

Optimal Management Requires Structural and Functional Analysis

Structural changes often predate functional loss.

BY ROCHELLE NATALONI, CONTRIBUTING EDITOR

THE PANEL



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In November 2003 during the AAO annual meeting, *Glaucoma Today* and The Dulaney Foundation presented a CME Dinner Seminar entitled, "The Roles of Structure and Function in Glaucoma." The take-home messages of the symposium were that progression of the disease varies greatly among patients and a "one-size-fits-all" treatment paradigm is inappropriate. For these reasons, technologies that focus on structure—such as Optical

Coherence Tomography (OCT) to detect changes in retinal thickness and ophthalmoscopy to view the optic nerve—are equally important to the diagnosis and management of glaucoma as technologies that focus on function, such as visual field testing and glaucoma progression software.

"We've been treating most glaucoma patients the same, and that's not correct," said Dr. Quigley, the session's moderator. "There are a lot of glaucoma patients who don't get

worse very fast, and there are those who are getting worse very fast. Our job is to separate them out so that we can tailor an aggressive treatment plan for some and a more conservative plan for others. Now that we have the technology to help us do that, there's going to be a big change in glaucoma therapy; we'll move away from the one-size-fits-all approach."

STATISTICALLY SPEAKING

Dr. Mills summed up visual field testing as an exercise in probability and stated, "the key to understanding probability is statistics." The Humphrey Field Analyzer II (Carl Zeiss Meditec, Inc., Dublin, CA) incorporates SITA and STATPAC, which, Dr. Mills pointed out, effectively aids statistical interpretation. He explained that STATPAC aims for diagnostic precision by using the largest worldwide normative database in perimetry, and he commented that STATPAC for Blue-Yellow testing (also known as SWAP) makes the interpretation of Blue-Yellow fields as easy as interpreting traditional white-on-white fields. Clinical studies by Pamela Sample, PhD, and Chris Johnson, PhD, among others, suggest that SWAP allows much earlier detection of visual field loss than does the traditional white-on-white method.

"SWAP has a real use, especially in mature practices with lots of ocular hypertensives in them," he added.

Describing frequency doubling technology as the new kid on the block with the new Humphrey Matrix (Carl Zeiss Meditec, Inc.), Dr. Mills asserted that the technology is less sensitive to nuclear sclerosis than SWAP and is therefore

more useful in an older patient population. He noted that practitioners have been using all these functional tools to detect the shift from a normal, undamaged optic nerve to glaucoma, and he argued that improvements in visual field testing for glaucoma detection and management are less likely than for structural tools in the years ahead.

"The visual field turnip has been wrung a lot harder than has the imaging turnip, and I think, therefore, that the increment of improvement that we'll be getting out of visual field testing is a small one compared to those that are anticipated in structural measures," he said.

INDIVIDUALIZATION

Like Dr. Quigley, Dr. Heijl emphasized the need for more individualized treatment plans.

"We need to tailor the patient's treatment much more to the individual than we used to do," he asserted. "The data from the modern trials show that interpatient variability is tremendously large. When a patient first comes to us and we don't have follow-up data, the initial treatment should be based on intraocular pressure plus risk factors other than intraocular pressure, but later it's very important to determine the patient's individual rate of progression."

Dr. Heijl stated that software such as the recently released Humphrey Glaucoma Progression Analysis (GPA) software (Carl Zeiss Meditec, Inc.) will start to play an important role in the management of glaucoma in the next 2 to 5 years.

"GPA helps you decide if the eye is stable or if [the disease] is progressing, and, if it is progressing, [GPA software] shows how fast it is progressing," commented Dr. Heijl, who went on to explain that knowing the rate of progression enables the practitioner to make the treatment decisions most suitable to the stage of disease of a particular eye (Figure 1).

CHANGE OVER TIME

Dr. Schuman asserted that "a device that detects progression should be able to assess subtle change over time." Dr. Heijl then pointed out that the GPA software is based on 10 years of experience from the Early Manifest Glaucoma Trial and has been adapted to SITA: "The nucleus of the new GPA is glaucoma change probability maps based on pattern deviations."

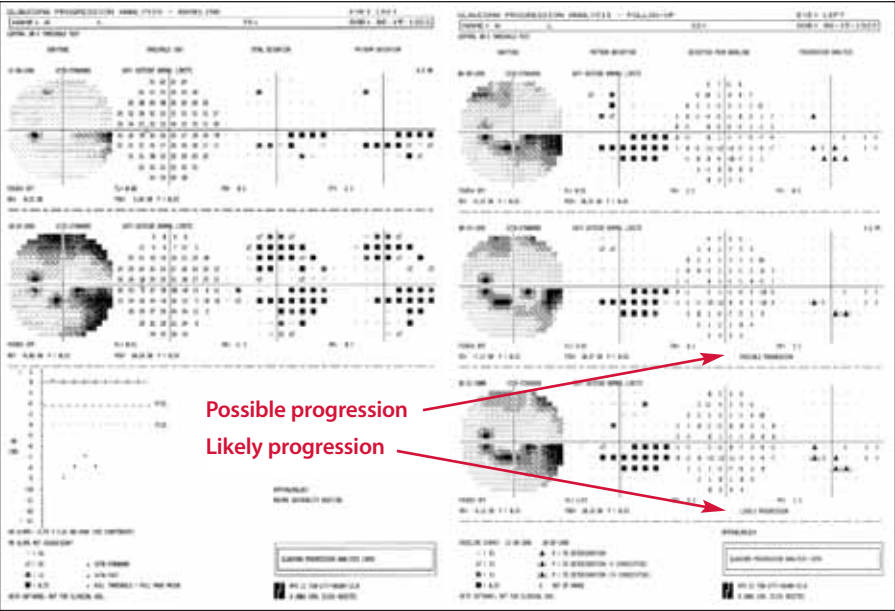


Figure 1. GPA software shows glaucomatous progression as symbols with clear text messages. The symbols in the released analysis package differ from those in the pre-release version (shown here).

He explained that the GPA software flags findings on a pointwise basis when they are reproducible and prints clear text messages of possible or likely progression. The software automatically eliminates unreliable fields, he said, "which here are fields with high numbers of false-positive answers." In addition, Dr. Heijl commented that the GPA software "automatically eliminates untrained first fields, if those are out of line with the following fields." It also provides a numerical and graphical display of the rate of progression.

According to Dr. Greenfield, glaucoma is not necessarily defined by a standard visual field defect.

"Most patients will develop standard visual field defects of white-on-white, but that's not the defining nature of this progressive, accelerated rate of ganglion cell death characterized by progressive structural change," he said. "I think there's substantial evidence that structural damage precedes functional loss. Now that we have so many options with which to acquire and disseminate normative data, I think we're in a position to clearly differentiate those patients who have disease from those who do not."

Determining whether progressive change is happening can be difficult without mechanical help, however, said Dr. Quigley.

"Many determinations that we would like to make require either measuring from photographs or using an imaging machine," he remarked. "Machines do some things much better than human observers, and there are now machines that will look at the thickness of the nerve fiber layer and display it graphically in a rather dramatic way" (Figure 2).

STRUCTURAL CHANGE/FUNCTIONAL LOSS

Although unproven, stated Dr. Greenfield, it is widely suspected that early detection and treatment in high-risk cases will likely reduce the incidence of later blindness in patients who have optic disc neuropathy. He added that short-wave-length perimetry can detect glaucomatous abnormalities

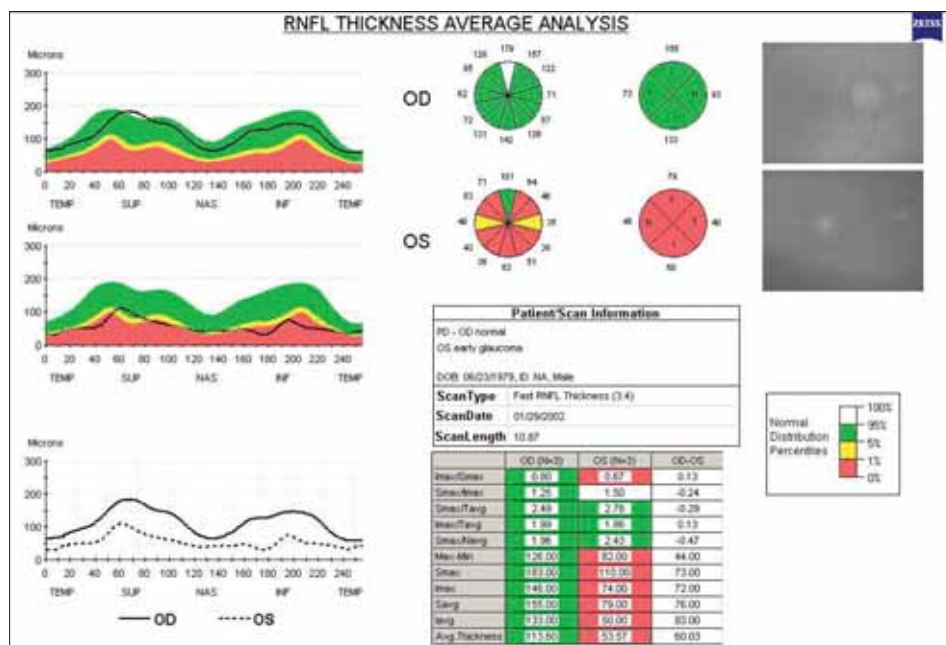


Figure 2. Using a stoplight color scheme based on age-matched normative data, the patient's RNFL thickness data (black line) is mapped against normals. The same color display is used for clock-hour and quadrant maps as well as tabular data.

long before the development of a white-on-white visual field defect.

"Last year, the investigators from the Ocular Hypertension Treatment Study¹ once again confirmed that structural changes often predate changes in white-on-white conventional perimetry and that 55% of the patients enrolled in this clinical trial actually developed progressive optic disc cupping without the development of an associated visual field defect," he said. "These data demonstrate that, in many patients, structural damage precedes functional loss as detected with standard automated perimetry."

Additionally, Dr. Greenfield cited a long-term study by Medeiros et al² in which investigators studied a population of eyes that had preperimetric glaucoma.

"They had definitive optic nerve damage without the development of a standard visual field defect," he said. "The population of eyes that had corneal thickness values below 545 µm at 7 years of follow-up showed that the rate of development of a standard visual field defect was 90%."

Dr. Greenfield stated that this finding illustrated that structural changes very often predate functional changes, particularly in eyes at risk for the development of conversion. He further maintained that the retinal nerve fiber layer often displays the earliest structural abnormality throughout the natural history of glaucoma and may be clinically measured using two commercially available imaging technologies. He discussed OCT as a posterior segment

imaging technology that allows physicians to generate sophisticated maps of the retinal nerve fiber layer and the macula. Dr. Greenfield commented that the technology is analogous to B-scan ultrasonography and is based on low-coherence interferometry. He noted that, "with this technology, a normative database is really essential. In fact, without a normative database, it's very difficult to judge differences between eyes that are suspected to have an abnormality and those eyes that really do." Carl Zeiss Meditec, Inc., introduced a normative database for its StratusOCT in the spring of 2003.

"Scanning laser polarimetry takes advantage of the fact that the retinal ganglion cells and their axons are birefringent tissues, and the birefringent shifts can be measured through a phenomenon known as retardation," Dr. Greenfield explained. "We know that there are other ocular birefringent structures—namely the cornea and to some degree the crystalline lens—so this technology has gone through a variety of iterations, the most recent of which is incorporating a means of neutralizing the anterior birefringence from patient to patient in a rather sophisticated way by capturing information within the macula."

"Now the anterior segment is really successfully neutralized from patient to patient, and we have a rather sophisticated way to look at the nerve fiber layer in the absence of any confounding effect of the anterior segment birefringence," he added. "Perhaps one of the most useful aspects of this technology is the incorporation of a probability map that not only tells us that an abnormality exists, but that an abnormality exists at a particular level of statistical significance. With this, we can judge whether that's a meaningful abnormality or not."

LARGE DISC CONCERNS

"If you have a large disc, you're going to have a large cup, and you have to be careful with devices where you're looking specifically at the optic nerve head, because the algorithm doesn't work particularly well when you're outside of a given range," emphasized Dr. Schuman.

With large disc areas (eg, greater than 2.7 mm), he suggested, it is wise "to take the analysis with a grain of salt." Dr. Schuman also commented that, although loss may occur in one area of the visual field, there will be a global loss of neural tissue, not just loss in the area of the visual field abnormality. Nevertheless, he said, the loss will be greatest in the area that corresponds to the visual field abnormality.

Dr. Schuman also noted that, in the Ocular Hypertension Treatment Study,¹ the optic nerve head was the most frequent parameter that changed, thereby showing progression to glaucoma. Within the study, he said, 55% of the progression events were by optic nerve head change, 35% were by visual field change, and just 10% showed both visual field

and optic nerve changes. According to Dr. Schuman, these results indicate that practitioners miss early damage with functional versus structural testing. He further stated that the patient who presents with worse damage is much more likely to progress than a patient with less damage.

In a study recently conducted at the UPMC Eye Center, University of Pittsburgh School of Medicine, and the New England Eye Center, Tufts University School of Medicine, Dr. Schuman and his colleagues "took a group of patients, and we set a cutoff for nerve fiber layer thickness [as measured with OCT] at 100 μ m and found that the people who had less than 100 μ m were much more likely to progress by visual field loss," he said. "If you take an even thinner cutoff of less than 80 μ m, you're much more likely still to have visual field progression than if you have a thicker nerve fiber layer baseline. So, the worse the disease is at baseline, the more likely it is that the patient will progress."

RETINAL CONNECTION

Dr. Schuman highlighted practitioners' ability to examine the retina at the cellular level and determine where damage has occurred.

"With OCT, we can look and see that the level of damage is at the photoreceptors and the outer nuclear layer in patients with retinitis pigmentosa or at the level of the nerve fiber layer and ganglion cell layer in patients with glaucoma," he commented. "There are a variety of technologies for looking at the optic nerve head and the nerve fiber layer. We can perhaps improve our measures by improving resolution as has been done with the StratusOCT as opposed to the earlier versions of this device. Imaging is useful for a number of purposes, most importantly, for taking care of our patients, but maybe for looking at outcome measures as well. ... I find that using imaging technology is quite beneficial in ruling out disease in addition to its utility ruling it in."

Regarding a potential difference in measurements of nerve fiber layer thickness with OCT versus scanning laser polarimetry, Dr. Schuman stated that all the machines studied to date "behave similarly in terms of discriminating the presence or absence of the disease." He commented that OCT may offer an advantage by providing "a direct cross-sectional image of the tissue, so you can look at nerve fiber layer, optic nerve, and the macula." □

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1. Kass MA, Heuer DK, Higginbotham EJ, et al. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. *Arch Ophthalmol*. 2002;120:701-713.

2. Medeiros FA, Sample PA, Zangwill LM, et al. Corneal thickness as a risk factor for visual field loss in patients with preperimetric glaucomatous optic neuropathy. *Am J Ophthalmol*. 2003;136:805-813.