Repeatability of vessel density measurements of optical coherence tomography angiography in normal and glaucoma eyes

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ABSTRACT

Aims To compare the intrasession repeatability of peripapillary and macular vessel density measurements of optical coherence tomography angiography (OCTA) in normal and glaucoma eyes, and to evaluate the effect of signal strength of OCTA scans on the repeatability.

Methods In a cross-sectional study, three optic nerve head scans each of 65 eyes (30 normal, 35 glaucoma eyes) and three macular scans each of 69 eyes (35 normal, 34 glaucoma eyes) acquired in the same session with OCTA were analysed. Repeatability was assessed using within-subject coefficient of repeatability (CRw) and variation (CVw). Effect of signal strength index (SSI) on repeatability was evaluated with repeated-measures mixed-effects models.

Results CRw (%) and CVw (%) of peripapillary measurements in normal eyes ranged between 3.3 and 7.0, and 2.5 and 4.4 respectively, and that in glaucoma eyes between 3.5 and 7.1, and 2.6 and 6.6. For the macular, these measurements ranged between 4.1 and 6.0, and 3.3 and 4.7 in normal eyes and 4.3 and 6.9, and 3.7 and 5.6 in glaucoma eyes. Repeatability estimates of most measurements were similar in normal and glaucoma eyes. Vessel densities of both peripapillary and macular regions significantly increased with increase in SSI of repeat scans (coefficients ranging from 0.15 to 0.38, $p<0.01$ for all associations).

Conclusions Repeatability estimates of OCTA measured peripapillary and macular vessel densities were similar in normal eyes and eyes with glaucoma. SSI values of the scans had a significant effect on the repeatability of OCTA with the vessel density values increasing in scans with higher SSI values.

INTRODUCTION

A relatively recent application of optical coherence tomography (OCT) has been the development of a three-dimensional angiography algorithm called split spectrum amplitude-decorrelation angiography for imaging the retinal and optic nerve head (ONH) microcirculation non-invasively.[1] Multiple studies have used optical coherence tomography angiography (OCTA) to report the vascular changes in common retinal pathologies such as diabetic retinopathy,[2] age-related macular degeneration[3 4] and retinal vein occlusions.[5] OCTA has also been used to demonstrate reduced ONH, peripapillary and macular vessel densities in patients with glaucoma.[6–11]

Although there are numerous studies on the use of OCTA in ocular pathologies, repeatability of these vessel density measurements in different diseases, and more importantly, the factors affecting the repeatability of measurements have not been well studied. Initial studies which evaluated the repeatability of OCTA measured vessel densities within the ONH found the repeatability to be better than previous methods of assessing vascular parameters of the eye.[6–8] Subsequent studies also evaluated the repeatability of OCTA-measured vessel densities in the peripapillary[9 12 13] and the macular regions.[13–15] However, the repeatability estimates in these studies were performed predominantly in normal subjects and on small samples. The purpose of the current study was to compare the intrasession repeatability of peripapillary and macular vessel density measurements of OCTA in normal and glaucoma eyes, and to evaluate the effect of signal strength of the OCTA scans on the repeatability.

METHODS

This was a prospective, cross-sectional study conducted at Narayana Nethralaya, a tertiary eye care centre in Bengaluru, South India, between February 2016 and November 2016. The methodology adhered to the tenets of the Declaration of Helsinki for research involving human subjects.

Participants of the study included control subjects, glaucoma suspects and patients with glaucoma. Control subjects were either hospital staff or subjects who consulted for a routine eye examination or a refractive error. Control subjects had no family history of glaucoma, intraocular pressure (IOP) ≤21 mm Hg, normal anterior and posterior segments on clinical examination by an ophthalmologist and non-glaucomatous optic discs, as assessed by glaucoma experts on masked examination of stereoscopic optic disc photographs. Glaucoma suspects either had an intraocular pressure >21 mm Hg or suspicious ONH as assessed on optic disc photographs. Patients with glaucoma had glaucomatous changes on ONH examination (focal or diffuse neuroretinal rim thinning, localised notching or retinal nerve fibre layer defects) as graded by experts on stereoscopic optic disc photographs. All types of patients with glaucoma (primary or secondary, open or angle closure) were

included. Inclusion criteria for all participants were age ≥18 years, corrected distance visual acuity of 20/40 or better and refractive error within ±5 D sphere and ±3 D cylinder. Exclusion criteria were presence of any media opacities that prevented good-quality OCT scans or any retinal or neurological disease other than glaucoma, which could confound the evaluation. All participants underwent a comprehensive ocular examination, which included a detailed medical history, corrected distance visual acuity measurement, slit-lamp biomicroscopy, Goldmann applanation tonometry, gonioscopy, dilated fundus examination, stereoscopic disc photography, visual field (VF) examination and OCTA imaging with RTVue-XR SD-OCT (Optovue, Fremont, California, USA).

Stereoscopic optic disc photographs were obtained by trained technicians using a digital fundus camera (Kowa nonmyd WX, Kowa Company, Japan). Each optic disc photograph was evaluated independently by two glaucoma experts (HLR and NKP) in a masked manner to determine the presence of glaucomatous changes (focal or diffuse neuroretinal rim thinning, localised notching or retinal nerve fiber layer defects). Discrepancy in the classification between the two experts was adjudicated by a third glaucoma expert (ZSP). Optic discs that could not be classified as normal or glaucomatous were classified as 'disc suspects'.

VF examination was performed using a Humphrey Field analyzer II, model 720i (Zeiss Humphrey Systems, Dublin, California, USA), with the Swedish interactive threshold algorithm standard 24-2 program. VFs were considered reliable if the fixation losses were <20%, and the false positive and false negative response rates were <15%.

OCTA imaging of the optic disc region and macula was performed using RTVue-XR SD-OCT (AngioVue, V.2016.1.0.26). Three scans each of the optic disc and the macular region were performed in the same session by the same technician in all these subjects. The procedure of OCTA imaging with RTVue-XR has been detailed previously.[11 16] The optic disc scan covers an area of 4.5×4.5 mm and the macular scan was performed using volumetric scans covering 3×3 mm. The software compares the consecutive B-scans at the same location to detect flow using motion contrast, thereby delineating blood vessels.[1] Vessel density is defined as the percentage area occupied by the large vessels and microvasculature in a particular region. Vessel densities are calculated over the entire scan area, that is, whole enface disc and whole enface macula, as well as defined areas within each scan as described below.

In the optic disc scan, the software automatically fits an ellipse to the optic disc margin. The peripapillary region is defined as a 0.75-mm-wide elliptical annulus extending from the optic disc boundary and the average vessel density within this region is calculated. The peripapillary vessel density was analysed from the 'radial peripapillary capillary (RPC) segment' which extends from the internal limiting membrane (ILM) to the posterior boundary of the nerve fibre layer. The peripapillary region is divided into six sectors based on the Garway-Heath map and the vessel density in each sector is calculated (nasal, inferonasal, inferotemporal, superotemporal, superonasal and temporal sectors).[17]

Macular vessel densities are analysed over a 1.5-mm-wide parafoveal, circular annulus centred on the macula. Macular vessel densities analysed in this study were of the superficial vascular plexus present in the inner layers of the retina (extending from the ILM to the inner plexiform layer). The parafoveal region is divided into four sectors of 90° each (temporal, superior, nasal and inferior sectors) and vessel density in each sector is calculated. Image quality was assessed for all OCTA scans. Poor-quality images, which were defined as those with a signal strength index (SSI) <45 or images with motion artefacts and segmentation errors were excluded from the analysis.

Statistical analysis

Descriptive statistics included mean and SD for normally distributed variables and median and IQR for non-normally distributed variables.

Repeatability was assessed by intraclass correlation coefficient (ICC), within-subject SD (Sw), coefficient of repeatability (CRw) and within-subject coefficient of variation (CVw). The Sw was calculated as the square root of the within-subject mean square of error (the unbiased estimator of the component of variance due to random error) in a mixed-effects model.[18] ICC was also calculated from the mixed-effects model.[19] The CRw was calculated as 2.77 times Sw. The CVw (100 × Sw/overall mean) was calculated according to the procedure described by Bland and Altman.[20] Effect of SSI on the repeatability of vessel density measurements was evaluated using linear mixed-effects models for repeated measures.[21] Statistical analyses were performed using the Stata V.13.1 statistical software. A p value of ≤0.05 was considered statistically significant.

RESULTS

In total, 134 eyes (60 normal, 31 glaucoma suspect and 43 glaucoma) of 80 subjects underwent three OCTA scans within the same session. Glaucoma suspects and patients with glaucoma were considered as a single group for the analysis. Among these, 22 eyes had poor-quality disc scans, 24 eyes had poor-quality macular scans and 41 eyes had poor-quality disc and macular scans, either in one or more of the three scans. These were excluded and the final analysis consisted of three good-quality optic disc scans of 65 eyes (30 normal and 35 glaucoma eyes) and three good-quality macular scans of 69 eyes (35 normal and 34 glaucoma eyes). These good-quality disc and macular scans were from 42 eyes of 27 normal subjects and 45 eyes of 26 patients with glaucoma. Table 1 shows the demographic, clinical and VF parameters of included subjects. Table 1 also shows the average values of the SSI and vessel densities from the three scans. Most of the vessel densities were significantly lesser in the glaucoma group compared with the control group.

Table 2 shows the repeatability estimates of the peripapillary vessel density measurements separately for normal and glaucoma eyes. ICCs of the inferior peripapillary measurements were greater in glaucoma compared with normal eyes. Other repeatability estimates were similar in normal and glaucoma eyes, except for the CVw of inferotemporal peripapillary sector which was significantly greater (worse) in the glaucoma eyes. Repeatability estimates of the peripapillary sectors were worse than that of the average and the whole enface vessel density measurement.

Table 3 shows the repeatability estimates of the macular vessel density measurements separately in normal and glaucoma eyes. Although the repeatability estimates were slightly greater (worse) in the glaucoma eyes, the differences were not statistically significant for any of the measurements. Like the peripapillary measurements, repeatability estimates of sector measurements were worse than the average parafoveal and whole enface vessel density measurements.

Table 4 shows the effect of SSI on the repeatability of vessel density measurements. The significant positive coefficients

Table 1 Clinical features, visual field parameters and vessel density measurements of the participants

	Control group (42 eyes, 27 subjects)	Glaucoma group (45 eyes, 26 patients)	p Value
Age (years)*	57.4 (39.2–60.4)	58.9 (55.3–64.3)	0.23
Gender (male:female)	16:11	23:3	0.02
Sphere (D)*	0.5 (0–1)	0.75 (0–1.5)	0.09
Cylinder (D)*	−0.75 (−1 to 0)	0 (−0.75 to 0)	0.04
Pseudophakia (n, %)	8 (19.1%)	6 (13.3%)	0.47
IOP at the scanning visit (mm Hg)	14.8±2.8	16.2±3.7	0.06
Hypertension (yes:no)	7:20	12:14	0.15
Diabetes mellitus (yes:no)	4:23	13:13	0.01
Mean deviation (dB)*	−2.4 (−3.7 to −0.2)	−4.7 (−11.0 to −2.6)	<0.001
Pattern SD (dB)*	1.8 (1.4 to 2.6)	3.2 (1.7 to 9.0)	<0.001
Visual field index (%)*	98 (97 to 100)	95 (72 to 98)	<0.001
	OCTA parameters		
SSI (optic disc scan)	58.1±6.4	57.1±5.7	0.50
Whole enface vessel density (disc scan, %)	52.3±3.1	49.3±5.4	0.01
Average peripapillary vessel density (%)	61.5±3.9	58.3±5.4	0.008
Nasal vessel density (%)	58.8±4.4	57.0±4.1	0.10
Inferonasal vessel density (%)	62.8±4.0	57.4±8.1	0.002
Inferotemporal vessel density (%)	65.0±4.3	56.4±12.4	0.001
Superotemporal vessel density (%)	65.8±4.7	61.5±9.3	0.03
Superonasal vessel density (%)	59.9±5.0	57.0±6.9	0.05
Temporal vessel density (%)	61.4±4.9	60.1±4.2	0.22
SSI (macula scan)	62.9±4.9	61.3±6.5	0.27
Whole enface vessel density (macula scan, %)	46.4±3.9	44.2±4.8	0.04
Parafoveal vessel density (%)	48.7±4.2	46.4±5.0	0.04
Temporal vessel density (%)	48.5±4.2	46.0±5.2	0.03
Superior vessel density (%)	49.1±4.2	47.2±5.2	0.11
Nasal vessel density (%)	48.3±4.1	46.7±4.7	0.13
Inferior vessel density (%)	49.1±4.8	45.8±5.7	0.01

All values represent mean ± SD unless specified.
*Median and IQR.
IOP, intraocular pressure; OCTA, optical coherence tomography angiography; SSI, signal strength index.

associated with SSI indicated that the vessel density significantly increased with an increase in the SSI values of the repeat scans.

DISCUSSION

The present study evaluated the repeatability of OCTA-measured peripapillary and macular vessel densities and found that the repeatability estimates were similar in normal and glaucoma eyes. Few studies have evaluated the repeatability of OCTA measured vessel densities in the peripapillary[9 12 13] and the macular regions.[13–15] However, the repeatability estimates in these studies were performed predominantly in normal subjects and on small samples. CVw was the only repeatability parameter estimated in these studies and, in most of the studies, repeatability was estimated only for the average vessel density measurements and not for sectors.

Wang *et al* evaluated the repeatability of average peripapillary vessel density in 15 normal eyes and reported a CVw of 1.21%.[13] Liu *et al* evaluated the repeatability of average peripapillary vessel density in 12 normal eyes and 12 glaucoma eyes and reported a CVw of 1.9% and 4%, respectively.[9] Unlike the previous studies which evaluated only the average peripapillary measurement, Hollo evaluated the repeatability of vessel density measurements of various peripapillary sectors in 18 glaucoma eyes (8 glaucoma and 10 ocular hypertensive eyes) and found that the CVw ranged from 3.51% (temporal sector measurement) to 5.12% (superotemporal sector measurement).[12] Summarising the results from the previous studies, it seemed that the CVw of peripapillary vessel density was better in normal compared with the glaucoma eyes, and the repeatability varied across different peripapillary sectors. However, in the current study, we found that the repeatability of peripapillary vessel densities was statistically similar in normal and glaucoma eyes, except for the CVw of inferotemporal sector measurement which was significantly worse in the glaucoma eyes. One possible reason for similar repeatability estimates in normal and glaucoma eyes in our study is that the severity of disease was mild in most of the glaucoma eyes and suspect eyes, which had normal VF, were also included in the glaucoma group. Similar to the findings of the study by Hollo,[12] we too found that the repeatability varied across different peripapillary sectors.

Yu *et al* evaluated the agreement (instead of repeatability) between two repeated measurements of average parafoveal vessel density in 15 normal eyes and reported that the 95% limits of agreement ranged between −8% and 11%.[14] Agemy *et al* evaluated the repeatability of average parafoveal vessel density in the superficial retinal, deep retinal and choroidal layers of five normal eyes and reported a CVw ranging from 0.1% to 6.8%; without reporting the CVw of different layers separately.[15] Wang *et al* evaluated the repeatability of average parafoveal vessel density in 15 normal eyes and reported a CVw of 4.55%.[13] This is similar to the CVw values found in normal eyes of our study. There are, however, no reports on the repeatability of macular vessel densities in eyes with glaucoma.

Table 2 Repeatability estimates of peripapillary vessel density measurements

	ICC		Sw (%)		CRw (%)		CVw (%)	
Vessel density	**Normal**	**Glaucoma**	**Normal**	**Glaucoma**	**Normal**	**Glaucoma**	**Normal**	**Glaucoma**
Whole enface disc	0.85 (0.75 to 0.92)	0.95 (0.91 to 0.97)	1.2 (1.0 to 1.5)	1.3 (1.1 to 1.5)	3.3 (2.8 to 3.9)	3.5 (3.0 to 4.1)	2.4 (1.8 to 2.9)	2.6 (2.2 to 3.0)
Peripapillary	0.86 (0.77 to 0.92)	0.93 (0.87 to 0.96)	1.5 (1.2 to 1.8)	1.5 (1.3 to 1.8)	4.1 (3.4 to 4.9)	4.1 (3.5 to 4.8)	2.5 (1.8 to 3.0)	2.6 (2.1 to 3.0)
Nasal	0.85 (0.74 to 0.91)	0.84 (0.74 to 0.91)	1.8 (1.5 to 2.2)	1.7 (1.5 to 2.1)	5.0 (4.2 to 6.0)	4.8 (4.1 to 5.7)	3.3 (2.4 to 4.0)	3.1 (2.6 to 3.5)
Inferonasal	0.71 (0.55 to 0.83)	0.93 (0.88 to 0.96)	2.4 (2.0 to 2.9)	2.2 (1.8 to 2.5)	6.6 (5.5 to 7.9)	6.0 (5.1 to 7.0)	4.0 (3.0 to 4.8)	4.1 (3.3 to 4.7)
Inferotemporal	0.75 (0.59 to 0.85)	0.96 (0.93 to 0.97)	2.3 (2.0 to 2.8)	2.6 (2.2 to 3.0)	6.5 (5.4 to 7.7)	7.1 (6.0 to 8.4)	3.7 (2.4 to 4.6)	6.6 (4.7 to 9.5)
Superotemporal	0.85 (0.75 to 0.92)	0.94 (0.89 to 0.96)	1.9 (1.6 to 2.3)	2.4 (2.0 to 2.8)	5.3 (4.4 to 6.3)	6.5 (5.5 to 7.7)	3.0 (2.3 to 3.6)	4.2 (3.1 to 5.1)
Superonasal	0.78 (0.64 to 0.87)	0.87 (0.79 to 0.93)	2.5 (2.1 to 3.0)	2.6 (2.2 to 3.0)	7.0 (5.8 to 8.4)	7.1 (6.0 to 8.4)	4.4 (2.6 to 5.6)	4.6 (3.6 to 5.5)
Temporal	0.78 (0.65 to 0.88)	0.71 (0.56 to 0.83)	2.4 (2.0 to 2.9)	2.5 (2.1 to 2.9)	6.7 (5.6 to 8.0)	6.9 (5.9 to 8.0)	4.2 (3.0 to 5.0)	4.1 (3.3 to 4.8)

Figures in parenthesis represent 95% CIs.
CRw, coefficient of repeatability; CVw, coefficient of variation; ICC, intraclass correlation coefficient; Sw, within-subject SD.

Table 3 Repeatability estimates of macular vessel density measurements

	ICC		Sw (%)		CRw (%)		CVw (%)	
Vessel density	**Normal**	**Glaucoma**	**Normal**	**Glaucoma**	**Normal**	**Glaucoma**	**Normal**	**Glaucoma**
Whole enface macula	0.87 (0.78 to 0.92)	0.90 (0.83 to 0.94)	1.5 (1.3 to 1.7)	1.6 (1.3 to 1.9)	4.1 (3.5 to 4.8)	4.3 (3.7 to 5.1)	3.3 (2.3 to 4.1)	3.7 (2.9 to 4.3)
Parafovea	0.87 (0.78 to 0.92)	0.87 (0.79 to 0.93)	1.6 (1.3 to 1.9)	1.8 (1.6 to 2.2)	4.4 (3.7 to 5.1)	5.1 (4.3 to 6.0)	3.4 (2.4 to 4.1)	4.1 (3.1 to 4.9)
Temporal	0.81 (0.70 to 0.89)	0.86 (0.76 to 0.92)	1.9 (1.6 to 2.3)	2.0 (1.7 to 2.4)	5.3 (4.5 to 6.3)	5.7 (4.8 to 6.7)	4.2 (3.0 to 5.2)	4.6 (3.7 to 5.3)
Superior	0.84 (0.74 to 0.91)	0.85 (0.75 to 0.91)	1.8 (1.5 to 2.1)	2.1 (1.8 to 2.5)	4.9 (4.2 to 5.8)	5.9 (5.0 to 7.0)	3.7 (2.8 to 4.5)	4.7 (3.8 to 5.4)
Nasal	0.80 (0.69 to 0.88)	0.75 (0.62 to 0.85)	1.9 (1.6 to 2.3)	2.5 (2.1 to 3.0)	5.4 (4.5 to 6.3)	6.9 (5.9 to 8.2)	4.2 (3.1 to 5.0)	5.6 (3.2 to 7.3)
Inferior	0.82 (0.71 to 0.89)	0.86 (0.77 to 0.92)	2.2 (1.8 to 2.6)	2.2 (1.9 to 2.6)	6.0 (5.1 to 7.1)	6.1 (5.2 to 7.2)	4.7 (2.6 to 6.1)	5.0 (4.0 to 5.8)

Figures in parenthesis represent 95% CIs.
CRw, coefficient of repeatability; CVw, coefficient of variation; ICC, intraclass correlation coefficient; Sw, within-subject SD.

Table 4 Effect of signal strength index on the repeatability of vessel density measurements of the peripapillary and macular regions

Vessel density	Coefficient (SE)	95% CI	p Value
Whole enface disc	0.21 (0.03)	0.15 to 0.26	<0.001
Peripapillary	0.23 (0.03)	0.17 to 0.29	<0.001
Nasal	0.25 (0.04)	0.17 to 0.32	<0.001
Inferonasal	0.19 (0.05)	0.08 to 0.29	0.001
Inferotemporal	0.20 (0.06)	0.07 to 0.32	0.002
Superotemporal	0.15 (0.05)	0.05 to 0.25	0.004
Superonasal	0.21 (0.06)	0.09 to 0.33	0.001
Temporal	0.35 (0.05)	0.26 to 0.45	<0.001
Whole enface macula	0.28 (0.04)	0.20 to 0.35	<0.001
Parafovea	0.31 (0.04)	0.23 to 0.39	<0.001
Temporal	0.30 (0.05)	0.20 to 0.39	<0.001
Superior	0.29 (0.05)	0.20 to 0.39	<0.001
Nasal	0.38 (0.05)	0.29 to 0.47	<0.001
Inferior	0.36 (0.05)	0.26 to 0.46	<0.001

In addition to CVw, we also evaluated CRw as an estimate of repeatability. Unlike CVw, CRw has greater relevance for clinicians as it represents the test–retest variability of the measurements.[18] CRw values of the most important peripapillary sectors (inferotemporal and superotemporal) were close to 7%. CRw of the parafoveal vessel densities also ranged between 4% and 7%. This would mean that any change in the peripapillary and parafoveal vessel density of <7% would fall within the test–retest variability and would be clinically insignificant. This has to be considered while interpreting any change in vessel densities longitudinally.

We evaluated the effect of SSI of the OCTA scans on the repeatability of vessel densities and found a significant positive association between the two. The vessel densities both in peripapillary and macular regions significantly increased with an increase in the SSI values of repeat scans. The coefficients ranged from 0.15 to 0.38 for peripapillary vessel densities which meant that the vessel densities increased by 1.5% to 3.8% if the SSI value of the repeat scan increased by 10 units. The coefficients were larger for the association between SSI and macular vessel densities and ranged from 0.28 to 0.38. Variability in SSI values of the repeat scans is likely to explain a significant part of the repeatability estimates seen in the present and previous studies. Therefore, SSI has to be considered while interpreting the changes in vessel density longitudinally.

There are some limitations of the OCTA technology which need to be considered while interpreting the results. A significant number of OCTA scans were excluded because of poor quality, which was either due to low SSI or residual motion artefacts. Some of the previous studies have also reported high numbers of poor-quality images with OCTA.[12 22 23] Real-time tracking is used in the current versions of the OCTA technology to reduce artefacts.[24] The OCTA algorithm, in its current form, includes large vessels along with capillaries in its estimation of vessel density. It is possible that the repeatability estimates are different for the measurement of large vessels compared with that of the capillaries. The peripapillary vessel densities can also be affected by parapapillary atrophy (PPA).[25] We did not record the presence of PPA or its extent in our subjects. However, the number of eyes with PPA in our study is unlikely to be significant as we had excluded high myopic subjects. Also, our results apply to OCTA imaging performed with RTVue and caution should be exercised while extrapolating the results to OCTA devices which use different platforms and algorithms for imaging blood vessels.

In conclusion, repeatability estimates of OCTA measured peripapillary and macular vessel densities were similar in normal and glaucomatous eyes. Changes in the peripapillary and parafoveal vessel density of <7% fall within the test–retest variability of the OCTA vessel density measurements and are therefore likely to be clinically insignificant. SSI values of the scans had a significant effect on the repeatability of OCTA measurements with the vessel density values increasing in scans with higher SSI values.

Contributors HLR was involved in conception and design, acquisition of data or analysis and interpretation of data; drafting the article or revising it critically for important intellectual content; and final approval of the version to be published. All the authors have contributed substantially to conception and design, acquisition of data and interpretation of data; revising it critically for important intellectual content; and final approval of the version to be published.

Competing interests HLR is a consultant for Pfizer, Santen and Cipla, RNW is a consultant for Aerie Pharmaceuticals, Allergan, Alcon, Eyenovia, Bausch & Lomb, Sensimed and Unity, KM is a consultant for Santen and Sensimed and CABW is a consultant for Alcon, Allergan, Santen and Pfizer. RNW has received financial support in form of instruments or research funding from Optovue, Topcon, Carl Zeiss, Heidelberg Engineering and Genentech, KM has received financial support in form of instruments or research funding from Topcon and Alcon, and CABW has received financial support in form of instruments or research funding from Alcon.

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