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Management of Glaucoma in the Era of Modern Imaging and Diagnostics

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1. Introduction

In light of a rapidly expanding geriatric demographic worldwide, and the concomitant increased prevalence of glaucoma, the need for reliable and reproducible methods for disease progression has become increasingly necessary. Given the high costs and morbidity of treatment, whether medical, laser, or incisional, the ability to detect disease and to further demonstrate progression allows glaucoma specialists to make more informed decisions regarding both the initiation, and advancement of therapeutic modalities. Furthermore, our ability to image both the anterior segment and the optic nerve head has allowed for better elucidation of anatomic variants and mechanisms of secondary glaucomas, along with better detection of subtle glaucomatous optic neuropathies and progression of nerve fiber layer defects.

The treatment of glaucoma has advanced rapidly over the past decades, yet remains a chronic disease requiring life long control. The expansion of the armamentarium of interventions possible to help retard progression of disease has allowed us to cater treatments to the specific needs of an individual patient. As glaucomatous damage is essentially irreversible, the holy grail of glaucoma treatment, regardless of etiology, is early detection of a progressive disease state. Intraocular pressure (IOP) remains the only modifiable risk factor for glaucoma patients, and continues to serve as the metric by which the success of therapeutic intervention is judged. The need for accuracy of these measurements has led to a better understanding of ocular tissue properties, and potentially their relative effects on disease progression.

In terms of diagnosis and management of glaucoma, progress has been made since the days when visual field testing remained the only option for the detection and documentation of disease and its progression. As traditional perimetry provides a functional assessment of a patient's disease state, the need for reliable structural measurements has resulted in the development of a multitude of technologies. The relationship between structural damage and functional loss, however, is often complicated, and much remains to be elucidated at the current time. Since structural and functional assessments give us different information, both are often used in conjunction for the detection and treatment of glaucoma. Understanding the limitations of both assessments is tantamount when considering various therapeutic algorithms. Ultimately, it remains the role of the clinician to determine an individual patient's risk of progression. This is optimally achieved by determining the level of intervention necessary to prevent functional loss, balancing the risks, side effects, and costs of treatment.

2. Assessment and measurement of intraocular pressure

As intraocular pressure (IOP) remains the only modifiable risk factor for glaucoma, the importance of consistent and accurate measurements cannot be overstated. Reduction of IOP remains the cornerstone for the treatment of glaucoma, as adequate and reproducible data on neuroprotective agents is currently lacking. Given that all forms of tonometry have limitations, the reference standard for IOP assessment continues to be Goldmann applanation tonometry (GAT). A brief review of the principle behind IOP measurement is provided here. GAT relies on the Imbert-Fick principle, and is in part based upon a standardized GAT applanation diameter of 3.06mm. The IOP is inferred from the force needed to flatten this standardized area of the central cornea. Therefore, it is intuitive that central corneal pathologies and properties will affect these IOP measurements.

For patients with high corneal astigmatism, it is important to take the average of two measurements 90 degrees apart by adjusting the applanation tip accordingly. GAT measurements need to be furthermore adjusted according to standard corneal pachymetry nomograms, although no one nomogram that exists that is universally accepted. A range of IOP correction from 1.1 to 7.14mm Hg/100 microns of corneal thickness exists in the current literature[1]. It is of interest that the clinical utility of these adjustments remains somewhat controversial, and that other corneal biomechanical properties may be of higher utility (See Ocular Response Analyzer below). Regardless, it is likely that corneal pachymetry measurements below 500 microns underestimate IOP, and those over 600 microns overestimate the measurement. A variety of tonometers have been developed in response to these properties, and some are discussed within this section.

2.1 Tonopen (Reichert technologies depew, NY)

The Tonopen is a modified Mackay-Marg tonometer, and is commercially sold as the Tonopen XL, and more recently, the Tonopen Avia. Mackay-Marg tonometers work on the principle that the applanating force to flatten a cornea (transuducer with a 1.5 mm applanation tip) must be equivalent to the counteracting force from within the eye. The transducer only measures the pressures at the center of the applanator, in contrast to the GAT, and is theorized to be less dependent on intrinsic corneal properties. The Tonopen contains a micro strain gauge attached to a 1.0 mm transducer, sampling at a rate of 500 measurements per second. This high sampling rate allows the Tonopen to provide accurate and reproducible IOP measurements. The Tonopen has several major advantages over GAT. It does not require a slit lamp, and is therefore not dependent on patient positioning, allowing for easy use outside the examnination room setting.. It further provides objective results, and requires less skill and training than GAT to perform. The Tonopen is particularly useful in children and non-cooperative patients. The surface area of applanation is one-third that of the GAT, and the ability to measure IOP from a non-central location may be an advantage in patients with certain corneal pathologies.

A study done in the earlier years of the Tonopen on 15 eyes which needed corneal glue, or had band keratopathy, demonstrated that the Tonopen was equivalent to the GAT when the unaffected area was applanated The study further concluded that the Tonopen grossly overestimated the IOP when the affected area was tested[2]. A large cross-sectional study of over 2000 primary care patients who were screened for ocular hypertension (OHTN) with the Tonopen described no adverse effects of tonometry, and further determined the incidence of OHTN and primary open angle glaucoma (POAG) to be 4.89% and 1.04%

respectively. Broman, et al.[3], examined 230 glaucomatous eyes with the Tonopen, GAT, Ocular Response Analyzer (ORA- see below), and further obtained measurements of central corneal thickness (CCT), axial length, corneal curvature, corneal astigmatism, central visual acuity, and refractive error. The IOP measured was noted to be lowest by the Tonopen, and highest by the ORA. Interestingly, it was found that the GAT was least affected by corneal pachymetry, and corneal hysteresis (see ORA below) was correlated with CCT. The authors concluded that corneal parameters affect tonometers in different ways. Lester, et al.[4] in an analysis of 104 patients found that the Tonopen XL gave similar results to GAT in only 62% of patients, and in subgroup analysis, found that the Tonopen XL underestimates IOP when GAT was above 20mm Hg.

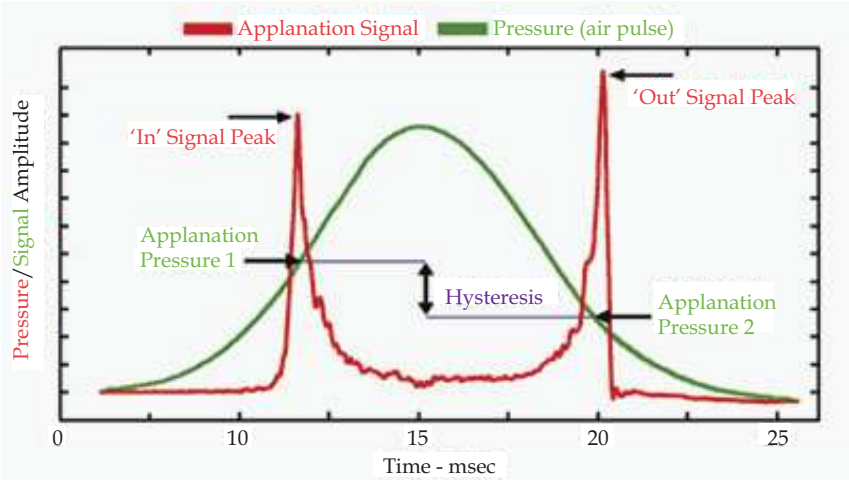
2.2 Ocular Response Analyzer (ORA: Reichert instruments, depew, NY)

The Ocular Response Analyzer is a modified non-contact tonometer, which measures previously un-recordable corneal biomechanical properties. These properties are thought to be the result of viscous damping of corneal tissue. The ORA utilizes a rapid air impulse, combined with a highly sensitive optical system, to record applanation pressures when the cornea is both maximally deformed inwards, and then once again on reformation. The *average* of the two IOP measurements is termed IOPg, to denote the fact that it is the equivalent of the correlated GAT. The *difference* between the two IOP measurements is termed corneal hysteresis (CH) (Figure 1-2). The ability to measure hysteresis allows for further derivations of other newer metrics, such as corneal-corrected IOP (IOPcc) and the corneal resistance factor (CRF). These derived metrics eliminate the need for corneal pachymetry compensation of IOP. The IOPcc is derived from a normative database of patients undergoing keratorefractive surgery, and "compensates" the IOP based on corneal properties, not corneal thickness. CRF is a measurement of the cumulative effects of both the viscous and elastic resistance encountered by the air jet while deforming the corneal surface, and is derived from CH measurements using various algorithms. ORA measurements have proven to be particularly useful in patients with corneal edema and some secondary glaucomas, where IOPg can serve as a surrogate for GAT when it is not possible. Patients with abnormal ORA hysteresis measurements may be at higher risk for corneal ectasia and possibly post keratorefractive surgery complications as well[5].

A study of 90 eyes (30 normal, 30 with POAG, 30 pseudoexfoliative) was recently performed with the ORA, and corneal hysteresis was found to be significantly lower in pseudoexfoliatives when compared to the controls and POAG patients[6]. Another recent review of 108 POAG patients demonstrated both lower corneal hysteresis and resistance factor measurements when compared to those of ocular hypertensives and controls[7]. In a prospective cross-sectional study of 117 POAG patients with asymmetric visual fields, Anand et al[8] demonstrated that abnormal ORA parameters were significantly associated with the eye with the greater visual field defect. Neither corneal pachymetry, nor GAT, were significantly different between the eyes. These findings suggest that the ORA is able to detect subtle differences in asymmetric glaucoma, when GAT and CCT measurements are symmetric.

Lastly, Ang et al performed a prospective comparative analysis of 40 patients with normal tension glaucoma (NTG) with 41 diagnosed with POAG, demonstrating higher hysteresis measurements in the NTG group. The highest recorded GAT measurement was also statistically significantly correlated with lower hysteresis and higher resistance factor values. These findings suggest that alterations in corneal biomechanical properties may

occur in response to chronically elevated IOP[9]. It is clear that the ORA is able to distinguish corneal biomechanical properties that were previously undetectable. As our understanding of the clinical relevance of these parameters improves, the predictive and diagnostic utility of ORA will likely lead to a greater adoption of this technology.



Ocular Response Analyzer(ocularresponseanalyzer.com), Reichert Industries website, 2011

Fig. 1. Ocular Response Analyzer (ORA). The ORA results from both eyes are displayed in graphical form, and are referred to as the "Signal Time Response" curves. The dynamic air puff to the cornea leads to two applanation events (inward and outwards), and the delays in these events are due to intrinsic corneal biomechanical properties. The Y-axis is the "Pressure/Signal Amplitude", and the X-axis is time in msec. The solid curve which peaks in the center of the plot is the pressure (air pulse). The bimodal peaked line represents the applanation signal. The first peak represents the "in-signal", when the cornea is flattened inwards by the air-puff. The second peak represents the "out-signal", when the cornea essentially "unflattens" back to its original state. The intersection of the pressure and signal plots at both peaks represents the two applanation measurements respectively. The average of the two pressures is the calculated IOPg, or Goldmann-correlated IOP. The difference between the two pressures is termed corneal hysteresis (CH), and is thought to be due to the viscous damping effects of the corneal tissue. The normal range of CH varies significantly from 8-16mm Hg, with the value of 11mm Hg considered normal. The IOPcc and CRF are derived from the CH. The IOPcc is the estimated IOP given the CH of a cornea, and is considered to be independent of pachymetry, etc. The CRF provides an estimate of the overall resistance of the cornea, and normal values range similar to the CH

2.3 Pascal dynamic contour tonometer (DCT)

The Pascal DCT (Zeimer Ophthalmics, Port, Switzerland) was developed in response to the large degree of variability of IOP measurements obtained by GAT, with respect to various corneal properties and biomechanics. It further eliminates the subjective nature of GAT by providing a slit-lamp mounted digital readout of the IOP. The advantages of the digital readout, along with the resultant reductions in intra-observer variability, are intuitive in a

busy clinical setting. Measurement of the ocular pulse amplitude (OPA) , a metric estimating the quality of ocular blood flow, is further displayed digitally. The SensorTip™ of the DCT is a concave applanator which houses a piezo resistant pressure sensor able to take approximately 100 measurements per second. A spring loaded Cantilever maintains a constant applanation force of 1 gram, reducing the likelihood of iatrogenic corneal injury as well. A major theoretical advantage of DCT, when compared to GAT, is that IOP measurements from DCT are not affected by corneal pachymetry. This difference is especially useful for keratorefractive and keratoconic[10]patients, where thin corneas and astigmatism greatly affect GAT measurements. The DCT clearly addresses many of the major shortcomings of standard GAT. DCT likely will play a larger role in glaucoma

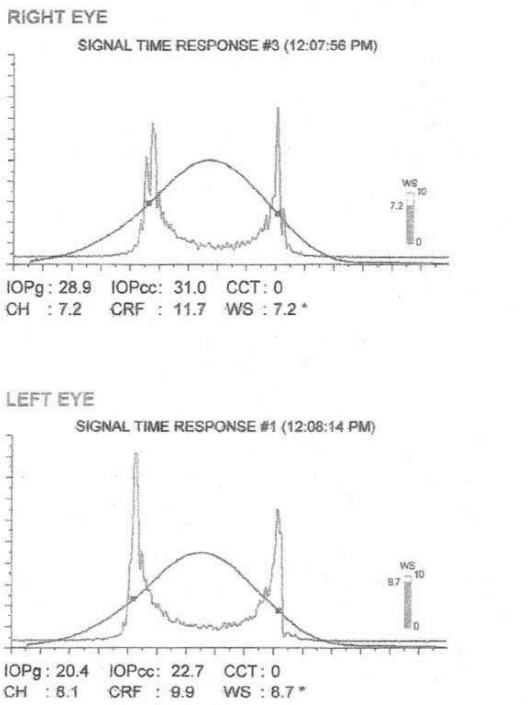


Fig. 2. ORA of glaucoma patient

The ORA scans of a patient show extremely an extremely high IOPg in both eyes, with the right eye being significantly higher than the Left (28.9 mm Hg, 20.4 mm Hg). CH values are low in both eyes, with an IOPcc even higher than IOPg (31.0 mm Hg OD, 22.7 mm Hg OS). The intraocular pressures of this patient by GAT have ranged from 12m Hg-18mm Hg on medical therapy, significantly lower than the measurements by the ORA. It is likely that the ORA is demonstrating a gross underestimation of this patient's IOP control. If functional and structural analysis continues to show progression, it is likely that this patient will need more aggressive IOP management than that being demonstrated by serial GAT. As with all testing, it is important to reproduce abnormal results prior to advancing to any therapeutic intervention

management, especially given that data generated from the DCT can be wirelessly integrated into many electronic medical record (EMR) systems. A hand-held DCT has been developed recently, and results have been shown to be consistent with the slit-lamp mounted model[11].
The DCT has been widely studied, and the current body of literature supports its use clinically. A retrospective review of 200 patients by Ang, et al.[9] demonstrated poor correlation of DCT with GAT measurements that had been corrected with six different pachymetry compensation formulae. Gunvant, et al[12] examined 120 eyes, and demonstrated that the Ehlers formula for GAT correction actually reduced agreement with DCT measurements. This study demonstrates that simple GAT corneal correction factors may be inadequate to compensate for complex corneal biomechanics. Kotecha, et al[13], examined 100 patients with GAT, ORA, and DCT, and concluded that the DCT demonstrated the best repeatability and reproducibility. Interestingly, ORA and DCT generally measured the IOP to be 2 mm higher than GAT in this study. Sullivan-Mee, et al[14] performed a similar analysis on 126 eyes, and found that all three forms of tonometry (GAT, ORA, and DCT) had similar repeatability and reproducibility, concluding from their data that the ORA and DCT are acceptable alternatives to GAT in routine clinical practice.

2.4 Icare® rebound tonometry (IRT)

Rebound tonometry, commercially available as the Icare tonometer TA01i (Tiolat Oy, Helsinki, Finland), has shown tremendous promise in the realm of pediatric ophthalmology and community screenings in particular. The Icare tonometer does not require topical anesthesia, and is able to provide rapid digital IOP measurements painlessly. The handheld device is first stabilized on the patient's forehead, and a small disposable rebounding probe briefly applanates the cornea. It is able to measure the IOP in microseconds, obviating the need for anesthesia and prolonged measurements, making the technology especially useful for children and special needs patients. The probe is briefly magnetized by an induction coil prior to firing, and the tonometer calculates and digitally displays the IOP from the generated induction current. It is important to note that IRT is likely subject to the same constraints as GAT with respect to various corneal parameters.
Flemmons et al[15]collected GAT and IRT measurements from 71 pediatric glaucoma patients, and found that the IRT measurements were within 3mm Hg of GAT in 63% of patients. It was further noted that the IOP was higher by IRT than GAT in 75% of patients measured. Scuderi, et al,[16] in a clinical study of 93 patients, examined the validity and limitations of IRT. They concluded that IRT was comparable to other nonconventional tonometers, and can replace GAT when it is not available. Munkwitz, et al[17] similarly examined 75 patients with GAT and IRT, and found that the IRT performed well within 3mm Hg for normotensive patients. However, in patients with IOPs ranging from 22-60 mm Hg, the IRT was shown to have larger variability than the GAT. This result potentially reduces the validity of IRT measurements in ocular hypertensive patients.
One of the most challenging aspects of glaucoma management is an absence of IOP data between office visits. Compliance rates likely change in the days preceding office visits, and extrapolating IOP over time from limited data points has serious limitations. In diabetic and hypertensive patients, inter-visit monitoring of blood pressure and blood glucose offers internists a great deal of information regarding the efficacy of treatment for these diseases. The possibility of home monitoring of IOP by IRT was addressed in a recent study by Asrani, et al. They observed excellent inter- and intra-observer variability (less than 3mm Hg) in 100 patients that performed IRT on themselves, compared with IRT and GAT

performed by a technician[18]. The possibility of home monitoring of IOP may have particular significance for patients where large diurnal IOP variability is suspected given normal measurements at office visits.

3. Standard automated perimetry (SAP) and short wavelength automated perimetry (SWAP) – Functional assessment of the glaucoma patient

SAP, or static perimetry, is most commonly performed by the Humphrey or Octopus perimeter. Alternately, manual (kinetic) perimetry, is most commonly performed with the Goldmann perimeter, although it is important to note that some automated perimeters do have kinetic testing functionality. SAP serves as a nonspecific assessment of visual function, and is designed to detect loss of sensitivity to light perception. This is traditionally done with a white stimulus on a standardized white background of uniform luminescence. However, newer testing paradigms which isolate specific wavelengths of light (see SWAP testing below) have been introduced for certain clinical indications. SAP serves as a global metric of functional loss. In clinical practice, this means that visual field deficits may represent a disease process anywhere from the ocular surface to the visual cortex. Characteristic patterns of deficit allow the practitioner to anatomically localize the site of injury, and are tremendously useful in the diagnosis and monitoring of many disease states. It is important to note that any visual field defect that is suspected to obey the vertical midline warrants further neurological assessment. The temporality and congruity of the field deficits further provide useful clues to the etiology of the defects. Bitemporal lesions generally localize pathology to the sella turcica adjacent to the optic chiasm, whereas homonomous defects are generally post-chiasmal. Highly congruous homonomous defects, especially with macular sparing, often localize to occipital pathology.

SAP testing relies on a variety of strategies, which ultimately determine the threshold necessary to reliably detect the presence of a stimulus in predetermined locations within the visual field. Algorithms and testing strategies have been constantly advancing to maximize sensitivity and specificity, while reducing test time and patient fatigue. Given the wide variety of options, it is imperative that the clinician not only chooses the correct test, but also furthermore accounts for an individual patient's ability to reliably perform that test.

The decision to advance treatment based on visual field analysis is inherently fraught with confounding factors. While the advent of structural analysis (see below) have allowed for some quantification of glaucomatous defect, the necessity for analysis and documentation of functional disease progression with perimetry remains a vital component of glaucoma management. This is especially the case when there are disparities between clinical examination, perimetry, and structural analysis. An improved understanding of the limitations of standard perimetry and structural analysis allows the astute clinician to avoid treatment errors. This is particularly important given the high levels of morbidity associated with many of the interventions presently available. The following sections aim to highlight the strengths and weaknesses of the wide range of testing modalities currently available.

3.1 Humphrey field analyzer (HFA)

One of the most commonly utilized perimetry devices is the HFA, with over 35,000 units in use currently worldwide. Indeed, many of the landmark glaucoma trials such as the Ocular Hypertensive Trial (OHTS)[19], Advanced Glaucoma Intervention Study (AGIS)[20], and Collaborative Initial Glaucoma Treatment Study (CIGTS)[21]to name a few, used this form of

perimetry to diagnose and detect functional glaucomatous progression. HFA analysis is the current gold standard for clinical trials, allowing for older studies to be appropriately compared. Recent advancements in progression analysis software by multiple vendors have increased the clinical utility of serial SAP testing by allowing for greater detection of subtle changes.

The choice of the most appropriate HVF should be based upon a wide variety of considerations. Some of these considerations include the extent of the visual field that needs to be tested, the intensity and size of the stimulus needed, and the best suited testing strategy for the clinical question being analyzed (i.e. screening vs. monitoring progression, etc.). An important caveat is that once a reliable visual field is obtained, it is advisable to utilize the same testing strategy as much as possible to reliably detect disease progression over time.

3.1.1 Degrees of visual field tested

The major options on standard HVF perimetry are 10-2, 24-2, 30-2, and the less commonly performed 60-2. The first number refers to the number of degrees around the fovea that will be tested (i.e. a 10-2 test 10 degrees of the visual field centered at the fovea). The second digit which is currently always "2", refers to the protocol type which tests points on either side of the horizontal and vertical meridians, as opposed to points on the meridians themselves. Testing points directly on the meridia is denoted with a "1" as the second digit. The "1" strategy is particularly useful in neuro-ophthalmic evaluation, to highlight the presence of vertical midline defects, for example. In general, the use of 10-2 testing is reserved for patients with very advanced glaucoma to detect subtle progression in an extremely constricted field, and for patients with suspected maculopathy. The 60-2 strategy can be applied in patients where peripheral defects detected by smaller field analyses require further confirmation, however patient fatigue and artifacts may limit the clinical utility of this strategy.

The choice between 24-2 and 30-2 is somewhat variable between practitioners, and there are advantages and disadvantages to each test. Many glaucoma specialists follow patients with 24-2 testing in lieu of full 30-2 testing as it has been demonstrated that both tests have approximately equal sensitivity and specificity[19] in the detection of glaucomatous field damage. The 30-2 paradigm can lead to significantly more fatigue for patients given the additional test spots in the periphery of the visual field. The 30-2 tests one more row of points in the peripheral visual field compared to the 24-2. This area of the field is most sensitive to rim, lid, and other artifacts, thereby reducing its clinical utility in some cases. As the detection of subtle field changes necessitates accurate testing (see below: reliability indices), the choice of a 24-2 paradigm may allow for improved reliability and more clinically meaningful data. Some clinicians choose to order a 30-2 test as the baseline, and assuming that it is normal, will follow patients with 24-2 testing. It is important to note that often multiple tests need to be performed to set a reliable baseline, as field testing accuracy generally improves along a variable learning curve. In patients having difficulty with increased test time, it is appropriate to set a baseline with the most extensive test that a patient can reasonably tolerate (see below: testing strategies) Important testing specifications are reviewed below:

- 10-2: The points adjacent to the horizontal and vertical meridians test 1 degree of the visual field; points tested peripheral to these points are 2 degrees apart

- 24-2 and 30-2: The points adjacent to the horizontal and vertical meridians test 3 degrees of the visual field; points tested peripheral to these points are 6 degrees apart

In a patient with a subtle maculopathy, affecting only a few degrees of the central visual field, defects can easily be missed by the 24-2 and 30-2 based on the aforementioned testing specifications, as the scotoma could fall in the region between the tested points. Alternately, dense paracentral/arcuate scotomas characteristic of glaucomatous optic neuropathies can "blacken" out an entire 10-2 field, and the 24-2 or 30-2 paradigms are far better suited.

a. Screening considerations

Screening protocols are variable amongst practitioners and practices. Large volume screenings for glaucoma are often performed with Humphrey Matrix Analyzers/ (FDT) based on the test time needed to perform the analysis. It is appropriate for "high risk" patients being screened (eg Strong family history of glaucoma, ocular hypertensives, IOP/cup-to-disc asymmetry, etc.) to perform more extensive perimetry with SITA-fast protocols (see below). Patients with positive screening tests warrant further work-up, often with structural and corneal biomechanical analyses.

b. Other considerations

As HFA analyses are based on age-matched controls, it is imperative that the correct birth date is entered prior to testing. The age groups of patients in the database are stratified into 10 year increments. For example, a 59 year old patient will be compared to age matched controls between the ages of 50-60. It is common, therefore, for patients to have deterioration of their visual field as they progress through each decade of life. Alternately, "improvements" in the visual field can be seen immediately after the patient's age increases to the next decade stratification. Furthermore, assessment of the mental and physical status of an elderly patient to determine whether they will be able to tolerate the high levels of concentration required to perform the test.

Refractive errors, especially presbyopic errors, need to be neutralized with the appropriate loose lenses, and vertex distances/head positioning optimized. Astigmatic correction over 1.25D should be neutralized along with spherical aberration. The HVF will determine the optimal neutralization from manifest refractions accounting for a target distance of 30cm. Reassessing head position relative to refractive neutralization is critical during testing, as rim artifacts can be generated by the lenses if head positioning is not adequately monitored. Furthermore, prismatic deviation caused by high power lenses need to be accounted for when testing is analyzed, and peripheral rim defects discounted appropriately in these cases. Pupil size is able to be measured by HFA, and is displayed with the results. Pupil size generally less than 2-3mm can lead to artifactual loss of threshold sensitivity of both central and peripheral fields[22]. This is of particular importance in following patients on miotic therapy for glaucoma. Pharmacological dilation of the pupil in these cases may help limit the effects of the miotic pupil. Patients should be consistently dilated for subsequent fields if this strategy is employed. Changes in the refractive error secondary to pharmacological dilation are likely negligible in the largely non-presbyopic patient demographic that commonly undergo perimetric evaluation.

A standard background light intensity of 31.5 asb (apostilbs) is used for the HVF, to match the scotopic light conditions outlined by Goldmann perimetry standards. HVF targets come in sizes ranging from 0.25 mm^2 to 64.00 mm^2 represented by Roman numerals I through V (see Goldmann Visual Fields below). Typically, a size III stimulus (4 mm^2) is used in patients

with good visual acuity (usually at least 20/200 or better). In these cases of decreased visual acuity, the use of larger size V (64 mm^2) test stimulus may be helpful, although many clinicians will opt for Goldmann Visual Fields for these low vision patients. Stimulus intensity, color, and duration can furthermore be varied by the operator based upon clinical needs.

Gaze tracking is possible with all HVF machines, and the reliability of an individual test can be further analyzed beyond the reliability indices calculated for each field. A real time fixation monitor is displayed at the bottom of each visual field printout. Upward deflections represent the moment a patient saccades away from a target, and downward deflections represent a tracking failure commonly secondary to blinking.

3.1.2 Testing algorithms – Swedish interactive testing algorithm (SITA)

SITA testing was designed to optimize visual field accuracy while reducing testing time. It is based on the concept of "threshold", which is a term that is defined as the intensity of light that a patient can detect 50% of the time. The threshold represents the minimal amount of light intensity that can be reliably detected. SITA testing determines this threshold by presenting points with varying intensities using a "bracketing" technique. Specifically, this technique involves measuring intensities above and below the threshold, as defined above. This technique is much more efficient than full threshold protocols, and generally is able to maintain a high degree of concordance in a much shorter time period. The SITA algorithm is dynamic, and the stimuli are timed based on an individual patient's response time. Algorithms are age-matched, so proper patient data entry is imperative. SITA-Fast and SITA standard algorithms remain options that can reduce test time by about 70% and 50%[23], respectively, when compared with full threshold tests. The differences between the protocols lies in the variability in response allowed when determining threshold values, with the SITA standard being more rigorous in repetition of points. In other words, the SITA-FAST strategy has a lower level of confidence needed to be achieved at each point relative to SITA-Standard. The SITA-fast protocol utilizes the expected thresholds based on normative population databases. The utilization of these normative assumptions increases the efficiency of the test, but is limited by the fact that it does not account for threshold variability at the individual level. The SITA fast protocol is generally more than adequate for screening examinations and for those patients who cannot perform SITA standard secondary to fatigue. Most glaucoma specialists rely on SITA standard testing to monitor for subtle changes indicating progression. This is particularly critical in the regions of the visual field surrounding an existing scotoma. A study by Budenz, et al demonstrated an overall sensitivity of 98% and 95% for SITA standard and SITA fast protocols when compared to full threshold testing. The same study demonstrated sensitivity in patients with mild glaucomatous damage as 92% and 85% respectively[24]. Specificity was determined to be 96% for both algorithms.

3.1.3 Short wavelength automated perimetry (SWAP) – Blue-on-yellow perimetry

SWAP testing is based upon the concept that glaucoma is characterized by damage to cells in the visual pathway that are more sensitive to blue light, with a peak activity at 440 nanometers. Blue cones in the photoreceptor layer of the retina eventually synapse in the koniocellular layers of the lateral geniculate body, via small bistratified retinal ganglion cells. The fact that SWAP testing isolates one type of ganglion cell should not imply that

these cells are necessarily the first to be affected by glaucomatous injury. Moreover, SWAP testing avoids the masking effects of inherent redundancies within the visual pathways by isolating one particular system.[25,26]

SWAP testing is generally more fatiguing than SAP, and is also much more affected by lens opacification and drusen in patients with macular degeneration. Recent development of SITA-SWAP testing has helped reduce test duration while maintaining sensitivity. The stimulus size for the blue target in SWAP testing is larger than that of SAP (equivalent to Goldmann V vs. III sized targets, respectively). More light is needed to activate the blue cone system[27], and although the blue target is generally less bright, the larger test stimulus size partially compensates for it. The caveat is, that a larger test stimulus can over estimate fixation losses in patients with relatively small blind spots, even though fixation maybe maintained.

Many studies have demonstrated the ability of SWAP testing to detect visual field abnormalities earlier than SAP testing[28,29]. A recent publication demonstrated less persuasive results regarding the early predictive abilities of SWAP testing. However, methodological differences between Johnson's original data from the prior decade may help explain the varied results[30]. Other reports indicate that patients with visual field defects on SAP demonstrate dramatically larger defects when tested with SWAP[31-33]. As data is continually being collected regarding SWAP testing in glaucoma patients, a better understanding of the protocol's benefits and limitations will help elucidate the role of SWAP testing in functional assessment of the glaucoma patient. At the time of this publication, SWAP testing largely remains the test most commonly used in younger patients with high clinical suspicion for glaucoma. This is especially the case in patients with previous normal SAP testing.

3.1.4 Reliability indices

In order to make determinations about clinically significant functional progression, it is imperative that visual fields are as reliable and reproducible as possible. Assessment of a glaucomatous scotoma by *reliable* perimetry is expected to fluctuate given the natural history of the disease and the manner in which we quantify defects. Alternately stated, seemingly progressive visual field loss can often "reverse" with serial testing, indicating that the etiology of the deterioration may indeed be non-physiological. The establishment of a blind spot corresponding to the position of the optic nerve is accomplished by placing testing points within this region during reliable fixation. It is even more challenging to separate fluctuation from progression when analyzing visual fields that are considered "unreliable". The establishment of an adequate baseline is important clinically, and essential if progression analysis is desired (see GPA below).

Fixation losses are measured by introducing stimuli into the physiological blind spot, and monitoring whether patients are able to detect them. A fixation loss indicates that the blind spot has moved (i.e. the patient has refixated to an alternate location within the perimeter). False positives are defined as patient responses when no stimulus is present. False negative responses are defined as a lack of detection of a suprathreshold stimulus (i.e. not being able to detect a more intense stimulus after the threshold is determined).

Reliable fields generally are recommended to have false positive and negative rates fewer than 35%, and fixation losses less than 20%. In clinical practice, many patients are not able to adequately perform the testing regardless of algorithm, and alternate means of documenting functional progression are necessary. Birt, et al.,[33] demonstrated in a review of 768 visual

field test from 106 glaucoma patients, that only 59.5% of test were considered reliable by the aforementioned criterion. Elevating the fixation loss threshold criterion from 20% to 33% increased the number of fields meeting reliability standards to over 75%. Newkirk[34], et al further demonstrated that artificially introducing false positives of 33% to a visual field improved the calculated mean deviation (MD) by 6dB; an amount that can easily mask progressive damage. Vingrys et al[35]demonstrated similar results, suggesting that the cutoffs for reliability of false positive results be reduced to 20% or less. Bengtsson, et al.[36], hve shown that false positive rates are the least variable in test-retest paradigms, and are likely to be the most reliable index of visual field accuracy based on the SITA algorithms.

3.1.5 Glaucoma Hemifield test/analysis (GHT)

The GHT was developed by Asman, et al in the early 1990s to measure asymmetries in threshold sensitivity around the horizontal meridian. It functionally analyzes five corresponding pairs of mirror image sectors in the superior and inferior horizontal fields, corresponding to the normal anatomy of the retinal nerve fiber layer. Outer edge, temporal, and blind spot points are excluded from the analysis, and can be used with either the 30- or 24-2 protocols. Abnormal GHT values indicate asymmetry around the horizontal meridian, and allows for rapid evaluation of zone defects that affect the superior or inferior hemifields in particular[37] The results are further stratified into 5 categories: "Outside Normal Limits", "Borderline", "Generalized Reduction of Sensitivity", "Abnormally High Sensitivity", and "Within Normal Limits". The definition of "Outside Normal Limits" is based upon defects between the respective upper and lower paired sectors greater than what would be expected in 1% of the normative database, or a sum difference at 0.5% normal population level. "Borderline" results indicate the same criterion at the 3% normal population level. Katz, et al analyzed the rate of incident field loss after one abnormal GHT, and found that GHT is not a consistent criterion for defining incident field loss. They further concluded that the use of two or three consecutive abnormal fields to define incident field loss makes it more likely that subsequent test results will be abnormal[38]. Susanna, et al. further analyzed the ability of the GHT to detect early glaucomatous changes, and found the sensitivity, specificity, and reproducibility of the GHT to be 100,100, and 83.3% respectively[39]. Johnson, et al more recently concluded that the GHT, GHT hemifield cluster, and Pattern Deviation plots provided the highest sensitivity and specificity of all the visual field metrics[40]

3.1.6 Glaucoma progression analysis (GPA)

Given the often large amounts of data provided by serial perimetry, the absolute need for automated detection of progressive visual field loss has lead to advancements in software that efficiently summarize function over time. This capability allows clinicians to rapidly detect areas of the visual field that have deteriorated from baseline threshold values. These are defined by the user as the first reliable field or fields (full threshold or SITA). The data output of GPA analysis summarizes the probability of the presence of glaucomatous progression. It factors in normal fluctuation from a large database, and subtracts out deficits secondary to media opacification as well. The data is summarized in probability plots, demonstrating the likelihood of functional progression with variably darkened triangular symbols. Triangles that are darker represent a portion of the visual field that has consistently worsened over multiple tests. A minimum of five examinations over at least three years must be included in GPA 2 for the linear regression results to be presented. The

open triangles represent deterioration from baseline with a 0.5 confidence interval, the half-shaded triangles represent deterioration at the same point on 2 visual fields, and finally the darkened triangle represents deterioration at the same location on 3 visual fields. Deterioration is defined as greater than that of the normal fluctuation that occurs within a normative database. Again, the lack of a uniform definition of deterioration is a severe limitation when comparing progression analyses. Consensus regarding this definition continues to be the source of much debate. Furthermore, the clinical relevance of any defined progression must be evaluated on an individual case basis to avoid errors in treatment strategy. Regardless of the definition of progression, it is widely accepted that the accuracy of progression rates is vastly improved with additional data points. This functionally translates into establishing a reliable baseline, repeating visual fields often, and using a longitudinal analysis to determine the rate of progression. In this manner, the likelihood of clinically relevant deterioration can be most accurately assessed.

As the assessment of glaucoma progression involves some degree of subjectivity, there are often discrepancies in patients who demonstrate mild changes in function. A recent review of 510 Humphrey visual fields of 83 eyes by 3 examiners demonstrated that clinician agreement of progression on sequential fields was actually better without the GPA analysis[41]. Clinician agreement (inter-observer reliability) obviously may not be an appropriate reference standard for the determination of disease progression given the subjective nature of the analysis. Another review of 90 eyes with greater than 5 reliable visual fields demonstrated that the GPA performed better in the detection of progression, when compared to a pattern deviation based visual field index (VFI)[42]. Another retrospective review of 93 glaucoma patients with 5 reliable fields concluded that there is a strong correlation between GPA identification of glaucomatous progression and a thorough objective clinical assessment of the visual fields. They further concluded that GPA could be a useful test to aid clinicians in the detection of glaucomatous progression, with high specificity, strong positive likelihood ratio, good sensitivity and negative likelihood ratio[43]. Diaz-Aleman, et al[44] examined 56 eyes of 42 patients with at least 7 reliable fields, and compared threshold noiseless trend (TNT) to GPA, and showed that TNT had a higher specificity and concordance with clinical examiners than GPA.

It is important to note that no universal definition of glaucoma, whether via a statistical package or point-by-point analysis, has been universally accepted. The optimal characterization of glaucomatous progression is the source of much of the research on perimetry that is currently being performed. Furthermore, as the perimetric definitions of progression vary significantly amongst many of the major landmark glaucoma studies, comparisons of results between the major trials has been limited. Clinically relevant models derived from these studies lack reproducibility, and no one index has been shown to be superior at the time of this publication (Figures 3-8).

While a useful adjunctive tool, GPA has had variable success when compared to other methodologies. It is our opinion that GPA serves as a useful tool in conjunction with other standard examination techniques when compared to grossly comparing serial HVF examinations without point by point analysis. The software will unlikely replace careful clinical examination utilizing a gestalt technique in its current clinical application. Monitoring the rate of visual field deterioration by multiple metrics, while accurately predicting the onset of functional loss with particular regard to projected life expectancy, is likely the optimal strategy in determining optimal treatment.

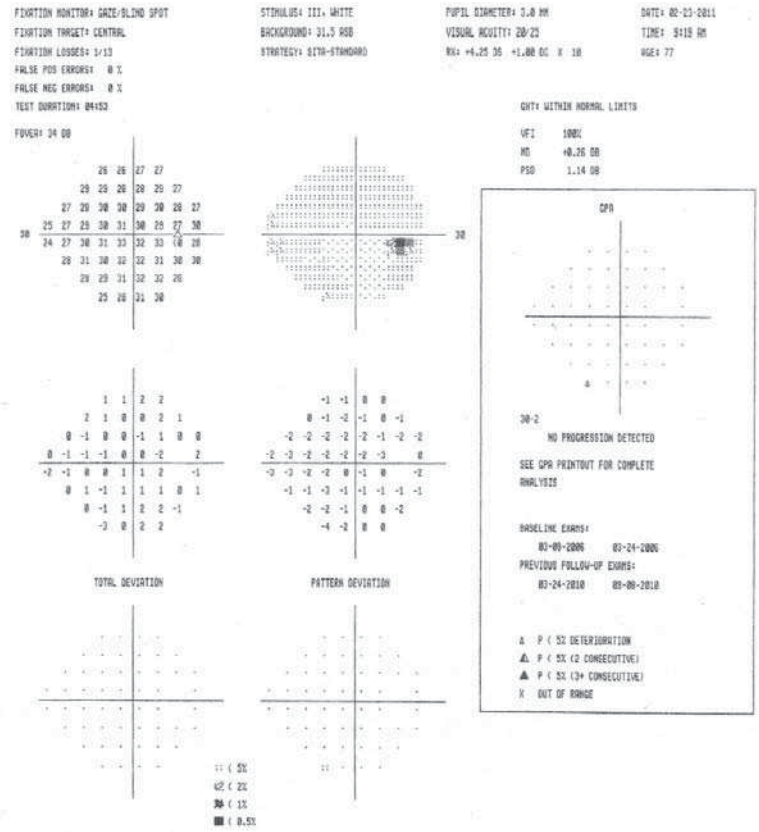


Fig. 3. HVF single field analysis with progression analysis summary: OD

This HVF is an example of the normal scan of the right eye of a patient being followed as a glaucoma suspect. Important demographic information is included at the top of the printout, including the date of birth. The type of visual field, in this case, Central 24-2 Threshold Test, is listed directly below. The type of Fixation Monitor (Gaze/Blind Spot), Stimulus Size (III) and Color (White stimulus on White Background), and the pupil diameter in mm (3.0 mm) is displayed in the next line, along with the date of the examination. The standard background intensity of 31.5 asb is used for this test, and the BCVA is further inputted from the chart. Reliability indices including Fixation Losses, False Positive and False Negative Errors, are displayed as a ratio and percentage respectively. The testing strategy is also displayed (SITA-Standard). Making clinical assessments of progression based upon serial analysis of fields utilizing different strategies should be avoided. The optimal refractive correction for the 30cm test distance is displayed, and it is one of the essential roles of the perimetrist to accurately correct the patient with large diameter loose lenses. The test duration is also recorded, and can give insight into a patient's performance. Longer test durations are likely to be prone to errors secondary to fatigue, and may have poorer reliability indices as well. Often the second eye tested will have lower test times, indicating the possibility of a learning curve effect during that perimetry session. Alternating the first eye tested for subsequent fields may "reverse" this phenomenon when unexplained

asymmetry is found. The threshold sensitivities, along with mean and pattern deviations are plotted along with probability analysis for a given defect. Darker shaded boxes within the field indicate a higher probability that the defect is valid compared to age-matched controls (range from 0.5% - 5%). The glaucoma hemifield test (GHT) is displayed in the upper right hand corner of this scan, indicating in this case that no asymmetry was found between the upper and lower sectors analyzed. Finally, the GPA summary plot is found in the boxed results section. In this case, no progression was detected. Symbols are placed at any test point location that has changed from baseline by more than the variability you would see in 19 out of 20 stable glaucoma patients at the approximately the same stage of the disease. The dates of the baseline and previous fields, used by the software to determine the likelihood of progression, are further displayed. The accuracy of the progression analysis improves dramatically with both a reliable baseline, and a larger number of follow-up fields.

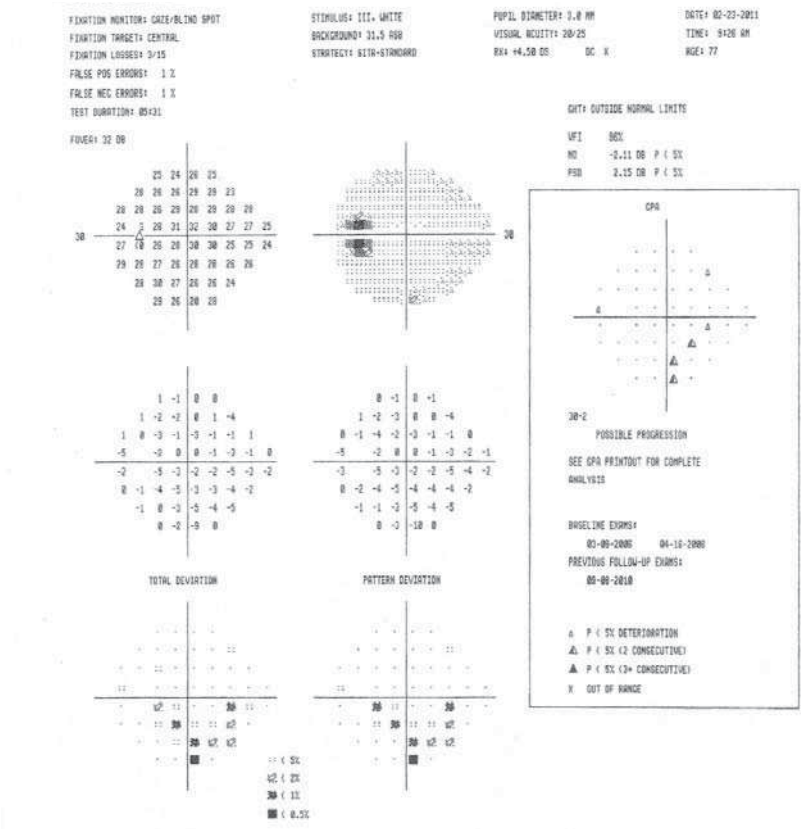


Fig. 4. Single field analysis: OS

In contrast to the right eye of the same patient, the left eye is demonstrating early changes in the pattern deviation of the inferior field (indicated by variably shaded boxes). The GHT is considered "Outside Normal Limits", and the GPA has determined the presence of "Possible Progression". The half-shaded triangles indicate p-values < 5% on 2 consecutive fields.

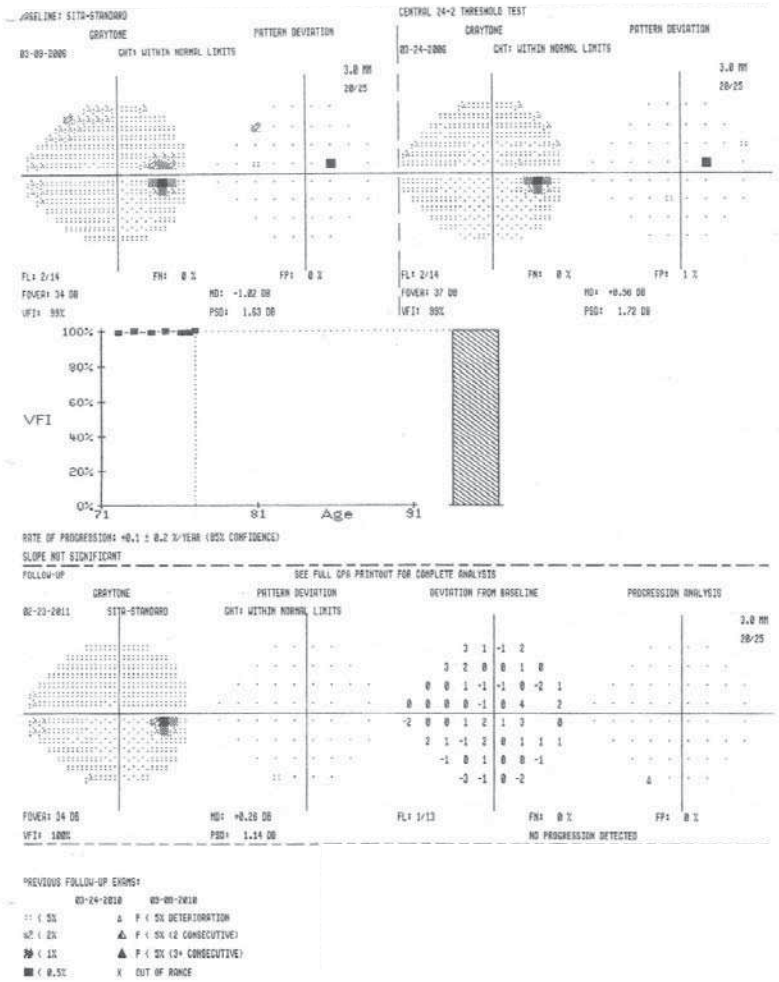


Fig. 5. GPA Summary OD

The GPA summary displays the grey scale for the baseline test, along with some of the indices for each of the tests displayed, including MD, PSD, GHT, Reliability Indices, Pupil size, and BCVA. The rate of change is also plotted over time (patient's age in years) against a visual field index (VFI). A VFI score of 100% represents a normal visual field, and 0% represents completely blackened perimetry. The VFI is calculated from pattern deviation plots, and was developed in response to the effects of media opacity on previous metrics. The rate of progression as a percentage is further displayed and analyzed. In this case, a +0.1 ± 0.2%/year was determined to be a normal slope. The shaded box at the far right of the plots is the extrapolated final VFI given a life expectancy of approximately 100 years old and the calculated rate of progression. The bottom half of the printout displays the results of the most recent exam, and provides probability plots for point-by-point likelihood of progression compared to baseline and prior follow-up examinations.

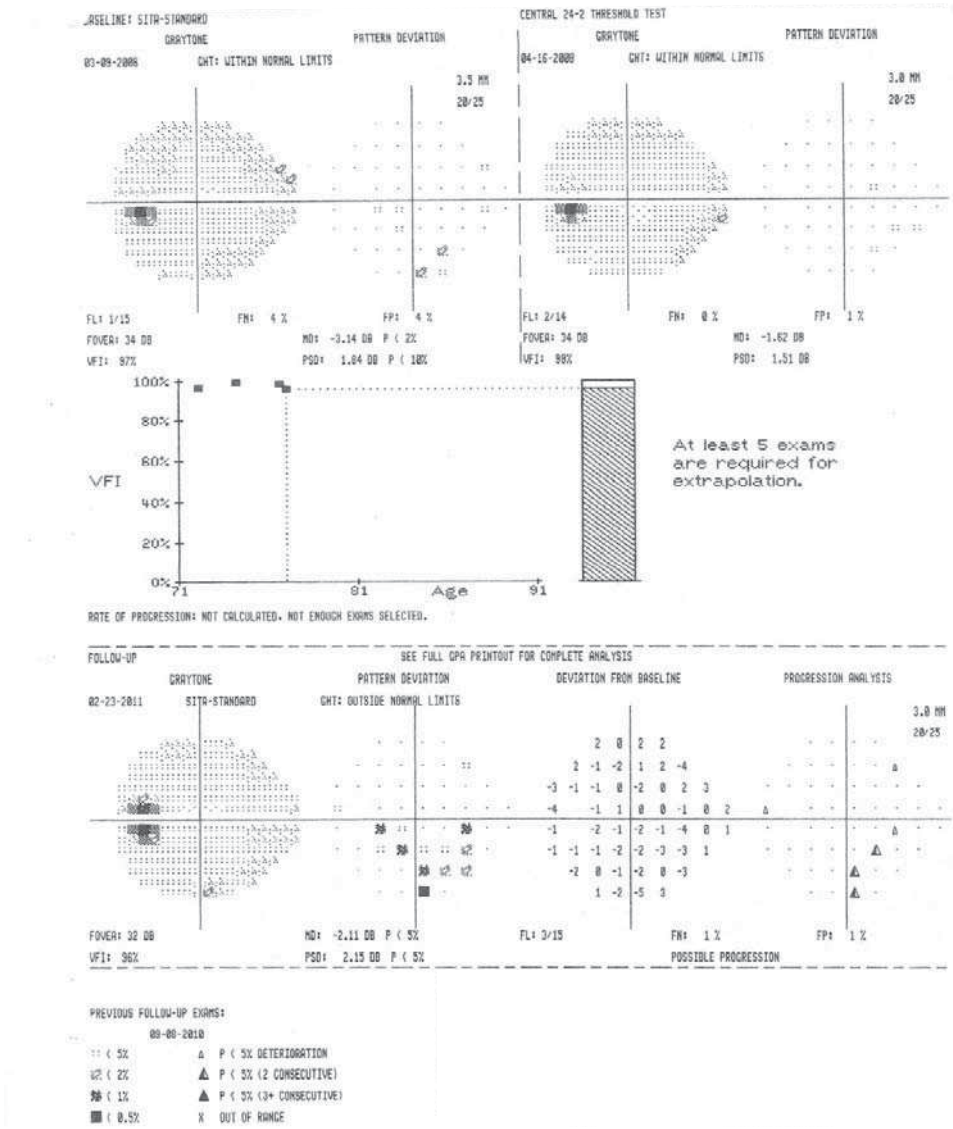


Fig. 6. GPA summary OS

In this case, it is demonstrated that the VFI extrapolation requires at least 5 consecutive tests to be considered reliable (only 4 visual fields are inputted), and a rate to be accurately calculated. The accuracy of this progression software significantly improves over time as additional fields are added to the analysis. The baseline visual fields in this patient are normal, in contrast to the defects noted in the most previous field detailed at the bottom of the printout. This patient is considered clinically to be at moderate risk of functional progression in this eye.

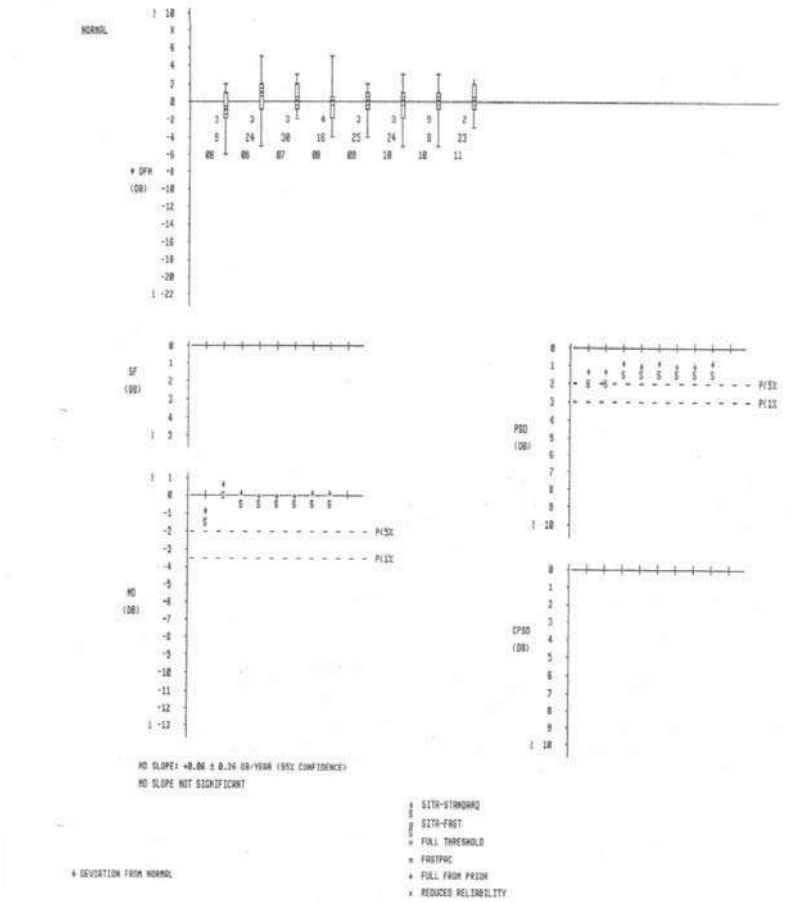


Fig. 7. Change analysis OD

The Change Analysis box plots display a variety of visual field metrics in the form of frequency distributions. The Y-axis is valued in Db, and represents the difference between the observed values relative to a normative database. The actual values observed are displayed in a chronological fashion centered on the 0 dB point (ie no deviation from normal). Positive deflections (above 0 db) indicate a "better than normal" threshold, and negative deflections indicate "worse than normal" threshold values. In this manner, the highest point (top of the "T") for each field represents the point with the highest threshold relative to normal. The shaded boxes for each data set indicate the percentile rank within each field. The highest value of the uppermost box for each data set is the 85th percentile, the middle represents the 50th percentile (ie half of the thresholds are above, and the other half below), and the bottom value represents the 15th percentile. The slope of the line for each visual field index is graphically displayed and then analyzed. In this example, the MD slope is calculated as +0.06 ± 0.26dB/year, indicating that no progression is noted during the testing interval. It is important to note that other diagnoses besides glaucoma can adversely affect the indices as well. Clinical correlation is always imperative.

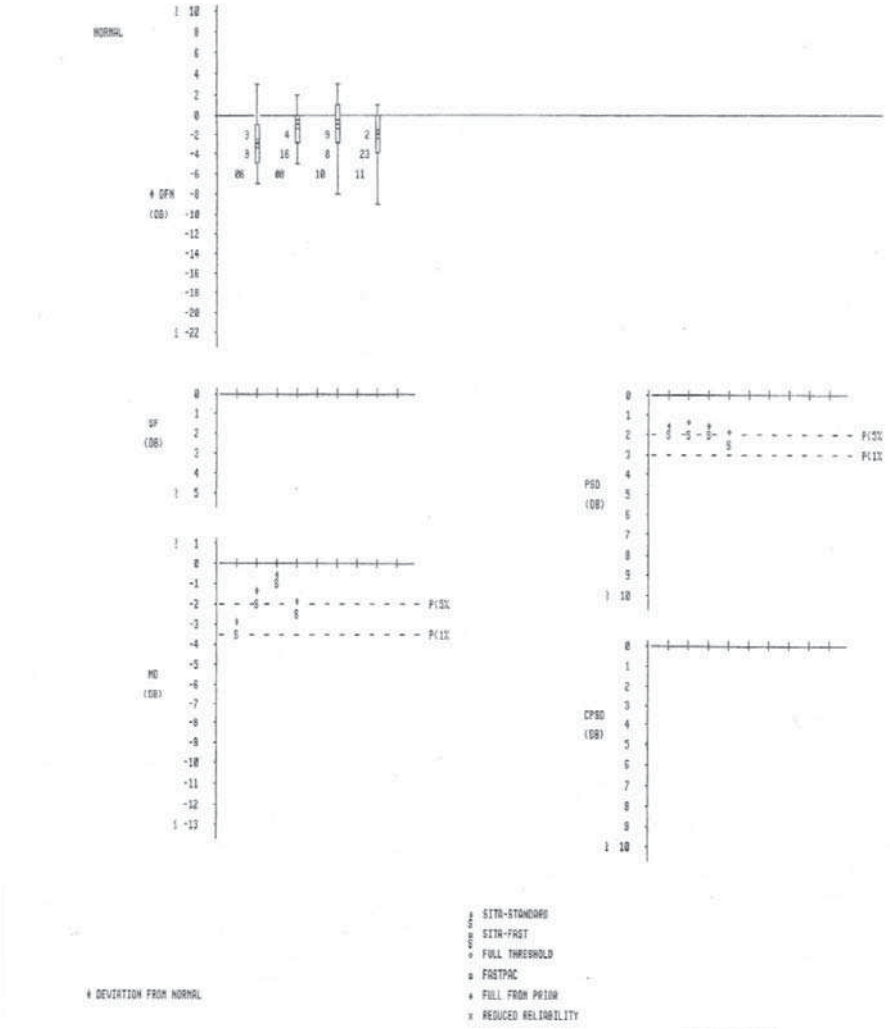


Fig. 8. Change analysis OS

In contrast to the right eye, the median values for the fields included are below the 0db line. The highest threshold points for each field (top of the "T") are above normal limits, however the range of percentile rankings tend to be below the 0 dB mark. The PSD plot further demonstrates possible worsening of the visual field, particularly in the latest examination.

3.2 Alternate functional assessment

When a patient is determined by multiple attempts and strategies to be a poor test taker by conventional SAP, alternate strategies may need to be employed to measure the visual field and establish an adequate baseline. As therapeutic algorithms are often advanced (ie topical therapy, laser, incisional surgery) based upon demonstration of functional progression of

disease, it is optimal for the clinician to exhaust any and all options available to determine the functional status of a patient. The Octopus perimeter is an alternative to the HVF, and offers many advantages in these patients. The Goldmann kinetic perimeter is an also relatively commonly used option in these patients for multiple reasons. As fixation can be manually monitored, patients are able to take breaks during testing, and receive coaching and encouragement on a point by point basis. Frequency Doubling Technology (FDT), Matrix analyzers, while much faster than traditional SAP, may not necessarily be appropriate as an alternate testing protocol for many patients. Simple confrontational visual fields provide only a gross estimate of visual function, and are clearly not an appropriate way to follow patients with, or at risk for glaucoma.

3.2.1 Octopus visual field analyzer

The Octopus visual field analyzer (Haag-Streit International, Koeniz, Switzerland) has had major advancements over the past decade, which largely developed in response to many of the limitations of the HVF. One of the key advancements in the technology is an improved fixation/blink monitor which continually tracks and accounts for fixation losses and eye blinking, along with automatic adjustments based on head and eye positioning relative to the perimeter. This additional functionality can dramatically improve the accuracy of the test, and further limit lens/rim artifacts that may occur with traditional SAP. Furthermore, the Tendency Oriented Perimeter (TOP) strategy employed by the Octopus reduces test duration for threshold analysis to an average of 2.5 minutes per eye, significantly reducing patient fatigue. The Octopus' EyeSuite™ Progression software offers intuitive plots demonstrating both global and cluster progression, and has the ability to integrate structural assessment as well. The Octopus test stimuli and background intensities are matched to those of Humphrey and Goldmann perimeters (See HFA above and GVF below).

Studies comparing the Octopus and Humphrey visual field analyzers have demonstrated variable results. King, et al[45] demonstrated that the SITA Fast and TOP strategies were highly correlated in a study of 76 glaucoma patients. They did note that although the TOP strategy was faster than the SITA protocol, it tended to underestimate the focal visual field defects. A recent analysis by Lan, et al[46] demonstrated a similar finding when comparing the Octopus to FDT (see below). Often times, the establishment of newer baselines with an alternate protocol proves to be a major barrier to adaptation. As with many technologies, ease of integration into electronic medical records has proven to be a driving force for changes in clinical practice. The utility of testing patients with multiple functional assessments remains to be determined given the likelihood of discordance.

3.2.2 Goldmann visual field (GVF)

The major difference between SAP and Goldmann visual field testing is that the SAP is a static visual field, whereas Goldmann visual field testing is kinetic, defined as perimetry utilizing a moving stimulus (3-5 degrees/second)[47]. It is important to note that the GVF may be used as a manual static perimeter as well, and is generally reserved for improved isolation of an existing scotoma. In the case of kinetic Goldmann perimetry, the moving stimulus is controlled by a skilled operator. This subjectivity is a major drawback, as subtle changes in the visual field can easily be missed given the summative variability of both the patient and operator[48]. However, given that each patient response can be carefully monitored, the added reliability of GVF testing makes the test clinically useful in patients who are unable to perform SAP. This is especially true in patients with poor central visual

acuity who are unable to reliably fixate for automated perimetry. This is indeed one of the most common reasons that GVF testing is ordered for glaucoma patients.
An additional advantage of the GVF is that it is it the only form of perimetry that is able to test the entire visual field. This encompasses 60 degrees superiorly and nasally, 75 degrees inferiorly, and 110 degrees temporally, although there are few clinical indications that demand testing far peripheral points. Neuro-ophthamic evaluation for functional visual loss and other central processes remains another common indication for GVF testing.
Definitions of stimuli and target sizes are summarized below.

Stimulus size	**Stimulus Intensity**
0 = 1/16 mm^2	1 – 4 : represent 5dB increments
I = 1/4 mm^2	a - e : represent 1 dB increments
II = 1 mm^2	
III = 4mm^2	
IV= 16mm^2	
V= 64 mm^2	

3.2.3 Frequency doubling technology (FDT) and the Matrix™ perimeter

FDT perimetry is based on a phenomenon that when an achromatic sinusoidal grating ,with low spatial frequency, flickers at a high temporal frequency, the apparent spatial frequency of the grating appears to be doubled[49]. Glaucoma is thought to preferentially effect cells in the magnocellular pathway, which have been demonstrated to be more sensitive to motion and flicker detection[50]. On the other hand, theories contend that the FDT illusion is based on higher cortical processing, and no retinal substrate exists to account for the phenomenon[51]. Regardless, the appeal of a technology that is theoretically able to preferentially detect damage to this visual pathway is obvious, and the clinical utility of FDT has advanced remarkably over the past decades. Current screening and full threshold strategies can be performed in minutes, reducing the inaccuracies of testing patients that are easily fatigued by the duration of SAP and similar strategies (Figures 9-10). Reproducibility of FDT results has further been demonstrated in multiple studies[52,53]. The reported sensitivity of FDT ranged from 0.51 to 1.00, and specificity from 0.58 to 1.00 determined by a meta-analysis of pooled data in 2006, with similar findings in more recent data.[54,55]
Nakagawa, et al.[56] recently examined 39 open angle glaucoma patients with low to moderate IOP, comparing FDT to SAP. With almost 5 years of follow-up, they determined that FDT was useful for monitoring defects detected in the SAP-normal hemifield in OAG eyes with low-to-normal IOP. A detailed study of 60 eyes with normal SAP ("pre-perimetric glaucoma") found that FDT testing was able to detect abnormalities in an astounding 65% of patients, of which 51% later developed defects by SAP over 4-27 months[57], a clear demonstration of the clinical utility of FDT in early detection of disease processes. Ferraras, et al[58] examined 278 subjects with pre-perimetric glaucoma by SAP, but with structural abnormalities by HRT, GDx-VCC, and OCT (see below). This study demonstrated that 20% of patients with structural loss had abnormalities on SWAP and FDT testing when SAP was found to be normal.
The Humphrey Matrix perimeter (Carl Zeiss Meditec, Dublin, Calif) was introduced in 2005, as a newer generation FDT perimetry option with the implementation of multiple efficiency measurements to reduce test taking duration. Fixation monitoring technology has been implemented, as have a wide variety of testing options ranging from screening to full

threshold algorithms. The option of smaller stimuli able to resolve subtle maculopathies, etc. is a further advancement from older generation FDT perimeters.

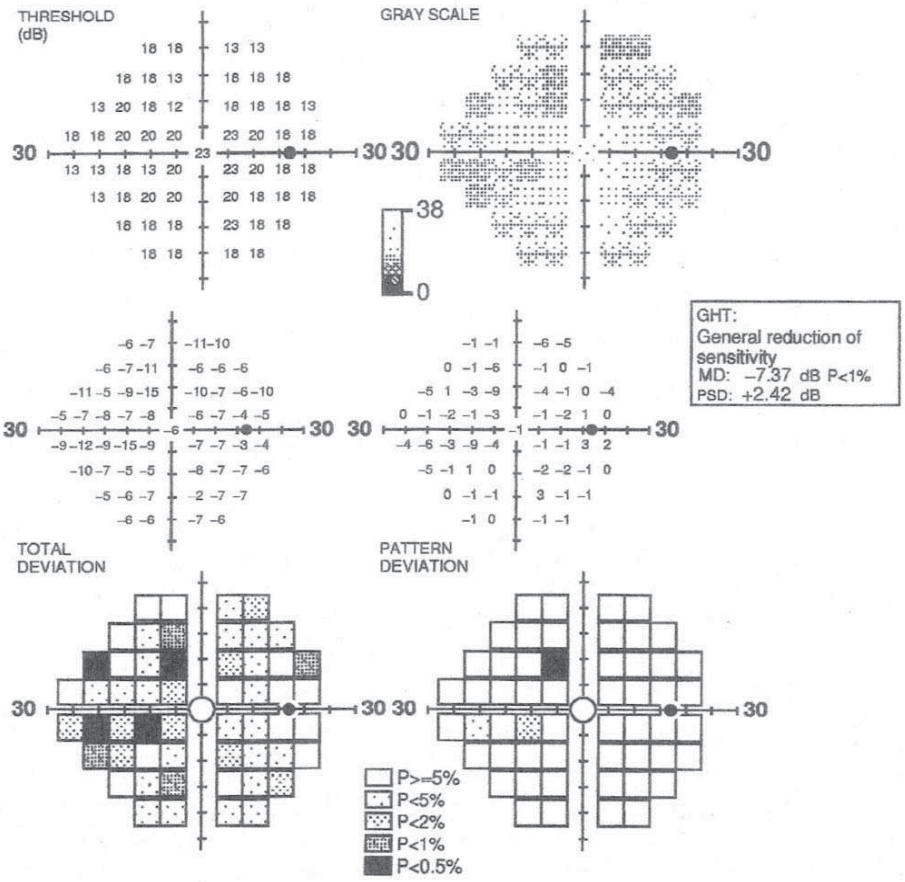


Fig. 9. Frequency doubling technology (FDT): Right eye of same patient on same day as HVF

The FDT plots of the right eye of the same patient show similar metrics to the HVF single field analysis (See Figure 1). The total deviation plot demonstrates more damage than the pattern deviation plot, likely indicating the presence of a media opacity in this patient. The pattern deviation plot demonstrates one point , in the superior field close to the vertical meridian, with a $p<0.5$ value not detected by the HVF. The significance of this point of visual field loss, as with any finding, needs to be correlated clinically with structural examination and careful ophthalmoscopy. This may indicate a false positive value, or possibly an early defect that the FDT was able to resolve prior to HVF change.

A recent prospective study of 115 glaucomatous eyes examined with the Humprey Matrix perimeterand SITA-SWAP demonstrated sensitivity of 87% for early glaucoma (pattern standard deviation was 94% and mean deviation was 91%); and nearly 100% sensitivity and specificity for moderate to advanced glaucoma when compared to SAP[59]. Another study

comparing FDT to SAP in 50 patients with confirmed glaucoma by SAP demonstrated excellent sensitivities of greater than 90%, and demonstrated that FDT had greater specificity than SAP in detecting more severe defects.[60] These recent results certainly demonstrate that FDT is a technology that likely will play an increasing role in the functional assessment of glaucoma patients.

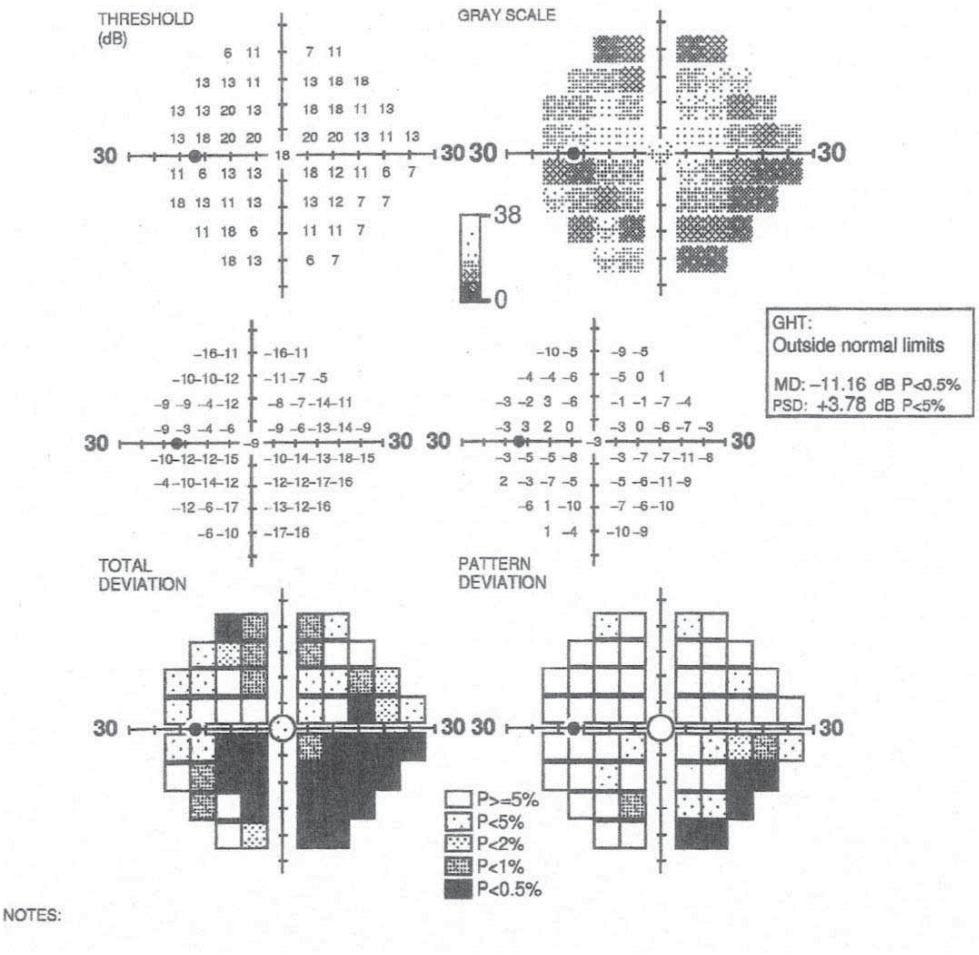


Fig. 10. Frequency doubling technology: Left eye of same patient on same day as HVF

The FDT plot clearly demonstrates a focal defect in the inferonasal field that corresponds to the HVF defects (See Figures 4-6). It is interesting to note that the MD is significantly lower (-11.16 dB) than that calculated from a HVF the same day (-2.11 dB). This large discrepancy may be indicative of the FDT's ability to detect disease at an earlier state. However, the rate of change demonstrated in subsequent FDT evaluations will provide more insight into the likelihood of clinical relevant progression.

4. Structural assessment of the glaucoma patient

The assessment of structural abnormalities of the anterior segment and the optic nerve can be performed utilizing a variety of technologies. Each of these diagnostic modalities offers a range of imaging resolutions, and the latest iterations offer extremely detailed images. Arguably, the largest advantage of adjunctive structural assessment is the fact that the measurements are purely objective (ie not subject to the inherent variability seen in all forms of subjective functional assessment). Another important ramification of these advancements is the ability to detect structural abnormalities prior to functional loss. In patients with documented functional loss, structural assessment further allows for quantification of the magnitude of defects. The detailed summary images rendered allow clinicians to actively engage patients in their diagnosis and treatment with simple color coded plots of the relevant anatomy. A great deal of research has been done utilizing these technologies, and it has clearly changed the manner in which clinicians diagnose, treat, and monitor disease progression. Furthermore, objective measurements are inherently less likely to be subject to test taking environments, and are therefore more translatable between practitioners. As structural assessments are not without limitations, it is the role of the clinician to reconcile discordant data, and make the most appropriate recommendations based on the totality of information available.

Prior to the modern imaging techniques further described below, clinicians relied on careful fundoscopic examination and red-free photography to visualize the retinal nerve fiber layer. A recent study by Suh, et al analyzed progressing normal tension glaucoma patients with red-free photography, visual fields, and stereo disc photography[61]. Four characteristic progression patterns were noted including: widening of the existing defect towards the macula, deepening of the defect without expansion, appearance of a new defect, and finally widening of a defect away from the macula. It was noted that almost 95% of these patients exhibited widening of the defect towards the macula, and deepening of the existing defect. Interestingly, no progression was clinically observed on the disc stereo photographs (n=65) or in the visual fields (n=55) in 64 eyes (98.5%) and 46 eyes (83.6%), respectively[61]. Although useful, reproducible high quality red-free images are often difficult and expensive to obtain. Serial red-free photography has largely been supplanted by the newer diagnostic modalities presented below for more routine cases.

4.1 Ocular coherence tomography (OCT)

OCT is one of the technologies that has absolutely revolutionized the field of ophthalmology. Clinicians are now able to resolve, at the micrometer level, exceptional three dimensional images of ocular tissues *in vivo*. These detailed images have allowed us to follow a variety of disease states with incredible accuracy, and help monitor the efficacy of therapeutic interventions. OCT is based upon the principle of interferometry, and provides a non-invasive "optical biopsy" of almost every aspect of the ocular anatomy. OCT is powered by low-coherence near infrared light (820nm), and renders images of microstructures based upon reflected signals. The light source at this wavelength offers excellent tissue penetration and has an exceptional safety profile. The super luminescent diode light source is split, simultaneously illuminating the ocular tissue specified,along with an internal reference mirror. The interference patterns of the backscattered light is detected by photo detectors, and then graphically interpreted into a standardized output format.

4.1.1 Time-domain OCT

This technology is used by the Stratus® OCT (Carl Zeiss Meditec, Dublin, CA), allowing for approximately 10 micrometer resolution at an acquisition rate of approximately 400 scans/second. This technology has recently been somewhat supplanted by higher generation OCT scanners in many practices. (see Spectral Domain OCT below). The most commonly used protocol for glaucoma management is the Fast Retinal Nerve Fiber (RNFL) scan, with thinning of the RNFL serving as a surrogate for the measurement of ganglion cell loss. The optic nerve head can be further analyzed to determine rim volume, depth, and cup to disc ratio, amongst other parameters. The Fast RNFL protocol measures the thickness of the RNFL in a circumferential fashion around the optic nerve at around a 3.4mm diameter. The thicknesses of the RNFL from both eyes are then compared to an age-matched normative database. The results are displayed in graphical form with a color coding system designed to represent the severity of the thinning. The average RNFL thickness is calculated from the thicknesses of individually displayed measurements from all four quadrants of the optic nerve. Time-domain OCT has limitations with regards to resolution and data acquisition speeds. This is based on the fact that the technology is limited by the velocity of movement of-a mirror-interferometer Kanamori, et al.[62] compared the RNFL scans and mean deviation (MD) from SAP of 237 glaucomatous eyes versus 160 controls, and found a significant correlation between RNFL thinning and greater MD. Furthermore, the average RNFL thickness proved to be the most reliable parameter in monitoring glaucomatous progression. Gupta, et al.[63] in a recent review in the neuro-ophthalmic literature, demonstrated that patients with non-glaucomatous optic neuropathies had a thinner RNFL thickness than patients with glaucomatous optic neuropathy. Leung, et al.[64] conducted a large study of 137 eyes obtaining 1373 Fast RNFL scans, 1373 normal RFNL scans, and 1236 visual fields over a median period of 4 years, and determined that the Fast RNFL protocol was the most reliable Stratus OCT protocol to detect and follow progression in glaucomatous eyes.

Given the objective nature of OCT scans, there is a tendency amongst clinicians to rely on these examinations more than functional assessment with perimetry. While this may be deemed appropriate in patients unable to perform perimetric evaluation reliably, the limitations of OCT must be taken into account as well. Reliable OCTs are often impossible in patients with severe surface disease, miotic pupils, dense media opacification, high axial length with associated peripapillary atrophy, and vitreous disease. Correlations should routinely be performed between OCT results and the clinical appearance of the optic nerve, as the scans may underestimate cupping when there is glaucomatous undermining under the rim tissue.

Our group[65] recently published a study further demonstrating the confounding effects of vitreous traction on the retinal nerve fiber layer. Approximately 110 eyes of patients were examined with Stratus OCT. Those noted to have partial vitreous detachments at the optic nerve head were found to have artifactually elevated RNFL measurements when matched to controls. Given the relatively high incidence of partial posterior vitreous detachments in the glaucoma group, it was hypothesized that RNFL damage from glaucoma may be masked by the effects of the vitreo-retinal interface. It was concluded from these results that both structural and functional assessments are imperative to determine the presence of glaucomatous damage in these patients in particular. Further investigation of the natural history of PVD, along with changes in the measured retinal nerve fiber layer by OCT, is currently underway. A corollary analysis of the effects of aging on vitreous separation is furthermore being investigated The vitreoretinal interface has been extensively examined by

OCT, particularly in diabetics. Ophir et al, amongst others, have performed multiple analyses utilizing 3-D SD-OCT (see below) to demonstrate that the subtleties of the vitreoretinal interface can be resolved accurately[66,67].

4.1.2 Spectral domain (SD) OCT

SD-OCT, also known as Fourier Domain OCT or High Definition OCT (HD-OCT), is the latest commercially available iteration of the OCT technology at the time of this publication. The commercially available Cirrus® OCT (Carl Zeiss Meditec, Inc.) has tremendous advantages over the Stratus OCT in the evaluation and management of many eye conditions. SD-OCT measures the cross-spectral density, a Fourier transformation aimed to estimate the spectral density from a sequence of time samples. The measurements are performed at the detection arm of the interferometer[68]. This allows for much higher resolution and lower test times, as there are no "moving-part" limitations within the interferometer. Furthermore, the ability of the SD-OCT to capture approximately 20,000 axial scans per second, compared to 400 scans/sec for the Stratus OCT, allows for significantly more accurate imaging. This further translates into scans that are less subject to micro-saccadic eye movements during data acquisition. The resultant axial resolution of the scans can be less than 6 micrometers. The Cirrus OCT is furthermore able to match anatomical landmarks from prior scans, minimizing the errors associated with scan misalignment. Misalignment errors are indeed an important source of confounding data with previous versions of the OCT. This is especially the case when longitudinal progression analysis is performed. Lastly the ability to render 3-Dimensional imaging of complex ocular anatomy is yet another major advancement.

Many ophthalmic practices have updated the Stratus OCT to one of the SD-OCT modules in the recent past. It is important to note that the aforementioned differences do not easily allow clinicians to compare RNFL measurements between the two technologies, and accurate correction factors are currently lacking. The re-establishment of a new baseline RNFL thickness with the SD-OCT is quite commonly done in many of these cases. Knight, et al.[69] compared the Stratus OCT to the Cirrus OCT RNFL measurements of 130 eyes with glaucoma relative to normal controls. They demonstrated that the RNFL thickness measured by the Stratus OCT tended to be higher than that of the Cirrus OCT. Sung, et al[70], performed a similar comparative study of 60 normals, 48 glaucoma suspects, and 55 glaucoma patients, They demonstrated that the Cirrus OCT had better sensitivity and specificity for disease than the Stratus OCT, and classified a significantly higher proportion of patients as abnormal. Specifically, Cirrus OCT demonstrated higher sensitivity and specificity (63.6% and 100%) than the Stratus OCT (40.0% and 96.7%) Leung, et al.[64], in a study of 128 glaucomatous eyes over 2 years, similarly concluded that the Cirrus OCT detected glaucomatous changes earlier and more often that the Stratus OCT. A portion of this difference can be attributed to decreased measurement variability with the Cirrus OCT.

Newer versions being developed will likely offer even greater sensitivity and specificity, improved resolution, and clinical progression analysis. Incorporation and evaluation of perimetry in the analysis will likely help bridge the current gap that exists between structural damage and functional loss These advancements will likely be in part possible with the exponentially growing adoption of electronic medical record (EMR) systems. At the time of this publication, significant barriers exist with respect to the interface between EMR, and the variety of functional and structural assessment tools that were traditionally designed as stand-alone technologies.

4.2 Confocal scanning laser ophthalmoscopy (SLO)

Retinal imaging with a confocal scanning laser ophthalmoscope (cSLO) involves scanning a small laser beam over the retina, and constructing an image from the descanned reflected light. By applying the confocal principle, tomographic images can be produced[71]. The confocal principle involves measurement of reflected laser light which is concentrated through a pinhole. SLO is based upon acquiring point-by-point images from a series of depths, and then reconstructing them into three-dimensional topographic images.. The Heidelberg Retinal Tomography (HRT) unit scans the fundus with a 670-nm diode laser, creating a three-dimensional map of the fundus and optic nerve. This is accomplished by obtaining multiple optical sections at different depths using a confocal aperture[72] The commercially available (HRT) unit has undergone advancements since the advent of the technology, to its current form as the HRT-III. HRT is used clinically in a similar manner to OCT scans in the evaluation and management of glaucoma. Exceptional imaging quality and newer iterations of progression analysis have made the HRT one of the leading structural analysis tools in practice today. HRT scans further employ eye tracking technology to improve the validity and reproducibility of serial examination. The analysis of the optic nerve head further includes a variety of metrics designed to document morphological variants (Figure 11). The clinical and predictive utility of these parameters continues to be the subject of a great deal of research and subsequent debate. As with any testing modality, data from the HRT needs to be correlated to an individual patient's clinical picture to determine its validity.

Kalabhoukhava, et al.[72], analyzed 59 subjects with ocular hypertension and glaucoma over 50 months with HRT, perimetry, and stereo disk photography. After expert review of the patients at the 50 month time point, subjects were grouped as either progressive or non-progressive. HRT parameters (cup shape measurement, classification index, the third moment in contour, cup/disc ratio, cup area, rim area, and area below reference) showed statistically significant morphological changes in only the progressive group (ie no change from baseline in the "stable" group). These results effectively demonstrate the high diagnostic utility of HRT testing as an adjunctive assessment tool for glaucoma evaluation. Kilintizis, et al[73], demonstrated that changes in HRT parameters of "length of contour" (LC) and "standard deviation of contour" (SDC) were of particular significance when comparing almost 100 glaucoma patients to controls. Balasubramanian, et al.[74] compared HRT I and II parameters in 380 eyes, and concluded that the stereometric parameters were not significantly altered by the newer generation scans. Another study by this same group performed an observational cohort study of 246 eyes followed with HRT, topographic change analysis (TCA), SAP, and stereo photography. It was concluded from the variability in results that there is a great deal of discordance in the detection of longitudinal change[75] between these modalities. Somewhat conflicting assessments of the utility of the HRT, as with all of the aforementioned diagnostic modalities, reminds us that the clinical utility of any data collected greatly relies on the clinician's subjective correlations.

4.3 Scanning laser polarimetry (SLP)

The original GDx (Laser Diagnostic Technologies, San Diego, CA), and newer versions with variable corneal compensation GDx-VCC (Carl Zeiss Meditec, Dublin, CA), analyze RNFL thickness with a different method than the OCT and HRT. The RNFL is birifringent secondary to the highly ordered microtubule arrays of the axon microtubules. As the near infrared laser light (780 nm) is split by the birifringent tissue, a phase shift phenomenon

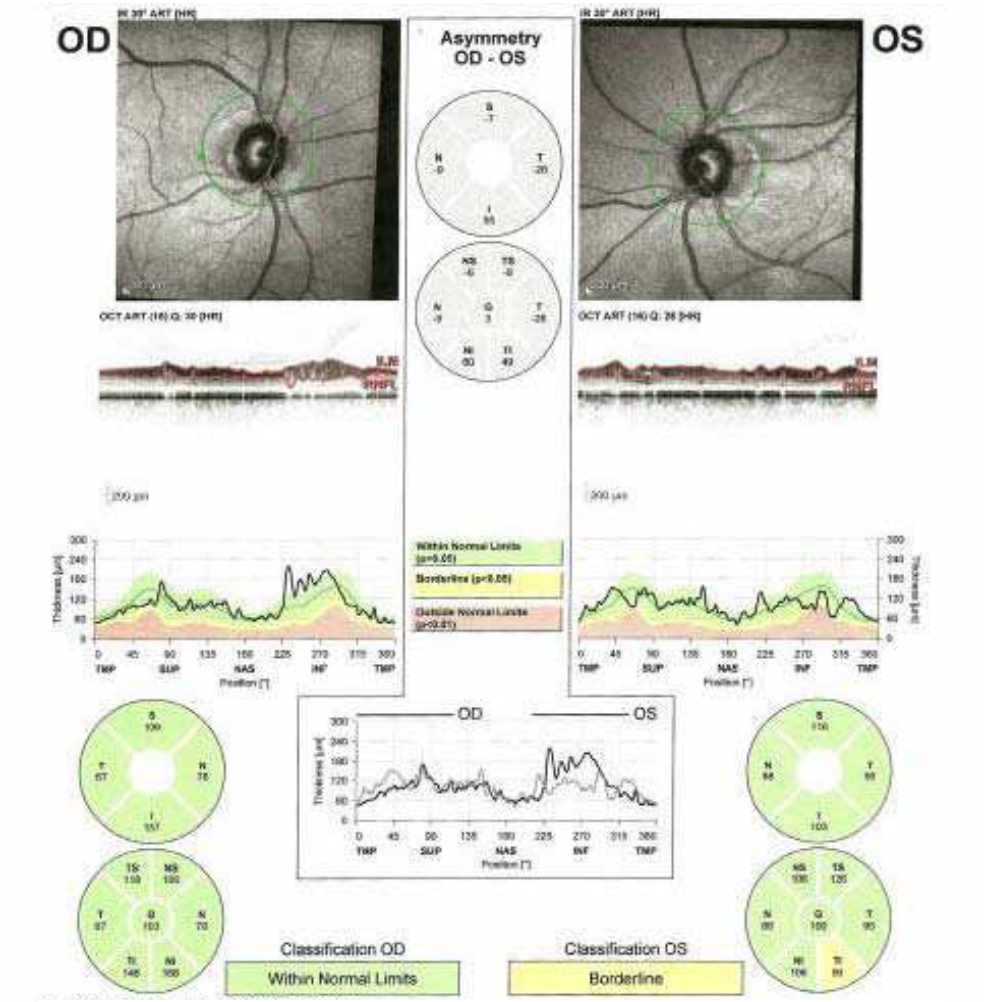


Fig. 11. Heidelberg retinal tomography (HRT) summary of RNFL of same patient on same day as HVF and FDT

Structural analysis may demonstrate an anatomical correlate to demonstrable visual field loss. The digital images are rendered at the top of the summary slide. The green circle demonstrates the limits of the area that is being examined. Centration is optimal in this case, and the newest generation HRT scanners are able to register and match previous scans to improve the reliability of progression analysis. The difference, or calculated asymmetry, between the two eyes is displayed in the top center of the summary printout. The difference in measure RNFL (OD – OS) is graphically displayed by location in the circumpapillary region with S= Superior, N= Nasal, I=Inferior, T=temporal, along with combinations in between the regions (ie TS = Temporal Superior, etc.). Negative values indicate that the left eye has a thicker RNFL, and positive values indicate the opposite. The circumpapillary RNFL.

occurs given the difference in velocity of the reflected light. RNFL thickness can be calculated based on the magnitude of this phase shift. As the anterior segment structures also demonstrate the property of biriferigence, it is necessary to subtract these effects, and newer versions with customized corneal compensation have proven to be much more accurate than prior versions utilizing a fixed compensation algorithm[76]. While the newest generation SLP is far more accurate than earlier versions, the technology is subject to some degree of variability in eyes that show so called "atypical birefringence patterns". Normal patterns of birefringence are generally characterized by the presence of high peripapillary retardation superiorly and inferiorly. This pattern corresponds histologically to the distribution of the superior and inferior arcuate nerve fiber bundles.[77] Abnormal patterns, that are considered normal variants, could therefore confound the data analysis and subsequent detection of disease.

Kim, et al.[78] measured the RNFL of 60 normal patients to 60 glaucoma patients with GDx VCCand Stratus OCT. The results demonstrated no significant differences between the instruments, with high correlations in the superior and inferior quadrants in particular. Pablo, et al[79]analyzed 181 eyes diagnosed with OHTN with GDx-VCC and Stratus OCT, and also found similar diagnostic accuracy between the two. Aptel, et al.[80], compared 120 eyes with Cirrus OCT and GDx-VCC (40 normals, 40 glaucoma suspects, 40 glaucoma) compared with visual field sensitivity, and found that the Cirrus OCT had a stronger correlation to function than the GDx-VCC. Lopez-Pena[81] performed a prospective study of 423 eyes 87 normal eyes, 192 ocular hypertensive eyes, 70 pre-perimetric glaucomas and 74 glaucomatous eyes) to compare SAP with GDx-VCC. The results of this large study showed only weak to moderate correlations with RNFL measurements and visual field defects in the glaucoma group. The relationship between HRT structural defects with functional visual field changes is clearly yet to be well defined.

5. Conclusions

The management of glaucoma in the modern era, despite the advent of a host of technologies, remains more of an art than a science in many respects. Improvements in tonometry will continue to improve the accuracy of IOP measurement, especially as the effects of corneal biomechanical properties continue to be elucidated. The potential for accurate home monitoring will allow for better assessment of diurnal and inter-visit IOP control. Similarly, improved imaging techniques will allow for earlier detection of disease with continually improving resolution and reproducibility. It is important to consider that early detection of glaucoma inherently carries the risk of over-diagnosis and subsequent overtreatment. Rates of progression, with all of the modalities described, need to be established prior to the initiation or advancement of therapy. Understanding the limitations of the testing is imperative when making assessments regarding both structure and function. A gestalt approach to glaucoma management allows the specialist to amalgamate a host of information, and effectively cater therapies based on the information available. The modern age of glaucoma care has had notable advancements, and the future of glaucoma management will allow for the optimal care of this globally disabling disease.

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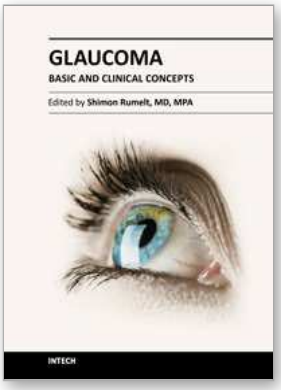

Glaucoma - Basic and Clinical Concepts
Edited by Dr Shimon Rumelt

ISBN 978-953-307-591-4
Hard cover, 590 pages
Publisher InTech
Published online 11, November, 2011
Published in print edition November, 2011

This book addresses the basic and clinical science of glaucomas, a group of diseases that affect the optic nerve and visual fields and is usually accompanied by increased intraocular pressure. The book incorporates the latest development as well as future perspectives in glaucoma, since it has expedited publication. It is aimed for specialists in glaucoma, researchers, general ophthalmologists and trainees to increase knowledge and encourage further progress in understanding and managing these complicated diseases.

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