

Prospects of Artificial Intelligence in Ophthalmic Practice

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Abstract

Artificial intelligence (AI) and machine learning (ML) were part of science fictions a decade before. But with ever evolving technology AI has made its way in our daily lives. AI also has brought paradigm shift in healthcare. Ophthalmology is a lucrative speciality for AI application as lot of imaging modality is being used to make diagnostic and therapeutic decisions. The application of AI in ophthalmology mainly focusses on disease with high incidence like diabetic retinopathy, age related macular degeneration, glaucoma, retinopathy of prematurity and cataract. In this review the current application of AI and its prospects is discussed in the ophthalmic practice.

Keywords: Artificial Intelligence; Ophthalmology; Diabetic Retinopathy; Cataract; Deep Learning; Machine Learning

Introduction

In this technology driven era, where does artificial intelligence (AI) stand in our daily personal and professional lives? The machines haven't taken over yet and may never be able to outsmart their creators but indeed they have seeped their way in our daily lives. Most common examples are voice powered personal assistant "Siri", "Alexa" and "Google assistant"; with "Tesla" rolling out cars with predictive capabilities, self-driving features; "Pandora" with musical DNA and "Nest", the thermostat by Google. AI has become an indispensable tool to better our daily lives. AI has already shown proof of concept in medical fields rooted in diagnostic imaging like radiology, pathology and dermatology. Ophthalmology also relies heavily on imaging like colour fundus photography, optical coherence tomography (OCT) and anterior segment photograph [1]. The advantages of AI in medicine are manifold. In ophthalmology it can assist in clinical practice to detect and learn features from large images, help to reduce diagnostic error. It can also help in providing personalized medicine. It can help us gain innovative scientific insight by recognizing disease specific patterns [2]. AI may also pave way for cost efficient telemedicine screening programs worldwide. The global estimated mean for ophthalmologist density is dismal and was estimated to be 31.7 per million populations [3].

The number of ophthalmologists is growing at half the rate of our population aged over 60 years, and there are 23 countries with less than one ophthalmologist per million population [4]. Various studies have demonstrated successful virtual clinic for various retinal disorders and glaucoma screening [5,6].

Understanding Artificial Intelligence

What really is AI? Artificial intelligence is the broadest term encompassing machine learning and deep learning. In simple terms AI is human like intelligence which a machine or computer acquires through various modalities. The term "artificial intelligence" was first coined by John McCarthy in 1955 [7]. He described it as 'the science and engineering of making intelligent machines. AI comprises of machine learning (ML), deep learning (DL), conventional machine learning (CML), natural language processing, computer vision, robotics, reasoning, general intelligence, expert system, automated learning, and scheduling [8].

Machine Learning

Machine learning (ML) is a subset of AI that enables computers to learn on their own with experience. Arthur Samuel, recognised as pioneer of ML, defined it as 'field of study that gives computers

the ability to learn without being explicitly programmed and has the ability to automatically learn' [9]. Therefore, machine learning is an ever evolving phenomenon.

Deep Learning

DL refers to machine learning which employs convolutional based neural networks (CNNs). It involves multiple levels of abstraction to process the input data without the need for manual feature engineering automatically and then the intricate structure is recognised through projection onto a lower dimensional manifold [10]. In conventional machine learning input image is classified from hand engineered features whereas in deep learning the features are both extracted and classified from the input directly allowing for fully end to end learning [11].

AI in Ophthalmic Practice: Where do we stand?

AI based algorithm has been widely investigated and published in diseases like diabetic retinopathy (DR), age related macular degeneration (AMD), cataract, refractive error, glaucoma, keratoconus and retinopathy of prematurity (ROP).

AI in Retina

In ophthalmic practice diagnosis in retina is heavily relied on

Table 1: Brief summary of various studies.

DL systems	Year	Test Data Sets	Number of Images	AUC	Sensitivity	Specificity	Comments
Abramoff et al. [16]	2016	Messidor 2	1748	0.98	96.8	87	Any DR
Gulshan et al. [17]	2016	Messidor 2	1748	0.99	87	98.5	
		Eye PACS 1	9963	0.991	90.3	98.1	Referable DR
Gargeya et al. [18]	2017	Messidor 2	1748	0.94	93	87	Any DR
Ting et al. [19]	2017	SIDRP 2010-2013	Multiple set of images	0.936	90.5	91.6	Referable DR
	2017	SIDRP 2010-2013	Multiple set of images	0.958	100	91.1	Vision threatening DR
Abramoff et al. [20]	2018		819		87.2	90.7	Any DR
Ramchandran et al. [21]	2018	Otago	485	0.901	84.6	79.7	Referable DR
		Messidor	485	0.98	96	90	
Shah et al. [22]	2020	Messidor	1200	0.907	90.37	91.03%	Any DR
			1200	0.969	94.68	97.4	Referable DR
			1200	0.923	91.67	92.92	Sight threatening DR

IDx-DR: It is the first FDA approved AI algorithm for detection of DR and is paired with non-mydratic retinal camera (TRC-NW400, Topcon). It can be used in the office of non-ophthalmic healthcare practitioners. The captured images are sent to a cloud-based server. The IDx-DR uses a deep learning algorithm to detect retinal findings suggestive of DR. The software provides either of the two results: (1) If more than mild DR detected, refer to an eyecare professional (ECP); (2) If the results are negative for more

color fundus photography and optical coherence tomography. These diagnostic tools allow non-invasive imaging of retinal vasculature and optic nerve head. Thus, the ample imaging in retina makes it a lucrative area of application of AI.

Diabetic Retinopathy

According to the International Diabetes Federation approximately 425 million people suffer from diabetes. The prevalence of diabetic retinopathy is approximately 28.5% in the United States and 18% in India [12,13]. Early detection and prompt treatment remain the mainstay for prevention of visual disability and effectively decreases the burden by 90%. In the current era, ophthalmologists screen the patients for DR but various logistical barrier, lack of trained ophthalmologist and cost of visit may limit the patients from getting the screening done. The other suggested way of addressing these issues are obtaining the colour fundus photo and sending it to ophthalmologist and optometrist to read the image thereby increasing the screening but involves time delay [14]. The limitations can be overcome by automated AI based grading systems. In April 2018, the US Food and Drug Administration (FDA) has approved an AI. AI algorithm, developed by IDx, used with Topcon Fundus camera (Topcon Medical) for DR identification [15-22]. Various studies have been outlined in Table 1.

than mild DR, rescreen in 12 months [23]. The FDA approval was based on a study involving 900 subjects in a primary care setting with automated image analysis of two 45-degree digital image based on optic nerve. The images were compared with the stereo, wide field fundus imaging interpreted by the Wisconsin Fundus Photograph Reading Centre (FPRC). AI was able to make a diagnosis in just 20 second after procurement of retinal images. A new entity minimal DR (mtmDR) was defined [24]. Various AI algorithm

developed for DR screening like Google AI, EyeArt and IDxDR work on platform based on cloud [16,17,20,25]. The AI algorithm by Medios Technologies (Singapore) is the first offline software for DR screening integrated with the smart phone-based fundus camera, the Remidio non-mydratic (NM) fundus-on-phone (FOP) [26]. The sensitivity and specificity of the AI algorithm in detecting referable DR (RDR) was 93% (95% CI 91.3% to 94.7%) and 92.5% (95% CI 90.8% to 94.2%) in Indian population [27].

AI in AMD

Approximately 288 million patients have been projected to suffer from AMD by 2040 and 10% of them will have intermediate AMD or worse [28,29]. There is an urgent clinical need to have a robust DL system to cater to the geriatric population to screen them for AMD and to further facilitate evaluation in tertiary care centres.

Ting et al reported a clinically acceptable DL system diagnostic performance in detecting referable AMD [19]. The DL system was trained and tested using 108 558 retinal images from 38 189 patients but this being primarily a DR centred study few patients of referable AMD was present. Fovea-centred images without macula segmentation were used in this study. Burlina et al. reported a diagnostic accuracy of between 88.4% and 91.6%, with an AUC of between 0.94 and 0.96 [30]. In this study macula was presegmented. Grassmann et al reported a sensitivity of 84.2% in the detection of any AMD [31]. All three abovementioned studies did not have any results for external validation on the individual DL systems. A predictive model also differentiated converting versus non converting eyes with a performance of 0.68 and 0.80 for CNV and GA, respectively [32].

Finally, AI is being studied as a support to therapy decision-making in AMD. Prahs et al. looked at AI to support therapy decisions for intravitreal injection and found that the deep CNN was able to correctly predict the need for anti-VEGF therapy in 95% of cases [33]. Schlegl et al. also designed an MLC using 1200 OCT images with a mean accuracy of 0.94 and an AUROC of 0.92 [34].

AI in Cataract

Table 2: Brief summary of AI studies in cataract.

Authors	Year	Slit Lamp Photograph /	No of Images for Training	No of Images for Testing	Performance
Li et al. [45]	2009	Slit lamp photograph	100	5490	Success rate of lens structure detection 1/4 95%
Xu et al. [46]	2013	Slit lamp photograph	100	5278	MAE= 0.336
Gao et al. [47]	2015	Slit lamp photograph	100	5278	MAE= 1/4 0.304
Wu et al. [48]	2019	Slit lamp photograph	30312	7506	AUC) of >99% for the capture mode recognition and cataract detection phase. AUC 0.9915 for evaluation of cataract severity. AUC was 1.00 for referral accuracy for pediatric cataracts with visual axis involvement (AUC 1.00).
Dong et al. [49]	2017	Color fundus photograph	5495	2355	Accuracy 94.07

AI in Other Retinal Condition

In 2018 DeepMind applied DL algorithm to OCT and successfully developed a model which automatically segmented tissue layers. The model achieved a diagnostic performance meeting and exceeding those of human expert graders for 50 common retinal conditions. This has paved a way for implementation in a real-world clinical pathway; the rapid access 'virtual' clinics that are now widely used for triaging of macular disease in the UK [5]. In the longer term, the system can be utilised by optometrist too, as OCT has become a common tool, in triaging the patient outside hospitals in community.

AI in Glaucoma

Glaucoma requires lifelong treatment and monitoring and is the second largest cause of irreversible blindness worldwide primarily affecting the elderly. It is projected that nearly 79.6million people will have glaucoma by 2020 [35,36]. The first aim is detection of glaucoma based on: classification of visual fields, optic nerve imaging or other clinical data. The second aim is to detect worsening earlier than conventional algorithms available. The last but not the least being able to study risk factors for glaucoma and quality of life based on AI models. Li et al. [37] and Ting et al. [19] trained computer algorithms to detect the glaucoma-like disc. Machine learning methods have been applied to distinguish glaucomatous nerve fibre layer damage from normal scans on wide-angle OCTs [38]. Elze et al. [39] developed an unsupervised computer program to analyse VF that recognises clinically relevant VF loss patterns and assigns a weighting coefficient for each of them and has proven useful in the detection of early VF loss from glaucoma [40]. Computer programs to detect VF progression exist along with sectoral VF analysis. But these approaches are often not aligned with clinical ground truth nor with one another [41,42]. Yousefi et al developed a machine-based algorithm that detected VF progression earlier than these conventional strategies [43]. More machine learning algorithms that provide quantitative information about regional VF progression can be expected in the future.

Ran et al. [50]	2018	Color fundus photograph	Details not present	Details not present	AUC 97.04 Sensitivity 97.26 Specificity 96.92
Pratap et al. [51]	2019	Color fundus photograph	400	400	Accuracy 100 For pre trained CNN for feature extraction

Cataract is the leading cause of visual impairment worldwide, accounting for 65.2 million cases of vision impairment and blindness globally [44]. These numbers are projected to increase to 70.5 million by 2020 worldwide as the population will age and therefore, they remain an important health concern. Various AI studies have been outlined in Table 2 [45-51]. Wu et al. utilized deep learning using residual neural network (ResNet) to establish a 3-step sequential AI algorithm for the diagnosis and referral of cataracts [48]. First, in the capture mode recognition phase, the AI system would first differentiate slit lamp photographs between mydriatic and nonmydriatic images, and between optical section and diffuse slit-lamp illumination. The second step would involve categorization of image into either normal (ie, no cataract), cataractous, or postoperative IOL. The third step would entail evaluation of type and severity of cataract based on the Lens Opacities Classification System II scale. A decision would be made whether to follow-up or refer the patient for tertiary care would be derived.

The system was validated using 37,638 photographs (18,819 eyes) from a Chinese cataract screening program, the AI achieved area under the receiver-operating characteristic curve (AUC

of >99% for both steps 1 and 2, AUCs for evaluation of cataract severity (step 3) were most optimal using mydriatic images with optical sections (AUC 0.9915) and least optimal using nonmydriatic images with diffuse illumination (AUC 0.9328), whereas AUCs for referral accuracy were highest for pediatric cataracts with visual axis involvement (AUC 1.00), and lowest for posterior capsular opacification with visual axis involvement (AUC 0.919). This AI algorithm was put on trial as part of a web-based platform, in a pilot study conducted in the Yuexiu district of Guangzhou, China. On comparing with ophthalmologist’s final diagnosis, sensitivity and specificity of the algorithm for cataract detection were 92.00% and 83.85%, respectively. Based on results of pilot study, the authors proposed to switch the first “point-of-care” from ophthalmologists to community-based health care facilities based on AI algorithm. Further AI is being used in IOL power calculation. A new machine learning technique by Gonzalez et al showed that the SD of the prediction error in order of lowest to highest was the new method (designated Karmona) (0.30), Haigis (0.36), Holladay 2 (0.38), Barrett Universal II (0.38), and Hill-RBF v2.0 (0.40). Using the Karmona method, 90.38% and 100% of eyes were within ±0.50 and ±1.00 D respectively [52].

AI for Corneal Diseases

Table 3: Various studies in corneal ectasias.

Authors	Year	Purpose	AUC	Sensitivity	Specificity
Souza et al. [56]	2010	Differentiate normal, astigmatic, photorefractive keratectomy and keratoconus corneas	0.98-0.99	0.98-1.00	0.98-1.00
Hidalgo et al. [57]	2017	Differentiate normal, keratoconus and sub-clinical corneal ectasia	keratoconus vs normal 0.998; subclinical vs normal 0.922	keratoconus vs normal:0.991 subclinical vs normal:0.791	keratoconus vs normal:0.998 subclinical vs normal:0.979
Arbelaez et al. [58]	2012	Differentiate normal, keratoconus and sub-clinical corneal ectasia	Not reported	keratoconus vs normal:0.950 subclinical vs normal:0.920	keratoconus vs normal:0.993 subclinical vs normal:0.977
Kovacs et al. [59]	2016	Differentiate normal, keratoconus and sub-clinical corneal ectasia using bilateral data)	keratoconus versus normal 0.99 subclinical versus normal:0.96	keratoconus vs normal:1.00subclinical vs normal: 0.90	keratoconus vs normal:0.95 subclinical vs normal:0.90
Ambrosio et al. [60]	2017	Differentiate normal, keratoconus and sub-clinical corneal ectasia using tomographic biomechanical index)	0.996	Detecting ectasia vs normal: 1.00 subclinical vs normal:0.904	Detecting ectasia vs normal:1.00 subclinical vs normal:0.960

Keratoconus being a progressive disease has attracted the attention of AI developers to detect it at the earliest. This can help in better preservation of vision in these patients. Also, with an increase in number of refractive surgeries the number of iatrogenic keratectasias is on the rise because of possible biomechanics failure which we were unable to pick before surgery. So to identify these

susceptible corneas various AI models have been developed (Table 1). In diabetic sensorimotor polyneuropathy with introduction of neural network and random forest models, the nerve can be fully segmented, and morphology can be studied hence allowing the development of an objective and precise method to early characterise the disease [53,54]. AI models can predict early

graft dislocation based on larger residual interface fluid following refractive surgery [55]. Identifying subclinical corneal ectasia is challenging but the topography and tomography provides data to the ophthalmologist for every cornea, but still subclinical keratoconus remains a diagnostic challenge. Often a decision is often made by individual ophthalmologist's subjective interpretation of patterns or empiric cut-off values, which vary from machine to machine thus is unreliable and time consuming. In this scenario AI could provide an alternative solution to recognising those patients most at risk and diagnosing subclinical ectasias (Table 3) [56-60].

AI in Paediatric Ophthalmology

Retinopathy of Prematurity (ROP)

It is intuitive to expect that AI in ROP has a colossal potential. ROP compared to DR is relatively limited by retinal findings but the complexity lies in the urgency of intervention in treatable ROP and in the management of systemic comorbidity in a neonate compared to adults with DR. Several semi-automated AI tools like Vessel Finder [61], VesselMap [62], ROptool [63], Retinal Image multiScale Analysis [64-66], Computer- Aided Image Analysis of the Retina [67,68], and IVAN [67,69] have been studied. These CNN models accurately assessed retinal fundus image quality in ROP in a manner comparable with the experts. The i-ROP deep learning [70] and DeepROP system [71] have been found to accurately identify diagnostic categories and overall disease severity in an automated fashion. This iROP DL system has only been trained on posterior pole vascular morphology. The data provides a proof to concept that a deep learning system can be used in an automated fashion to diagnose ROP. These tools when incorporated in successful tele-ROP programs can be revolutionary as it will help in early and rapid triage of infants needing treatment even in rural areas. AI in ROP is going to have a tremendous impact in a country like India where preterm births have crossed 3.5 million mark annually more than any other country. Estimated 215 specialist that is even less than 1% of the ophthalmologists are engaged in ROP services directly. AI seems to provide us with the solutions and mend road ahead for optimal ROP care

Eye as a Window

For long philosophers has defined the eye as a window to the soul before scientists addressed this cliché to prove its scientific basis and clinical relevance. Recent work has applied DNN on retinal OCT and fundus images for assessing age, gender, systolic blood pressure, smoking status, haemoglobin A1c, and likelihood of having a major adverse cardiac event. The AUC for gender was found to be 0.97 while the others were in the range of 0.70. This suggests that through further advancements many more information can be gathered by these images using AI based algorithms [72]. AI has widespread application in ophthalmological practice. AI still is in its stage of infancy. There are three main limitation of AI which needs consideration [73]. Usually, the studies use homogenous population data as training data sets. This leads to their

questionable generalisation in diverse population and different ethnicity. The second pitfall being the "black box" nature of the AI where the physician is not able to understand the algorithm being used. This leads to trust issues with the AI platforms. The third being the power calculation done for an independent data sets used in these studies. This brings a questionable calibration of the algorithm being used in these AI platforms. In addition, the medico-legal aspects and the regulatory approvals vary in different countries and need to be addressed.

Nonetheless, with development of the Eye Grader clinician interface a new era has ushered where an immediate grading report for clinicians are generated in an integrated and automated fashion that can function both online and offline. Eye Grader has been designed to grade for four common blinding eye diseases including referable DR, suspect glaucoma, wet AMD, and cataract. The feasibility and acceptability of the Eye Grader system has been pilot-tested in real-world settings in Australia with great success and commendable patient satisfaction [74]. These AI systems will help bridge the significant patient doctor ratio gap. Even the patient in remote areas would be able to access the specialised healthcare system. The AI platforms also will enable health care providers like physicians and endocrinologist, who are first point contact in systemic diseases, to perform screening procedures in their patient at the earliest. Even non eye health care professional would be able to actively involved in the screening and diagnosis in the early stage of disease. This in turn will lead to timely diagnosis and treatment thereby bringing down the burden of visual impairment and blindness.

Conclusion

AI is the next big leap in ophthalmology. With combined clinical skill of ophthalmologists and AI platforms the medicine field is all set for the next big revolution. The long lived dream of medical care for everyone, at every doorstep has been an ever alluding dream since long but with each passing day we are inching closer to get this dream fulfilled with mankind's one of the great invention "AI".

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Conflict of Interest

No conflict of interest.

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