Role of artificial intelligence and machine learning in ophthalmology

ABSTRACT

Artificial intelligence (AI) and machine learning (ML) have entered several avenues of modern life, and health care is just one of them. Ophthalmology is a field with a lot of imaging and measurable data, thus ideal for application of AI and ML. Many of these are still in research stage, but show promising results. The ophthalmic diseases where AI is being used are diabetic retinopathy, glaucoma, age-related macular degeneration, retinopathy of prematurity, retinal vascular occlusions, keratoconus, cataract, refractive errors, retinal detachment, squint, and ocular cancers. It is also useful for intraocular lens power calculation, planning squint surgeries, and planning intravitreal antivascular endothelial growth factor injections. In addition, AI can detect cognitive impairment, dementia, Alzheimer's disease, stroke risk, and so on from fundus photographs and optical coherence tomography. We will surely see many more innovations in this rapidly growing field.

Keywords: Artificial intelligence, convolutional neural networks, deep learning, glaucoma artificial intelligence, machine learning

INTRODUCTION

John McCarthy described artificial intelligence (AI) as the "science of creating intelligent machines which replicated human behaviour." That had remained very much a part of science fiction until recently when more powerful computer hardware allowed the development of computing intensive algorithms and machine learning (ML) programming. This is now a part of the Fourth Industrial Revolution, which includes AI, autonomous vehicles, blockchain, robotics, internet of things, advanced biotechnology, and three-dimensional (3D) printing.[1] ML is a subtype of AI, where the software learns from large volumes of example data by trial and error without explicit instructions on how to derive the required output. Deep learning (DL) is a subtype of ML, which uses multiple layers of convolutional neural networks (CNNs), which are made of software-defined "neurons" which together try to figure out the instructions to process data to get information [Figure 1].

Generative adversarial networks (GANs) are a class of ML system that can generate new data based on training data. They are paired neural networks used for unsupervised ML, where the generative neural network generates images or other data and the discriminative neural network evaluates it and gives feedback to help in the learning process. It is also useful for semi-supervised learning, fully supervised learning, and reinforcement learning. They can potentially be used to make deepfakes such as fake fundus lesions on a normal fundus photograph. Israeli researchers showed how they could insert or remove fake lung cancer lesions in a normal computed tomography (CT) scan in milliseconds.[2] They showed how the hospital's CT scan and picture archiving and communication system was easily compromised using a cheap Raspberry Pi with a fake 3D-printed logo of the CT scan

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company. This was done on high-resolution volumetric CT scans, so doing this on fundus photographs is much simpler.

Computer programming has typically depended on a series of precise sequential instructions written by a programmer. The software programmer had to know in advance what sort of input data the software would receive and how to process the data to produce the information that is required. However, with ML, the computer program figures out the instructions by itself based on example inputs and outputs. Once the software has finished learning, it is often not apparent to the programmer how exactly the ML program that they had written generates the required output. This is called the black box problem and the source of much of the trust issues with AI-generated reports. Newer AI software opens up the black box using an Integrated Gradients Explanation algorithm to show a heatmap or attention map as Google researchers demonstrated [Figure 2].[3]

A typical AI solution is a software installed on a powerful computer (ML server), which is accessed via the internet. The input data are uploaded onto the ML server, which takes some time to process it (seconds to minutes depending on complexity of data analysis and processing speed of the server). The output can be accessed via the internet.

In the medical field, ophthalmology,[4] radiology,[5] dermatology,[6] pathology,[7] pediatrics,[8] gynecology,[9] oncology,[10] endocrinology,[11] and cardiology[12] have joined the AI revolution. Most of this is because of the huge volume of nonstandardized image processing required in these fields, which is very difficult in conventional programming but much simpler to implement with ML. In addition to image processing, analysis of big data, making predictions, and finding efficient use of resources are other areas where ML can help in the medical field.

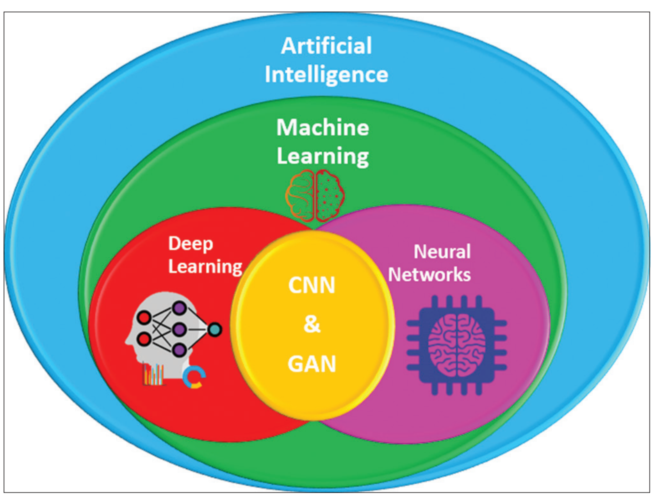

Figure 1: Relationship between artificial intelligence, machine learning, deep learning, convolutional neural networks, and generative adversarial networks

For ophthalmology in particular, the most common use of AI has been in analysis of retinal fundus[13] images for diabetic retinopathy (DR), followed by age-related macular degeneration (ARMD), glaucoma, and retinopathy of prematurity (ROP). Huge advancements have been made in this field with the advent of offline AI which can now run the final algorithm on a smartphone, whereas earlier a powerful server computer was required. However, fundus image analysis is the only part of the picture, as various other arenas of ophthalmology from intraocular lens (IOL) calculation to myopia prediction to smart electronic medical records (EMRs) are now based on AI.

Major tech companies have taken an interest in AI for ophthalmic use. Google's DeepMind Health, in a research with Moorfields Eye Hospital, showed that it can detect fifty eye diseases[14] from optical coherence tomography (OCT) scans for referral. IBM's AI can predict visual field data from OCT scans.[15] Microsoft Intelligent Network for Eyecare[16] is a collaboration to apply AI to eliminate avoidable blindness and scale eyecare delivery systems. Several authors have reviewed the current state of AI in ophthalmology, but newer applications are coming out every few months.[17-24] The current commercially available AI solutions include Netra.AI (Leben Care Technologies Pte., Ltd.),[25] Pegasus (Visulytix Ltd.),[26] Medios AI (Remidio Pvt., Ltd.),[27] and IDx-DR (IDx Technologies Inc.).[28]

Let us look at some of the applications of AI and ML in ophthalmology.

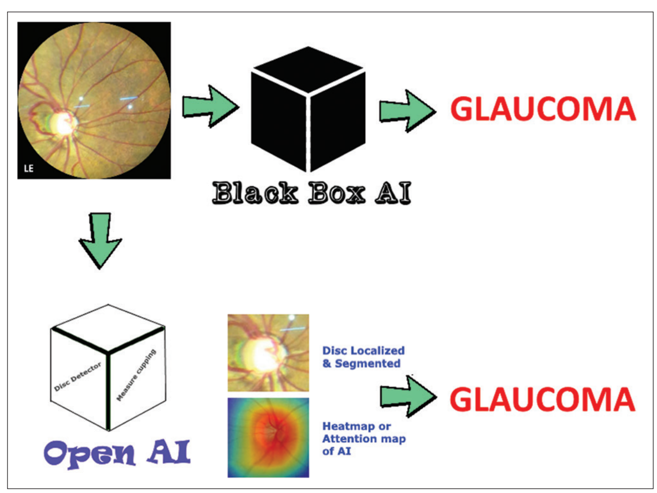

Figure 2: Representation of black box problem in artificial intelligence. Typical artificial intelligence does not show how the analysis works. By modifying the internal working, "Open" artificial intelligence shows the segmentation and heatmap by which the image was analyzed and arrived at a diagnosis

Diabetic retinopathy

The most widely known use of AI in ophthalmology is for the evaluation of DR from fundus photographs, which has several studies and reviews [Figure 3].[29-36]

The first US Food and Drug Administration-approved autonomous AI diagnostic device was IDX-DR for detecting "more than mild" DR and diabetic macular edema.[37]

Typically, ML systems run on a powerful server computer. Fundus images taken using a fundus camera are collected and evaluated later or they are uploaded through the internet to the powerful server which generates the report and sends it back to the device. With the advent of low-cost smartphone-based fundus cameras such as DIYretcam,[38] T3retcam,[39] MIIretcam,[40] JaizRetcam, and Hopescope, quick image analysis would be invaluable. In a recent study, Sosale *et al*. evaluated an offline AI (Medios AI) on a Remidio Fundus-on-Phone (Remidio Innovative Solutions Pvt. Ltd., Bengaluru, Karnataka, India) and showed a high sensitivity (93%) and specificity (92.5%).[41] Offline AI would make this technology accessible in areas with poor network connectivity.

Glaucoma

Glaucoma evaluation involves measurement of intraocular pressure, optic disc cupping, visual fields, gonioscopy, and optical coherence tomography for retinal nerve fiber layer (RNFL) and ganglion cell layer (GCL) thickness. We fail to recognize that the regular OCT machines automatically measure disc size, cupping, neuroretinal rim area, RNFL thickness, and GCL thickness and all such parameters using AI image processing techniques called segmentation. A comprehensive AI for glaucoma should evaluate all the parameters including IOP, disc, gonioscopy, fields, and OCT together; however, such an AI system is not ready yet. Several studies evaluated various AI and ML systems for glaucoma.[42,43]

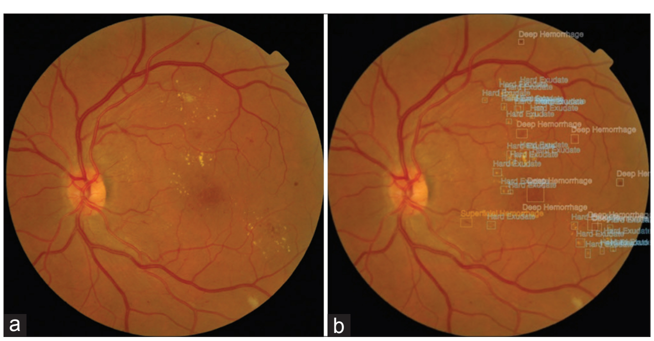

Figure 3: (a) Retinal fundus photo of the left eye of a diabetic patient. (b) Same image after artificial intelligence analysis by Netra.AI (Leben Care Technologies Pte., Ltd.) with the superficial hemorrhages, deep hemorrhages, and hard exudates

Martin *et al*. analyzed pooled data from 24 prospective clinical trials of a contact lens sensor for intraocular pressure monitoring (SENSIMED Triggerfish, Sensimed AG, Lausanne, Switzerland).[44] They used an ML approach called random forest modeling to identify the parameters associated with the primary open-angle glaucoma patients.

Niwas *et al*. evaluated a fully automated model to classify angle closure glaucoma from anterior segment OCT scans and showed an accuracy of 89.2%.[45]

For fundus photographs, Li *et al*. evaluated a DL algorithm that showed a high sensitivity (95.6%) and specificity (92%) to detect referable glaucomatous optic neuropathy.[46] The disadvantage was that high myopia caused false negatives and physiological cupping caused false positives. Al-Aswad *et al*. evaluated Pegasus (Visulytix Ltd., London, UK), a DL system to detect glaucomatous optic neuropathy from color fundus photographs and showed that it outperformed 5 out of 6 ophthalmologists in the study.[47] Netra.AI (Leben Care Technologies Pte., Ltd.) is another AI that evaluates glaucomatous fundus photographs [Figure 4]. Several other studies also looked at different techniques to detect glaucomatous optic neuropathy from disc photographs [Figure 5].[48-50]

Muhammad *et al*. showed that a hybrid deep learning method on a single, wide-field swept-source OCT had 93.1% sensitivity in detecting glaucoma suspects.[51] Asaoka *et al*. evaluated a DL algorithm with pretraining that diagnosed glaucoma based on macular OCT for RNFL and GCL.[52] Other studies evaluated unsupervised ML, ML classifiers (MLCs), artificial neural networks (ANNs), support vector machines, and segmentation methods for glaucoma OCT.[53-56]

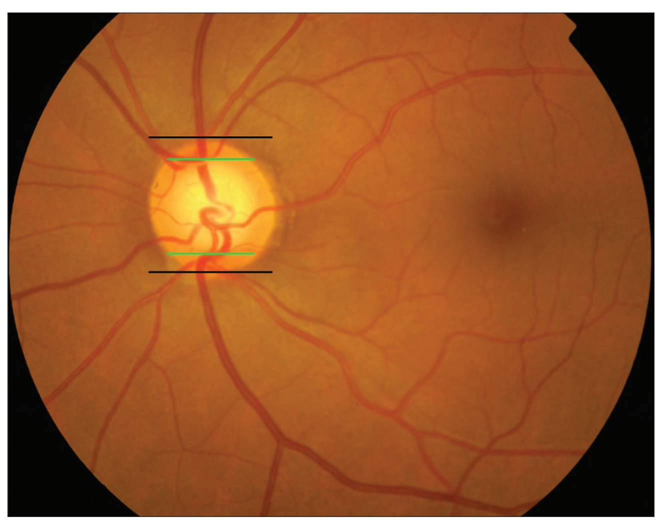

Figure 4: Retinal fundus photo of the left eye of a glaucoma patient in which the vertical disc and cup margins have been demarcated by the Netra.AI (Leben Care Technologies Pte., Ltd.)

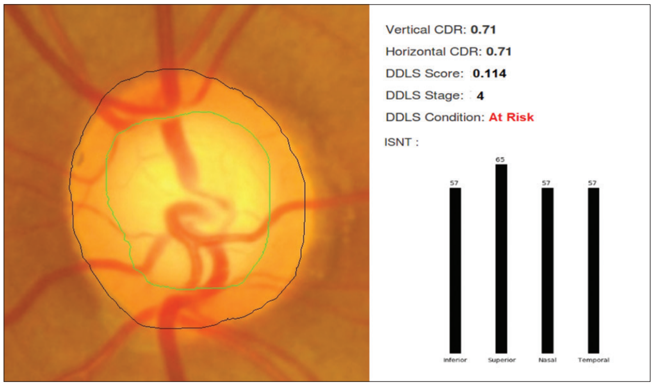

Figure 5: Localized and segmented image of disc from previous fundus image in which disc and cup margins are segmented. On the right, vertical cup: disc ratio, horizontal cup: disc ratio, and disc damage likelihood stage are shown along with the violated ISNT rule graph (inferior superior nasal and temporal neuroretinal rim) (Image courtesy: Leben Care Technologies Pte., Ltd.)

Visual fields are difficult to interpret, so AI help would be appreciated in this context. Asaoka *et al*. used a feedforward neural network to identify preperimetric visual fields which did not meet Anderson–Patella's criteria from healthy visual fields.[57] Li *et al*. evaluated a CNN to automatically differentiate glaucoma VF from nonglaucoma VF.[58] Goldbaum *et al*. used unsupervised ML and variational Bayesian independent component analysis mixture model (vB-ICA-mm) to analyze VF defects.[59] Andersson *et al*. showed that a trained ANN obtained 93% sensitivity and 91% specificity in evaluating glaucoma VF and performed at least as well as clinicians.[60] Bowd *et al*. successfully used vB-ICA-mm, an unsupervised MLC, to analyze frequency-doubling technology perimetry data.[61]

For visual field progression analysis, Goldbaum *et al*. used progression of patterns, an MLC algorithm.[62] Yousefi *et al*. showed that ML detects VF progressing consistently, without confirmation visits and even slow progression.[63] All these methods would ideally run on portable perimetry devices like the smartphone-based virtual reality perimetry such as PeriScreener, VirtualEye, and C3FA.[64]

Wen *et al*. trained a DL system with 32,443 visual fields (24-2 HVFs) taken between 1998 and 2018, and the resulting CascadeNet-5 model was able to predict future visual fields for up to 5.5 years based on a single input visual field.[65] Kazemian *et al*. developed and validated Kalman filters, which could predict personalized trajectory of progression of mean deviation of visual fields at different target IOPs.[66] This would guide ophthalmologists in choosing a specific patient's target IOP.

Retinopathy of prematurity

AI tools for ROP screening[67-69] from fundus images from cameras such as RetCam (Massie Research Laboratories, Inc., Dublin, California) include ROPTool,[70] retinal image multiscale analysis,[71] computer-assisted image analysis of the retina,[72] and imaging and informatics in ROP (i-ROP).[73] Diagnostic accuracy of the i-ROP system (95%), which incorporated tortuosity of arteries and veins, was comparable to expert ophthalmologists.[73]

Age-related macular degeneration

Some ML algorithms have been trained to detect and grade ARMD from color fundus photographs.[74-78] Some other ML algorithms can detect ARMD from OCT scans.[79-82] A few other ML systems can predict visual acuity[83,84] and requirement of antivascular endothelial growth factor (VEGF)[85] from OCT scans.

Retinal vascular occlusions

ML algorithms can detect central retinal vein occlusion[86] and branch retinal vein occlusion[87] from wide-field fundus photographs or from fluorescein angiograms[88] and quantify the resulting macular edema[81] by OCT. Another study also used ML to evaluate the impact of vitreomacular adhesion on anti-VEGF therapy for retinal vein occlusions.[89]

Optical coherence tomography

Inbuilt segmentation of scans in OCT machines is a type of AI. OCT scans can be evaluated for glaucoma, DR, and several other retinal diseases. Kuwayama *et al*. showed the feasibility of automated detection of macular diseases such as epiretinal membrane, DR, and ARMD from OCT and found that image augmentation is effective when the number of training images is low.[90]

Sumaroka *et al*. used a supervised ML to predict perimetry results from OCT scans of retinitis pigmentosa and Leber congenital amaurosis patients.[91]

Fluid intelligence is a mobile AI app that runs on Android or iPhone, which allows you to take a photo of an OCT scan and detect macular edema or subretinal fluid. Odaibo *et al*. evaluated this app and found a sensitivity of 89.3% and specificity of 81.25% [Figure 6].[92]

Other retinal diseases

Ohsugi *et al*. showed that DL can detect rhegmatogenous retinal detachment from ultra-wide-field fundus photographs with a sensitivity of 97.6% and specificity of 95.6%.[93]

Xu *et al*. evaluated a dual-stage DL system to identify and segment pigment epithelial detachment (PED) in polypoidal choroidal vasculopathy (PCV) from OCT scans.[94]

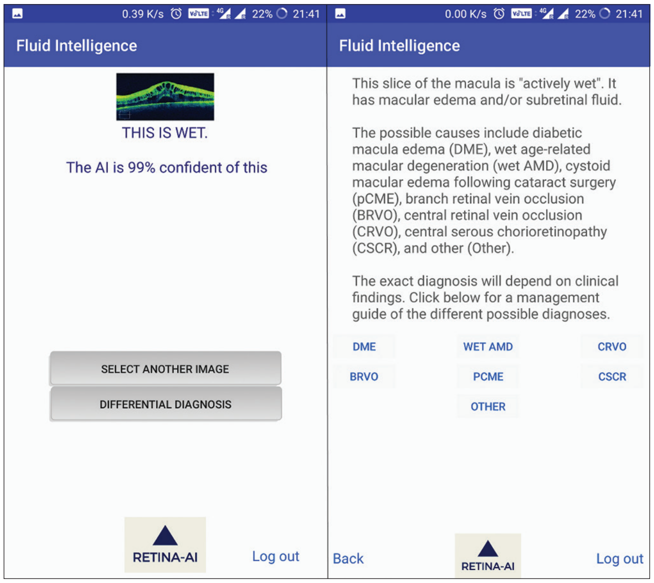

Figure 6: Screenshots of Fluid Intelligence App on Android after evaluating optical coherence tomography scans uploaded from mobile (Image courtesy: Fluid Intelligence App)

Keratoconus

AI has been used to detect keratoconus and forme fruste keratoconus[95] from Placido topography, Scheimpflug tomography,[96] SD-ASOCT, and biomechanical metrics (Corvis ST, corneal hysteresis).[97] Data from Pentacam,[98] Sirius,[99] Orbscan II,[100] Galilei,[101] and TMS-1[102] topographers and tomographers have been studied using ML algorithms to detect early keratoconus.

Other corneal diseases

Ambrósio *et al*. evaluated AI-based tomographic and biomechanical index (TBI), which combines Scheimpflug-based corneal tomography and biomechanics (Corvis ST) for enhancing ectasia detection.[103] Sharif *et al*. showed that confocal microscopy images of the cornea can be evaluated in detail using a committee machine formed from ANNs and adaptive neuro-fuzzy inference systems that can detect abnormalities with high accuracy and can visualize in 3D.[104]

Cataract grading

Mahesh Kumar and Gunasundari developed a computer-aided diagnosis system to detect corneal arcus and cataract from the photographs of eyes taken with a standard digital camera.[105] Gao *et al*. proposed a system to automatically grade cataract from slit-lamp images.[106]

Caixinha *et al*. proposed grading of cataract hardness using ultrasound in an animal model using ML.[107] Yang *et al*. demonstrated grading of cataract from clarity of retinal fundus photographs with an accuracy of 93.2% in detecting cataract and 84.5% in grading cataract.[108] Zhang *et al*. reported a similar accuracy of 93.52% for detecting cataract and 86.69% for grading cataract with their method using fundus photographs.[109]

Mohammadi *et al*. predicted the risk for posterior capsule opacification (PCO) using AI with an accuracy of 87%.[110]

Gillner *et al*. demonstrated automated segmentation of an accommodative intraocular lens in a biomechanical eye model using OCT.[111] This can potentially be used to study the working of accommodative lens and design better IOLs.

Pediatric ophthalmology

AI and ML have been used for congenital cataract diagnosis,[112] collaborative management,[113] and prediction of surgical complications of pediatric cataract surgery.[114]

It can also be used to detect strabismus[115] and refractive error, predict future high myopia, and diagnose reading disability.[116] There have also been studies to automatically detect leukocoria in children from recreational smartphone or digital camera photographs, which suggests ocular pathology that requires screening.[117,118]

Almeida *et al*. presented a methodology based on support vector regression for planning surgical resections and recessions for horizontal strabismus surgeries which showed good accuracy.[119]

Ocular oncology

A technique to demarcate the boundary of ocular surface squamous neoplasia from unstained biopsy specimens using multispectral imaging and ML was described by Habibalahi *et al*.[120] This can potentially be used intraoperatively for rapid assessment of cancer-free margins.

Tan *et al*. showed that a supervised ML decision tree model was able to predict the complexity of reconstructive surgery after excision of periocular basal cell carcinoma.[121]

Refractive error prediction

Das *et al*. from LV Prasad Eye Institute, India, presented a study that predicted the progression of myopia and refractive error in children using ML on data such as age, gender, onset of refractive error, current refractive error, visual acuity, and other clinical information.[122] Zhang *et al*. validated the accuracy of a model to predict onset of myopia in children using ocular biometry, height, weight, and presenting visual acuity.[123] Lin *et al*. developed an algorithm to use refraction data from EMRs to predict refraction values at future time points.[124]

Surprisingly, Varadarajan *et al*. from Google used DL using TensorFlow for predicting refractive error from only retinal fundus photographs.[125] The attention map which opens up the black box of the ML algorithm showed that features on the fovea were important to predict refractive error including spherical equivalent, spherical, and cylindrical powers. Liu *et al*. presented the Pathological Myopia Detection Through Peripapillary Atrophy system to detect pathological myopia from retinal images by the detection of parapapillary atrophy.[126] Zhang *et al*. further demonstrated the diagnosis of pathological myopia by combining heterogeneous biomedical data, including demographic data, fundus imaging data, and single-nucleotide polymorphism data.[127]

Koprowski *et al*. demonstrated the use of ANNs to predict the corneal power after myopic refractive surgery with good accuracy (0.16 ± 0.14 diopters).[128]

Intraocular lens power calculation

IOL power calculations have always been an approximate estimate from several parameters and are thus suited for ML algorithms. AI-powered IOL calculations include Hill-Radial Basis Function (RBF),[129] Ladas Super Formula,[130,131] Clarke Neural Network,[132] and FullMonte Method. A few other studies have also attempted to use AI for IOL calculation.[133-135] Kane *et al*., in 2017, had compared the accuracy of Hill-RBF, Ladas Super Formula, and FullMonte with that of Holladay 1 and Barrett Universal II, but did not find them to be more accurate.[136]

The best known AI formula is the Hill-RBF formula[129] by Dr. Warren Hill, available online at https://rbfcalculator.com/online/, which uses pattern recognition and data interpolation. It is currently in version 2.0 and uses data from 12,419 eyes. Biometry data required include axial length, anterior chamber depth, and keratometry values and their axes. Optional data which can improve accuracy include central corneal thickness, lens thickness, and white-to-white [Figure 7].

Dementia and Alzheimer's disease

Retinal vascular changes not detectable by human ophthalmologists are present in neurological diseases[137] such as cognitive impairment,[138] dementia,[139-141] and Alzheimer's disease,[142-144] which can be detected by ML algorithms from fundus photography and OCT. Carl Zeiss Meditech holds a patent for a method and system for detecting the effects of Alzheimer's disease in the human retina.[145]

Predicting cardiovascular and stroke risk

In a study by Google, Poplin *et al*. trained a DL AI using data from 284,335 patients and validated on two independent datasets of 12,026 and 999 patients. From fundus photographs, the AI was able to predict age (mean error of 3.26 years), gender (AUC = 0.97), smoking status (AUC = 0.71), systolic blood pressure (mean error of 11.23 mmHg), and major adverse cardiac events (AUC = 0.70). They noted that AI used anatomical features of the fundus photo such as optic disc and blood vessels to make the predictions. This can potentially help humans to learn from the AI regarding how to predict these from fundus photos.

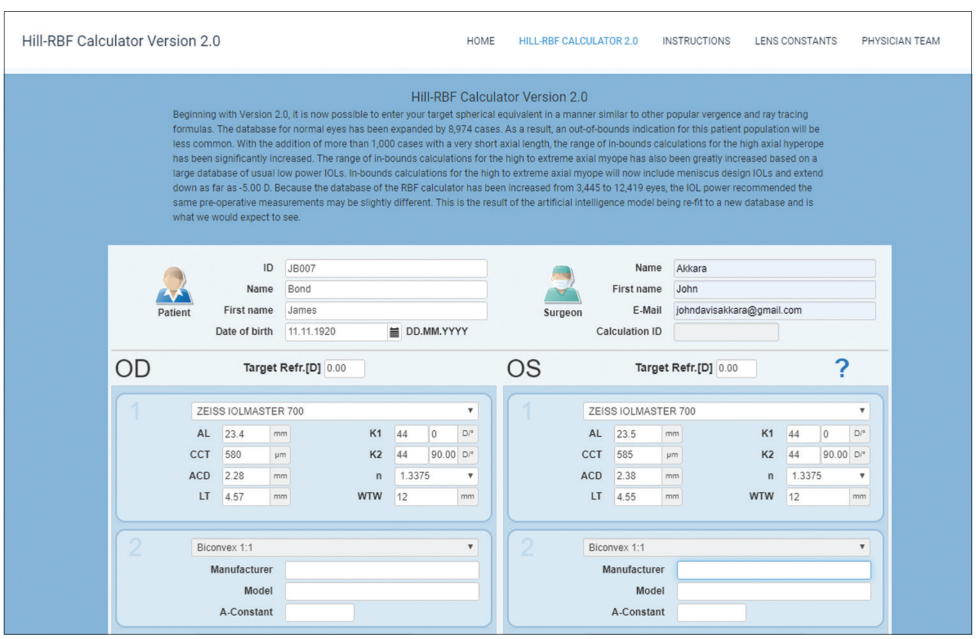

Figure 7: Website of artificial intelligence based Hill-Radial Basis Function intraocular lens power calculator showing the parameters entered (image courtesy: rbfcalculator.com)

Automatic retinal image analysis of fundus photos by an ML algorithm can predict the presence of white matter hyperintensities on magnetic resonance imaging brain, which is a risk for cerebral small vessel disease and stroke.[146]

CONCLUSION

The age of AI and ML has definitely arrived. However, the accuracy and reliability of the systems in a real-world clinical scenario is questionable. AI and ML should augment the clinician skill and can only be considered a tool. AI in ophthalmology would probably find the best application in screening camps and teleophthalmology.[147] This could also be applied in virtual clinics[148] to reduce the number of onward referrals to higher centers. Currently available medical diagnosis apps include Ada (available on Android and Apple phones), Babylon, and Your.MD, and though they sometimes give correct diagnosis, they cannot be relied on for critical decisions. Fundus photographs can be analyzed on Orbis Cybersight Consult website in the clinical cases section. Many newer fundus cameras and OCT machines might come inbuilt AI software. EMRs may be integrated with a cloud AI system.

Ophthalmologists should know about the AI resources available to them and make judicious use of them when understanding their limitations.

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Conflicts of interest

There are no conflicts of interest.

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