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Contents

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EDITORIAL

- 1 New Year's greeting and overview of *Artificial Intelligence in Medical Imaging* in 2021
Wu YXJ, Shen J

MINIREVIEWS

- 5 Artificial intelligence in ophthalmology: A new era is beginning
Panda BB, Thakur S, Mohapatra S, Parida S

Contents

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ABOUT COVER

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AIMS AND SCOPE

The primary aim of *Artificial Intelligence in Medical Imaging* (AIMI, *Artif Intell Med Imaging*) is to provide scholars and readers from various fields of artificial intelligence in medical imaging with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

AIMI mainly publishes articles reporting research results obtained in the field of artificial intelligence in medical imaging and covering a wide range of topics, including artificial intelligence in radiology, pathology image analysis, endoscopy, molecular imaging, and ultrasonography.

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Artificial intelligence in ophthalmology: A new era is beginning

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Abstract

The use of artificial intelligence (AI) in ophthalmology is not very new and its use is expanding into various subspecialties of the eye like retina and glaucoma, thereby helping ophthalmologists to diagnose and treat diseases better than before. Incorporating "deep learning" (a subfield of AI) into image-based systems such as optical coherence tomography has dramatically improved the machine's ability to screen and identify stages of diabetic retinopathy accurately. Similar applications have been tried in the field of retinopathy of prematurity and age-related macular degeneration, a silent retinal condition that needs to be diagnosed early to prevent progression. The advent of AI into glaucoma diagnostics in analyzing visual fields and assessing disease progression also holds a promising role. The ability of the software to detect even a subtle defect that the human eye can miss has led to a revolution in the management of certain ocular conditions. However, there are few significant challenges in the AI systems, such as the incorporation of quality images, training sets and the black box dilemma. Nevertheless, despite the existing differences, there is always a chance of improving the machines/software to potentiate their efficacy and standards. This review article shall discuss the current applications of AI in ophthalmology, significant challenges and the prospects as to how both science and medicine can work together.

Key Words: Artificial intelligence; Retina; Diabetic retinopathy; Glaucoma; Retinopathy of prematurity; Image-based learning

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Core Tip: Artificial intelligence has improved the diagnostic ability in the ophthalmology field, thereby improving patient care. The in-depth image recognition in diabetic retinopathy, retinopathy of prematurity and age-related macular degeneration has helped in early diagnosis and prevention. The detection of visual field

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defect even at its minute stage in glaucoma and other ocular conditions has accurately staged the disease with the prediction of its severity. Still, many challenges need to be addressed, such as image incorporation, training sets and the black box dilemma. Nevertheless, despite the existing differences, there is always a chance of improving machines to potentiate their efficacy and standards.

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INTRODUCTION

Artificial intelligence (AI) software can perform cognitive functions like problem-solving and learning by processing and analyzing a large amount of data; in other words, the machine can gain experience as humans do. It came into existence in 1956 and in no time spread its roots into many medical fields, including ophthalmology in the late 1990s when colour fundus photography had started gaining importance in diabetic retinopathy (DR) screening^[1]. Later on, its use was not limited to but tried extensively in many subspecialties of the eye such as cataract, myopia and glaucoma screening, corneal ectasia, keratoconus, retinopathy of prematurity (ROP) and ocular reconstruction. It can also be used in calculating intraocular lens power and while planning squint surgery and intravitreal injections. AI can even detect cognitive loss, Alzheimer's disease and cerebrovascular stroke risk from fundus photographs and optical coherence tomography (OCT). AI in ophthalmology started with machine learning (ML), which meant automatic behaviour modification after exposure to several inputs. Deep learning (DL) is a subset of ML that uses convolutional neural networks (CNN) to add decision-making capability. When incorporated into OCT, these features can help in the diagnosis of many anterior and posterior segment diseases.

AI AND DR

The disease burden of diabetes mellitus increases day by day, and millions of people are affected. According to published data, the present disease burden is 463 million^[2] and likely to rise to 642 million by 2040. DR is a microvascular complication affecting the retina's blood vessels, leading to progressive damage and irreversible blindness. These patients need to be diagnosed early, and prompt treatment should be started regardless of the type of diabetes. Routine dilated fundus screening in these patients with ophthalmoscopy and colour fundus photographs is the need of the hour and, therefore, eases the burden on the retina specialists. AI has shown promising results in the automated grading of DR based on ML and DL models, the CNN and the massive-training artificial neural network. The lesions in DR are recognized by ML as different colours like red (microaneurysms, haemorrhage, venous abnormalities, intraretinal microvascular abnormalities, new vessels, *etc.*), yellow (hard exudates, drusen) and white (cotton wool spots, fibrous proliferation, retinal oedema)^[3]. Staging in DR is usually done by the Davis staging practiced worldwide^[4]. In 2017, Takahashi *et al*^[5] developed a modified Davis staging adopting the DL criterion. The DL approach increases the possibility of identifying neovascularization or other features of proliferative DR (PDR) outside a 45° angle to the posterior pole by detecting non-verbalizable unclear signals. A major breakthrough in this arena was the United States Food and Drug Administration approval of IDx-DR in 2018^[6]. A CNN DL algorithm-based AI system to be used along with a Topcon fundus camera has now been proven to be an essential tool in non-ophthalmic healthcare places where it can diagnose DR in just a matter of 20 sec. Lately, the automated DR image accessing system has been applied in conditions affecting the macula such as PDR and clinically significant macular oedema. Another new entity has evolved termed as mtmDR (more than minimal DR), which is defined as the presence of Early Treatment Diabetic Retinopathy Study level 35 or higher, *i.e.* showing microaneurysms, hard exudates,

cotton wool spots and mild retinal haemorrhages and presence of macular oedema in at least one eye^[7].

Abràmoff *et al*^[8] reported that DL enhanced algorithm for automated detection of DR has better sensitivity than the Iowa Detection Program—without DL components. The sensitivity and specificity of DL-based automated DR detection algorithm was 96.8% [95% confidence interval (CI): 93.3%-98.8%] and 87.0% (95% CI: 84.2%-89.4%) with 6/874 false negatives, resulting in a negative predictive value of 99.0% (95% CI: 97.8%-99.6%). The authors did not miss a single case of severe non-proliferative DR, PDR or macular oedema with DL technology^[8]. Gargeya *et al*^[9] developed a data-driven DL algorithm where the colour fundus images were classified as healthy (no-retinopathy) or DR. Their model achieved a 0.97 area under the curve with a 94% and 98% sensitivity and specificity, respectively^[9].

Several studies came out with different proposals of classifying DR stages, some of which are worth mentioning^[10]. A three-layer feed-forward neural network based on identifying microaneurysms and haemorrhages was proposed by Wong *et al*^[11] to stage DR. A novel technique known as morphological component analysis was formulated by Imani *et al*^[12] to detect oedema and haemorrhages. Yazid *et al*^[13] used inverse surface thresholding and Lattice Neural Network with Dendritic Processing or enhancement techniques to identify hard exudates and optic disc pathologies. Akyol *et al*^[14] tried using key point detection, texture analysis and visual dictionary techniques to detect automatically the optic disc changes from fundus images. The sensitivity and specificity of these studies ranged from 75% to 94.7%. Few studies have used the Eye Art software smartphone-based fundus photography with a sensitivity of around 95% and specificity of 91.5%. The EyeNuk software using the desktop fundus cameras to evaluate retinal images showed that EyeArt's sensitivity for DR screening was 91.7% and specificity was 91.5%^[15-17]. Ting *et al*^[18] validated the DL algorithm with retinal images taken with conventional fundus cameras that had high sensitivity and specificity for identifying DR and age-related macular degeneration (AMD). The intelligent retinal imaging system is another milestone achieved in the field of AI. It is a tele-retinal DR screening program that compares non-mydratic retinal images taken by a fundus camera with a standard set of images from Early Treatment Diabetic Retinopathy Study to recommend referral in selected cases of severe non-proliferative DR or more advanced vision-threatening disease^[19].

Wong *et al*^[20] pointed out certain limitations of DL technology in AI for the screening of DR. There is no simple, standardized algorithm to follow. The technology can talk about the referral cases but fail to detect severe sight-threatening DR that need urgent attention. The software may fail to detect associated glaucoma and AMD while screening for DR. The most severe problem is the development of the faith of the physicians on the machine. The heterogeneous population, different races and variability in pupil dilatation, cataract severity and media opacities may befool the machine and can be one of the reasons for refusal of the technology by the physicians^[20].

AI AND ROP

ROP is one of the leading causes of childhood blindness throughout the world. This vasoproliferative condition affects preterm infants with low gestational age and those with low birth weight. This condition should be diagnosed promptly so that timely intervention can be done. This can be abetted with the help of AI, which provides an automated, quantifiable and highly objective diagnosis in plus disease in ROP^[21]. One more area of application of AI in ROP is the utilization of the DL algorithms into medical training to standardize ROP training and education through tele-education. However, there are few clinical and technical challenges in the implementation of AI in the actual scenario.

According to International Classification of Retinopathy of Prematurity, ROP is classified based on the location, extent and severity of disease^[22]. However, there is much inter-observer variability in the subjective and qualitative assessment of disease severity (zone, stage and plus-disease) due to wide disparities among the diagnosing abilities of ophthalmologists attending these preterm babies. Therefore, there is a need to add objective methods of diagnosis and record-keeping for future comparisons to improve accuracy. Today, digital fundus photography using telemedicine has already paved the way for screening at-risk preterm babies at any geographical location that can be evaluated by a trained retina specialist sitting at another location.

Earlier systems of computer-based ROP diagnosis as described by Wittenberg *et al*^[23]

(2012) include the ROP-Tool, retinal image multiScale analysis, vessel map and computer-assisted image analysis of the retina, which were feature extraction-based systems. These systems could quantify vessel type, dilation and tortuosity into some value that had a variable diagnostic agreement with the clinical diagnosis of ROP.

Newer ML-based systems used a support vector machine that is trained to combine the features (vessel tortuosity) and the field of view (six-disc diameter radius) and then provide the diagnosis, quite similar to what an expert can do. This improved machine efficacy and accuracy to almost 85%-95%^[24,25]. However, there were few limitations as they required manual drawings for input. In 2018, Brown *et al*^[24] described a fully automated convoluted neural networks-based system known as the i-ROP DL system for the diagnosis of plus-ROP that can diagnose plus disease with a sensitivity and specificity of 93% and 94%, respectively. Taylor *et al*^[25] used the i-ROP DL algorithm to create a scoring system related to vascular tortuosity and termed it as continuous ROP vascular severity score (1-9), which could classify ROP as no ROP, mild ROP, type 2 ROP and pre-plus disease or type 1 ROP. This scoring system could help augment treatment regimens by better predicting the preterm infants at risk for treatment failure and disease recurrence. However, few regulatory and medicolegal issues in utilizing the DL systems for ROP diagnosis need to be resolved for proper implication.

AI AND AMD

AMD is considered the leading cause of central vision loss in the elderly age group. The challenges in diagnosing and managing this silent progressive retinal condition have led to the rising prevalence of the disease. AI has evolved to help in the automated detection of drusens in the very early stages and stratify the disease's progression. AMD is clinically characterized by the presence of drusens and retinal pigment epithelium changes progressing into geographic atrophy and neovascularization.

Many of the studies related to incorporating AI in the screening of AMD have used colour fundus images as input materials and then extract features of early, intermediate and late AMD to differentiate from the healthy ones with relatively high accuracy and sensitivity ranging from 87%-100%^[26,27]. They found this technique much cheaper than using OCT to stage the disease. Fang *et al*^[28] proposed a spectral-domain OCT combined with DL system that could determine the macular fluid quantity of neovascular AMD and the segmentation of the retinal layers of dry AMD and validated the accuracy as 100%. Bogunovic *et al*^[29] developed an algorithm to evaluate the response to treatment using OCT images. More recently, Bhuiyan *et al*^[30] did pioneer research in creating and validating AI-based models for AMD screening (accuracy 99.2%) and predicting late dry and wet AMD progression within 1 and 2 years (accuracy 66%-83%). They used the DL screening methods on the Age-related Eye Disease Study (AREDS) dataset to classify their colour fundus photos into no, early, intermediate or advanced AMD and further classified them along the AREDS 12 Level severity scale^[30]. They combined the AMD scores with sociodemographic, clinical data and other automatically extracted imaging data by a logistic model tree ML technique to predict risk for progression to late AMD.

AI AND GLAUCOMA

Glaucoma is a progressive optic neuropathy caused by high intra-ocular pressure leading to retinal nerve fibre loss and irreversible blindness. Early treatment can retard the progression of the disease. AI can help in identifying the borderline cases and predict the course of the disease. Many studies have tried to apply ML to identify the disease. A comprehensive AI for glaucoma should be able to evaluate all the necessary parameters such as optic disc changes, intraocular pressure (IOP), gonioscopy, retinal nerve fiber layer thickness, visual fields *etc.* However, such a comprehensive package is yet to come to the real-time world. The application of AI in measuring IOP is now limited to the Sensimed Triggerfish, a contact lens-based continuous IOP monitoring device that measures the corneal strain changes induced by IOP fluctuations. Martin *et al*^[31] used data from 24 prospective studies of Triggerfish using Random Forest Modelling (a ML method) to identify the parameters associated with glaucoma patients.

Omodaka *et al*^[32] developed a ML algorithm based on the segmentation technique where the parameters such as optic disc cupping, neuroretinal rim thickness and

ganglion cell thickness could be quantified with the help of swept-source OCT to the accuracy as high as 87%. Other studies by Christopher *et al*^[33], Barella *et al*^[34], Bizios *et al*^[35] and Larrosa *et al*^[36] evaluated unsupervised ML, ML classifiers, artificial neural networks, support vector machines and segmentation methods for glaucoma OCT.

Many studies have evaluated a DL algorithm to detect glaucomatous optic disc changes from colour fundus photographs with high sensitivity and specificity^[37,38]. The available AI devices for detecting glaucomatous optic neuropathy from fundus photos are the Pegasus (Orbis Cybersight Consult Platform), NetraAI (Leben Care Technologies Pte Ltd) and the Retinal Image Analysis - Glaucoma (RIA-G). RIA-G is the AI device based on DL made by the Indian startup Kalpah Innovations (Vishakapatnam, India). It is a cloud-based software that uses advanced image processing algorithms to measure the cup disc size and ratio, NeuroRetinal Rim Thickness and Disc Damage Likelihood Score^[39].

AI can also augment the interpretation of visual fields in studies showed by Asaoka *et al*^[40] and Andersson *et al*^[41] using a Feed-Forward Neural Network to identify pre-perimetric visual fields (VF). Goldbaum *et al*^[42] used unsupervised ML and variational Bayesian independent component analysis mixture model (vB-ICA-mm) to analyze VF defects. Bowd *et al*^[43] used the variational Bayesian independent component analysis-mixture model, which is an unsupervised machine-learning classifier and can be used in the analysis of frequency doubling technology perimetry data^[43].

AI AND CATARACT

Studies have described techniques to grade nuclear cataracts by the help of AI using algorithms based on ML or DL systems that work as efficiently as a clinician's grading. Gao *et al*^[44] proposed a system that could process slit-lamp images to grade cataracts. Liu *et al*^[45] focused on identifying and categorizing pediatric cataracts with excellent accuracy and sensitivity. Wu *et al*^[46] developed a universal AI platform and multilevel collaborative pattern that could perform effectively in diagnostic and referral service for pediatric and age-related cataracts. Dong *et al*^[47] have proposed the automated detection and grading of cataracts from colour fundus photographs using a combination of a DL system to extract images (Caffe software) followed by a ML algorithm (called as Softmax function) for severity grading. AI has also been tried in residents' cataract surgery training due to recognizing different phases of cataract surgery^[48,49]. Some researchers have derived new AI-based calculation formulae for pre-cataract surgery intraocular lens power, *e.g.*, the Hill-Radial basis function method and the Kane formula, which are reported to be able to estimate individual eye's intraocular lens power with promising results with further improvements needed for short axial length eyes^[50-52].

CONCLUSION

AI-assisted screening and diagnosis of high incidence diseases will help in better medical care and reduce the limitations to access ophthalmic care at remote areas devoid of ophthalmologists. In doing so, it will also reduce the overburdened healthcare system. However, this project at its infancy is nonetheless riddled with certain limitations. The assessment is highly dependent on image quality. Hence, patient factors such as head and eyeball movement and poor fixation may lead to a substandard image and a wrong assessment. However, this is the basis of ML, and in future, we expect a much more robust system. A certain degree of human supervision is required to find the subtle variations and atypical findings missed by AI. Computational cost and running expenses could be over the roof. AI mainly targets diseases with high incidence and morbidity, but not much effective for rare diseases with fewer incidences.

Future outlook

Not only for screening and diagnosis, AI has also been found to be instrumental in maintaining Electronic Health Record (EHR) data. Given the plethora of diagnostic tests that patients undergo, these collected EHR data could be fed into the AI system and trained through exposure to normal and pathological clinical data. Therefore, it could be used for risk assessment as well as to predict postoperative complications and outcome.

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