CAPTURING THE SILENT THIEF OF SIGHT: AN ARTIFICIAL INTELLIGENCE SCREENING SYSTEM FOR GLAUCOMA

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HIGHLIGHTS

- Glaucoma is the global leading cause of irreversible blindness
- At present, glaucoma screening is conducted mainly through opportunistic case identification in eye clinics, or amongst people having regular eye check-ups
- Three-dimensional (3D) spectral-domain optical coherence tomography (SDOCT) is a common ophthalmic modality used to identify glaucomatous structural damages
- An artificial intelligence (AI) based system for SDOCT image interpretation that has similar performance to trained experts has the potential to reduce the time and human resources required for glaucoma screening

Glaucoma is the global leading cause of irreversible blindness and the second cause of blindness after cataracts.[1] The current estimated global prevalence of glaucoma for the population aged 40-80 years is 3.54% (95% CI: 2.09-5.82) and is projected to increase in the aging population.[2] Screening for glaucoma is predominantly opportunistic due to its low prevalence and lack of early symptoms. In a recent interview with *Omnihealth Practice*, Dr. Carol Cheung and Dr. Anran Ran shared their research on the first artificial intelligence (AI) based system to analyze three-dimensional (3D) spectral-domain optical coherence tomography (SDOCT) volumetric images for identifying glaucomatous optic neuropathy (GON).

Glaucoma Overview

Glaucoma is an optic neuropathy characterized by progressive structural and functional changes of the optic nerve that leads to irreversible damage if left untreated.[2] Often associated with a long and asymptomatic initial phase, glaucoma usually progresses unnoticed until extensive and irreversible vision loss has occurred. When presented to ophthalmologists at this late disease stage, medical and surgical treatment often produce unsatisfactory results, and glaucoma patients are usually placed on lifelong management to prevent further loss of vision.[2]

From 1990 to 2007, the disability-adjusted life-years (DALYs) of glaucoma has increased by 81%.[2] By 2040, the number of people with glaucoma worldwide is expected to increase to 111.8 million and approximately 1 in 38 of those aged over 40 will be affected by glaucoma.[1,3] As about 1 in 4 cases of permanent blindness in Hong Kong can be attributed to glaucoma, its timely detection and management are critical to minimize irreversible vision loss.[4]

Current population screening for glaucoma is neither cost-effective nor practical

Despite being a treatable disease where early intervention can reduce vision loss and possibly prevent blindness, glaucoma screening programs are rare due to low cost-effectiveness and lack of appropriate screening tests.[5] The low cost-effectiveness can be attributed to the low overall prevalence of glaucoma and the requirement for multiple expensive diagnostic testing including a subjective examination of the optic nerve head where experts often do not agree, especially for the early asymptomatic cases.[5] At present, most glaucoma is detected through opportunistic screening in eye clinics, or amongst asymptomatic people having routine eye check-ups.[5]

In primary prevention, early detection and management of conditions such as ocular hypertension (OHT) and primary angle closure suspect (PACS) can reduce the incidence of glaucoma.[5] However, the absolute risk reduction of developing primary open angle glaucoma by managing these conditions are only 5.1% and 0.38%, respectively.[5] Thus, the screening of OHT and PACS would be of limited utility in glaucoma prevention and would not be considered cost-effective.

In secondary prevention, the aim shifts to prevent undiagnosed glaucoma before it becomes symptomatic.[5] While challenging to define what level of visual impairment qualifies as 'symptomatic', screening is often done with tests that look at structural changes in the optic nerve head and retinal nerve fiber layer, as well as fluid pressure of the eye. These structural changes often precede functional defects in glaucoma.[5,6] Optical coherence tomography (OCT) is one such non-contact, non-invasive structural screening technique that captures images of the optic nerve head in three-dimensional (3D) view within seconds. In eye clinics, 3D SDOCT is increasingly widely used by ophthalmologists to identify glaucomatous structural damages, i.e. GON.

Despite providing objective and quantitative measures with high validity, OCT is expensive, not easily portable, and requires sequenced segmentation of structures of interest to extract appropriate measurements.[7] While the OCT software performs segmentation automatically, a segmentation error of 19.9% and an artifact rate of 46.3% have been reported with the use of 3D SDOCT.[7] Although manual review and correction of these segmentation errors are possible, the process is time-consuming and is not feasible in a busy clinical practice.[7] Additionally, ophthalmologists are typically required to integrate multiple parameters and data in diagnosing glaucoma, possibly leading to interpretation errors.[7] Given these limitations, a deep learning model may provide alternative ways to quantify structural damages without relying on pre-defined features derived from the automated segmentation software and provides a more accurate identification of GON.[7]

Deep learning 3D SDOCT for the early detection of GON

Deep learning is a branch of AI where a computer trains itself to process and learn from data.[7] While traditional machine learning algorithms require human coding to transform raw data into input features, deep-learning algorithms are able to learn the most relevant features from data automatically and may identify more subtle and comprehensive features than manual data curation.[7] The application of deep-learning algorithms is particularly useful in ophthalmology as the diagnosis is highly dependent on ancillary imaging. Previously, several deep learning algorithms have been developed to detect glaucoma in two-dimensional (2D) OCT scans and fundus photographs.[8–10]

However, 2D view of the optic nerve is limited in information and is unable to include certain glaucoma-related features such as the entire retinal layered structure or the optic nerve head structure in the 3D cube.[11] To address this limitation, there is a need for a 3D deep learning algorithm to better assist the screening of glaucoma.

Ran and Cheung et al. developed the first 3D AI deep learning system trained on 4,877 SDOCT volumetric scans of optic disc collected at the Chinese University of Hong Kong Eye Centre and the Hong Kong Eye Hospital. 60% of these volumetric scans were used for training, 20% for testing, and 20% for primary validation. Three independent datasets, including 546,267 and 1,231 scans, respectively, were collected from different eye settings in Hong Kong and the United States as external validation.[11] All the volumetric scans were labeled by glaucoma specialists with more than ten years' experience in glaucoma management, and visual field reports that illustrated glaucomatous functional changes were also reviewed for a more accurate grading.

In primary validation, the algorithm achieved an area under the receiver operating curve (AUROC) value of 0.97 (95% CI: 0.96-0.98), a sensitivity of 89% (95% CI: 83-93), specificity of 96% (95% CI: 92-99), and accuracy of 91% (95% CI: 89-93) (Table 1). In external validation, the algorithm achieved AUROC values of 0.89-0.90, sensitivities of 78-90%, specificities of 79-86%, and accuracies of 80-86%.[11] Heatmaps were generated to show the discriminative regions for the AI system to detect GON, and the learned features used to detect abnormalities by the 3D AI system were shown to be similar to what clinicians usually review (Figure 1).[11]

Further subgroup analysis confirmed that image signal strength, age, eye (i.e. left vs. right), sex, and race or ethnicity did not significantly affect the diagnostic performance of the deep learning system.[11] Compared to conventional screening techniques, 3D deep learning systems can review cases much faster than experienced specialists, can be done automatically, and do not require a large number of trained personnel on-site to analyze multitudes of OCT data. Thus, with a validated performance similar to experienced glaucoma specialists, this automated AI-based 3D SDOCT screening system has a huge potential to facilitate clinically feasible, diagnostically accurate and more cost-effective glaucoma screening.

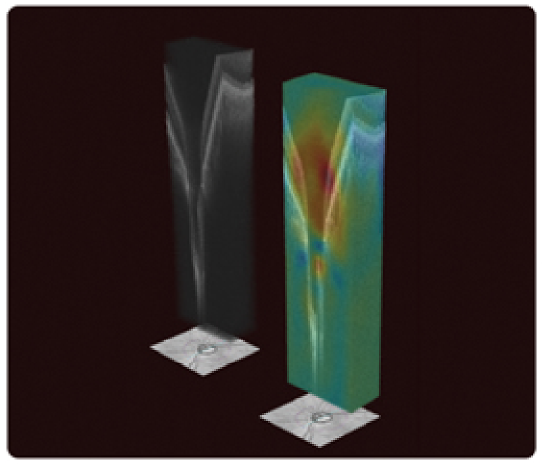

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Figure 1. The example of an SDOCT volumetric scan labeled as glaucomatous optic neuropathy (GON) and its corresponding heatmap. The red-orange colored regions represented the area with most discriminative power for the 3D deep learning system to detect GON, i.e., retinal nerve fiber layer, neuro-retinal rim area, and lamina cribrosa

	AUROC (95% CI)	*p*-value	Sensitivity (95% CI)	Specificity (95% CI)	Accuracy (95% CI)
Primary validation dataset					
3D deep-learning system	0.969 (0.960-0.979)	-	89% (83-93)	96% (92-99)	91% (89-93)
2D deep-learning system	0.921 (0.905-0.937)	<0.0001	85% (77-89)	85% (79-91)	84% (82-87)
Glaucoma specialist 1	0.933 (0.924-0.943)	<0.0001	89% (86-92)	94% (91-97)	91% (89-93)
Glaucoma specialist 2	0.937 (0.928-0.946)	<0.0001	87% (84-90)	96% (93-98)	90% (88-93)

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Table 1. Comparison of the 3D deep learning system, 2D deep learning system, and assessments by two glaucoma specialists in the primary validation dataset

AUROC: Area under the receiver operating curve

Future directions

A prospective validation study is underway to test and refine the AI algorithm by including more SDOCT volumetric scans from a broader range of disease stages and optic disc sizes. More participants with pre-perimetric glaucoma can be recruited to further refine the AI algorithm.[5,11] Based on preliminary estimations, the AI algorithm is expected to have a sensitivity and specificity above 85% in any of the unseen datasets.[11] Additionally, the study will estimate screening cost-effectiveness – opportunistically, among at-risk individuals, or in the general population – and help determine the incremental cost-effectiveness of incorporating this AI-based model for glaucoma screening.[11] Ultimately, through the AI algorithm, patients at risk can be effectively identified for further investigation and referred for appropriate management.

Message to physicians and conclusion

Early detection and timely treatment for glaucoma can prevent disease progression, avoid vision loss, and improve patients' quality of life. Using deep learning AI for identifying GON from 3D SDOCT has the potential to automate and accelerate the glaucoma screening process. It is hoped that the advances in AI deep learning systems will bring significant improvements to community glaucoma screening, particularly in the rural or low-resource areas. This will significantly advance the vision of preventing irreversible blindness in the future.

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