

# PERSPECTIVE

## Detection of Glaucoma Deterioration in the Macular Region with Optical Coherence Tomography: Challenges and Solutions



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- **PURPOSE:** Macular imaging with optical coherence tomography (OCT) measures the most critical retinal ganglion cells (RGCs) in the human eye. The goal of this perspective is to review the challenges to detection of glaucoma progression with macular OCT imaging and propose ways to enhance its performance.
- **DESIGN:** Perspective with review of relevant literature.
- **METHODS:** Review of challenges and issues related to detection of change on macular OCT images in glaucoma eyes. The primary outcome measures were confounding factors affecting the detection of change on macular OCT images.
- **RESULTS:** The main challenges to detection of structural progression in the macula consist of the magnitude of and the variable amount of test–retest variability among patients, the confounding effect of aging, lack of a reliable and easy-to-measure functional outcome or external standard, the confounding effects of concurrent macular conditions including myopia, and the measurement floor of macular structural outcomes. Potential solutions to these challenges include controlling head tilt or torsion during imaging, estimating within-eye variability for individual patients, improved data visualization, the use of artificial intelligence methods, and the implementation of statistical approaches suitable for multidimensional longitudinal data.
- **CONCLUSIONS:** Macular OCT imaging is a crucial structural imaging modality for assessing central RGCs. Addressing the current shortcomings in acquisition and analysis of macular volume scans can enhance its utility for measuring the health of central RGCs and therefore assist clinicians with timely institution of appropriate treatment. (Am J Ophthalmol 2021;222:277–284. © 2020 Elsevier Inc. All rights reserved.)

STRUCTURAL BIOMARKERS CAN NOW BE MEASURED IN patients with glaucoma in the peripapillary region and macula with unprecedented accuracy and precision with optical coherence tomography (OCT).<sup>1</sup> Disease progression in glaucoma manifests itself mainly as thinning of neural tissues, although other markers such as schisis of the inner retinal layers or changes in tissue density have been reported.<sup>2</sup> Detection of progressive tissue thinning seems a simpler endeavor compared with the detection of pathologic changes in macular retinal disorders. However, clinicians are still grappling with detecting change at all stages of glaucoma in a consistent and timely manner. Also, a direct correlation of progressive structural thinning as measured with OCT imaging with functional loss is yet to be established longitudinally.<sup>3</sup> We review the challenges involved in timely detection of structural decay in glaucoma with an emphasis on macular OCT imaging and propose steps to potentially facilitate this task for monitoring of patients with glaucoma.

### THE CHALLENGES

- **THE VARIABLE AMOUNT OF NOISE AMONG PATIENTS:** Test–retest variability of macular OCT measurements tends to be low but varies in individual eyes.<sup>4,5</sup> Between-visit variability of OCT measures is the main determinant of how accurately and quickly we can detect changes in macular thickness over time. Detection of the smallest structural changes could be of significant practical interest especially in eyes with advanced glaucoma.<sup>6,7</sup> Visit-to-visit variability within local areas of the macula can be large enough to make detection of change within an eye problematic. Estimating individual measurement variability may be of particular interest because sampling variability may vary from person to person.

Sources of test–retest variability include procedural factors, such as head tilt/turn, image centration, and focusing among others. Patient factors consist of poor ocular surface, media opacity, presence of high myopia, and other anatomical issues. Technical factors include incorrect segmentation related to poor image quality or ocular conditions,

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such as peripapillary atrophy and confounding retinal disorders—the latter specifically affect macular OCT measurements.

• **THE SLOW AND VARIABLE AMOUNT OF CHANGE IN PATIENTS WITH GLAUCOMA:** Ledolter and Kardon<sup>8</sup> recently provided an elegant review on using repeated measures random effects models in ophthalmology, illustrating their methods on longitudinal data from the Variability in Perimetry study.<sup>8</sup> Such models can estimate population baseline levels and rates of change over time, which is important when we wish to compare populations distinguished by some characteristic, such as demographic variables or by different treatments. More importantly for individual patients, repeated measures random effects models can estimate subject-specific measures including an individual's baseline level and the individual's rate of change over time for structural and functional outcomes measures. Rates of change estimates from repeated measures random effects models will be more accurately estimated than from regression models that only use data from an individual patient. Importantly, these models can provide estimates on the uncertainty in the estimation of these subject-specific parameters. These models can be potentially used for prediction purposes to assign individual eyes to stable or progressing groups based on one or more feature(s), such as rates of change in various structural domains. Ledolter and Kardon<sup>8</sup> found no significant difference in the rates of change between the normal and glaucoma cohorts although the glaucoma group had a slightly faster average rate of change for the global ganglion cell/inner plexiform layer (GCIPL) and a somewhat slower mean rate of change for the average retinal nerve fiber layer (RNFL). Random effects models are but one of many classes of models for modeling the covariances between the repeated measures within a person.<sup>9</sup> It is important to properly model the covariances between the repeated measures because this is what provides appropriate inferences about individual slopes. Adding autocorrelation between consecutive observations to a random effects model is an important and sometimes useful elaboration of random effects models.<sup>9</sup> Interestingly, in the Variability in Perimetry dataset, the autocorrelations of the residuals were small ( $\rho = 0.19$  for RNFL and  $= 0.15$  for GCIPL for a lag of 1.0 year), and therefore the added model complexity may not warrant considering autocorrelation of residuals.

• **THE CONFOUNDING EFFECT OF AGING:** Age-related loss of retinal ganglion cells (RGCs) is not uniform among subjects nor across the macula. Current evidence suggests that it is a function of the existing number of RGCs at any given time.<sup>10</sup> Leung and associates<sup>11</sup> estimated rates of change for the inner retina, outer retina, GCIPL, and full macular thickness measurements over time with a linear mixed model. They used a fixed-effect interaction term (baseline thickness  $\times$  follow-up duration) for adjusting the estimated

rates of change for the influence of baseline thickness measurements. However, they used the 95% prediction intervals from their normal cohort to correct the rates of change in glaucoma eyes. If one were to accept that the rates of change are affected by the baseline thickness for most structural parameters, which is a plausible assumption based on available data,<sup>12</sup> using the rates of change in normal eyes for correcting age-related decay in glaucoma eyes would be expected to overestimate the influence of aging and underestimate true rates of disease progression in eyes with established glaucoma. Zhang and associates<sup>13</sup> reported a slowing of ganglion cell complex (GCC) loss beyond 65 years of age, which amounted to a third of that seen in their youngest age group (40-55 years of age,  $-0.31$  vs  $-0.11$   $\mu\text{m}/\text{year}$ ). The authors could not rule out variations because of chance given the magnitude of the reduction in the rates of change. They also did not consider a random slope along with the random intercept, which means that they likely underestimated the uncertainty in the slopes.

Tong and associates<sup>14</sup> described clusters in the central macula based on age-related rates of ganglion cell layer (GCL) thinning in a cross-sectional group of 254 normal subjects. An average GCL thinning rate of 0.26% per year was reported within the central 20 degrees of the macula beyond the late 30s. Their work is based on the macular volume scans from Spectralis OCT, which provides an  $8 \times 8$  array of  $3^\circ \times 3^\circ$  superpixels within the central 24 degrees of the macula (Figure 1). They defined clusters of superpixel based on the age-related rates of change. Regardless of the clustering method(s) used, the superpixels demonstrating similar age-related rates of change were clustered in a pericentral pattern with thicker regions (superpixels) displaying larger absolute age-related rates of change. This is supported by Yoshioka and associates<sup>10</sup> findings, in which the normalized rates of change were found to be uniform; the investigators normalized rates of change to the highest thickness measurements for the superpixels of interest. A recent study by Chauhan and associates<sup>5</sup> on white subjects confirms that age-related changes seem to be a function of average thickness in the central macula (Figures 2 and 3). The overall smaller confidence intervals for prediction of functional outcomes from structural measurements with the defined clusters in Tong and associates' study<sup>14</sup> supports the potential utility of clustering superpixels for prediction of functional deterioration from structural changes. More than likely, baseline levels and time trends of superpixels belonging to the same cluster are more highly correlated than superpixels from different clusters; however, the superpixels from different clusters are not uncorrelated, but the correlations are low.

• **EVIDENCE FROM HISTOLOGICAL STUDIES:** Some histological studies have provided evidence for age-related decay in the number of RGCs<sup>16-20</sup> but others have not.<sup>21,22</sup> The number of eyes included have been generally

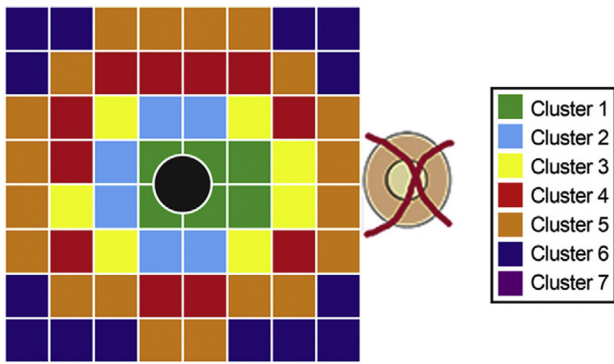


FIGURE 1. An example of clustering of the superpixels from the macular volume scan of the Spectralis optical coherence tomography (OCT) based on age-related rates of change in normal subjects. The Posterior Pole Algorithm of the Spectralis OCT provides an  $8 \times 8$  array of  $3^\circ \times 3^\circ$  superpixels within the central 24 degrees of the macula. In this example, the superpixels demonstrating similar age-related rates of change in the ganglion cell layer were clustered in a pericentral pattern, with thicker superpixels displaying larger absolute age-related rates of change. This particular set of clusters was derived from hierarchical clustering using 5- and 10-year age brackets and *k*-means clustering using 10-year age brackets. Data from the foveal pit were excluded from analysis (black circle) because there are no retinal ganglion cells in this area. (Reprinted from Tong and associates,<sup>14</sup> with permission from Elsevier.)

small (12-22 eyes), and therefore these studies had low power to detect age-related changes. For example, when 12 of 16 eyes reported by Balazsi and associates<sup>16</sup> were reanalyzed with automated methods, the influence of age became nonsignificant.<sup>21</sup> Other confounding factors may have influenced the results of histological studies. Repka and Quigley<sup>22</sup> reported signs of autolysis in up to 80% of 19 eyes they studied. Also, in their study, the average axonal count was roughly 700,000, which is significantly below the average reported in most other studies. Jonas and associates<sup>23</sup> reported an age-related loss of optic nerve fibers of about 0.5% per year. Gao and Hollyfield<sup>24</sup> found that macular RGCs decreased by about 0.3% per year, amounting to about 16% total RGC loss from the second through the sixth decades of life. However, the results were based only on 6 eyes and specific to a localized region nasal to the fovea.<sup>24</sup>

• **PATTERNS OF CHANGE FOR THE INNER MACULAR LAYERS HAVE NOT BEEN WELL DEFINED:** Most if not all studies reporting structural rates of change have assumed a linear decay for structural measures, including macular thickness outcomes. While this may be a practical and convenient assumption, and indeed reasonable over short time periods of time, it needs to be formally verified, especially in untreated cohorts of patients with suspected (or established) glaucoma. The effect of treatment remains a

significant confounding factor in published studies of treated glaucoma cohorts.

• **LACK OF ESTABLISHED REGION OF INTEREST APPROACHES FOR MACULAR OCT IMAGES:** There has been a lack of automated and customized approaches for defining and delineating regions of interest (ROI) in the macula or elsewhere for detection of glaucoma deterioration. Hood and associates<sup>25</sup> reported that a manual ROI approach was better able to detect the extent of progression in the macular region. The task of defining the ROI would be potentially useful so as to outline regions where structural measurements are still above their measurement floor and therefore, identification of change would be possible and detected change is plausible. The measurement floor may vary among different eyes and this has to be taken into account when defining ROIs.

• **LACK OF A RELIABLE AND EASY-TO-MEASURE FUNCTIONAL OUTCOME:** The lengthy testing time and fairly sparse sampling of the central retina with the 10-2 visual field test along with the observed high test-retest variability remain important barriers for reliable assessment of the central visual function in a time-efficient manner. In addition, no clinically established methods are yet widely available for measuring central functional progression although significant advances have been reported.<sup>26-28</sup>

• **LACK OF OPTIMIZED DATA VISUALIZATION:** To date, clinicians still must rely on proprietary software developed by OCT manufacturers for visualizing changes of macular thickness measures over time. The complexity and user friendliness of such software and the macular outcome measure used vary among different OCT devices. None provides the ability to rapidly sort through series of images and almost all are still limited to a single thickness measure, ie, GCC, GCIPL, or GCL. Our preliminary studies have shown that macular outcome measures are not equal regarding identification of progression. Rabiolo and associates<sup>29</sup> recently demonstrated that GCC thickness measurements were more likely to identify statistically significant rates of change in eyes with central or advanced damage at baseline compared with GCIPL or GCL regardless of the level of damage at baseline. This is likely related to the less demanding segmentation task involved in delineating GCC compared with GCIPL or GCL. In addition, our team has recently provided evidence that trend analysis of GCC thickness within macular superpixels can detect statistically significant change over time earlier than the same technique applied to total deviation values at corresponding 10-2 visual field test locations.<sup>3</sup>

• **LACK OF ALTERNATIVE OUTCOME MEASURES OTHER THAN TISSUE THICKNESS:** There have been reports on the potential utility of changes in tissue density in the RNFL<sup>30</sup>; however, no other biomarker has proven to be superior to macular thickness measures and the utility of

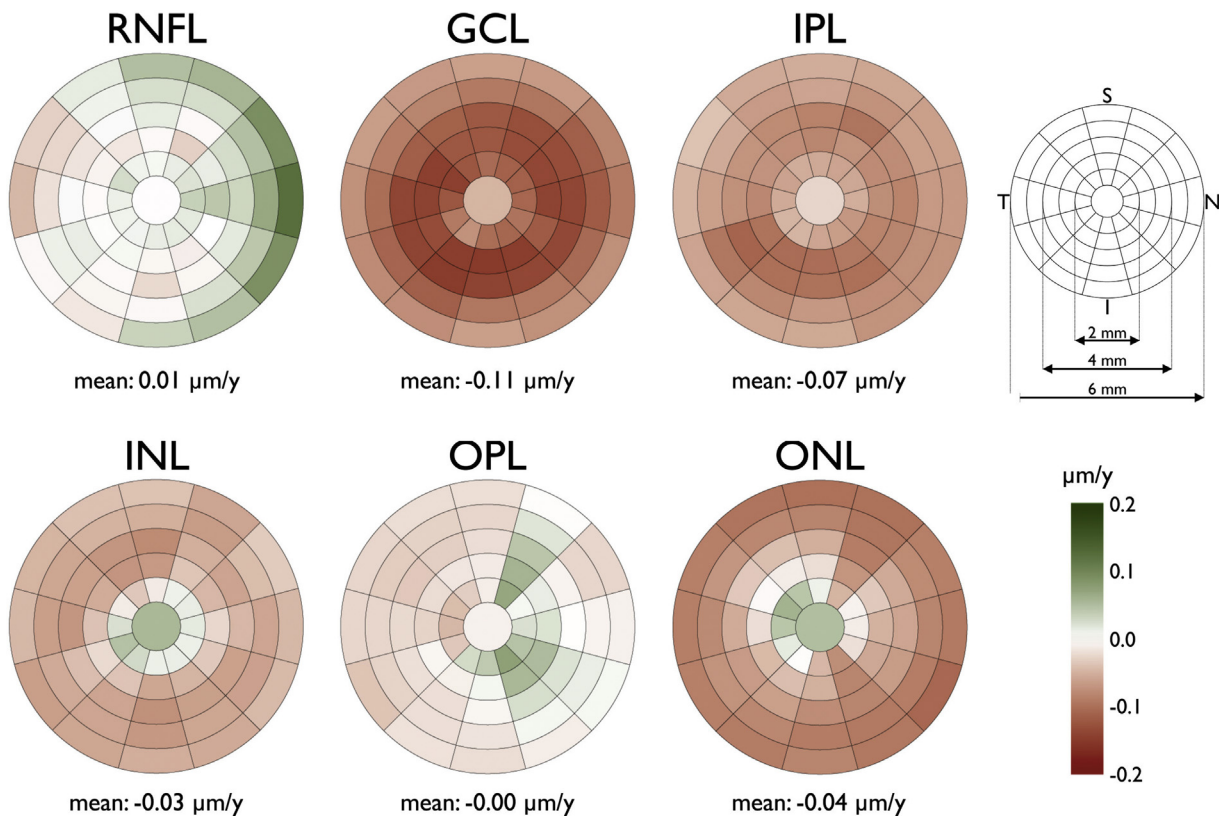


FIGURE 2. Sectoral absolute mean age-related rates of change of the macular retinal nerve fiber layer (RNFL), ganglion cell layer (GCL), inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer (OPL), and outer nuclear layer (ONL) thickness (right eye format). The innermost circle has a diameter of 1 mm with an incremental increase of 1 mm in the diameter of each concentric circle (key, upper right). Each circle, except the most central one, is divided into twelve 30-degree sectors. The darker red colors denote faster negative rates and darker green sectors show faster positive rates (key, bottom right). Rates were calculated based on a cross-sectional group of 246 white subjects. I = inferior; N = nasal; S = superior; T = temporal. (Reprinted from Chauhan and associates,<sup>15</sup> with permission from Elsevier.)

tissue density within the macular retina has yet to be explored. OCT angiography (OCTA) is a promising modality for measuring vascular density as a proxy for blood flow both in the circumpapillary and macular regions. It has provided researchers with new potential biomarkers for measuring the health of the macular RGCs. Findings from diagnostic studies using macular OCTA to discriminate between healthy eyes and eyes with suspected or established glaucoma and the association of vessel density, the main outcome of interest, with functional findings are promising.<sup>31–33</sup> Shoji and associates<sup>34</sup> recently reported that macular OCTA was able to detect longitudinal changes in macular vessel density after an average follow-up of 14 months in eyes with established glaucoma, whereas no changes in GGC thickness could be detected during the same time interval. Validation of these findings in larger cohorts with longer follow-up is needed before OCTA can be recognized as a clinical tool for detection of disease progression in the macula.

- **THE CONFOUNDING EFFECT OF MACULAR DISEASES INCLUDING MYOPIA:** One major limitation of macular OCT imaging is that various retinal macular pathologies can disrupt inner retinal structural integrity and affect measurements of the inner retina. The influence of milder degrees of outer retinal pathologies on inner retinal measurements, such as drusen or retinal pigment epithelial atrophy, has yet to be studied. Progressive thinning of the posterior eye wall is a common feature observed in myopia of varying severity. Enlargement and expansion of the posterior pole leads to thinning of the retina, including the inner retinal layers. Increasing axial length has been consistently associated with thinning of the inner or full retinal thickness measurements in the macula.<sup>35,36</sup> Part of this apparent thinning of the retinal layers is related to the optical magnification observed in myopic eyes.<sup>37</sup> Macular inner thickness measurements have been shown to perform as well as circumpapillary RNFL measurements for detection of glaucoma in highly myopic eyes.<sup>38,39</sup> The



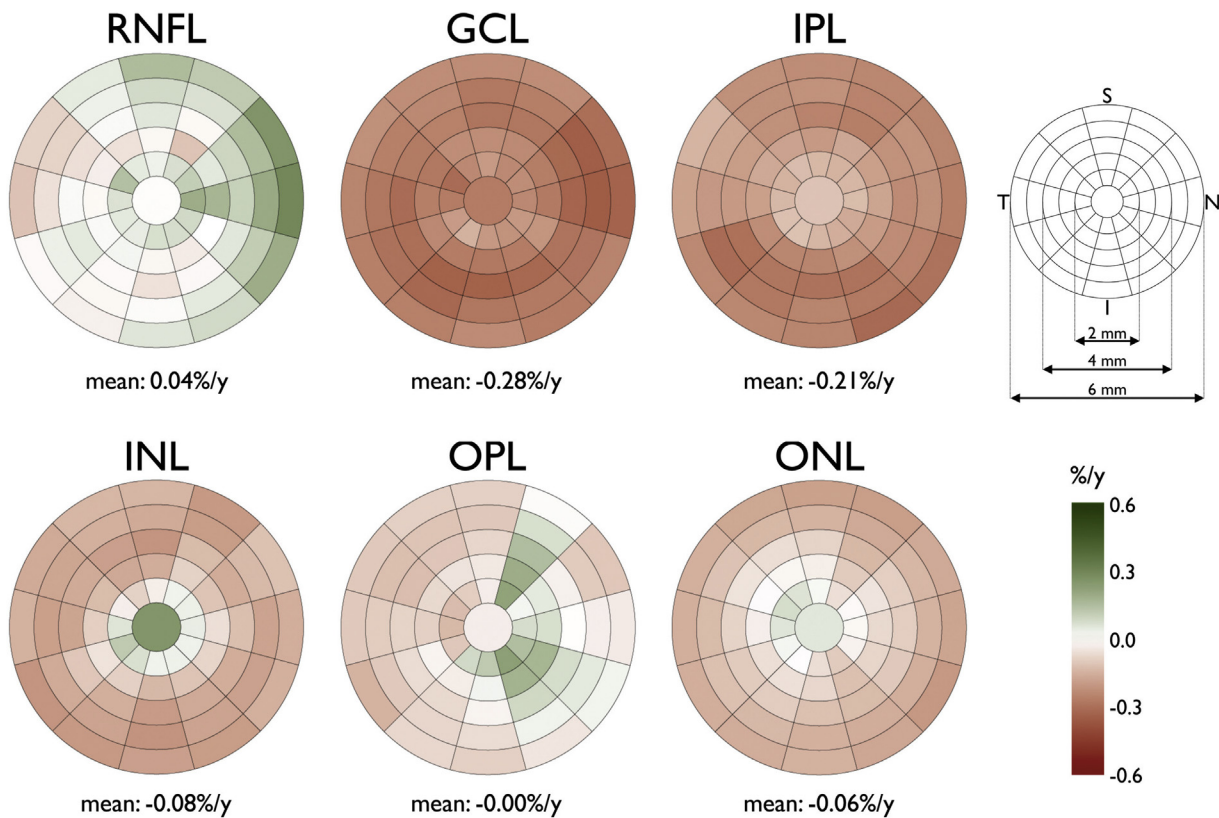


FIGURE 3. Sectoral relative mean age-related rate change of the macular retinal nerve fiber layer (RNFL), ganglion cell layer (GCL), inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer (OPL), and outer nuclear layer (ONL) thickness expressed in percent loss (right eye format). The innermost circle has a diameter of 1 mm with an incremental increase of 1 mm in the diameter of each concentric circle (key, upper right). Each circle, except the most central one, is divided into twelve 30-degree sectors. The darker red colors denote more negative rates and darker green sectors show faster positive rates (key, bottom right). Rates were calculated based on a cross-sectional group of 246 white subjects. I = inferior; N = nasal; S = superior; T = temporal. (Reprinted from Chauhan and associates,<sup>15</sup> with permission from Elsevier.)

main challenges in detection of disease progression with macular OCT imaging are potentially inadequate quality of the OCT images related to signal roll off in eyes with longer axial lengths, presence of significant retinal atrophy confounding macular segmentation and thickness measurements, and possible progression of myopia during the follow-up period, especially in younger patients. Because of tilting of the posterior pole in some myopic eyes, measuring retinal thickness consistently over time may also present a problem in some eyes.<sup>40</sup>

• **JOINT MODELING OF STRUCTURE AND FUNCTION:** Recent work from Hood and associates<sup>41</sup> has provided important insight on the correspondence of structural and functional damage in patients with glaucoma. Medeiros and associates<sup>42</sup> and other investigators have explored Bayesian models for enhancing detection of glaucoma using OCT RNFL thickness measurements.<sup>43,44</sup> Various Bayesian approaches have been proposed, ranging from combining event and trend analyses for visual fields to

using structural change as prior information for modeling of visual field progression. Bayesian methods may allow for inferential quantities of interest that clinicians could find useful. For example, Bayesian methods can allow for inferences such as the probability that progression (or no progression) is occurring in a given time frame in a given superpixel or clusters of superpixels. While Bayesian approaches seem promising, none have been fully developed and therefore, are not available routinely to clinicians. Further work on this topic is needed to bring such approaches into routine clinical use.

• **THE FLOOR EFFECT:** All OCT structural thickness measures are known to reach their floor after about an 8-10 dB decline in perimetric threshold sensitivity has occurred at corresponding test locations or regions. Macular measures are not an exception.<sup>45-48</sup> Central RGC damage can occur early during the course of glaucoma at the same time as the earliest sign of RNFL or neuroretinal rim loss are identified; however, because of the redundancy of the

central macular RGCs, the central macula is the only region of the retina where the residual RGC mass can be measured in later stages of the disease.<sup>49</sup>

• **THE RELATIONSHIP BETWEEN MACULAR RATES OF CHANGE AND BASELINE THICKNESS:** Rates of change for any structural outcome measure, such as macular OCT thickness measurements, typically depend on the initial value of the outcome of interest for 2 reasons: first, there is frequently a measurement floor below which such measures cannot fall. The closer the initial measurement is to the floor, the smaller any detected change would be. Measurement of percent change from baseline has been proposed to address this issue. Percent change also allows comparison of rates of change among competing structural measures in glaucoma.<sup>50</sup> One of the problems of using percent change in this setting is that smaller amounts of change can be magnified as any given outcome measure approaches its measurement floor. Second, where one starts measuring determines the denominator of the percent change calculation; people who enter a study after significant macular damage have a different reference point than people who enter before any decrease. Third, the baseline measurement is usually not informative about the floor level; the floor level will be a different percentage change from initial values for different people. Exponential decay models with random effects are more difficult to fit than linear random effects models. Linear random effects models can be adapted to approximate nonlinear time trends using splines and similar nonlinear curve fitting techniques. The better approach for modeling time trends has not been determined.

Analysis of covariance has been proposed to account for the influence of initial values of a physiologic variable and to compare rates of change across groups.<sup>51</sup> Analysis of covariance is flawed, however, because a baseline measure is likely to have different predictive ability for follow-up observations depending on the time lag of prediction, ROI, and progression of the disease in the cohort under study.

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## POTENTIAL SOLUTIONS

• **HEAD TILT OR TORSION:** Controlling head tilt and turn at every imaging session would be expected to decrease between-visit variability for OCT measurements. While device software handles smaller degrees of head tilt or turn, larger changes in these factors can potentially introduce significant noise and variability into the measurements. A head- or spectacles-mounted sensor-based device could potentially be used for this purpose and is under development.

• **ESTIMATING WITHIN-EYE VARIABILITY:** Although our previous work has demonstrated that the amount of mea-

surement variability is fairly uniform among subjects and within the central region of the macula,<sup>4</sup> some patients manifest higher variability for various reasons. On the other hand, other eyes demonstrate low variability and therefore estimating variability in individual eyes could improve detection of change over time. Our team has shown that variability in inner macular thickness measurements over time was similar to within-session repeated measurement variability.<sup>7</sup> Repeat imaging of a given eye during the initial 1 or 2 visits could provide a good estimate of test–retest variability in thickness measurements and individualized prediction intervals could then be created to optimize detection of change.

• **SOFTWARE AND ACCESS TO RAW DATA:** Despite significant advances in OCT imaging over the last 2 decades, available software algorithms on OCT devices remain inaccessible and are designed with limited input from clinicians and statisticians. Also, options for modifying data visualization in real time are restricted. The ideal software would be able to estimate 95% prediction limits for within-eye variability, so that true change can be distinguished from noise, would allow visualization of the change on macular OCT images at different resolutions, and would provide sliding scale cutoff points for flagging change from baseline by flipping through images or as a short animated series. It would also perform trend analysis on superpixel sizes of choice or clusters with appropriate predictions so that localized information would not be lost. Real-time hierarchical analyses and data visualization based on more sophisticated statistical models and large data sets could be potentially useful in this setting.

Any change analysis algorithm should also allow for the possibility of tissue thickening. Microcystic macular changes in the inner nuclear layer can occur in advanced glaucoma especially in younger patients.<sup>52,53</sup> Also, the possibility of an improvement in macular thickness after marked reduction of the intraocular pressure should be considered. Improvements in the extent of visual field damage and optic nerve appearance after surgical treatment of glaucoma are well established.<sup>54,55</sup>

• **USE OF ARTIFICIAL INTELLIGENCE METHODS:** Use of artificial intelligence in glaucoma diagnostics is still in its infancy, but results from early investigations have been promising. Berchuck and associates<sup>56</sup> recently found that deep learning models could improve estimation of future visual field rates and trajectories from OCT RNFL thickness measurements compared with traditional statistical methods. Unpublished data from our laboratory have also provided evidence that use of AI approaches could enhance our understanding of linking of structure and function in the macula, improve prediction of functional from structural measurements, and potentially pave the way for improvements in detection of progression.<sup>57</sup>

In summary, while macular OCT imaging has significantly advanced the field of glaucoma diagnostics, further optimization of imaging procedures, analyses, and data visualization could move the field ahead

and enhance clinicians' ability to detect glaucoma deterioration in a timely manner and facilitate clinical research by shortening time to detection of progression endpoints.

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