Linking structure and function in glaucoma

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This article will give an overview of the latest imaging technology available to assess the optic disc. This will then be compared with the information provided by visual field assessment including standard automated perimetry (SAP), short-wavelength automated perimetry (SWAP) and frequency doubling technology (FDT). The different mechanisms for each type of perimetry will be discussed.

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Learning objectives
To understand different approaches when undertaking visual field assessment (Group 3.1.5)
To recognise when to refer patients with suspected glaucoma based upon clinical findings (Group 6.1.8)
To understand the needs of patients with advanced disease when examining visual fields (Group 7.1.7)

Learning objectives
To understand the instruments involved in visual field analysis (Group 3.1.5)
To understand the implications of glaucoma manifestations (Group 8.1.5)

About the author
Numerous instruments to capture images of the fundus have been developed in recent years, enabling the practitioner to undertake objective assessment of the optic disc. This article will give an overview of the latest imaging technology available, comparing this with information obtained by visual field assessment.
Introduction

Glaucoma is a progressive optic neuropathy, associated with characteristic visual field defects, caused by structural changes in the optic nerve head and peripapillary retinal nerve fibre layer (see Figure 1). Research in an established glaucoma referral refinement pathway has shown a decline in referral accuracy by optometrists with no special interest in glaucoma as opposed to those with additional training. Specifically, this relates to the detection of disc abnormalities and abnormal intraocular pressure (IOP) following the publication of the National Institute for Health and Clinical Excellence (NICE) glaucoma guidelines. Monitoring optic disc changes, and more specifically, assessing the retinal nerve fibre layer (RNFL), can provide predictive data on which patients with elevated IOP will go on to develop glaucoma. Over the past two decades there have been considerable advances in technology, leading to the development of a vast array of equipment for fundus imaging. Structural changes to the optic disc and retinal nerve fibre layer often precede visual field defects, which can be measured with standard achromatic perimetry in early glaucoma. This could lead to the conclusion that visual field tests, particularly standard automated perimetry (SAP), are not the ideal screening tools for optometrists. However, structural and functional measures in glaucoma contribute different and, arguably, equally important information for assessing the eye, despite the variable correlation between these techniques, in relation to the disease stage.

Standard automated perimetry (SAP)

SAP is the ‘gold standard’ measure for visual fields. The most effective detection criteria for glaucomatous visual field loss are localised loss for individual points, hemifield clusters, or asymmetrical sensitivity across the horizontal meridian. SAP is not selective for a particular ganglion cell type, therefore, any of the primary ganglion cell types can respond to the achromatic stimulus presented on a white background. A significant amount of ganglion cell loss can occur before SAP can identify functional deficits. However, progression of visual field defects can be difficult to quantify due to high test-retest variability. This was highlighted in the ocular hypertension study where 85.9% of initial field assessments showing defects were found to be normal on repeat testing. The findings in this study led to the recommendation of three consecutive tests. However, even with this more stringent criteria applied, some eyes still produce normal visual field tests on further follow-up. Approximately one third of the variability in SAP test results can be accounted for by the severity of the defect, its location and the patient’s diagnosis. However, factors such as patient performance and reliability, fixation losses, fatigue, learning effects, changes in pupil size, improper refractive correction, and true physiological variability also play a part. The Swedish Interactive Thresholding Algorithm (SITA) uses an adaptive algorithm based on the patient’s responses, which significantly decreases testing time (to four or five minutes for 24-2) without compromising accuracy, as compared to much longer, full-

Figure 1 Glaucoma progression as a continuum. Reprinted from Weinreb et al. Am J Ophthalmol, 2004;138(3);458–467

Figure 2 The GDxPRO Scanning Laser Polarimeter. Image courtesy of Carl Zeiss, Meditec
threshold testing. The SITA fast 24-2 reduces testing time further, to just over three minutes. However, this is at the expense of precision as it allows for a greater variability in responses on individual point re-testing.

**Short wavelength automated perimetry (SWAP)**

SWAP projects a Goldmann size V blue target against a bright yellow background. The background reduces the sensitivity of the green and red cones, therefore the blue (short-wavelength sensitive) cones and their small, bistratified retinal ganglion cells are isolated (the koniocellular pathway). Longitudinal studies have shown that SWAP defects may occur three to five years before abnormalities are seen on full-threshold SAP, and are predictive of both the onset and location of future SAP defects. Approximately 10% of ganglion cells are of the bistratified variety. The most widely accepted theory suggests that by testing fewer sparsely distributed cells with large retinal fields, the results are less likely to be masked by other pathways. SWAP has traditionally been recommended as a test to evaluate visual function in younger glaucoma patients. This is due to the yellow tone of the nuclear cataract acting as a blue filter and causing significant diffuse depression of sensitivity. The limitations of prolonged testing have largely been overcome with the introduction of the SWAP SITA. However, the yellow background and the blue spot target of SWAP are still more difficult to recognise than the white-on-white test, leading to increased patient fatigue and discomfort during the test. Testing the blue test, leading to increased patient fatigue and difficulty to recognise than the white-on-white test, SWAP have comparable performance. However, there are also reports that FDT identifies field loss before SAP. FDT has shown lower test-retest variability than SAP and appears to have higher sensitivity than SWAP at a comparable level of specificity. Disadvantages include: fading of the testing screen due to the Troxler phenomenon (where stimuli away from the fixation point may seem to disappear) and unreliable results in patients with cataracts, high myopia or small pupils.

**Frequency doubling technology (FDT)**

When a low spatial frequency sinusoidal grating (less than one cycle per degree) undergoes high temporal frequency counterphase flicker (greater than 15 Hz), the stimulus appears to have twice as many light and dark bars than are physically present – a phenomenon known as frequency doubling. The origins of this response are thought to be cortical, although it has been reported that FDT selectively tests the contrast sensitivity of the magnocellular cells. Magnocellular retinal ganglion cells are primarily involved in motion and flicker detection and comprise approximately 10% of the entire retinal ganglion cell population. Evidence of a reduced ability of the visual system to use other subsets of retinal ganglion cells to compensate for damaged retinal ganglion cells of the type being tested supports the utility of the test. A 24-2 version using an algorithm called Zippy Estimation of Sequential Thresholds (ZEST) with similar forecasting principles to SITA is available, and has comparable performance. However, there are also reports that FDT identifies field loss before SAP. FDT has shown lower

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**Figure 3** HRT takes data from a 3D stack of tomographic images of the optic nerve and RNFL, aligns the images and computes a 3D topographic map of the retinal surface. Image courtesy of Heidelberg Engineering
and some elderly patients can show an atypical retardation pattern.22 In addition, the cornea (and to a lesser extent, the lens) are also bi-refrangent. When assessing RNFL retardation, anterior segment retardation must be neutralised. However, both atypical retardation and residual anterior segment bi-refrangement can have a detrimental effect on the accuracy of measurements taken by SLP. Fixed and variable corneal compensators have been utilised to cancel bi-refrangement arising from the anterior segment, based on population averages and individual, eye-specific compensation. Enhanced corneal compensation (ECC) uses an algorithm to further improve the signal-to-noise ratio of RNFL retardation, reducing the errors associated with atypical scan results.21,24,25

Images of the fundus are obtained by a scanning beam of near-infrared laser light (780nm), which moves in a raster pattern to include the peripapillary and macular regions of the eye. The latest SLP devices such as the GDx PRO (Carl Zeiss Meditec) can compare retinal nerve fibre thickness at the optic nerve head and indicate significant thinning or thickening of the RNFL (see Figure 2). The nerve fibre index (NFI) is an algorithm that takes this thickness information and combines it with other variables to give a value indicating disease status. The device also provides characterisation of the microstructures within the RNFL as it has been shown that changes in the orientation and density of the microtubules occur before thickness changes become apparent.26,27

How does SLP compare with perimetry?
SLP with variable corneal compensation has been shown to correlate well with perimetry performed by the Humphrey Field Analyser, using the 24-2 full threshold or 24-2 SITA standard programme.28 The ocular hypertensive treatment study demonstrated that lowering intraocular pressure in eyes with ocular hypertension without glaucomatous optic neuropathy or visual field damage decreased the incidence of primary open angle glaucoma (POAG) by 50%.29 The average velocity of visual field change in untreated ocular hypertension is generally slow. However, this is significantly reduced following the application of topical therapy, regardless of whether they develop POAG.20

Confocal scanning laser opthalmoscopy (CSLO)
The Heidelberg Retina Tomograph III (HRT III; Heidelberg Engineering) is the latest commercially available CSLO. The device uses a diode laser (670nm wavelength) to sequentially scan 15° x 15° areas of the retinal surface in horizontal and vertical directions in multiple focal planes. The coronal (longitudinal) planes are effectively ‘stacked up’ (see Figure 3) and this re-assembly enables an assessment of the optic nerve head topography.30 Three sets of scans are acquired in rapid succession and, after the images are aligned, the average measurement is used for analysis. The operator must then outline the optic nerve head margin to enable the device to define a reference plane. Parameters can then be calculated to quantify the optic nerve head region and produce a reflectance image overlaid with a topographic map. The reference plane is automatically generated by the CSLO software and calculated as 50µm below the mean retinal surface level. All structures within the contour line and above the reference plane are considered to be neuro-retinal rim, and all structures below the reference plane are considered to be the cup. The glaucoma probability score (GPS) is also provided, although interestingly, this does not rely on manual delineation of the optic disc margin. Rather, a predefined model of the optic nerve head structure is used. As the name suggests, confocal scanning laser opthalmoscopy provides a global and sectorial quantification of the region. However, there are limitations to the technique and the investigators who derived the calculation noted that the early pattern of glaucomatous change may be different to the most substantially altered shape parameters they identified in the study.22 An alternative method of analysis – the Moorfields regression analysis (MRA) – requires manual outlining of the disc boundaries. However, the diagnostic performance of the methods appear to be similar, with accuracy for classification dependent on optic disc size and glaucoma severity.31 The development of an ethnic-specific normative database may improve sensitivity and specificity in cases with very large or small discs.32

Advantages of HRT include good image quality through undilated pupils (though dilation may be necessary at times), and the ability to upgrade existing machines with newer software, allowing the clinician to build upon long-term databases. Most importantly, the sophisticated registration capability of HRT to superimpose baseline and follow-up images allows for change to the ONH to be detected automatically. The use of HRT in the ancillary study to the ocular hypertension treatment study has resulted in a well-characterised data set which is beneficial for future investigations of this technique.

How does CSLO compare with perimetry?
An interesting study using pattern-recognition algorithms known as machine learning classifiers, has been applied to optic disc imaging results and visual field data. Machine learning classifiers are well suited for evaluating these large data as they summarise the information in order to detect complex patterns and trends. This method has shown improved accuracy in glaucoma diagnosis for combined optimised HRT and SWAP data.33 A study investigating...
structure-function relationships using perimetry and scanning laser ophthalmoscopy in glaucoma patients showed correlations are strongest in temporal areas where glaucomatous damage tends to occur first, particularly for FDT compared with SAP.\(^{35}\)

**Optical coherence tomography**

OCT works in a similar way to ultrasound, using near-infrared light instead of sound waves to produce high resolution, cross-sectional images. Time domain OCT has been superseded by the higher quality spectral domain (SD-OCT), which permits direct, real-time visualisation of retinal pathology.

SD-OCT also provides quantitative measurements of retinal architecture at higher resolutions than CSL and SLP (see Figure 4). The increased speed reduces motion artefacts and improves patient compliance, although patients may still require dilation and image quality can be compromised in patients with ocular opacities. Repeatability of nerve fibre layer thickness measurements in patients with glaucoma and healthy volunteers has shown good intra- and inter-observer repeatability in comparison with time domain OCT.\(^{36}\) SD-OCT has been used to quantify the loss of retinal ganglion cells in experimentally induced anterior ischemic optic neuropathy, and high-penetration OCT using long wavelengths has been used to characterise choroidal thickness in highly myopic eyes with normal tension glaucoma.\(^{37}\) This may have implications for refining diagnostic parameters as reduced choroidal thickness appears to be the most influential factor on the occurrence of normal tension glaucoma in high myopes.\(^{38}\)

**How does SD-OCT compare with perimetry?**

The RNFL assessment with SD-OCT performed well in detecting pre-perimetric glaucomatous damage in a cohort of glaucoma suspects and delivered a better performance than CSL.\(^{39}\) For diagnostic purposes, machine learning classifiers trained on OCT and SAP data can successfully discriminate between healthy and glaucomatous eyes. When combined, these measurements improved diagnostic accuracy compared with OCT data alone.\(^{40}\) A study evaluating the relationship between SAP, changes in estimated retinal ganglion cell (RGC) counts and measures of RNFL thickness showed the same amount of RGC loss corresponded to the mean deviation (MD) change depending on the stage of the disease, that is, small changes in MD, but relatively larger changes in RNFL thickness for early disease stages as opposed to larger changes in MD, but only small or no changes in average RNFL thickness in later disease stages.\(^{41}\)

**Conclusion**

Imaging allows an objective, non-contact measure that is more reproducible than a subjective examination and permits the measurement of features not otherwise possible using other methods. The technology allows for an expert examination by non-experts, however, this relies on quality control measures being carried out by the instrument software to establish accurate diagnosis and change criteria. The operator’s level of skill at the time of image acquisition and careful interpretation are vital. Scans containing artefacts from movements or areas with signal dropout cannot be interpreted correctly as it is impossible for the analysis algorithm to accurately predict measurement details. Certain cases, such as high myopes or tilted discs, are not suitable for comparison with data from a normative database and may be normal, but flagged as abnormal by the statistical analysis failing to recognise that they fit at the low end of the distribution.

In summary, imaging findings should never be accepted as the absolute measure and must be considered alongside more ‘low-tech’ examination findings. Combined method analysis can prove to be more sensitive and specific, however, they are not readily available to non-research optometrists. Therefore, simply assessing correspondence between multiple techniques (even if they are individually variable) is far more likely to give an accurate and more complete overview of the patient’s disease status.

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**References** Visit www.optometry.co.uk/clinical, click on the article title and then on ‘references’ to download.

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