

## Review article

# Detecting optic nerve head deformation and retinal nerve fiber layer thinning in glaucoma progression



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## ABSTRACT

The application of digital imaging technologies including confocal scanning laser ophthalmoscopy (CSLO), optical coherence tomography (OCT), and scanning laser polarimetry (SLP) has significantly improved the detection of optic nerve head (ONH) deformation and progressive retinal nerve fiber layer (RNFL) thinning for assessment of glaucoma progression. Algorithms for change analysis such as topographic change analysis and guided progression analysis perform event analysis of serial ONH surface height topology maps and RNFL thickness/RNFL retardance maps, respectively, providing a topographical display of the location of significant change. With spectral-domain OCT, it is feasible to delineate and measure the lamina cribrosa surface depth in addition to ONH surface depth and RNFL thickness. Growing evidence from experimental and clinical studies indicates that ONH and lamina cribrosa deformation can be observed prior to detectable RNFL thinning and functional loss in glaucoma. These findings lend support to the notion that upon detection of ONH/lamina cribrosa deformation, a time window for therapeutic intervention for better outcomes may exist. The ONH and the lamina cribrosa are therefore important targets for monitoring glaucoma progression. This review summarizes the latest findings comparing the performance of OCT, CSLO, and SLP for detection of progressive ONH and RNFL damages in glaucoma patients and the clinical implication and limitations of studying the morphological alteration of the ONH, lamina cribrosa, and RNFL in the assessment of glaucoma progression.

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## 1. Introduction

Glaucoma is the most common form of chronic, progressive optic neuropathy. A previous report indicates that the number of people with glaucoma would increase to 79.6 million by 2020.<sup>1</sup> Early detection of optic nerve damage in glaucoma is pertinent to formulation of treatment plan to prevent or slow down irreversible loss of vision. Although all forms of optic neuropathies demonstrate loss of retinal ganglion cells and thinning of the retinal nerve fiber layer (RNFL), glaucoma is unique in exhibiting progressive deformation of the optic nerve head (ONH). Growing evidence suggests that ONH deformation occurs prior to RNFL and functional loss in glaucoma.<sup>2–7</sup> Deformation of the ONH and lamina cribrosa surfaces has been consistently demonstrated in nonhuman primates

induced with experimental glaucoma by laser photocoagulation of the trabecular meshwork.<sup>2–5,8–11</sup> Proposed to be the primary site of optic nerve damage in glaucoma,<sup>12</sup> the lamina cribrosa represents a strategic location for early detection of disease deterioration behavior. Progressive deformation of the lamina cribrosa may represent an early biomarker for glaucoma development and progression. This review summarizes the digital imaging technologies and algorithms available in the clinic for evaluation of progressive ONH and RNFL changes, experimental and clinical studies that investigated ONH deformation and RNFL thinning in glaucoma progression, and the implication of detection of structural changes of the ONH in the management of glaucoma.

## 2. Imaging technologies for evaluation of ONH deformation and RNFL thinning

### 2.1. Confocal scanning laser ophthalmoscopy

Confocal scanning laser ophthalmoscopy (CSLO) is the most long-standing digital imaging instrument for evaluation of the ONH

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surface topology. The Heidelberg Retinal Tomograph 3 (HRT 3; Heidelberg Engineering, Heidelberg, Germany) is the latest commercially available model of CSLO. It constructs three-dimensional surface topographic image consisting of up to 384 pixels  $\times$  384 pixels  $\times$  64 pixels from multiple focal images captured axially along the ONH. Because CSLO does not collect any data below the retinal and ONH surfaces, it can only be used to monitor ONH surface deformation but not lamina cribrosa deformation nor RNFL thinning. Measurement of the neuroretinal rim area is feasible with HRT but the measurement is dictated by an arbitrary reference plane, which is defined 50  $\mu$ m posterior to the mean retinal height between 350° and 356° along a manually drawn contour line along the clinically visible optic disk margin. The topographic change analysis (TCA; Heidelberg Engineering), developed by Chauhan and colleagues,<sup>13</sup> is a well-established algorithm for measurement of progressive ONH surface height change in glaucoma patients. The TCA analyzes serial ONH topography images at a resolution of 96 superpixels  $\times$  96 superpixels (1 superpixel = 4  $\times$  4 pixels). Individual superpixel ONH surface height measurements obtained in the baseline and follow-up visits are compared with the within-subject measurement variability. Superpixels with significant ONH surface depression and elevation are encoded in red and green, respectively, in the significance map, which is a topographical display of the location and the magnitude of ONH surface deformation (the saturation of the color increases with the degree of change; Fig. 1D). However, there is no consensus regarding the area and the depth of ONH surface height change that should be considered as clinically relevant. It is worth noting that ONH surface depression measured by the HRT may indicate the presence of ONH surface deformation, lamina cribrosa deformation, loss of the prelaminar tissue, or a combination of all these. HRT is not capable of delineating the individual components of the ONH changes.

## 2.2. Spectral-domain optical coherence tomography

### 2.2.1. Analysis of progressive RNFL thinning

Spectral-domain optical coherence tomography (SD-OCT) has gained popularity over the CSLO because of its higher scan speed, higher image resolution, and being able to quantify both the RNFL and ONH parameters. Whereas all the commercially available SD-OCT instruments have a scan speed >20,000 A-scans/second and an axial resolution of  $\sim$ 5  $\mu$ m, the Cirrus high-definition OCT (HD-OCT; Carl Zeiss Meditec, Dublin, CA, USA) is unique in having the most mature technology for detection of progressive RNFL thinning. The RNFL is conventionally imaged and measured using a circumpapillary scan with a diameter of approximately 3.45 mm. The Cirrus HD-OCT measures the RNFL thicknesses in an area of 6  $\times$  6 mm<sup>2</sup>, comprising 200 pixels  $\times$  200 pixels, displays the distribution of the RNFL in the RNFL thickness map, and reveals locations of RNFL abnormalities in the RNFL thickness deviation map.<sup>14</sup> For progression analysis, the guided progression analysis (GPA; Carl Zeiss Meditec) computes the differences of RNFL thickness measurements in serial RNFL thickness maps and reports the location of significant change in the RNFL thickness change map (Fig. 1B).<sup>15</sup> The GPA aligns and registers two baseline and the follow-up RNFL thickness maps, and compares the RNFL thickness differences of the individual superpixel (1 superpixel = 4 pixels  $\times$  4 pixels) locations between the baseline and the follow-up measurements with an estimate of test–retest variability. Superpixels are encoded in yellow in the OCT RNFL thickness change map if the RNFL thickness differences between the two baseline and follow-up examinations are greater than the test–retest variability. Superpixels are encoded in red if the change is confirmed in a consecutive visit. It has already been demonstrated that GPA of the

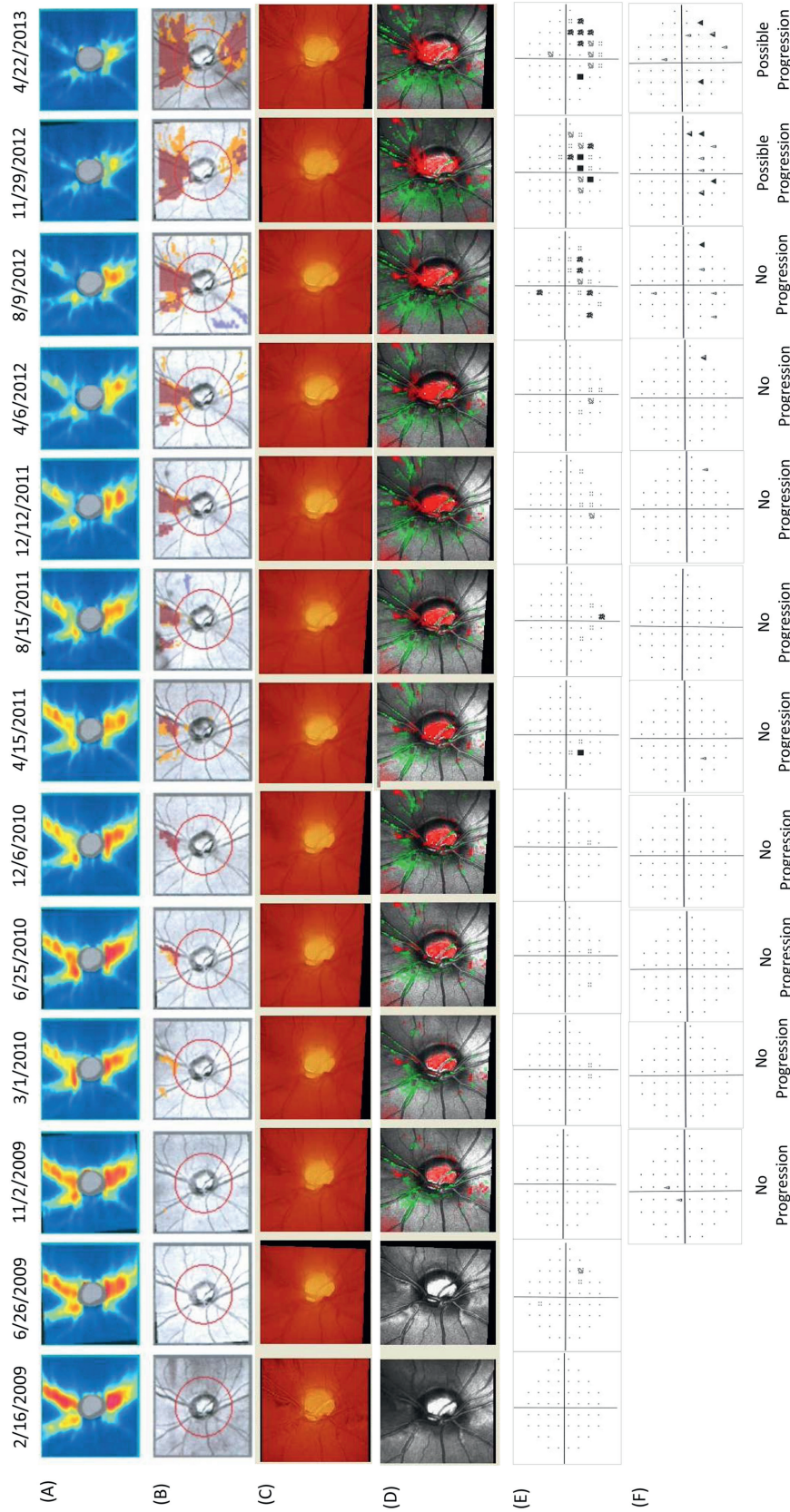
RNFL thickness maps is useful to discern different patterns of progressive RNFL thinning including widening and deepening of RNFL defects.<sup>15</sup> Although GPA also provides a trend analysis of the average superior and inferior RNFL thicknesses, these analyses are limited to the circumpapillary RNFL measurement. Trend analysis of the RNFL thickness map has not yet been developed for routine clinical use.

### 2.2.2. Analysis of progressive ONH changes

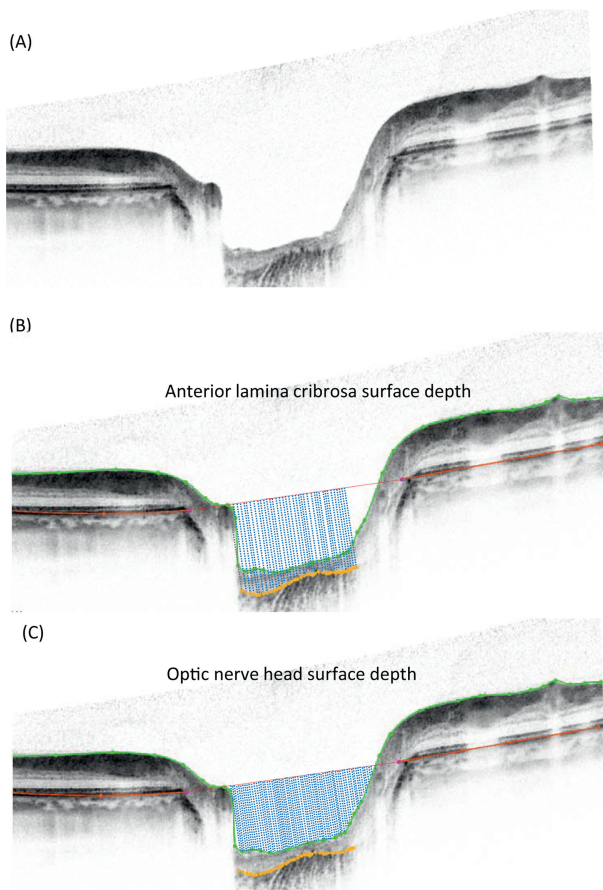
Analysis of progressive deformation of the ONH surface and the lamina cribrosa surface is less straightforward with OCT as no image and statistical analysis package for detection of ONH and lamina cribrosa surface change has been incorporated into the existing OCT platforms. With enhanced depth imaging of the SPECTRALIS OCT (Heidelberg Engineering) and the swept-source OCT (e.g., the Atlantis OCT, Tokyo, Japan), clear visualization of the anterior (and sometimes posterior) lamina cribrosa surface and reliable estimation of the lamina cribrosa surface depth have become possible. OCT B scans can be exported from the OCT instrument for measurement of lamina cribrosa surface depth and optic nerve head surface depth (ONHSD) using a customized developed computer program. Anterior lamina cribrosa surface depth (ALCSD) and ONHSD are most often measured with reference to the Bruch's membrane opening (BMO) in experimental and clinical studies measuring deep ONH changes in glaucoma.<sup>2–5,9–11</sup> The ALCSD represents the perpendicular distances from a line joining the BMO, the reference line, to the discernible anterior lamina surface, which can be identified as the intersection between the horizontal high-intensity signal below the disk surface and the high-intensity vertical striations (Fig. 2B).<sup>2</sup> The ONHSD represents the perpendicular distances from the reference line to the ONH surface (Fig. 2C). Because the scan locations are registered at the baseline, it is feasible to image the same locations in the follow-up visits and track the changes of the ONH structures. It is uncertain, however, what type (radial vs. raster scans) and how many B scans are required to reliably detect ONH and lamina cribrosa surface change. Localized changes would be missed if the B-scan sampling density is low. Although the BMO reference line/plane is a widely adopted standard for measurement of ALCSD and ONHSD, the long-term stability of the BMO reference line/plane remains unclear. Age-related choroidal thinning may lead to anterior displacement of the ONH and lamina surfaces, confounding change analysis of ALCSD and ONHSD in glaucoma progression.<sup>16</sup>

## 2.3. Scanning laser polarimetry

The scanning laser polarimetry (SLP) uses polarized light to measure the relative phase retardance of the RNFL. The GDx enhanced corneal compensation (ECC; Carl Zeiss Meditec) is the latest generation of SLP. It introduces a known bias retarder, which then is removed mathematically to compensate for the retardance signal induced by the crystalline lens and the cornea. The GDx ECC uses the same GPA as that in the Cirrus HD-OCT for detection of progressive loss of RNFL retardance (Fig. 3). Although it has been shown that loss of RNFL retardance detected by SLP preceded RNFL thinning detected by OCT in nonhuman primates induced with experimental glaucoma,<sup>3,17</sup> a prospective clinical study demonstrated otherwise. Following 116 glaucoma patients for an average of 55 months with GDx ECC measurement of RNFL retardance and Cirrus HD-OCT measurement of RNFL thickness at 4-month intervals, we observed that progressive RNFL thinning was detected more frequently than progressive reduction of RNFL retardance at a similar level of specificity (14.6% and 4.3% of eyes showed progressive reduction of RNFL thickness and RNFL retardance, respectively).<sup>18</sup> For eyes with loss of RNFL thickness and RNFL



**Fig. 1.** (A) Serial retinal nerve fiber layer (RNFL) thickness maps, (B) RNFL thickness change maps, (C) optic nerve head (ONH) surface topography, (D) ONH significance maps, (E) visual field pattern deviation plots, and (F) guided progression analysis (Early Manifest Glaucoma Trial criteria) of the left eye of a 27-year-old glaucoma patient followed for 50.4 months. Diffuse ONH surface depression was detected on November 2, 2009, which was then followed by superior (June 25, 2010) and inferior (November 29, 2012) RNFL thinning and visual field progression. Note: From "Optic nerve head deformation in glaucoma: the temporal relationship between optic nerve head surface depression and retinal nerve fiber layer thinning," G. Xu, R.N. Weinreb, and C.K. Leung, 2014, *Ophthalmology*, 121, p. 2362–2370. Copyright 2014. Elsevier. Reprinted with permission.



**Fig. 2.** (A) An optical coherence tomography cross-sectional image of the optic nerve head illustrating the measurement of (B) the anterior lamina cribrosa surface depth and (C) optic nerve head surface depth after manual detection of the Bruch's membrane opening (pink dots), internal limiting membrane/optic nerve head surface (green), and anterior lamina cribrosa surface (orange). The reference line (pink) is a line joining the Bruch's membrane opening.

retardance evident at the latest follow-up visit, the former preceded the latter (Fig. 3). SD-OCT may outperform SLP in providing a wider dynamic range and having a lower measurement variability for detection of RNFL damage.<sup>19</sup>

### 3. ONH deformation precedes RNFL thinning

#### 3.1. Experimental evidence

Experimental studies investigating ONH and lamina cribrosa changes in nonhuman primates have consistently indicated that ONH and lamina cribrosa deformation preceded reduction in RNFL thickness and visual function. Strouthidis and colleagues<sup>2</sup> serially imaged the ONH with CSLO and the RNFL with SD-OCT in nine rhesus macaques with intraocular pressure elevation induced by laser photocoagulation of the trabecular meshwork. At the onset of CSLO-detected ONH surface depression at approximately 1.2–5.8 months following induction of experimental glaucoma, there was no significant change in RNFL thickness. Significant RNFL thinning was only detected at approximately 7.1–14.0 months. Two studies by Fortune and colleagues<sup>3,4</sup> confirmed this observation in 33 and 68 rhesus macaques, respectively, induced with experimental glaucoma using the same imaging instruments. On average, progressive ONH surface depression was detected approximately 1–2 months earlier than progressive RNFL thinning. In a recent study, He et al<sup>5</sup> measured the ALCSA with SD-OCT in eight rhesus

macaques at the baseline and then every 2 weeks following elevation of intraocular pressure and showed that detectable ALCSA change occurred prior to detectable RNFL thinning and deterioration in visual function measured by multifocal electroretinography. These experimental studies indicate that there is a time lag between ONH/lamina cribrosa deformation and reduction in RNFL thickness and visual function in experimental model of glaucoma. Notably, a key shortcoming in the experimental glaucoma model is intraocular pressure spikes, which can be up to 50–60 mmHg following laser photocoagulation of the trabecular meshwork. Acute increases of intraocular pressure may result in morphological alteration of the ONH and ischemic damage of retinal ganglion cells independent of glaucomatous damage.

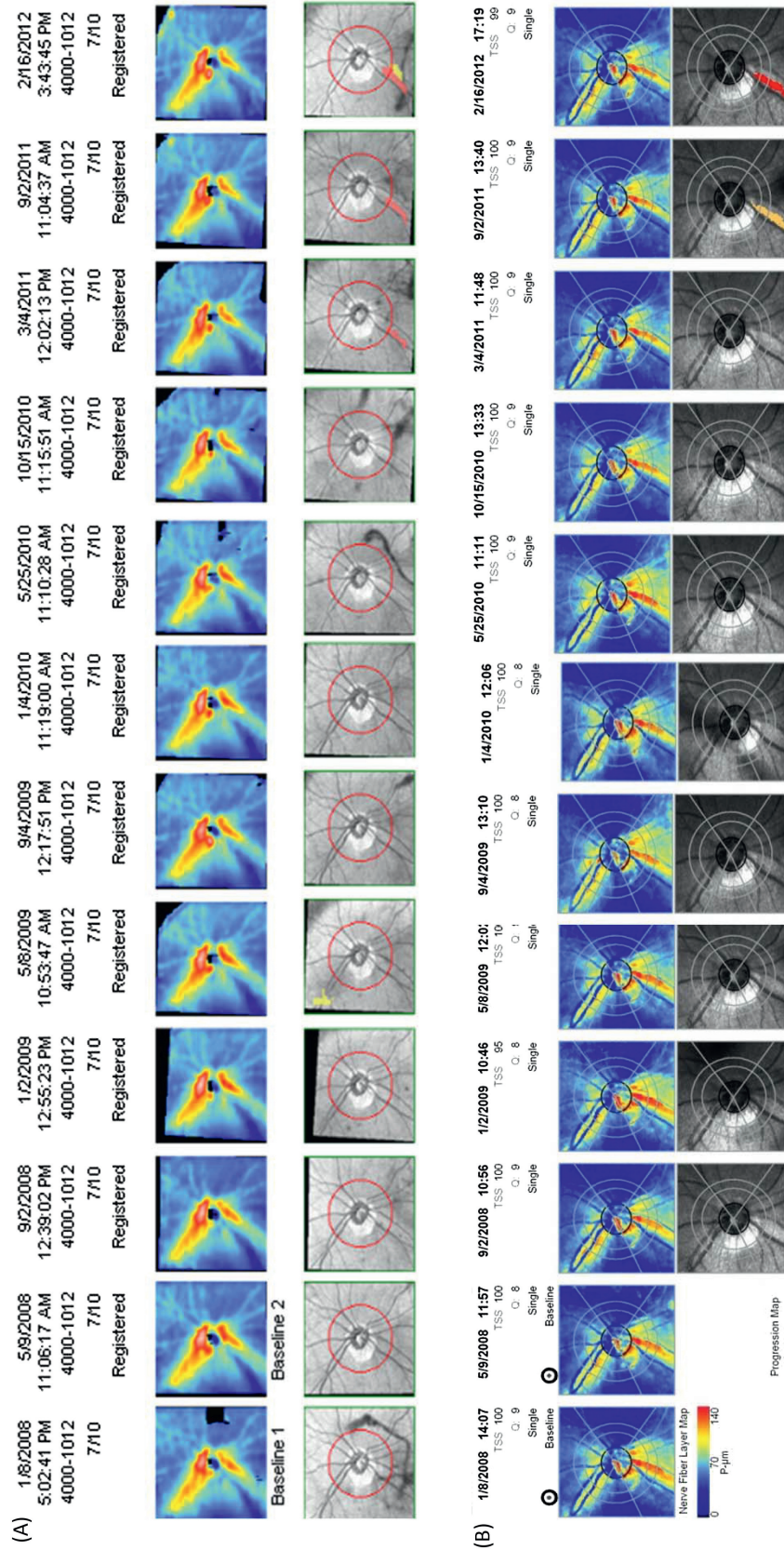
#### 3.2. Clinical evidence and implication

At least three longitudinal studies have demonstrated that progressive ONH change detected by stereophotography or CSLO occurs before identifiable visual field progression in glaucoma patients. Medeiros and colleagues<sup>6</sup> followed 639 eyes of 407 patients with suspected glaucoma with visual field testing and optic disk photography performed every year for an average of 8 years and showed that progressive optic disk damage was a strong predictor for development of visual field defects. Eyes with progressive optic disk changes carry a 25.8-fold (95% confidence interval: 16.0–41.7) increase in risk of development of visual field defects compared with those without. Using the CSLO, Chauhan and colleagues<sup>7</sup> imaged the ONH every 6 months for a median of 11 years in 81 open-angle glaucoma progression cases and reported that eyes having visual field progression were three times more likely to have prior ONH surface change detected by the TCA. In a recent study, we examined 146 eyes of 90 glaucoma patients and imaged the ONH with CSLO and the RNFL with SD-OCT at 4-month intervals for an average of 5.4 years and investigated the temporal relationship between ONH deformation and RNFL thinning.<sup>20</sup> Among the 23 eyes demonstrating both ONH deformation and RNFL thinning at the latest follow-up visit, 82.6% had ONH surface depression detected before RNFL thinning and the median lag time was 15.2 months. For eyes with concomitant ONH deformation, RNFL thinning, and visual field loss, ONH deformation always occurred before visual field progression. This study underscores the importance of ONH imaging and the significance of ONH deformation in predicting RNFL and visual field loss in glaucoma.

The need for new end points to evaluate glaucoma therapies has been widely discussed in major ophthalmology conferences including the World Glaucoma Association Consensus meetings and the National Eye Institute/Food and Drug Administration Glaucoma Clinical Trial Design and Endpoints Symposium.<sup>21</sup> Regulatory agencies consider structural parameters as outcome measures for glaucoma clinical trials only when there is evidence supporting that the new outcome measure is predictive of functional change. Active investigation is ongoing to investigate whether progressive ONH surface and/or lamina cribrosa surface deformation are reliable structural end points to indicate subsequent change in visual function and more importantly, whether glaucoma treatment initiated or augmented at the time of ONH/lamina cribrosa deformation would slow down visual field loss and preserve vision.

### 4. Summary

Digital imaging technologies have considerably improved the visualization and detection of ONH and RNFL changes in glaucoma progression. For detection of progressive RNFL thinning, the GPA (Carl Zeiss Meditec) provides event analysis of RNFL measurements



**Fig. 3.** Serial retinal nerve fiber layer (RNFL) thickness maps (A, upper panel), RNFL retardance maps (B, lower panel), and RNFL retardance change maps (B, lower panel) of a glaucomatous eye. Progression was evident in the RNFL thickness change map (on March 4, 2011) approximately 11 months before it became noticeable in the RNFL retardance change map (on February 16, 2012). Note: From "Retinal nerve fiber layer progression in glaucoma: a comparison between retinal nerve fiber layer thickness and retardance," G. Xu, R.N. Weinreb and C.K. Leung, 2013, *Ophthalmology*, 120, p. 2493–2500. Copyright 2013. Elsevier. Reprinted with permission.

in the RNFL thickness map. For detection of progressive ONH surface change, the TCA (Heidelberg Engineering) performs event analysis of the ONH surface heights in the ONH surface topology map. The OCT GPA and the HRT TCA are important clinical tools to detect and monitor localized and diffused changes of the RNFL profile and ONH surface topology. Currently, change analysis of the lamina cribrosa requires manual detection of the lamina cribrosa surface and BMO, which could be time consuming and labor intensive, particularly when a large volume of OCT scans are collected over time. The fact that deformation of ONH surface/lamina cribrosa surface precedes irreversible loss of the RNFL and visual function lends support to the notion that ONH and/or lamina cribrosa deformation may well serve as an early biomarker for disease deterioration behavior. A time window may be available for therapeutic intervention in many patients upon detection of ONH deformation.

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