Assessment of rates of structural change in glaucoma using imaging technologies

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CAMBRIDGE OPHTHALMOLOGICAL SYMPOSIUM

Abstract

Purpose To review the ability of current imaging technologies to provide estimates of rates of structural change in glaucoma patients.

Patients and methods Review of literature.

Results Imaging technologies, such as confocal scanning laser ophthalmoscopy (CSLO), scanning laser polarimetry (SLP), and optical coherence tomography (OCT), provide quantifiable and reproducible measurements of the optic disc and parapapillary retinal nerve fibre layer (RNFL). Rates of change as quantified by the rim area (RA) (for CSLO) and RNFL thickness (for SLP and OCT) are related to glaucoma progression as detected by conventional methods (eg, visual fields and optic disc photography). Evidence shows that rates of RNFL and RA loss are significantly faster in progressing compared with non-progressing glaucoma patients.

Conclusion Measurements of rates of optic disc and RNFL change are becoming increasingly precise and individualized. Currently available imaging technologies have the ability to detect and quantify progression in glaucoma, and their measurements may be suitable end points in glaucoma clinical trials.

Eye (2011) **25,** 269–277; doi:10.1038/eye.2010.202; published online 7 January 2011

Introduction

Glaucoma is a complex and progressive disease characterized by an optic neuropathy that is usually associated with typical visual function loss.[1] Although most glaucoma patients will show some evidence of progression, if followed long enough, the rate of deterioration can be highly variable among them. Some patients may progress slowly over the course of many years or decades with minimal impact on the quality of vision, whereas others may have aggressive disease with rapid rates of change that can eventually result in blindness or substantial impairment unless appropriate interventions take place. Therefore, the evaluation of rates of change in glaucoma is essential to allow proper allocation of resources towards the patients who are most likely to develop impairment. In fact, according to the Consensus on Medical Treatment from the World Glaucoma Association, glaucoma treatment is indicated for patients whose rates of progression will most likely result in loss in vision-related quality of life over the projected remaining years of life.[2]

A complete assessment of rates of disease progression requires both structural and functional measures, as it is known that many patients seem to progress by one method and not the other.[3–6] Although functional outcomes have an unquestionable relevance to patients, it has been shown that structural changes can often precede functional losses and be an earlier marker of deterioration. More importantly, a recent study showed that structural changes observed on optic disc stereophotographs are predictive of future functional losses and, therefore, carry clinically relevant prognostic information.[7] However, although optic disc stereophotographs have been considered the gold standard for evaluation of structural damage in glaucoma, evaluation of rates of structural change using stereophotographs is difficult because of the qualitative and subjective nature of this assessment.

Over the past two decades, several technologies, such as confocal scanning laser

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ophthalmoscopy (CSLO), scanning laser polarimetry (SLP), and optical coherence tomography (OCT), have been used to quantitatively and objectively measure the topography of the optic disc and thickness of the parapapillary retinal nerve fibre layer (RNFL).[8] Results from these imaging technologies can be used to predict glaucoma development,[9–13] and have the potential to detect and measure structural progression.[7,14–24] Recent literature has focused on the ability of these instruments to provide estimates of rates of change over time. In this review, we discuss the evidence with regard to the ability of current imaging technologies in measuring rates of structural change in glaucoma and their relationship to conventional methods for assessment of disease progression.

CSLO

CSLO was introduced more than 20 years ago. It enables reproducible measurements of the surface height of the optic nerve head (ONH) and parapapillary retina.[9] The most recent implementation of this technology (Heidelberg Retina Tomograph (HRT), Heidelberg Engineering GmbH, Heidelberg, Germany) has been widely used to evaluate topographic changes of the ONH to detect progression of glaucoma.[13,24–26] Although different stereometric parameters have been suggested as useful markers of progression, some studies have suggested that the neuroretinal rim area (RA) is the most reliable and reproducible measure for detection of change.[27,28] Changes in RA have been demonstrated in glaucoma patients followed over time and are associated with disease progression.[14,15,22,28–34] Baseline measurements obtained by the HRT have also been shown to predict future conversion to glaucoma in patients suspected of having the disease, although the predictive accuracy of the measurements on individual patients is generally low.[13]

CSLO measurements have been used to evaluate rates of glaucoma progression in several studies. Strouthidis et al[22] initially used rates of change in RA to compare detection of progression by visual fields and CSLO in patients with ocular hypertension. They did not, however, report absolute values of change. See et al,[33] observing 94 glaucoma patients and 54 normal controls over 8.6 ± 2.9 years, found a rate of change (RA loss/ year) of -0.0053 and $-0.0012\,\text{mm}^2/\text{year}$, respectively (Figure 1). Strouthidis et al[35] found that the rate of RA loss was greatest in the inferotemporal ($-1.43\%/\text{year}$) and superotemporal sectors ($-1.05\%/\text{year}$). Poli et al[36] also assessed rates of change with the CSLO. In 31 subjects with ocular hypertension and reproducible visual field loss and 19 normal subjects, they reported global RA mean slopes of $-0.0123\,\text{mm}^2/\text{year}$.

Alencar et al[15] studied 629 eyes of 390 patients. Over an average of 3.3 ± 0.7 years of follow-up, the average rate of RA decline was not significantly different between glaucoma progressors and non-progressors (-0.0058 vs $-0.0073\,\text{mm}^2/\text{year}$, respectively; $P = 0.727$). The area under the receiver-operating characteristic (ROC) curve for this parameter showed a poor discriminatory ability, no better than chance. However, when eyes that had undergone glaucoma surgery were excluded, the rates of RA loss became significantly different between progressors ($-0.020\,\text{mm}^2/\text{year}$) and non-progressors ($-0.007\,\text{mm}^2/\text{year}$; $P = 0.015$). This is probably explained by the effect of intraocular pressure (IOP) reduction in causing a significant reversal of ONH cupping, which may be interpreted as an increase in RA by the CSLO and confound evaluation of RA change in patients who underwent surgery during follow-up.[29,37,38]

A shortcoming of the CSLO technology stems from the variation induced by tracing a contour line to outline the optic disc. Alternative approaches for detecting progression in series of CSLO images, such as the topographic change analysis,[26,31,39,40] the glaucoma probability score,[14,25,41,42] and statistic image mapping,[43,44] have been developed and obviate the need for a contour line. These methods, however, exhibit only moderate agreement with each other and have poor agreement with expert-assessed change in optic disc stereophotographs.[45]

In the context of detecting progressive glaucoma, one advantage of the CSLO, when comparing it to other imaging devices, is that latest commercially available versions of the instrument have shown relatively good compatibility with older ones, which is of significant benefit to clinicians and researchers who need to follow up patients for long periods of time.

SLP

SLP (GDx; Carl Zeiss Meditec Inc., Dublin, CA, USA) is a confocal scanning laser ophthalmoscope with an integrated polarimeter that measures the amount of retardation (phase shift) of a polarized near-infrared laser beam as it passes through the RNFL.[45] Changes in RNFL have been suggested to be the earliest sign of glaucoma development in many patients and to precede visual field loss.[46] The SLP enables clinicians to evaluate the parapapillary RNFL objectively and quantitatively. This technology has been shown to provide reproducible RNFL measurements and to differentiate glaucoma patients from normal subjects with sensitivities and specificities between 72 and 78%, and 56 and 92%, respectively.[47–52]

Imaging artifacts such as a poorly compensated corneal birefringence can hamper the accuracy of the
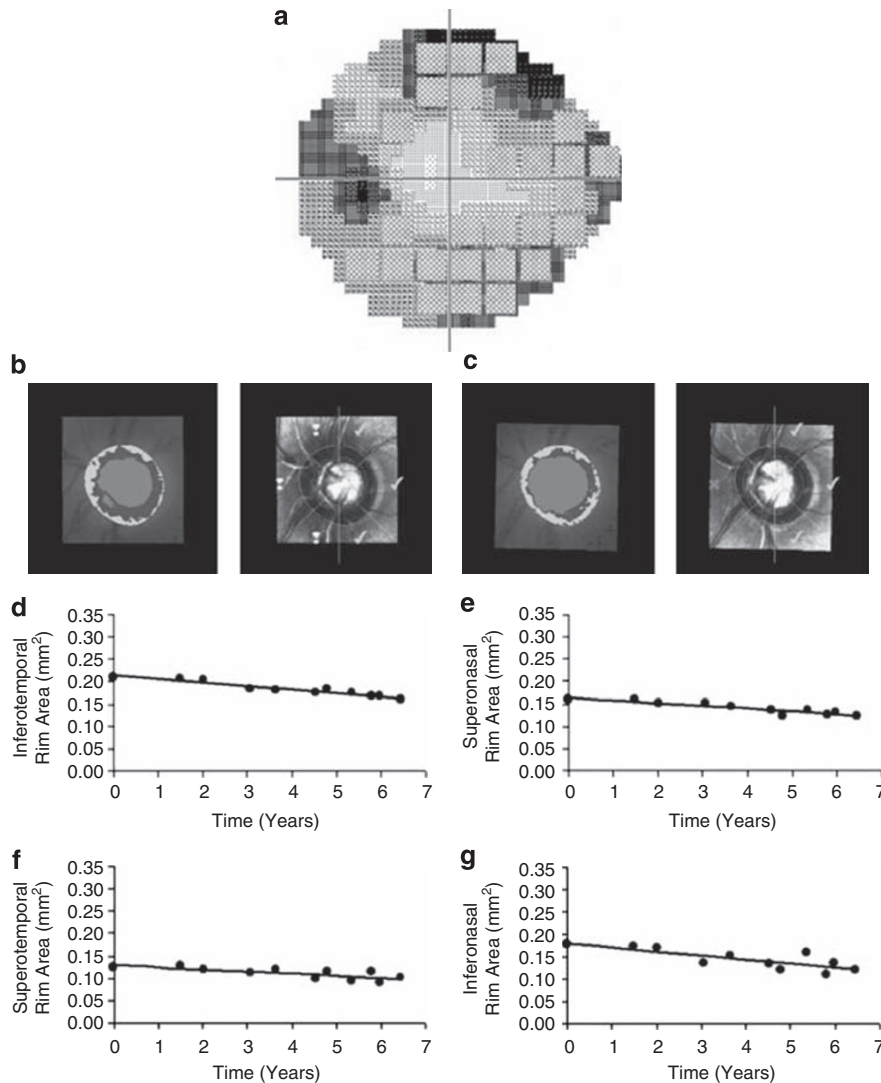
Figure 1 Disc and field progression in subject 9. (a) Visual field grey scale at the conclusion of the study; the hatched squares indicate the test points flagged as progressing according to the standard PLR criteria; (b) HRT baseline mean topography; (c) HRT mean topography at the conclusion of the study period. (d–g) Scatterplots with regression line for sectoral RA against time. (From Strouthidis *et al*[22]).

device in clinical practice.[53] The introduction of a variable corneal polarization compensator (GDxVCC) attempted to alleviate this problem and resulted in improved diagnostic accuracy.[54] The GDxVCC scans, however, were found to be limited by atypical retardation patterns (ARPs). ARPs result from poor noise-to-signal ratio as a consequence of light scattering in the eye. Medeiros *et al*[18] have shown that the presence of ARP on SLP scans adversely affects the detection of progressive glaucomatous RNFL loss. The most recent commercially available version (GDxPRO) is a modification of the GDxVCC and provides an enhanced corneal compensation (ECC) to eliminate artifacts associated with ARP.[54,55]

The GDx software has been recently upgraded with the addition of a guided progression analysis (GPA). The GPA software compares SLP images acquired during follow-up and reports a summary analysis for progression in an individual eye after automated consideration of the expected test–retest variability. It has been shown to be able to identify a significant proportion of glaucoma progression with 50% sensitivity and 96% specificity compared with optic disc stereophotographs and visual fields.[16] Repeatability of GDxVCC was demonstrated to be stable for all stages of disease severity with a repeatability coefficient within $4\,\mu m$ (compared with $6\,\mu m$ with Stratus OCT, Carl Zeiss Meditec Inc.).[42]

Recently, several authors calculated rates of change for the GDx. Using GDxVCC, Medeiros et al[17] imaged individuals with suspected and established glaucoma. They reported an average loss of RNFL thickness of $-0.70 \mu m$/year in glaucoma progressors (based on GPA software for standard automated perimetry (SAP)) vs $-0.14 \mu m$/year in non-progressors ($P < 0.001$), very similar to rates of change reported elsewhere by the

same group (-0.65 and $-0.11 \mu m$/year, respectively).[15] Da Pozzo et al,[56] in a cross-sectional design estimated the age-related loss of RNFL thickness in 384 healthy adults and found a rate of $-0.08 \mu m$/year attributed to ageing.

To date, four longitudinal studies have evaluated GDxECC for detection of progression in glaucoma, with two of them comparing measurements obtained by GDxECC with GDxVCC.[19,21,57,58] Medeiros et al[19] evaluated the relationship between IOP and progressive RNFL loss in a cohort recruited from the Diagnostic Innovations in Glaucoma Study (DIGS). Patients who manifested progression of glaucoma on SAP–GPA showed a significantly higher rate of RNFL change compared with non-progressors (-0.95 vs $-0.17 \mu m$/year; $P = 0.001$). Considering an average baseline thickness of $47 \mu m$ for the RNFL, this amount of loss in progressors would represent an almost 2% loss per year. Each 1-mmHg higher IOP was associated with an additional RNFL loss of $0.13 \mu m$/year in progressors compared with $0.05 \mu m$/year overall. They further showed that rates of change were higher in inferior and temporal sectors, which is in agreement with the expected pattern of glaucomatous damage to the RNFL and to the neuroretinal rim (Figure 2).[59] The same investigators in a subsequent publication reported an average rate of decline for RNFL thickness measurements of $-1.24 \mu m$/year in progressors vs $-0.34 \mu m$/year in non-progressors, with a significantly higher area under the ROC curve for detecting change for ECC compared with VCC (0.89 vs 0.65; $P < 0.001$) (Figure 3).[21] Grewal
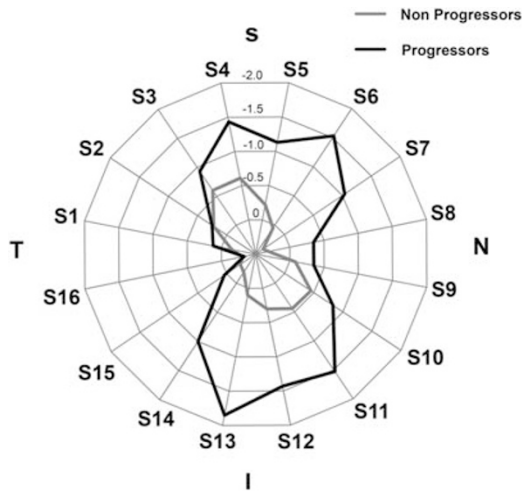

Figure 2 Radar plot illustrating the rates of change in SLP with ECC retinal nerve fibre layer measurements according to the sectors around the optic disc. Eyes that showed progression on visual fields and/or optic disc stereophotographs had greater loss of the RNFL in the inferior and superior sectors. I, inferior; N, nasal; S, superior; T, temporal. (From Medeiros et al[19]).
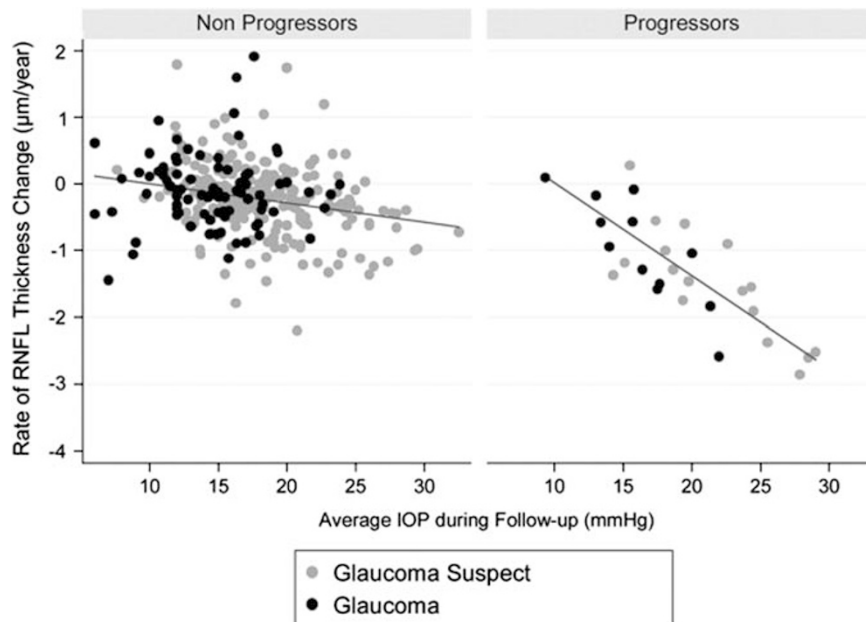

Figure 3 Scatterplot illustrating the relationship between rates of change in the SLP with ECC parameter temporal–superior–nasal–inferior–temporal average and IOP. Rates of change are shown for eyes that progressed by visual fields and/or stereophotographs (progressors) as well as for eyes that did not (non-progressors). (From Medeiros et al[19]).

et al[57] demonstrated that ECC identified more cases of progression than VCC (11.8 vs 8.8%), with only moderate agreement ($\kappa = 0.57$). In a subsequent publication,[58] the same investigators using ECC found rates of annual RNFL loss of $-1.11\,\mu m$/year (progressors) vs $-0.41\,\mu m$/year (non-progressors), when progression was defined based on the SAP visual field index.

A significant limitation of SLP is the lack of interchangeability among serial generations of the commercial instrument. RNFL thickness measurements obtained with the GDxVCC and GDxECC are not interchangeable. Thus, a new baseline must be established in the case of conversion to GDxECC.

OCT

OCT is a non-contact and non-invasive technique for examination of the human retina. Briefly, the instrument uses a super luminescent diode light and works similar to a B-scan ultrasound, using light instead of sound. Unlike the CSLO and the SLP, OCTs are currently available from several different manufactures, with different axial resolution and lower acquisition time. We focus, herein, on the Stratus OCT because very little longitudinal data are currently available for the spectral-domain OCTs.

Wollstein et al[60] showed the potential use of OCT in detecting glaucomatous progression with an event-based approach (ie, a change greater than the expected variability was considered progression). Using a prototype, they concluded that the OCT was more sensitive than standard visual fields for the detection of progression. In fact, 22% of eyes had a significant change measured by the OCT without corresponding deterioration of the visual fields. However, it was not clear whether these eyes were true progressors undetected by visual fields or false positives due to variability of the measurements or age-related thinning of the RNFL.

Medeiros et al[20] evaluated the ability of RNFL thickness, ONH, and macular thickness measurements to detect glaucomatous progression. In their study, progression was determined by SAP and longitudinal assessment of optic disc stereophotographs. They reported the RNFL thickness parameters as having better ability than ONH and macular thickness parameters to detect progression (Figure 4). This is in agreement with previous cross-sectional studies that showed a poor performance of Stratus OCT-derived macular and ONH parameters for cross-sectional detection of glaucoma.[61] For average RNFL thickness, a rate of change of $-0.72\,\mu m$ ($\sim 1\%$)/year for the progressors compared with $0.14\,\mu m$/year in non-progressors was reported. The authors found a wide variation of rates of change, which has also been reported by Leung et al[62] in a study evaluating the GPA software of Stratus OCT. Although this wide range can be explained by individual characteristics, such as stage of disease and response to treatment, it is possible that non-centered scans and signal strength affected the ability to detect change.[63,64] Nonetheless, the wide individual variation should be considered when evaluating patients on a case-by-case basis.
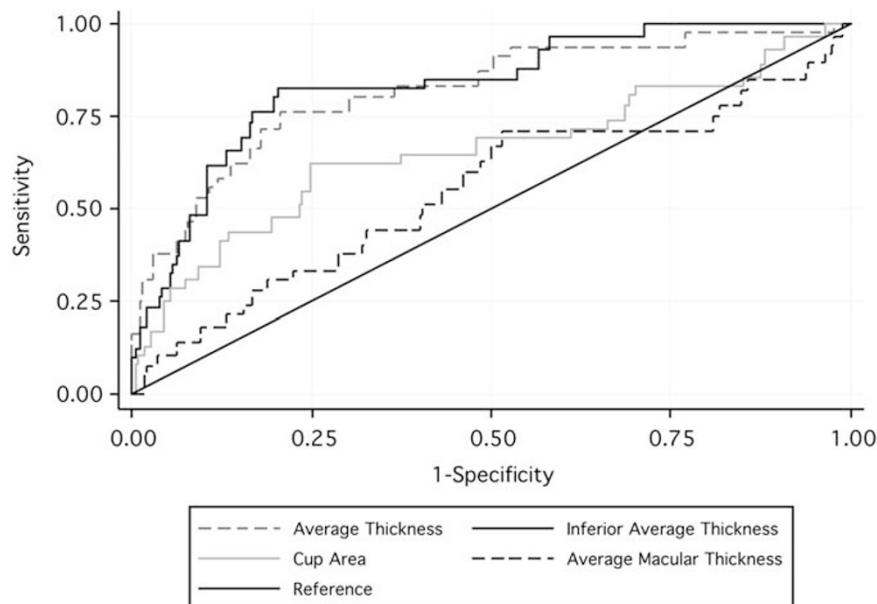

Figure 4 ROC curves of rates of change for discriminating progressors from non-progressors of the three parameters with largest areas under the ROC curves in each scanning area and the average RNFL thickness. (From Medeiros et al[20]).

The recent introduction of spectral domain OCT (SDOCT) has enhanced resolution and decreased scan acquisition time compared with Stratus OCT. With more reproducible images,[65,66] there is potential for improved ability to detect glaucomatous progression. Further, with this higher resolution, new scan types are now possible. One example is the ganglion cell complex (GCC) that selectively measures the inner retina in the macular region. The GCCs have shown similar diagnostic accuracy for detecting glaucoma as the RNFL thickness, and may be useful for monitoring the disease.[67] Recently, Leung et al (Leung CK et al, personal communication) evaluated the ability to detect RNFL progression using Stratus OCT and SDOCT. A total of 128 eyes were followed for a minimum of 24 months. They found more progressors using SDOCT compared with Stratus OCT (23.5% of patients with SDOCT vs 4.9% with Stratus OCT). The agreement with visual field progression was also better with SDOCT. In addition, five eyes had an increasing RNFL thickness with Stratus OCT, indicating an inherent measurement variability of the instrument. The agreement for detection of RNFL progression was poor between the two instruments ($k = 0.188$). The rate of change ranged between -1.52 and $-5.03\,\mu m/year$ with SDOCT, and between -2.22 and $-7.60\,\mu m/year$ with Stratus OCT.

Table 1 summarizes the ability of all the three imaging technologies to provide rates of change.

Summary and future directions

Currently available imaging technologies have been demonstrated to detect and quantify glaucomatous progression in a reproducible manner. Rates of change in RNFL thickness and optic disc topographic measurements as measured by different instruments have been shown to correlate significantly with conventional methods for assessment of change, such as SAP and optic disc stereophotographs. Several studies have shown that rates of structural damage are faster in eyes with progressive glaucoma, and show a correlation with important risk factors for the disease such as IOP.

Advances in the assessment of change with imaging devices may shift the macroscopic standard of optic disc photographs towards the microscopic and three-dimensional imaging of the retinal layers. With the increasing resolution and reliability of imaging technologies, it is likely that the estimation of these rates of change will be more precise and individualized in the near future. In addition, advances and implementation of image stabilization technologies should improve reproducibility of structural measurements to enable better differentiation of variability from true progression.

At present, the Food and Drug Administration (FDA) recognizes IOP as an efficacy end point for IOP-lowering drugs and visual field testing, visual acuity, contrast sensitivity, and colour vision as functional end points.[68] IOP is an imperfect surrogate for the clinical outcomes of glaucoma, as disease can progress despite low IOP or remain stable despite IOP levels considered high.[69–71] The use of visual fields as an end point is potentially limited by the need for large samples, long follow-up, variability of results, and inconsistency in criteria for defining progression.[72] The absence of regulatory support for other glaucoma end points has been

Table 1 Mean rates of change for patients with progressive glaucoma as measured by CLSO, SLP (GDxVCC and GDxECC), and Stratus OCT

Imaging technology	Study	Parameter	Mean rates of change		AROC
			Progressors	Non-progressors	
CSLO	Alencar et al[1]	RA average (mm²/year)	−0.0058	−0.0073	0.51 (95% CI, 0.40–0.61)
	Poli et al[2a]	RA average (mm²/year)	−0.0123	NA	NA
	See et al[3]	RA average (mm²/year)	−0.0053	−0.0012	NA
GDxECC	Medeiros et al[4]	TSNIT average (μm/year)	−0.95	−0.17	NA
	Medeiros et al[5]	TSNIT average (μm/year)	−1.24	−0.34	0.89 (95% CI, 0.83–0.95)
	Grewal et al[6b]	TSNIT average (μm/year)	−1.11	−0.41	NA
GDxVCC	Medeiros et al[7c]	TSNIT average (μm/year)	−0.70	−0.14	NA
	Medeiros et al[5d]	TSNIT average (μm/year)	−0.46	−0.15	0.65 (95% CI, 0.53–0.77)
	Alencar et al[1]	TSNIT average (μm/year)	−0.65	−0.11	0.81 (95% CI, 0.74–0.88)
Stratus OCT	Medeiros et al[8]	TSNIT average (μm/year)	−0.72	−0.14	0.83 (95% CI, 0.72–0.92)
	Leung et al[9]	TSINT average (μm/year)	−3.30 (median)	NA	NA

Abbreviations: AROC, area under the receiver operating characteristic curve; ARP, atypical patterns of retardation; CI, confidence interval; CLSO, confocal scanning laser ophthalmoscopy; ECC, enhanced corneal compensation; NA, not applicable; OCT, optical coherence tomography; RA, rim area; SAP, standard automated perimetry; SLP, scanning laser polarimetry; TSNIT, temporal–superior–nasal–inferior–temporal.
[a]Calculated for 'converters' (defined as normal or ocular hypertensive subjects who progressed to glaucoma).
[b]Progression was defined by the slope of the visual field index on SAP.
[c]Included scans with ARP.
[d]Excluded scans with ARP.

identified as a weakness in exploring candidate agents for neuroprotective therapy and alternative surrogate end points have been sought. Structural measurements obtained by imaging technologies have the potential to overcome these obstacles, and could potentially act as useful biomarkers and surrogate end points to be used in glaucoma clinical trials. Future research should be directed at evaluating, quantifying, and comparing the abilities of structural change measured by different imaging technologies in predicting clinically relevant outcomes in glaucoma.

Conflict of interest

K Mansouri, none; MT Leite, none; FA Medeiros, Carl Zeiss Meditec Inc. (F, R), Alcon (C, R), Allergan (C, F), Merck (C, F), Pfizer Inc. (C, F, R), and Reichert Inc. (R); RN Weinreb, Carl Zeiss Meditec Inc. (C, F); Heidelberg Engineering, GmbH (F); Optovue Inc. (C, F); and Topcon Medical Systems Inc. (F, R).

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