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Use of optical coherence tomography by non-expert personnel as a screening approach for glaucoma

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Abstract

Purpose—Pilot study to assess optical coherence tomography (OCT) as a screening tool for glaucoma when used by non-expert personnel.

Methods—This prospective case control study included 54 patients with open angle glaucoma and 54 age matched comparison individuals. Optovue iVue SD-OCT imaging was performed by non-professional photographers on undilated patients. The sensitivity, specificity, negative predictive value, and positive predictive value of iVue scan parameters for detecting open angle glaucoma were evaluated.

Results—The iVue cup to disc vertical ratio had a sensitivity of 0.96 (95% CI 0.90-1.00) at 90% specificity and was strongly correlated with both the Cirrus HD-OCT cup to disc vertical ratio (Pearson coefficient=0.84) and the cup to disc ratio observed on dilated clinical examination by faculty ophthalmologists (Pearson coefficient=0.80). The retinal nerve fiber layer (RNFL) parameters performed robustly, but the ganglion cell complex (GCC) parameters showed limited diagnostic value. The inferior quadrant thickness was among the best performing RNFL parameters, with a sensitivity of 0.87 (95% CI 0.78-0.96) and a specificity of 0.88 (95% CI 0.80-0.97) using the iVue normative database thresholds for abnormality.

Conclusions—OCT imaging may be performed by non-professional photographers on undilated patients, and quantitative parameters derived from the resultant images, particularly the vertical cup to disc ratio and the RNFL inferior quadrant thickness, demonstrate sensitivities and specificities that may be adequately robust for glaucoma screening in the community setting.

Keywords

glaucoma; optical coherence tomography; screening

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Introduction

Glaucoma is the second leading cause of blindness, and the number of individuals affected worldwide is expected to rise to nearly 80 million by 2040.¹ Due in part to inadequate access to eye care services and the painless, gradual vision loss that is characteristic of glaucoma, many patients go undiagnosed and untreated until their disease progresses to advanced stages. Studies have estimated that at least half of the glaucoma cases in the United States are undiagnosed.² Glaucoma is associated with decreased vision related quality of life,³ and reducing the burden of this disease is a pressing public health need. Community based vision screening is one of the many approaches being used to help address this issue. However, the most commonly used screening methods, including measurement of intraocular pressure, visual field testing, and optic nerve head examination, have low sensitivity and specificity, limiting the overall efficacy and cost-effectiveness of community-based glaucoma screenings.^{4,5}

Optical coherence tomography (OCT)⁶ is now frequently used in clinical ophthalmological diagnosis and management. In addition to quantitatively measuring retinal nerve fiber layer thickness and cup to disc ratio, OCT generates images of the optic nerve head and retina. As OCT imaging is widely available, non-invasive, and rapid, it has the potential to be a useful tool in community-based screening for glaucoma. Although the role of OCT in glaucoma diagnosis has been extensively studied in the clinical setting, there are several factors that have limited the feasibility of widely implementing commonly used spectral domain OCT (SD-OCT) instruments in the community setting. Their table-based platforms are expensive, may be sensitive to vibration during travel, and are difficult to transport without disassembly and reassembly. Previous systematic reviews of the effectiveness of various screening tools for glaucoma have excluded OCT from their analyses, possibly because of these limitations.^{4,7}

The Optovue iVue SD-OCT (iVue; Optovue, Inc., Fremont, CA) is an FDA-approved instrument that is compact and sufficiently portable for use in the screening setting. One published study evaluating the utility of the iVue for the detection of open angle glaucoma (OAG)⁸ found modest predictive power for its quantitative measurements of retinal nerve fiber layer (RNFL) and ganglion cell complex (GCC) thickness in a community-based, cross-sectional population in the United Kingdom. In their cohort, only 5.1% had OAG and the iVue imaging was performed by an experienced technician. We have already carried out imaging with the iVue in a series of community-based screenings, showing its feasibility and durability for this purpose. The results of those examinations will be published in a future report. However, as the number of definitive OAG cases in screening programs is typically small, the predictive power of the approach must be initially estimated by studies with larger numbers of OAG patients. The present investigation is a clinic-based assessment of the identification of OAG by iVue imaging performed by non-expert personnel, as it might be implemented in community screening. We compared known OAG patients to a mixed group of persons who were either being seen in a retina clinic or who were controls, without detectable eye disease, accompanying patients to the clinic. The ability of OCT to detect OAG has been well documented, but to our knowledge, this is the first proof of concept

study demonstrating the feasibility of using a transportable device and non-professional personnel to acquire OCT images that are of sufficient quality for OAG discrimination.

Methods

This study was approved by the Johns Hopkins University School of Medicine Institutional Review Board, adhered to the tenets of the Declaration of Helsinki, and complied with the Health Insurance Portability and Accountability Act. All subjects provided written informed consent to participate. Subjects were recruited prospectively from the clinics of two faculty ophthalmologists (HAQ and AWS) at the Wilmer Eye Institute of the Johns Hopkins University School of Medicine between February, 2015 and April, 2016.

OAG patients were eligible for participation if they were English speaking, 18 years of age or older, and were scheduled to obtain OCT imaging by Cirrus SD-OCT (Carl Zeiss Meditec, Inc., Dublin, CA) as part of their routine care on that day. All OAG subjects met the definition of glaucoma in published criteria, including their optic disc findings and visual field loss.⁹ Briefly, glaucoma was diagnosed based on the presence of either cup to disc ratio >0.7 or cup to disc ratio asymmetry >0.2 and evidence of a visual field defect characteristic of glaucoma, such as an “outside normal limits” glaucoma hemifield test or a reproducible cluster of points at the 5% level on a pattern deviation plot from Humphrey HFA II-24-2 field testing (Carl Zeiss Meditec, Inc., Dublin, CA). Clinical examination by a glaucoma specialist was also performed to rule out other conditions that may affect the optic disc or retinal nerve fiber layer and to confirm that the observed disc changes and field deficits were due to glaucoma. The comparison group to those with OAG were English speaking, 18 years of age or older, had no prior diagnosis of OAG and were either patients in a retina clinic or controls with no known eye disease. Individuals who were included for comparison to OAG subjects and had no diagnosed eye disease were required to have visual acuity of 20/25 or better with habitual correction using the standard Early Treatment Diabetic Retinopathy Study (ETDRS) chart.

The iVue imaging was performed using the iVue GCC thickness, optic nerve head RNFL, and optic nerve head 3D scan protocols in both eyes without dilation. All iVue imaging was completely and independently performed by non-professional photographers (MML or CC, medical students, Johns Hopkins University School of Medicine) who had no experience in ophthalmic imaging prior to the study, aside from a single session of basic hands-on training for iVue scan acquisition. After iVue imaging, OAG patients proceeded with routine care, including clinical examination and Cirrus SD-OCT imaging (Optic Disc Cube 200×200 scan protocol) performed by a professional photographer or technical staff member. Comparison group patients did not receive Cirrus SD-OCT imaging. Patient characteristics, including age, race, gender, visual acuity with habitual correction, clinical exam findings, and past ocular history were recorded. Exam findings recorded from chart data included past ocular history and visual field findings from Humphrey HFA II-24-2 field testing (Carl Zeiss Meditec, Inc., Dublin, CA).

The sensitivity and specificity of iVue GCC and RNFL scan parameters to separate OAG from the comparison group were evaluated. Recognizing that measurements from the right

and left eyes of a single individual are correlated, for individuals imaged in both eyes, the more abnormal value for each individual test parameter was used for analysis. For each parameter, a receiver operator characteristic (ROC) curve was constructed using a nonlinear, weighted least squares model. The sensitivity at 90% or 95% specificity and the area under the ROC curve were used to compare the performance of the parameters. The iVue software incorporates a normative database, which allows for age-adjusted categorization of test parameters as “within normal”, “borderline”, or “outside normal” relative to healthy individuals. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the “outside normal” categorization were evaluated for each parameter. Since disease prevalence in this case-control study did not represent the disease prevalence in the population, predictive values and the associated standard errors for population screening were calculated using standard formulas.¹⁰ Combinations of two parameters were also considered. Statistical analyses were performed using R (version 3.2.2).

Results

A total of 112 individuals were enrolled. Four of these individuals were excluded due to an inability to obtain iVue images, indicating 96% successful acquisition of all images. The remaining 108 individuals included 54 OAG and 54 comparison individuals, whose demographic and clinical characteristics are summarized in Table 1. In 3 comparison group individuals, the iVue RNFL scans were obtained, but not the GCC scans, and in 2 comparison group individuals and 1 OAG patient there were successful GCC scans, but not RNFL scans. Thus, 105 study participants provided data for evaluation of each RNFL and GCC parameter.

The majority of all study participants were European-derived (n=87, 81%) and female (n=64, 59%). A significant proportion of study eyes were pseudophakic (n=96, 44%) or had some degree of cataract described in the clinical record (n=71, 33%). Among the comparison group, 16 were controls with no existing eye disease, while 38 were diagnosed with some retinal disease, including age-related macular degeneration, diabetic macular edema, epiretinal membrane, or macular hole, in one or both eyes. The severity of OAG in those individuals included in the study was estimated by the means of their mean deviation index (-6.5 ± 4.9 dB) and their pattern standard deviation index (6.1 ± 3.0 dB). Of these individuals, 52% (n=28) had mean deviation better than -6 dB, but a broad spectrum of disease severity was represented in this study (Figure, Supplemental Digital Content 1).

All analyzed iVue images were of sufficient quality for the autosegmentation software to calculate quantitative scan parameters. The iVue cup to disc vertical ratio value performed robustly, with a sensitivity of 0.96 (95% CI 0.90-1.00) at 90% specificity, and its area cup to disc ratio was almost equally sensitive and specific (Table 2). The thresholds for abnormality at 90% sensitivity were 0.78 for cup to disc vertical ratio and 0.63 for area cup to disc ratio. The sensitivity and specificity for a statistical grading of “outside normal” cup to disc vertical ratio were substantially lower, at 0.72 (95% CI 0.60-0.84) and 0.94 (95% CI 0.88-1.00), respectively (Table 3). To confirm that the iVue values for optic nerve head parameters were valid, we compared them to the cup to disc ratios determined by both

clinical exam (available for OAG subjects and retinal disease comparison group subjects) and the Cirrus SD-OCT (available for OAG subjects only). The iVue vertical cup to disc ratio and the Cirrus HD-OCT vertical cup to disc ratio were strongly correlated (Pearson correlation coefficient=0.84), and iVue and clinical cup to disc ratios observed by faculty ophthalmologists were also highly correlated (Pearson correlation coefficient=0.80) (Figure 1).

The iVue RNFL and iVue GCC test parameters were treated as continuous quantitative variables, and ROC curves were constructed (Figure 2 and see Figure, Supplemental Digital Content 2). The sensitivity at 90% and 95% specificity and the area under the ROC curve for each parameter were determined (Table 2). Based on these metrics, the RNFL parameters performed better than the GCC parameters, but not as well as the best optic nerve head parameters. The RNFL parameters with the highest sensitivity at 90% specificity were average thickness (0.83, 95% CI 0.73-0.93), average superior hemisphere thickness (0.82, 95% CI 0.72-0.92), average inferior hemisphere thickness (0.78, 95% CI 0.67-0.89), and inferior quadrant thickness (0.79, 95% CI 0.68-0.90).

Using the iVue normative database, sensitivity, specificity, PPV, and NPV were calculated for the GCC and RNFL test parameters (Table 3). Consistent with the findings from the ROC analysis, the RNFL sensitivities were again higher than those of the GCC, including average inferior hemisphere thickness (0.87, 95% CI 0.78-0.96), inferior quadrant thickness (0.87, 95% CI 0.78-0.96), and average superior hemisphere thickness (0.85, 95% CI 0.75-0.95). The specificities for these parameters were all 0.87 or greater. The PPV and NPV, calculated using the study sample prevalence of glaucoma (50%), were greater than 0.87 and 0.85, respectively. As PPV and NPV are dependent on prevalence, PPV and NPV were also calculated assuming an estimated screening population prevalence of 4% for OAG in an adult population of these demographics (Table 4). Under these conditions, the NPV values were higher, but the PPV values were significantly lower. Interestingly, the optic nerve head rim area and the optic nerve head cup volume both had 100% PPV.

In an effort to maximize specificity and PPV, combinations of RNFL metrics with the optic nerve head rim area value were evaluated. Sensitivity, specificity, PPV, and NPV for requiring a RNFL test parameter and the optic nerve head rim area to both be “outside normal” are shown in Table 5. Specificity and PPV were 100% for all combination metrics, but at the cost of decreased sensitivity relative to using the RNFL test parameter alone. When assuming glaucoma prevalence of 4%, PPV and NPV for the combination metrics were all nearly 100% (Table 6).

Discussion

We evaluated the performance of iVue scan parameters for the identification of glaucoma in a known clinical population of OAG subjects compared to a comparison group of age-matched persons. All but 4% of subjects had suitable imaging data acquired by a non-professional with limited training in ophthalmic photography. We have shown that a lay person with no prior experience may be trained in less than 30 minutes to competently and rapidly set up and acquire images using the iVue. This indicates the likely practicality of

using this instrument with non-professional operators in the field, especially given its relatively small size and portability compared to other imaging modalities. Whereas the Cirrus HD-OCT has a footprint of 26 inches $\times$ 18 inches and weighs approximately 80 pounds, the iVue base and control box have footprints of 14 in $\times$ 8 in and 14 in $\times$ 5 in, respectively, and together weigh less than 50 pounds. The iVue components fit in a padded case with wheels specifically designed for iVue disassembly, storage, and transport. Although the role of OCT in glaucoma diagnosis is well demonstrated, this is the first pilot study to show that this modality can be effectively implemented by non-professionals.

The vertical cup to disc ratio value as measured by iVue had the highest sensitivity at 90% specificity, as well as the second largest area under an ROC curve. The iVue cup to disc measurements were highly correlated to both the clinician grading and Cirrus OCT measure of the cup size. Furthermore, the iVue cup to disc parameters had similar sensitivity and specificity to the clinician's cup gradings, done by experts with stereo-ophthalmoscopy and dilated pupils. More than 95% of those with glaucoma were identified and only 7-9% of non-glaucoma comparison subjects were identified. This showed a 34% positive predictive value when an estimated 4% of a screened population have OAG. When the statistical abnormality of vertical cup to disc ratio against the iVue normative database was used, it retained the best balance of sensitivity, specificity, and predictive values among optic nerve head parameters. However, using statistical abnormality, the RNFL thickness measures had similar or even slightly better sensitivity and negative predictive values than those of cup to disc ratio gradings of outside normal limits. This suggests that further testing of iVue imaging in a non-clinic based setting would be potentially a valuable approach, as its better performing measures would simulate the assessment of the optic disc by an expert, but could be carried out by a lay person with modest training.

Several RNFL parameters, particularly the inferior quadrant thickness, had impressive sensitivity and specificity and may be useful in the context of glaucoma screening. In particular, the inferior RNFL quadrant was in each analysis the best or among the best performing in identifying glaucoma. A prior study evaluating the iVue for glaucoma detection⁸ also found the inferior quadrant thickness was the strongest performing single parameter. That study also found that the GCC focal loss volume was a parameter with high sensitivity and specificity, but among our imaging data, none of the GCC measures performed well. There is considerable evidence that the inferior zone of the optic nerve is most susceptible to glaucoma damage,¹¹⁻¹⁴ probably explaining the value of this local zone. Among OCT instruments, the division of RNFL data into quadrants is done with some variation, so regional comparisons among instruments must take this into account.

We found that a combination of nerve head data and RNFL data could reduce the false positive rate of simulated screening, but only by reducing the sensitivity of the combined measure. When subjects need to be abnormal on both parameters, the number of non-OAG persons identified is few to none, but at a cost of missing 40% or more of the OAG subjects. Under some conditions, this trade-off may be an acceptable solution. Where the expense of post-screening re-examination, transport, and care are high or limited, such as the developing world, referral of OAG subjects alone may be a pragmatic choice.

Diagnostic performance has been systematically reviewed for common glaucoma screening tools, including ophthalmoscopy (sensitivity 60% [95% credible interval (CrI) 34-83%], specificity 94% [95% CrI 76-99%]), FDT C-20-5 (sensitivity 78% [95% CrI 19-99%], specificity 75% [95% CrI 57-87%]), and Goldmann applanation tonometry (sensitivity 46% [95% CrI 22-71%], specificity 95% [95% CrI 89-97%]).⁷ In this context, the performance of the iVue parameters compares favorably and suggests that this OCT implementation is among the most robust of the available screening tools for glaucoma.

The conditions under which this study was performed also mirror some of the realities and challenges that would exist with glaucoma screening in the community setting. All imaging was performed by non-professional individuals in subjects with undilated pupils. Study participants were not excluded if they had other ocular diseases, and, as might be the case in a general population, a notable proportion of both the glaucoma and control groups had some cataract and/or retinal pathology. One limitation of the study is that the control group had a higher prevalence of retinal disease than the glaucoma group. The control population represented a convenience sample of similar age persons to the OAG group, but it is recognized that the presence of retinal disease in some subjects may affect parameters used to identify OAG. While this may be a potential confounding feature, it is more likely to reduce than to inflate the predictive power for OAG identification of the methods used, and its most likely effect would have been to lower our estimates of specificity, as it has been shown that the macular ganglion cell-inner plexiform layer and peripapillary RNFL are thinned in AMD.¹⁵ Furthermore, for the age group seen in community screening of elderly adults, retinal disease would be a common finding, thereby making this comparison group more realistic than a control group consisting of purely normal subjects.

As the control group did not undergo testing to confirm that they were not individuals with undiagnosed glaucoma, it is possible that glaucoma subjects were included in the control group. The theoretical effect of their inclusion would have been to lower our estimate of positive predictive value and increase our estimate of negative predictive value. However, given that the control group was a mix of individuals with and without known retinal disease, the prevalence of OAG in this group is estimated to be less than 5% on a population basis, and the resultant impact is expected to be small.¹⁶ Finally, it is generally accepted that clinic-based assessments of screening approaches give more favorable results than when the same methods are utilized in the community setting. One factor contributing to the 96% successful image acquisition rate may be the large proportion of pseudophakic eyes in the study population, as the absence of cataracts may facilitate image acquisition and quality. Our findings need further validation in follow up studies. We have accumulated hundreds of iVue images in actual non-clinical locations as part of a medical student initiated screening. These data will be analyzable with the present findings to test their durability outside the clinic.

In summary, we have demonstrated that the portable iVue SD-OCT may be utilized by non-expert personnel on undilated patients and that the quantitative and categorical parameters from the resultant scans, in particular the vertical cup to disc ratio and the RNFL inferior quadrant thickness, demonstrate highly encouraging performance metrics. Our findings suggest that with limited training, non-expert personnel can acquire these images, which

may be useful in screening for glaucoma. With the aging population in the United States, there is an increasingly pressing need for novel public health approaches to reduce the disease burden of glaucoma. Although this pilot study requires replication, it demonstrates the potential of an OCT based community glaucoma screening approach, in which imaging is performed by lay personnel with minimal training in image acquisition. Binary scan derived parameters can be used to identify high risk individuals at the time of screening, and only those high risk individuals are referred for formal evaluation by a glaucoma specialist. This approach may be particularly suited for screening minority and medically underserved groups, which experience unique barriers to specialty health care access.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Correlation of cup to disc between A) iVue and clinical exam and B) Cirrus and iVue.

Figure 2.

Receiver operator characteristic (ROC) curves for selected iVue OCT parameters.

C.D_V_RATIO: Cup to disc vertical ratio (iVue); C.D_AREA_RATIO: Cup to disc area ratio (iVue); AVG_INFERIOR_RNFL_UM: RNFL average inferior hemisphere thickness; RNFL_INFERIOR_QUADRANT_UM: RNFL inferior quadrant thickness; GCC_INFERIOR_UM: GCC inferior hemisphere thickness; GCC_TOTAL_UM: GCC total thickness.

Table 1
Characteristics of study participants

	OAG (n=54)	Comparison (n=54)
Age, mean $\pm$ SD	71.9 $\pm$ 12.2	69.3 $\pm$ 10.9
Gender, n (%)		
Men	20 (37.0)	24 (44.4)
Women	34 (63.0)	30 (55.6)
Race, n (%)		
European-derived	42 (77.7)	45 (83.3)
African-derived	8 (14.8)	7 (13.0)
Hispanic	1 (1.9)	1 (1.9)
Asian	2 (3.7)	1 (1.9)
Other	1 (1.9)	0 (0.0)
Diabetes, n (%) *	5 (9.3)	23 (42.6)
Hypertension, n (%) *	14 (25.9)	28 (51.9)
Retinal Disease, n (%) *	5 (9.3)	38 (70.4)
Intraocular pressure, mean $\pm$ SD * [†]	12.0 $\pm$ 3.7	14.5 $\pm$ 3.4 [‡]
Visual field parameters, mean $\pm$ SD [†]		
Mean deviation	-6.5 $\pm$ 4.9	ND
Pattern standard deviation	6.1 $\pm$ 3.0	ND
Lens status, n (%) * [§]		
No cataract	17 (15.7)	32 (29.6)
Cataract	37 (34.3)	34 (31.5)
Pseudophakic	54 (50.0)	42 (38.9)

* p<0.05 by Fisher's exact test (diabetes, hypertension, retinal disease, lens status) or Wilcoxon two sample rank sum test (intraocular pressure) for OAG vs Comparison

[†] Measurements from left and right eyes were averaged for each individual

[‡] Mean for all measured individuals (n=38)

[§] Reported using the eye as the unit (OAG n=108; Comparison n=108)

Table 2
Sensitivity at 90% and 95% specificity and area under the curve for iVue OCT parameters

Variable	Sensitivity at 90% specificity (95% CI)	Sensitivity at 95% specificity (95% CI)	Area under the curve (95% CI)
Optic nerve head			
Cup to disc ratio (clinical exam)	0.95 (0.89, 1.00)	0.78 (0.67, 0.89)	0.96 (0.91, 1.00)
Cup to disc vertical ratio (iVue)	0.96 (0.90, 1.00)	0.79 (0.68, 0.90)	0.93 (0.87, 0.98)
Cup to disc area ratio (iVue)	0.95 (0.89, 1.00)	0.77 (0.66, 0.88)	0.91 (0.85, 0.96)
Optic nerve head rim area (iVue)	0.74 (0.62, 0.86)	0.49 (0.36, 0.63)	0.88 (0.82, 0.95)
Cup to disc horizontal ratio (iVue)	0.51 (0.38, 0.65)	0.30 (0.18, 0.43)	0.85 (0.78, 0.92)
Optic nerve head cup volume (iVue)	0.50 (0.37, 0.64)	0.30 (0.17, 0.42)	0.85 (0.77, 0.92)
Retinal nerve fiber layer			
Average inferior hemisphere Thickness	0.78 (0.67, 0.89)	0.54 (0.40, 0.67)	0.94 (0.89, 0.99)
Inferior quadrant thickness	0.79 (0.68, 0.90)	0.54 (0.40, 0.67)	0.93 (0.87, 0.98)
Average thickness	0.83 (0.73, 0.93)	0.58 (0.45, 0.72)	0.92 (0.87, 0.98)
Average superior hemisphere Thickness	0.82 (0.72, 0.92)	0.58 (0.44, 0.71)	0.90 (0.84, 0.96)
Temporal quadrant thickness	0.56 (0.43, 0.70)	0.34 (0.21, 0.47)	0.88 (0.81, 0.94)
Superior quadrant thickness	0.64 (0.51, 0.77)	0.40 (0.27, 0.53)	0.86 (0.79, 0.94)
Nasal quadrant thickness	0.46 (0.33, 0.60)	0.27 (0.15, 0.39)	0.83 (0.75, 0.91)
Ganglion cell complex			
Inferior hemisphere thickness	0.62 (0.49, 0.75)	0.38 (0.25, 0.51)	0.90 (0.84, 0.96)
Total thickness	0.59 (0.46, 0.72)	0.36 (0.23, 0.49)	0.90 (0.84, 0.97)
Global loss volume	0.50 (0.37, 0.64)	0.29 (0.17, 0.42)	0.87 (0.80, 0.94)
Superior hemisphere thickness	0.47 (0.34, 0.61)	0.27 (0.15, 0.39)	0.84 (0.76, 0.92)
Focal loss volume	0.26 (0.14, 0.38)	0.14 (0.05, 0.23)	0.75 (0.65, 0.85)

Table 3
Sensitivity, specificity, positive predictive value, and negative predictive value for iVue OCT parameters using normative database thresholds

Variable	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)
Optic nerve head				
Cup to disc vertical ratio	0.72 (0.60, 0.84)	0.94 (0.88, 1.00)	0.93 (0.85, 1.00)	0.77 (0.66, 0.87)
Cup to disc area ratio	0.60 (0.47, 0.74)	0.94 (0.88, 1.00)	0.91 (0.82, 1.00)	0.70 (0.59, 0.81)
Optic nerve head rim area	0.58 (0.45, 0.72)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	0.70 (0.60, 0.81)
Optic nerve head cup volume	0.21 (0.10, 0.32)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	0.55 (0.45, 0.65)
Cup to disc horizontal ratio	0.13 (0.04, 0.22)	0.96 (0.91, 1.00)	0.78 (0.51, 1.00)	0.52 (0.42, 0.62)
Retinal nerve fiber layer				
Average thickness	0.89 (0.80, 0.97)	0.83 (0.72, 0.93)	0.84 (0.74, 0.94)	0.88 (0.79, 0.97)
Average inferior hemisphere thickness	0.87 (0.78, 0.96)	0.88 (0.80, 0.97)	0.88 (0.80, 0.97)	0.87 (0.78, 0.96)
Inferior quadrant thickness	0.87 (0.78, 0.96)	0.88 (0.80, 0.97)	0.88 (0.80, 0.97)	0.87 (0.78, 0.96)
Average superior hemisphere thickness	0.85 (0.75, 0.95)	0.87 (0.77, 0.96)	0.87 (0.77, 0.96)	0.85 (0.75, 0.95)
Superior quadrant thickness	0.72 (0.60, 0.84)	0.85 (0.75, 0.94)	0.83 (0.72, 0.94)	0.75 (0.63, 0.86)
Temporal quadrant thickness	0.49 (0.36, 0.63)	0.94 (0.88, 1.00)	0.90 (0.79, 1.00)	0.64 (0.54, 0.75)
Nasal quadrant thickness	0.42 (0.28, 0.55)	0.90 (0.82, 0.98)	0.81 (0.67, 0.96)	0.60 (0.49, 0.71)
Ganglion cell complex				
Focal loss volume	0.80 (0.69, 0.90)	0.65 (0.52, 0.78)	0.70 (0.59, 0.82)	0.75 (0.62, 0.88)
Inferior hemisphere thickness	0.78 (0.67, 0.89)	0.84 (0.74, 0.94)	0.84 (0.74, 0.94)	0.78 (0.67, 0.89)
Total thickness	0.76 (0.65, 0.87)	0.86 (0.77, 0.96)	0.85 (0.75, 0.95)	0.77 (0.66, 0.88)
Superior hemisphere thickness	0.61 (0.48, 0.74)	0.86 (0.77, 0.96)	0.82 (0.71, 0.94)	0.68 (0.56, 0.79)
Global loss volume	0.48 (0.35, 0.61)	0.92 (0.85, 1.00)	0.87 (0.75, 0.99)	0.63 (0.52, 0.74)

Table 4
Positive predictive value and negative predictive value for iVue OCT parameters with
glaucoma prevalence of 4%

Variable	Positive predictive value (95% CI)	Negative predictive value (95% CI)
Optic nerve head		
Optic nerve head rim area	1.00 (1.00, 1.00)	0.98 (0.98, 0.99)
Optic nerve head cup volume	1.00 (1.00, 1.00)	0.97 (0.96, 0.97)
Cup to disc vertical ratio	0.34 (0.09, 0.59)	0.99 (0.98, 0.99)
Cup to disc area ratio	0.30 (0.07, 0.54)	0.98 (0.98, 0.99)
Cup to disc horizontal ratio	0.13 (0.00, 0.29)	0.96 (0.96, 0.97)
Retinal nerve fiber layer		
Temporal quadrant thickness	0.26 (0.04, 0.48)	0.98 (0.97, 0.98)
Average inferior hemisphere thickness	0.24 (0.10, 0.38)	0.99 (0.99, 1.00)
Inferior quadrant thickness	0.24 (0.10, 0.38)	0.99 (0.99, 1.00)
Average superior hemisphere thickness	0.21 (0.09, 0.32)	0.99 (0.99, 1.00)
Average thickness	0.18 (0.09, 0.26)	0.99 (0.99, 1.00)
Superior quadrant thickness	0.16 (0.07, 0.25)	0.99 (0.98, 0.99)
Nasal quadrant thickness	0.15 (0.04, 0.27)	0.97 (0.97, 0.98)
Ganglion cell complex		
Global loss volume	0.20 (0.04, 0.36)	0.98 (0.97, 0.98)
Total thickness	0.19 (0.08, 0.29)	0.99 (0.98, 0.99)
Inferior hemisphere thickness	0.17 (0.08, 0.26)	0.99 (0.98, 0.99)
Superior hemisphere thickness	0.16 (0.06, 0.25)	0.98 (0.98, 0.99)
Focal loss volume	0.09 (0.05, 0.12)	0.99 (0.98, 0.99)

Table 5
Sensitivity, specificity, positive predictive value, and negative predictive value for iVue
RNFL parameters combined with abnormal optic nerve head rim area

Variable	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)
Retinal nerve fiber layer				
Average thickness	0.58 (0.45, 0.72)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	0.70 (0.60, 0.81)
Average superior hemisphere thickness	0.57 (0.43, 0.70)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	0.69 (0.59, 0.80)
Average inferior hemisphere thickness	0.55 (0.41, 0.68)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	0.68 (0.58, 0.79)
Inferior quadrant thickness	0.55 (0.41, 0.68)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	0.68 (0.58, 0.79)
Superior quadrant thickness	0.53 (0.39, 0.66)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	0.68 (0.57, 0.78)
Temporal quadrant thickness	0.32 (0.20, 0.45)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	0.59 (0.49, 0.69)
Nasal quadrant thickness	0.28 (0.16, 0.40)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	0.58 (0.48, 0.68)

Table 6
Positive predictive value and negative predictive value for iVue RNFL parameters
combined with abnormal optic nerve head rim area with glaucoma prevalence of 4%

Variable	Positive predictive value (95% CI)	Negative predictive value (95% CI)
Retinal nerve fiber layer		
Average thickness	1.00 (1.00, 1.00)	0.98 (0.98, 0.99)
Average superior hemisphere thickness	1.00 (1.00, 1.00)	0.98 (0.98, 0.99)
Average inferior hemisphere thickness	1.00 (1.00, 1.00)	0.98 (0.98, 0.99)
Inferior quadrant thickness	1.00 (1.00, 1.00)	0.98 (0.98, 0.99)
Superior quadrant thickness	1.00 (1.00, 1.00)	0.98 (0.98, 0.99)
Temporal quadrant thickness	1.00 (1.00, 1.00)	0.97 (0.97, 0.98)
Nasal quadrant thickness	1.00 (1.00, 1.00)	0.97 (0.97, 0.98)