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Financial Disclosures: The authors have no proprietary or commercial interest in any materials discussed in this article.

Available online: August 20, 2020.

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Re: Wu et al.: Wide-field trend-based progression analysis of combined retinal nerve fiber layer and ganglion cell inner plexiform layer thickness

(*Ophthalmology*. 2020;127:1322-1330)

TO THE EDITOR: We read the article by Wu et al.[1] Attempts to use wide-field OCT data for evaluating the structural progression of glaucoma are interesting and necessary for understanding the spatial relationship between the peripapillary and macular areas. Our group also introduced a combination method that integrates the peripapillary retinal nerve fiber layer (RNFL) and macular ganglion cell−inner plexiform layer (GCIPL) guided progression analysis (GPA) progression maps (Cirrus HD-OCT software, version 10.0, Carl Zeiss Meditec, Inc) into a single image (we refer to this map as a "wide-field GPA map" or "GPA PanoMap"), which helps us to evaluate the temporal sequence or patterns of the glaucomatous structural progression.[2,3]

However, we would like to make a few comments on the authors' methodology for handling wide-field OCT data and offer some suggestions for highlighting this new method's superiority.

First, the wide-field scan covered an area of 12 × 9 mm. The actual eyeball is 3-dimensional (3D), but the software-generated wide-field OCT images are 2-dimensional. As the scan area widens, the image becomes more distorted when a 2-dimensional projection is made. For image superimposition to compare the wide-field images, 3D registration or 3D processing are necessary. To overcome this weakness, we use our self-produced Visual C++, Visual Studio Community software (Version 2015; Microsoft).[4] Have the authors considered these technical issues in their study?

Second, Topcon software also provides wide-field progression maps as a "Trend" function (Differential map in IMAGEnet, Topcon Corporation). In those maps, although their algorithm makes some modifications for superimposition, thickened (presented as red) and thinned areas (presented as blue) are mixed and displayed. If the superimposition is perfect—theoretically—no thickened area will exist in patients with glaucoma. Being Topcon OCT users ourselves, owing to these limitations, we cannot use the "Trend" function of the Topcon software as effectively as Cirrus GPA in a clinical setting. This limitation may also be related to the first issue presented. Looking at the authors' representative cases, portions with increased thickness were not presented. Only the decreased portion was presented as the thinning rate (μm/year). We were wondering if there was no actual increase, or if the increased portions were not displayed, and what technical method was used to minimize these areas.

Third, it seems that the central conclusion of this study was that RNFL−GCIPL (ganglion cell complex) trend-based progression analysis (TPA) is superior to existing RNFL or GCIPL TPAs because of its ability to detect progression early on. The advantages of a wide-field scan do not seem to be mentioned enough.[5] We wonder if there were any cases with visualization of progression in areas that cannot be covered by conventional methods, as the authors analyzed progression in a wider area.

Although these issues are difficult to analyze because of their methodologic complexity, they need to be discussed to maximize the benefits of wide-field TPA and promote extensive use of this method in the near future.

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Financial Disclosures: The authors have no proprietary or commercial interest in any materials discussed in this article.
Supported by the Bio & Medical Technology Development Program of the National Research Foundation (NRF) funded by the Korean government (MSIT) (No. NRF-2019M3E5D1A01069352).

Available online: September 10, 2020.

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REPLY: We thank Dr Lee et al for their interest in our study.[1] We are well aware of their cardinal work in applying guided progression analysis (GPA; Carl Zeiss Meditec), an event-based analysis, to evaluate changes in parapapillary retinal nerve fiber layer (RNFL) thickness and macular ganglion cell inner plexiform layer (GCIPL) thickness in patients with glaucoma. As shown in our earlier studies,[2,3] trend-based progression analysis (TPA) outperforms GPA in enabling earlier detection of progressive RNFL thinning and providing spatial information of its rates of change. Our present study highlights combining RNFL and GCIPL as a single layer (RNFL–GCIPL) for TPA over a wide-field, covering the macula and the parapapillary region, to be a more effective strategy to detect glaucoma progression compared with TPA of RNFL thickness or GCIPL thickness alone.

Lee et al rightly pointed out the advantages of 3-dimensional over 2-dimensional registration of OCT scans in examining the morphology of the optic nerve head in extreme eye positions—abduction and adduction. However, because eyes are typically imaged in primary gaze position, the benefit of 3-dimensional over 2-dimensional registration in improving the test-retest variability of RNFL/GCIPL thickness measurements and detecting glaucoma progression remains to be investigated. A key element that dictates the test–retest variability of the RNFL/GCIPL thickness measurements is the signal-to-noise ratio of OCT scans. Ocular surface disease, a prevalent condition in glaucoma patients, often compromises tear film integrity which in turn decreases the signal-to-noise ratio of OCT scans and thereby underestimates RNFL/GCIPL thickness.[4,5] Increases in RNFL/GCIPL thickness would be observed if the signal-to-noise ratio of OCT scans increases over time, with an improvement in the ocular surface (e.g., following glaucoma surgery and cessation of topical glaucoma medication).

In our 3-year study, the proportions of eyes in the glaucoma group identified with progressive RNFL/GCIPL thickening (i.e., having $\geq$20 contiguous superpixels with a significant [$P < 0.05$] positive trend between RNFL/GCIPL thickness and time in the RNFL/GCIPL thickness change map) ranged between 0.2% and 4.1% (Table 1), suggesting high specificities of TPA to detect progressive RNFL/GCIPL thinning. Whereas wide-field TPA is able to discern progressive RNFL/GCIPL thinning outside the macula and the parapapillary region, isolated foci of RNFL/GCIPL thinning at the peripheral retina are uncommon. Nevertheless, spatial analysis of progressive RNFL/GCIPL thinning over a wide-field undoubtedly adds diagnostic precision to identify focal RNFL/GCIPL thinning and to study regional association with visual function. We entirely agree with Lee et al in advocating wide-field TPA to assist detection of glaucoma progression in clinical practice.

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Financial Disclosures: The author made the following disclosures: C.K.S.L.: Patent – Carl Zeiss Meditec, relevant to the work submitted; Consultant – Quark, Aerie, Allergan, Novartis, Santen, Galimedix, Novartis; Grants – Alcon, Novartis, Glaukos, to the institution; Speakers bureau – Topcon, Heidelberg Engineering, Santen, Global Engineering outside the submitted work.

Available online: September 10, 2020.

Table 1. Proportions of Eyes Detected with Progressive RNFL/GCIPL Thickening by TPA

No. of Contiguous Superpixels to Define Progressive RNFL/GCIPL Thinning	20	50	150	250
	Number and proportion of eyes detected with progressive RNFL/GCIPL thinning			
Progressive RNFL-GCIPL thickening (95% CI)	18 (4.1%) (2.4%–6.4%)	16 (3.6%) (2.1%–5.8%)	12 (2.7%) (1.4%–4.7%)	9 (2.0%) (1.0%–3.9%)
Progressive RNFL thickening (95% CI)	9 (2.0%)(1.0%–3.9%)	5 (1.1%) (0.4%–2.6%)	2 (0.5%) (0.1%–1.6%)	1 (0.2%)(0.0%–1.3%)
Progressive GCIPL thickening (95% CI)	10 (2.3%)(1.1%–4.1%)	9 (2.0%) (1.0%–3.9%)	5 (1.1%) (0.4%–2.6%)	5 (1.1%) (0.4%–2.6%)

CI = confidence interval; GCIPL = ganglion cell inner plexiform layer; RNFL = retinal nerve fiber layer; TPA = trend-based progression analysis.