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Detecting Visual Field Progression

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Timely detection of glaucomatous progression is crucial in the delivery of glaucoma care. Clinical judgment may be used to make this assessment, but relatively modest agreement among practitioners supports the use of complementary methods. Event-based analyses take into account expected localized test–retest variabilities in sensitivity, and trend-based analyses are helpful for determining and predicting overall visual function. Landmark clinical trials have used various visual field progression criteria as end points with variable performances. Short- and long-term fluctuations as well as inadequate testing frequency are limitations in visual field analysis for glaucomatous progression. Ongoing improvements in statistical techniques as well as incorporation of functional and structural measures into a single model likely will lead to an enhanced ability to detect glaucomatous progression and will allow for more timely and appropriate therapy. *Ophthalmology 2017;124:S51-S56 © 2017 by the American Academy of Ophthalmology*

Glaucoma is the leading cause of irreversible blindness worldwide.[1] Progression of the disease to this state is associated with significant economic and psychological burdens as well as a negatively affected quality of life.[2–4] Intraocular pressure lowering has been proven to delay or halt glaucomatous progression.[5–7] Therefore, detection of glaucomatous progression at the earliest possible time is crucial, because proven therapies are available and the sequelae of an advanced disease state are profound.

Glaucomatous progression may be detected using serial structural or functional testing, or both, of the optic nerve and neural pathway. Structural testing measures include stereoscopic optic disc photography and optical coherence tomography studies of the optic nerve, peripapillary retinal nerve fiber layer, and macula. Functional testing typically involves automated visual field testing. This article aims to describe current methods for the detection of glaucomatous progression using standard achromatic automated visual field testing techniques because these strategies are used most commonly in clinical trials and practice. In selecting articles for inclusion in this review, a literature search using the PubMed database was carried out initially using the following keywords: (*glaucoma**) AND (*visual field** OR *progression** OR *perimetry**). Articles retrieved with this search as well as cross-referenced articles relevant to the clinical methodologies described below then were selected. Original manuscripts describing randomized clinical trial design and methodology also were retrieved for appropriate referencing where applicable. We did not use any date or language restrictions in the electronic searches. The electronic database was last searched on February 9, 2017.

Methods for Visual Field Progression Detection

A number of methods and criteria may be used for determining the presence of glaucomatous progression with automated visual field testing. Some of these methods are better suited for direct clinical care, whereas others are more applicable as a clinical trial end point.

Clinical Methods

Methods for the detection of visual field progression that are used in routine clinical care include clinical judgment, event-based analysis, and trend-based analysis. Each of these methods has unique advantages and disadvantages and therefore may be used in a complementary manner.

Clinical Judgment. Clinical judgment is likely the most common method used by all eye care practitioners to assess visual field progression.[8] This practice involves manual subjective review of serial visual field tests by the practitioner and the use of nonstandardized criteria to assess progression. In studies investigating agreement among clinicians using subjective judgment in determining the presence or absence of glaucomatous progression, weighted κ statistics typically are used to report the results. Viswanathan et al[9] provided 5 expert clinicians with 27 visual field series, each containing more than 19 Humphrey Visual Field (Carl Zeiss Meditec, Inc., Dublin, CA) printouts. Relatively strict criteria were used for the selection of visual field data because each test was deemed reliable by standard criteria and the macular threshold of each field test was required to be at least 30 dB. The clinicians were instructed to grade each series as definitely stable, probably stable, probably progressing, or definitely progressing. The clinicians were not given formal instructions or guidelines for making their respective determination. Despite the relatively strict criteria for visual field selection, which likely does not simulate a routine clinical scenario, poor agreement (median $\kappa = 0.32$) was found among the practitioners. In another study determining both interobserver agreement and intraobserver reproducibility of subjective visual field assessment for glaucomatous progression, Tanna et al[10] provided 5 expert glaucoma subspecialists with 5 visual field tests from each of 100 eyes of 83 patients. The practitioners were asked to classify each set of visual fields with respect to progression as none, questionable, probable, or definite. The series then were reordered randomly and presented again, without advance

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knowledge, to the practitioners 1 month later for re-evaluation and grading. For the purposes of data analysis, raw progression classification of the 4 progression categories was performed in addition to dichotomized data analysis in which the probable and definite categories were considered as progressed and the none and questionable categories were considered as nonprogressed. Although intraobserver reproducibility was found to be good to excellent ($\kappa = 0.62-0.78$) for the raw data and moderate to good ($\kappa = 0.58-0.71$) for the dichotomized data, agreement among the experts was only moderate under both analyses ($\kappa = 0.45$ and 0.55, respectively). The poor and modest levels of agreement discovered by Viswanathan et al and Tanna et al, respectively, may result from 2 factors described by Spry and Johnson.[11] First, different experts likely use different criteria for the determination of visual field progression, and second, the wealth of data provided to visual field graders may increase the chance that subtle features are detected to a variable degree.

Event-Based Analysis. Event-based analysis broadly refers to the comparison of follow-up test results with initial, baseline examinations. The most commonly used event-based analysis for the determination of progressive glaucoma is the Guided Progression Analysis (GPA; Carl Zeiss Meditec, Inc.) protocol. The GPA method is derived from the Early Manifest Glaucoma Trial (EMGT) protocol and compares the pattern deviation value of each test location with an average of the threshold values from the same point in 2 baseline studies.[12] Worsening is determined when the value in the subsequent study exceeds deterioration outside of the 95% confidence interval for expected test–retest variability in a group of stable glaucoma patients.[13] As soon as the same 3 (not necessarily contiguous) points have reached this criterion on 2 separate tests, a determination of possible progression is indicated on the GPA printout (Fig 1). Upon confirmation with 3 separate tests, likely progression is indicated on the printout. The GPA offers an automated method for the detection of visual field progression that takes into account expected variability for each respective testing location. In addition, use of the pattern deviation plot for the analysis allows for emphasis on focal defects characteristic for glaucoma, rather than diffuse defects that may signify progressive cataract, ocular surface disease, or both.

In a study of 30 glaucomatous patients who underwent 10 visual field studies within a 3-month period, the GPA technique was found to have a relatively low false-positive rate (2.6%) when using the likely progression indicator for progressive disease. However, a wide range (<0.1%–20%) was found among patients because of differences in visual field variability and reliability indices.[14] Other limitations of the GPA method include an inability to determine progression for severely depressed points and the reliance on high-quality baseline studies.[15]

Trend-Based Analysis. Trend-based methods involve sequential analysis of global measures of visual field function using linear regression models. Global measures used for the analyses may include mean deviation, pattern standard deviation, or visual field index (VFI). Advantages of the VFI include less influence by progressive cataracts and greater weighting of centrally located points that are more likely to affect visual function.[16] The VFI is reported as a percentage, where 100% represents a normal visual field and 0% represents a perimetrically blind field. Regression analysis using the VFI parameter allows for an assessment of the rate, or velocity, of progressive loss. This is important because a high rate of progressive loss indicates higher risk for further progression.[17] Computerized extrapolation of the VFI trend also allows for prediction of expected loss of visual field over a given period[18] (Fig 2). This feature is useful in a clinical scenario when deciding on the risk-to-benefit ratio of further intraocular pressure–lowering in light of a given patient's life expectancy and activities of daily living. Furthermore, the trend line may be interpreted easily by patients to allow for involvement in decision making. A limitation of trend-based analysis is lower sensitivity for the detection of glaucomatous progression in early stages of the disease.[19]

A trend-based analysis that may increase sensitivity for glaucomatous progression in early disease involves linear regression analysis of the sensitivity values of individual test points, or pointwise linear regression (PLR). This method is available commercially as the Progressor software package (Medisoft, Ltd., Leeds, UK) and generates a slope indicating the rate of sensitivity change for each test location.[20] Varying progression criteria have been reported using pointwise regression analysis with the Progressor package. The most commonly used criteria make a determination of glaucomatous progression after a negative rate of change of approximately 1 dB per year for at least 2 test locations has been reached with 95% confidence.[15,21,22] This approach generally has been rendered to research studies as the analysis requires software external to the Humphrey Visual Field package. Furthermore, more than 8 visual fields may be required for the analysis to perform adequately.[23]

Comparison of Clinical Methods. A number of studies have sought to compare clinical judgment, event-based, and trend-based methods with respect to levels of agreement, sensitivity, and specificity for determining glaucomatous progression. Tanna et al[24] performed a comparison of GPA and subjective analysis of serial visual fields by a group of glaucoma experts with regard to overall agreement. The dichotomized method of analysis, as described above, was used. In this study, the level of agreement between clinical judgment by consensus agreement and the GPA method was fair ($\kappa = 0.52$). Expert consensus was more likely to deem a given series of visual fields as progressed compared with GPA ($P < 0.002$). When experts were presented with the GPA results for a given series and asked to make another determination for the same visual field series, agreement remained fair ($\kappa = 0.62$). In a separate study by Viswanathan et al,[9] agreement among clinicians was found to increase with the addition of Progressor software (PLR) results to a series of standard visual field printouts ($\kappa = 0.32$ vs. $\kappa = 0.59$, respectively; $P = 0.006$).

Several studies suggest that PLR is capable of detecting glaucomatous progression at an earlier point than global indices such as the VFI.[25,26] This has been attributed to PLR detection of focal changes that occur more rapidly than diffuse changes, which may mask underlying focal loss.[25] Furthermore, unlike the GPA technique, PLR uses visual field data from all tests rather than solely baseline examinations, and therefore is likely more sensitive to gradual progressive visual field loss within a focal area.[27]

Anton et al[28] performed a prospective study of 37 eyes followed up for 36 months with biannual visual field testing. The sensitivities, specificities, and levels of agreement using trend-based (VFI), event-based (GPA), and expert subjective analyses then were determined. Expert analysis was the benchmark gold standard for the purposes of the study. The levels of agreement between expert analysis and trend-based and event-based methods were high ($\kappa = 0.82$) and moderate ($\kappa = 0.57$), respectively. The level of agreement between trend-based and event-based methods was moderate ($\kappa = 0.53$). Sensitivities and specificities were found to be 57% and 71% for trend-based analyses and 93% and 96% for event-based analyses, respectively. Because most patients enrolled in this study had earlier stages of glaucoma, the findings support the view that event-based analyses may be more sensitive for glaucomatous progression detection in early disease states, whereas