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Frequency of Testing to Detect Visual Field Progression Derived Using a Longitudinal Cohort of Glaucoma Patients

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Purpose: To determine the time required to detect statistically significant progression for different rates of visual field loss using standard automated perimetry (SAP) when considering different frequencies of testing using a follow-up scheme that resembles clinical practice.

Design: Observational cohort study.

Participants: One thousand seventy-two eyes of 665 patients with glaucoma followed up over an average of 4.3±0.9 years.

Methods: Participants with 5 or more visual field tests over a 2- to 5-year period were included to derive the longitudinal measurement variability of SAP mean deviation (MD) using linear regressions. Estimates of variability then were used to reconstruct real-world visual field data by computer simulation to evaluate the time required to detect progression for various rates of visual field loss and different frequencies of testing. The evaluation was performed using a follow-up scheme that resembled clinical practice by requiring a set of 2 baseline tests and a confirmatory test to identify progression.

Main Outcome Measures: Time (in years) required to detect progression.

Results: The time required to detect a statistically significant negative MD slope decreased as the frequency of testing increased, albeit not proportionally. For example, 80% of eyes with an MD loss of −2 dB/year would be detected after 3.3, 2.4, and 2.1 years when testing is performed once, twice, and thrice per year, respectively. For eyes with an MD loss of −0.5 dB/year, progression can be detected with 80% power after 7.3, 5.7, and 5.0 years, respectively.

Conclusions: This study provides information on the time required to detect progression using MD trend analysis in glaucoma eyes when different testing frequencies are used. The smaller gains in the time to detect progression when testing is increased from twice to thrice per year suggests that obtaining 2 reliable tests at baseline followed by semiannual testing and confirmation of progression through repeat testing in the initial years of follow-up may provide a good compromise for detecting progression, while minimizing the burden on health care resources in clinical practice. *Ophthalmology 2017;■:1−7 © 2017 by the American Academy of Ophthalmology*

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Visual field testing using standard automated perimetry (SAP) remains the most important clinical tool for characterizing the level of visual loss in eyes with glaucoma and for detecting progressive damage in the disease. However, the accurate and timely detection of progressive changes can be difficult because of the inherent variability of SAP testing.[1–4] The time required to detect progressive visual field loss depends on the frequency of testing[5] and follow-up scheme used.[6–9] As such, evidence-based guidance on the frequency of testing required to accurately distinguish the presence of progressive visual field losses from measurement variability remains elusive, but would be of immense benefit for the clinical management of patients with glaucoma.

In a previous study, Chauhan et al[5] sought to provide such guidance by using computer simulations to estimate the time required to detect a significant negative slope for visual field mean deviation (MD) when different rates of loss were simulated and different testing frequencies were considered. It is well known that the ability to detect trend-based progression is dependent on the measurement variability, the number of tests included, and the follow-up duration. However, a recent report by Crabb et al[10] highlighted how the findings presented in this previous study were misleading because they failed to account correctly for the follow-up duration in the simulations and consequently underestimated the actual time required to detect progression.

Nonetheless, the findings presented by Chauhan et al[5] provided a useful initial guideline, and further refinements to their methodology can be made to reflect clinical practice patterns better. For instance, the importance of

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obtaining reliable baseline visual field measurements is acknowledged widely because the subsequent tests often are compared with these reference measurements. Obtaining 2 reliable tests within a short time frame at baseline has been the protocol used in a number of landmark glaucoma clinical interventional trials[11–13] and is recommended for event-based analyses of visual field progression.[14] Although not imperative for trend-based analyses, its inclusion would provide guidelines on the time required to detect progression using a follow-up scheme that better captures ideal clinical practice patterns. In addition, confirming the presence of progressive loss through repeated testing is also recommended to reduce the probability of incorrectly diagnosing progression.[15–18] Therefore, this study sought to determine the time required to detect visual field progression, defined as a statistically significant negative slope for visual field MD, when considering different underlying true rates of loss and different testing frequencies with a follow-up scheme that more closely resembles clinical practice.

Methods

Participants

This study included participants who were evaluated in a longitudinal study designed to investigate structural and functional damage in glaucoma.[19] Institutional review board approval was obtained and written informed consent was obtained from all participants. This study adhered to tenets of the Declaration of Helsinki and was conducted in accordance with the Health Insurance Portability and Accountability Act.

All participants underwent a comprehensive ophthalmologic examination, including a review of their medical history, visual acuity and visual field testing, slit-lamp biomicroscopy, ophthalmoscopic examination, intraocular pressure measurements, gonioscopy, and stereoscopic optic disc photography. Inclusion criteria required open angles on gonioscopy, a best-corrected visual acuity of 20/40 or better, and being 18 years of age or older. Participants were excluded if they showed any other ocular or systemic disease that could affect the optic nerve or the visual field.

This study included only participants with eyes that had glaucoma, which was defined on the basis of masked grading of the optic nerve appearance on stereophotographs, using methods described previously.[19] Eyes were also considered to have glaucoma if there was evidence of progressive optic disc changes on masked grading of the stereophotographs[20] or if they had 3 or more consecutive abnormal visual field test results (defined as having a pattern standard deviation value at $P < 0.05$ or glaucoma hemifield test results outside normal limits).[21]

Visual Field Testing

Visual field testing was performed using the Swedish Interactive Threshold Algorithm with the 24-2 standard strategy on the Humphrey Field Analyzer II-i (Carl Zeiss Meditec, Inc., Dublin, CA). All visual fields were evaluated by the University of California, San Diego, Visual Field Assessment Center[22] for artifacts including eyelid or rim artifacts, fatigue or learning effects, inappropriate fixation, evidence that the visual field results were caused by a disease other than glaucoma (e.g., homonymous hemianopia), and inattention; tests or eyes with such artifacts were excluded from this study. Visual fields were considered unreliable and were excluded if they showed more than 33% fixation losses or false-negative errors (with the exception for false-negative errors when visual field MD was less than −12 dB), or more than 15% false-positive errors. Only eyes with at least 5 eligible tests within a period of 2 to 5 years were included.

Computer Simulations

To create computer simulations to evaluate the specificity of different clinical testing protocols and the time required to detect different rates of visual field progression, the first step was to derive the expected variability (or noise) of SAP MD in the longitudinal clinical data. This was obtained by fitting an ordinary least squares regression to the MD values over time, and the residuals were obtained (by subtracting the measured value from the fitted value) and grouped in 1-dB bins according to the fitted values; the distributions of these residuals at 4 representative fitted MD bins are shown in Figure S1 (available at www.aaojournal.org). For each test during each sequence of the simulations, the noise component then was added randomly to the true simulated sensitivity using these residuals, thus providing a reconstruction of how the visual field tests would appear in real-world clinical practice, in a similar manner as performed previously for SAP MD.[6]

In this study, we first evaluated the specificity of clinical protocols that required 0, 1, or 2 confirmatory tests meeting the definition of visual field progression (a statistically significant slope less than 0 at $P < 0.05$ for a 2-tailed test using ordinary least squares regression). All clinical protocols included 2 baseline visual field tests, and for the clinical protocols that required confirmatory tests, the visual field tests were repeated at the same time point. The simulated eyes continued to be tested at the specified regular intervals if the criterion for progression was not met, and the test was repeated at the next time point when the definition of visual field progression was met again. The clinical protocol where testing was performed twice yearly and that required 1 additional confirmatory test to define progression is illustrated with an example in Figure 2. For each of these clinical protocols, 10 000 sequences were generated that specified a baseline MD of −3 dB (representing early to moderate visual field damage) and a progression rate of 0 dB/year to simulate glaucoma eyes that were truly stable, so that the specificity of the clinical paradigms could be evaluated.

For all subsequent simulations, a clinical protocol that included 2 baseline visual field tests and a criterion that required 1 confirmatory test as having met the definition of visual field progression was used (see "Results"). This protocol was applied to sequences that assumed progression rates of −0.25, −0.50, −1.00, and −2.00 dB/year from a baseline MD of −3 dB when visual field testing was performed once, twice, and thrice per year. A total of 10 000 sequences was generated for each of these conditions, and the average time and the time when 80% and 90% of simulated eyes were detected as having progressed were recorded. The percentages of simulated eyes detected as having progressed after 2 and 5 years were also recorded.

Results

Participant Characteristics

A total of 8240 tests from 1072 eyes of 665 participants with glaucoma were included. The mean age ± standard deviation of the participants was 60.9±12.0 years (range, 18–90 years) at the first visit, and they were seen at a mean ± standard deviation of 7.7±2.7 visits (range, 5–22 visits) over 4.3±0.9 years (range, 2–5