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ARTIFICIAL INTELLIGENCE

The upcoming role of Artificial Intelligence (AI) for retinal and glaucomatous diseases

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Abstract In recent years, the role of artificial intelligence (AI) and deep learning (DL) models is attracting increasing global interest in the field of ophthalmology. DL models are considered the current state-of-art among the AI technologies. In fact, DL systems have the capability to recognize, quantify and describe pathological clinical features. Their role is currently being investigated for the early diagnosis and management of several retinal diseases and glaucoma. The application of DL models to fundus photographs, visual fields and optical coherence tomography (OCT) imaging has provided promising results in the early detection of diabetic retinopathy (DR), wet age-related macular degeneration (w-AMD), retinopathy of prematurity (ROP) and glaucoma.

In this review we analyze the current evidence of AI applied to these ocular diseases, as well as discuss the possible future developments and potential clinical implications, without neglecting the present limitations and challenges in order to adopt AI and DL models as powerful tools in the everyday routine clinical practice.

Introduction

Considering the growing average age of the population and the subsequent increased prevalence of age-related ophthalmic diseases, the importance of early diagnosis and appropriate treatment of ophthalmic diseases has never been greater.[1] In fact, in spite of the several technological advances in retinal imaging, including the advent of developed optical coherence tomography (OCT) and OCT angiography (OCTA) devices, the interpretation and management of retinal diseases has become largely more complex for ophthalmologists, in virtue of the large accumulation of

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images and findings leading to a 'big data' challenge.[2-4] In this regard, the deep integration of artificial intelligence (AI), machine learning (ML) and deep learning (DL) into the ophthalmic field may improve the preexisting diagnostic system and may help to create a more efficient health care service in ophthalmology.[5]

AI is a subfield of computer science, which was developed in the late 50s by Arthur Samuel with the aim to produce intelligent machines.[6] ML is a branch of AI, in which algorithms are needed to learn the rules through a set of examples, instead of being manually encoded.[7] Instead, DL is based on a system of artificial neural networks (ANN), which imitates the functional structure of the central nervous system. In DL, a single deep neural network has not only the capability of collecting data, but also of learning to both extract features that are suitable for a given classification problem and to subsequently categorize them.[8,9] Hence, the difference between ML and DL systems is that the former (ML) is related to computers learning from data using algorithms to perform a task without being explicitly programmed, while DL adopts a complex structure of algorithms modeled on the human brain.

In the field of ophthalmology, DL has shown to be a useful tool for screening and follow-up of several diseases, including diabetic retinopathy (DR), retinopathy of prematurity (ROP), wet-age related maculopathy (w-AMD) and glaucoma.[5] In fact, the combination between DL and telemedicine may help to overcome the high costs related to manpower and financial resources, thus improving the process of screening and follow-up of these chronic ocular diseases; in addition, AI offers the possibility to adopt efficient algorithms able to detect and learn different clinical features, extrapolated from a huge amount of data.[10]

In this review, we summarized all the clinical applications of AI and in particular DL, especially focusing on frequent ocular diseases including DR, w-AMD and glaucoma.

AI in diabetic retinopathy

DR is one of the leading causes of blindness in Western countries. An estimated 600 million people will have diabetes by 2040, and at least a third will develop DR.[11] For this reason, early screening for DR, with timely referral and treatment remains the most accepted strategy to combat blindness in these patients.[12] Despite the global need for retinal screening examinations, due to issues such as implementation, availability of human accessors and financial sustainability, many people still today remain undiagnosed. Nonetheless, the diagnosis and grading of DR is allowed by the adoption of multimodal imaging, including fundoscopy, OCT and OCT angiography for detecting the presence of diabetic macular edema (DME) and fluorescein angiography (FA), which is particularly useful for describing the presence of ischemic areas and new pathologic vessels in the posterior pole and in the retinal periphery.[13]

Nowadays, to improve the early diagnosis of DR, AI and in particular teleretinal screening, has become a growing possibility to automate DR screening.[14]

In recent years, DL-based technologies have proved to be equivalent to, if not superior to, the diagnostic performance of clinical specialists. In this regard, many studies have proven that DL systems and algorithms can accurately identify DR.[15] Abràmoff et al. reported a sensitivity of 96.8% and a specificity of 87% and an area under the receiver operating characteristic curve (AUC) of 0.980, for detecting referable DR on the publicly available Messidor-2 data set.[16]

Gargeya and Leng et al. DL algorithm achieved a 0.97 AUC with a sensitivity of 94% and specificity of 98%, on a 5-fold cross-validation using their local data set and 0.94 and 0.95 AUC when tested against the Messidor- 2 and E-Ophtha databases, respectively. They showed that a DL-based grading algorithm could be adopted for screening fundus photographs in diabetic patients and could reliably refer those cases, which needed further clinical evaluation, to an ophthalmologist.[14] Gulshan and colleagues also developed a DL algorithm able to detect referable diabetic retinopathy with an AUC of 0.991 for EyePACS-1 dataset and 0.990 for Messidor-2. These promising results led to multiple AI algorithms being approved for market.[17]

In April 2018, the United States Food and Drug Administration (FDA) approved the autonomous DR and diabetic macular edema detection software (IDx-DR). IDx-DR is a software device developed to be adopted by health care providers for screening more than mild diabetic retinopathy in adults with diabetes who have not been previously diagnosed with diabetic retinopathy. The device is indicated for use with fundus photographs.[18]

Afterwards, Eye Art became the second AI-based DR in-clinic screening platform to receive FDA approval in 2020.[19]

More recently, there has been a significant advancement in smartphone-based AI. The world's first smartphone retinal imaging system (Remidio Fundus On Phone Non Mydriatic (FOP NM-10) device received FDA approval as an out of clinic device to diagnose diabetic retinopathy.[20,21]

Other smartphone-based AI devices include the i-Examiner (Welch Allyn, Skaneateles Falls, NY), which has already received FDA approval, as well as the Peek Retina and Volk iNview.[22] These out-of-clinic devices have the potential to increase diabetic retinopathy screening program access and coverage, especially in places where people may not have access to a routine ophthalmological examination.[23,24]

Despite the very promising results in DL-based AI for DR detection as determined by screening performance metrics, there are still many practical challenges to be resolved. Firstly, there is large concern from clinicians over the interpretability, complexity, and time-effectiveness of AI implementations. Secondly, different visualization methods, such as cameras with varying resolutions, may not necessarily produce the same results. Third, from a legal standpoint, clinicians are concerned about the threat of legal liability arising from incorrect AI analyses. Even though systems like IDx-DR and Eye Art have already been approved by the FDA for DR detection, the repercussions of a possible AI misdiagnosis are still to be assessed.[25]

Currently, the combination of humans and AI is able to provide the best care, than either alone.[26] In fact, while AI is detail-oriented and fatigue resistant, humans have a higher-level metacognition and intuition that allows them to recognize anomalies more readily as well as be aware of the sometimes-overlapping features of different retinal pathologies, particularly in more advanced stages of the disease. A major drawback in fact is that most of these algorithms are excellent at detecting moderate to severe DR but worse at grading the severity of DR, and in detecting early stages pre-

diabetic retinopathy. Moreover, another possible limitation is represented by the possible misdiagnosis or false negatives when other ocular comorbidities (together with DR) are present.[27]

Because most DL systems are evaluated on specific data sets rather than on a real-world setting, big worldwide datasets with patients of various ethnicities should be employed for algorithm optimization. Also, integration of different parameters including age, duration of diabetes, serum HbA1C percentage, blood cholesterol, blood pressure and genetic risk information may improve diagnostic accuracy.[28]

Multimodal imaging has recently been investigated to predict various retinal vascular illnesses, and while Hayreh et al. DL model had good overall accuracy, the model provided incorrect predictions particularly for eyes with advanced-stage disorders or coexisting retinal conditions.[29] The additional complexity that is inevitable with DL algorithms analysing different retinal diseases makes real world implementation of AI challenging, somewhat making one pathology detection-based algorithms less enticing.[30]

For the above-mentioned reasons, despite the promising results and capabilities of AI, clinicians and the scientific community remain cautiously optimistic.

AI in macular degeneration

Age-related macular degeneration (AMD) represents nowadays one of the major causes of central vision loss in developed countries. Worldwide, the number of people affected by AMD is predicted to increase from 196 million in 2020 to 288 million by 2040.[31] It can be classified as dry, wet, early, or advanced based on the presence of intraretinal or subretinal fluid. Both early and advanced stages can be associated with atrophic changes on the retinal pigment epithelium. Recently, the Classification of Atrophy Meetings (CAM) group elaborated the definitions of geographic atrophy in AMD and characterized its subtypes with histological correlates and clinical validation. In combination with OCT imaging, other imaging techniques, including fundus autofluorescence, near-infrared reflectance, and color imaging, may provide complementary information to describe the atrophy. In this regard, a novel OCT-based classification has been proposed to identify a complete outer retinal atrophy (cRORA) according to the following criteria (1) a region of hypertransmission of at least 250 μm in diameter, (2) a zone of attenuation or disruption of the RPE of at least 250 μm in diameter, (3) evidence of overlying photoreceptor degeneration, and (4) absence of scrolled RPE or other signs of an RPE tear.[32,33]

In this regard, DL has been shown to have the ability to detect the different stages of atrophy. In a recent study, the first DL segmentation model was studied in relation to consensus definitions for the detection, classification, and quantification of geographic atrophy by OCT features. This model reported potential for clinical utility through high performance in a real-life external validation. Furthermore, a predictive performance was reported in comparison with that shown by clinical experts.[89]

Over the last 20 years a lot of progress has been made in terms of diagnosis and treatment modalities. Before the advent of OCT devices, careful fundal assessment was the only way to diagnose macular abnormalities. With advancements being made in OCT technology, we are now able to assess the macular region based on microscopical changes caused by AMD.[33] Standard treatment for wet AMD remains anti-VEGF intravitreal injections. This treatment leads to patients' vision stabilization as well as some vision improvement in some circumstances. Of particular importance, are also the timing and the number of injections as it has proven to be relevant for the patients visual outcome.[34-42]

Several studies have been published recently regarding the use of AI in patients affected by AMD; however, to date, there is still no consensus about its use on fundus photographs, whether associated or not with an OCT scan.[5]

Several studies have demonstrated AI ability to detect findings not otherwise visible.[43,] Some authors have even suggested the use of AI-based algorithms from fundus photographs as a form of screening and diagnostic tool by itself. In this regard, a major challenge is that retinal photographs captured from real-world clinical settings may show worse quality in comparison with the retinal photographs carefully curated and used specifically in the developments of DL algorithms. Hence, to overcome these limits, some studies developed specific DL algorithms to assess image quality, field of view, and laterality of the eye of retinal photographs, showing an excellent performance.[44]

Currently, retinography represents an important diagnostic tool in the evaluation of AMD in the clinic, allowing satisfactory screening of patients. Other studies showed an improved sensitivity in AMD diagnosis when used in concomitance with OCT scan.[45] In fact, such double device approach likely increases the reliability of the results.[46]

Recently, it has been demonstrated the clinical utility of AI in the decision-making process on whether to promptly treat or postpone treatment in patients affected by wet AMD (w-AMD). AI algorithms can indeed be considered a helpful adjunct tool, especially for non-retina specialists in the interpretation of OCT scans.[47]

In a large, retrospective study, the predictive usefulness of quantitative imaging biomarkers, acquired automatically from OCT scans were evaluated in 6467 eyes of 3261 patients with wet AMD. They found that the automatic segmentation may allow to have a rapid acquisition of quantitative and reproducible OCT biomarkers and may help to inform treatment decisions in the management of wet AMD.[48]

Although AI-based algorithms are rapidly evolving and are being increasingly implemented to aid in AMD detection and diagnosis, there are still several significant limitations. In fact, the presence of a poor image quality due to media opacity, long axial length, poor vision and/or patients' general condition may significantly affect the reliability of the algorithms.[49]

In the next years one of the leading focuses of AI technology should consist in developing more accurate algorithms able to predict the presence of w-AMD and its evolution and/or progression. Already different studies have described the clinical course of AMD in patients treated with anti-VEGF drugs.[50] In addition, a novel retinal imaging technology (Detection of Apoptosing Retinal Cells (DARC)) was recently developed, able to detect stressed and apoptotic cells in the living eye. This technology with an AI-aided algorithm gave promising results in detecting AMD and there is potential for this technology to be used as a biomarker, although further

studies are needed to validate the findings. This system may also help to monitor and predict the clinical course of the contralateral, unaffected eye.[51]

AI in glaucoma

Glaucoma is one of the leading causes of irreversible blindness, whose global prevalence in people aged 40-80 years is estimated to be 3.5%. Moreover, it has been a predicted that 112 million people will be affected by glaucoma worldwide by 2040.[52] Glaucoma is characterized by the progressive degeneration of the optic nerve, with loss of retinal ganglion cells, thinning of the retinal nerve fiber layer, and progressive excavation of the optic disc. Early diagnosis and an accurate monitoring of glaucoma progression are key to provide the most accurate and targeted treatment. This is particularly important given that the visual loss caused by glaucoma is irreversible.[53]

In the last decade, AI diagnostic algorithms that detect, monitor and predict glaucoma have increased exponentially; furthermore, several different parameters including intraocular pressure (IOP), optic disc evaluation, retinal nerve fiber layer measurement, gonioscopy and visual field have been evaluated as 'markers' to identify and monitor this disease through DL systems.[54]

IOP remains the main modifiable risk factor for developing glaucoma and it is associated with its progression; thus, developing devices that can constantly monitor IOP remains crucial.[55] In the study published by Martin et al., 24-h profiles of ocular volume changes were recorded using the contact lens sensor (CLS) monitoring device (Sensimed Triggerfish). The CLS parameters feature was able to discriminate primary open angle glaucoma from healthy eyes with mean ROC AUCs of 0.611.[56]

Several other studies have evaluated the accuracy of other algorithms in detecting glaucoma from fundus photography, mostly by evaluating the optic disc to cup ratio. Al-Aswad et al. demonstrated the superiority of the Pegasus DL system (Visulytix Ltd., London UK) that outperformed five out of six ophthalmologists in the diagnosis of glaucomatous optic neuropathy.[57] Li et al. described a DL algorithm with a comparable performance in detecting glaucoma from fundus photography, with a sensitivity of 95.6% and specificity of 92%.[58]

In another study, Haleem et *al*. further optimized the ability to detect the contour of optic disc and cup boundary using their Region Classification Model (RCM), which provides a more individualized system that allows to detect the precise contour of the optic disc, compared to the circular or ellipse fitting often used in standard approaches.[59]

Despite the excellent performances of current algorithms, major drawbacks remain when detecting glaucoma in high myopic eyes. The peripapillary atrophy, shallow cups, and tilting/torsion of the optic disc, features often present in high grade myopia, were in fact the leading cause of false negatives and positives in several studies. Poor quality images also may hinder the accuracy of the algorithm.[60]

OCT also proved to be valuable in the detection of glaucomatous damage as retinal nerve fibers layer (RNFL) thickness measurement remains one of the most important features to discriminate between normal and glaucomatous eyes.[61,62]

In other studies, DL algorithms were able to effectively detect glaucomatous eyes from a single wide field swept source OCT (SS-OCT), by analyzing the RNFL as main parameter.[63,64]

In addition to the dichotomous classification (glaucomatous vs healthy eyes) often used to evaluate algorithm performance, detecting the progression of glaucoma has also been of major interest.[65] Various artificial neural network and DL methods demonstrated high accuracy in distinguishing glaucoma visual fields (VF) from healthy VFs as well as in monitoring glaucoma progression[66,67] Wang et al. reported an algorithm able to recognize early stages of glaucoma and track VF progression using archetypal analysis. The study recognized relevant VF loss patterns and assigned a weighting coefficient for each pattern loss to grade and quantify glaucoma progression.[68]

Combination approaches have also been implemented to enhance diagnosis and monitor glaucoma progression. For instance, a study integrated both non-ophthalmologic factors (sex, age, menopause, and duration of hypertension) and ophthalmologic factors (IOP, spherical equivalent refractive errors, vertical cup-to-disc ratio, presence of supertemporal and inferotemporal RNFL defect) to predict glaucoma, providing a more personalized and holistic approach in glaucoma detection.[69]

Furthermore, Kazemian et al. was able to develop a clinical forecasting tool by combining tonometry and VF data that could predict the disease trajectories at different IOPs.[69]

In the near future, these combination approach models are expected to classify patients into subgroups, taking into account both general health and ocular parameters; furthermore, these models are expected to become critical tools to help guide clinicians to adopt the most effective strategy to treat glaucoma. Although the performances of current algorithms often outperform that of clinicians, a major challenge remains their general applicability to systems and setting beyond the site of development. The access to a greater pool of training images as well as inclusion of images from patients of different ethnicities may likely increase the accuracy of DLS. The next stage for AI in glaucoma will most likely be the integration of the genome, lifestyle behavior, medical history, and ophthalmological parameters into a unified algorithm.

AI in retinopathy of prematurity

Retinopathy of prematurity (ROP) is a leading cause of childhood blindness worldwide, affecting extremely preterm infants.[70] Low gestational age and low birth weight are the two strongest risk factors for the development of ROP.[71] The pathology occurs in a percentage of premature births varying from 5-10% to 73% depending on the study and accounts for 6—18% of blindness registrations.[72] Early treatment has proven to be highly beneficial, thus screening and regular monitoring are crucial for the optimal management of the disease.[73]

In 2021, participants in ICROP3 decided to refine classification metrics (e.g. posterior zone II, notch, subcategorization of stage, and recognition that a continuous spectrum of

vascular abnormality exists from normal to plus disease) and to include the definition of aggressive ROP to replace aggressive-posterior ROP.[74]

The role of AI in ROP has significantly grown since its application in the field, ranging from the development of ROPtool (FocusROP), Retinal Image multiScale Analysis (RISA), Vessel Map, Computer Assisted Image Analysis of the Retina (CAIAR), to the most recent Imaging and Informatics in ROP (i-ROP) and i-ROP DL.[75] In detail, i-ROP presents 2 main advantages in comparison with the other image analysis systems. Firstly, most previous Computer-Based Image Analysis (CBIA) systems, which is a well-established interdisciplinary research unit that primarily attends to the development and benchmarking of algorithms for the analysis and synthesis of cell microscopy image data, have focused on a two-level classification (i.e., plus versus not plus), whereas i-ROP is able to discriminate among 3 categories (i.e., plus, preplus and normal). Secondly, previous studies used a simple threshold-based classification, instead of a Gaussian mixture models-based feature representation, which is shown to perform better than using regular statistics of image features in classification.[76] The results of i-ROP have shown to be highly promising, since its accuracy (95%) in diagnosing ROP was higher than 10 out of 11 individually evaluating trained clinical experts and comparable to the whole group of experts together (97%).[77] Despite the promising results, there were still some improvements to be done. First, i-ROP has been trained using manually segmented images, therefore, it was not a fully automated procedure. Moreover, the data set employed in the study needed to be validated against other data sets.[77] Recently, fully automated systems employing convolutional neural networks (CNNs) have been developed. In 2016, Worrall et *al*. presented the first fully automated ROP detection system.[78] Later, Brown et al. presented a CNN-based DL trained on more than 5000 images from 8 different academic institutions, which was a fully automated system. In this study, its accuracy was 91% against the mean of 82% achieved by 8 experts. The i-ROP DL algorithm outperformed not only most experts, but also all prior CBIA systems in ROP.[76]

In a meta-analysis including 9 studies on DL models for automated diagnosis of ROP, Zhang et al. reported accuracy values based on AUC are over 0.97, which is classified as high when above 0.9. Hence, DL models have been shown to display an important role in detecting and grading ROP with high sensitivity, specificity, and repeatability[79]; however, the systems still present some limitations, linked to the fact that CNN are only as robust as the data on which they are trained. Moreover, they currently classify only the plus disease, which represents only one component of the International Classification of Retinopathy Of Prematurity (ICROP) system, while a fully automated ROP screening platform should ideally classify zone, stage, and the overall disease category as well as predict the need for treatment. Nonetheless, CNN features are not fully transparent or explainable.[80]

To improve these limitations, Yildiz et al. introduced i-ROP ASSIST, which combines some of the advantages of a CNN model for identification of the relevant vascular structures with a feature-extraction algorithm previously developed.[80,81] The system calculated the area under the curve (AUC), which consists of a reliable measure of the ability of a classifier to distinguish between classes and therefore the higher is he AUC, the better is the performance of the model at distinguishing between the classes. In their study, the authors reported AUC values of 0.88 and 0.94 for predicting pre-plus or worse versus normal and plus versus not-plus disease, respectively, similarly to 0.94 and 0.98 AUC, obtained by a CNN-based approach.[80]

Other CBIA systems have been introduced for several purposes: DeepROP aims to improve the accuracy of i-ROP DL. It is based on a larger dataset and obtained 97% as the highest accuracy.[82] Other algorithms have been proven to identify zone 1 through RetCam images 6 and to outline the demarcation line.[78,83] Moreover, quantitative ROP vascular severity score extrapolated from CBIA systems can be used to track clinical disease progression and post-treatment regression.[84] A higher score is also associated with more posterior disease, higher disease stage, and higher extent of stage 3 disease.[85]

The use of CBIA systems may offer an alternative and even more valid method to diagnose ROP, for both methodological and economic reasons. Finally, AI has enabled the development of a ROP severity score that correlates with ICROP disease classification and shows promise for quantitative disease monitoring, improved risk prediction, and post-treatment identification of treatment failure and recurrence. Being comparable to human evaluation, CBIA systems can be useful in saving the time of highly specialized ophthalmologists, reducing the screening burden by up to 80%.[86] Furthermore, the instrument may be implemented in telemedicine consults, in order to offer a cheap screening telemedicine tool for diagnosing ROP in low- and middle-income countries, where prevention still presents many flaws. The introduction of CBIA systems in routine clinical practice is expected to impact the outcomes of patients with ROP; further studies are needed to provide more evidence in this regard.

Conclusions

AI-based models provided high levels of accuracy in different ophthalmological fields; however, in spite of these achievements, there are still some challenges to be overcome. First, most of the studies on AI and DL-based models have adopted training data sets extrapolated from relatively homogeneous populations.[10] In fact, these data sets are subjected to several variables, including the different quality of the images, field of view, image magnification and ethnicities of the patients; thus, an important issue is to diversify the features of the data as well as enlarge the data set analyzed by AI-models.

Second, other important issues are represented by the relatively poor availability of data concerning rare ophthalmological diseases, including ocular tumors, and inherited retinal dystrophies.[5] Another important limitation is that although many studies have provided consistent evidence in favor of DL models in the early detection and diagnostic capability in the ophthalmological field, often the power calculation of independent data sets has not provided. Hence, further studies should provide evidence on the power calculation used, including prevalence of the disease and type 1 and 2 errors calculation.[87]

Lastly, many ophthalmologists are concerned about AI and DL being 'black-boxes' systems; in fact, clinical decision

cannot be guided solely by a quantitative algorithmic performance, but it should also consider the underlying clinical features in order to improve physician acceptance.[88]

In conclusion, DL models have been proven to be the current state-of-art in the field of AI applied to ophthalmology. In fact, D-models have provided promising results in the diagnostic process for several retinal diseases (DR, w-AMD and ROP) and for glaucoma. To date, despite promising results from DL models, some challenges persist, and further clinical studies are needed to overcome these limitations as well as to accurately assess the impact of AI and DL models applied to the ophthalmological field.

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Declaration of Competing Interest

The authors have no conflicts of interests.

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