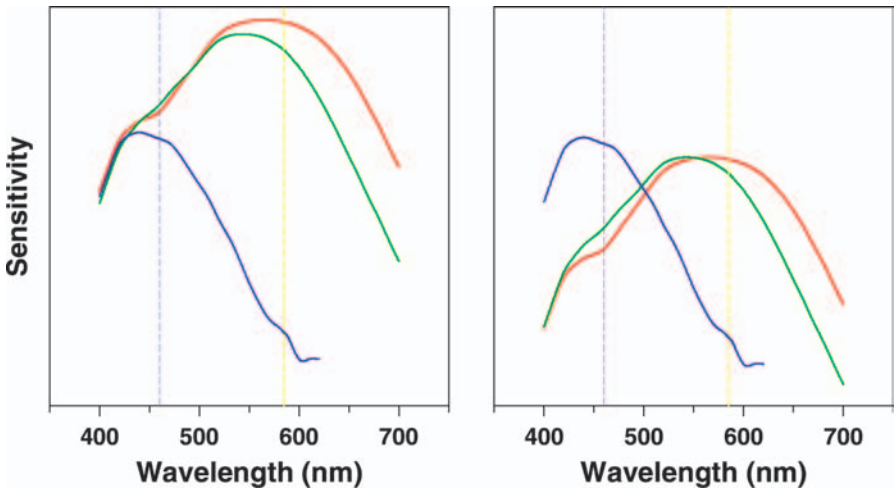

Fig. 1. The left panel shows the relative sensitivity of the long wavelength-sensitive (red curve), medium wavelength-sensitive (green curve) and short wavelength-sensitive cones (blue curve) under dim, neutral illumination, such as the background in standard automated perimetry. It can be seen that the l and m cones are more sensitive to short wavelengths (blue vertical dashed line) than the s cones. The right panel shows the effect of the bright yellow background used in SWAP, which is to decrease the sensitivity of the l and m cones, leaving the s cones now more sensitive to the short wavelength stimulus.

same disease process as SAP.[5] Several candidate hypotheses have been advanced.[6-8]

Instrumentation

SWAP is performed using the same instrumentation and programs as SAP. Different colored filters are used for the stimulus and background, and a different background intensity is also employed.[4]

Pitfalls and limitations

Limitations to SWAP testing are a relatively greater influence of pre-retinal light absorption on test results, and greater variability. Lens yellowing, light scatter[9,10] and macular pigmentation differences[11] within the population produce wider limits of normality compared to SAP. There also appears to be greater short- and long-term psychophysical variability for vision mediated through the SWS pathway.[1, 12-14] Effects of pre-retinal absorption tend to be diffuse, or limited to the macular region. These factors make it unwise to pay much regard to SWAP total deviation values. Diffuse glaucomatous damage is difficult to detect with SWAP as pre-retinal factors confound this interpretation. For the best interpretation of SWAP results, lens density measurements should be made.[5,15-18] Alternatively, emphasis can be placed on asymmetry indices, such as the Glaucoma Hemifield Test (GHT).[19,20]

Percentage of glaucoma patients in whom satisfactory results can be obtained

These data do not appear in the literature. However, it can be assumed that SWAP will be less able to provide satisfactory results in patients with advanced glaucoma and coexisting significant cataract.[21]

Available studies

Many studies that investigate SWAP have been published. Laboratory science regarding the chromatic mechanisms involved and the amount of isolation are available.[4,22-26] Non-human primate studies looking at the effect of RGC loss on SWAP thresholds have been published.[27] Investigations of learning effects and effects of pre-retinal light absorption and cataract are available,[9-11,28,29] as are investigations of short- and long-term variability.[1,12,14,30,31] Prospective, cross-sectional and longitudinal clinical science studies examining the performance of SWAP compared to other forms of perimetry (SAP, HRP, motion, flicker

and FDT)[5,32-46] and electrophysiological techniques (PERG) are available.[44] Comparisons between SWAP and non-visual/structural indicators of glaucomatous loss (HRT, SLP, stereo nervehead photos, RNFL photos and clinician assessment) have been reported.[17,42,47-56] Studies examining the ability of SWAP to determine glaucomatous progression have also been performed and reported.[33,35]

Level of evidence (see Finnish Guidelines, Acta Opthalmologica 81:3, 2003)

Much of the evidence regarding SWAP is B-level evidence. Some studies represent C- and D-level evidence. Generally, studies regarding SWAP have been well controlled with moderately large numbers of participants, with many of them being prospective. Independent laboratories and investigators from many countries have generally reported homogeneous findings. Many studies on SWAP lack a non-functional classifier, *i.e.*, the test results are interpreted in the light of participant classification, based on another functional test.

Reproducibility

SWAP is more variable than SAP, both for short- and long-term fluctuation within an individual, and variability between individuals within a population.[1,12,14,30,31] SWAP also appears to have a more rapid age-related decline in sensitivity even when pre-retinal factors are accounted for.[57]

Sensitivity/specificity for early, moderate and advanced glaucoma, and for measuring progression

SWAP has good sensitivity and specificity when careful criteria are applied.[58,59] Many studies do not stratify the diagnostic performance by disease severity. Sensitivity and specificity for early damage have both been reported to be as high as 90%. One study has reported a lower sensitivity for early glaucoma in SWAP than SAP.[60] Reports of SWAP's ability to detect abnormal nerves, often with normal SAP, range from 18-74%, depending on the population and criteria used.

Effects of intraocular pressure changes, media, and refraction

There is some evidence that the effect of asymmetric intraocular pressure (IOP) on SWAP is similar to its effect on SAP.[61] The effects of media have been well investigated for SWAP. Generally, denser or yellower media reduce SWAP thresholds diffusely and limit the available mechanistic isolation. SWAP ap-

pears to be very resistant to the effect of refractive blur with minimal threshold change (approximately 2 dB) with up to 8 D of blur.[62] Chromatic aberration should result in best SWAP refractions being approximately 1 D more minus than best refraction for SAP.

Type of environment/setting where instrument is used

Physically, SWAP needs a moderately darkened environment to be administered effectively. It is suited to supplying additional information in patients with mild glaucoma or for use with glaucoma suspects. SWAP is currently not regarded as a tool for primary care, but is better suited to secondary and tertiary settings. It can be used to assist practitioners in deciding which patients are at highest risk of converting to glaucoma or those with glaucoma most likely to progress. It can therefore assist in the decision as to who are the best candidates for initiating therapy or who requires more aggressive therapy.

Conclusions

SWAP has been thoroughly investigated in laboratory and clinical science investigations. Study conclusions can be summarized as follows: SWAP is more variable than SAP both within individual patients and within the population; SWAP testing has been repeatedly shown to detect glaucomatous defects prior to SAP in many patients, in spite of its greater variability; mappable SWAP defects convey high predictive capacity for future SAP defects; SWAP testing may show earlier evidence of progression than SAP, although this is still contentious; the results of SWAP testing are more likely to mirror the early, subtle changes evident at the nerve head and in the retinal nerve fiber layer than SAP, particularly early in the glaucomatous disease process.

When/where should it be used

SWAP should be used in secondary and tertiary settings, and to provide additional information in glaucoma suspects and those at risk. With shorter test times and less variable algorithms (SITA SWAP), it may take on a primary role.

Unanswered questions

Firstly, the use of SWAP with a screening algorithm, although this may be less pressing with the advent of a faster thresholding algorithm. Only longitudinal

studies can address whether SWAP defects without glaucomatous optic neuropathy or SAP defects are predictive of future glaucoma. Another unanswered question is whether SWAP has sufficient mechanistic isolation to offer an alternate glaucoma change analysis, although there is evidence suggesting that SWAP isolation is likely to be maintained into moderate and perhaps even severe disease.[25]

Studies needed

Further investigation is needed into the ability of SWAP to quantify glaucoma progression, together with further investigation of normative databases appropriate for SWAP testing, particularly for the central ten degrees.

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FREQUENCY DOUBLING TECHNOLOGY (FDT) PERIMETRY

Chris A. Johnson, Murray Fingeret and Aiko Iwase

Chris A. Johnson

Summary

- Frequency doubling technology (FDT) testing has high sensitivity and specificity for the detection of retinal disease, glaucoma and neuro-ophthalmological disorders.
- FDT testing has many clinical benefits for those administering the test, and patients prefer it to other visual field test procedures.
- Some investigations indicate that FDT can detect early glaucomatous damage prior to standard automated perimetry, but additional studies would be desirable.
- FDT testing has a test/retest variability that is equal to or better than standard automated perimetry, especially for visual fields with sensitivity loss.
- Longitudinal studies for evaluating the ability of FDT to determine progressive visual field loss are needed.
- Further studies of new FDT test procedures, as implemented on the Humphrey Matrix, are also needed.

Method

Frequency doubling technology (FDT) perimetry uses a low spatial frequency (< 1 cycle per degree) sinusoidal grating as a target that undergoes high temporal frequency (> 15 Hz) counterphase flicker.[1] FDT targets are displayed at various positions in the central visual field and the observer's task is to press a response button each time a stimulus is detected. Both threshold and screening tests are available. The original FDT perimeter presents 17 (C-20 test, with four 10 x 10 degree targets per quadrant plus a five-degree diameter central stimulus) or 19 (N-30 test, using the C-20 targets plus two additional targets above and below the nasal horizontal midline at 20-30 degrees eccentricity) stimuli throughout the central visual field. The new FDT perimeter, called the Humphrey Matrix, has all the test procedures used by the original FDT perimeter plus four additional test patterns similar to the 30-2 (69 stimuli), 24-2 (55 stimuli), 10-2 (44 stimuli) and Macula (16 stimuli) tests. In order to produce these new stimulus patterns, the target size was reduced to 5 x 5 degrees, and

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the spatial and temporal characteristics were slightly altered. For the 10-2 and Macula tests, the procedure does not generate frequency doubled targets, and these tests predominantly evaluate flicker sensitivity. Flicker sensitivity refers to the ability to determine that a stimulus is undergoing light and dark alternations, rather than having stable illumination. Flicker sensitivity is the amount of contrast (difference between light and dark alternations) needed to distinguish alterations in stimulus luminance over time. Ganzfeld blankout and Troxler image fading refer to the reduced visibility of stimuli when all or most of the visual field is uniformly illuminated (Ganzfeld blankout) or a target is fixated for a prolonged period of time (Troxler image fading).

Threshold estimates for the Humphrey Matrix are obtained using the ZEST (zippy estimation of sequential thresholds) algorithm,[2] a procedure that is similar to the SITA (Swedish interactive threshold algorithm) procedure.[3] The Humphrey Matrix also has an eye monitor and improved capabilities for permanently storing and analyzing test results.

Mechanism

Maddess and Henry[4] reported that the frequency doubling effect was produced by a subset of retinal ganglion cells known as My cells that project to the magnocellular layers of the lateral geniculate nucleus and have nonlinear response properties. However, recent evidence[5] showed no electrophysiological support for a distinct My cell class in primates, and psychophysical human studies indicated that the frequency doubling effect was mediated by the interaction of more than one group of retinal ganglion cells at higher visual centers in conjunction with a loss of phase discrimination for high temporal frequen-

cies. Martin *et al.*,[6] also reported no evidence of a selective loss of specific types of retinal ganglion cells in glaucoma, as evidenced by frequency doubling and other perimetric tests.

Instrumentation

The FDT perimeter was launched about seven years ago by Welch Allyn (Skaneateles, NY) and Carl Zeiss Meditec (Dublin, CA). There are currently more than 10,000 of these instruments worldwide. The Humphrey Matrix was introduced in March 2003 (Figure 1).

Pitfalls

There are several factors other than neural deficits that can affect FDT test results, including cataract and other media opacities, high myopia, low background luminance, small pupils, Ganzfield blankout, experience and incomplete light adaptation.[7-12] In addition, FDT perimetry may provide less than optimal characterization of the vertical steps for chiasmal and post-chiasmal visual deficits.

Percentage of glaucoma patients who can provide results

Most patients prefer FDT perimetry to testing with conventional automated static perimetry, and find it easier to perform. As a general rule, it can be

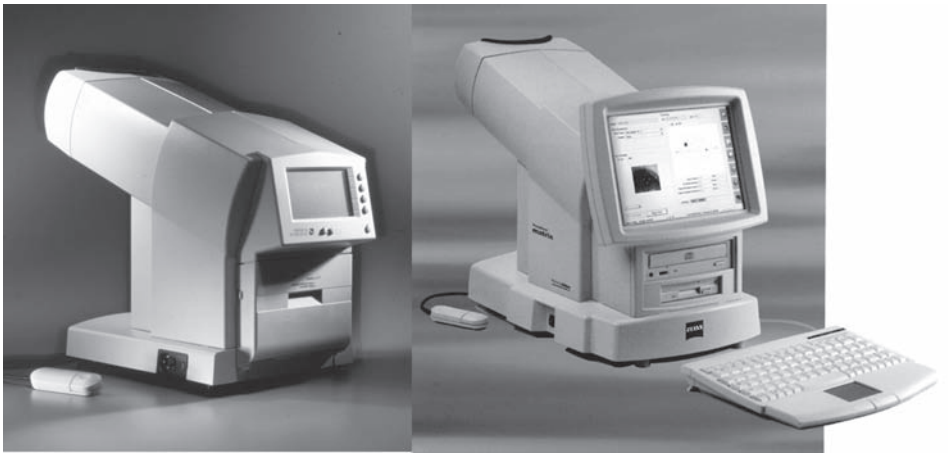

Fig. 1. The original Frequency Doubling Technology (FDT) perimeter (left) and the new Humphrey Matrix FDT perimeter (right).

assumed that individuals who are able to perform conventional static automated perimetry will also be able to undergo FDT perimetry. Some observers who are not able to perform conventional automated static perimetry will be able to perform FDT perimetry. Although ocular dominance and Troxler image fading influence the test procedure, test results do not appear to be influenced by them to any appreciable extent.

Available studies

There are a number of investigations that have now been reported for the original FDT perimeter and its use for various ocular and neurological disorders, which are summarized in a recent publication.[12] Most of these studies report very good sensitivity and specificity for the detection of visual field loss produced by retinal, optic nerve, chiasmal and post-chiasmal disorders. FDT can also be used successfully to test older patients and young children. Most publications indicate that FDT perimetry is an effective procedure for screening for ocular and neurological disorders. There are two rapid screening procedures for FDT, which take between 30 and 90 seconds per eye to complete, and which have good sensitivity and specificity (85% or higher).

Level of evidence

Using the Finnish evidence-based guidelines for open angle glaucoma, most studies of the original FDT perimeter provide evidence in grade A to B for studies describing the detection of glaucomatous visual field loss and perimetric deficits produced by other ocular and neurological disorders. The Humphrey Matrix FDT device is new, and therefore difficult to classify at this time.

Reproducibility

Recent investigations have reported that FDT perimetry demonstrates very good short- and long-term variability. For the original FDT perimeter tests and the new 24-2 test procedure, there is only a modest increase in test-retest variability (20-30%) for damaged visual field locations, compared to the substantial (250-350%) increases in variability for evaluation of moderate visual field loss with conventional automated static perimetry.[14-17]

Sensitivity/specificity

For threshold estimates in a clinical setting, most studies report very good sensitivity and specificity for the ability of FDT perimetry to detect visual field

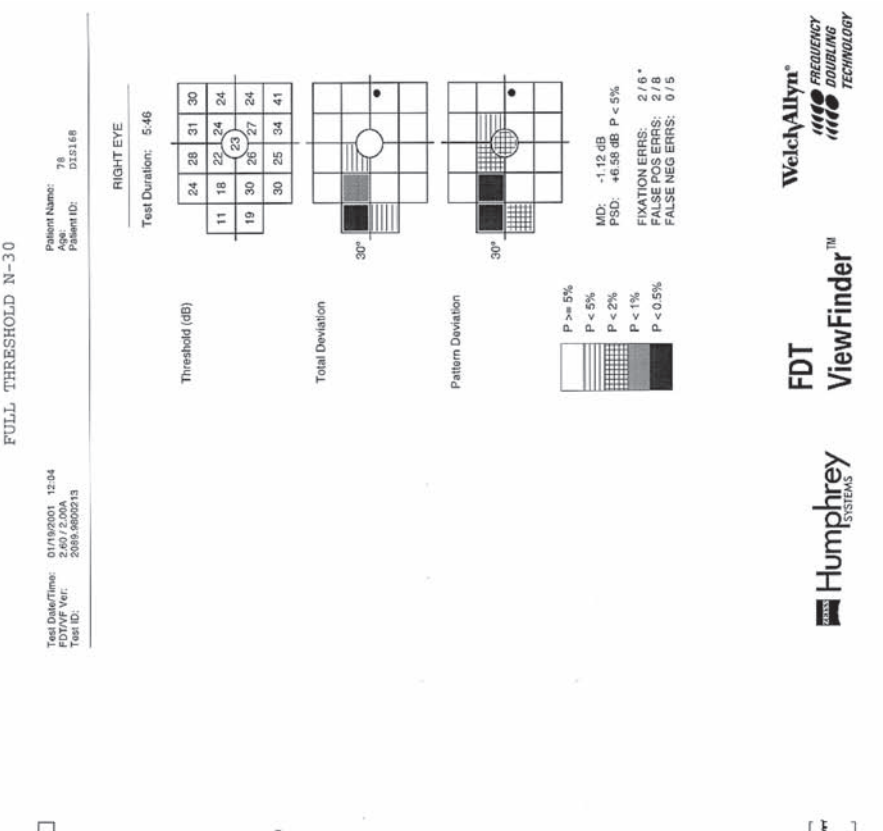

Fig. 2. Humphrey Field Analyzer SITA-Standard results (bottom) and FDT results (top) for the right eye of a patient with a superior arcuate nerve fiber bundle defect from glaucoma.

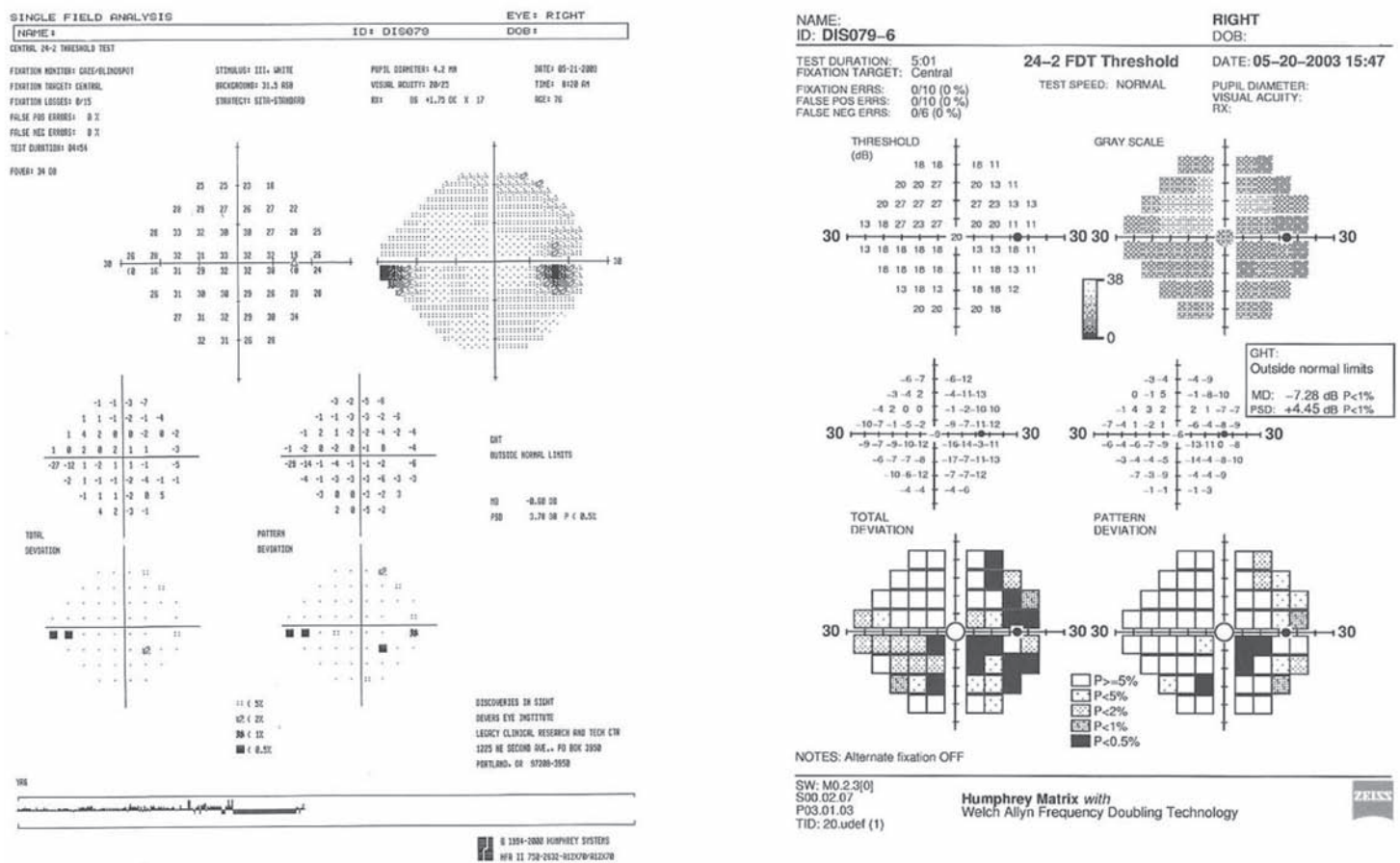

Fig. 3. Humphrey Field Analyzer SITA-Standard results (bottom) and Humphrey Matrix 24-2 FDT results (top) for the right eye of a patient with an inferior partial arcuate glaucomatous visual field defect.

loss in a variety of ocular and neurological disorders (summarized in Anderson and Johnson[12]). Rapid screening procedures exhibit modestly lower sensitivity and specificity values, and screening FDT tests performed for a general population under non-optimal test conditions yield poorer sensitivity and specificity results. FDT perimetry appears to be able to distinguish very well between mild, moderate, and severe visual field loss.[1,18,19] For moderate and advanced glaucoma, sensitivity and specificity are better than 95%. For early glaucoma, sensitivity is about 85% or higher, and specificity about 90% or better. In comparison to standard automated perimetry (SAP) and short wavelength automated perimetry (SWAP), FDT perimetry has been shown to be able to detect glaucomatous visual field loss modestly better.[20] (See Figures 2 and 3.)

Measuring the progression of glaucoma

At the present time, there is only limited information available on the ability of FDT perimetry to evaluate the progression of glaucomatous visual field loss, and there is no information on the reversibility of FDT sensitivity loss related to treatment. Presently, there is insufficient data to estimate the minimum number of fibers damaged when the first FDT abnormality is detected. Also, there is a new FDT device (Humphrey Matrix) that has just been developed with new test presentation patterns and strategies. When more research becomes available for this device, we may be able to obtain additional information about early FDT losses in relation to fiber damage.

Effects of intraocular pressure, refraction, and media

To date, there is limited evidence as to whether or not intraocular pressure (IOP) variations affect FDT test results. Cataract and other media opacities tend to reduce stimulus contrast and degrade FDT sensitivity.[21] Although high refractive errors (6 D or more for the original FDT perimeter, 3 D for the Humphrey Matrix) will diminish FDT sensitivity, lower refractive errors have a negligible influence on FDT results.[12,13,21,22]

Type of environment/setting

As a general rule, FDT perimetry can be performed in a variety of settings. The FDT device is constructed in a manner that restricts the amount of ambient room light presented to the eye during testing. In most circumstances, this provides a satisfactory test environment. If ambient light levels are too high, the FDT device has a monitoring system that generates a warning message. FDT testing that is performed under unusual circumstances (*e.g.*, outdoors in

the midday sun) may require the use of a shroud or light occlusion device to be placed around the FDT perimeter and the observer.

Conclusions

The original FDT perimeter has been shown to be a useful instrument for the detection and evaluation of visual field loss. It has been shown to be a rapid and easy-to-use perimetric device. At the present time, there are several areas in which additional studies are needed. The limited amount of longitudinal information concerning FDT should be addressed by new investigations. Also, the development of more statistical analysis packages for FDT perimetry would be useful, as would evaluation of the new Humphrey Matrix.

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COMPARISON OF FUNCTIONAL METHODS

Pamela Sample, Balwantray Chauhan, Makoto Araie and Chris A. Johnson

Pamela Sample

Summary

- Functional testing to detect abnormality and documentation is essential and should be performed in all patients.
- It is unlikely that one functional test covers the whole dynamic range.
- There is little evidence to support the use of a particular selective visual function test over another in clinical practice because there are few studies with adequate comparisons.
- With an appropriate normative database, there is good evidence for SWAP and some evidence for frequency doubling technology (FDT) for improved early diagnosis.
- Standard automated perimetry (SAP) is not optimal for early detection; further studies are needed.

Intra-function working group position

Methods

In this section, we will cover the comparison of methods for evaluating visual function in glaucoma. The emphasis will be placed on the three clinically and commercially available, standardized procedures of standard automated perimetry (SAP), short-wavelength automated perimetry (SWAP) and frequency doubling technology perimetry (FDT), which were discussed by the consensus 1 groups. Other tests such as high-pass resolution, flicker, motion perimetry, peripheral displacement and pattern displacement perimetry have also been described in the literature. The newer tests, FDT and SWAP, had already been compared individually to SAP by the earlier consensus stage, so this report will focus on comparisons among the three, and in some instances with other tests.

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Mechanisms/how do comparisons work?

There are two primary goals for studies comparing various visual function tests. The first is to determine the relative utility of the tests for the diagnosis and follow-up of glaucoma. The second is to understand the relative effects of glaucoma on retinal ganglion cell populations, although it is also important to determine this from a histopathological perspective. As was mentioned by the consensus 1 groups, SAP's target is detectable by all three of the main ganglion cell subtypes, the magnocellular, parvocellular, and small bistratified ganglion cells that project through the primary visual pathway. On the other hand, SWAP and FDT are visual function-specific tests designed to primarily assess vision mediated by only one ganglion cell subtype. This holds until some level of deficit allows another subtype to assist with detection of the target. For example, approximately 15 dB of sensitivity must be lost for the SWAP target before the next most sensitive system will take over detection.

Instrumentation

Already described in previous section.

Pitfalls and limitations

Limitation: As mentioned in the previous section, the main limitation of intra-function comparison studies is that many use SAP either to classify the sub-

jects included in the study or as the 'gold standard' against which the other tests are compared. This assumes that SAP is the best and that no other test will ever perform as well. Conversely, when patients are selected as being normal on SAP and then the percentage of those found to be abnormal on the visual function specific tests is computed, SAP suffers by comparison. There are few studies that have used a non-function 'gold standard'. They also have their limitations. For example, Sample *et al.*[1] (acceptable quality; single site study) used the presence of glaucomatous optic neuropathy as the 'gold standard' for glaucoma when comparing SAP, SWAP, FDT and motion perimetry. This allows for a fairer comparison of the different visual function tests, but limits the comparison to those with GON. Additionally, because of the potential overlap in optic disc appearance between glaucoma patients and healthy persons, there is a possibility of classification error in patients who are ostensibly normal by currently recognized definitions (*e.g.*, healthy looking discs and normal SAP field), but who show an abnormality on one of the visual function specific tests. Another study addressed the 'gold standard' issue in a different way[2] (acceptable quality, single site study, overlap in subjects for two gold standards). Separate evaluation of SWAP and FDT parameters, and of structural OCT and SLP parameters, was carried out using two different gold standards, one based on optic disc appearance (photos), the other on SAP fields. The results found that the most sensitive FDT parameters tended to be more sensitive than SWAP parameters at set specificities of ≥ 90% and ≥ 70%. ROC areas for FDT and SWAP when the optic disc was the gold standard were 0.88 and 0.78, respectively. When SAP used as the gold standard, these were 0.87 and 0.76, respectively. Structural measurements based on OCT were also more sensitive than SWAP measurements. However, the study also found very little agreement in diagnosis (normal versus glaucoma) among the instruments at specificities ≥ 90%.

Without an external and independent classifier of glaucoma, clinical studies may be subject to bias.

Remedy: Longitudinal follow-up to verify the progression of disease in those identified as abnormal without GON.

Limitation: The full threshold SWAP normative database included in STATPAC for Humphrey is not accurate[3] so that only centers with their own large normative databases can evaluate SWAP accurately.

Remedy: The normative database for SITA-SWAP should be accurate.

Limitation: The use of different versions of each test. For example, FDT has undergone several changes since its relatively recent introduction, going from program C-20 with only 17 locations, to the N-30 which added two locations in the nasal field, to its most recent program with a full 24-2 pattern, which mimics the 24-2 pattern with SAP. The switch from full threshold to SITA for SAP and soon for SWAP will also make ongoing longitudinal analyses difficult.

Remedy: Both the N-30 and 24-2 FDT are promising and should be compared to other functional and structural indicators of damage for their diagnostic sensitivity and for their ability to assess progressive loss of function. SITA and the expected improvements in SITA-SWAP mean we may have to wait for answers until longitudinal comparisons are available. Studies should also be performed on assessing the consequences of switching from full-threshold to SITA in follow-up.

Limitation: Learning effects of the newer tests are not addressed by sufficient practice to equal the experience with SAP, and abnormal results are not repeated to ensure that they are real.
Remedy: While many studies have addressed the learning effects of SWAP and FDT, there is a lack of consensus as to what constitutes adequate learning. Prospectively designed studies should carry out enough tests to ensure that there are sufficient examinations built into the protocol to allow for learning and confirmation of change.

Limitation: There may be some effect of IOP on visual function, *i.e.*, some of the fluctuation in test results may be due to fluctuations in IOP. This is suggested by results of FDT in a study in which 46% of OHT eyes were abnormal when healthy eyes showed a specificity of 88%.[1] However, to the best of our knowledge this has not been evaluated for any of the function tests.
Remedy: This needs to be evaluated in order to determine whether it is true. If it is true, studies are needed to determine whether it is a transient effect of IOP and whether all visual function tests are similarly affected.

Percentage of glaucoma patients in whom satisfactory results can be obtained

Already addressed in the chapters SAP, SWAP and FDT. Studies comparing tests are generally carried out on participants who are willing to enroll in research and to undergo several perimetric procedures over a short period of time.

Available studies

Only six studies were found[1-6] that offered comparisons of more than one visual function-specific test where SAP, SWAP and FDT are concerned (each visual function specific test compared individually to SAP was covered in the chapters on SWAP and FDT and one study compared SAP, FDT and high pass resolution perimetry (HPRP)).[7] Four of the six studies suffered from the lack of an identifiable gold standard that did not include one of the functional tests (lower quality). Only one of these tests addressed this in part by longitudinal follow-up, but only in part because progression on SAP was used as the gold standard.[4]

Level of evidence

None of the studies met the higher quality classification, since progressive optic nerve damage was not used as the gold standard. The few comparisons studies were of lower or acceptable quality. At this time, no-one is really proposing the use of only one visual function test versus another for clinical use in the diagnosis and management of glaucoma. However, for understanding the loss of ganglion cell function, four studies have addressed this.[1,4,7,8] Only two studies have reported sensitivity for SAP, SWAP, and FDT in eyes with GON not specific for level of severity, but with specificity set near 90%.[1,2] These single site studies are of acceptable quality. In another acceptable study, glaucomatous progression was defined by progressive SAP defects rather than by optic nerve structural progression.[4] The findings from these studies supported the notion that both magnocellular and small bistratified cells are affected early in glaucoma. Furthermore, there are two studies that include comparisons between visual function specific tests targeting the parvocellular ganglion cells (*e.g.*, HRP) and those targeting magnocellular ganglion cells (*e.g.*, FDT), with both suggesting that both systems are affected in the early and moderate stages of glaucoma.[7,8] The early effects on ganglion cell subtypes are supported by neuropathological findings in a monkey model of glaucoma.[9] Currently, there are no publications that include comparisons between visual function specific tests targeting the parvocellular ganglion cells (*e.g.*, high pass resolution perimetry) and those targeting magnocellular or small bistratified ganglion cells, although such studies are being conducted. In all studies, the control subjects may not be representative of the patients for whom diagnostic testing is needed to rule out disease.

None of the studies included here report likelihood ratios, but in one study with a gold standard that did not include one of the functional tests, it is possible to compute these for SWAP and FDT, however, with some caution.[2] This paper did not address the use of combinations of parameters, which is more common for clinical diagnosis, but it is possible to compute LR for single parameters. Given that, the best SWAP parameter at 90% specificity was pattern deviation points ≤ 5%. This parameter yielded a positive likelihood ratio (sensitivity/(1-specificity)) of 5.38. However, the sensitivities and specificities were derived from the ROC curves, so no information on how many points must be ≤ 5% is given. The negative likelihood ratio ((1-sensitivity)/specificity) was 0.62. For FDT, the best positive LR was 16.33 for superior total deviation points ≤ 5%, with a negative LR of 0.53. Other parameters also did well, and it would be nice to reassess these data using combinations of criteria for abnormality. In summary, the overall evidence was moderate (B) because the manuscripts available for review were of lower to acceptable quality.

Reproducibility

There are too few studies using the same test procedures and similar methods at this time.

Sensitivity/specificity for early, moderate and advanced glaucoma, and for measuring progression

One study showing sensitivity for eyes with GON not specific for level of severity, but with specificity set near 90% showed 46% for SAP, 61% for SWAP, and 79% for FDT.[1] A consideration in this study is that the same criteria for abnormality were used for SAP and SWAP, but different normative databases for all tests and different criteria for FDT were used because of its later arrival and the difference in the number of tested locations. One study which followed patients with bilateral SAP defects found that SWAP showed progression in 79.6% of 54 eyes six to 24 months prior to progression with SAP, according to CNTG criteria, and in 74.1% of 54 eyes with FDT 12 to 24 months earlier (note C-20 version of FDT was used).[4]

Effects of intraocular pressure changes, media, and refraction

See chapters on SAP, SWAP and FDT.

Type of environment/setting where the instrument is used

See chapters on SAP, SWAP and FDT.

When/where should they be used

Comparison studies should be undertaken in centers with diverse populations, including patients who are OHT, suspect, and on through to advanced glaucoma. Well-designed, prospective, longitudinal studies are required to address all the concerns raised so far.

Unanswered questions, comments and responses

For clinical use

- Will one visual function specific test be best for both detection and progression?

This most important question generated all the discussion in this section. Erik Greve replied that the problem is indeed the non-existant 'gold standard', but we must decide which tests to use and whether they are the same for detection and follow-up. How many tests can we realistically carry out? Do we have sufficient evidence for the choice? He also stated that there is little doubt that at least one function test has to be included, and he then voted for SAP because it can be utilized in the advanced stages of the disease, but at the price of later detection. Daniel Grigera responded that he thinks it is possible to use more than one visual function test, one for earlier detection, another for later on in the disease. Also, use of a second test may be more informative than repeating SAP to verify a change in visual field status. For example, he suggested that FDT/SWAP detect damage earlier than SAP, so FDT (or SWAP) could be performed after a normal SAP in a glaucoma suspect. Pam Sample offered an alternative solution to Dr Greve's choice of SAP in line with Dr Grigera's comments. She suggested using a more sensitive test, SWAP, for the initial evaluation and follow-up for as long as it is possible. SITA-SWAP should alleviate the problem of increased test time and will help lengthen possible follow-up with its increased dynamic range. Then, when the damage has progressed to the point where the individual can no longer be followed with SWAP, the clinician could switch to SAP. This is presently done with SAP when the 24-2 field is so advanced that a switch is made to the 10-2. Since SWAP is available on the same device as SAP, this approach would not involve any additional expense. This first unanswered question is of great clinical significance and research efforts should focus on finding the solution.

- What is the sensitivity and specificity for these tests and for SAP when SAP is not used as the gold standard?
- Does IOP influence the test results for any of the function tests?
- What are the trade-offs between sensitivity/specificity and patient acceptance of the test?

For understanding loss of ganglion cell function

- Are all ganglion cell subtypes equally affected by glaucoma?
- If neuroprotective agents are developed, will they protect all subtypes equally, since each is unique in its anatomy, physiology, and morphology?

Studies needed

Well-designed, prospective, longitudinal studies are required to address all the concerns raised so far.

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COMPARISON OF STRUCTURAL METHODS

Linda M. Zangwill, Christopher Girkin, Stefano Miglior, Remo Susanna and Ravi Thomas

Linda M. Zangwill

Summary

- Little comparative information is available on reproducibility in the same population.
- The sensitivity and specificity of imaging instruments for the detection of early glaucoma is comparable to that of stereo color photography.
- At specificities of over 95%, sensitivities decreased to around 60%.
- At high specificities, imaging techniques do not show concordance in detecting the same glaucoma patients.
- The current literature does not provide the requisite evidence to validate any of these imaging instruments for widespread routine clinical use.

The AIGS consensus documents on structural methods summarize what is known about optic disc and retinal nerve fiber layer (RNFL) photography, and HRT, GDx and OCT imaging instruments. Comparison of results across studies can be difficult because of differences in study design, definition and severity of glaucoma, operator input, and general characteristics of the study population. In order to reduce the effect of these issues on results, it is valuable to compare techniques in one study population. This report focuses on studies that directly compare at least two imaging instruments, or at least one imaging instrument, to photography.

Instrumentation: how does it work?

This is well summarized in 'the structural methods' reports.

Minimal damage that can be detected

Little information is available. See 'the structural methods' reports for more details.

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Percentage of glaucoma patients in whom satisfactory results can be obtained

Few studies state the proportion of patients with usable images or photographs. In one clinic-based study, RNFL photographs had a lower proportion of usable results (70%) than GDx (93%).[1] The same proportion of usable GDx images (93%) was reported in subjects from the population-based Baltimore Eye Follow-up Study.[2] All 55 eyes in a clinic-based study had usable OCT images.[3]

Reproducibility

Reproducibility is well summarized for individual instruments in 'the structural methods' reports. However, little information is available comparing the reproducibility of techniques in the same population.

Comparing imaging and photography

The intraobserver variability in estimating disc and rim areas is similar for optic disc photos assessed by planimetry and HRT.[4] HRT shows better interobserver reproducibility compared to planimetric measurements of optic disc photographs.[4] However, the variation in disc margin definition, together with the subsequent variation in reference height and cup definition, leads to a variation in rim area. This variation may be clinically significant in cross-sectional studies. This variation can be reduced if clinical optic disc photographs are used to help in outlining the optic disc margin.[5]

Comparing imaging instruments

The reproducibility of interpretation of clinical printouts of HRT, GDx and OCT has been moderate to substantial, with kappas ranging from 0.5 to 0.77.[6]

Sensitivity/specificity for detecting early, moderate and advanced glaucoma: comparing imaging and photography

1. There is limited, but consistent evidence from different investigators that HRT, GDx and OCT can detect early to moderate glaucoma, as well as standardized, expert qualitative assessment of stereoscopic optic disc and RNFL photographs in clinical research settings. Specifically, the areas under the ROC curve for stereophotographs, HRT, GDx and OCT were 0.93, 0.92, 0.94 and 0.88, respectively.[7] The sensitivity and specificity for detecting glaucoma by assessment of photographs and HRT was 0.71/0.94 and 0.84/0.96, respectively.[8] At fixed specificities of 85% and 90%, respectively, the sensitivity of HRT (81 and 63%), GDx (66 and 54%), and OCT (76 and 71%) was similar to that of expert assessment of photographs (80%).[9] Other studies also found equivalent ability of HRT and stereophotograph assessment for detecting glaucoma defined by standard visual fields.[10,11] One study observed that the presence of RNFL abnormality based on semiquantitative grading of RNFL photos in either hemiretina can give high sensitivity and specificity (95 and 82%, respectively) for normal and glaucoma eyes, but when specificity is increased to 94%, sensitivity drops to 59%.[1] In this same report, the best GDx parameter (the Number) yielded a sensitivity of 62% and a specificity of 96%.
2. Although there is moderate to good correlation between photographic-based assessment and CSLO topographic measurements of the optic nerve head, there are differences in the absolute measurements obtained. Specifically, compared to planimetric measurements on optic disc photographs, HRT estimated a larger neuroretinal rim area,[10,11] and frequently defined a different location of greatest cup depth.[12] Cup-to-disc ratio measurements with HRT are smaller than a clinician's mean vertical and horizontal cup-to-disc ratio estimates.[13] Differences are smaller when evaluating patients with glaucoma compared to normal subjects, and may depend on disc area, cup size, glaucoma stage and clinician. Parts of the central retinal vessel trunk that are defined as neuroretinal rim in the HRT algorithm may account for at least some of these differences. Another possible explanation for the differences may be due to the calculation of the cup-rim boundary which is defined based on the mean height contour measurement along a small temporal section of the contour line (350-356 degrees). In the detection of peripapillary changes associated with glaucoma, HRT detected nine of 12 focal RNFL defects using individual reflectivity images,[14] and correlated with planimetric estimates of peripapillary atrophy.[15]
3. There is limited, but consistent evidence of a good correlation between semiquantitative assessment of RNFL photographs and OCT RNFL measurements

(r^2 values of 36-55%) compared to a poor correlation to SLP with fixed corneal compensation RNFL measurements (maximum r^2 values of 28%).[16,17] A handful of studies compared SLP or OCT with conventional RNFL photography, finding good correlation to local retinal nerve fiber layer defects with the OCT,[18,19] and a higher correlation to the mean defect of conventional perimetry (MD) than subjectively scored RNFL photographs.[20] In a more recent study, SLP measurements of RNFL thickness were significantly correlated to morphological change determined by optic disc stereo-photography.[21] Correlation between OCT and SLP measurements is not strong, with OCT measuring thicker RNFL values in normals, and thinner values in glaucoma eyes than GDx.[22]

Comparing imaging instruments

There is a limited number of studies directly comparing the diagnostic accuracy of imaging instruments in the same study population. In general, the areas under the ROC curve for the best parameters of OCT, SLP and HRT are similar, with estimates ranging from 0.79-0.93.[7,9,23] However, at high specificities, estimates of sensitivities differ across studies, and each instrument identifies different eyes as having glaucoma.[7,9,23] The sensitivity and specificity of three expert observers reviewing standard printouts ranged from 64-75% and 68-80%, respectively, for HRT, from 72-82% and 56-82%, respectively, for GDx, and from 76-79% and 68-81% for OCT.[6] In the same study,[6] likelihood ratios of a positive test (calculated from published sensitivities and specificities[24]) range from 1.9-4.0, while likelihood ratios of a negative test range from 0.30-0.53. Likelihood ratios (calculated from published sensitivities and specificities) from two studies comparing imaging instruments were better. At specificities of between 85 and 95%, the likelihood ratios of a positive test ranged from 5.8-8.4 for HRT, from 4.7-8.1 for GDx, and from 5.4-11.8 for OCT, and the likelihood ratios of a negative test ranged from 0.18-0.76 for HRT, from 0.21-0.71 for GDx, and from 0.28-0.37 for OCT.[7,9] A likelihood ratio of > 10 or < 0.1 usually generates large and conclusive changes from pre- to post-test probabilities, while a likelihood ratio of 5-10 and 0.1-0.2 generates moderate shifts in pre- to post-test probabilities.[24]

Measuring progression

Comparing imaging and photography

Few studies are available. The LSU experimental glaucoma study demonstrated that TopSS CSLO imaging may meet or exceed the ability of fellowship-trained glaucoma specialists to detect progressive disc damage in a high pressure primate model.[25] In a clinical study, concordance between HRT probability map

analysis and qualitative assessment of stereophotograph for the determination of glaucomatous progression was seen in 13 (80%) of 16 eyes followed with both techniques.[26]

Comparing imaging instruments

No information is available.

Effects of intraocular pressure changes, media, refraction

No studies are available comparing these effects in the same population. Optic disc topographical measurements are influenced by intraocular pressure (IOP). The influence of refraction and media opacities needs to be studied.

Type of environment/setting where instrument is used

Most of these studies were completed in academic glaucoma subspecialty clinics. It may not be possible to generalize the results to general ophthalmology and optometry clinics.

Levels of evidence

None of the studies met the 'high quality' classification, since progressive optic nerve damage (or field damage) was not used as the gold standard. Most studies met the 'acceptable quality' classification, since the gold standard used for glaucoma diagnosis was the presence of repeatable abnormal standard automated perimetry results, a standard independent of the diagnostic test being evaluated. In most of these studies, the imaging and photography results did not influence the decision to perform the gold standard. Likelihood ratios can be calculated for some of these studies (*see* Comparing imaging instruments under Sensitivity/specificity for detecting early, moderate and advanced glaucoma section). Both these criteria are required for acceptably demonstrating validity of a diagnostic test according to the Evidence-Based Medicine Working Group.[24] A common problem with most of these studies is their relatively small sample size, and therefore, their limited power for detecting true differences in diagnostic techniques. In addition, the control subjects used in the studies may not be representative of the patients for which diagnostic testing is needed to rule out the disease.

Conclusions

The exciting literature comparing qualitative and quantitative methods demonstrate good correspondence between these modalities, with no significant differences in their discriminatory ability. However, most of these evaluations were carried out with small sample sizes using older version of the imaging instruments. Their comparative effectiveness in detecting progression awaits future longitudinal observational studies.

There was general agreement that the current literature does not provide the requisite evidence to validate any of these imaging instruments for widespread routine clinical use, since the techniques have not been shown to be better than standard clinical testing or a dilated examination by a trained clinician. However, in the hands of an experienced clinician who understands the strengths and limitations of the instruments, information may be helpful in many clinical situations.

Unanswered questions

- If photography and imaging instruments are capable of detecting the early stages of glaucoma, (*i.e.*, pre perimetric glaucoma), should they not be capable of detecting *all* those with early and moderate field damage? That is, they should have 100% sensitivity for eyes with moderate glaucoma. However, none of the structural instruments have shown this.
- More information is needed on the characteristics of eyes with field defects that are being missed by imaging instruments and photographs.
- Will the patient be better off as a result of the test? In the hands of a specialist? Generalist?
- Does the cost of the possible misinterpretation of results from imaging instruments to diagnose glaucoma (and the possible over treatment due to false positives) outweigh the benefits of providing optic disc and RNFL information to the general ophthalmologist and optometrist, who would otherwise not assess the optic disc and RNFL of their glaucoma patients?
- Why do the instruments, despite having similar overall discriminating ability, identify different patients as has having glaucoma? On follow-up too, different patients are labeled as progressing by different instruments.

Studies needed

- Studies are needed to determine how the recent improvements in imaging instruments effect their reproducibility, percentage of glaucoma patients in whom satisfactory results can be obtained, sensitivity and specificity, and ability to detect progression.

- Studies are needed to determine the minimum detectable damage.
- Longitudinal studies are needed to determine whether imaging instruments can reproducibility detect glaucomatous changes in the optic disc and RNFL which eventually lead to functional loss.
- Studies comparing the costs and benefits of these techniques.
- Meta-analyses to combine results across studies in order to provide more robust estimates of the discriminating abilities of these techniques.

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COMPARISON OF STRUCTURAL AND FUNCTIONAL METHODS – I

David F. Garway-Heath

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Summary

- The weight of evidence seems to point to a linear relationship between RGC numbers and linear (un-logged decibel) visual field sensitivity at field locations outside the central 15 degrees (36 of the 52 non-blind spot locations in a 24-2 Humphrey field). The precise relationship remains to be determined and is likely to vary according to the type of structural measurement and imaging device used to estimate RGC numbers.
- Within the central 15 degrees, the structure/function relationship is likely to remain non-linear as a result of spatial summation effects.
- The use of a logarithmic (decibel) scale to express visual field sensitivity results in the curvilinear relationship to structural measurements. This explains the impression of a functional reserve, with large changes in structure corresponding to small changes in decibel visual field values early in disease, and small changes in structure corresponding to large changes in decibel field values late in disease.
- Given likely linear relationship between structural and functional parameters, the facility to identify damage early in disease will depend on the precision of the measurements (test retest variability), the spread of normal values, and the closeness of the measured parameter to disease-related damage.
- The facility to measure progression will depend on the precision of the measurements and the linearity of the measured parameter with respect to disease-related damage.
- How well the parameter matches the 'stage of disease' depends on the classification system and the perspective of the observer. If the clinician is concerned about the functioning of the individual in his or her environment, then early disease might be equated with standard automated perimetry loss up to, say, -10 dB (Heijl *et al.*[1]). If the clinician is a ganglion cell counter, then –3 dB might seem disastrous!

Introduction

Clinicians use tests of visual function and instruments that measure aspects of retinal structure in order to aid in the diagnosis of glaucoma, to stage the disease, and to measure disease progression. Different tests, or different parameters from the same test, may be more or less appropriate for each of these purposes. For example, we may want a test of visual function that is sensitive

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in early disease, one that is able to make measurements across the range of disease, or one that reflects the functioning of an individual in his or her visual environment. We may want an instrument that is able to measure specific layers within the retina, deformation of the optic nerve head (ONH), or even changes in structure that relate to dysfunction of cells. Glaucoma is viewed as a disease primarily affecting ganglion cells (RGCs) and the tests of visual function used in clinical practice are designed to measure the psychophysical or electrophysiological responses to RGC stimulation (whether RGC class specific or non-specific). At present, it is not possible to measure RGCs as individual structures and we therefore measure larger structures such as the retinal nerve fiber layer (RNFL) and ONH.

Measurements that are useful for classifying ('diagnosing') or staging or measuring progression do not necessarily have to relate directly or wholly to RGC loss. For instance, measurements of ONH structure are related to RGC axon numbers,[2] and may also provide information of ONH deformation unrelated to RGC loss,[3] but which is nevertheless useful. However, when we want to relate structural and functional measurements to each other, it is more useful if the parameters chosen for comparison both relate closely to RGC numbers.[4] For this reason, when considering ONH parameters, it is more meaningful to consider neuroretinal rim area than cup area or volume or cup shape measure. When considering the RNFL, thickness measurements are more meaningful than the neural network summary parameter or modulation or ratio measurements.

It is necessary to know the relationship of the parameter measurement to the disease variable across the range of that variable. When relating structural and functional measurements of glaucoma, the variable is the number of remaining RGCs. We need to know if the structural measurement or the measurement of function is linearly or non-linearly related to RGC numbers, and whether the dynamic range of the measurement is more suited to early or late disease. We also need to be aware of components of the structural measurement that are not related to RGC numbers, such as blood vessels and supporting tissue, and the effect of ONH tilt in scanning laser tomography measurements of neuroretinal rim, RNFL and non-RNFL factors that affect ocular birefringence in scanning laser polarimetry measurements of the RNFL, or blood vessels and supporting glial tissue in optical coherence measurements of the RNFL. Likewise, we need to be aware of components of the functional measurement that are not related to RGC numbers, such as lens opacity, refractive error, pupil size, and cognitive function. Each of these will degrade the relationship between structural and functional measurements. To these effects needs to be added the imprecision of the measurements (test-retest variability).

A further consideration is the spatial relationship between the measurements – the sampling pattern of the structural or functional test. Typically, structural measurements are made symmetrically around the center of the ONH. However, conventional tests of RGC function, such as standard automated perim-

etry, sample some regions of the retina in much greater detail than others.[5] There are relatively few test points (six), in relation to RGC density, in the central macular region that relate to the 90-degree segment of the temporal ONH. Similarly, the visual field that relates to the nasal aspect of the ONH is poorly sampled (Fig. 1). Fifty percentof the retinal ganglion cells are found in the central 20 degrees of the retina, yet only 12 (22%) of the Humphrey test points lie in this region. These differences in sampling may distort apparent structure/function relationships. This distortion is compounded by differences in the slope of the structure/function relationship, which varies with eccentricity (*see* Harwerth, Clinical Basic 1, and below). The identification of certain patterns in the topographical relationship between structure and function may be useful to aid in the evaluation of glaucomatous damage, although the pattern is characterized by considerable interindividual variability.[6]

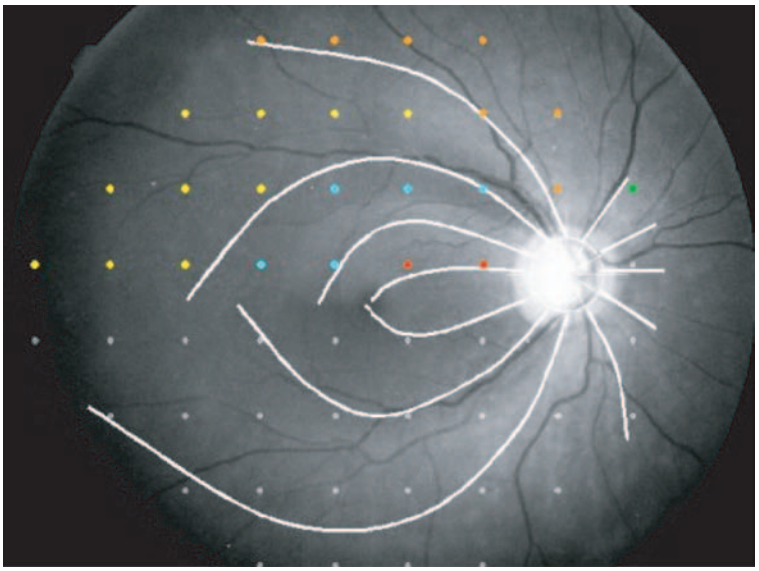

Fig. 1. Representation of the relationship between visual field locations and optic disc sectors.

Clinical studies of the structure/function relationship in glaucoma are difficult because of the almost inevitable introduction of selection biases.[7] The substrate for studies is usually a clinic-based population of glaucoma patients. These patients have been identified on the basis of particular patterns of structural and functional abnormality that meet certain preconceived notions. These preconceptions will bias the outcome of comparisons. For instance, if the inclusion criteria for a study restrict the glaucoma patients to those that have recognizable patterns of visual field loss with corresponding damage to the optic nerve head or RNFL, structure/function concordance is likely to be increased (because clinically non-concordant cases have been excluded). Studies

involving ocular hypertensive patients are often selected on the basis of normal visual fields and varying structural criteria, ranging from none to 'normal appearing ONH or RNFL'. These approaches are likely to lessen the concordance between structural and functional measurements.

Structure/function relationships in the literature

Clinical studies

With these caveats in mind, the evidence in the literature concerning the relationship between structural and functional measurements can be reviewed. Many studies have compared structural and functional loss in glaucoma. This review will be restricted to those that consider the pattern and quantitative relationship between the two.

Airaksinen and Drance[8] considered the relationship between neuroretinal rim area, measured by planimetry, and mean damage in decibels, measured by Octopus perimetry, in 23 normal subjects, 49 glaucoma suspects and 51 glaucoma patients. He found that the relationship was non-linear: adding a quadratic function to the regression model improved the fit from $r^2 = 0.32$ to $r^2 = 0.41$.

Jonas and Grundler[9] correlated mean visual field defect in decibels, measured by Octopus perimetry, and neuroretinal rim area, measured by planimetry, in 410 patients with glaucoma. He found that the correlation was similar to a logarithmic function.

Garway-Heath *et al.*[10] correlated visual field mean sensitivity in decibels, measured by Humphrey perimetry, with neuroretinal rim area, measured by scanning laser tomography, in 33 glaucoma patients and 69 normal subjects. They reported a curvilinear relationship that became linear if the decibel values were un-logged.

Bartz-Schmidt *et al.*[11] correlated the relative rim area loss (calculated from the standardized rim/disc area ratio), measured by scanning laser tomography, with the mean defect in decibels, measured by computerized static perimetry, in 90 glaucoma patients, ten ocular hypertensive patients, and ten normal subjects. They reported an exponential relationship between the two.

Garway-Heath *et al.*[12] correlated visual field mean sensitivity in decibels, measured by Humphrey perimetry, with RNFL thickness measurements, measured by a prototype scanning laser polarimeter, in 51 normal subjects and 54 glaucoma patients. They reported a logarithmic relationship that became linear when the decibel values were un-logged.

Similarly, Lemij and Reus[13] correlated visual field mean sensitivity in decibels, measured by Humphrey perimetry, with RNFL thickness measurements, measured by scanning laser polarimetry, in 51 normal subjects and 91 glaucoma patients. They reported a logarithmic relationship that became linear when the decibel values were un-logged.

The above reports support the concept of a non-linear relationship between structural measurements that are related to RGC numbers and decibel light sensitivity.

In contrast, Racette *et al.*[14] correlated the temporal neuroretinal rim area, measured by scanning laser tomography, with the decibel mean threshold of the 16 central visual field locations in 149 normal subjects and 54 glaucoma patients, and found no evidence for a non-linear relationship.

Electrophysiological measurements of retinal function have been compared to conventional perimetric thresholds. Garway-Heath *et al.*[15] correlated the amplitude of the pattern electroretinogram (PERG) with the mean threshold of the 16 central visual field locations in 34 normal subjects and 40 patients with glaucoma. They reported a curvilinear relationship when visual field sensitivity was scaled in decibels, and a linear relationship when scaled in linear (unlogged) units. Hood *et al.*[16] correlated the signal-to-noise ratio of the multifocal visual evoked potential (mfVEP) to the Humphrey visual field mean defect in 20 eyes with glaucoma or ischemic optic neuropathy, and concluded that there is a linear relationship between the signal portion of the mfVEP and linear HFV loss (the antilog of decibel values). Hood and Greenstein,[17] in considering the model for mfVEP amplitude analysis, stated, "the … model implies that the same relationship exists between the reduction of the mfVEP signal amplitude and ganglion cell loss, on the one hand, and linear visual field loss (antilog of dB loss) and ganglion cell loss on the other".

Histological studies

These clinical studies only give us the relationship between visual function and an indirect anatomical estimate of RGC numbers. A gold-standard study would be to relate perimetric (or electrophysiological) measures of function to the actual numbers of ganglions cells. This can only be done in post-mortem human or experimental animal studies. Kerrigan-Baumrind *et al.*[18] compared the RGC density in 17 eyes of 13 individuals with a history of glaucoma (relative to the RGC density in 17 eyes of 17 individuals with no history of glaucoma) to visual field sensitivity measured by Humphrey automated perimetry. The data were analyzed in several ways. When the relative RGC density for every point in all eyes was compared to the threshold loss at each point, a significant correlation was found, although the regression explained only a small fraction of the variance ($r^2 = 0.03$). When mean relative RGC density for each eye was compared to the global visual field indices, there was a 6-dB loss of sensitivity at 100% relative RGC density, and a linear loss of 0.05-dB sensitivity for each 1% RGC loss. These figures suggest a 6-dB loss of sensitivity without RGC loss, and then a further 5-dB loss of sensitivity for 100% RGC loss. Analysis of hemifield RGC density and visual field sensitivity across subjects provided a slope of 0.084-dB loss for each 1% of RGC loss. Within-eye hemifield differences in relative RGC density and visual field density provided a slope of

0.2 dB for each 1% of RGC loss (approximately 5 dB for 25% RGC loss). This latter analysis is broadly in line with previous estimates.[19] Variability in the plots of relative RGC numbers and visual field loss precludes the recognition of any particular pattern (linear versus non-linear) in the relationship. There are many potential sources of variability in the data, in addition to the variability inherent in psychophysical testing. The size of the retinal trephine, from which RGC density was calculated, was 190 times larger than the Goldmann size III visual field test spot and "the variance of data at each individual data point for RGC counting was substantial".[18] The time from visual field to histology was relatively long with a mean of 1.2 years (five eyes longer than one year, one eye longer than two years). Also of note is that, although RGC and axon counts from the same eyes agreed reasonably well, counts in the normal eyes were at the lower end of ranges previously reported. As RGC loss in the glaucoma eyes was calculated relative to the normal eyes, an underestimation of RGC density in normal eyes would result in the underestimation of RGC loss in the glaucoma eyes.

Harwerth *et al.*[20] has correlated visual field loss, measured by behavioral perimetry, with RGC loss in a monkey model of glaucoma. In this high-pressure model of glaucoma, there was an approximate 6-dB loss in sensitivity before any RGC loss. The sensitivity loss and RGC loss data were fitted with a bilinear function, with no relationship between sensitivity and RGC loss between 0% and about 45% RGC loss, and then a linear relationship for greater RGC loss with a slope of about 0.4 dB for each 1% of RGC loss. The same data, with both visual field loss and RGC loss plotted in decibels for test points of all eccentricities, demonstrate a single linear relationship with a slope of 1.3-dB loss of sensitivity for each 1-dB loss in RGC.[21] More recently, Harwerth *et al.*[22] have reported that this slope varies with eccentricity, with a slope of about 2 dB/dB at an eccentricity of 15 x 15 degrees (*see* Consensus Basic 1). This is consistent with the finding of Bartz-Schmidt and Weber,[23] who reported that a 6-dB loss in intensity thresholds corresponded to a 3-dB loss in spatial resolution (equivalent to RGC density), as measured by high pass resolution perimetry.

Theoretical studies

The relationship between perimetric light sensitivity and RGC numbers has been modeled from a report of RGC counts in normal eyes and a report of normal Humphrey perimetric differential light sensitivity thresholds.[24] The model demonstrated, for normal eyes, a curvilinear relationship between dB visual field sensitivity and ganglion cell numbers (Fig. 2), and a linear relationship between ganglion cell numbers and linear visual field sensitivity (un-logged dB values) once the effects of spatial summation were taken into account. Swanson *et al.*[25] re-plotted the same data with visual field sensitivity and RGC numbers

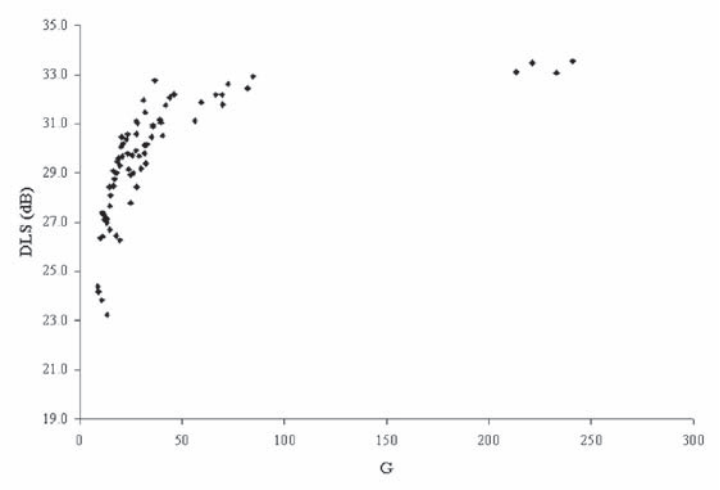

Fig. 2. Physiological relationship between dB visual field sensitivity and the number of ganglion cells within a size III test spot.

both in the decibel scale. This plot was fitted with a bilinear function, with an initial slope of 1 and a second slope of 0.25. This is consistent with Ricco's law of complete summation within a certain critical area, when ganglion cell numbers are below a particular number, and Piper's law of probability summation with a slope of 0.25 outside that critical area. The relationship with a slope of 1 is predicted for locations more peripheral than 15 degrees from fixation for the Goldmann size III stimulus. Swanson *et al.*[26] developed a quantitative neural model that predicts a wide range of perimetric data in the literature. The model predicts a non-linear relation between ganglion cell numbers and decibel light sensitivity, and a linear relation if both are scaled in linear or both in logarithmic units.

The predicted structure/function relationship will be modified if ganglion cells are present, but dysfunctional. It is possible that ganglion cell dysfunction might explain the deviation of Harwerth's results from the expected RGC dB/light sensitivity dB slope value of 1.

The theoretical models make the assumption that the physiological structure/function relationship is maintained in glaucoma. It is possible that remodeling of the central detection mechanisms may occur in response to RGC loss, however, available data suggest little or no change in perimetric spatial summation in glaucoma.

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COMPARISON OF STRUCTURAL AND FUNCTIONAL METHODS – II

Balwantray C. Chauhan

Balwantray C. Chauhan

Summary

- There is no independent qualifier of glaucoma or its progression.
- Statistical and biological progression are probably different entities.
- With the tools we have today, tests of structure and function provide largely independent information on progression.
- We should talk about *disc change* and *field change*, but perhaps not glaucoma progression.

Introduction

Correlating structural and functional changes in glaucoma has both clinical and scientific importance. For example, determining the temporal sequence of optic disc and visual field changes can influence the management of individual patients, while determining this correlation in a group of patients in scientific studies may shed some light on the nature of disease progression and the relative efficacy of various diagnostic tests used for measuring structural parameters in the optic disc or retinal nerve fiber layer, and visual function.

Since the primary neuronal damage in glaucoma is loss of retinal ganglion cells (RGCs), ideally we wish to study the correlation between structure (say, some form of cellular or intra-cellular imaging) and function (say, single cell electrophysiology or axon conduction velocity) of individual RGCs. Currently we have no means to conduct this type of study *in vivo*. Instead, clinicians and scientists rely on surrogates of structural and functional loss. For structural measures, these include rim area, cup volume, and so on, obtained with morphometric measurements using optic disc imaging techniques, or retinal nerve fiber layer thickness measurements using other imaging modalities. For functional measures, these include mean sensitivity, mean deviation, individual pointwise sensitivity values, and so on, using a variety of perimetric tests, including standard automated perimetry as well as the newer psychophysical tests.

Currently, we have no evidence to demonstrate how well these clinical surrogates represent neuronal integrity, but it is certain that there are confounding

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edited by Robert N. Weinreb and Erik L. Greve

factors in these parameters. For example, clinical and experimental studies have shown that despite complete optic nerve transection, the optic disc does not 'cup out' completely. Visual field measures can be affected by many retinal and pre-retinal factors that may be independent of RGC integrity.

Types of structure-function correlations in clinical studies

There is a distinction between structure-function correlations obtained in cross-sectional studies and those obtained in longitudinal studies. There are numerous reports on the former topic, but there is a scarcity of reports on the temporal relationship between optic disc (and or nerve fiber layer) changes and the visual field. Structural parameters have been obtained from both conventional disc photography and modern imaging techniques, such as scanning laser tomography, scanning laser polarimetry and optical coherence tomography. On the other hand, the functional correlates include static white-on-white perimetry, as well as perimetric techniques based on high-pass resolution, blue-on-yellow contrast, and frequency doubling, among others.

In cross-sectional studies, the statistical strength of the relationship can depend critically on the inclusion criteria. The correlation is expected to be high if patients range from having very early to advanced damage on the structural and functional scale due to an 'anchoring' effect. Moreover, many studies have elected to include normal control subjects and ocular hypertension (or glaucoma suspect) patients in the analysis with the range of glaucoma patients, which undoubtedly adds to the anchoring effect. The inclusion of these three classes of subjects in the same analysis may be more appropriate if we assume that there is a transition from normality to advanced glaucoma. Clearly this

Report authors: David Garway Heath and Linda Zangwill (ex Balwantray Chauhan, presenter)

assumption is not valid for the included subjects. Indeed, when subjects include only patients with either early, moderate, or advanced damage (based either on a structural or functional parameter), the correlation is substantially worse.

Longitudinal studies in glaucoma subjects comparing structural and functional measures are critical but, to date, are lacking in number. However, data from many laboratories will be forthcoming over the next five to ten years. One of the prime limitations of these studies is that the technology that is used to determine the functional and structural measures is evolving. The most striking of these is in the quantification of the optic disc. The modern imaging techniques have undergone several iterations in hardware and longitudinal data gathered with older technology, which can be sound and scientifically rigorous, may be obsolete.

Correlating structural and functional change

Whether structural changes precede functional changes depends on whether a given structural change precedes a change in function that is related to the structural change. For example, does a progressive change in the already damaged inferior temporal sector of the rim 12 months prior to a change in an already damaged superior nasal visual field mean that disc changes precede field change? It may, however an equally plausible scenario is that the optic disc change measured was the result of a visual field change that occurred six months prior to the patient being enrolled in the study (or seen in the clinic).

It is also assumed that one progressive event with one technique is equivalent to one progressive event with the other. While these event-based analyses are based on logical statistical rules, it cannot be ruled out that one progressive event with one technique may be equivalent to several progressive events with another, and that the analysis techniques with the former are sub-optimal. In addition to event-based analyses, we can evaluate the relationship between the trends with two techniques. In this case, the scaling issue and analysis of the correct parameter becomes critical. However, it is likely that there is no relationship between the statistically defined events or trends and biological change.

As mentioned above, the correlation between structural and functional measurements is limited to the clinical measurements which are only surrogates of the true neuronal structure and function. On a cellular level, there is presumably a correlation between the two. The death of an individual RGC should be clearly measurable by a single cell electrophysiological technique. Perhaps even dysfunction of the RGC can be measured by alterations in axon conduction velocity. But, it is likely that our clinical estimates are not accurate, and may partly explain the often poor nature of the correlation as well as the large variance among patients in this correlation.

Many of the considerations above apply to the temporal relationship be-

tween structure and function. In clinical studies, it has been widely reported that large changes in optic disc morphology take place prior to demonstrable visual field damage. Recently, it has been shown in monkeys trained to perform perimetry that visual field sensitivity remains unchanged despite RGC loss. While accurate techniques have been used to quantify RGCs, is measurement of perimetric sensitivity an adequate (or even fair) functional equivalent? It is apparent that conventional perimetry may not be an accurate or sensitive estimate of RGC function. On the other hand, issues have been raised regarding the scaling of perimetric sensitivity, where altering the scale has been shown to linearize the relationship between structural and functional loss. However, this transformation does not affect the variability in the correlation between structural and functional measurements in patients.

In the final analysis, we have no independent qualifier of glaucoma or its progression, since the very tests that are used to measure its severity or progression are the ones that are used to define it. Statistical progression, which is what we are limited to measuring, is very likely different from biological progression, which is ultimately what we would like to measure.

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COMPARISON OF STRUCTURAL AND FUNCTIONAL METHODS – III

Linda M. Zangwill

Linda M. Zangwill

Summary

- As no single examination method alone is adequate for glaucoma diagnosis, both structural and functional testing are needed.
- Perimetry and optic nerve evaluation and documentation – by photography or digital imaging – remain essential for managing glaucoma.
- Digital imaging is recommended as a clinical tool to augment and facilitate assessment of the optic disc and retinal nerve fiber layer (RNFL) in the management of glaucoma.

The theoretical issues that influence our ability to evaluate the structure function relationship in glaucoma have been outlined in AIGS documents by Drs Chauhan and Garway-Heath (see Clinical 3 structure-function). In brief, the ability to evaluate the structural-function relationship depends on the available techniques for measuring surrogates to the parameter of interest, retinal ganglion cell functioning. Our assumptions about the clinical techniques utilized to measure structure and function, together with the study population and stage of disease included in the evaluation, can often bias our conclusions about the nature of the structure-function relationship in glaucoma. Furthermore, one of the most important and fundamental methodological issues, the lack of an external independent gold standard (independent of both structural and functional criteria) for defining glaucoma and its progression, impedes our ability to objectively evaluate and compare different techniques.

The relevant longitudinal and cross-sectional studies available on the correlation of the retinal nerve fiber layer (RNFL), optic disc and visual field changes have, been reviewed in the AIGS structural and functional documents. To summarize, there is consistent evidence suggesting that photographic determination of RNFL and optic disc damage is often detectable before SAP damage;[1-5] some longitudinal studies found that RNFL is a better predictor of damage than cup/disc ratio,[1-3] while other cross-sectional studies suggested that RNFL and cup/disc ratio have similar prediction capabilities.[6,7] However, the largest randomized clinical trial of individuals without detectable optic disc and visual field damage at baseline, the Ocular Hypertension Treatment Study (OHTS),

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found that repeatable visual field damage is detected before optic disc damage in over one-third of subjects with ocular hypertension. Specifically, although the majority of patients (54%) reached a photography-based optic disc endpoint before a visual field endpoint, a substantial proportion (37%) of patients reached a standard automated perimetry (SAP) endpoint before optic disc damage was detected, with approximately 9% showing concurrent disc and field damage.[8] Therefore, at least in the very early stages of glaucoma, if we only focus only on structural assessment, one-third of glaucomatous damage may be missed, while if only visual fields were monitored, over half the glaucoma could be missed. Moreover, the OHTS, with its large sample size and standardized enrollment criteria, is less likely to be subject to selection bias and other methodological limitations than many of the smaller single clinic-based studies. In most large multi-centered clinical trials of treatment for glaucoma, progression of optic disc damage was not considered a primary endpoint. Therefore, many studies, that included patients with later stages of glaucoma, such as AGIS and CITGS, have not yet reported their results on progression of optic disc damage, based on assessment of stereophotographs.

A limited number of small longitudinal studies have reported results comparing the newer structural and functional techniques. Among these reports are three studies utilizing imaging techniques to detect structural change over time.[9-11] In one study, after approximately five years of follow-up, significant, repeatable retinal height 'charges', based on HRT Change Probability Map Analysis, were detected in 40% of 77 eyes with normal visual fields and optic discs at baseline.[11] In this study, another 4% of eyes showed repeatable SAP damage only, 29% of the eyes showed HRT and SAP progression at the same time, and 27% did not progress by either criteria. Agreement between repeatable Change Probability Map results and subjective assessment of stereoscopic photographs

for change and was found in 80% of the 16 eyes with comparable photographic documentation. A second study, defining significant changes in HRT optic disc parameters as being those outside the limits of variability of HRT parameters in healthy eyes measured on multiple visits, found that 13 (62%) of 21 eyes that converted to glaucomatous visual fields showed concurrent changes in HRT parameters.[10] Finally, a third study calculated baseline variability of sectoral neuroretinal rim area measurements (30-degree rim sectors, dependent on an eye-specific reference plane) in individual eyes to determine whether changes in rim area measurements over time from baseline examinations exceeded the baseline variability in two of three consecutive examinations.[12] Using this technique, 18 (90%) of 20 ocular hypertensive eyes that converted to glaucomatous visual fields during three years of follow-up had rim changes. However, seven (35%) of 20 longitudinally studied healthy eyes were also identified as being changed, resulting in a low specificity (65%).

There are few studies reporting agreement of functional measurements in eyes with documented structural change based on photographic assessment. One study[13] compared SWAP and SAP changes in a group of 22 eyes with progressive change by stereophotographs and 25 eyes without progressive structural change. There was a statistically significant difference in the mean change in Advanced Glaucoma Intervention Study scores for both standard perimetry ($p < 0.004$) and SWAP ($p < 0.001$) between the progressed and non-progressed groups. SWAP identified more patients than SAP as having progressive glaucomatous changes of the optic disc.

Given the available evidence, and with the above-mentioned caveats in mind, both structural and functional measurements should be utilized to monitor glaucoma. The difficult, clinically relevant question is which structural and functional examinations should be included in everyday practice? In another words, is there sufficient evidence to recommend changes to the current clinical gold standard of functional assessment by standard automated perimetry and structural assessment by stereophotography? At the present time, there is insufficient evidence to change from the current gold standard structural and functional examinations.

As the intra-function AIGS document states, “there is little evidence to support the use of a particular visual function specific test over another in clinical practice. That said, it does seem that SAP is not ideal for early detection and follow-up of progression….” As the intra-structure AIGS document states, “There was general agreement that the current literature does not provide the requisite evidence to validate any of these imaging instruments for widespread routine clinical use, as the techniques have not been shown to be better than standard clinical testing or a dilated examination from a trained clinician. However, in the hands of an experienced clinician who understands the strengths and limitations of the instruments, information may be helpful in many clinical situations.” Unfortunately, it is unlikely that general ophthalmologists examine the optic disc and/or nerve fiber layer with the same degree of expertise as a

glaucoma sub-specialist. In a recent survey of 395 US managed care patients, only 53% of patients received an optic disc photograph or drawing at their initial visit.[14]

Given the relative low rate of evaluation of structural damage in glaucoma management, and the evidence (albeit limited) of concordance between photography and imaging instruments, particularly with HRT[11,15] (*see* intrastructure AIGS document), it can be argued that imaging can be recommended as a routine clinical tool as it will increase the assessment of the optic disc and RNFL in the management of glaucoma. However, as stated in the AIGS intrastructure document, it is important to consider whether the cost of possible misinterpretation of results from imaging instruments to diagnose glaucoma (and the possible over treatment due to false positives), outweighs the benefits of providing optic disc and RNFL information to the general ophthalmologist and optometrist, who would otherwise not assess the optic disc and RNFL of their glaucoma patients.

Regardless of the methods utilized, it is essential for clinicians to understand the strengths and limitations of the technique used, and to rely on good quality information. Educated clinicians know that, at best, limited information can be obtained from poor quality optic disc photographs, and unreliable visual fields. Clinicians can identify spurious visual field defects due to ptosis or other conditions. Similarly, caution should be used when interpreting poor quality images from optical imaging instruments. Several imaging instruments currently provide automated image quality assessment and feedback to the operator during or immediately after image acquisition. Although this feedback facilitates the acquisition of high quality images, there will likely be some patients for whom good quality scans are very difficult or impossible to obtain. Therefore, it is necessary to evaluate the quality of the structural and functional examinations before using the measurements derived from it.

What studies are needed?

- Longitudinal studies comparing structural and functional measurements for detecting glaucoma and its progression that include:
  - o assessment of the specificity and sensitivity of the measurements
  - o analysis of the rate and pattern of structural and functional changes
  - o analysis of the temporal relationship between detectable structural and functional changes
  - o analysis of the characteristics of eyes with field defects, which are being missed by structural assessment, and characteristics of eyes with structural damage without detectable functional damage
- Studies reporting on and comparing the reproducibility of the techniques.
- Studies comparing long-term variation in normal and glaucoma patients.
- Studies comparing possible confounding effects on test results (media opacity, IOP variation, pupil size, etc.).

- Studies reporting on the proportion of eyes for which satisfactory results can be obtained.
- Studies determining the minimum detectable damage.
- Studies comparing the costs and benefits of the techniques

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CONSENSUS STATEMENTS

Structure:

o 1 A method for detecting abnormality and also documenting optic nerve structure should be part of routine clinical management of glaucoma.

Explanation: It is known that documentation of optic nerve structure is often missing in routine ophthalmology practice.

o 2 According to limited evidence available sensitivity and specificity of imaging instruments for detection of glaucoma are comparable to that of expert interpretation of stereo colour-photography and should be considered when such expert advice is not available.

Explanation: Experts evaluating stereophotographs are those who have had specialized training and experience in this technique.

o 3 Digital imaging is recommended as a clinical tool to enhance and facilitate the assessment of the optic disc and retinal nerve fibre layer in the management of glaucoma.

Explanation: Digital imaging is available for scanning laser tomography, scanning laser polarimetry and optical coherence tomography. Digital imaging also is possible for photography, but assessment remains largely subjective.

o 4 Automated analysis of results using appropriate databases is helpful for identifying abnormalities consistent with glaucoma.

Explanation: The comparison of results of examination of individual patients with those of an appropriate database can delineate the likelihood of abnormality. Structural assessment should preferably include such a biostatistical analysis.

o 5 Different imaging technologies may be complementary, and detect different abnormal features in the same patients.

Note 1: At this time, evidence does not preferentially support any one of the above structural tests for diagnosing glaucoma

Function

o 6 A method for detecting abnormality and documenting functional status should be part of routine clinical management of glaucoma.

o 7 It is unlikely that one functional test assesses the whole dynamic range.

o 8 Standard Automated Perimetry (SAP), as usually employed in clinical practice, is not optimal for early detection.

o 9 With an appropriate normative database, there is emerging evidence that short wavelength automated perimetry (SWAP) and possibly also frequency doubling technology perimetry (FDT) may accurately detect glaucoma earlier than SAP.

Explanation: Earlier detection of glaucomatous damage with SWAP and FDT than with SAP has been consistently demonstrated.

o 10 There is little evidence to support the use of a particular selective visual function test over another in clinical practice because there are few studies with adequate comparisons

Explanation: At this time, there is no evidence to support the superiority of either SWAP vs. FDT.

Function & Structure:

o 11 Published literature often lags behind the introduction of new technology. Therefore literature based on previous versions of current technology should be viewed with caution.

o 12 In different cases, either structural examination or functional testing may provide more definitive evidence of glaucoma, so both are needed for detection and confirmation of the subtle early stages of the disease.

Note 2: Data from both functional and structural examinations always should be evaluated in relation to all other clinical data

CONCLUDING REMARKS

In evidence based diagnosis the ideal studies compare an experimental test to a Gold Standard. Although standard white on white perimetry has frequently been used as a Gold Standard the limitations of this method often render it unsuitable for this purpose. The committee on evidence based glaucoma of this consensus meeting has proposed "progressive structural optic nerve damage" as the Gold Standard. The matter of the Gold Standard was not discussed during this Consensus Meeting. However, it seems prudent that any Gold Standard includes a measure of progression whether assessed by structural or functional methods. This implies the need of longitudinal diagnostic studies of which unfortunately there are few. The highest level of evidence was therefore difficult to reach for this consensus. The good news is that several diagnostic longitudinal studies are ongoing and should allow both an upgrading of evidence levels and the conclusions in the foreseeable future.

R.N. Weinreb
E.L. Greve

A serious and good philosophical work could be written consisting entirely of jokes.
Ludwig Wittgenstein

FINANCIAL DISCLOSURE

Descriptions of the abbreviations used are listed below:

Accumat	- A	Consultant	- 1
Canon	- B	Honoraria	- 2
C. Zeiss Meditec	- C	Stock	- 3
Haag-Streit	- D	Research support	- 4
Heidelberg	- E	Travel support	- 5
LDT	- F	Other	- 6
Nidek	- G		
Talia	- H		
Topcon	- I		
Welch-Allyn	- J		

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Balwantray Chauhan E-4, J-4
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Shaban Demirel C-4, J-4
Robert Fechtner F-1, 4
Murray Fingeret C-2, 4, 5; E-2, 5; F-2, 4, 5; J-2, 4, 5
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David Garway Heath C-4; E-2, 4; F-2, 4; H-4
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1, 2, 5, 6. Audience

4. AIGS Executive Committee

3. Consensus Developmental Panel

1, 4, 6. At the Hamilton Glaucoma Center
5. Doug Anderson getting ready for the Consensus meeting
3, 2. Audience

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