HHS Public Access

Author manuscript

*Expert Rev Ophthalmol*. Author manuscript; available in PMC 2017 September 14.

Published in final edited form as:

*Expert Rev Ophthalmol*. 2016 ; 11(5): 367–376. doi:10.1080/17469899.2016.1229599.

# Structural and Functional Evaluations for the Early Detection of Glaucoma

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## Abstract

The early detection of glaucoma is imperative in order to preserve functional vision. Structural and functional methods are utilized to detect and monitor glaucomatous damage and the vision loss it causes. The relationship between these detection measures is complex and differs between individuals, especially in early glaucoma. Using both measures together is advised in order to ensure the highest probability of glaucoma detection, and new testing methods are continuously developed with the goals of earlier disease detection and improvement of disease monitoring. The purpose of this review is to explore the relationship between structural and functional glaucoma detection and discuss important technological advances for early glaucoma detection.

### Keywords

Glaucoma; OCT; Standard Automated Perimetry; OCT Angiography; Ganglion Cell Inner Plexiform Layer; Bruch's Membrane Opening; Lamina Cribrosa; Frequency Doubling Perimetry; Flicker Defined Form Perimetry; Multifocal Visual Evoked Potential; Pattern Electroretinography

## 1. Introduction

Glaucoma is a neurodegenerative disease of the optic nerve involving the death of retinal ganglion cells and their axons, which leads to irreversible visual impairment, and if untreated causes blindness. Due to the aging population, the prevalence of glaucoma has increased and is expected to affect 80 million people worldwide by 2020.[1] Many people with glaucoma remain undiagnosed. The disease typically progresses slowly, and remains asymptomatic until a substantial amount of vision has already been lost. Early detection of the disease is therefore challenging but is critically important in order to preserve functional vision.

Diagnosis of glaucoma is based on signs of functional vision loss associated with characteristic morphological changes of the optic nerve head (ONH) and retinal nerve fiber layer (RNFL). A variety of structural and functional testing methods have been developed to

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**Declaration of interest**

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aid in the detection of glaucoma. The purpose of this review is to discuss the relationship between structural and functional glaucoma detection and to highlight important recent innovations in early glaucoma detection.

## 2. Functional Testing

The most commonly used functional testing in the context of glaucoma evaluation is standard automated perimetry (SAP), which is considered the clinical gold standard for the assessment of visual function. The Humphrey field analyzer Swedish interactive threshold algorithm (SITA) 24-2 standard strategy in particular is widely used for glaucoma diagnosis and monitoring, giving clinicians a systematic and reproducible method to assess the regions of a patient's field of vision affected by glaucoma and the severity of vision loss. The device projects light with various intensities throughout the the central 24 degrees from central fixation (30 degrees in the nasal direction), and the test taker is instructed to indicate when the stimuli is detected by pressing a button. This method allows a thorough mapping of the central visual field and provides both localized threshold sensitivity and global information.

## 3. Structural Testing

Clinical examination of the ONH and the use of fundus photography have long given clinicians a method to assess the severity of damage to the optic nerve. Typical glaucomatous damage includes enlarged cupping, localized neuroretinal rim thinning, barring of the blood vessels, vascular diameter irregularity, nasalization of the major blood vessels, peripapillary atrophy and RNFL defects. Advancements in ocular imaging have made it possible to obtain high-resolution, real time, in vivo images of the eye with automated quantification of various parameters. This provides a way to detect and monitor glaucomatous structural changes using reliable measurements of the optic nerve, macula, and anterior eye.

Scanning Laser Polarimetry (SLP), Confocal Scanning Laser Ophthalmoscopy (CSLO), and Optical Coherence Tomography (OCT) are three imaging technologies that have been widely utilized over the past two decades for glaucoma evaluation. Scanning Laser Polarimetry (SLP) uses the birefringence of polarized light to determine tissue thickness. The spatial organization of the axons in the nerve fiber layer have a parallel orientation of fibers, causing a phase delay when light is reflected back from the eye that is proportional to tissue thickness.[2],[3] Confocal Scanning laser ophthalmoscopy (CSLO) filters back scattered light through a confocal pinhole in front of a photodetector at a focal conjugate, giving topographical information about the posterior eye. Optical coherence tomography (OCT) operates based on the principles of low-coherence interferometry. Differences in tissue reflectivity with depth produces a virtual cross section of the imaged tissue. Time domain (TD)-OCT was the first iteration of this technology, but its requirement for a moving reference mirror limited scanning speed greatly. The currently available iteration of OCT, Spectral domain (SD)-OCT, eliminated the need for a moving mirror by using Fourier transform technology to resolve depth reflectivity information, allowing OCT technology to perform at faster speeds and to have a higher axial resolution. All three technologies provide

automated quantification of structures in the ONH, peripapillary and/or macula region which have been shown to allow excellent glaucoma diagnostic capabilities.[4],[5],[6],[7],[8]

## 4. Structure – Function Relationship

The relationship between glaucomatous structural and functional changes has been shown to be complex.[9],[10],[11],[12] The association between structural and functional measures increases with severity of disease, with RNFL thickness linearly related to SAP loss at advanced disease.[11],[13] The relationship is harder to define in early glaucoma, and it is debated whether initially structure changes before function or whether the reverse or a simultaneous change is closer to the actual biological process. Limitations of current testing methods, such as increased measurement variability within the normal range of the visual field, could be the source of the temporal disconnect. It is also possible that glaucoma may present differently for each patient, since the same amount of structural loss sometimes results in very different degrees of visual field loss.

The Early Manifest Glaucoma Trial in 1999 and the European Glaucoma Prevention Study in 2005 reported that 86% and 60% of subjects, respectively, developed a detectable visual field defect before a structural defect.[14],[15] However, many other studies have shown evidence that structural damage often precedes the detection of functional changes. Through the use of fundus photography, RNFL atrophy[16] and ONH cupping[17] have been shown up to six years earlier than vision loss was detected with SAP. Structural abnormalities have also been recently shown to more often precede vision loss when using the three most commonly used ocular imaging technologies, OCT,[18],[19],[20][21],[22] (Figure 1) CSLO[23],[24] and SLP.[25],[26]

## 5. Disagreement Between Structure and Function

One possible cause of the disagreement between structural and functional glaucoma detection measures is the redundancy of the visual system. Neighboring retinal ganglion cells compensate for cells nearby that are dead or dying until most of the cells in a region are not functional anymore, and only at this point is a change in functional vision detectable. SAP is not sensitive enough detect these very early glaucomatous changes due to this redundancy.

Kerrigan-Baumrind et al.[27] reported that at least 25% to 35% RGC loss is needed before SAP abnormalities develop. This calculation was based upon histological estimation of retinal ganglion cell bodies in retinal sections and counts of axons passing through the ONH in post mortem control and glaucoma eyes. These cell and axon estimations were then compared to the global SAP indices obtained before the subject’s death that corresponded to the sampling location of the histology. Based on the analysis of 112 eyes from 72 healthy and 40 glaucoma subjects, it was reported that approximately 17% of structure loss was necessary before functional abnormalities were seen, and that the average RNFL thickness at this point was 77μm.[*28] This RNFL value, or the tipping point, is the threshold at which enough structural loss has occurred for functional changes to begin to be detectable.

Another possible reason for the disconnect between structural and functional testing is that retinal ganglion cells exhibit a period of dysfunction before death. This could potentially lead to variability in SAP testing and a general reduction in visual field sensitivity since sometimes dysfunctional cells could be functioning while at other times they may not be. Structural measurements may therefore not be representative of the number of functioning ganglion cells. Buckingham et al.[29] reported that retinal ganglion cells experienced somal shrinkage, retrograde labeling deficits, and down regulation of retinal ganglion cell specific genetic programs before total cell death in a mouse model. In a study by Ventura et. al,[30] improvement in pattern electroretinogram (PERG) testing was seen after the reduction of intraocular pressure (IOP) in glaucomatous and ocular hypertension eyes. This suggests that retinal ganglion cells could become dysfunctional in response to pressure, and that function could be at least partially restored after the lowering of IOP.

There are several other factors that should be considered when discussing the variability of SAP testing. SAP is a subjective test, therefore poor patient compliance can greatly influence the reliability of SAP results. Media opacities can also influence SAP testing, confounding vision loss due to glaucoma. Many studies have found that cataracts can cause diffuse visual field loss but do not produce actual scotomas.[31],[32],[33] This evidence is strengthened by the visual field restoration often seen after cataract extraction and intraocular lens implantation.[34],[35]

It has been suggested that using both structural and functional measures maximizes the likelihood of glaucoma detection. It’s possible that changes can be detected simultaneously with more precise testing methods, and it is also possible that the order of structural and functional glaucoma progression may inherently differ between individuals.[36] New forms of structural and functional testing are continuously being developed in order to improve glaucoma detection so that clinicians can have the most accurate information possible in order to detect early signs of glaucoma and direct clinical management accordingly in order to preserve sight.

## 6. Innovations in Glaucoma Evaluation

### 6.1 Retinal Vasculature

Elevated IOP has long been considered the most important risk factor for glaucoma, but with the recognition that some patients develop glaucoma with an IOP within the normal range, other causal factors have been explored. There is evidence that vascular dysfunction may be related to the development of glaucoma.[37],[38],[39],[40],[41] Efforts have therefore been made to quantify retinal vessel density through structural measurements of the vasculature and also to estimate functional perfusion and blood flow indexes. A decrease in ocular perfusion has been seen in glaucoma eyes compared to healthy or ocular hypertensive eyes,[42],[43] and this decrease in perfusion may even precede RNFL and functional defects in early glaucoma.[42],[44] Without adequate ocular blood flow, ocular cells do not receive the oxygen and nutrients necessary for their metabolic needs, potentially leading to cell death.

Fluorescein angiography (FA) and Doppler optical coherence tomography (DOCT) are established methods to assess functional ocular blood flow. FA involves the intravenous

injection of a dye such as sodium fluorescein or indocyanine green into the bloodstream, allowing the vessels to be visualized by illuminating the dye within them. However, this method is invasive with the risk of adverse side effects. DOCT is a noninvasive method to measure blood perfusion that uses OCT technology coupled with phase information. When illuminated, the light that scatters off of moving red blood cells does so at various frequencies that depend on the speed and direction of the original moving cell. Since light that scatters from stationary cells does not have a phase shift, it is possible to separate the two kinds of signal in order to obtain details about the moving blood cells. DOCT detects blood flow in major vessels,[45],[46],[47],[48] but is less sensitive to capillary circulation or demonstrating leakage from the vessels.[49],[50] Laser doppler flowmetry[51] and laser speckle flowgraphy[52] are two other non-invasive technologies that are used to measure ocular blood flow.

OCT angiography (OCTA) is a reproducible, non-invasive imaging technique that has been developed to visualize the vascular network and can also be used to measure perfusion.[53] OCTA therefore achieves both functional and structural assessment of the retina through the same scan. Figure 2 shows an OCTA image of a glaucomatous ONH at various retinal depths, taken from a commercial software. There is evidence that OCTA is useful in distinguishing between healthy and glaucoma eyes, which might make it a useful tool in glaucoma diagnosis and monitoring, especially for normal tension glaucoma.[49],[50],[54],[55] OCTA is less susceptible to random noise and is able to obtain information from deep retinal layers and microcirculation, expanding the application of vascular imaging. Jia et al. [**49] used OCTA to quantify optic disc perfusion, and found that perfusion was significantly decreased in glaucomatous eyes compared to healthy controls, similar to previous reports. In glaucoma eyes, the microvascular network is noticeably attenuated, and disc flow is lower by approximately 25%. Wang et al.[56] have shown that a decrease in optic disc perfusion and vessel density were correlated with glaucoma severity as well as visual field mean deviation (MD) and peripapillary RNFL and macular ganglion cell complex thickness thinning. Further evaluation of the role of this technology in early glaucoma diagnosis is still underway at the time of this writing.

## 7. Innovations in Structural Testing

### 7.1 Ganglion Cell Analysis

While structural imaging in glaucoma usually focuses on the ONH and peripapillary retinal layers, more than half of all retinal ganglion cells lie in the macula, making this an important region for glaucoma assessment as well.[57] Total macular thickness thinning is strongly associated with glaucoma, but not as strongly as peripapillary RNFL thickness thinning, which is regarded as the most robust structural parameter by which to diagnose glaucoma.[58],[59],[60],[61] Advancements in OCT technology now allow the analysis of only the ganglion cell and inner plexiform layers (GCIPL), consisting of the bodies and dendrites of retinal ganglion cells. In some devices the segmentation also includes the RNFL and is called the ganglion cell complex (GCC). Both GCIPL and GCC have been shown to be quantifiable with high accuracy and reproducibility.[62],[63] The analysis of these layers targets only the portion of the macula that is specifically affected by glaucoma,

circumventing the influence of non-glaucomatous retinal pathologies that affect the macula. Ganglion cell layer measurements have been proven to be more sensitive to early glaucomatous damage in the macula than total macular thickness, as seen in Figure 3. Minimum GCIPL, or the thinnest GCIPL thickness among 360 spokes measured around the fovea, has been reported to more accurately detect early localized glaucomatous change than total average GCIPL thickness.[64] The glaucoma diagnostic ability of the GCIPL and GCC are comparable to circumpapillary RNFL thickness performance.[65],[66],[67] The diagnostic ability of these layers is improved in the presence of a central or paracentral scotoma in comparison with early peripheral abnormalities that might not be detectable in this scanned region.[68]

Ganglion cell analysis can be an especially useful tool for glaucoma diagnosis in myopic eyes. The detection of glaucoma in myopic eyes is complicated by common presence of a tilted disc, an optic cup that is shallow and large, and atrophy of the peripapillary crescent. Shin et al.[*69] reported that minimum GCIPL thickness performed statistically significantly better than circumpapillary RNFL in discriminating between healthy and early glaucomatous eyes with myopia. Several other studies have also shown the utility of ganglion cell thickness parameters for the detection of glaucoma in subjects with high myopia.[70],[71],[72] Therefore, ganglion cell analysis parameters should be considered along with the optic nerve and peripapillary parameters to ensure the most accurate glaucoma diagnosis.

### 7.2 Bruch's Membrane Opening and Minimum Rim Width

Traditionally, the neuroretinal rim in the optic nerve has been defined as the space from the termination of the retinal pigment epithelium to the edge of the cup. This measurement is an important parameter in the assessment of the ONH in glaucoma, used in the calculation of parameters such as rim area and rim volume. Recent analyses of this clinical construct have shown that the borders of the neuroretinal rim do not accurately represent the anatomical structure of this area of the ONH.[73] The configuration of the border tissue of Elschnig, the connective tissue that extends from the edge of the anterior sclera to Bruch's membrane, can obscure the visibility of the border of the optic disc margin. The location at which Bruch's membrane ends, also known as the Bruch's membrane opening (BMO), is a more consistently and accurately observed parameter that should be used as the anatomic indicator of the neuroretinal rim border.[74]

The axons of all ganglion cells pass through the ONH rim on their way to the brain. The shortest distance connecting the BMO with the ONH surface, the minimal rim width (MRW), is the narrowest rim space through which the axons need to pass and thus provides a reliable quantification of the axons passing over this area.[75] MRW measurements have been shown to closely correspond with the ONH morphology, RNFL thickness, and VF findings.[**75],[76] It is possible that rim calculations using BMO-based parameters may be better diagnostic indicators than traditional rim parameters due to their increased accuracy, [74] making it a novel marker by which to assess early structural glaucomatous changes.

### 7.3 RNFL Reflectance

The reflectivity of optical tissue has proven useful in the assessment of ocular tissue through the development of OCT technology. The internal reflectivity of the RNFL may also prove useful in the distinction between healthy and glaucomatous eyes. The reflectance of the RNFL depends on the orientation and properties of the microtubules that make up the axonal cytoskeleton of the RNFL,[77],[78] and distortion of the axonal cytoskeleton has been shown to occur in a rat model of glaucoma.[79] Huang et al.[80] and Dwelle et al.[81] found that increased IOP caused a decrease in RNFL reflectance in a rat and non-human primate model of glaucoma, respectively. Preliminary information suggests that reduction in tissue reflectance might be an indicator for early glaucomatous changes[82] and a predictor of future functional changes.[83] More research is needed to further explore the utility of this parameter for glaucoma diagnosis.

### 7.4 Lamina Cribrosa Imaging

The lamina cribrosa (LC) is the porous structure within the ONH through which all retinal ganglion cells pass through on their way to the brain. Evaluation of the LC is of great interest as this region is thought to be involved in the pathogenesis of glaucoma.[84],[85] Recent advances in optical imaging have allowed for deeper signal penetration, making it possible to better visualize both the macrostructure and microstructure of this region. New analysis tools have been developed to automatically analyze the shape of the LC along with the beam and pore microstructure of the LC.[86],[87],[88] Assessment of this structure may allow the observation of the ONH changes that initially damage retinal ganglion cell axons and lead to cell death.

Differences in the morphology of the LC between healthy and glaucomatous eyes have been previously reported. Wang et al. reported that in 19 healthy and 49 glaucoma eyes, the LC microstructure of glaucomatous eyes featured a larger beam to pore ratio than seen in healthy eyes.[88] Glaucoma eyes also had a higher standard deviation in microstructure measurements, which may indicate that focal remodeling of the LC occurs with disease. Ivers et al. identified changes in mean anterior LC surface depth, mean BMO MRW and anterior LC surface microstructure in a nonhuman primate model of early glaucoma.[89] More studies focusing on the LC microstructure are required before the effects of glaucoma on this structure can be fully defined and understood. Park et al. measured the total laminar thickness in 144 glaucoma subjects and 65 healthy controls.[*90] Glaucoma subjects had thinner LC measurements than healthy controls, and in normal tension glaucoma in particular, LC thickness significantly improved discrimination between healthy eyes and eyes with early glaucoma. They reported that statistically, laminar thickness had a diagnostic ability comparable to peripapillary RNFL thickness. This could provide another parameter by which to diagnose early glaucoma in the future. However, the posterior boundary of the LC is often difficult to detect with current OCT imaging without advanced post-processing of the image, therefore further validation and technological advances are required before this finding can be translated to clinical practice.

Another area of LC research investigates LC defects, defined as a large irregularity of the anterior LC surface that manifests as a hole or laminar disinsertion that violates the U- or W-

shaped contour typical of healthy eye anatomy. LC defects have been associated with localized RNFL defects and neuroretinal rim thinning[91],[*92],[93],[94] and VF progression.[95] In a study by You et al.[*92] that examined 185 eyes with varying stages of glaucoma, 11 laminar holes and 36 laminar disinsertions were discovered in 40 of the eyes. LC defects were detected using OCT images, reconstructed, then superimposed onto disc photographs. LC defects corresponded spatially to focal neuroretinal rim loss or optic disc pits. More research is required to better understand the role of LC defects in glaucoma, and whether LC defects can be used as a parameter to aid in the detection of glaucoma.

At the time of this writing, these assessments of the LC require advanced image analysis tools are needed in order to integrate the observation of these structural changes into routine glaucoma detection. The role of LC abnormalities in predicting future structural and functional changes requires further investigation.

## 8. Innovations in Functional Testing

### 8.1 Frequency-Doubling Perimetry

While SAP is the clinical gold standard for assessing functional vision, alternative forms of perimetry have also been developed. Frequency-doubling perimetry (FDP) uses a stimulus of a sinuosoidal grating composed of alternating black and white bands that is flickered at a high frequency. This creates the optical illusion that there are twice as many bars, which tests a subset of large, magnocular retinal ganglion cells that may be selectively damaged early in glaucoma.[96] The test is administered in a similar way to SAP. Studies have found that the ability of FDP to detect visual field abnormalities is effective at distinguishing between healthy eyes and eyes of varying degrees of glaucoma.[87],[98] The usefulness of this technology for glaucoma diagnosis has not reached a consensus. Many studies suggest that early glaucomatous abnormalities can be detected using this technique earlier than is possible with SAP, and that FDP can predict future SAP defects.[99],[100],[101],[102],[103] Other studies did not find a significant difference in the abilities of SAP and FDT to detect glaucoma.[104],[105] At this time, more research is needed to fully understand the potential of this technology.

### 8.2 Flicker Defined Form Perimetry

Another alternative form of perimetry is known as flicker defined form perimetry (FDF). This technology uses a stimulus of randomly positioned black and white dots that flicker at a high frequency. The black dots become white dots and the white dots become black dots with each flicker, and at high frequencies it creating the illusion that the subject is looking at a grey area with a circular edge in the center.[**106] This form of perimetry was designed to differentially stimulate the same subset of magnocular retinal ganglion cells that FDP stimulates, and it is administered similarly to SAP and FDP. FDF has been shown to be capable of distinguishing between healthy and glaucomatous eyes, although the ability of FDF to make this distinction worsens with worsening vision.[107] Therefore, the utility of FDF is in the detection of early glaucomatous damage, and during this early stage FDF may detect changes in vision earlier than SAP testing.[**106],[108],[109],[110] The defects detected with FDF have been shown to be correlated with RNFL measurements.[**106],

[111] The commercially available form of this test has been shown to be a useful tool in glaucoma diagnosis, and may become an important clinical tool in glaucoma management.[112],[113]

### 8.3 Multifocal visual evoked potential

Visual evoked potential (VEP) records the gross electrical potential generated by cells in the occipital cortex in response to brief light stimuli, often in the form of reversing checkerboard patterns. This gives a measure of the integrity of the visual pathway. The test is performed using scalp electrodes placed over the occipital cortex, therefore this test is less subjective than perimetry. Multifocal visual evoked potential (mfVEP) is a more recent iteration of VEP, and has the ability to record many spatially local VEP responses, making this technology a useful tool for detecting disruptions of the visual system caused by glaucoma, as the region corresponding to the ONH can be focused on.[114] mfVEP had shown a comparable diagnostic ability to that of SAP,[115],[116],[117] but it has been estimated that in up to 20% of subjects there is disagreement between the exact results of the two forms of testing, which might reflect differences in the what is being detected by the two devices.[116] It has therefore been suggested in a study by Moraes et al.[*118] that mfVEP may be most clinically useful when SAP and clinical examination prove insufficient to diagnose glaucoma.

### 8.4 Electroretinography

The electroretinogram (ERG) measures the electrical response of retinal cells. The pattern ERG (PERG) is a form of the test that is particularly useful in glaucoma because it selectively measures the function of retinal ganglion cells. Similar to VEP testing, ERG uses electrodes, which are applied to the cornea using a contact lens or are applied to the skin near the eye. Also similar to VEP testing, a black and white reversing pattern (usually alternating stripes or a checkerboard) stimulus is used. The results of the test yield a waveform that can be broken down into different components that reflect the response of different cells in the retinal layers. The a-wave reflects the function of the cone photoreceptors, the b-wave reflects the function of the cone bipolar cells including Muller cells.[119] PERG results have been shown to be abnormal in glaucoma subjects compared to normal subjects, making the test a successful indicator of disease.[120],[121],[122] Some studies have shown that abnormal PERG results can be predictive of future visual field loss detected with SAP.[123],[124],[125],[126]

Another component of this waveform, the phototopic negative response (PhNR), can be seen following the b-wave. This wave is thought to be caused by a spike in retinal ganglion cell activity.[127] Experimentally induced glaucoma in non-human primates eliminated this portion of the waveform from the ERG. The amplitude of the PhNR has since been shown to be smaller in ocular hypertensive and glaucoma subjects than in healthy subjects. The degree of PhNR abnormality has been correlated linearly to severity of visual field loss and RNFL thinning.[119],[127],[128] [*129] Analyzing the PhNR instead of looking at the general results of the PERG has been shown to have similar glaucoma detection ability.[130] ERG technology may prove useful in the future of glaucoma detection and monitoring, especially in subjects with suspected glaucoma or unreliable SAP testing.

## 9. Summary

Disagreement between structural and functional glaucoma detection methods often occurs in early stages of the disease. The use of both testing measures is the most robust way to ensure the detection of glaucoma. Recent advancements in structural testing methods have focused on new parameters by which to detect early glaucoma. OCTA, GCIPL and GGC measurements, BMO MRW, RNFL reflectance, and LC measurements may help clinicians detect glaucoma earlier and with more sensitivity and specificity. Advancements in functional testing have focused on detecting changes in vision during the early period of the disease when SAP testing is not sensitive enough to detect visual field defects. FDP and FDF are two forms of perimetry that may have the potential to detect visual changes earlier than SAP testing. mfVEP and ERG technology offers an objective way to measure visual function, and may also be more useful in detecting early glaucomatous changes than SAP. New advances in structural and functional testing increase our ability to detect early glaucoma, improving glaucoma management.

## 10. Expert Commentary

The use of both structural and functional glaucoma detection methods is of great importance for glaucoma management. Innovative technologies such as OCT angiography give clinicians a way to accurately track changes in retinal vasculature in glaucomatous eyes and use this information to predict future progression. Structural measurements of structures such as the GCC, GCIPL and MRW adds another important piece of information in glaucoma diagnosis, especially in eyes that are confounded by co-morbidities such as myopia or non-glaucomatous retinal pathologies. Through the targeting of retinal ganglion cells that are specifically prone to very early glaucomatous damage, new forms of perimetry including FDP and FDF have the potential to detect vision loss earlier than was possible with SAP. These new forms of structural and functional glaucoma detection methods will complement established testing methods and supplement the information available to clinicians, allowing clinicians to make the most informed decisions possible to manage glaucoma.

## 11. Five-year view

The analysis of the structure-function relationship in glaucoma is likely to further improve in the future. Future technologies will be focused on early glaucoma detection, novel parameters to distinguish between healthy and glaucomatous eyes, and advancement in the sensitivity and specificity of the technologies that are used to currently assess important parameters. OCT technology in particular has allowed for the novel investigation of many aspects of glaucoma, making it possible to perform advanced segmentation and analysis of structures such as the retinal layers and lamina cribrosa microstructure. This technology is only expected to advance with respect to scanning speed, tissue penetration, and resolution. Advancements in posterior eye imaging may lead to the clinical accessibility of parameters involving the lamina cribrosa, choroid and possibly even individual retinal ganglion cells. It is also expected that new, more sensitive methods to assess early changes in visual function will be developed to compensate for the lack of sensitivity seen with SAP. It is likely that

research focused on combining structural and functional measures will be honed, and new algorithms will be developed to better combine the complementary information that can be obtained from both forms of testing.

## Acknowledgments

**Funding**

Funding was received from the U.S. Department of Health and Human Services, the National Eye Institute and the NIH, grant numbers R01-EY013178, R01-EY025011

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## 12. Key Issues

- The structure-function relationship in the early stages of glaucoma is complexly associated.
- Causal factors for this complicated relationship could include the redundancy of the visual system, retinal ganglion cell dysfunction before total cell death and limitations in the sensitivity of standard automated perimetry.
- OCT angiography (OCTA) provides a non-invasive method to visualize the retinal vasculature and measure perfusion. Decreased optic disc perfusion has been associated with glaucoma, making OCTA a potential diagnostic tool.
- The ganglion cell analysis allows the analysis of macular layers that are specifically prone to glaucomatous damage, giving clinicians a way to accurately observe retinal ganglion cell loss in situations where RNFL measurements could be confounded, such as in patients with high myopia.
- Neuroretinal rim parameters, such as rim area, calculated using Bruch's membrane minimum rim width have (BMO-MRW) been shown to provide a more anatomically accurate estimate of these measurements.
- Decreased RNFL reflectivity may be a predictor of future structural and functional glaucomatous damage.
- Changes in lamina cribrosa structure (LC) can be quantified using imaging devices, and has been associated with glaucoma.
- New forms of functional glaucoma detection methods such as frequency doubling perimetry (FDP), flicker defined form perimetry (FDF), multifocal visual evoked potential (mfVEP), and electroretinography (ERG) may be useful for specific diagnostic situations, but their overall utility in glaucoma diagnosis is yet to be determined.

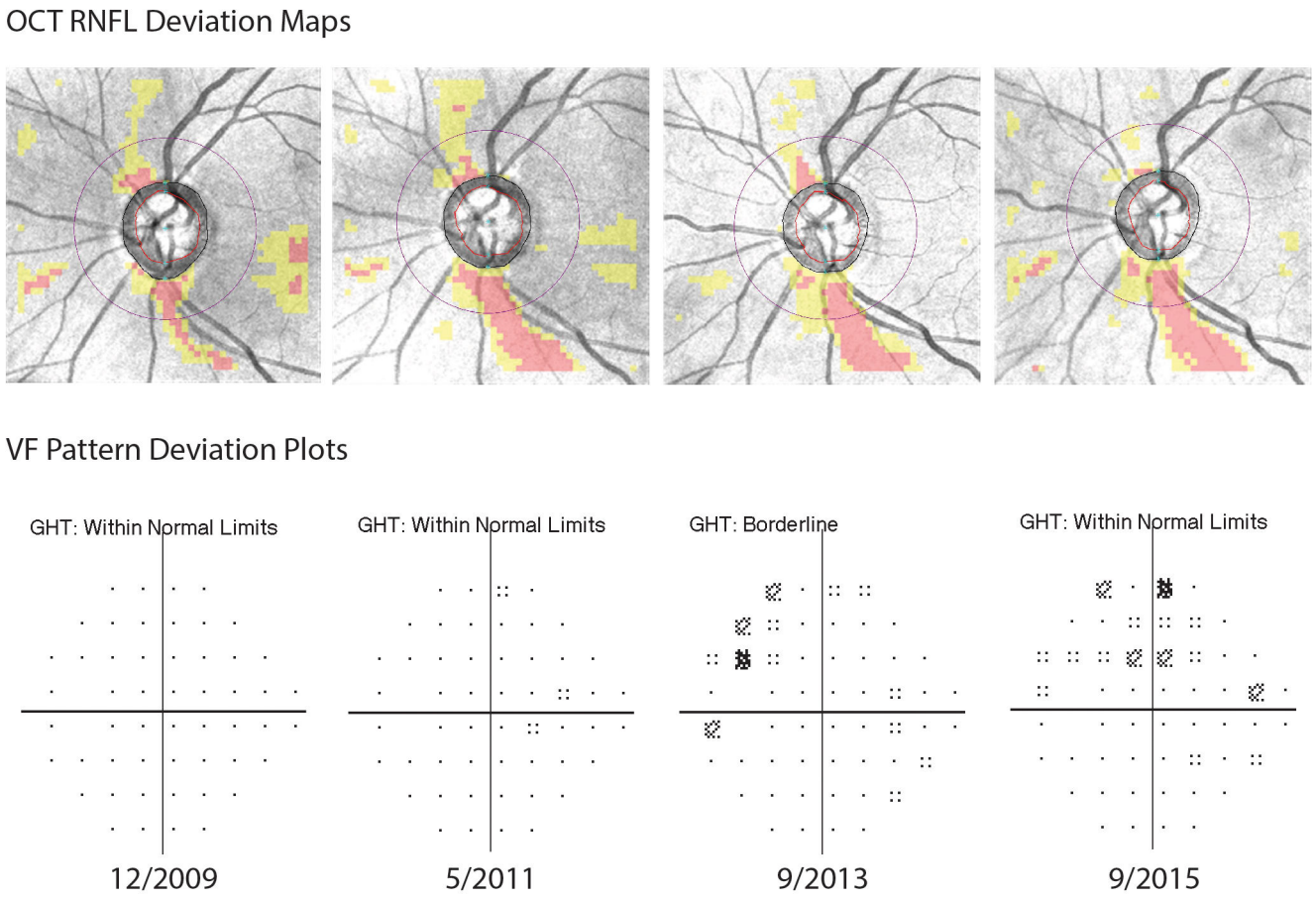


**Figure 1. Structural RNFL Defect Detected with OCT before Functional Defect detected with Humphrey Visual Field 24-2**

Significant thinning of the RNFL (denoted with yellow at the first occurrence and red at each subsequently matching occurrence) is seen during the baseline exam and progresses over the course of follow-up. An abnormality is detected using perimetry nearly 4 years later.

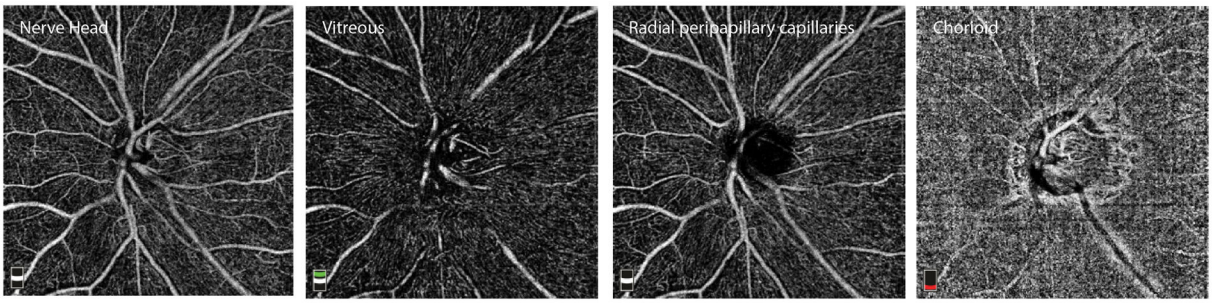


**Figure 2. OCT Angiography of a Glaucomatous Optic Nerve Head**

The vasculature of the optic disc is seen as a projection (nerve head) and three different specific retinal layers (vitreous, radial peripapillary capillaries, choroid).

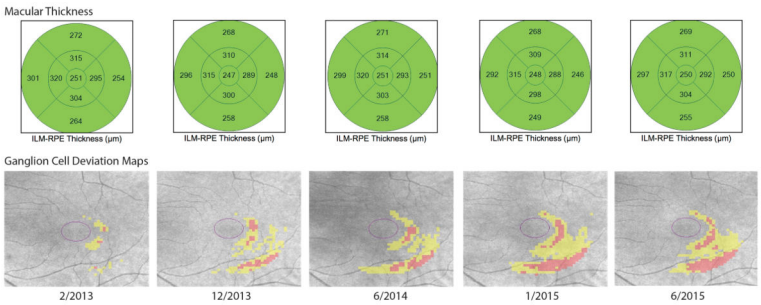


**Figure 3.**

Ganglion Cell Analysis Detects Damage Missed by Total Macular Thickness Analysis

Abnormality detected in the inferior ganglion cell inner plexiform layer (GCIPL) that is reproducible and worsens over time (bottom). Thinning is not detected by analysis of total macular thickness (top).