5 Detection of Glaucomatous Changes in the Optic Disc

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INTRODUCTION

The role of any imaging device for the optic disc in glaucoma is to determine the likelihood of a disc being abnormal and whether the appearance of the disc has changed over a period of time.

The ability to objectively and correctly detect a normal or glaucomatous disc using a single examination depends on the overlap of the distribution of some quantitative measure (such as cup/disc ratio) in unselected glaucoma and normal populations. If the distribution of cup/disc ratios in this population of glaucoma subjects overlaps widely with that of nonglaucomatous subjects, then the utility of this parameter is limited. If, on the other hand, another parameter were to separate the glaucomatous and nonglaucomatous populations into two distinct groups, then the utility of this parameter is likely to be high.

Detection of change depends largely on the ability of an imaging device to detect a meaningful difference that is over and above the measurement variability in a given optic disc. For example, if the variability of measurements of a disc parameter is so large that it encompasses the true change that can occur in a progressing disc, then its utility is likely to be limited. On the other hand, if the measurement variability is low, then small changes may be detected.

IMPORTANCE OF DETECTING OPTIC DISC CHANGES

Detecting optic disc progression is one of the most important aspects of glaucoma management. Accurate and early detection of disc change allows the clinician to make appropriate clinical decisions and, if necessary, monitor and adjust the patients' treatment regimen.

It should be noted that detection of early disc change can be used for making a diagnostic decision. As mentioned above, the inter-individual variation in optic disc parameters is considerable, and many individuals who are not glaucomatous may be classified as glaucomatous. More importantly, individuals who are in the statistically normal range may undergo optic disc change over time and still remain within the normal range when analyses of single examinations alone are done. For example, a patient with an initial cup/disc ratio of 0.5 in a large disc may have a concentric enlargement of the cup such that the cup/disc ratio is now 0.6. While the disc has clearly changed, analyses based on single examinations would classify the disc as normal on both occasions. Hence, in such situations, the fact that the disc has changed may be used as a diagnostic cue that the patient is abnormal and, depending on other clinical factors, an early diagnosis of glaucoma may be made on the strength of the disc change.

The availability of serial optic disc images is a powerful clinical tool in the management of glaucoma (Figure 5.1). The ability to perform sophisticated analysis online provides the clinician with important information that has not been available until now.

OPTIONS FOR DETECTING OPTIC DISC CHANGE

Summary indices

Clinicians are familiar with classical indices of optic disc morphology such as cup/disc ratio, cup volume, and neuroretinal rim area. These summary indices are clinically intuitive and convenient to use. Modern imaging devices such as the Heidelberg Retina Tomograph (HRT) automatically calculate stereometric parameters after a contour line demarking the optic disc has been drawn. When a series of images over time have been obtained and carefully aligned, any change in these parameters can be examined by comparing the values from any follow-up examination to the baseline. If many images are available, a trend analysis that examines whether the change is statistically significant over time (and, more importantly, the rate of change over time) can be calculated.

Optic disc changes usually occur in a non-uniform manner across the disc—that is, progression may be more rapid in some disc sectors compared to others. For this reason, it is useful to divide the disc into sectors in which the summary parameters can be analyzed over time. In this manner, changes in, say, the temporal sector alone become more obvious than in a global analysis in that variability or noise from measurements in the other sectors that are not changing can mask the localized changes in the temporal sector.

INDIVIDUAL TOPOGRAPHIC VALUES

The HRT and the HRT II provide a rich matrix of topographic height values (256 x 256 and 384 x 384 pixels respectively) for each single or mean image. An alternative or additional approach to using the summary measures is to examine the height changes in these individual values to determine whether there has been a change. Because analysis of many thousands of values has to be made, care must be taken during both the statistical analysis and interpretation of the results.

The advantage of this approach is that it places no reliance on a contour line or reference plane. Furthermore, the analysis can be performed over the whole image and not restricted to the optic disc.

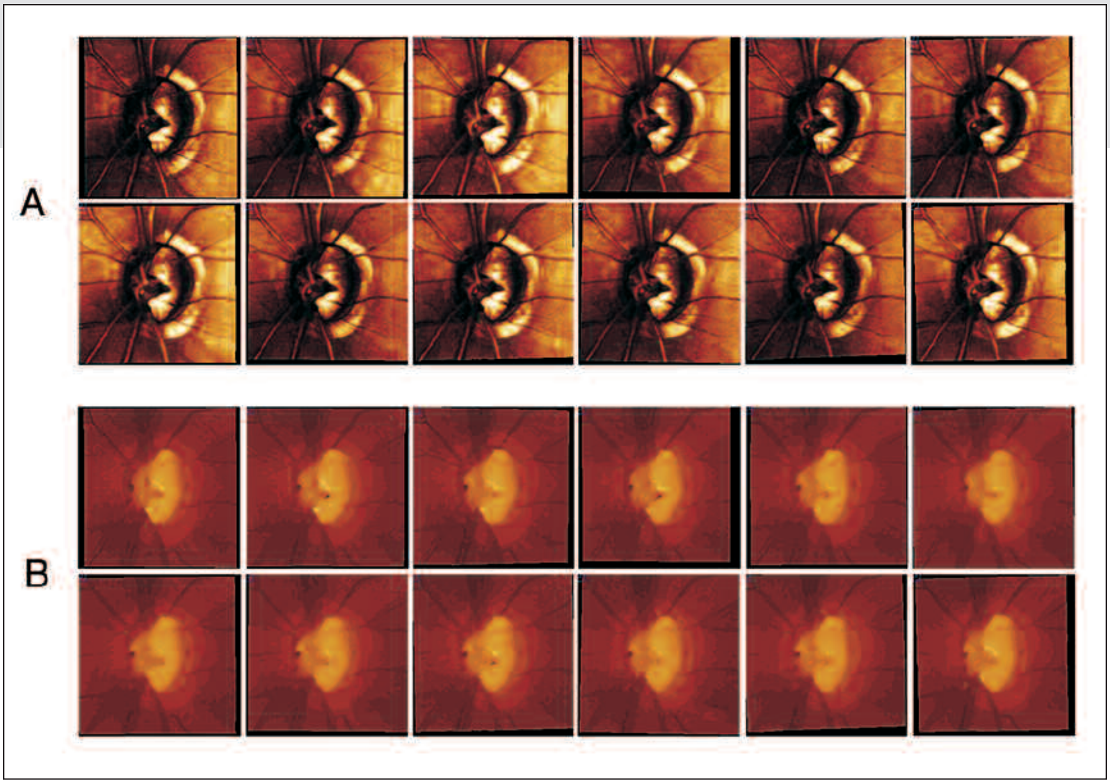

Figure 5.1

HRT images from a four-year follow-up of the left eye of a glaucoma patient examined every four months.

A. Reflectivity images from the series beginning with the baseline image (September 1999, top left) and ending with the final image (October 2003, bottom right).

B. Topography images from the series (baseline [top left] to final [bottom right]).

ANALYSIS OF THE STEREOMETRIC PARAMETERS

The HRT computes a variety of stereometric summary parameters, which have been described in previous chapters. When there are sufficient examinations in the follow-up, the parameters, either singly or in combination, can be observed over time. The number of examinations required before this analysis can be performed depends on the degree of change observed. In cases where large and rapid changes in the optic disc have occurred, quantitative analysis may be possible in as few as three or four examinations, while in cases where the variability of the images is high and/or the changes are small, a larger number of examinations would be required. Generally, as is the case in all types of diagnostic tests, the higher the number of examinations, the better the confidence with the data can be used clinically.

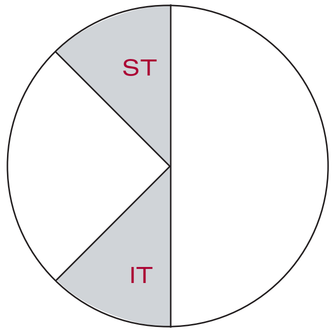

Figure 5.2A

Superior temporal (ST) and inferior temporal (IT) segments, with each segment subtending 45°.

DIVISION OF DISC SECTORS FOR ANALYSIS

The HRT software allows three types of division of disc sectors (Figures 5.2A, B, C) for analysis of the parameters over time (Figures 5.3A, B). In the first, analysis can be done in the superior temporal and inferior temporal sectors; in the second, in the superior and inferior sectors; and in the third, in the entire upper or entire lower disc. In each case, analysis of the entire or global value or values is also performed.

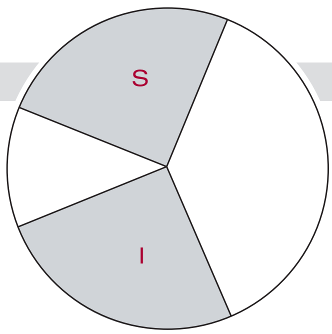

Figure 5.2B

Superior (S) and inferior (I) segments, with each segment subtending 90°.

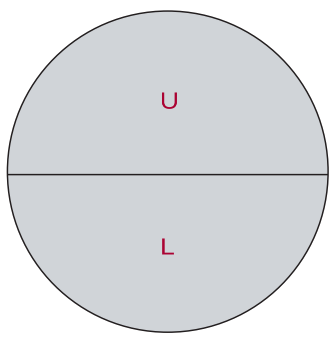

Figure 5.2C

Upper (U) and lower (L) segments, with each segment subtending 180°. Format for the right eye is shown.

ANALYSIS AND INTERPRETATION OF THE PARAMETERS

When performing a trend analysis, the following parameters can be examined over time:

1. Rim area
2. Rim volume
3. Cup volume
4. Cup shape
5. Mean retinal nerve fiber layer thickness
6. Mean height of contour
7. Mean contour elevation
8. Contour line modulation temporal
9. Mean cup depth
10. Mean height inside contour line
11. A combination or average of the above parameters

The actual values of the parameters are not shown in the trend analysis, but instead the normalized change from baseline is shown (Figures 5.3A, B). The normalization is done in order to place the change from baseline in all parameters on the same scale from +1 (maximum improvement) to −1 (maximum deterioration). The basis of the normalization is a ratio of (the difference between a given value and baseline) to (the difference between the average value in a normal eye and an advanced glaucomatous eye).

The horizontal axis can be displayed on a real-time scale with examination dates or simply by examination number irrespective of the time interval between examinations. A formal regression analysis is not performed; therefore, the user should adopt empirical rules for the interpretation of change. Previous experience has shown that a downward trend in three consecutive examinations is suggestive of change; however, confirmations in further examinations are always very useful.

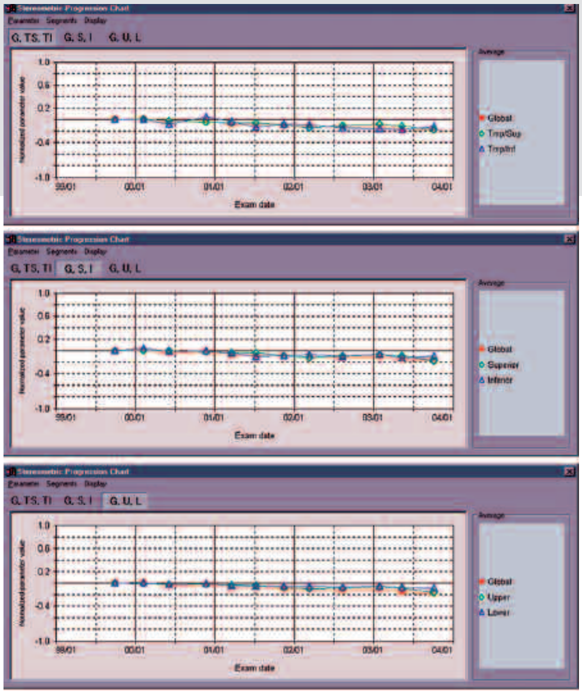

Figure 5.3A

Trend analysis of the parameters of the follow-up shown in Figure 5.1. Analysis of the average of the 10 parameters with the three divisions of disc sectors (top to bottom respectively) as shown in Figures 5.2A, B, C.

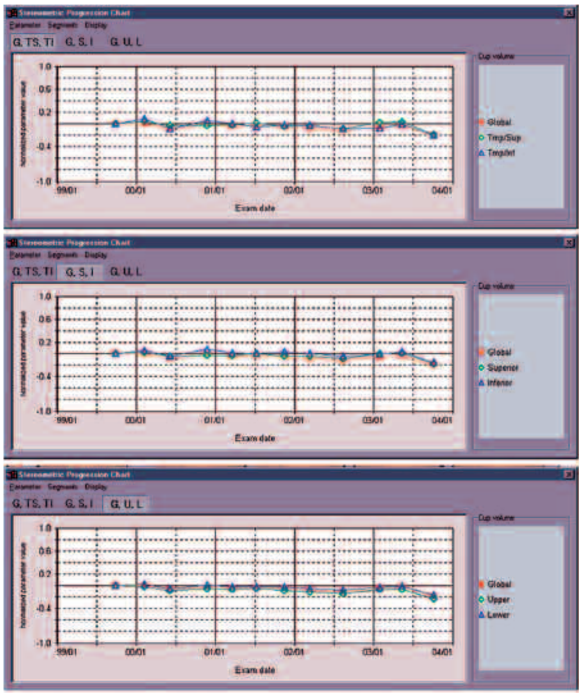

Figure 5.3B

Respective analysis of cup volume. The analysis of the average of the parameters shows a very subtle but definite trend toward worsening values, which is not apparent in the analysis of cup volume.

TOPOGRAPHIC CHANGE ANALYSIS

Topographic change analysis (TCA) is a statistical method to compare the topographic values in discrete areas of the image called superpixels, which contain 4 x 4 (or 16 pixels) at two points in time.[1] Typically, after a series over time has been obtained and aligned, comparison of each follow-up image is made to the baseline.

There are many differences between the trend analysis previously described and TCA, the most important being that TCA does not require a contour line or a reference plane. The analysis is performed on the raw topography values. TCA computes, at each superpixel, the probability of the difference in height values between the two time points occurring by chance alone. Hence, a high probability value (when p is high) indicates that the likelihood of a change is low. On the other hand, a low probability (when $p < 0.05$) indicates that there is little chance that the difference was due to chance alone and that the change was likely to be real. The key determinant in TCA is the variability in topography values within the superpixel over the two sets of three images for each comparison. If the local variability is high, a much larger height difference between the two time points will be required to reach statistical significance, and vice versa. Typically the variability of measurements is highest at the edge of the optic cup and along blood vessels, and lowest in the topographically flatter peripapillary retina. Therefore, relatively larger changes will be required to reach significance in the former case and relatively smaller changes in the latter.

TCA DISPLAY

TCA is automatically performed (Figure 5.4) when there is one mean baseline image and at least two mean follow-up images, with each mean containing at least three individual images.

The main analysis from TCA is contained in the Change Probability Maps, which show each of the follow-up images either in a single display showing each of the reflectivity or topography images (Figure 5.5) or individually (Figure 5.6). In the individual Change Probability Map it is possible to display the baseline reflectivity or topography image as well as the respective follow-up images, in addition to the gray scale of the p values from the analysis and the Absolute Change Map (Figure 5.6). The Reflectivity Map is overlaid with red and green symbols that show superpixels in which the p values are significant, with red demonstrating depression and green demonstrating elevation (Figures 5.5 and 5.6). It is important to note that, by default, only those superpixels where the p values are significant over three consecutive examinations are shown. It is highly recommended that this option (“3 consecutives” as opposed to “2 consecutives”) is used.

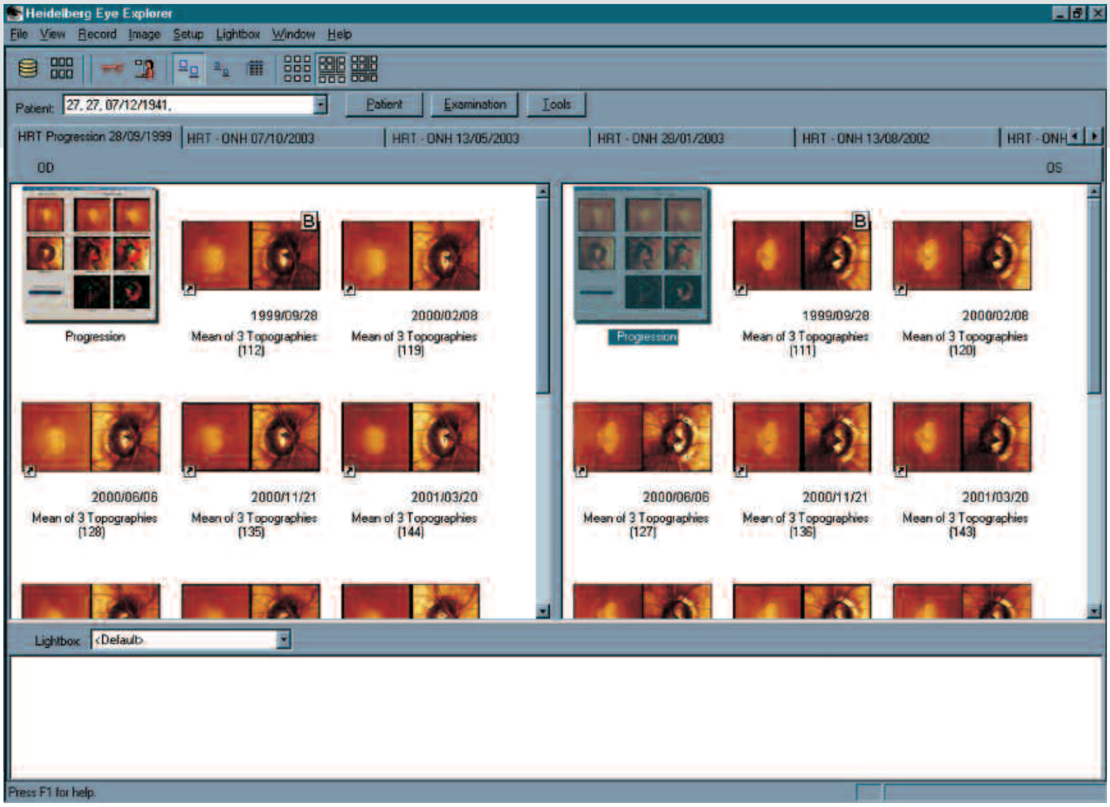

Figure 5.4

A window from the HRT software showing the examinations in the follow-up of each eye in addition to the Progression icon to initiate TCA and trend analysis.

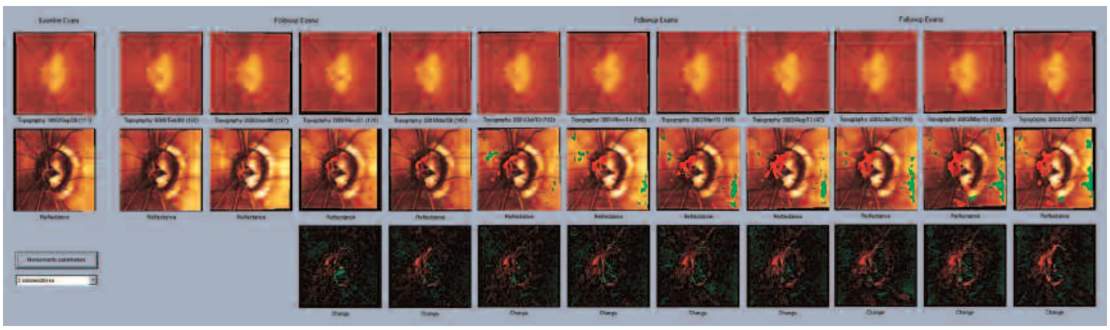

Figure 5.5

Initial window from TCA showing the serial topography images (top), the reflectivity images with the superimposed red and green probability symbols showing areas of depression and elevation respectively (middle), and the absolute difference (from baseline) images color-coded such that the redder or greener the superpixels, the greater the depression or elevation respectively (bottom). This disc shows clear change both supero-nasally and inferiorly (see probability and difference maps). While there are significant green superpixels, they are limited mostly to the edge of the image, where there are likely some alignment errors. The change in these locations is also very small (bottom). Finally, the changes in this disc are more evident with TCA than in the trend analysis (Figure 5.3A) or in inspection of the reflectivity or topography images (Figure 5.1).

Figure 5.6

Window from TCA after mouse-clicking on any of the follow-up reflectivity images. In addition to the disc change supero-nasally compared to baseline, the nerve fiber layer defect infero-temporally appears more pronounced. The user can toggle between the baseline reflectivity and topography images by mouse-clicking on the respective thumbnail image under the main window and also between the follow-up Raw Probability Map, Absolute Change Map, topography, and reflectivity respectively by mouse-clicking on the respective thumbnail image under the main window.

The user can determine the change in local areas by mouse-clicking any area on the follow-up image to reveal the change, pooled standard deviation, and p value in that superpixel (Figure 5.7).

INTERPRETATION OF TCA

TCA is a powerful analysis that has been demonstrated to detect very small changes in optic disc and peripapillary retinal topography. There are, however, no rules regarding when the change detected becomes clinically significant. In a recent study,[2] the criterion for significant change was the presence of a cluster of 20 superpixels derived from cutoff values obtained as the 95th percentile in a group of normal subjects followed over time. It is very important to distinguish between criteria for progression in research studies and in individual patients in a clinical setting. In the latter situation, the criteria may be different for different patients depending on the individual risk.

TCA is a statistical analysis and therefore while a given amount of change in one patient may be highly significant, in another it may not reach significance for a variety of reasons. Even though findings are significant, one should examine the magnitude of change to determine whether the rate or amount of change is meaningful. On the other hand, the absolute change or rate of change in another patient may be high; however, due to variability, the change may not reach statistical significance. These changes cannot be entirely disregarded, and efforts should be made to ensure that the variability of the images is the lowest it can be. Unfortunately, to date, there are no proven guidelines on what degree or rate of change in absolute units (i.e., µm or µm per year) is clinically significant principally because we do not have an external or gold standard for progression.

Figure 5.7

Window from TCA after mouse-clicking anywhere on the follow-up reflectivity image. The outer blue square contains 4 X 4 (16) superpixels or 16 X 16 (256) pixels. The center blue square contains one superpixel. The height change, pooled standard deviation (of the six constituent values), and the p value in that superpixel are shown in the bottom right of the window.

PRACTICAL ISSUES AND TIPS FOR USING THE HRT TO DETECT CHANGE

Image acquisition

- Image quality is paramount. Remember that garbage in = garbage out.
- Ensure that the utmost care is taken to obtain the best possible quality images. Do not rush the acquisition process and if in doubt obtain more images than necessary. Only the best quality images can then be used in the analysis and the others discarded. This is much easier than asking the patient to return to the clinic in case the only set of images obtained was unsatisfactory.
- During image acquisition ensure that the:
  - Patient is given a fixation target if the internal fixation target is difficult to see and/or if the disc cannot be centered in the image frame (see below).
  - Laserbeam enters through the center of the pupil.
  - Fundus is illuminated as evenly as possible.
  - Optic disc is in the center of the image frame. This is crucial for follow-up because it ensures that there is maximum overlap in the area of the aligned images and also that the reference ring (different from the reference plane), which is used to align the serial images, is well away from the disc edge.
  - Optic disc is well enclosed within the image frame with at least 0.5 disc diameters of peripapillary retina visible. If not, switch to a wider scan angle (HRT only, since the scan angle with the HRT II is fixed to 15°).
- Before computing the mean topography, ensure that there are no significant eye movements (especially slow drift or pursuit movements). Use the "Show movie" option of the image series.
- When performing an analysis of the parameters or using TCA, ensure that the serial images are properly aligned. This can be done by mouse-clicking the control buttons on the top right of the screen (Figure 5.6) and cycling between the images. If there are obvious alignment errors, specific images can be removed from the series and/or the manual alignment method should be used. Remember, good alignment of serial images is critical for TCA to perform optimally. Poor alignment will also affect the analysis of parameters.

FREQUENCY OF EXAMINATIONS

- Generally, the more images during the follow-up, the better the analysis. Having a large number of examinations also allows the removal of obviously poor ones for the analysis. This has less of an impact on any change analysis if there are many examinations available in the first place.
- Because examinations are relatively quick, they should ideally be performed routinely in the same way that intraocular pressure or visual acuity is measured.
- Obtain a good set of baseline images (up to three sets). Usually the image quality at baseline is more variable or poorer in quality. Having more images means that the user is not limited to one set.
- When change is suspected, more examinations should be performed over a shorter period of time. In this way the TCA can be used in a shorter time period.

INTERPRETATION

- The greatest utility of the HRT is in the detection of change. Detection of change can be used both for the diagnosis of glaucoma and progression of disc damage.
- Examine all the results carefully. Remember, the quality and options offered by the software are much better than the printout. Always examine the results on the computer monitor and never rely on the printout alone.
- Obtain as many high-quality images as possible.
- Be judicious about excluding images of poor quality and alignment. The inclusion of these images often leads to erroneous results.
- Many patients show changes with the HRT. While this change is not normal, it does not always mean there is clinically significant progression. On the other hand, if there are other signs of disc progression (determined by clinical examination or disc photographs), do not assume the HRT is correct. There are potential reasons why the HRT may miss optic disc change.
- In clinical care, the HRT is a powerful tool that should be used with other clinical tools and measures. In the final analysis, machines do not replace sound clinical judgment.

REFERENCES

1. Chauhan BC, Blanchard JW, Hamilton DC, LeBlanc RP. Technique for detecting serial topographic changes in the optic disc and peripapillary retina using scanning laser tomography. *Invest Ophthalmol Vis Sci.* 2000;41:775-782.
2. Chauhan BC, McCormick TA, Nicolela MT, LeBlanc RP. Optic disc and visual field changes in a prospective longitudinal study of patients with glaucoma: comparison of scanning laser tomography with conventional perimetry and optic disc photography. *Arch Ophthalmol.* 2001;119:1492-1499.