

Optical Imaging Update

Current, improved imaging technologies affect diagnostic uncertainty but should not be used in lieu of thorough examination and visual function testing.

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Over the past 5 years, several new-generation optical imaging techniques have become available for detecting and monitoring glaucoma. They include the HRT II (Heidelberg Engineering, Dossenheim, Germany), the StratusOCT (Carl Zeiss Meditec Inc., Dublin, CA), and the GDx VCC (Carl Zeiss Meditec Inc.). Each instrument has been updated from previous versions to become more useful for detecting and monitoring glaucoma. This article focuses on the pros and cons of each instrument as well as the devices' relevance to clinical practice.

HRT II

This confocal scanning laser ophthalmoscope relies on the same general principles as its predecessor, the HRT (Heidelberg Engineering),¹ but it was designed specifically for imaging the optic nerve head in glaucoma. The hardware has been ergonomically refined, introducing a much smaller, angled scanning head that simplifies the acquisition of images. Software changes include the automated capture of three consecutive images (the variability of which is used to define progression in follow-up examinations), the inclusion of a new glaucoma classification system, the Moorfields Regression Analysis (MRA) that assesses measured disc area sectorally in comparison with an internal normative database, and a refined progression analysis that displays areas of significant change (Topographic Change Analysis [TCA]) from baseline across the retinal surface using color-coded super pixels. Results with the MRA² and TCA^{3,4} have mostly been positive.

The most recent HRT software (version 3.0) includes a new glaucoma detection algorithm called the *Glaucoma Probability Score (GPS)* (Figure 1). Unlike the MRA, the GPS and the TCA are independent of a user-placed contour line to define the margin of the optic disc, a characteristic that makes these analyses independent of the user. The GPS analysis provides a probability of glaucoma by means of an

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advanced machine learning classification algorithm called *Relevance Vector Machine* that is trained on a large population of glaucomatous and healthy eyes. The analysis is based on the steepness, shape, and depth of the automatically defined cup as well as the horizontal and vertical curvature of the entire retinal surface. Other software changes in version 3.0 include an improved alignment algorithm that should decrease variability in baseline images, which may allow the detection of smaller amounts of change in follow-up images, and the introduction of a larger race-based normative database. No empirical evaluation of the GPS has yet appeared in a peer-reviewed journal, but preliminary results should be reported soon.

One limitation of the HRT II is that many measurements, including the MRA, are calculated relative to the previously described user-defined contour line. Although reports have described good agreement in the placement of the contour line among independent observers and little effect of small changes in the contour line's size on HRT parameters,^{5,6} the disc margin is defined subjectively. The introduction of the TCA and GPS addresses this issue, but it is possible that both analyses will be affected by alterations in IOP, which have been shown to significantly change topography.^{7,8}

STRATUSOCT

The current optical coherence tomograph relies on the same general principles as its predecessors.¹ The instrument's primary application for glaucoma—measuring the

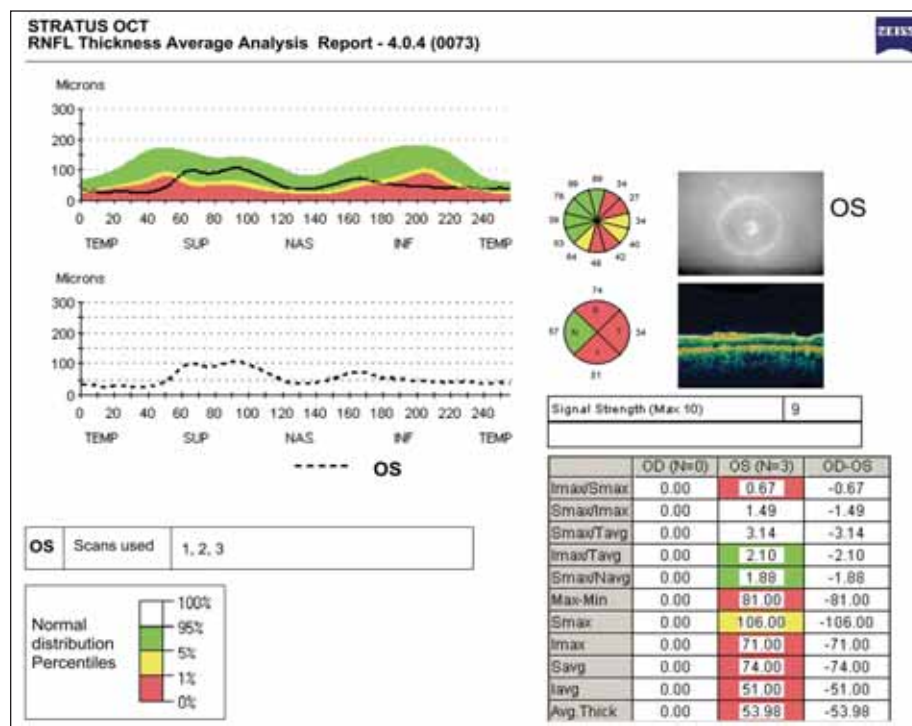


Figure 2. This RNFL printout from the StratusOCT shows the left eye of a glaucoma patient. The results indicate superior, temporal, and inferior RNFL thinning outside normal limits. Several RNFL sectors and parameters are also outside normal limits or borderline relative to the internal normative database.

ments over time. More sophisticated analyses involving the registration of images and a comparison of inter- or intra-eye variability over time are needed.

GDx VCC

The GDx VCC derives RNFL thickness measurements based on the birefringent properties of the RNFL,¹ but the technique for isolating the effects of corneal and lenticular birefringence is new. The previous method assumed a standardized correction for all eyes, but several studies showed that this correction was inadequate for many eyes.^{10,11} The new technique, called *Variable Corneal Compensation* (VCC), automatically isolates the anterior chamber's birefringence by imaging the macula, where birefringence is minimal, and subtracting the residuum, presumably caused by the cornea and lens, from circumpapillary RNFL measurements.¹²

Studies using the GDx VCC (or a similar prototype) showed better diagnostic accuracy for discriminating between healthy and glaucomatous eyes and showed a stronger association with functional measurements (ie, visual sensitivity measured using standard automated perimetry) compared with the earlier GDx NFA (Laser Diagnostic Technologies, Inc.) with a fixed corneal compensator.¹³⁻¹⁵

The GDx VCC (Figure 3) currently includes comparisons of measurements with an internal normative database and a summary parameter that assigns eyes a likelihood-of-glaucoma score ranging from 1 (unlikely glaucoma) to 100 (extremely likely glaucoma). This parameter, called the *Nerve Fiber Indicator* (NFI), is derived using a machine learning classification algorithm called *Support Vector Machine* trained on GDx VCC measurements from a large population of glaucomatous and healthy eyes.

Currently, the GDx VCC does not provide any progression analyses beyond a subtraction of measurements over time (similar to the StratusOCT), although the development of such analyses is reportedly underway. According to

recent research, a significant percentage of eyes imaged with the GDx VCC exhibit an unusual appearance in which elevated patterns of birefringence appear in unexpected regions (eg, temporally, nasally, and peripherally, called *atypical scans*), a situation likely causing inaccurate measurements of thickness.^{16,17} A software-based correction for atypical scans is currently under development,¹⁸ and preliminary evidence suggests that this technique will improve diagnostic accuracy for discriminating between healthy and glaucomatous eyes.¹⁹

A COMPARISON

One study has compared the diagnostic accuracy of the HRT II, StratusOCT, and GDx VCC for discriminating between healthy eyes and those with glaucomatous visual field defects in the same population.²⁰ The investigators showed similar discrimination between the most accurate parameter from each instrument with receiver operating characteristic curve areas of 0.86 for the HRT II, 0.92 for the StratusOCT, and 0.91 for the GDx VCC. Sensitivities at 95% specificity were 59%, 64%, and 61%, respectively.

Likelihood ratios are the probability of a given test result (eg, outside normal limits) in patients with a disease, divid-

ed by the probability of the same test result in those without the disease (positive likelihood ratio = sensitivity / (1 - specificity), negative likelihood ratio = 1 - sensitivity / specificity). In the aforementioned study, positive likelihood ratios were very high (eg, > 20) for all instruments, a finding suggesting that a result outside normal limits on any of the tests greatly increases the probability that an eye has glaucoma compared with the pretest probability. Moreover, negative likelihood ratios for results within normal limits were small, indicating that these instruments are of limited value for eliminating the probability of disease. These results suggest that the HRT II, StratusOCT, and GDx VCC all can make significant contributions to clinical diagnosis by reducing uncertainty about disease, if the results are interpreted properly.

THE EFFECT OF DISEASE SEVERITY FOR GLAUCOMA'S DETECTION

We recently investigated the effect of glaucoma severity (defined as a standard automated perimetry Advanced Glaucoma Intervention Study [AGIS] score²¹) on the diagnostic accuracy of the HRT II, StratusOCT, and GDx VCC for discriminating between healthy and glaucomatous eyes. Our aim was to determine if the instruments differ in their accuracy at different stages of the disease.²² The sensitivity for detecting glaucoma grew with increasing AGIS scores for all of the instruments, but the sensitivity was somewhat lower for the HRT II's MRA than for the StratusOCT's average RNFL thickness and the GDx VCC's NFI. In eyes with large optic discs, however, the HRT's MRA and GDx VCC's NFI proved somewhat more sensitive than the StratusOCT's average thickness. These results indicate that clinicians should consider the disease's severity and the optic disc's size when interpreting the results with these imaging technologies.

PREDICTING AND DETECTING PROGRESSION

Recently, several studies have reported that imaging instruments can detect abnormalities in the eyes of glaucoma suspects followed longitudinally before they develop repeatable visual field defects. Baseline (ie, at study enrollment) HRT-measured abnormalities were detectable an average of 3 to 4 years before the development of visual field defects in ocular hypertensive eyes²³ and suspect eyes (ocular hypertensive and those with glaucomatous-appearing discs)²⁴ with normal visual fields at the

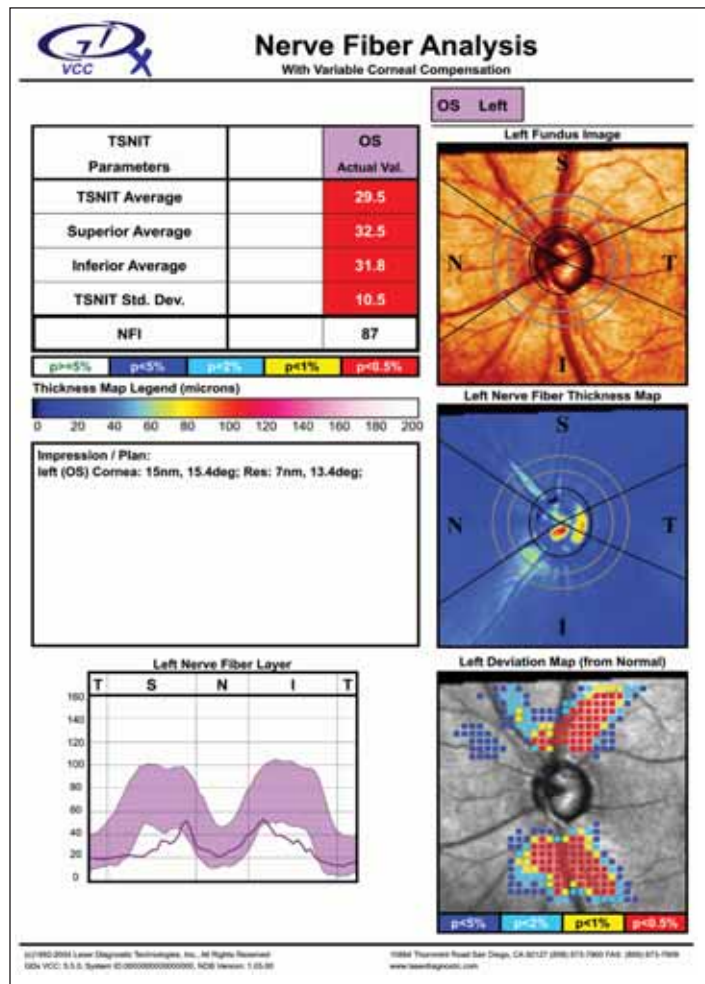


Figure 3. This GDx VCC printout shows the left eye of a glaucoma patient with pronounced superior and inferior RNFL thinning, evidenced by the Nerve Fiber Thickness map, the Deviation Map, and the Nerve Fiber Layer graph. All parameters are outside normal limits, and the NFI is 87, indicating a high likelihood of glaucoma.

time of baseline imaging. Additionally, these abnormalities were predictive of which eyes converted to glaucomatous visual fields and which did not based on proportional hazards analysis. Similar results have been reported for GDx measurements using the GDx NFA.²⁵

Few studies have investigated change over time in glaucomatous eyes using optical imaging instruments, because extensive follow-up is required. In addition, changes in OCT and GDx technology have cut short the follow-up time necessary to allow a thorough testing of the instruments' abilities to detect change. For the HRT II, studies have shown that standard parameters and TCA results change in eyes that also show an alteration in the appearance of the optic disc and/or visual fields.^{4,26-29} Further, it appears that change in the HRT II's TCA is more frequent

than change in visual fields over the same follow-up time.⁴ Because there currently is no standard reference for glaucomatous progression, however, it is difficult to determine if this change is real or falsely positive.

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CONCLUSION

The HRT II, StratusOCT, and GDx VCC seem to be similarly able to discriminate between healthy and glaucomatous eyes. For instance, abnormal results from any instrument may increase the likelihood of treatment in an ocular hypertensive patient with a family history of glaucoma. Currently, however, we do not recommend making diagnostic and treatment decisions based on optical imaging results alone. Although the information from these devices can decrease diagnostic uncertainty if used properly, they should not replace thorough clinical examination and visual function testing.

Regarding progression, there is currently no strong evidence to suggest that optical imaging instruments are more sensitive for detecting change over time than careful clinical follow-up. Several longitudinal studies sponsored by the National Eye Institute, including the multicenter Ocular Hypertension Treatment Study, are underway to further assess this issue. Although the instruments are attractive for their ease of use and refined detection and progression (in the case of the HRT II) algorithms, they should be used only in conjunction with regular clinical examinations. □

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