Special Focus:
Optimal testing, technologies to detect glaucoma damage and progression

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Core Concepts
• There are 2 global indices of visual field sensitivity: mean deviation (MD) and pattern standard deviation (PSD). Once glaucoma has been diagnosed MD and PSD provide data on disease severity.
• To be useful, tests must be reliable with few fixation losses and few false positive/false negative responses.
• Data on disease severity with measured visual field deterioration, along with patient age and health status should be used to estimate likelihood of visual impairment.
• Progression detection algorithms available are GPA I and II.
• Frequency of follow-up testing should be dictated by the relative risk of progression. The higher the risk, the more frequently testing should take place.
• The World Glaucoma Association Consensus Group on Glaucomatous Progression suggests at least 2 reliable fields in the first 6 months after diagnosis and at least 2 more fields within the next 18 months.
• Increased testing from baseline up to 2 years identifies more rapidly progressing patients with a lower false positive rate.
• When central vision is compromised it may be useful to obtain 10-2 visual fields that use a 2-degree spacing.

Technologies to Detect Glaucomatous Visual Field Damage
There are several ways to identify glaucomatous defects from standard automated perimetry (SAP) print outs (Figure 1). Firstly, inspect sensitivity thresholds at each test point. It is not particularly useful to identify defects, because these values are not age-corrected. In older patients low thresholds could be attributable entirely to age. More meaningful information is available in the total deviation (TD) and pattern deviation (PD) probability plots (Figure 2). The TD probability plot shows the point-by-point probability of abnormality (in grey scale) compared with an age corrected normative database. The PD probability plot provides similar information adjusted for both age and generalized depression that could be caused by other pathologies (e.g. cataract). So in the PD plot, localized defects most likely from glaucoma are highlighted. Localized patterns of abnormality, identified on the PD probability plot, can be assessed to determine if they are what is considered characteristic for glaucoma (e.g. nasal step, superior or inferior arcuate patterns of defect). Odd-looking patterns

Figure 1 shows all of the information available on a standard automated perimetry print out.
might result from a test-taking artifact or patient inattention.

Two global indices of visual field sensitivity are available. Mean deviation (MD) is the weighted average of the point-by-point decibel deviations from normal that are shown in the TD plot. Pattern standard deviation (PSD) represents the relative point-by-point decibel deviations from normal across the visual field. PSD increases as the point-by-point deviations from normal across the visual field become more variable. PSD increases in the presence of localized defects. Although these global indices are not used for diagnosis, a PSD outside normal limits is likely to be more informative than an MD outside of normal limits because it is more likely to detect local defects earlier. Once glaucoma has been diagnosed, MD and PSD provide a general idea of the severity of the disease.

The Glaucoma Hemifield Test1 is a summary parameter that describes the relative difference in sensitivity in five zones of the superior hemifield compared with five corresponding zones in the inferior hemifield. Results are either “outside normal limits”, “borderline” or “within normal limits”. This parameter is particularly useful to detect early to moderate disease because glaucomatous visual field defects usually manifest asymmetrically across the visual field horizontal midline. The Visual Field Index (VFI) is another summary parameter; it is based on geographically weighted PD probability map values with emphasis on the central test points; it has been reported to represent the percentage of remaining useful vision.2 Theoretically the VFI ranges from 100 in a healthy eye to zero in a seriously damaged eye. There is no suggested abnormality cut-off for this parameter.

Consider other important items to identify glaucomatous defects. Firstly, tests must be reliable, with few fixation losses and few false positive and false negative responses. The latter reliability criterion is less important in individuals with advanced disease because a reported false negative may be a truly unseen test point that is the result of a severe defect. Secondly, observed abnormalities should be repeatable and consecutive abnormal tests should have the same general patterns of defect. In the Ocular Hypertension Treatment Study, 86% of 702 initial abnormal SAP tests did not show a subsequent abnormal test. In fact, 66% of these eyes had all indices within normal limits on follow-up testing3, thus the importance of repeatable abnormal results to identify true glaucomatous defects. Finally, visual field results are quite variable and learning effects, artifact caused by drooping eyelids, small

Figure 2 shows the Total Deviation and Pattern Deviation probability plots from an eye with a moderate to severe inferior visual field defect. Global indices are also shown.

Figure 3 shows the Total Deviation and Pattern Deviation probability plots from an eye with a small pupil. This pattern of defect generally is not characteristic of glaucoma.

Figure 4 shows the first incidence of possible and likely progression, based on GPA analysis, in an eye with a developing inferior temporal visual field defect. Half filled triangles represent test points progressed, relative to baseline variability, in two consecutive tests (possible progression). Filled triangles represent progression in three consecutive tests (likely progression).
pupils and by inattention can result in different patterns of defects that are not disease related; hence the need to check for similar and recognizable patterns of defect in consecutive tests (Figure 3).

**Technologies to Detect Glaucomatous Progression**

Glaucoma management aims to preserve visual function for an individual's lifetime. To this end, clinicians need to monitor closely the magnitude and rate of visual fields changes so that appropriate treatment can be initiated to preserve visual function. Information on the rate of visual field deterioration along with the severity of the disease at diagnosis and the patient's age and general health status (i.e. likely longevity) should be used to estimate the likelihood of visual impairment.

Similar to detection of disease using SAP, disease progression also can be assessed subjectively based on information available in TD and PD probability plots. To do this, a longitudinal series of TD or PD plots can be compared for increases in scotoma size and/or depth or the development of new scotomas. Because of the large variability in SAP results, this information is not always meaningful. Two useful progression detection algorithms currently are available in the Humphrey Statpac software: Guided Progression Analysis (GPA) and linear regression of Visual Field Index (VFI).

GPA is a PD plot-based event analysis calculation that relies on the comparison of change at each test location to the variability observed between two baseline tests at the same location (Figure 4). According to the Early Manifest Glaucoma Trial criteria, " Likely Progression" is assigned to a visual field if at least three test points are flagged as significantly progressing at the same location over three consecutive tests ("Possible Progression" is assigned if the same three points have progressed over two consecutive tests). GPA is attractive because it is objective, but it relies on the variability between baseline tests. Because of this, its sensitivity to change can be variable. Also, it does not require the progressing points to be contiguous, so the observed change may not represent the predicted increase in scotoma size that is associated with disease progression. Once a GPA result of "Likely Progression" has been assigned, new baseline examinations should be obtained to allow identification of a subsequent progression event. As suggested by the 2011 World Glaucoma Association Consensus Group, new baseline examinations should also be obtained after any significant therapeutic intervention.

Unlike the GPA, linear regression of the VFI can provide the rate of change over time (i.e. change in VFI value per year) and, because it is derived from PD and not MD, it likely is fairly resistant to the effects of developing/worsening cataracts. Knowing the rate of progression is more important for long-term disease management than simply knowing if a patient has progressed or not (Figure 5). This is in part because faster progression is a predictor for future progression and increases the likelihood of visual impairment in one's lifetime. Like GPA, VFI is not perfect. For instance, using linear regression to suggest a predicted rate of change over time assumes that change over time is linear; this may not be true.

It also assumes a stable treatment regimen and it does not consider intervening surgical procedures. Finally, assuming change over time is linear estimates of change of VFI over time (i.e. estimates of the negative slope of VFI) will be more accurate when more tests are included in the regression equation. This is because adding more test points will result in a better ("tighter") linear fit.

Another available progression detection technique uses ordinary least squares linear regression and is implemented using Progressor® software. Based on five or more consecutive tests, Progressor software performs linear regression (like regression of VFI) of threshold sensitivity on a point-by-point basis using all test points in the 24-2 test pattern. Individual points are defined as progressed if the negative slope of the point-wise change in sensitivity meets or exceeds a user-selected cut-off. A global progression event can be assigned (similar to GPA) based on a user-defined global progression criterion (e.g. ≥ of the same test points with a slope ≥ 1.0 dB/year for inner points and ≥ 2.0 dB for edge points, confirmed in three consecutive exams). No matter the technique used for progression detection, as suggested by the 2011 World Glaucoma Association Consensus Group statements, frequency of follow-up testing should be dictated by the relative risk of significant progression (based on extent of damage, life expectancy and any other relevant clinical observations, such as structural change and IOP control), with frequency increasing with increasing risk.

**Optimal Testing**

Several critical clinical questions must be answered to determine how best to "monitor closely" visual function in glaucoma patients, using any or all of the techniques described above. How many visual fields are really needed? How often should visual field tests be obtained? Given the variability of visual field results, a sufficient number of visual field tests must be obtained in order confidently to identify changes that are greater than the variability of the measurement. More visual fields, offer a better estimate of the rate of visual field progression. But how many visual field tests are needed over what period of time? According to Chauhan et al, to detect relatively slow progression (~0.50 dB/yr) in 2 years, 7 visual fields are needed each year; clearly more than is practical. On

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**Figure 5** shows the VFI regression analysis results from the same eye shown in Figure 4.
the other hand, to detect fast progressing glaucoma (-0.20 dB/yr), Chauhan et al recommend that newly diagnosed patients complete visual field testing three times per year during the first two years after glaucoma diagnosis.13 These recommendations were adopted by The European Glaucoma Society in 2008.14 The 2011 World Glaucoma Association Consensus Group6 on Glaucomatous Progression recently developed similar guidelines on the optimal number of visual field tests required with newly diagnosed glaucoma patients. Specifically, during the first two years after a diagnosis of glaucoma “at least two reliable visual fields is optimal in the first six months... and at least two further visual fields should be performed within the next 18 months. Where the lifetime risk of visual disability is high, such as those who already have advanced damage, three baseline visual fields may be necessary.”

After the initial two years following a diagnosis of glaucoma, the frequency of visual field testing should be based on the risk of visual impairment during the patient’s lifetime. The 2011 World Glaucoma Association Consensus Group6 recommends that, “In low and moderate risk patients, subsequent visual field frequency should be one visual field per year... and, as a rule, repeated sooner... if other clinical observations are suggestive of possible progression or increased risk of progression.” However, “In high risk patients, subsequent visual field frequency should be two visual fields per year and repeated sooner if possible progression is identified on the basis of an ‘event’ analysis, or if other clinical observations are suggestive of progression or increased risk of progression.”

Recently, computer simulation has been used to determine the optimal spacing for the intervals between testing for detection of rapidly progressing glaucoma (rate of loss: -2dB/yr). Crabb and Garway-Heath15 suggest that compared with evenly-spaced follow-up every six months, visual field testing 2 or 3 times at baseline and at the end of a 2 year period identifies more patients with rapidly progressing visual fields (58% and 62%, respectively) with a lower false positive rate (5.9% and 4.0%, respectively). By aggregating the visual field testing earlier and later in the follow-up period, there is increased efficiency to reduce the false positive rate, and to estimate the rate of visual field loss. This “wait and see” approach, developed using “moderate” variability of the visual fields in the computer simulation to detect fast progression, is being tested in longitudinal studies.

The number of fields and intervals between them can also influence the methods used to measure the rate of change. For example, Medeiros et al.15 recently reported that a Bayesian-based slope estimate technique was more predictive of future impairment than ordinary least square regression, particularly in eyes with moderate to fast rates of change. Most patients can be monitored using the 6-degree by 6-degree grid spacing of 24-2 visual field test pattern. However, when central vision is compromised or threatened, it may be useful to obtain 10-2 visual fields that use 2-degree by 2-degree spacing to better document how glaucoma is affecting central vision.16, 17 Using a relatively small number of eyes, Hood et al.17 reported evidence of visual field damage in the central visual field using 10-2 test pattern that is not detected in the peripheral field using 24-2 testing. Zhang et al.16 documented that the 10-2 test pattern results are useful to make clinical management decisions; in about one third of visual fields considered to threaten fixation based on 30-2 or 24-2 test patterns, the threat, based on 10-2 testing was not imminent. In some patients, 10-2 testing can be important to determine the level of visual impairment expected from glaucomatous visual field loss in the central and peripheral visual field.

References