Detection of glaucoma progression by population and individual derived variability criteria

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ABSTRACT

Purpose Ocular imaging devices provide quantitative structural information that might improve glaucoma progression detection. This study examined scanning laser polarimetry (SLP) population-derived versus individual-derived cut-off criteria for detecting progression.

Methods Forty-eight healthy, glaucoma suspect and glaucoma subjects, providing 76 eyes were used. All subjects had reliable visual field (VF) and SLP scans acquired at the same visits from ≥4 visits. VF progression was defined by guided progression analysis (GPA) and by the VF index. SLP measurements were analysed by fast mode (FM) GPA, compared with the population rate of progression, and extended mode (EM) GPA, compared with the individual variability. The agreement between progression detection methods was measured.

Results Poor agreement was observed between progression defined by VF and FM and EM. The difference in temporal-superior-nasal-inferior-temporal (TSNIT) average rate of change between VF defined progressors and non-progressors for both FM (p=0.010) and EM (p=0.015) was statistically significant.

Conclusions There is poor agreement between VF and SLP progression regardless of the use of population derived or individual variability criteria. The best SLP progression detection method could not be ascertained, therefore, acquiring three SLP scans per visit is recommended.

The detection of glaucoma progression poses a significant clinical challenge. Glaucoma progresses slowly with high variability in the progressive trends of the disease. Perimetry testing is the current preferred method for detecting glaucoma progression; however, studies have shown structural damage to occur prior to vision loss in many eyes.[1–3] Optic disc stereophotography has also been used to assess glaucoma progression, though minor structural changes have been shown to be difficult to detect.[4–6] Imaging devices provide quantitative and reproducible measurements of ocular structure and may improve progression detection ability. Their ability to measure structural changes to the retinal nerve fibre layer (RNFL) and optic nerve head (ONH) removes the subjectivity associated with perimetry. Additionally, structures can be measured over time to detect minor disease related changes.

Scanning laser polarimetry (SLP) is an imaging device used to assess glaucoma progression. The commercially available SLP technology, GDx (Carl Zeiss Meditec (CZM), Dublin, California, USA), includes guided progression analysis (GPA) software. This analysis uses a cut-off criterion for progression that is derived either from the population variability or from the individual tested eye variability. Previous studies have shown the ability of SLP to detect glaucoma progression.[7–10] The purpose of this study was to examine the outcome of population-derived versus individual-derived cut-off criteria for detecting progression using SLP data.

METHODS

Subjects

Subjects were recruited from the University of Pittsburgh Medical Center Eye Center. The study was approved by the University of Pittsburgh Institutional Review Board, and adhered to the Declaration of Helsinki and Health Insurance Portability and Accountability Act Regulations. Informed consent was obtained from all subjects.

Study protocol

Healthy, glaucoma suspect and glaucoma subjects enrolled in the Pittsburgh Imaging Technology Trial (PITT) were included in this study. At each biannual visit, participants underwent a full ocular examination including intraocular pressure measurement (IOP), gonioscopy, visual field (VF) testing, fundus photography and imaging with GDx-Enhanced Corneal Compensation (ECC; CZM; software V.5.5.0). Subjects must have completed 4 or more testing visits to be included in the study. Exclusion criteria included history of ocular trauma, best corrected visual acuity worse than 20/60, refractive error less than 8 dioptres, media opacity, ocular diseases other than glaucoma, or non-glaucomatous causes of VF abnormalities. Subjects were excluded if they had surgery other than non-complicated cataract surgery, or glaucoma surgery during enrolment resulting in less than 4 consecutive follow-up visits either before or after the surgery. Both eyes were used if eligible for the study.

Clinical diagnosis

Healthy eyes were categorised as those with no history of intraocular surgery or retinal disease, IOP≤21 mmHg, normal appearing ONH and full VF. The glaucoma suspect group included subjects with IOP from 22–30 mm Hg, vertical cup to disc ratio (VCDR) >0.7, asymmetric ONH cupping (difference in VCDR between the eyes ≥0.2) or abnormal appearing ONH all in the presence of a full VF. Glaucomatous eyes were defined as those having a glaucomatous VF defect at baseline.

Visual field testing

Swedish interactive thresholding algorithm 24-2 perimetry (SITA; Humphrey Field Analyzer; CZM, Dublin, CA, USA) was used for VF testing. Reliable VF tests were designated as those with less than 30% fixation losses, false positive and false negative responses. A full VF is defined as one with glaucoma hemifield test within normal limits and no clusters of 3 or more adjacent points deviating from normal range with a probability of less than 5% or clusters of 2 or more adjacent points with probability less than 1% in a typical non-edge glaucoma pattern on the pattern deviation map.

VF progression was determined by the VF GPA software. Eyes with a likely or possible GPA outcome or a statistically significant ($p<0.05$) negative VF index (VFI) slope, at the final visit, were defined as progressors.

SLP image acquisition and analysis

The principles of SLP have been previously described.[11 12] In brief, SLP uses a polarisation-modulated light source directed on the retina, where a phase shift is caused by the organised, parallel structure of microtubules within the RNFL. This measurable shift, or retardation, can be acquired across a transverse plane in the peripapillary region and is linearly related to RNFL thickness. To determine RNFL thickness progression with SLP, multiple longitudinal peripapillary scans are obtained. The imaging device identifies RNFL change when a measured value exceeds the measurement variability and reports it as a true change.

Each subject underwent a GDx Corneal scan at the onset of study inclusion to determine the birefringence of the anterior segment. This consisted of one scan of the macular region, which was applied to all subsequent ECC scans to account for the birefringence of the anterior segment. Three GDx-ECC scans were performed for each eye, at every visit. Scans were reviewed to ensure an image quality score greater than or equal to 8, a typical scan score greater than or equal to 70, proper centration and focus. SLP parameters were obtained from the retardation measurements acquired at each visit, including; temporal-superior-nasal-inferior-temporal (TSNIT), superior and inferior thickness.

SLP progression assessment

Progression for SLP was defined as a 'Likely Progression' classification by the device's GPA software at the last visit. An eye was considered progressing by SLP if any of the three methods (Image Progression Map, TSNIT Progression Graph, TSNIT Summary Parameter Chart) resulted in a 'Likely Progression' outcome.

The Image Progression Map, uses a fundus image with pixel clusters that represent significant change from baseline. Clusters greater than or equal to 150 pixels shown in two consecutive scans are reported as likely progression. The TSNIT Progression Graph displays the RNFL thickness along the sampling circle. This analysis clusters the circumpapillary circle into 64 regions, where likely progression is indicated if significant change occurs in 4 or more adjacent regions. The RNFL Summary Parameter Charts utilise a linear regression to determine the TSNIT, superior, and inferior average RNFL change over time. Only those eyes with decreasing rates of change, statistically significantly different than zero, are given a quantitative progression rate. All other TSNIT, superior, and inferior linear regressions were computed manually.

The GDx GPA was computed by using both the Fast Mode (FM) and the Extended Mode (EM) software analysis. FM progression is defined as a change from baseline exceeding the predetermined measurement variability based on population-derived data. For FM the average of one scan from the first two visits is used as baseline, a change in follow-up visits is considered significant if it exceeds the population measurement variability for all three methods of progression assessment. The FM GPA only utilises a single test in each visit; therefore, at each visit the best quality scan was selected for analysis.

EM progression is defined based on the measurement variability of each individual eye, determined by the variability among the three scans obtained in the first two baseline visits. The change from baseline approach is used to identify progression for the Image Progression Map, where change exceeding individual eye variability, is considered significant. The TSNIT Progression Graph and RNFL Summary Parameters Charts use the individual eye variability to determine progression, relying on Statistical Image Mapping (SIM).[13]

Statistical analysis

Linear mixed effect modelling was used to account for clustering of the data, that is, using multiple scans from subjects and both eyes of subjects. TSNIT average slopes were compared between VF defined progressors and non-progressors and between groups classified by diagnosis.

Statistical analysis was performed using R Language and Environment for Statistical Computing package *nlme*.[14] $p<0.05$ was considered statistically significant.

RESULTS

Sixteen healthy, 34 glaucoma suspect and 26 glaucoma eyes from 48 subjects were included in the study. The mean length of follow-up of the entire group was 3.94 years (range: 1.6–5.5) with a mean of 6.13 visits (range: 4–8). Table 1 summarises the baseline characteristics of the subjects. Table 2 shows the diagnosis group differences. All baseline parameters of healthy and glaucoma suspect eyes were statistically significantly different than glaucoma eyes. Ten eyes were identified as VF progressors (7 glaucoma and 3 glaucoma suspect). Two healthy eyes progressed by FM and 2 progressed by EM.

Table 1 Study population characteristics at baseline. All parameters are reported as mean and 95% CIs (linear mixed effect modelling)

	Healthy (n=16)	Glaucoma suspect (n=34)	Glaucoma (n=26)
Age (years)	49.37 (45.53 to 53.20)	55.78 (53.15 to 58.41)	63.01 (60.00 to 66.02)
Visual field MD (dB)	−0.47 (−1.67 to 0.73)	−0.43 (−1.25 to 0.40)	−3.09 (−4.04 to −2.15)
Visual field PSD (dB)	1.61 (0.48 to 2.75)	1.71 (0.93 to 2.49)	4.21 (3.31 to 5.10)
FM TSNIT average (μm)	55.85 (52.12 to 59.59)	52.93 (50.43 to 55.43)	47.93 (45.08 to 50.79)
EM TSNIT average (μm)	55.09 (51.42 to 58.77)	52.55 (50.11 to 55.00)	47.19 (44.40 to 49.97)

EM, extended mode; FM, fast mode; MD, mean deviation; PSD, pattern SD; TSNIT, temporal-superior-nasal-inferior-temporal.

Table 2 Difference (p value*) in baseline parameters between clinical groups

	Age (years)	Visual field MD (dB)	Visual field PSD (dB)	FM TSNIT average (μm)	EM TSNIT average (μm)
Glaucoma suspect—healthy	6.41 (0.008)	0.04 (0.958)	0.10 (0.889)	−2.93 (0.202)	−2.54 (0.257)
Glaucoma—healthy	13.65 (<0.001)	−2.62 (0.002)	2.59 (0.001)	−7.92 (0.002)	−7.91 (0.002)
Glaucoma—glaucoma suspect	7.23 (0.001)	−2.66 (<0.001)	2.50 (<0.001)	−4.99 (0.008)	−5.37 (0.004)

*Linear mixed effect modelling.
EM, extended mode; FM, fast mode; PSD, pattern SD; TSNIT, temporal-superior-nasal-inferior-temporal.

Progression detection agreement

Proportional area diagrams summarise the progression agreement as defined by VF, FM and EM GPA criteria (figures 1 and 2). Ten eyes were defined as progressors by VF with half of these eyes showing progression with GDx GPA analysis. Four out of the remaining five eyes that were defined as VF progression but did not show GDx GPA progression had advanced structural damage as reflected by baseline average TSNIT less than 38 μm. In 3 out of the 12 eyes where progression was detected by both FM and EM the timing of progression detection was identical. In six eyes FM progression occurred prior to EM and in three eyes EM progression preceded FM. Three eyes were VF progressors and progressed by both EM and FM. In one of the three eyes all methods detected progression simultaneously. Progression was detected in the second eye in the order: VF, EM, and FM, at three consecutive visits. Progression in the third eye was detected by VF and FM simultaneously, with EM detection at a subsequent visit. One eye progressed by VF and EM only. One eye progressed by VF and FM only, where progression was determined at the same visit in both cases.

Figure 3 shows an example of a glaucoma subject where FM indicated likely progression for all three methods. EM only indicated possible progression in the superonasal region of the TSNIT Progression Graph. The printouts highlight the diagnostic differences that can result when using EM and FM.

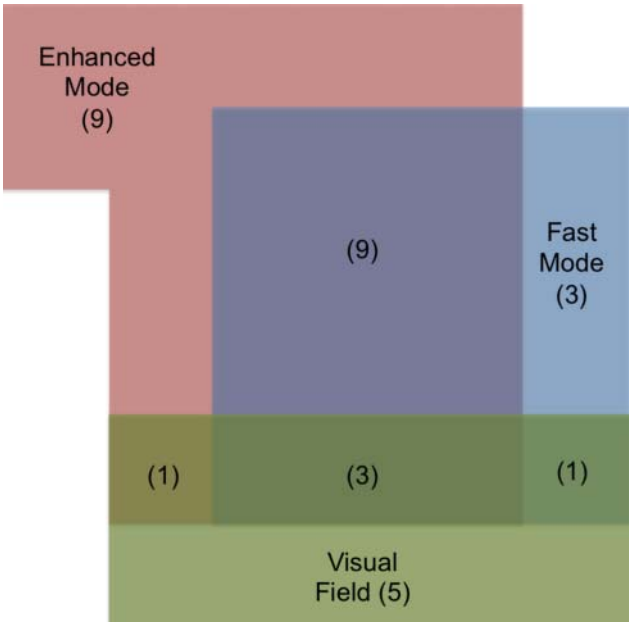

Figure 1 Proportional area diagram for visual field progression and progression by at least one of the GDx Guided Progression Analysis criteria.

Mixed effects model

The TSNIT average rates of change as measured by linear mixed effects models for the different clinical diagnoses were healthy=0.13 μm/year (95% CI −0.21 to 0.47), glaucoma suspect=−0.43 μm/year (95% CI −0.69 to −0.18), and glaucoma=−0.22 μm/year (95% CI −0.47 to 0.03) for FM and healthy=0.18 μm/year (95% CI −0.12 to 0.48), glaucoma suspect=−0.45 μm/year (95% CI −0.67 to −0.23), and glaucoma=−0.31 μm/year (95% CI −0.54 to −0.09) for EM. A negative slope signifies thinning of the RNFL over time. There was a statistically significant difference between the rate of change for the glaucoma suspect compared with the healthy group for both EM (p<0.001) and FM (p=0.010). Additionally, there was a statistically significant difference between the rate of change for the glaucoma group compared with the healthy group for EM (p=0.010), but not for FM. Linear mixed effects models showed the VFI rate of change for healthy=0.11 (−0.28, 0.50), glaucoma suspect=0.13 (−0.16, 0.41) and glaucoma=−0.62 (−0.92, −0.32). There was a statistically significant difference in VFI rate of change between healthy and glaucoma eyes (p=0.004), and glaucoma suspect and glaucoma eyes (p=0.001).

Linear mixed effects models showed the TSNIT average rates of change for FM progressors=−0.73 μm/year (−1.14, −0.32) and non-progressors=−0.14 μm/year (−0.31, 0.03). For EM, progressors=−0.69 μm/year (−1.06, −0.32) and non-progressors=−0.19 μm/year (−0.34, −0.03). A statistically significant difference existed in the TSNIT average rate of change between VF defined progressors and non-progressors for both FM (p=0.010) and EM (p=0.015).

DISCUSSION

This study was designed to evaluate the preferred method for detecting glaucoma progression when comparing population- and individual-derived cut-off criteria. Similar to a previous study, we observed poor agreement between VF and GDx GPA regardless of the use of population- or individual-derived variability criteria.[10] However, RNFL thickness slope was significantly different between VF defined progressors and non-progressors.

Of the 10 eyes progressing by VF, 4 were detected as progressing by EM and 4 by FM. Most of the remaining five eyes that demonstrated VF progression without corresponding GDx GPA progression had advanced structural damage that might indicate that the structural changes precede the functional changes or that functional assessment is more sensitive to detect changes in advanced stages of glaucoma. These results agree with previous studies reporting limited agreement between structural and functional progression detection methods.[2 10 15–17] In a study by Alencar *et al*,[9] the GDx GPA was only able to identify 50% of the eyes that were detected as progressing by VF and stereophotographs. As we have shown, vision loss and RNFL changes occur at different times and exhibit different rates of progression, making agreement difficult to detect.[18] A model that

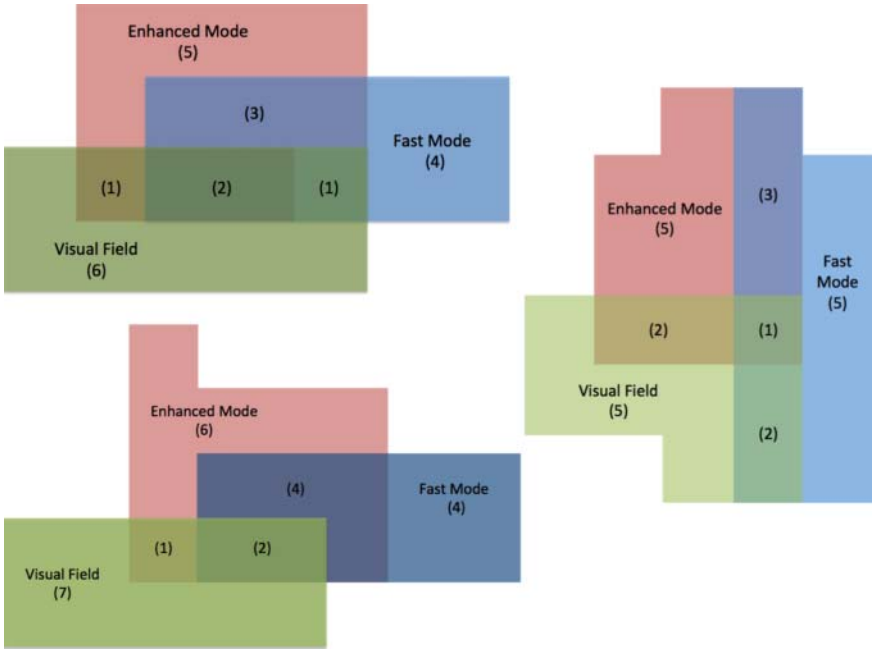

Figure 2 Proportional area diagram for progression by the Image Progression Map (top left), temporal-superior-nasal-inferior-temporal Progression Graph (top right), and Summary Parameter Charts (bottom left) GDx Guided Progression Analysis criteria.

accounts for these differences and relates structural and functional changes in glaucoma may provide a better assessment of disease.

In this study, we report of statistically significantly higher rate of RNFL thinning for eyes that were defined as VF progressors compared with eyes that were defined as non-progressors with both FM and EM. These findings are in line with Medeiros *et al*,[7] who reported a statistically significantly difference in the rate of GDx-VCC FM progressors (−0.70 µm/year) compared with the non-progressing group (−0.14 µm/ year; p=0.001). This implies that eyes that showed a faster rate of VF deterioration also had a faster rate of RNFL thinning as measured by GDx, compared with non-VF-progressing eyes. We were also able to detect differences in the rates of RNFL change between glaucoma suspect and healthy subjects for both FM and EM. Because the glaucoma suspect group is a heterogenic mix of healthy and early glaucoma subjects, the ability of GDx to detect a difference in the progression rate between these groups

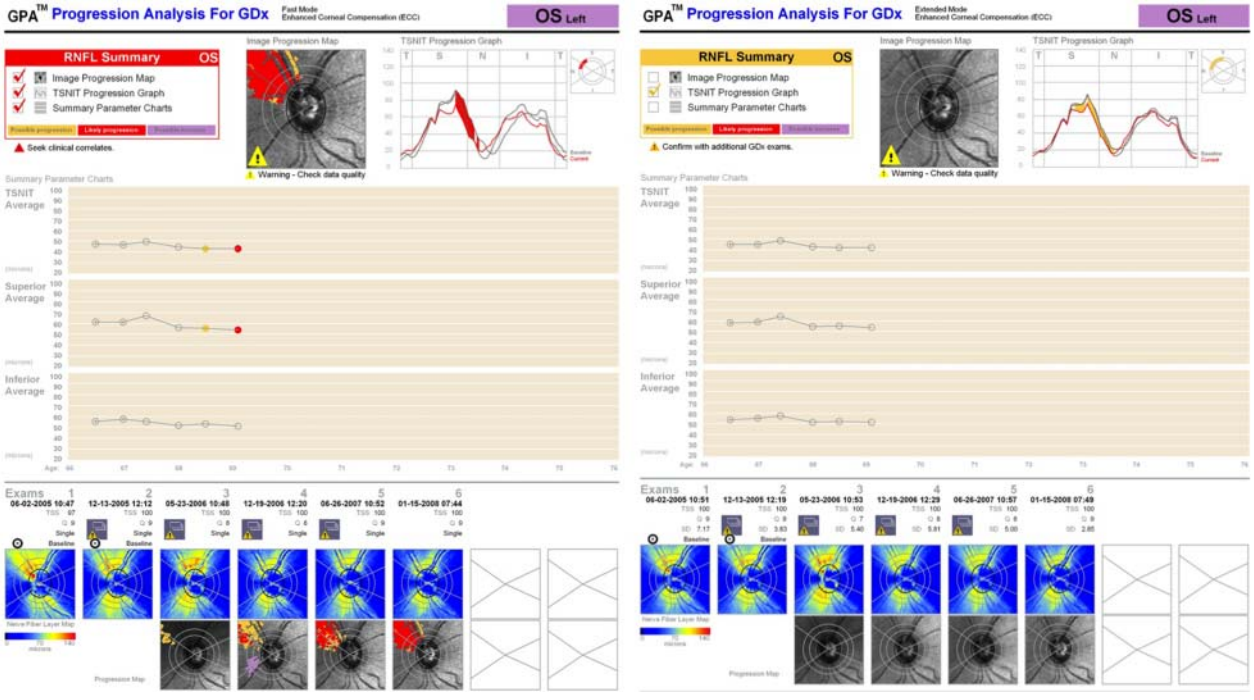

Figure 3 GDx Guided Progression Analysis (GPA) reports for glaucoma subject showing likely progression with Fast Mode (left) and possible progression for Extended Mode (right). Fast Mode shows likely progression for all three GPA detection methods, where extended mode only shows possible progression for the temporal-superior-nasal-inferior-temporal Progression Graph.

highlights the strength of this analysis. However, only EM was able to detect a difference in the rate of RNFL change between glaucoma and healthy subjects, which indicates an advantage to the diagnostic ability of EM. We evaluated the difference in VFI rate of change between diagnoses because glaucoma suspects had the greatest TSNIT rate of change. We found the glaucoma group to have a statistically significantly larger VFI rate of change than both the healthy and glaucoma suspect groups. This does not explain the TSNIT average findings, however, the difference in the TSNIT rate of change between glaucoma suspect and glaucoma eyes, for both EM and FM, was not significant.

The differences in the performance of FM and EM stem from the different cut-off criteria utilised as determined from individual compared with population variability. Additionally, all scans were included in EM while only one scan at each visit was used in FM. Kjaergaard *et al*,[10] have demonstrated that selection of the tests to be included in the FM analysis is affecting the outcome of the GPA analysis, resulting in further GPA differences observed in our study. The analysis method employed in the TSNIT Progression Graph and Summary Parameter Charts is also different for the FM compared with EM. For FM, change is detected based on a difference from baseline analysis (an event analysis). EM analysis is determined by the SIM method, which is based on trend analysis.

While EM theoretically 'tailors' progression detection to individual eye variability, there was a trend of earlier progression detection by FM in cases where both methods detected progression. Additionally, EM and FM showed a similar level of specificity, reflected by the same number of healthy eyes detected as progressors. A total of 21 eyes were detected as progressing by GDx GPA and not VF, which might indicate pre-perimetric progressing or a false positive result, further follow-up is required.

A limitation of this study is the low incidence of progression. Since GDx-ECC is a relatively new software modification to SLP, our follow-up time was limited by scan availability. The limited number of progressing subjects is a result of careful clinical management, an inevitable ethical limitation when studying longitudinal trends of treatable diseases, along with a relatively short follow-up duration for a typically slowly progressing disease.

While FM had the tendency to detect progression earlier than EM, only EM could demonstrate a significant difference for the progression rate between healthy and glaucomatous eyes. Taken together, we cannot ascertain the most effective SLP method of progression detection. It is therefore recommended to acquire three SLP scans at each visit, to allow either EM or FM to be performed.

Contributors Design of the study (LSF, GW, HI, JSS), conduct of the study (LSF, JK), data analysis and interpretation (LSF, GW, RAB, YL), manuscript preparation (LSF), manuscript review (GW, HI, LK, JSS), manuscript final approval (GW, HI, JSS).

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Competing interests JSS received royalties for intellectual property licensed by Massachusetts Institute of Technology to Carl Zeiss Meditec.

Ethics approval The study was approved by the institutional review board and ethics committee (prospective approval) of the University of Pittsburgh and informed consent was obtained from all subjects. This study followed the tenets of the Declaration of Helsinki and was conducted in compliance with the Health Insurance Portability and Accountability Act.

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