Supplement to

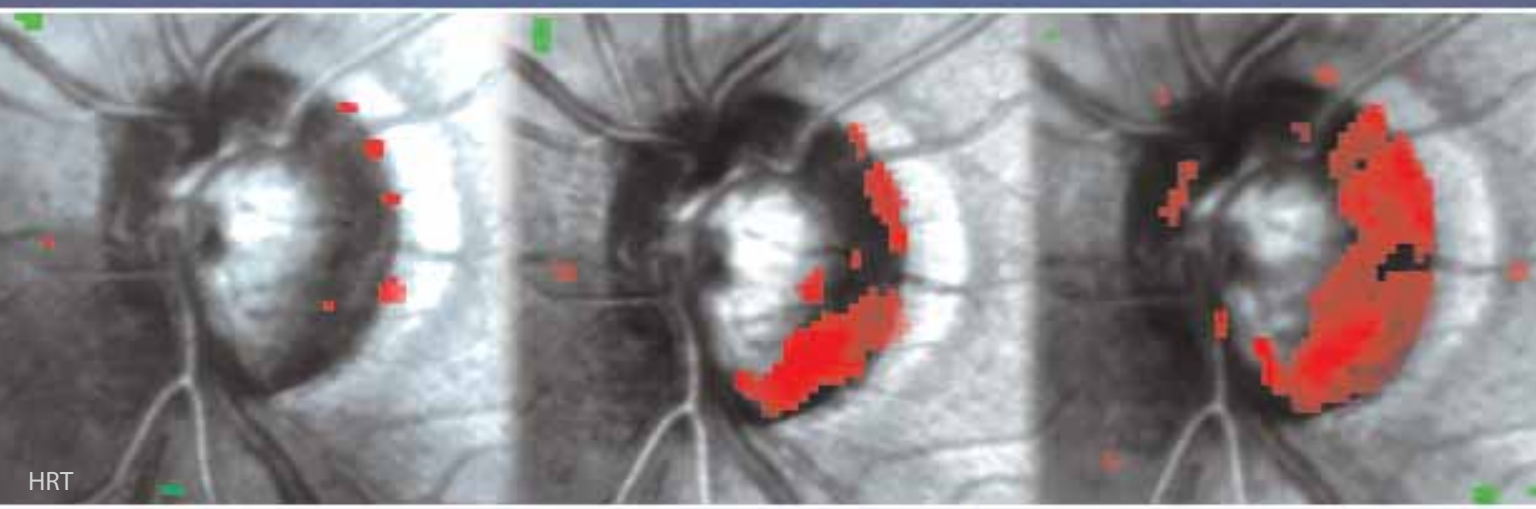
Sponsored by an unrestricted educational grant from Heidelberg Engineering, Inc.

Glaucoma TODAY

March/April 2007

Glaucomatous Progression

The relationship of structural and functional change.



PANEL

Robert J. Noecker, MD, MBA, Moderator

L. Jay Katz, MD

Jody Piltz-Seymour, MD

Theodore Krupin, MD

Thomas W. Samuelson, MD

Introduction

Clinicians' use of imaging in glaucoma has increased substantially in the past several years. It is well recognized that a thorough examination of the optic nerve and nerve fiber layer are requisite parts of any evaluation, and the available imaging modalities have proven to be useful at various stages of evaluation and treatment. Nonetheless, although the promise of being able to provide quantitative information about the structure of the optic nerve and retina is enticing, there remains a great deal of misinformation or lack of data to support the utility of these devices in daily clinical practice. While the ability to produce digital images is helpful at one level, it also introduces a dilemma for the clinician as to how to use the data once they are obtained. Finally, practitioners must understand what sort of artifact may be introduced with each machine and how easy it is to acquire images with each device. Poor scans provide useless or misleading information that confounds clinical care.

The purpose of this supplement is to share with readers the insights of several experts in the field of glaucoma who use imaging in daily practice. The panelists discuss the strengths and weaknesses of the various technologies and the ability of each unit to diagnose and follow patients for glaucomatous progression. We also address practical issues such as transferring old data forward into newer versions of the devices and the need for pupillary dilation during image acquisition. Lastly, we share several real-world cases that illustrate how imaging was helpful in our decision-making process.

I think that readers will find this supplement to be a useful reference on the implementation of imaging technologies in their clinical practices.

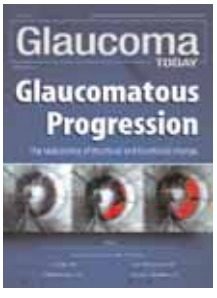
Robert J. Noecker, MD, MBA, Moderator

The Panel

Robert J. Noecker, MD, MBA, moderator, is Director of the Glaucoma Service and Associate Professor/Vice Chair at the Department of Ophthalmology at the University of Pittsburgh. He has received honoraria from Heidelberg Engineering, Inc. Dr. Noecker may be reached at (412) 647-2152; noeckerrj@upmc.edu.

L. Jay Katz, MD, is Director of the Glaucoma Service at Wills Eye Hospital and Professor of Ophthalmology at Jefferson Medical College, both in Philadelphia. He has been in the speakers program of Heidelberg Engineering, Inc. Dr. Katz may be reached at (215) 928-3197; ljk22222@aol.com.

Theodore Krupin, MD, is Clinical Professor, Department of Ophthalmology, Feinberg School of Medicine, Northwestern University, Chicago. He has received honoraria from Heidelberg Engineering, Inc. Dr. Krupin may be reached at (312) 475-1000; krupin@northwestern.edu.



ABOUT THE COVER

The cover includes three scans using the HRT Topographic Change Analysis. The visual fields are courtesy of Robert J. Noecker, MD, MBA.

Jody Piltz-Seymour, MD, is in private practice at the Glaucoma Care Center Keystone Eye Associates Subspecialty Center in Philadelphia. She is a consultant for Heidelberg Engineering, Inc. Dr. Piltz-Seymour may be reached at (215) 552-8331.

Thomas W. Samuelson, MD, is Adjunct Associate Professor at the University of Minnesota in Minneapolis and Attending Surgeon at Minnesota Eye Consultants/Phillips Eye Institute in Minneapolis. He is on the speakers bureaus for Heidelberg Engineering, Inc., and Carl Zeiss Meditec, Inc. Dr. Samuelson may be reached at (612) 813-3628; twsamuelson@mneye.com.

CONTENTS

Analyzing the Relationship Between Structure and Function 3
Assessing Structure in Daily Practice 3
Comparing Imaging Devices 5
Ensuring a Quality Scan 6
Diagnosis Versus the Detection of Progression 8
The Literature 8
The HRT II Versus the HRT3 10
Case Studies 11
Closing Thoughts 15

ANALYZING THE RELATIONSHIP BETWEEN STRUCTURE AND FUNCTION

Noecker: The ancillary testing we perform today is certainly different from a decade ago. Before we evaluate the pluses and minuses of today's imaging technologies, let's begin by discussing the relationship between structure and function.

> *"I am convinced that structural change precedes functional loss [in glaucoma]."*
> *—Theodore Krupin, MD*

Krupin: As far as the glaucomatous process, either development or progression, I am convinced that structural change precedes functional loss. We have come a long way from looking only at functional change in the visual field. For example, the large (5,000 glaucoma suspects), NEI-funded, multicenter Collaborative Glaucoma Study that was performed in the 1970s defined the development of open-angle glaucoma as visual field loss.[1] The importance of evaluating the optic nerve in glaucoma did not surface until the early 1980s. Although you cannot monitor patients without assessing visual function, I put a lot more emphasis on structural changes to the optic nerve.

Samuelson: I have been in practice for 15 years now. One thing that has become increasingly evident to me during that time is that structural changes occur earlier than functional changes in the vast majority of patients, as demonstrated by Balwantray Chauhan, PhD,[2] and the Ocular Hypertension Treatment Study (OHTS).[3] If you rely on functional parameters to make the diagnosis of glaucoma, you are picking things up pretty late in the game structurally. The significance of this is not yet entirely understood. Is it simply that there is redundancy in the neural network and, therefore, a significant percentage of ganglion cells can be lost without functional consequence, or are patients losing function that we are not good at measuring yet? I suspect the latter may be true. I think a lot of people who are asymptomatic and have normal white-on-white visual fields have abnormal elements to their visual function that we cannot yet pinpoint. We know that we can measure such loss earlier with other testing modalities such as Frequency Doubling Technology or Short Wavelength Automated Perimetry (both from Carl Zeiss Meditec, Inc., Dublin, CA), but the consequences of such a loss on function in the activities of daily living are not yet well known.

Piltz-Seymour: The OHTS showed clearly that, in the majority of patients who developed glaucoma, the disease manifested first in the optic disc.[4] Photographing the optic nerve is important, and imaging plays an important role as well.

Katz: I think that the definition of glaucoma is changing. We used to say that there had to be characteristic visual field defects before we diagnosed glaucoma. A functional deficit is not a requisite to make the diagnosis now. That is why the glaucoma community has introduced and embraced the term *preperimetric glaucoma*.

Noecker: It appears that there is a consensus among the experts that there is a need to detect abnormalities and changes in the optic nerve as early as possible. Now, on a practical level, let's discuss how we translate this into the care of our glaucoma patients.

ASSESSING STRUCTURE IN DAILY PRACTICE

Noecker: In your daily clinical practice, how do you assess structural changes?

Samuelson: My evaluation begins with the clinical examination, which includes a careful stereoscopic view of the optic disc under high magnification. I use a 60.00 D lens for an eye with a widely dilated pupil and clear media. I use a 90.00 D lens in eyes with cloudy media. I also routinely look at the nerve fiber layer (NFL) with a red-free light and high magnification. I look for hemorrhages and notching of the optic nerve. I like to look at the NFL and the neuroretinal rim rather than simply document a cup-to-disc ratio. I think that the cup has been overemphasized in the past. Although I describe the optic nerve in the chart much like George Spaeth, MD, does with his Disc Damage Likelihood Scale,[5] I think it is important to memorialize the structures to facilitate comparisons in the future. I do not think we can simply rely on our drawings and descriptions. We need to tap into the technology that is able to record lasting and reproducible images. I have three different imaging platforms: the HRT3 (Heidelberg Engineering GmbH, Heidelberg, Germany); the Stratus OCT (Carl Zeiss Meditec, Inc.); and the GDx VCC (Carl Zeiss Meditec, Inc.). I find them all useful in different ways.

Noecker: Jody, do you look at the NFL at every visit, and what do you look for?

Piltz-Seymour: I look at the optic nerve at most visits. The optic nerve examination is key to the glaucoma examination. If you do nothing else, you must look at the optic nerve and really have a sense of it over time. Your interpretation of what you see provides the most important informa-

tion to determine optimal glaucoma management.

It is important to look at the nerve in different ways. I view it under high magnification and bring a slit beam across the optic nerve. What may look like rim may disappear as the beam passes. Rims may have different qualities. They may be dense and compact or moth eaten. I really like to bring highly magnified, digital photographs up on a computer screen. Patients get involved in their care by looking at these images. I have taught disc interpretation to so many patients now using the doughnut model (look at the rim, not the hole). I have the HRT and Stratus OCT at my practice and have used the GDx in the past.

> *"In the majority of [OHTS] patients who developed glaucoma, the disease manifested first in the optic disc."*
> *—Jody Piltz-Seymour, MD*

Katz: The panelists (all glaucoma specialists) look at the optic nerve very carefully, but there are articles suggesting that our colleagues who are general ophthalmologists do not quite share our enthusiasm for carefully examining and recording the appearance of the optic nerve and NFL in patients with glaucoma.[6] They may not think doing so is important, they may be too busy, or they may find the optic nerve hard to see. I think that the introduction of imaging technology has refocused the ophthalmic community at large on looking at the optic nerve. The imaging software provides a lot of data and analysis.

Piltz-Seymour: Many practitioners will not document anything about the optic disc. It is important to teach people to look at the optic nerve and to offer them alternatives that may get them to analyze the nerve if they are not looking at it directly.

Noecker: Ted, what do you think the standard of care is for a general ophthalmologist?

Krupin: First, I would stress the optic nerve examination. One of the major advantages of these imaging devices may be that they provide a way to document the optic nerve for the busy clinician, but they surely do not diminish the importance of the examination. I look at the nerve every time a patient comes in. It takes me a second. If you do not look, you are going to miss an optic disc hemorrhage.

How often do you all use the ISNT rule[7,8] when examining the optic nerve on a new patient? I think I am about 95% accurate in my diagnosis of glaucoma just by looking at the optic nerve.

Piltz-Seymour: The ISNT rule is not always accurate, especially if the optic nerve is tilted, very large, or tiny. With the average optic nerve, however, the ISNT rule can guide you. An inferior rim that is thinner than the other rims is suspicious.

Krupin: The ISNT rule reinforces the examination of the optic nerve. That is why I think it is important.

Noecker: I think the key point is that there are multiple components to the optic nerve's evaluation, starting with noting the size of the disc, the contour of the rim, and the presence of NFL hemorrhages. You have to put together the whole picture.

Katz: When you list 20 different things to look for to diagnose optic neuropathy with glaucoma, it is too much initially. If you start by teaching the ISNT rule to residents, they will look and notice a disc hemorrhage or abnormal disc cupping.

Samuelson: One of the things I discourage residents and fellows from doing is drawing the optic nerve when viewing it through a small pupil. When pupils are undilated, I use subjective comments like *no notching* or *rim intact*. If I do draw the optic nerve in undilated eyes, I make a note that it was an undilated view so that, if it differs from my drawing of the dilated eye, I know to trust the latter more.

Krupin: I agree, but, when I am judging the cup-to-disc ratio, I am not looking at what I did before. You know the variability you have.

Katz: Do you ever record the cup-to-disc ratio?

Krupin: I do it the first time.

Samuelson: I do it if I write 1.0. Otherwise, I describe the rim in four to six locations around the disc (eg, 0.1 @ 10 o'clock, 0.2 at 12 o'clock, 0.1 @ 2 o'clock). It helps to have a scribe recording information as you describe what you are seeing. For me, this is the most reproducible method of examining the optic disc.

Krupin: I document the size, because I think it is so important to our analysis of the optic nerve.

Katz: Do you perform imaging to document the optic nerve's size, or do you merely make a comment after the clinical evaluation?

Krupin: I look for asymmetry in disc size, which is common.

Noecker: Do you use disc photographs? Are they the gold standard?

Katz: I no longer get disc photographs for every patient.

Krupin: I obtain simultaneous stereoscopic photographs on every glaucoma and ocular hypertensive patient and on patients with suspicious optic nerves. I think the technology of imaging is here to stay, and it is just going to get better. When I see a patient referred in, I ask, "Has anyone ever taken a picture of your nerve?" I would love to see a picture from 10 years ago. I rarely repeat photographs.

Samuelson: I use disc photographs on occasion, especially for younger patients or interesting cases that I will use for teaching purposes. I do not usually take disc photographs of everyone, because I typically image them with the HRT, Stratus OCT, or GDx unless, of course, the damage to the disc is far advanced. In such cases, I rely more on visual fields. I agree, however, that properly used photographs, especially in the digital era, remain a great way to monitor patients.

Piltz-Seymour: I take disc photographs of every patient at baseline.

Krupin: A baseline photograph is better than imaging, because imaging technology changes. Some of the technology is not convertible. The photograph is always there. I routinely take three copies. When patients are leaving the practice, I tell them to take the photographs with them.

> *"Imaging now seems to be an integral part of the structural evaluation of the optic nerve."*
> *—Robert J. Noecker, MD, MBA*

Noecker: We get baseline photographs, too, but typically document change by other methods.

Katz: I do not disagree but will point out that we all trained in the era of getting disc photographs. I would like to note the limitations, however, of qualitative evaluations of the optic nerve. There is a lot of evidence that we really do not know how to look at disc photographs in series very well.[9-11] We are terribly biased in how we read them. Knowing the chronology, we overcall change by 50%.[11]

Samuelson: We have all said that having a photograph from 10 or 15 years ago is great. That is partly because imaging was not very good not that long ago. If we had a high-quality HRT, Stratus OCT, or GDx scan, we would probably find that quite valuable as well.

> *"Heidelberg Engineering GmbH should be congratulated on their longitudinal stability in terms of their platform."*
> *—Thomas W. Samuelson, MD*

Noecker: It appears that the methods by which we assess the optic nerve and NFL have changed. Imaging now seems to be an integral part of the structural evaluation of the optic nerve. The quantitative data about nerve size and rim area can confirm our clinical impressions and help us to objectively measure damage and progression.

COMPARING IMAGING DEVICES

Noecker: Tom, since you use all three technologies, would you mind briefly contrasting how they work?

Samuelson: The units may be divided into two main types, those that image the NFL well and those that image the disc well. The Stratus OCT is generally considered to image the NFL well but less so the optic disc. It does much better in the z axis than the x-y axis. I think that the HRT3 does the best job by far with the disc, and the device provides an assessment of the NFL as well. Because I do not have each imaging system at every office location, I choose the technology based on which office I am using; two of my offices have HRT3 units, and the other has the Stratus OCT. The GDx supplements either of those two technologies. I would emphasize the need to be certain that you are obtaining quality scans with all of the devices, but this is especially important with the GDx. There is a "tie-dyed" artifact that I see all too frequently in my Scandinavian population in Minnesota. Given the artifact's frequency, I would not rely on the GDx VCC as my sole imaging device. When I do get a quality scan, perhaps 90% of the time, I like the GDx's ability to assess the NFL.

Piltz-Seymour: I have experience with all three devices as well. Most often, I use the HRT II but look forward to upgrading to the HRT3. The HRT has the best database, the best long-term follow-up data, and the best progression program. It is also the device that concentrates on the optic nerve. I use the HRT most frequently to evaluate progression. I do not use it as much for diagnosis as for follow-up, although I think it is a useful diagnostic tool for general ophthalmologists. I use the Stratus OCT when I want to look more at the NFL. It is a balancing act. I would like to look at

a Stratus OCT and an HRT scan for every person, but I must be practical. Because I have the Stratus OCT, I do not miss the GDx. Ensuring quality data is important with every instrument. You need to be sure that you are looking at quality scans.

Samuelson: I can look at a GDx scan and tell if it is a reliable image just by its appearance. The HRT3 and earlier versions of the technology have excellent standard deviation readings to help the clinician judge the image's quality. I also look at the contour line and the image of the HRT printout to assess the quality of the scan. In my opinion, assessing the image's quality is most difficult with the Stratus OCT. The addition of the "signal strength" parameter helps, but it can still be challenging. Heidelberg Engineering GmbH should be congratulated on their longitudinal stability in terms of their platform, which does allow you to look at progression better than with the other units, even from different versions of the HRT.

Katz: We have looked at the optic nerve for many years, whether with stereo disc photography or clinical examination. The glaucoma community has never embraced NFL photography, despite the reported value of red-free photographs in noting glaucomatous NFL dropout.[12,13] Along those lines, technology that relies solely on looking at the NFL was not that attractive to me. The GDx was never really used much in my institution. As Tom mentioned, HRT technology has been very stable, so my colleagues and I have gone through the original HRT to the HRT II and now to the HRT3. We have relied clinically on the HRT for our follow-up with glaucoma suspects and patients. Doing a Stratus OCT scan is not easy. I myself tried it and saw how difficult it was. The technicians have a hard time getting quality images with this device as opposed to the HRT. For all of those practical considerations, my colleagues and I have relied much more on the HRT for our clinical practice. The Stratus OCT has been relegated primarily to retinal examinations.

Krupin: I agree with Jay. I would only add that all of the technologies are very dependent on technician acquisition, as are visual fields.

Samuelson: If I just get the NFL, I feel like I missed disc analysis and vice versa. I do like looking at the NFL, and Harry Quigley, MD, Alfred Sommer, MD, and the group at the Wilmer Eye Institute in Baltimore have emphasized the usefulness of the NFL examination. Unfortunately, our ability to image the disc well with photographs is significantly easier than imaging the NFL. To have devices that image the NFL well is quite helpful and far superior than what we can do with photographs.

Krupin: I think I do as well looking at the disc as at the NFL. Where the NFL is gone, the blood vessels stand out. It is not quantitative, but I do look at it.

Samuelson: I think that is true with focal loss. With diffuse loss, it is pretty hard, especially with a light-colored fundus.

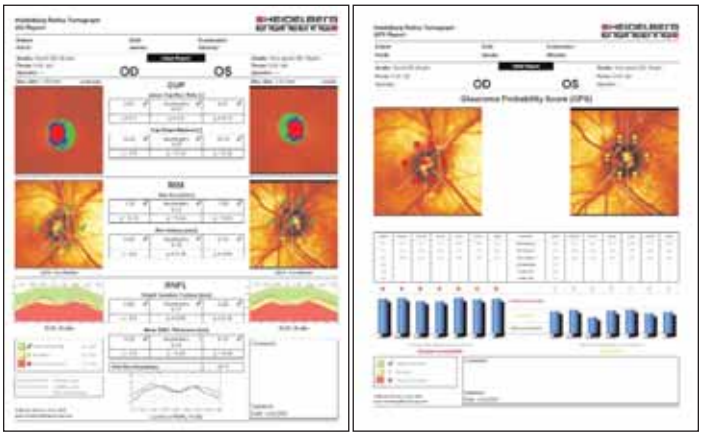
Piltz-Seymour: For years, I tried to work with our photographers to take consistent photographs of the NFL. Sometimes, their photographs were gorgeous. Other times, they were terrible. I think photography was discouraging as a tool for evaluating NFL loss, but the NFL is still a wonderful place to look for damage. With darkly pigmented fundi, a great color photograph will show NFL loss if you look for it closely.

> *"The HRT3 has databases for different ethnicities that help standardize disc size, which can vary by race."*
> *—Thomas W. Samuelson, MD*

Noecker: It is important to understand what each technology is measuring. The units are not just competing brands but have different physics behind them. Simply put, with the Stratus OCT, you are acquiring a B-scan–like image of the retina using light to look at the different layers of the retina based on reflectance of the different layers. The NFL is highly reflective, which makes it convenient for use in glaucoma. With the HRT3, you end up with more of a topographic map made of a composite of serial images at different depths. The GDx gives you information about the NFL looking at the polarization of light. One of the problems with the original GDx was that those scans were largely useless, because the technology did not compensate for the polarization in the cornea, lens, and vitreous. The GDx with VCC and ECC are better. In clinical practice, however, I would have to agree that the GDx only gives information about the NFL and is probably the most prone to artifact. Also, it is still an indirect measurement. With the availability of the HRT3 and the Stratus OCT, I do not see a role for the GDx in my clinical practice.

ENSURING A QUALITY SCAN

Noecker: It is important to discuss practical issues such as how to judge a good scan and the different types of likely artifacts. The HRT3 functions at 24 milliseconds per scan, whereas the Stratus OCT is at 320 milliseconds. I think we can talk about the artifacts that may be introduced as a result of scan speed.



(Courtesy of Heidelberg Engineering, Inc.)

Figure 1. The HRT3's OU Report summarizes cup, rim, and retinal nerve fiber layer (RNFL) information while quantifying asymmetry. The HRT3's Glaucoma Probability Score (GPS) is a new approach to analyzing HRT data based on the 3-D shape of the optic disc and peripapillary retinal nerve fiber layer. Producing an easy way to understand the probability of disease, the GPS gives immediate results without drawing a contour line.

Samuelson: As I mentioned earlier, it is most difficult for me to assess scan quality with the Stratus OCT, although signal strength helps. It is very technician dependent. To make acquiring images easier, I have changed my routine regarding when I dilate patients' pupils in my office that has the Stratus OCT. I always used to perform dilation when patients had visual fields so I could perform a comprehensive assessment. Because I believe that scan quality is better for the Stratus OCT with a dilated pupil, however, I tend to perform dilation when patients have ocular coherence tomography and less often when they have their visual fields. I will stagger testing so patients have imaging at one visit and functional testing at the next. I tend to stop imaging when people have significant field loss. I find it to be less useful, although that may ultimately prove to be wrong.

The HRT3 has the new GPS software (Heidelberg Engineering GmbH) that does not require a contour line, which I think is helpful. I find the GPS software to be very sensitive. I am not yet certain about its specificity, because it is calling a lot of discs abnormal that look okay based upon my examination. Which is correct time will tell. When assessing image quality with follow-up examinations using the HRT3, I first make sure that the disc area is the same as on the baseline, because it indicates that the original contour line was carried forward. If they are different, I try to find out why.

Piltz-Seymour: To ensure a good scan with the Stratus OCT, in addition to signal strength, I will look at centration. With the HRT3, I look for a low standard deviation and will make sure the image is centered. If you are still using the Moorfields program, you have to make sure your patient is compatible with this database, meaning the optic nerve is not too big or small and the patient is white. The new printout with the HRT3's GPS software is wonderful (Figure 1). The most important theoretical advantage is that you do not have to draw the contour line, which is where I saw the greatest number of systematic errors in HRT interpretation. In terms of interpretation, I would stress that the HRT examination does not exist in isolation but rather in the context of a patient. Even with a good scan, we must consider all aspects of the examination when interpreting results.

Katz: The evolution of the data's presentation has been critical. I remember the original HRT simplistically classified patients as normal and glaucoma. The latest HRT3 Glaucoma software is packaging data in a more manageable way, and it forces you to consider the information in the categories of cup, rim, and NFL (Figure 1). You also have to compare the two eyes side by side as the HRT3 looks for asymmetry.

Samuelson: Both Ted and Jay have alluded to the importance of looking at the right and left discs of a given patient and comparing them with regard to their size. Obviously, the refractive state influences the size of the disc that is imaged. Thus, assuming that you standardized for refractive influence, variability in disc size in the same patient is one of the most common causes of cup asymmetry and, in my experience, is one of the most frequent reasons that a patient may be misdiagnosed with glaucoma. Asymmetry in disc size is only one characteristic to watch for; overall size is just as important. Small discs mean that the neural tissue is crowded together, and you can see visual field defects without classic notching. With a big disc, you can have a 0.9 cup and completely normal neural tissue. Our ability to judge disc size is greatly enhanced by imaging technology. You can do it with photographs, but you do not get quite the same quantitative measurements of disc area.

The HRT3 has databases for different ethnicities that help standardize disc size, which can vary by race. There are examples in which patients were imaged on three different databases (Caucasian, African, Indian) and were found to be normal only when the appropriate race was applied (data on file with Heidelberg Engineering GmbH).

Noecker: I think misinterpretations are common. We have done a study looking at corneal drying.[14] You have to be really careful, especially with the Stratus OCT, if the patient has had a dilated examination, had his pressures checked, and then got imaging, the signal strength will have deteriorated, and the NFL will appear thinner. There can be

a wide range of variability in individuals based on whether they have anesthetic in their eyes. I think, when you have good technicians, they always have a drop of artificial tears nearby to help minimize the corneal drying. You must also be careful interpreting the scans of patients who may have undergone too much testing in one day with imaging scheduled last. I always have my patients do the imaging first, before almost everything else in their examination.

It can be difficult to obtain quality scans in patients with nystagmus, but even normal saccades, microsaccades, or macrosaccades can affect consistency in imaging. It can be difficult to have consistently good-quality scans in that patient. With the Stratus OCT, patients who have poor macular function may have difficulty fixating on the little green light, which can produce problems with centration and misdiagnoses of glaucomatous progression. Image acquisition can be a major source of variability.

DIAGNOSIS VERSUS THE DETECTION OF PROGRESSION

Krupin: Rob, are you using imaging devices to make the diagnosis, or are you looking at progression?

Noecker: Both. What do you do?

Krupin: I think the major strength of these technologies is with progression. Regarding the diagnosis, I think I do as well as the machines as far as detecting disc asymmetry, cupping, and notching and even picking up some NFL thinning.

Samuelson: That is a compliment to the machines to say that they do as well as someone with your expertise as a glaucoma specialist. One study found that the machines did as well as a glaucoma specialist with disc photographs.[15] If you could elevate the standard of care in the eye care community to that same level, that would be quite an accomplishment.

Noecker: One of the arguments for using imaging technologies is to bring a non-expert to the level of an expert.

> *"I can use scans from 1994 on the original HRT. That is ... not possible with the other imaging technologies."*
> *—Jody Piltz-Seymour, MD*

Samuelson: Exactly, yet I have not seen that universally by any means. I see a lot of misinterpretation, overinterpretation, and overcalling with the technology. It is incumbent on the ophthalmologists and optometrists who are using these devices to make sure they understand what they are looking at.

Noecker: They also must not use the technologies in a vacuum. Imaging is not the only thing you do. Examining the optic nerve may be the primary thing, but you are still going to get visual fields.

Krupin: The clinician makes the diagnosis, not the machine. I use imaging as an ancillary test that will help me make a diagnosis. Progression is different.

Katz: So, you are using imaging just the way you would photographs. Do you envision that the technology will one day pick up something that you will not?

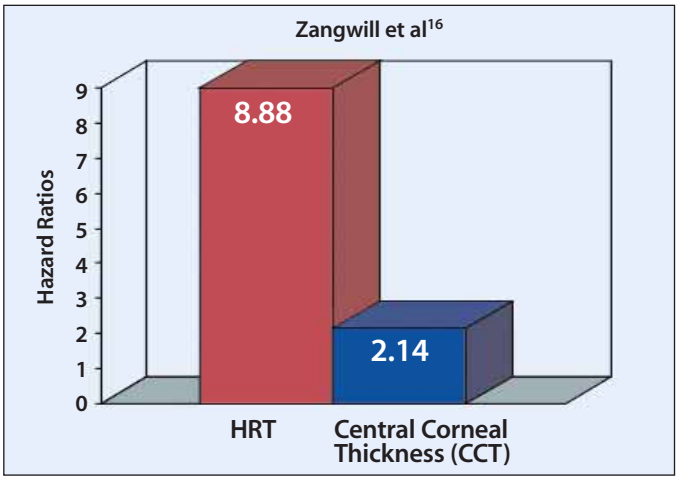
Piltz-Seymour: If the machine found something at diagnosis that I did not, I should be able to go back to the patient and see it if it was real.

Noecker: I think it works both ways. I would argue that there are times you can find something that the machine cannot. A focal defect in the NFL can be averaged away with software analysis.

THE LITERATURE

Noecker: Jay, would you mind summarizing the ancillary study for the OHTS?

Katz: A subpopulation had serial imaging with the HRT. One article has been published on those results, and another is about to be. The first article looked at the baseline characteristics with imaging, HRT in particular.[16] The investigators noted that an abnormal



(Courtesy of Heidelberg Engineering, Inc.)

Figure 2. The data illustrated in this graph are adapted from Zangwill et al.[16]

(Courtesy of Jody Piltz-Seymour, MD.)

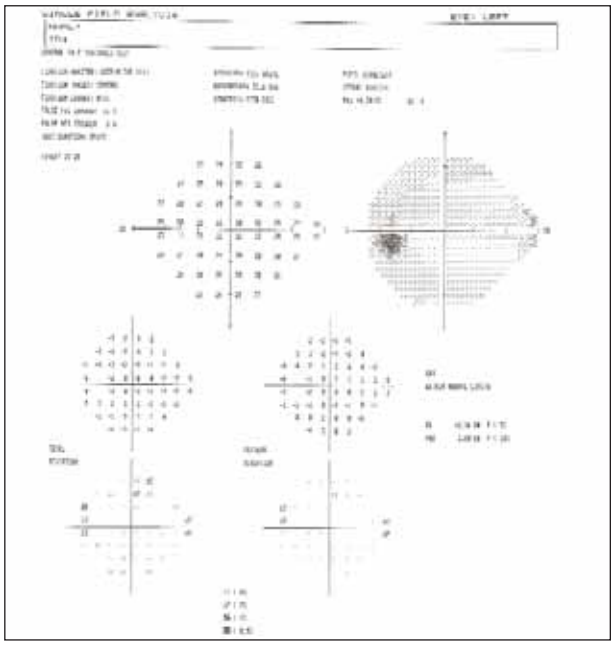


Figure 3. This patient's visual field was within normal limits.

Moorfields regression analysis on baseline examination was strongly predictive for later glaucomatous development with optic nerve progression or the development of an abnormal visual field test. Maybe subjects already had undiagnosed, early-stage, preperimetric glaucoma instead of being a high-risk population. An abnormal baseline HRT scan proved to be a more predictive risk factor than any other variables such as corneal thickness, age, or IOP in this population.

Noecker: When we look at the relative risk of progression to glaucoma, the abnormal HRT was a bigger risk factor than central corneal thickness (CCT) (Figure 2).

Katz: This should not be a huge surprise, because the cup-to-disc ratio is also predictive.

Krupin: The OHTS investigators were looking for high-risk patients. Importantly, some of the OHTS subjects had glaucomatous optic neuropathy but normal fields.

Katz: Do you think that is really true, or do you think it is just the disc anatomy that predisposes them to it?

Samuelson: I think some of the subjects whose fields seemed to have progressed without structural change probably had experienced structural change prior to entry in the study.

Piltz-Seymour: The field criteria for the OHTS were incredibly stringent.

Katz: I think some people experience functional change before structural change.

Samuelson: I agree that is likely in some cases, but we really do not know. These patients did not have imaging 10 years prior to enrollment. Perhaps they were initially considered normal but had already changed from their inherent baseline.

Krupin: I do not think that all visual field defects are necessarily permanent.

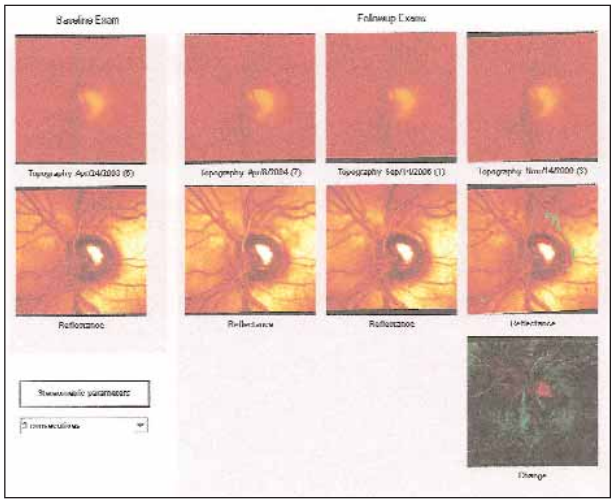
Samuelson: I think that, once you see a classic nerve fiber bundle layer type defect, it is likely there. You may not pick it up on subsequent tests.

Katz: I think the density may be different in terms of the depth and size of the scotoma and may be variable depending on how aggressively you treat a patient.

Samuelson: That could well be.

Katz: The reversibility of visual field defects in glaucoma has been talked about for many years. In the OHTS, we talk about the structural changes preceding functional loss. If I remember correctly, approximately one third of subjects had no structural change but did have visual changes.

Samuelson: There is no way to know if, prior to entering the study, the structural change occurred. There may be different levels of dysfunction of a dying axon. It may be particularly dysfunctional at a certain IOP level or a certain neurotrophic concentration level within the milieu and then less dysfunctional at other times.



(Courtesy of Jody Piltz-Seymour, MD.)

Figure 4. The physician was able to combine databases to compare HRT scans over time for the patient whose visual field appears in Figure 3.

(Courtesy of Jody Piltz-Seymour, MD.)

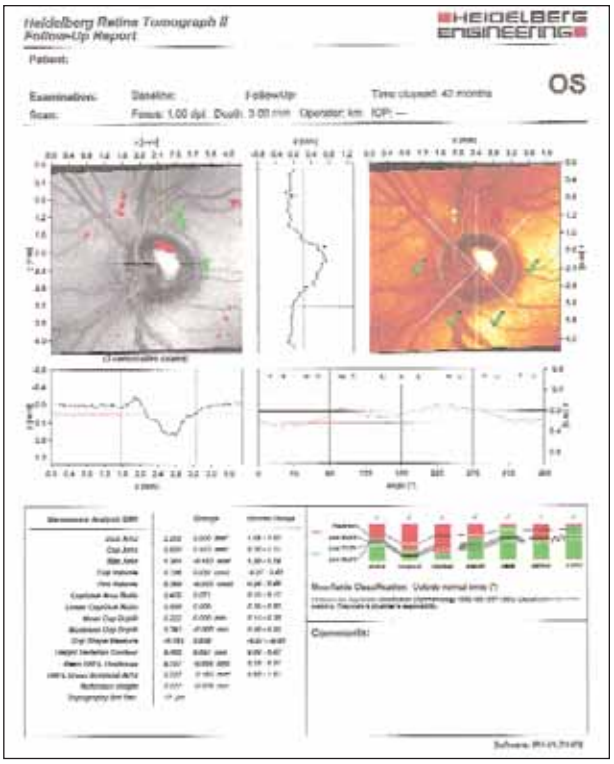


Figure 5. Reproducible change is evident for the patient shown in Figures 3 and 4.

Katz: I think that not all axons die. Some are sick and may not function well on perimetry at high pressure, and the neurons "recover" and work better at a lower pressure.

Noecker: Let's look at a recent study out of San Diego.[17] It is similar to the OHTS but not quite as big or powerful. This study looked at the ability of ocular coherence tomography to predict the development of glaucoma and found that it did have predictive value. Its ability was slightly less than CCT, the most significant risk factor identified in the OHTS,[18] whereas, in the ancillary study to the OHTS, abnormal HRT scans had more power than CCT in predicting the development of glaucoma[19] (Figure 2).

The point is that you can do similar things with the Stratus OCT. In this set of data, it appears that the HRT does better with ocular hypertensives in declaring them as having progressed to glaucoma patients.

Samuelson: In terms of the percentage of progression with the OHTS, I think we have to keep in mind that certain entry criteria, specifically elevated IOP without regard to CCT, may have inadvertently allowed a disproportionate number of enrolled subjects who were probably more resistant to glaucomatous progression. That is, they really were not ocular hypertensives in the true sense. They simply had increased IOP because they had thick corneas. The biomechanics of the cornea are complex. It is far more than just thickness. It is distensability and elasticity. We do not yet know how to incorporate the role of the cornea on IOP measurements. I think, however, that we can all agree that probably the thicker corneas are more resistant to damage than thin corneas at the same measured IOP.

THE HRT II VERSUS THE HRT3

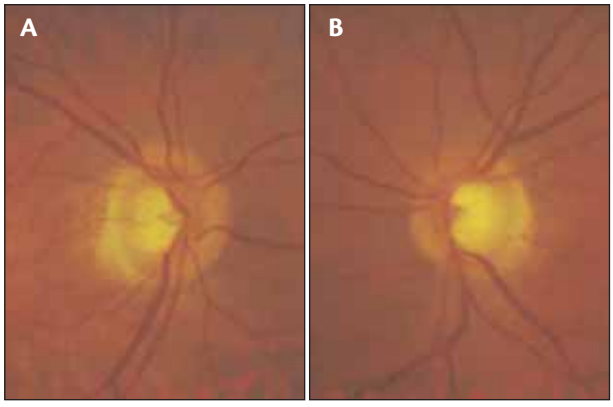
Noecker: Tom, do you prefer the HRT3 to the HRT II?

Samuelson: I like the improved database that includes race. I also like the printout, which I think is more readable and provides a better eye-to-eye comparison. I have not had the GPS software long enough to know whether it is in fact more sensitive. It does label patients abnormal more often than the prior strategy. I do not know if it is too sensitive and therefore loses specificity or if these patients will eventually prove to have glaucoma. I do like that the GPS software does not require a contour line and that it uses the contour assessment of the entire image better.

Piltz-Seymour: I agree with everything Tom said. I would add that the alignment software is also somewhat improved as is the use of information about the whole shape of the optic nerve. I am hopeful that the software will help improve diagnosis and the detection of progression.

Katz: I think the GPS software is a big advance. There is also an integration of data concerning the optic nerve rim, cup, and NFL by a "smart algorithm" that contrasts normal architecture with typical glaucomatous topography (Figure 1).

Piltz-Seymour: I think that Heidelberg Engineering GmbH should be congratulated for making software that is back-



(Courtesy of Theodore Krupin, MD.)

Figure 6. Both of the patient's optic nerves are large with a tilted insertion (right, A; left, B). Large optic nerves have large cups. The superior vessels have an anomalous entry through the rim. This developmental condition presents difficulty with the ISNT rule.

(Courtesy of Theodore Krupin, MD.)

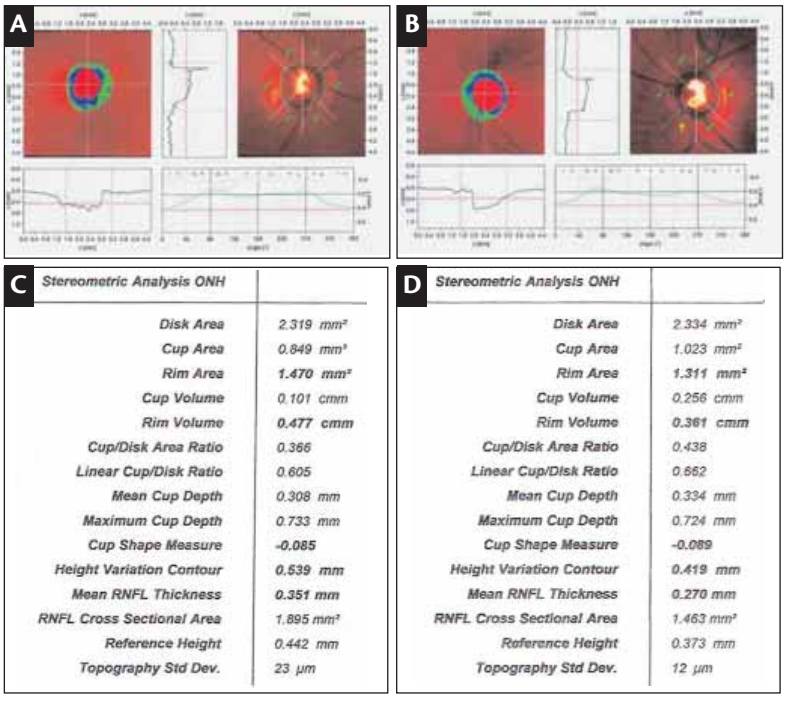


Figure 7. The HRT scans (A, B) demonstrate the tilted configuration seen in Figure 6 and confirm large optic nerves: disc areas of 2.319 mm^2 OD and 2.334 mm^2 OS. The calculated cup-to-disc area ratios are similar (0.366 OD and 0.438 OS) (C, D), and the images suggest an intact ISNT rule.

ward compatible. I can use scans from 1994 on the original HRT. That is an amazing achievement and not possible with the other imaging technologies.

CASE STUDIES

Noecker: All of you have done a great job of summarizing the lay of the land in imaging. Now, I think it may be helpful to look at some real-world examples of how glaucoma experts use imaging in daily clinical practice.

(Courtesy of Theodore Krupin, MD.)

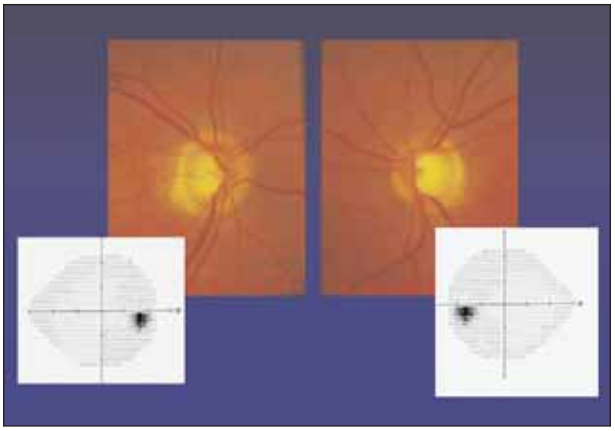


Figure 8. Humphrey visual fields (24-2 Swedish Interactive Threshold Algorithm [SITA] full-threshold) are normal for the patient shown in Figures 6 and 7.

No. 1

Piltz-Seymour: A 60-year-old female presents with a history of pseudoexfoliation (PXF). She has been followed as a glaucoma suspect for 8 years. Her maximum IOPs were 24 mm Hg OD and 25 mm Hg OS. Her grandmother became blind from glaucoma, and her sister is on medical therapy but with no known loss of visual function. The patient has no significant medical problems. Her visual acuity is 20/25 OU, and both corneas measure 610 µm. Currently, her IOP measures approximately 20 mm Hg OU, and gonioscopy reveals widely open angles.

Upon examination, the right optic nerve looks fine, but there appears to be mild thinning and some sloping of the superior rim in the patient's left eye. Visual fields with SITA-Fast (Carl Zeiss Meditec, Inc.) were all within normal limits (Figure 3). The patient's chart included HRT II scans performed at different offices. They were all single scans rather than progression scans. By combining databases, I could show change over time (Figure 4). A reproducible change over three consecutive scans was detected (Figure 5). There is a progression of the optic nerve without visual field changes. This is a case of documented preperimetric glaucomatous optic nerve progression. This finding goes along with my observations that the patient has significant risk factors for glaucoma.

Katz: Did the eye that progressed have a slightly higher IOP?

Piltz-Seymour: Yes, her right eye had an IOP of 19 mm Hg versus 21 mm Hg in her left when she presented, but the pressures were relatively symmetric throughout her chart.

Samuelson: Importantly, this patient's CCTs were over 600 µm. Too often, people are reassured by that. There is no question that it helps to interpret the measured IOP, but plenty of patients with thick corneas develop glaucoma. The other caveat from this particular patient is that patients with PXF always warrant increased suspicion and surveillance. You should never let your guard down with such individuals. They are lifelong strong glaucoma suspects in my opinion.

Krupin: Would this patient's independent risk factors alter your treatment plan?

Piltz-Seymour: Absolutely. I felt confident from the start that this was an abnormal optic nerve. The change over time on the HRT test helped. This case highlights that it is critical to get the digital scans, not just the paper printouts.

Samuelson: Did you have to change the contour line to account for the different scans?

Piltz-Seymour: The megapixel progression analysis does not require the contour line.

Krupin: Did you compare the patient's two eyes?

Piltz-Seymour: This is the HRT II software, so we need to manually compare the scans from the two eyes. The appearances of the superior rims were clinically different. There was definite asymmetry.

Krupin: This is the time you want to make a diagnosis in this patient, before there are perimetric changes.

No. 2

Krupin: A patient was referred for a glaucoma evaluation. His visual acuity was 20/20 OU with a -2.50 D correction. His IOPs were normal, with a high of 18 mm Hg. Cupping was evident, and the left optic nerve appeared to be tilted. The examination was unremarkable, and the CCTs were normal (552 µm OD, 557 µm OS). I sensed a difference in the size and shape of the patient's optic nerves (Figure 6). Vessels were apparent through the rim, a finding that frequently indicates an anomalous optic nerve. That is often a congenital rather than an acquired situation. Humphrey visual fields (SITA-Standard; Carl Zeiss Meditec, Inc.) were normal, and HRT scans were performed (Figures 7 and 8).

Noecker: Which numbers on the scans do you use?

Krupin: I look at the disc area at the top for sure and at the standard deviation on the bottom to determine the quality of the scan. Based on the nerve's size, I will evaluate the cup-to-disc ratio and compare the parameters between the two eyes.

Katz: Which of these gets highlighted now?

Noecker: I like cup shape measure.

Krupin: I like the cup shape measure, too, but I do not do that as a start.

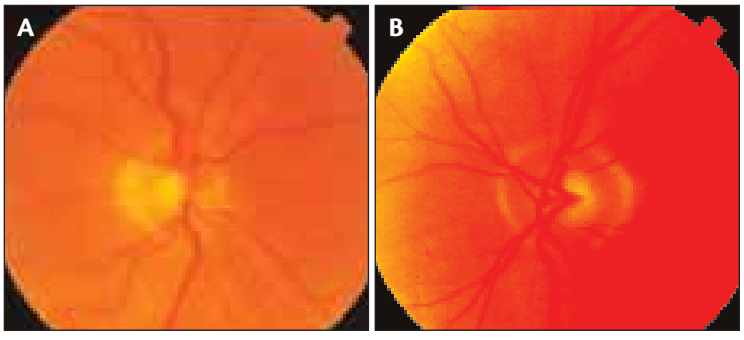
Samuelson: The other one in the OHTS that came back with a good predictive value was the mean height contour.

Krupin: I did not put this case in the HRT3's software but should have. This case demonstrates asymmetry in the disc area between the two eyes that accounts for the perceived difference in cupping between the eyes. Large optic nerves have large cups.

Katz: If you are looking for change over time, do you just perform the progression analysis, or do you look at the global parameters in terms of change of time? You print them out as well?

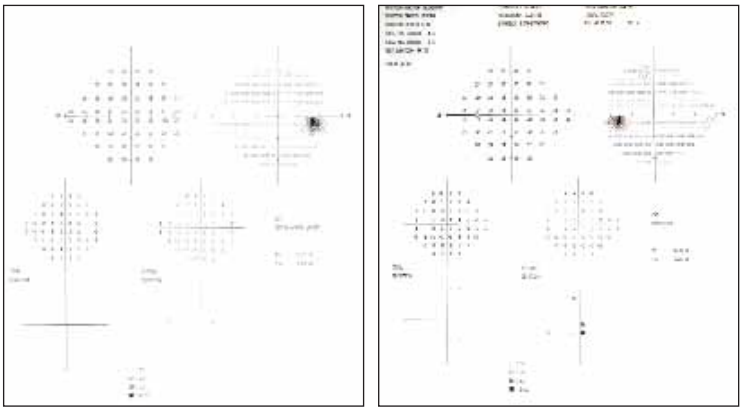
Krupin: For change over time, I look at the printout's parameters over time and the Trend Report as well as the TCA Overview on the computer.

Katz: I think I have seen changes in the global stereo-



(Courtesy of L. Jay Katz, MD.)

Figure 9. An 82-year-old, myopic, white male has IOPs of 29 mm Hg OD and 34 mm Hg OS. His cup-to-disc ratios measure 0.4 OD (A) and 0.6 OS (B). A telltale, isolated disc hemorrhage is visible at the 5-o'clock position in the patient's left eye.



(Courtesy of L. Jay Katz, MD.)

Figure 10. The clinician deemed the results of visual field testing for the patient shown in Figure 9 to be fairly normal.

(Courtesy of L. Jay Katz, MD.)

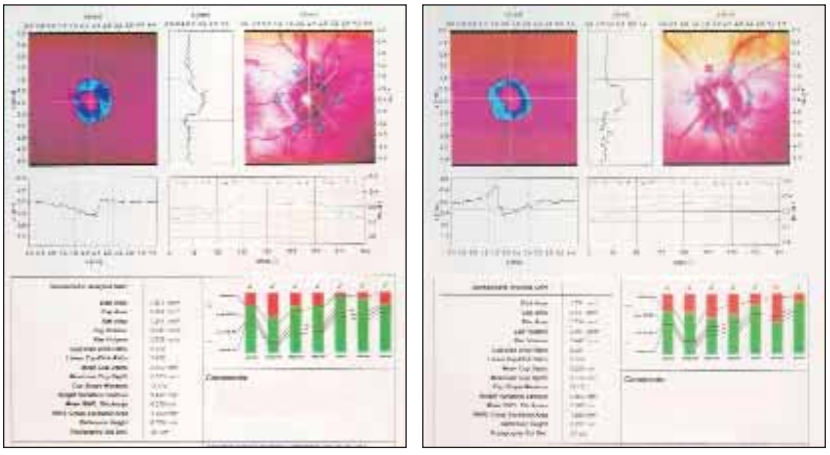


Figure 11. The Moorfields regression analysis with the HRT II detected abnormality in the superior area of the left optic nerve for the patient shown in Figures 9 and 10.

> *"The HRT machine picked up a thin rim area that I probably missed on my first clinical examination."*
> *—L. Jay Katz, MD*

metric parameters that I do not pick up looking at a focal change in the progression analysis program.

Krupin: We did not diagnose glaucoma and followed the patient. Short Wavelength Automated Perimetry was also normal.

Samuelson: For these extreme myopes, we really have to compare them to themselves, because the database excluded patients with extreme refractive errors. It is therefore misleading to compare them statistically to the normative data. This is less of an issue on progression analysis in which patients are compared to their own baselines.

No. 3

Katz: The following case showed me that the HRT II may highlight something that I may miss. This 82-year-old male had a family history of glaucoma. He had markedly elevated pressures. His optic discs were slightly asymmetric (Figure 9), and I called his visual fields normal (Figure 10). There is an isolated disc hemorrhage (Figure 9), a finding that I think makes the diagnosis pretty easy. Let's forget about the disc hemorrhage for the moment, however.

Krupin: There is a big difference between the optic nerves of the two eyes. The left nerve has a horizontal rotation versus a more vertical nerve in the patient's right eye.

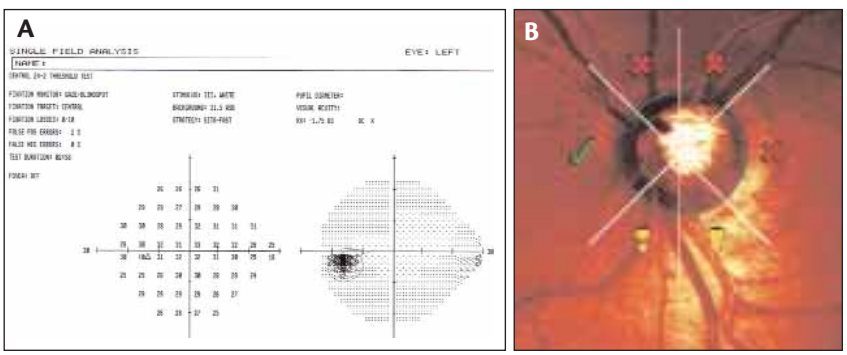
Katz: I called the automated perimetry fairly normal just looking at the gray scale, although there are a couple of slightly depressed points in the inferior paracentral region. On the Moorfields regression program, the superior region of the optic nerve was abnormal. If you go back to the photographs, the rim is fairly thin superiorly in the patient's left eye, as pinpointed by the HRT II Moorfields regression program (Figure 11). I did not appreciate the thinning until I went back and looked at it more carefully after reviewing the HRT data. On the other hand, I can pick up the disc hemorrhage, and the machine cannot. The HRT machine picked up a thin rim area that I probably missed on my first clinical examination. This case definitely increased my respect for HRT technology.

Krupin: Without additional information, how many would have started treatment on this patient?

Noecker: That patient gets treated.

Krupin: So, you are not using other ancillary tests to help confirm the diagnosis.

Katz: It fits the total package. Say the patient's IOP were instead 24 mm Hg in his left eye, and there were no disc hemorrhage.



(Courtesy of Thomas W. Samuelson, MD.)

Figure 12. This patient's right eye has a normal visual field (A) but a very abnormal HRT scan (B). Faced with such a discrepancy, physicians must use their clinical judgment to reconcile the test results. This case reflects a typical structural/functional disparity.

(Courtesy of Thomas W. Samuelson, MD.)

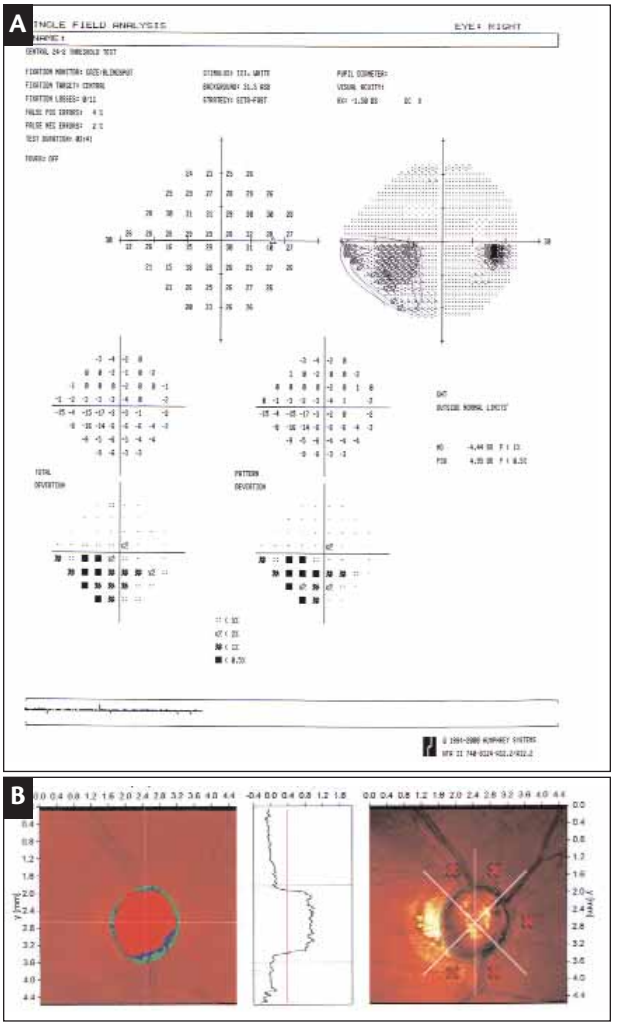


Figure 13. For the fellow eye of the patient shown in Figure 12, both the visual field (A) and HRT scan (B) are abnormal. The visual field changes are relatively mild, whereas the HRT scan is markedly abnormal. Clearly, when viewed in the context of the patient's left eye, his right eye (Figure 12) has glaucoma, and the HRT is demonstrating abnormality earlier than the visual field.

Noecker: But he did have that area of thinning?

Katz: An IOP at 34 mm Hg makes this case pretty easy in terms of deciding whether to treat the patient. The question is, what would I have done if the pressure had been lower and there were no disc hemorrhage?

Noecker: I would have treated him.

Katz: I would have treated him, too.

Krupin: I would have initiated treatment for an IOP of 34 mm Hg and repeated the visual field at the follow-up visit. If the pressure were 24 mm Hg, you would have time to repeat the field before starting treatment in this 84-year-old patient.

Piltz-Seymour: If you could treat this patient with a prostaglandin, that would be great. Treating this patient with a beta-blocker might worsen his quality of life.

Krupin: Yes, but in this kind of patient, you could make a decision or at least think of doing a laser treatment.

No. 4

Samuelson: This is less a case presentation than a way to stimulate discussion. When we look at the HRT scan and visual field, we have no idea if this patient has glaucoma or not (Figure 12). Certainly, the HRT scan gets our attention. By Moorfields regression analysis, there is less than a 0.1% chance that this disc is normal. Upon viewing the patient's fellow (left) eye (Figure 13), the results lend considerable credence to the fact that the HRT is probably correct in diagnosing glaucoma in the patient's right eye. The right visual field has remained normal despite considerable structural change.

Katz: Is the IOP relevant?

Samuelson: The patient's IOP was in the low 20s. One of my favorite questions in this case is whether this patient's glaucoma is early, moderate, or late. Clearly, we are measuring only mild functional loss despite late structural damage.

Krupin: Why do you perform SITA-Fast?

Samuelson: It depends on the patient. I use SITA-Fast for someone who I believe is going to have trouble sitting through a SITA-Standard test. In general, my preferred test format for most patients is the SITA-Standard.

Krupin: Too many people are using the SITA-Fast program for screening and following glaucoma patients.

Katz: My institution uses SITA-Fast maybe 1% of the time.

Samuelson: My default is always SITA-Standard.

Krupin: You are calling this an early case?

Samuelson: Only in terms of the field loss. If asked, this patient might contend that he was asymptomatic and that his vision was normal. If he went from his normal complement of ganglion cells to this level of structural change in a matter of minutes or even seconds, as in ischemic optic neuropathy, however, there is no question in my mind that

this would be a symptomatic disease. Given the insidious nature of the process, this patient would probably contend that his visual function was pretty normal. Just because someone does not have symptoms, however, does not mean he is normal. Sometimes we forget that. We see that all the time with cataracts. Patients forget how well they used to see.

Katz: Patients are not necessarily asymptomatic. We may not know to elicit the right symptoms.

Krupin: When do we ever treat symptoms in glaucoma? When do we ever make anyone feel better because we start therapy?

Katz: I am saying we begin treatment to keep them from getting worse.

Krupin: I do not think anybody would recommend not treating this patient. He has glaucoma in both eyes.

CLOSING THOUGHTS

Katz: During the past 20 years, imaging technology has gone from a research tool to an accepted modality for providing good clinical care for patients. It has helped put the emphasis back on looking at the optic nerve and the NFL. The software is evolving rapidly to the point where the presentation of data is more useful to clinicians, and the technology is fairly stable now.

Noecker: Imaging is here to stay, but clinicians must have a plan for how they will use the information. They must also ensure the quality of that information and realize the capabilities of each device. Learning how to use the software of each machine, especially for detecting progression, is key.

Katz: The bottom line is that the machine does not tell you what to do. The clinician incorporates the data from image analysis into an overall assessment and the accompanying decision making for patient care.

Samuelson: We do not want to hold the machine to a standard that does not exist for any other test, either. Perfect sensitivity and specificity do not exist for IOP measurements or visual fields, and it does not exist for imaging technology. Clinicians' interpretations, therefore, remain the most critical element and discriminating aspect of the assessment.

Noecker: Training the technicians on data acquisition is important, too. Often, they need more than having a representative visit the practice for a day. Physicians must also have quality control and understand the essence of reproducibility. The HRT3 does some quality control, at least in terms of aligning the images, but, as with all devices, we still need to get good images.

Katz: Imaging technology is not a substitute for a good clinical examination, assessment of the optic disc, or visual field testing. ■

1. Armaly MF, Krueger DE, Maunder L, et al. Biostatistical analysis of the Collaborative Glaucoma Study. I. Summary report of the risk factors for glaucomatous visual-field defects. *Arch Ophthalmol.* 1980;98:2163-2171.
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.
3. Keltner JL, Johnson CA, Anderson DR, et al; Ocular Hypertension Treatment Study Group. The association between glaucomatous visual fields and optic nerve head features in the Ocular Hypertension Treatment Study. *Ophthalmology.* 2006;113:1603-1612.
4. 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; discussion: 829-830.
5. Bayer A, Harasymowycz P, Henderer JD, et al. Validity of a new disk grading scale for estimating glaucomatous damage: correlation with visual field damage. *Am J Ophthalmol.* 2002;133:758-763.
6. Fremont AM, Lee PP, Mangione CM, et al. Patterns of care for open-angle glaucoma in managed care. *Arch Ophthalmol.* 2003;121:777-783.
7. Jonas JB, Gusek GC, Naumann GO. Optic disc, cup and neuroretinal rim size, configuration and correlations in normal eyes [published corrections appear in *Invest Ophthalmol Vis Sci.* 1991;32:1893. and *Invest Ophthalmol Vis Sci.* 1992;32:474-475]. *Invest Ophthalmol Vis Sci.* 1988;29:1151-1158.
8. Harizman N, Oliveira C, Chiang A, et al. The ISNT rule and differentiation of normal from glaucomatous eyes. *Arch Ophthalmol.* 2006;124:1579-1583.
9. Gaasterland DE, Blackwell B, Dally LG, et al; Advanced Glaucoma Intervention Study Investigators. The Advanced Glaucoma Intervention Study (AGIS): 10. Variability among academic glaucoma subspecialists in assessing optic disc notching. *Trans Am Ophthalmol Soc.* 2001;99:177-184; discussion: 184-185.
10. Altangerel U, Bayer A, Henderer JD, et al. Knowledge of chronology of optic disc stereophotographs influences the determination of glaucomatous change. *Ophthalmology.* 2005;112:40-43.
11. Zeyen T, Miglior S, Pfeiffer N, et al; European Glaucoma Prevention Study Group. Reproducibility of evaluation of optic disc change for glaucoma with stereo optic disc photographs. *Ophthalmology.* 2003;110:340-344.
12. Quigley HA, Miller NR, George T. Clinical evaluation of nerve fiber layer atrophy as an indicator of glaucomatous optic nerve damage. *Arch Ophthalmol.* 1980;98:1564-1571.
13. Sommer A, Quigley HA, Robin AL, et al. Evaluation of nerve fiber layer assessment. *Arch Ophthalmol.* 1984;102:1766-1771.
14. Stein DM, Wollstein G, Ishikawa H, et al. Effect of corneal drying on optical coherence tomography. *Ophthalmology.* 2006;113:985-991.
15. Correnti AJ, Wollstein G, Price LL, Schuman JS. Comparison of optic nerve head assessment with a digital stereoscopic camera (discam), scanning laser ophthalmoscopy, and stereophotography. *Ophthalmology.* 2003;110:1499-1505.
16. Zangwill LM, Weinreb RN, Beiser JA, et al. Baseline topographic optic disc measurements are associated with the development of primary open-angle glaucoma: the Confocal Scanning Laser Ophthalmoscopy Ancillary Study to the Ocular Hypertension Treatment Study. *Arch Ophthalmol.* 2005;123:1188-1197.
17. Lalezary M, Medeiros FA, Weinreb RN, et al. Baseline optical coherence tomography predicts the development of glaucomatous change in glaucoma suspect. *Am J Ophthalmol.* 2006;142:576-582.
18. Gordon MO, Beiser JA, Brandt JD, et al. The Ocular Hypertension Treatment Study: baseline factors that predict the onset of primary open-angle glaucoma. *Arch Ophthalmol.* 2002;120:714-720.
19. Zangwill LM, Weinreb RN, Berry CC, et al; OHTS CSLO Ancillary Study Group. The Confocal Scanning Laser Ophthalmoscopy Ancillary Study to the Ocular Hypertension Treatment Study: study design and baseline factors. *Am J Ophthalmol.* 2004;137:219-227.

Glaucoma TODAY

02.08.07.850