Infrequent Confirmation of Visual Field Progression

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Objective: To evaluate the effects of the repeatability criteria on the detection of change in visual fields by six progression algorithms used in standard automated perimetry.

Design: Retrospective, observational case series

Participants: Fifty-one glaucoma patients, each with multiple visual fields performed between May 1990 and December 1998, were included.

Methods: Each patient's set of visual fields were analyzed using the glaucoma change probability, the Early Manifest Glaucoma Trial (EMGT) algorithm, a modified glaucoma change probability score, a modified EMGT score, the Advanced Glaucoma Intervention Study algorithm, and the Collaborative Initial Glaucoma Treatment Study algorithm.

Main Outcome Measures: The effects of repeatability on the detection of field change, the level of agreement among algorithms, as well as the number of eyes identified as changed with each algorithm, were assessed.

Results: Mean follow-up was 34 months (range, 12–87 months). The average percentage of eyes with change based on three consecutive follow-up fields was 8.2% (4.0%–12.5%). However, of those showing change on the initial follow-up, this change from baseline was observed in subsequent examinations on average in 23% (18%–33%), depending on the algorithm. When change was based on just one field, four of the six algorithms noted a significantly greater number of eyes with change. The algorithms, however, did not differ significantly when confirmation of field change required two versus three consecutive follow-up visual fields.

Conclusions: Although current algorithms may help identify change, there are inconsistencies among them. We found that requiring repeatable change from baseline significantly reduces the number of changed eyes identified with each subsequent follow-up field. Identification and confirmation of change in visual fields plays an important role in helping to identify true glaucoma progression; however, the specific methods to do so have yet to be determined. *Ophthalmology 2002;109:1059–1065 © 2002 by the American Academy of Ophthalmology.*

Identifying and quantifying glaucomatous progression in serial automated, achromatic perimetry is a crucial step in the management of glaucoma. However, because of inherent intertest variability, patient fatigue, physiologic variation resulting from glaucoma, grader subjectivity, and other factors, fluctuations in visual field results have made the assessment of change difficult.[1–7] Even experienced clinicians have difficulty reaching a consensus on whether change has occurred in a given clinical case.[8,9]

To differentiate true change from random fluctuation, it has been recommended that evidence for progression in visual fields should be repeatable on subsequent visual fields. For example, several National Eye Institute-sponsored clinical trials, the Advanced Glaucoma Intervention Study (AGIS), the Collaborative Initial Glaucoma Treatment Study (CIGTS), and the Early Manifest Glaucoma Trial (EMGT) require that change from baseline be observed in three consecutive follow-up visual fields before progression is verified.[10–12] Each of these ongoing trials was designed for a different group of glaucoma patients and each study's end point was based on a different progression algorithm. Such differences make it difficult to compare across algorithms. However, Katz et al[13] compared these progression algorithms in the same group of visual fields and found that EMGT and CIGTS had rates of progression twice those of AGIS and that each algorithm identified a different group of patients as progressing. Currently, no single algorithm for identifying and quantifying progression in serial visual fields has gained wide acceptance.[13–16] There is currently no quantifiable gold standard to deter-

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mine if the changes seen on each algorithm are indeed evidence of progression resulting from glaucoma.

Repeatability of visual field results may help establish whether there is true change. However, increasing the number of required follow-up visual fields potentially will delay treatment. The purpose of this study was to evaluate six progression algorithms in the same group of patients to determine whether repeatable changes on three follow-up visual fields are indeed necessary, or whether fewer follow-up visual fields can provide similar results.

Materials and Methods

Patients

We reviewed our research database for records of a group of patients diagnosed with glaucoma based on: (1) an abnormal, glaucomatous-appearing optic disc showing notching, excavation, cup-to-disc asymmetry of more than 0.2, or characteristic nerve fiber layer defects; and (2) repeatable, abnormal standard visual fields on two separate visits (i.e., corrected pattern standard deviation outside 95% normal limits or glaucoma hemifield test "outside normal limits"). The patients were followed up at the Glaucoma Center, University of California at San Diego, and 14 other locations as part of a multicenter clinical trial. To be included, patients had to have long-term follow-up with four or more standard, achromatic visual fields; a best-corrected visual acuity of 20/40 or better throughout follow-up; a spherical refraction within ±5.0 diopters (D); and a cylinder correction within ±3.0 D. Any history of ocular trauma, intraocular surgeries, or refractive corneal procedures; a history of diabetes mellitus; or concomitant use of systemic medications that may affect the intraocular pressure were grounds for exclusion. To reduce the learning curve effect, all patients had experience with automated perimetry before the fields used in this analysis. In addition, only visual fields with false-negative responses, false-positive responses, and fixation loss rates all less than 25% were included. In cases where both eyes were eligible, one eye was randomly selected. Fifty-one eyes of 51 patients were included in the study. Each had two reliable abnormal baseline visual fields and at least two reliable follow-up visual fields. Of these 51 eyes, 48 eyes had at least three reliable follow-up visual fields. The total included 19 right and 32 left eyes. The mean age at the start of study was 57.7 ± 11 years (range, 38–76 years). All visual fields were performed between May 1990 and December 1998. The mean number of visual fields performed per eye was 6.7 ± 1.8 (range, 4–13). The mean follow-up period between the first and last visual fields was 34 ± 20 months (range, 12–87 months). The interval between the average of the first two and the average of the last two visual fields was 26 ± 14 months (range, 9–70 months).

Visual Fields

All standard, achromatic visual fields were performed on the Humphrey Field Analyzer (Humphrey Instruments, Dublin, CA) and were administered by trained technicians using either the 24–2 or 30–2 full-threshold program. The additional locations tested by the 30–2 program and the two locations nearest the blind spot were not used in calculating visual field scores. Each patient's set of visual fields was analyzed using six progression algorithms. The first two and the last three reliable visual fields were used in the analysis, even in cases where patients had more than five visual fields.

The Progression Algorithms

The glaucoma change probability (GCP) analysis included in Statpac2 (Humphrey Instruments, Dublin, CA)[17,18] assesses progression by comparing the average of two reliable baseline visual fields with subsequent tests. Based on the total deviation probability map, a drop in sensitivity more than the long-term fluctuation found in a group of stable glaucoma patients at the <5% limit is required to trigger deterioration at that particular location.[19,20] Deterioration is noted with a black triangle (Fig 1). The GCP analysis currently provided by Statpac2 does not provide a definition of progression; it only identifies test locations that may have deteriorated relative to the baseline. For this study, we adopted a progression criterion similar to that used by the EMGT (see below). Progression required that at least three locations anywhere in the field show a black triangle and that at least three of the changed locations be identical on the follow-up fields.

The EMGT, a National Eye Institute-sponsored study, was designed to compare the effect of immediate therapy to lower intraocular pressure versus late or no treatment on the progression of newly diagnosed patients with open-angle glaucoma.[12] The progression algorithm for the EMGT also uses the GCP plot. However, a special version of GCP was developed for the EMGT study. Change is triggered based on the pattern deviation plot rather than the total deviation plot. The change in pattern deviation is thought to provide a more accurate assessment of visual field progression resulting from glaucoma, because this type of plot is less influenced by shifts in the global hill of vision resulting from cataract, pupil size changes, or refractive errors. Progression for the EMGT study requires deterioration in at least three same locations, which do not have to be contiguous, on three consecutive follow-up visual fields.

The AGIS algorithm was developed to determine eligibility for the AGIS study and to evaluate visual field progression in patients with advanced glaucoma. The AGIS scoring system is based on the concepts that: (1) multiple defects can occur in the upper, lower, and nasal hemifields; (2) a defective region requires two or more adjacent defective locations; (3) the severity of depression must be greater than the normal variability limits in serial visual fields; and (4) the defect must be caused by glaucoma. Calculation of the AGIS score has been explained in full previously.[10] In brief, the AGIS score is calculated by totaling the number of adjacent depressed test locations on the total deviation plot found in the upper, lower, and nasal hemifields. The final AGIS score for each field ranges from 0 to 20. Progression requires an increase in score of 4 or more points between the average score of the two baseline visual fields and the score on each of three consecutive follow-up fields.

The CIGTS algorithm[11] is a modification of the AGIS scoring system. The CIGTS is a multicenter, randomized clinical trial designed to compare initial medical versus initial surgical treatment for patients newly diagnosed with open-angle glaucoma. The scoring is based on the following: (1) the total deviation probability plot after adjusting the total deviation values at each location relative to the most normal region in the visual field; (2) each abnormal test location must be accompanied by at least two adjacent abnormal locations ($P < 5\%$); and (3) each abnormal location is given a score from 1 to 4 if the depressed location is accompanied by two contiguous abnormal locations with a probability level of 5% to 0.5%. The two most depressed neighboring locations are used for scoring when a particular location is surrounded by more than two neighboring depressed locations. When a depressed location does not have any contiguous, abnormal locations, a score of 0 is assigned. The value for each of the 52 locations within the visual field is combined to obtain a maximum possible score of 208. The total score is then multiplied by a

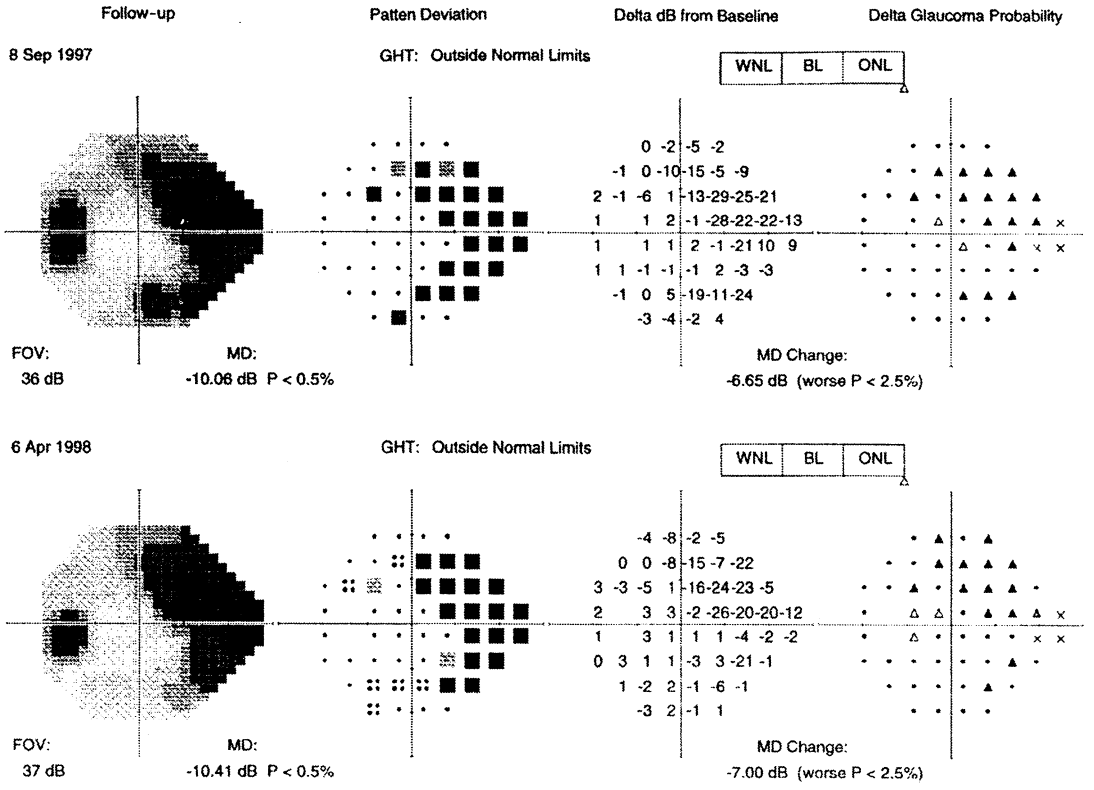

Figure 1. Example of glaucoma change probability printout for two follow-up visual fields. Filled triangles = worsening; open triangles = improvement.

conversion factor (0.096) to obtain a final score ranging from 0 to 20. The difference between the averaged two baseline visual field scores and each follow-up visual field score is then calculated. For progression, CIGTS requires a score increase of 3 or more on three consecutive visual fields.

Modified Scoring Procedures. The GCP and EMGT analyses do not take into account improvement in locations within the visual field that may coexist with other deteriorating locations. For this study, we developed an additional definition of progression for GCP and EMGT to quantify better the degree of progression by also taking into account locations that improved. We call these the "modified GCP score" and the "modified EMGT score." The modified GCP score is calculated by taking the difference between the number of black triangles (areas of deterioration) and the number of white triangles (areas of improvement) shown on the GCP printout (Fig 1). The modified EMGT score is calculated in the same manner, except that it is based on the pattern deviation probability plot. For both scoring systems, triangles were considered in the scoring only if they were repeatable on three follow-up visual fields. The difference score between the two averaged baselines and three follow-up visual fields must be +3 or more (three or more total progressed locations than improved locations) for an eye to qualify as having progressed.

Data Analysis

The statistical analysis was performed using JMP software (SAS Institute Inc., Cary, NC). Scatter diagrams were plotted for each pair of algorithms, and linear regression was applied to all pairwise comparisons and correlation coefficients calculated. The r^2 value was reported, which quantifies the amount of variation explained by the analysis. The effect of modifications in the criteria for repeatability on the number of visual fields identified with change by each algorithm was analyzed. A McNemar's test was performed to determine whether the number of eyes called "changed" by each of the six algorithms was statistically different and whether there was any difference in results when scoring was based on one, two, and three follow-up visual fields.

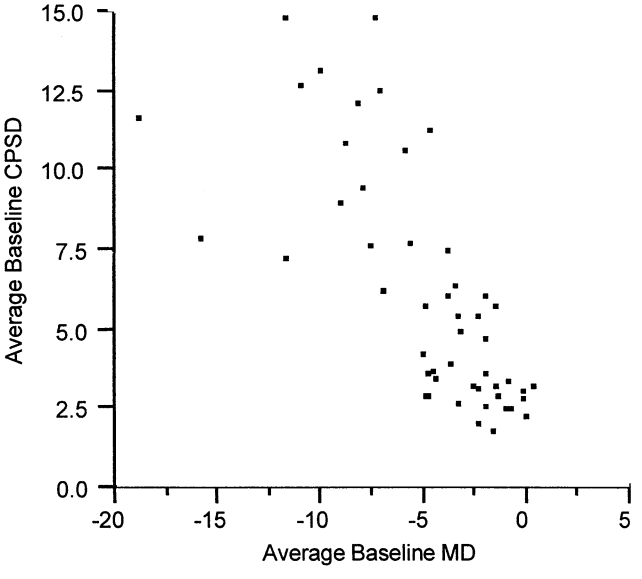

Figure 2. Scatterplot of average of two baseline mean deviations versus average of two baseline corrected pattern standard deviations.

Table 1. Correlation between Algorithms (All $P < 0.001$)

	Modified Glaucoma Change Probability Score	Early Manifest Glaucoma Trial Score	Advanced Glaucoma Intervention Study	Collaborative Initial Glaucoma Treatment Study
Modified Glaucoma Change Probability score				
Modified Early Manifest Glaucoma Trial score	$r^2 = 0.626$			
Advanced Glaucoma Intervention Study	$r^2 = 0.551$	$r^2 = 0.546$		
Collaborative Initial Glaucoma Treatment Study	$r^2 = 0.495$	$r^2 = 0.318$	$r^2 = 0.774$	

Results

Patients showed a wide range of visual field loss. Figure 2 shows the average of the two baseline mean deviations plotted against the average of the two baseline corrected pattern standard deviations. The mean of the average of the two baseline mean deviations was −4.7 dB ± 4.1 dB (range, −18.5 dB to +0.4 dB; median, −3.7 dB). The mean of the average of the two baseline corrected pattern standard deviations was 6.1 dB ± 3.8 dB (range, 1.8 dB–14.9 dB; median, 5.0 dB). The mean of the average of the two baseline AGIS scores was 4.2 ± 3.5 (range, 0–16). The mean of the average of the two CIGTS baseline scores was 3.8 ± 3.7 (range, 0–16).

Differences between the average of the two baseline and three follow-up visual fields for each of the progression algorithms ranged from −4.0 to 7.0 for AGIS, −3.9 to 7.5 for CIGTS, −6 to 13 for modified GCP, and −2 to 11 for modified EMGT. It is important to note that all three follow-up visual fields individually must have a score more than 4 and 3 for a series of fields to be considered to have changed based on AGIS and CIGTS, respectively. An average score of the three follow-up visual fields more than 4 or 3 for AGIS and CIGTS, respectively, does not necessarily indicate that an eye has changed.

Correlations among Algorithms for Identifying Change

The GCP and EMGT algorithms provide a yes-or-no answer for change. The modified GCP and EMGT, as well as the AGIS and CIGTS algorithms, provide a numerical difference score, which can be used to assess better the correlation among the algorithms. Table 1 summarizes the results. The highest correlations in the difference between baseline and follow-up visual fields were found between AGIS and CIGTS ($r^2 = 0.774$, $P < 0.001$; Fig 3A) and between the modified GCP score and the modified EMGT score ($r^2 = 0.626$, $P < 0.001$; Fig 3B). A high correlation is expected between AGIS and CIGTS, because CIGTS is a modification of AGIS. The lowest correlation was found between CIGTS and the modified EMGT score ($r^2 = 0.318$, $P < 0.001$; Fig 3C).

Initial Change

Table 2 shows the number of eyes identified with change. The modified GCP score, modified EMGT score, GCP, EMGT, AGIS, and CIGTS algorithms identified 23, 13, 37, 25, 6, and 11 eyes with change on follow-up visual field 1, respectively. The GCP identified the most eyes when scoring was based on one follow-up visual field. Pairwise comparisons, using the McNemar's test, between the six algorithms were all significantly different ($P < 0.05$), except for AGIS versus CIGTS ($P = 0.18$), CIGTS versus modified EMGT score ($P = 0.75$), and EMGT versus modified GCP score ($P = 0.79$).

Confirming Change

Of the patients with change on the first follow-up visual field, Table 2 gives the number (and percentage) of eyes with repeatable change on the second and third follow-up visual fields. A large percentage of eyes did not have repeatable change. Of the 37 eyes found to have change based on GCP on the initial visual field, only 27% had repeatable change on a second follow-up visual field, whereas 16% of eyes with change on the initial follow-up visual field had change on both the second and third follow-up visual fields (Table 2). As expected, the modified GCP score called change in fewer eyes, initially, as compared with the GCP. However, when confirmation of change required a second and a third visual field, the modified GCP score performed similarly to the GCP. Of the 23 eyes identified by the modified GCP score, 43% and 26% had change on the second and third follow-up visual field, respectively. Twenty-eight percent and 16% of eyes shown by EMGT to have change on the first follow-up visual field had change from baseline that was observed on a second and third follow-up visual field. Although the modified EMGT score identified change in fewer eyes, 43% and 26% of eyes with change on initial follow-up visual field had change that was observed on the second and third follow-up visual fields. The AGIS and CIGTS identified the fewest number of eyes with change. However, 67% of eyes with change on initial follow-up visual field based on AGIS had repeatable change on a second follow-up visual field, whereas CIGTS had 45%. Thirty-three percent and 18% of eyes

Table 2. Number of Visual Fields Changed from Baseline Observed on Follow-up Visual Fields

	Follow-up 1 (n = 51)	Follow-up 2 (n = 51)	Follow-up 3 (n = 48)
Modified Glaucoma Change Probability score	23	10 (43%)	6 (26%)
Modified Early Manifest Glaucoma Trial score	13	5 (38%)	4 (31%)
Glaucoma Change Probability	37	10 (27%)	6 (16%)
Early Manifest Glaucoma Trial	25	7 (28%)	4 (16%)
Advanced Glaucoma Intervention Study	6	4 (67%)	2 (33%)
Collaborative Initial Glaucoma Treatment Study	11	5 (45%)	2 (18%)

Of those fields with change on follow-up 1, the percentage of fields identified as having changed in follow-up 2 or 3 is given in parenthesis.

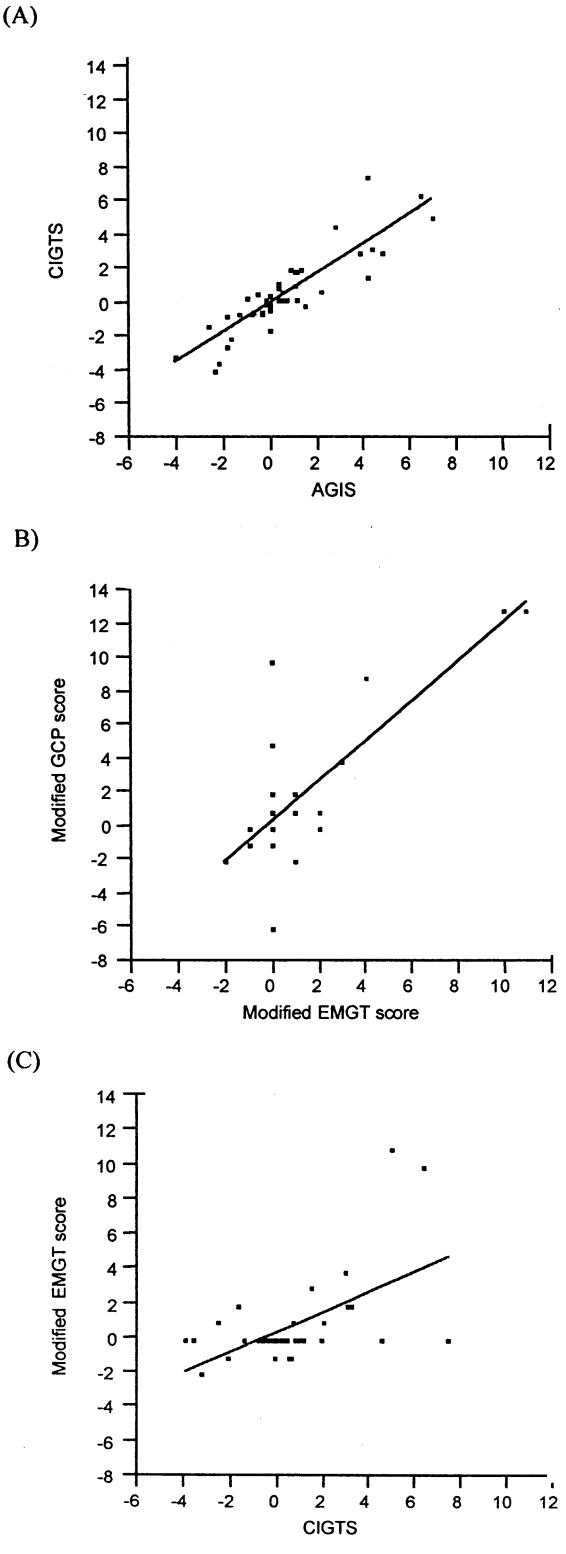

Figure 3. Scatterplot of change between baseline and follow-up for (**A**) Advanced Glaucoma Intervention Study score versus Collaborative Initial Glaucoma Treatment Study score ($r^2 = 0.774$); (**B**) modified Early Manifest Glaucoma Trial (EMGT) score versus modified glaucoma change probability score ($r^2 = 0.626$); and (**C**) Collaborative Initial Glaucoma Treatment Study score versus modified EMGT score ($r^2 = 0.318$).

shown by AGIS and CIGTS, respectively, to have changed on initial follow-up visual field had change on all three follow-up visual fields. The same two eyes had repeatable change for both algorithms when deterioration in three follow-up visual fields was required. After correction for multiple comparisons, there was no difference in the number of eyes identified by the six algorithms when scoring of visual fields was based on either two or three follow-up fields.

Six of 48 eyes (13%) had repeatable change based on any one of the six algorithms when scoring was based on three follow-up visual fields. All six eyes showed change on two or more algorithms, whereas two eyes showed change on all six algorithms. Both GCP and the modified GCP score identified change in all six eyes, whereas the EMGT and the modified EMGT score called change in the same four of the six eyes. The AGIS and CIGTS identified the same two of the six eyes (Table 3).

We should note that the incidence of repeatable improvement among the eyes studied was very low, at 0% (0/51), 2% (1/51), 2% (1/51), and 0% (0/51) for the AGIS, CIGTS, modified GCP score, and modified EMGT score, respectively. Improvement in the visual field required a decrease in score of four or more for AGIS and three or more for CIGTS for each follow-up visual field. The modified GCP and EMGT scores required an overall score of -3 or less. The same eye was identified by both the CIGTS and modified GCP score to have improved. We did not expect much improvement in visual fields attributable to the learning effects, because all patients had undergone at least two visual fields before their baseline examinations.

Other Explanations for Visual Field Changes

Changes in visual fields were not the result of changes in pupil size (mean baseline pupil size, 4.1 ± 1.1 mm; mean follow-up pupil size, 4.1 ± 1.0 mm; mean difference between baseline and follow-up pupil size, 0.06 ± 0.86 mm) or refraction (mean difference between baseline and follow-up refraction, 0.29 ± 0.67 D). All patients were screened for any history of intraocular surgeries, refractive corneal procedures, or diabetes mellitus before enrollment into the study. In addition, patients found to have any clinical evidence of lens changes were disqualified from the study.

Discussion

Confirmation of change on additional visual fields after initial detection is important to ensure that the detected changes are more likely to be real. We found the six algorithms to vary in their assessment of change in serial visual fields. All six algorithms identified more eyes with change when scoring was based on any one visual field. On initial follow-up of the 51 eyes, the three algorithms that identified the most eyes as having changed were: GCP (37 eyes), modified GCP (23 eyes), and EMGT (25 eyes). When change was assessed based on two follow-ups, 10 (27%), 10 (43%), and 7 (28%) of those eyes initially found to have changed were repeatable, respectively. AGIS, CIGTS, and the modified EMGT identified a smaller number of visual fields with change initially: 6, 11, and 13, respectively. When a second follow-up visual field was required to confirm a change, 4 (67%), 5 (45%), and 5 (38%) eyes were repeatable, respectively. In all cases, fewer eyes were identified when a third visual field was required to confirm a change. Although our study did not find a significant dif-

Table 3. Overall Results for the Six Patients with Change Identified on Three Follow-up Examinations by Any One of the Six Algorithms

		Algorithms					
		Advanced Glaucoma Intervention Study	*Collaborative Initial Glaucoma Treatment Study*	*Glaucoma Change Probability*	*Early Manifest Glaucoma Trial*	*Modified Glaucoma Change Probability Score*	*Modified Early Manifest Glaucoma Trial Score*
Progressed Eyes	1	0	0	+	+	+	+
	2	+	+	+	+	+	+
	3	0	0	+	0	+	0
	4	+	+	+	+	+	+
	5	0	0	+	+	+	+
	6	0	0	+	0	+	0

+ = change; 0 = no change.

ference in the results when scoring was based on two versus three consecutive follow-up visual fields, this may be the result of the small overall number of eyes with change from baseline observed on subsequent visual fields.

Differences in the results among the six algorithms are not surprising. The AGIS, CIGTS, and EMGT each were developed to assess a different study population. The AGIS and CIGTS identified less change than GCP or EMGT; Hence, their criteria for change are stricter. For AGIS, a cluster of three or more adjacent, depressed locations within a hemifield must be present before a point can be added to the score. In addition, half or more of depressed locations must have declined by 12 dB or more before a point can be added for severity. Finally, a change in overall score of 4 or more in each follow-up visual field is required for change. For CIGTS, points are given only if a depressed location is accompanied by two contiguous abnormal locations. Change requires an increase or decrease in overall score of 3 or more. The GCP and EMGT require change in any three points in the visual field. Requiring the same three points to be changed on subsequent fields strengthens the criteria and reduces the differences among the algorithms.

Given the small number of patients who had detectable visual field change in this study, additional studies looking at a larger patient population followed up over a longer period are needed to evaluate whether the results obtained using two follow-up visual fields are indeed comparable with those scored using three or more visual fields. Such results can have an impact on the decision when to initiate or modify treatment, because the diagnosis of visual field change may be made earlier if fewer visual fields are required to confirm change. It is important to point out that some of these fluctuations in results may be explained by visit-to-visit glaucoma-related variations in the fields or true changes in the disease state or individual and are not an artifact of testing. In addition, each of these algorithms defines change based on specified cutoff values. A lack of repeatability does not necessarily mean the person has returned to baseline performance. It may simply be that the individual is straddling just above and below the algorithm's cutoff values from one test to the next. Much work is still needed to improve our ability to assess the fluctuating changes resulting from glaucoma.

Katz et al[13] showed that the number of patients identified as having field progression in the same group of glaucoma patients among the AGIS, CIGTS, and EMGT progression algorithms were variable. Although subjective clinical impressions of visual fields are currently relied on to assess change, King et al[18] showed in their study a median interobserver agreement of only 61% (median κ, 0.52). Another group found that in only 15 of their 30 subjects did at least five of six experienced clinician graders agree on behavior of the visual fields.[17] In the absence of a "gold standard," we cannot determine the true rate of glaucoma progression nor the true sensitivity and specificity of each algorithm.

In summary, this study shows the effects of varying the repeatability criteria on the overall detection of change in visual fields among six progression algorithms when applied to the same group of patients. Three of the algorithms used are now part of clinical trials, and the modified versions are available commercially with the Humphrey Visual Field Analyzer and the Glaucoma Change Probability program. It is important to be able to assess the results of studies using these algorithms. Our study compares these algorithms in the same well-defined group of patient eyes. Although confirmation of visual field change is important in differentiating true progression from random fluctuations, it is unclear how many fields are necessary to best confirm change. In addition, although the current algorithms and indices may help to identify early change, we cannot conclude that any one of them is best for identifying true visual field change.

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