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The primary aim of *World Journal of Diabetes* (*WJD*, *World J Diabetes*) is to provide scholars and readers from various fields of diabetes with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

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Everything real about unreal artificial intelligence in diabetic retinopathy and in ocular pathologies

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Abstract

Artificial Intelligence is a multidisciplinary field with the aim of building platforms that can make machines act, perceive, reason intelligently and whose goal is to automate activities that presently require human intelligence. From the cornea to the retina, artificial intelligence (AI) is expected to help ophthalmologists diagnose and treat ocular diseases. In ophthalmology, computerized analytics are being viewed as efficient and more objective ways to interpret the series of images and come to a conclusion. AI can be used to diagnose and grade diabetic retinopathy, glaucoma, age-related macular degeneration, cataracts, IOL power calculation, retinopathy of prematurity and keratoconus. This review article intends to discuss various aspects of artificial intelligence in ophthalmology.

Key Words: Artificial intelligence; Diabetic retinopathy; Deep learning; Machine learning; Ophthalmology

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Core Tip: It is said that necessity is the mother of all inventions and converging global trends make multiplying eye care efficiency an increasingly urgent necessity. Artificial intelligence refers to an artificial creation of human-like intelligence of computer machines that can learn, reason, plan, perceive or process natural language.

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INTRODUCTION

Artificial intelligence (AI) refers to a machine's ability to mimic human cognitive functions, such as learning, reasoning, problem-solving, knowledge representation, social intelligence and general intelligence. It represents a significant advance in computer science and enables doing tasks using a computer with little human mind involvement following human training. AI was developed in the 1940s, but major advances ensued during the 1990s with significant improvements in machine learning, multi-agent planning, case-based reasoning, scheduling, data mining, natural language understanding and translation, vision, virtual reality, games, *etc.* Researchers have created an algorithm that can guess whether patients with cardiovascular diseases have lived or died based on their condition within a year. The algorithm could predict patient survival in 85% of cases based on data obtained by measuring the heart's electrical activity using electrocardiography. The rapid development in AI technology requires physicians and computer scientists to have a good mutual understanding of the technology and the medical practice to improve medical care. This review article presents the role of AI in various fields of ophthalmology.

METHODOLOGY

We searched highly cited articles in PubMed, Scopus database, Google Scholar, Web of Science, Cochrane library and Embase database on Artificial - Intelligence in Diabetic - Retinopathy, Age-related macular degeneration, Glaucoma, Keratoconus, Cataract, Dry Eye and other common ocular diseases published between the year 2000 to 2021. We also used Reference Citation Tool (RCA) for searching the keywords and articles were ranked based on the "Impact Index Per Article." The latest highlighted articles were selected for review. Only articles published in English were considered and the rest were rejected.

ARTIFICIAL INTELLIGENCE BASICS

Machine learning

Machine learning (ML) is a core AI branch that aims to provide computers with the ability to learn without being explicitly programmed[1]. ML focuses on developing algorithms that can analyze data and make predictions[2] (Figure 1).

Deep learning

Deep learning (DL) differs from ML in that DL uses neural networks for making predictions and decisions. These neural networks were inspired by the biological neural networks of animal brains. They use the statistical probability principle derived from large data volumes to learn how to improve their accuracy, making DL a valuable tool for aiding physicians in clinical practice.

Generative adversarial network

Generative adversarial networks (GANs) are paired neural networks used for unsupervised ML. They can generate images or other data for the discriminative neural network to evaluate the data and provide feedback to aid the learning process[3].

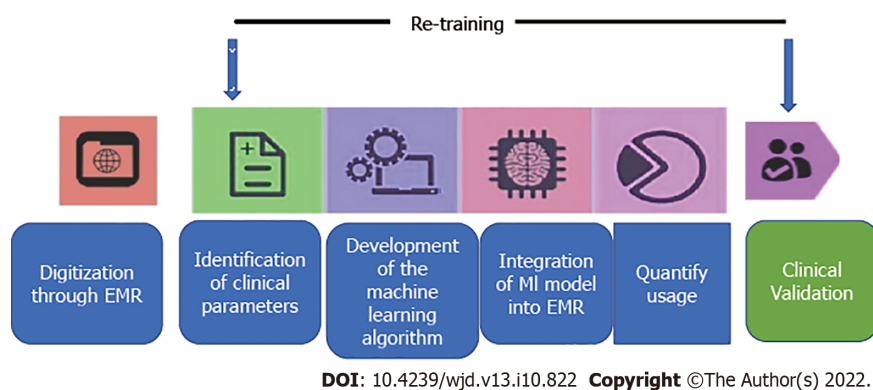


Figure 1 Steps of machine learning algorithms that forms to analyze data and make predictions.

ARTIFICIAL INTELLIGENCE PLATFORMS

Algorithms resemble the AI software, whereas platforms resemble the computer hardware in which algorithms are installed and work to predict and make decisions. AI platforms simulate cognitive functions of the human mind including learning, reasoning, problem-solving, social intelligence and general intelligence[4].

Top Artificial intelligence platforms

The top AI platforms include Google, Microsoft Azure, TensorFlow, Railbird, Infosys Nia, Wipro HOLMES, Premonition, Dialogflow, Ayasdi, MindMeld, MeYa, KAI and Vital A.I. Following the initial learning steps, the system or machine is taught to advance its initial learning for more accuracy and efficiency. This learning is further compounded by using complex mathematical equations to understand nonlinear relationships between different variables through an information flow called “neural networks.” This “higher training” form enables AI to judge and weigh different outcome possibilities.

USE OF ARTIFICIAL INTELLIGENCE IN OPHTHALMOLOGY

From the back of the eye to the front, AI is expected to provide ophthalmologists with novel automated tools to diagnose and treat ocular diseases. Recently, the application of AI in medicine has garnered much attention from big players in the digital world, such as Google and IBM. This is expected to stimulate research and development for disease diagnosis and treatment. Researchers in the field of AI ophthalmology view computerized analytics as the path toward more efficient and objective ways of image interpretation compared with modern eye care practice.

Diabetic retinopathy

Patients with diabetes require regular and repetitive screening to detect and treat diabetic retinopathy (DR)[4,5]. Conventionally, this screening is performed by dilated fundus examination or color fundus photography using conventional fundus cameras (mydriatic or nonmydriatic). The primary issue in this screening is retinal image grading by retinal specialists or trained personnel, who are few compared with the patient load requiring screening. Another problem is that most patients reside in rural areas. Finally, constant follow-ups are needed for several years[4].

DR, a complication of chronic diabetes, is a vasculopathy affecting one-third of patients with diabetes and possibly leading to irreversible blindness[6,7]. Most AIs have been evaluated for their application in DR detection with the primary goal of assisting the development of a mass and rapid screening tool with high sensitivity and specificity. Considering the huge diversity in the clinical presentation of DR, it is essential for an AI neural network to be multilayered and extensively trained. This requires the use of multiple images evaluated against the ground truth.

Most studies have used the International Clinical Diabetic Retinopathy Disease severity scale, a 5-point scale [no apparent retinopathy, mild non-proliferative DR (NPDR), moderate NPDR, severe NPDR and proliferative diabetic retinopathy (PDR)]. Referable DR is defined as moderate or severe DR as disease management often changes from yearly screening to closer follow-up for moderate disease severity. A recent study by Shah *et al*[8] used an AI algorithm with a deep convolutional neural network (DCNN). It assessed its sensitivity and specificity with double validation, *i.e.* external and internal validation. External validation was performed using the Methods to Evaluate Segmentation and Indexing Techniques in the Retinal Ophthalmology dataset, *i.e.* the MESSIDOR dataset. In contrast,

internal validation was performed by two retinal specialists. The main advantage of this study was that 112489 images, acquired from various fundus cameras taking pictures of both mydriatic and nonmydriatic eyes, were fed into AI, thereby giving a multiethnicity advantage to the dataset. The agreement between AI and internal/external validation was high for ANY DR and REFERRAL DR, with a sensitivity of > 95%. The agreement for sight-threatening DR between AI and external validation was high but moderate between AI and internal validation. However, this did not affect the conclusion that AI proved to be a useful screening tool and detected referral DR cases with high specificity.

Valverde *et al*[9] reviewed the available algorithms and detailed the methods for segmenting exudates, red lesions and screening systems. These segmentation methods were used to develop a computer-aided diagnosis for automated DR detection, such as Retmarker DR, Retalyze System, IDx-DR (first FDA-approved system), iGradingM and Telemedical Retinal Image Analysis and Diagnosis Network. Overall, all these systems achieved high sensitivity and specificity, provided that the segmentation of exudates was used to screen for DR rather than the segmentation of red lesions. Medios, an offline AI, was developed and studied by Sosale *et al*[10]. This offline algorithm was created because of Internet access limitations and the high computational power required for all cloud-based AIs in a developing country. Fundus photographs were captured using Remidio Non-Mydriatic Fundus on Phone 10 (NM FOP 10) and image processing was directly performed on the smartphone graphics processing unit. The sensitivity and specificity of the AI algorithm for detecting referral DR were 98% and 86%, respectively. For any DR, its sensitivity and specificity were 86% and 95%, respectively. Compared with other online cloud-based software, such as EyeArt and IDx-DR, Medios had better sensitivity and equivalent specificity (Figure 2). The specific abnormalities that can be detected using continuous machine learning (CML) are macular edema[11,12], exudates[13], cotton-wool spots[14], microaneurysms and optic disc neovascularization[15]. Commercially available DR detection and analysis technologies include Retalyze System, IDx-DR, iGradingM and RetmarkerDR. The difference is that only a few modalities use lesion-based grading, whereas the others use image-based grading. The sensitivity of this system has reached around 80%, but its specificity remains lower than 90%.

A DL GAN can be trained to map anatomical features from different image modalities, *i.e.* fundus photographs and fluorescein angiography (FA) images, onto a shared feature manifold to generate one image modality from another[16]. Using GAN, detailed retinal vascular structures can be produced without the requirement of FA to avoid its potential side effects. The inferred structural measurements of retinal vasculature may allow clinicians to identify the natural history of changes in the retinal vasculature and the clinical outcomes of retinal diseases, as previously reported by direct fundus image analysis, but with the accuracy of FA or even optical coherence tomography angiography image analysis[17].

Morya *et al*[18] evaluated the first smartphone-based online annotation in the world, a tool for rapid and accurate image labeling, using AI-based DL for DR. This DL model evaluated its accuracy based on a binary referral DR classification system, depending on whether a retinal image had referral DR or not. A total of 32 ophthalmologists used the tool for over 55000 images. The data analysis proved considerable flexibility and portability with favorable grader variability in concurrence with image annotation. Table 1 demonstrates the collective data of various studies on DR-related AI. This table has been reproduced from the article by Padhy *et al*[19].

AGE-RELATED MACULAR DEGENERATION

Age-related macular degeneration (AMD) is the cause of approximately 9% of cases of blindness globally[20]. The worldwide number of people with AMD was projected to be 196 million in 2020, which is expected to substantially increase to 288 million in 2040[20]. The age-related eye disease study (AREDS) developed a simplified severity scale for AMD[22]. This scale combines the risk factors from both eyes to generate an overall score for the individual based on the presence of one or more large drusen (diameter of > 125 μ m) or AMD pigmentary abnormalities in the macula of each eye. The simplified severity scale is also clinically useful because it allows ophthalmologists to predict an individual's 5-year risk of developing late AMD[23]. AMD detection and prediction are essential for individualized treatment. Using AI in cases of AMD could increase the detection rate of lesions such as drusen, with the presence of fluid and reticular pseudo-drusen and geographic atrophy.

Several DL systems have been developed for classifying color fundus photographs based on AMD severity scales. These severity scales include referable and non-referable AMD[22] and multiclass AMD classification systems (*e.g.*, 9-step AREDS severity scale and 4-class). Recent studies have shown the robust performance of automated AMD classification systems based on optical coherence tomography (OCT) scans[24].

DeepSeeNet is based on color fundus photography and uses three networks-Drusen-Net, Pigment-Net and Late AMD-Net (Figure 3). These three networks were designed as DCNNs, each with an Inception-v3 architecture and a state-of-the-art convolutional neural network (CNN) model for image classification. Similar to the study by De Fauw *et al*[25], DeepSeeNet includes two stages by design for improved performance and increased transparency. Images were obtained from the AREDS dataset,

Table 1 Comparative analysis of various studies done on artificial intelligence in diabetic retinopathy[19]

Ref.	Sensitivity, specificity or accuracy of the study	Total fundus images examined	Types of AI used	Main objective
Wong <i>et al</i> [20]	Area under the curve were 0.97 and 0.92 for microaneurysm and hemorrhages respectively	143 images	A three-layer feed forward neural network	Deals with detecting the microaneurysm and hemorrhages. Frangi filter used
Imani <i>et al</i> [57]	Sensitivity of 75.02%-75.24%; Specificity of 97.45%-97.53%	60 images	MCA	Detected the exudation and blood vessel
Yazid <i>et al</i> [58]	97.8% in sensitivity, 99% in specificity and 83.3% in predictivity for STARE database. 90.7% in sensitivity, 99.4% in specificity and 74% in predictivity for the custom database	30 images	Inverse surface thresholding	Detected both hard and soft exudates
Akyol <i>et al</i> [59]	Percentage accuracy of disc detection ranged from 90%-94.38% using different data set	239 images	Key point detection, texture analysis, and visual dictionary techniques	Detected the optic disc of fundus images
Niemeijer <i>et al</i> [13]	Accuracy in 99.9% cases in finding the disc	1000 images	Combined k-nearest neighbor and cues	Fast detection of the optic disc
Rajalakshmi <i>et al</i> [60], Smart phone based study	95.8% sensitivity and 80.2% specificity for detecting any DR. 99.1% sensitivity and 80.4% specificity in detecting STD	Retinal images of 296 patients	Eye Art AI Dr screening software used	Retinal photography with Remidio 'Fundus on Phone'
Eye Nuk study	Sensitivity was 91.7%; Specificity was 91.5%	40542 images	Eye PAC Stelescreening system	Retinal images taken with traditional desktop fundus cameras
Ting <i>et al</i> [61]	Sensitivity and specificity for RDR was 90.5% and 91.6%; For STD the sensitivity was 100% and the specificity was 91.1%	494661 retinal images	Deep learning system	Multiple Retinal images taken with conventional fundus cameras
IRIS	Sensitivity of the IRIS algorithm in detecting STD was 66.4% with false-negative rate of 2% and the specificity was 72.8%. Positive Predictive value of 10.8% and negative predictive value 97.8%	15015 patients	Intelligent Retinal Imaging System (IRIS)	Retinal screening examination and nonmydriatic fundus photography

This table has been reproduced from the article by Padhy *et al*[19]. Citation: Padhy SK, Takkar B, Chawla R, Kumar A. Artificial intelligence in diabetic retinopathy: A natural step to the future. *Indian J Ophthalmol* 2019; 67: 1004-1009. Copyright© The Authors 2019. Published by *Indian Journal of Ophthalmology*. The authors have obtained the permission for table using from the Indian Journal of Ophthalmology Publishing Group ([Supplementary material](#)). AI: Artificial intelligence; MCA: Morphological component analysis.

comprising approximately 60000 retinal images. DeepSeeNet operates by first detecting individual risk factors (drusen and pigmentary abnormalities) in each eye and then combining values from both eyes to assign an AMD score for the patient. Therefore, DeepSeeNet closely matches the clinical decision-making process ([Figure 3](#)). The accuracy of Fine-Tuned DeepSeeNet (FT-DSN) was superior to that of human retinal specialists (67% *vs* 60%). On further analysis, the overall accuracy of FT-DSN was superior. However, subgroup analysis showed that FT-DSN correctly classified participants with severity scale scores of 0-4 more often than the retinal specialists. In contrast, the retinal specialists correctly classified those with late AMD more often than FT-DSN. Lee *et al*[26] developed an AMD screening system to differentiate between normal and AMD OCT images. They trained their CML using 48312 normal and 52690 AMD images. Their CML had a peak sensitivity and specificity of 92% and 93%, respectively. Treder *et al*[27] used OCT images (1112 images) to develop a CML that could differentiate a healthy macula from a macula showing exudative AMD, with a sensitivity of 100% and a specificity of 92%.

Bogunovic *et al*[28] developed a data-driven interpretable predictive model to predict the progression risk in those with intermediate AMD. Drusen regression, an anatomic intermediate AMD endpoint, and advanced AMD onset can be predicted using this specifically designed, fully automated, ML-based classifier. Treder *et al*[27] fed corresponding OCT images of patients with low or high anti-vascular endothelial growth factor (VEGF) injection requirements into a random forest (RF) classifier to develop a predictive model. The treatment requirement prediction showed an area under the curve (AUC) of 70%-80%. Prahs *et al*[29] trained a DCNN on OCT images to facilitate decision-making regarding anti-VEGF injection, and the outcomes were better than those using CML. These studies are an essential step toward image-guided prediction of treatment intervals in neovascular AMD or PDR management. In addition to screening, some studies have focused on grading AMD and predicting visual acuity from OCT images. This will aid clinicians in formulating a visual prognosis and support them in their

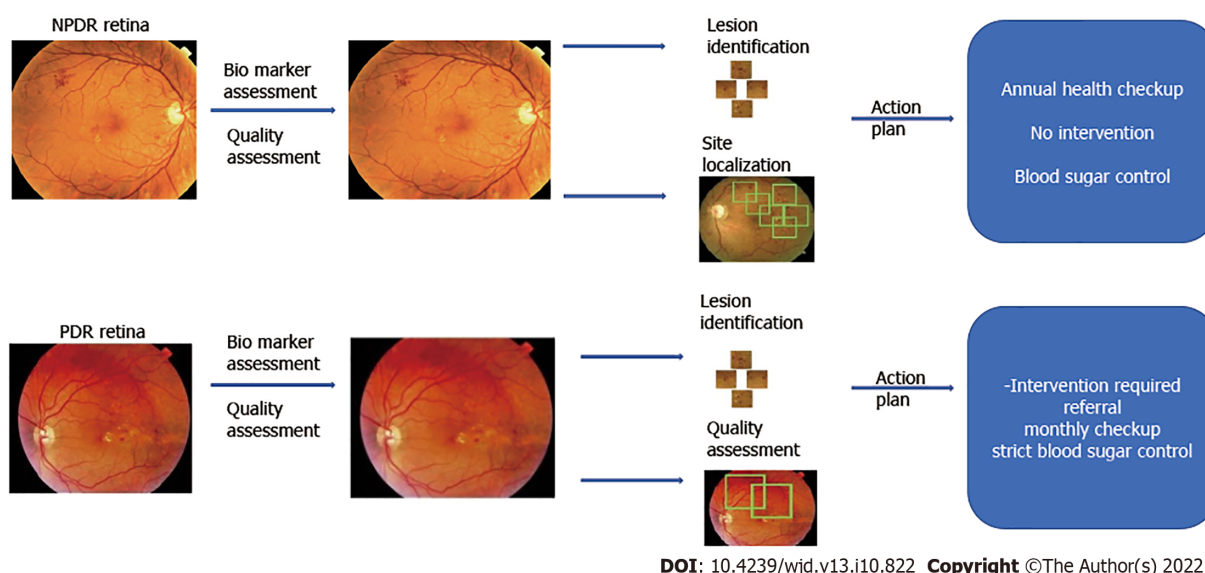


Figure 2 AI software assess the diabetic retinopathy into referable and non-referable interventions.

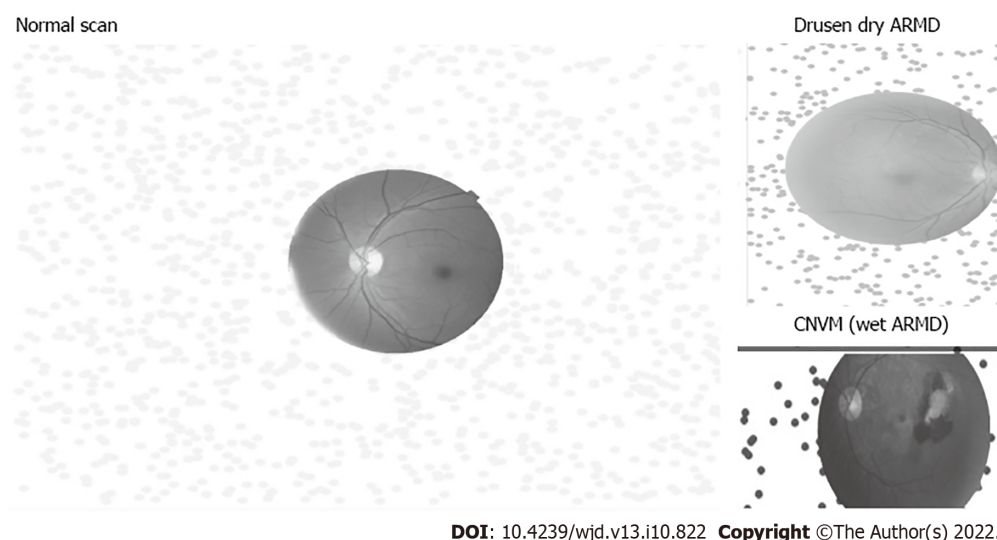


Figure 3 Deep Sea net classify age-related macular degeneration (AMD) into dry AMD and wet AMD based on fundus photograph.

decision-making. Aslam *et al*[30] and Schmidt-Erfurth *et al*[31] developed CMLs that could estimate visual acuity. Aslam *et al*[30] trained their CML on data from 847 OCT scans, whereas Schmidt-Erfurth *et al*[31] trained their CML on data from 2456 OCT scans (from 614 eyes).

AI systems can be trained to perform segmentation, classification and prediction using retinal OCT images. Several AI systems were demonstrated to display high accuracy for segmentation which is essential to quantify intraretinal fluid, subretinal fluid and pigment epithelial detachment. Compared with noncomputerized segmentation techniques, the DL algorithm developed by Lee *et al*[26] accurately differentiated fluid accumulation from other abnormal retinal findings. Further, De Fauw *et al*[25] confirmed the ability of DL to detect > 50 retinal conditions and the robustness of the AI system in triaging the urgency of referrals for patients with retinal diseases. Table 2 is a summary of AI algorithms used for AMD.

Glaucoma

Glaucoma, also known as the silent sight killer, is the leading cause of preventable and irreversible blindness worldwide. The disease remains asymptomatic and an estimated 50%-90% of individuals with glaucoma remain undiagnosed. Thus, glaucoma screening is recommended for its early detection and treatment. Cup-disk ratio (CDR) can be calculated to assist early-stage glaucoma diagnosis using AI models[32]. After locating the coarse disk margin using a spatial correlation smoothness constraint, a support vector machine (SVM) model is trained to find the patches on OCT images to identify a

Table 2 Summary of artificial intelligence algorithm used in age-related macular degeneration

Ref.	Sensitivity	Specificity	Diagnostic accuracy	Output
Grassman <i>et al</i> [62]	84.20	94.30	63.3, Kappa of 92%	Final probability value for referable <i>vs</i> not referable
Ting <i>et al</i> [61]	93.20	88.70	Area under curve-0.932	Identifying referable AMD and advanced AMD
Lee <i>et al</i> [26]	84.60	91.50	87.60	Prediction of binary segmentation map
Treder <i>et al</i> [27]	100	92	96	AMD testing score-score of 0.98 or greater adequate for diagnosis of AMD

AMD: Age-related macular degeneration.

reference plane that can calculate the CDR[33].

In 2013, Yousefi *et al*[16] published an AI study on the progression of primary open-angle glaucoma (POAG) in 180 patients using many different CMLs and independent features. They found that retinal nerve fiber layer features provided sufficient information for CMLs to differentiate between stable POAG and progressing POAG at an early-moderate disease stage. RF tree and lazy K star were the most sensitive CMLs. Chen *et al*[34] developed a CNN using two different datasets [ORIGA dataset: 650 images (99 for training and 551 for validation) and SCES dataset: 1676 images (entirely used for validation as the images in the ORIGA set were used for training)] to detect POAG based on optic disk images. They reported the area under the receiver operating characteristic curve values of 0.831 and 0.887 for ORIGA and SCES datasets, respectively. Kim *et al*[35] and Raghavendra focused on detecting glaucoma *vs* normal fundus images. They reported an accuracy of 87.9%, equivalent to the accuracy of human experts, demonstrating an efficient method for glaucoma screening. Raghavendra *et al*[36] tested their CML on 589 normal and 837 glaucoma images and obtained a score of 0.98 for sensitivity, specificity and accuracy.

DL performs better than CML in detecting pre-perimetric open-angle glaucoma[36]. Holistic and local features of the optic disc on fundus images have been used to mitigate the influence of optic disk misalignment for glaucoma diagnosis[37]. Li *et al*[38] demonstrated that DL could be used to identify referable glaucomatous optic neuropathy with high sensitivity and specificity. Table 3 is a summary of studies using AI to detect progression in eyes with glaucoma.

Retinopathy of prematurity

Retinopathy of prematurity (ROP) is a leading cause of treatable childhood blindness, provided it is diagnosed timely[39]. This disease necessitates strict follow-up and screening which are very tedious and demanding. Repeated ROP screening and follow-up consume substantial manpower and energy. Therefore, the application of AI in ROP screening may improve the efficiency of care for ROP.

Wang *et al*[40] developed an automated ROP detection system called DeepROP using deep neural networks (DNNs). ROP detection was divided into ROP identification and grading tasks. Two specific DNN models-Id-Net and Gr-Net-were designed for the identification and grading tasks, respectively. Id-Net achieved a sensitivity of 96.62% and a specificity of 99.32% for ROP identification, whereas Gr-Net attained a sensitivity of 88.46% and a specificity of 92.31% for ROP grading. In another 552 cases, the developed DNNs outperformed some human experts[41].

A similar AI, developed by Tan Z, achieved similar accuracy for detecting plus ROP. They reported that this AI could distinguish the plus disease with 95% accuracy, comparable to the diagnoses of experts and much more precise than those of non-experts. Various studies have reported promising results, most of which were based on two-level sorting (plus or not plus disease).

Keratoconus

There are significant obstacles in distinguishing patients with very early keratoconus signs from the normal population. This is attributed to the limited availability of samples owing to low disease prevalence. For this purpose, the application of AI in corneal topography interpretation has been attempted. The methods used discriminative classifiers that, given a set of independent machine-derived variables from corneal topography (*e.g.*, simulated K readings and topographic asymmetries), can be trained to differentiate between two or more classes of topography (*e.g.*, normal, astigmatic and keratoconus).

AI has been used to detect keratoconus and forme fruste keratoconus[42] based on data from Placido topography, Scheimpflug tomography[43], anterior segment spectral domain OCT and biomechanical metrics (CorvisST and corneal hysteresis). Further, data from Pentacam[44], Sirius[45], Orbscan II, Galilei and TMS-1 have been studied using ML algorithms to detect early keratoconus.

The Pentacam RF index (PRFI) is an RF model built using data from Pentacam HR (Oculus, Wetzlar, Germany). It was the only model trained using the preoperative examination data of patients that developed ectasia. The index already available on the device (BAD-D) presented a sensitivity of 55.3%, whereas PRFI identified 80% of the cases correctly. In the external validation set, the model showed an

Table 3 Summary of studies using artificial intelligence to detect progression in Glaucomatous eyes

Ref.	No. of eyes	Instrument	Approach	Comments
Lin <i>et al</i> [63]	80	SAP	Supervised ML	Sensitivity-86%; Specificity-88%
Goldbaum <i>et al</i> [64]	478 suspects; 150 glaucoma; 55 stable glaucoma	SAP	Unsupervised ML	Specificity-98.4%, AROC not available; Use of variational Bayesian. Independent component analysis mixture model in indentifying patterns of glaucomatous visual field defects and its validation
Wang <i>et al</i> [65]	11817 (method developing cohort) and 397 (clinical evaluation cohort)	SAP	Unsupervised ML	AROC of the archetype method 0.77
Yousefi <i>et al</i> [16]	939 Abnormal SAP and 1146 normal SAP in the cross section and 270 glaucoma in the longitudinal database	SAP	Unsupervised ML	Sensitivity 34.5%-63.4% at specificity 87% Comment: it took 3.5 years for ML analysis to detect progression while it took over 3.5 years for other methods to detect progression in 25% of eyes
Belghith <i>et al</i>	27- progressing; 26-stable glaucoma and 40 healthy controls		SD OCT Supervised ML	Sensitivity -78% Specificity in normal eyes-93%; 94% in non-progressive eyes

ML: Machine learning; OCT: Optical coherence tomography.

accuracy of 85% for detecting the normal topographic eye of very asymmetric cases (VAE-NT), reaching a specificity of 96.6%[46].

A single decision tree method was proposed based on the data obtained from the Galilei Dual Scheimpflug Analyzer (Ziemer Ophthalmic Systems AG, Port, Switzerland). This index showed a sensitivity of 90% and a specificity of 86% for detecting early disease forms[47]. Discriminant linear models were also successfully used to analyze the data obtained from Orbscan II (Technolas, Munich, Germany) with a sensitivity of 92% and a specificity of 96% in the first validation set and a sensitivity of 70.8%, and a specificity of 98.1% in a different ethnic background population[48].

Ambrósio *et al*[48] evaluated AI-based tomographic and biomechanical index (TBI), which combines Scheimpflug-based corneal tomography and biomechanics (Corvis ST) for improving ectasia detection. The Kerato Detect algorithm analyzes the corneal eye topography using a CNN that can extract and learn the features of a keratoconus eye. The results ensure high-level performance yielding an accuracy of 99.33% for the test dataset. Neural networks have been used to evaluate the waveform signals of the Ocular Response Analyzer (Reichert Ophthalmic Instruments, Buffalo, United States) yielding high accuracy for the study validation sample comprising early keratoconus forms (AUC, 0.978). The RF model called TBI achieved a sensitivity of 90.3% and a specificity of 96% for detecting VAE-NT. The combination of tomographic and biomechanical parameters was superior to either method used alone.

Sharif *et al*[49] showed that corneal images obtained *via* confocal microscopy could be assessed in detail using a committee machine developed from artificial neural networks and adaptive neuro-fuzzy inference systems that can detect abnormalities with high accuracy and enable 3D visualization. Nevertheless, considering that the research on these aspects is limited, there is a possibility that the characteristics learned in AI training may not be similar to those in another clinical population. When using tomographic data rather than Placido topographic data, researchers have found that combining biomechanical or additional imaging data is necessary to enhance the performance for detecting early keratoconus signs.

CORNEAL DYSTROPHIES AND DYSPLASIA

Eleiwa *et al*[50] used AI to differentiate Fuchs endothelial corneal dystrophy (FECD, without corneal edema) from late-stage FECD (with corneal edema) based on high-definition OCT images. The model they developed had a sensitivity of 99% and a specificity of 98% in differentiating normal cornea from FECD (early or late).

Gu *et al*[51] reported an AUC of 0.939 for detecting corneal dystrophy or degeneration using a slit-lamp photograph-based DL model. They included ocular surface disorders such as limbal dermoid, papilloma, pterygium, conjunctival dermolipoma, conjunctival nevus and conjunctival melanocytic tumors to differentiate ocular surface neoplasms. However, considering the limited existing evidence, the use of AI for detecting ocular surface neoplasms warrants further exploration. Kessel *et al*[52] created trained DL algorithms to detect and analyze amyloid deposition in corneal sections in patients with familial amyloidosis undergoing full-thickness keratoplasty.

Dry eye

Dry eye disease is a common condition that affects 8% of the global population and is caused by the reduced quantity or quality of tears. Left untreated, dry eye can result in pain, ulcers and even corneal

scars. Therefore, rapid diagnosis is essential and clinically based on tear production measurement and a tear film stability evaluation.

In a recent study, researchers used infrared thermal images of the eye along with the ML algorithms Gabor transform and Discrete Wavelet Transform (DWT) to detect dry eyes[53]. These ML methodologies were used to extract features from specific image frames, further segmented into eye regions, and the data were analyzed accordingly. Principal component analysis was ranked using a t-value and fed into the SVM classifier. Using the 1st, 5th, and 10th after the first blink, they achieved classification accuracies of: (1) 82.3%, 89.2% and 88.2% for the left eye; and (2) 93.4%, 81.5% and 84.4% for the right eye, respectively. Similarly, using the 1st, 5th, and 10th frames of the lower half of the ocular region, they achieved accuracies of: (1) 95.0%, 95.0% and 89.2%; and (2) 91.2%, 97.0% and 92.2% for the left and right eyes, respectively. This study showed that the lower half of the ocular region is superior to the upper half of the ocular region.

This method offers several advantages, such as being semiautomatic and making it less susceptible to interobserver variability. It is more accurate than standard clinical tools, more convenient for the patient and does not require a special dye. Gabor transform and DWT are methodologies for automatic feature extraction from biomedical images.

Cataract

Cataract refers to the clouding of the eye lens. It is the leading cause of blindness worldwide. Therefore, automatic detection for the diagnosis of this disease will be cost-effective.

Srivastava *et al*[54] proposed a system that automatically grades the severity of nuclear cataracts based on slit-lamp images. First, the lens region of interest is identified, following which the CNN filters randomly selected image patches, generating local representations *via* an iteration process with random weights. They named it ACASIA-NC_v0.10 (*i.e.*, Automatic Cataract Screening from Image Analysis-Nuclear Cataract, version 0.10) and specifically used the “visibility cue” for nuclear cataract grading C. Their system used visible features of the nucleus, such as sutures and demarcation lines, in greyscale. With the help of the software, they could analyze the number of visible features. ACASIA-NC_v0.10 achieved a similarity of > 70% against clinical grading and reduced the error by > 8.5%. Other studies similar to Liu *et al*[55] mainly focused on identifying pediatric cataracts. They reported exceptional accuracy and sensitivity for lens classification and density. In addition, cataract grading can also be achieved automatically based on lens OCT findings.

SMARTPHONE-BASED APPS USING AI IN OPHTHALMOLOGY

The advantages of using smartphones are many, including having built-in internal data storage and cloud storage capabilities[56]. Pegasus VISULTIX, an inexpensive smartphone clip-on optic nerve scanner expected to aid the diagnosis and treatment of those with chronic blinding diseases, such as glaucoma, using AI, is being adapted. Pegasus could detect glaucomatous optic neuropathy with an accuracy of 83.4%, comparable to the average accuracies of ophthalmologists (80.5%) and optometrists (80%) using the same images.

CC-Cruiser was developed to study the application of AI in congenital cataracts (CC). CCs cause irreversible vision loss and breakthroughs in the research on CCs have substantially contributed to the field of medicine. Researchers have developed a three-fold AI system that includes identification networks for CC screening in populations, evaluation networks for risk stratification of patients with CC and strategist networks to assist ophthalmologists in making treatment decisions.

Shaw created a ComputeR Assisted Detector LEukocoria (CRADLE) app that uses AI to identify white eyes indicative of several serious eye diseases. The sensitivity of CRADLE for detecting white eyes in children aged ≤ 2 years surpassed 80%, which was substantially higher than the sensitivity of physical examination (8%). This new smartphone app takes advantage of parents’ fondness for snapping pictures of their children to identify signs of a severe eye disease that the child might be developing. On average, the app detected white eyes in pictures collected 1.3 years before diagnosis.

FUTURE OF ARTIFICIAL INTELLIGENCE APPLICATION

The AI-based platform provides an intelligent diagnosis of eye diseases at present. It focuses on binary classification problems, whereas visiting patients suffer multi-categorical retinal disorders in clinical settings. Multimodal clinical images, such as OCTA, visual field and fundus images should be integrated to build a generalized AI system for more reliable AI diagnosis. The challenge is coordinating multicenter collaborations to build good quality and extensive data collection to train and improve AI models. AI is an instrument to upturn clinical decision power with many possible applications for ophthalmologists.

LIMITATIONS OF ARTIFICIAL INTELLIGENCE

Any software design is not perfect, and so artificial intelligence is also not bias-proof. Five distinct types of machine learning bias that we need to be aware of and guard against: (1) Sample bias: poor data collection for training. Example: Labeling other vascular retinopathies as DR; (2) Prejudice bias: Prejudice bias results from training data that is influenced by stereotypes. For example, a large cup is always glaucoma; (3) Measurement bias. For example, fundus photo color, different cameras give different color measurements; best avoided by having multiple or similar measuring devices and humans trained to compare the output of these devices when developing the algorithm; (4) Algorithm bias: Choosing the wrong software algorithm for a specific disease; and (5) The quality control of images for prediction.

CONCLUSION

With the substantial advances in AI in the field of ophthalmology, it can be assumed that now is the dawn of AI in ophthalmology. With the advent of technologies based on different AI modules, such as DL, ML and GAN, it can be assumed that AI has a promising role in the diagnosis of DR, ARMD, dry eye, glaucoma, keratoconus and cataracts. In particular, these AI-based applications are more relevant during the present coronavirus disease 2019 era and for serving the remotest of areas worldwide. Compared with conventional tests performed at tertiary ophthalmic centers, AI performs better in the screening and diagnosis of various eye diseases. After considering all the facts and overcoming challenges in its application, it can be said that AI in the field of ophthalmology is here to stay and revolutionize eye care in the 21st century. Nonetheless, researchers in the field of ophthalmology need to develop more robust AI modules with better verification and validation. Further, we must not rely only on near-real AI as no modality can possibly replace the level of affection, care and sensitivity as that provided by human caregivers.

FOOTNOTES

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