Detection of Progression With 10-2 Standard Automated Perimetry: Development and Validation of an Event-Based Algorithm

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• PURPOSE: To describe the development of a new algorithm for detecting progressive changes in 10-2 visual field (VF) tests using event-based analysis and to test its validity in a second, independent glaucoma cohort.

• DESIGN: Prospective cohort study.

• METHODS: Patients with established open-angle glaucoma from the Macular Assessment and Progression Study (MAPS; development cohort, n = 151), and the African Descent and Glaucoma Evaluation Study (ADAGES; validation cohort, n = 52) were evaluated. The 10-2 VF results from MAPS were obtained during 4 test-retest sessions within a 4-month period. For the validation analysis, 10-2 VF results from ADAGES performed on at least 5 visits were used. The event-based pointwise changes on 10-2 tests in the validation cohort were determined using 2 progression criteria: at least 3 progressing VF locations on 2 or 3 consecutive tests ("possible" or "likely" progression). Linear mixed-effects models were used to evaluate VF progression.

• RESULTS: In the validation cohort, the mean (SD) follow-up time was 2.3 (0.7) years. The number of eyes experiencing 10-2 VF progression based on "possible" and "likely" progression was 36 (54.5%) and 11 (16.6%), respectively. Eyes experiencing "possible" progression had MD changes (−0.60 dB/year [95% confidence interval (CI): −0.93 to −0.28]) faster than those not meeting this criterion ($P < .001$), whereas for those with "likely" progression the difference was −0.91 dB/year (95% CI: −1.26 to −0.56, $P < .001$).

• CONCLUSIONS: A new event-based progression algorithm using the 10-2 VF can identify eyes experiencing more rapid MD progression and may be used as a tool to assess progressive macular functional changes in glaucoma. (Am J Ophthalmol 2020;216:37–43. © 2020 Published by Elsevier Inc.)

STANDARD AUTOMATED PERIMETRY (SAP) BASED ON the 24-2 and 30-2 grids is currently the reference method to define and monitor progressive visual field loss in glaucoma. However, there is no consensus on how to define significant visual field progression with those tests. In clinical practice, and in major randomized clinical trials in glaucoma, different approaches have been employed to define whether a patient changed from a normal to an abnormal visual field status or whether deterioration from a pre-existing abnormality was significant.[1,2] One of the challenges to reaching a consensus on what represents significant progression is the fact that SAP is a behavioral test, the variability of which is dependent on patient- and disease-specific characteristics.[3] For instance, test-retest variability of global and local SAP indexes increases as a function of disease severity.[4]

To overcome this, and other limitations of SAP, clinicians have relied on their judgment of glaucomatous visual field progression based on statistical packages that incorporate measures of variability derived from a reference database in which patients with different levels of glaucomatous damage were tested at short intervals—assuming that changes in such a short period were likely attributable to "noise" and not true progression.[5,6]

One such package used clinically is the Guided Progression Analysis (GPA) software (Carl Zeiss Meditec, Inc, Dublin, California, USA). The GPA is based on a database of glaucoma patients tested multiple times over a short period (Heijl and associates, 1989[4]). For the event-based analysis of progression, a test location is deemed as progressing if the change from the average of 2 baseline tests exceeds the lower limit of test-retest variability for

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that location (with a similar level of damage) derived from the reference database. The GPA software then assesses the repeatability of 3 or more test locations and reports "possible progression" if 2 consecutive visual field tests show 3 or more of the same locations that changed from baseline, and reports "likely progression" if 3 consecutive tests show change at the same 3 or more locations.

Recent structural and functional evidence has suggested that macular damage occurs even in early glaucoma.[7] Functional monitoring of the macula is clinically important because the macular region, defined here as the central 8° around the fovea, includes about 30% of all retinal ganglion cells.[7,8] Nevertheless, glaucomatous damage to the macula can be missed if only 24-2 or 30-2 visual fields and peripapillary optical coherence tomography (OCT) scans are performed.[9–12] Additionally, macular damage is frequently present and is more easily detected in early glaucoma if assessed with 10-2 visual fields tests[9,11,13,14] and OCT cube scans of the macula.[7,10,15,16]

Despite the growing interest in the assessment of macular damage in glaucoma, GPA does not include a reference database of 10-2 visual field tests that could be used to define an event-based determination of macular progression. Given the increasing interest in the role of 10-2 visual fields in early glaucoma, it will become critical to have a tool to detect significant change in a manner similar to what has been done with 24-2 and 30-2 tests. In the present study, we describe the development of such a reference database, and then validate it in an independent sample to establish whether its results can determine glaucoma progression in the central visual field.

METHODS

DATA FROM 2 NATIONAL EYE INSTITUTE–FUNDED COHORTS were analyzed in this prospective cohort study: The Macular Assessment and Progression Study (MAPS) and the African Descent and Glaucoma Evaluation Study (ADAGES) (clinicaltrials.gov identifiers: NCT02547740 and NCT00221923).

• **MACULAR ASSESSMENT AND PROGRESSION STUDY (DEVELOPMENT COHORT):** This 1-site prospective study has been conducted at the Edward S. Harkness Eye Institute at Columbia University Medical Center. The institutional review board approved the study methodology, which adheres to the tenets of the Declaration of Helsinki and to the Health Insurance Portability and Accountability Act. All participants gave written informed consent. MAPS enrollment began in August 2015 and is ongoing. Data collected until January 2019 were included in the present analysis.

• **AFRICAN DESCENT AND GLAUCOMA EVALUATION STUDY (VALIDATION COHORT):** The 3-site ADAGES collaboration includes the Hamilton Glaucoma Center at the Department of Ophthalmology, University of California–San Diego (data coordinating center); Edward S. Harkness Eye Institute at Columbia University Medical Center; and the Department of Ophthalmology, University of Alabama-Birmingham. The institutional review boards at all sites approved the study methodology, which adheres to the tenets of the Declaration of Helsinki and to the Health Insurance Portability and Accountability Act. All participants gave written informed consent. ADAGES enrollment began in January 2003 and ended in July 2006, while follow-up included in this analysis through 2017.

• **INCLUSION CRITERIA AT BASELINE:** In both studies, participants older than 18 years, with open angles, a best-corrected visual acuity ≥20/40, and a refractive error <5.0 diopters sphere and <3.0 diopters cylinder were included. At least 1 high-quality stereophotograph and 2 reliable SAP Humphrey 24-2 field test results at baseline were required, defined as <15% false-positives, <30% false-negatives, and <20% fixation losses. Although 10-2 tests were not employed at baseline in ADAGES, they had to meet the same reliability criteria as 24-2 tests. In addition, MAPS participants were required to have a baseline 24-2 mean deviation (MD) better than −6 dB at the screening visit. Diabetic participants without evidence of retinopathy were included.

• **EXCLUSION CRITERIA:** In both studies, participants were excluded if they had a history of intraocular surgery other than an uncomplicated cataract or glaucoma surgery; secondary causes of glaucoma; other systemic or ocular diseases known to affect the visual field (including neurologic diseases and cognitive impairment) or potentially preclude retention in the study; ocular disorders other than glaucoma affecting color vision; or an inability in performing reliable visual field examinations.

• **DEFINITIONS:** For the present study, only patients from both cohorts with glaucomatous optic neuropathy and abnormal visual fields were included.

Glaucomatous optic neuropathy was defined as excavation, neuroretinal rim thinning or notching, localized or diffuse retinal nerve fiber layer defect, or vertical cup-to-disc ratio asymmetry >0.2 between eyes (not explained by differences in disc size) based on masked grading of stereophotographs by 2 experienced graders at the Imaging Data Evaluation and Analysis Center (ADAGES) and 2 glaucoma specialists (MAPS). Disagreement regarding glaucomatous optic neuropathy status was resolved by adjudication by a third experienced grader or by consensus. Only photographs of adequate quality were used for evaluation.

SAP 24-2 visual field results were considered abnormal if the pattern standard deviation had a $P < 5\%$ or the

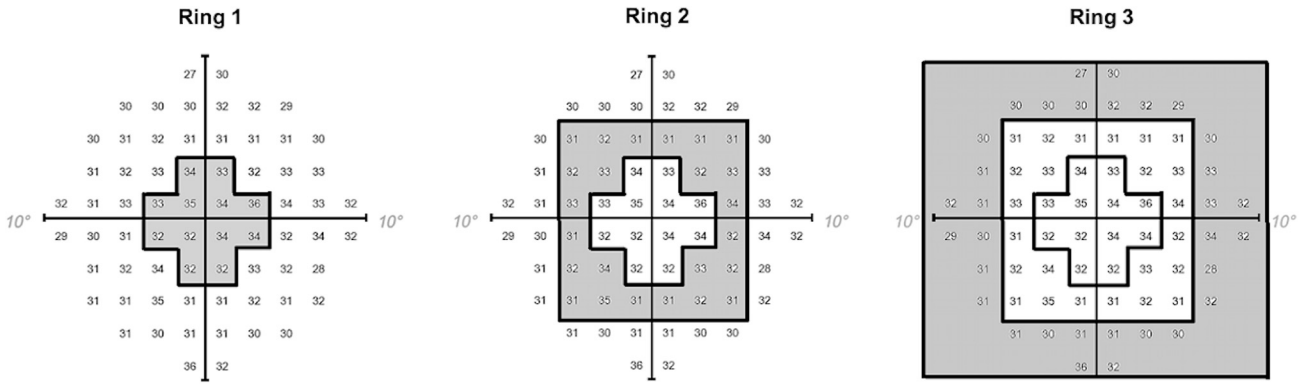

FIGURE 1. Schematic representation of the 3 concentric areas (rings) used in the 10-2 visual field tests from the development cohort for calculation of the sectorial limits of variability.

Glaucoma Hemifield Test result was "outside normal limits" (ADAGES) or based on expert evaluation (MAPS). Abnormality had to be confirmed with an additional visual field test.

• **TESTING:** The detailed procedures completed for ADAGES have been described elsewhere.[17] MAPS followed a similar protocol with the exception of a test-retest period that required 4 visits during 4 months, which included both 24-2 and 10-2 visual field tests. In addition, MAPS participants classified as healthy subjects and glaucoma suspects were asked to return every 6 months while glaucoma patients were tested at 4-month intervals. Participants of both studies underwent a comprehensive ophthalmic examination, including annual review of medical history, best-corrected visual acuity, slit-lamp biomicroscopy, intraocular pressure, dilated funduscopy examination, pachymetry, simultaneous stereoscopic optic disc photography, and SAP with Swedish interactive threshold algorithm (Humphrey Field Analyzer; Carl Zeiss Meditec, Inc, Dublin, California, USA).

• **DEVELOPMENT OF AN EVENT-BASED PROGRESSION ALGORITHM:** Only the 4 test-retest 10-2 SAP data from MAPS were included in the definition of limits of variability. For each test, we defined 3 concentric visual field areas ("rings"). These were determined from the 68 points tested in the 10-2 pattern deviation (PD) plots as follows: ring 1, the 12 inner central points; ring 2, the 24 middle points; and ring 3, the 32 outer points (Figure 1). For each ring, the pooled retested results from each point were plotted with quantile regression analysis to calculate the 5% and the 95% quantile limits of variability, taking the results from the first test as the baseline PD values. Similar methodology was employed in the development of the GPA.[5] These limits were then used to further determine whether PD values measured in a follow-up period were significantly different from baseline in the validation (ADAGES) cohort.

• **VALIDATION OF AN EVENT-BASED PROGRESSION ALGORITHM:** For the pointwise analysis, baseline PD sensitivity values for each visual field location from ADAGES were calculated using the average of the 2 initial tests. Then, predictions from the quantile regression models derived from MAPS were used to define the fifth percentile limits of variability for each test location of each ADAGES participant, considering the 3 rings proposed. PD values during follow-up that exceeded the lower fifth percentile were considered as "progressing locations."

For comparison purposes, and analogous to the GPA, progression was categorized based on the number of consecutive tests confirming significant change: at least 3 progressing visual field locations on 2 consecutive tests ("possible" progression) and at least 3 progressing visual field locations on 3 consecutive tests ("likely" progression).

The "specificity" of the above criteria was estimated based on the number of tests locations experiencing improvement relative to the limits of variability. For such, PD values during follow-up that exceeded the upper fifth percentile were considered as "improving locations." If the eye had at least 3 improving visual field locations on 2 consecutive tests it was deemed "possible" improvement, whereas at least 3 improving locations on 3 consecutive tests was deemed "likely" improvement.

• **STATISTICAL ANALYSES:** Continuous variables are described as means and standard deviation (SD). Linear mixed-effects models were used to verify progressing eyes ("possible" or "likely" progression) in the validation cohort. This type of model takes into account random effects associated with intercepts and slopes, which adjust for the inclusion of both eyes of the same patient, and the correlation of residuals in longitudinal data. The interaction term "Progression" × "Time" describes the difference in slopes of 10-2 visual field PD values between stable and both "possible" and "likely" progressing eyes. The relationship between duration of follow-up and meeting the progression and improvement criteria was tested with

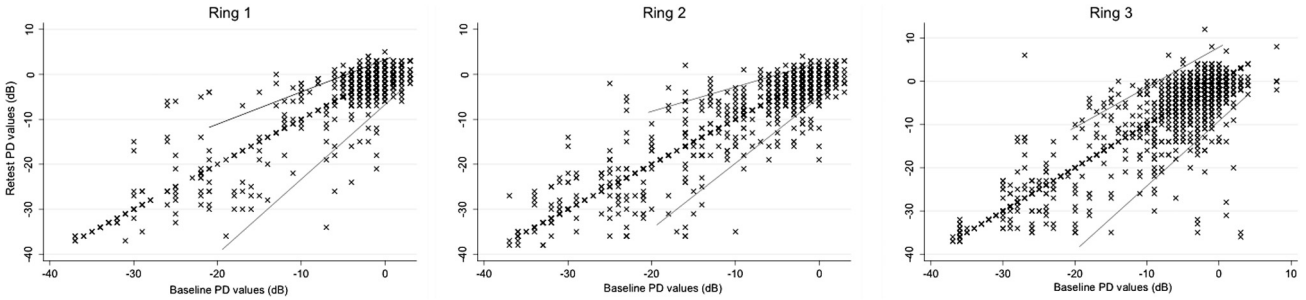

FIGURE 2. Dispersion of the test-retest pattern deviation (PD) results with the 5th and 95th quantile regression models, using the baseline PD values from the development cohort in the 3 concentric rings.

logistic regression with binary outcomes. Because there is currently no definition of what constitutes an early or an advanced 10-2 visual field result, we divided our sample based on a median split using the median of the baseline 10-2 MD values for evaluating influences of disease severity on detection rates. Statistical analyses were performed using commercially available software (STATA, version 14; StataCorp LP, College Station, Texas, USA). Statistical significance was defined at $P < .05$.

RESULTS

THE DEVELOPMENT COHORT INCLUDED 151 EYES WITH open-angle glaucoma from MAPS (age, 65.8 ± 11.0 years), with mean baseline 10-2 visual field MD of −2.9 ± 4.0 dB (range, −25.8 to 1.7 dB). The validation cohort included 66 eyes of 52 open-angle patients from ADAGES (mean age at baseline, 67.9 ± 10.4 years) who underwent at least 5 reliable 10-2 visual field tests (mean baseline MD, −6.3 ± 6.5 dB; range, −26.3 to 1.1 dB).

Figure 2 shows the dispersion of the test-retest session with PD values with the 5th and 95th quantile regression models, using the baseline PD values from development cohort in the 3 concentric rings. Of note, the development cohort included pointwise PD values that spanned the entire range of sensitivities (from approximately 0 to −30 dB).

In the validation cohort, the mean follow-up time was 2.3 ± 0.7 years (range, 0.9 to 5.0 years). The number of eyes experiencing 10-2 visual field progression based on "possible" and "likely" progression was 36 (54.5%) and 11 (16.6%), respectively. Eyes experiencing "possible" progression had MD slopes −0.60 dB/year (95% confidence interval [CI]: −0.93 to −0.28) faster than those not meeting this criterion ($P < .001$) whereas for those with "likely" progression the difference was −0.91 dB/year (95% CI: −1.26 to −0.56, $P < .001$) (Table 1). Given the differences in disease severity between the 2 cohorts, we investigated the role of disease severity on detection rates. Among eyes with baseline 10-2 MD values better (more positive) than −4.4 dB (which is the median of the sample), 3 of 32 (9.3%) and 12 of 32 (37.5%) experienced "likely" and "possible" progression, respectively. Among those with 10-2 MD values worse than the median, these numbers were 8 of 34 (23.5%) and 24 of 34 (70.5%).

For the "specificity" analysis, 16 eyes (24.2%) experienced "possible" improvement and 3 eyes (4.5%) experienced "likely" improvement. There was significant association between total follow-up time and the likelihood of experiencing "likely" progression or improvement (odds ratio [OR] = 4.17/year; 95% CI = 1.53 to 11.33, $P = .005$; OR = 4.40; 95% CI = 1.19 to 16.24; $P = .026$; respectively). Regarding changes observed in the different rings, the number of likely progression points was larger in the periphery (ring 3), followed by ring 2 and ring 1, while the number of points showing improvement was more similar in the 3 rings with a more diffuse pattern consistent with noise (Table 2). Moreover, there was no significant difference in MD slopes between eyes experiencing "possible" improvement and those that did not (difference in slopes = −0.01 dB/year, 95% CI = −0.42 to 0.39, $P = .950$), which was also true among those experiencing "likely" improvement (difference in slopes = 0.39 dB/year, 95% CI = −0.35 to 1.15, $P = .303$).

DISCUSSION

THERE IS CURRENTLY NO COMMERCIALLY AVAILABLE pointwise event-based analysis for 10-2 visual fields. We tested the hypothesis that one such algorithm derived from the 10-2 visual field PD values could differentiate progressing from nonprogressing based on the rates of change of functional metrics derived from the macular area. Based on the limits of test-retest variability from an independent sample, our algorithm was able to detect groups of eyes experiencing significantly different rates of trend-based progression based on the 10-2 MD values. To the best of our knowledge, this is the first report of an event-based analysis of progression using Humphrey 10-2 visual fields in glaucoma.

TABLE 1. Mean Deviation Slopes of 10-2 Visual Fields of Eyes Categorized as Progressing and Nonprogressing, According to the Event-Based Pointwise Changes

Progression	"Possible" (dB/Year)	"Likely"(dB/Year)
Progressing eye	−0.64 (−0.91 to −0.38)	−1.06 (−1.38 to −0.73)
Nonprogressing eye	−0.04 (−0.10 to 0.11)	−0.19 (−0.31 to −0.06)
P value	<.001	<.001

Data are presented as mean (95% confidence interval).

TABLE 2. Distribution of the Number of Points With Confirmed Progression and Improvement on Rings 1, 2, and 3 of 10-2 Visual Fields, According to the Event-Based Pointwise Algorithm Used

Eccentricity	Confirmed Progression	Confirmed Improvement
Ring 1 (mean, range)	0.04 (0-2)	0.02 (0-2)
Ring 2 (mean, range)	0.13 (0-8)	0.04 (0-2)
Ring 3 (mean, range)	0.23 (0-6)	0.05 (0-4)

Central visual field defects may be present in early glaucoma[7,11,14,18] and are not uncommon.[10,13,15,19] When present at the baseline examination, they have been reported to be predictive of more rapid global (24-2) visual field progression.[20] Many studies have also pointed out the important role of central field damage, associated with macular function (with[19,20] or without[21,22] spatially consistent OCT damage), on vision-related quality of life in glaucoma. Putting these findings together with the growing use of 10-2 visual fields in clinical practice, a robust tool for discriminating progression in a sequence of 10-2 tests from early disease stages is needed.

In this study, the event-based rather than the trend-based approach was chosen owing to the widespread use of the former in clinical practice as well as its ease and familiarity of interpretation. We have previously developed a trend-based algorithm to measure global rates of change of 10-2 fields, which was significantly associated with follow-up intraocular pressure and was minimally affected by the presence of cataract.[23] In another study using principal component analyses, we identified clusters of 10-2 locations that progressed more rapidly based on pointwise linear regression analysis.[24] More recently, Asano and associates[25] reported that a new binomial pointwise linear regression method detected glaucomatous 10-2 visual field progression in the central 10° significantly earlier than other methods, including trend analyses of the 10-2 MD.

For the present event-based analysis of progression, a test location was deemed as progressing if the change from the average of 2 baseline tests exceeds the chosen lower limit of test-retest variability for that location. Variability was adjusted for different depths of sensitivity as well as eccentricity given their known role on 24-2 and 30-2 patterns.[3,4] We employed the same rationale and proposed the lower fifth percentile as the limit of test-retest for each location in 3 concentric rings to develop the current algorithm. Consistent with previous studies,[5,26] the requirement of confirmation on consecutive tests improved the specificity to detect significant progression on 10-2 fields as well. This observation was also reported for the GPA by Artes and associates,[27] who estimated the false-positive rates of "possible" and "likely" progression with the 24-2 GPA to be on average 18.5% and 2.6%, respectively, over a sequence of 10 tests. Notably, and consistent with our findings, these rates increase as a function of time.[27]

Limitations of this study include the lack of eyes in the development cohort with 24-2 MD worse than −6 dB at baseline. Although 10-2 *pointwise* PD values had a broader range, the small number of eyes with more severe visual fields may pose a limitation to detect progression in more advanced glaucoma using the present algorithm. We are currently expanding the inclusion criteria to enable a more robust algorithm. Another limitation was our estimation of specificity based on improving locations. Given the lack of a gold standard to define glaucomatous progression (and hence stability), studies have employed different methods to estimate the specificity of different progression criteria. Among such methods, simulations of stable fields[28,29] or the assessment of improving locations have been reported.[30,31] Whether visual fields improve owing to a "true" pathophysiologic phenomenon involving ganglion cell recovery or owing to purely stochastic reasons is open to debate. The improving locations may also change over time as a biased consequence of our analyses. Considering the more specific criteria ("likely" improvement), the distribution of the 95% CI was more positive; this suggests a trend toward improvement. However, the small sample size may have prevented detection of such effects. Alternatively, perhaps improving locations based on events may be occurring just by chance without affecting the global status of the visual field. Despite the above limitations, the present algorithm was able to identify eyes experiencing rapid progression in the validation cohort, which included the entire range of glaucoma severity with reasonable *estimated* specificity (4.5% for "likely" criteria). Further, new visual field tests that map the sensitivity of the macular region, and also do not depend on fixation, could help improve the detection of glaucomatous progression.[32]

Of note, progression based on our criteria was more common among eyes with more severe macular visual field damage. This finding could be attributable either to differences in disease severity between the development and validation cohorts or to a true effect of visual field severity

on the likelihood of progression, as has been demonstrated with conventional 24-2 visual fields in previous studies.

In conclusion, we developed a robust algorithm for detecting glaucoma progression using the 10-2 visual field based on a pointwise event-based approach. Future studies are needed to better assess its added value in clinical practice and how it compares to the more conventional 24-2 grid.

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