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Ophthalmic Technology Assessment

Spectral-Domain OCT: Helping the Clinician Diagnose Glaucoma

A Report by the American Academy of Ophthalmology

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Purpose: To review the current published literature on the use of spectral domain (SD) OCT to help detect changes associated with the diagnosis of glaucoma.

Methods: Searches of the peer-reviewed literature were conducted on June 11, 2014, November 7, 2016, August 8, 2017, and April 19, 2018, in the PubMed and Cochrane Library databases and included only articles published since the last glaucoma imaging Ophthalmic Technology Assessment, which included articles up until February 2006. The abstracts of these 708 articles were examined to exclude reviews and non-English articles. After inclusion and exclusion criteria were applied, 74 articles were selected, and the panel methodologist (K.N.-M.) assigned ratings to them according to the level of evidence. Two articles were rated level I, 57 articles were rated level II, and the 15 level III articles were excluded.

Results: Spectral-domain OCT is capable of detecting damage to the retinal nerve fiber layer (RNFL), macula, and optic nerve in patients with preperimetric and perimetric glaucoma (level I and II evidence). The most commonly studied single parameter was RNFL thickness. Of note, RNFL thickness measurements are not interchangeable between instruments. Various commercially available SD OCT instruments have similar abilities to distinguish patients with known glaucoma from normal subjects. Despite different software protocols, all SD OCT instruments are able to detect the same typical pattern of glaucomatous RNFL loss that affects primarily the inferior, inferior temporal, superior, and superior temporal regions of the optic nerve (level II evidence). Across many SD OCT instruments, macular imaging also can detect a preferential inferior, inferior temporal, and superior temporal thinning in patients with glaucoma compared with controls. Best disc parameters for detecting glaucomatous nerve damage are global rim area, inferior rim area, and vertical cup-to-disc ratio. Studies suggest that newer reference-plane independent optic nerve parameters may have the same or better detection capability when compared with older reference-plane dependent disc parameters (level II evidence).

Conclusions: Structural glaucomatous damage can be detected by SD OCT. Optic nerve, RNFL, and macular parameters can help the clinician distinguish the anatomic changes that are associated with patients with glaucoma when compared with normal subjects. *Ophthalmology* 2018;■:1–11 © 2018 by the American Academy of Ophthalmology

The American Academy of Ophthalmology prepares Ophthalmic Technology Assessments to evaluate new and existing procedures, drugs, and diagnostic and screening tests. The goal of an Ophthalmic Technology Assessment is to systematically review the available research for clinical efficacy and safety. After review by members of the Ophthalmic Technology Assessment Committee, other Academy committees, relevant subspecialty societies, and legal counsel, assessments are submitted to the Academy's Board of Trustees for consideration as official Academy statements. The purpose of this assessment is to evaluate the

current published literature on the ability of spectral-domain (SD) OCT to help the clinician diagnose glaucoma.

Background

OCT allows for noninvasive imaging of ocular structures.¹ It is similar to ultrasound technology but uses light instead of sound. OCT images are based on the varying reflectivity of different ocular structures to light. However, unlike sound, light travels so fast that a fundamentally different way to

process the information is needed. First described in 1991, the typical time-domain OCT (TD OCT) system includes a superluminescent diode light source.² The superluminescent diode light travels via a beam splitter to the eye and a reference mirror. When the light comes back from the eye and the reference mirror, the interference pattern is processed by a photodetector, and the data are then used to create a 2-dimensional (2D) image. The limitations of TD OCT technology include low resolution (i.e., $\sim 10\ \mu\text{m}$) and slow acquisition speeds (i.e., ~ 1.3 seconds to produce a 2D image).

To achieve simultaneous ultrahigh resolutions and ultrahigh acquisition speeds, a fundamentally new technology was developed in 2003, called “video-rate SD OCT” or “Fourier domain OCT.”^{3,4} The term “video-rate” is synonymous with 3-dimensional (3D) imaging, because earlier attempts at SD OCT were limited to 2D imaging. The fundamental difference between TD OCT and SD OCT is in how the light is processed as it returns from the eye and the reference mirror. Instead of being processed by a photodetector as with TD OCT, SD OCT processes the reflected light from the eye and reference mirror by a spectrometer, which is more efficient than a photodetector. The information is then analyzed using Fourier transform to create an image, thus the term “Fourier domain OCT.”³ The higher sensitivity of SD OCT technology allows for weaker signal detection and faster data acquisition.¹ Where an A-line is a 1-dimensional unit of OCT data, SD OCT allows for scan speeds of 25 000 to 50 000 A-lines per second compared with TD OCT with scan speeds of 400 A-lines per second. Commercially available SD OCT machines also have improved resolutions of 5 to 7 μm in tissue compared with the 10 μm resolution of TD OCT. Unlike early 2D SD OCT images, video-rate SD OCT heralded the transition from 2D to 3D imaging.^{3,4} When 3D volume scan protocols are described for each machine, the first number usually refers to the number of A-scans or A-lines that compose a B-scan, and the second number usually refers to the number of B-scans or frames that compose the volume scan. For example, a Macular Cube 512 $\times$ 128 protocol uses 512 A-lines to compose a single B-scan, and there are 128 B-scans that make up this volume cube scan.

In the clinical evaluation of patients with glaucoma, SD OCT is used primarily to image 3 structures: (1) the optic nerve, (2) the peripapillary retinal nerve fiber layer (RNFL), and (3) the macula. The optic nerve undergoes characteristic changes with glaucoma that consist of classic features, such as cupping and neuroretinal rim thinning that can be imaged with SD OCT. Of these 3 regions, the RNFL thickness measurement is the most commonly used OCT parameter and is usually measured along a peripapillary circular scan. Last, the retina in the macular region also demonstrates thinning with glaucoma. Because glaucoma damages the retinal ganglion cells (RGCs), macular SD OCT measurements may reflect RGC loss, because the macular region contains approximately 50% of the RGCs and is where the ganglion cell layer (GCL) is more than 1 cell layer thick.⁵ This Ophthalmic Technology Assessment evaluates devices from the 4 most commonly used manufacturers based on the articles included from the literature search.

Question for Assessment

The purpose of this assessment is to address the following question: Is SD OCT able to help the clinician detect glaucomatous damage to the RNFL, macular, and optic nerve; and is it, therefore, able to help detect changes associated with the diagnosis of glaucoma?

Description of Evidence

Searches of the peer-reviewed literature were conducted on June 11, 2014, November 7, 2016, August 8, 2017, and April 19, 2018, in the PubMed and Cochrane Library databases and included only articles published since the last glaucoma imaging Ophthalmic Technology Assessment, which included articles up until February 2006.⁶ The abstracts of these 708 articles were examined to exclude reviews and non-English articles. The remaining articles were reviewed in full text by the Glaucoma Panel to select only those that met the following inclusion criteria: (1) SD OCT was the technology focus of the study; (2) the study reported on imaging of the RNFL, optic nerve head, or macula; (3) the study represented original research; (4) the study reported on the ability of SD OCT to help detect changes associated with the diagnosis of glaucoma; (5) the study subjects were adults; and (6) the study had at least 125 patients.

Application of these criteria yielded 74 articles, and the panel methodologist (K.N.-M.) assigned ratings to them according to the level of evidence. A level I rating was assigned to well-designed and well-conducted randomized clinical trials; a level II rating was assigned to well-designed case-control and cohort studies and poor-quality randomized studies; and a level III rating was assigned to case series, case reports, and poor-quality cohort and case-control studies. Two articles were rated level I, and 57 articles were rated level II. The 15 level III articles were excluded.

Published Results

Overview of SD OCT Machines and Associated Glaucoma Software Protocols

The 4 manufacturers' instruments covered in this assessment include the following: (1) Cirrus High-Definition (HD) OCT (Carl Zeiss Meditec, Inc., Dublin, CA), (2) RTVue-100 (Optovue Inc., Fremont, CA), (3) Spectralis SD OCT (Heidelberg Engineering Inc., Heidelberg, Germany), and (4) 3D OCT-1000 and 3D OCT-2000 (Topcon Corporation, Tokyo, Japan). Table 1 provides an overview of the SD OCT glaucoma software protocols for these instruments.

The Cirrus HD-OCT has a scanning rate of 27 000 A-lines per second with 5- μm axial resolution.⁷⁻¹² Most Cirrus studies required a signal strength of at least 6¹³⁻²² or 7^{9,11,20,23,24} of a maximum signal strength of 10. The Optic Disc cube 200 $\times$ 200 protocol scans a 6 $\times$ 6-mm area and allows for RNFL thickness and optic nerve parameters (Table 1).^{8,9,11-19,21-23,25-30} Using a reference plane of 200 μm above the retinal pigment epithelium (RPE),³¹ disc parameters can be calculated and can include disc area,

Table 1. Overview of Spectral-Domain OCT Glaucoma Software Protocols*

Instrument	Retinal Nerve Fiber Layer Thickness	Optic Nerve Parameters	Macular Parameters
Cirrus HD-OCT (Carl Zeiss Meditec, Inc., Dublin, CA)	RNFL thickness generated along 256 points along a 3.46-mm diameter circle from the Optic Disc Cube protocol	Optic nerve parameters calculated from a reference plane 200 μ m above the RPE from Optic Disc Cube protocol	From the Macular Cube protocol, GCA calculates GCIPL = GCL+IPL and GCC = RNFL+GCL+IPL
RTVue-100 (Optovue Inc., Fremont, CA)	RNFL thickness generated along a 3.45-mm diameter circle from the optic nerve head scan protocol	Optic nerve parameters calculated from a reference plane 150 μ m above the RPE from optic nerve head scan protocol	GCC = RNFL + GCL + IPL from macular scan protocol
Spectralis (Heidelberg Engineering Inc., Heidelberg, Germany)	RNFL thickness along a 12° arc (i.e., 3.45-mm circle scan for typical eye length)	Reference-plane independent BMO-MRW neuroretinal rim measurement	PPAA 30°×25° volume scan of retinal thickness
3D OCT-1000 and 3D OCT-2000 (Topcon Corporation, Tokyo, Japan)	RNFL thickness along a 3.4-mm or 3.46-mm diameter circle from the disc scan protocol	Optic nerve parameters calculated from a reference plane 120 μ m above the RPE from 3D disc analysis	NFL GCL + IPL NFL + GCL + IPL

3D = three dimensional; BMO-MRW = Bruch's membrane opening-minimum rim width; GCA = ganglion cell analysis; GCC = ganglion cell complex; GCIPL = ganglion cell inner plexiform layer; GCL = ganglion cell layer; HD = high definition; IPL = inner plexiform layer; NFL = macular RNFL (mRNFL); PPAA = posterior pole asymmetry analysis; RNFL = retinal nerve fiber layer; RPE = retinal pigment epithelium.

*The Table is a select but not comprehensive list of software.

rim area, average cup-to-disc ratio, vertical cup-to-disc ratio, and cup volume.^{13,17,18} From the Macular Cube 200×200 protocol^{11,13,17,26,29,30} and 512×128 protocol,^{14,18,23,28} ganglion cell analysis (GCA) can be performed (Table 1). The GCA algorithm determines macular parameters in an elliptical annulus delimited by an inner oval border (vertical diameter of 1 mm and horizontal diameter of 1.2 mm) and outer oval border (vertical diameter of 4 mm and outer horizontal diameter of 4.8 mm).^{10,13,17,26} Calculated ganglion cell inner plexiform layer (GCIPL) parameters include average GCIPL thickness, minimum GCIPL thickness, and GCIPL thickness in 6 sectoral GCIPL regions (i.e., superior, inferior, superonasal, inferonasal, superotemporal, inferotemporal).^{13,17,18,26} The GCA algorithm can also calculate the ganglion cell complex (GCC) or a summation that includes the combined thickness of 3 layers: the RNFL, GCL, and inner plexiform layer (IPL).^{7,11} These 3 layers, respectively, comprise the ganglion cell axons, cell bodies, and dendrites.

The RTVue device has a speed of 26 000 A-lines per second^{7,32-36} with 5- μ m axial resolution.³³⁻³⁶ Most articles required a minimum signal strength of 30^{7,32,33,37-45} or 45^{12,38,46} of a maximum signal strength of 100 for inclusion in the study. The optic nerve head scan protocol (Table 1) consists of a combination of 12 radial scans (3.4 mm in length, 452 A-scans each) and 6 concentric circle scans ranging from 2.5 to 4.0 mm in diameter^{37,39-42,44} or 13 concentric circle scans ranging from 1.3 to 4.9 mm in diameter.³⁴ From the optic nerve head scan protocol, RNFL thickness values are generated along a 3.45-mm diameter circle (at 775^{47,48} or 2325^{33,37} points along the circle). Using a reference plane 150 μ m above the RPE,^{34,37,40,42,44} disc parameters that can be generated include disc area, cup area, rim area, rim volume, nerve head volume, cup volume, cup disc area ratio, horizontal cup-disc ratio, and vertical

cup-disc ratio.^{37,38,42} The GCC macular protocol (Table 1) scans a 7×7-mm square area, consisting of a single horizontal 7-mm line scan (467 A-lines) followed by 15 vertical 7-mm line scans (400 A-lines) spaced at 0.5-mm intervals, centered 0.75 mm^{34,35} to 1 mm^{32,36,37,48,49} temporal to the fovea. From this macular scan protocol, the RTVue system calculates GCC thickness within a 6-mm diameter circular macular area.⁷ Newer pattern-based parameters include GCC global and focal-loss volume.^{35,36,38,49}

The Spectralis SD OCT instrument has a scan rate of 40 000 A-lines per second.^{33,50-52} with 7- μ m axial resolution.⁵² Most studies required a signal strength of at least 15^{33,51-54} of a maximum signal strength of 40. A dual-beam imaging system with simultaneous confocal scanning laser ophthalmoscopy allows for real-time eye tracking that corrects saccadic eye motion and improves reproducibility.⁵¹ In the Spectralis RNFL circle scan protocol (Table 1), RNFL thickness measurements are obtained along a peripapillary scan circle spanning 12° of arc, and the final diameter is dependent on the axial length.^{43,50} Some studies have suggested that this usually translates to a 3.45-mm circle manually centered on the disc in an eye with typical axial length.^{33,51,55} Unlike in the Cirrus and RTVue systems, these RNFL measurements are not interpolated from a volumetric scan protocol. Rather, the measurements are obtained directly from manual centration of a circular RNFL scan. In 2016, the U.S. Food and Drug Administration approved the Spectralis Glaucoma Module Premium Edition (GMPE) software. In this GMPE scan protocol, 3 circumpapillary scans are obtained with diameters of 3.5 mm, 4.1 mm, and 4.6 to 4.7 mm (i.e., 12°/14°/16° for the emmetropic eye with axial length of 23 mm), with scan circles centered over Bruch's membrane opening (BMO).^{50,56} The GMPE scan protocol uses 24 radial scans to calculate a neuroretinal rim parameter, BMO-minimum

rim width (BMO-MRW, Table 1), a 360° region bordered internally by the cup surface and externally by the BMO and that represents the minimum distance between these 2 boundaries. First, the foveal-BMO axis is determined, and then both quadrant and sectoral measurements are calculated relative to this axis.⁵⁰ A similar but earlier neuroretinal rim parameter (i.e., the minimum distance band [MDB]) is derived from a high-density optic nerve 512×193 volume scan protocol. This MDB is a 360° band bound internally by the cup surface and externally by the RPE/BMO complex.^{3,53,54} Unlike in the Cirrus and RTVue systems, Spectralis neuroretinal rim parameters are not reference-plane dependent (i.e., BMO-MRW and MDB).⁵⁷ The Spectralis posterior pole asymmetry analysis (PPAA) software (Table 1)⁵⁸ calculates total retinal thickness for each cell of an 8×8 grid that is oriented along the foveal-BMO axis. Asymmetry between eyes and between hemispheres of each eye is then determined using darker cells to represent regions of greater asymmetry.⁵⁹

The 3D OCT-1000 has a scan speed of 18 000 A-lines per second.⁶⁰ The newer version 3D OCT-2000 has a scan speed of 50 000 A-lines per second^{7,32,61} with a 5-μm axial resolution.⁶¹ Most studies required a signal strength of 60 or higher of a maximum signal strength of 160.^{7,32,62} The disc scan protocol (Table 1) consists of a 6×6-mm (512×128) volume scan^{3,6} or a 7×7-mm volume scan.^{7,62} From this raster scan, the software calculates RNFL thickness along a diameter circle of 3.4 or 3.46 mm.^{7,32,61,62} A peripapillary RNFL thickness map is generated from the disc scan protocol. The macular scan protocol (Table 1) consists of a 7×7-mm (512×128) volume scan that is obtained to measure a 6×6-mm area via 3D OCT-2000 software.^{7,32,61} Macular parameters may include macular RNFL (mRNFL), GCL/IPL, and the GCC (sum of the RNFL, GCL, and IPL).

Overview Description of SD OCT Diagnostic Studies

In the 59 SD OCT glaucoma studies that used the 4 manufacturers' instruments, the most commonly studied parameter for glaucoma diagnosis was RNFL thickness (56 studies), followed by specific parameters in the macular region (36 studies) and the optic nerve (23 studies). This Ophthalmic Technology Assessment did not evaluate SD OCT studies of the lamina cribosa or assessments of relevant blood flow. Although RNFL thickness is the most commonly used diagnostic parameter, it is important to realize that RNFL thickness values are not interchangeable between different machines. For example, in a study of normal eyes by Seibold et al,⁶³ the average (± standard deviation) RNFL thickness was measured at 110.1±12.8 μm with Stratus OCT, 98.7±10.9 μm with Cirrus HD-OCT, 106.6±12.8 μm with Spectralis SD OCT, and 112.8±13.2 μm with RTVue.⁶³ Because values between machines are not interchangeable, the capability of the 4 most commonly used manufacturers' instruments to aid in diagnosis are discussed separately.

Most SD OCT studies quantify the ability to help detect changes associated with the diagnosis of glaucoma as an area

under the receiver operating characteristic curve (AUROC) value. The receiver operating characteristic curve is created by plotting the true positive rate (i.e., sensitivity) against the false-positive rate (1 – specificity) at various threshold settings. The accuracy of a test can then be quantified by AUROC values between 0 and 1, where 1 represents a perfect test and 0.5 represents an uninformative test. An excellent test generally has AUROC values between 0.90 and 1, a good test between 0.80 and 0.90, a fair test between 0.70 and 0.80, and a poor test between 0.60 and 0.70.

Cirrus Diagnostic Studies. Twenty-six articles evaluated the RNFL thickness parameter that was measured using the Cirrus HD-OCT instrument,^{7-19,21-30,32,33,47} and the study by Larrosa et al¹³ was the only one with a level I rating.¹ Global or average RNFL thickness can help the clinician distinguish normal subjects from patients with glaucoma, and AUROC values ranged from 0.677 to 0.969.^{7-11,13-17,19,22,23,26,27,30,32,47} Of the specific RNFL quadrants or clock-hour sectors, the best diagnostic data provided were associated with the inferior and superior regions with the AUROC values of 0.686 to 0.963 and 0.601 to 0.944, respectively.^{7,10,13-19,23,24,26,27,30,32} For average RNFL thickness, higher AUROC values were associated with worse disease severity:⁸ 0.752 to 0.860 for preperimetric glaucoma,^{10,19} 0.813 to 0.943 for early to moderate glaucoma,^{14,19,22,27,29,30,47} and 0.936 to 0.981 for advanced glaucoma.^{13,22,29,47}

In studies that compared Cirrus SD OCT with Stratus TD OCT (Carl Zeiss Meditec, Inc., Dublin, CA), RNFL thickness measurements consistently showed that the Cirrus SD OCT exhibited the same^{9,12,19,54} or better^{15,24,25,27} AUROC curve values than Stratus TD OCT. In addition, the Cirrus SD OCT had other demonstrated advantages over the Stratus TD OCT machine, including better axial resolution (i.e., 5 vs. 10 μm),³³ faster acquisition rates,³³ better scan quality (i.e., 1.9% of Cirrus scans vs. 23% of Stratus scans with poor signal strength in 216 patients),¹⁶ less measurement variability (i.e., coefficient of variation <6.4% for Cirrus vs. <12.8% for Stratus OCT),⁹ and the availability of RNFL thickness deviation maps with their associated spatial information (i.e., RNFL defect angular width and area).^{12,19,24} Some authors suggest that RNFL deviation maps are better able to help detect changes associated with the diagnosis of glaucoma and better characterize RNFL defects compared with conventional circumpapillary RNFL thickness measurements.^{12,19,24} Specifically, authors have suggested that RNFL defects could be characterized by using a 5-point grading scale for size, shape, depth, location, and disc margin distance. A defect that exhibits all 5 criteria, or a map score of 5, would have both high sensitivity (95%) and specificity (95.1%).²⁴ Notably, Cirrus and Stratus color codes do not agree and are not interchangeable.²¹

Macular parameters were evaluated in 14 Cirrus studies.^{7,10,11,13,14,17,18,20,23,26,28-30,32} The parameters with the best diagnostic data included minimum GCIPL thickness (0.702–0.980),^{10,13,14,17,18,23,26,29} inferotemporal GCIPL thickness (0.752–0.970),^{10,11,13,14,17,18,23} average GCIPL thickness (0.703–0.960),^{10,11,13,14,17,18,20,23,26,32} inferior

GCIPL thickness (0.702–0.950),^{7,10,11,13,14,17,18,20,23,26,32} and superotemporal GCIPL thickness (0.652–0.9320).^{10,11,13,14,17,18,23} There are fewer articles on GCC than GCIPL, yet studies have demonstrated that the better GCC parameters were average GCC (0.901–0.945),^{7,11,32} inferotemporal GCC (0.922),¹¹ superotemporal GCC (0.910),¹¹ and inferior GCC (0.904–0.908).^{7,11} One study of 132 healthy eyes and 131 early glaucoma eyes cautioned that GCA may be associated with both false negatives (19.8%, 12.2%, and 20.6% for GCA sector, deviation, and thickness maps, respectively) and false positives (21.2%, 28.0%, and 15.2% for GCA sector, deviation, and thickness maps, respectively).²⁸

Intra-eye macular asymmetry analyses have also been used for detecting glaucoma.^{20,23} In 1 study,²³ customized software was used to test a novel GCIPL hemifield test to help detect glaucomatous damage in 195 myopic eyes of 195 subjects with myopia worse than –6.50 spherical equivalent. This new GCIPL hemifield parameter tested for asymmetry across the temporal raphe and provided significantly better diagnostic data than best RNFL and GCIPL parameters (i.e., GCIPL hemifield 0.938 vs. average RNFL 0.784 and minimum GCIPL 0.818, $P < 0.001$ for all measurements). This study suggested that intra-eye GCIPL asymmetry may help the clinician diagnose glaucoma in highly myopic eyes.²³ In another study,²⁰ GCIPL thickness differences across the superior and inferior hemispheres were calculated, as well as a GCIPL asymmetry index (i.e., absolute log₁₀ of inferior hemisphere thickness over superior hemisphere thickness). The authors suggested that the GCIPL thickness difference and the asymmetry index were more helpful for detecting changes associated with the diagnosis of glaucoma than other GCIPL parameters only in the early stages of glaucoma ($P < 0.05$).

Optic disc parameters were analyzed in 8 Cirrus studies.^{10,13,14,17,18,22,29,30} Of the studies that compared multiple Cirrus disc parameters for detecting glaucomatous damage (i.e., rim area, disc area, average cup-to-disc ratio, vertical cup-to-disc ratio, and cup volume), the best Cirrus disc parameters included rim area and vertical cup-to-disc ratio, and both parameters were consistently better than disc area and cup volume.^{13,14,17,22,29,30} The AUROC values for best Cirrus disc parameters were 0.655 to 0.960 for rim area^{10,13,14,17,18,22,29,30} and 0.400 to 0.962 for vertical cup-to-disc ratio.^{10,13,14,17,18,30} The AUROC curve values were highest with advanced glaucomatous disease (rim area: 0.937; vertical cup-to-disc ratio: 0.911–0.941).^{13,22} Lower AUROC values were noted for preperimetric, early, and moderate glaucoma patients (rim area: 0.655–0.910; vertical cup-to-disc ratio: 0.400–0.962).^{13,14,17,22,29,30}

Multiple parameters (i.e., RNFL thickness, disc parameters, or macular parameters) were compared in 13 Cirrus studies.^{7,10,11,13,14,17,18,22,23,26,29,30,32} A majority of these studies suggest that there are no significant differences in diagnostic data generated between best macular, RNFL, or disc parameters.^{10,11,13,18,26,29,30} Average RNFL thickness and GCC thickness also appear to provide similar diagnostic information.^{7,32} Only 2 studies suggest that inferotemporal GCIPL and average RNFL thickness parameters may be

better than other parameters for myopic eyes and early glaucoma eyes, respectively.^{17,22} For example, when comparing inferotemporal GCIPL with RNFL thickness and disc parameters, inferotemporal GCIPL was significantly better than best RNFL parameters for helping to discriminate myopic glaucoma from myopia alone (inferotemporal GCIPL 0.752 vs. inferior RNFL 0.686; $P = 0.036$).¹⁷ Another study suggested that average RNFL thickness was significantly better than optic nerve head parameters (i.e., AUROC 0.957 RNFL thickness vs. 0.871 rim area; $P < 0.001$); however, this finding was true only in the early glaucoma subgroup yet not in the moderate to advanced glaucoma subgroup.²²

RTVue Diagnostic Studies. Nineteen articles evaluated the RNFL thickness parameter that was measured using the RTVue instrument.^{7,32,34,36,42,44,46–49,64–66} The best RNFL thickness parameters for helping the clinician to diagnose perimetric glaucoma were as follows, in descending order: (1) average RNFL thickness (AUROC 0.828–0.977),^{7,32,33,37,41,47,48,65,67} (2) inferior RNFL thickness (0.823–0.982),^{7,32,33,37,65,67} and (3) superior RNFL thickness (0.805–0.944).^{7,32,33,37,38,65,67} For average RNFL thickness values, higher AUROC values were associated with worse disease severity:⁴² 0.720 to 0.820 for preperimetric glaucoma,^{44,46} 0.782 to 0.924 for early and moderate glaucoma,^{36,40,47,48} and 0.936 to 0.977 for advanced glaucoma.^{36,47,48} Improved diagnostic data from RNFL thickness measurements were associated with improved RTVue signal strength index (SSI) values.³⁹ For example, AUROC values for average RNFL thickness for mild glaucoma and advanced glaucoma improved, respectively, from 0.678 and 0.890 with an SSI of 30 to 0.962 and 0.994 with an SSI of 70.³⁹

Macular parameters were evaluated in 19 RTVue studies.^{7,32,34–40,42,44–46,48,49,64–67} The best macular parameters to detect perimetric glaucoma were average GCC thickness and inferior GCC thickness, with AUROC values ranging from 0.642 to 0.957^{7,32,35,37,38,67} for average GCC and 0.743 to 0.949^{7,32,37,67} for inferior GCC thickness. Better AUROC values for average GCC thickness were generally associated with more severe disease: 0.720 to 0.780 for preperimetric glaucoma,⁴⁴ 0.642 to 0.895 for early to moderate glaucoma,^{36,40} and 0.916 for advanced glaucoma.³⁶ Better ability to help detect changes associated with the diagnosis of glaucoma for average GCC thickness measurements were also associated with better RTVue signal strength values.³⁹ For example, AUROC values for average GCC thickness for mild glaucoma and advanced glaucoma improved, respectively, from 0.726 and 0.873 with an SSI of 30 to 0.886 and 0.959 with an SSI of 70.³⁹

For imaging in myopes, 2 RTVue studies^{34,49} suggest that macular parameters may provide better diagnostic value than RNFL thickness parameters for patients with longer axial lengths. In 1 study,⁴⁹ the ability of RNFL thickness to help detect changes associated with the diagnosis of glaucoma decreased with increasing axial length. In contrast, the ability of macular parameters (i.e., macular GCC thickness and GCC focal loss volume) to help detect changes associated with the diagnosis of glaucoma was not affected by increasing axial length.⁴⁹ A second study³⁴

also suggested that the ability of GCC thickness, unlike RNFL thickness, to help detect changes associated with the diagnosis of glaucoma did not significantly decrease with myopia of 5.0 diopters or worse (i.e., RNFL thickness: AUROC 0.939 vs. 0.827, $P = 0.028$; GCC thickness: AUROC 0.933 vs. 0.935; $P = 0.959$).

In 2009, Tan et al³⁵ studied a novel GCC pattern-based parameter, GCC global loss volume, which was calculated using the authors' customized software. This GCC global loss volume was reported to have a significantly higher AUROC value of 0.920 compared with average GCC thickness at 0.900 ($P = 0.01$).³⁵ Newer pattern-based parameters of GCC global and focal loss volume are now available in the RTVue-100 software package, where global loss volume is the sum of negative fractional deviations over the entire scan area and where focal loss volume is the integral of deviation in areas of significant focal GCC loss divided by the map area.^{38,49} Three subsequent studies^{36,46,67} have since noted that AUROC values for these pattern-based parameters are higher than AUROC GCC thickness values, but these differences may not be statistically significant.

Kita et al⁴⁸ proposed a new parameter called the "G/T ratio" (i.e., GCC thickness to total retinal thickness ratio) and suggested that it may be more helpful for detecting changes associated with the diagnosis of glaucoma than both RNFL thickness and total retinal thickness (AUROC 0.982 G/T ratio vs. 0.942 RNFL thickness and 0.841 total retinal thickness, $P < 0.05$). In this study, the AUROC of GCC thickness was 0.968. However, a subsequent study by Holló et al⁶⁵ suggested that, in contrast to Japanese eyes, in white European eyes G/T ratio does not improve detection ability (AUROC 0.887 G/T ratio vs. 0.925 average RNFL thickness and 0.914 average GCC thickness).

Optic disc parameters were analyzed in 8 RTVue studies.^{37-40,42,44,64,67} Of the studies that compared multiple RTVue disc parameters for detecting preperimetric and perimetric glaucoma (i.e., cup area, disc area, rim area, rim volume, nerve head volume, cup volume, cup disc area ratio, horizontal cup-to-disc ratio, and vertical cup-to-disc ratio), the most useful RTVue disc parameters were inferior rim area and vertical cup-to-disc ratio. Best AUROC curve values for RTVue disc parameters were 0.720 to 0.960 for inferior rim area^{37,44} and 0.621 to 0.970 for vertical cup-to-disc ratio.^{37,38,40,44,67}

The diagnostic ability of rim area increased as disease severity increased.⁴² Improved ability to help detect changes associated with the diagnosis of glaucoma for rim area measurements were also associated with improved RTVue signal strength.³⁹ For example, AUROC values for rim area for mild glaucoma and advanced glaucoma improved, respectively, from 0.651 and 0.747 with an SSI of 30 to 0.873 and 0.922 with an SSI of 70.³⁹

Multiple parameters (i.e., RNFL thickness parameter, disc parameters, or macular parameters) were evaluated in 17 RTVue studies.^{7,32,34,36-40,42,44,46,48,49,64-67} However, only some of these studies directly compared the ability of these 3 parameters to help detect changes associated with the diagnosis of glaucoma.^{7,32,34,36,38,42,46,48,49,64,67} Four of

these studies suggested that RNFL thickness and GCC thickness had similar abilities to help detect changes associated with the diagnosis of glaucoma.^{7,32,36,48} Two other studies further suggested that RNFL, macular, and disc parameters had similar detection abilities.^{42,67} One study noted that combining parameters improved the ability of the RTVue machine to help detect changes associated with the diagnosis of glaucoma.³⁸ Of the studies that claimed that 1 of the 3 parameters may be significantly different, 2 studies suggested that disc parameters were worse than RNFL and macular parameters.^{37,64} The other 2 studies suggested that, for imaging in myopes, macular parameters are more helpful than RNFL thickness parameters.^{34,49}

Spectralis Diagnostic Studies. Twelve articles evaluated the RNFL thickness parameter that was measured using the Spectralis machine.^{5,33,43,50-56,68,69} The study by Schweitzer et al⁵⁵ was the only level I study. Best RNFL thickness parameters that were most useful for helping the clinician detect changes associated with the diagnosis of perimetric glaucoma were global RNFL thickness (AUROC 0.880–0.978),^{33,50-56} inferior RNFL thickness (0.850–0.958),^{33,53,54} superior RNFL thickness (0.880–0.936),^{33,52-54} temporal-inferior RNFL thickness (0.855–0.959),⁵⁰⁻⁵⁶ and temporal-superior RNFL thickness (0.803–0.951).⁵⁰⁻⁵⁶ For average RNFL thickness values, lower AUROC values were associated with early glaucoma: AUROC 0.839 for preperimetric glaucoma⁵⁶ and 0.895 to 0.928 for early glaucoma.^{52,53}

Two studies evaluated whether certain RNFL scan protocols were better than others for detecting glaucoma.^{43,49} In 1 study, when the 3 RNFL scan circle sizes were compared ($12^\circ/14^\circ/16^\circ$), the smallest circle diameter provided the best diagnostic data.⁵⁶ In the other study, when RNFL thickness measurements manually centered on the disc (RNFL_{Di}) were compared with RNFL thickness values automatically centered at the BMO (RNFL_{BMO}), the glaucoma diagnostic abilities were generally comparable.⁵⁰ However, RNFL_{BMO} was superior to RNFL_{Di} in eyes with a larger width ($>250\ \mu\text{m}$) of externally oblique border tissue, such as seen in tilted optic discs. The discrepancy between RNFL_{BMO} measurements and RNFL_{Di} measurements were usually due to the automated BMO disc margin being more temporal compared with the manually determined disc margin. Notably, of the original 261 subjects in the study, 77 subjects were excluded because of the failure of the OCT algorithm to detect BMO.⁵⁰

Optic disc parameters were analyzed in 6 Spectralis studies.^{43,53,54,56,68,69} Neither of the optic nerve parameters (i.e., BMO-MRW and MDB thickness) rely on a reference plane to determine the average thickness of a 3D band of neuroretinal rim tissue. Three variations of these reference-plane independent parameters that quantify 3D neuroretinal rim tissue have been reported (minimum circumpapillary band area),⁵⁷ validated (MDB thickness and area),³ and then commercialized (BMO-MRW and area).^{43,56,68,69}

Three studies evaluated the BMO-MRW neuroretinal rim parameter, which had good ability to help detect the changes associated with glaucoma diagnosis (0.929–0.960).^{43,56,68} In an initial study, BMO-MRW demonstrated better AUROC values compared with RNFL thickness values

(BMO-MRW 0.960 with a 95% confidence interval of 0.920–1.00 vs. RNFL thickness 0.920 with a confidence interval of 0.880–0.960); however, it is unclear if this difference was statistically significant because no *P* values were reported in the article.⁴³ The ability of the BMO-MRW sectoral analysis to help detect the changes associated with glaucoma was equivalent to total BMO-MRW analysis.⁶⁸ Two subsequent studies observed no statistically significant differences between RNFL thickness and BMO-MRW for detecting changes associated with preperimetric and perimetric glaucoma ($P = 0.727$; $P > 0.5$).^{56,69}

Two studies evaluated the neuroretinal rim parameter MDB thickness.^{53,54} The MDB parameter is similar to the BMO-MRW parameter, but it uses the RPE/BMO complex as the OCT-based disc border instead of the BMO alone. The RPE/BMO complex is used because the RPE and BMO are often indistinguishable on OCT scans⁷⁰ and because Bruch's membrane is only 1 to 5 μm thick, which is smaller than the resolution of most commercially available SD OCT machines. For MDB thickness measurements, a higher-density 193 raster scan protocol is used rather than the BMO-MRW 24-line radial scan protocol, and this affords the opportunity for simultaneous high-density evaluation of the peripapillary region for retinal thickness, retinal volume, and RNFL volume.^{59,71,72} Both studies suggested that MDB thickness was better than RNFL thickness for helping to detect changes associated with the diagnosis of glaucoma;^{53,54} MDB thickness is significantly better than RNFL thickness in the nasal ($P = 0.004$ –0.023), temporal (0.026), inferonasal ($P = 0.011$ –0.49), and superonasal sectors (0.012–0.023), whereas in other regions the thicknesses were similar.^{53,54}

Two Spectralis disc studies suggest that reference-plane independent parameters (i.e., BMO-MRW and MDB thickness) may be more helpful in detecting changes associated with the diagnosis of glaucoma than some reference-plane dependent parameters (i.e., BMO-horizontal rim width or BMO-HRW, rim volume, rim area, and rim thickness).^{43,54}

Studies that evaluated multiple parameters (i.e., RNFL thickness and disc parameters) suggest that RNFL thickness is statistically similar to optic nerve parameters (i.e., BMO-MRW, MDB thickness)^{53,54,56,69} or worse than optic nerve parameters (i.e. MDB thickness).^{53,54} Improved ability to detect glaucomatous damage is achieved by combining data from abnormal RNFL parameters or disc parameters.^{52,53,56}

Macular parameters were studied in 2 Spectralis studies.^{5,73} One study⁷³ used 3 circular grid sizes from the GMPE software to determine mRNFL, GCL, IPL, GCIPL, and GCC volume and thickness. After manual correction of segmentation errors by a glaucoma specialist, the authors noted that isolated macular GCL was as good as GCC and GCIPL in glaucoma diagnosis, whereas IPL was not. They also suggested that the larger 6-mm macular grid may provide better data to detect glaucoma than the 3-mm and 3.45-mm grids. In the other study,⁵ macular PPAA was used to determine retinal thickness in a $30^\circ \times 25^\circ$ scan region, which was divided into an 8×8

grid. The best macular retinal thickness parameter was as helpful as the best RNFL parameter (i.e., 0.833 for inferior macular thickness vs. 0.858 for inferotemporal RNFL thickness; $P = 0.5$) for detecting the changes associated with the diagnosis of glaucoma. Although only patients with unilateral glaucoma were included, PPAA parameters were not as helpful as retinal thickness parameters in detecting the changes associated with glaucoma diagnosis (i.e., 0.427 for right-left asymmetry and 0.499 for hemispheric asymmetry vs. 0.825 to 0.833 for total macular thickness, average inferior macular thickness, and average superior macular thickness).

Three-Dimensional OCT Diagnostic Studies. Four articles evaluated the RNFL thickness parameter that was measured using the 3D OCT-1000 or 3D OCT-2000.^{7,32,61,62} The best RNFL thickness parameters to help detect changes associated with diagnosis of perimetric glaucoma were as follows, in descending order: (1) average RNFL (AUROC, 0.931–0.974),^{7,32,62} (2) inferior RNFL thickness (0.909–0.964),^{7,32,61,62} (3) global RNFL thickness (0.890–0.957),^{7,32,61,62} and (4) superior RNFL thickness (0.826–0.909).^{7,32,61,62} Retinal nerve fiber layer thickness and significance maps improved the ability to detect localized RNFL defects when defined by angular width and area (0.975–0.992).⁶¹

Macular parameters were evaluated in four 3D OCT studies.^{7,32,61,62} In addition to the aforementioned mRNFL, best macular parameters were average GC/IPL (0.830–0.954),^{7,32,61,62} and inferior GC/IPL (0.856–0.954),^{7,32,61,62} as well as average GCC (0.872–0.968)^{7,32,61} and inferior GCC (0.888–0.969).^{7,32,61} Concurrent analysis of multiple SD OCT parameters significantly improved the clinician's ability to diagnose glaucoma compared with using any single-best SD OCT measurement (i.e., average RNFL thickness, inferior GC/IPL, total mRNFL) in 1 study.⁶²

Studies Comparing the Diagnostic Capabilities of Different Spectral-Domain OCT Machines. All 4 studies that compared different SD OCT machines (i.e., Cirrus, RTVue, Spectralis, 3D OCT) found that the SD OCT machines of interest had similar abilities to help the clinician detect changes associated with the diagnosis of glaucoma.^{7,32,33,47} Minor differences in these studies did not reveal any consistent trends for superiority of 1 machine over another.^{7,32,33,47} Retinal nerve fiber layer thickness values between machines were not interchangeable.⁴⁷

Conclusions

The following conclusions are summarized from the literature review and are not the conclusions or opinions of the Ophthalmic Technology Assessment Committee Glaucoma Panel.

The most commonly studied glaucoma OCT parameters were the RNFL thickness parameter, followed by macular parameters and then optic nerve parameters. The most commonly studied SD OCT machine was the Cirrus, followed by the RTVue, the Spectralis, and the 3D OCT.

The Cirrus SD OCT system is a widely used platform for the analysis of glaucomatous damage. The best evidence-based parameters include RNFL thickness, GCIPL thickness, rim area, and vertical cup-to-disc ratio, with evidence of damage primarily manifesting in the inferior, superior, inferotemporal, and superotemporal regions. Most Cirrus studies suggest that RNFL, macular, and disc parameters were similar in their ability to help detect changes associated with the diagnosis of glaucoma. The Cirrus SD OCT RNFL thickness measurements were similarly helpful compared with Stratus TD OCT RNFL thickness measurements, but the Cirrus SD OCT instrument provides better axial resolution, faster acquisition rates, better scan quality, better reproducibility, and RNFL thickness and deviation maps.

The RTVue SD OCT system can reliably detect glaucomatous damage. The best RNFL parameters include average RNFL thickness, inferior RNFL thickness, and superior RNFL thickness. The best macular parameters were average GCC and inferior GCC. Newer macular parameters such as GCC pattern-based parameters (global and focal loss volume) also may be helpful. The best RTVue disc parameters were inferior rim area and vertical cup-to-disc ratio. Although most RTVue studies suggest that the 3 parameters have similar abilities to help detect changes associated with the diagnosis of glaucoma (i.e., RNFL, disc, and macular parameters), 2 studies suggested that for myopic patients, macular parameters might be better than RNFL thickness parameters.

The Spectralis SD OCT machine also performs well for detecting changes associated with the diagnosis of glaucoma. The most useful RNFL thickness parameters for helping the clinician detect changes associated with diagnosis of perimetric glaucoma were global RNFL thickness, inferior RNFL thickness, superior RNFL thickness, temporal-inferior RNFL thickness, and temporal-superior RNFL thickness. When the 3 RNFL scan circle sizes were compared ($12^\circ/14^\circ/16^\circ$), the smallest circle diameter showed the highest accuracy in detecting the changes associated with the diagnosis of glaucoma. Spectralis optic nerve studies suggest that reference plane-independent neuroretinal rim parameters (i.e., BMO-MRW and MDB thickness) can have the same or better diagnostic performance when compared with RNFL thickness or some reference plane-dependent parameters. Improved ability to detect glaucomatous damage may be achieved by combining the use of both newer disc parameters and older RNFL thickness measurements. Spectralis macular studies are limited but suggest that macular GCL is as good as GCC and GCIPL for detecting glaucomatous damage when using a circular grid scan protocol. When using the PPAA scan protocol, the best macular retinal thickness parameter (i.e., inferior macular thickness) is similar to the best RNFL parameter (i.e., inferotemporal RNFL thickness) for detecting the changes associated with glaucoma diagnosis, and retinal thickness parameters are better than asymmetry analyses (i.e., right-left asymmetry and hemispheric asymmetry) for detecting glaucomatous damage.

The 3D OCT system is also a good tool to help detect changes associated with glaucomatous damage. Best RNFL

thickness parameters for detecting perimetric glaucoma were mRNFL thickness, inferior RNFL thickness, global RNFL thickness, and superior RNFL thickness. Best macular parameters included average and inferior GCC and average and inferior hemiretinal GC/IPL. Analyzing multiple SD OCT parameters concurrently enhance detection accuracy over any single parameter alone.

All the SD OCT machines appear to be similar in their ability to help the clinician diagnose glaucoma, according to the 4 studies that compared the different SD OCT machines (i.e., Cirrus, RTVue, Spectralis, 3D OCT). The RNFL thickness values between machines are not interchangeable. Studies with the Cirrus, RTVue, and Spectralis machines demonstrated that lower AUROC curve values for RNFL thickness were associated with preperimetric glaucoma and early glaucoma, whereas higher AUROC curve values were associated with advanced glaucoma.

Future Research

The studies in this assessment demonstrated that SD OCT can help the clinician detect glaucomatous damage to the optic nerve and the surrounding retina. The conclusions of this review are largely based on cross-sectional studies; therefore, future longitudinal SD OCT studies would better elucidate the prognostic ability of certain parameters as well as to better define the characteristic progressive structural changes that occur with glaucoma. Current prospective longitudinal studies include but are not limited to the Advanced Imaging in Glaucoma Study, the Diagnostic Innovations in Glaucoma Study, the Portland Progression Project, and the Spectral-domain OCT in Glaucoma Study, all of which have at least 5 years of follow-up data. Although using SD OCT to monitor glaucoma progression is outside the scope of this review, longitudinal evidence shows that SD OCT is a sensitive test for monitoring glaucoma progression and can be more sensitive than visual field testing, particularly early in the disease.^{74,75} This is consistent with the consensus that SD OCT can sometimes detect structural changes before functional visual field changes. Software in SD OCT machines is already Food and Drug Administration approved to monitor for disease progression. The upcoming years should yield more publications describing the longitudinal data from these studies of glaucoma, a lifelong disease.

Because SD OCT is an integral part of diagnosing glaucoma and detecting disease progression, it is important for the clinician to be aware of factors that may influence SD OCT test results, such as testing artifacts, false positives, false negatives, refractive error, racial variation, known measurement variability, and normal aging changes. Future studies should also focus on the development of better 3D software and novel 3D imaging parameters (e.g., peripapillary retinal thickness, peripapillary retinal volume, and RNFL volume). Further studies that evaluate the relevant vasculature would also help to elucidate the vascular theories of glaucoma pathophysiology. Evaluation of better glaucoma biomarkers may also be possible with new imaging research. Finally, development of new imaging

technologies, as well as improved ancillary clinical testing, can allow us to better understand the mechanisms of glaucomatous disease and to improve the clinical care of patients with glaucoma.

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Abbreviations and Acronyms:

AUROC = area under the receiver operating characteristic curve; BMO-MRW = Bruch's membrane opening-minimum rim width; GCA = ganglion cell analysis; GCC = ganglion cell complex; GCIPL = ganglion cell inner plexiform layer; GCL = ganglion cell layer; GMPE = Glaucoma Module Premium Edition; HD = high-definition; IPL = inner plexiform layer; MDB = minimum distance band; mRNFL = macular RNFL; PPAA = posterior pole asymmetry analysis; RGC = retinal ganglion cell; RNFL = retinal nerve fiber layer; RPE = retinal pigment epithelium; SD = spectral domain; SSI = signal strength index; TD = time domain; 2D = 2-dimensional; 3D = 3-dimensional.

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