Refinement of Pointwise Linear Regression Criteria for Determining Glaucoma Progression

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PURPOSE. A variety of pointwise linear regression (PLR) criteria have been proposed for determining glaucomatous visual field progression. However, alternative PLR criteria have only been assessed on a limited basis. The purpose of this study was to evaluate a range of PLR slope and significance criteria to define a clinically useful progression decision rule for longitudinal visual field examinations.

METHODS. Visual field data for each of 140 eyes (one per participant among 96 cases and 44 controls) were evaluated using the Humphrey Field Analyzer II program 24-2 Swedish interactive thresholding algorithm standard test strategy and Goldmann size III stimuli. The pointwise linear regression A2 (PLRA2) method was used to analyze the data, which included nine visual field examinations performed every 6 months for 4 years. Data from the Ocular Hypertension Treatment Study (OHTS) were used to validate the decision rule.

RESULTS. Several slope criteria produced specificities of 0.90 or higher, particularly slope criteria of less than -1.2 dB/y. The use of the slope criterion less than -1.2 dB/y at a significance level of $P < 0.04$ for classification resulted in a hit rate of 0.38, more than a 2-fold increase compared with a commonly used standard slope criterion of less than -1.0 dB/y at a significance level of $P < 0.01$. A similar increase in the hit rate was shown for a slope of less than -1.2 dB/y and $P < 0.04$ compared with the standard criterion in the independent OHTS validation data.

CONCLUSIONS. When systematically evaluating criteria for detecting glaucoma progression, PLR criteria can be refined by requiring a stricter slope criterion such as less than -1.2 dB/y and relaxing the significance criterion to $P < 0.04$. Increasing the hit rate of PLR will be useful for early detection and treatment of glaucoma.

Keywords: pointwise linear regression, glaucoma progression, perimetry, trend analysis, visual field

The determination of glaucoma progression is based on a variety of clinical signs and measures, which include the assessment of visual field status over time. Two commonly used definitions of visual field change over time for individual or grouped visual field test locations are based on event analysis (change from baseline) and trend analysis (change in visual field function over time).¹ Subjective assessment by experienced, knowledgeable glaucoma specialists and classification (staging) systems has also been used, although this is not as clinically helpful as event and trend analyses because of low interrater and intrarater agreement.²⁻⁴

The natural history of glaucoma progression includes a linear pattern of gradual loss perceived through trend analyses (e.g., using PROGRESSOR; Institute of Ophthalmology, University College London, and Moorfields Eye Hospital National Health System Foundation Trust, London, UK) and a stepwise pattern of decay perceived through glaucoma change probability analyses (e.g., using StatPac2; StatPac, Inc., Bloomington MN).⁵ The two approaches are similar in that they are

pointwise analytic methods to identify locations of the visual field that indicate significant visual loss. The trend analysis approach to glaucoma progression detection was used in the present study primarily because gradual loss over time has been shown to occur more often than abrupt change.⁶ The mean deviation (MD) is a weighted mean of the total deviation values in the visual field, indicating the overall amount of visual field damage compared with a normative database. Trend analyses can be based on one of several possible dependent outcomes, including either MD or pointwise sensitivity within location. Individual pointwise sensitivities at each location in the visual field were used for the present study because they indicate specific areas of the visual field that may be deteriorating (or improving) and are useful in detecting more subtle changes in visual field test results over time.

Pointwise linear regression (PLR) analysis involves the regression of visual field data at each test location as the dependent variable versus time as the independent variable. A location is considered to be progressing if it fulfills specified

slope and significance criteria. The frequently applied criterion is a slope of less than -1.0 dB/y with an associated $P < 0.01$ significance level,⁷ a rule originally proposed by Fitzke et al.⁸ and later validated by Viswanathan et al.⁹ To date, few evaluations of alternative decision rules defined by a range of slope and significance level criteria have been conducted. Justification for the current standard criterion of slope less than -1.0 dB/y and $P < 0.01$ is that this strict slope criterion increases the probability that the observed statistically significant decline is actually clinically meaningful, and the $P < 0.01$ significance level criterion limits the risk of a type I error.¹⁰ Selection of a criterion to define a decision rule for determining progression can affect the performance of the visual field analyses.^{7,11–14}

Nouri-Mahdavi et al.¹⁴ found that PLR methods may better agree with clinical assessment than other methods of determining progression. Several PLR-based algorithms requiring a certain number of contiguous visual field examinations at which the criterion for progression is satisfied have been proposed, including two of two,¹⁵ three of three,¹⁶ two of three (Wescott MC, et al. *IOVS* 2001;42:ARVO Abstract 3005), and three of four.^{17,18} In addition, some PLR methods use a location criterion that requires a specified number (usually two or three) of locations to be flagged by the criterion to classify the eye as demonstrating progressive glaucomatous visual field decline.

The pointwise linear regression A2 (PLRA2) method used in this study is defined as two or more locations (which need not be contiguous) within the visual field satisfying the standard criterion at three of four consecutive visual field examinations. This method has been found to be highly specific⁷ and identifies a clinically meaningful number of eyes as progressing. However, the statistical significance criterion needed to achieve optimal results can be influenced by the number of visual field examinations at which data are collected.⁷ Generally, a minimum of seven to eight visual field examinations is needed to attain acceptable performance of PLR.^{11,19,20}

The purpose of this study was to compare the classification performance for a range of PLR slope and significance level criteria. The study aimed to define a primary decision rule for the determination of glaucomatous visual field progression.

METHODS

Study Design

Adult patients with glaucoma were recruited from the glaucoma clinic at the University of Iowa Department of Ophthalmology and Visual Sciences. The research was approved by the University of Iowa and Veterans Affairs institutional review boards, and informed consent was obtained from all patients after an explanation of the study. Data were collected between 2003 and 2009. Inclusion criteria for cases were as follows: (1) the clinical diagnosis of glaucoma determined by the presence of glaucomatous optic disc changes confirmed through the examination of fundus images and (2) the presence of visual field defects (MD between 0 and -20 dB on standard automated perimetry, as well as either three adjacent locations in a clinically suspicious area falling outside the deviation limits compared with normative data at $P < 0.05$ or two adjacent locations at $P < 0.01$). Cases were not required to have elevated intraocular pressure, but they were excluded if there were cataracts causing visual acuity worse than 20/30, they were younger than 19 years, or they had a pupil size of less than 2.5 mm. If both eyes qualified, one eye was randomly selected for inclusion in the study.

Ocularly healthy adults (controls) were recruited using advertisements inviting participation in a research study. Inclusion criteria for controls were as follows: (1) no history of eye disease, (2) refractive error within a ± 5 -diopter sphere and ± 2 -diopter cylinder, (3) no history of diabetes mellitus or systemic arterial hypertension, and (4) a normal ophthalmologic examination result, including 20/30 or better visual acuity. An examination by an ophthalmologist on the day of testing or the results of a complete eye examination within 2 years of the testing date was used to confirm normal ocular health. One eye was randomly selected for the study. If a control developed a pattern of visual loss leading to an ophthalmologic diagnosis other than refractive error, the individual was not included in the analysis. This research adhered to the tenets of the Declaration of Helsinki.

For all participants, threshold data for 54 locations of the visual field were obtained using the 24-2 program of the Humphrey Field Analyzer II (Carl Zeiss Meditec, Dublin, CA). Results within the usual location for the physiologic blind spot (X, Y locations at 15° , 3° , and 15° , -3° from the fixation point) were excluded. Goldmann size III (0.43° diameter) stimuli were used with the standard 24-2 Swedish interactive thresholding algorithm (SITA).²¹

Visual field data from the Ocular Hypertension Treatment Study (OHTS) were used for the validation of the PLR criterion found to be optimal in our study. Details of the OHTS protocol can be found in previous literature²² and online at <https://vrcc.wustl.edu/> (in the public domain). Eligible for inclusion in our validation study were 850 of 1493 participants with ocular hypertension (24–32 mm Hg in one eye and 21–32 mm Hg in the other eye) and no evidence of glaucomatous damage at baseline who were enrolled in the OHTS and had nine or more visual field examinations using the SITA thresholding algorithm. One eye was randomly selected for each patient independent of disease status at the OHTS end point. Data were originally collected using the Humphrey 30-2 program. Consequently, the 54 locations that occur on the 24-2 program were extracted from the total of 76 locations that occur on the 30-2 program, and the physiological blind spots were excluded. The remaining 52 locations were analyzed using the same methods as the original data (see the Statistical Analysis subsection). Of 850 OHTS study eyes included in the validation study, 120 (14.1%) were diagnosed as having primary open-angle glaucoma (POAG) at the OHTS end point. Any determination of POAG using the OHTS criteria²² in the randomly selected study eye was used to define case status.

Statistical Analysis

No gold standard independent of visual field testing exists for the detection of glaucoma progression,^{1,23} although definite change in the optic disc is considered a strong indicator. A decline in a patient's visual field function across a minimum of seven to eight examinations can be identified using trend analysis (i.e., analysis of the pattern of visual field test results over time). Glaucomatous progression at a location is assumed when the decay over time is "steep enough" at a prespecified significance level. Using PLR, a simple linear regression model of visual field data versus time is fit at each location, and the estimate and significance of the slope are used to assess the extent of visual decay over time.

The hit rate is defined as the proportion of patients with glaucoma found to be progressing, while the specificity is defined as the proportion of ocularly healthy individuals determined to have no progression. The hit rates and specificities over a range of slope criteria varying by 0.2 dB/y in the interval $(-2.0, 0)$ were estimated compared with case status. For each slope criterion (11 in all), the effect of a range

FIGURE 1. Visual field location flagged as progressing by PLR analysis. The first progression found by PLR is at time point seven. The PLRA2 then fits a regression model incorporating visual field examinations eight and then nine to confirm the determination of progression at time point seven.

of significance levels from 0.01 to 0.10 in increments of 0.01 was explored, resulting in the construction of a family of 11 curves similar to receiver operating characteristic (ROC) curves,²⁴ which are graphical plots illustrating the performance of a classification system as the significance criterion is varied. The area under the ROC curve (AUC) was calculated for each slope criterion.

The PLRA2 algorithm was used to classify individuals as progressing or having stable visual function. At all locations separately, PLRA2 tests threshold sensitivities; for each time point within location, a linear model is fit to all data from baseline to that time point. If the slope and significance criteria of that linear model are met, then a separate regression model is fit from the baseline measure to each of three additional visual field examinations (Fig. 1). If the slope and significance criteria are met for two of the three additional visual field examinations, then visual field decline at the original time point is confirmed. Overall, if two or more locations within the eye are significantly declining, PLRA2 classifies the eye as progressing.

Because the use of standard clinical software for PLR analysis (e.g., PROGRESSOR) would be inefficient for analyzing a large number of patients using PLRA2, an iterative R program using R statistical software (<http://www.R-project.org/> in the public domain) was written by CMK to reproduce the algorithm and expand the method to explore the range of criteria considered in our study. The baseline and subsequent two visual field examinations were regressed, and then successive examinations were regressed iteratively to determine the first point of visual field decay. More than 5 million regression analyses of visual field data versus time (140 individuals $\times$ 52 locations per individual $\times$ 7 iterative

regressions per location $\times$ 110 criteria) were performed. For the validation study using the OHTS data, approximately 1 million additional regression analyses were performed and summarized. The estimated slope and corresponding significance level were recorded for each analysis to be used for classification based on the PLRA2 definition.

The visual field threshold value at each time point was compared with a database of normally sighted individuals of similar age as part of the Humphrey Field Analyzer II program. From this comparison, the value for the threshold at this location was classified as being normal or abnormal at a probability level of 5%, 2%, 1%, or 0.5%. For each location, a deviation was calculated from the expected threshold value for a person of the same race/ethnicity and age using the Humphrey program. The average of these deviations across all 54 visual field locations is referred to as the MD. Individuals who are able to see dimmer stimuli on average than others of similar age and race/ethnicity will have positive MD values. Those who require more intense stimuli on average will have negative MD values. The average MD for cases and controls was calculated at baseline and at the conclusion of the study. For this study, a specificity of 0.90 or higher was considered clinically acceptable because a high specificity is of more importance than statistical optimization to avoid exposing controls to potentially damaging treatments (presumed false positives).

A difference in age between cases and controls was tested using a two-sample *t*-test with the Satterthwaite approximation of the *df*, since it does not assume equal variance.²⁵ SAS software version 9.2 (SAS Institute, Inc., Cary, NC) was used for data management, and R statistical software version 2.13.1 was

TABLE 1. Characteristics of Case and Control Individuals (Data From One Eye per Individual Were Used in the Study)

Characteristic	Cases, <i>n</i> = 96	Controls, <i>n</i> = 44
Age, mean (SD) [range], y	64.6 (8.8) [38–81]	57.8 (8.4) [40–78]
Eye, <i>n</i>		
Right	53	20
Left	43	24
MD, dB		
At baseline	−6.67	0.65
At conclusion	−8.14	0.40

used for the PLR analysis and for computation of hit rate and specificity.

RESULTS

One hundred forty individuals, one eye per participant, provided sufficient data to be included in our study, comprising 96 cases with a clinical diagnosis of glaucoma and 44 ocularly healthy controls. The mean (SD) age for cases was 64.6 (8.8) years compared with a mean (SD) age of 57.8 (8.4) years for controls ($P < 0.0001$). Data analyzed included nine visual field examinations performed every 6 months for 4 years for cases and controls. The average MD of cases at baseline was −6.67 and declined to an average of −8.14 by the conclusion of the study; in contrast, controls had average MDs of 0.65 and 0.40, respectively (Table 1).

Several slope and significance level criteria, particularly slope criteria of less than −1.2 dB/y, produced a specificity of

0.90 or higher, indicating that no more than 10% of control eyes were identified as progressing. The hit rate and specificity of PLRA2 for each slope and significance level criterion are given in Table 2.

As expected, the use of slope criteria in the range of less than 0.0 dB/y to less than −0.8 dB/y produced specificity below optimal level (<0.90) for all but the most strict significance level criterion of $P < 0.01$; in addition, the 0.15 hit rate was low at $P < 0.01$. Applying the standard criterion of slope less than −1.0 dB/y and $P < 0.01$ significance level, all controls were classified as not progressing by PLRA2 (specificity of 1.00); however, the associated hit rate was very low at 0.10. When the significance level was set at $P < 0.02$, the hit rate for the slope criterion of less than −1.0 dB/y increased to 0.25. All other significance criteria for the slope criterion of less than −1.0 dB/y resulted in specificities of less than 0.90.

For the slope criterion of less than −1.2 dB/y, the significance level of $P < 0.04$ resulted in the highest hit rate of 0.38, while maintaining a 0.93 specificity. The hit rates for the slope criteria of less than −1.4 dB/y and less than −1.6 dB/y were both highest using a $P < 0.05$ significance level criterion.

Overall, the highest hit rate for a criterion maintaining a specificity of 0.90 or higher was found using the slope criterion of less than −1.8 dB/y and a significance level of $P < 0.10$, which yielded a hit rate of 0.48 and a specificity of 0.93. The specificity using the PLRA2 algorithm was found to be 1.00 for all significance levels of the slope criterion less than −2.0 dB/y, and the highest hit rate for this slope criterion was 0.44, found at the significance level criterion of $P < 0.10$. The use of the following criteria produced hit rates of 0.35 or higher and specificities of greater than 0.90: slope of less than −1.2 dB/y and $P < 0.04$, slope of less than −1.4 dB/y and $P < 0.05$, slope

TABLE 2. Hit Rates and Specificities With Nine Visual Field Examinations Among 140 Eyes Using PLRA2 Analysis of Longitudinal Goldmann Size III SITA Full-Threshold Visual Field Data

Slope, dB/y	Variable	<i>P</i> Value of Slope										AUC
		0.01	0.02	0.03	0.04	0.05	0.06	0.07	0.08	0.09	0.10	
0.0	Hit rate	0.15‡	0.31†	0.47†	0.52*	0.57*	0.64*	0.69*	0.71*	0.77*	0.81*	0.6953
	Specificity	1.00‡	1.00†	1.00†	1.00*	1.00*	1.00*	1.00*	1.00*	1.00*	1.00*	
−0.2	Hit rate	0.15‡	0.31†	0.47†	0.52*	0.57*	0.64*	0.69*	0.71*	0.77*	0.81*	0.6953
	Specificity	0.98‡	0.86†	0.82†	0.75*	0.70*	0.59*	0.57*	0.52*	0.48*	0.48*	
−0.4	Hit rate	0.15‡	0.31†	0.47†	0.52*	0.56*	0.64*	0.69*	0.71*	0.77*	0.81*	0.7006
	Specificity	0.98‡	0.86†	0.82†	0.75*	0.70*	0.61*	0.59*	0.55*	0.50*	0.50*	
−0.6	Hit rate	0.15‡	0.31†	0.45†	0.51*	0.55*	0.60*	0.66*	0.69*	0.75*	0.79*	0.7083
	Specificity	0.98‡	0.86†	0.84†	0.77*	0.77*	0.70*	0.64*	0.59*	0.57*	0.57*	
−0.8	Hit rate	0.13‡	0.28†	0.42†	0.47*	0.53*	0.57*	0.60*	0.64*	0.71*	0.75*	0.7216
	Specificity	1.00‡	0.86†	0.84†	0.77*	0.77*	0.70*	0.68*	0.64*	0.64*	0.64*	
−1.0	Hit rate	0.10‡	0.25‡	0.36†	0.44†	0.50†	0.55*	0.58*	0.60*	0.69*	0.73*	0.7249
	Specificity	1.00‡	0.91‡	0.89†	0.86†	0.80†	0.73*	0.70*	0.66*	0.66*	0.64*	
−1.2	Hit rate	0.08‡	0.21‡	0.31‡	0.38‡	0.42†	0.48*	0.53*	0.55*	0.63*	0.67*	0.7394
	Specificity	1.00‡	0.98‡	0.98‡	0.93‡	0.89†	0.77*	0.77*	0.75*	0.75*	0.75*	
−1.4	Hit rate	0.07‡	0.19‡	0.25‡	0.31‡	0.38‡	0.44†	0.46†	0.49†	0.55†	0.58†	0.7127
	Specificity	1.00‡	0.98‡	0.98‡	0.95‡	0.91‡	0.80†	0.80†	0.80†	0.80†	0.80†	
−1.6	Hit rate	0.06‡	0.16‡	0.24‡	0.30‡	0.36‡	0.43†	0.44†	0.47†	0.52†	0.54†	0.7120
	Specificity	1.00‡	1.00‡	1.00‡	1.00‡	0.98‡	0.86†	0.86†	0.86†	0.84†	0.84†	
−1.8	Hit rate	0.05‡	0.15‡	0.22‡	0.28‡	0.31‡	0.39‡	0.40‡	0.42‡	0.46‡	0.48‡	0.7019
	Specificity	1.00‡	1.00‡	1.00‡	1.00‡	0.98‡	0.93‡	0.93‡	0.93‡	0.93‡	0.93‡	
−2.0	Hit rate	0.04‡	0.14‡	0.21‡	0.27‡	0.29‡	0.35‡	0.36‡	0.39‡	0.42‡	0.44‡	0.7072
	Specificity	1.00‡	1.00‡	1.00‡	1.00‡	1.00‡	1.00‡	1.00‡	1.00‡	1.00‡	1.00‡	

The hit rate is defined as the proportion of patients with glaucoma who were found to be progressing, while the specificity is defined as the proportion of ocularly healthy individuals determined to have no progression. Slope is the parameter estimate from the ordinary least squares linear regression model of visual field on time, with the P value from the two-sided test of the null hypothesis that slope equals 0.

* Criteria that yield higher hit rate but clinically unacceptable specificity (<0.80).

† Criteria with specificity in the interval (0.80, 0.90).

‡ Criteria with clinically acceptable levels of specificity (>0.90).

TABLE 3. Validation of New PLR Slope and Significance Criteria Using an Independent Data Set From the OHTS

Slope and Significance Criteria	Original Data Set, <i>n</i> = 140		OHTS Validation Data Set, <i>n</i> = 850	
	Hit Rate	Specificity	Hit Rate	Specificity
Standard, slope less than -1.0 dB/y and $P < 0.01$	0.10	1.00	0.06	0.96
Optimized, slope less than -1.2 dB/y and $P < 0.04$	0.38	0.93	0.19	0.90

of less than -1.6 dB/y and $P < 0.05$, slope of less than -1.8 dB/y and $P < 0.06$ to $P < 0.10$, and slope of less than -2.0 dB/y and $P < 0.06$ to $P < 0.10$.

When the AUC was considered (Table 2), the optimal slope criterion was less than -1.2 dB/y (AUC of 0.74). The use of the criterion slope less than -1.2 dB/y and $P < 0.04$ for classification resulted in a hit rate of 0.38 and a specificity of 0.93. In summary, more than a 2-fold increase in the hit rate was found for the criterion of slope less than -1.2 dB/y and $P < 0.04$ compared with a commonly used standard criterion of slope less than -1.0 dB/y and $P < 0.01$.

To determine if these results could be expanded to other data, the best performing criterion observed in this study (slope of less than -1.2 dB/y and $P < 0.04$) was tested on an independent longitudinal visual field examination data set from the OHTS. The OHTS data are from enrolled individuals with ocular hypertension and no evidence of glaucomatous damage at baseline, with longitudinal follow-up examination for visual field or optic nerve change. As in the original data set, the OHTS data showed more than a 2-fold increase in the hit rate (19% with slope of less than -1.2 dB/y and $P < 0.04$ compared with the standard criteria hit rate of 6%). As expected, the hit rate was low overall in the OHTS data from patients with earlier disease. Specificity was lower with the new criterion compared with the standard; however, it still remained at the level of 90%. The results of the validation study are summarized in Table 3.

DISCUSSION

Pointwise linear regression analysis is frequently used for evaluation of longitudinal visual field series. It has been shown to perform well as a curve-fitting technique and to be useful for predicting threshold sensitivities and detecting both gradual and sudden changes.²⁶ Until a standard that is independent of visual field testing is established, the true sensitivity of PLR techniques for determining glaucoma progression will remain unknown. A comparison with published rates of progression or the determination of agreement between different methods for detecting glaucomatous progression is one method of assessing proposed new PLR criteria. Rates of progression have been found to be 30% to 39% using PLR methods in studies^{27,28} of patients with glaucoma having 6 to 8 years of follow-up examinations, while methods of event-based analyses (primarily glaucoma change probability) have shown rates of progression among cases to be 26% to 50% in 3 to 6 years of follow-up examinations.^{11,14,29,30} The nonparametric-based method of permutation analyses of pointwise linear regression,³¹ which estimates the significance of visual field deterioration from patient-specific data, found a progression rate of 42% for patients measured an average of 10 times over 8 years.

Our study examined a range of PLR slope and significance level criteria for the classification of patients with glaucoma, and the results corroborate previous studies in finding that PLR was highly specific,⁷ with relatively low rates of progression detected using the standard criterion.³² The commonly used standard criterion of slope less than -1.0 dB/y and $P < 0.01$

significance level was found to classify all ocularly healthy individuals as not progressing; however, only 10% of patients with glaucoma were classified as progressing. The standard criterion may be too conservative in identifying glaucoma progression given that this is a lower rate of progression among patients having glaucoma with 4 years of follow-up examinations than would be expected from a comparison with published literature. Another criterion of slope less than -1.0 dB/y and $P < 0.05$ used in previous studies^{8,9} resulted in a hit rate of 0.50, slightly higher than progression rates found in comparable investigations; however, the results of the present study indicate a specificity of 0.80, which may allow for incorrect classification at too high a rate in the controls (who represented individuals not progressing in this study).

Our results suggest that a higher hit rate (in the range of 30%–40% found in other investigations) could be achieved, while maintaining a high specificity by further restricting the slope criterion (declines in the range of -1.2 dB/y or steeper) and relaxing the significance level criterion. In Figure 2, visual field series are shown from locations not flagged by the standard criterion of slope less than -1.0 dB/y and $P < 0.01$ but were flagged by slope of less than -1.2 dB/y and $P < 0.04$. In this study, these thresholds succeeded in correctly identifying a large proportion of ocularly healthy controls (specificity of ≥ 0.90) and identified approximately 35% of patients as progressing (hit rate of approximately 0.35). Validation of our results in an independent data set (OHTS) showed a similar increase in the hit rate with the new criterion (slope of less than -1.2 dB/y and $P < 0.04$) over previously used criteria, strengthening the argument that hit rates can be improved even in patients with early glaucoma.

While this study focused on significant decline in threshold sensitivities over time, there is a possibility that locations may have significantly improved over the study period. Improvement may be a result of chance and the large number of test points in the visual field (i.e., type I error); on the other hand, significant improvements may be results of successful treatment of glaucoma or resolution of other ocular conditions such as cataract.

Strengths of this study include the longitudinal collection of control data, allowing for the estimation and control of the false-positive rate with each criterion, regular administration of visual field examinations at 6-month intervals, and minimal attrition. Independence of sample data was achieved by the use of one randomly selected eye per individual for control individuals and cases with glaucoma in both eyes. For cases affected with glaucoma in only one eye, this eye was used for the study. The difference in age between the cases and controls in this study is a limitation and may inflate the estimates of specificity because controls were significantly younger than cases. The results of this study are to some degree a function of the study population, the number of visual field examinations, and of course the inherent test-retest variability of the Goldmann size III SITA visual field examination. Some patients were undergoing treatment during the study, which has been shown to significantly reduce the rate of visual field progression over time.³³ Also, the use of a longer time series and various stimuli and stimulus sizes may require different optimal criteria. These facts will need to be considered in

FIGURE 2. Locations satisfying the criterion of slope less than -1.2 dB/y and $P < 0.04$ but not satisfying the criterion of slope less than -1.0 dB/y and $P < 0.01$. The PLR with the refined criterion would classify these individuals as progressing, whereas PLR with the standard criterion would not classify progression. (A) and (B) are two locations from the same patient with glaucoma, and (C) and (D) are two locations from the same control.

generalizing the results of this study. For an accurate clinical decision concerning progression of glaucomatous damage, the results of trend analyses such as PLR should be used in combination with all aspects of the clinical glaucoma examination.

A previous PLR standard criterion is a sensitivity loss of 1 dB/y at $P < 0.01$, defining the classification of deterioration at any location. Because visual sensitivity data are measured on the logarithmic scale, loss of 1 dB/y is approximately 10 times the normal age-related rate of sensitivity decay. Sensitivity loss also has different implications depending on disease severity; a loss of 2 dB from 32 to 30 dB on the logarithmic scale is 10 times greater on the linear scale than a loss of 2 dB from 22 to 20 dB. Likewise, retinal ganglion cell loss, which has been shown to be linearly related to visual field sensitivity on a linear scale, varies based on disease status.³⁴ Measurement of the rate of loss is important clinically because patients would not

benefit from treatments if a low rate of decay is found and are not likely to experience visual impairment in their lifetime.

Other variants of PLR have been proposed such as two-omitting and three-omitting methods, which remove points and refit the linear model to determine if loss is sustained. These have been shown to increase specificity substantially using the standard criterion of slope less than -1.0 dB/y and $P < 0.01$ significance level.³² Future studies are needed to determine whether considering various slope and significance level criteria for other variants of the standard PLR approach would contribute to an increase in the hit rate, while maintaining a high specificity.

These results show that visual field trend analysis using PLR can be refined by adjusting the standard slope-based and significance level-based criteria. By considering more restrictive declines in visual field data (e.g., less than -1.2 dB/y, which is approximately 12 times the normal rate of age-related decay)

and relaxing the significance criterion of the PLR slopes to $P < 0.04$, a high specificity can be maintained, while increasing the hit rate of PLR. Maximizing the performance of PLR, a commonly used clinical measure in the detection of visual field decay, will contribute to the early detection and treatment of glaucoma.

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