Screening for Glaucoma in High-Risk Populations Using Optical Coherence Tomography

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Objective: To estimate the diagnostic accuracy of Stratus optical coherence tomography (OCT) for glaucoma screening in high-risk populations.

Design: Cross-sectional evaluation of a diagnostic test for screening.

Participants: Three hundred thirty-three community-based volunteer participants with risk factors for glaucoma.

Methods: The optic nerve and peripapillary retinal nerve fiber layer (RNFL) of participants' eyes were scanned using the Stratus OCT. Based on an ophthalmologic examination and frequency doubling perimetry, eyes were classified into 4 categories: normal, possible glaucoma, probable glaucoma, and definitive glaucoma.

Main Outcome Measures: The sensitivities, specificities, positive and negative likelihood ratios of the RNFL, optic disc parameters, and their combinations were calculated.

Results: The right eyes were retained for analyses. After excluding eyes with missing data or with poor quality scans, the data of 210 right eyes were analyzed. Six eyes had definitive glaucoma. Combining the best performing optic nerve head parameters (cup diameter or cup/disc vertical ratio or cup/disc area ratio) and RNFL parameters (superior average or inferior average or overall average) using AND-logic resulted in a sensitivity of 67% (95% confidence interval [CI], 24%–94%), specificity of 96% (95% CI, 92%–98%), a positive likelihood ratio of 17.08 (95% CI, 7.06–41.4), and a negative likelihood ratio of 0.35 (95% CI, 0.11–1.08).

Conclusions: When adequate quality scans may be obtained, the Stratus has moderate sensitivity and high specificity for definitive glaucoma. Specificity is increased when parameters from both the optic nerve head and RNFL scans are combined.

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Glaucoma is the primary cause of irreversible blindness worldwide. In the United States, >2 million people were estimated to be affected in 2000 and the number affected is projected to increase to 3.6 million by 2020 as the population ages.[1]

Current recommendations for glaucoma screening remain equivocal.[2] The United States Preventive Services Task Force Recommendation Statement regarding screening for glaucoma cites insufficient evidence to "determine the extent to which screening would reduce impairment in vision related function or quality of life."[3,4] Meanwhile, the Recommendation Statement acknowledged the potential benefit of screening high-risk groups such as older African Americans.

Known risk factors for glaucoma include age, race, and family history. The prevalence rates of chronic open angle glaucoma increase from 1.5% in the 40- to 49-year-old age group to 5.1% in 70- to 79-year-olds.[1] The Los Angeles Latino Eye Study showed significantly higher prevalence rates among Hispanics of Mexican ancestry compared with whites particularly in those >70 years old.[5] The Baltimore Eye Survey showed a 3- to 4-fold higher prevalence for every age group in blacks compared with whites.[6] Having a first-degree relative (parent, sibling, or child) with glaucoma has been consistently associated with an increased risk of chronic open-angle glaucoma in prevalence surveys.[7–9] Selective screening in high-risk groups may be a more cost-effective option than comprehensive, population-based screening.

A recent systematic review of cost-effectiveness studies regarding glaucoma screening also cited insufficient evidence to reach a conclusion.[10] The uncertainty was partly attributed to technological advances in glaucoma diagnostic imaging devices, which had not been adequately evaluated for screening purposes.

Glaucoma diagnostic imaging with optical coherence tomography provides quantitative measurements of the optic nerve head and peripapillary retinal nerve fiber layer (RNFL). The earliest observable defect in glaucoma is atrophy of the RNFL.[11] Optic nerve cupping has also been shown to precede visual field (VF) loss.[12–14] Thus, imaging enables early detection of the disease and treatment initiation. Early treatment of glaucoma has been shown to reduce the incidence of VF loss.[15,16]

The Stratus optical coherence tomography (Stratus OCT; Carl Zeiss Meditec Inc., Dublin, CA) can provide high-

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resolution (8–10 μm), cross-sectional images of the RNFL and optic nerve head (Stratus OCT Software Version 4.0: Real Answers in Real Time. available: http://www.meditec.zeiss.com; accessed October 10, 2008). The RNFL parameters found to be most useful for detecting glaucoma were the overall average, inferior, and superior quadrants. These parameters were associated with area under the receiver operating curves (AUC) ranging from 0.86 to 0.89.[17,18] The best optic nerve head parameter in 1 study was the cup/disc area ratio with an AUCs of 0.88.[19] These and many previous studies on the diagnostic accuracy of the Stratus were conducted among eye clinic or glaucoma service patients.[17,20–23] The sensitivity and specificity of diagnostic tests have been shown to depend on the disease spectrum in the population in which they are used.[24] The severity of VF loss has been shown to significantly influence the sensitivity of glaucoma imaging devices. The sensitivity of the Stratus OCT and scanning laser polarimetry improve with more severe disease.[23] Patients seen in eye clinics or by glaucoma services likely have more advanced disease than volunteer participants from the community neither referred nor previously evaluated for glaucoma. The purpose of our study was to evaluate the performance of the Stratus fast RNFL and fast optic disc parameters to screen for glaucoma in high-risk populations neither referred nor followed by ophthalmologists.

Methods

The Standards for Reporting of Diagnostic Accuracy were reviewed and followed.[25]

Patient Population

This observational, cross-sectional study was performed in Montreal, Quebec, Canada. The study protocol was approved by the ethics committee of Maisonneuve-Rosemont Hospital, a University of Montreal affiliated hospital. Informed consent was obtained from all study participants and the research protocol adhered to the tenets of the Declaration of Helsinki. Data collection was planned before the date of enrollment and before testing was performed.

To be eligible, subjects had to fulfill ≥1 of the following inclusion criteria: (1) self-described Caribbean, African, or Hispanic origin, (2) >50 years of age, or (3) positive family history of glaucoma. For example, a 60-year-old Caucasian man with no family history of glaucoma would have been included as a case because he fulfilled 1 of the criteria. The exclusion criteria were an inability to give informed consent and an inability to complete an ophthalmic examination or OCT scan.

Participants were recruited and examined consecutively at the following locations: a Caribbean community church, an outdoor summer festival, a community park, the Judith Jasmin Chronic Care Nursing Centre, the Eye Clinic of Maisonneuve-Rosemont Hospital, and the Glaucoma Institute of Montreal between August 2003 and May 2008. Participants examined at the first 3 sites were recruited by setting up kiosks and recruiting passersbys. Participants examined at the Judith Jasmin Centre were approached on the ward and offered free glaucoma screening. At these 4 sites, participants were examined in a mobile clinic that included a Stratus OCT and underwent scanning the same day. Participants who were examined at Maisonneuve-Rosemont Hospital and the Glaucoma Institute of Montreal were volunteer participants who either responded to advertisements placed in clinic waiting areas, hospital circulars, and local newspapers, or were approached by study coordinators offering free screening tests for family members accompanying glaucoma patients. These participants were examined at the hospital or the Glaucoma Institute and underwent scanning the same day or, when an ophthalmic technician was unavailable, within 1 month of their examination.

After informed consent was obtained, an interviewer completed a questionnaire regarding family, medical, and ocular history. Family history of glaucoma was considered positive if the participant reported a first-degree relative (parent, sibling, or child) diagnosed with glaucoma.

Clinical Examination

Subjects underwent a complete eye examination by 1 of 2 glaucoma specialists (PH, GL) who were masked to the results of the Stratus scan and perimetry. The ocular examination included pachymetry, gonioscopy, slit-lamp examination, intraocular pressure (IOP), and a stereo examination of the optic nerve head, RNFL, and retina. The optic nerve head examination was performed using a 78-diopter lens and documented using the vertical cup-to-disc ratio and the Disc Damage Likelihood Scale,[26] where stage 0 represents no optic nerve damage and stage 7 represents advanced rim loss. Pupils were only dilated for the clinical examination when visualization of the optic nerve head was difficult undilated. Patients also underwent confocal scanning laser ophthalmoscopy of the optic nerve head with a Heidelberg Retina Tomograph (HRTII or HRTIII; Heidelberg Engineering, Heidelberg, Germany) for a separate ongoing study.[27] Based on the Disc Damage Likelihood Scale, individual eyes were then classified by the examiner as normal, glaucoma suspect, or glaucoma.

Frequency Doubling Technology

At the same visit, patients performed a VF test in both eyes using the frequency doubling technology (FDT) screening C-20-5 program (Humphrey Instruments, Dublin, CA) or the 24-2 FDT Matrix threshold program (FDT2, Humphrey Matrix; Carl-Zeiss Meditec). The test has been described previously.[28] Testing was performed in a dark room. Both eyes were tested according to the instrument protocol. The test was orally explained to each subject and a preview of the target stimuli was shown at the beginning. The test was administered by a physician-researcher trained in FDT testing or a VF technician with ≥1 year experience with the machine. For the C-20-5 program, 17 targets including sixteen 10° square stimuli (4 per quadrant) plus a central 5° diameter circular stimulus were presented to each eye.[28] The test printout classifications ('within normal limits,' 'mild relative loss,' 'moderate relative loss,' and 'severe loss') based on comparisons with an age-related normative database for each target were documented. An FDT with ≥2 adjacent squares of relative loss was considered abnormal using the C-20-5.[29] The FDT2 24-2 program consists of 54 test points covering the central field out to 24°, except nasally, where it extends to 30°. The 24-2 program printout shows the number and areas of decreased sensitivity, the glaucoma hemifield test results (within normal limits, borderline, or outside normal limits), the pattern standard deviation, and the mean deviation.[30] A glaucoma hemifield test outside normal limits or borderline was considered abnormal.

Final Diagnostic Classifications

The data of eyes classified as "glaucoma suspect" or "glaucoma" were reviewed in combination with the FDT results (but blinding to the Stratus scan results was maintained) to assess whether areas

Table 1. Diagnostic Classifications Based on Clinical Examination and Frequency Doubling Technology (FDT)

Diagnostic Classification	Examination Results	
	Ophthalmic Examination	*FDT*
Normal	Normal	Normal
Possible glaucoma	Normal	Abnormal
	Glaucoma suspect	Normal
Probable glaucoma	Glaucoma suspect	Abnormal
	Glaucoma	Normal
Definitive glaucoma	Glaucoma	Abnormal

of neuroretinal rim thinning were compatible with the locations of VF defects using an optic disc-VF map.[31] For example, inferotemporal rim thinning accompanied by a superonasal step was considered definitive glaucoma. Eyes were then classified into 4 categories based on the optic disc appearance and perimetry results (Table 1). Definitive glaucoma was used as the gold standard for glaucoma diagnosis.

Optical Coherence Tomography Scan

Detailed principles of the OCT have been published previously.[32] Unless dilation was required to visualize the optic nerve head, nondilated OCT scans were performed by a photographer masked to the results of the clinical and FDT examination. Spectacle correction was noted. Scans with a signal strength <6 were considered to be of inadequate quality and were not analyzed. In eyes where pupillary dilation was required for the optic nerve head examination, OCT scans were performed before and after dilation.

Both the Fast RNFL and the Fast Optic Disc scan protocols of the Stratus were performed (Stratus OCT, Software Version 4.0; Carl Zeiss Meditec, Inc.). The Fast RNFL scan performs circular scans of 3.4 mm diameter around the optic nerve head and provides measurements of the RNFL in the peripapillary region. Measurements are provided for clock-hour sectors, quadrant averages (superior, inferior, nasal, temporal), and overall averages of the circular scan. These measurements are compared with a normative database which is divided into percentiles. Measurements below the 5th percentile and 1st percentile are indicated in yellow and red, respectively.

The Fast Optic Disc scan performs 6 radial line scans through the optic disc, which provides cross-sectional information on cupping and rim area. Disc margins are identified from the termination of the retinal pigment epithelium. The following parameters are directly measured: rim area (vertical cross-section), average nerve width at disc, disc diameter, cup diameter, and rim length (horizontal). The following optic nerve head parameters are derived from the 6 radial line scans: vertical integrated rim area, horizontal integrated rim width, disc area, cup area, rim area, cup/disc area ratio, cup/disc horizontal ratio, and cup/disc vertical area ratio. There is no normative database for this scanning protocol.

Outcome Measures

For the purposes of this study, the assumed gold standard to which scan results were compared was definitive glaucoma. However, analysis was also performed for the combined grouping of probable and definitive glaucoma to evaluate the performance of the Stratus for earlier forms of glaucoma. From the Fast RNFL scan, we combined the superior average, inferior average, and overall average using OR logic. More specifically, a scan was considered

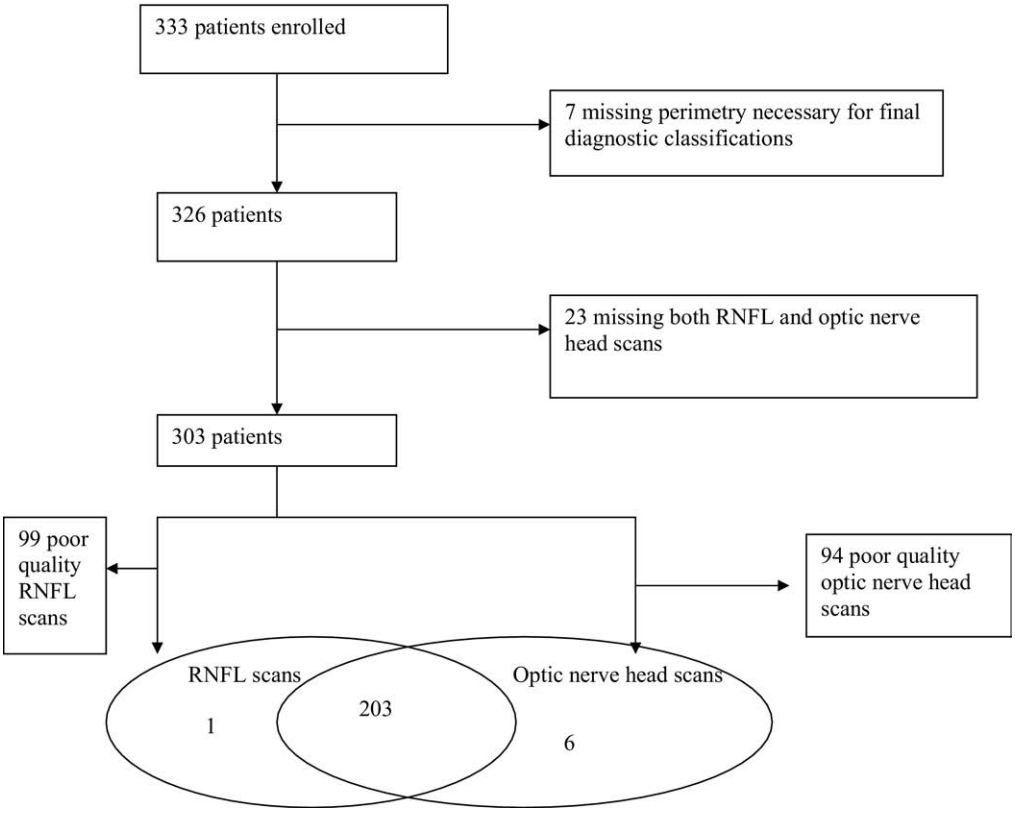

Figure 1. Patient enrollment and exclusion. RNFL = retinal nerve fiber layer.

positive for glaucoma if at least 1 or more of these 3 parameters fell below the percentile cutoffs. We compared the percentile classifications (5th and 1st) to the assumed gold standard. Sensitivity, specificity, positive likelihood ratio (PLR), and negative likelihood ratio (NLR) were calculated.

To evaluate the performance of the Fast Optic Disc scan, the 3 best performing parameters were identified by selecting those with the highest sensitivity–specificity combinations. Threshold values associated with the highest combination of sensitivity and specificity for detection of definitive glaucoma were chosen as cutoffs. The 3 best performing parameters were then combined using OR logic and compared with the assumed gold standard. The sensitivity, specificity, PLR, and NLR were calculated. Areas under the receiver operating characteristic curves were also calculated to enable comparisons with previous studies.

The 3 RNFL and 3 optic nerve head parameters were then combined to detect glaucoma using an AND logic gate. More specifically, the combined scans were considered positive for glaucoma when ≥1 of the 3 RNFL parameters and ≥1 of the 3 optic nerve head parameters were below the cutoffs. We calculated sensitivity, specificity, PLR, and NLR for this combination of the Fast RNFL and Fast Optic Disc scans.

Statistical Analyses

We arbitrarily selected the right eyes for analysis. Analyses were performed only on eyes that had undergone the clinical examination, the FDT VF, and the Stratus scan with a signal strength ≥6. Statistical analyses were performed using STATA software version 9.0 (StatCorp, College Station, TX).

The following performance parameters of diagnostic tests were calculated as follows:

$$\text{sensitivity} = [\text{true positives}/(\text{true positives} + \text{false negatives})],$$

$$\text{specificity} = [\text{true negatives}/(\text{true negatives} + \text{false positives})],$$

$$\text{PLR} = [\text{sensitivity}/(1 - \text{specificity})], \text{ and}$$

$$\text{NLR} = [(1 - \text{sensitivity})/\text{specificity}].$$

Confidence intervals (CI) were calculated for all parameter estimates.

Results

All subjects met ≥1 high-risk inclusion criterion. Of 333 participants who were examined, 30 were excluded owing to missing data: 7 subjects had a missing FDT VF and 23 had missing Stratus scans. Of the remaining 303 patients, 51 were examined and tested at the hospital (Rosemont pavilion where the eye clinic was located until 2005), 77 were examined and tested at the new ambulatory eye clinic of the hospital (Centre de santé ambulatoire, which opened in 2005), 127 at the Glaucoma Institute of Montreal (an outside office and surgical facility), and 48 during mobile screening clinics.

For Stratus RNFL scan analysis, data from 99 eyes were excluded because of poor signal strength (<6) leaving 204 RNFL scans for analysis. For Stratus optic nerve head scan analysis, 94 eyes were excluded owing to inadequate scan quality (<6; Fig 1), leaving 209 optic nerve head scans for analysis. In some patients, the RNFL scan was of adequate quality whereas the optic nerve head scan was not and vice versa; therefore, only 203 eyes had both a good quality RNFL and optic nerve head scan. In total, the scan data of 210 eyes were analyzed: either RNFL scan data or optic nerve scan data or data from both scans.

Scans performed during mobile screening clinics where the Stratus OCT was transported to the examination site were more likely to have poor quality scans. Of Stratus scans performed during mobile clinics, 72.9% (35/48) had signal strengths <6. In contrast, 13.3% of scans performed at the Glaucoma Institute of Montreal (a clinical and surgical facility) had poor quality scans. The difference in proportions of poor quality scans from mobile clinics compared with the Glaucoma Institute was 59.6% (95% CI, 45.8%–73.6%). Meanwhile, 27.3% of scans performed at the new eye clinic (as of 2005) had poor signal strength. The difference in proportions of poor quality scans from mobile clinics compared with the new eye clinic was 45.6% (95% CI, 29.6%–61.6%).The association between an inability to fixate and poor signal strength was also assessed. Twenty eyes with inadequate signal strength had best corrected visual acuities <20/70, which could potentially explain a diminished signal. The majority of eyes (72%) with poor signal strength had 0 fixation losses during FDT.

Of the patients examined, 10.3% required pupillary dilation to better visualize the posterior pole. However, even after dilation, the signal strength was poor and these eyes were not included in the analyses.

The characteristics of the study population are summarized in Table 2. The mean ± standard deviation age was 61.01±8.73 years. The mean IOP was 15.8±3.6 mmHg in both eyes. The mean disc area of study eyes, as measured by the OCT Fast Optic Disc Scan, was 2.29 mm^2 (Table 2). More than 70% of participants were female and 38.3% had a self-reported family history of glaucoma. The majority of patients (91.43%) were Caucasian. Of 210 eyes, 6 were considered to have definitive glaucoma.

Among excluded eyes owing to a missing (n = 23) or poor quality RNFL scan (n = 99), 3 of these 122 (2.45%) eyes had definitive glaucoma, 7 (5.74%) had probable glaucoma, 37 (30.33%) had possible glaucoma, and 75 (61.48%) had normal eyes. The mean age of patients whose eyes were excluded was 62.22 years (standard deviation, 11.93). The majority were female (84/122 [68.85%]). Eighteen patients (14.75%) were of African

Table 2. Study Population Characteristics

Total number of eyes analyzed	210
Demographics	
Age (yrs)	
Mean ± SD	61.01±8.73
Range	22–87
Gender	
Female	157 (74.76%)
Male	53 (25.24%)
Race	
Black	15 (7.14%)
White	192 (91.43%)
Hispanic	2 (0.95%)
Other	1 (0.48%)
Positive family history for glaucoma	81
Ocular characteristics	
Mean IOP ± SD (mmHg)	15.82±3.59
Mean refractive error (spherical equivalent) ± SD (D)	+0.50±1.75
Range (D)	−5.25 to +5.75
Mean disc area (mm^2) ± SD (mm^2)	2.29±0.47
Range (mm^2)	1.32–3.94
Clinical diagnoses, no. eyes (%)	
a = Normal	121 (57.62)
b = Possible glaucoma	71 (33.80)
c = Probable glaucoma	12 (5.71)
d = Definitive glaucoma	6 (2.86)

D = diopters; IOP = intraocular pressure; SD = standard deviation.

Table 3. Performance of Combined Superior Average, Inferior Average, and Overall Retinal Nerve Fiber Layer Thickness Parameters Using OR Logic to Detect Definitive Glaucoma Using the Stratus (right eye; n = 204)

Stratus Classifications	5th Percentile Cutoff	1st Percentile Cutoff
Sensitivity (95% CI)	0.67 (0.24–0.94)	0.5 (0.19–0.81)
Specificity (95% CI)	0.85 (0.79–0.90)	0.94 (0.89–0.97)
Positive likelihood ratio	4.55 (2.12–9.04)	8.25 (2.87–21.90)
Negative likelihood ratio	0.39 (0.21–1.16)	0.53 (0.32–1.15)

CI = confidence interval.

origin and 104 (85.25%) were Caucasian. The mean IOP was 16.46±3.51 mmHg. The mean refractive error (spherical equivalent) was −0.50±2.53 diopters. The mean disc area of excluded eyes was 2.43±0.54 mm^2.

When an abnormal test result was defined as RNFL measurements below the 5th percentile cutoff in the superior quadrant or inferior quadrant or overall average RNFL thickness (OR logic), the Stratus had acceptable specificity (0.85), but low sensitivity (0.67) for a screening test (Table 3). When the 1st percentile cutoff was used, the sensitivity decreased, but the specificity and likelihood ratios improved (Table 3).

To assess the performance of the Stratus RNFL parameters in detecting less advanced cases of glaucoma, the diagnostic classification was changed to include probable and definitive glaucoma. Sensitivity decreased to 0.35 (95% CI, 0.15–0.61), specificity remained similar at 0.86 (95% CI, 0.79–0.90), the PLR was 2.44 (95% CI, 1.16–5.20), and the NLR was 0.76 (95% CI, 0.58–1.07).

The 3 best performing optic nerve head parameters were the cup diameter, the cup/disc vertical ratio, and the cup area (Table 4), which were associated with the highest sensitivity and specificity. The cutoffs for glaucoma detection (Table 4) were selected based on the thresholds associated with the highest sensitivity and specificity combinations (Fig 2A–C). Combining the best performing optic nerve head parameters using OR logic resulted in improved sensitivity (1.00) compared with RNFL parameters, but decreased specificity (0.75; Table 5).

The combination of the 3 RNFL and 3 optic nerve head parameters performed best in detecting definitive glaucoma (Table 6). The sensitivity was similar to that of the 3 combined RNFL parameters, but the specificity increased from 0.85 (95% CI, 0.79–0.90) to 0.96 (95% CI, 0.93–0.98). Compared with the 3 RNFL parameters, the PLRs of the combined RNFL and optic nerve scan parameters improved (from 4.55 to 17.10).

Discussion

Glaucoma imaging is currently used as an adjunct to other clinical parameters important in glaucoma diagnosis and progression.[33] The performance of the Stratus for glaucoma detection has been evaluated in patients followed in eye clinics. Within this population, the sensitivity of the best performing RNFL parameters ranges between 75% and 85% for specificities >88%.[17,22,34–37] However, patients followed in eye clinics by glaucoma specialists have more advanced disease than in a screening population. The sensitivity and specificity of diagnostic tests have been shown to depend on the disease spectrum in the population in which they are used.[24] The severity of VF loss has been shown to significantly influence the sensitivity of confocal scanning laser ophthalmoscopy, scanning laser polarimetry, and Stratus OCT. More severe disease was associated with increased sensitivity.[23] The aim of our study was to assess the performance of the Stratus in a screening population.

We have shown a sensitivity of 0.67 (95% CI, 0.24–0.94) and a specificity of 0.85 (95% CI, 0.79–0.90) for the combination of superior quadrant, inferior quadrant, and overall RNFL using the 5th percentile cutoff. This combination of parameters was based on the study by Lu et al,[17] which showed this combination achieved optimal diagnostic accuracy. They showed a sensitivity–specificity combination of 0.65–0.97 at the 5th percentile cutoff for perimetric glaucoma. The inclusion of additional RNFL parameters increased specificity, but decreased sensitivity. Furthermore, the OR logic combinations can be easily performed from the scan printout without requiring additional statistical software, which would not be feasible in a population screening program. Direct comparisons between studies are

Table 4. Sensitivity, Specificity, and Area Under the Receiver Operating Curves (AUC) of Stratus Optic Nerve Head Parameters to Detect Definitive Glaucoma (right eye; n = 210)

Optic Nerve Head Parameter	Cutoff for Detection of Definitive Glaucoma	Sensitivity (%)	Specificity (%)	AUC (95% CI)
Cup diameter	≥1.16	83.33	84.39	0.91 (0.82–0.99)
Cup/disc vertical ratio	≥0.68	83.33	81.95	0.88 (0.80–0.95)
Cup area	≥1.33	83.33	81.46	0.86 (0.78–0.93)
Cup/disc area ratio	≥0.49	83.33	75.61	0.86 (0.78–0.95)
Cup/disc horizontal ratio	≥0.70	83.33	71.71	0.84 (0.75–0.93)
Disc diameter	≥1.75	83.33	45.37	0.64 (0.40–0.89)
Disc area	≥1.95	83.33	28.29	0.64 (0.33–0.95)
Rim area	≥0.54	83.33	6.83	0.23 (0.03–0.42)
Average nerve width at disc	≥0.22	83.33	1.46	0.17 (0.00–0.42)
Horizontal integrated rim width (area)	≥1.02	83.33	1.46	0.14 (0.00–0.33)
Rim length (horizontal)	≥0.28	83.33	0.98	0.17 (0.01–0.34)
Rim area (vertical cross section)	≥0.02	83.33	0.98	0.14 (0.00–0.35)
Vertical integrated rim area (volume)	≥0.07	83.33	0.49	0.08 (0.00–0.20)

CI = confidence interval.

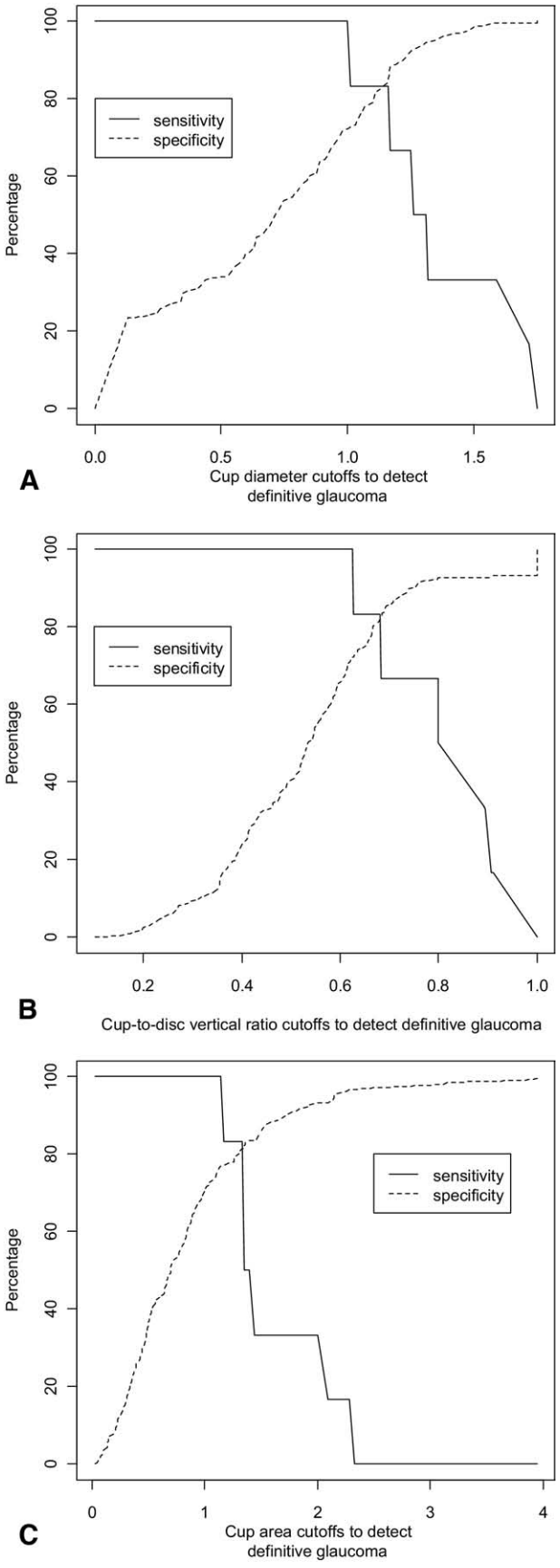

Table 5. Performance of Combined Cup Diameter, Cup/Disc Vertical Ratio, Cup Area Ratio Optic Nerve Head Parameters to Detect Definitive Glaucoma Using OR Logic (right eye; n = 210)

	Classification Using 3 Optic Nerve Head Parameters
Sensitivity (95% CI)	1.00 (0.54–1.00)
Specificity (95% CI)	0.75 (0.69–0.81)
Positive likelihood ratio	4.02 (3.17–5.10)
Negative likelihood ratio	0

CI = confidence interval.

difficult because of the use of different gold standards and VF machines.

We also evaluated optic nerve head parameters. Our 3 best performing parameters were the cup diameter, the cup/disc vertical ratio, and the cup area. Other studies consistently confirm the cup/disc vertical ratio to be among the best performing parameters.[38,39] Medeiros et al did not assess cup diameter, but found the highest AUCs using cup/disc vertical ratio (0.88) and cup/disc area ratio (0.88).[17,40] In a study by Brusini et al, the cup/disc area ratio had the highest AUC (0.88), followed by horizontal integrated rim width (0.87), vertical integrated rim area (0.86), and cup/disc vertical ratio (0.84).[19] The 3 optic nerve head parameters with the highest AUCs in a study by Wollstein et al were rim area (0.97), horizontal integrated rim width (0.96) and vertical integrated rim area (0.95). The AUC for the cup/disc vertical ratio was high (0.93); cup diameter was not assessed.[41]

A combination of RNFL and optic nerve head parameters improved specificity and the PLR compared with RNFL or optic nerve head parameters alone.

The PLR allows the clinician to update the probability of disease after a particular test result is obtained. Before the test result is known, the prior probability may be the prevalence of disease and is revised to a posterior probability once the test result is obtained.[42] For example, to calculate the posterior probability of having definitive glaucoma if the combination of RNFL and optic nerve head parameters are abnormal (Table 6), we consider the prior probability of definitive glaucoma to be 2.9%, the prevalence in our study population (Table 2). Using the likelihood ratio, we calculate:

$$\text{Prior odds} = \text{prior probability}/(1 - \text{prior probability})$$

$$\text{Posterior odds} = \text{prior odds} \times \text{PLR}$$

$$\text{Posterior probability} = \text{posterior odds}/(1 + \text{posterior odds})$$

Figure 2. A, Sensitivity and specificity of cup diameter cutoffs to detect definitive glaucoma (right eye; n = 209). **B,** Sensitivity and specificity of cup-to-disc vertical ratio cutoffs to detect definitive glaucoma (right eye; n = 209). **C,** Sensitivity and specificity of cup area cutoffs to detect definitive glaucoma (right eye; n = 209).

Table 6. Performance of Combined Retinal Nerve Fiber Layer and Optic Nerve Head Parameters Using AND Logic to Detect Definitive Glaucoma (right eye; n = 210)

	Classification Using 3 Retinal Nerve Fiber Layer and 3 Optic Nerve Head Parameters
Sensitivity (95% CI)	0.67 (0.22–0.96)
Specificity (95% CI)	0.96 (0.93–0.98)
Positive likelihood ratio	17.10 (7.06–41.40)
Negative likelihood ratio	0.35 (0.11–1.08)

CI = confidence interval.

The prior odds are therefore 0.03 [= 0.029/(1 − 0.029)]. The posterior odds are 0.51 (= 0.03 × 17.10 from Table 6). The posterior probability of having definitive glaucoma is then 0.34 (= 0.51/[1 + 0.51]). In our population, a negative test result is more informative because the specificity (96%) is high. When the patient does not have definitive glaucoma, the test is normal 96% of the time. The high specificity of the test is potentially useful to eliminate unnecessary visits with an ophthalmologist or additional testing, thereby decreasing health care costs.

Other glaucoma imaging devices have been evaluated for screening. The HRT II (Heidelberg Engineering) is a confocal scanning laser ophthalmoscope that produces 3-dimensional measurements of the optic nerve head. The HRT II has been shown to have a sensitivity of up to 85% (95% CI, 54%–97%) for a specificity of 96% (95% CI, 92%–98%) in a high-risk volunteer population using the clinical examination as the gold standard.[27] The scanning laser polarimeter (GDx-VCC; Carl Zeiss Meditec Inc.) measures peripapillary RNFL thickness and showed high specificity (97%; CI unavailable), but low sensitivity (25.6%; CI unavailable) in a self-recruited high-risk population for its best performing parameter, the Nerve Fiber Index.[43] Combining the Nerve Fiber Index with Matrix FDT improved sensitivity to 12%; specificity remained high at 99.6%. Glaucoma was defined by typical optic nerve changes and VF abnormalities. Because different devices measure different areas involved in glaucomatous damage, there is imperfect agreement between devices with no test able to detect all cases.[40]

The performance of the Stratus depends partly on the gold standard used. The gold standard for glaucoma diagnosis is documented progression over time in the form of changes on optic disc photographs or the development of VF defects on achromatic automated perimetry (AAO Preferred Practice Patterns Committee Glaucoma Panel. Primary open angle glaucoma suspect. AAO Annual Meeting, 2002; San Francisco). However, in a screening scenario, this longitudinal follow-up is not feasible. The next best gold standard possible is correlating structural (optic nerve head) and functional (VF) defects. The optic nerve head examination was performed by a glaucoma specialist and documented using the disc damage likelihood scale, which has been shown to have an AUC of 0.95 for perimetric glaucoma and an interobserver reproducibility of 85%.[26,44,45] We used FDT perimetry as we hypothesized a screening population would have less advanced disease requiring detection at the earliest possible stage. Frequency doubling technology has been reported to be a good predictor of future standard automated perimetry VF defects.[46–48] We considered ≥2 adjacent squares of relative loss as abnormal using the C-20-5. This definition is associated with a specificity of 85% and a sensitivity of 66.7% for glaucoma.[29] Therefore, by using this cutoff, the prevalence of glaucoma may have been underestimated.

One of the limitations of our study include the data derived thresholds for glaucoma detection using the Fast Optic Disk scan. Because these cutoffs were based on our data, they may not perform as well in another dataset.

Another limitation was the loss of data owing to poor signal strength. We have shown poorer signal strength was observed with mobile clinics where the Stratus was moved from 1 site to another. We have also observed poor signal strength that improved after replacing the superluminescent diode light source. The most consistently high signal strengths were observed at the Glaucoma Institute of Montreal, a semiprivate office. The Stratus may not be adapted for use in mobile glaucoma screening clinics, but requires a site where regular maintenance can be ensured. Another factor influencing signal strength is pupillary dilation. Smith et al[49] showed acquisition of high-quality OCT images was not possible in 9.5 of 38 (25%) patients when undilated. An inability to obtain adequate signal strength through an undilated pupil was associated with smaller pupil size and increasing cataract.[49] In our study, approximately one third of scans had inadequate signal strength and were not analyzed. Up to one third of patients may require dilation to achieve adequate signal strength when using the Stratus.

The loss of one third of participants raises the potential for bias. To evaluate this potential, we analyzed the prevalence of glaucoma among excluded patients owing to poor signal strength, characterized their risk factors for glaucoma and evaluated ocular measurements that could influence the performance of the Stratus. The prevalence of definitive glaucoma among excluded eyes was similar to that of included eyes (2.45% vs 2.86%). Differences in mean IOP, refractive errors, and disc areas were not significant. Larger optic disc areas have been associated with decreased sensitivity for the RNFL parameter average thickness, whereas smaller discs have been associated with increased sensitivity.[23] The demographic profiles were similar in both groups except for racial distribution. Whereas 7% of included patients were of African origin, approximately 15% of excluded patients were of African descent. There was no clear association with fixation loss in the majority of these patients; 72% had 0 fixation losses during FDT. Further studies would be necessary to confirm these findings.

We did not use scan tracking coordinates, which could have improved centration around the optic disc. Recent evidence shows that scan centration may be improved by using scan tracking coordinates during image acquisition.[50] Optimizing scan centration may have improved the accuracy of measurements within the different quadrants.

In conclusion, Stratus images with the highest signal scores were obtained in nonmobile settings. When adequate quality images are obtained, the Stratus may be useful for

glaucoma screening in high-risk groups. The device has inadequate sensitivity to be used alone, but may be useful as an initial test to exclude patients who do not require further screening tests or an evaluation by an ophthalmologist.

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