Longitudinal reproducibility of spectral domain optical coherence tomography in children with physiologic cupping and stable glaucoma

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PURPOSE To determine whether Spectralis (Heidelberg, Germany) spectral domain optical coherence tomography (SD-OCT) measurements are reproducible over time in children with physiologic cupping and stable glaucoma.

METHODS Subjects were identified from a subset of participants in an earlier retrospective study conducted by our group and included children (<18 years of age) with physiologic cupping and stable primary congenital glaucoma (PCG) having had at least 2 SD-OCTs over a period of more than 1 between April 2010 and September 2015. Thicknesses of average peripapillary retinal nerve fiber layer (pRNFL) and six individual sectors and volumes of three segmented retinal layers and total retina were measured. Spectralis review software was used for segmentation. Intraclass correlation coefficients (ICC) and coefficient of variation (COV) were calculated.

RESULTS A total of 35 eyes of 35 children were included: 15 eyes had physiologic cupping; 20 eyes, PCG. Mean ages at initial SD-OCT were 11.2 ± 3.3 years and 9.7 ± 3.3, respectively; mean intervals between first and last imaging were 2.2 ± 1.1 and 3.0 ± 1.4 years, respectively. ICCs across three visits for both groups for average and sectoral pRNFL thicknesses were 0.887-0.997 and for segmented retinal volumes were 0.806-0.993. ICCs for total retinal volume for physiologic cupping and PCG were 0.993 and 0.954, respectively. COVs for average pRNFL thickness were 0.9% and 1.7%, respectively. For all other measurements, COVs ranged from 0.3% to 5.4%.

CONCLUSIONS Reproducibility of longitudinal SD-OCT measurements for average pRNFL thickness in children with stable glaucoma over about 2 years is comparable to short-term reproducibility (COV) in normal children (1.16%) and normal and glaucoma adults (1.62%-3.4%). (J AAPOS 2019;23:262.e1-6)

Primary congenital glaucoma (PCG) is difficult to manage, let alone assess. Reliable visual field information, which furnishes important information for managing many adult glaucoma patients, is often unavailable in children. Assessment of nerve damage progression via funduscopy or fundus photography also presents challenges, especially in young children and those with nystagmus. Spectralis spectral domain optical coherence tomography (SD-OCT; Heidelberg-Engineering, Heidelberg, Germany) has previously shown good reproducibility for measurements of both peripapillary retinal nerve fiber layer (pRNFL) and macular thicknesses in adults with known or suspected glaucoma as well as in children with healthy eyes and with non-glaucomatous optic neuropathies.[1-5] In adults with known or suspected stable glaucoma, previous studies have shown that SD-OCT demonstrates good reproducibility in both the short term (>3 months) and in the long term (>2 years).[1,3,4]

By contrast, in children, good reproducibility of OCT imaging has been shown only in children with normal eyes and with nonglaucomatous optic neuropathies, and these studies have been limited to a period of up to 4 months between imaging studies,[2,5] save for a single study using time domain OCT.[6] These studies in pediatric glaucoma

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patients have, however, reported good intra-visit reproducibility in both pRNFL and total macular measurements.

As OCT imaging quality and software interpretation have improved over the past few years, interest in analysis of the ganglion cell complex (GCC) for the diagnosis and monitoring of glaucoma in adults has increased as well.[7-10] Studies have shown change in the GCC in glaucoma, whereas the outer retinal layers are unaffected, because the axons, soma, and dendrites of the retinal ganglion cells are present in the nerve fiber layer (NFL), ganglion cell layer (GCL), and inner plexiform layer (IPL), respectively, which comprise the GCC.[8] Examining these layers rather than the macula as a whole may increase the specificity in glaucoma detection and monitoring. Thus far, studies in adults examining the GCC have reported diagnostic capabilities comparable to pRNFL measurements and good repeatability.[7,9,10] In the pediatric population, Silverstein and colleagues[11] showed a significant difference in GCC volume between children with and without glaucoma. The purpose of this study is to determine whether Spectralis SD-OCT measurements of the pRNFL and macula are reproducible over time in children with physiologic cupping and stable glaucoma.

Subjects and Methods

This retrospective cohort study was approved by the Duke University Institutional Review Board and was conducted in compliance with the US Health Insurance Portability and Accountability Act of 1996. Included were pediatric patients with diagnoses of physiologic cupping or primary congenital glaucoma with favorable response to surgical intervention, now considered stable, presenting to a single pediatric glaucoma specialist (SFF). Patients <18 years of age at their initial imaging session underwent clinically indicated SD-OCT imaging of the pRNFL and macula as part of the standard of care between April 2010 and September 2015. Study subjects were identified from a subset of participants in an earlier retrospective study conducted by our group that showed that the segmented inner macular layers were significantly thinner in pediatric eyes with glaucoma than in eyes without glaucoma by Silverstein and colleagues.[11] The present study included only children who had at least one subsequent SD-OCT imaging session to monitor for disease stability, with more than one year between scans. Imaging studies of good quality, such that they can be automatically segmented by in-built Spectralis review software (version 1.9.10.0, Heidelberg-Engineering, Heidelberg, Germany), were also identified as part of this original study.

Physiologic cupping was defined in eyes with intraocular pressure (IOP) of ≤21 mm Hg on repeated testing having clinically determined cup:disk ratio ≥0.5 with symmetric rim (cup:disk asymmetry of <0.1) and no other finding suggestive of glaucoma, as in our previous studies.[12] Clinical diagnoses of glaucoma were made by a pediatric glaucoma specialist (SFF) in eyes with IOP of >21 mm Hg and also had at least one suggestive anatomic finding on physical examination (corneal enlargement, asymmetrical progressive myopic shift accompanied by enlargement of corneal diameter and/or axial length, increased optic nerve cup:disk ratio by ≥0.2, or IOP control necessitating surgical procedures), consistent with published criteria.[13,14] Specifically, stable PCG was defined as diagnosis of glaucoma presenting before age 2 years, now considered stable due to early intervention. Only eyes with clinically controlled, stable glaucoma without the need for additional intervention between initial and subsequent standard-of-care SD-OCT imaging studies were considered eligible for study inclusion. Only the right eye of each participant was included.

Excluded were patients with clinically evident progression as measured by cup:disk ratio, IOP, or need for surgical intervention. Patients with diagnosis of juvenile open-angle glaucoma were excluded, because it is considered an inherently progressive disease. Additionally, original study exclusion criteria included premature birth (<36 weeks' gestational age) and neurologic disorder as well as eyes with aphakia, pseudophakia, and refractive error (spherical equivalent) >5 D, because these ocular features have been reported to confound measurements of macular and RNFL thicknesses obtained by OCT.[15-17] Eyes with retinal abnormalities on OCT imaging were also excluded as part of the original study because they have been shown to be more commonly associated with nonglaucomatous optic atrophy and thinner pRNFL.[18] All excluded cases were reviewed for causes of exclusion, and no patient data was excluded on the basis of OCT progression.

Furthermore, serial fundus photographs of all patients with glaucoma or physiologic cupping were reviewed in a masked fashion by one pediatric glaucoma specialist (SFF) and one adult glaucoma specialist (KWM) looking for any changes in the optic nerve structure or color. All eyes included in this study were deemed stable by fundus photography.

Image and Data Acquisition

All SD-OCT images were acquired using Spectralis SD-OCT by experienced ophthalmic imagers at the Duke Eye Center. Two areas were imaged using SD-OCT: (1) 12° scans of the peripapillary region of the RNFL and (2) macular retinal scans centered on the foveal pit. The first consisted of 768 A-scans along a 3.5 mm diameter peripapillary circle and divided into six sectors totaling 360° (90° temporal and nasal regions; 45° superotemporal, superonasal, inferonasal, and inferotemporal regions).[2] Average thickness for the entire circle is also reported in the center. The macular retinal scans were segmented via native Spectralis review software into NFL, GCL, IPL, inner nuclear layer (INL), outer plexiform layer (OPL), outer nuclear layer (ONL), and retinal pigment epithelium (RPE). See Figure 1. Mean thicknesses of the region, according to the Early Treatment Diabetic Retinopathy Study map (consisting of a central 1 mm diameter circle and two concentric circles with diameters measuring 3 mm and 6 mm, each with superior, inferior, nasal, and temporal quadrants) were recorded for each segmented retinal layer and the total retina.[19] The volumes for the inner three segmented retinal layers (NFL, GCL, and IPL) comprising the GCC and the total retina within the 6 mm diameter outer ring were then used for analysis, as only the inner layers have been shown to be affected by glaucoma.[11]

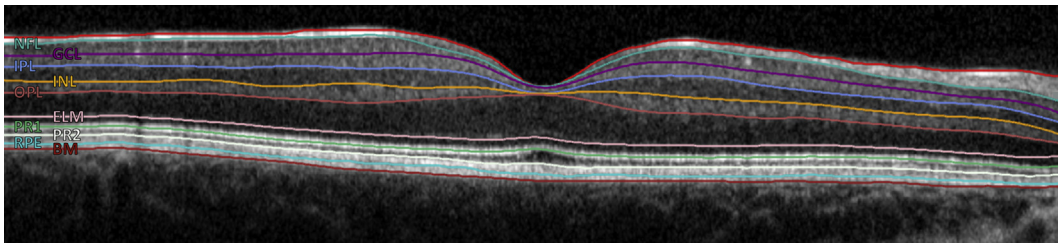

FIG 1. Typical Spectralis optical coherence tomography segmentation map through the center of the fovea. Each colored line represents the lower boundary of the respective segmented layer. From superior to inferior, the layers are nerve fiber layer (*NFL*), ganglion cell layer (*GCL*), inner plexiform layer (*IPL*), inner nuclear layer (*INL*), outer plexiform layer (*OPL*), external limiting membrane (*ELM*), photoreceptor layer 1 (*PL1*), photoreceptor layer 2 (*PL2*), retinal pigment epithelium (*RPE*), and Bruch's membrane (*BM*).

Table 1. Summary of subject demographics and clinical features for all diagnostic groups

Study parameter	Physiologic cupping (n = 15)	PCG (n = 20)	*P* value	95% CI
Demographics, no. (%)				
Asian	2	0	—	—
Black or African American	6	12	—	—
Hispanic or Latino	0	1	—	—
White	6	8	—	—
More than one race	1	0	—	—
Males	6 (40)	11 (55)	—	—
Clinical features				
Age at initial imaging, years				
Mean ± SD	11.2 ± 3.3	9.7 ± 3.3	0.18	−0.75, 3.87
Median (range)	10.8 (6.0-16.6)	8.9 (4.6-16.9)	0.19	—
Time between scans 1 and 2, years				
Mean ± SD	1.5 ± 0.5	1.9 ± 0.9	0.19	−0.88, 0.18
Median (range)	1.5 (1.0-2.6)	2.0 (0.3-3.5)	0.45	—
Time between 1st and last scans, years				
Mean ± SD	2.2 ± 1.1	3.0 ± 1.4	0.08	−1.71, 0.09
Median (range)	2.1 (1.0-4.6)	3.3 (1.0-5.2)	0.11	—
IOP, mm Hg, mean ± SD	16.5 ± 2.5	15.4 ± 3.6	0.3	−1.05, 3.41
Cup:disk ratio ± SD	0.7 ± 0.1	0.4 ± 0.2	0.0005	0.11, 0.37

CI, confidence interval of difference in means; *IOP*, intraocular pressure; *PCG*, primary congenital glaucoma; *SD*, standard deviation.

Statistical Analysis

Excel 2013 (Microsoft, Redmond, WA), SPSS Statistics 23 (IBM, Armonk, NY), and JMP 12 (SAS Institute, Cary, NC) were used to analyze data for OCT measurements and demographics. For each diagnostic group, reproducibility was evaluated using intraclass correlation coefficients (ICC) and coefficients of variation (COV) for each of the above measurements across both 2 and 3 visits, when possible. The ICC is a statistic that describes how strongly units in the same group resemble one another. According to Munro's classification of reliability coefficients, 0.26-0.49 was classified as low correlation; 0.50-0.69, as moderate correlation; 0.70-0.89, as high correlation; and 0.90-1.00, as very high correlation.[20] The COV is a measure of spread that describes the amount of variability relative to the mean.

Test–retest variability was also calculated (1.96 times inter-visit standard deviation) across 3 visits. The *t* test and Wilcoxon rank sum test were performed for analysis of significance of demographics data and one-way analysis of variance (ANOVA) for mean SD-OCT measurements. The Wilcoxon rank-sum test was also performed for analysis of significance of average inter-visit variabilities for thicknesses of average pRNFL and 6 individual pRNFL sectors and total volumes for macular retina and 3 individual segmented retinal layers. For comparisons of the 6 individual RNFL sectors, Bonferroni correction was applied (0.008, or *P*-value divided by 6).

Results

In total, 35 right eyes of 35 children (<18 years of age) with physiologic cupping (n = 15) or PCG (n = 20) were included. Table 1 outlines demographic information and baseline clinical features of subjects. Only cup:disk ratio was significantly different between the two groups (Table 1). The means and inter-visit ICCs across two and three visits for all OCT measurements are shown in Table 2. The inter-visit ICCs across two visits for the average and sectoral RNFL thicknesses were very good for both groups, ranging from 0.815 to 0.994. Inter-visit ICCs for the three segmented retinal layer volumes were also quite good, ranging from 0.778 to 0.990 for both groups. Inter-visit ICCs for total macular retinal volume were excellent. When measurements for those patients who had three SD-OCT imaging studies were included, the majority of ICCs improved.

Table 2. Optical coherence tomography measurements for all diagnostic groups

OCT parameter	Visit 1 Mean ± SD	Visit 2 Mean ± SD	Visit 3 Mean ± SD	ANOVA *P* value	Inter-visit ICC 2-visit	Inter-visit ICC 3-visit
pRNFL thickness, μm						
Physiologic cupping					(n = 15)	(n = 6)
Average	101.1 ± 10.1	102.3 ± 10.3	100.5 ± 5.9	0.9106	0.979	0.953
Superotemporal	136.5 ± 20.9	136.2 ± 20.6	139.5 ± 21.6	0.9444	0.992	0.997
Temporal	73.1 ± 13.2	74.5 ± 14.9	78.7 ± 16.8	0.7295	0.988	0.987
Inferotemporal	145.6 ± 15.3	147.6 ± 15.0	148.8 ± 18.4	0.8945	0.966	0.971
Inferonasal	117.7 ± 31.6	120.9 ± 32.5	109.5 ± 20.8	0.7440	0.986	0.964
Nasal	76.7 ± 11.9	77.9 ± 13.0	72.7 ± 10.3	0.6768	0.960	0.937
Superonasal	108.6 ± 27.3	108.7 ± 27.9	102.2 ± 22.6	0.8647	0.994	0.994
PCG					(n = 20)	(n = 14)
Average	96.6 ± 21.8	94.9 ± 20.2	98.1 ± 15.6	0.8903	0.979	0.994
Superotemporal	122.8 ± 38.1	122.2 ± 38.0	126.9 ± 38.4	0.9325	0.993	0.996
Temporal	72.5 ± 23.0	69.9 ± 21.4	68.2 ± 13.6	0.8253	0.981	0.986
Inferotemporal	137.7 ± 43.2	127.0 ± 42.0	137.0 ± 37.0	0.6708	0.815	0.996
Inferonasal	117.6 ± 41.2	117.3 ± 39.5	112.9 ± 37.2	0.9351	0.965	0.887
Nasal	72.2 ± 19.5	72.4 ± 19.5	74.3 ± 17.8	0.9451	0.982	0.986
Superonasal	104.7 ± 42.3	108.0 ± 38.6	116.1 ± 36.9	0.7077	0.976	0.988
Retinal total volume, mm^3						
Physiologic cupping					(n = 15)	(n = 6)
Total macula	8.59 ± 0.53	8.55 ± 0.45	8.68 ± 0.44	0.8569	0.974	0.993
NFL	0.93 ± 0.13	0.90 ± 0.09	0.92 ± 0.08	0.7263	0.778	0.963
GCL	1.09 ± 0.08	1.10 ± 0.10	1.10 ± 0.11	0.9881	0.942	0.975
IPL	0.91 ± 0.06	0.90 ± 0.06	0.91 ± 0.08	0.8910	0.959	0.987
PCG					(n = 20)	(n = 14)
Total macula	8.43 ± 0.75	8.48 ± 0.60	8.53 ± 0.54	0.8949	0.933	0.954
NFL	0.89 ± 0.20	0.87 ± 0.18	0.90 ± 0.11	0.8766	0.870	0.806
GCL	1.04 ± 0.18	1.04 ± 0.17	1.06 ± 0.15	0.9033	0.975	0.989
IPL	0.87 ± 0.13	0.86 ± 0.12	0.88 ± 0.09	0.9460	0.990	0.988

ANOVA, analysis of variance; *GCL*, ganglion cell layer; *ICC*, intraclass correlation; *IPL*, inner plexiform layer; *NFL*, nerve fiber layer; *OCT*, optical coherence tomography; *PCG*, primary congenital glaucoma; *pRNFL*, peripapillary retinal nerve fiber layer; *SD*, standard deviation.

Table 3. Average inter-visit variability for all diagnostic groups

OCT Parameter	Physiologic cupping Mean ± SD	Physiologic cupping 95% CI	PCG Mean ± SD	PCG 95% CI	*P* value
pRNFL thickness (μm)					
Average	3.99 ± 2.11	2.92, 5.06	5.55 ± 5.94	2.95, 8.15	0.95
Superotemporal	4.11 ± 2.41	2.90, 5.33	7.05 ± 4.58	5.04, 9.05	0.03
Temporal	3.38 ± 3.11	1.81, 4.95	5.65 ± 6.01	3.01, 8.28	0.10
Inferotemporal	6.40 ± 4.80	3.97, 8.83	18.59 ± 44.17	−0.76, 37.95	0.56
Inferonasal	9.53 ± 5.84	6.58, 12.48	16.88 ± 26.97	5.06, 28.70	0.58
Nasal	5.85 ± 4.64	3.50, 8.19	5.27 ± 3.91	3.55, 6.98	0.80
Superonasal	4.25 ± 3.23	2.61, 5.88	9.65 ± 12.45	4.19, 15.11	0.12
Retinal total volume, mm^3					
Total macula	0.16 ± 0.16	0.08, 0.24	0.23 ± 0.34	0.08, 0.38	0.95
NFL	0.07 ± 0.11	0.01, 0.13	0.09 ± 0.13	0.03, 0.15	0.80
GCL	0.04 ± 0.03	0.03, 0.06	0.05 ± 0.05	0.03, 0.07	0.99
IPL	0.03 ± 0.02	0.02, 0.04	0.03 ± 0.02	0.02, 0.04	0.99

CI, confidence interval; *GCL*, ganglion cell layer; *IPL*, inner plexiform layer; *NFL*, nerve fiber layer; *OCT*, optical coherence tomography; *PCG*, primary congenital glaucoma; *pRNFL*, peripapillary retinal nerve fiber layer; *SD*, standard deviation.

Average inter-visit variabilities are shown in Table 3. Although the physiologic cupping group shows lower variability for pRNFL thickness, with the exception of the nasal region, this difference did not reach statistical significance, given Bonferroni correction ($P > 0.008$). Average inter-visit variabilities for total macular retinal and segmented (NFL, GCL, IPL) volumes were also not significantly different ($P > 0.05$). Inter-visit COV for average RNFL thickness was smaller for physiologic cupping (0.89%) compared with PCG (1.7%). For all other measurements, inter-visit COV ranged from 0.3% to 5.3% across the diagnostic groups (Table 4).

Table 4. Inter-visit coefficient of variation for all diagnostic groups

OCT parameter	Inter-visit COV	
	Physiologic cupping (%)	PCG (%)
pRNFL thickness, μm		
Average	0.89	1.71
Superotemporal	1.32	2.06
Temporal	3.87	3.08
Inferotemporal	1.11	4.47
Inferonasal	5.08	2.24
Nasal	3.61	1.58
Superonasal	3.52	5.35
Retinal total voume, mm^3		
Total Macula	0.78	0.62
NFL	1.71	1.71
GCL	0.34	1.30
IPL	0.65	0.81

COV, coefficient of variation; *GCL*, ganglion cell layer; *IPL*, inner plexiform layer; *NFL*, nerve fiber layer; *OCT*, optical coherence tomography; *PCG*, primary congenital glaucoma; *pRNFL*, peripapillary retinal nerve fiber layer.

Discussion

Our study found that longitudinal reproducibility of the pRNFL and inner retinal layers in children with physiologic cupping and with stable glaucoma is comparable to reported short-term reproducibility in children and adults as well as to long-term reproducibility in adults. To our knowledge, the present study is the first to report long-term reproducibility of segmented retinal volumes in pediatric patients.

All SD-OCT measurements demonstrated excellent reproducibility, with ICCs across two visits ranging from 0.778 to 0.994 and three visits ranging from 0.806 to 0.997, corresponding to high to very high correlation. In parallel, we found that reproducibility of average pRNFL in the present study was also comparable to that reported previously for adults in the short- and long-term and for children in the short-term with and without pathology.[1-4,21] We found test–retest variabilities were low and similar between the two diagnostic groups, at 3.99 μm and 5.55 μm for mean pRNFL thickness in physiologic cupping and PCG, respectively. Previous studies reported inter-visit variabilities in adults with and without glaucoma over the short-term to range from 1.85 μm to 4.85 μm,[2,3] whereas in normal children over the short-term, inter-visit variability was 2.31 μm.[2] Additionally, we report values of 0.89% COV for physiologic cupping and 1.7% for PCG versus short-term reproducibility (up to 6 months) reported in previous studies of 1.16% for children with normal eyes by Ghasia and colleagues,[2] and 1.3% to 3.1% COV in children with pathology.[5,21] COV in the present study are also in the same ballpark as those reported for adults with both normal eyes and with glaucoma, which ranged from 1.62% to 2.70% COV in the short term[2,3] and from 3.0% to 3.4% in the long term.[1,4]

For all other measurements, COVs ranged from 0.3% to 5.3% between the diagnostic groups, with most COVs falling below 5%, suggesting they are clinically applicable. Previous studies in adults have reported that in terms of diagnostic ability, GCC measurements were not significantly different from pRNFL thickness.[9,22] For long-term monitoring, we found that volumes of the layers comprising the GCC showed comparable or better reproducibility to pRNFL thickness in terms of COV.

Another important consideration when applying the results of this study to clinical practice is the confirmation of longitudinal variance, which better indicates when retinal thinning found on SD-OCT imaging should be considered clinically significant glaucoma progression. This information may be especially useful in following children with less severe glaucomatous optic nerve damage, where functional decline may be difficult to measure. Our findings suggest pRNFL thickness change exceeding approximately 8 μm should be considered a likely sign of probable clinical change. In growing children, the pRNFL thickness may become reduced secondary to physiologic growth in axial length. Fortunately, based on the mean axial length in normal eyes of children over a 3.3-year span, the corresponding change in pRNFL thickness is considerably less than the variability reported in this study and should not be clinically significant.[6,23] Because we also report very good reproducibility in the segmented macular layer volumes, changes in NFL, GCL, and IPL volumes exceeding 0.1 mm^3, 0.05 mm^3, and 0.03 mm^3, respectively, should also be considered when evaluating glaucoma progression.

The present study was limited by its retrospective nature; lack of axial length data did not allow for quantitation of change between imaging sessions for a given eye. Another limitation was relatively small sample size. However, pediatric glaucoma is rare, and good-quality imaging is limited by nystagmus or poor fixation, media opacity, and other barriers to segmentation, such as concurrent outer retinal pathology.[18] Finally, generalizability is limited by use of physiologic cupping rather than "normal" eyes as the control group. Because this study was retrospective in nature, our access to data was limited to those patients who received repeated SD-OCT imaging as part of standard of care, as was the case for patients with physiologic cupping but not other "normal" eyes. Finally, the finding that reproducibility is worse in eyes with glaucoma compared to the physiologic cupping is due to limitation of the machine's segmentation software, and our findings are similar to those reported in adults.[2,4]

In conclusion, we report that Spectralis SD-OCT shows longitudinal reproducibility in eyes of growing children in both physiologic cupping and stable glaucoma that is comparable to results in adults. Further study involving a larger sample size with control group consisting of children with normal eyes and possibly a subgroup who showed true clinical progression would allow for better assessment of the reproducibility as well as analysis of sensitivity and specificity of a change if detected.

Literature Search

The authors searched PubMed (MEDLINE) for English-language only articles for the period 1946 to 2018 using

combinations of the following search terms: *pediatric glaucoma*, *OCT* OR *optical coherence tomography*, *reproducible* OR *reproducibility*, *intraclass correlation coefficient* OR *ICC*, *ganglion cell complex* OR *GCC*, *retinal nerve fiber layer* OR *RNFL*, and *segmentation*.

References

1. Kim KE, Yoo BW, Jeoung JW, Park KH. Long-term reproducibility of macular ganglion cell analysis in clinically stable glaucoma patients. Invest Ophthalmol Vis Sci 2015;56:4857-64.
2. Ghasia FF, El-Dairi M, Freedman SF, Rajani A, Asrani S. Reproducibility of spectral-domain optical coherence tomography measurements in adult and pediatric glaucoma. J Glaucoma 2015;24:55-63.
3. Vazirani J, Kaushik S, Pandav SS, Gupta P. Reproducibility of retinal nerve fiber layer measurements across the glaucoma spectrum using optical coherence tomography. Indian J Ophthalmol 2015;63:300-305.
4. Roh KH, Jeoung JW, Park KH, Yoo BW, Kim DM. Long-term reproducibility of cirrus HD optical coherence tomography deviation map in clinically stable glaucomatous eyes. Ophthalmology 2013;120:969-77.
5. Rajjoub RD, Trimboli-Heidler C, Packer RJ, Avery RA. Reproducibility of retinal nerve fiber layer thickness measures using eye tracking in children with nonglaucomatous optic neuropathy. Am J Ophthalmol 2015;159:71-77.e1.
6. Prakalapakorn SG, Freedman SF, Lokhnygina Y, et al. Longitudinal reproducibility of optical coherence tomography measurements in children. J AAPOS 2012;16:523-8.
7. Tan O, Chopra V, Lu AT, et al. Detection of macular ganglion cell loss in glaucoma by Fourier-domain optical coherence tomography. Ophthalmology 2009;116:2305-2314.e1-e2.
8. Tan O, Li G, Lu AT, Varma R, Huang D; Advanced Imaging for Glaucoma Study Group. Mapping of macular substructures with optical coherence tomography for glaucoma diagnosis. Ophthalmology 2008;115:949-56.
9. Kim NR, Lee ES, Seong GJ, Kim JH, An HG, Kim CY. Structure-function relationship and diagnostic value of macular ganglion cell complex measurement using Fourier-domain OCT in glaucoma. Invest Ophthalmol Vis Sci 2010;51:4646-51.
10. Seong M, Sung KR, Choi EH, et al. Macular and peripapillary retinal nerve fiber layer measurements by spectral domain optical coherence tomography in normal-tension glaucoma. Invest Ophthalmol Vis Sci 2010;51:1446-52.
11. Silverstein E, Freedman S, Zéhil GP, Jiramongkolchai K, El-Dairi M. The macula in pediatric glaucoma: quantifying the inner and outer layers via optical coherence tomography automatic segmentation. J AAPOS 2016;20:332-6.
12. Ghasia FF, Freedman SF, Rajani A, Holgado S, Asrani S, El-Dairi M. Optical coherence tomography in paediatric glaucoma: time domain versus spectral domain. Br J Ophthalmol 2013;97:837-42.
13. Beck AD, Freedman SF, Lynn MJ, Bothun E, Neely DE, Lambert SR, Infant Aphakia Treatment Study Group. Glaucoma-related adverse events in the Infant Aphakia Treatment Study: 1-year results. Arch Ophthalmol 2012;130:300-305.
14. Weinreb RN, Grajewski AL, Papadopoulos M, Grigg J, Freedman SF. Childhood Glaucoma: The 9th Consensus Report of the World Glaucoma Association. The Netherlands: Kugler Publications; 2013.
15. Barrio-Barrio J, Noval S, Galdós M, et al. Multicenter Spanish study of spectral-domain optical coherence tomography in normal children. Acta Ophthalmol 2013;91:e56-63.
16. Rao A, Sahoo B, Kumar M, Varshney G, Kumar R. Retinal nerve fiber layer thickness in children <18 years by spectral-domain optical coherence tomography. Semin Ophthalmol 2013;28:97-102.
17. Al-Haddad C, Barikian A, Jaroudi M, Massoud V, Tamim H, Noureddin B. Spectral domain optical coherence tomography in children: normative data and biometric correlations. BMC Ophthalmology 2014;14:53.
18. Jiramongkolchai K, Freedman SF, El-Dairi MA. Retinal changes in pediatric glaucoma and nonglaucomatous optic atrophy. Am J Ophthalmol 2016;161:188-195.e1.
19. Grading diabetic retinopathy from stereoscopic color fundus photographs—an extension of the modified Airlie House classification. ETDRS report number 10. Early Treatment Diabetic Retinopathy Study Research Group. Ophthalmology 1991;98:786-806.
20. Munro BH. Statistical Methods for Health Care Research. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2005.
21. Avery RA, Cnaan A, Schuman JS, et al. Reproducibility of circumpapillary retinal nerve fiber layer measurements using handheld optical coherence tomography in sedated children. Am J Ophthalmol 2014;158:780-787.e1.
22. Schulze A, Lamparter J, Pfeiffer N, Berisha F, Schmidtmann I, Hoffmann EM. Diagnostic ability of retinal ganglion cell complex, retinal nerve fiber layer, and optic nerve head measurements by Fourier-domain optical coherence tomography. Graefe's Arch Clin Exp Ophthalmol 2011;249:1039-45.
23. El-Dairi MA, Asrani SG, Enyedi LB, Freedman SF. Optical coherence tomography in the eyes of normal children. Arch Ophthalmol 2009;127:50-58.