

Deep Learning Based Analysis of Ophthalmology: A Systematic Review

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Abstract

INTRODUCTION: Diagnosis of medical-related problems is the biggest issue in every era. In past decades, due to less number of technologies and equipment's it was challenging to diagnose it. As time passes, technologies i.e. Artificial Intelligence (AI) grow and became popular in the medical field especially in ophthalmology at proliferating rate. But, still, many of the diseases are diagnose manually. (i.e., eye disease disorder) which is time consuming, expensive, and tedious task. Existing prediction systems can resolve medical issues such as ocular disorder but the accuracy of prediction is very less.

OBJECTIVES: This study gives a brief overview of the analysis of traditional systems with modern approaches. Further, this study highlights the different allied techniques and impact of transfer learning on ophthalmology for the detection of various eye diseases i.e., Diabetic Retinopathy (DR), Age-related Macular Degeneration (AMD), Glaucoma, etc.

METHODS: AI and Machine Learning Technique are used to conduct this research for analysis.

RESULTS: The result of this paper concludes AI with allied techniques may reshape and revolutionize the medical community especially in the area of ophthalmology.

CONCLUSION: This paper presented a comprehensive review of AI with allied techniques in ophthalmology. In ML and DL-based approaches, CNN provides the most promising results.

Keywords: Deep Learning, Machine Learning, Diabetic Retinopathy, Age-related Macular Degeneration, Glaucoma.

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1. Introduction

Ophthalmology is a branch of medical science which deals with the scientific study of diseases, diagnosis, and treatment of various eyes disorder. In past, ocular disorders were diagnosed manually by ophthalmologists which takes a lot of time [1]. Therefore, it might lead to a delay in the treatment. Further, the error margin was still massive and as a consequence misdiagnosis of treatment also occurred. As era changes, medical sciences and computer science work jointly to solve disease diagnosis and treatment of various medical field related problems.

In computer science, AI with different allied techniques such as Machine Learning (ML) and Deep Learning (DL) plays a vital role. In the present situation, AI with allied techniques has emerged as an impressive tool for the automatic detection of complex patterns from the ocular disorders. Therefore, with the help of the above-mentioned tools, ophthalmologists and trained experts can find sufficient information for analyzing the eye disease diagnosis and treatment of various ocular disorders.

In the present situation, medical sciences and computer science are uplifting together in the diagnosis of medical-related problems with the help of images. With the help of this, an anonymous amount of data has been

generated for further analysis for clinical practitioners, healthcare professionals, researchers, etc. related to the diagnosis of respective diseases [2]. The methodology shown in figure 1, evolved as an extraordinary mechanism for clinicians and practitioners for the study of various diseases, diagnosis, and treatments. Optical Coherence Tomography (OCT) images [3], Fundus Fluorescein Angiography (FFA) image, 2D Color Fundus Photography (CFP) [4], B-Scan Images and many more scans are mainly using by the majority of ophthalmologist to erect the intelligent decision but still required more attention to analyze it [5-6]. This study gives an analysis of allied techniques in classification, segmentation, and prediction of various ocular disorders. So far, innumerable research articles have been published which emphasizing the potential of AI with allied techniques in different disease diagnosis [7-9]. Also, in the field of ophthalmology, lots of manuscripts showed the potential of AI in automated applications for classification, segmentation, prediction of various eye disease diagnosis and detection. After the analysis of different researchers views on the ophthalmology-, Diabetic Retinopathy (DR) [10-11], Age-related Macular Degeneration (AMD) [12], Glaucoma [13], Diabetic Macular Edema (DME) [14] etc. eye diseases are the leading causes of blindness in the mostly aging populaces. Also, as per the World Health Organization (WHO) report, the aging population is increasing in the world, it's expected that patients suffering from ocular diseases will also escalation in the same proportion [15-16]. So there is a specific interest in this application of AI to improve ophthalmologic care as well as to decrease healthcare cost especially when initiatives of telemedicine integrated [17].

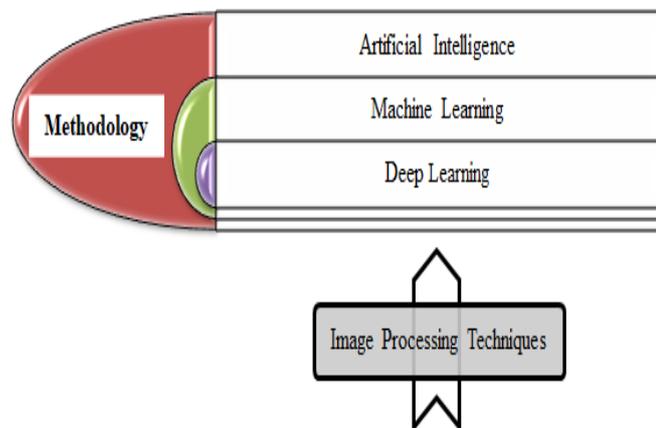


Figure 1. Methodology [5]

Section 2 focuses on the motivation and problem statements of deep learning based analysis of ophthalmology. Section 3 comprehended an anatomy of eye, various eye diseases, and applications of AI such as classification, segmentation and prediction in retinal images. Section 4 discusses in details the literature about the techniques based analysis of ophthalmology. Comparative analysis of techniques and results produced

by different researchers in the field of ophthalmology are furthermore discussed in this part (Table 2 and 3). This section further expands the analysis of three leading eye blindness diseases namely DR, AMD, and Glaucoma (Table 4).

Section 5 discussed the potential challenges and impacts of allied techniques in the field of ophthalmology. Section 6 concludes the review by highlighting the clinical applications, further research work and pathways to study the various diseases, diagnosis, and treatment of eyes disorder.

2. Motivations and Problem Statement

The primary motivation to work in the field of ophthalmology is the concern of human health. It is evident that the eyes are one of the most important organs of sense because the eyes play a vital role in collecting the data from the environment and sends to the brain for further processing. Then brain converts the light received by the eye into usable information. Therefore, the eyes are the key organs that tell us about the world, learn new things, do some creative processes, and also make wonderful memories.

In today's industrialized environment lots of work to be done by using various electronic devices such as tablets, laptops, mobiles, and many more to name. Also, last year, due to the impact of covid-19, most human beings are mainly doing their work from home by using various online platforms. Due to all of these circumstances, most of the peoples are suffering from eyesight issues. Further, the people having a visionary issue are more likely to prone to other diseases such as diabetes, heart-related problems, high blood pressure, stroke, etc., and also have more chances for falling, injury, and depression [18]. Thus, there is a global concern to be addressed because as per the various recent articles, surveys [19], and medical reports, a large number of patients have been diagnosed with various eye diseases such as DR, AMD, Cataract, Glaucoma, Choroidal Neovascularization, Drusen, Keratoconus, and many more to name [20-21]. As per the WHO report, medical experts, and researchers views, these eye diseases are the leading causes of blindness in human beings and their growth will be expanded exponentially as the number of aging populaces are increasing in the world [15].

AI allied techniques have been applied to diagnosis, as well as to predict the prognosis of various ophthalmic/ocular diseases, but still, the lot of potential of AI just needs to be uncovered. As the aspect of AI just started to be revealed, it would be a good prospect for the healthcare industry because AI allied techniques will completely revolutionize vision care. So there is a specific interest in this application of AI to improve ophthalmologic care as well as to decrease healthcare cost. This review dives deeper to study various allied techniques and datasets to cope with the further advancement in the field of ophthalmology. Hence the

motivation of this paper is to pave way for young researchers to perceive eye ocular disorder and to work in the field of ophthalmology to develop a fully autonomous system.

3. Eye Diseases and Application of AI in Retina

To understand and interpret the diagnostic results in a more appropriate way, we should also know about the exact structure of the eye and various types of disease that effected the human eyes. Also, lots of applications of AI in retina images are addressed by the researchers by applying the various AI allied techniques. These are the basis for clinical management decisions that need to understand because further the various processes such as feature extraction, preprocessing of images which includes contrast enhancement, resizing of images, and so on are based on this. Therefore, this section discusses the anatomy of the eye, various eye diseases, and the various application of AI in retina images.

3.1. Anatomy of Eye

Eye is the most highly developed sensory organ of a human body. In-fact, a far larger part of the brain is dedicated to vision than to hearing, taste, touch, or smell combined. When we capture an image, light of that image enters first into pupil and then it reports to the retina which converts that light signal into an electrical signal and then the brain participate in this to make world visible to human [22-23]. Refracting tissue, light-sensitive tissue, and support tissue makes our visionary system [22-23] and enable the humans to see as shown in figure 2.

Refracting tissue- It gives us a clear image by focusing on light. Refracting tissue consists of:

- **Pupil:** The pupil does the same work as the aperture of a camera. It allows the light to enter into the eye. Due to the pupil, the amount of light is controlled in dark bright conditions.
- **Lens:** Behind the pupil, lens is present. The lens can change shape according to the conditions.
- **Ciliary muscles:** The main job of muscle is to render accommodation that change in the shape of the lens.
- **Cornea:** It is mainly responsible for the eye focusing power. Mostly refracting errors of the eyes are due to the abnormality in the cornea.

Light sensitive tissue- Retina is covered in light-sensitive tissue. The working of the retina is to convert light signals into electrical signals and then send the signals to brain for further processing and makes the vision.

Support tissue- It includes:

- **Sclera:** Provide support to the eyeball.

- **Choroid:** Connective tissue between retina and sclera.

So it can be concluded that vision is a very complex process that runs fluently in humans as shown in figure 3. Eyes allows humans to perceive every movement of this colorful world and allow humans to experience each movement of life. Our main connectivity with the surrounding is only because of our vision.

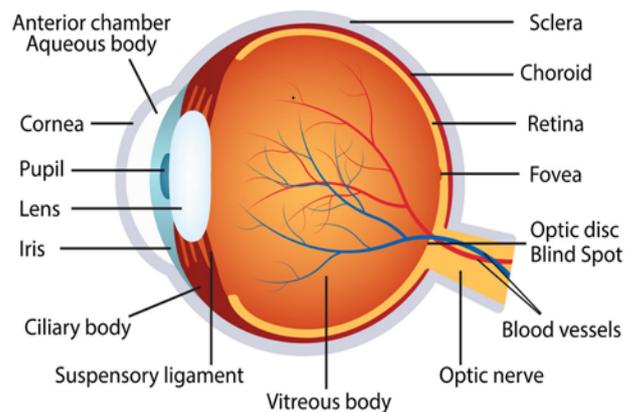


Figure 2. Eye Anatomy [24]

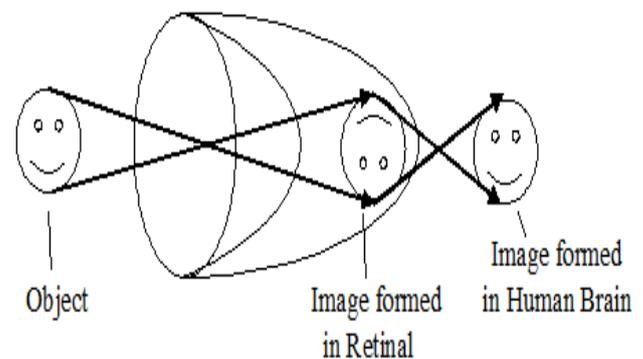


Figure 3. Eye Image Formulation [25]

3.2. Eye Diseases

At present, most of the population suffering from eye diseases is relatively huge in number as compared to the number of medical facilities available [26-27]. As already discussed in the introductory section, the most widespread reasons for blindness in the today's world are:

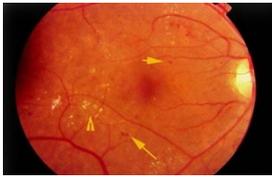
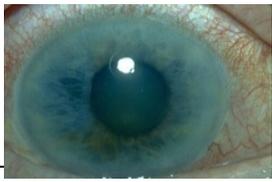
- Diabetic Retinopathy [28]
- Age-related Macular Degeneration
- Glaucoma
- Cataracts
- Macular Edema
- Choroidal Neovascularization (CNV)

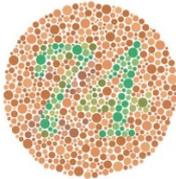
- Retinal Detachment etc.

For the detection of eye diseases, ophthalmologists, a skilled experts perform the eye analysis. They mainly diagnose eye disease, treat it & prescribe the medicines as and when required. In severe cases, the professional perform the eye surgery as well. But at the same instance,

different ophthalmologists have diverse opinions and different treatments are given for the same diseases because some of the diseases related to eye possess the similar symptoms. A list of various types of eye diseases with their causes, sign and symptoms are summarized in table 1.

Table 1. List of Eye Disease and their sign and symptoms [28-29]

S. No.	Disease	Causes	Sign and Symptoms	Images
1	Age-related Macular Degeneration	Damage to the central portion of the retina known as macula.	<ul style="list-style-type: none"> ▪ Blurriness of central vision ▪ Problems seeing in dim light ▪ Objects appearing smaller than their actual size as viewed with one eye and then the other ▪ Appearance of the straight line as distorted 	
2	Diabetic Retinopathy	Diabetes for a long time with fluctuating blood sugar levels.	<ul style="list-style-type: none"> ▪ Fluctuating vision ▪ Blurred vision ▪ Vision loss ▪ Impaired color recognition ▪ Dark spots or strings floating through your vision 	
3	Glaucoma	Flow of fluid in the eye is not the way it should be.	<ul style="list-style-type: none"> ▪ Tunnel Vision ▪ Peripheral vision loss ▪ Sudden vision disturbance in low light condition ▪ Blurred vision ▪ Redness of eyes 	
4	Cataracts	Light cannot pass through to the retina smoothly enough.	<ul style="list-style-type: none"> ▪ Blurred vision or clouded vision ▪ Redness of eyes ▪ Problems seeing at night ▪ Faded view of colors ▪ Seeing 'halos' around lights 	
5	Conjunctivitis (Pinkeye)	Inflames the tissues lining the back of eyelids and covering the sclera.	<ul style="list-style-type: none"> ▪ Blurred vision ▪ Redness appearing in the eyelid or through the white of the eye ▪ Swelling in the conjunctiva ▪ Excessive tearing ▪ Thick yellowish discharge, covering whole eyelashes 	
6	Retinal Detachment	The retina is detached from its underlying tissue holding it in its place.	<ul style="list-style-type: none"> ▪ Suddenly appearance of floaters in the infected eye ▪ Suddenly unexpected appearance of light flashes in one or both the eyes. ▪ Blurred vision ▪ Appearance of a curtain-like shadow. 	
7	Uveities	Group of eye diseases causing inflammation in the uvea.	<ul style="list-style-type: none"> ▪ Blurred vision ▪ Redness of eyes ▪ Pain in eye ▪ Sensitivity to light 	

8	Color Blindness	Pigments found in eye cones have some problems and not able to see the color.	<ul style="list-style-type: none"> ▪ Trouble distinguish between different shades ▪ Failure in seeing different tones or shades of the same color 	
9	Eye Floaters	Jelly like substance (vitreous) within eyes turning into more liquid.	<ul style="list-style-type: none"> ▪ Appearance of dark specks or transparent strings ▪ Movement of the spots in correspondence with the movement of eyes ▪ High visibility of the spots when looked at against a plain bright background like a white wall or blue sky 	
10	Strabismus (Crossed Eyes)	Muscles control the eye, eyelid movement fail to do in coordination.	<ul style="list-style-type: none"> ▪ Double vision ▪ Eye's movement not coordinated with each other ▪ Loss of depth perception ▪ Not able to focus on a particular point at the same instance 	
11	Nearsightedness (Myopia)	Irregular bending of light due to the shape of the eyes.	<ul style="list-style-type: none"> ▪ Blurriness of vision at a distinct object ▪ Eyestrain leading to headaches ▪ At the time of driving, difficulty to identify objects 	
12	Farsightedness (Hypermetropia)	Tiredness in eyes with difficulty focusing on a close object.	<ul style="list-style-type: none"> ▪ Blurriness of vision for close object ▪ Need to squint for getting a better vision ▪ Headache after tasks needing focus on close by objects 	
13	Astigmatism	Vision gets out of focus due to abnormally curved cornea.	<ul style="list-style-type: none"> ▪ Blurriness of vision for close as well as for far object ▪ Headache ▪ Eyestrain leading to headaches ▪ Eye irritation ▪ Difficult to identify object especially at night 	
14	Macular Edema	An unwanted build-up of fluids in the central region of the retina known as macula.	<ul style="list-style-type: none"> ▪ Blurred or wavy vision ▪ Faded view of colors 	
15	Dry Eye Syndrome	Tears failed to provide adequate lubrication for the eyes.	<ul style="list-style-type: none"> ▪ Burning, scratchy or stinging sensation in eyes ▪ Redness of eyes ▪ Blurred vision ▪ Sensitivity to light ▪ Mucus production in or around the eyes 	

Further, one of the leading cause of blindness in today's most of the developing countries or industrialized world is purely dominant by the DR specially in the working adults [30]. DR advancement basically denoted by four stages in medical term namely:

- Mild non-proliferative retinopathy

- Moderate non-proliferative retinopathy
- Severe non-proliferative retinopathy
- Proliferative diabetic retinopathy [31]

Diabetic Macular Edema (DME) is the another most widespread critical form of blindness and almost develops in half of the people having DR [32]. DME may occur at any progress stage of DR.

3.3. Applications of AI in Retina Images

Supervised learning is mainly dominant in the applications of AI. In retina image applications, three principal use case scenarios *classification, segmentation, and prediction* are represented in figure 4.

- **Classification scenarios** are mainly used in retinal image analysis either in binary or multi-class like automatic screening or diagnosis of disease stage or type. ML and DL techniques are applied in this scenario depending on the level of interpretability needed or the size of the dataset available.
- **Segmentation-based** methods are mainly focused on to subdivides the objects in an image. The basic aim of this method is to study the anatomical structure or extracting the meaningful pattern or structure of interest from an image such as like boundaries in 2-dimensional or 3-dimensional images.
- **Prediction scenarios** are mainly focused on the disease progression, future outcome of treatment from an image, and so on. For representing the local region of retain, the prediction method can be used as well.

4. Technique based Analysis of Ophthalmology

In the past decade, numerous articles on the above-highlighted diseases have been published. Various ML and DL algorithms/architecture such as Support vector machine (SVM), K-Means, Decision tree, Alex Net, Vgg-16/19, Inception V3, ResNet etc. have been used in AI eye disease diagnosis. Therefore, the main focus of this section is to review the various techniques proposed by the researcher to diagnose the various eye diseases.

4.1. Systematic review Analysis for Ophthalmology using AI with Allied Techniques

Lee et al. [33] proposed a DL method for effectively classifying the OCT images of normal and AMD people. VGG-16 (Visual Geometry Group-16) convolutional neural network of twenty-one layers with rectified linear unit (ReLU) activation was used for classification. The proposed model achieved an accuracy of 87.63% for the independent image level. Pratt et al. [34] used the computational ability of a deep convolutional neural network to predict the classification accuracy of DR. The proposed model used various data augmentation, normalization which recognizes the various complicated features like exudates, haemorrhages, micro-aneurysms from the retinal images that were not identified by the naked eye. The proposed model was applied on a large dataset consisting of approximately eighty thousand images and achieved a classification accuracy of 75% but the network was not capable enough to learn deep complicated features from retinal images which may relate to some more aspects of DR. Bruijne [35] analysis the various approach of ML and their futuristic applications in the medical domain. The author suggested the two most emerging applications of the medical field namely Neurodegenerative and DR in which ML may use for diagnosis. Nilashi et al. [36] proposed a hybrid knowledge-based system for disease diagnostics. They used the principal component analysis (PCA), Gaussian Mixture model, Classification and regression trees (CART), and fuzzy rule-based techniques for disease prediction. Xu et al. [37] proposed a convolutional neural network approach for the automatic detection of DR. They used various data augmentation such as shearing, rotation, translation, flipping, rescaling for classification. As a result, network performance was enhanced by 94.5% for classifying the hard exudates, red lesions, micro-aneurysms, and blood vessel features. Rakhlin [38] suggested a convolutional neural network classification framework of DL for detecting DR. This approach was applied to Messidor and Kaggle dataset that's available publically. Various preprocessing methods such as normalization, scaling, cropping, etc were applied to the dataset. For enhancing the image quality various data augmentation method such as rotation, flipping, shearing, rescaling, translation, etc. were applied, and then for the final diagnosis, scores were obtained from pre-stages combined in the final stage. As a result proposed framework achieved sensitivity and specificity for Messidor and Kaggle dataset were 99%, 92 % and, 71%, 72% respectively.

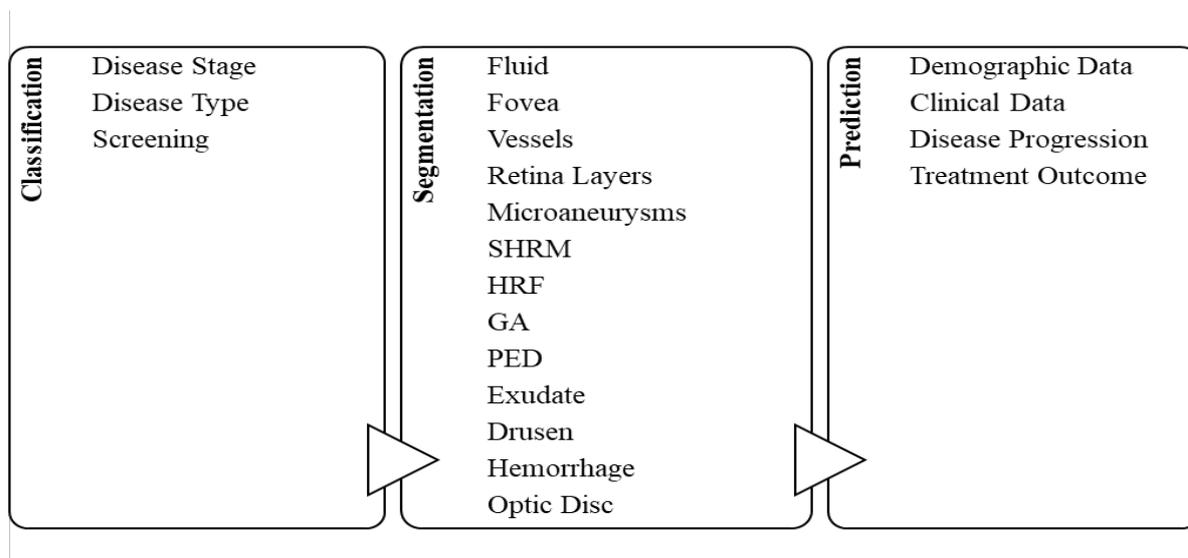


Figure 4. Application of AI in Retina Images [5] (Subretinal hyperreflective material (SHRM), Geographicatrophy (GA), hyperreflective foci (HRF), pigment epithelial detachment (PED))

Kermany et al. [39] proposed an efficient DL method for classifying normal, choroidal neovascularization, diabetic macular edema, and drusen eye disease. The authors used the transfer learning technique with feed-forward on Inception V3 architecture. The proposed model achieved a classification accuracy of 94%. Grssmann et al. [40] suggested a DL algorithm for the prediction of eye diseases such as AMD and Cataract. They trained the various DL architectures by using thirteen classes of a dataset which include nine classes of age-related eye diseases; three stages of late AMD and one class for the un-gradable image. As a result accuracy and k statistics of the proposed model were increased and reached up to 84.2% for the patient who showed the symptoms of either early or late AMD. Kwasigroch et al. [41] proposed a special class coding approach in a deep convolutional neural network that detects and provides the stage of DR of eye disease. The stages of disease were defined numerically such as 0 for No DR, 1 for Mild DR, 2 for Moderate DR, 3 for Severe DR, and 4 for Proliferative DR respectively where level 1 indicates the starting stage of the disease and level 4 indicates the most severe stage of the disease. Detection of DR accuracy and accessing stage of the proposed model was reached up to 82% and 51% respectively and kappa value indicated up to 0.776. Mahiba et al. [42] proposed a hybrid structure descriptor by using the modified convolutional neural network for analysis of the severity of DR in retinal images. This model predicts the stage of glaucoma which was defined as PDR, mellow, moderate, and serious class. Han et al. [43] proposed a support vector machine (SVM) parameter optimization algorithm for classifying the DR. Then K-fold cross-validation (K-CV) with genetic algorithm and grid search were further applied for parameter optimization. The proposed model achieved a

classification accuracy of 98.33% in 31.13 seconds. Kamble et al. [44] suggested an approach by using the convolutional neural network with fine-tuning for automatic detection for diabetic macular edema versus the normal cases on OCT images. The Authors use the effective fine-tuning method with Inception-Resnet-V2 CNN and tested the proposed model on Singapore eye research institute and Chinese university Hong-Kong datasets which are accessible publically.

Wan et al. [45] suggested an approach by using a convolutional neural network (CNN) power with transfer learning and hyper-parameter for automatic detection of DR for fundus images. They include the hyper-parameter with transfer learning to analyze the result on AlexNet, VggNet(-s,-16,-19), GoogleNet, Resnet. The best model i.e VggNet-s with hyperparameter tuning achieved a classification accuracy of 95.68%. Jena et al. [46] proposed an approach for the detection of DR. The proposed model of neural network has only six convolutional layers with a Rectified linear unit (ReLU) and max pooling. Faster training and reduction in computational complexities were the major importance of the proposed model. The proposed model achieved an accuracy of only 91.66% which was far better than some existing models such as medium KNN, Naïve Bayes, and quadratic SVM, etc. Rehman et al. [47] proposed a customized convolutional neural network classification framework for detecting DR. In this approach they suggested a customized five-layer CNN model having two convolutional layers and three fully connected neural layers. AlexNet, VGG-16, and SqueezeNet CNN approaches were applied for the classification of OCT images for DR achieved a classification accuracy of 98.15%. The overall summary of these articles with their silent features are described in table 2.

Table 2. List of studied papers and their salient features including author and year

Authors	Year	Disease Prediction	Pros	Cons
Cecilia S. Lee et al. [33]	2016	Macular Degeneration (Age-Related)	Increase the accuracy of the proposed model.	Used the OCT images captured from a single device, not include the images having distorted or poor eminence and used only those OCT images which go with certain criteria.
Harry Pratt et al. [34]	2016	Diabetic retinopathy	The proposed model applied on a large dataset consisting of approximately eighty thousand images.	The network was not cable enough to learn deep complicated features from retinal images which may relate to some more aspects of DR.
Marleen de Bruijne [35]	2016	Suggested the two most emerging applications of medical filed namely Neurodegenerative and Diabetic retinopathy.	Futuristic applications in the medical domain.	How the result will apply in actual medical practice for treatment because the result having the reliability and interpretability issue and secondly how the system will be learned from week labels.
Mehrbakhsh Nilashi et al. [36]	2017	Diabetes, Breast Cancer prediction	The model achieved an efficient accuracy using a combination of fuzzy rule-based classification and regression trees with noise removal and clustering.	Datasets were not large enough and also not in complex nature. So more interest should be paid to the dataset for disease classification.
Kele Xu et al. [37]	2017	Diabetic retinopathy	A neural network with data augmentation enhances the performance for classifying the hard exudates, red lesions, micro-aneurysms and blood vessel features.	Dataset was the major setback of the system because the system was analyzed only 1000 images.
Alexander Rakhlin [38]	2017	Diabetic retinopathy	Proposed Model uses the Messidor and Kaggle dataset in which the images having the 100 % and 75% gradable quality.ds	The framework has some drawbacks such as its not cable enough to learn deep complicated features from retinal images, used the OCT images captured from a single device and not include the images having distorted or poor eminence.
Daniel S. Kermany et al. [39]	2018	Macular Degeneration and diabetic retinopathy	Increase the accuracy of the proposed model.	Model not achieved state-of-art accuracy i.e. 96% The whole training time was required at least four days. The best model was formed after 300 epochs.
Felix Grssmann et al. [40]	2018	Macular Degeneration (Age Related) Cataract	Accuracy and k statistics of the proposed model is increased.	The algorithm is not capable enough to specify those diseases that were not related to AMD The dataset includes the fundus images of eye disease for only those patients whose ages were more the fifty-five years.
Arkadiusz Kwasiroch et	2018	Diabetic retinopathy (Detection and assessing	Special class coding techniques applied for the detection of DR	The extremely unbalanced dataset was the major setback of the

al. [41]		Stage)	and the accessing stage enhanced the performance of the proposed model.	proposed system.
C. Mahiba et al. [42]	2018	Glaucoma Class comparison of various stages (PDR, mellow, moderate, Serious) Diabetic retinopathy	Hybrid color and texture features with modified convolutional neural network, multiclass lesion classification approach is established which enhanced the classification accuracy	Dataset was the major setback of the system because the system was evaluated on 550 images only out of which 135 images of normal eye indicated no sign of glaucoma disease.
Jiangxue Han et al. [43]	2018	Diabetic retinopathy	Classification accuracy of the proposed model Increase.	Dataset having only 120 images was the major setback for the proposed system.
Ravi M. Kamble et al. [44]	2018	Diabetic Macular Edema	This model may be used for small dataset disease prediction.	Small dataset and fine-tuning constraint such as train the layer from scratch if change the filter configuration were the major setback for the proposed system.
Shaohua Wan et al. [45]	2018	Diabetic retinopathy	Hyper-parameter was coupled with transfer learning to resolve the over-fitting problem and to classify the image more accurately.	The extremely unbalanced dataset was the major setback of the proposed system.
Manaswini Jena et al. [46]	2018	Diabetic retinopathy	Faster training and reduction in computational complexities was the major importance of the proposed model.	Dataset was not large enough and also not in complex nature.
Mobeen-ur-Rehman et al. [47]	2019	Diabetic retinopathy	The proposed model is faster enough because utilize only 2 convolutional layers.	Dataset having only 1200 images was the major area of concern for the proposed system.

4.2. Parameter for Performance Measure

The main aim to evaluate a model on futuristic data or unseen data to estimate the generalization accuracy of a model. The basic parameters to evaluate the performance of the model are:

- Accuracy [48]
- Sensitivity / Recall Rate
- Specificity

- Precision / Positive predictive value
- Kappa Value
- Confusion Matrix
- Roc
- F1 Score etc.

Since the past & present studies mainly focus on these listed parameters for the model performance measure, the same parameters have been analyzed in the presented comparative analysis and described in table 3.

Table 3. Comparative Analysis including Performance Measure

Study	Technique	Architecture	Dataset	Accuracy	Sensitivity	Specificity	Area under ROC Curve
[33]	Deep Convolutional Neural Network	VGG-16	OCT scans from 2006 to 2016 Heidelberg Spectralis (Heidelberg Engineering, Heidelberg, Germany) imaging database	Independent image level : 87.63% Macula level : 88.98% Patient level : 93.45%	92.64%	93.69%	Independent image level : 92.78% Macula level : 93.83% Patient level : 97.45%

[34]	Deep Convolutional Neural Network	x ¹	Kaggle	75.00%	30.00%	95.00%	Not Given
[35]	Suggested the two most emerging applications of medical filed namely Neurodegenerative and Diabetic retinopathy.	x	X	Not Given	Not Given	Not Given	Not Given
[36]	Principal component analysis (PCA), Gaussian Mixture model, Classification and regression trees (CART) and fuzzy rule-based techniques.	x	Pima Indian Diabetes, Mesothelioma, WDBC, StatLog, Cleveland and Parkinson's telemonitoring datasets	Not Given	Not Given	Not Given	Not Given
[37]	Convolutional Neural Network	x	Kaggle	94.50%	Not Given	Not Given	Not Given
[38]	Deep Convolutional Neural Network	x	Kaggle Messidor-2	Not Given	Messidor-2 : 99.00% Kaggle : 92.00%	Messidor-2 : 71.00% Kaggle : 72.00%	Messidor-2 : 97.00% Kaggle : 92.00%
[39]	Deep Convolutional Neural Network	Inception V3	OCT (Kaggle)	94.00%	97.80%	97.40%	99.90%
[40]	Deep Convolutional Neural Network	x	1: Fundus images from the AREDS are available at dbGAP (http://dbgap.ncbi.nlm.nih.gov) accession, phs000001.v3.p1). 2: KORA data are available on an individual project agreement with KORA at (https://epi.helmholtz-muenchen.de/) 3: publicly available at(https://github.com/RegensburgMedicalImageComputing/ARIANNA). 4: National Institute of Health	Healthy Fundus Images : 94.3% Fundus Images with the sign of early or late AMD : 84.2%	Not Given	Not Given	Not Given

[41]	Deep Convolutional Neural Network	x	Eyepacs http://www.eyepacs.com/ https://nei.nih.gov/health/diabetic/retinopathy	82.00%	Not Given	Not Given	Not Given
[42]	Deep Convolutional Neural Network	x	Government Medical College	98.41%	Not Given	Not Given	Not Given
[43]	Support Vector Machine (SVM) K-fold cross-validation (K-CV) with genetic algorithm and grid search were further applied for parameter optimization.	x	Messidor	98.33%	Not Given	Not Given	Not Given
[44]	Convolutional Neural Network	Inception-Resnet-V2 CNN	Singapore eye research institute Chinese university HongKong dataset	100.00%	Not Given	Not Given	Not Given
[45]	Deep Convolutional Neural Network	VggNet-s	Kaggle	95.68%	Not Given	Not Given	Not Given
[46]	Convolutional Neural Network	x	Publically available High-Resolution Fundus (HRF) dataset	91.66%	Not Given	Not Given	Not Given
[47]	Convolutional Neural Network	AlexNet, VGG-16, and SqueezeNet CNN	Messidor	98.15%	98.94%	97.87%	Not Given

†

1

4.3. Analysis of DR, AMD and Glaucoma detection through Deep learning Approach

Diabetic Retinopathy, Age-related Macular Degeneration, and Glaucoma are the three leading causes of blindness in adults & the elderly as per the researcher's views in ophthalmology. Therefore, the results of some studies related to ophthalmology based on three leading eye diseases have been comprehended in table 4.

4.3.1. Diabetic Retinopathy (DR)

DR is the leading cause of vision loss which is growing exponentially in the working age populace of adulthood. It's a common cause of diabetic complications. Blood

vessels are affected by the impact of this disease which further affects the light-sensitive tissues of retina. The basic reason for the progression of this disease is lack of enough oxygen being received by the retina [29]. The advancement of DR is mainly denoted by four stages in medical terms namely: mild non-proliferative retinopathy, moderate non-proliferative retinopathy, severe non-proliferative retinopathy, and proliferative diabetic retinopathy [49] as shown in figure 5. As compared to early stages like mild, moderate non-proliferative retinopathy, later stages are the more severe form in which new fragile blood vessels are growing. These blood vessels leak the blood into vitreous which affects the vision of person. Various symptoms are exhibited by this disease [29] such as blurry vision, impaired color recognition, dark spots or strings floating through your vision, fluctuating vision, etc..

4.3.2. Age-Related Macular Degeneration (AMD)

AMD is one of the other severe causes of vision loss in the human beings which impact normally at the age of

† x – Not Available

fifty years or more. The macula is adversely impacted by the effect of this disease which is the central portion of the retina. AMD diseases are further classified into two categories namely 'Wet' and 'Dry' [29]. Blood vessel abnormally grows under the retina when the person is impacted by Wet AMD. In the case of Dry AMD, light-sensitive cells or tissues degenerate under the macula. At the earlier stage no clear signs and symptoms possessed by this disease other than the degradation of light vision. But at the later stage this disease shows many symptoms [29] such as appearing of object size smaller when viewed by one eye as compared to other eye, difficult to view in low light, the formation of blind spots, etc.

4.3.3. Glaucoma

Glaucoma is another cause of blindness which damage the optic nerve system of eyes [50]. It's impact on the eye fluid by increasing the intraocular pressure so that the optic nerve system is not able to transmit the images in the brain. This disease grows exponentially day by day and as a result permanent vision loss in a few years can be reported. Glaucoma is further classified into two categories known as *open / wide-angle glaucoma* and *angle-closure glaucoma* [50]. In wide-angle eye conditions, flows of fluid within the eyes behave abnormally but the trabecular meshwork looks normal

which is the drain structure of an eye [50]. In angle-closure glaucoma which also known as acute or chronic or narrow-angle glaucoma, intraocular pressure increase in massive amount which affects the drainage on the eyes. Redness in the eyes, severe pains, blurry vision, tunnel vision, vision disturbance in low light, etc. are the symptoms obsessed by this disease [29], [50].

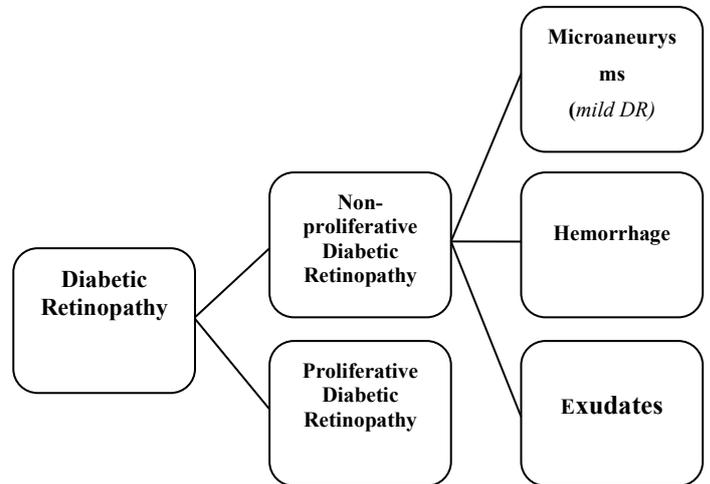


Figure 5. Classification of Diabetic Retinopathy

Table 4. Comparative analysis of DR, AMD and Glaucoma detection through Deep Learning approaches

Authors	Year	Disease Prediction	Architecture Algorithm /	Dataset	Accuracy %	Sensitivity %	Specificity %	Area under ROC Curve
Abramoff et al. [51]	2016	DR	Alex Net / VGG Net	Messidor-2	x	96.8	87	0.98
Gulshan et al. [52]	2016	DR	Inception V3	Messidor-2 & EyePacs-1	x	87	98.5	0.99
Acharya et al. [53]	2016	DR	SVM	Kasturba Medical College	88.63	86.2	91	x
Lee et al. [33]	2016	AMD (Exudate)	VGG-16	x	87.6	84.6	91.5	0.92
Gargeya R, Leng T [54]	2017	DR	Customized CNN	Kaggle	x	x	x	0.97
Ting et al. [55]	2017	Glaucoma	VGG-19	SiDRP	x	96.4	93.2	0.94
Ting et al. [55]	2017	AMD	VGG-19	SiDRP	x	93.2	88.7	0.93
Burlina et al. [4]	2017	AMD	Alex Net	AREDS	x	x	x	0.96
Abramoff et al. [56]	2018	DR	Alex Net / VGG Net	USA	x	87.2	90.7	x

Li et al. [57]	2018	Glaucoma	Not Given	Guangdong	x	95.6	92	0.98
Grassman et al. [40]	2018	AMD	Alex Net / VGG Net / Google Net / Inception V3 / Res Net	AREDS	x	84.2	94.3	x
Treder et al. [58]	2018	AMD (Exudate)	Inception V3	x	100	x	x	0.98
Kermany et al. [39]	2018	DR & AMD	Inception V3	Kaggle	94	97.8	97.4	99.9
Soorya M et al. [59]	2018	Glaucoma	Customized (Novel Blood Vessel Detection)	VIER	97	x	x	x
Jiangxue Han et al. [43]	2018	DR	SVM	Messidor	98.33	x	x	x
Mobeen-ur-Rehman et al. [47]	2019	DR	AlexNet / VGG-16 / SqueezeNet CNN	Messidor	98.1	98.9	97.8	x

As per the above analysis, CNN models provide the most encouraging results. Also, these learning algorithms mainly use the FFA and OCT images for the analysis purpose. Authors have used different datasets for result demonstrations and the same has been listed in the comparative analysis.

4.4. Transfer Learning

Transfer of learning means the reuse of previously acquired knowledge and skills or pre-trained model in new learning of problem-solving situations [5]. Transfer learning techniques are very useful in data sciences to solve real-world problems because, generally in real-time scenario do not have a million of labeled data to train complex model. Therefore, transfer learning is very popular in DL because by using comparatively small data, a deep neural network can be trained [60]. In general, there are three types of transfer learning: *from prior knowledge to learning, from learning to new learning, and from learning to application.*

In these approaches, instead of training a model from the scratch or CNN as a fixed feature extractor, pre-trained model weights can be additionally fine-tuned as shown in figure 6. But the major concern while applying this particular approach that a large amount of training data are required from the target domain for the successful implementation of fine-tuning [5]. Researchers have used the concept of transfer learning to detect various ocular disorders. For instance, Grinsven et al. [61] used this concept to detect hemorrhages from color fundus images. Takahashi et al. [62] detected the stages of DR by using the transfer learning technique. Ting et al. [63] also proposed the system for detecting DR, AMD, and

Glaucoma by using this concept. Therefore, various researchers have used the transfer learning techniques to detect the ocular disorder but still, the potential of the approach needs to be uncovered.

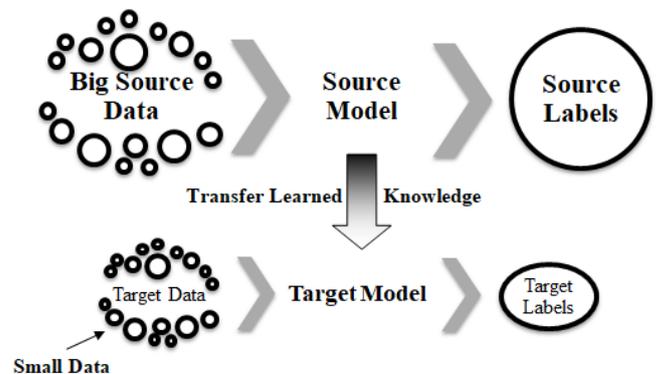


Figure 6. Transfer Learning Technique

5. Potential Challenges faced in Ophthalmology

In the health care organization, AI with allied techniques have shown promising results but none of them achieve the appropriate accuracy, sensitivity, specificity, etc. that can be used for autonomous disease diagnosis in a real environment. Therefore, the deployment of these models for real-time clinical practitioner purposes is still a challenging task. DL has revolutionized the present era but still, lots of improvement is required to enhance the

quality of listed parameters in the area as described in the above tables.

The other main challenges being faced by these techniques include: ethical challenges, applying image preprocessing techniques for either filtration or contrast enhancement, making a cost-effective system for the health care industry/organization, reducing the training time of the model etc. And many more to say, the datasets used for training purposes are gathered from homogeneous populations only. Also, the unavailability of the dataset of some rare diseases like retinoblastoma, ocular tumours, etc., and some common diseases which are not captured frequently like cataracts, etc., affect the development in the area of AI.

5. Conclusion and Future Scope

This paper presented a comprehensive review of AI with allied techniques in ophthalmology. In ML and DL-based approaches, CNN provides the most promising results. In further research work, healthcare organizations, authorities, and ophthalmologists should work jointly to embrace these technologies and techniques, which may deeply impact the medical/clinical society and may also facilitate the promising medical practitioners in the future. Patients in different remote areas may remotely access the resources that can be provided by the AI with allied techniques applications. To increase the reliability and stability of the modernistic system, OCT, FFA, images are required to be incorporated together because most of the patients suffer from multiple diseases. Future research is intended towards model deployment for clinical practitioners and for designing the cost-effective autonomous DL system. The integration of DL with cloud and telemedicine is another futuristic pathway for the modern society lifestyle. Also, by using the potential of transfer learning, the time and cost of healthcare can be reduced. To conclude, AI with allied techniques may reshape and revolutionize the medical community especially in the area of ophthalmology.

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