



## Detecting Structural Progression in Glaucoma with Optical Coherence Tomography

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Optical coherence tomography (OCT) is increasingly used to obtain objective measurements of the retinal nerve fiber layer (RNFL), optic nerve head, and macula for assessing glaucoma progression. Although OCT has been adopted widely in clinical practice, uncertainty remains concerning its optimal role. Questions include: What is the best structure to measure? What quantity of change is significant? Are structural changes relevant to the patient? How are longitudinal measurements affected by aging? How can changes resulting from aging be differentiated from true progression? How best should OCT be used alongside visual fields, and how often should OCT be performed? Recent studies have addressed some of these questions. Important developments include appreciation of the need to use a consistent point of reference for structural measurements, leading to the introduction of Bruch's membrane opening (BMO)–based measurements, including BMO–minimum rim width and BMO–minimum rim area. Commercially available OCT devices also permit analysis of macular changes over time, for example, changes in the ganglion cell and inner plexiform layers, the sites of the retinal ganglion cell bodies and dendrites, respectively. Several longitudinal studies have compared rates of change in RNFL and macular measurements, with some suggesting that the relative value of each parameter may differ at different stages of disease. In early disease, looking for change over time also may be useful for glaucoma diagnosis, with advantages over classifying eyes using cross-sectional normative databases. Optimal glaucoma management requires information from imaging and visual fields, and efforts have been made to combine information, reducing the noise inherent in both tests to benefit from their different performances according to the stage of disease. Combining information from different structural measurements may also be useful. There is now substantial evidence that progressive structural changes are of direct clinical relevance, with progressive changes on OCT often preceding functional loss and patients with faster change on OCT at increased risk of worsening visual losses. Identification of such patients offers the possibility of commencing or escalating treatment at an earlier stage. This review appraises recent developments in the use of OCT for assessing glaucoma progression. Ophthalmology 2017;124:S57-S65 © 2017 by the American Academy of Ophthalmology

Detecting and assessing rates of progression are indispensable constituents of glaucoma management as they provide a means to identify rapidly progressing patients who are at high risk of visual disability and who may require escalation in treatment. Progression is measured conventionally by monitoring for changes in visual field sensitivity; however, many patients have changes to the optic disc or retinal nerve fiber layer (RNFL) in the absence of deterioration on automated perimetry, providing an opportunity to commence or increase treatment before significant decline in vision.<sup>1,2</sup>

Detecting structural change over time is also useful for diagnosing glaucoma, with advantages over classifying an eye as normal, abnormal, or borderline by comparing a single scan with a normative database. Normative databases have strict inclusion criteria, consist largely of patients of European ancestry, and exclude those with high refractive error or ocular comorbidities. Normal structural measurements vary widely between individuals, increasing the chances of misclassification. In some cases, because of the wide range of normal, significant neural losses may occur before a patient is deemed to be outside normal limits. Establishing baseline structural measurements and observing for change over time has great value as an aid to diagnosis, particularly in glaucoma suspects.

Detection of glaucomatous structural changes traditionally has relied on assessment of optic disc photographs; however, agreement among glaucoma specialists in judging change on disc photographs is only slight to fair, and photographs do not allow quantification of rates of change.<sup>3</sup> Optical coherence tomography (OCT) overcomes some of the limitations of optic disc photography and can be used to provide objective measurements of the RNFL, optic nerve head (ONH), and macula, useful for glaucoma diagnosis and progression analysis. Although OCT has been adopted widely in glaucoma clinics, uncertainty remains concerning how best to use OCT to detect glaucoma progression. Pertinent, and only partially answered, questions include: What is the best structure to measure? What quantity of change is significant? Are structural changes relevant to the patient? How are

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longitudinal measurements affected by aging, and how can changes resulting from aging be differentiated from true progression? What are the best ways to use OCT alongside visual fields and how often should OCT be performed?

### What Is the Best Structure to Measure?

The ideal parameter for measuring glaucoma progression should be highly reproducible and useful at all stages of disease. OCT measurements of rates of change in glaucoma have focused largely on circumpapillary RNFL (cpRNFL) thickness, which is also the most widely used parameter in clinical practice. However, recent studies have indicated that additional information can be gleaned from examining changes in RNFL in other regions, for example, by examining the topography of RNFL loss across a  $6 \times 6$ -mm<sup>2</sup> optic disc cube scan RNFL map.<sup>4</sup> OCT devices now also provide the ability to quantify changes to the glaucomatous macula using measurements such as ganglion cell inner plexiform layer and ganglion cell complex thickness, which includes the ganglion cell layer, inner plexiform layer, and RNFL-the sites of retinal ganglion cell bodies, dendrites, and axons, respectively. Macular measures are of special interest because of the density of retinal ganglion cells located in this region and the realization that, contrary to conventional teaching, the macula often is involved early in the glaucomatous process.<sup>5,6</sup> Some OCT devices now also include the ability to obtain novel ONH metrics such as Bruch's membrane opening (BMO)-minimum rim width (MRW) and BMO-minimum rim area,<sup>7-9</sup> which use BMO as an anatomic point of reference for measurements and are discussed in more detail below.

The first report of OCT to examine glaucoma progression used a prototype time-domain OCT device to measure changes in RNFL thickness over time.<sup>10</sup> The device was limited by poor reproducibility, which may have resulted in false-positive assumptions of progression; however, the study demonstrated the potential of OCT for detecting longitudinal change. Using a commercially available timedomain OCT device (Stratus OCT; Carl Zeiss Meditec, Inc, Dublin, CA), Medeiros et al<sup>11</sup> compared the ability of cpRNFL, ONH, and macular measurements to differentiate eyes progressing on standard automated perimetry (SAP) and optic disc stereophotographs from those that remained stable using conventional tests. Circumpapillary RNFL performed significantly better than ONH and macular parameters at discriminating progressing and stable eyes, with faster rates of cpRNFL thinning observed in progressing eyes ( $-0.72 \mu m$ /year vs. 0.14  $\mu$ m/year; P = 0.004).

Time-domain OCT now has been superseded by spectral-domain (SD) OCT, which has an improved scan speed and a higher resolution, and incorporates innovations such as real-time eye tracking to compensate for eye movements during data acquisition and to reduce motion artifacts. Time-domain OCT was limited by its inability to register images on follow-up scans, meaning measurements from disparate retinal locations could be included in analyses of change over time. In contrast, SD OCT devices can center follow-up scans automatically on previously scanned locations by identifying retinal land-marks, which results in improved reproducibility and better ability to detect progression compared with time-domain OCT.<sup>12,13</sup>

Several studies have used SD OCT to evaluate the role of cpRNFL and macular measurements for assessing glaucoma progression (Table 1).<sup>14–23</sup> However, it is difficult to determine whether one parameter is better than another because of the lack of a gold standard, and although all glaucomatous changes reflect loss of retinal ganglion cells, there is still poor understanding of the temporal relationship between changes to the ONH, RNFL, and macula. Studies either have compared rates of structural change occurring in glaucomatous eyes with rates in healthy participants  $^{17,18,20,22-25}$  or have examined the association between rates of change on OCT and contemporaneous or future changes on conventional structural or functional assessments.<sup>14,16,19,26–28</sup> Overall, both cpRNFL and macular measures show faster rates of loss in glaucomatous eyes compared with controls; however, there is wide variation in reported rates of change. This is to be expected, however, because trend-based analyses of visual field sensitivities also have demonstrated disparate slopes among different individuals.<sup>29</sup> It is also inappropriate to compare rates of change directly between studies and between parameters because of different baseline thicknesses and dynamic ranges. One approach that helps overcome this problem is to examine rates of change with values normalized for dynamic range. Using this approach to study 97 glaucomatous eyes followed up for an average of 3.2 years, Hammel et al<sup>23</sup> found normalized cpRNFL thickness to decrease by 1.7% per year compared with only a 1.3% per year decrease in macular ganglion cell inner plexiform layer (mGCIPL) thickness. This 1.3-fold faster rate of cpRNFL loss suggests that cpRNFL may be a more sensitive index of progression; however, among eyes with advanced glaucoma, where no further change in cpRNFL was observed, there was significant downward slope in mGCIPL thickness. Therefore, the relative value of cpRNFL and mGCIPL measurements may vary at different stages of disease, with macular measurements possibly of value for monitoring eyes with advanced glaucoma, beyond the floor observed in cpRNFL measurements.<sup>30</sup> These findings also were supported by Sung et al,<sup>16</sup> who found eyes with advanced glaucoma with visual field progression had significantly faster rates of macular thickness loss compared with nonprogressing eyes, whereas there was no significant difference in rate of cpRNFL change between groups. However, it is important to exercise caution in interpreting the results of these studies because the rate of change is not the only variable of importance in determining which parameter could be of most value for detecting progression. For example, a faster rate of change in cpRNFL compared with mGCIPL may be offset by differences in reproducibility of cpRNFL and mGCIPL measurements.

With an increasing number of OCT parameters available to monitor glaucoma progression, there may be confusion as to which parameter to use. To date, evidence suggests that

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Study	Participants	No. of Eyes	Average Baseline Mean Deviation (dB)	Follow-up (yrs)	Parameters	Device	Mean Rate of Change (µm/yr)	Comments
Leung et al (2011) <sup>23,24</sup>	Glaucoma	128	-9.43	2 to 2.75	cpRNFL	Cirrus, Stratus	-1.52 to $-5.03and -2.22 to -7.60$	SD OCT outperformed TD
Leung et al (2012) <sup>25</sup>	Healthy	35	N/A	2.5	cpRNFL	Cirrus	$-0.52 \pm 0.34$	Mean rates of change of superior and inferior cpRNFL were $-1.35 \pm 0.7$ and $-1.25 \pm 0.5$ um/vr
Na et al (2012) <sup>14</sup>	Preperimetric glaucoma	103	-3.50	2.13	mGCIPL, cpRNFL	Cirrus	Not reported	38 of 114 eyes (27%) showed progression
	Perimetric glaucoma	38	-0.28		mGCIPL, cpRNFL		Progression was defined as	by optic disc photographs or VF
	Healthy	61	0.17			significant negative slop in OCT measures ov time.	significant negative slope in OCT measures over time.	during follow-up. There was poor agreement between loss of mGCIPL or cpRNFL and progression using conventional
Na et al (2013) <sup>15</sup>	Progressing	63	-4.3	2.2	cpRNFL, rim area, macular thickness	Cirrus	-1.26, -0.016 mm <sup>2</sup> /yr. $-1.82$	Progressing glaucoma was defined by the
(2013)	glaucoma Nonprogressing glaucoma	216	-0.8		cpRNFL, rim area, macular thickness	mm /yr, -1 -0.94, -0.006 mm <sup>2</sup> /yr, -1	-0.94, -0.006 mm <sup>2</sup> /yr, -1.51	was defined by the presence of changes on optic disc photographs $\pm$ VF
Sung et al (2012) <sup>16</sup>	Advanced glaucoma	98	-14.3	2.2	Macular thickness, cpRNFL	Cirrus	$\begin{array}{c} -2.43 \pm 4.28, \\ -0.98 \pm 2.45 \end{array}$	Eyes progressing on VF had faster rates of macular thickness loss than eyes not progressing on VF $(-4.74 \pm 4.40 \text{ vs.} -0.53 \pm 1.44 \mu \text{m/yr})$ . Rates of cpRNFL loss were similar between groups
Leung et al (2013) <sup>17</sup>	Glaucoma Healthy	150 72	Not reported*	3.8	cpRNFL, mGCIPL cpRNFL, mGCIPL	Cirrus	-1.53, -0.81 -0.057, -0.32	Age-related change in mGCIPL, but not cpRNFL, was related to baseline thickness measurements. *Average baseline cpRNFL and mGCC thicknesses were 70.6 μm and 98.1 μm, respectively, in glaucomatous eves
Wessel et al $(2012)^{26}$	Progressing glaucoma Nonprogressing glaucoma Healthy	13	-2.8	3	cpRNFL	Spectralis	-2.12	Patients showing
(2013)		25	-4.6				-1.18	disc photographs had significantly
		24	-0.2				-0.60	faster rates of cpRNFL loss compared with those not showing progression and with healthy participants.

Table 1.	Summary	of Studies	Using	Spectral-I	Domain	Optical	Coherence	Tomograp	hy to	Examine	Longitudinal	Structural	Changes i	in
					Gl	aucomat	ous and He	althy Eyes						

(Continued)

Study	Participants	No. of Eyes	Average Baseline Mean Deviation (dB)	Follow-up (yrs)	Parameters	Device	Mean Rate of Change (µm/yr)	Comments
Iverson et al (2014) <sup>18</sup>	Glaucoma suspects and preperimetric	74	-0.3	3.6	cpRNFL, mGCC	RTVue	-1.15, -0.52	Approximately half of cpRNFL and mGCC measurements
	Healthy	23	-0.4	3.7	cpRNFL, mGCC		-0.91, -0.75	classified as outside normal limits were not replicated on subsequent scans
Naghizadeh et al (2014) <sup>19</sup>	Glaucoma Healthy	51 17	-10.2 -0.9	2.0	cpRNFL, mGCC cpRNFL, mGCC	RTVue	-0.33, -0.20 -0.24, -0.02	Ten of 51 glaucoma patients showed VF progression during follow-up. mGCC loss, but not cpRNFL loss, was significantly faster in glaucomatous eyes with VF progression compared with glaucomatous eyes with cpkle VFc
Miki et al (2014) <sup>28</sup>	Glaucoma suspects showing VF defect	40	-0.8	2.2	cpRNFL	Spectralis	-2.02	The rate of cpRNFL loss was more than twice as fast in eyes that showed a VF
	Glaucoma suspects not showing VF defect	414	-0.3				-0.82	defect during follow-up compared with those that did not.
Na et al (2015) <sup>20</sup>	Preperimetric glaucoma Perimetric glaucoma	87 40	-0.88 -3.98	2.5	cpRNFL, macular thickness cpRNFL, macular thickness	Cirrus	-0.62, -1.56 -0.69, -1.18	Eyes with perimetric glaucoma had significantly faster rates of change in the fovea and inferior macula than eyes with preperimetric glaucoma, but there was no significant difference in rates of change in cpRNFL
Gardiner et al (2015) <sup>21</sup>	Glaucoma and OHT	157	−1.2 (most recent)		MRW, MRA, cpRNFL	Spectralis	-1.6 (95% range, -9.4 to 3.3), -0.005 mm²/yr (95% range, -0.035 to 0.020 mm²/yr), -1.0 (-3.2 to 1.0)	thickness. cpRNFL had a better longitudinal signal- to-noise ratio ( $-0.58$ y <sup>-1</sup> ) than MRW ( $-0.24$ y <sup>-1</sup> ) or MRA ( $-0.23$ y <sup>-1</sup> ), meaning true change may be easier to differentiate from
Holló et al (2016) <sup>22</sup>	Healthy	34	-1.1	5.3	cpRNFL, mGCC	RTVue	$\begin{array}{c} -0.33 \pm 0.51, \\ -0.53 \pm 0.36 \end{array}$	cpRNFL loss of $> -1.5 \ \mu m/yr$ or
	OHT	34	0.1		cpRNFL, mGCC	$\begin{array}{c} -0.44 \pm \ 0.62, \\ -0.54 \ \pm \ 0.52 \end{array}$	$-0.44 \pm 0.62,$ $-0.54 \pm 0.52$	mGCC loss $> -1.3$ µm/yr were deemed
	Glaucoma	122	-10.1		cpRNFL, mGCC		$\begin{array}{c} -0.69 \pm 0.93, \\ -0.80 \pm 0.78 \end{array}$	strongly suggestive of uncontrolled glaucomatous progression.

Table 1. (Continued.)

Study	Participants	No. of Eyes	Average Baseline Mean Deviation (dB)	Follow-up (yrs)	Parameters	Device	Mean Rate of Change (µm/yr)	Comments
Zhang et al (2016) <sup>49</sup>	Healthy	192	N/A	2.5	mGCC, cpRNFL	RTVue	$\begin{array}{c} -0.25 \pm 0.05, \\ -0.14 \pm 0.07 \end{array}$	Age-related rates of thinning in mGCC and cpRNFL were approximately 0.2%/yr. There was no significant effect of IOP on rates of age-related loss in healthy participants
Yu et al (2016) <sup>27</sup>	Glaucoma	240	-9.5	5.8	cpRNFL	Cirrus	Eyes with and without cpRNFL thinning on GPA had -0.76%/yr and -0.26%/yr deterioration in VFI, respectively (P = 0.019)	Progressive RNFL thinning on trend- based progression analysis was strongly predictive of subsequent VF loss, with a 9-fold increased risk of VF progression using EMGT criteria for eyes showing progression on RNFL GPA.
Hammel et al (2017) <sup>23</sup>	Healthy Glaucoma	28 97	-0.1 -4.3	1.7 3.2	cpRNFL, mGCIPL cpRNFL, mGCIPL	Cirrus	N/A, N/A $-0.98 \pm 0.22$ $(-1.7 \pm 0.4\%)$ yr), $-0.57 \pm$ $0.16 (-1.3 \pm$ 0.4%/yr)	Normalized rates of progression were faster for cpRNFL than mGCIPL. Progressive loss of mGCIPL, but not cpRNFL, was detectable in eyes with advanced glaucoma.

Table 1. (Continued.)

cpRNFL = circumpapillary retinal nerve fiber layer thickness; EMGT = Early Manifest Glaucoma Trial; GPA = Guided Progression Analysis; GS = glaucoma suspect; mGCC = macular ganglion cell complex; mGCIPL = macular ganglion cell inner plexiform layer; N/A = not applicable; OHT = ocular hypertension; MRA = minimum rim area; MRW = minimum rim width; SD OCT = spectral-domain optical coherence tomography; TD OCT = time-domain optical coherence tomography; VF = visual field; VFI = visual field index.

measures of the RNFL, ONH, and macula are complimentary and that using multiple parameters will increase sensitivity for detecting change. However, the use of multiple parameters may increase the number of eyes falsely labelled as progressing. The availability of multiple structural parameters therefore presents an opportunity and a challenge, which may be addressed best by combining results into a single metric. For example, Mwanza et al<sup>31</sup> found that an index that combined information from macula and ONH OCT scans was better able to differentiate healthy eyes from those with early glaucoma compared with individual measures.

#### What Quantity of Change Is Significant?

It is important to quantify the reproducibility of measurements because timely detection of progression depends on the ability to differentiate true change from the noise of test—retest variability. Several studies have shown SD OCT cpRNFL measurements have excellent short-term reproducibility.<sup>32–35</sup> Using Cirrus OCT (Zeiss Meditec, Dublin, CA), Mwanza et al<sup>34</sup> reported average cpRNFL thickness to have an intervisit

intraclass correlation coefficient of 97.2%. Macular measurements also had excellent reproducibility, with mGCIPL thickness using Cirrus OCT achieving an intervisit intraclass correlation coefficient of 98.0%, with a test-retest standard deviation of only 1.16 µm.35 It was suggested that a short-term change in average cpRNFL thickness of 4 µm may be considered as suspicious of glaucoma progression, which was similar to the change of 5  $\mu$ m suggested by Leung et al.<sup>32</sup> However, it is important to exercise some caution when interpreting such cutoffs; confidence in detecting true change can be increased by having 2 or more baseline measurements and confirming the change on subsequent scans. Because of the lower reproducibility of sectorial compared with average cpRNFL thickness, relatively greater change would be needed in sectors for similar confidence of true change (approximately 7 µm for temporal, superior, and inferior quadrants and 8  $\mu$ m for the nasal quadrant).<sup>3</sup> Considering that the current dynamic OCT RNFL thickness measurements range from a maximum of approximately 80 to 100 µm in healthy participants to a floor of approximately 50 µm, an intervisit variability of 5 µm represents more than 10% of the dynamic range, which could reduce the value of

OCT for detecting change considerably if relying on such guidelines.

It is also important to acknowledge that most studies examining reproducibility excluded poor-quality scans and analyzed short-term, rather than long-term, reproducibility, which may increase variability further. Nevertheless, a study examining 6-month reproducibility in stable glaucoma patients still reported good reproducibility with intraclass correlation coefficients for average cpRNFL and mGCIPL thickness of 0.97 and 0.99, respectively, with reproducibility not influenced by glaucoma severity.<sup>36</sup> A tolerance limit of a 4-µm change in mGCIPL thickness was suggested as a likely indictor of progression. Also, OCT cpRNFL measurements have been shown to have lower longitudinal signal-to-noise ratios than standard automated perimetry, which is an important factor in identifying true change.<sup>37</sup>

OCT technology also is evolving rapidly, and there are likely to be future improvements in measurement reproducibility, and possibly enhanced dynamic range, which may improve the ability to detect change. For example, decentration of the cpRNFL scan is a common artefact, reported in more than 1 in 4 SD OCT scans.<sup>38-40</sup> Decentration of the circle scan by just 0.1 mm can result in a  $2.3\pm2.0$ -µm error in average RNFL thickness, with sectorial measures even more vulnerable to displacement error because the RNFL is thinner farther from the ONH.<sup>39</sup> Previously, cpRNFL circle scans were centered manually on the optic disc; however, subjective location of the disc margin has been found to correspond poorly to a defined structure on OCT.<sup>6</sup> In contrast, an alternative landmark, the BMO, can be identified automatically on radial OCT scans of the ONH, the orientation of the scan can be adjusted according to the BMO-fovea axis to account for difference in cyclotorsion, and the cpRNFL scan can be centered on the BMO (RNFL-BMO). A recent study has shown that although overall RNFL-BMO measurements have similar ability to detect glaucoma compared with traditional RNFL measurements, RNFL-BMO performed better in eyes with larger width externally oblique border tissue, a feature of tilted optic discs.<sup>41</sup> However, there is a lack of studies examining the long-term reproducibly of RNFL-BMO and its ability to detect progression.

Other parameters also can be measured relative to the BMO, for example, the BMO-MRW (the minimum distance from BMO to the internal limiting membrane) and BMO-minimum rim area, which overcomes the inverse relationship between disc size and BMO-MRW.<sup>9,42</sup> It has been shown that the BMO-MRW can be used to differentiate glaucomatous and healthy eyes accurately, in one study performing better than cpRNFL thickness.<sup>7,8</sup> One might suppose that measurements taken relative to BMO would perform better than conventional structural measures at detecting glaucoma progression, given the relative stability of the BMO as a point of reference for repeat scans. However, a recent study by Gardiner et al<sup>21</sup> has suggested that BMO-MRW and BMO-minimum rim area may be less able to detect change because of a relatively low longitudinal signal-to-noise ratio compared with cpRNFL. This observation may have been the result of changes in the location of the BMO over time, possibly related to fluctuations in IOP or because of connective tissue remodeling with glaucoma

progression. Recently, based on a cross-sectional analysis, Johnstone et al<sup>43</sup> reported that the BMO is located more posteriorly in older compared with younger individuals, suggesting that it may migrate posteriorly with age and be a less stable landmark than hoped. However, in contrast, a longitudinal study following up 95 eyes for a period of 3 to 4 years found the location of the BMO to be stable over time.<sup>44</sup> Longer-duration studies are needed to determine whether the BMO can be used as a long-term stable reference from which to measure glaucomatous changes and to evaluate the potential benefits of orientating scans using the fovea–BMO axis.

# Are Structural Changes Relevant to the Patient?

Regardless of which parameter may be best, there is now a large body of evidence that progressive changes on OCT are clinically relevant. Several studies have shown good agreement between progressive cpRNFL loss on OCT and changes on optic disc photographs.<sup>11,26</sup> For example, Wessel et al<sup>26</sup> found eyes with progressive changes on optic disc photographs had significantly faster rates of cpRNFL loss than glaucomatous eyes not progressing on photographs, with others reporting a similar faster rate of change in macular measurements.<sup>19</sup> Faster rates of cpRNFL loss on OCT also are associated with higher risk of future development of visual field defects. In a study of 554 eyes suspected of having glaucoma at baseline but with normal visual fields, Miki et al<sup>28</sup> found that faster rates of cpRNFL loss were associated strongly with subsequent development of a visual field defect. Each 1-µm/year faster rate of cpRNFL loss corresponded to a 2.05-times higher risk of a visual field defect developing. Yu et al<sup>27</sup> found similar results in eyes with established glaucoma, with progressive RNFL thinning on trend-based progression analysis strongly predictive of visual field loss. Displacement of the lamina cribrosa relative to the BMO also may be a useful marker of progression, with a report of a higher risk of visual field progression in eyes with faster increasing posterior displacement of the anterior lamina cribrosa and ONH surface.<sup>45</sup> Faster rates of cpRNFL loss also are associated with faster decline in quality of life and worse performance on driving simulation, with information from OCT offering additional predictive value compared with information from visual field testing alone.46,47 OCT progression analysis therefore offers the possibility of detecting patients at high risk of worsening visual function and of providing an objective means of quantifying glaucomatous neural losses directly related to quality of life.

### How Are Measurements Affected by Aging?

Glaucoma progression must be differentiated from normal age-related changes to cpRNFL and the macula.<sup>17,25,48,49</sup> Leung et al<sup>25</sup> found mean rates of change in average, superior, and inferior cpRNFL thickness of  $-0.52 \ \mu m$  (95% confidence interval [CI], -0.86 to  $-0.17 \ \mu m$ ),

 $-1.35 \ \mu m \ (95\% \ CI, -2.05 \ to -0.65 \ \mu m)$ , and  $-1.25 \ \mu m \ (95\% \ CI, -1.78 \ to -0.7 \ \mu m)$  per year, although the average follow-up was only 30 months. Age-related average mGCIPL losses were  $-0.32 \ \mu m$  per year.<sup>17</sup> In a subsequent study that followed up 90 patients (150 eyes) for an average of 46 months, 50% of glaucomatous eyes showed progressive mGCIPL loss; however, when the lower 95% CI for age-related changes was applied, the proportion progressing decreased to only 15%. In the future, it may be helpful to have longitudinal reference databases of healthy participants to help determine whether an observed rate of change is pathologic or an expected change for age.

It is important to note that high rates of false-positive detection of progression may occur when progression is considered to have occurred merely if a statistically significant negative slope of change is present (i.e., a slope that is statistically significantly different from 0 with P < 0.05). For instance, with 5 years of annual testing, up to 25% of normal eyes can be identified falsely as having progressed if such criteria is used for RNFL thickness change.<sup>50</sup> A suggestion has been made that trend-based analysis of RNFL thickness change should involve at least testing the statistical significance of its change relative to the mean estimate of age-related changes.<sup>50</sup> This would be analogous to evaluating visual field progression using mean deviation instead of mean sensitivity (with the former being an age-adjusted parameter), and could be described as an RNFL mean deviation trend analysis.

# What Are the Best Ways to Use OCT alongside Visual Fields?

Although OCT has a valuable role in assessing glaucoma progression, visual field testing remains the primary method of assessing glaucomatous damage, and some patients demonstrate visual field changes before detectable structural changes. The ability to detect progression by perimetry versus OCT is influenced significantly by the stage of disease, with eyes with less severe disease at baseline having a higher chance of being detected as progressing by OCT, but not SAP, and eyes with more advanced disease having a higher chance of being detected as progressing by SAP, but not OCT.<sup>2</sup> This phenomenon is partly the result of the different measurement scales of the devices, with SAP using a logarithmic scale that compresses results in early disease, reducing the ability to detect change; however, differences in dynamic range also contribute.<sup>51</sup> The result is that simultaneous detection of change in structural and functional measurements is rare,<sup>13,52</sup> and therefore it is the consensus that both structural and functional tests should be monitored with equal diligence for optimal assessment of glaucoma progression.

This raises the question of the best ways to use OCT to complement assessment of visual function. One approach is to use a Bayesian probability theorem to allow information derived from OCT to influence inferences obtained from automated perimetry, and recent studies using this approach have shown that progression slopes obtained from integrated measurements are better able to predict future visual field status than isolated information from either structural or functional domains.<sup>53,54</sup> In another approach, OCT and perimetry data were combined into a single index after transforming the measurements to a common scale reflecting neural losses. The combined structure-function index has been shown to be able to improve detection, staging, prediction, and assessment of progression compared with isolated measures from structure and function. 55-57 Future research should concentrate on developing these approaches further to determine the most clinically effective and cost-effective frequency of testing and combination of tests for detecting change at various stages of disease. Not only would these approaches potentially improve our ability to detect change, combining information from structural and functional tests or from different structural measurements, but they also provide an opportunity to simplify and simultaneously present results from an increasing range of tests.

In conclusion, since the introduction of OCT more than 25 years ago, our ability to detect and quantify glaucomatous structural changes has been greatly enhanced. OCT provides a means to obtain reproducible measures of the RNFL, ONH, and macula, each of which are of value in quantifying glaucoma progression. Although visual function is what matters most to patients, progressive structural changes can precede functional loss, and patients with faster changes on OCT are at increased risk of worsening visual losses, offering the possibility of escalating treatment at an earlier stage to preserve vision better. The ability to assess glaucoma progression is likely to be improved further by novel approaches to incorporate information from OCT and visual fields, reducing the noise inherent in both tests, and the next few years are likely to see such strategies included on commercial devices. However, there are important questions that still need to be addressed, particularly regarding testing strategies, to ensure the most effective use of OCT in clinical practice.

#### References

- Keltner JL, Johnson CA, Anderson DR, et al; Ocular Hypertension Treatment Study Group. The association between glaucomatous visual fields and optic nerve head features in the Ocular Hypertension Treatment Study. *Ophthalmology*. 2006;113(9):1603-1612.
- 2. Abe RY, Diniz-Filho A, Zangwill LM, et al. The relative odds of progressing by structural and functional tests in glaucoma. *Invest Ophthalmol Vis Sci.* 2016;57(9):421-428.
- **3.** Jampel HD, Friedman D, Quigley H, et al. Agreement among glaucoma specialists in assessing progressive disc changes from photographs in open-angle glaucoma patients. *Am J Ophthalmol.* 2009;147(1):39-44.
- 4. Lin C, Mak H, Yu M, et al. Trend-based progression analysis for examination of the topography of rates of retinal nerve fiber layer thinning in glaucoma. *JAMA Ophthalmol.* 2017;135(3): 189-195.
- 5. Curcio CA, Allen KA. Topography of ganglion cells in human retina. *J Comp Neurol*. 1990;300(1):5-25.
- 6. Hood DC, Raza AS, de Moraes CG, et al. Glaucomatous damage of the macula. *Prog Retin Eye Res.* 2013;32:1-21.
- 7. Reis AS, Sharpe GP, Yang H, et al. Optic disc margin anatomy in patients with glaucoma and normal controls with spectral

domain optical coherence tomography. *Ophthalmology*. 2012;119(4):738-747.

- 8. Chauhan BC, O'Leary N, Almobarak FA, et al. Enhanced detection of open-angle glaucoma with an anatomically accurate optical coherence tomography-derived neuroretinal rim parameter. *Ophthalmology*. 2013;120(3):535-543.
- **9.** Gardiner SK, Ren R, Yang H, et al. A method to estimate the amount of neuroretinal rim tissue in glaucoma: comparison with current methods for measuring rim area. *Am J Ophthalmol.* 2014;157(3):540-549.
- Wollstein G, Schuman JS, Price LL, et al. Optical coherence tomography longitudinal evaluation of retinal nerve fiber layer thickness in glaucoma. *Arch Ophthalmol.* 2005;123(4):464-470.
- Medeiros FA, Zangwill LM, Alencar LM, et al. Detection of glaucoma progression with stratus OCT retinal nerve fiber layer, optic nerve head, and macular thickness measurements. *Invest Ophthalmol Vis Sci.* 2009;50(12):5741-5748.
- 12. Langenegger SJ, Funk J, Töteberg-Harms M. Reproducibility of retinal nerve fiber layer thickness measurements using the eye tracker and the retest function of Spectralis SD-OCT in glaucomatous and healthy control eyes. *Invest Ophthalmol Vis Sci.* 2011;52(6):3338-3344.
- 13. Leung CK, Cheung CY, Weinreb RN, et al. Evaluation of retinal nerve fiber layer progression in glaucoma: a comparison between the fast and the regular retinal nerve fiber layer scans. *Ophthalmology*. 2011;118(4):763-767.
- 14. Na JH, Sung KR, Baek S, et al. Detection of glaucoma progression by assessment of segmented macular thickness data obtained using spectral domain optical coherence tomography. *Invest Ophthalmol Vis Sci.* 2012;53(7):3817-3826.
- 15. Na JH, Sung KR, Lee JR, et al. Detection of glaucomatous progression by spectral-domain optical coherence tomography. *Ophthalmology*. 2013;120(7):1388-1395.
- **16.** Sung KR, Na JH, Lee Y. Glaucoma diagnostic capabilities of optic nerve head parameters as determined by Cirrus HD optical coherence tomography. *J Glaucoma*. 2012;21(7): 498-504.
- 17. Leung CK, Ye C, Weinreb RN, et al. Impact of age-related change of retinal nerve fiber layer and macular thicknesses on evaluation of glaucoma progression. *Ophthalmology*. 2013;120(12):2485-2492.
- 18. Iverson SM, Feuer WJ, Shi W, et al. Frequency of abnormal retinal nerve fibre layer and ganglion cell layer SDOCT scans in healthy eyes and glaucoma suspects in a prospective longitudinal study. *Br J Ophthalmol.* 2014;98(7):920-925.
- **19.** Naghizadeh F, Garas A, Vargha P, Holló G. Detection of early glaucomatous progression with different parameters of the RTVue optical coherence tomograph. *J Glaucoma*. 2014;23(4):195-198.
- **20.** Na JH, Sung KR, Baek SH, et al. Rates and patterns of macular and circumpapillary retinal nerve fiber layer thinning in preperimetric and perimetric glaucomatous eyes. *J Glaucoma*. 2015;24(4):278-285.
- 21. Gardiner SK, Boey PY, Yang H, et al. Structural measurements for monitoring change in glaucoma: comparing retinal nerve fiber layer thickness with minimum rim width and area. *Invest Ophthalmol Vis Sci.* 2015;56(11):6886-6891.
- 22. Holló G, Zhou Q. Evaluation of retinal nerve fiber layer thickness and ganglion cell complex progression rates in healthy, ocular hypertensive, and glaucoma eyes with the Avanti RTVue-XR optical coherence tomograph based on 5-year follow-up. *J Glaucoma*. 2016;25(10):e905-e909.
- 23. Hammel N, Belghith A, Weinreb RN, et al. Comparing the rates of retinal nerve fiber layer and ganglion cell-inner

plexiform layer loss in healthy eyes and in glaucoma eyes. *Am J Ophthalmol.* 2017;178:38-50.

- 24. Leung CK, Chiu V, Weinreb RN, et al. Evaluation of retinal nerve fiber layer progression in glaucoma: a comparison between spectral-domain and time-domain optical coherence tomography. *Ophthalmology*. 2011;118(8):1558-1562.
- 25. Leung CK, Yu M, Weinreb RN, et al. Retinal nerve fiber layer imaging with spectral-domain optical coherence tomography: a prospective analysis of age-related loss. *Ophthalmology*. 2012;119(4):731-737.
- 26. Wessel JM, Horn FK, Tornow RP, et al. Longitudinal analysis of progression in glaucoma using spectral-domain optical coherence tomography. *Invest Ophthalmol Vis Sci.* 2013;54(5):3613-3620.
- 27. Yu M, Lin C, Weinreb RN, et al. Risk of visual field progression in glaucoma patients with progressive retinal nerve fiber layer thinning: a 5-year prospective study. *Ophthalmology*. 2016;123(6):1201-1210.
- 28. Miki A, Medeiros FA, Weinreb RN, et al. Rates of retinal nerve fiber layer thinning in glaucoma suspect eyes. *Ophthalmology*. 2014;121(7):1350-1358.
- 29. Chauhan BC, Malik R, Shuba LM, et al. Rates of glaucomatous visual field change in a large clinical population. *Invest Ophthalmol Vis Sci.* 2014;55(7):4135-4143.
- **30.** Bowd C, Zangwill LM, Weinreb RN, et al. Estimating optical coherence tomography structural measurement floors to improve detection of progression in advanced glaucoma. *Am J Ophthalmol.* 2017;175:37-44.
- **31.** Mwanza JC, Warren JL, Budenz DL. Combining spectral domain optical coherence tomography structural parameters for the diagnosis of glaucoma with early visual field loss. *Invest Ophthalmol Vis Sci.* 2013;54(13):8393-8400.
- **32.** Leung CK, Cheung CY, Weinreb RN, et al. Retinal nerve fiber layer imaging with spectral-domain optical coherence tomography: a variability and diagnostic performance study. *Ophthalmology*. 2009;116(7):1257-1263.
- **33.** González-García AO, Vizzeri G, Bowd C, et al. Reproducibility of RTVue retinal nerve fiber layer thickness and optic disc measurements and agreement with Stratus optical coherence tomography measurements. *Am J Ophthalmol.* 2009;147(6):1067-1074.
- 34. Mwanza JC, Chang RT, Budenz DL, et al. Reproducibility of peripapillary retinal nerve fiber layer thickness and optic nerve head parameters measured with cirrus HD-OCT in glaucomatous eyes. *Invest Ophthalmol Vis Sci.* 2010;51(11):5724-5730.
- 35. Mwanza JC, Oakley JD, Budenz DL, Anderson DR; Cirrus Optical Coherence Tomography Normative Database Study Group. Ability of cirrus HD-OCT optic nerve head parameters to discriminate normal from glaucomatous eyes. *Ophthalmology*. 2011;118(2):241-248.e1.
- 36. Kim KE, Yoo BW, Jeoung JW, Park KH. Long-term reproducibility of macular ganglion cell analysis in clinically stable glaucoma patients. *Invest Ophthalmol Vis Sci.* 2015;56(8): 4857-4864.
- 37. Gardiner SK, Fortune B, Demirel S. Signal-to-noise ratios for structural and functional tests in glaucoma. *Transl Vis Sci Technol.* 2013;2(6):3.
- 38. Liu Y, Simavli H, Que CJ, et al. Patient characteristics associated with artifacts in Spectralis optical coherence tomography imaging of the retinal nerve fiber layer in glaucoma. *Am J Ophthalmol.* 2015;159(3):565-576.
- **39.** Cheung CY, Yiu CK, Weinreb RN, et al. Effects of scan circle displacement in optical coherence tomography retinal nerve

fibre layer thickness measurement: a RNFL modelling study. *Eye (Lond)*. 2009;23(6):1436-1441.

- **40.** Vizzeri G, Bowd C, Medeiros FA, et al. Effect of improper scan alignment on retinal nerve fiber layer thickness measurements using Stratus optical coherence tomograph. *J Glaucoma*. 2008;17(5):341-349.
- 41. Lee EJ, Lee KM, Kim H, Kim TW. Glaucoma diagnostic ability of the new circumpapillary retinal nerve fiber layer thickness analysis based on Bruch's membrane opening. *Invest Ophthalmol Vis Sci.* 2016;57(10):4194-4204.
- 42. Enders P, Adler W, Schaub F, et al. Novel Bruch's membrane opening minimum rim area equalizes disc size dependency and offers high diagnostic power for glaucoma. *Invest Ophthalmol Vis Sci.* 2016;57(15):6596-6603.
- **43.** Johnstone J, Fazio M, Rojananuangnit K, et al. Variation of the axial location of Bruch's membrane opening with age, choroidal thickness, and race. *Invest Ophthalmol Vis Sci.* 2014;55(3):2004-2009.
- 44. Belghith A, Bowd C, Medeiros FA, et al. Does the location of Bruch's membrane opening change over time? Longitudinal analysis using San Diego Automated Layer Segmentation Algorithm (SALSA) stability of Bruch's membrane opening location over time. *Invest Ophthalmol Vis Sci.* 2016;57(2):675-682.
- **45.** Wu Z, Lin C, Crowther M, et al. Impact of rates of change of lamina cribrosa and optic nerve head surface depths on visual field progression in glaucoma. *Invest Ophthalmol Vis Sci.* 2017;58(3):1825-1833.
- **46.** Gracitelli CP, Abe RY, Tatham AJ, et al. Association between progressive retinal nerve fiber layer loss and longitudinal change in quality of life in glaucoma. *JAMA Ophthalmol.* 2015;133(4):384-390.
- **47.** Tatham AJ, Boer ER, Rosen PN, et al. Glaucomatous retinal nerve fiber layer thickness loss is associated with slower reaction times under a divided attention task. *Am J Ophthalmol.* 2014;158(5):1008-1017.
- **48.** Sung KR, Wollstein G, Bilonick RA, et al. Effects of age on optical coherence tomography measurements of healthy retinal

#### Footnotes and Financial Disclosures

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- **49.** Zhang X, Francis BA, Dastiridou A, et al; Advanced Imaging for Glaucoma Study Group. Longitudinal and cross-sectional analyses of age effects on retinal nerve fiber layer and ganglion cell complex thickness by Fourier-domain OCT. *Transl Vis Sci Technol.* 2016;5(2):1.
- Wu Z, Saunders L, Zangwill LM, et al. Impact of normal aging and progression definitions on the specificity of detecting retinal nerve fiber layer thinning. *Am J Ophthalmol.* 2017;181: 106-113.
- **51.** Medeiros FA, Zangwill LM, Bowd C, et al. The structure and function relationship in glaucoma: implications for detection of progression and measurement of rates of change. *Invest Ophthalmol Vis Sci.* 2012;53(11):6939-6946.
- 52. Medeiros FA, Tatham AJ. Structure versus function in glaucoma: the debate that doesn't need to be. *Ophthalmology*. 2016;123(6):1170-1172.
- 53. Medeiros FA, Leite MT, Zangwill LM, Weinreb RN. Combining structural and functional measurements to improve detection of glaucoma progression using Bayesian hierarchical models. *Invest Ophthalmol Vis Sci.* 2011;52(8): 5794-5803.
- 54. Russell RA, Malik R, Chauhan BC, et al. Improved estimates of visual field progression using Bayesian linear regression to integrate structural information in patients with ocular hypertension. *Invest Ophthalmol Vis Sci.* 2012;53(6): 2760-2769.
- 55. Medeiros FA, Lisboa R, Weinreb RN, et al. A combined index of structure and function for staging glaucomatous damage. *Arch Ophthalmol.* 2012;130(9):1107-1116.
- 56. Medeiros FA, Zangwill LM, Anderson DR, et al. Estimating the rate of retinal ganglion cell loss in glaucoma. *Am J Ophthalmol.* 2012;154(5):814-824.
- 57. Meira-Freitas D, Lisboa R, Tatham A, et al. Predicting progression in glaucoma suspects with longitudinal estimates of retinal ganglion cell counts. *Invest Ophthalmol Vis Sci.* 2013;54(6):4174-4183.

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Abbreviations and Acronyms:

BMO = Bruch's membrane opening; CI = confidence interval; cpRNFL = circumpapillary retinal nerve fiber layer; mGCIPL = macularganglion cell inner plexiform layer; MRW = minimum rim width;<math>OCT = optical coherence tomography; ONH = optic nerve head; RNFL = retinal nerve fiber layer; SAP = standard automated perimetry; SD = spectral-domain.

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