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Promising Artificial Intelligence-Machine Learning-Deep Learning Algorithms in Ophthalmology

Balyen L[1,2], Peto T[2]

[1]Kafkas University, Faculty of Medicine, Department of Ophthalmology, Kars, Turkey

[2]Queen's University Belfast, School of Medicine, Centre for Public Health, Institute of Clinical Science, Department of Ophthalmology, Belfast, United Kingdom

Abstract

The lifestyle of modern society has changed significantly with the emergence of artificial intelligence (AI), machine learning (ML) and deep learning (DL) technologies recently. There are many innovations concerning novel automated technologies including unmanned plane, autonomous vehicles, face and image recognition, automatic speech recognition, natural language processing, bioinformatics, military settings, drug discovery and toxicology. AI is a multi-dimensional technology with various components such as advanced algorithms, ML and DL. AI, ML, and DL are expected to provide recent automated devices to ophthalmologists for early diagnosing and treating ocular disorders in the near future. In fact, AI, ML, and DL are being used in ophthalmic setting to validate the diagnosis of diseases, read images, corneal topographic mapping, and IOL calculations. Diabetic retinopathy (DR), age-related macular degeneration (AMD), and glaucoma are the three most common causes of irreversible blindness on a global scale. Ophthalmic imaging provides a way to diagnose and objectively detect the progression of a number of pathologies including DR, AMD, glaucoma and other ophthalmic disorders. There are two methods of imaging generally used as diagnostic methods in ophthalmic practice, including fundus digital photography and optical coherence tomography (OCT). Particularly, OCT has become the most widely used practical imaging modality in ophthalmology settings across developed world. Changes in population demographics and life style, extension of average lifespan, and the changing pattern of chronic diseases, such as obesity, diabetes mellitus (DM), DR, AMD, and glaucoma create a rising demand for such images. Furthermore, the limitation of availability of retina specialists and trained human graders is a major problem in many countries. Consequently, given the current population growth trends, it is inevitable that analysing of such images is time consuming, costly, and prone to human error. Therefore, the detection and treatment of DR, AMD, glaucoma and other ophthalmic disorders will be inevitable through unmanned automated applications system in the near future. Namely, these challenges may be only resolved through unmanned automated applications of novel analysis methods without the need of ophthalmologists, retina specialists and human graders.

We therefore provide an overview of the potential effects of the current AI, ML and DL methods and their applications on the early detection and treatment of DR, AMD, glaucoma and other ophthalmic diseases.

Keywords: Artificial intelligence, machine learning, deep learning, diabetic retinopathy, age-related macular degeneration, glaucoma, ophthalmic disorders, health care service, future

1. Introduction

Population aging is increasing worldwide, so patients suffering from eye diseases are expected to increase at the same rate. Early diagnosis and appropriate treatment of ophthalmic diseases are of great importance to prevent needless visual loss and improve quality of life. However, conventional ophthalmic diagnostic methods are profoundly depend on physicians' professional experience and knowledge, leading to a high rate of misdiagnosis and wasted too much medical data. Therefore, the deep integration of ophthalmology and artificial intelligence (AI), machine learning (ML), and deep learning (DL) have the potential to revolutionize the existing disease diagnosis system and create a significant clinical effect in ophthalmic health care service.[1] The name of ML was first coined by Arthur Samuel in 1959. Arthur Samuel defined in 1959, ML is an application of AI that provides systems the ability to automatically learn and improve from experience without being explicitly programmed.[2] AI is a technique that enables computer to mimic human behaviour and it is divided into artificial narrow intelligence (ANI), artificial general intelligence (AGI), and artificial super intelligence (ASI). AI contains ML, DL, conventional machine learning (CML), natural language processing (NLP), computer vision, robotics, reasoning, general intelligence, expert system, automated learning and scheduling.[1,3]

As mentioned previously, ML is a subfield of AI technology that systematically implements algorithms to synthesize the underlying interrelation between data and information.[4] ML, the scientific discipline, is focusing on how computers learn from data and ML is also an artificial computer intelligence system that allows computers to learn automatically without programming and without human intervention or assistance. ML has become an important component of the information technology revolution affecting our daily lives for 25 years. There are great numbers of successful applications of ML, such as medicine practice, recognizing speech, handwriting, and machine translation. However, DL and CML are subfield of ML methods. DL learns underlying features in data using neural networks. DL can be supervised, semi-supervised or unsupervised learning setting, regarding with task-specific algorithms inspired by the structure and function of the human brain.[5-7]

Considering current population growth trends, the limitation of availability of retina specialists and trained human graders, manual segmentation is time consuming, costly, prone to bias, and disadvantageous in a clinical ophthalmic health care service. Therefore, the ophthalmic health care system exceptionally needs an automatic, rapid, cost-effective, yet highly sensitive and specific method to detect diabetic retinopathy (DR), age-related macular degeneration (AMD), glaucoma and other ophthalmic disorders. Unfortunately, due to numerous patients are not diagnosed in time, they lose their sight needlessly.[8-10]

It is fact that in comparison to all medicine fields, due to special structure of eye, the ophthalmology is relatively more practical application for AI, ML and DL-assisted automated screening and diagnosis and more open to high technology. Therefore, in the near future, for detecting and treatment of DR, AMD, glaucoma, and other ophthalmic disorders, the unmanned automated applications of AI, ML, and DL will be utilized as a potential alternative to ophthalmologists, retina specialists, and trained human graders.

In this review, we systematically reviewed the potential promising clinical applications of AI, ML, and DL in diagnosing DR, AMD, glaucoma and other ophthalmic disorders and introduced the current AI, ML, and DL technologies with the ophthalmic imaging modalities. We believe that this review may provide both ophthalmologists and computer scientists a significant and detailed summary on AI, ML, and DL applications in ophthalmology field and facilitate the potential promising clinical applications of AI, ML and DL projects in the ophthalmology health care system.

2. Subjects and Methods

With the use of the following keywords: "artificial intelligence", "machine learning", "deep learning", "diabetic retinopathy", "age-related macular degeneration", "glaucoma", and "ophthalmic disorders", we searched various literatures, potential eligible research articles and reviews studies regarding ophthalmology published on the PubMed, Cochrane Library, Embase, Science Direct, Web of Science, and Google Scholar databases. This review is regarding the potentially promising clinical automated applications of AI, ML and DL technologies in ophthalmic health care settings. These automated applications mainly focus on diseases with high prevalence and incidence, such as DR, AMD, and glaucoma, and also partly on some ophthalmic disorders. The search was limited to specific years particularly recent years and English language was applied. We gave classification, statistic, sensitivity, specificity, validation, overall accuracy, repeatability, reliability, Cohen's kappa, and the area under receiver operator characteristic curve (AUC) regarding these diseases subsequently.

3. Results

3.1. The application of the novel methods in the ophthalmic disorders

A variety of articles concerning AI, ML, and DL automated applications in diagnosing ophthalmic diseases have been published recently. The majority of these studies are related to DR, AMD and glaucoma researches, which are the three most prevalent causes of irreversible global blindness. In many recent studies, AI, ML and DL techniques have been shown to be an effective diagnostic tool for detecting and identifying various eye diseases in ophthalmic health care services. AI, ML and DL applications can make a great contribution to providing support to patients in remote areas where there are no experts, medical devices and adequate infrastructure. These studies have indicated that AI, ML, and DL applications with high accuracy are capable of detecting and diagnosing multiple retina disorders and promising results in automated image analysis.[11]

3.2. Artificial Intelligence-Machine Learning-Deep Learning in Diabetic Retinopathy

Diabetes mellitus (DM) has an increasing prevalence and incidence, affecting more than 415 million people worldwide, namely 1 out of every 11 adults is approximately affected. However, by 2040, approximately 600 million people are expected to have DM. DM is being the most leading causes of adulthood blindness among the working-age population.[1,12-14] Because of progressions in the treatment of DM, the surveillance of patients has improved and thus the frequency of DR and DME has increased. DR and DME cause blurring of central vision due to the developing retinal microvascular complications and the leakage of fluid from abnormal blood vessels in the retina of diabetic individuals. DR, a prevalent microvascular complication of DM, affects one-third of diabetic patients, leading to irreversible blindness. Undiagnosed and untreated DME is the major leading causes of severe visual impairment and blindness in working-age population.[1,15,16] Therefore, there is an urgent need for large-scale screening of DR to detect potentially threatening changes at an early stage that would benefit management and treatment. It is known that early intervention is the most cost-effective choice.[17] Therefore, in order to prevent vision loss in time due to sight-threatening retinopathy, it is very essential that early detection of DR and DME through regular and close surveillance by clinical examination or grading of retinal photographs. Annual screening of the retina with fundus digital photography, FFA, and OCT is recommended but presents a huge challenge and a problematic issue in many countries. Given the increased global prevalence of DM and DR, the limitation of availability of ophthalmologists, retina specialists, and trained human graders, the delivery of optimal diabetic screening will be a problematic procedure for current global health care management. The analysing of such images is also time consuming, costly, and prone to human error. Therefore, these challenges may be only resolved through unmanned automated applications of novel analysis methods without the need of ophthalmologists, retina specialists and human graders. In this perspective, it is inevitable that DR and DME will be detected by the automated retinal image analysis systems in the near future.[18-22] The screening of DR is so crucial and a universal strategy for preventable blindness coupled with timely diagnosis and treatment. However, DR screening programs are not being processed healthily, because of organizational practices, lack of human graders and financial problems.[14]

Given the current population growth trends and the high prevalence of DR and DME in the community, the applications of automated screening and diagnosis are inevitable in ophthalmic health care settings. In order to improve the management of DR patients and to alleviate the social burden, automatic retinal screening techniques for the diagnosis of DR have been researched. Multiple AI, ML and DL techniques have been applied to automatically diagnose and grade DR and the most effective automated applications are based on studies over the past three years. In recent studies regarding DR revealed that AI, ML and DL demonstrated high accuracy, sensitivity and specificity for the detection of DR.[14,21,23-25]

The prevalence and incidence of DR increase often around the World. There is no doubt that early diagnosis and treatment of DR is very important for preventing or treating avoidable blindness. Considering the increasing diabetic patient populations, the shortage of retina specialists and ophthalmologists, and the shortage of trained graders, the automated retinal image applications are very important in terms of costeffectivity and time. If the accuracy, sensitivity and specificity of these applications are acceptable, these automated retinal image applications will be more valuable in the health care settings. The results of some studies on DR based on AI, ML, and DL modalities are given in detail below.

Ting et al,[14] assessed the deep learning system (DLS) performance, a ML technology with high potential for screening and detecting RDR, vision-threatening DR, AMD, and possible glaucoma, using 494 661 retinal images. In this study, for RDR, the AUC of the DLS was 0.936, sensitivity was 90.5%, and specificity was 91.6%. For vision-threatening DR, the AUC was 0.958, sensitivity was 100%, and specificity was 91.1%. For AMD, AUC was 0.931, sensitivity was 93.2%, and specificity was 88.7%. For possible glaucoma, AUC was 0.942, sensitivity was 96.4%, and specificity was 87.2%. They claimed that the retinal images from multiethnic cohorts of patients with DM, the DLS had high sensitivity and specificity for recognizing DR and related eye diseases, but additional studies were required to assess the applicability and validation of the DLS in the ophthalmic health care settings.

Tufail et al,[21] detected that the sensitivity point calculations of the screening performance of the automated retinal image analysis systems (ARIAS) were as follows: in EyeArt 94.7% for any retinopathy, 93.8% for referable diabetic retinopathy (RDR), 99.6% for proliferative retinopathy; in Retmarker 73.0% for any retinopathy, 85.0% for RDR, 97.9% for proliferative retinopathy. They stated that Retmarker and EyeArt systems achieved acceptable sensitivity for RDR compared with human graders and that ARIAS had a high potential for clinically effective for rapid detection of DR and cost-effective in the health care systems. ARIAS could be safely introduced into DR scanning programs to replace human graders and help remote health care applications.

Abramoff et al,[23] evaluated the sensitivity and specificity of the Iowa Detection Program (IDP) for detecting RDR by using automated analysis of retinal images. In this study, the AUC was 0.937. The sensitivity and the specificity of IDP were 96.8%, 59.4%, respectively. However, the sensitivity and specificity of the retina specialists were 0.80/0.98, 0.71/1.00, and 0.91/0.95, and the average intergrader or interobserver difference (κ) was 0.822. They claimed that the IDP had high sensitivity and specificity for automated detection of RDR. They also claimed that it could be performed safely into DR screening program, potentially improving access to ophthalmic health care screening program and reducing sight loss thanks to early diagnosis and treatment of DR.

Deep learning algorithm (DLA) is expected to be a routine application in ophthalmic health care practice in the immediate future. However, further studies are needed to elucidate the applicability and validation of this algorithm in the clinical ophthalmic health care setting and to elucidate whether use of this algorithm could result in improved care and results compared to current ophthalmologic appraisal.[24] Gulshan et al,[24] developed a DLA for automated screening and detection of DR and DME in 128 175 retinal images by using a deep convolutional neural network (DCNN). In this study, for detecting RDR, the algorithm of the AUC was 0.991 for EyePACS-1 data set and 0.990 for Messidor-2 data set. Utilization a first operating cut point with high specificity in the data set, the sensitivity and the specificity were 90.3%, 98.1%, respectively for EyePACS-1 data set. Nevertheless, the sensitivity and the specificity were 87.0%, 98.5%, respectively for Messidor-2 data set. Utilization the second operating cut point with high sensitivity in the data set, the sensitivity and the specificity were 97.5%, 93.4%, respectively for EyePACS-1data set. Nevertheless, the sensitivity and the specificity were 96.1%, 93.9%, respectively for Messidor-2 data set. They claimed that ML and DL algorithms had high sensitivity and specificity for detecting RDR. However, they indicated that further studies were needed to elucidate the applicability and validation of these algorithms in the clinical ophthalmic health care settings and to elucidate whether use of this algorithm could result in improved care and results compared to current ophthalmologic appraisal.

The detection of DR on the basis of color fundus photographs has been performed for years. The vast majority of studies of automated applications of AI, ML and DL have focused mainly on the analysis of fundus photographs. If the validation, accuracy, reliability, sensitivity and specificity of an AI-based, DLA are reasonable, this application will be costeffective and rapid in the health care settings. Without doubt, this technology will offer potential to increase the efficiency, sustainability and accessibility of DR screening programs worldwide. Li et al,[25] developed an AI-based on DLA for the detection of referable DR on the basis of color fundus photographs. In the internal validation data set, the AUC, sensitivity, and specificity of the DLA for vision-threatening RDR were 0.989, 97.0%, and 91.4%, respectively. Testing against the independent, multiethnic data set the AUC, sensitivity, and specificity of 0.955, 92.5%, and 98.5%, respectively. However, due to a misclassification of mild or moderate DR the false-positive cases were by 85.6%. Unobserved intraretinal microvascular abnormalities corresponded with 77.3% of all false-negative cases. They claimed that AI-based DLA could be used with a good accuracy and reliability in the detection of vision-threatening RDR in retinal images and that DLA technology had also a potential to increase the efficiency and accessibility of DR screening programs worldwide.

In fact, these automated application systems can help doctors understand DR predictions better and increase the applicability of intelligent diagnostic models in real clinical practice. In the perspective of these studies, with AI, ML and DL, the accuracy, validation, sensitivity and specificity of the evaluation of automated analysis of retinal images for detection of DR were very high and the diagnostic performance of AI, ML and DL was clinically acceptable and highly reproducible for validation dataset. However, further studies are needed to elucidate the applicability and validity of these algorithms in clinical ophthalmic healthcare, and to clarify whether the use of this algorithm will lead to better care and outcomes compared to the current ophthalmological evaluation.

3.3. Artificial Intelligence-Machine Learning-Deep Learning in Age-Related Macular Degeneration

AMD, a significant cause of visual loss in the world, is a chronic macular disease characterized by drusen, retinal pigment changes, choroidal neovascularisation, haemorrhage, exudation, and sometimes geographic atrophy which is an irreversible serious condition.[26] It effects elderly population, resulting in visual impairment, depression, a decrease in quality of life, and mortality.[27,28] In fact, AMD and DR are the leading causes of blindness in adults over the age of 50 years in the US.[29] Basically, macular degeneration is induced by drusen inside or outside the retinal pigment epithelium and generally leading to visual deterioration in AMD. There are two types of drusen, including hard drusen or soft drusen. Hard drusen can be found in all age groups and may progress to soft drusen. However, soft drusen is mostly found among the elderly and may develop choroidal neovascularization leading visual impairment. Therefore, the quantitative measurement of drusen is very substantial in order to prevent macular degeneration. However, traditional manual drusen measurements with current visual examination take a lot of time, require considerable effort and less reliable.[30-32] Therefore, there are predictions based on drusen with AI, ML, and DL algorithms for making individualized predictions in AMD. These algorithms can predict about drusen underneath the retina in AMD. AI, ML, and DL algorithms provide automated detection of drusen, fluid, and geographic atrophy concerning AMD lesions to improve AMD diagnosis and treatment by using fundus images and SD-OCT.[33-37] The automatic drusen detection with AI, ML and

DL is likely to help ophthalmologists to improve the early and rapid diagnostic performance on fundus images[30]. The accuracy is usually over 80% and AI, ML, and DL-based automated assessment of AMD is consistency with manual professional evaluation and the agreement can reach 90%.[33,36-38]

Intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) drugs is very important in the current management of neovascular-AMD (nAMD) and close follow-up observation is also very important. The use of AI, ML, and DL to predict anti-VEGF injection requirements for patients with nAMD and proliferative DR (PDR) can alleviate the economic burden of patients and facilitate resource management.[39]

Given the social population aging and the severity of this disease, it's necessary to perform AMD screening regularly. Automatic AMD diagnosis may apparently reduce the work burden of clinicians and thus may increase productivity.[40] Most of AI, ML, and DL techniques have been applied to automatically diagnose and grade AMD and the most effective automated applications are based on studies in the past year. In recent studies regarding AMD revealed that AI, ML and DL demonstrated high accuracy, sensitivity and specificity for the detection of AMD.[41-45] The results of some studies on AMD based on AI, ML, and DL modalities are given in detail below.

Burlina et al,[41] developed an automated grading for detecting of AMD from color fundus images by using DL methods and AI; namely, DCNN. They detected that the DCNN method gave accuracy (88.4% and 91.6%), the AUC (0.94 and 0.96), and kappa coefficient (0.764 and 0.829). They claimed that a DL-based automated assessment of AMD Was consistency with manual professional evaluation and that automated algorithms could play a critical role in the present management of AMD, costs of screening or monitoring, access to healthcare, and the appraisal of novel treatments.

Schlegl et al,[42] developed a fully DL automated method to detect and quantify macular fluid caused by AMD, DME, and RVO in conventional OCT images. It was demonstrated an automated diagnostic method based on DL achieved optimal accuracy for the detection and quantification of intraretinal cystoid fluid (IRC) for AMD, DME, and RVO average accurate with an AUC of 0.94. However, the detection and measurement of subretinal fluid (SRF) were also highly accurate with an AUC of 0.92, with superior performance in neovascular AMD and RVO compared to DME. Consequently, they detected that the high correlation was verified between automated and manual fluid localization and quantification and the mean Pearson's correlation coefficient was 0.90 for IRC and 0.96 for SRF. They indicated that the detection and quantification of macular fluid based on DL could produce similar results to human performance levels. In addition, they claimed that DL automated analysis of retinal OCT image ensured a promising horizon in improving accuracy and reliability of retinal diagnosis for clinical studies, practices, and care in the ophthalmic settings.

Burlina et al,[43] used the DL for severity characterization and estimation of 5-year risk of AMD patients by using 67 401 color fundus images. The weighted κ scores were 0.77 for the 4-step and 0.74 for the 9-step AMD severity scales. The overall average estimation error for the 5-year risk ranged from 3.5% to 5.3%. In the perspective of these findings, they suggested that DL based automated assessment of AMD grading had performance comparable with that of human performance levels. Consequently, they claimed that DL had a potential to assist for clinical researches, care, and disease progression and public screening all around the world.

Grassmann et al,[44] developed a DLA for prediction of the severity scale of AMD based on color fundus photography. They pointed out that the algorithm detected 84.2% of all fundus images with signs of early or late AMD and 94.3% of healthy fundus images were categorized accurately. In this study, their DLA showed a weighted κ outperforming of human graders in the AMD study and was appropriate to categorize AMD fundus images in other datasets individuals over 55 years of age.

Peng et al,[45] assessed the severity and the risk of progression of late AMD with DeepSeeNet which is a DL model for automated classification of AMD severity from color fundus photographs. They measured of the outcome of the overall accuracy, specificity, sensitivity, Cohen’s kappa, and the AUC. In this study, the performance of DeepSeeNet was compared to that of retina specialists. They demonstrated that DeepSeeNet was with high AUCs in the detection of large drusen (0.94), pigmentary abnormalities (0.93) and late AMD (0.97) and that DeepSeeNet (accuracy=0.671; kappa=0.558) performed better than retina specialists (accuracy=0.599; kappa=0.467). DeepSeeNet also performed better than retina specialists in the detection of large drusen (accuracy 0.742 vs 0.696; kappa 0.601 vs 0.517) and pigmentary abnormalities (accuracy 0.890 vs 0.813; kappa 0.723 vs 0.535). However, it showed lower performance in the detection of late AMD (accuracy 0.967 vs 0.973; kappa 0.663 vs 0.754). In this study, DeepSeeNet had a high reliability and accuracy in the automated AMD risk categories. As a result, they claimed that DL systems had a potential to assist and enhance clinical decision of early AMD detection and risk prediction of the late AMD development.

In the light of these studies of the research on AMD, AI, ML and DL have shown high accuracy, sensitivity and specificity in the detection of AMD. These automated applications have provided similar results with trained human graders. Therefore, these automated applications will be a routine practice method in the diagnosis and treatment of AMD in the near future.

3.4. Artificial Intelligence-Machine Learning-Deep Learning in Glaucoma

Glaucoma, the second most common cause of blindness worldwide, is characterized by progressive neurodegenerative of retinal ganglion cells (RGCs) and irreversible loss of axons from the optic nerve. Early diagnosis and treatment of glaucoma is hugely important for preventing needless blindness. It is very important that optic nerve head (ONH) and retinal nerve fiber layer (RNFL) around the optic disc is evaluated for early diagnosis of glaucoma. It is possible to evaluate glaucomatous structural changes quantitatively with OCT. However, a remarkable limitation of retinal imaging devices, retina specialists, general ophthalmologists, ophthalmic graders, eye clinics or hospitals pose a great problem in developed and developing countries. In addition, patients with glaucoma suffer from availability, accessibility, affordability and sustainability of ophthalmic health care services problems in poorer countries. It is therefore very important that automatically detecting of glaucoma via AI, ML, and DL.[46,47]

The visual field (VF) defect is the main parameter of visual function during glaucoma progression. In order to construct the AI, ML, and DL based glaucomatous diagnostic models; VFs, fundus images, and OCT scans have been used. Although a standard automated VF test is important in the diagnosis and management of glaucoma, it is a disadvantage that it consumes a lot of time and resources. Moreover, such a manual procedure performed by patients is subjective and has been challenging in epidemiological studies. AI, ML and DL methods have shown excellent performance in the classification of glaucoma and healthy eyes in a short time. Ophthalmologists can refer to these automated results and make better decisions in clinical practice.[1,48]

AI, ML, and DL have a potential revolution for the screening, diagnosis and classification of early detection of glaucoma. In addition, AI, ML, and DL have the potential to recognize the development, progression and treatment of glaucoma by identifying and assessing new risk factors. However, there is no clearly defined gold standard of these algorithms for determining the presence and severity of glaucoma. Therefore, in future studies, more robust disease definitions should be used to develop and optimize current methodologies and data inputs for AI, ML and DL analyses, and improve information acquisition methods from learned results.[49] Multiple AI, ML and DL techniques have been applied to automatically diagnose and grade glaucoma and the most effective automated applications are based on studies in the past three years. In recent studies regarding glaucoma revealed that AI, ML and DL demonstrated high accuracy, sensitivity and specificity for the detection of glaucoma.[10,50-53] The results of some studies on glaucoma based on AI, ML, and DL modalities are given in detail below.

Devalla et al,[10] developed a DLS to digitally stain OCT images of the ONH and automatically measure structural parameters of the ONH. They achieved that the RNFL + prelamina, the RPE, all other retinal layers, the choroid, and the peripapillary sclera and lamina cribrosa were being stained digitally via DLA. For all tissues, the averge of the dice coefficient, sensitivity, specificity, intersection over union (IU), and accuracy were 0.84 ± 0.03, 0.92 ± 0.03, 0.99 ± 0.00, 0.89 ± 0.03, and 0.94 ± 0.02, respectively. They demonstrated that DLA can simultaneously stain the neural and connective tissues of the ONH. Furthermore, they indicated that digital staining also performed well on OCT images of both glaucoma and healthy individuals and that could offer very high reliability and accuracy for glaucoma management.

Li et al,[50] evaluated the performance and the efficacy of a DLA for detecting and automated classification of referable glaucomatous optic neuropathy (GON) based nearly 48 116 on colour fundus photographs. They detected that DLS achieved referable GON in an AUC of 0.986 with sensitivity of 95.6% and specificity of 92.0%. However, coexistence of eye disorders especially pathologic or high myopia was the most common cause resulting in false-negative results. Besides, physiologic cupping of optic disc was the most common reasons for false-positive results in their study.

Asaoka et al,[51] by using standard automated perimetry with a DL modality, differentiated the VFs of preperimetric open-angle glaucoma (OAG) patients from the VFs of healthy eyes. They obtained a significantly larger AUC of 92.6% by using the deep feed-forward neural network (FNN) classifier compared to all other ML methods: 79.0% with RF, 77.6% with gradient boosting, 71.2%, and 66.7% with neural network (NN). They, using a deep FNN classifier, indicated that preperimetric glaucoma VFs could be differentiated from healthy VFs with a good reliability and accuracy.

Kim et al,[52] aimed to develop ML models that have strong prediction power and interpretability for diagnosis of glaucoma based on RNFL thickness and visual field (VF). They indicated the classification accuracy, sensitivity, specificity, and the AUC are 0.98, 0.983, 0.975, and 0.979, respectively. The developed prediction models show high accuracy, sensitivity, specificity, and the AUC in classifying among glaucoma and healthy eyes. They claimed that ML would be used for predicting glaucoma and clinicians could be able to make better decisions in this way.

Asaoka et al,[53]constructed that a DL model to diagnose early glaucoma from SD-OCT images for the input features of the 8 x 8 grid macular RNFL thickness and ganglion cell complex layer thickness. The AUC, the random forests (RF), and the support vector machine (SVM) were used for diagnostic accuracy. They demonstrated that the AUC with the DL (DCNN) model was 93.7 %. The AUC was significantly reduced by 76.6% and 78.8% without preliminary training. Significantly smaller AUCs were obtained with RF and SVM (82.0% and 67.4%, respectively). Consequently, they detected that a DL model for glaucoma offers a substantive increase in diagnostic performance by using SD-OCT.

In the perspective of overall studies, it is shown that the automated applications of AI, ML and DL are successfully effective and have the potential to support the impending challenge of DR, AMD and glaucoma screenings in developed, as well as in developing countries. It is certain that the advent of these novel automated applications is incredibly impressive. There is no doubt that the AI, ML and DL algorithms can revolutionize ophthalmology health care system in the near future. In addition, the emergence of AI, ML and DL in ophthalmic health care settings may help make for prevention of DR, AMD and glaucoma-associated irreversible blindness. However, further studies are needed to determine the actual accuracy, sensitivity, specificity and validity of these automated applications for diagnosis and detection of DR, AMD and glaucoma.

4. Discussion

In many areas of specialties, accurate and rapid evaluation of clinical images is not only for diagnosis, but also for treatment. However, repeatability, validation, accuracy, reliability, sensitivity and specificity of clinical images are very important in clinical health care practices. For this reason, the development of vision algorithms with computers is crucial to help in the analysis of biomedical images. However, retina specialists in many ophthalmological settings currently determine retinal evaluation. In fact, that is not an objective evaluation; immensely time consuming with variable interpretation, repeatability, and interobserver agreement variation.[54] DL is a promising class of ML models that has become a popular subject over the past decade in science setting. DL has been used successfully for signal processing, pattern recognition, and statistical analysis. In addition, image processing and segmentation have been eased with DCNN. Undoubtedly, these results will have clinical implications and will positively reflect medical imaging procedures.[7,54,55] AI technology application depends mainly on ML, which is represented by mathematical algorithms and models generated by many input experiences. AI can originally efficiently conduct ophthalmological image processing, mainly based on the fundus photographs. In fact, AI is likely to achieve a promising accuracy comparable with clinical experts.[40,56] For example, it has been demonstrated that by using automatic ML algorithm for reticular pseudodrusen detection and quantification using multimodal information performed within the same range as the human graders.[36] Consequently, in recent years, a variety of studies have highlighted that AI, ML and DL algorithms were successfully used for automated retinal images applications.

It is certain that promising computer algorithms will make retinal disorders more objective than before. In addition to DR,[14,21,23-25] AMD,[41-45] and glaucoma[10,50-53]; AI, ML, and DL has also been used to diagnose other retinal diseases, including central retinal vein occlusion (CRVO),[57] rhegmatogenous retinal detachment (RRD),[58] retinopathy of prematurity (ROP),[59] and reticular pseudodrusen.[36] Apart from retina, AI-based systems have been improved in order to better identify or appraise other ophthalmic disorders, including paediatric cataract,[60] keratoconus (KC),[61] corneal ectasia,[62] oculoplastic reconstruction[63], evaluation of corneal power after myopic corneal refractive surgery,[64] making surgical plans in horizontal strabismus,[65] and determining of pigment epithelium detachment in polypoidal choroidal vasculopathy (PVC).[66] The results of some studies on CRVO, RRD, ROP, KC, and cataract based on AI, ML, and DL modalities are given in detail below.

CRVO, a vascular disease of the retina, leads to substantial visual morbidity and vision loss in the aging population.[67] The CRVO shows up with dilated tortuous retinal veins, retinal haemorrhages, cotton-wool spots, macular edema, and optic edema.[68] It was used DL technology in order to show presence of CRVO with Optos images. It has been indicated that DL model has higher sensitivity, specificity, and AUC values for detecting CRVO in Optos fundus photographs.[57] This technology may have an important potential clinical benefit to reach large areas without retina specialists.[57] Therefore, early diagnosis and intervention of CRVO patients living in areas with inadequate ophthalmic care is very crucial for visual recovery. As with other ophthalmic diseases, automatic diagnosis in CRVO will also be potentially beneficial for both patients and ophthalmologists.[57]

RRD, a severe condition, causes visual loss. Therefore, the early diagnosis and treatment of RRD is crucial. RRD is basically treatable, if treated appropriately and early. However, if left untreated and proliferative changes develop; it can turn into an uncontrollable state called proliferative vitreoretinopathy (PVR). The Optos, the ultrawide field scanning laser ophthalmoscope (Optos 200Tx; Optos PLC, Dunfermline, United Kingdom), can provide non-invasive, nonmydriatic, widefield fundus images and has been used for diagnosis or follow-up of multiple fundus disorders and treatment assessment.[58, 69-71] However, due to rising social security costs and lack of retina specialists, the establishment of vitreoretinal centers providing modern ophthalmological procedures is not truly feasible.[58] Ohsugi et al,[58] found that the DL model's sensitivity of RRD was 97.6% and specificity was 96.5%, and the AUC was 0.988. However, the support vector machine (SVM) model's sensitivity was 97.5%, specificity was 89.3% and AUC was 0.976. In this study, the sensitivity and specificity of the detecting RRD on the Optos fundus photographs were high with DL technology.

ROP, a vasoproliferative disease affecting premature infants, is a leading cause of childhood blindness worldwide and may be successfully treated with appropriate and timely diagnosis.[40,59] Clinical studies have shown that ROP requires close observation and timely treatment to prevent blindness. However, the rigorous and arduous repeated screening and follow-up of the ROP consumes quite a lot of manpower and energy. Therefore, the application of AI in ROP screening may increase the effectiveness of ROP care.[40,72,73] Campbell et al,[59] demonstrated that the diagnostic accuracy of the imaging and informatics in ROP (i-ROP) computer-based system was 95%, while the result of 11 expert physicians was mean 87%. Therefore, in the perspective of this study, it is possible to perform a computer-based image analysis system comparable to retina specialists of the ROP.

KC, a bilateral and non-inflammatory, is an eye disease characterized by progressive thinning, protrusion and scarring of the cornea. However, the deterioration of cornea may be progressive, asymmetric, and thus resulting in distorted and decreased vision.[74,75] Although the underlying cause of the disorder is still unknown, it mostly becomes clinically manifest at puberty in both sexes and may be related to various factors such as atopic disease, eye rubbing, contact lens use, connective tissue disease, tapetoretinal degeneration, inheritance, and Down syndrome.[74] ML models have already been used in KC and other corneal disorders detection. In addition, artificial neural networks and discriminant analysis are ML techniques have already been used to describe the topographical models of KC.[75,76] For instance, Carvalho,[76] indicated that developed an artificial neural network and in this study, the sensitivity, specificity and precision of these parameters were 78.75, 97.81, and 94%, respectively.

Cataract characterized by clouding of the lens is one of the prevalent diseases, causing of bilateral blindness across the world.[40,77] Ultraviolet and infrared rays or electromagnetic waves, smoking, diabetes, alcohol consumption, steroid medications, hormonal replacement therapy, malnutrition, synthetic chemical and pharmaceutical toxins, poor living conditions, hypoparathyroidism, galactosemia, eye surgery, inflammation and injury of the eye can lead to cataracts.[78] Early diagnosis and treatment can regain vision and improve quality of life for cataract patients. By applying ML algorithms such as RF and SVM, the diagnosis and grading of cataract has been made by utilizing fundus images, ultrasound images and visible wavelength eye images.[79,80] The risk estimation model for posterior capsular opasification after phacoemulsification surgery is also predicted by algorithms.[81] Using DL models, senile cataract can be diagnosed.[82] There is a more impressive study about the paediatric cataract that is the one of the primary causes of childhood blindness, if it is not detected early.[83] It is not surprising that the application of ML for anterior segment diseases will become a frequent modality of ophthalmic settings.[60,84,85,86] Given the prevalent of cataract in society, the automatic recognition will be rapid, cost-effective and more reliable.

Consequently, the medical decision-making with computers has increasingly performed recently. There is no doubt that AI, ML, and DL methods have recently demonstrated significant advances in medicine.[49] There are many goals of AI, including ML, DL, CML, NLP, computer vision, robotics, reasoning, general intelligence, expert system, automated learning and scheduling. Considering the fact that population aging has a large demographic trend around the world, it is expected that patients suffering from eye diseases will increase in an upright manner. Early diagnosis and appropriate treatment of eye diseases are known to be of great importance in order to prevent visual loss and improve quality of life. Due to lack of ophthalmologists, retina specialists, graders and optimal eye devices, conventional diagnostic methods of the eye are inadequate. In addition, the conventional diagnostic methods depend on the professional experience and knowledge of physicians, leading to a high rate of misdiagnosis and wasting too much medical data. Therefore, the deep integration and adaptation of ophthalmology and AI / ML / DL has the potential to revolutionize current disease diagnose pattern and create a significant clinical impact.[1]

Future of the automated applications (AI, ML, and DL) in ophthalmic clinical trials

In recent years, AI, ML and DL techniques have been shown in various scientific studies as an effective diagnostic tool to identify various diseases in health care services. The accuracy of the models is incredibly promising, and AI, ML and DL applications can provide a great contribution to providing support to patients in remote areas by sharing expert knowledge and limited resources. For creating a more reliable AI, ML and DL systems; OCT, OCTA, VF, and fundus images need to be integrated together. Most of the current studies regarding intelligent diagnosis of eye diseases focus on dual classification problems, while many patients suffer from multiple categorical retinal diseases in the clinical setting. It is therefore need to be had a model for detecting and distinguishing DR, AMD, glaucoma, and other retinal disorders simultaneously. Therefore, in order to detect and diagnose different retinal diseases with high accuracy, it is necessary to build further intelligent systems in clinic practice.[1]

It is certain that the advent of AI, ML, and DL applications is incredibly impressive. Although AI, ML, and DL are not yet mature enough to be implemented in the clinical setting, it seems to be a unique revolutionary breakthrough in the health care applications. For this reason, further studies are needed to elucidate the algorithms based on AI, ML, and DL whether their sensitivity, specificity, and clinically validity of these technologies for detecting of DR, DME, AMD, glaucoma, and other ophthalmic disorders. In addition, further researches are essential to identify the applicability of these algorithms in the clinical setting and to identify whether the use of these algorithms could lead to improved healthcare and to identify their outcomes compared with current ophthalmologic assessment. However, it is feasible in the near future that with AI, ML and DL-assisted automated screening and diagnosis can help minimize doctors' burden and maximize the role of doctors' at the ophthalmology clinics.[40] AI, ML and DL platforms can provide patients with more medical opportunities and reduce barriers to access to an eye care clinic without an ophthalmologist.[40] In addition, new technologies based on AI, ML and DL can reduce social inequalities.[87] AI, ML and DL supported systems may be a potential solution for overburdened health care system problems.[40] It seems that the health care industry will be begun to reshape by AI, ML and DL completely in the near future. There is another problematic issue with artificial neural networks. As AI, ML, and DL gradually move from the virtual into the real world, research and experience demonstrates that artificial neural networks are vulnerable to cyber threat, hacks and deception.

Despite everything, the intelligent systems will be adopted in some specific clinical ophthalmic studies in the near future. Although ethics, regulatory and legal issues are challenging, AI, ML and DL will revolutionize the diagnosis and treatment of diseases and will have a significant clinical impact in the health system in the near future.

5. Conclusion

Automated retinal imaging technologies may potentially reduce the barriers to access to health care system and health screening, and thus it may gradually help reduce needless blindness across the world. If these technologies are widely and embraced by health care system authorities and ophthalmologists, it will have an immense favourable impact on medicine community and on ophthalmology society. However, it is very important that the repeatability, validation, accuracy, reliability, sensitivity, specificity, and correct disease staging of retinal scanning algorithms based on AI, ML, and DL in the clinical health care practice. On the other hand, as AI becomes more sophisticated, there may be many ethical challenges occur, including transparency, bias, human values, data protection and intellectual property, social dislocation, cyber security, decision making, liability, legal and regulatory issue. Although such issues arise, AI, ML, and DL will contribute significantly to make a breakthrough current disease diagnostic and treatment pattern and create a substantial clinical impact in the near future. However, by creating more interpretable AI, ML, and DL methods using advanced ophthalmic scanning algorithms with high reproducibility, validity, accuracy, reliability, sensitivity, and specificity; by enhancing the applicability, availability and accessibility of AI, ML, and DL, but with this way, these novel technologies can be widely enabled in ophthalmic setting. With this perspective, it may lead to the adoption of intelligent systems in ophthalmic or specific clinical trials.

We believe that this review may provide detailed, important, interesting and diverse information to both ophthalmologists and computer scientists about the AI, ML and DL applications in the ophthalmology health care platforms. We believe that it may also shed light on the new projects of AI, ML and DL in the ophthalmology health care system and facilitate future promising clinical practices.

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7. Author Contributions

L.B. and T.P. wrote the main manuscript text. L.B. and T.P. designed the research. L.B. conducted the research. L.B. collected the data. Both authors reviewed the manuscript.

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9. Conflicts of Interest

There is no conflict of interest.

10. References

1. Lu W, Tong Y, Yu Y, et al. Applications of artificial Intelligence in ophthalmology: general overview. *J Ophthalmol.* 2018; 2018: 5278196.
2. Samuel AL. Some studies in machine learning using the game of checkers. I. In: Levy DNL, editor. Computer Games I. Springer, New York, NY 1988: 335–65.
3. Mesko B, Hetényi G, Gyorffy Z. Will artificial intelligence solve the human resource crisis in healthcare? *BMC Health Serv Res.* 2018; 18(1): 545.

4. Awad M, Khanna R. Efficient learning machines: theories, concepts, and applications for engineers and system designers. Apress, Berkeley, CA. 2015: 1-18.
5. Bengio Y, Courville A, Vincent P. Representation learning: a review and new perspectives. *IEEE Trans Pattern Anal Mach Intell.* 2013; 35(8): 1798-828.
6. Schmidhuber J. Deep learning in neural networks: an overview. *Neural Netw.* 2015; 61: 85-117.
7. LeCun Y, Bengio Y, Hinton G. Deep learning. *Nature.* 2015; 521(7553): 436-44.
8. Lang A, Carass A, Hauser M, et al. Retinal layer segmentation of macular OCT images using boundary classification. *Biomed Opt Express.* 2013; 4(7): 1133–52.
9. Gaiarsa VM, Cardenas D, Furuie SS. Approaches to segment stent area from intravascular optical coherence tomography. *Res Biomed Eng*. 2017; 33(1): 11–20.
10. Devalla SK, Chin KS, Mari JM, et al. A deep learning approach to digitally stain optical coherence tomography images of the optic nerve head. *Invest Ophthalmol Vis Sci.* 2018; 59(1): 63-74.
11. Rahimy E. Deep learning applications in ophthalmology. *Curr Opin Ophthalmol.* 2018; 29(3): 254-60.
12. Gargeya R, Leng T. Automated identification of diabetic retinopathy using deep learning. *Ophthalmology.* 2017; 124(7): 962–9.
13. Congdon NG, Friedman DS, Lietman T. Important causes of visual impairment in the world today. *JAMA.* 2003; 290(15): 2057–60.
14. Ting DSW, Cheung CY, Lim G, et al. Development and validation of a deep learning system for diabetic retinopathy and related eye diseases using retinal images from multiethnic populations with diabetes. *JAMA.* 2017; 318(22): 2211-23.
15. Yau JW, Rogers SL, Kawasaki R, et al.. Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care.* 2012; 35(3): 556-64.

16. Sabanayagam C, Banu R, Chee ML, et al. Incidence and progression of diabetic retinopathy: a systematic review. *Lancet Diabetes Endocrinol.* 2018 pii: S2213-8587(18)30128-1.
17. Bek T, Erlandsen M. Visual prognosis after panretinal photocoagulation for proliferative diabetic retinopathy. *Acta Ophthalmol Scand*. 2006; 84(1): 16–20.
18. Aiello LP, Gardner TW, King GL, et al. Diabetic retinopathy. *Diabetes Care.* 1998 ;21(1):143-56.
19. Mohamed Q, Gillies MC, Wong TY. Management of diabetic retinopathy: a systematic review. *JAMA.* 2007; 298(8): 902-16.
20. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Res Clin Pract.* 2010; 87(1): 4-14.
21. Tufail A, Rudisill C, Egan C, at al. Automated diabetic retinopathy image assessment software: diagnostic accuracy and cost-effectiveness compared with human graders. *Ophthalmology.* 2017; 124(3): 343-35
22. Balyen L, Ünlü K, Deniz Balyen LS. Outcomes of intravitreal triamcinolone acetonide injection in patients with diabetic macular edema. Van Med J. 2018; 25: 28-33.
23. Abramoff MD, Folk JC, Han DP, et al. Automated analysis of retinal images for detection of referable diabetic retinopathy. *JAMA Ophthalmol.* 2013 ;131(3): 351-7.
24. Gulshan V, Peng L, Coram M, et al. Development and validation of a deep learning algorithm for detection of diabetic retinopathy in retinal fundus photographs. *JAMA.* 2016; 316(22): 2402-2410.
25. Li Z, Keel S, Liu C, et al. An automated grading system for detection of vision-threatening referable diabetic retinopathy on the basis of color fundus photographs. *Diabetes Care.* 2018; 41(12): 2509-16.
26. Ferris FL, Wilkinson CP, Bird A, et al, on behalf of the Beckman initiative for macular research classification committee. Clinical classification of age-related macular degeneration. *Ophthalmology.* 2013; 120(4): 844–51.

27. Brody BL., Gamst AC, Williams RA, et al. Depression, visual acuity, comorbidity, and disability associated with age-related macular degeneration. *Ophthalmology.* 2001; 108(10): 1893–1900.
28. Tseng VL, Yu F, Lum F, et al. Risk of fractures following cataract surgery in medicare beneficiaries. *The Journal of the American Medical Association.* 2012; 308(5): 493–501.
29. Jiang S, Franco YL, Zhou Y, et al. Nanotechnology in retinal drug delivery. *Int J Ophthalmol.* 2018; 11(6): 1038-44.
30. Schlanitz FG, Baumann B., Kundi M., et al. Drusen volume development over time and its relevance to the course of age-related macular degeneration. *British Journal of Ophthalmology.* 2017; 101(2): 198–203.
31. Algvere PV, Kvanta A, Seregard S. Drusen maculopathy: a risk factor for visual deterioration. *Acta Ophthalmologica.* 2016; 94(5): 427–433.
32. Kim YJ, Kim KG. Automated segmentation methods of drusen to diagnose age-related macular degeneration screening in retinal images. *Comput Math Methods Med.* 2018: 12; 2018: 6084798.
33. Chen Q., Leng T., Zheng L., et al. Automated drusen segmentation and quantification in SD-OCT images. *Medical Image Analysis.* 2013; 17(8): 1058–72.
34. Bogunovic H., Montuoro A., Baratsits M., et al. Machine learning of the progression of intermediate age-related macular degeneration based on OCT imaging. *Investigative Opthalmology & Visual Science.* 2017; 58(6): O141–O150.
35. Chakravarthy U., Goldenberg D., Young G., et al. Automated identification of lesion activity in neovascular age-related macular degeneration. Ophthalmology. 2016; 123(8): 1731–6.

36. van Grinsven M. J., Buitendijk G. H., Brussee C., et al. Automatic identification of reticular pseudodrusen using multimodal retinal image analysis. *Investigative Ophthalmology & Visual Science*. 2015; 56(1): 633–9.

37. Feeny AK, Tadarati M, Freund DE, et al. Automated segmentation of geographic atrophy of the retinal epithelium via random forests in AREDS color fundus images. *Computers in Biology and Medicine*. 2015; 65: 124–36.

38. Lahmiri S., Boukadoum M. Automated detection of circinate exudates in retina digital images using empirical mode decomposition and the entropy and uniformity of the intrinsic mode functions. *Biomedical Engineering*. 2014; 59(4): 5527–35.

39. Wong TY, Liew G, Mitchell P. Clinical update new treatments for age-related macular degeneration. Lancet.2007; 370(9583): 204–6.

40. Du XL, Li WB, Hu BJ. Application of artificial intelligence in ophthalmology. *Int J Ophthalmol*. 2018; 11(9): 1555-61.

41. Burlina PM, Joshi N, Pekala M, Pacheco KD, Freund DE, Bressler NM. Automated Grading of Age-Related Macular Degeneration From Color Fundus Images Using Deep Convolutional Neural Networks. JAMA Ophthalmol. 2017 Nov 1;135(11):1170-1176.

42. Schlegl T, Waldstein SM, Bogunovic H, Endstraßer F, Sadeghipour A, Philip AM, Podkowinski D, Gerendas BS, Langs G, Schmidt-Erfurth U. Fully Automated Detection and Quantification of Macular Fluid in OCT Using Deep Learning. Ophthalmology. 2018 Apr;125(4):549-558.

43. Burlina PM, Joshi N, Pacheco KD, Freund DE, Kong J, Bressler NM. Use of Deep Learning for Detailed Severity Characterization and Estimation of 5-Year Risk Among Patients With Age-Related Macular Degeneration. JAMA Ophthalmol. 2018 Sep 14. doi: 10.1001/jamaophthalmol.2018.4118

44. Grassmann F, Mengelkamp J, Brandl C, Harsch S, Zimmermann ME, Linkohr B, Peters A, Heid IM, Palm C, Weber BHF. A Deep Learning Algorithm for Prediction of Age-Related Eye Disease Study Severity Scale for Age-Related Macular Degeneration from Color Fundus Photography. Ophthalmology. 2018 ; 125(9):1410-1420.

45. Peng Y, Dharssi S, Chen Q, Keenan TD, Agrón E, Wong WT, Chew EY, Lu Z. A deep learning model for automated classification of patient-based age-related macular degeneration severity from color fundus photographs. Ophthalmology. 2018 Nov 21. pii: S0161-6420(18)32185-7.
46. L Shahsuvaryan M. Glaucomatous optic neuropathy management: the role of neuroprotective agents. *Med Hypothesis Discov Innov Ophthalmol.* 2013; 2(2): 41-6.
47. Shibata N, Tanito M, Mitsuhashi K, et al. Development of a deep residual learning algorithm to screen for glaucoma from fundus photography. *Sci Rep.* 2018; 8(1): 14665.
48. Oh E, Yoo TK, Hong S. Artificial neural network approach for differentiating open-angle glaucoma from glaucoma suspect without a visual field test. *Invest Ophthalmol Vis Sci.* 2015; 56(6): 3957-66.
49. Zheng C, Johnson TV, Garg A, et al. Artificial intelligence in glaucoma. *Curr Opin Ophthalmol.* 2018 Dec 12. doi: 10.1097/ICU.0000000000000552.
50. Li Z, He Y, Keel S, et al. Efficacy of a deep learning system for detecting glaucomatous optic neuropathy based on color fundus photographs. *Ophthalmology.* 2018; 125(8): 1199-206.
51. Asaoka R, Murata H, Iwase A, Araie M. Detecting Preperimetric Glaucoma with Standard Automated Perimetry Using a Deep Learning Classifier. *Ophthalmology.* 2016 Sep;123(9):1974-80.
52. Kim SJ, Cho KJ, Oh S. Development of machine learning models for diagnosis of glaucoma. PLoS One 2017;12(5):e0177726.
53. Asaoka R, Murata H, Hirasawa K, et al. Using deep learning and transform learning to accurately diagnose early-onset glaucoma from macular optical coherence tomography images. *Am J Ophthalmol.* 2018 Oct 11. pii: S0002-9394(18)30589-0.
54. Lee CS, Tyring AJ, Deruyter NP, et al. Deep-learning based, automated segmentation of macular edema in optical coherence tomography. *Biomed Opt Express.* 2017; 8(7): 3440-8.

55. Mitchell JB. Machine learning methods in chemoinformatics. *Wiley Interdiscip Rev Comput Mol Sci*. 2014; 4(5): 468-81.

56. Lee A, Taylor P, Kalpathy-Cramer J, et al. Machine learning has arrived. *Ophthalmology*. 2017; 124(12): 1726–8

57. Nagasato D, Tabuchi H, Ohsugi H, et al. Deep neural network-based method for detecting central retinal vein occlusion using ultrawide-field fundus ophthalmoscopy. *J Ophthalmol*. 2018; 2018: 1875431

58. Ohsugi H, Tabuchi H, Enno H, et al. Accuracy of deep learning, a machine-learning technology, using ultra-wide-field fundus ophthalmoscopy for detecting rhegmatogenous retinal detachment. *Sci Rep*. 2017; 7(1): 9425.

59. Campbell JP, Ataer-Cansizoglu E, Bolon-Canedo V, et al. Imaging and informatics in ROP (i-ROP) research consortium.expert diagnosis of plus disease in retinopathy of prematurity from computer-based image analysis. *JAMA Ophthalmol*. 2016; 134(6): 651-7.

60. Liu X, Jiang J, Zhang K, et al. Localization and diagnosis framework for paediatric cataracts based on slit-lamp images using deep features of a convolutional neural network. *PLoS One*. 2017; 12(3): e0168606.

61. Ruiz Hidalgo I, Rozema JJ, Saad A, et al. Validation of an objective keratoconus detection system implemented in a scheimpflug tomographer and comparison with other methods. *Cornea*. 2017; 36(6): 689-95.

62. Ambrósio R Jr, Lopes BT, Faria-Correia F, et al. Integration of scheimpflug-based corneal tomography and biomechanical assessments for enhancing ectasia detection. *J Refract Surg*. 2017; 33(7): 434-43.

63. Tan E, Lin F, Sheck L, et al. A practical decision-tree model to predict complexity of reconstructive surgery after periocular basal cell carcinoma excision. *J Eur Acad Dermatol Venereol*. 2017; 31(4): 717-23.

64. Koprowski R, Lanza M, Irregolare C. Corneal power evaluation after myopic corneal refractive surgery using artificial neural networks. *Biomed Eng Online.* 2016; 15(1): 121.

65. Almeida JD, Silva AC, Teixeira JA, Paiva AC, Gattass M. Surgical planning for horizontal strabismus using Support Vector Regression. *Comput Biol Med.* 2015; 63: 178-86.

66. Xu Y, Yan K, Kim J, Wang X, Li C, Su L, Yu S, Xu X, Feng DD. Dual-stage deep learning framework for pigment epithelium detachment segmentation in polypoidal choroidal vasculopathy. Biomed Opt Express. 2017; 8(9): 4061-76.

67. Yau JW, Lee P, Wong TY, et al. Retinal vein occlusion: an approach to diagnosis, systemic risk factors and management. Intern Med J. 2008; 38(12): 904-10.

68. Hayreh SS, Zimmerman MB. Fundus changes in central retinal vein occlusion. Retina. 2015; 35(1): 29-42.

69. Nagiel A, Lalane RA, Sadda SR, et al. Ultra-widefield fundus imaging: a review of clinical applications and future trends. *Retina.* 2016;36:660–678.

70. Miki D, Hida T, Hotta K, et al. Comparison of scleral buckling and vitrectomy for retinal detachment resulting from flap tears in superior quadrants. *Jpn. J. Ophthalmol.* 2001;45:187–191.

71. Heussen N, Feltgen N, Walter P, et al; SPR Study Group. Scleral buckling versus primary vitrectomy in rhegmatogenous retinal detachment study (SPR Study): predictive factors for functional outcome. Study report no. 6. Graefes Arch Clin Exp Ophthalmol. 2011; 249(8): 1129-36.

72. Gilbert C, Fielder A, Gordillo L, et al. International NO-ROP group characteristics of infants with severe ROP in countries with low, moderate, and high levels of development implications for screening programs. *Pediatrics.* 2005; 115(5): e518–e25.

73. Hardy RJ, Good WV, Dobson V, et al. The early treatment for retinopathy of prematurity clinical trial: presentation by subgroups versus analysis within subgroups. *Br J Ophthalmol*. 2006; 90(11): 1341-2.
74. Krachmer JH, Feder RS, Belin MW. Keratoconus and related noninflammatory corneal thinning disorders. *Surv Ophthalmol.* 1984; 28: 293–322.
75. Souza MB, Medeiros FW, Souza DB, et al. Evaluation of machine learning classifiers in keratoconus detection from orbscan II examinations. *Clinics (Sao Paulo).* 2010; 65(12): 1223-8.
76. Carvalho LA. Preliminary results of neural networks and Zernike polynomials for classification of videokeratography maps. *Optom Vis Sci.* 2005; 82: 151–8.
77. Waltz KL, Featherstone K, Tsai L, et al. Clinical outcomes of TECNIS toric intraocular lens implantation after cataract removal in patients with corneal astigmatism. Ophthalmology. 2015; 122(1): 39-47.
78. Gupta VB, Rajagopala M, Ravishankar B. Etiopathogenesis of cataract: an appraisal. Indian J Ophthalmol. 2014; 62(2): 103-10.
79. Yang JJ, Li J, Shen R, et al. Exploiting ensemble learning for automatic cataract detection and grading. Computer Methods and Programs in Biomedicine. 2016; 124: 45–57.
80. MK SV, Gunasundari R. Computer-aided diagnosis of anterior segment eye abnormalities using visible wavelength image analysis based machine learning. Journal of Medical Systems. 2018;42(7) doi: 10.1007/s10916-018-0980-
81. Mohammadi S., Sabbaghi M., Z-Mehrjardi H., et al. Using artificial intelligence to predict the risk for posterior capsule opacification after phacoemulsification. Journal of Cataract and Refractive Surgery.2012;38(3):403–408.

82. Gao X., Lin S., Wong T. Y. Automatic feature learning to grade nuclear cataracts based on deep learning. *IEEE Transactions on Biomedical Engineering*. 2015; 62(11): 2693–2701.

83. Lin D., Chen J., Lin Z., et al. 10-Year overview of the hospital-based prevalence and treatment of congenital cataracts: the CCPMOH experience. *PLoS One*. 2015;10(11) doi: 10.1371/journal.pone.0142298.e142298

84. Gao X, Lin S, Wong TY. Automatic feature learning to grade nuclear cataracts based on deep learning. *IEEE Trans Biomed Eng*. 2015; 62(11): 2693–701.

85. Gillner M, Eppig T, Langenbucher A. Automatic intraocular lens segmentation and detection in optical coherence tomography images. *Z Med Phys*. 2014; 24(2): 104–11.

86. Ohnell H, Heijl A, Brenner L, et al. Structural and functional progression in the early manifest glaucoma trial. *Ophthalmology*. 2016; 123(6): 1173–80.

87. Heidary F, Gharebaghi R. Ideas to assist the underprivileged dispossessed individuals. *Med Hypothesis Discov Innov Ophthalmol*. 2012; 1(3): 43–4.