Detection of Progressive Retinal Nerve Fiber Layer Loss in Glaucoma Using Scanning Laser Polarimetry with Variable Corneal Compensation

Felipe A. Medeiros, Luciana M. Alencar, Linda M. Zangwill, Christopher Bowd, Gianmarco Vizzeri, Pamela A. Sample, and Robert N. Weinreb

Purpose. To evaluate the ability of scanning laser polarimetry with variable corneal compensation to detect progressive retinal nerve fiber layer (RNFL) loss in glaucoma patients and patients suspected of having the disease.

Methods. This was an observational cohort study that included 335 eyes of 195 patients. Images were obtained annually with the GDx VCC scanning laser polarimeter, along with optic disc stereophotographs and standard automated perimetry (SAP) visual fields. The median follow-up time was 3.94 years. Progression was determined using commercial software for SAP and by masked assessment of optic disc stereophotographs performed by expert graders. Random coefficient models were used to evaluate the relationship between RNFL thickness measurements over time and progression as determined by SAP and/or stereophotographs.

Results. From the 335 eyes, 34 (10%) showed progression over time by stereophotographs and/or SAP. Average GDx VCC measurements decreased significantly over time for both progressors as well as non-progressors. However, the rate of decline was significantly higher in the progressing group (−0.70 μm/year) compared to the non-progressing group (−0.14 μm/year; $P = 0.001$). Black race and male sex were significantly associated with higher rates of RNFL loss during follow-up.

Conclusions. The GDx VCC scanning laser polarimeter was able to identify longitudinal RNFL loss in eyes that showed progression in optic disc stereophotographs and/or visual fields. These findings suggest that this technology could be useful to detect and monitor progressive disease in patients with established diagnosis of glaucoma or suspected of having the disease. (*Invest Ophthalmol Vis Sci.* 2009;50:1675–1681) DOI:10.1167/iovs.08-2712

Glaucoma is a progressive disease characterized by pathologic loss of ganglion cells and retinal nerve fiber layer with or without associated visual field loss.[1] Current management of glaucoma is focused on reducing intraocular pressure, and treatment is considered effective if it is able to slow or halt disease progression. Accurate methods for detecting disease progression are therefore essential to monitor patients and evaluate the efficacy of therapy. Although automated perimetry has been the standard method for detecting progressive disease, it is known that many patients can have progressive structural damage that precedes detectable associated changes in the visual field.[2,3] Evaluation of progressive structural damage in glaucoma can be performed by comparing the appearance of the optic disc on longitudinal stereophotographs. This method, however, is limited by the need for subjective evaluation performed by skilled examiners, requirement for pupillary dilation, and may also offer suboptimal evaluation of the retinal nerve fiber layer (RNFL).

Several imaging technologies have become available to objectively evaluate the optic disc and the RNFL. One of these technologies, scanning laser polarimetry (SLP), provides quantitative estimates of the thickness of the RNFL with potential use for diagnosis and follow-up of glaucoma patients.[4,5] It is based on the principle that polarized light passing through the birefringent RNFL undergoes a measurable phase shift, known as retardation, which is linearly related to histologically measured RNFL tissue thickness.[6] The introduction of variable corneal compensation (VCC) in a commercially available scanning laser polarimeter (GDx VCC, software version 5.5.1; Carl-Zeiss Meditec, Inc., Dublin, CA) has resulted in improved diagnostic accuracy compared to earlier versions of this technology, which used fixed corneal compensation.[7–12] GDx VCC measurements are reproducible[13,14] and detect RNFL loss in patients with glaucomatous visual field damage as well as in glaucoma suspects.[11,15–18] However, the ability of this technology to monitor progressive RNFL loss in a longitudinal study has not yet been reported.

The purpose of this study was to evaluate the ability of the GDx VCC to detect progressive RNFL loss in glaucoma patients and patients suspected of having the disease. We report on the ability of the GDx VCC to detect progressive disease, as well as on the factors influencing longitudinal measurements of the RNFL thickness obtained by this instrument.

Methods

This was an observational cohort study. Participants from this study were included in the Diagnostic Innovations in Glaucoma Study (DIGS), a prospective longitudinal study designed to evaluate optic nerve structure and visual function in glaucoma conducted at the Hamilton Glaucoma Center, University of California, San Diego. Participants in the DIGS were longitudinally evaluated according to a preestablished protocol that included regular follow-up visits in which patients underwent clinical examination and several other imaging and functional tests. All the data were entered in a computer database. All participants from the DIGS study who met the inclusion criteria described below were enrolled in the present study. Informed consent was obtained from all participants. The University of California San

From the Hamilton Glaucoma Center and Department of Ophthalmology, University of California, San Diego, California.

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Corresponding author: Felipe A. Medeiros, Hamilton Glaucoma Center, University of California, San Diego, 9500 Gilman Drive, La Jolla, CA 92093-0946; fmedeiros@eyecenter.ucsd.edu.

Diego Human Subjects Committee approved all protocols and the methods described adhered to the tenets of the Declaration of Helsinki.

At each visit during follow-up, subjects underwent a comprehensive ophthalmologic examination including review of medical history, best-corrected visual acuity, slit-lamp biomicroscopy, intraocular pressure (IOP) measurement, gonioscopy, dilated fundoscopic examination, stereoscopic optic disc photography, and automated perimetry using either 24-2 full-threshold or Swedish Interactive Threshold Algorithm (SITA). Axial length measurements were acquired (IOLMaster; Carl-Zeiss Meditec). Only subjects with open angles on gonioscopy were included. Subjects were excluded if they presented best-corrected visual acuity $<20/40$, spherical refraction outside ± 5.0 diopters and/or cylinder correction outside 3.0 diopters, or any other ocular or systemic disease that could affect the optic nerve or the visual field. Patients included in the study had no history of refractive surgery.

The study included patients diagnosed with glaucoma as well as patients suspected of having the disease, as determined on the baseline visit. Eyes were classified as glaucomatous if they had repeatable (two consecutive) abnormal visual field test results on the baseline visits, defined as a PSD outside of the 95% normal confidence limits, or a Glaucoma Hemifield Test result outside normal limits, regardless of the appearance of the optic disc. Eyes were classified as glaucoma suspects if they had a history of elevated intraocular pressure (>21 mm Hg) and/or suspicious or glaucomatous appearance of the optic nerve but normal and reliable visual field results on the baseline visits. If both eyes from the same patient were eligible for the study, both eyes were included in the analysis, and statistical procedures were used to take into account the correlation between measurements within the same patient.

A minimum follow-up period of 1 year with GDx VCC and a minimum of two separate visits were required in the study. GDx VCC images were obtained annually during follow-up. The median follow-up time was 3.94 years (first quartile: 3.01 years, third quartile: 4.44 years). In some visits, more than one image was available for analysis. The existence of multiple images during the same visit was taken into account during statistical analysis and used to evaluate the variability of GDx VCC measurements. From the 1565 GDx VCC visits during follow-up, 1386 (89%) had at least two images obtained on the same day and 1196 (76%) had at least three images obtained on the same day. For 179 (11%) GDx VCC visits, only one image was available for analysis on those visits. Therefore, a total of 4885 GDx VCC images were available for analysis in the whole study.

Eligible subjects were required to have had a visual field examination and optic disc stereophotographs taken close in time to the baseline and last GDx VCC scans. Baseline was set at the first occurrence of this matching and the GDx VCC date was used as the baseline date. During follow-up time, each patient was treated at the discretion of the attending ophthalmologist.

Standard Automated Perimetry

Standard automated perimetry (SAP) visual fields were obtained using the SITA (Humphrey Field Analyzer [HFA]; Carl Zeiss Meditec) strategy during follow-up. Only reliable tests ($\leq$33% fixation losses and false negatives, and <15% false positives) were included. Glaucomatous visual field progression was assessed using commercial software (HFA Guided Progression Analysis [GPA]; Carl Zeiss Meditec). Progression by SAP GPA was defined as a significant decrease from baseline (two exams) pattern deviation at three or more of the same test points on three consecutive tests.[19]

Stereophotograph Grading

Simultaneous stereoscopic optic disc photographs (TRC-SS; Topcon Instrument Corp of America, Paramus, NJ) were reviewed using a stereoscopic viewer (Asahi Pentax Stereo Viewer II; Asahi Optical Co., Tokyo, Japan). For progression assessment, each patient's most recent stereophotograph was compared to their baseline stereophotograph. Definition of change was based on focal or diffuse thinning of the neuroretinal rim and increased excavation, appearance, or enlargement of RNFL defects. Evidence of progression was based on masked (patient name, diagnosis, temporal order of photographs) comparison between the baseline and most recent photograph, by two observers. If these observers disagreed, a third observer served as an adjudicator. Overall agreement among observers in the evaluation of progression was 0.91.

Scanning Laser Polarimetry

Patients were imaged using a commercially available scanning laser polarimeter with variable corneal compensation (GDx VCC, software version 5.5.1, Carl-Zeiss Meditec). The general principles of scanning laser polarimetry and the algorithm used for variable corneal compensation have been described in detail elsewhere.[4,6,7] Assessment of GDx VCC image quality was performed by an experienced examiner masked to the subject's identity and results of the other tests. To be classified as good quality, an image required a focused and evenly illuminated reflectance image with a centered optic disc. To be acceptable, the mean image also had to have residual anterior segment retardation $\leq$15 nm and a typical scan score (TSS) $\geq$80.[20]

RNFL retardation measurements were obtained on a 3.2 mm diameter calculation circle around the optic nerve head. Three parameters were calculated from RNFL measures obtained within this calculation circle and used in this study: TSNIT average (average of RNFL measurements obtained on the 360° around the optic nerve [T stands for temporal, S stands for superior, N stands for nasal, and I stands for inferior]), inferior average, and superior average. These parameters are provided on the standard GDx VCC printout. To evaluate changes in GDx VCC RNFL measurements in localized sectors, the calculation circle was also divided into 16 sectors (22.5° each) and the average retardation was recorded for each of these sectors. There were eight sectors for the superior hemiretina and eight sectors for the inferior hemiretina, with sectors numbered in a clockwise fashion and sector S1 corresponding to the most temporal sector of the superior hemiretina. The GDx VCC provides measurements of RNFL retardation, which are converted to estimated RNFL thickness using a fixed conversion factor.

Statistical Analysis

Random coefficient models were used to evaluate the relationship between RNFL thickness measurements over time and progression as determined by SAP or stereophotographs. These models are a type of linear mixed model that involves both random intercepts and random slopes and that takes into account the clustered structure of the data, allowing the residuals associated with the longitudinal measures on the same unit of analysis to be correlated. For the initial model, we assumed progression to have occurred if progression was either observed on stereophotographs or SAP GPA. Subsequently, we constructed separate models for progression occurring with each one of these methods separately. Below we describe in more detail the model used for analysis. Further information on the statistical modeling principles can be found in the literature.[21,22]

GDx VCC RNFL thickness measurements were considered as the dependent variable. Progression as assessed by stereophotographs and SAP was included as a fixed-effect covariate (variable PROG in the model below) with a value of 1 if the eye progressed by stereophotographs and/or SAP and a value of 0 if the eye did not show progression with any of these methods. Time (variable TIME) was included as a continuous predictor. The significance of the coefficients associated with the variable TIME indicates whether there is a significant trend in GDx measurements over time; that is, whether GDx measurements tend to decrease or increase significantly over time. The two-way interaction between TIME and PROG was included in the model to evaluate whether there was a significant difference in longitudinal GDx measurements over time between progressors and non-progressors. Baseline GDx measurements (variable BASELINE) and the interaction

TABLE 1. Baseline Measurements for the GDx VCC Parameters in Eyes That Progressed by Visual Fields and/or Stereophotographs and in Eyes That Remained Stable

	Progressors (n = 34)	Non-progressors (n = 301)	P
TSNIT average	44.2 ± 7.2	49.7 ± 6.5	<0.001
Superior average	51.8 ± 12.5	59.3 ± 10.0	<0.001
Inferior average	50.6 ± 9.0	57.9 ± 9.3	<0.001
S1	26.8 ± 7.7	25.3 ± 7.2	0.273
S2	33.0 ± 9.9	32.2 ± 9.40	0.882
S3	46.9 ± 16.7	51.0 ± 15.7	0.157
S4	57.8 ± 19.0	67.8 ± 16.4	0.001
S5	55.3 ± 16.2	63.7 ± 15.4	0.003
S6	56.7 ± 14.2	64.6 ± 14.4	0.003
S7	44.0 ± 11.9	49.6 ± 13.3	0.019
S8	28.9 ± 6.8	31.3 ± 9.8	0.076
S9	28.3 ± 6.1	31.2 ± 8.9	0.016
S10	45.1 ± 11.2	49.8 ± 14.3	0.062
S11	61.4 ± 13.8	68.2 ± 15.6	0.016
S12	62.0 ± 13.2	69.6 ± 15.1	0.005
S13	54.5 ± 15.1	65.1 ± 14.6	<0.001
S14	42.1 ± 14.0	49.4 ± 15.4	0.009
S15	26.4 ± 7.6	26.8 ± 9.0	0.843
S16	24.1 ± 7.3	22.2 ± 6.7	0.103

term with time (BASELINE × TIME) were included as fixed-effects covariates to evaluate whether there was an influence of baseline measurements on detection of RNFL loss over time with the GDx VCC. The following random components were added to the model: random patient-specific effects associated with both the intercept and slope (i.e., the effect of time) for each patient, random specific effects associated with both the intercept and slope for each eye nested within patient, and random effects associated with the intercept for each visit nested within eye (due to the multiples images acquired on each visit for each eye). The general form of the model for an individual GDx measurement y at visit t (t represents time during follow-up) on eye i nested within patient j (denoted by GDx_{ytij}) is

$$GDx_{ytij} = \beta_0 + \beta_1 \times TIME_{tij} + \beta_2 \times PROG_{ij} + \beta_3 \times TIME_{tij} \times PROG_{ij} + \beta_4 \times BASELINE_{ij} + \beta_5 \times BASELINE_{ij} \times TIME_{tij} + \zeta_{0j} + \zeta_{1j} \times TIME_{tij} + \zeta_{0i|j} + \zeta_{1i|j} \times TIME_{tij} + \zeta_{0|i|j} + \varepsilon_{ytij} \quad (1)$$

where parameters β_0 through β_5 represented the fixed effects associated with the intercept, time, progression, baseline measurements, and their two-way interactions with time; ζ_{0j} and ζ_{1j} were random patient effects associated with the intercept and time slope, respectively; $\zeta_{0i|j}$ and $\zeta_{1i|j}$ were the random effects (intercept and slope, respectively) associated with eye nested within patient; $\zeta_{0t|i|j}$ represented the random effects associated with multiples measures during the same visit or time t; and ε_{ytij} represented the residual.

Random coefficient models were also used to evaluate the relationship between baseline age, race, sex, refraction (spherical equivalent), and axial length with rate of RNFL change over time.

Statistical analyses were performed (STATA v. 10.0; StataCorp, College Station, TX and SPSS v.16.0; SPSS Inc., Chicago, IL). The alpha level (type I error) was set at 0.05.

RESULTS

The study included 335 eyes of 195 patients with a mean ± SD age of 63 ± 12 years. Of the 195 patients, 118 (61%) patients were female. The group consisted of 121 white patients (62%), 70 black patients (36%), and four patients of Asian descent (2%). From the 335 eyes included in the study, 95 (28%) had a diagnosis of glaucoma and 240 (72%) were considered as glaucoma suspects. Median (first quartile, third quartile) MD and PSD of the visual field closest to the baseline imaging test date in glaucomatous eyes were −4.08 dB (−6.44 dB, −2.14 dB) and 3.76 dB (2.57 dB, 7.79 dB). Corresponding values for glaucoma suspect eyes were −0.76 dB (−1.60 dB, −0.04 dB) and 1.62 dB (1.41 dB, 1.88 dB).

From the 335 eyes, 34 (10%) showed progression over time. From the 34 progressing eyes, 14 (41%) progressed only by SAP GPA, 13 (38%) progressed only by optic disc stereophotographs and seven (21%) progressed by both methods. Baseline GDx VCC measurements in progressing and non-progressing eyes are shown on Table 1. Eyes that showed progression with SAP or stereophotos had significantly lower RNFL thickness measurements at baseline than non-progressing eyes for most parameters, except for the sectors related to measurements on the most nasal and temporal locations. Differences in baseline measurements were taken into account and adjusted for in the models used to investigate longitudinal RNFL loss after baseline.

Table 2 shows results of the random coefficient model when applied to investigate changes in the GDx VCC TSNIT average parameter. The model shows a significant decrease in GDx VCC measurements over time for both progressors and non-progressors. However, the rate of decline was significantly higher in the progressing group (−0.70 μm/year) compared to the non-progressing group (−0.14 μm/year). The significant P value (P = 0.001) for the interaction term (β_2; PROG × TIME) indicates that the difference between rates of RNFL loss over time in the two groups was statistically significant. As the non-progressor group was used as reference category (0 in the variable PROG), the coefficient of the variable TIME (β_1) indicates the rate of loss in the non-progressing group (as the interaction term PROG × TIME will be zero). To obtain the rate of loss in the progressing group, it is necessary to add the coefficient β_2 (−0.14 μm/year) to that of the interaction term β_3 (−0.56 μm/year), which results in −0.70 μm/year. Baseline measurements had a significant influence on change over time

TABLE 2. Results of the Random Coefficient Model for the GDx VCC Parameter TSNIT Average

Parameter	Coefficient	Estimate	95% CI	P
Intercept	β_0	0.26	(−0.07–0.60)	0.127
PROG	β_1	0.56	(−0.43–1.56)	0.268
TIME	β_2	−0.14	(−0.26–−0.02)	0.020
PROG × TIME	β_3	−0.56	(−0.90–−0.23)	0.001
BASELINE	β_4	0.99	(0.94–1.04)	<0.001
BASELINE × TIME	β_5	−0.03	(−0.05–−0.02)	<0.001

* The variable TSNIT average was centered on its mean value (50 μm). See text for description of the variables in the model.

TABLE 3. Results of the Random Coefficient Model for the GDx VCC Parameter Superior Average

Parameter	Coefficient	Estimate	95% CI	*P*
Intercept	β_0	0.49	(−0.02–0.99)	0.060
PROG	β_1	0.35	(−1.14–1.84)	0.646
TIME	β_2	−0.20	(−0.37–−0.03)	0.021
PROG × TIME	β_3	−0.61	(−1.07–−0.15)	0.010
BASELINE	β_4	0.98	(0.93–1.00)	<0.001
BASELINE × TIME	β_5	−0.03	(−0.05–−0.02)	<0.001

* The variable superior average was centered on its mean value (58 μm). See text for description of the variables in the model.

in GDx VCC measurements. Higher baseline measurements were associated with greater change over time, whereas lower measurements were associated with smaller changes in GDx VCC measurements over time. This is indicated by the negative coefficient of the interaction term between baseline measurements and time (β_5; −0.03).

Tables 3 and 4 show results for similar models constructed using superior average and inferior average, respectively. The results are similar to the model using TSNIT average. For superior average, the rate of change in progressing eyes was significantly higher than that in non-progressing eyes (−0.81 μm/year vs. −0.20 μm/year, respectively; $P = 0.01$). For inferior average, the rate of change was also significantly higher in progressing eyes compared to non-progressing eyes (−0.90 μm/year vs. −0.16 μm/year, respectively; $P = 0.008$). Figure 1 shows a polar plot illustrating the rates of GDx VCC RNFL measurement changes in progressing eyes according to the sectors around the optic disc. As expected, rates of change were higher on temporal inferior and superior sectors.

Separate models were constructed for eyes progressing by visual fields or stereophotographs only. For eyes progressing only by SAP GPA, the rate of change in TSNIT average was −0.56 μm/year and it was significantly different from that for eyes not detected as progressing by visual fields (−0.14 μm/year; $P = 0.047$). For eyes progressing only by optic disc stereophotographs, the rate of change in TSNIT average was −0.82 μm/year and it was significantly different from that for eyes not detected as progressing by stereophotographs (−0.14 μm/year; $P = 0.001$).

We also investigated whether the diagnosis of glaucoma versus suspect had any influence on the detection of RNFL loss over time with the GDx VCC in progressing eyes. In a model that did not adjust for baseline GDx VCC measurements, glaucomatous eyes that had progression on SAP or stereophotographs tended to have smaller rate of change on TSNIT average (−0.40 μm/year) than eyes that were suspected of having glaucoma at baseline, but showed progression on SAP or stereophotos over time (−0.61 μm/year), although the difference did not reach statistical significance ($P = 0.083$). When adjusted for GDx VCC baseline measurements, there was no statistically significant difference in rates of change between glaucomatous eyes and eyes suspected of having glaucoma that showed progression (−0.68 μm/year vs. −0.71 μm/year, respectively; $P = 0.799$).

Black patients had a significantly higher overall rate of change in the GDx VCC parameter TSNIT Average compared to white patients (−0.31 μm/year vs. −0.03 μm/year; $P = 0.005$). Male patients also had significantly higher overall rate of change for this parameter than females (−0.28 μm/year vs. −0.04 μm/year). This effect was present event after adjustment for baseline age and race. Baseline age, spherical equivalent and axial length had no significant effect on the rate of change of the GDx VCC TSNIT average parameter (*P* values of 0.155, 0.092, and 0.416 for the interaction terms with TIME, respectively).

Figure 2 shows the GDx VCC retardation maps and parameter values during follow-up for an eye that showed progression on optic disc stereophotographs.

DISCUSSION

To our knowledge, this is the first cohort study to report an evaluation of longitudinal RNFL loss with the GDx VCC in glaucoma. Eyes that showed progression by standard methods (i.e., SAP visual fields and optic disc stereophotographs) had significantly higher rates of RNFL loss over time as measured by the GDx VCC compared to eyes that remained stable. These findings may have significant implications for the use of this instrument to evaluate and monitor progression in glaucomatous patients and patients suspected of having the disease.

For the average global RNFL thickness, represented by the parameter TSNIT average, the rate of RNFL loss over time in progressing eyes was five times higher than that in non-progressing eyes. The rates of RNFL loss with GDx VCC in progressing eyes were particularly higher in the inferior temporal and superior temporal sectors, which is in agreement with the expected pattern of RNFL and neuroretinal rim loss in glau-

TABLE 4. Results of the Random Coefficient Model for the GDx VCC Parameter Inferior Average

Parameter	Coefficient	Estimate	95% CI	*P*
Intercept	β_0	0.41	(−0.10–0.92)	0.113
PROG	β_1	0.38	(−1.22–1.98)	0.643
TIME	β_2	−0.16	(−0.35–0.03)	0.096
PROG × TIME	β_3	−0.74	(−1.29–−0.20)	0.008
BASELINE	β_4	0.98	(0.92–1.03)	<0.001
BASELINE × TIME	β_5	−0.03	(−0.05–−0.01)	<0.001

* The variable Inferior Average was centered on its mean value (57 μm). See text for description of the variables in the model.

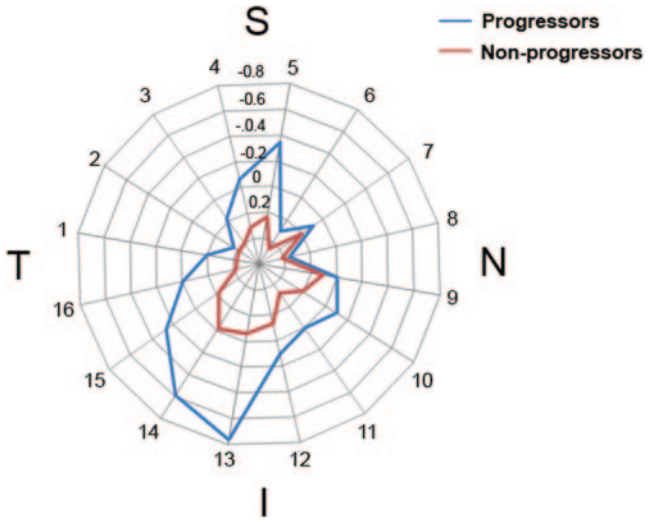

FIGURE 1. Polar plot illustrating the rate of change in GDx VCC retinal nerve fiber layer (RNFL) measurements according to the sectors around the optic disc. Eyes that showed progression on visual fields and/or optic disc stereophotographs had greater loss of the RNFL in the inferior temporal and superior sectors.

coma.[23] It is interesting to note that eyes that were not detected as progressing by SAP or optic disc stereophotographs also had a statistically significant decline in GDx VCC RNFL measurements over time. This could potentially represent progressive glaucomatous damage that was not detected by the conventional methods. In fact, there is some evidence that there can be observed changes in the RNFL before the optic nerve or visual fields.[24] On the other hand, the decline in GDx VCC measurements over time in non-progressing eyes could also represent age-related loss of the RNFL. Using the GDx VCC, Da Pozzo et al.[25] imaged 384 eyes of 384 healthy subjects and estimated an age-related loss of 0.08 μm/year in the average RNFL thickness. These estimates are somewhat lower than the rate of decline found in our study for non-progressing eyes, and could support the hypothesis that some of these eyes actually had glaucomatous progression not detected by conventional methods. However, the estimates from Da Pozzo et al.[25] are derived from a cross-sectional study and suffer from the limitations introduced by between-subject variability. No longitudinal study has yet been performed estimating the age-related loss of RNFL with the GDx VCC.

The rate of GDx VCC RNFL loss in progressing eyes was lower for eyes that had lower values of baseline GDx VCC measurements. This seems to indicate that the GDx VCC is more sensitive to detect progression during early stages of the disease. In patients with advanced glaucomatous damage, the instrument would be less sensitive to detect deterioration. In fact, when the models were not adjusted for baseline RNFL measurements, eyes with glaucomatous visual field defects at baseline that had progression on SAP or stereophotographs tended to have smaller rates of change than eyes that were suspected of having glaucoma at baseline and showed progression on SAP or stereophotos over time. This effect could be inherent to the GDx VCC and represent a floor effect for detection of RNFL loss with this instrument. Alternatively, it could reflect the natural history of progression in glaucoma, with greater detectable rates of RNFL loss in the earlier stages of disease. This seems to be supported by a model relating structure and function in glaucoma proposed by Hood and colleagues.[26] According to this model, changes in the RNFL would be better detected in patients without advanced visual field loss. It is important to emphasize, however, that RNFL estimates in the Hood et al.[26] model were obtained by an imaging technology (optical coherence tomography) and probably incorporate limitations inherent to this technology for assessment of the RNFL.

In our study, both SAP visual fields and optic disc stereophotographs were used to assess progression. Recent results from several clinical trials have indicated that both structure and function should be used to monitor patients over time. In the Ocular Hypertension Treatment Study,[2] 55% of the patients with ocular hypertension that converted to glaucoma showed a change first in optic disc photographs, whereas in 35% of the cases changes were seen first on the visual fields, and in 10% of the cases, changes were seen in both tests at the same time. In our study, we also found that a small proportion of eyes progressed by both methods at the same time (21%), whereas 41% progressed only by SAP GPA and 38% progressed only by optic disc stereophotographs. To evaluate whether there was a difference in the rate of RNFL loss in patients progressing by visual fields or optic disc, we also conducted analysis separately for patients progressing by each method. In both cases, the rates of change in RNFL over time were statistically significant. However, the rates of GDx VCC RNFL change tended to be higher for eyes progressing by stereophotos compared to visual fields, which is probably explained by a higher correlation between two structural tests compared to the correlation between a structural and a functional test.

We found significantly higher rates of change for GDx VCC parameters in black patients compared to white patients, which is in agreement with previously reported higher rates of progressive disease in that racial group.[27,28] In the Collaborative Initial Glaucoma Treatment Study (CIGTS), nonwhite patients (85.6% of whom were black) had a 50% increased risk relative to white patients of experiencing visual field progression from baseline, irrespective of treatment.[28] We also found that males had significantly higher rates of RNFL loss than females. Although a few populational studies have suggested that glaucoma is more prevalent in males than females,[29–31] other studies have reported opposite findings.[32] In the OHTS, male sex was a significant risk factor for progression from ocular hypertension to glaucoma, but only in univariate analysis.[33] It is important to note, however, that the confidence interval for the hazard ratio of sex in the OHTS multivariate analysis was large and reflects a possible lack of power of the study to evaluate this issue. Further studies are necessary to clarify the controversial relationship between sex and glaucoma damage.

We used statistical models to evaluate whether the GDx VCC was able to detect longitudinal change in the RNFL of eyes with progressive disease detected by conventional methods. The positive findings of our study should be seen as an initial step toward validation of this technology for monitoring glaucoma. However, future research should evaluate methods for detecting progressive damage on the GDx VCC that could be incorporated into clinical practice. These methods should be able to detect progression in individual patients taking into account the expected variability over time. One such method, the GDx Guided Progression Analysis Software (GDx GPA) has been recently released commercially. Studies will be necessary to evaluate the agreement between GDx GPA and standard methods to evaluate progression. Also, for patients progressing by GDx and not by standard methods, it will be important to determine whether the progression detected by the GDx has clinical relevance in terms of the outcome of these patients.

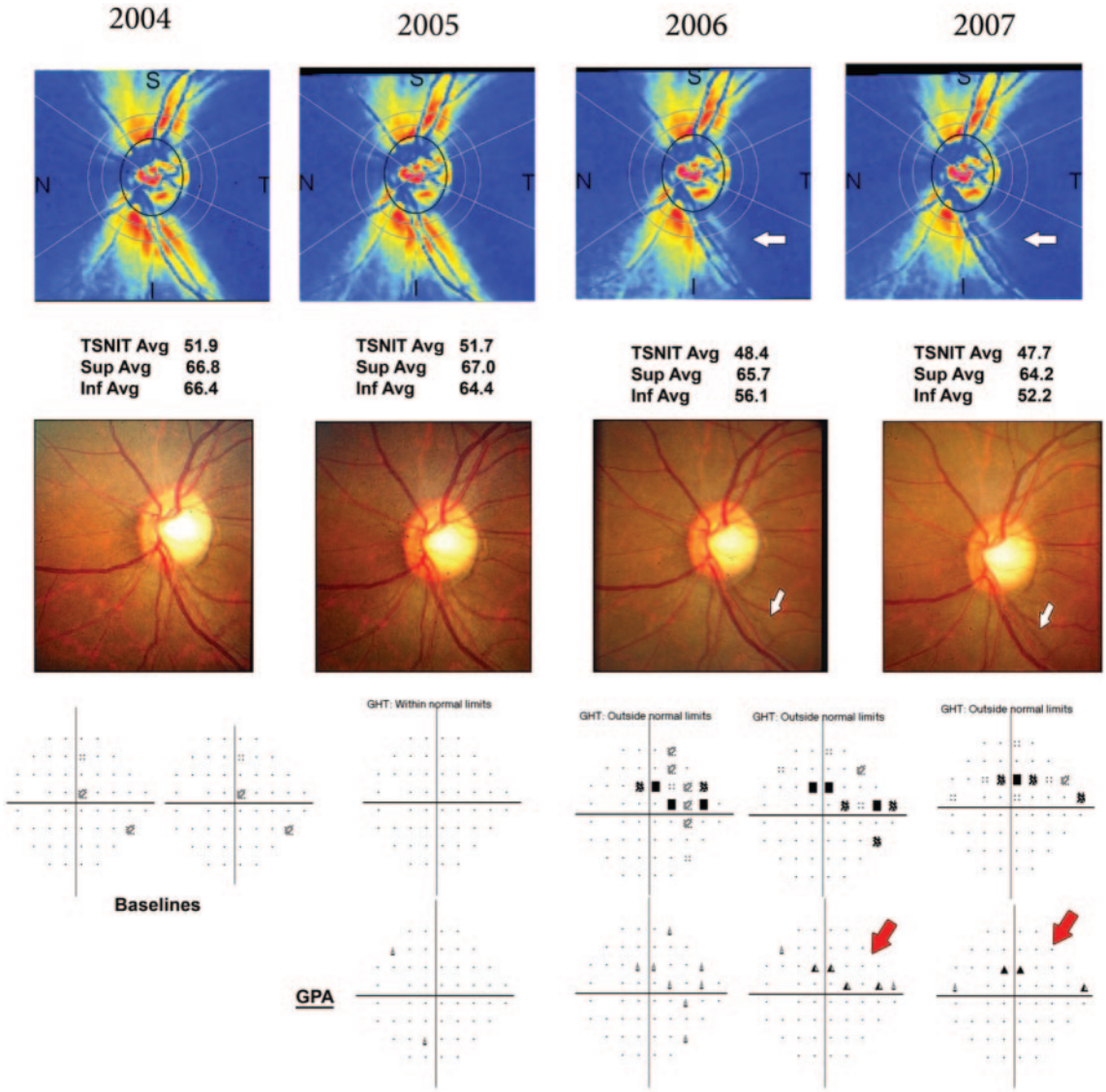

FIGURE 2. GDx VCC measurements in an eye that showed progression on optic disc stereophotographs. The optic disc photographs (*middle row*) show progressive development and enlargement of an inferior temporal localized retinal nerve fiber layer defect. The standard automated perimetry Guided Progression Analysis (SAP GPA; *bottom row*) shows corresponding progression on the superior nasal portion of the visual field; however, as only two points showed repeatable change by this method, it was not sufficient to be flagged as likely progression. The GDx VCC retardation maps (*upper row*) show progressive loss of the RNFL in the inferior temporal location. The inferior average parameter decreased by approximately 14 μm from 2004 to 2007.

In conclusion, the GDx VCC scanning laser polarimeter was able to identify longitudinal RNFL loss in eyes that showed progression in optic disc stereophotographs and/or visual fields. These findings suggest that this technology could be useful to detect and monitor progressive disease in patients with an established diagnosis of glaucoma or suspected of having the disease.

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