Patterns of Glaucomatous Visual Field Progression Identified by Three Progression Criteria

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• PURPOSE: **To determine typical patterns of repeatable glaucomatous visual field progression.**
• DESIGN: **Retrospective analysis of data obtained from two prospective studies.**
• METHODS: **Included were 72 eyes of 72 patients tested up to six times over 2 years, and 40 eyes of 40 patients followed annually for up to 12 years. Each patient had two abnormal baseline visual fields, abnormal optic nerves, and serial fields. Progression was identified using three methods: by glaucoma change probability using total deviation (GCP-TD) and pattern deviation (GCP-PD) plots and by a clinical criteria. Progression was categorized as deepening or expansion of an existing scotoma, or a new scotoma.**
• RESULTS: **The percentage of eyes repeatably progressed ranged from 17% to 27%. The most common pattern of progression was a deepening of an existing scotoma in the annual group, followed by expansion. With two follow-ups required, percentages for deepening only were 20% (clinical classifier). A combination of expansion and deepening was most common for the GCP criteria: 15% (GCP-TD classifier), and 10% (GCP-PD classifier) for the annual group. For the semiannual group, deepening was most common with the clinical criteria (11% of eyes), and deepening with expansion was most common by GCP criteria (14%, GCP-TD and GCP-PD). No eyes showed repeatable new scotomas.**
• CONCLUSIONS: **Glaucomatous visual fields progress in the area of the visual field where baseline testing showed an existing scotoma. Follow-up testing might be improved by concentrating on already defective locations and using sparser test patterns or screening algorithms in normal areas of the visual field. (Am J Ophthalmol 2004;138: 1029–1036. © 2004 by Elsevier Inc. All rights reserved.)**

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THE ACCURATE IDENTIFICATION OF TRUE GLAUCOMATOUS progression is an ongoing challenge in glaucoma clinical practice and research. Identifying progression by functional means is difficult because visual fields that appear to have deteriorated over a period of follow-up may improve at subsequent visits. Separating true progression from fluctuations in visual field results due to learning effects, fatigue, changes in the physiologic state of the eye, and the long-term fluctuation inherent in the test is extremely difficult.[1–3]

It is well recognized that identification of a visual field defect requires comparison of patient results to a large well-defined normative population. Taking into account age-related changes to normal vision improves the detection of field abnormalities. Perimetry is used both to identify abnormal fields and to assess deterioration of vision during the course of follow-up care. It has been accepted practice to use the same testing strategy and pattern of test locations for both defect identification and monitoring progression regardless of qualitative findings that progression tends to occur in areas damaged previously.[4] Monitoring progression of vision loss may be better served by focusing on regions of the field at high risk for progression. Mikelberg and Drance[4] showed that visual field defects tend to deepen over time, more so than emerging in a new location in the field. Several multicentered clinical trials sponsored by the National Eye Institute have developed their own progression algorithms for use with different patient populations. These include the Ocular Hypertension Treatment Study (OHTS),[5] the Early Manifest Glaucoma Trial study (EMGT),[6] the Advanced Glaucoma

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Intervention Study (AGIS),[7] and the Collaborative Initial Glaucoma Treatment Study (CITGS).[8]

To our knowledge, patterns of visual field progression have not been systematically evaluated with automated perimetry. We sought to confirm Mikelberg and Drance's finding using automated perimetry with current progression algorithms.[9] In this study, we used three algorithms for identifying change in visual fields (EMGT criteria, Glaucoma Change Probability (GCP) of the Statpac 2 software on the Humphrey Visual Field Analyzer, and clinical criteria) to determine where progression was most likely to occur. Two criteria were selected because they are clinically available (clinical criteria and GCP–total deviation [TD]). GCP–pattern deviation (PD) is a modification of the GCP available on the Humphrey Visual Field Analyzer and is thought to be less susceptible to diffuse depression of the visual field over time due to factors such as cataract. Our goal was to identify the mode of progression (deepening, expansion, new scotoma) rather than to compare progression algorithms.

METHODS

Subjects. Included in this analysis of serial visual fields were 112 eyes of 112 patients with glaucoma. The study

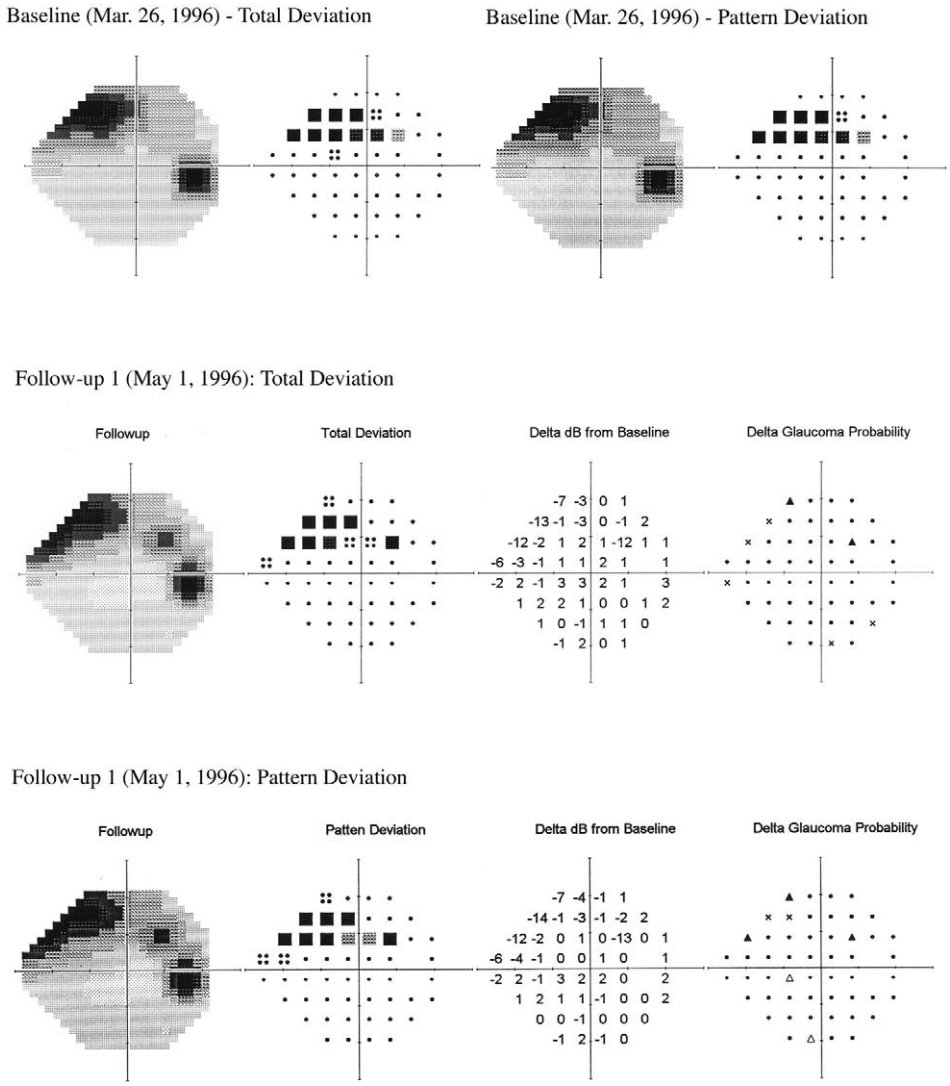

FIGURE 1. Results of the glaucoma change probability (GCP) analysis for one glaucoma patient's right eye. The gray-scale and probability plots from one of the two baseline fields is shown on the top row. The baseline based on total deviation (TD) are shown top row left and the comparable baseline based on pattern deviation (PD) are shown top row right. The second row (total deviation) and third row (pattern deviation) show the results of the GCP for this patient's first follow-up visual field. Visual field locations with significant change for the worse (filled triangles) and points with significant improvement (open triangles) are plotted by the GCP. Points that deteriorate or improve near the limits of the dynamic range of the instrument so change is difficult to judge are marked with an x. The change for the worse occurs as a deepening of the existing scotoma.

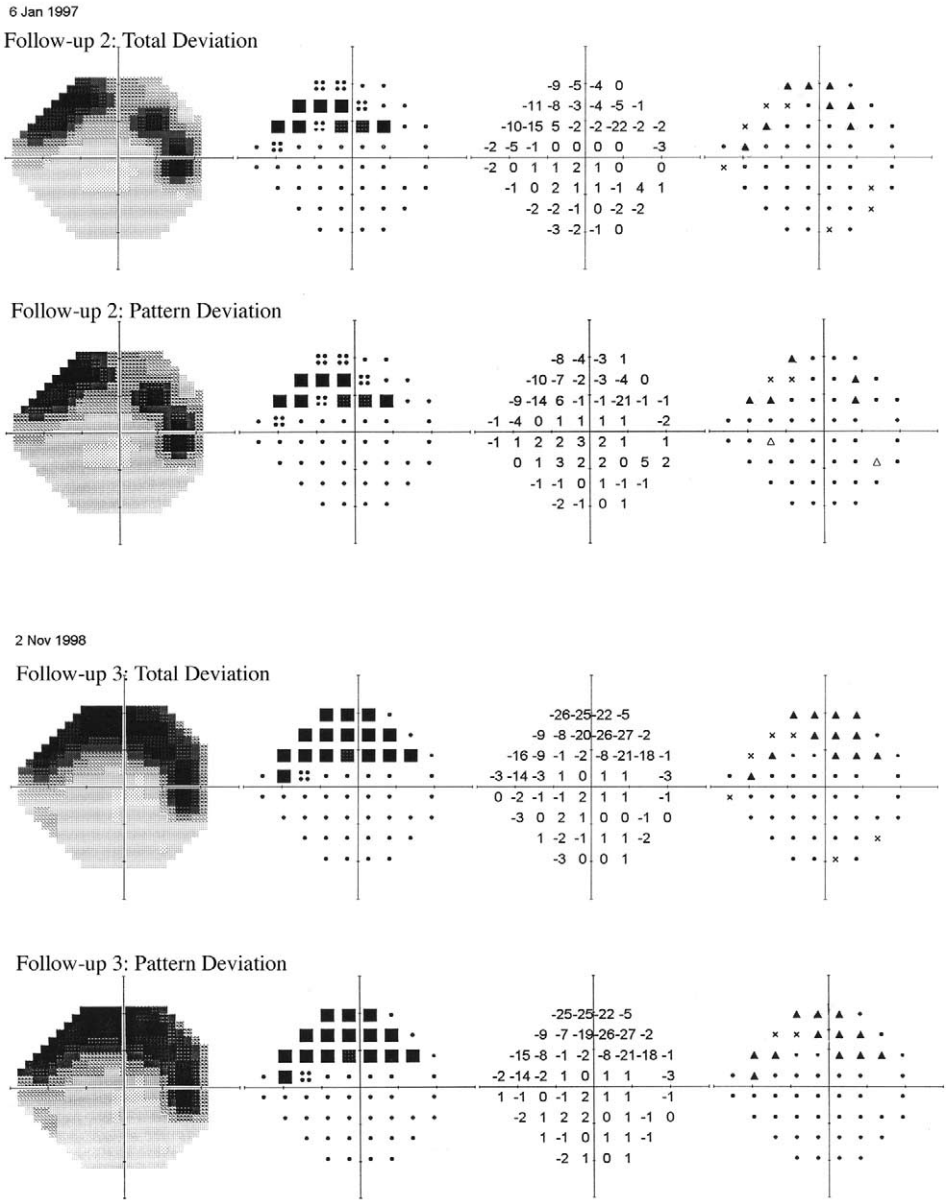

FIGURE 2. Two additional follow-up fields for the same individual as shown in Figure 1. The total deviation version of the GCP and the pattern deviation version for the same test date are shown in the first and second rows, respectively. The bottom two rows show the same data for a later test date. The change is repeatable on all follow-ups for this individual, showing both a deepening and expansion of the baseline scotoma. Note that more filled triangles are present on the total deviation version of the program. Also, note that the worsening in threshold dB values also meets the clinical definition of progression used in this study.

eye was selected randomly. These patients came from two studies. The first was a prospective multicenter study in which 72 patients were followed at 3, 6, 12, 18, and 24 months. Hereafter, this group will be referred to as the "semiannual" group. Progression on visual fields was defined by the clinical criteria listed below. When progression was noted, a follow-up field was scheduled within one month. The other 40 patients came from a prospectively designed and ongoing longitudinal study at the University of California, San Diego—Diagnostic Innovations in Glaucoma Studies (DIGS). These patients were followed annually (the "annual" group). This study was approved by the Human Subjects Committee of the University of California, San Diego, and by the appropriate review board for each site of the multicenter study. The study adhered to the Declaration of Helsinki with informed written consent.

The two groups were comparable in average age, baseline mean defect (MD), corrected pattern standard deviation (CPSD), and severity of field loss. Baseline ages (mean ± SD years) were 61.0 ± 1.2 and 60.9 ± 1.6 for the semiannual and annual groups respectively (*t* test, $P >$

TABLE 1. Progressed Eyes Showing a Deepening (D), Expansion (E), New, or Combined (D + E) Change From Baseline Scotoma for Each of the Three Classifiers

	Semiannual Group (n = 72)			Annual Group (n = 40)		
	Clinical n (%)	GCP-TD* n (%)	GCP-PD n (%)	Clinical n (%)	GCP-TD* n (%)	GCP-PD n (%)
D	8 (11)	8 (11)	1 (1)	8 (20)	1 (2)	1 (2)
E	1 (1)	2 (3)	0 (0)	1 (2)	0 (0)	2 (5)
D + E	3 (4)	10 (14)	10 (14)	2 (5)	6 (15)	4 (10)
New	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Stable	61 (85)	53 (74)	62 (86)	29 (73)	33 (83)	33 (83)

Progression required two consecutive progressed fields. GCP-TD = glaucoma change probability using total deviation; GCP-PD = glaucoma change probability using pattern deviation.

*One participant had two points showing deepening and one new abnormal pattern deviation point at $P < .05\%$ repeatable who was labeled nonprogressing. A second participant showed a new scotoma on the total deviation plot but not on the pattern deviation plot. These examples indicate that new regions of the field might be defective in some patients, although not by the criteria employed in this study.

TABLE 2. Kappa Tables, Values (Standard Error) Comparing Pairs of Progression Criteria Requiring Two Consecutive Progressed Fields

	Semi-Annual Group (n = 73)						Annual Group (n = 40)					
	Clinical			GCP-TD			Clinical			GCP-TD		
	Yes	No	Kappa	Yes	No	Kappa	Yes	No	Kappa	Yes	No	Kappa
GCP-TD Yes	9	11	0.45 ± 0.12				6	1	0.58 ± 0.15			
GCP-TD No	3	49					5	28				
GCP-PD Yes	5	6	0.33 ± 0.15	10	1	0.56 ± 0.11	7	0	0.72 ± 0.13	4	3	0.48 ± 0.18
GCP-PD No	7	54		10	51		4	29		3	30	

GCP-TD = glaucoma change probability using total deviation; GCP-PD = glaucoma change probability using pattern deviation.

5%). Baseline average MDs were −4.3 ± 2.4 dB and −5.3 ± 4.0 dB (*t* test, $P > 5\%$) for the semiannual and annual groups, respectively. Baseline average CPSDs were 5.8 ± 3.1 dB and 6.8 ± 3.9 dB, respectively (*t* test, $P > 5\%$). Thirty-two percent of eyes were classified as early field loss and 68% as moderate in the semiannual group, and 29% as early and 71% as moderate in the annual group. In these studies, early visual field loss has a mean defect better than or equal to −6 dB and a CPSD < 5% but no worse than the 1% probability level. Moderate field loss has a mean defect worse than −6 dB, but better than or equal to −15 dB or a CPSD worse than the 1% probability level.

Each subject underwent a complete ophthalmologic examination that included review of relevant medical history, best-corrected visual acuity, slit-lamp biomicroscopy (including gonioscopy), applanation tonometry, dilated funduscopy, and fundus photography.

Inclusion and Exclusion Criteria. All subjects had primary open angle glaucoma, a best corrected acuity of 20/30 or better, a spherical refraction within ± 5.0 diopters, and cylinder correction within ± 3.0 diopters. Treatment during the study was only with topical intraocular-pressure-lowering medication. Only patients without a significant lens opacity as determined by the examining specialist at the baseline clinical examination and without a change noted during the study period on follow-up ophthalmologic examinations were included. Patients with other disorders known to affect visual fields were excluded.

Visual Fields. To minimize a learning effect, each patient had had at least two prior standard achromatic visual fields before study entry and baseline testing. All visual fields were obtained on a Humphrey Visual Field Analyzer using program 24 to 2 with a full-thresholding algorithm (Carl-Zeiss Meditec, Dublin, California). This program uses 54 test locations (the two locations near the blind spot locations were not included, leaving 52 test locations) presented in a six-degree grid. Each included eye had two reliable baseline visual fields classified as abnormal based on a glaucoma hemifield test outside the normal limits or a corrected pattern standard deviation at the 5% probability or worse. Eyes also had a mean defect (MD) better than −15 dB on both baseline examinations to allow room to show progression. In addition, each eye had to have two or more reliable follow-up visual fields. Fields were considered

TABLE 3. Progressed Eyes Showing a Deepening (D), Expansion (E), New, or Combined (D + E) Change From Baseline Scotoma for Each of the Three Classifiers

	Semiannual Group (n = 72)			Annual Group (n = 40)		
	Clinical n (%)	GCP-TD n (%)	GCP-PD n (%)	Clinical n (%)	GCP-TD n (%)	GCP-PD n (%)
D	6 (8)	5 (7)	1 (1)	4 (10)	2 (5)	0 (0)
E	1 (1)	2 (3)	0 (0)	2 (5)	0 (0)	2 (5)
D + E	0 (0)	1 (1)	1 (1)	0 (0)	4 (10)	2 (5)
New	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Stable	66 (90)	65 (89)	71 (97)	34 (85)	34 (85)	36 (90)

Progression required three consecutive progressed fields. GCP-TD = glaucoma change probability using total deviation; GCP-PD = glaucoma change probability using pattern deviation.

TABLE 4. Kappa Tables, Values (Standard Error) Comparing Pairs of Progression Criteria Requiring Three Consecutive Progressed Fields

	Semi-Annual Group (n = 73)						Annual Group (n = 40)					
	Clinical			GCP-TD			Clinical			GCP-TD		
	Yes	No	Kappa	Yes	No	Kappa	Yes	No	Kappa	Yes	No	Kappa
GCP-TD Yes	2	6	0.18 ± 0.16				5	0	0.89 ± 0.10			
GCP-TD No	5	59					1	34				
GCP-PD Yes	1	1	0.19 ± 0.18	2	0	0.37 ± 0.19	4	0	0.87 ± 0.12	4	0	0.77 ± 0.15
GCP-PD No	6	64		6	64		1	35		2	34	

GCP-TD = glaucoma change probability using total deviation; GCP-PD = glaucoma change probability using pattern deviation.

reliable if they had fixation losses, false negatives, or false positive of less than or equal to 25%.

Optic Disk. Included eyes also had to have abnormal baseline stereophotos determined independently on masked review by two trained graders at the Optic Disk Reading Center at the University of California, San Diego. Disagreements were resolved by consensus. Optic discs were considered abnormal when one or more of the following was found: excavation or undermining of the neural rim, nerve fiber layer defects, notching, rim thinning, or cup-to-disk asymmetry between eyes > 0.2.

Clinical Definition of Progression. Baseline scotomas were defined as 3 adjacent points with a $P < 5\%$, with at least 1 point having a $P < 1\%$ on the pattern deviation plot on first and second baseline fields. At least one overlapping location had to be defective on both baseline fields, and the other two defective locations had to overlap or be adjacent to defective points on the first baseline's scotoma. Points with a PD $< 5\%$ on either of the two baseline fields in adjacent locations were considered to be part of the "baseline scotoma."

Our clinical criteria for progression were derived from the multicenter study from which we received our semiannual visual field data (unpublished study, see Acknowledgments). At the start of this study, clinical criteria for progression were defined as follows: 1) deepening of an existing scotoma: two or more points $\geq$ 10 dB poorer in the same locations as the baseline scotoma; 2) expansion of an existing scotoma: two or more points $\geq$ 10 dB poorer adjacent to the baseline scotoma; 3) new scotoma: two or more adjacent points not within or adjacent to the baseline scotoma, now showing a probability on the pattern deviation plot at $P < 1\%$ or worse, or 1 point within the central 10 degrees that declined by $\geq$ 10 dB in a previously normal location; 4) combinations of these criteria. For a combination of deepening and expansion, for instance, there had to be at least 1 location that met the criteria for deepening and at least 1 location that met the criteria for expansion. The criteria had to be met on two (or three, discussed later) consecutive fields at exactly the same locations for all modes of progression. When progression was noted for the semiannual group, a follow-up visual field was scheduled within 1 month and the progression had to be confirmed. The next annual visit served as the confirmatory field in the annual group.

For the analysis reported here, we used the clinical definition described here, as well as defining progression based on the GCP plot provided within the Statpac 2 analysis of the Humphrey Visual Field Analyzer. It is well known that different progression algorithms will identify

different eyes and different percentages of a population as progressed.[10,11] It was not our purpose to compare these methods again, but rather to employ three commonly employed methods and see if the mode of the progression might differ (deepening, expansion, or new defect) with the method employed. We have analyzed our results with two consecutive fields versus three consecutive fields.

GCP Definitions of Progression. To improve detection of glaucomatous visual field progression, statistical methods for analysis of visual fields have been developed. The GCP plot of Statpac 2 compares an individual patient's series of visual fields (two baselines and one or more subsequent fields) to the change seen in a series of fields from a group of stable glaucoma eyes.[12] The assumption is that any change in the latter group is due to long-term fluctuation, rather than glaucomatous progression.[13] Change in an individual's visual field test locations must exceed the long-term fluctuation in the stable group at that location to be considered outside the normal limits of variability.[14,15] Several authors have verified that the "noise" (fluctuation) is greater for visual field locations located more eccentrically and those with deeper defects, so that a change in "noisy" locations needs to be of a greater magnitude to exceed normal limits of fluctuation than a change in "quiet" locations.[16–19] The GCP analysis takes this into account for each visual field location. If there is a change in threshold greater than the test-retest variability found for a group of stable glaucoma patients at a probability of $P < 5\%$, the program denotes it by placing a triangle at that location on the GCP printout (Figures 1 and 2). A filled triangle denotes deterioration and an open triangle denotes improvement in the sensitivity from baseline (also at a probability of $P < 5\%$).

We used two versions of the GCP analysis. One is currently available on Humphrey Field Analyzers and is based on change seen using the total deviation plot. The second version is a modification made for use in the EMGT study,[6] where change is evaluated based on the pattern deviation plot. The rationale for using the pattern deviation plot is that it will reduce the effects of factors that cause a diffuse change in the visual field, such as cataract, change in refraction, or pupil size.[20] However, it will also obscure any diffuse change caused by glaucoma.

Definitions for progression using the GCP analysis (both TD and PD) were as follows: 1) deepening of an existing scotoma: three or more filled triangles in the same locations as the baseline scotoma; 2) expansion of an existing scotoma: three or more filled triangles adjacent to the baseline scotoma; 3) new scotoma: two or more adjacent points not within or adjacent to the baseline scotoma, now showing a probability on the pattern deviation plot at $P < 1\%$ or worse, or 1 point within the central 10 degrees that declined by ≥ 10 dB in a previously normal location; and 4) combinations of these criteria. Confirmation of progression required at least three identical locations with filled triangles on the field suspected of showing progression and the confirmatory field(s). Three locations that are flagged as progressed (that is, outside the variability in a stable glaucoma group at $P < 95\%$) are recommended by the EMGT study for the GCP-PD. The EMGT study uses the Humphrey 30 to 2 full-threshold program and requires three consecutive progressed fields before determining a change is real; two confirming fields are also recommended by several National Eye Institute (NEI)-sponsored studies of progression.[21,22] We have analyzed our results with two consecutive fields versus three consecutive fields.

RESULTS

BASELINE MEAN DEVIATIONS FOR ABNORMAL AND PROgressed visual field locations versus abnormal and nonprogressed locations were within 1.0 dB (-5.3 ± 5.6 and -4.4 ± 5.0, respectively). Eyes in the semiannual group had a minimum of four fields and a maximum of six fields. Eyes in the annual group had a minimum of four and a maximum of 17 follow-up fields.

Progression Based on Two Sequential Progressed Fields (Semiannual Group, n = 72): Seventy-one percent (51 of 72) of the eyes were considered stable by all criteria. Seventeen percent (12 of 72) progressed by clinical criteria, 28% (20 of 72 eyes) progressed using the GCP total deviation, and 15% (11 of 72) progressed using the GCP pattern deviation criteria (note that some eyes converted by more than 1 criteria). Only 7% (5 of 72) of eyes progressed by all three criteria. By all criteria, the majority of progressed eyes showed a deepening of an existing scotoma; 11% (8 of 72 eyes) by clinical criteria, 11% (8 of 72 eyes) GCP-TD criteria, and 1% (1 of 72) GCP-PD (Table 1). The next most common finding was a combination of expansion and deepening of an existing scotoma (Table 1). No eyes showed a new scotoma. Kappa values for pairs of progression criteria are given in Table 2. The agreement between algorithms is fair to moderate.[23] The percentage of eyes classified the same (either progressed or nonprogressed) by the clinical criteria and GCP-TD was 82%. It was 83% by the clinical criteria and GCP-PD and 86% for the two versions of the GCP.

Progression Based on Two Sequential Progressed Fields (Annual Group, n = 40): Seventy percent of eyes (28 of 40) were considered stable by all criteria. Thirty percent (11 of 40) progressed by the clinical criteria, 18% (7 of 40) by the GCP-TD criteria, and 18% (7 of 40) by the GCP-PD criteria. Eight percent of eyes (3 of 40) were considered progressed by all criteria. By clinical criteria, most eyes showed deepening of an existing scotoma (20%, 8 of 40). By the GCP criteria, deepening and expansion were most common: 15% (6 of 40 eyes) by GCP-TD

criteria and 10% (4 of 40) by GCP-PD (Table 1). Pure expansion was the next most common pattern of progression (Table 1). No eyes developed a new scotoma. Kappa values for pairs of progression criteria are given in Table 2. The agreement between algorithms is fair to moderate.[23] The percentage of eyes classified the same (either progressed or nonprogressed) by the clinical criteria and GCP-TD was 85%. It was 90% by the clinical criteria and GCP-PD and 85% for the two versions of the GCP.

Progression Based on Three Sequential Progressed Fields (Semiannual Group, n = 72): Eighty-nine percent (64/72) of the eyes were considered stable by all criteria. Of the 12 eyes that showed progression by at least 1 criteria, 7 (10%) eyes progressed by clinical criteria, 8 (11%) eyes by GCP-TD and 2 (3%) eyes by GCP-PD. Only 1% of eyes (1 of 72) progressed by all three criteria. No eyes showed evidence of a new scotoma (Table 3). Most progressed eyes showed deepening by clinical and GCP-TD criteria; 8% (6 of 72) by clinical criteria and 7% (5 of 72) by GCP-TD criteria. Of the two eyes progressed by GCP-PD, one showed deepening and expansion and the other showed pure deepening (Table 3). Kappa values for pairs of progression criteria are given in Table 4. The agreement between algorithms is fair to moderate.[23] The percentage of eyes classified the same (either progressed or nonprogressed) by both the clinical criteria and GCP-TD was 86%. It was 92% by both the clinical criteria and GCP-PD and 93% for the two versions of the GCP.

Progression Based on Three Sequential Progressed Fields (Annual Group, n = 40): The majority (85%) of eyes (34 of 40) were considered stable by all criteria. Of the eyes that did show progression by one or more of our progression criteria, 6 (15%) progressed by clinical criteria, 6 (15%) by GCP-TD, and 4 (10%) by GCP-PD. A small percentage (10%, 4 of 40) of those eyes progressed by all three criteria. No eyes acquired a new scotoma when the criteria for progression required three fields (Table 3). Once again, most eyes that progressed showed deepening of an existing scotoma by clinical criteria (10%, 4 of 40). Deepening and expansion was most common by GCP criteria: 10% (4 of 40) GCP-TD criteria, and 5% (2 of 40) GCP-PD (Table 3). Kappa values for pairs of progression criteria are given in Table 4. The agreement between algorithms is fair to moderate.[23] The percentage of eyes classified the same (either progressed or nonprogressed) by the clinical criteria and GCP-TD was 98%. It was 98% by the clinical criteria and GCP-PD and 95% for the two versions of the GCP.

DISCUSSION

AS HAS BEEN SHOWN IN EARLIER STUDIES, PROGRESSION criteria comparable to those in our study do not always identify the same eyes as progressed or even the same number of progressed eyes.[10,11,18,24] For instance, clinical criteria for progression similar to those employed here tend to indicate more eyes as progressed than the GCP using total deviation. Additionally, the GCP using the total deviation plot tends to signal more eyes as progressed than does the GCP using pattern deviation. The two GCP criteria identify a different subset of eyes.[10,11,24] Our results also showed only fair to moderate agreement among algorithms. Despite the disparities in verdicts from these progression algorithms, all eyes identified as changed with two confirming fields showed either a deepening or expansion of an existing scotoma or a combination of these, regardless of the progression algorithm we employed in this study. This was true whether patients were tested over a short or long time. No eyes showed a new scotoma.

Using the same type of test for both detection of abnormality and for follow-up ignores known information about the location, depth, and size of the patient's baseline defect and the fact that these previously defective areas tend to progress first. Our results and previous results using Goldmann perimetry[9] suggest that when a defect is already present, concentrating on certain locations within the visual field to emphasize the area where the initial defect was identified and to allot more time to verify thresholds in this area might improve identification and confirmation of true change.

Devoting the same amount of time to testing abnormal areas of the visual field, which are most likely to change, as that devoted to testing normal areas, which are unlikely to change, is not making optimal use of examination time.[25] With existing technology, it should be possible to structure follow-up visual fields to examine more closely previously determined areas of damage. Furthermore, they could also be structured to screen normal areas of the visual field rapidly to rule out emergence of the rare new scotoma. This trade-off could be accomplished without increasing the length of the visual field examination, and might even shorten it. For example, a three-degree grid could be used in the quadrant or hemifield with known damage and a screening algorithm used elsewhere. Another modification could be to increase the number of crossovers from seen to unseen before threshold is determined in those locations that are at high risk. Studies with these modifications are needed to verify our hypothesis.

Although detection of visual field progression has always been important for effective management of glaucoma, it is attracting further attention as clinical trials seek to determine whether existing or new treatments can prevent or slow visual field loss. A difficult challenge lies in determining treatment effectiveness by identifying small reliable changes in the visual field within a relatively short time frame. Taking more advantage of what is known about an individual patient's visual field at study onset should improve the detection of true change in that eye.

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