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## The Retina Module

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A noninvasive, objective, and quantitative approach to the assessment of retinal edema is both timely and important for the future management of retinal disease, in particular diabetic macular edema.<sup>1-9</sup> It has been predicted that over the next 20 years there will be an unprecedented increase in the prevalence of diabetes and its complications. When this is considered along with the limitations of current clinical standards for the detection of retinal edema, the need for new objective imaging techniques becomes clear. Fundus biomicroscopy and stereophotography both rely upon the subjective evaluation of retinal thickening, which makes it particularly difficult to distinguish the development of retinal edema from normal inter-subject variation<sup>8,10</sup> and detect change in the amount of retinal edema. Even in patients with clinically significant diabetic macular edema, the leading cause of visual impairment in diabetic eye disease, it has been reported that there are dramatic differences between retinal specialists when defining the extent and location of the edema.<sup>8</sup>

The Retina Module of the Heidelberg Retina Tomograph II (HRT II) (Heidelberg Engineering, Heidelberg, Germany) acquires a series of 16 lateral retinal images for every millimeter of scan depth along the axial plane, or z-axis. Once the sections are aligned, the amount of light returned from the eye and falling on the instrument's detector, known as the reflectance intensity, can be plotted for each pixel as a function of scan depth. This plot of reflectance intensity per unit depth is called the confocal intensity profile, or z-profile (Figure 7.1). The standard topographic surface is generated by establishing the position of peak reflectance intensity along the confocal intensity profile for each pixel. This corresponds to the position of greatest refractive index change, i.e., the interface between the vitreous and the internal limiting membrane (for further details see Chapter 1). We previously demonstrated that measuring the width of the confocal intensity profile could provide objective maps of retinal thickening in selected patients with clinically defined macular edema.<sup>6</sup> It was also found that peak reflectance intensity of the profile decreased in areas of edema.<sup>6,7</sup> This was thought to be a result of the reduced change in refractive index found when going between the vitreous and areas of retinal edema. Consequently, an edema index has been proposed that is sensitive to both the increase in signal width and localized change in peak reflectance. The resultant Edema Maps offer a high-resolution image of the extent and magnitude of retinal edema.<sup>7-9,11</sup>

## THEORETICAL ASPECTS OF RETINAL EDEMA MAPPING

Edema Maps (EMs) are generated by calculating an edema index (EI) for each pixel location such that:

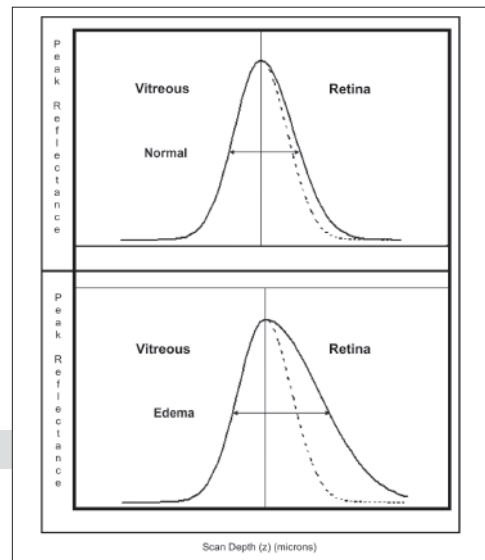
$$\text{Edema index}_{x,y} = \text{SW}_{x,y} / \text{IN}_{x,y}$$

where  $\text{SW}_{x,y}$  is the signal width of the confocal intensity profile at 50% peak reflectance intensity for a given pixel location  $(x,y)$  and  $\text{IN}_{x,y}$  is the peak reflectance intensity for pixel location  $(x,y)$  normalized across all image pixel locations (Figure 7.2). The normalization procedure compensates for variation in absolute reflectance intensity between images, caused by eye and head movement, tear film quality, pupil size, and laser/detector alignment.<sup>6,12</sup> By incorporating two aspects of the effect of edema on the confocal intensity profile, the resultant edema index is sensitive to early retinal edema. The edema index is therefore quantified in arbitrary units.

Signal width ( $\text{SW}_{x,y}$ ) is calculated by fitting a 16th order polynomial to the confocal intensity profile and measuring the signal width at 50% of the peak reflectance. The curve-fitting algorithm also enables aspects of quality control. Pixels are considered invalid, appear black in the Edema Map, and are not used in any of the analysis when the polynomial is unable to model the data. This happens with hemorrhage, when much of the signal is absorbed; exudate, when the signal is reflected; and extensive detachment.

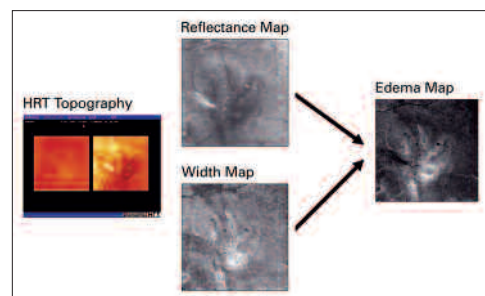
## IMAGE ACQUISITION

When using the Retina Module it is essential that care and attention is given to the process of image acquisition and that the image quality is optimal. In particular it is important that the image is appropriately focused and that the brightness across the image is even, with attention being given to the corners of the live image prior to acquisition. Each of these steps in the acquisition process are similar to that advised for optic nerve head imaging. The patient should be positioned comfortably on the chin and brow rest. Decrease the distance between the objective and the



**Figure 7.1**

In the normal retina, the shape of the confocal intensity profile is slightly asymmetric, with a longer tail toward deeper layers. This is due to light scattered from the deeper retinal tissue, which adds to the high signal of the internal limiting membrane. When edema is present, the amount of scatter from within the edematous retina increases and the peak intensity is reduced. The tail of the confocal intensity profile extends toward the deeper layers, the profile becomes more asymmetric, and its width increases.



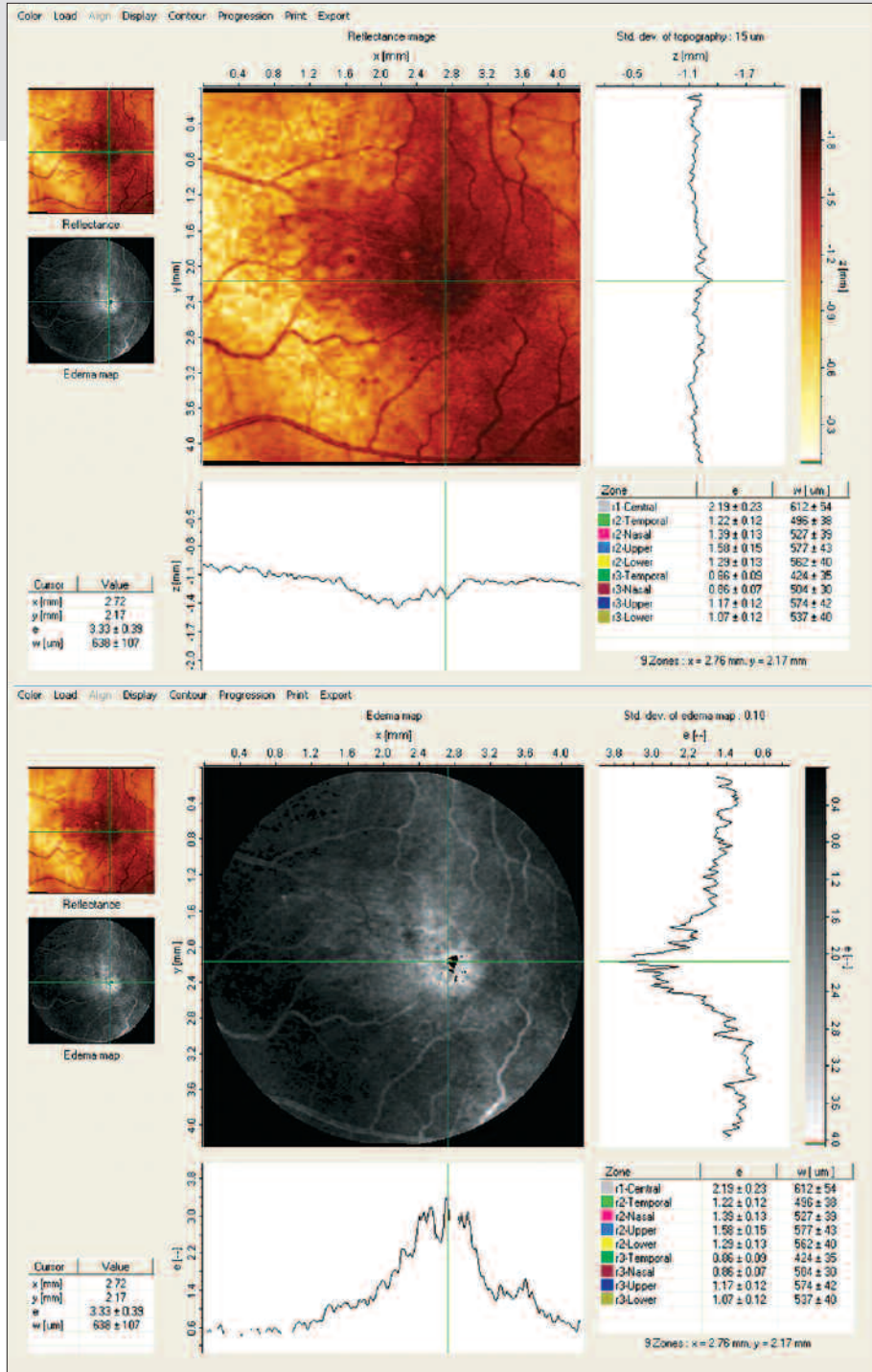
**Figure 7.2**

The Edema Map is generated by combining information from the Reflectance and Width Maps.

eye until the laser beam appears as a stable, sharp circle on the iris. Then move the laser beam into the center of the pupil. Adjust the camera head position and focus until the brightest, most evenly illuminated image has been found. Recheck the position of the laser beam at the center of the pupil throughout this adjustment period. Focus should be optimized for the retinal vasculature. An external fixation light is required in order to center the retinal area of interest, for example the fovea when screening for diabetic macular edema. If the patient has more than a diopter of astigmatism, it is important to use the HRT astigmatic correction lenses, as the signal width and edema index will otherwise be artifactually increased. Once all these steps have been successfully completed, image acquisition will automatically store three separate image series. If tear film quality is poor, particularly if small circular discontinuities are seen on the video image, use artificial tears to aid image quality. The reflectance topographic standard deviation should be as low as possible and preferably below 30  $\mu\text{m}$ .

## IMAGE ANALYSIS

Enter the Heyex Eye Explorer database and select the patient of interest. Once the image icons have appeared in the image window, right-click on the icon and select “Show Movie.” If the three image series appear to be well aligned and of similar intensity, then right-click on the icon and select “Compute Retina Map.” Figure 7.3 illustrates the window that appears at the end of this process. Select the Reflectance Map and choose one of the four “Contour” options. The cross gives simple crosshairs, with the corresponding profiles being displayed adjacent to the reflectance image (Figure 7.3). The circle gives a default 500- $\mu\text{m}$ -radius circle, corresponding to the Early Treatment of Diabetic Retinopathy Study (ETDRS) criterion for definitions of clinically significant diabetic macular edema.<sup>13,14</sup> If a larger measurement circle is required, select the box at the right side of the circle and drag to the desired radius. The x/y position of the circle and its radius are interactively displayed in millimeters at the bottom right corner of the window. The mean average edema index and signal width for valid pixels within the circle are displayed in the table above. The 9-Zone grid automatically analyzes and tabulates nine regions of the image (Figure 7.4). The center circle has a 500- $\mu\text{m}$  radius. The two larger circles are at 1000 and 1500  $\mu\text{m}$ . As with the circle, the 9-Zone grid can be moved within the image by selecting the box at the center of the display using the left button of the mouse. Note that when positioning the contour a normal fovea will appear as a discrete peak on the reflectance profiles, rather than a pit. This can be a useful anatomic landmark. The final option is a freehand grid that works in a similar way to the contour line drawing utility for the optic nerve. The area of interest can be encapsulated by surrounding with clicks of the left mouse button. This feature is particularly useful when monitoring large, confluent areas of edema, for example as found in branch vein occlusion. Once the contour of choice is appropriately positioned, it can be “Accepted” and the Edema Map selected. Ensure that the Edema Map scale is set to “0 to 4,” unless edema index values are extreme. Note that black pixels within the Edema Maps are locations that are considered artifactual. This is due to a variety of reasons including that the signal width could not be modeled ( $r < 0.85$ ), the pixel was one of the brightest 5%,



**Figure 7.3**

The Retina Module enables the clinician to choose the Reflectance Map or the Edema Map. The crosshairs can be positioned within the image. The profiles are illustrated and associated values are tabulated in the bottom left corner. The case illustrates an example of clinically significant diabetic macular edema.

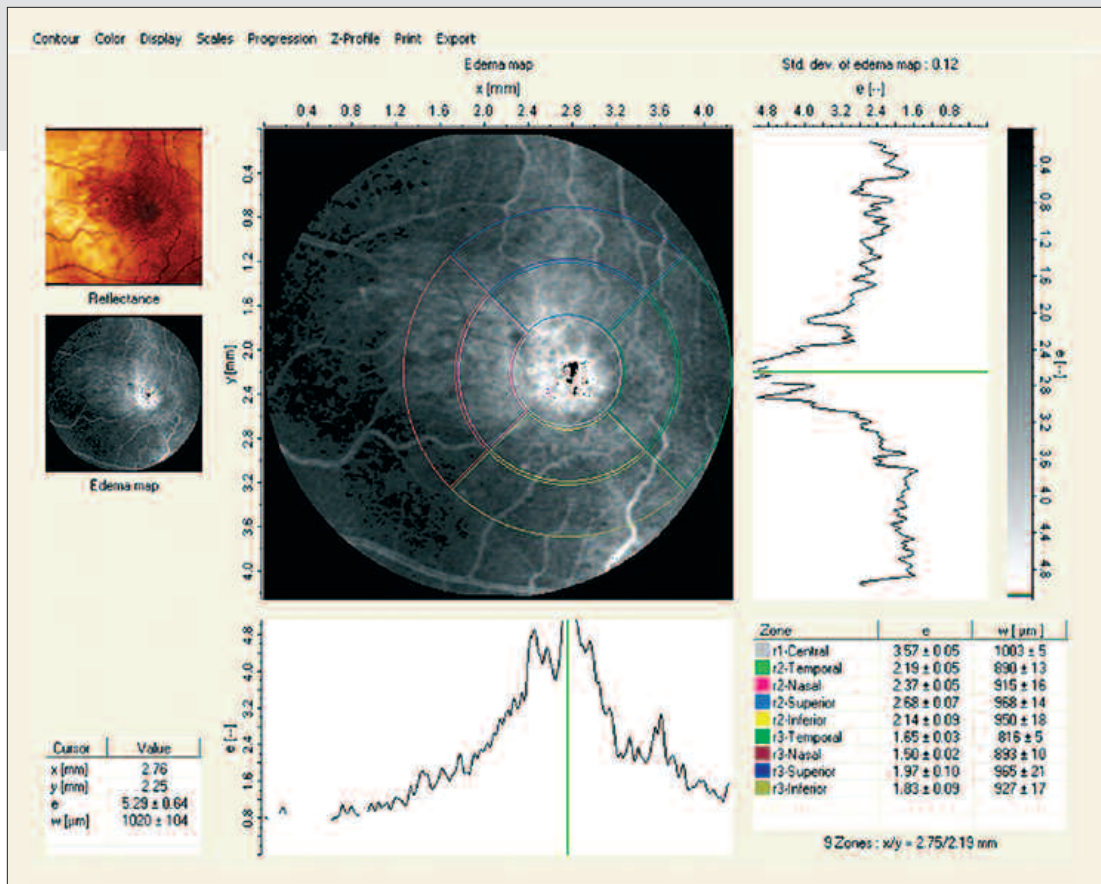


Figure 7.4

The 9-Zone grid is positioned within the Reflectance Map or Edema Map, and values for each area are tabulated in the bottom left corner. The central circle has a diameter of 500 µm. The two larger circles have radii of 1000 and 1500 µm.

and that the pixel was overexposed (gray value > 251). These pixels are labeled as nonvalid and do not influence the edema index calculations. The summary data will be displayed on the printout and can be exported into an Excel® spreadsheet. A table in the bottom left corner of the active window displays the position, edema index, and signal width for the center point of the contour.

Excel is a registered trademark of Microsoft Corporation.

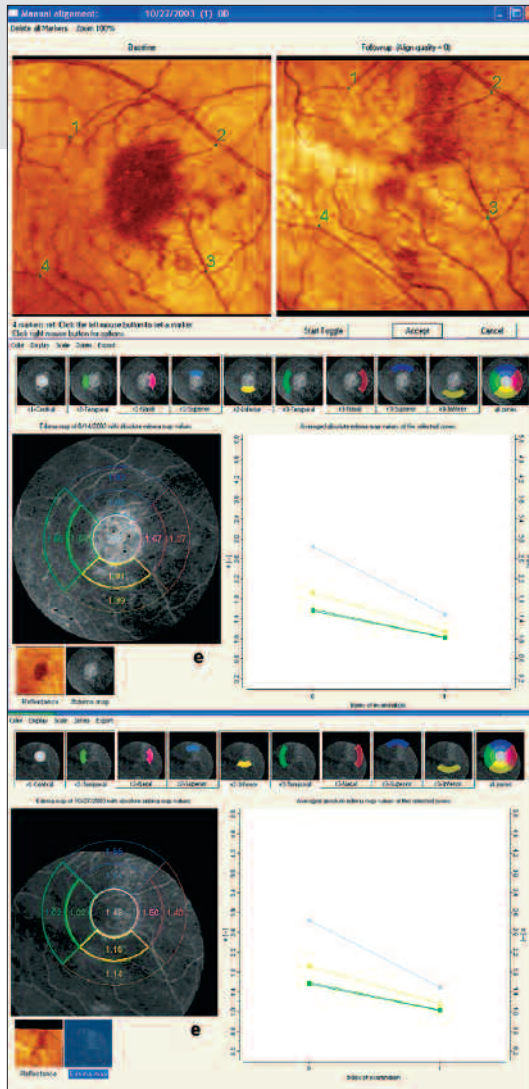
## PROGRESSION ANALYSIS

If a retinal condition is being monitored, then the images require alignment to the original baseline image. Unlike the optic nerve module this process is not automatic, due to the diversity and complexity of retinal imaging and the frequent sparsity of anatomical landmarks. To perform the alignment procedure, select the follow-up image in the light box, right-click the mouse, and select “Align.” The window that opens will display the baseline and follow-up image and will request that you select four landmarks that are common to both images. It is possible to magnify the image so that locations can be more accurately matched. A number is also displayed that shows the percentage of successful matching in order to assist in optimizing the alignment (100 being the best). It is advisable to use vessel bifurcations and to select a landmark within each quadrant of the images. Once images are aligned and a contour (e.g., the 9-Zone grid) has been positioned on the baseline image, it will be automatically positioned on all subsequent images. A Trend Analysis Graph will be displayed (Figure 7.5).

## INTERPRETATION

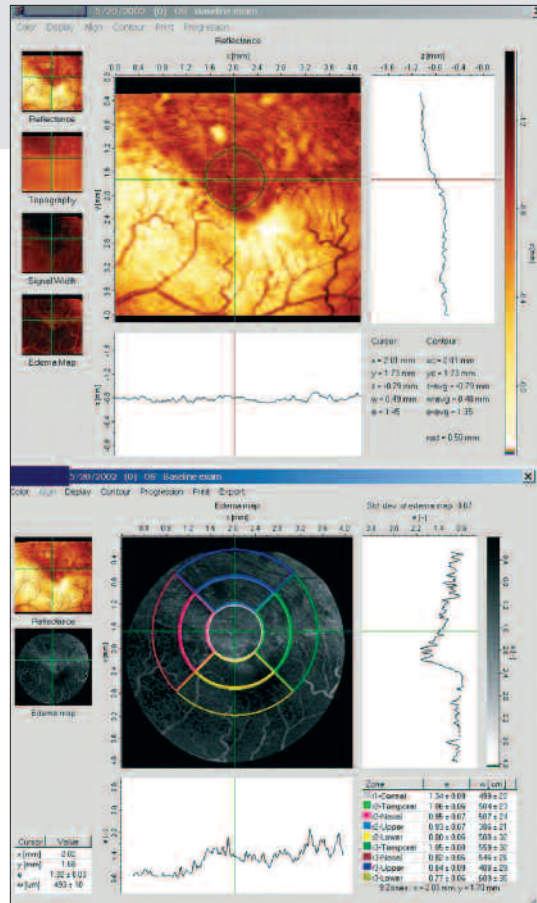
Normal edema index values for the central 500- $\mu\text{m}$ -radius circle change little with age, and have a value of approximately  $1.10 \pm 0.30$  arbitrary units (au). Normal values are similar for all of the 9-Zone sectors. A value between 1.50 and 1.80 should be considered as borderline and above 1.80 as being outside of normal limits ( $p < 0.05$ ). However, the edema index values are of secondary diagnostic importance to the mapping of discrete areas of increased edema within an image.

It is important to understand that the Edema Maps were developed specifically to map the development of early diabetic edema and its progression. It is assumed that the retina is pigmented, and the edema index will not be calculated reliably in areas of retinal pigment epithelium dropout. The technique can be useful in identifying and monitoring nondiabetic retinal edema, e.g., cystoid macular edema and the edema associated with vein occlusions (Figure 7.6), but will be less useful in macular degeneration. Retinal nevi and prominent macular pigmentation can give artifactually increased edema values, but these are easily identified clinically. In the future it is likely that an estimate of retinal thickness, in micrometers ( $\mu\text{m}$ ), will be included in the Retina Module as a Thickness Map (Figure 7.7).



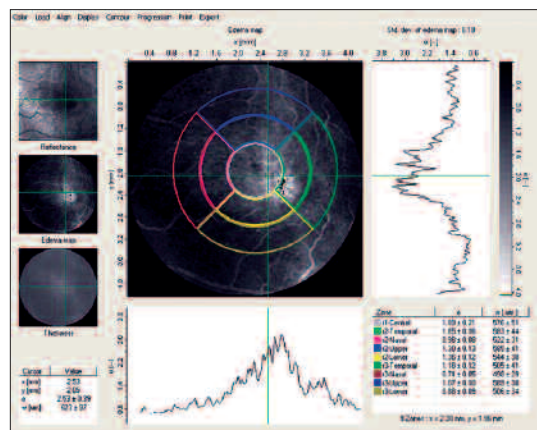
**Figure 7.5**

Progression Analysis: The upper panel shows the window for the manual alignment utility. Four landmarks are selected that are common to both the baseline image (left) and follow-up image (right). Following alignment the Trend Analysis window will appear after selecting "Progression." The middle panel shows the baseline image for a patient with diabetic macular edema. The lower panel shows a follow-up image taken 14 months later, with a clear reduction in the amount and extent of the edema.



**Figure 7.6**

Reflectance Map (upper) and Edema Map (lower) showing a case of branch retinal vein occlusion.



**Figure 7.7**

Retina Module analysis of a patient with diabetic macular edema (as in Figure 7.4) showing the prototype of the Retinal Thickness Map.

## CONCLUSION

In summary, the Retina Module offers a unique and sensitive analysis of the optical effects of edema within the retina. It does so by combining the increase in the signal width experienced as the laser light works its way through the retina, with the reduction in peak reflectance experienced over areas of retinal edema. It does not measure retinal thickness, although retinal edema and retinal thickness are often correlated. The agreement with clinical assessment is good,<sup>9,11</sup> and it is capable of identifying diabetic macular edema prior to its clinical detection.<sup>8,9,11</sup>

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## REFERENCES

1. Bresnick GH. Diabetic macular edema. *Ophthalmology*. 1986;93:989-997.
2. Bartsch DU, Intaglietta M, Bille JF, Dreher AW, Gharib M, Freeman WR. Confocal laser tomographic analysis of the retina in eyes with macular hole formation and other focal macular diseases. *Am J Ophthalmol*. 1989;108:277-287.
3. Shahidi M, Ogura Y, Blair NP, Zeimer R. Retinal thickness change after focal laser treatment of diabetic macular oedema. *Br J Ophthalmol*. 1994;78:827-830.
4. Puliafito CA, Hee MR, Lin CP, et al. Imaging of macular diseases with optical coherence tomography. *Ophthalmology*. 1995;102:217-229.
5. Hudson C, Charles SJ, Flanagan JG, Brahma AK, Turner GS, McLeod D. Objective morphological assessment of macular hole surgery by scanning laser tomography. *Br J Ophthalmol*. 1997;81:107-116.
6. Hudson C, Flanagan JG, McLeod D, Turner GS. Scanning laser tomography z-profile signal width as an objective index of macular retinal thickening. *Br J Ophthalmol*. 1998;82:121-130.
7. Hudson C, Flanagan JG, Turner GS, Chen H, Young L, McLeod D. Scanning laser-derived edema index topographic maps. In: Wall M, Wild JM, eds. *Perimetry Update 1998/1999*. The Hague: Kugler Publications; 1999:503-510.
8. Hudson C, Flanagan JG, McLeod D. A clinical vision science perspective of the management of diabetic macular oedema. *Excerpta Medica. Focus on Diabetic Retinopathy*. 8:1:4-9.2000.
9. Hudson C, Flanagan JG, Turner GS, Chen HC, Young L, McLeod D. Correlation of a scanning laser derived oedema index and visual function following grid laser treatment for diabetic macular oedema. *Br J Ophthalmol*. 2003;87:455-461.
10. Ferris FL III, Patz A. Macular edema. A complication of diabetic retinopathy. *Surv Ophthalmol*. 1984;28:452-461.
11. Guan K, Hudson C, Flanagan JG. Comparison of the Heidelberg Retina Tomograph II and Retinal Thickness Analyzer in the assessment of diabetic macular edema. *Invest Ophthalmol Vis Sci*. 2004;45:610-616.
12. Eikelboom RH, Cooper RL, Barry CJ. A study of variance in densitometry of retinal nerve fiber layer photographs in normals and glaucoma suspects. *Invest Ophthalmol Vis Sci*. 1990;31:2373-2383.
13. ETDRS Research Group. Early photocoagulation for diabetic retinopathy. ETDRS report number 9. *Ophthalmology*. 1991;98:766-785.
14. Kinyoun J, Barton F, Fisher M, Hubbard L, Aiello L, Ferris F. Detection of diabetic macular edema. Ophthalmoscopy versus photography. ETDRS report number 5. *Ophthalmology*. 1989;96:746-751.