RNFL Progression Analysis with the RTVue

Software version 4.0

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Glaucoma is a progressive optic neuropathy characterized by a loss of retinal ganglion cells, thinning of the retinal nerve fiber layer (RNFL), thinning of the neuro-retinal rim, and enlarged cupping. Scanning laser devices like the OCT can be helpful to detect these changes. In fact, because of the high level of reproducibility of the quantitative results from these scanning laser devices, small changes may be detected more reliably with them than through direct clinical examination or with stereo-photographs. Several studies have found the accuracy for detecting glaucoma progression with optic-disc photographs is poor, mainly because the reproducibility of judging the discs is poor (Coleman et al., 1996; Azuara-Blanco et al. 2003). These structural changes can help determine not only whether a patient is progressing or stable, but they can also help with the initial diagnosis as well. When diagnosing glaucoma, imaging devices are helpful because they provide a quantitative assessment of retinal structures (e.g., RNFL thickness) and can determine where a given patient stands in relation to a pre-defined normative range based on a normative database. The normative database is used to set cut-offs based on the statistical distribution of normal eyes, a patient's result is then compared to this normal distribution and when their value falls outside the normal range the software flags this result. The cut-offs used by the normative database are typically the bottom 5% of the normal distribution for a classification of 'Borderline' and 1% for a classification of 'Outside Normal Limits'. However the number of ganglion cells in a normal eye can vary up to two-fold, from approximately 750,000 to 1.5 million. So the normal range can be very large, requiring a loss of a majority of ganglion cells before the value falls outside the normal range for many patients. However progression analysis can potentially detect much smaller changes and therefore the diagnosis of glaucoma can be made before a substantial loss of ganglion cells occurs, even though the absolute value may still be within the normal range. The key issue is the ability to detect significant change from a patient's own baseline result.

In order to detect progression in glaucoma, the following three criteria must be met: 1) the measurements must be reproducible, 2) the images must be accurately registered to each other, and 3) a statistical test must be performed to differentiate true biological change from normal measurement variability. Another important feature of meaningful progression analysis is to determine not only whether significant change has occurred, but also the rate of change. Although both are important, the rate of change may be more clinically meaningful because it can differentiate more stable patients from those that are progressing more quickly. Data regarding rate of change can have direct clinical relevance in regard to treatment strategies when related to the patient's age and life expectancy. Investigators have shown that a small, but significant number of patients may show rapid glaucomatous changes (fast progressors), who can lose several decibels of vision each year (Artes 2008). These are the patients who are likely to go blind if they are young at diagnosis and non-aggressive therapy is used. Conversely, a slowly progressing patient diagnosed at an older age may be treated less aggressively. The rate of change in a patient is also helpful when determining how aggressively a patient should be followed.

Criteria 1: Reproducibility

Several independent investigators have shown the RTVue to have excellent reproducibility. For reproducibility studies, most investigators report either the Coefficient of Variance (lower is better), or the Intraclass correlation coefficient (higher is better). David Huang and his colleagues found the Coefficient of Variance (CV) of the RTVue was 1.6% for normals, 1.7% for pre-perimetric glaucoma patients, and 2.1% for perimetric glaucoma patients (i.e., patients with reproducible visual field defects) (Tan, Lu, Chopra, Varma, Ishikawa, Wollstein, Schuman, Huang, 2008). A study from UCSD also reported excellent reproducibility, with the CV of the RTVue for average RNFL thickness to be 2.1%, and the intraclass correlation coefficient was 0.97 (Gonzalez-Garcia, Vizzeri, Bowd, Medeiros, Zangwill, Weinreb, 2008). In addition, studies have compared the RTVue reproducibility with other imaging instruments. Aliyeva, Berisha, Roshdy, Pfeiffer, and Hoffmann (2008) found the inter-observer agreement was significantly better for the RTVue compared to the HRT, and Tan et al. (2008) found the RTVue had better reproducibility than the Stratus (lower CV). One likely explanation for the improved reproducibility compared to the Stratus comes from the fact that the Stratus takes a single circular scan around the optic nerve head. The exact position of this circle can affect the RNFL results (see Figure 1.)

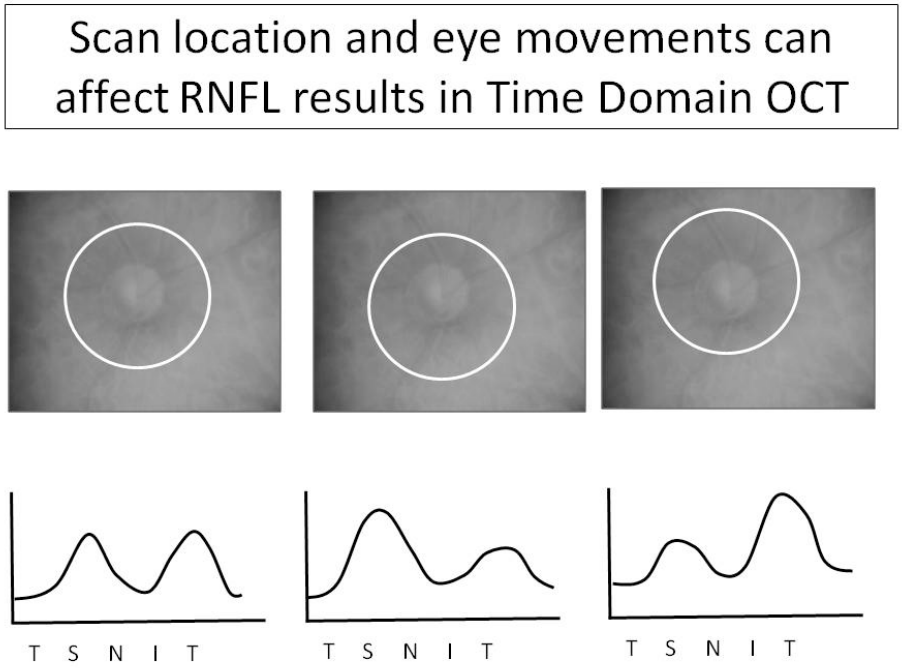


Figure 1. A comparison of the scan circle location on the RNFL thickness values. In a normal eye, when the scan is well centered, the TSNIT will show a double-hump pattern (far left). However if the scan circle is not well centered and is too low, then the RNFL thickness in the TSNIT is increased superiorly and decreased inferiorly (middle pattern). The opposite affect will occur if the scan circle is too high. This is caused by the distance from the scan circle to the disc margin.

If the operator does not have the scan perfectly centered over the optic nerve head (ONH), or if there are eye movements during the scan, spurious RNFL thickness values can result which can make a normal eye look glaucomatous and vice versa. For example in the middle panel of Figure 1, the scan circle is too low relative to the center of the optic disc. This makes the superior part of the scan circle closer to the disc, artificially increasing the RNFL thickness, and the inferior part farther from the disc, making the RNFL artificially thinner.

The RTVue is not affected by this limitation because the RNFL map is made up of more data points covering a large area around the ONH. The RNFL map covers a 5 mm diameter circle around the ONH. The TSNIT graph is generated from a 3.45 mm diameter circle that is always centered on

the ONH. If the scan pattern is not perfectly centered on the ONH during the scan acquisition, the location of the TSNIT circle can be adjusted left, right, up, or down, so that it is centered on the center of the ONH. This is possible because of the large RNFL map that is collected, rather than a single circle. Because there is a large RNFL map covering a large area, the exact location of the TSNIT circle can be adjusted so that it is always centered on the optic disc. This is not possible with a single circle scan acquired in the Time Domain Stratus. The time for the RTVue to collect the larger RNFL map is still less compared to the time required for a single circle with the Time Domain OCT (due to a faster scan speed of 26,000 A scans/sec. vs 400 A scans/sec with Time Domain OCT).

Criteria 2: Registration

A series of scans are automatically aligned and registered to each other based on matching the blood vessel pattern from one scan to the next. Blood vessel based registration is likely the most accurate method because adjustments can be made vertically, horizontally, and also rotationally in order to precisely align one scan to the next. This ensures the same location is compared over time for the most accurate change analysis possible.

The procedure for automatic image registration is as follows:

Step 1) A 3-D scan of the optic disc is captured and the software automatically delineates the optic disc margin. This is based on software algorithms that automatically detect the end of the RPE or Bruch's membrane at the disc margin (see Figure 2). This automatic detection is then displayed and the operator can accept or modify the data points if necessary.

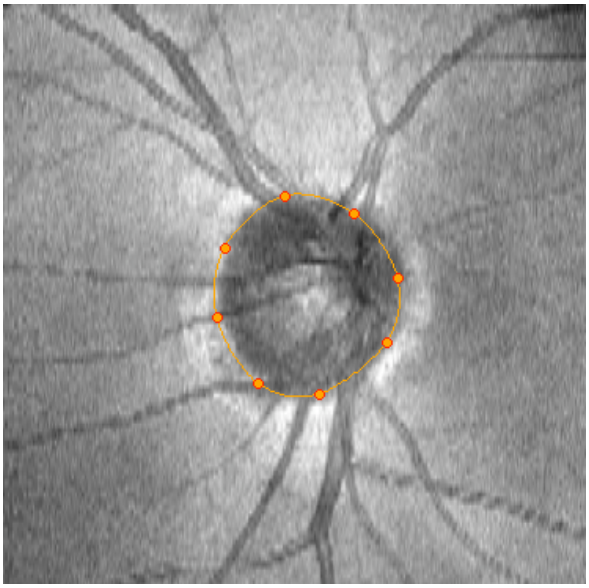
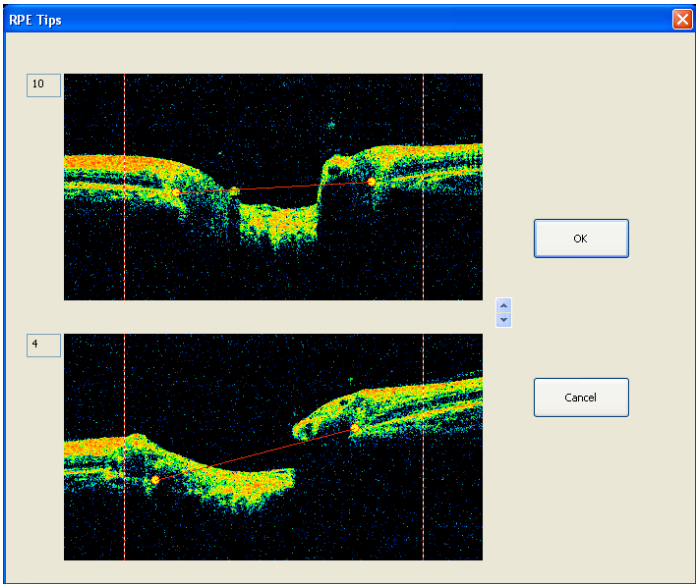


Figure 2. A display of the result from the automatic optic disc margin detection in a 3-D optic disc scan. The software displays the results and allows the operator to verify accuracy and modify data points if necessary. The disc margin drawing is saved and is used for all follow-up exams.

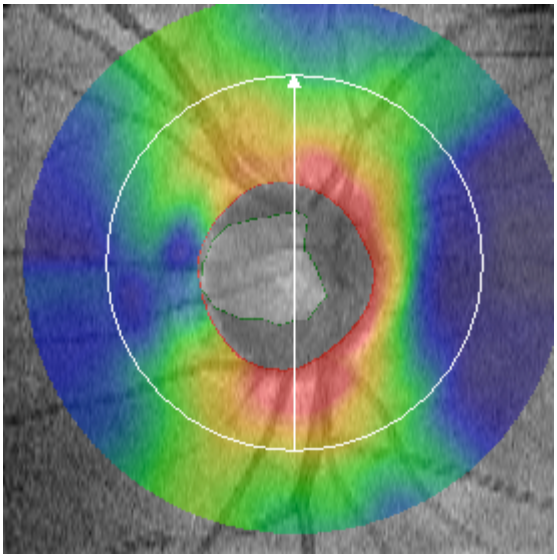
Step 2) Next, the new ONH scan is taken in order to get the optic disc parameters and the RNFL map. The new software automatically detects the RPE/Bruch's membrane end and displays this result to the user in order to verify accuracy (Figure 3). This screen display is similar to the old software version, however the detection process is now automatic instead of manual.

Figure 3. The results of the automatic detection of the RPE/Bruch's membrane end at the disc margin. The software displays the results and allows the operator to verify accuracy and modify data points if necessary. This process is performed after every ONH scan.



Once the optic disc margin has been detected from the 3-D scan, and the RNFL/Bruch's membrane endpoint have been detected in the ONH scan, the software places the disc margin circle over the ONH scan results and calculates the optic disc parameters and RNFL map. In this way, an accurate drawing of the optic disc margin is obtained, and the quantification of RNFL thickness and optic disc parameters (e.g., cup area and rime area) is calculated. Figure 4 shows the RNFL thickness map and optic disc cup and rim area superimposed on the 3-D scan. The disc margin is outlined in red, and the light gray region inside the disc is cup, and the dark gray region is rim. The RNFL thickness map is color coded where thicker RNFL values are colored red and yellow and thinner are blue and green),

Figure 4. The result of registration of the ONH scan to the 3-D optic disc scan. Notice the disc margin drawing from the 3-D scan is shown and outlined in red. The cup and rim areas are shown inside the disc margin as light gray and dark gray respectively. The RNFL thickness map is shown in color with brighter colors representing thicker areas and darker colors representing thinner areas.



For follow-up exams, only the ONH scan needs to be taken, the 3-D optic disc scan needs to be taken at the initial visit only. The disc margin drawing from the 3-D scan is automatically placed on all subsequent ONH scans.

Figure 4. The ONH RNFL thickness map superimposed on the 3-D scan. Registration is performed based on the blood vessel pattern identified in both scans. The RNFL thickness map is color-coded based on thickness where red and yellow represent thicker regions and blue and green represent thinner regions.

Step 3) The blood vessel map for each ONH scan is determined using the en-face view of the ONH scan. When viewed from the top-down perspective, or en-face, the blood vessel pattern around the optic nerve is readily apparent, and can be detected and mapped automatically with software algorithms. This mapping can be seen in Figure 5.

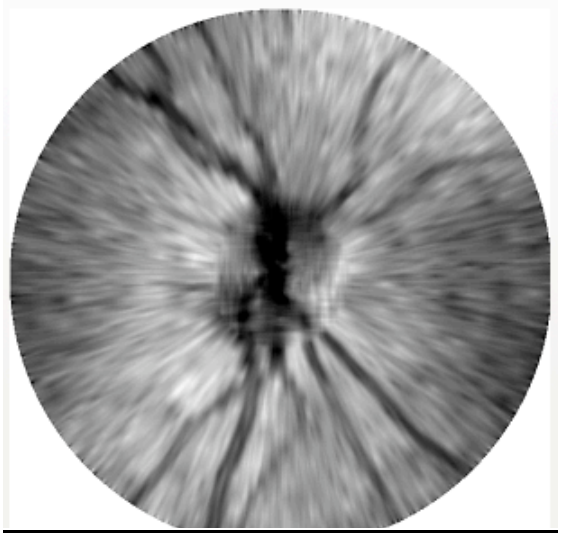


Figure 5. The en face view of the ONH scan reveals the blood vessel pattern around the optic nerve head. The 4.0 software automatically detects this pattern and registers all scans in a series to each other based on this pattern.

Criteria 3: Statistical Analysis

The progression analysis of the ONH scans employs a rigorous statistical analysis to a series of scans in order to determine whether significant change has occurred and also to determine the rate of change in microns/year. The statistical test used is called Statistic Image Mapping (SIM) adapted from neuro-imaging and applied to retinal imaging data by Dr. Garway-Heath and colleagues at Moorfields Eye Hospital (Patterson, Garway-Heath, Strouthidis, Crabb, 2005). This technique has been found to be more accurate for both sensitivity to detecting true change, and specificity for detecting no change in stable eyes, than the Topographical Change Analysis (TCA) utilized in the Heidelberg Retinal Topographer (HRT). The SIM method demonstrates a specificity of 90% vs 85% for TCA (specificity means accurately detecting no change in stable eyes). Likewise the SIM method demonstrates a 73% sensitivity for detecting change in ocular hypertensive converters compared to 53% for TCA (sensitivity is the ability to detect change in eyes that converted to glaucoma). The authors conclude, "SIM has better diagnostic precision in detecting change in a series of HRT images when compared to current quantitative techniques" (Patterson, Garway-Heath, Strouthidis, Crabb, 2005).

The statistical approach used in the SIM method is straightforward. First, a series of data points is identified for analysis. These points can theoretically be anything, from a global parameter such as average RNFL thickness, down to a single pixel. In the current software (version 4.0), there are 6 RNFL sectors that are analyzed (Superior Temporal, Superior Nasal, Nasal, Inferior Nasal, Inferior Temporal, and Temporal), as well as the global RNFL thickness parameter (see figure 3). After the images are aligned based on the blood vessel registration algorithm, the data points at a given location are arranged in order and subjected to a trend analysis. A regression line is created along with a standard error based on the "goodness of fit of the regression line" to the actual data points (better fit means smaller standard error). The slope is determined from the regression analysis. A simple test statistic is created by taking the slope and dividing it by the standard error. If

the slope is large, and the error is small, the test statistic will be large and indicates likely progression. In the next step of the analysis, the data points are randomly re-arranged. After the random shuffling of the data, a new regression line and slope are calculated from this new data re-arrangement, along with a new error term. This random permutation of the data and re-calculation of the possible slopes and error terms is repeated 1,000 times in order to create 1,000 unique test statistics. Then a frequency distribution is created based on all generated test statistics from this random permutation process (a histogram with 1,000 points). Next, the typical cut-off points are determined from this distribution, notably the 5% and 1% levels. Finally the actual test-statistic is compared to the distribution and cut-off values. If the true test statistic exceeds the level of the 5% cut-off, it is colored yellow and labeled, "Possible Progression", if the true test statistic exceeds the level of the 1% cut-off, it is colored red and labeled, "Likely Progression", otherwise it is colored green to indicate no significant progression was detected. The results are presented in a new printout format showing the data points, regression line, slope, and total change for each RNFL sector analyzed (See Figure 5).

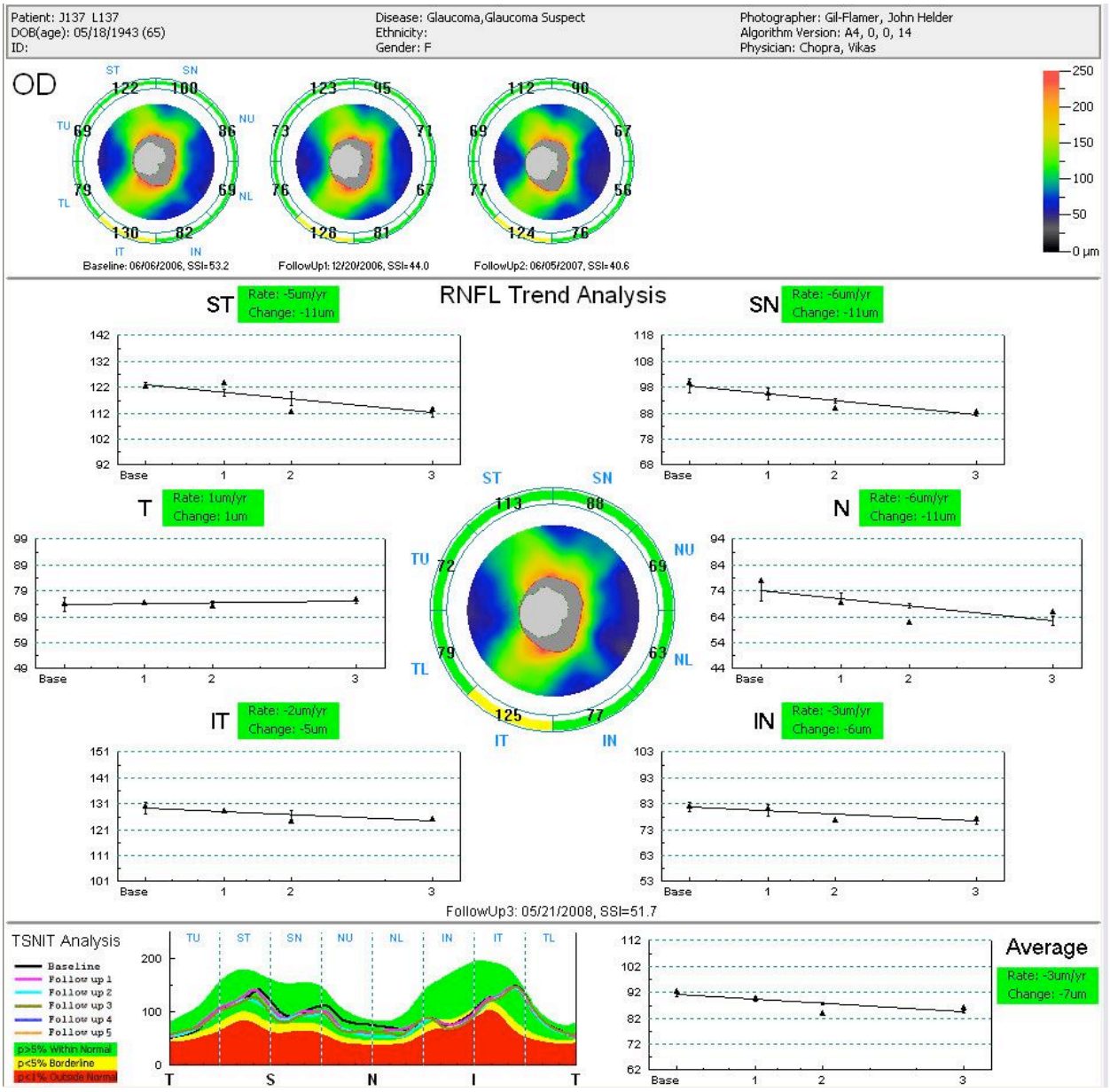


Figure 5. The printout for the RNFL progression analysis. At the top the individual exam thickness maps are presented. The baseline or initial exam is on the left, and each follow-up is to the right. The most recent follow-up is presented in the middle of the printout. The trend analysis graphs for each local region are shown surrounding the thickness map for the most recent follow-up (middle). The individual data points are shown in each graph, along with a regression line. The slope and total change are adjacent to each graph and color coded based on the statistical analysis (see text for details). At the bottom the TSNIT graph is shown with all exams plotted together. On the bottom right is the trend analysis for the average RNFL thickness.

Scan Pattern Details for Progression Analysis

The RNFL and optic nerve scan pattern used for the progression analysis has been slightly modified in software version 4.0. The original RNFL and optic nerve scan pattern in older software

versions was called NHM4, and consisted of an RNFL map and optic disc analysis based on a scan pattern with 12 radial lines and 6 concentric circles with a maximum diameter of 4 mm. The new scan pattern in version 4.0 is now called ONH (for optic nerve head) and provides a larger scan area, out to 4.9 mm. This creates a larger RNFL map and allows for more optic disc decentration than the older scan pattern. This will be helpful for progression analysis where scans must be registered to each other and some area of the RNFL map may not be included in all scans do to scan alignment. The details of the new ONH scan pattern are as follows: Area scanned is 4.9 mm centered on the optic disc, scan pattern is made up of 13 concentric circles with diameter from 1.3mm to 4.9 mm with 0.3mm interval and 12 radial lines, total data points is 14241, and the scan time is 0.55 seconds. The software will allow progression analysis to be performed with both scan patterns, so a patient can be followed that started with the NHM4 scan pattern, and then swithched to the ONH scan pattern without any problem.

References

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