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Detection of retinal Nerve Fiber Layer Progression: Comparison of the Fast and Extended Modes of GDx Guided Progression Analysis

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Abstract

Purpose—To compare detection of retinal nerve fiber layer (RNFL) changes using GDx Guided Progression Analysis (GPA) fast mode (which assumes fixed variability of a reference population) and extended mode (which measures individual variability) and to determine how they compare to photography and visual field based conventional methods for identifying glaucoma progression.

Methods—172 eyes from 117 participants in the Diagnostic Innovations in Glaucoma Study (DIGS) (12 healthy, 108 glaucoma suspect and 52 glaucoma eyes) with 4 GDx VCC visits and 3 good quality GDx VCC scans at each visit were included. Results: Agreement between the GDx GPA fast mode and GDx GPA extended mode was limited. The GDx fast mode and extended mode detected 15 and 18 eyes, respectively as “likely progression” but only 7 of them agreed. The conventional reference standard (stereophotograph based optic disc and/or visual field progression) identified 9 eyes as progressing of which 2 eyes were also identified by the GDx fast and 3 eyes by the extended mode. In the GDx fast mode, we found that the progression detection varies depending on which 2 scans are included in the baseline and follow-up images. Conclusion: There was limited agreement between the GDx fast mode and the GDx extended mode for progression detection, and between different scans included in the GDx fast mode progression analysis. Longer follow-up is needed to determine the proportion of eyes classified as “likely progression” by the GDx analysis that are early change and the proportion that are false positive results.

Keywords

glaucoma; imaging; diagnostic tests/investigation

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Introduction

Over the last decade, imaging instruments have been studied and employed for glaucoma diagnosis and optic disc and RNFL progression detection.¹⁻⁹ One of these instruments, the scanning laser polarimeter (SLP, GDx VCC, Carl Zeiss Meditec Inc.) has been shown to be effective in differentiating between glaucomatous and healthy eyes.^{10, 11, 12} Recently, the rate of RNFL change measured with the GDx VCC has been shown to be faster in eyes progressing by visual field and stereophotographs than in eyes that remain stable.¹³ Although this study showed that the GDx RNFL measurements can be used to measure the rate of RNFL change in groups of eyes, evaluation of tools to assess progression in individual patients in clinical practice is still needed.

The GDx now includes a new software algorithm, the Guided Progression Analysis (GPA) for detecting glaucoma progression. GPA uses two different modes, the “fast mode” and the “extended mode” to compare follow-up to baseline images to determine the likelihood of progression. An advantage of the extended mode is that it uses measured variability from the 3 scans of an individual's eye. In contrast, the fast mode uses variability from an external cohort to compare the two baseline scans with the final two follow-up scans. It has been shown that the GDx “fast mode” detected glaucoma progression in a significant number of eyes showing progression by conventional methods.¹⁴ Based on these results, the authors suggested that the GDx fast mode could be used to complement clinical evaluation in detection of glaucoma progression.¹⁴ The aim of the current study was to compare the agreement in detection of glaucoma progression between the GDx GPA fast mode and GDx GPA extended mode, and to determine how they compare to conventional methods for detecting glaucoma progression.

Methods

Participants included in this prospective study were enrolled from the Diagnostic Innovations in Glaucoma Study (DIGS). Participants gave written informed consent and all methods were approved by the University of California, San Diego (UCSD) Human Subjects Committee.

All participants met DIGS inclusion and exclusion criteria; best corrected acuity worse than 20/40, spherical refraction within ± 5 D, cylinder correction within ± 3 D, good quality optic disc stereophotographs and reliable SITA standard automated perimetry (SAP) 24-2 tests ($\geq 33\%$ fixation losses, false negatives and false positives).^{13, 15} Ophthalmologic examinations and testing were completed annually and participants excluded if they no longer met inclusion criteria.^{13, 15}

Subjects were required to have at least 4 GDx VCC visits with 3 good quality scans at each visit so that the GDx extended mode could be calculated.

Diagnostic Classification

All patients with at least 2 repeatable abnormal SAP at baseline were classified as glaucomatous. Abnormal visual fields were defined as a PSD with $P < 0.05$ or a Glaucoma Hemifield Test “outside normal limits”. The glaucoma suspects did not have abnormal baseline SAP visual fields but had at least one of the following indications in at least one eye: glaucomatous optic disc appearance based on masked review of stereophotographs by 2 experienced graders, elevated IOP (> 21 mmHg), or were under treatment with IOP lowering medication.

Individuals classified as normal were recruited from the general population through advertisement, as well as from UCSD staff. All normal participants had no abnormal clinical, optic disc photography and SAP findings in both eyes, and no history of increased IOP.

The definition of “likely progression” as defined by the SAP GPA (a significant decrease from baseline pattern deviation of 3 identical test points on 3 consecutive tests) was used.¹⁶ All progression cases were evaluated by a masked glaucoma specialist and did not show evidence of artifacts or non-glaucomatous progression.

Baseline simultaneous stereoscopic optic disc photographs were graded as glaucomatous or normal based on the presence or absence of neuroretinal rim thinning, RNFL thinning, or cupping characteristic of glaucoma. To detect progressive glaucomatous optic neuropathy, the photographs closest (within 1 year) to the baseline and last GDx date were reviewed by two experienced masked graders for evidence of progressive glaucomatous change (neuroretinal rim or RNFL thinning, or increased cupping). In cases of disagreement, a third observer adjudicated the decision.

Instrumentation

Scanning Laser Polarimetry—Images were acquired with the GDx VCC (software version 5.0) and analyzed with the GDx GPA algorithm (software version 6.0).

The GDx GPA report uses color-coded checkmarks in the summary box to display results of 3 different progression detection methods. When significant change is detected, “Possible progression” (yellow checkmark) is flagged, when change is confirmed in two consecutive exams “Likely progression” (red checkmark) is flagged. An increase in RNFL is reported as “Possible increase” (purple checkmark).

Eyes flagged as “likely progression” in at least one of the 3 maps were considered progressing.

1. The Image Progression Map, designed to be sensitive to focal RNFL loss, displays a fundus image with color-coded areas showing RNFL change compared to the two baselines. At least 150 adjacent points clusters must show statistically significant change for the map to flag progression,
2. The TSNIT (temporal, superior, nasal, inferior, temporal) Progression Graph, designed to be sensitive to broader focal change, plots RNFL thickness around the optic disc with the most recent examination in red. Statistically significant change in 4 adjacent segments from the calculation circle (from a total of 64 segments) are required for the map to flag progression.
3. The Summary Parameter Charts, designed to be most sensitive to diffuse change, plots three parameters over time, TSNIT Average, Superior Average and Inferior Average. If there is a significant linear trend ($p < 0.05$) a regression line is drawn and the rate of change is displayed in micrometers/year.

The GDx GPA has two different methods for detecting “statistically significant” change, the fast and extended mode. Fast mode requires only single images from each visit, while the extended mode requires at least 3 images from each visit. In the fast mode, the observed change is compared to variability derived from an independent outside sample population. In the extended mode, the observed change is compared to the test-retest variability measured on that same eye.

The “Change From Baseline” algorithm, which is used in all fast mode maps and in the “Image Progression Map” for the extended mode, is an event-based algorithm that compares change from the mean of the two baselines to measurement variability. The “Change from Baseline” algorithm uses only the first two visits and last two visits to determine change and is most sensitive when the variability between the two baselines is small. The fast mode can detect the earliest changes only after the third test; the first two are used for defining the average baseline value and the third test is compared to this measurement. In contrast, the trend based algorithm, “Statistical Image Mapping” used in the “TSNIT Progression Graph” and “Summary Parameter Chart” of the extended mode has the advantage that all visits contribute to determining whether change is significant.

Eligible subjects were included based on the ability to run the extended mode (i.e. subjects had 3 good quality images from 4 different visits). We only used images that were evenly illuminated, well focused, centered and with quality score 7 or higher. Scans with poor registration, standard deviation > 11.5 and typical scan score (TSS) <80 were excluded. Scans with TSS $\geq$ 80 have been shown to have minimal atypical retardation profiles.^{17, 18} TSS provides a measure of how typical the RNFL image is and ranges from 0 (very atypical) to 100 (very typical). To ensure comparability of the analysis we included the same baseline and follow up dates for each method.

Since 3 GDx scans were acquired at each visit, we were able to analyze whether the choice of scans could influence the GDx GPA fast mode results. Specifically, the fast mode uses 2 scans for the baseline and 2 for the last follow-up examination. To compare GDx GPA fast mode results using different scan combinations, we interchanged the scans included in the baseline and the last follow-up and ran the analysis three ways, using first and second scans acquired (scans 1 and 2), scans 2 and 3 and scans 1 and 3, respectively.

Statistical analysis

Statistical analysis was performed using JMP (version 8.0.1; SAS Institute Inc., Cary, NC). Random effects models were used to estimate differences in the change in GDx measurements in progressing and non-progressing eyes to account for the lack of independence between eyes.

Results

We included 172 eyes (108 glaucoma suspect eyes, 52 glaucoma eyes and 12 healthy eyes) from 117 individuals. 70 (60%) individuals were female. Most participants were Caucasian (78 (67%)) or African-American (36 (31%)). Table 1 shows the baseline demographic information, visual field indices and GDx RNFL parameters for participants at study entry.

The GDx fast mode detected 15 eyes as “likely progression” and the GDx extended mode detected 18, but only 7 of them agreed. Two of the fast mode progressing eyes and three of the extended mode progressing eyes agreed with the conventional reference standard (Figure 1). Overall agreement for detection of progressing and non-progressing eyes between the conventional methods and the GDx fast mode and the extended mode was observed in 152/172 (88.4%) and 151/172 (87.8%), respectively. Overall agreement between the fast and the extended mode was 153/172 (89.0%). The number of eyes identified as progressing by the Image Progression Map, TSNIT Progression Map, and Summary Parameter Chart for the GDx fast mode was 3, 9 and 10, respectively, and for the GDx extended mode was 8, 10 and 10, respectively.

We also evaluated the number of false positives in the group of the 12 healthy eyes (12 subjects) that were followed for an average of 38 (95% CI, 29–47) months. None of the

healthy eyes showed progression by the fast mode while one eye showed progression by the extended mode.

In the GDx fast mode, we found that progression detection varies depending on which 2 scans are included in the baseline and follow-up analysis (Figure 2). We evaluated 3 possibilities, using the first and second scan (scans 1 and 2), using the second and third scan (scans 2 and 3) and using the first and third scan (scans 1 and 3). Of the total 25 eyes flagged with “likely progression” using either scan combination, only 8 (32%) eyes were identified by all three combinations. The change in RNFL parameters over time is presented in Table 2. We found consistent significantly larger RNFL change in progressing eyes compared to non-progressing eyes as defined by GDx fast mode and GDx extended mode (most p-values 0.002), but not when progression was defined by conventional methods (most p-values 0.05).

Figure 3 presents three different case examples illustrating agreement between the GDx fast and extended mode in eyes without SAP and stereophotographs progression. In Figure 3a, the fast mode reports “likely progression”, whereas the extended mode does not. Figure 3b shows the extended mode detecting “likely progression”, but the fast mode does not and Figure 3c shows both modes showing “likely progression”.

Discussion

We found limited agreement between the GDx fast mode and the GDx extended mode for progression detection (Figure 1). In addition, our results suggest that the GDx fast mode results can vary depending on the scans selected for analysis in the baseline and the last follow-up examinations. To our knowledge, this is the first report comparing progression detection using the fast and extended mode, and also the first assessing the effect of scan selection on GDx fast mode progression detection.

There are several possible explanations for the limited agreement between the GDx fast and extended modes for detecting glaucoma progression. First, the method for calculating the variability differs between the two modes. The GPA extended mode is based on the measured variability of an individual's scans, while the GPA fast mode is based on a fixed variability using an outside reference population. Therefore, if an eye has higher measurement variability than the average variability of reference population used in the fast mode, the fast mode might detect progression whereas the extended mode may not. Conversely, if an eye has lower variability than the reference population, the fast mode might not detect change while the GDx extended mode may identify progression.

The fast and the extended mode of the GDx each have their advantages and limitations. An advantage of the fast mode is that fewer scans are required at each visit, so image acquisition is less time consuming than the extended mode. If three scans are not available at each visit, then only the GDx fast mode can be calculated. Limitations of the fast mode include its dependence at least in part on which scans were included in the analysis (Figure 2). In addition, GDx change algorithms (both modes) do not account for RNFL loss due to aging. Aging changes should be considered when interpreting any automated change detection method. The lack of objective interpretation of photographs and the variability of visual field results are among the limitations of conventional methods for progression detection.

We also found limited agreement between both GDx GPA modes and conventional methods for detecting glaucoma progression. Other investigators have also reported limited agreement between the GDx fast mode and stereophotograph or visual field based progression detection methods, and between other imaging techniques and conventional methods for progression detection.¹⁹⁻²⁴ One explanation is that RNFL loss might be

preceded by changes in birefringence from alterations of the cytoarchitecture of RNFL and that the SLP might detect birefringence changes before change in RNFL thickness can be detected.²⁵ This may at least in part explain why the GDx GPA software detects some progressing eyes that are not detected with stereophotograph or visual field assessment and why RNFL parameter changes do not differ between progressing and non-progressing eyes as defined by conventional methods. One study¹⁹ reported better agreement between GPA fast mode and conventional methods (50%) than the current study (22%). Possible explanations for this inconsistency include longer length of follow-up and larger sample size than the current study.

Even though the SLP is available for almost a decade, assessment of progression is difficult because hardware and software improvements have made current scanning protocols incompatible with earlier scans for automated change detection. The newest SLP version, the GDx ECC with enhanced corneal compensator^{13, 27} reduces atypical retardation patterns (ARPs) measured by TSS.^{18, 28, 29} The ability of SLP to discriminate between healthy and glaucomatous eyes has been shown to decrease when ARPs are present.^{6, 17, 30} Moreover, ARPs are not necessarily stable over time,¹⁸ and can therefore either mask true progressing eyes (if ARP increases over time) or cause the GPA to detect false progression (if ARP decreases over time). However, this same study suggests that GPA GDx VCC can be used to detect progression in eyes with minimal ARP. Since we limited our analysis to scans with TSS ≥ 80 , and the baseline TSS in this study was high, with mean (95% CI) TSS score was 96.1 (95.2, 99.0) we believe the influence of change in TSS on progression detection is unlikely.¹⁸

In summary, we found limited agreement between the GDx fast and extended mode, and between both GDx modes and conventional methods for progression detection in glaucoma suspects and early to moderate glaucoma patients. Moreover, we found that fast mode results can vary depending on which scans are used in the baseline and the last follow-up examination. Each of the two GDx GPA modes have their strengths and limitations and should be used with visual field testing and a thorough clinical examination for patient management decisions.^{3, 26, 31}

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Figure 1.

Venn diagram showing agreement between the GDx VCC GPA extended mode, GDx VCC GPA fast mode and conventional methods of change detection by standardized photographic and visual field assessment.

Figure 2.

Venn diagram showing agreement between using different individual scans in the baseline and follow up of the GDx VCC GPA fast mode analysis. Using scans 1 and 2, scans 1 and 3, and scans 2 and 3 identified different eyes as “likely progression”.

Figure 3a.

Print out of the fast mode (left) and extended mode (right) results for the left eye of a 61-year-old male glaucoma suspect with normal visual fields and photographs at baseline. The fast mode reports “likely progression” in the “Summary Parameter Charts”, whereas the extended mode does not. No progression was found based on GPA analysis of the visual fields or by standardized assessment of stereophotographs.

Figure 3b.

Print out of the fast mode (left) and extended mode (right) results for the right eye of a 54 year old male glaucoma patient with glaucomatous appearing optic disc and visual fields at baseline. The “Extended Mode” print out indicates “likely progression” in the “TSNIT Progression Graph”, but the fast mode does not. No progression was found based on GPA analysis of the visual fields or by standardized assessment of stereophotographs.

Figure 3c.

Print out of the fast mode (left) and extended mode (right) results for the right eye of a 51-year-old female glaucoma suspect with glaucomatous appearing optic disc and normal visual fields at baseline. Both the “Fast Mode” print out and the “Extended Mode” print out show progression. The “Fast Mode” (left) shows progression in the “Image Progression Map”, “TSNIT Progression Graph” and the “Summary Parameter Charts”. The “Extended Mode” shows “Likely Progression on the “TSNIT Progression Graph” only.

Table 1

Demographics and Clinical Characteristics, Based on the Diagnostic Classification at Baseline, for 172 Eyes of 117 Study Participants.*

	Healthy 12 eyes	Suspects 108 eyes	Glaucomatous 52 eyes
Progression by:			
Conventional methods	0(0%)	2(2%)	7(13%)
Visual field	0	0	5
Optic disc	0	2	2
GDx GPA Fast mode	0(0%)	11(10%)	4(8%)
GDx GPA Extended mode	1(8%)	13(12%)	4(8%)
Both GDx GPA Fast and Extended Mode	0 (0%)	6 (6%)	1 (2%)
Follow-up (months) Median (1st, 3 th quartile)	33.5 (30.8 – 53.5)	40.9 (34.7 – 60.0)	40.0 (33.6 – 57.8)
Age at baseline (years) Median (1st, 3 th quartile)	65.5 (51.3 – 74.9)	60.6 (51.9 – 68.6)	66.2 (55.7 – 70.2)
Baseline GDx Fast mode			
NFI	19.7 (16.2 – 23.1)	23.9 (21.8 – 26.0)	39.1 (33.3 – 44.9)
TSNIT Average (μm)	54.0 (52.2 – 55.7)	51.0 (50.0 – 52.1)	46.7 (44.0 – 48.3)
Superior Average(μm)	64.5 (61.4 – 67.6)	60.9 (59.3 – 62.5)	54.2 (50.8 – 57.6)
Inferior Average (μm)	64.7 (61.5 – 67.8)	59.5 (58.0 – 61.0)	52.8 (49.8 – 55.8)
TSNIT Std. Deviation (μm)	24.8 (22.0 – 27.7)	21.2 (20.4 – 22.1)	19.1 (17.3 – 20.8)
Baseline GDx Extended mode			
NFI	19.9 (16.6 – 23.3)	24.1 (22.1 – 26.2)	39.2 (33.6 – 44.8)
TSNIT Average (μm)	53.2 (51.5 – 54.9)	50.5 (49.5 – 51.6)	45.7 (43.6 – 47.7)
Superior Average(μm)	63.9 (60.4 – 67.5)	60.7 (59.1 – 62.3)	53.8 (50.5 – 57.0)
Inferior Average (μm)	63.8 (61.0 – 66.6)	59.2 (57.8 – 60.7)	52.3 (49.4 – 55.1)
TSNIT Std. Deviation (μm)	24.9 (22.2 – 27.6)	21.2 (20.4 – 22.0)	18.5 (17.0 – 20.0)
Typical scan Score	97.3 (95.0 – 100.0)	96.3 (95.2 – 97.4)	95.2 (93.6 – 96.9)
Baseline Visual Field			
MD median dB (Quartiles)	–1.02 (–3.87, –0.30)	–0.71(–1.67, 0.00)	–2.70 (–5.10, –1.71)
PSD Median dB (Quartiles)	1.56 (1.47, 2.17)	1.56 (1.32, 1.79)	3.05 (2.12, 6.26)
Baseline stereophotographs			
Glaucomatous optic neuropathy	0 (0%)	31 (28.7%)	34 (65.4%)

GPA = Guided Progression Analysis; NFI = nerve fiber indicator; TSNIT = temporal superior nasal inferior temporal; MD = mean deviation; PSD = pattern standard deviation.

* Unless otherwise specified, results are given as mean (95% confidence intervals).

Table 2

Change in RNFL Parameters during the Follow-up Time, Stratified by the Method that Detected Progression.*

	Conventional methods			GDx Fast mode			GDx Extended mode		
	Progression	Not progression	p	Progression	Not progression	p	Progression	Not progression	p
Eyes (n)	9	163		15	157		18	154	
GDx Fast mode: Difference from baseline									
NFI	4.1 (−6.3 – 14.6)	0.7 (−0.45 – 1.8)	0.257	6.7 (−0.9 – 14.4)	0.3 (−0.8 – 1.4)	0.004	8.4 (4.1 – 12.7)	−0.01 (−1.2 – 1.2)	<0.001
TSNIT av. (μm)	−1.0 (−4.7 – 2.8)	−0.3 (−0.8 – 0.2)	0.688	−3.8 (−6.8 – −0.8)	0.0 (−0.5 – 0.5)	<0.001	−4.0 (−5.8 – −2.1)	0.1 (−0.4 – 0.6)	<0.001
Superior av.(μm)	−2.5 (−8.1 – 3.1)	−0.5 (−1.2 – 0.2)	0.227	−5.0 (−9.7 – −0.3)	−0.2 (−0.8 – 0.4)	0.0005	−5.0 (−8.3 – −1.9)	0.0 (−0.8 – 0.6)	<0.001
Inferior av.(μm)	−0.8 (−4.5 – 3.0)	−0.1 (−0.9 – 0.6)	0.971	−4.2 (−8.6 – −0.2)	0.2 (−0.5 – 0.9)	0.004	−4.9 (−6.9 – −2.9)	0.4 (−0.4 – 1.2)	<0.001
TSNIT S.D. (μm)	−1.0 (−4.7 – 2.8)	−0.3 (−0.8 – 0.2)	0.687	−3.8 (−6.8 – −0.8)	0.0 (−0.5 – 0.5)	<0.001	−4.0 (−5.8 – −2.1)	0.1 (−0.4 – 0.6)	<0.001
GDx Extended mode: Difference from baseline									
NFI	7.9 (−1.5 – 17.3)	1.2 (0.2 – 2.2)	0.007	7.6 (0.8 – 14.4)	1.0 (0.1 – 1.9)	<0.001	7.4 (4.1 – 13.3)	0.7 (−0.2 – 1.7)	<0.001
TSNIT av. (μm)	−1.8 (−5.0 – 1.5)	−0.2 (−0.7 – 0.2)	0.184	−3.4 (−6.2 – −0.7)	0.0 (−0.4 – 0.4)	<0.001	−3.6 (−5.6 – −1.7)	0.1 (−0.3 – 0.5)	<0.001
Superior av.(μm)	−3.4 (−8.4 – 1.5)	−0.6 (−1.2 – 0.1)	0.050	−5.0 (−9.2 – −0.7)	−0.3 (−0.9 – 0.2)	<0.001	−5.5 (−8.4 – −2.6)	−0.2 (−0.8 – 0.4)	<0.001
Inferior av.(μm)	−2.3 (−5.5 – 1.0)	−0.1 (−0.7 – 0.6)	0.203	−3.9 (−7.4 – −0.5)	0.2 (−0.4 – 0.8)	<0.001	−4.1 (−6.3 – −2.0)	0.3 (−0.4 – 0.9)	<0.001
TSNIT S.D. (μm)	−1.5 (−3.6 – 0.6)	−0.4 (−0.9 – 0.0)	0.294	−1.9 (−5.0 – −1.1)	−0.4 (−0.4 – 0.0)	0.064	−2.6 (−3.9 – −1.3)	−0.3 (−0.7 – 0.2)	0.002

NFI = nerve fiber indicator, TSNIT = temporal superior nasal inferior temporal, S.D. = standard deviation.

p-values represent the statistical significance of the difference between the parameters of the progressors and non-progressors diagnosed with each method determined by mixed effects models controlling for lack of independence between eyes.

* Unless otherwise specified, results are given as mean (95% confidence intervals).