Did the OCT Show Progression Since the Last Visit?

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Abstract: Identifying progression is of fundamental importance to the management of glaucoma. It is also a challenge. The most sophisticated, and probably the most useful, commercially available clinical tool for identifying progression is the Guided Progression Analysis (GPA), which was initially developed to identify progression using 24-2 visual field tests. More recently, it has been extended to retinal nerve fiber layer (RNFL) and ganglion cell–inner plexiform layer (GCIP) thicknesses, like the GPA for 24-2 test, based on the assumption that one needs a minimum of 4 tests to detect “likely” progression.

Thus, the GPA OCT report, like the GPA 24-2 visual field report, is not designed to answer a fundamental clinical question important to both the patient and the clinician, namely: Did damage progress since the last visit? Our purpose here is to first review the OCT GPA and to illustrate how its design limits answering this fundamental question, and second to discuss approaches for answering this question, including the need to evaluate both RNFL and ganglion cell layer (GCL) probability maps, and to scrutinize circumpapillary OCT B-scans.

THE 24-2 VISUAL FIELD AND THE GPA

The GPA is undoubtedly the most sophisticated, and probably the most useful, clinical tool for identifying progression based on multiple 24-2 visual fields. Figure 1 provides an example of the GPA Summary Report for the 24-2 test. The key aspect of this report is the progression analysis, shown within the red rectangle in Figure 1A. It is enlarged and presented in Figure 1B. An open triangle indicates that the sensitivity at that point on the current test (TC1) has decreased at the P-value <5% level as compared with the average of 2 baseline tests (first row in Fig. 1). In this example, 3 points met this criterion. Note, it takes 3 tests to analyze whether the sensitivity at a given point has decreased, 2 baseline tests and the test at TC1. If on the test at time 2 (TC2), one of the locations satisfied this criterion, then a half-filled triangle appears. In this example, one of the locations satisfied this criterion, as is shown by the progression analysis for TC2 in Figure 1C. If that point were significant on a fifth test (TC5), again compared with the baseline tests, then a filled triangle would appear at that location. The GPA uses the Early Manifest Glaucoma Trial criteria for progression, namely, 3 or more half-filled locations denote “possible loss (progression),” and 3 or more filled triangles denote “likely loss (progression).” In other words, a minimum of 4 tests (ie, 2 baseline tests plus 2 subsequent tests) are needed to determine “possible progression” and a minimum of 5 tests are needed to determine “likely progression.”

Although the GPA approach is statistically sound, it does not answer the question: Did the eye show progression of damage since the last test? To answer this question, the
FIGURE 1. A, The Guided Progression Analysis (GPA) Summary Report for the 24-2 test for a patient tested on 3 dates. B, The progression analysis within the red rectangle in (A) is shown enlarged. The small triangles indicate that the sensitivity at that location is significantly lower compared with the 2 baseline tests. C, The progression analysis for the fourth test. The open triangle, as in (B), indicates that the sensitivity at that location is significantly lower compared with the 2 baseline tests, and the half-filled triangle indicates that that location was also 1 of the 3 significant locations (open triangles) on test 3 (B). FL indicates loss of fixation; FN, false negative; FP, false positive; GHT, glaucoma hemifield test; MD, mean deviation; PSD, pattern standard deviation; VFI, Visual Field Index.
clinician is left to interpret the reports for the 24-2 while taking into consideration other information such as intraocular pressure, fundus examination/photography, other risk factors (eg, disc hemorrhage, central corneal thickness, family history), and, often, OCT data.

THE OCT AND THE GPA

The GPA and RNFL Thickness

As with the visual fields, the challenge when using OCT tests is to distinguish real loss (ie, progression) from test-retest variability. Again, the most sophisticated, commercially available statistical approach based on multiple tests is the Zeiss OCT GPA. Figure 2A is the top half of the GPA report for an OCT disc scan obtained on TC1 for the same eye tested as in Figure 1. The top row shows the RNFL thickness maps in pseudo-color. The second row shows the “Change Map.” The Change Map is similar to the progression analysis reports in Figures 1B and C. In the case of the OCT Change Map, an individual location is a superpixel on the RNFL thickness map. A yellow region, like the open triangle in Figures 1B and C, indicates that for this superpixel, the third test was significantly different than the 2 baseline tests. This location/superpixel is said to show “possible loss.” If the same superpixel is also significantly different from baseline on the next (fourth) test, then it is coded red (likely loss). Figure 2B shows the top half of the report for the fourth test on TC2. The red regions contain superpixels that were significantly different from the baseline tests obtained on both TC1 and TC2. Overall, there must be at least 20 adjacent yellow or red superpixels for the change maps to be classified as “possible loss” or “likely loss.” Thus, an eye is likely progressing if a large enough region turns red and stays red. For the eye in our example, test 3 (TC1) showed yellow regions (yellow arrows, Fig. 2A) suggesting “possible loss/progression.” On test 4 (TC2), most of these same regions were now red (red arrows in Fig. 2B) suggesting “likely loss/progression.” Thus, based on the OCT RNFL analysis, we can now say, after a minimum of 4 tests (ie, 2 baseline tests plus 2

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**FIGURE 2.** A, The Guided Progression Analysis (GPA) Summary Report for the retinal nerve fiber layer thickness plots (top row) from optical coherence tomography cube scans centered on the disc. The Change Map is similar to the progression analysis in Figure 1. In this case, yellow indicates that the third visit was significantly different than the 2 baseline examinations. This location/superpixel is said to show “possible loss” (yellow arrows). If the same superpixel is also significantly different from baseline on the next (fourth) test, then it is coded red (likely loss) as shown in (B) (red arrows), the GPA Report for test 4.
require at least 4 tests to conclude modi are important improvements, which should be considered as and measuring the combined RNFL+GCIPL thickness.8 These progressive RNFL thinning.5 This same group has also argued that progression can be detected sooner (ie, with fewer tests) if baseline tests and the test at TC1, with a “likely progression.” But, did this eye progress between test 3 (T_{C1}: 8/25/2014) and test 4 (T_{C2}: 2/24/2017)?

The GPA and GCIPL Thickness

More recently, the same logic has been applied to GCIPL thickness measures obtained from OCT cube scan centered on the fovea. Figure 3 shows Change Maps, for the same eye and test dates as in Figure 2B. After 4 tests, the Change Maps indicate “likely progression,” as indicated by the red regions on the Change Map for test 4 (Fig. 3, lower right panel). But, again did this eye progress between test 3 (T_{C1}; 8/25/2014) and test 4 (T_{C2}: 2/24/2017)?

Recent Advances in OCT and GPA

Recently, 2 groups have suggested substantial improvements to the OCT GPA approach. Leung and colleagues5,6 have proposed replacing the “event-based” comparison between baseline tests and the test at T_{C1}, with a “trend-based progression analysis” (TPA). TPA uses linear regression analysis based on all tests between baseline 1 and T_{C}, the current test. They demonstrated that compared with GPA, TPA detected more eyes with progressive RNFL thinning.5 This same group has also argued that progression can be detected sooner (ie, with fewer tests) if RNFL and GCIPL results are combined either by way of separate analyses as in Figures 2 and 3,7 or by using a wide-field scan and measuring the combined RNFL+GCIPL thickness.8 These are important improvements, which should be considered as modifications to the standard GPA analysis. However, they still require at least 4 tests to conclude “likely progression.”

Lee and colleagues9–11 have also argued for using trend-based analysis, and information from both OCT RFNL and GCIPL thickness measures. For reasons to be discussed below, the Lee et al’s10 study is particularly important for our purposes here. They compared four methods for determining whether an eye had progressed. Figure 4A, from their study, shows the series of RNFL thickness maps, (1) RNFL and (2) GCIPL. On the basis of both GPA analyses, this eye showed “likely progression” by test 6, as indicated by the red regions on the change maps [red arrows in (1) and (2) of Fig. 4A]. Their other 2 methods involved a “qualitative” judgment of progression by glaucoma experts. In method 3, they viewed the series of RNFL thickness maps, shown as (3) of Figure 4A. In method 4, a similar judgment was made of the deviation maps, shown as (4) of Figure 4A. In general, thickness maps and deviation maps are available from a commercial report, the Zeiss Panomap. The Lee and colleagues’ study found that expert assessment of the deviation maps had the highest accuracy, although the results were not significantly different from the traditional GPA of the RNFL (1). [Note: the “deviation” maps are “probability” maps, where the yellow and red colors refer to regions significantly different from healthy controls at the 5% (yellow) and 1% (red) levels.]

**BUT IS THERE PROGRESSION SINCE THE LAST TEST?**

The Clinical Problem

Glaucoma is usually a progressive disease if left untreated, and progression can occur despite treatment. Hence, over time changes in treatment are needed in virtually all patients with diagnosed or suspected glaucoma. Because of the irreversible nature of glaucomatous damage, clinicians do not have the time to wait for documented, confirmed progression before escalating therapy. In fact, being behind (and not ahead) of the disease has been argued to be a main reason that patients continue to go blind from glaucoma.12 Therefore, although repeating tests multiple times and waiting for confirmation has its merits, in daily practice a decision often needs to be made relative to the most recent visit(s). However, there is no standard procedure for evaluating OCT changes between 2 test dates, although there are at least 3 different general approaches used by clinicians. We consider these 3 approaches next.

**Viewing B-scan Images and Circumpapillary Retinal Nerve Fiber Layer (cpRNFL) Thickness Plots**

One approach involves looking at B-scans before evaluating cpRNFL thickness plots. We have argued that, for

FIGURE 3. The Guided Progression Analysis (GPA) Summary Report for ganglion cell-inner plexiform layer (GCIPL) thickness plots (top row) from optical coherence tomography cube scans centered on the fovea. The Change Map is similar to the Change Map in Figure 2.
detecting and understanding glaucoma, the clinician should closely examine B-scan images, especially circumpapillary images. Progression between 2 visits can also be assessed with circumpapillary B-scan images. However, in the case of progression the situation is more complicated as the B-scan images from 2 sessions must be aligned. There are 2 ways to accomplished this. First, when the circumpapillary B-scan is derived from a cube scan, the scans from 2 test dates can be centered in the same optic disc location after acquisition. The circumpapillary B-scan images in Figure 5A, from a Topcon OCT instrument (Topcon Inc., Tokyo, Japan) were derived from cube scans after centering of the optic disc. Successful alignment can be confirmed by the common location of the blood vessel shadows. Note that a subtle local thinning of the RNFL is visible on the derived B-scan images within the red rectangle. This is easier to visualize in the inset to the right of Figure 5A, which shows the region within the red rectangle enlarged (see the study by Sun et al for more examples).

A second approach involves obtaining the second circle scan at the “same” location used in the earlier scan. This is best obtained with some type of eye tracking to assure accurate placement of the second scan. Because both a circle and a cube scan must be obtained, this scanning protocol typically takes more time. However, it produces a better circumpapillary image as the circle scan can now be averaged. Figure 6 shows B-scans obtained with a circle scan and.
FIGURE 5. A, Derived circumpapillary B-scans from cube scans obtained at 2 different visits. These are the same as shown in panel 1 of (B) and (C) below. The circumpapillary retinal nerve fiber layer (RNFL) thickness for the 2 dates are superimposed in the lower panel of (A), where the faint gray curve is from time 1. Insets to the right show the portion of the panels within the red rectangle. B, A 1-page report using a wide-field, swept-source optical coherence tomography cube scan as input.18 The probability maps for RNFL (4) and ganglion cell layer (GCL) inner plexiform layer (6) are shown in the red rectangles. These maps are based on the thickness maps in (3) and (5), but are shown in field view [inferior retina/superior visual field (VF) on top]. Red arrows point to topographically similar locations with thinned RNFL. Black arrows point to locations of the GCL inner plexiform layer, which are part of the same defect. C, The report for the same eye obtained 1.2 years later. The regions indicated by the arrows can be seen to have progressed.
a Spectralis OCT instrument (Heidelberg Engineering Inc., Heidelberg, Germany). There is a local thinning of the cpRNFL in the region within the red rectangle in Figure 6A, which is visible on the B-scans (orange arrow). This defect can be better appreciated in Figure 6B, which contains enlarged images of the regions within the red rectangle in Figure 6A.
Furthermore, the thinning of the cpRNFL is clearly visible on the cpRNFL thickness plot (red arrow). Examination of the B-scans within the red rectangle indicates that the cpRNFL thinning is not because of a segmentation error, as the segmentation is similar on both test dates (see the study by Eguia et al\textsuperscript{16} for more examples).

In many eyes, lack of progression between 2 scan dates can be seen with the same approach. In particular, if the 2 cpRNFL thickness plots are essentially superimposed then it is extremely unlikely that there is significant progression. This is illustrated in Figure 7, where the black (time 2) and gray (time 1) curves in the bottom panel of Figure 7 are nearly superimposed.

In sum, B-scans can be used to assess progression in many eyes with glaucoma. However, it is likely that most of the clinicians currently looking at circumpapillary B-scan images are those using the Heidelberg Spectralis. Until recently, B-scan images in the reports of other manufacturers were either not present and/or too small to be of use. However, the images shown in Figure 5 demonstrate that derived circumpapillary images can be of sufficient quality to detect changes, especially when used with the cpRNFL thickness plot. If clinicians start using these images, as we suggest, the manufacturers will improve the quality of them either through the addition of a circle scan and/or software enhancements.

**Change in Global Thickness of the cpRNFL**

Many clinicians make use of summary statistics when determining the presence or absence of progression. Whether the circumpapillary B-scan image is obtained from a circle scan (Figs. 6, 7) or derived from a cube scan (Fig. 5), all OCT instruments show a plot of the thickness of the cpRNFL as a function of distance around the disc, as shown by the black and gray curves in the lower panels of Figures 5A, 6A, and 7. Some clinicians have advocated using changes in the average (global) thickness of this cpRNFL thickness plot. For example, the so-called “rule of 5,” based on 95% confidence intervals,\textsuperscript{19}–\textsuperscript{22} stipulates that if the global RNFL thickness (G) changes by $>5\mu m$ between 2 tests, then statistically significant progression has taken place. However, this rule has been shown to have both poor sensitivity and specificity for detecting progression.\textsuperscript{16,17,22,23} In fact, as we have recently documented, no criterion $\Delta G$ value will produce good sensitivity and specificity.\textsuperscript{16} The reason is simple. On the one hand, the $\Delta G$ produced by a significant local change in cpRNFL may be $<2\mu m$, whereas subtle changes in segmentation of the cpRNFL and/or the centering/alignment of the circle scan can result in larger changes in $\Delta G$.\textsuperscript{16,17} Figure 6 illustrates both problems. The $\Delta G$ for this eye was only $-3\mu m$. Thus, the defect, which is clearly seen within the red rectangle (Figs. 6A, B), would not be flagged as progression. The segmentation error within the green rectangle (Figs. 6A, C) also helped obscure the loss of cpRNFL. In any case, it is clear that one should not use $\Delta G$ measures without scrutinizing the B-scan image to assess the alignment and segmentation errors.\textsuperscript{16,17} Further, these errors severely limit the use of $\Delta G$ for the purpose of detecting progression as they are very common and often difficult to impossible to correct.\textsuperscript{16,17}

**Evaluating Probability and Thickness Maps**

When assessing progression between visits, many clinicians now look at RNFL and GCL thickness and/or deviation/
probability maps, which are available on all major OCT instruments. The Lee et al.\textsuperscript{3,10} study discussed above supplied evidence that experts can do as well as, or better than, the GPA by viewing only deviation/probability maps. Their study also opens the possibility that experts using deviation maps may need fewer tests. For example, notice in Figure 4A that the GPA for both the RNFL (1) and GCIPL (2) required all 6 tests to reach “likely progression” (red arrows in bottom row of Fig. 4A). Their study design did not include a determination of the number tests needed by the experts. However, in this example, progression is fairly obvious in the deviation maps well before the sixth test. This can be more easily visualized in Figure 4B, where the images from panel 4 of Figure 4A are enlarged. For example, consider the region within the red rectangles. Note that the red and yellow areas in this region increase between baseline 2 (black arrow) and test 3 (red arrow), and between test 3 (red arrow) and test 4 (red arrow). That is, there is clear change well before the GPA criteria for “likely progression” is met on test 6.

Another example is shown in Figure 4C, which contains deviation maps from the Zeiss Panomaps for the eye in Figures 1–3. There is a clear change in deviation maps (red arrows) between examinations 3 and 4. These examples illustrate that a comparison of deviation maps may allow an assessment of progression between visits in at least some eyes.

Our group has advocated for the importance of probability maps in detecting early glaucoma.\textsuperscript{16,24–27} Figures 5B and C is our 1-page report using a wide-field OCT cube scan as input.\textsuperscript{18} [A version of this report is available in some Topcon instruments (Topcon Inc.).] In Figures 5B and C, the probability maps for RNFL (4) and GCIPL (6) are shown in red rectangles. Although these maps are very similar to the deviation maps of the Panomap Report in Figures 4A–C, there are 3 differences. One, the RNFL and GCIPL probability maps are shown separately in our report, whereas they are combined in the Panomap. Two, our probability maps are displayed in field view, that is, rotated around the horizontal meridian to allow for a comparison with visual field. Finally, in our probability maps, the scale is continuous from 10% (green) to 0.1% (dark red), whereas the Panomap deviation map has 2 colors (yellow and red) and 2 probability levels.

Recently, we have presented evidence that the report in Figures 5B and C can be used to identify progression occurring between 2 sessions, at least in some eyes. In particular, Wu et al.\textsuperscript{15} found that an expert assessing the reports from 2 test days outperformed an event-based analysis of the global cpRNFL thickness, a metric commonly used to detect change between 2 tests. In the Wu and colleagues’ study, experts flickered between the reports from the 2 test days. This approach is similar to the flickering between disc photos that has long been used to help detect progression. Figures 5B and C shows the reports for 2 days from Wu and colleagues. Note that there is an indication of progression in the region of the red arrows on RNFL thickness and probability maps (panels 3 and 4). There is also a suggestion of progression on GCIPL thickness and probability maps (black arrows in panels 5 and 6), and in the thickness of the cpRNFL seen in the region of red arrows on the B-scan image (panel 1—upper) and cpRNFL thickness plot (panel 1—lower).

Taken together, the evidence above suggests that at least in some eyes, progression can be assessed between 2 sessions by an expert viewing OCT probability maps within OCT reports such as seen in Figures 5 and 8, discussed below.

### Structure-Structure Agreement: Combining Viewing B-scan Images and cpRNFL Thickness Plots With Probability Maps

The need for multiple 24-2 visual field tests, and the 24-2 GPA, is due to the inherent variability in visual field measures. OCT measures, such as global thickness, also show variability. However, when it comes to overcoming measurement error, the OCT has 2 major advantages compared with visual fields. First, by examining circle scans as in Figures 5–8, it is often possible to identify the source of the variability (eg, a segmentation error), and then correct for it, either by correcting the segmentation or, more practically, by taking it into consideration when making a clinical judgment. Second, the different analyses of the OCT scans, as seen in the OCT reports in Figures 5 and 8, provide >1 source of information. For example, GCL thickness/probability maps, RNFL thickness/probability maps, and cpRNFL images/thickness provide related, but different views, of possible damage. Subtle damage or progression on one of these may not be convincing. However, topographical comparison among different analyses of OCT scans should reduce the need for multiple OCT tests.

This is illustrated by the OCT reports in Figures 5 and 8, from 2 different instruments and for 2 different patients. In these figures, there are subtle signs of progression associated with red and black arrows on the various parts of each report. The red arrows point to locations that topographically correspond to the defect seen on the B-scan in panel 1 (upper), and the black arrows are a second location near fixation that is topographically consistent with an arcuate defect that includes the red arrows. The changes on each of these individual maps/plots by themselves might be ignored, as they are subtle. However, together they strongly suggest progression. Note that some of the most common sources of variability will affect these maps/plots differently. For example, segmentation errors that result in an artifactual larger GCL thickness by mistakenly including the RNFL will result in an RNFL thinner than expected. Other errors due to centering of scans on the disc or fovea, pathological conditions such as epiretinal membranes or retinoschisis or anatomical variations caused by variation in the shape of the fovea or location of major blood vessels, can be identified as well.

### Structure-Function Comparisons

The same argument can be made for comparing OCT (structure) and visual field (function) results. Subtle changes consistent with progression seen with either OCT or visual field tests may or may not be due to random variability. However, if these changes are in the corresponding regions of the visual field and retina, then these subtle changes together likely make true progress. Consistent with this argument, we have recently shown that comparing visual field and OCT probability maps can improve the identification of early glaucoma compared with either alone.\textsuperscript{28,29} Similarly, it should be possible to reduce the number of OCT and visual field tests needed to identify progression by topographically comparing progressing regions on visual fields with those on OCT probability maps. In addition, these topographical structure-structure and structure-function comparisons can be enhanced with a model of RNFL projections.\textsuperscript{30}

### NEED FOR RESEARCH

There are at least 5 areas that need more study. First, until automated procedures and/or OCT reading centers
FIGURE 8. A 1-page report using a spectral domain optical coherence tomography cube scan as input. The probability maps for retinal nerve fiber layer (4) and ganglion cell-inner plexiform layer (6) are shown in black rectangles. These maps are based on the thickness maps in (3) and (5), but are shown in field view (inferior retina/superior visual field on top). Red arrows point to topographically similar locations with thinned retinal nerve fiber layer. Black arrows point to locations of the ganglion cell-inner plexiform layer which are part of the same defect. The report for the same eye obtained 12 (B) and 47 (C) months later. The regions indicated by the arrows can be seen to progress. Insets to the right show enlarged images of the B-scans in panel 1 for the region within the red rectangles. Note: this report is not available in this form for use in the United States.
become common, we need to develop methods for training eye care providers to make better use of the information in OCT scans. This includes examining circumpapillary B-scans in every patient. Second, there is a need for refinement and validation of the so-called qualitative methods, such as those involved in evaluating the reports in Figures 6 and 8.28,29,39 These methods are actually based on extensive quantitative analyses. Thus, calling them “qualitative” is misleading. In any case, ultimately the clinician is making a decision based on information from various sources. The best way to integrate visual field and OCT information into this decision process is still an open question. Third, we need to test our hypothesis that in many eyes a pair of OCT is sufficient to make a decision concerning progression. Fourth, for clinical trials and screening we need to search for, and validate, objective metrics for identifying glaucoma and its progression. The current methods of using summary metrics such as mean deviation, pattern standard deviation, and glaucoma hemifield test of visual fields, and global/average or regional/sector thickness of OCT RNFL and GCIIPL are clearly inadequate and insufficient.13,27,31–38 In contrast, combining topographical related information within and between visual field and OCT probability maps may help.28,29,39 Finally, many believe that deep-learning, convolutional neural networks may be the answer. Interestingly, RNFL probability maps are a particularly good input to these models.32,40 However, while the current work with convolutional neural network models is encouraging, much work needs to be done to make them clinically useful.

Until then, we need to develop methods that allow clinicians to make decisions about changes without requiring long follow-up with multiple tests. On the basis of the approaches described here, this is possible and practical even when looking at a pair of good quality OCT examinations and enables detection of rapid progressors.

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