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Review Article

Using artificial intelligence in diabetic retinopathy

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ABSTRACT

Diabetic retinopathy (DR), a microvascular complication of diabetes, is a leading cause of blindness in India. Regular and timely screening for DR is recommended for the early diagnosis and appropriate treatment. However, mass screening for DR poses a significant challenge. Artificial intelligence (AI) is an important tool which has been used for diagnosing and grading diabetic retinopathy and aids in mass DR screening thus helping in faster and earlier screening of DR. This article aims to describe how AI is used in DR, software that are available for screening and the limitations and challenges in implementation of AI in health-care settings.

Keywords: Diabetic retinopathy, Artificial intelligence, Deep learning, Diabetic macular edema, Diabetic retinopathy screening

INTRODUCTION

Diabetes mellitus is a chronic non-communicable disease that can impact various organs in the body including the eye. Diabetic retinopathy (DR) is one of the complications of diabetes and a leading cause of visual impairment in India. Since it is asymptomatic in early stages with irreversible sight loss later, screening for DR is important to detect sight threatening disease and manage appropriately to prevent avoidable blindness. People with diabetes also require regular and repetitive annual retinal screening for timely detection of DR in addition to DM assessment. DR is clinically diagnosed through fundus examination or imaging methods such as fundus photography (FP) and optical coherence tomography (OCT). Mydriatic fundus examination for all patients with diabetes can be time-consuming. Fundus photos taken by digital cameras can be assessed by retina specialists which helps fasten the screening process, but this can also be time-consuming especially in countries with high incidence of diabetes. Early detection, diagnosis, and proper screening can decrease risk of visual loss to 57% and decrease overall cost of treatment.[1]

ARTIFICIAL INTELLIGENCE (AI)

AI, a concept first proposed in 1956 by McCarthy *et al.*,[2] is a system, in which machines mimic the cognitive function of the human mind. Machine learning is employed to generate and improve the machine's ability to improve its own decision-making by learning from data provided to it. Deep learning (DL) is composed of algorithms that use a cascade of multilayered artificial neural networks to independently perform feature extraction from data.[3] Convolutional neural network (CNN) is a DL model suitable for processing images, and it is mainly composed of convolutional layers, pooling layers, and fully connected layers. Many studies haverevealed that AI has high sensitivity and specificity to recognize stages of DR from fundus photos.[4-6]

AI IN DR

The current utility of AI in DR is limited to preventive care, that is, in screening, with a rising interest in predictive features toward disease advancement and treatment burden. The American Diabetes Association has suggested that AI systems that detect more than mild DR and diabetic macular edema (DME) represent an alternative to traditional screening approaches.[7] These AI programs can also be applied on smartphone-based fundus cameras thus providing a low cost and effective method of screening for DR.[7] They have several advantages over human-based screening: they can grade thousands of images without fatigue, provide results within seconds to minutes, and reduce barriers to access in areas, where image graders/doctors are not present and decreased overall health burden.[3,8]

AI ALGORITHM DEVELOPMENT FOR DR

A good AI program needs to have an adequate balance between sensitivity and specificity. In DR screening, images of fundus are uploaded to the computer and DR lesions are detected by basic software. Depending on the system, the output is different DR present/absent, referable DR present/absent, no DR/referable DR/Sight-threatening DR outcome, or others. There are many databases for screening of fundus photographs. The two major ones are Digital retinal images for vessel extraction and Messidor (Methods for evaluation segmentation and indexing techniques dedicated to retinal ophthalmology). Other databases include EyePacs, E-Ophtha, and Singapore Integrated DR program.[9] The dataset should be divided into training, validation, and test sets which should not overlap. The training set is to train the algorithm, the validation set is used for parameter selection and tuning, and the testing set is used to evaluate the actual performance of the AI system in clinical scenarios.[10]

[Figure 1] shows how a normal AI process works.

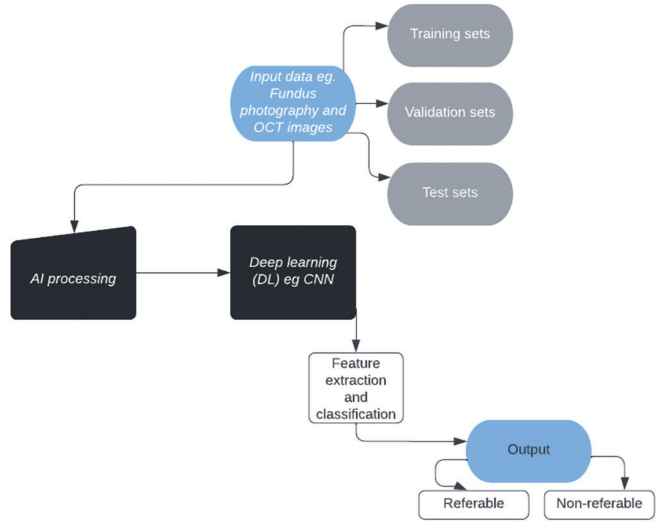

Figure 1: Flow chart explaining the artificial intelligence process.

AVAILABLE AI SOFTWARE PROGRAMMES

IDx-DR was the first FDA approved AI software program which uses pictures from a non-mydriatic retinal camera (TRC-NW400, Topcon) and then uses an AI program to diagnose DR. The images taken are sent to a cloud-based server which utilizes the software and a DL algorithm to detect retinal findings in DR based on comparison with a large set of representative fundus images. If more than mild DR is detected, the patient is referred. If less than mild DR is detected, the patient is rescreened in 1 year.[7] It has shown good sensitivity and specificity. Abràmoff *et al.* reported that it had a sensitivity of 87.2% and specificity of 90.7% in detection of referable DR.[4] EyeArt by EyeNuk inc. was FDA approved in August 2020.[11] Rajalakshmi *et al.* validated a smartphone-based fundus photograph system for DR screening. They assessed the role of an automated AI algorithm for detecting DR and vision threatening DR. The EyeArt software was used to analyze images from dilated eyes. The results showed that the AI software exhibited 96% sensitivity and 80% specificity in detecting any DR and 99% sensitivity and 80% specificity in detecting vision-threatening DR.[5] Gulshan *et al.* from Google AI healthcare reported an AI system based on DL with excellent diagnostic capabilities called Inception V-3. A large training dataset of 128,175 images to test was used to validate themodel. It shows a high sensitivity (>96%) and specificity (>93%) and area under the receiver operating characteristic curve (AUC) >0.99 in the external validation using two public databases.[6] Intelligent retinal imaging system (IRIS) is a type of AI system which is used an automated tele-retinal DR screening program which compared non-mydriatic fundus images with a standard data set from ETDRS and gave recommendations for referral, such as any patient with severe NPDR or more advanced disease. This program reported good sensitivity and a low false-negative rate.[12] The IRIS software is combined with Remidio's handheld camera to provide instantaneous image gradeability. [Table 1] shows a list of some of the AI systems available with their sensitivities and specificities. Vision-threatening DR, for example, PDR and DME is important to identify as it requires prompt referral and management. DL algorithms have found reliability of grading up to 95% and sensitivities of 90.5–97% and the probability of missing severe NPDR, PDR, or macular edema is <1%. Roy *et al.* conducted the first pilot study in India which demonstrated the efficacy of automated DR imaging in screening studies in Indian population. Retmarker was used to analyze images of 1445 patients, of which images of 1207 patients had no evidence of DR (83.52%), which helped in initial screening

Table 1: List of Artificial intelligence software available in detection of diabetic retinopathy.

AI system	Authors	Algorithm	Type of camera	Mydriatic or non-mydriatic	AUC	Sensitivity	Specificity
IDx-DR	Abràmoff *et al*.[4]	CNN	TRC-NW400, Topcon	Non-mydriatic	N/A	87.2	90.7
	Van der Heijden *et al*.[22]	AlexNet, VGG net	TRC-NW400, Topcon	Non-mydriatic	0.94/0.87	91/68	84/86
Retmarker DR	Oliviera *et al*.[23]	Recognition of characteristic lesions	Cannon CR6-45NM fundus camera attached to a Sony power HD 3CDD digital color camera	Non-mydriatic	0.849	95.8	63.2
EyeArt	Solanki *et al*.[24]	Image analysis technology	Canon CR-2 AF	N/A	0.941	93.8	72.2
	Rajalakshmi *et al*.[5]	Image analysis technology	Remidio fundus on phone (FOP), Remidio	Mydriatic	N/A	99.3	68.8
	Bhaskaranand.[25]	Image analysis technology	Multiple fundus cameras	Both	0.879	90	63.2
	Bhaskaranand.[26]	Image analysis technology	Multiple fundus cameras	Both	0.965	91.3	91.1
Google	Gulshan *et al*.[6]	Inception V3	1st data set: Multiple cameras 2nd data set:Topcon TRC NW6	Both	0.990–0.991	87.00–97.50	93.9–98.5
	Gulshan *et al*.[27]	Inception V4	NM TRC, Topcon	Non-mydriatic	0.963–0.980	88.90–92.10	92.20–95.20
IDP	Abràmoff *et al*.[28]	Non-DL	Topcon TRC NW6 fundus camera+color video 3CCD camera	Non-mydriatic	0.980	96.8	87
	Hansen *et al*.[29]	Non-DL	Topcon NW6S Fundus Camera	Mydriatic	0.878	86.7	70
Airdoc	He *et al*.[30]	Inception V4	Topcon TRC-NW400 Fundus camera	Non-mydriatic	0.95	91.8	98.79
	Huang *et al*.[31]	Inception V3 , SVM			0.94	95.3	79.5
VoxelCloud Retina	Zhang *et al*.[32]	Inception-Res Net V2	Multiple cameras	Non-mydriatic	N/A	83.3	92.5
VeriSee	Hseih *et al*.[33]	Inception V4, resnet	Canon CR-2	Non-mydriatic	0.95	89.2	90.1
Eyegrader	Keel *et al*.[34]	Inception V3	Digital Retinography System (DRS, CenterVue)	Non-mydriatic	0.937–0.989	92.3	93.7
PhelcomNet	Malerbi *et al*.[35]	CNN	Smartphone-based hand held devices	Mydriatic	0.89	97.8	61.4
Retianalyze Bosch DL	Bawankar *et al*.[36]	CNN	Bosch non-mydriatic fundus camera	Non-mydriatic	N/A	91.18	96.91
Singapore SERI NUS	Ting *et al*.[37]	VGGNet	Multiple cameras	N/A	0.889–0.983	91.4–100.00	73.3–92.20
EyeWisdom V1	Zhang *et al*.[38]	Resnet-34, Inception V3	Topcon TRC NW6S, Cannon CR2, KOWA Non-myd a-DIII 8300	Non-mydriatic	0.958	92.96	93.32
Others	Gargeya and Leng.[39]	Data driven DL algorithm	Multiple cameras	N/A	0.97	94	98
	Li *et al*.[40]	Inception-v3	Multiple cameras	N/A	0.955	92.5	98.5
	Cao *et al*.[41]	Bayesian model	Topcon TRC-NW6S/7S Fundus camera	Mydriatic	0.938	94.9	92.8

(*Contd...*)

Table 1: (*Continued*).

AI system	Authors	Algorithm	Type of camera	Mydriatic or non-mydriatic	AUC	Sensitivity	Specificity
	Sahlsten *et al.*[42]	Inception-v3	Canon CR2	Mydriatic	0.987	89.6	97.4
	Krause *et al.*[43]	Inception-v3	Centervue DRS, Optovue iCam, Canon CR1/ DGi/CR2, and TopconNWusing	N/A	0.986	97.1	92.3
Ultrawidefield imaging							
EyeArt	Wang *et al.*	Image analysis technology	Optos Daytona UWF system	Mydriatic	0.873/0.851	91.7/90.3	50.0/53.6
	Nagawasa *et al.*	CNN	Optos Daytona UWF system	Mydriatic	0.969	94.7	97.2
	Tang *et al.*	CNN	Optos Daytona UWF system	Mydriatic	0.923–0.966	79.6–94.9	70.4–95.8

CNN: Conventional neural networks, UWF: Ultra wide field, N/A: Data not available

of DR.[13] In a nationwide, DR screening program in Thailand DL versus human graders was compared for classifying DR. The study showed that relative to human graders, for detecting referable DR (moderate NPDR or worse), the DL algorithm had significantly higher sensitivity and a slightly lower specificity.[14]

AI WITH OCT AND ULTRA-WIDEFIELD (UWF) IMAGING

Most current AI-based diagnostic systems are based on fundus photo. The disadvantage is that they can only recognize hard exudates in the posterior pole and may miss cases which have DME. OCT can also be used by AI for detecting of DME. Hassan *et al.* used both fundus and OCT images to achieve a sensitivity of 97% and specificity of 92% for referable DME detection. Zheng *et al.* devised an automated identification program DME examined by OCT which had good intraobserver and interobserver consistency. Lee *et al.* developed a CNN algorithm to detect intraretinal fluid on OCT. There are various other systems which combine OCT and AI techniques to detect DME. UWF imaging provides fast evaluation of non-mydriatic pupils to evaluate the peripheral retina which can recognize early damage of DR in the periphery. Wang *et al.* used a model with EyeArt software with an automated algorithm to detect referral warranting retinopathy with a sensitivity of 90.3%, specificity of 53.6%, and AUC of 0.851.[15] Nagasawa *et al.* also trained a CNN model to detect treatment naïve PDR in UWF images with a sensitivity of 94.7% and a high specificity of 97.2%, with an AUC of 0.969.[16] Tang *et al.* also validated a DL system which provided automated image quality assessment and detection of referable DR and vision-threatening DR from UWF-SLO images with high sensitivity and specificity.[17] DME is a common cause of visual impairment in diabetics and is treated with intravitreal anti-vascular endothelial growth factor (VEGF) injections. A major challenge associated with this treatment is determining an optimal treatment regimen and differentiating responders and non-responders to anti-VEGF. ML- or DL-based algorithms can be used to identify DME in fundus photo or OCT and predict patient's response to an anti-VEGF agent. These AI-based prediction models can help in reducing the disease burden and offer the best line of treatment for the patient.[18]

AI IN REAL-WORLD SETTINGS

Adoption of AI technology is dependent on how it performs in the real-world clinical settings. Ruamviboonsuk *et al.* performed a prospective intervention cohort study to evaluate the real-world performance and feasibility of using a DL system into the healthcare system of Thailand. A total of 7940 patients were included for screening and 2412 patients were referred for DR, DME, ungradable images or low visual acuity. For vision-threatening DR, the deep-learning system had an accuracy of 94.7% (95% CI 93.0–96.2), sensitivity of 91.4% (87.1–95.0), and specificity of 95.4% (94.1–96.7) versus accuracy of 93.5%, sensitivity of 84.8%, and specificity of 95.5% in the retina specialist over-readers. This showed that a DL system can deliver real-time DR detection similar to retina specialists.[19] A computer-assisted customized algorithm was used for detection of DR in a tertiary eye care hospital in India which shows 78–79% sensitivity and 55–57% specificity in detecting DR. The algorithm was tested under physiological dilatation thus resembling real world settings.[20] Raman *et al.* proposed a step-wise algorithm for DR: From development to clinical use. This includes assessment of problem to be addressed by AI → Availability of data and data collection → Implementation costs →Deployment of AI in clinical settings → Clinical uptake → Maintenance over time. Each of these steps needs proper policies for useful functioning.[21]

LIMITATIONS AND CHALLENGES FOR AI IN DR

The very basis of building AI machines is that it learns from the information fed to it over the years by pattern recognition; however, there is lack of large databases of high-quality retinal images with proper annotations. Human graders are required to label and standardize images for further reference. This comes at a cost of time and manpower. There is also inter/intra grader variability which is not accounted for. Further, AI algorithms are validated on this highly curated data which is not representative of real life screening scenarios.[44] There is a requirement for cameras with similar imaging systems and resolutions and pixels for large scale adoption along with image standardization. In ophthalmology in general, the ocular imaging consists of many different modalities such as color fundus photos, OCT, and Ultrasound images. Despite American academy of Ophthalmology and Asia pacific academy of ophthalmology guidelines, there is low compliance of ophthalmic imaging systems to adhere to the Digital Imaging and Communications in Medicine standards which are applied in radiological imaging.[45,46] At present, there is no easy way of sharing digital imaging data, and therefore, standardization of ophthalmic images is very central to what we indent to do with AI. With a few FDA approved machines and a few more being developed, another inherent hurdle is the comparison between different AI machines. This is due to lack of Key performance indicators. Different researchers have used different key indices to measure any AI model's performance. Depending on the machine, the output might be different, for example, IDx –DR generates an overall per patient result, on the other hand, Retinalyse generates a per image result. Additional challenge in comparing the sensitivity and specificity of 2 machines is that studies use different cutoff values for Referable DR which may not always correspond with the same ETDRS grading levels.[44] Another confounding factor is demographic characteristics for instance many developers that have excluded individuals aged <40 years which risks the AI being unable to deal with highly reflective internal limiting membrane in young's, hence decreasing the sensitivity of detecting referable DR in that age group.[6] AI opens many doors in its aim to provide better health facilities to the rural parts of the nation but it comes with its own cons. Like a lower specificity will identify more people without the disease who may in fact have changes of DR which will lead to a false sense of security to the people; on the other hand, a lower sensitivity may identify people with the disease who might not have it and that fails the entire purpose of building AI machines to decrease health burden. Downside of AI in DR so far is that it detects referable DR only by means of fundus photographs and macular optical tomography scans, but these machines should be made sensitive to other DR related changes like neovascularization of Iris or Angles. Therefore, algorithms based on comprehensive eye examination are required. At present, there are various screening programs already in practice such as computer programs, browser-based solutions, and even mobile applications which are already being used so it more on AI to integrate such programs and provide a more wholesome screening. In future, the results of artificial screening might surpass that of human graders, but can human graders be taken as an absolute objective truth? Some of the researchers, therefore, proposed patient outcome based truth rather than clinician's agreement as an algorithm to build AI and showed that it works better than human graders.[4,28] There are considerable legal issues associated with development and implementation of AI algorithms such as product liability, medical malpractice, data security, and availability of consent, which can have serious implications. Developing countries economic burden in terms of cost of setting up the equipment which is in addition to the highly trained staff required to operate these equipment's limits its use in already resource deprived parts of the nation. Several intergovernmental organizations and countries have proposed principles and guidelines for ethical use of AI, convergence was found on transparency, justice, fairness, non-maleficence, and responsibility. Several governments are introducing national policies and laws to govern the use of AI in healthcare. Organization for Economic cooperation and Development (OECD) launched a policy observatory in 2020 that "aims to help countries enable, nurture, and monitor the responsible development of trustworthy AI systems for benefit of society." India is now the 27th member of this organization. AI is playing an ever expanding role worldwide and its alignment with regional policies, following rules and regulations adopted by OECD is the way forward.[47]

FUTURE OF AI IN DR

AI devices can provide screening decision without requiring a trained ophthalmologist. The integration of AI into healthcare will help in larger coverage for screening for DR. Following factors need to be considered in implementation of AI in healthcare settings: Policy setting which involves a risk adjust policy, technological implementation, and medical and economic impact quantification.[48] There are several challenges that stand in the way of wider adoption of AI. These include: Workflow integration, enhanced explainability and interpretability, workforce education on how to use AI, appropriate regulatory mechanisms, problem identification and focusing on intervention drive AI, understanding the potential impact of AI on clinician and patient relationship and data quality, access, and sharing and compliance with privacy. These factors are critical to implementation of AI in healthcare settings.[49] AI can ease the pressure on the healthcare system, particularly in nations with large spread and unequitable resources having high projected burden of diabetes. Automated DR screening methods can make the screening process more efficient, cost-effective, reproducible, and accessible.[50]

CONCLUSION

Almost 30–50% of individuals with diabetes do not adhere to screening recommendations and thus screening programs with non-mydriatic cameras can help in improving the screening process. AI technology can be used as for triaging to differentiate between urgent and non-urgent referrals. It also helps in the early detection of DR as screening can be conducted by all healthcare professionals and not just by the ophthalmologist. This helps in early and appropriate management, thus preventing loss of vision. Timely detection and early intervention are needed. The use of AI seems like a natural step in the future that can increase detection rates and reduce clinician's burden at the same time. The aim is to reduce number of visits to an ophthalmologist, reduce overall cost of treatment, and optimize the number of patients needing referral.

However, it is important to realize that current medical knowledge is derived from decades of observational data gathering, hypothesizing, and validating the same by means of clinical research. Therefore, we cannot simply take a finding of AI without validating it to be consistent with our acquired medicine knowledge. To facilitate real word integration of AI programs, more studies are required to evaluate health professional's acceptance and interpretability of AI to identify barriers to adoption and further to develop targeted solutions accordingly. The ultimate goal, here, is not replace a patient doctor relationship which is built on trust and compassion but to must complement it allowing quality medical services to people who need it the most.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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