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Current roles of artificial intelligence in ophthalmology

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Abstract

Artificial intelligence (AI) studies are increasingly reporting successful results in the diagnosis and prognosis prediction of ophthalmological diseases as well as systemic disorders. The goal of this review is to detail how AI can be utilized in making diagnostic predictions to enhance the clinical setting. It is crucial to keep improving methods that emphasize clarity in AI models. This makes it possible to evaluate the information obtained from ocular imaging and easily incorporate it into therapeutic decision-making procedures. This will contribute to the wider acceptance and adoption of AI-based ocular imaging in healthcare settings combining advanced machine learning and deep learning techniques with new developments. Multiple studies were reviewed and evaluated, including AI-based algorithms, retinal images, fundus and optic nerve head (ONH) photographs, and extensive expert reviews. In these studies, carried out in various countries and laboratories of the world, it is seen those complex diagnoses, which can be detected systemic diseases from ophthalmological images, can be made much faster and with higher predictability, accuracy, sensitivity, and specificity, in addition to ophthalmological diseases, by comparing large numbers of images and teaching them to the computer. It is now clear that it can be taken advantage of AI to achieve diagnostic certainty. Collaboration between the fields of medicine and engineering foresees promising advances in improving the predictive accuracy and precision of future medical diagnoses achieved by training machines with this information. However, it is important to keep in mind that each new development requires new additions or updates to various social, psychological, ethical, and legal regulations.

Keywords

Artificial intelligence, ophthalmology, machine learning, deep learning, computer-aided diagnosis, algorithm

Introduction

With the incorporation of artificial intelligence (AI) into clinical practice, healthcare professionals get ready to face innovations. The U.S. Food and Drug Administration first approved an AI diagnostic device in 2018 that doesn't require a specialist doctor to interpret the results. The software program, called IDx-DR, was able to detect a type of eye disease by looking at retinal photos. After this event, the field that AI started to cover in ophthalmology began to expand rapidly [1].

AI has become one of the most influential information technology revolutions of our time. The field of AI is essentially the use of machines to perform tasks that typically require human intelligence. It encompasses machine learning (ML), where machines can learn by experience and acquire skills without human intervention [deep learning (DL)]. AI enables a technical system of human-like behavior that consists of retrieving, interpreting, and learning from data before achieving a specific goal. Among the methods of AI, the intricacies of ML and DL come first [2, 3].

DL is a state-of-the-art ML technique in the last few years that has had a great impact all over the world. DL uses representation-learning methods with multiple levels of abstraction to process input data without the need for manual feature engineering and automatically recognizes complex structures in high-dimensional data by projecting them onto a lower-dimensional manifold [4]. Compared to traditional techniques, DL has been shown to achieve significantly higher accuracies in many areas, including natural language processing, computer vision [3–5], and voice recognition [6].

This study will review the current roles of AI applications in ophthalmology.

Core components in AI system

Most ophthalmologists and clinicians unrelated to computer science can become overwhelmed with AI work because of the complex technical terminology. Not all AI readers need to fully understand all technical architecture or mathematical formulas. However, it is important to evaluate the essential components of AI systems required for clinical translation. An AI system consists of 2 phases: (1) training and validation, and (2) testing. Training and validation in the AI system require 2 main components: (1) a training dataset of images and clinical data, and (2) the selection of a technical network [7, 8]. Without regard to splitting the training and validation datasets into their components, it's more important to have enough robust and preferably several independent test datasets [9, 10].

ML and DL techniques

In AI studies, there are several technical methods to develop and train an algorithm, it largely depends on the question of the research and training dataset type. In general, the training dataset is based on only clinical data, images, or multimodal models. Many research groups have used conventional methods of ML and statistical methods to analyze clinical data [9]. These conventional methods seem adequate to build robust predictive algorithms to train the model. A newer method, DL, can be adopted for predictive and longitudinal clinical problems with temporal sequence [11]. On the other hand, for image-based training data [optical coherent tomography (OCT) or fundus photographs], the most preferred technique is DL by far because of its ingenerate diagnostic capability. Readers can encounter DL algorithms named convolutional neural networks (CNNs) made up of neuron-like quantitative layers that could have various numbers of layers. In addition, a technique known as transfer learning has been used to increase the performance of diagnosis. In this method, CNNs are usually pre-trained via the ImageNet database (a database containing millions of photos, such as animals, cars, etc.) before applying them to a particular dataset [9].

ML and DL in ophthalmology

The field of ophthalmology is well-placed to tap into the power of AI [12]. A subset of ML, DL consists of a network of interconnected algorithms called neural networks. These networks allow "filtered learning" from large datasets crossing multiple layers of algorithms to automatically extract features. The goal is to closely align the classification or regression outputs with the target output provided by the training set [13]. In ophthalmology, AI algorithms have been developed for the detection of diabetic retinopathy (DR) [14], glaucoma [15], age-related macular degeneration [16], and retinopathy of prematurity [17]. There have been many recent studies on the diagnosis, prognosis, and post-treatment predictions of the mentioned diseases.

Ahn et al. [18] obtained a total of 1,542 photos (786 normal controls, 467 advanced glaucoma, and 289 early glaucoma patients) by fundus photography. Datasets were used to construct simple logistic classification and convolutional neural networks using TensorFlow. The same datasets were used to fine tune pre-trained GoogleNet Inception v3 model. The convolutional neural network achieved accuracy and area under the receiver operating characteristic curve (AUROC) of 92.2% and 0.98 on the training data, 88.6% and 0.95 on the validation data, and 87.9% and 0.94 on the test data. Transfer-learned GoogleNet Inception v3 model achieved accuracy and AUROC of 99.7% and 0.99 on training data, 87.7% and 0.95 on validation data, and 84.5% and 0.93 on test data. The ML algorithm was able to accurately identify both advanced and early glaucoma using fundus photos alone. Compared to previously published models, their new model—which is trained using a convolutional neural network—was more effective at diagnosing early glaucoma.

In the field of ophthalmology, especially in diseases that cause blindness and diseases with a high incidence, AI-assisted medical scanning, and image-based diagnosis emerge in various sub-branches. AI combined with medicine can make the physician’s job more precise and effective.

AI for identifying DR

Ryu et al. [19] developed a fully automated classification algorithm to diagnose DR and determine referral status using OCT angiography (OCTA) images with a CNN model and validated its feasibility by comparing its performance to a traditional ML model. In their study, they presented an end-to-end deep CNN-based method for classifying DR severity automatically from OCTA images. Baseline facts for classifications were based on ultra-wide-field fluorescent angiography to improve the accuracy of data description. The proposed CNN classifier achieved 91–98% accuracy, 86–97% sensitivity, 94–99% specificity, and 0.919–0.976 area under the curve (AUC). In external validation, overall similar performances were also obtained. The results were similar regardless of the size and depth of the OCTA images; this indicates that DR can be satisfactorily classified even with images containing a narrow area of the macular region and a single image plate of the retina. CNN-based classification using OCTA is expected to create a new diagnostic workflow for DR detection and referral. This study demonstrates the idea that the high accuracy, sensitivity, and specificity rates shown in previous studies [20, 21] can be advanced by using new modalities and programs.

Early diagnosis of DR can provide rapid treatment that effectively prevents irreversible vision loss. For this reason, as a precautionary measure, the American Diabetes Association and the American Academy of Ophthalmology recommended that patients with diabetes who do not yet have retinopathy in their eyes should undergo a fundus examination once a year. For patients who have developed retinopathy with intraretinal bleeding or another complication (e.g., diabetic macular edema), follow-up visits are required at more frequent intervals, such as every 1 to 6 months, depending on the severity of the disease [22].

The results of the study by Wongchaisuwat et al. [23] suggest that “Patients will be evaluated early and treated quickly before the disease progresses to irreversible blindness. DL models have confirmed their clinical efficacy in screening for referrable DR and improving visual outcomes.”

Prediction of postoperative visual acuity after vitrectomy using DL-based AI

Macular holes (MHs) are vertical full-thickness defects of the neurosensorial retina in the fovea. Various factors have been shown to affect the visual acuity (VA) after the operation, namely the patient’s age, size of the MH, duration of the symptoms, pre-operative VA, and vascular density of the fovea [24]. In clinical practice, pre-operative VA is an indicative factor for prognosis, often considered the strongest predictor of postoperative VA [25]. However, only the pre-operative VA is not sufficient for the prediction of postoperative VA.

Obata et al. [26] constructed a model for the estimation of postoperative VA from preoperative OCT images using DL-based AI and compared the results with predictions made using a sequential multinomial logistic regression model based on pre-operative VA and pre-operative factors. The methods of DL-based AI indicated a little bit better accuracy but better correlation with actual post-operative VA than the postoperative VA estimating based on pre-operative VA alone. Moreover, DL-based AI methods indicated a little bit better accuracy but better correlation with actual post-operative VA than the estimation of postoperative VA using a multivariate linear regression model or an ordinal multinomial logistic regression.

The results of this study can be considered important because it not only supports the success of AI in the correct identification of diseases, but also inspires the prediction of post-treatment outcomes.

Advances in imaging pathologic myopia using AI

One of the causes of permanent visual impairment is pathological myopia. There has been a great increase in the prevalence of myopia in the world in recent years. This is a sign that the incidence of pathological myopia will increase in the future. Therefore, it has become important to be able to predict the progression of myopia more accurately in order to detect pathological changes early and to provide early intervention when necessary. For these reasons, imaging of myopic eyes becomes a priority.

Significant advances have been made recently in OCT techniques. Thus, it contributed to improving clinical management and phenotyping determinations and renewing the grading system for maculopathy in myopia and traction maculopathy in pathological myopia. The ability to perform wide-field fundus and OCT imaging has made significant progress in detecting posterior staphyloma. Non-invasive OCTA provided a more in-depth visualization of choroidal neovascularization in myopia [27].

Among the globally increasing myopic human population, DL algorithms are effective for the classification and screening of high-risk myopia and for detecting macular degeneration in myopic people. To this end, the blockchain platform can act as a reliable platform for the performance testing of AI models among future medical applications [28].

AI has made very useful contributions to the detection of pathological myopia and the identification of myopia-related complications. Imaging capability has advanced with the help of assistive AI analytics. Thus, it can provide important developments in monitoring the progress of pathological myopia and using it as a guide in treatment. In a review by Li et al. [29], the classification of pathological myopia, the detection and clinical evaluation of myopia-related complications by imaging, and how imaging improves management were tried to be presented in detail.

Thus, a broad update was provided on the development of AI algorithms for pathological myopia detection, classification, and clinical evaluation of myopia-related complications.

Automatic detection of glaucoma via fundus imaging and AI

One of the irreversible visual impairments worldwide is glaucoma. Cases of glaucoma are on the rise worldwide. Visual loss can be prevented if timely treatment and intervention can be made. Therefore, early diagnosis is extremely important. Diagnosis provided through the analysis of medical images using a computer is known as computer-aided diagnosis (CAD). In the past years, various techniques have been proposed to develop an effective CAD system for glaucoma detection. The CAD system can assist the ophthalmologist in batch screening of glaucoma. They outlined the lessons that can be drawn from existing approaches using segmentation, non-segmentation, and classification methods through studies conducted at many research centers around the world and the limitations that need to be addressed to develop a robust CAD for glaucoma detection [30].

In order to detect glaucoma promptly, it is important to evaluate the optic nerve head (ONH) and optic disc margins. Fundus oculi imaging is a non-invasive, low-cost but very important examination. Image review is a subjective assessment most of the time. It is therefore based on time-consuming and costly expert evaluations [31].

This is exactly why it is an important question whether AI can imitate glaucoma assessments made by experts by AI. That is, can AI automatically find the boundaries of the ONH and disc like an expert? Can it then use the segmented image to identify glaucoma with high accuracy?

Glaucoma detection by a clinician

Structural changes with slow but progressive narrowing of the neuroretinal margin, signaling degeneration of ganglion cell axons of the retina and astrocytes of the optic nerve [32]. The clinician determines the narrowing of the neuro-retinal border by evaluating the optic disc cupping and the border contours of the disc. These determinations help explain the rationale of the diagnosis made to the patient afterward. Thus, it allows the patient to participate in the discussion of his or her condition and treatment decisions.

Detecting glaucoma via AI

The use of telemedicine in glaucoma was reviewed in a recent review [33] due to the coronavirus disease 2019 (COVID-19) pandemic. As a result of this study, it was emphasized that this type of machine which is operated by less experienced personnel can also give objective results. Another study confirmed that a DL algorithm could be useful to automatically screen for glaucoma via smartphone-based fundus photos. This algorithm showed a high diagnosis ability, especially in the eyes of advanced glaucoma patients [34].

Thus, a computer-based diagnostic system using image processing algorithms has been implemented to screen large populations for glaucoma disease at less cost, reducing human error and thus making the diagnosis more objective.

AI helps anterior segment diseases of the eye

AI in medicine has the potential to help with the early detection, quantification, and monitoring of diseases affecting the anterior segment of the eye, including microbial keratitis, keratoconus (KCN), dry eye syndrome (DES), and Fuchs endothelial dystrophy (FED). To identify and categorize different forms of microbial keratitis as well as to quantify characteristics related to microbial keratitis, algorithms have been developed.

Numerous advancements have been made in the identification, division, and quantification of traits associated with FED and DES. Studies examining the application of AI in the screening, diagnosis, staging, or treatment of corneal conditions, with a focus on conditions like microbial keratitis, KCN, DES, and issues like meibomian gland dysfunction (MGD) and FED [35].

Detection of microbial keratitis

A recent study [36] has focused on the primary detection of microbial keratitis and the distinction of microbial keratitis from other diseases and normal eyes. The study used slit lamp photography (SLP) and smartphone photography to detect keratitis from normal eyes with high performance. SLP and smartphone photography were used to detect keratitis using pre-existing CNN software. The best model recognized microbial keratitis from normal eyes and other corneal diseases with an AUC of 0.998 [36].

Detection of KCN

Several investigations have been conducted to detect KCN, forme fruste KCN (ffKCN), and normal eyes. Most studies used corneal tomography images to train models, with encouraging results. Al-Timemy et al. [37] constructed a hybrid-CNN DL model to recognize characteristics, which they subsequently utilized to train a support vector machine (SVM) to detect KCN. Two investigations utilized CNN models to correctly distinguish normal, ffKCN, and KCN eyes (99% [38], 95% [39]), while another successfully recognized KCN from normal and post-refractive eyes (99% [40]). Given the clinical need to detect progression early so that surgical therapies can be offered, some research focused exclusively on detecting ffKCN. Furthermore, feature detection was done; the models identified ffKCN patterns such as asymmetric bowtie, inferior steepening, and the existence of a center cone.

Another group used baseline OCT data to train an unsupervised ML model to predict the need for keratoplasty and published the normalized likelihoods of receiving various types of transplants; however, algorithm performance was not reported. AI may be able to help clinicians decide when to intervene for KCN [41].

Quantifying DES features via AI

A recent paper [42] describes CNN models based on SLP for detecting and quantifying surface keratopathy. Su et al. [42] developed a model that automatically measured and staged keratopathy in DES patients and found it to be 97% accurate in detecting keratopathy.

With promising findings, many recent AI approaches have focused on quantifying MGD features by training models based on meibography pictures using both machine [43] and deep [44–46] learning methods.

Detection of FED

Eleiwa et al. [47] used AI-OCT images to train a CNN model to detect cases without clinically visible corneal edema (termed early-FED) and showed great performance in discriminating early-FED, late-FED, and normal corneas (AUCs > 0.97, sensitivities and specificities > 91%). This study detects subclinical corneal edema in FED patients using a DL algorithm trained on anterior segment OCT images. The model achieved high accuracy in differentiating early-FED, late-FED, and normal corneas.

Shilpashree et al. [48] successfully trained a CNN model to segregate endothelial cell density, coefficient of variation, and proportion of guttae (AUROC 140.967, accuracy 1,488%). The researchers used specular microscopy pictures to train a CNN model to segment critical aspects of FED such as endothelial cell density, coefficient of variation, and percentage of guttae with excellent accuracy.

AI applications and cataract management

AI-based software has various uses in all aspects of cataract management, including diagnosis, prognosis, and planning in the field of cataract surgery complications and follow-up.

Based on slit lamp image processing, Li and colleagues [49] developed a computer-aided approach for the diagnosis of nuclear cataracts. They achieved 95% and 96.9% success rates in lens structure recognition and localization, respectively.

The SVM-based CAD program created by Mahesh Kumar and coworkers [50] had high values of sensitivity (97%), specificity (99%), and predicted accuracy (96.96%).

Despite the use of checklists, the danger of medical errors, such as wrong-site procedures, exists, particularly in high-volume settings and in the presence of concomitant co-morbidities. Yoo and colleagues [51] assigned a deep-learning-based smart speaker to corroborate surgical information in ocular surgery, including age-related cataract surgery, particularly during the time-out period.

Artificial models and neural networks have also been used to improve patient care in terms of diagnosis, prognosis, and planning in the field of cataract surgery complications. Antibiotic injection into the anterior chamber is thought to be an effective method for lowering the risk of postoperative endophthalmitis. Despite the use of antibiotics intraoperatively, the development of a posterior capsular rupture is a well-known risk factor for postoperative endophthalmitis after cataract surgery [52, 53].

Before they can be used in the real world, these AI algorithms must be tested in randomized trials to determine their safety, cost-effectiveness, and efficacy in clinical contexts.

AI helps neuro-ophthalmology practice

The visual system extends from the eyes to the most posterior parts of the brain (occipital cortex). As a result, intracranial pathologies often lead to visual disturbances, prompting patients to consult an ophthalmologist. Neuro-ophthalmology is an integrative medical discipline that includes the study of pathologies along the visual pathway. The most common neuro-ophthalmic conditions are:

(1) Those affecting the afferent system: conditions affecting the afferent visual system lead to various visual dysfunctions.

(2) Affecting the efferent system: These are conditions that cause central ocular-motor disorders, ocular-motor cranial neuropathies, gaze instability, and pupillary disorders in addition to systemic dysfunctions affecting the neuromuscular junction or extraocular muscles [1].

Papilledema, pseudopapilledema, and other ONH abnormalities

Akbar et al. [54] developed an automated system to detect papilledema from healthy ONH images using classical ML and graded its severity as "mild to severe" using 160 retrospectively collected fundus photographs. Four feature classes (textural, color, disc dimming, and vascular) were extracted from ONH photographs and then processed through an SVM classifier and radial basis function kernel. This system provided 92.9% and 97.9% accuracy for the detection and grading of papilledema, respectively.

The high accuracy of Akbar's supervised ML algorithm for papilledema detection is further advanced than the previous findings of Fatima et al. [55], which explored combinations of the same 4 features above and achieved an accuracy of 87.8% for papilledema detection using a supervised SVM classifier.

Other studies using different combinations of ONH feature extraction and ML algorithms showed a good fit for papilledema grading by a specialist neuro-ophthalmologist (Kappa score, 0.71) and comparing ONH volume with OCT values (Pearson correlation coefficient, $r = 0.77$) [56].

Ahn et al. [57] developed a model using AI to differentiate optic neuropathies from pseudo papilledema (PPE). In their models, 295 images of optic neuropathies, 295 PPE images, and 779 control images were used. Four ML classifiers and 50-layer Deep Relic Learning (ResNet) were compared. The accuracy and the AUROC were analyzed [57]. The accuracy of the ML classifiers ranged from 95.89% to 98.63%. A high AUROC score was recorded on both ResNet and 19-layer Very Deep Convolution Network from Visual Geometry group (VGG, 0.999). It was concluded that ML techniques could be combined with fundus photography as an effective approach to differentiate PPE from high optic discs associated with optic neuropathy.

Optic disc pallor

In addition to the swollen appearance, ONH may appear pale and/or atrophic in patients with chronic optic neuropathy. Unlike ONH swelling, ONH pallor has no severity grading and no standard diagnosis. Even among partially trained ophthalmologists, criteria are difficult to establish because of the subjective nature of ONH assessment [58] and anatomical differences between patients (pseudophakia, physiological temporal pallor, peripapillary atrophy, and oblique disc). Yang et al. [59] developed a CAD system to detect ONH wilt using color fundus photographs using the classical ML method. This system achieved 96.1% accuracy, 95.3% sensitivity, and 96.7% specificity in detecting ONH pallor from normal discs in color fundus photographs.

Brain and optic nerve study with AI

The brain and optic nerve study with AI (BONSAI) consortium was carried out in 2019 in a major collaborative effort at 24 ophthalmology centers in 15 countries which led to the development of a DL system (DLS) capable of classifying papilledema and other ONH abnormalities [60]. Consisting of segmentation (U-Net) and classification (DenseNet) networks, DLS was trained to classify ONHs into 3 classes: (1) normal, (2) papilledema, and (3) other ONH abnormalities using a dataset of 14,341 mydriatic fundus photographs retrospectively collected from 6,779 patients of various ethnicities from 19 centers worldwide. The training dataset consisted of 9,156 normal ONH, 2,148 papilledema, and 3,037 ONH images with other abnormalities. Next, the classification performance of DLS was evaluated on an external test dataset of 1,505 photographs from 5 other independent centers. BONSAI-DLS, the AUC 0.96 [95% confidence interval (CI): 0.95–0.97], sensitivity 96.4% (95% CI: 93.9–98.3) and 84%, specificity (95% CI: 82.3–87.1). BONSAI-DLS was also able to reveal features of normal discs and other abnormalities (e.g., optic disc atrophy, non-arteritic ischemic optic neuropathy, optic disc drusen, etc.) with high specificity.

ML at ocular myasthenia gravis

Ocular myasthenia gravis (OMG) is a subgroup of myasthenia gravis that specifically affects the extraocular and eyelid muscles. Myasthenia gravis is the most common primary disorder of neuromuscular transmission. Acetylcholine receptor (AChR) antibodies are detected in the serum of more than 80–90% of patients with generalized myasthenia gravis, about 50% with purely ocular myasthenia, and rarely in healthy people [61]. Affected patients are typically present with variable, fatigable ptosis and/or ophthalmoplegia. The diagnosis of OMG in the clinical setting can be difficult, and there is no single test that can diagnose absolute myasthenia [62].

Liu et al. [63] developed a CAD system that uses facial images and video of OMG patients' extraocular movements and eyelid positions taken during surgery. To aid in OMG diagnosis, the neostigmine test, and image segmentation software called OMG-net was developed by the team and MobileNet served as the backbone of the encoder-decoder network. The program was able to successfully determine the parameters of the globe and eyelid positions (palpebral aperture, scleral distance) compared with the manual measurement results of the doctors. Although this work potentially serves as a platform from which more complex algorithms can be built, the authors acknowledged that image segmentation in this model could be improved.

Detection of eye movement disorders

The ocular deviation in infantile and acquired strabismus observed in children and adults may be associated with muscle restriction, lack of convergence or divergence, or refractive errors. Ocular misalignment can be detected clinically with the Hirschberg test and Krimsky test, among other methods, and the gold standard is the prism covering test (PCT). Eye movements are affected by cortical control, subcortical centers, premotor coordination of conjugated eye movements, ocular motor cranial nerves (especially cranial nerves III, IV, and VI), and extraocular muscles. This comprehensive system aims to create stable binocular single vision. Any damage to the ocular motor pathways can lead to ocular misalignment, concomitant gaze abnormalities, or abnormal involuntary oscillating movements of the eyes called nystagmus [64].

Strabismus and conjugate gaze abnormalities

Detection of ocular misalignment or strabismus using AI has been described in technical studies predominantly using patient photographs of eye movement [65], videos of lid tests [66], retinal birefringence scanning [67], or PCT measurements [68]. Face photos, different AI techniques have also been used to detect strabismus. Sousa de Almeida et al. [69] proposed a CAD to detect and diagnose strabismus based on the Hirschberg reflex in clinical photographs of 40 adult patients in 5 gaze positions (primary, upward gaze, down gaze, left gaze, and right gaze). Five steps were used: segmentation of the face, detection of the eye region, the position of the eyes, the position of the limbus and brightness, and finally the diagnosis of strabismus based on the distance of the corneal center to the light reflex. The accuracy of detecting ocular misalignment was 100% in exotropia, 88% in esotropia, 80% in hypertropia, and 83% in hypotropia.

de Figueiredo et al. [70] used a DL algorithm to objectively classify eye versions from adult face photos via a mobile application. The model was first trained in 9 gaze positions and processed through ResNet-50 as the neural network architecture. The application achieved an accuracy ranging from 42% to 92% and an accuracy ranging from 28% to 84%, depending on the type of eye version.

Recently, Zheng et al. [71] also developed a DL approach to screen for steerable horizontal strabismus in children based on primary gaze photographs. A total of 7,026 images were used to train the model and 277 images from an independent dataset were tested. The algorithm achieved an accuracy of 95%, outperforming established ophthalmologists.

In an attempt to promote automated self-scanning, in 2018 Lu et al. [72] developed a deep neural network for the detection of strabismus in a telemedicine setting using self-made eye photos of patients. It achieved 93.9% accuracy, 93.3% sensitivity, and 96.2% specificity for detecting strabismus.

A study by Yang et al. [73] used an infrared camera with a special shutter that blocks the subject's vision and all visible light, but selectively transmits infrared light, to measure horizontal deviations of esotropia and exotropia in children and adults. In this program, a strong positive correlation ($r = 0.90$, $P < 0.001$) was obtained with manual PCT measurements performed by 2 independent ophthalmologists.

Localization of central nervous system lesions

Extraocular movement abnormalities can be used to localize central nervous system lesions [74]. In the study of Viikki et al. [75], decision tree induction was used to model the relationships between oculomotor test parameters of conjugated eye movements and lesion location in patients with operated cerebellopontine angle tumor, operated hemangioblastoma, and cerebellum-brainstem infarction. Meniere's disease and control subjects' ocular motor assessment included random follow-up eye movements and saccadic eye movements recorded by electrooculography with skin electrodes. When patients were divided into 3 classes (control, central lesion, and peripheral lesion), the program gave an average classification accuracy of 91%. When using 5 classes (control subject, brainstem lesion, cerebellar lesion, cerebellum-brainstem lesion, and peripheral lesion) the classification accuracy was 88%.

Nystagmus

Nystagmus may be congenital or acquired and may result from central nervous system pathologies, peripheral vestibular disease, or severe vision loss. A wide variety of nystagmus waveform types have been described in the clinical literature, and features of nystagmus may occasionally point to the etiology of the condition [76].

In nystagmus, especially in young children, it is extremely difficult to obtain images to document eye position and movements. D'Addio et al. [77] designed a predictive model based on 2 algorithms to investigate the relationship between different parameters of congenital nystagmus: 1) random forest and 2) logistic regression tree. Electro-oculography of 20 patients (adults and children) was recorded and signals were extracted using custom-made software. The model was able to predict VA and eye positioning variability with the coefficient of determination values of 0.70 and 0.73, respectively. This study could potentially serve as a framework for investigating other types of nystagmus.

The use of AI for the detection and diagnosis of ocular misalignment or conjugated gaze abnormalities is promising for applications in both pediatric ophthalmology and neuro-ophthalmology. However, larger studies potentially using publicly available datasets with solid ground truth are needed before an application in clinical practice or telemedicine programs.

Additional applications for AI in conditions with neuro-ophthalmology

Although not directly seen in a neuro-ophthalmology clinic, various diseases such as neurodegenerative, neurodevelopmental, trauma, etc. can show ocular symptoms. In such cases, ML techniques have been considered in the parameters of view for neurodegenerative [78] [e.g., Parkinson's disease (PD), and Alzheimer's disease (AD)] and neuro-psychiatric diseases [79]. DL techniques related to pupillometry have been used in the investigation of psychiatric and neurodevelopmental disorders. Moreover, visually evoked potential (VEP) responses taken during intracranial surgery, particularly in the sellar region, can be automatically evaluated by neural network algorithms, directing real-time monitoring during surgical removal [80].

Detecting systemic diseases using AI from ocular images

Since the 20th century, research has used color fundus photography (CFP) as a standard screening technique for retinal diseases. AI-based on ophthalmological images has the potential to diagnose some systemic diseases. In this way, it has been shown that chronic kidney diseases (CKDs) can be detected in the early stages [81]. Large amounts of fundus photos give a possibility to assess predicting models, and the recent development of smartphone-based and handheld CFP cameras enhanced the utility of CFP [82]. However, the traditional use of information from CFP images through subjective judgments or simple statistics made by the human eye is limited compared to the use of AI. AI offers opportunities to supply key features from retinal images with ML and DL algorithms. This worthy information can be used as a chooser via heatmaps according to retinal specialists' interests [83].

However, more research is needed to validate these models for real-world application. With the increasing number of relationships found between the eye and other body systems, it would be useful to explore the possibility of a universal scanning tool using ocular images.

Studies using other ocular images

The OCTA studies have discovered additional underlying issues in the small blood vessels of the retina and choroid in individuals with cardiovascular disease (CVD). In patients with coronary artery disease, the density of both the superficial and deep capillary networks in the central area of the retina and the capillaries in the choroid was found to be reduced. This decrease was associated with Gensini scores and aligned with the risk assessment system of the American Heart Association (AHA) [84]. In their research, Zhong et al. [85] went further in exploring the diagnostic value of OCTA images in assessing coronary artery disease occurrence, along with combining electrocardiogram findings and clinical OCTA parameters using a technique called least absolute shrinkage and selection operator (LASSO) regression.

However, choroidal, and retinal vessel densities have been plucked down in hypertension [86, 87] stroke, degenerative nerve diseases, and diabetes [88]. CVD can be identified by the distinct pattern of neurovascular changes on the retina [89].

For these reasons, the specificity of retinal microvascular change alone is limited. On the other hand, OCT studies have found that retinal neural damage is mediated by microvascular thinning [90]. However, additional studies are required to prove that OCTA is specific in accurately identifying CVDs.

Detection of central nervous system diseases

In addition to cerebrovascular diseases, degenerative neural conditions like AD, PD, and dementia are also associated with changes in the retinal neurovasculature. These changes involve the loss of retinal ganglion cells (RGC) and thinning of retinal layers due to the accumulation of amyloid-beta protein in AD patients, as evidenced by various OCT studies. Moreover, research has indicated that degenerative neural disorders, including AD or non-AD dementia, PD, and mild cognitive impairment, lead to a decrease in photoreceptors in the outer retina as well [91]. Given the relatively quick and repeatable nature of ocular examinations, ocular images can be valuable in detecting degenerative neural diseases such as AD and cognitive impairment during routine health check-ups [92].

There has been a notable increase in the number of children being diagnosed with autism spectrum disorder (ASD) in recent years. One of the most pressing challenges related to ASD is the lack of an objective screening method that would enable earlier intervention, ultimately improving the individual's quality of life [93]. Recent discoveries regarding the variation in retinal nerve fiber layer (RNFL) thickness between high-functioning ASD individuals and those with other forms of ASD have provided new insights into distinct patterns of neural structural development [94]. As a result, researchers have developed a DL model based on OCT images to extract features from images, which, when combined with automatically generated features from automatic retinal image analysis (ARIA), can predict ASD. The model's performance, assessed through 10-fold cross-validation, achieved a sensitivity of 95.7% and a specificity of 91.3% [95]. In comparison to the lengthy observation periods typically required for ASD diagnosis, AI-enhanced ocular imaging offers a promising approach for early ASD screening in a patient's early years.

Detection of endocrinological disorder

In addition to DR, another significant complication of diabetes is diabetic peripheral neuropathy (DPN), which can lead to disabilities such as diabetic foot ulcers and amputations in diabetic patients [96]. DPN tends to occur concurrently with the progression of DR and is closely associated with different stages of DR [97].

These results highlighted the superiority of DL algorithms over traditional ML models. Further clinical trials should be conducted to investigate whether AI based on ocular imaging can serve as an additional diagnostic tool for DPN.

Detection of kidney diseases and renal function

The impaired kidney function in individuals with CKD also has an impact on the structures of the macula, leading to the accumulation of intraretinal vascular leakage and the development of macular edema [98].

In OCTA studies, it has been observed that there is a reduction in retinal and choroidal microvascular density and an increase in macular thickness correlated with elevated urine albumin/creatinine ratio (UACR), which is a risk factor for endothelial dysfunction (ED) [99].

These findings suggest that ocular image-based AI has the potential to play a role in monitoring CKD patients, starting from the early stages of the disease and progressing to end-stage CKD. By leveraging retinal images and employing DL algorithms, healthcare providers may be able to enhance their ability to detect and manage CKD, offering a non-invasive and potentially more efficient approach to patient monitoring.

Detection of hematological diseases

Anemia is known to cause hypoxia in the eye, resulting in various ocular manifestations such as increased venous tortuosity, chronic inflammation, and the development of extravascular lesions like hemorrhages, exudates, and cotton-wool spots. Previous studies have primarily utilized images of the eyelid conjunctiva to predict anemia, but these images are scarce and rely on subjective judgments.

Recent studies utilizing OCT and OCTA have revealed that children with iron deficiency anemia (IDA) exhibit significantly lower retinal vessel density and lighter reflectance of the vessels on OCT images [100]. Building upon these findings, a study utilized a ML algorithm to extract texture features from OCT images to classify anemia [101]. This approach showed promising results.

Detection of hepatobiliary disease

Hepatobiliary diseases, including hepatitis B virus, hepatitis C virus, obesity, and type 2 diabetes mellitus (T2DM), remain a significant public health concern. Screening for these conditions is crucial, and ocular signs have been observed in various hepatobiliary diseases [102]. Examples include the presence of a Kayser-Fleischer ring in Wilson disease and the yellowing of the sclera during hyperbilirubinemia. These ocular manifestations indicate that retinal images can provide valuable insights into the impact of hepatobiliary diseases on macro and microvasculature and neural tissue.

Zhang et al. [103] developed a multitask DL model to predict total bilirubin (T-BIL) and direct bilirubin (D-BIL) levels using CFP images. Xiao et al. [104] constructed six DL models based on ResNet-101 architecture, utilizing slit-lamp external eye images and CFP images to screen for six major hepatobiliary diseases.

The conjunctiva was identified as the most prominent area in the image input, as it exhibited pathological changes like jaundice and telangiectasis, which are characteristic of hepatobiliary diseases.

Future directions

By integrating prior clinical knowledge with ocular image data in the ML models, it is possible to enhance the transparency and interpretability of the AI models. This approach can provide insights into how the models arrive at their predictions. It also helps establish a clearer understanding of the correlations between ocular characteristics and systemic diseases. Enhancing AI model transparency fosters trust and reliability in clinical settings, reducing reporting bias and correlation errors.

A major concern that should be raised is the lack of explainability in AI models, especially when they are applied to systemic diseases for which correlation with retinal features may not have been established through clinical trials. To address this issue, a combination of previous clinical knowledge and ocular image data can be leveraged using ML methodologies such as the deep regressor model [105].

Neuro-ophthalmologic studies benefit significantly from AI systems. These systems are valuable for screening and characterizing ONH structure and function and, to a lesser extent, certain eye movement disorders. These systems automate complex diagnostic procedures, ensuring timely and accurate results. They are particularly valuable in neuro-ophthalmological conditions, where ocular dysfunctions may signal underlying life-threatening or systemic diseases. Today, there's a growing need for prospective, multicenter studies to assess the practical value of AI systems in both neuro-ophthalmic and non-neuro-ophthalmic settings, where experts may face readiness challenges. Furthermore, there's a growing emphasis on DL-guided quality assessment of retinal images to minimize non-diagnostic datasets. This is an even more important consideration in neuro-ophthalmology, where data are scarce [106]. In the long term, ophthalmologists may leverage personalized treatments through "AI-assisted prognosis and disease monitoring". This could enable more effective patient care. Simultaneously, non-ophthalmologists may benefit from AI-powered ocular exams, facilitating the automatic detection of neurological and systemic conditions.

It is imperative to continue developing methodologies that prioritize explainability in AI models. This ensures that insights derived from ocular imaging are interpretable and can be effectively integrated into clinical decision-making. Such transparency is crucial for the broader acceptance and adoption of AI-based ocular imaging in healthcare settings. A critical point to emphasize is the need for generalizability in predictive models for systemic diseases. While internal validation methods are valuable for proof-of-concept and initial AI implementation studies, they may not suffice for real-world deployment. To establish the robustness and viability of these models, external validation datasets comprising diverse and representative real-world data are essential. External validation datasets offer a more accurate representation of societal demographics, accounting for variations in race and ethnicity. These factors can significantly impact the performance of prediction models. For instance, retinal pigmentation varies among different populations, such as Asians and Europeans, with observable differences in the loss of retinal pigment cells and rod photoreceptors as individuals age [107]. This implies that age prediction models trained on a population with less retinal pigmentation may have lower performance when applied to a population with more retinal pigmentation.

To enhance the generalizability of AI models for systemic diseases, future studies should prioritize training datasets that exhibit greater biodiversity and closer resemblance to the intended validation datasets. This approach helps ensure that the models can perform effectively across diverse populations and minimizes biases associated with specific demographics. By incorporating a wider range of demographic characteristics and variations into the training data, the models are more likely to achieve superior generalizability. As a result, they can reliably produce predictions when applied to real-world scenarios.

While the potential of AI to enhance medical practice is promising, there is limited research on its influence on the relationship between healthcare providers and patients. From a psychosocial perspective, emerging technologies have the potential to reshape the dynamics between clinicians and patients in several ways. The integration of AI into healthcare settings is revolutionizing the delivery of care to patients. AI-generated information regarding diagnosis, treatment, and medications is increasingly guiding decisions across the entire healthcare spectrum. This includes choices related to treatment options, lifestyle changes, disclosure of health information to family members, and even the communication of unfortunate news.

As AI is poised to play a significant role in medical practice in the foreseeable future, it becomes crucial to comprehend its influence on shared decision-making and the overall patient-doctor relationship. In many healthcare systems worldwide, patients have the right to be informed about the tools, resources, and approaches employed to address their medical conditions. Patients will increasingly need to be aware that their diagnosis or medical prescriptions may originate from a machine, complementing the expertise and efforts of human doctors [108]. While the field of medicine inherently embraces innovation and technology, it's noteworthy that certain healthcare professionals hold reservations about technology in patient care. Their concerns primarily stem from the perceived risk of dehumanizing patients and the fear that unfamiliar tools may be used against them in medical controversies [109].

The data clearly demonstrate that the process of technological innovation in the healthcare field is rarely seamless, even when dealing with technologies different from AI. While the benefits of AI and ML devices in improving the technical aspects of medicine, such as diagnostic accuracy, are evident, their influence on the patient-doctor relationship remains largely uncharted. It is presumed that the mere awareness of the presence of a "machine" in the healthcare process could influence the attitudes of both doctors and patients. From a psychological perspective, attitudes towards something can develop even before direct experience with it.

Conclusions

When considering the integration of AI into the diagnosis and treatment identification process, it becomes conceivable that the concept of "shared decision-making" should evolve to incorporate the contributions of artificial entities. AI will no longer be viewed as just another "app" on doctors' devices; it will be seen as an active interlocutor capable of providing diagnoses, prognoses, and intervention recommendations to both doctors and patients. The implementation of AI in healthcare holds significant potential for positive effects, contingent upon the attitudes of doctors. For instance, if AI were to handle administrative and technical tasks in medicine, doctors would gain the opportunity to reclaim valuable time for consultation and empathetic listening to their patients, thus enhancing shared decision-making [108]. In this context, AI would serve as an active intermediary between healthcare providers and patients. Furthermore, patients must receive appropriate information regarding these important concepts. Many patients may not be familiar with the concept of over-diagnosis, which can make it challenging for them to assess the relative risks of unnecessary diagnosis and treatment compared to the risk of missing a cancer diagnosis. Additionally, patients may not always have clear preferences regarding these outcomes.

As AI advances through ML and DL, addressing factors like ethnicity, race, and gender remains a challenge which signifies that AI's journey is far from complete [110]. As a result, it is critical to develop algorithms that prioritize patient well-being and dignity. Such a strategy is essential for improving AI's implementation and integration in the healthcare industry. Hence, it becomes essential to define a reasonable default decision threshold for situations in which patients either choose not to express their preferences or do not have specific preferences [111].

At present, the scientific literature lacks sufficient research data to comprehensively address these questions. However, by drawing upon studies examining healthcare providers' responses to technological innovation and insights from the field of medical psychology, it can be anticipated certain social-psychological phenomena that may emerge in future healthcare scenarios. Understanding these phenomena is crucial for preparing and managing any potential undesirable side effects. These developments will not only trigger social and psychological events but also inevitable ethical and legal consequences. As such, they demand evaluation from a comprehensive perspective that encompasses these aspects. By using these assessments, it is possible to guarantee that the required preparations are completed on time [112].

Abbreviations

AD: Alzheimer's disease

AI: artificial intelligence

ASD: autism spectrum disorder

AUC: area under the curve

AUROC: area under the receiver operating characteristic curve

BONSAI: brain and optic nerve study with artificial intelligence

CAD: computer-aided diagnosis

CFP: color fundus photography

CI: confidence interval

CKDs: chronic kidney diseases

CNNs: convolutional neural networks

CVD: cardiovascular disease

DES: dry eye syndrome

DL: deep learning

DLS: deep learning system

DPN: diabetic peripheral neuropathy

DR: diabetic retinopathy

FED: Fuchs endothelial dystrophy

ffKCN: forme fruste keratoconus

KCN: keratoconus

ML: machine learning

OCT: optical coherent tomography

OCTA: optical coherent tomography angiography

OMG: ocular myasthenia gravis

ONH: optic nerve head

PCT: prism covering test

PD: Parkinson's disease

PPE: pseudo papilledema

SLP: slit lamp photography

SVM: support vector machine

VA: visual acuity

Declarations

Author contributions

KHK: Conceptualization, Investigation, Writing—original draft, Writing—review & editing, Validation, Supervision. The author read and approved the submitted version.

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The author declares that he has no conflicts of interest.

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