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Detecting structural progression in glaucoma with optical coherence tomography

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Abstract

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 widely adopted in clinical practice, uncertainty remains concerning how it should be best utilized. 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, and how can changes due to aging be differentiated from true progression? How 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 measures 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 the relative value of each parameter may differ at different stages of disease. In early disease, looking for change over time may also 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 the disease. Combining information from different structural measurement 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.

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PRECIS

This review addresses critical questions related to the use of optical coherence tomography for assessing glaucoma progression with retinal nerve fiber layer, macular and optic nerve head measurements.

Detecting and assessing rates of progression is an indispensable constituent of glaucoma management as it provides a means to identify rapidly progressing patients who are at high risk of visual disability, and who may require escalation in treatment. Progression is conventionally measured by observing 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.[1,2] 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 to 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 co-morbidities. Normal structural measurements vary widely between individuals increasing the chances of misclassification. In some cases, due to 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 has traditionally 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.[3] Optical coherence tomography (OCT) overcomes some of the limitations of optic disc photography and can be used to provide objective measurements of the retinal nerve fiber layer (RNFL), optic nerve head (ONH) and macula, useful for glaucoma diagnosis and progression analysis. Although OCT has been widely adopted in glaucoma clinics, uncertainty remains concerning how OCT should be best used 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 longitudinal measurements affected by aging, and how can changes due to aging be differentiated from true progression? How should OCT be best used 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. Recent studies have however 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 6×6 mm^2 optic disc cube scan RNFL map.[4] OCT devices now also provide the ability to quantify changes to the

glaucomatous macula using measurements such as ganglion cell inner plexiform layer (GCIPL) and ganglion cell complex (GCC) 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 due to the density of retinal ganglion cells located in this region and the realization that, contrary to conventional teaching, the macula is often involved early in the glaucomatous process.[5,6] Some OCT devices now also include the ability to obtain novel optic nerve head metrics such as Bruch's membrane opening-minimum rim width and Bruch's membrane opening -minimum rim area (BMO-MRW, BMO-MRA).[7–9], which use Bruch's membrane opening (BMO) as an anatomical point of reference landmark for measurements and are discussed in more detail below.

The first report of OCT to examine glaucoma progression used a prototype time domain OCT (TDOCT) device to measure changes in RNFL thickness over time.[10] 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 TDOCT device (Stratus OCT, Carl Zeiss Meditec Inc, Dublin, CA), Medeiros and colleagues 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.[11] cpRNFL 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 vs. 0.14 μm/year; P = 0.004).

TDOCT has now been superseded by spectral domain OCT (SDOCT), which has improved scan speed and higher resolution, and incorporates innovations such as real-time eye-tracking to compensate for eye movements during data acquisition and reduce motion artifacts. TDOCT was limited by 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, SDOCT devices can automatically center follow-up scans on previously scanned locations by identifying retinal landmarks, which results in improved reproducibility and better ability to detect progression compared to TDOCT.[12,13]

Several studies have used SDOCT to evaluate the role of cpRNFL and macular measurements for assessing glaucoma progression (Table 1).[14–23] It is however difficult to determine whether one parameter is better than another due to 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 have either compared rates of structural change occurring in glaucomatous eyes to rates in healthy subjects[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.[14,16,19,26–28] Overall, both cpRNFL and macular measures show faster rates of loss in glaucomatous eyes compared to controls, however, there is wide variation in reported rates of change. This is to be expected though as trend-based analyses of visual field sensitivities have also demonstrated disparate slopes among different individuals.[29] It is also inappropriate to directly compare rates of change between studies

and between parameters due to 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 for an average of 3.2 years, Hammel et al. found normalized cpRNFL thickness to decrease by 1.7% per year compared only a 1.3% per year decrease in mGCIPL thickness.[23] 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.[30] These findings were also supported by Sung et al. who found eyes with advanced glaucoma with visual field progression had significantly faster rates of macular thickness loss compared to non-progressing eyes, whereas there was no significant difference in rate of cpRNFL change between groups.[16] It is however important to exercise caution in interpreting the results of these studies as 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 to 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 measures of RNFL, ONH and macular are complimentary and that using multiple parameters will increase sensitivity for detecting change. On the other hand, 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 best addressed by combining results into a single metric. For example, Mwanza and colleagues found an index that combined information from macula and ONH OCT scans was better able to differentiate healthy eyes from those with early glaucoma compared to individual measures.[31]

What quantity of change is significant?

It is important to quantify the reproducibility of measurements as timely detection of progression depends on the ability to differentiate true change from the noise of test-retest variability. Several studies have shown SDOCT cpRNFL measurements have excellent short term reproducibility.[32–35] Using Cirrus OCT (Zeiss Meditec, Dublin, CA), Mwanza et al. reported average cpRNFL thickness to have an intervisit intraclass correlation coefficient (ICC) of 97.2%.[34] Macular measurements also had excellent reproducibility, with mGCIPL thickness using Cirrus OCT achieving an intervisit ICC 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 μm suggested by Leung et al.[32] It is however important to exercise some caution when interpreting such cut-offs and confidence of detecting true change can be increased by having two or more baseline measurements and confirming change on subsequent scans. Due to lower reproducibility of sectorial compared to 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 μm for the nasal quadrant).[34] Considering that the current dynamic range of OCT RNFL thickness measurements ranges from a maximum of approximately 80 to 100 μm in healthy subjects to a floor of approximately 50 μm, an intervisit variability of 5 μm, represents more than 10% of the dynamic range, which could considerably reduce the value of OCT for detecting change if relying on such guidelines.

It is also important to acknowledge that most studies examining reproducibility excluded poor quality scans and examined short, rather than long term reproducibility, which may further increase variability. Nevertheless, a study examining 6-month reproducibility in stable glaucoma patients still reported good reproducibility with ICCs for average cpRNFL and mGCIPL thickness of 0.97 and 0.99 respectively, with reproducibility not influenced by glaucoma severity.[36] A tolerance limit of 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.[37]

OCT technology is also rapidly evolving and there are likely to be future improvements in measurement reproducibility, and possibly enhanced dynamic range, which may improve ability to detect change. For example, de-centration of the cpRNFL scan is a common artefact, reported over one in four SDOCT scans.[38,39,40] De-centration of the circle scan by just 0.1mm can result in a 2.3 ± 2.0 μm error in average RNFL thickness, with sectorial measures even more vulnerable to displacement error as the RNFL is thinner further from the optic nerve head.[39] 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.[6] In contrast, an alternative landmark, the BMO, can be identified automatically on radial OCT scans of the optic nerve head, the orientation of the scan can be adjusted according to the BMO-fovea axis to account for difference in cyclotorsion, and the cpRNFL scan centered on the BMO (RNFL-BMO). A recent study has shown that although overall RNFL-BMO measurements have similar ability to detect glaucoma compared to traditional RNFL measurements, RNFL-BMO performed better in eyes with larger width externally oblique border tissue, a feature of titled optic discs.[41] There is however a lack of studies examining the long term reproducibly of RNFL-BMO and its ability to detect progression.

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

due to changes in the location of the BMO over time, possibly related to fluctuations in IOP or due to connective tissue remodeling with glaucoma progression. Recently, based on a cross-sectional analysis, Johnstone et al. reported that the BMO is located more posteriorly in older compared to younger individuals, suggesting that it might migrate posteriorly with age and be a less stable landmark than hoped.[43] However, in contrast, a longitudinal study following 95 eyes for a period of 3 to 4 years found the location of the BMO to be stable over time.[44] Longer duration studies are needed to confirm 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 might 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.[11,26] For example, Wessel et al. found eyes with progressive changes on optic disc photographs had significantly faster rates of cpRNFL loss than glaucomatous eyes not progressing on photographs,[26] with others reporting a similar faster rate of change in macular measurements.[19] Faster rates of cpRNFL loss on OCT are also 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. found faster rates of cpRNFL loss were strongly associated with subsequent development of a visual field defect.[28] Each 1 μm/year faster rate of cpRNFL loss corresponded to a 2.05 times higher risk of developing a VF defect. Yu et al found similar results in eyes with established glaucoma, with progressive RNFL thinning on trend-based progression analysis strongly predictive of VF loss.[27] Displacement of the lamina cribrosa relative to the BMO may also 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.[45] Faster rates of cpRNFL loss are also associated with faster decline in quality of life and worse performance on driving simulation, with information from OCT offering additional predictive value compared to information from visual field testing alone.[46,47] OCT progression analysis therefore offers the possibility to detect patients at high risk of worsening visual function, and provide 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 macula.[17,25,48,49] Leung et al. found mean rates of change in average, superior, and inferior cpRNFL thickness of −0.52 (95% CI −0.86 to −0.17), −1.35 (95% CI, −2.05 to −0.65) and −1.25 (95% CI, −1.78 to −0.7) μm per year, although the average follow up was only 30 months.[25] Age-related average mGCIPL losses were −0.32 μm per year.[17] In a subsequent study, which followed 90 patients (150 eyes) for an average of 46 months, 50% of glaucomatous eyes had progressive mGCIPL loss, however, when the lower 95% confidence interval 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 subjects to help determine whether an observed rate of change is pathological 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 than zero with P<5%). For instance, with 5 years of annual testing, up to 25% of normal eyes can be falsely identified as having progressed if such criterion is employed for RNFL thickness change.[50] A suggestion has been made that trend-based analysis of RNFL thickness change should at least involve testing the statistical significance of its change relative to the mean estimate of age-related changes.[50] This would be analogous to evaluating visual field progression using mean deviation (MD) instead of mean sensitivity (with the former being an age-adjusted parameter), and could be described as an RNFL “mean deviation” trend analysis.

How should OCT be best used 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 develop visual field changes before detectable structural changes. The ability to detect progression by perimetry versus OCT is significantly influenced 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.[2] This phenomenon is due partly due to 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.[51] The result is that simultaneous detection of change in structural and functional measurements is rare [13,52] and it is therefore 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 how OCT should be best used to complement assessment of visual function. One approach is to use Bayesian probability theorem to allow information derived from OCT to influence inferences obtained from automated perimetry, and recent studies using this approach have shown progression slopes obtained from integrated measurements are better able to predict future visual field status than isolated information from either structural or functional domains.[53,54] 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 to isolated measures from structure and function.[55–57] Future research should concentrate on further developing these approaches to determine the most efficacious 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, provides an opportunity to simplify and simultaneously present results from an increasing range of tests.

In conclusion, since the introduction of OCT over 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 change on OCT are at increased risk of worsening visual losses, offering the possibility of escalating treatment at an earlier stage to better preserve vision. The ability to assess glaucoma progression is likely to be further improved 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. There are however, important questions that still need to be addressed, particularly regarding testing strategies, to ensure the most effective use of OCT in clinical practice.

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Table 1.

Summary of studies using SDOCT to examine longitudinal structural changes in glaucomatous and healthy eyes.

Study	Subjects	Number of eyes	Average Baseline MD (dB)	Follow-up (years)	Parameters	Device	Mean rate of change (μm/year)	Comments
Leung 2011[23]	Glaucoma	128	−9.43	2 to 2.75	cpRNFL	Cirrus	Ranged from −1.52 to −5.03	SDOCT outperformed TDOCT
						Stratus	Ranged from −2.22 to −7.60	
Leung 2012[24]	Healthy	35	N/A	2.5	cpRNFL	Cirrus	−0.52 ± 0.34	Mean rates of change of superior and inferior cpRNFL were −1.35 ± 0.7 and −1.25 ± 0.5 μm/year.
Na 2012[13]	Preperimetric Glaucoma	103	−3.50	2.13	mGCIPL	Cirrus	Not reported.	38 of 114 eyes (27%) showed progression by optic disc photographs or VF during follow up. There was poor agreement between loss of mGCIPL or cpRNFL and progression using conventional measures.
					cpRNFL			
	Perimetric Glaucoma	38	−0.28		mGCIPL		Progression was defined as significant negative slope in OCT measures over time.	
					cpRNFL			
	Healthy	61	0.17					
Na 2013[14]	Progressing glaucoma	63	−4.3	2.2	cpRNFL	Cirrus	−1.26	Progressing glaucoma was defined by the presence of changes on optic disc photographs ± VF progression analysis.
					Rim area		−0.016 mm^2/year	
					Macular thickness		−1.82	
	Non-progressing glaucoma	216	−0.8		cpRNFL		−0.94	
					Rim area		−0.006 mm^2/year	
					Macular thickness		−1.51	
Sung 2012[15]	Advanced Glaucoma	98	−14.3	2.2	Macular thickness	Cirrus	−2.43 ± 4.28	Eyes progressing on VF had faster rates of macular thickness loss than eyes not progressing on VF (−4.74 ± 4.40 versus −0.53 +/− 1.44 μm/ year). Rates of cpRNFL loss were similar between groups.
					cpRNFL		−0.98 ± 2.45	
Leung 2013[16]	Glaucoma	150	Not reported*	3.8	cpRNFL	Cirrus	−1.53	Age-related change in mGCIPL but not cpRNFL was related to baseline thickness measurements.
					mGCIPL		−0.81	
	Healthy	72			cpRNFL		−0.057	*Average baseline cpRNFL and mGCC thicknesses were 70.6 μm and 98.1 μm in glaucomatous eyes.
					mGCIPL		−0.32	

Study	Subjects	Number of eyes	Average Baseline MD (dB)	Follow-up (years)	Parameters	Device	Mean rate of change (μm/year)	Comments
Wessel 2013[25]	Progressing glaucoma	13	−2.8	3	cpRNFL	Spectralis	−2.12	Patients progressing on optic disc photographs had significantly faster rates of cpRNFL loss compared to those not progressing and healthy subjects.
	Non-progressing glaucoma	25	−4.6				−1.18	
	Healthy	24	−0.2				−0.60	
Iverson 2014[17]	Glaucoma suspects and Preperimetric Glaucoma	74	−0.3	3.6	cpRNFL	RTVue	−1.15	Approximately half of cpRNFL and mGCC measurements classified as outside normal limits were not replicated on subsequent scans.
					mGCC		−0.52	
	Healthy	23	−0.4	3.7	cpRNFL		−0.91	
					mGCC		−0.75	
Naghizadeh 2014[18]	Glaucoma	51	−10.2	2.0	cpRNFL	RTVue	−0.33	10 of 51 glaucoma patients had VF progression during follow up. mGCC but not cpRNFL loss was significantly faster in glaucomatous eyes with VF progression compared to glaucomatous eyes with stable VFs.
					mGCC		−0.20	
	Healthy	17	−0.9		cpRNFL		−0.24	
					mGCC		−0.02	
Miki 2014[27]	Glaucoma suspects developing 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 developed a VF defect during follow up compared to those that did not.
	Glaucoma Suspects not developing VF defect	414	−0.3				−0.82	
Na 2015[19]	Preperimetric Glaucoma	87	−0.88	2.5	cpRNFL	Cirrus	−0.62	Eyes with perimetric glaucoma had significantly faster rates of change in the fovea and inferior macular than eyes with preperimetric glaucoma but there was no significant difference in rates of change in cpRNFL thickness
					Macular thickness		−1.56	
		40	−3.98		cpRNFL		−0.69	
	Perimetric Glaucoma				Macular thickness		−1.18	
Gardiner 2015[20]	Glaucoma and OHT	157	−1.2 (most recent)		MRW	Spectralis	−1.6 (95% range −9.4 to 3.3)	cpRNFL had a better longitudinal signal to noise ratio ($-0.58y^{-1)}$ than MRW ($-0.44y^{-1}$) or MRA ($-0.23y^{-1}$) meaning true change may be easier to differentiate from noise using cpRNFL.
					MRA			
					cpRNFL		−0.005mm2/year (95% range −0.035 to 0.020)	

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Study	Subjects	Number of eyes	Average Baseline MD (dB)	Follow-up (years)	Parameters	Device	Mean rate of change (μm/year)	Comments
							−1.0 (−3.2 to 1.0)	
Holló 2016[21]	Healthy	34	−1.1	5.3	cpRNFL	RTVue	−0.33 ± 0.51	cpRNFL loss of > −1.5 μm/year or mGCC loss > −1.3 μm/year were deemed strongly suggestive of uncontrolled glaucomatous progression.
					mGCC		−0.53 ± 0.36	
	OHT	34	0.1		cpRNFL		−0.44± 0.62	
					mGCC		−0.54 ± 0.52	
	Glaucoma	122	−10.1		cpRNFL		−0.69 ± 0.93	
					mGCC		−0.80 ± 0.78	
Zhang 2016[47]	Healthy	192	N/A	2.5	mGCC	RTVue	−0.25 ± 0.05	Age-related rates of thinning in mGCC and cpRNFL were approximately 0.2% per year. There was no significant effect of IOP on rates of age-related loss in healthy subjects.
					cpRNFL		−0.14 ± 0.07	
Yu 2016[26]	Glaucoma	240	−9.5	5.8	cpRNFL	Cirrus	Eyes with and without cpRNFL thinning on GPA had −0.76%/year and −0.26%/year 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 progressing on RNFL GPA.
Hammel 2017[22]	Healthy	28	−0.1	1.7	cpRNFL	Cirrus	N/A	Normalized rates of progression were faster for cpRNFL than mGCIPL. Progressive loss of mGCIPL but not cpRNFL was detectable in eyes with advanced glaucoma.
					mGCIPL		N/A	
	Glaucoma	97	−4.3	3.2	cpRNFL		−0.98 ± 0.22 (−1.7 ± 0.4%/year)	
					mGCIPL		−0.57 ± 0.16 (−1.3 ± 0.4%/year)	

Abbreviations: GS = Glaucoma Suspect, OHT = Ocular hypertension, cpRNFL = circumpapillary retinal nerve fiber layer thickness, mGCC = macular ganglion cell complex, mGCIPL = macular ganglion cell inner plexiform layer, VF= visual field, EMGT = Early Manifest Glaucoma Trial. GPA =Guided Progression Analysis.