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Diagnostic Capability of Spectral Domain Optical Coherence Tomography for Glaucoma

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Abstract

Purpose—To determine the diagnostic capability of spectral domain optical coherence tomography (OCT) in glaucoma patients with visual field (VF) defects.

Design—Prospective, cross-sectional study.

Setting: Participants were recruited from a university hospital clinic.

Study Population: One eye of 85 normal subjects and 61 glaucoma patients [with average VF mean deviation (MD) of -9.61 ± 8.76 dB] were randomly selected for the study. A subgroup of the glaucoma patients with early VF defects was calculated separately.

Observation Procedures: Spectralis OCT circular scans were performed to obtain peripapillary retinal nerve fiber layer (RNFL) thicknesses. The RNFL diagnostic parameters based on the normative database were used alone or in combination for identifying glaucomatous RNFL thinning.

Main Outcome Measures: To evaluate diagnostic performance, calculations included areas under the receiver operating characteristic curve (AROC), sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio.

Results—Overall RNFL thickness had the highest AROC value (0.952 for all patients, 0.895 for the early glaucoma subgroup). For all patients, the highest sensitivity (98.4%, CI 96.3–100%) was achieved by using two criteria: 1 RNFL sectors being abnormal at the $< 5\%$ level, and overall classification of borderline or outside normal limits, with specificities of 88.9% (CI 84.0–94.0%) and 87.1% (CI 81.6–92.5%) respectively for these two criteria.

Conclusions—Statistical parameters for evaluating the diagnostic performance of the Spectralis spectral domain OCT were good for early perimetric glaucoma and excellent for moderately-advanced perimetric glaucoma.

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Introduction

Glaucoma is characterized by irreversible damage to the retinal nerve fiber layer (RNFL) and ganglion cell layer with corresponding typical visual field (VF) changes.¹ In the evaluation of glaucoma, RNFL thickness assessment is relevant, because thinning of the RNFL is directly correlated with loss of ganglion cells, which is assumed to be a primary site of glaucomatous damage.² RNFL assessment is also potentially useful for the early detection of glaucoma, because RNFL thinning often occurs prior to clinically detectable vision loss. For example, histological evaluation of the RNFL has shown that up to 50% of the RNFL may be lost prior to the initial appearance of VF loss.³ In addition, clinical evaluation of the RNFL from red-free photographs has suggested that RNFL thinning can be detected in 60% of photos up to 6 years prior to the appearance of a VF defect.⁴ Optical coherence tomography (OCT) is an imaging technology that can image and measure glaucomatous RNFL thinning.⁵

OCT, first described by Huang et al in 1991,⁶ allows for in vivo noninvasive quantitative evaluation of RNFL thickness.^{5,7,8} With the ability to directly measure RNFL thickness with axial resolutions of approximately 10 μm and scan speeds of 400 A-lines per second, time-domain OCT (Stratus OCT; Carl Zeiss Meditec Inc., Dublin, CA) has become a common imaging instrument for glaucoma evaluation.⁸⁻²¹ Using best RNFL thickness parameters, time-domain OCT has reported sensitivities and specificities for glaucoma diagnosis of 66% to 90% and 80% to 100% respectively.^{8,14-16,18}

Spectral domain OCT (SD-OCT) is a new technology which affords unprecedented ultra-high resolution ultra-high speed RNFL imaging.^{5,22} Using the Cirrus HD-OCT (Carl Zeiss Meditec Inc., Dublin, CA) machine, the area under the receiver operating characteristic curves (AROCs) were reported to be 0.837 to 0.963 using best RNFL thickness parameters.²³⁻²⁶ Using the RTVue (Optovue Inc, Fremont, CA) SD-OCT machine, the best AROC value using RNFL thickness determinations was found to be 0.94 for inferior RNFL thickness.²⁷

Spectralis OCT (Heidelberg Engineering, Inc., Heidelberg, Germany) is one of the many commercially available SD-OCT instruments. It has a scan speed of 40,000 A-lines per second. In addition, Spectralis OCT has the advantage of eye tracking technology which enables simultaneous real-time imaging with eye movement tracking. With faster scan speeds and with the eye tracking system, Spectralis OCT may reduce RNFL thickness measurement variability secondary to movement artifact and may improve measurement accuracy.²⁸ The current study is to evaluate the performance of Spectralis SD-OCT RNFL thickness values for diagnosing glaucoma. The following variables were determined: area under the receiver operating characteristic curve (AROC), sensitivity, specificity, positive predictive value (PPV), negative predictive value, positive likelihood ratio, and negative likelihood ratio.

Methods

Participants and examinations

All study subjects were recruited from the Glaucoma Service at the Massachusetts Eye and Ear Infirmary (MEEI) between January 2009 to July 2009. All study subjects underwent a complete eye examination by a glaucoma specialist (TCC) which included history, visual acuity testing, refraction, Goldmann applanation tonometry, slit-lamp biomicroscopy, gonioscopy, ultrasonic pachymetry, dilated ophthalmoscopy, stereo disc photography [Visucam Pro NM (Carl Zeiss Meditec, Dublin, CA)], VF testing [Swedish Interactive Threshold Algorithm (SITA) 24-2 test of the Humphrey visual field analyzer 750i, Carl

Zeiss Meditec, Dublin, CA] and peripapillary RNFL thickness measurements using the Spectralis OCT (Spectralis software version 4.0).

Inclusion criteria included patients with a spherical equivalent between -5.0 diopters and +5.0 diopters and with a best corrected visual acuity of 20/40 or better. The study only included patients with reliable VF testing with less than 33% fixation losses,²⁹ less than 20% false positives, and less than 20% false negatives. Patients were excluded if they had discernable congenital anomalies of the anterior chamber, corneal scarring or opacities, diabetic proliferative or severe non-proliferative retinopathy, VF loss attributable to a non-glaucoma condition, or a dilated pupil diameter of less than 2 mm.

Glaucoma patients were defined as having characteristic changes of the optic nerve head with corresponding abnormal VF defects. The VF was considered to be abnormal if three or more contiguous test locations in the pattern standard deviation plot were depressed significantly at the $P < 5\%$ level with at least 1 at the $P < 1\%$ level on the same side of the horizontal meridian and if the VF defect corresponded to the optic nerve appearance.³⁰ Except for traumatic glaucoma, all types of glaucoma were included. VF abnormalities were classified as mild (mean deviation [MD] > -6 decibels [dB]), moderate ($-12 \text{ dB} < \text{MD} < -6 \text{ dB}$), or severe ($\text{MD} < -12 \text{ dB}$). Normal subjects were those without ocular disease, except for mild cataracts, and those with normal VF test results, as defined by pattern standard deviation (PSD) $> 5\%$ and glaucoma hemifield test (GHT) within normal limits.²⁹ If both eyes were eligible for the study, one eye was selected by the investigator who was masked to the OCT results at the time selection was made and who used a random number generator statistical table.

Spectralis OCT Peripapillary Retinal Nerve Fiber Layer Measurement

All SD-OCT imaging was performed after pupillary dilation with the Spectralis OCT (version 4.0), which has an acquisition rate of 40,000 A-lines per second, an axial resolution of 7 μm in tissue, and an 870 nm superluminescent diode source. More details of the SD-OCT technique have been described elsewhere.^{22,31} The circular scan pattern was used for peripapillary RNFL thickness measurements. The scan circle was 12 degrees in diameter, and the scan circle diameter in millimeters is primarily dependent on the axial eye length. For a typical eye length, the circle is approximately 3.5 to 3.6 mm in diameter.³² Images were acquired by different operators but on the same day as the VF examination.

Spectralis OCT provides an Automatic Real-Time (ART) function with an eye tracking system which can increase image quality. With ART activated, multiple frames of the same scanning location are obtained. This data is then averaged for noise reduction, and eye motion artifacts are reduced. In this study, 16 frames were acquired per eye with ART on. As suggested by the manufacturer, scans with signal strength of less than 15 (range, 0–40) were excluded from the analysis.³² In addition, criteria for determining adequate scan quality were as follows: a clear fundus image with good optic disc and scan circle visibility before and during image acquisition, RNFL visible and without interruptions, and a continuous scan pattern without missing or blank areas.

The Spectralis OCT software calculates the average RNFL thickness for the overall globe (360 degrees), for quadrants (i.e. superior [S], inferior [I], nasal [N], and temporal [T], each 90 degrees), and additionally for four sectors (i.e. superior-temporal [TS], superior-nasal [NS], inferior-nasal [NI], and inferior-temporal [TI]) (Figure 1). In the Spectralis OCT RNFL printouts, not only are the RNFL thickness values for the above areas shown, but the classifications are also displayed in three different colors (Figure 1). The green, yellow and red areas are determined by comparing the patient's RNFL thickness values to a normative database,³³ with green representing the 95% normal range, yellow ("borderline

classification”) representing values outside the 95% confidence interval but within the 99% confidence interval of the normal distribution ($0.01 < p < 0.05$), and red (“outside normal limits”) representing values outside the 99% confidence interval of the normal distribution.³² The colored bar at the bottom of the printout indicates the overall classification. The bar is red (“outside normal limits”) if the RNFL thickness of one or more sectors (TS, NS, NI, TI), T quadrant or N quadrant, or overall global (G) is outside normal limits. The bar is yellow (“borderline”) if the RNFL thickness of one or more sectors (TS, NS, NI, TI), temporal or nasal quadrant, or overall global average is classified as borderline but none as outside normal limits. If all sectors, temporal and nasal quadrant, and overall global average RNFL thickness are classified as within normal limits, the bar will appear green (“within normal limits”).

Statistical Analysis

Demographic characteristics of the normal and glaucoma groups were compared using chi-square tests and non-paired 2-tailed Student's *t* tests for categorical and continuous variables respectively. Receiver operating characteristic (ROC) curves and AROCs were calculated for the RNFL thickness parameters of the overall globe, 4 quadrants, and 4 sectors. A statistical tool (MedCalc version 11.5.1, MedCalc Software bvba, Mariakerke, Belgium) was used when comparing AROCs.

Using RNFL thickness parameters, sensitivity, specificity, PPV, negative predictive value, positive likelihood ratio and negative likelihood ratio of six criteria were tested: 1) average overall globe RNFL thickness abnormal at the $< 5\%$ level; 2) average overall globe RNFL thickness abnormal at the $< 1\%$ level; 3) 1 quadrants abnormal at the $< 5\%$ level; 4) 1 quadrants abnormal at the $< 1\%$ level; 5) 1 sectors [TS, TI, NS and NI] abnormal at the $< 5\%$ level; 6) 1 sectors [TS, TI, NS and NI] abnormal at the $< 1\%$ level.

Sensitivity, specificity, PPV, negative predictive value, positive likelihood ratio and negative likelihood ratio were also evaluated for ten additional diagnostic criteria which combined the parameters with the best AROC values. These ten diagnostic criteria were 1) overall classification (provided by Spectralis software) of “outside normal limits”; 2) overall classification of “borderline” or “outside normal limits”; 3) overall, superior or inferior quadrants with RNFL thickness values abnormal at the $< 5\%$ level; 4) overall, superior or inferior quadrants with RNFL thickness values abnormal at the $< 1\%$ level; 5) superior or inferior quadrants with RNFL thickness values abnormal at the $< 5\%$ level; 6) superior or inferior quadrants with RNFL thickness values abnormal at the $< 1\%$ level; 7) overall, TS or TI sectors with RNFL thickness values abnormal at the $< 5\%$ level; 8) overall, TS or TI sectors with RNFL thickness values abnormal at the $< 1\%$ level; 9) TS or TI sectors with RNFL thickness values abnormal at the $< 5\%$ level; 10) and TS or TI sectors with RNFL thickness values abnormal at the $< 1\%$ level.

Sensitivity, specificity, PPV and negative predictive value were calculated using conventional 2×2 tables.³⁴ The use of likelihood ratio tests has been promoted to assist in interpreting diagnostic tests in medicine.³⁵ Positive likelihood ratio and negative likelihood ratio were calculated using the formulae positive likelihood ratio = sensitivity / (1 – specificity) and negative likelihood ratio = (1 – sensitivity) / specificity. A large positive likelihood ratio (for example a value more than 10) helps rule in disease, and a small negative likelihood ratio (for example a value less than 0.1) helps rule out disease.³⁶ In the current study, the criteria of positive likelihood ratio > 10 and negative likelihood ratio < 0.1 were used to determine whether Spectralis SD-OCT RNFL thickness measurements were good for diagnosing glaucoma. Statistical analyses were performed using SPSS version 15.0 (SPSS, Inc., Chicago, IL). $P < 0.05$ was considered to be statistically significant, and $P < 0.001$ was considered to be highly statistically significant.

Results

A total of 146 participants (85 normal subjects and 61 glaucoma patients) were studied. The characteristics of the study population are listed in Table 1. Types of glaucoma included primary open angle glaucoma (41 of 61 patients, 67.2%), normal tension glaucoma (6 of 61 patients, 9.8%), pseudoexfoliation glaucoma (6 of 61 patients, 9.8%), chronic angle closure glaucoma (4 of 61 patients, 6.6%), inflammatory glaucoma (1 of 61 patients, 1.6%), pigmentary glaucoma (1 of 61 patients, 1.6%), juvenile open angle glaucoma (1 of 61 patients, 1.6%), and iridocorneal endothelial syndrome with glaucoma (1 of 61 patients, 1.6%). Severity of VF defects was equally distributed among mild (23 of 61 patients, 37.7%), moderate (17 of 61 patients, 27.9%), and severe VF defects (21 of 61 patients, 34.4%).

Table 2 compares the mean RNFL thickness values for normal versus glaucoma patients. The mean overall RNFL thickness was $94.3 \pm 8.8\mu\text{m}$ for normal subjects and $65.3 \pm 16.5\mu\text{m}$ for glaucoma patients.

Table 3 summarizes AROC data for all RNFL thickness parameters. Table 3 lists the AROC for each parameter generated by the Spectralis OCT peripapillary RNFL scan for two groups: 1) all glaucoma patients and 2) early glaucoma patients with mild VF defects. In the group of all the glaucoma patients, the overall RNFL thickness had the highest AROC value (0.952), followed by the TI sector (0.947), superior quadrant (0.925), TS sector (0.911), and inferior quadrant (0.905), and these latter four values were not significantly lower than the highest value. The AROC value for overall RNFL thickness was significantly higher than those for the temporal and nasal quadrants as well as the NS and NI sectors. In the group of glaucoma patients with mild VF defects, overall RNFL thickness had the highest AROC (0.895). Other RNFL parameters with similarly high AROC values were the TI sector (0.888), TS sector (0.873), superior quadrant (0.864), and inferior quadrant (0.861).

Tables 4 and 5 lists the calculated sensitivities, specificities, PPVs, negative predictive values, positive likelihood ratio, and negative likelihood ratio for 6 RNFL thickness criteria. Table 4 lists these diagnostic parameters for all glaucoma patients, and table 5 lists these diagnostic parameters for early glaucoma patients with mild VF defects. Of the 6 RNFL thickness criteria for the glaucoma group (Table 4), best sensitivity (98.4%) and negative predictive value (98.6%) were achieved when 1 of the RNFL thickness sectors were abnormal at the $< 5\%$ level. The best specificity (100%) and PPV (100%) were achieved when overall globe RNFL thickness was abnormal at $< 1\%$ level. The only criteria with both positive likelihood ratio > 10 and negative likelihood ratio < 0.1 was 1 RNFL sectors abnormal at the $< 1\%$ level. Of the 6 RNFL thickness criteria for the early glaucoma group with mild VF defects (Table 5), similar results were obtained. The only RNFL criteria with both positive likelihood ratio > 10 and negative likelihood ratio < 0.1 was 1 RNFL sectors abnormal at $< 1\%$ level.

The diagnostic abilities of the 10 different combinations of RNFL thickness parameters with the best AROC values were evaluated for all glaucoma patients (Table 6) and for early glaucoma patients with mild VF defects (Table 7). The criteria of overall classification was provided by the Spectralis OCT circular scan software and is shown in the printout (Figure 1). Ten different combinations or criteria were established (Tables 6 and 7) by using the 5 best single parameters (i.e. overall globe, superior and inferior quadrants, and TS and TI sectors) based on their AROC values (Table 3) using an either-or-combination. In table 6, only four of the ten combined RNFL criteria for potential glaucoma diagnosis had both positive likelihood ratio > 10 and negative likelihood ratio < 0.1 : 1) overall classification of outside normal limits, 2) overall, superior or inferior quadrants with RNFL thickness

abnormal at the $< 1\%$ level, and 3) overall, TS or TI sectors with RNFL thickness abnormal at the $< 5\%$ and 4) at the $< 1\%$ level. In contrast, when analyzing these ten combination RNFL criteria for diagnosing early glaucoma with mild VF defects (Table 7), none of the combined criteria had both positive likelihood ratio > 10 and negative likelihood ratio < 0.1 , but the criteria of “overall classification of outside normal limits” was possibly the best with a positive likelihood ratio of 18.48 and negative likelihood ratio of 0.14.

Discussion

By providing objective, quantitative, and reproducible measurements of RNFL thickness, OCT provides supplemental information that may help differentiate glaucomatous eyes from normal eyes.^{8-21,23-27} In the current study, the diagnostic performance of the Spectralis SD-OCT was evaluated. SD-OCT RNFL thickness values were able to distinguish normal eyes from glaucomatous eyes with VF defects (Tables 2-7).

Best diagnostic ability and best ROC curves were achieved by analyzing the overall globe RNFL, the superior and inferior RNFL quadrants, and the temporal RNFL sectors (i.e. TI and TS) for both glaucomatous eyes with mild VF loss (Table 3) and glaucomatous eyes with mild, moderate, and severe VF loss (Table 3). This is consistent with known glaucoma pathophysiology, which preferentially affects the inferior and superior RNFLs before the nasal and temporal RNFLs.

In addition to ROC curves, likelihood ratio tests are used to evaluate diagnostic tests in medicine.³⁵ Positive likelihood ratio demonstrates how more often a positive test result occurs in persons with the target condition compared to those without the target condition, and negative likelihood ratio means how less likely a negative test result is in persons with the target condition compared to those without the target condition. A likelihood ratio of 1 indicates no diagnostic value. Positive likelihood ratio greater than 10 is usually regarded as a strong positive test result, and negative likelihood ratio less than 0.1 are usually regarded as a strong negative test result.³⁶ For the glaucomatous eyes with mild, moderate, and severe VF loss in this study (Tables 4 and 6), there were five RNFL criteria that had good diagnostic value (i.e. positive likelihood ratio > 10 and negative likelihood ratio < 0.1): 1) 1 RNFL sectors abnormal at the $< 1\%$ level, 2) overall classification of outside normal limits, 3) overall, superior or inferior quadrants with RNFL thickness abnormal at the $< 1\%$ level, and 4) overall, TS or TI sectors with RNFL thickness abnormal either at the $< 5\%$ level or 5) at the $< 1\%$ level. In summary, a diagnosis of glaucoma was usually associated with an overall RNFL classification of red (“outside normal limits”). A diagnosis of glaucoma was also associated with abnormal thinning of the overall RNFL, superior and/or inferior RNFL quadrants, and TS and/or TI sectors at either the $< 5\%$ or $< 1\%$ level.

The diagnostic performance of structural tests such as OCT RNFL measurements may be more critical for early stage glaucoma diagnosis compared to late stage glaucoma, because the diagnosis of late stage glaucoma is easier due more obvious clinical evidence of cupping and functional visual field test abnormalities. Therefore, a subset of early glaucoma patients with mild VF defects⁸ were analyzed separately in this study (Tables 5 and 7). For these early glaucoma patients, only one RNFL criterion was considered a good diagnostic criterion (i.e. 1 RNFL sectors abnormal at the $< 1\%$ level; Table 5) by likelihood ratio tests.

Over the past decade, many studies have evaluated the diagnostic accuracy of Stratus OCT RNFL thickness measurements for diagnosing glaucoma.⁸⁻²¹ In one study of 109 normal subjects (109 eyes) and 63 glaucoma patients (63 eyes) with the average MD of -8.4 ± 6.0 dB, Budenz et al investigated the sensitivity and specificity of RNFL thickness

measurements using Stratus OCT in perimetric glaucoma patients.⁸ They found that the RNFL parameters having the higher AROC values were mean RNFL thickness (0.966), superior quadrant (0.952), inferior quadrant (0.971), TI clock hour (0.959), 6-o'clock hour position (0.940), TS clock hour (0.935), and 12-o'clock hour position (0.924).⁸ In the current study using Spectralis SD-OCT, the RNFL parameters with the highest AROCs were in similar locations as those in the Stratus OCT study (i.e. overall RNFL thickness [0.952], the superior quadrant [0.925], the inferior quadrant [0.905], the TS sector [0.911], and the TI sector [0.947]; Table 3).

In study populations with similar degrees of VF loss, AROC values appear to be similar for time domain OCT and SD-OCT machines. For example, comparable diagnostic performance for glaucoma has been reported for the Stratus time domain OCT machine and the Cirrus and RTVue SD-OCT machines.^{27,37} It is possible that the stage of our glaucoma cohort, which had an average VF mean deviation of -9.61 dB, may have contributed in part to our inability to better differentiate normal eyes from glaucomatous eyes with SD-OCT.²⁷ The ability to discriminate normal from glaucomatous results is directly proportional to the magnitude of disease severity, and this observation in part will contribute to the high AROC values identified for both time domain OCT and SD-OCT.²⁷ The other possible reason for similar results with time domain and SD-OCT is that it is theoretically possible with Stratus OCT to have perfect operator scan circle centration techniques and perfect patient cooperation, which would theoretically enable the exact same data to be obtained each time.³⁷ Lastly, extracting only peripapillary RNFL data from SD-OCT machines may not result in improved perimetric glaucoma detection, because extracting only peripapillary RNFL data with SD-OCT does not even begin to fully utilize the three-dimensional high-resolution potential of SD-OCT imaging.

In another study of 89 age-matched normal subjects and 89 perimetric glaucoma eyes, Lu et al identified the best combination of Stratus OCT RNFL thickness parameters for the detection of glaucoma.²⁰ The RNFL diagnostic parameters were combined using either or-logic or and-logic approaches in their study. They found that the highest AROC value (0.92) was achieved by the or-logic combination of overall, inferior, and superior quadrant RNFL thicknesses.²⁰ Since it has been proven that the AROC values for and-logic combinations were uniformly worse than the equivalent or-logic combination in Lu et al's study,²⁰ we only used or-logic in the current study for combining the best single RNFL parameters (first columns of Tables 6 and 7). In the current study, a diagnosis of glaucoma was associated with abnormal thinning of the overall RNFL, superior and/or inferior RNFL quadrants, and TS and/or TI sectors at either the <5% or <1% level. In Lu et al's study,²⁰ similar RNFL locations (i.e. overall, inferior and superior quadrants) were noted to be important for diagnostic criteria when using the or-logic combination.

There are only a few studies evaluating the diagnostic accuracy of SD-OCT machines for glaucoma.²³⁻²⁷ Two studies using Cirrus HD-OCT RNFL thickness parameters have reported AROC values of 0.962²³ and 0.953²⁶ for overall average RNFL thickness, 0.963²³ and 0.926²⁶ for superior quadrant RNFL thickness, and 0.949²³ and 0.963²⁶ for inferior quadrant RNFL thickness. The mean MDs for these studies were -8.66 ± 8.10 dB²³ and -6.67 ± 5.80 dB.²⁶ In a study of 50 healthy subjects (50 eyes) and 50 glaucoma patients (50 eyes) with a mean MD of -9.2 ± 7.1 dB using the RTVue system, Sehi et al reported RNFL thickness AROC values of 0.88 (average RNFL), 0.80 (superior RNFL), and 0.94 (inferior RNFL).²⁷ Using the Spectralis OCT in the current study (Table 3), our AROC values were 0.952 (overall average), 0.925 (superior quadrant), and 0.905 (inferior quadrant). Therefore, our Spectralis OCT AROC values were similar to those obtained by the Cirrus HD-OCT^{23,26} and the RTVue OCT.²⁷

With the eye tracking system of Spectralis OCT, multiple frames of the same scan location are obtained. This data is then averaged for noise reduction, and eye motion artifacts are reduced. In theory, the eye tracking system can increase image quality and may improve diagnostic performance. Studies which have utilized other SD-OCT machines (i.e. Cirrus HD-OCT and RTVue OCT) for glaucoma detection did use strict criteria to guarantee the image quality.²³⁻²⁷ For example, in Cirrus HD-OCT studies, images were excluded if horizontal eye motion was observed within the measurement circle during scan acquisition.^{23,26} Because good diagnostic performance by these other SD-OCT machines were demonstrated, the advantages of the eye tracking system in the Spectralis SD-OCT is not yet proven for glaucoma diagnosis. In theory, eye tracking may be better for longitudinal evaluation of glaucomatous structural changes, but further studies which directly compare machines with and without tracking for both glaucoma diagnosis and for the longitudinal evaluation of glaucomatous structural progression need to be done.

A potential limitation of this and other diagnostic studies is that the glaucoma patients evaluated all had VF defects, so the diagnostic accuracy of SD-OCT has only been evaluated so far for perimetric glaucoma. Further studies are needed to evaluate the diagnostic accuracy of Spectralis OCT and other SD-OCT machines for pre-perimetric glaucoma.

In conclusion, although the statistical parameters for evaluating the diagnostic of Spectralis SD-OCT were good for early perimetric glaucoma and excellent for moderately-advanced perimetric glaucoma, the diagnostic performance of SD-OCT technology appears to be similar across all instruments in single imaging studies. Based on our results, five RNFL criteria may be particularly useful for glaucoma diagnosis. They are 1) 1 RNFL sectors abnormal at the < 1% level; 2) overall classification of red (“outside normal limits”); 3) overall, superior or inferior quadrants with RNFL thicknesses abnormal at the < 1% level; 4) overall, TS or TI sectors with RNFL thicknesses abnormal at the < 5% level; and 5) overall, TS or TI sectors with RNFL thickness abnormal at the < 1% level. For early glaucoma patients with mild VF defects, the criteria of 1 sectors with RNFL thicknesses abnormal at the < 1% level is the best one. In summary, a diagnosis of glaucoma is usually associated with an overall RNFL classification of red (“outside normal limits”) and with abnormal thinning of the overall RNFL, superior and/or inferior RNFL quadrants, and TS and/or TI sectors at either the <5% or <1% level.

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Biography

Teresa C. Chen, MD is an Associate Professor of Ophthalmology at the Harvard Medical School. She works in the Glaucoma Service at the Massachusetts Eye and Ear Infirmary. Her research expertise is in imaging and the pediatric glaucomas. She edited the book *Glaucoma Surgery* and has published over 100 original articles, major reviews, and book chapters. Drs. de Boer and Chen were the first to image a glaucoma eye with spectral domain optical coherence tomography.

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References

1. Wollstein, G.; Beaton, S.; Paunescu, A., et al. Optical coherence tomography in glaucoma.. In: Schuman, JS.; Puliafito, CA.; Fujimoto, JG., editors. Optical coherence tomography of ocular diseases. SLACK Incorporated; Thorofare, NJ: 2004. p. 483-610.
2. Blumenthal EZ, Weinreb RN. Assessment of the retinal nerve fiber layer in clinical trials of glaucoma neuroprotection. *Surv Ophthalmol.* 2001; 45(Suppl 3):S305–12. discussion S332–4. [PubMed: 11377454]
3. Quigley HA, Addicks EM, Green WR. Optic nerve damage in human glaucoma. III. Quantitative correlation of nerve fiber loss and visual field defect in glaucoma, ischemic neuropathy, papilledema, and toxic neuropathy. *Arch Ophthalmol.* 1982; 100(1):135–46. [PubMed: 7055464]
4. Sommer A, Katz J, Quigley HA, et al. Clinically detectable nerve fiber atrophy precedes the onset of glaucomatous field loss. *Arch Ophthalmol.* 1991; 109(1):77–83. [PubMed: 1987954]
5. Chen TC, Zeng A, Sun W, Mujat M, de Boer JF. Spectral domain optical coherence tomography and glaucoma. *Int Ophthalmol Clin.* 2008; 48(4):29–45. [PubMed: 18936635]
6. Huang D, Swanson EA, Lin CP, et al. Optical coherence tomography. *Science.* 1991; 254:1178–81. [PubMed: 1957169]
7. Mujat M, Chan RC, Cense B, Park BH, Joo C, Akkin T, Chen TC, de Boer JF. Retinal Nerve Fiber Layer Thickness Map Determined from Optical Coherence Tomography Images. *Optics Express.* 2005; 13(23):9480–91. [PubMed: 19503151]

8. Budenz DL, Michael A, Chang RT, McSoley J, Katz J. Sensitivity and specificity of the Stratus OCT for perimetric glaucoma. *Ophthalmology*. 2005; 112(1):3–9. [PubMed: 15629813]
9. Medeiros FA, Zangwill LM, Bowd C, Weinreb RN. Comparison of the GDx VCC scanning laser polarimeter, HRT II confocal scanning laser ophthalmoscope, and stratus OCT optical coherence tomograph for the detection of glaucoma. *Arch Ophthalmol*. 2004; 122(6):827–37. [PubMed: 15197057]
10. Chen HY, Huang ML. Discrimination between normal and glaucomatous eyes using Stratus optical coherence tomography in Taiwan Chinese subjects. *Graefes Arch Clin Exp Ophthalmol*. 2005; 243:894–902. [PubMed: 15834602]
11. Medeiros FA, Zangwill LM, Bowd C, et al. Evaluation of retinal nerve fiber layer, optic nerve head, and macular thickness measurements for glaucoma detection using optical coherence tomography. *Am J Ophthalmol*. 2005; 139:44–55. [PubMed: 15652827]
12. Wollstein G, Ishikawa H, Wang J, Beaton SA, Schuman JS. Comparison of three optical coherence tomography scanning areas for detection of glaucomatous damage. *Am J Ophthalmol*. 2005; 139(1):39–43. [PubMed: 15652826]
13. Brusini P, Salvatet ML, Zeppieri M, et al. Comparison between GDx VCC scanning laser polarimetry and Stratus OCT optical coherence tomography in the diagnosis of chronic glaucoma. *Acta Ophthalmol Scand*. 2006; 84(5):650–5. [PubMed: 16965496]
14. Chen HY, Huang ML, Hung PT. Logistic regression analysis for glaucoma diagnosis using Stratus Optical Coherence Tomography. *Optom Vis Sci*. 2006; 83(7):527–34. [PubMed: 16840878]
15. Hougaard JL, Heijl A, Bengtsson B. Glaucoma detection using different Stratus optical coherence tomography protocols. *Acta Ophthalmol Scand*. 2007; 85(3):251–6. [PubMed: 17343690]
16. Pueyo V, Polo V, Larrosa JM, et al. Diagnostic ability of the Heidelberg retina tomograph, optical coherence tomograph, and scanning laser polarimeter in open-angle glaucoma. *J Glaucoma*. 2007; 16(2):173–7. [PubMed: 17473725]
17. Anton A, Moreno-Montañés J, Blázquez F, et al. Usefulness of optical coherence tomography parameters of the optic disc and the retinal nerve fiber layer to differentiate glaucomatous, ocular hypertensive, and normal eyes. *J Glaucoma*. 2007; 16(1):1–8. [PubMed: 17224742]
18. Hougaard JL, Heijl A, Bengtsson B. Glaucoma detection by Stratus OCT. *J Glaucoma*. 2007; 16(3):302–6. [PubMed: 17438424]
19. Parikh RS, Parikh S, Sekhar GC, et al. Diagnostic capability of optical coherence tomography (Stratus OCT 3) in early glaucoma. *Ophthalmology*. 2007; 114(12):2238–43. [PubMed: 17561260]
20. Lu AT, Wang M, Varma R, et al. Combining nerve fiber layer parameters to optimize glaucoma diagnosis with optical coherence tomography. *Ophthalmology*. 2008; 115(8):1352–7. 1357, e1–2. [PubMed: 18514318]
21. Lee EJ, Kim TW, Park KH, et al. Ability of Stratus OCT to detect progressive retinal nerve fiber layer atrophy in glaucoma. *Invest Ophthalmol Vis Sci*. 2009; 50(2):662–8. [PubMed: 18824734]
22. Chen TC, Cense B, Pierce MC, et al. Spectral domain optical coherence tomography: ultrahigh-speed, ultrahigh-resolution ophthalmic imaging. *Arch Ophthalmol*. 2005; 123(12):1715–1720. [PubMed: 16344444]
23. Leung CK, Cheung CY, Weinreb RN, et al. Retinal nerve fiber layer imaging with spectral-domain optical coherence tomography: a variability and diagnostic performance study. *Ophthalmology*. 2009; 116(7):1257–63. 1263, e1–2. [PubMed: 19464061]
24. Sung KR, Kim DY, Park SB, Kook MS. Comparison of retinal nerve fiber layer thickness measured by Cirrus HD and Stratus optical coherence tomography. *Ophthalmology*. 2009; 116(7):1264–70. 1270, e1. [PubMed: 19427696]
25. Moreno-Montañés J, Olmo N, Alvarez A, et al. Cirrus high-definition optical coherence tomography compared with Stratus optical coherence tomography in glaucoma diagnosis. *Invest Ophthalmol Vis Sci*. 2010; 51(1):335–43. Epub 2009 Sep 8. [PubMed: 19737881]
26. Park SB, Sung KR, Kang SY, Kim KR, Kook MS. Comparison of glaucoma diagnostic Capabilities of Cirrus HD and Stratus optical coherence tomography. *Arch Ophthalmol*. 2009; 127(12):1603–9. [PubMed: 20008715]

27. Sehi M, Grewal DS, Sheets CW, Greenfield DS. Diagnostic Ability of Fourier-Domain vs Time-Domain Optical Coherence Tomography for Glaucoma Detection. *Am J Ophthalmol*. 2009; 148(4):597–605. [PubMed: 19589493]
28. Wolf-Schnurrbusch UE, Ceklic L, Brinkmann CK, et al. Macular thickness measurements in healthy eyes using six different optical coherence tomography instruments. *Invest Ophthalmol Vis Sci*. 2009; 50(7):3432–7. [PubMed: 19234346]
29. Gordon MO, Kass MA. The Ocular Hypertension Treatment Study: design and baseline description of the participants. *Arch Ophthalmol*. 1999; 117(5):573–83. [PubMed: 10326953]
30. Katz J, Sommer A, Gaasterland DE, Anderson DR. Comparison of analytic algorithms for detecting glaucomatous visual field loss. *Arch Ophthalmol*. 1991; 109:1684–9. [PubMed: 1841576]
31. Cense B, Nassif N, Chen TC, et al. Ultrahigh-resolution high-speed retinal imaging using spectral-domain optical coherence tomography. *Opt Express*. 2004; 12(11):2435–47. [PubMed: 19475080]
32. Heidelberg Engineering. OCT Acquisition Window1 –Overview. Spectralis OCT QuickGuide (Software Version 4.0). 2008:10.
33. Bendschneider D, Tornow RP, Horn FK, et al. Retinal nerve fiber layer thickness in normals measured by spectral domain OCT. *J Glaucoma*. 2010; 19(7):475–82. [PubMed: 20051888]
34. Sackett, DL.; Haynes, RB.; Guyatt, GH.; Tugwell, P. *Clinical Epidemiology: A Basic Science for Clinical Medicine*. 2nd ed.. Little, Brown; Boston, MA: 1991. p. 67-152.
35. Jaeschke R, Guyatt GH, Sackett DL. Users' guides to the medical literature. III. How to use an article about a diagnostic test. B. What are the results and will they help me in caring for my patients? The Evidence-Based Medicine Working Group. *JAMA*. 1994; 271(9):703–7. [PubMed: 8309035]
36. McGee S. Simplifying likelihood ratios. *J Gen Intern Med*. 2002; 17(8):646–9. [PubMed: 12213147]
37. Chang RT, Knight OJ, Feuer WJ, Budenz DL. Sensitivity and specificity of time-domain versus spectral-domain optical coherence tomography in diagnosing early to moderate glaucoma. *Ophthalmology*. 2009; 116(12):2294–9. Epub 2009 Oct 2. [PubMed: 19800694]

Figure 1.

A sample printout of a Spectralis optical coherence tomography (OCT) Basic Retinal Nerve Fiber Layer (RNFL) Report. This patient has glaucoma of the left eye. The top pie charts display classification results for the 4 RNFL quadrants, and the bottom pie charts display 4 RNFL sectors (i.e. superior-temporal [TS], inferior-temporal [TI], superior-nasal [NS], and inferior-nasal [NI]) and 2 RNFL quadrants (nasal [N] and temporal [T]). The black font numbers are the average RNFL thickness measurement values for each sector, quadrant, and the overall global average (G). The colored bars underneath the pie charts indicate the overall classification.

G: 360°; 4 quadrants (i.e. superior [S], inferior [I], N, and T): each 90°; sector TS: 45°-90°, sector NS: 90°-135°, sector NI: 225°-270°, and sector TI: 270°-315°. OD: right eye; OS: left eye.

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Table 1

Demographics of the study population of normal and glaucoma patients.

	normal	glaucoma	all	p values ^a
number of eyes	85	61	146	
number of right eyes (% total)	60.0%	62.3%	61.0%	0.779
age (range)	63.5 ± 14.0 (18-90)	69.2 ± 13.0 (18-89)	66.4 ± 13.8 (18-90)	0.054
female (% total)	52.9%	59.0%	55.5%	0.466
race (Caucasian % total)	74.1%	67.2%	71.2%	0.363
refractive error (spherical equivalent in diopters)	-0.95 ± 1.94	-1.33 ± 1.74		0.067
VF mean deviation (dB)	-1.25 ± 1.74	-9.61 ± 8.76		<0.001
VF pattern standard deviation (dB)	1.82 ± 1.31	6.14 ± 3.43		<0.001

Results are expressed as the mean ± standard deviation.

VF: visual field; dB: decibel

^aWhen comparing normal and glaucoma groups, chi-square tests were used for categorical variables and non-paired 2-tailed Student's *t* tests were used for continuous variables.

Table 2

Spectralis optical coherence tomography (OCT) retinal nerve fiber layer (RNFL) thickness (μm) values in normal and glaucomatous eyes

RNFL thickness (μm)	normal (n = 85) (mean $\pm$ SD)	glaucoma (n = 61) (mean $\pm$ SD)
overall global average	94.3 $\pm$ 8.8	65.3 $\pm$ 16.5 ^a
superior quadrant	111.5 $\pm$ 14.4	73.4 $\pm$ 21.9 ^a
temporal quadrant	70.3 $\pm$ 10.6	54.9 $\pm$ 13.9 ^a
inferior quadrant	119.7 $\pm$ 15.9	75.3 $\pm$ 27.3 ^a
nasal quadrant	74.9 $\pm$ 11.6	57.2 $\pm$ 18.0 ^a
TS sector	124.5 $\pm$ 16.4	78.0 $\pm$ 28.5 ^a
TI sector	136.0 $\pm$ 20.5	76.9 $\pm$ 29.3 ^a
NS sector	98.7 $\pm$ 19.9	68.8 $\pm$ 23.0 ^a
NI sector	103.9 $\pm$ 20.8	73.8 $\pm$ 29.7 ^a

SD: standard deviation; TS: superior-temporal; TI: inferior-temporal; NS: superior-nasal; NI: inferior-nasal

^aSignificantly different ($P < 0.001$) when compared to the normal group (analysis of variance)

Table 3

Areas under the receiving operator characteristic curve (AROCs) for Spectralis optical coherence tomography (OCT) retinal nerve fiber layer (RNFL) thickness circular scan parameters

OCT parameter	all glaucoma patients		glaucoma patients with mild VF loss	
	AROC (95% CI)	p value ^a	AROC (95% CI)	p value ^a
overall RNFL thickness	0.952 (0.915-0.990)		0.895 (0.807-0.983)	
superior RNFL thickness	0.925 (0.881-0.969)	0.3530	0.864 (0.773-0.955)	0.6300
temporal RNFL thickness	0.808 (0.734-0.881)	< 0.001	0.718 (0.589-0.847)	< 0.05
inferior RNFL thickness	0.905 (0.848-0.963)	0.1752	0.861 (0.755-0.967)	0.6286
nasal RNFL thickness	0.801 (0.726-0.877)	< 0.001	0.707 (0.577-0.836)	<0.05
TS RNFL thickness	0.911 (0.859-0.963)	0.2029	0.873 (0.774-0.972)	0.7463
TI RNFL thickness	0.947 (0.906-0.988)	0.8599	0.888 (0.792-0.985)	0.9162
NS RNFL thickness	0.847 (0.781-0.914)	< 0.05	0.725 (0.593-0.857)	< 0.05
NI RNFL thickness	0.819 (0.739-0.898)	< 0.05	0.739 (0.605-0.873)	0.0583

VF: visual field; CI: confidence interval; TS: superior-temporal; TI: inferior-temporal; NS: superior-nasal; NI: inferior-nasal

^aBased on comparison with overall RNFL.

Table 4

Performance of Spectralis optical coherence tomography (OCT) retinal nerve fiber layer (RNFL) thickness parameters for diagnosing glaucoma

OCT parameter	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	LRP (95% CI)	LRN (95% CI)
overall global RNFL thickness abnormal at < 5% level	80.3 (73.9-86.85)	92.9 (88.8-97.1)	89.1 (84.0-94.1)	86.8 (81.3-92.3)	11.38 (6.59-29.88)	0.21 (0.14-0.29)
overall global RNFL thickness abnormal at < 1% level	67.2 (59.6-74.8)	100	100	81.0 (74.6-87.3)	+ ∞	0.33 (0.25-0.40)
1 quadrants with RNFL thickness abnormal at < 5% level	96.7 (93.8-99.6)	85.9 (80.2-91.5)	83.1 (77.0-89.2)	97.3 (94.7-99.9)	6.85 (4.75 -11.76)	0.04 (0-0.08)
1 quadrants with RNFL thickness abnormal at < 1% level	88.5 (83.4-93.7)	95.3 (91.9-98.7)	93.1 (89.0-97.2)	92.0 (87.7-96.4)	18.81 (10.24-73.73)	0.12 (0.06-0.18)
1 sectors of TS, TI, NS, NI with RNFL thickness abnormal at < 5% level	98.4 (96.3-100)	88.9 (84.0-94.0)	87.0 (81.5-92.4)	98.6 (96.7-100)	8.85 (5.94-16.70)	0.02 (0-0.04)
1 sectors of TS, TI, NS, NI with RNFL thickness abnormal at < 1% level	93.4 (89.4-97.5)	95.3 (91.9-98.7)	93.4 (89.4-97.5)	95.3 (91.9-98.7)	19.86 (10.98-76.69)	0.07 (0.03-0.12)

PPV: positive predictive value; NPV: negative predictive value; LRP: likelihood ratio positive; LRN: likelihood ratio negative; CI: confidence interval; TS: superior-temporal; TI: inferior-temporal; NS: superior-nasal; NI: inferior-nasal.

Table 5

Performance of Spectralis optical coherence tomography (OCT) retinal nerve fiber layer (RNFL) thickness parameters for diagnosing early glaucoma patients with mild visual field loss

OCT parameter	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	LRP(95% CI)	LRN(95% CI)
overall global RNFL thickness abnormal at < 5% level	65.2 (57.5-72.9)	92.9 (88.8-97.1)	71.4 (64.1-78.8)	90.8 (86.1-95.5)	9.24 (5.13-25.12)	0.37 (0.28-0.48)
overall global RNFL thickness abnormal at < 1% level	47.8 (39.7-55.9)	100	100	87.6 (82.3-93.0)	+ ∞	0.52 (0.44-0.60)
1 quadrants ith RNFL thickness abnormal at < 5% level	91.3 (86.7-95.9)	85.9 (80.2-91.5)	63.6 (55.8-71.4)	97.3 (94.7-99.9)	6.47 (4.39-11.32)	0.10 (0.05-0.17)
1 quadrants with RNFL thickness abnormal at < 1% level	78.3 (71.6-85.0)	95.3 (91.9-98.7)	81.8 (75.6-88.1)	94.2 (90.4-98.0)	16.63 (8.79-66.85)	0.23 (0.15-0.31)
1 sectors of TS, TI, NS, NI with RNFL thickness abnormal at < 5% level	95.2 (91.8-98.7)	88.9 (84.0-94.0)	69.0 (61.5-76.5)	98.6 (96.7-100)	8.57 (5.67-16.41)	0.05 (0.01-0.10)
1 sectors of TS, TI, NS, NI with RNFL thickness abnormal at < 1% level	91.3 (86.7-95.9)	95.3 (91.9-98.7)	84.0 (78.1-89.9)	97.6 (95.1-100)	19.40 (10.65-75.44)	0.09 (0.04-0.14)

Positive predictive value (PPV); negative predictive value (NPV); likelihood ratio positive (LRP); likelihood ratio negative (LRN); CI: confidence interval; TS: superior-temporal; TI: inferior-temporal; NS: superior-nasal; NI: inferior-nasal.

Table 6

Performance of combinations of Spectralis optical coherence tomography (OCT) retinal nerve fiber layer (RNFL) thickness parameters for diagnosing glaucoma

Spectralis OCT diagnostic criteria	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	LRP (95% CI)	LRN (95% CI)
overall classification of borderline or outside normal limits	98.4 (96.3-100)	87.1 (81.6-92.5)	84.5 (78.6-90.4)	98.7 (96.8-100)	7.60 (5.24-13.40)	0.02 (0-0.05)
overall classification of outside normal limits	95.0 (91.6-98.6)	95.3 (91.9-98.7)	93.5 (89.6-97.5)	96.4 (93.4-99.4)	20.20 (11.25-77.58)	0.05 (0.01-0.09)
overall global, superior or inferior quadrants with RNFL thickness abnormal at < 5% level	96.7 (93.8-99.6)	85.9 (80.2-91.5)	83.1 (77.0-89.2)	97.3 (94.7-99.9)	6.85 (4.75-11.76)	0.04 (0-0.08)
overall global, superior or inferior quadrants with RNFL thickness abnormal at < 1% level	90.2 (85.3-95.0)	95.3 (91.9-98.7)	93.5 (89.1-97.3)	96.4 (89.0-97.2)	19.16 (10.48-74.75)	0.09 (0.05-0.16)
superior or inferior quadrants with RNFL thickness abnormal at < 5% level	95.1 (91.6-98.6)	88.2 (83.0-93.5)	85.3 (79.5-91.0)	96.2 (93.0-99.3)	8.08 (5.39-15.08)	0.06 (0.02-0.10)
superior or inferior quadrants with RNFL thickness abnormal at < 1% level	88.5 (83.4-93.7)	96.5 (93.5-99.5)	94.7 (91.1-98.4)	92.1 (87.8-96.5)	25.08 (12.78-174.72)	0.12 (0.06-0.18)
overall global, TS or TI sectors with RNFL thickness abnormal at < 5% level	96.7 (93.8-99.6)	92.9 (88.8-97.1)	90.8 (86.1-95.5)	97.5 (95.0-100)	13.70 (8.37-34.30)	0.04 (0-0.07)
overall global, TS or TI sectors with RNFL thickness abnormal at < 1% level	91.8 (87.4-96.3)	95.3 (91.9-98.7)	93.3 (89.3-97.4)	94.2 (90.4-98.0)	19.51 (10.73-75.74)	0.09 (0.04-0.14)
TS or TI sector with RNFL thickness abnormal at < 5% level	88.5 (83.4-93.7)	91.8 (87.3-96.2)	88.5 (83.4-93.7)	91.8 (87.3-96.2)	10.75 (6.57-24.81)	0.13 (0.07-0.19)
TS or TI sector with RNFL thickness abnormal at < 1% level	67.2 (59.6-74.8)	95.3 (91.9-98.7)	91.1 (86.5-95.7)	80.2 (73.7-86.7)	14.28 (7.32-58.88)	0.34 (0.25-0.44)

CI: confidence interval; positive predictive value: PPV; negative predictive value: NPV; likelihood ratio positive: LRP; likelihood ratio negative: LRN; TS: superior-temporal; TI: inferior-temporal; NS: superior-nasal; NI: inferior-nasal.

Table 7

Performance of combinations of Spectralis optical coherence tomography (OCT) retinal nerve fiber layer (RNFL) thickness parameters for diagnosing early glaucoma patients with mild visual field loss

Spectralis OCT diagnostic criteria	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	LRP (95% CI)	LRN (95% CI)
overall classification of borderline or outside normal limits	95.7 (92.3-99.0)	87.1 (81.6-92.5)	66.7 (59.0-74.3)	98.7 (96.8-100)	7.39 (5.02-13.20)	0.05 (0.01-0.09)
overall classification of outside normal limits	87.0 (81.5-92.4)	95.3 (91.9-98.7)	83.3 (77.3-89.4)	96.4 (93.4-99.4)	18.48 (10.01-72.72)	0.14 (0.08-0.20)
overall global, superior or inferior quadrants with RNFL thickness abnormal at < 5% level	87.0 (81.5-92.4)	85.9 (80.2-91.5)	62.5 (54.6-70.4)	96.1 (92.9-99.2)	6.16 (4.12-10.91)	0.15 (0.08-0.23)
overall global, superior or inferior quadrants with RNFL thickness abnormal at < 1% level	73.9 (66.8-81.0)	95.3 (91.9-98.7)	81.0 (74.6-87.3)	93.1 (89.0-97.2)	15.71 (8.20-63.77)	0.27 (0.19-0.36)
superior or inferior quadrants with RNFL thickness abnormal at < 5% level	87.0 (81.5-92.4)	88.2 (83.0-93.5)	66.7 (59.0-74.3)	96.2 (93.0-99.3)	7.39 (4.80-14.13)	0.15 (0.08-0.22)
superior or inferior quadrants with RNFL thickness abnormal at < 1% level	73.9 (66.8-81.0)	96.5 (93.5-99.5)	85.0 (79.2-90.8)	93.2 (89.1-97.3)	20.94 (10.24-151.11)	0.27 (0.19-0.36)
overall global, TS or TI sectors with RNFL thickness abnormal at < 5% level	87.0 (81.5-92.4)	92.9 (88.8-97.1)	69.0 (61.5-76.5)	96.2 (93.0-99.3)	8.21 (5.23-16.51)	0.15 (0.08-0.22)
overall global, TS or TI sectors with RNFL thickness abnormal at < 1% level	69.6 (62.1-77.0)	95.3 (91.9-98.7)	80.0 (73.5-86.5)	92.0 (87.7-96.4)	14.78 (7.63-60.61)	0.32 (0.23-0.41)
TS or TI sector with RNFL thickness abnormal at < 5% level	69.6 (62.1-77.0)	91.8 (87.3-96.2)	84.2 (78.3-90.1)	92.1 (87.8-96.5)	19.71 (9.52-143.64)	0.32 (0.23-0.41)
TS or TI sector with RNFL thickness abnormal at < 1% level	52.2 (44.1-60.3)	95.3 (91.9-98.7)	57.1 (49.1-65.2)	87.4 (82.0-92.7)	4.93 (2.83-10.77)	0.53 (0.42-0.66)

CI: confidence interval; positive predictive value (PPV); negative predictive value (NPV); likelihood ratio positive (LRP); likelihood ratio negative (LRN); TS: superior-temporal; TI: inferior-temporal; NS: superior-nasal; NI: inferior-nasal.