1) Introduction

Glaucoma is a multifactorial neurodegenerative disorder characterized by progressive structural and functional injury of the optic nerve complex (optic nerve + parapapillary region) for which intraocular pressure (IOP) remains the only proven modifiable risk factor. Assessments of both structure and function of the optic nerve are indispensable aspects of the glaucoma examination and disease detection, monitoring, and management. Since the main goal of treatment is to either halt or slow disease progression, clinicians must be able to identify patients at increased risk of progression and, most importantly, be able to detect and measure progression when it occurs.

Glaucomatous progression can be detected clinically either by structural or functional tests, with change detected by either event-based or trend-based analysis.

2) New Technologies/ Software

A. Functional Tests

Standard automated perimetry (SAP) is the most widely used method to assess visual function in glaucoma and correlates well with patient quality of life and vision. SAP has also been used in the major randomized clinical trials (RCT) to determine glaucoma functional change or progression endpoints.

Different types of event-based VF progression criteria were used by each of these trials. However, a widely used statistical package of event-based analysis is automatically provided by the Humphrey Field Analyzer (HFA, Carl Zeiss Meditec, Inc., Dublin, CA) and is called Guided Progression Analysis™ (GPA) (Carl Zeiss Meditec, Inc., Dublin, CA). The Humphrey Field Analyzer II-i with the new GPA software additionally provides a trend-based analysis using the Visual Field Index™ (VFI) (Carl Zeiss Meditec, Inc., Dublin, CA) described by Bengtsson and Heijl, along with the more familiar event-based analysis.[2]

The VFI is an age-adjusted index that summarizes the global VF status for each test of the VF series. Briefly, the VFI calculation is based on the pattern standard deviation (PSD) probability maps with a greater weighting for more central points. Therefore, the final index which ranges from 0 (blind) to 100% (normal) has a greater weight of the central points relative to the paracentral and peripheral points. (Figure 1). A minimum of five exams over at least three years must be included in GPA 2 for the linear regression results to be presented.

Another option to perform trend analysis with HFA data is the Progressor™ software (Medisoft, Inc., London, UK). A) Selection of visual field test dates to be analyzed. B) Definition of progression criteria. C) Graphic output showing pointwise rates of change and their significance. D) Display showing number of points reaching the predefined progression criteria, global and localized rates of change (dB/yr).

Fitzke et al. described a graphical method of measuring rates of VF change using pointwise linear regression (PLR) analysis which was further employed to build the Progressor™ software package.[3] At least five tests are necessary for the analysis to provide the global rates of change (dB/yr) and p values. The software also allows one to define different progression criteria (Figure 2 B). If any of the tested points meets the chosen criteria a graphical display shows the lo-
cation of the progressing point(s) on the VF, as well as the level of significance of the slope (p) (Figure 2 C and D).

For those who use the Octopus Perimeter (Haag Streit, Berne, Switzerland), the PeriTrend™ provides a trend-analysis; this is part of the device’s standard statistical package. Similar to GPA 2, this is a form of trend-analysis based on global indices and therefore has the limitation of not detecting focal change.

B. Structural tests

Stereo disc photographs

Review of simultaneous or non-simultaneous stereophotographs of the optic disc and retinal nerve fiber layer (RNFL) remains the most widely used method to detect structural change in glaucoma. Masked photograph review was used by some of the major RCTs to determine structural progression.[4-6]

HRT

New imaging technologies have been developed to evaluate objectively the optic disc and retinal nerve fiber layer and to enhance identification of structural progression. (Figure 3). Confocal Scanning Laser Ophthalmoscopy (Heidelberg Retina Tomograph, [HRT], Heidelberg Engineering, GmbH, Heidelberg, Germany) was among the first devices designed to do this. The Topographic Change Analysis™ (TCA) program was developed to allow objective measurements of topographic change in a series of HRT examinations. Due to its stable platform, data from the older version of HRT (HRT II) can also be analyzed using the current version of the software (HRT III). (Figure 4). TCA currently also provides objective, trend-based measurements of rates of changes (mm2/yr). Moreover, a regression line is provided both globally as well as for each stereometric parameter on the printout. Recent reports have applied linear regression to HRT longitudinal data suggesting that this method may be useful to quantify rates of progression using the HRT. [7,8]

GDX

Scanning Laser Polarimetry (GDx-VCC and GDx-ECC, Carl Zeiss Meditec, Inc., Dublin, CA, USA) is an additional technology used to detect structural progression. The new Guided Progression Analysis™ (GPA) software provides both an event- and trend-based analysis of longitudinal change of the RNFL thickness. A colored map with a classification system resembling the HFA GPA is also provided: yellow, possible progression; red, likely progression; and purple, possible increase (RNFL “thickening”). Graphical images of the linear regression (microns/yr) of values for the average RNFL thickness as well as for the various RNFL sectors are also shown along with its extrapolation over time, assuming the rate remains constant (Figure 5). There is a good correlation between RNFL thickness change shown on Gdx and conventional progression endpoints (SAP and photograph review).[9]

OCT

Time-domain optical coherence tomography (Stratus OCT, Carl Zeiss Meditec, Inc., Dublin, CA, USA) has also been reported to be able to assess structural progression. The new version of the software, the GPA Advanced Serial Analysis, provides the rates of RNFL thickness change (microns/yr) and their level of significance (p) both globally and by clock-hours (Figure 6). This feature may
allow topographic correlations between localized RNFL loss and VF progression. Detection of structural progression using time-domain OCT has been demonstrated using both topographic and RNFL parameters of the device. [10]

Improvements in the OCT technology (Fourier-domain OCT) are available and due to their rapid image acquisition with high-resolution, may improve performance of the devices from several companies, to detect structural change.

in a subset of the Advanced Glaucoma Intervention Study (AGIS) population and found results consistent with the pre-existing literature regarding the previously documented importance of risk factors for progression (e.g., intraocular pressure [IOP] and age).[11] In the Diagnostic Innovations in Glaucoma Study (DIGS), rates of structural loss using different technologies can be measured in glaucoma patients and suspects; these values correlate well with the follow-up IOP and SAP/optic disc endpoints. [9,10] Large studies involving real-world patients have shown that trend-analysis may be an effective method to determine progression with results consistent with the major clinical trials.

4) Conclusion
These functional and structural methods to determine rates of progression ought to be tested in populations enrolled in the major clinical trials in order to assess their performance and consistency with previously reported risk factors. New, more accurate, and improved software algorithms should continue to be developed to allow clinicians to detect better structural and functional changes in glaucoma so that treatment paradigms can be modified to prevent visual disability.

References

Core Concepts
- Progression can be detected either by structural or functional tests with change detected by either using event-based or trend-based analyses.
- Standard automated perimetry is currently the most widely used method to assess visual function.
- The Humphrey Visual Field Analyzer with the new GPA software provides a trend based analysis using the Visual Field Index.
- The Visual field Index ranges from 0 (blind) to 100% (normal).
- Structural tests are stereo disc photographs, HRT (Heidelberg Retina Tomograph), GDX (Scanning Laser Polarimetry) and OCT (optical coherence tomography).
- HRT and topographic change analysis enables an objective measurement of topographic change in HRT examinations.
- GDX and OCT can both be used with the new Guided Progression Analysis (GPA) to provide both event- and trend-based analysis of longitudinal change of the RNFL thickness.
- All methods described should be tested in populations enrolled in major clinical trials.
- New, more accurate and improved software algorithms should continue to be developed.

Figure 6: Guided Progression Analysis™, Advanced Serial Analysis, Time-domain Optical Coherence Tomography (OCT, Carl Zeiss Meditec, Inc., Dublin, CA).

3) Guidance from clinical trial outcomes
Most glaucoma clinical trials have evaluated progression by means of event-analysis using SAP and photographic review. In a post-hoc analysis, Nouri-Madahvi et al. employed pointwise linear regression (PLR) to determine VF progression with topographic analysis from stereo disc photographs, HRT (Heidelberg Retina Tomograph), GDX (Scanning Laser Polarimetry) and OCT (optical coherence tomography).