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Glaucoma

Detecting Established Glaucoma Using OCT Alone: Utilizing an OCT Reading Center in a Real-World Clinical Setting

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Purpose: We evaluated the ability of an optical coherence tomography (OCT)-based reading center for glaucoma (ORG) to detect established glaucoma using OCT alone.

Methods: This study included eyes from 70 consecutive patients with established glaucoma (i.e. moderate or severe glaucoma according to the International Classification of Diseases [ICD]-10 guidelines) and 20 consecutive healthy subjects, who had no evidence of glaucomatous optic neuropathy (GON) or visual field (VF) loss in either eye. Using a standardized ORG quality assessment, 33 eyes were excluded due to media opacity (12), poor image quality (13), or epiretinal membrane (8). Of the remaining 147 eyes, 86 had established glaucoma and 36 were from healthy controls (total $n = 122$). Based on the OCT report alone and applying a previously described evaluation method, the presence of GON in each eye was determined by two masked ORG graders. The main outcome measures were sensitivity and specificity for detection of eyes with established glaucoma.

Results: Of the 86 eyes with established glaucoma (average mean deviation [MD] $= -10.9 \pm 7.7$ dB, range $= -0.5$ to -31.5 dB), only one eye (MD $= -0.46$) was missed (sensitivity $= 98.8\%$). However, the other eye of this patient was correctly classified as GON. Therefore, at a patient level, sensitivity was 100%. None of the 36 healthy eyes was classified as GON by the ORG (specificity $= 100\%$).

Conclusions: An OCT-based reading center is able to identify eyes with established glaucoma using OCT alone with high sensitivity and specificity.

Translational Relevance: Our study validates the use of a systematic OCT-based approach for glaucoma detection in a real-world setting.

Introduction

Glaucoma is the leading cause of irreversible blindness worldwide.[1] The standard approach for glaucoma detection involves a comprehensive history, an eye examination, and a variety of ancillary tests to identify signs of structural and functional optic nerve damage. Because there is no litmus test for glaucoma, the diagnosis is based on clinical interpretation and integration of various sources of information. Often, this requires agreement or corroboration of findings across multiple modalities to reach a sufficient level of diagnostic confidence. However, this approach can result in inconsistencies and disagreements even among glaucoma experts, especially in borderline cases or cases of early glaucoma.[2–6] Specifically, the lack of consensus for the definition of what constitutes clinically significant glaucomatous optic neuropathy (GON) poses a significant limitation for clinical studies and assuring reproducible inclusion criteria. Clinical trials that utilize optic nerve appearance as an entry

criterion or for end point determination often rely on Optic Disc Reading Centers with masked, trained personnel to provide objectivity and consistency.[7]

Optical coherence tomography (OCT) has become a cornerstone of glaucoma assessment.[8–11] It provides high resolution, objective, quantifiable, and reproducible structural information on the retinal nerve fiber layer (RNFL) and ganglion cell layer (GCL) and thus reflects damage to the retinal ganglion cells and their axons. However, glaucoma screening tactics that

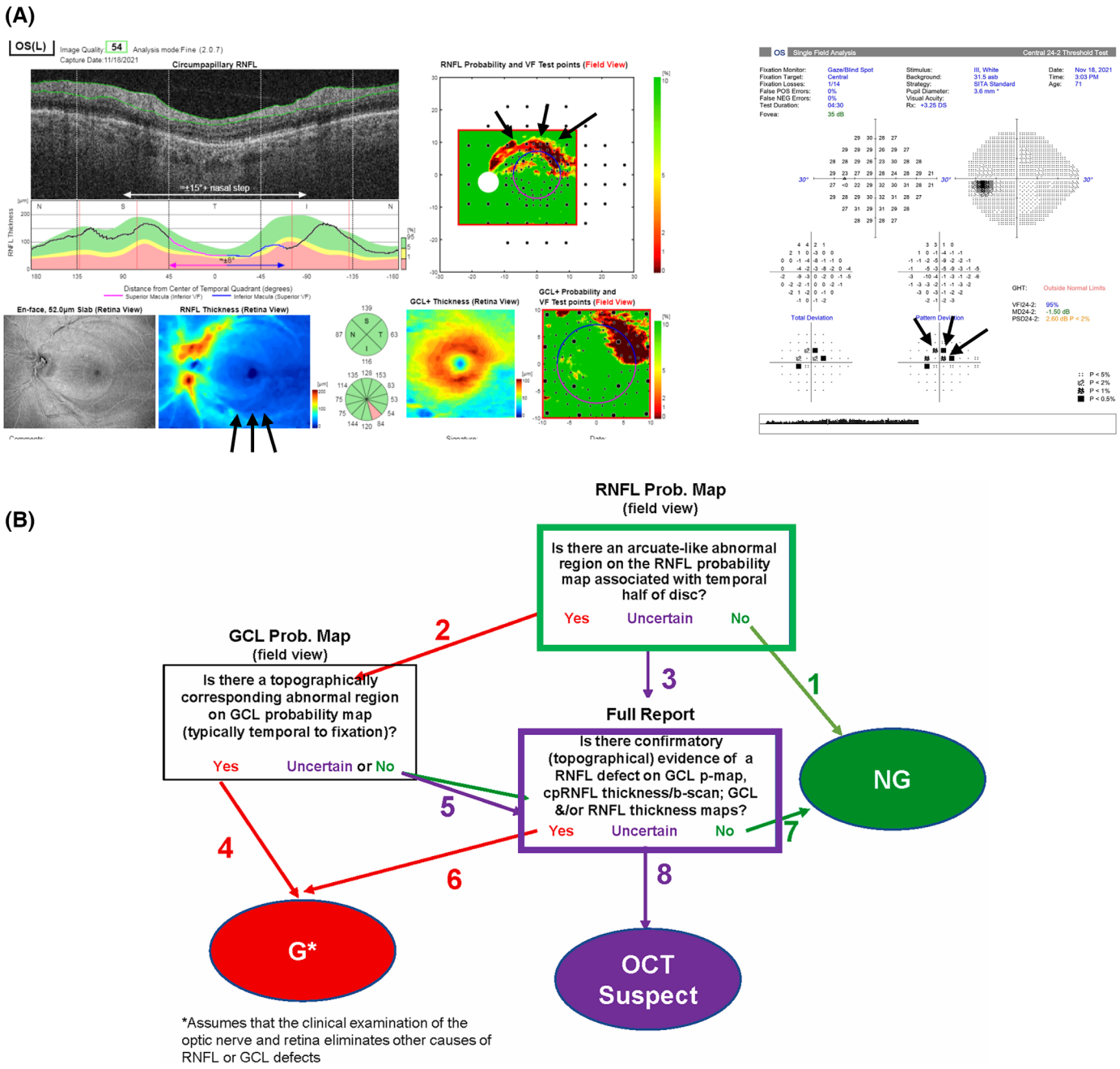

Figure 1. Example of the one-page wide-field "Hood Report" (**A**) and the CU method decision tree (**B**). (**A**) Example of the Topcon commercial OCT "Hood report" (*left*) and corresponding 24-2 VF (*right*). The OCT report is composed of probability and thickness maps for the RNFL and GCL as well as circumpapillary RNFL B-scan and thickness plot, all of which are used for classification by the CU method. It is important to note that the GCL and RNFL thickness maps are presented in retina view, whereas the probability maps are in field view. That is meant to make it easier for the clinician to match the structural damage with the functional defects. For example, in this case, there is an arcuate-like on the inferior hemi-retina which corresponds to the superior arcuate defect on the 24-2 visual field (*black arrows*). (**B**) The CU method decision tree, reproduced with permission from Hood et al. 2022.[16] The decision tree is explained in the methods section and in more detail in Refs. 15 and 16.

rely on OCT-based summary metrics have been found to have inadequate sensitivity and specificity.[12–14] To aid in the detection of GON, Hood and Raza et al.[15,16] proposed a format that illustrates valuable information from OCT scans in a single-page report (Fig. 1A). Using only this OCT report, experienced OCT readers had excellent inter-rater repeatability and diagnostic ability relative to glaucoma specialists who had typical clinical information, namely stereophotographs, 24-2 VFs, and commercially available OCT optic nerve images.[17] The Columbia University OCT-based method (CU method) is a systematic approach that utilizes this single-page OCT report to aid in the detection of GON.[18,19] This method was shown to have excellent specificity (96-98%) and extremely high sensitivity for glaucoma detection (94% for early glaucoma and 100% for advanced glaucoma).[19]

Based on these promising results, the Columbia University OCT Reading Center for Glaucoma (ORG) developed a protocol whose foundation is the CU method and allows reviewers to evaluate OCT images and reports for the presence of GON. To date, however, studies investigating the CU method have relied on known research subjects rather than individuals being recruited from clinical practice. The focus of this study was to evaluate the performance of the ORG for the detection of established glaucoma, based only on a one-page OCT report and applying the CU method.

Methods

Subjects

This study was approved by the Institutional Review Board for Human Research of Columbia University Irving Medical Center. The study followed the tenets of the Declaration of Helsinki and the Health Insurance Portability and Accountability Act. All scans were completely de-identified prior to extraction and all data were saved on secure local servers.

The study group included 70 consecutive patients with glaucoma (age [mean ± SD] = 72.4 ± 12.7 years, 54.2% female patients) classified using International Classification of Diseases, Tenth Revision (ICD-10) guidelines as moderate or severe glaucoma ("established glaucoma") in at least one eye.[20] We used this definition for two reasons. First, to ensure that the ORG would be able to identify eyes with the highest risk for irreversible blindness. Second, whereas there is no litmus test for glaucoma, it is unlikely that cases showing structural glaucomatous damage consistent with visual field loss would be misdiagnosed. The control group included 20 consecutive individuals (age = 59.7 ± 16.1 years, 50% female patients) that underwent screening for glaucoma and were found to be healthy (i.e. no clinical evidence of GON or visual field loss). The indication for screening was ocular hypertension (5), anatomic narrow angle (5), family history of glaucoma (5), pseudoexfoliation syndrome (2), pigment dispersion syndrome (2), and a suspicious disc (1). Four patients also had high myopia in both eyes (SE < −6 diopters [D]). None of these eyes had a history of ocular surgery or treatment with ocular hypotensive treatments (pharmacological or laser).

The OCT Reports and Grading

All eyes were scanned using wide field (12 × 9 mm) swept-source OCT (Triton; Topcon, Inc., Paramus, NJ, USA), which includes both the macula and the optic disc. The commercial single-page "Hood Report"[15,16] was generated by Topcon's proprietary software "ImageNet 6" (see Fig. 1A). Note that, in this report, the OCT probability maps are flipped along the horizontal meridian to field view to make it easier to compare with the visual field (VF) report. As per standard care, each eye is scanned two to three times on each visit to ensure that at least one scan would be of sufficient quality for reliable evaluation. Of those, the best-quality scan, based on qualitative assessment, was used.

The Reading Center

All OCT images were processed through the ORG. The ORG's systematic procedures allow for the quality review of OCT scans and reports, and their evaluation for the presence of GON. Part of this procedure is the classification based on the CU method, which is the focus of this study (see Fig. 1A).

Each of the OCT reports was reviewed for their quality and subsequently graded by two of the ORG's graders (authors D.C.H. and E.T.). Both graders are OCT experts with extensive experience in interpreting OCT reports for glaucoma as well as the application of the CU method. Each grader independently applied the rules of the CU method for glaucoma detection on each one-page OCT report. A detailed explanation of the method can be found in Liebmann et al.[18] and Hood et al.[16] In brief, the CU method is applied to classify eyes as GON, non-glaucomatous optic neuropathy (non-GON) or OCT-suspect (OCT-S) based on a one-page OCT report (see Fig. 1A).[15–19] Three questions are asked (Fig. 1b). First, "Is there an arcuate-like abnormal region on the RNFL probability map associated with temporal half of disc?" (see the "red near the disc rule" Fig. 1b green box).

To clarify, the abnormal region can be either focal or diffuse, respecting the arcuate-like distribution of the RNFL fibers. If the answer is "No," then the eye is considered non-GON. If the answer is "Yes," the grader moves to the second question: "Is there a topographically corresponding abnormal region on GCL probability map?" If the answer is "Yes," then the eye is considered GON. When the answer for the first question is "Uncertain" or the answer for the second questions is "No" or "Uncertain" the grader is directed to question 3: "Is there confirmatory (topographical) evidence of a RNFL defect on GCL probability map, cpRNFL thickness/b-scan, GCL+ and/or RNFL thickness maps?" (see Fig. 1b purple box). To answer this question, the grader uses all available information on the report from the OCT circle and cube scans to identify patterns of glaucomatous damage (i.e. arcuate damage on the RNFL probability map) with corroboration using spatial structure-structure agreement. Based on the response to question 3, the eye can be classified as GON ("Yes"), non-GON ("No"), or OCT-S ("Uncertain").[18,19] For the purpose of this study, OCT-S was defined as eyes in which the presence of GON cannot be determined by the OCT and thus does not meet the ORG criteria for "glaucoma."

Based on the quality assessment, scans and reports from 33 eyes were excluded due to media opacity (12 eyes); poor image quality (13); or epiretinal membrane (8). That is, 147 eyes with acceptable image quality scans and without confounding ophthalmic pathology were further reviewed. Of the 147 eyes, 86 had established glaucoma and 36 were healthy controls. These 122 eyes are the focus of our study.

The graders were masked to the purpose of the study as well as the diagnosis and any additional information that does not appear on the OCT report. In 8 of the 122 eyes (6.5%), there was disagreement between the graders regarding the classification. These cases were discussed and adjudicated. It is worth noting that there were no cases of total disagreement (i.e. one grader classified the eye as GON and the other non-GON). Their final decisions were used for the analysis.

Outcome Measures

The main outcome measures were the sensitivity for detection of eyes with established glaucoma defined as moderate or severe stage by the ICD-10, and the specificity for the healthy control eyes. The rate of detection of patients with clinically significant VF loss (24-2 mean deviation [MD] of −6 dB or worse) was evaluated as well.

Results

Table summarizes the clinical characteristics of the 86 eyes with established glaucoma.

Overall, 85 of the 86 eyes with established glaucoma (98.8%) were classified by the ORG as GON. It is worth highlighting that all 53 eyes with significant glaucomatous VF loss (MD worse than −6 dB) were correctly classified as GON. One eye was missed and classified as OCT-S (Fig. 2). However, the other eye of the patient was labeled as GON based on the CU method. Therefore, if the ORG was used as a screening tool, the patient would not be missed because they would be "referred" based on their other eye.

Depending on the answers provided to the three questions of the CU method, one can potentially follow eight different paths to eventually reach a decision of GON, non-GON, or OCT-S (see Fig. 1b). Two of these paths, the ["Yes" to both questions 1 and 2] (see arrows 2 and 4 in Fig. 1b) and ["No" to question 1] (see arrow 1 in Fig. 1b), imply high confidence in the decision of GON and non-GON, respectively. The majority of eyes in our cohort (97/121, 80%) were

Table. Demographics and Patient Characteristics

Variable		*N* (%)
Lens status	Phakic	43/86 (50)
	Pseudophakic	43/86 (50)
24-2 MD	Better than −3 dB	5/86 (5.8)
	Between −3 and −6 dB	24/86 (27.9)
	Between −6 and −12 dB	30/86 (34.9)
	Worse than −12 dB	27/86 (31.4)
Glaucoma Surgical History	None	63/86 (73.2)
	Trabeculectomy	15/86 (17.4)
	Trabeculectomy + GDD	3/86 (3.5)
	GDD	3/86 (3.5)
	Angle surgery	2/86 (2.3)
Glaucoma subtype	POAG	57/86 (66.3)
	PXFG	11/86 (12.8)
	PDG	4/86 (3.5)
	CACG	9/86 (10.5)
	JOAG	4/86 (3.5)
	Secondary OAG	2/86 (2.3)
Number of IOP lowering medications	0*	15/86 (17.4)
	1	27/86 (31.4)
	2	10/86 (11.6)
	3	20/86 (23.3)
	4	14/86 (16.3)

CACG, chronic angle closure glaucoma; GDD, glaucoma drainage device; IOP, intraocular pressure; JOAG, juvenile open angle glaucoma; MD, mean deviation; OAG, open angle glaucoma; PDG, pigmentary dispersion glaucoma; POAG, primary open angle glaucoma; PXFG, pseudoexfoliation glaucoma.

*Eyes that maintained target pressure without medication after surgical intervention.

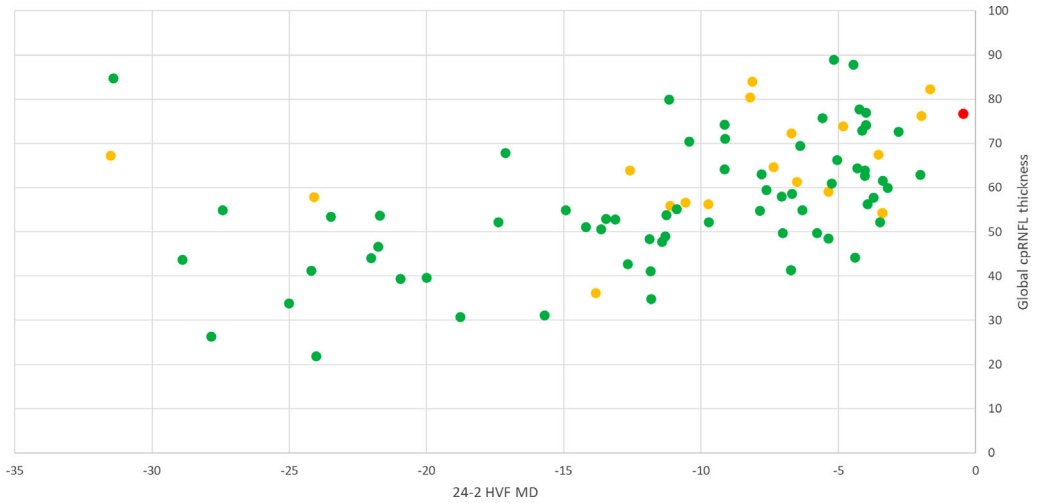

Figure 2. Distribution of cases with established glaucoma based on 24-2 MD and global cpRNFL thickness. Color indicates the CU method classification pathway (Fig. 1b): *Green* = eyes that were classified by the ORG as GON based on "Yes" to both questions 1 and 2 (pathway: 2 and 4); *Orange* = eyes that were classified by the ORG as GON where question 3 was required (pathways 2, 5, and 6 and 3 and 6); *Red* = eyes that were classified by the ORG as OCT-S (pathways 2, 5, and 8, and 3, and 8).

classified through these two paths. The first, ["Yes" to both questions 1 and 2], indicates clear evidence of GON based on established presence of an arcuate RNFL defect accompanied by macular GCL damage that topographically agrees with the RNFL arcuate. This was the case for the majority of the eyes classified as GON by the ORG (67/85, 79%). The severity of VF loss in the eyes that were classified by this path in 24-2 MD ranged between −2.0 and −31.4 dB (median = −9.1 dB). The remaining 19 patient eyes (MD range between −0.5 and −31.5 dB, media = n −8.1) required the evaluation of the full report (see question 3, in Fig. 1b, purple box) for evidence of topographic agreement of a defect on cpRNFL thickness/b-scan, GCL and/or RNFL thickness maps, and GCL or RNFL probability maps. For these eyes, full report evaluation was needed due to an "uncertain" response to either question 1 (arrow 3, $N = 14$) or question 2 (arrow 5, $N = 5$). All of these eyes were eventually classified as GON (arrow 6) apart from one case (MD = −0.5) which was classified as OCT-S by the ORG (i.e. the responses to questions 1 and 3 were both "uncertain", arrows 3 and 8). Figure 2 shows the distribution of all cases of established glaucoma based on MD and global cpRNFL thickness. As can be appreciated, the extent of structural and functional severity of eyes that were classified based on a "Yes" response to question 3 had a similar distribution as the eyes that were classified based on a "Yes" response to both questions 1 and 2. In addition, the one case of established glaucoma that was classified by the ORG as OCT-S had the mildest severity based on the 24-2 MD and a global cpRNFL thickness that is considered to be within the normal range.

The other direct path, ["No" to question 1] (see the arrow 1, in Fig. 1b), indicates lack of the strongest sign of glaucomatous damage, which is the arcuate-like defect on the RNFL. The majority of the healthy eyes (30/36, 83%) were classified as non-GON based on this path. In the remaining 6 (20%) healthy eyes, the response to question 3 was "No" in 3 eyes (i.e. eventually classified correctly as non-GON, arrows 3 and 7), and "uncertain" in the other 3 eyes (i.e. eventually classified as OCT-S, arrows 3 and 8).

Discussion

This study demonstrates that an OCT-based reading center applying the standardized CU-method for evaluation of OCT images can detect established glaucoma in a real-world clinical setting with high sensitivity and specificity. Our data suggests that an OCT-based reading center can be used to efficiently categorize eyes based on the presence or lack of GON in a systematic and reproducible approach. Possible applications of this technique include validation of inclusion or exclusion criteria related to the presence of GON for clinical trials, or screening out individuals who do not have clear evidence of GON. In addition, it can be used for detection of patients at risk of functional visual field loss and blindness (i.e. "established glaucoma" at the time of diagnosis).

Our cohort included a diverse range of patients, both in terms of demographic characteristics (e.g. age and sex), and was not restricted to a specific type of glaucoma. More importantly, we included eyes with a wide range of glaucomatous damage, both in terms of functional damage (24-2 MD median −8.0, range = between −0.5 and −31.5 dB) and structural damage (RNFL thickness median 56.5, range = 21.9–89.0 microns). In addition, the only exclusion criteria were having scans of poor quality that do not allow interpretation or reliable evaluation. Nevertheless, the sensitivity and specificity rates found here are consistent with those reported by Hood et al. who evaluated the accuracy of the CU method on a controlled study population.[19] Similar to their report, we also found that the vast majority (80%) of eyes were classified based on the relatively straightforward paths (i.e. ["Yes" to both questions 1 and 2] or ["No" to question 1]). For the remaining cases, in which evaluation of the full report is needed (i.e. question 3), a good understanding of the pathophysiology of glaucoma, the underlying models of the loss of RGC axons that travel through the RNFL in bundles and cause thinning in the cpRNFL region, and how these are illustrated on OCT images and reports is necessary. Therefore, the final outcomes and responses to the third question of the CU method may vary, depending on the variety of those that utilize this approach: from the experienced graders, such as the OCT experts of the CU OCT reading center, through technicians and clinicians that are well-educated in the ways of reading and understanding OCT images and reports, to users that are inexperienced with the OCT technology. With the recent advancements in artificial intelligence (AI) it is possible that, in the near future, such programs might be able to aid the human graders in the classification of the OCT reports and standardize the grading process.[19] This will depend on sufficient evidence that the AI performance is equivalent to the OCT expert graders in diagnosing glaucoma.

Implications for Screening

The performance of the ORG applying the CU method alone to identify eyes with established glaucoma in a real-life clinical setting has several advantages. First, none of the eyes with moderate or severe VF loss (i.e. 24-2 MD worse than −6 dB) were missed. This is particularly important given that such eyes with clinically significant VF loss are likely at risk for severe vision loss and blindness.[21] Second, all patients with GON were judged by the ORG as having at least one eye categorized as GON. In other words, if the CU method was used for screening of the individuals within our cohort, it would not have missed any. That is, it detected all patients with established glaucoma in at least one eye. The high sensitivity and specificity found here highlights the potential of the ORG to enable timely referral of individuals with established glaucoma as well as avoiding unnecessary visits of those who are found to be healthy. Although cost analysis evaluation of this approach is beyond the scope of the current study, it underscores the necessity for future studies that will assess the economic implications of this approach.

Note that according to the methodology of this study, only one eye was presented to the OCT graders at a time to eliminate possible bias. This is, of course, not representative of a real-world clinical setting, where both eyes are evaluated simultaneously. Although the detection rate for patients was 100%, as judged by the classification of individual eyes, the presentation and evaluation of OCT reports from both eyes at the same time has the potential to eliminate the risk of missing glaucoma at the patient level and/or reduce the number of both OCT-S and wrong referrals (false positive results) in healthy eyes. For example, the three healthy controls of this study that were judged as OCT-S, share similar patterns in the RNFL and/or GCL probability maps and are hard to distinguish between lower end of normal structural thickness or diffuse glaucomatous loss. The OCT report from the other eye often helps with the correct categorization of such eyes, as it offers an intra-patient approach of comparing structural thickness.

Although the data for this study were collected from a tertiary glaucoma center, the application of this type of screening method would be most effective for providers who are not glaucoma specialists (e.g. community optometrists or screening centers) to determine who should be referred for further glaucoma evaluation and the possible need for treatment. It is important to mention that the CU method is designed to help establish the presence of optic neuropathy. Here, the method was applied based on the assumption that all eyes have undergone thorough clinical evaluation that ruled out the presence of non-glaucomatous causes. However, based on the CU method alone, the ORG can determine the presence of optic neuropathy but not the exact etiology that caused it. In a screening scenario, the presence of GON detected by the ORG must be confirmed by clinical examination to exclude other non-glaucomatous causes.

Limitations

Although the inclusion criteria in this study were broad in an attempt to encompass the wide variety of patients with glaucoma, our cohort is still limited by

sample size and the geodemographic patient population seen in our clinics. Whereas the sample of patients was quite diverse, double-blinded case-control studies using a larger sample size in a variety of patient populations are needed to confirm our results. In addition, our study focused on the detection of eyes with established glaucoma, which are at the highest risk for developing irreversible blindness. Prior studies[19,22] suggest that the CU method has a similar level of accuracy in detection of cases at the earlier stages of glaucoma, however, further investigation is needed to validate these findings in a real-world setting. It is worth noting that the reading center did not classify the scans of very poor quality or eyes with retinal co-morbidities (i.e. extensive epiretinal membranes [ERMs]) which precluded reliable interpretation of the OCT report. This limitation is to be expected in a real-world clinical setting, especially in a referral-based tertiary care center managing relatively more advanced cases. Although this limits the applicability of an OCT-based reading center, it is mostly a technical limitation of the OCT device and ability to acquire reliable measurements of the RNFL and GCL. Although currently there are some eyes in which the OCT might be less useful, future technological advances in OCT imaging might be able to overcome this issue. It should be noted that the high level of accuracy of the ORG was obtained thanks to gradings of two highly experienced OCT experts, familiar with the CU method, and as such likely represent the best possible outcome of the CU method. Future studies may consider using a greater number of graders. In addition, here, we used an OCT report produced by one commercial instrument. Although preliminary data suggests that the performance of the CU method is similar across devices,[22,23] further studies are needed to validate that this approach can be extrapolated to other instruments.

Conclusions

An OCT-based reading center is able to identify eyes with established glaucoma based on OCT alone using the CU method with high sensitivity and specificity and is singularly effective in eyes with MD loss of −6 dB or worse, which are at highest risk of blindness.

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