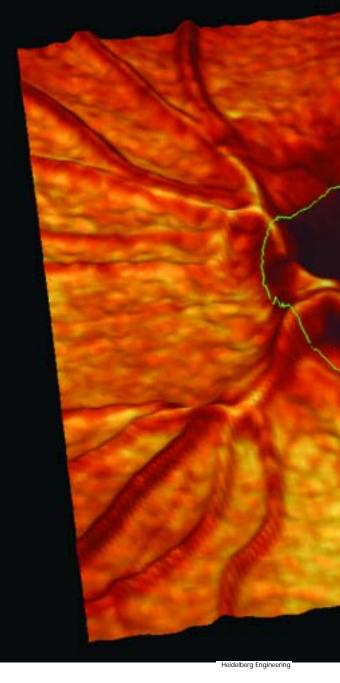
## Diagnosing Glaucoma With Laser Precision

Odette Callender

Three laser-based technologies are being applied with success to the diagnosis and monitoring of glaucoma.

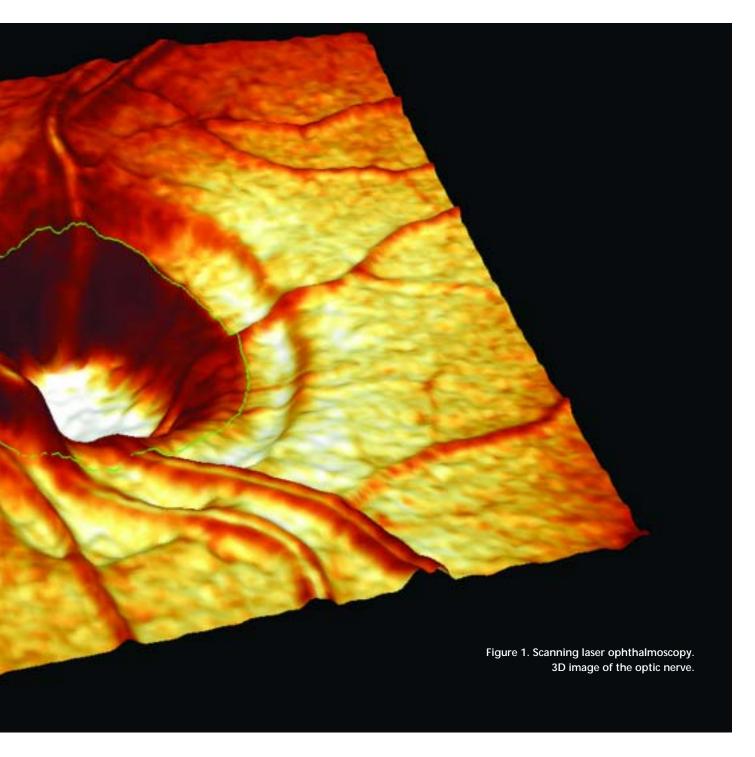


laucoma is the second leading cause of irreversible blindness in the world and the leading cause of blindness in the African-American and Hispanic populations of the United States. Worldwide, it is estimated that 67 million people have glaucoma and that 6.7 million of them are blind in both eyes because of the disease. The risk of developing glaucoma increases with age and with a family history of glaucoma: a recent study found that the lifetime risk of developing glaucoma was

9.2 times higher in siblings and offspring of patients than in the rest of the population.

In glaucoma, the pressure in the eye builds to a level that eventually causes permanent damage to the fibers of the optic nerve, known as the retinal nerve fiber layer (RNFL). But because the level of pressure capable of causing damage may vary from person to person, in the diagnosis and management of glaucoma, doctors cannot rely solely on the measurement of eye pressure.

Nerve damage from glaucoma initially causes small blind spots in peripheral vision that eventually creep inwards, destroying central vision as well. Because the loss of peripheral vision is gradual, the process usually goes unnoticed by patients until a significant amount of vision has been lost. Most forms of glaucoma are not associated with pain, redness, swelling or blurred vision. Precisely because it is asymptomatic in its early stages, glaucoma has often been called the "sneak thief of sight": approximately



50 percent of the people affected by glaucoma don't even realize they have it.

Blind spots in peripheral vision can be revealed by a computerized test during which lights of varying intensities are presented to numerous locations in the peripheral field. In the test the patient, while concentrating on a central fixation target, must acknowledge seeing the lights by pressing a button. Visual field testing can be difficult for patients, a factor which can make the results unreliable. To diagnose or monitor glaucoma, in

addition to testing peripheral vision, doctors evaluate the appearance of the optic nerve. But since variants of normal in the appearance of the optic nerve can be confused with glaucoma, it may be difficult to detect subtle changes. For these reasons, determining whether or not a person has glaucomatous nerve damage or whether a person with known glaucoma is stable or worsening often presents a challenge for doctors.

New laser-based technologies may offer a solution in the form of a more

objective assessment of the optic nerve which is less dependent on patient cooperation and physician judgment. Three instruments that use laser technology are scanning laser polarimetry (GDx), scanning laser ophthalmoscopy (HRT II) and optical coherence tomography (OCT).

Laser Diagnostic Technology makes a scanning laser polarimeter (GDx) that uses "form birefringence" to assess the thickness of the fibers radiating from the optic nerve. When polarized light passes through a birefringent medium it splits



Figure 2. Scanning laser ophthalmoscopy progression overlays. The red areas are those in which there has been progressive loss of the retinal nerve fiber layer between Feb. 8, 2002 and April 3, 2003.

into two rays, one of which is parallel to the fibers and proceeds unimpeded. another that is perpendicular to the fibers and undergoes a phase shift and slows down. The slowing process is known as retardation. The retina is considered form birefringent because of its arrangement of parallel structures—microtubules—each of which are of smaller diameter than the incident light.

In scanning laser polarimetry, a polarized diode laser light source (780 nm) is used to perform 20 scans measuring 256 x 256 pixels in a 15-20 degree grid centered on the head of the optic nerve. A detector measures the amount of retardation between the unshifted rays and the phase-shifted rays which is directly proportional to the thickness of the retinal nerve fiber layer. The total signal detected represents the birefringence of the entire eye, including the signal from the retinal nerve fiber layer, the cornea and, to a much smaller degree, the lens. A proprietary compensator in the instrument removes the portion of the signal resulting from the cornea. The resulting

net signal is the retardation from the retinal nerve fiber laver. The system then generates a two-dimensional (2D) colorcoded image of each eye, in which each pixel has its own specific measurement of retardation. Areas in which the nerve fiber layer is thick are shown in yellow, orange and red; thinner areas are shown in blue and green.

Each patient's results are compared to an extensive gender-, age- and ancestryadjusted normative database that provides the location and magnitude of RNFL abnormalities based on probability of normality (p-values). A temporalsuperior-nasal-inferior-temporal (TSNIT) map displays the thickness measurements along the optic nerve. In the TSNIT map, the values that characterize each patient are superimposed on normal values; the result is depicted as a shaded, double-humped pattern. Localized changes in the RNFL or asymmetry between the patient's own eyes can be easily detected by analyzing tables provided in addition to the color-coded images (see Fig. 3). By comparing serial

studies on any given patient, stability or progressive changes in the RNFL can be assessed; areas of change are color-coded in the printout.

Heidelberg Engineering produces a scanning laser ophthalmoscope (HRT II) that indirectly measures the thickness of the RNFL by measuring its height above a reference plane in the eye. The reference plane in the eye is the area between the optic nerve and the macula that controls central vision. Diode laser light  $(\lambda = 670 \text{ nm})$  is projected through a condensing lens and the pupil onto a precise plane on the retina that covers a 15 degree area. The beam is reflected back through the condensing lens onto a beam splitter and then through a small pinhole aperture onto a photodetector. Only light at a particular focusing plane will go through the aperture onto the photodetector.

During scanning, the focusing plane is varied to change the depth, a process which produces a series of sections focused at different layers on the back of the eye. Inside the 15 degree area of retina that is scanned, 16 to 64 optical sections are obtained, each of which consists of 384 x 384 pixels (147,456 data points). In the color-coded image produced, green is used to represent areas in which the RNFL is intact: red is used to show areas in which it is absent. Stereometric analysis, in which an absolute quantification of various parameters of the optic nerve is generated, is performed on the scan results. In addition, the RNFL is divided into six sectors, each of which is compared to a normal database and classified by linear regression analysis based on probability of normality (confidence interval limits).

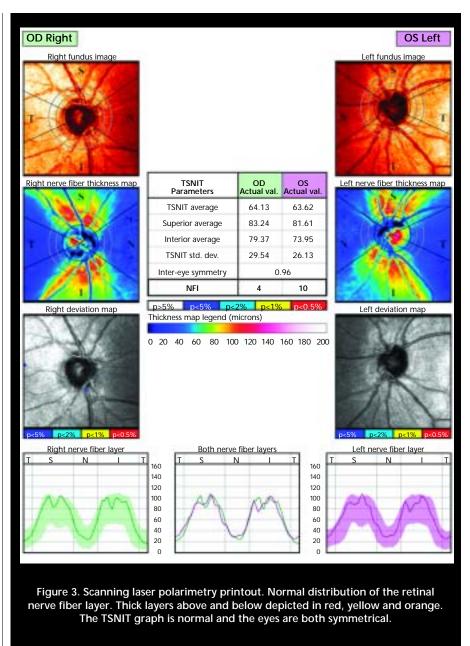
The results of the analysis are depicted in a graph with red and green vertical bars. Each whole column represents the total area of the optic nerve head for a specific sector, green for areas in the sectors in which the nerve fiber layer is intact and red for areas in the sectors in which it is absent. Serial studies can be used to detect progressive changes in the RNFL; areas of loss of the nerve fiber layer are shown in red (see Fig. 2). A quick-view printout on a single page displays images of the optic nerve, along with a table that contains the key stereometric analysis parameters of both eyes.

Carl Zeiss Meditec makes an optical coherence tomographer (OCT). The technology works in a way that is similar to ultrasound but uses light at a wavelength of 820 nm instead of sound to image tissue. Light produces higher spatial resolution than sound without the need for physical contact with the eye.

With this system, a beam of laser light is simultaneously sent to the eye and to a reference mirror, a process which produces reference and measurement beams that travel back to a photosensitive detector. By scanning an area approximately 3.4 mm in diameter around the optic nerve, samples of tissue on the X-Y axis are taken every 5-60 µm, producing up to 512 data points; tissue samples with 1,024 data points over a 2 mm depth are taken on the Z axis. The measurement beam penetrates the ocular tissue layers and is reflected back according to the thickness, distance and reflectivity of the tissue it strikes. The delay times of the reflected measurement beams are compared to the reference beam, which allows for a computer reconstruction of the underlying tissue as high resolution cross-sectional images. The RNFL is differentiated from surrounding structures by an algorithm for margin recognition and its thickness is calculated by counting pixels between the anterior and posterior margins. The RNFL is shown in red and white in the image produced. A normative database, to which various sectors of the patient's optic nerve can be compared, was recently developed.

Visual field testing provides a functional assessment of the RNFL. If there is significant loss of the RNFL, areas in the peripheral vision will be affected. As noted above, the effectiveness of traditional diagnostic methods is often limited by a patient's ability to perform the test. Direct viewing of the optic nerve or photos can provide an anatomical assessment but are limited by the ability of the human eye to detect small changes and judge subtle differences between normal and abnormal.

The newer laser technologies described above offer a much more detailed, objective and reproducible way of evaluating the optic nerve. Despite their potential, however, these new forms of technology are not without their limi-



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tations. Thus far, we cannot unequivocally distinguish between variability in results that can occur with repeated testing from true changes in the retinal nerve fiber layer. Corneal disease, dense cataracts, major fluctuations in eye pressure and some normal variants in optic nerve appearance can all affect results. Though the laser-based methods are far less dependent on patient cooperation, for accurate results to be obtained, patients must be able to maintain shortterm fixation. At present, the new tests appear to be useful in determining whether glaucoma is progressing in a person who already has the disease and in distinguishing a normal patient from one with glaucoma. They are less helpful in assessing whether someone with findings suspicious for glaucoma really has the disease or not. In the future, it is hoped that these new laser-based technologies will be consistent, reliable tools for definitively diagnosing and managing glaucoma.

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