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Review

Ophthalmic diagnosis using deep learning with fundus images – A critical review

Sourya Sengupta[a,b,*], Amitojdeep Singh[a,b], Henry A. Leopold[a,b], Tanmay Gulati[c], Vasudevan Lakshminarayanan[a,b]

[a] Theoretical and Experimental Epistemology Lab, School of Optometry and Vision Science, University of Waterloo, Ontario, Canada
[b] Department of Systems Design Engineering, University of Waterloo, Ontario, Canada
[c] Department of Computer Science and Engineering, Manipal Institute of Technology, India

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ABSTRACT

An overview of the applications of deep learning for ophthalmic diagnosis using retinal fundus images is presented. We describe various retinal image datasets that can be used for deep learning purposes. Applications of deep learning for segmentation of optic disk, optic cup, blood vessels as well as detection of lesions are reviewed. Recent deep learning models for classification of diseases such as age-related macular degeneration, glaucoma, and diabetic retinopathy are also discussed. Important critical insights and future research directions are given.

1. Introduction

In the United States, more than 40 million people suffer from acute eye related diseases that may lead to complete vision loss if left untreated [1]. Many of these diseases involve the retina. Glaucoma, diabetic retinopathy and age-related macular degeneration are some of the most common retinal diseases. Fig. 1 is a fundus photograph of the retina with various structures and disease manifestations.

Glaucoma is one of the major causes of blindness; it is estimated that by 2020 glaucoma will affect almost 80 million people in the world [2]. The two main types of this disease are *open-angle* glaucoma and *angle closure* glaucoma. About 90% of the affected people suffer from primary open-angle glaucoma [3]. Traditionally glaucoma is diagnosed by calculating what is called the optic cup to disk ratio. Neuroretinal rim loss, visual fields, and retinal nerve fiber layer defects are also some of the measures used by ophthalmologists for diagnosis. Diabetic retinopathy (DR) is another common cause of human vision loss. It is expected that the percentage of diabetic patients worldwide will increase from 2.8% in 2000 to 4.4% in 2030. Diabetes is quite common in persons above the age of 30; uncontrolled diabetes can lead to DR [4]. Early stages of DR are less severe and clinically managed. It is characterized by various abnormalities in the retina such as microaneurysms (MA) and other small lesions caused by rupture of thin retinal capillaries; these are early indicators for DR. Some of the other manifestations include hard exudates, soft exudates or cotton wool spots (CWS), hemorrhages (HEM), neovascularization (NV) and macular edema (ME) (see Fig. 1) [5]. Age-related macular degeneration (AMD) is another common vision related problem. It can result in loss of vision in the middle of the visual field in the human eye, and with time there is a complete loss of central vision [6]. In the United States, about 0.4% people from age range 50 to 60 suffer from this disease and around 12% people who are over 80 years old are affected [7]. Health-care in most countries suffers from a low doctor to patient ratio. Due to an overburdened patient-care system, diagnosis and proper treatment becomes error-prone and time-intensive. On the other hand, sufficient amount of data are generated every day in various health clinics and hospitals, but it is rarely utilized for computer aided diagnostics (CAD) applications and not available publicly [5]. During the past few years, artificial intelligence algorithms have been used in classifying different types of data including images. In retinal image analysis, the traditional CAD system architectures takes several predefined templates and kernels to compare with manually annotated and segmented parts of these images. Deep learning models are extremely powerful architectures to find patterns between different nonlinear combinations of different types of data. It derives relevant necessary representations from the data without the requirement of manual feature extraction. In recent years, deep learning algorithms are replacing most of the traditional machine learning algorithms and in most of the cases outperforming the traditional classifiers. General

* Corresponding author at: Theoretical and Experimental Epistemology Lab, School of Optometry and Vision Science, University of Waterloo, Ontario, Canada.
E-mail address: s28sengu@uwaterloo.ca (S. Sengupta).

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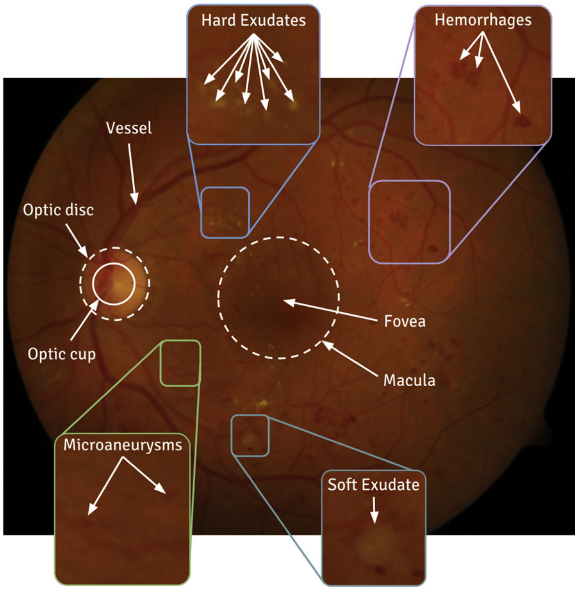


Fig. 1. Fundus photograph showing retinal morphologies and pathologies [5].

details of the different deep learning architectures like Alexnet [8], VGG [9], Sparse Autoencoder [10] can be found in [11].

Among different retinal imaging modalities, fundus imaging is widely used. The biomarkers play an important role in clinical intervention and different biomarkers corresponding to different retinal diseases can be detected by inspection of a fundus image. Optic disc (OD) to optic cup (OC) diameter ratio is very crucial for glaucoma diagnosis and hemorrhages are important biomarkers for diabetic retinopathy (DR) diagnosis. Hence detection of the biomarkers in the fundus image is crucial and sometimes it is necessary to segment some specific parts of the fundus images prior to diagnosis. Segmentation is an important step to crop the region of interest for further processing. An image may possess some unwanted distortions which hamper proper processing. Noise can be present in the images and the illumination may not be uniform across the image. Hence for proper visualization, different parts of an image should be segmented.

In this review, we will discuss recent articles (starting from year the 2014) where different deep learning architectures have been implemented on retinal fundus images for applications in clinical ophthalmology. In addition we also review computer-aided image segmentation methods for fundus images. Fig. 2 shows yearwise trends in the published literature and also number of papers for different application areas. It can be seen that the number of publications on deep learning for fundus imaging for ophthalmic diagnosis has increased significantly since 2014 (the plot shows trend up to 2018 as all the papers have not come out of 2019). Papers published in medical imaging conferences, e.g. MICCAI, IPMI, ISBI, SPIE Medical Imaging, EMBC, CVPR and journals like IEEE TMI, IEEE TBME, Elsevier AIIM, and Pattern Recognition are included in this review. Papers were also collected through search queries on Google scholar and Pubmed with various keywords, e.g. deep learning, ophthalmology, image segmentation, classification, fundus photos, image datasets (e.g. MESSIDOR, DRIVE, STARE, EYEPACS, RIGA, etc.), retina. The different available datasets are summarized in Table 1. Papers are classified into subsections according to the classification and segmentation task. The three segmentation tasks are OD, OC segmentation, lesion segmentation, and blood vessel segmentation which are the primary steps towards glaucoma and diabetic retinopathy diagnosis respectively. Separate papers for major retinal disease (e.g. glaucoma, DR, AMD) diagnosis are the other 3 sections. Each of these sections is divided according to the architecture of the deep learning model. Different performance measures like accuracy (Acc), sensitivity (SN), specificity (SP), area under curve (AUC), F1 score, DICE Score are mentioned for different application areas. Please, refer to [12] for details on the performance indicators discussed herein. Table 1 gives an overview of existing fundus image datasets which are commonly used in deep learning models. Section 2 reviews the commonly used deep learning architecture, Section 3 consists of various applications of deep learning for detection and diagnosis of ophthalmic diseases from retinal fundus images. We conclude with a comprehensive discussions and critical insight followed by a brief overview of future research direction.

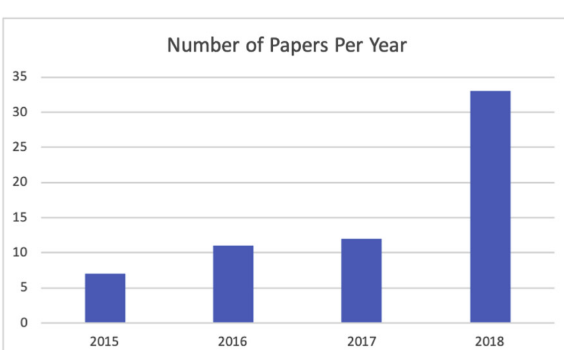
2. Deep learning background

Deep learning is a category of machine learning algorithms which use deep neural networks to learn different tasks. Convolutional neural networks (CNN) are the most popular deep learning models used for computer vision tasks including medical imaging. Other deep learning algorithms implemented in the works include ensemble of CNN, transfer learning, combination of CNN with conventional machine learning, fully convolutional neural networks and autoencoders. In this section commonly used deep learning architectures and methods of training are discussed in brief. More details can be found in [13].

2.1. Types of deep learning architectures

This subsection briefly introduces various deep learning architectures used in the literature.

Convolutional neural networks (CNN): CNN models are typically comprised of four types of layers - Convolutional layer, Dense layer, Pooling layer, and Dense layer. Activation functions provide non-linearity to the model and replicate firing of a neuron. Backpropagation is the algorithm to tune weights and make the model learn. Batch normalization and dropout are the common ways to achieve faster convergence and avoid overfitting. The various layers used in typical CNN are:



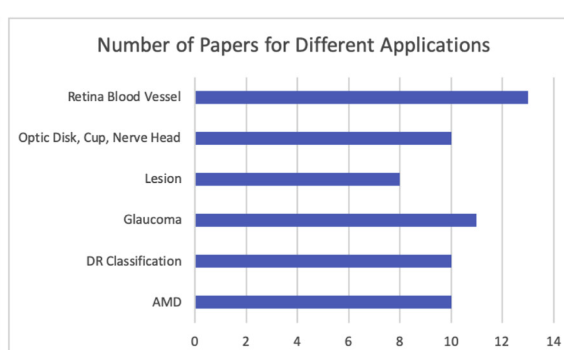


Fig. 2. Analysis of reviewed articles.

Table 1
Fundus image dataset information.

Dataset name	Annotations	Camera	Availability
Glaucoma detection, OD, ON segmentation			
ACHIKO-K [14]	258 manually annotated images, 114 glaucoma, 144 normal		Available online
DRIONS-DB [15]	110 images, 23.1% chronic glaucoma and 76.9% eye hypertension		Available online
DRISHTI-GS [16]	101 images	Fundus camera with FOV 30°	Available online
HRF [17]	45 images, 15 images each of healthy, DR, glaucomatous patients	Canon CR-1 fundus camera with FOV 45°	Available online
SEED [18]	235 images, 43 glaucoma and 192 normal		Not available online
ORIGA [19]	650 retinal images		Not available online
RIGA [20]	760 retinal fundus images		Available online
REFUGE [21]	1200 annotated images		Available online
CLEOPATRA [22]	298 images		Not available publicly
MESSIDOR [23]	1200 images	Color video 3CCD camera with FOV 45°	Available online MESSIDOR-2 upon request
ONHSD [24]	99 images	Canon CR6 45MMNf with FOV 45°	Available online
RIM-ONE [25]	783 images	Nidek AFC-210 Can EOS 5D Mark II	Not Available publicly
DR and lesion detection			
DIARETDB1 [26]	88 images, 84 DR and 4 normal	Fundus camera FOV 50°	Available online
DIARETDB0 [27]	130 images, 20 normal and 110 DR		Available online
Kaggle/ EyePACS [28]	35126 images		Available on registration
e-optha [29]	47 images with exudates, 35 without. 233 normal images and 148 MA images		Available online
Retinopathy Online Challenge [30]	100 fundus images	Topcon NW 100, Topcon NW 200, Canon CR5-45NM	Available on registration
MESSIDOR [23]	1200 images	Color video 3CCD camera with FOV 45°	Available online MESSIDOR-2 upon request
AMD detection			
AREDS [31]	Approx. 206,500 images		Upon request
KORA [32]	images from 2840 patients		Available online
Blood vessel segmentation			
CHASE [33]	28 images		Available online
DRIVE [34]	40 images, 33 normal and 7 mild DR	Canon CR5 non-mydriatic 3CCD camera with FOV 45°	Available online
STARE [35]	400 images, blood vessel annotation on 40 images	TRV50 fundus camera with FOV 35°	Available online

1. Convolutional layer: Performs convolution with a given kernel size and step to generate feature maps.
2. Activation layer: Applies an activation function like ReLU on the output of convolutional layer.
3. Pooling layer: Pooling is used to reduce the feature size. Typically the convolutional layer after pooling has twice the number of kernels than the previous layer to preserve the information.
4. Fully connected layer: It is the same as the feed forward neural network and it is used as the final layer for classification. CNN without a fully connected layer are called fully convolutional networks and are used in tasks like image segmentation.

Fully convolutional networks: As evident from the name, these are made of locally connected convolutional layers like downsampling (convolution), upsampling (deconvolution) and pooling. The absence of a dense layer leads to faster computation and reduced number of parameters. Typically these have a downsampling path made of convolutional layers and an upsampling path made of deconvolutional layers. These can include skip connections which bypass more than one layer and transfer information across layers with different resolution for better learning.

Autoencoders: It is an unsupervised neural network that is used to efficiently compress and encode data and then reconstruct data from the reduced encoded representation. It is comprised of an encoder which reduces the dimensions, a bottleneck which has the lowest dimensions of input data, a decoder which learns to reconstruct the data from the encoding and reconstruction loss which is used to measure the performance of the decoder's output with respect to the original data. The network is trained using backpropagation to minimize the reconstruction loss in order to get the reconstructed data to be as similar to the original data as possible.

2.2. Training methods

Training of a neural network is usually performed by initializing random weights and tuning them using stochastic gradient descent and backpropagation. Following are some techniques to train a neural network employed in literature on ophthalmic diagnosis using fundus images.

Transfer learning: Deep learning algorithms usually require large datasets for efficient training. The datasets available in ophthalmic diagnosis are usually small and can lead to overfitting of the model. Transfer learning presents a solution to this by initializing the weights by fitting on a large dataset, often of a dissimilar domain. This is followed by finetuning of weights of some or all of the layers of the model on the target dataset.

Ensemble learning: This involves training several deep learning models independently and then polling their results for a given data sample to get the prediction for it. Majority voting which involves selecting the most frequent result as the final prediction is the commonly applied approach. It is based on the assumption that errors of independently trained models are not likely to coincide.

3. Application in retinal image processing techniques

To the best of our knowledge, the very first application of computer-aided methods to clinical ophthalmology was by Goldbaum et al. in 1994 [36]. The authors concluded that a neural network could be trained and modeled as efficiently as a trained reader for glaucoma visual field interpretation. Another early application was the use of a neural network to predict astigmatism after cataract surgery [37].

3.1. Fundus image applications

3.1.1. Optic disc (OD), cup (OC) and nerve head segmentation (ONH)

CNN based methods: The first implementation of deep learning architecture in OD segmentation was proposed by Lim et al. [38] in 2015. During this time (2015) CNN had already been successfully implemented in various biomedical segmentation problems [39,40]. The authors developed CNN for calculating cup-to-disc ratio as a measure of the presence of glaucoma to overcome the need for hand-crafted feature extraction methods of shallow machine learning algorithms. Since this publication, there have been significant advances in deep learning architectures. Maninis et al. [41] experimented on fundus images to segment both blood vessels and OD together using the VGG model [9] with a smaller modification of layers. Feng et al. [42] performed both OD and exudates segmentation. Utilizing the concept of unified segmentation architecture like [41] or [42], Al-Bander et al. [43] proposed deep learning based segmentation architecture for both OD and fovea together. Recently Mitra et al. [44] reported some drawbacks of Al-Bander et al. [43], as Al-Bander et al. used grayscale images which resulted in some data loss. Their proposed architecture in [43] utilized dropout layers at different stages which arbitrarily dropped neurons resulting in further data loss. To address and overcome these shortcomings, [44] used batch-normalization in CNN for OD detection. More recently Liu et al. [45] used fundus images to implement deep learning based segmentation architectures to segment glaucomatous OD. A previously trained model with ImageNet database was used and the output layer was replaced by a new output layer with 2 nodes for 2 different classes – normal and glaucoma. In contrast with the previous studies, this work gathered a larger amount of data from different sources with different image qualities and resolutions. Hence this model can be considered as more robust than most of the other works.

Fully convolutional neural networks: A fully convolutional neural network (FCN) of U-Net architecture, very popular for biomedical image segmentation problems [46], was modified by replacing convolutional layers with residual blocks, (inspired by He et al. [47]) and used to build a unified architecture. Sevastopolsky [48] also used U-Net architecture (with reduced number of filters in each convolutional layer) to segment both OD and OC decreasing both time and space complexity. In [48] the authors segmented both OD and OC separately. Edupuganti et al. [49] implemented one-shot segmentation pipeline for segmenting OD and OC for glaucoma analysis. ImageNet (http://www.image-net.org/) was used for initialization of the FCN encoder. Sun et al. [50] employed a faster R-CNN architecture as a deep object detection architecture to segment OD from fundus.

Self organizing maps (unsupervised learning): Ghassabi et al. [51] introduced a consolidated approach of ONH and cup segmentation using Self Organizing Maps (SOM) for glaucoma assessment. It was effective even when there were non-obvious neuroretinal rim, peripapillary atrophy and low intensities of the optic cup as it gave a better performance (as shown by the overlapping error). The various methods to segment OD, OC, and ONH are compared in Table 2.

3.1.2. Lesion segmentation and detection

Lesion detection is an important step for DR screening. Different deep learning based studies on lesion detection and segmentation are discussed below.

CNN based methods: Haloi [53] was the first to implement deep neural network to detect MA for DR screening. He used a 5 layer pixel based deep neural network to detect MA. Grinven et al. [54] proposed a methodology to detect hemorrhages in retinal fundus images by classifying the lesions. CNN was implemented and a selective sampling algorithm was introduced to dynamically select misclassified training

Table 2
Summary of OC, OD and ONH segmentation results.

Reference	Architecture	Dataset	Acc	SN	SP	AUC	F1 score	DICE score	Overlapping error
Lim et al. [38]	3-class CNN	MESSIDOR, SEED-DB				0.847			
Maninis et al. [41]	CNN DRIU	DRIVE, STARE, DRIONS-DB, RIM-ONE					0.822, 0.831, 0.971, 0.959		
Feng et al. [42]	FCN	DRIONS-DB		93.12%	99.56%		0.9093		
Sevastopolsky [48]	U-Net with lesser filters	DRIONS-DB, RIM-ONE						0.94, 0.95	
Edupuganti et al. [49]	VGG16 FCN	Drishti-GS					0.967		
Al-Bander et al. [43]	CNN	MESSIDOR	96.89%						
Mitra et al. [44]	CNN	MESSIDOR, EyePACS	99.05%, 98.78%		99.14%, 98.17%				
Sun et al. [50]	Faster R-CNN	ORIGA Dataset	93.1%						
Liu et al. [45]	ResNet50 FCN	3 centers from Sydney, HRF, RIM-ONE	91.6%	86.7%	96.5%	0.97			
Ghassabi et al. [51]	WTA neural network, SOM neural network	Stein Eye Institute, Labbafi Nedjad hospital of Iran, RIMONE, DIARETDBO							9.6% (ONH seg.) & 25.1% (cup seg.)
Tan et al. [52]	10-layer CNN	CLEOPATRA-DB		87.58%-exudates 71.58%-dark lesions					

samples. It was found to decrease the time of epochs and also to enhance the AUC as compared for the CNN with no selective sampling. All previous studies [53,55,54] tried to detect different lesions separately, Tan et al. [52] applied a 10 layer CNN to automatically segment exudates, MA and hemorrhages using a single framework. [56] Deep learned feature vectors using 4 convolutional layers and 1 fully connected layer from CNN (trained using LeNet architecture) were created by combining handcrafted features drawn from the green channel of the normalized and equalized image. Lam et al. [57] used a deep learning architecture to detect the presence of five classes of red lesions, i.e. normal, microaneurysms, hemorrhages, exudates, retinal neovascularization using EyePACS. The CNN was trained with 1050 images using GoogleNet architecture [11]. Patches were extracted with varying shapes and sizes according to the size of the lesions. For testing, a sliding window was introduced to make a full scan over the whole image by the CNN to give a multiclass outcome probability. Son et al. [58] proposed a cost-effective method to localize lesions which improved precision during training by using regional annotation of findings. Khojasteh et al. [59] introduced an innovative framework and architecture for CNN by inserting a pre-processing layer for recognition of HE and MAs. Chudzik et al. [60] presented a segmentation method which utilized similar a combination of CNN and codebook structure.

Autoencoders: Shan et al. [55] found biological cell nuclei detection and MA detection problems quite similar and employed stacked sparse autoencoder (SSAE) proposed in a nuclei detection problem [61]. Classification was done for MA and non-MA patches. Image patches were passed through the SSAE to obtain features and a softmax layer was used to classify the labels. The previous studies mainly addressed detection of MA, but in DR screening bigger hemorrhages are also important. Badar et al. [62] used an encoder-decoder based FCN architecture calculating pixel-wise segmentation of multi-class retinal pathologies (exudates, hemorrhages & cotton wool spots) and achieved state of the art results.

CNN and conventional machine learning (hybrid model: Orlando et al. [63] also worked on detection of both MA and HE together using 3 different data-sets combining hand-crafted feature and deep features learned from CNN. Previously there were very few studies analyzing the effectiveness of combining two feature methods. The different techniques for lesion segmentation and detection are compared in Table 3.

3.1.3. Retinal blood vessel segmentation

Retinal blood vessels are important for eye disease diagnosis. In this section we will discuss different results on vessel segmentation from retinal fundus images.

Autoencoders and random forest: In one of the first studies in this domain, Maji et al. [64] used a hybrid of random forest and deep neural network (DNN) for blood vessel segmentation. The DNN performed unsupervised learning of vessel dictionaries using sparse trained denoising auto-encoders (DAE). It was followed by supervised learning of random forest on the DNN response. However this method could not outperform the conventional approaches.

CNN based methods: Around the same time as [64], Liskowski et al. [65] proposed a deep learning based blood vessel segmentation framework of retinal fundus images datasets. Images were standardized by subtracting the mean from every patch and dividing it by the standard deviation to avoid contrast and brightness fluctuations in the image pixels. It outperformed many existing approaches. In another pioneering work, Melinscak et al. [66] used a deep neural network, inspired by a similar problem of segmenting neuronal membranes [67] using DNN as pixel classifier. To improve the performance proposed in [64], Maji et al. [68] used an ensemble of 12 CNNs to segment retinal blood vessels. The networks were trained individually on the dataset of 60,000 randomly chosen $3 \times 31 \times 31$ patches. During inference, the responses were averaged to form the final segmentation. RMSProp was used as the optimizer and a minibatch size of 200 was used. Leopold et al. [69] investigated use of CNN to segment blood vessels using ADAM parameter optimization. The green channel of each image was used for classifying vessels and non-vessels image pixels. The model gave the probability maps of every pixel to classify between vessel and non-vessel. Gabor filters were used to smooth and finalize the decision. Liu et al. [70] used densely Connected CNN to segment blood vessels in fundus images. A 17 layer architecture was used and the layer number X got input from the output of the previous $X - 1$ layers and thus used the back layers of the network as features of the front layer.

Fully convolutional neural networks: Fu et al. [71] found several disadvantages in [66] as it used pixel based approach and hence Fu et al. proposed a fully CNN architecture based on image-to-image training system. Multi-scale and multi-level CNN was used and combined with conditional random field (CRF) as recurrent neural network (RNN) to model the long-range interactions between pixels. Zhang et al. [72] applied U-Net which was also used in other works for OD segmentation [42,48]. The authors proposed a modified U-Net based architecture to segment blood vessels from fundus images. By adding some additional labels on boundary areas the problem was converted into a multi-class task. Stochastic gradient descent (SGD) was used to optimize model parameters. Oliveira et al. [73] implemented deep learning architecture for blood vessel segmentation. Previous deep learning architectures only processed raw data but here, initially, stationary wavelet transform was applied to each training image to keep multi-resolution information. A fully convolutional network was used to generate feature maps. Stochastic Gradient Descent with Nesterov momentum was implemented during training to decrease the cross-entropy loss function. The final probability maps for all of the image patches were merged and averaged to get a final value and thresholding was done to get the ultimate unique segmentation. Lepetit-Aimon et al. [74] introduced the LRFFCN which did better than the U-Net [46]in retinal artery and vein classification and manifested high sensitivity in comparison to other state-of-the-art algorithms to segment vessels.

Table 3
Summary of lesion detection and segmentation results.

Reference	Architecture	Dataset	Acc	SN	SP	AUC
Haloi [53]	5 layer CNN	MESSIDOR, ROC	96%	97%	96%	0.982, 0.98
Shan et al. [55]	Transfer learning (SSAE)	DIARETDB	91.38%			0.916
Grinven et al. [54]	CNN using OxfordNet	MESSIDOR, EyePACS		91.9%, 83.7%	91.8%, 85.1%	0.972, 0.895
Tan et al. [52]	10 layer CNN	CLEOPATRA	87.58%, 71.58%			
Orlando et al. [63]	CNN using LeNet architecture	e-optha, MESSIDOR				0.8812, 0.8932
Lam et al. [57]	CNN using GoogleNet3	EyePACS, e-optha	98%			0.95
Son et al. [58]	CNN with residual, reduction, avg. pooling, atrous pyramid pooling layers	Seoul National University Bundang Hospital				0.9895
Badar et al. [62]	Encoder–decoder based FCN	MESSIDOR	97.86%	80.93%	98.54%	
Khojasteh et al. [59]	CNN with preprocessing after 1st conv layer	DIARETDB1	90.0%			
Chudzik et al. [60]	FCNN &Auxiliary Codebook	E-Optha MA &E-Optha EX		0.8666	0.9998	0.982

Table 4
Summary of retinal blood vessel segmentation results.

Reference	Architecture	Dataset	Acc	SN	SP	AUC
Maji et al. [64]	RF and DNN	DRIVE	93.27%			0.9195
Liskowski et al. [65]	CNN	DRIVE, STARE, CHASE_DB	97%			0.99
Maji et al. [68]	ConvNet ensemble	DRIVE	94.7%			0.9283
Fu et al. [71]	Multi-scale and multi-level CNN	DRIVE, STARE, CHASE_DB1	95.23%, 95.85%, 94.89%	.7603%.7412%.7130%		
Leopold et al. [69]	FCN using RETSEG13	DRIVE	94.78%	68.23%	98.01%	0.9707
Zhang et al. [72]	CNN(U-Net)	DRIVE, STARE, CHASE_DB1	95.04%, 97.12%, 97.7%	87.23%, 76.73%, 76.7%	96.18%, 99.01%, 99.09%	0.9799, 0.9882, 0.99
Oliveira et al. [73]	CNN	DRIVE, STARE, CHASE_DB1	95.76%, 96.94%, 96.53%	80.39%, 83.15%, 77.79%	98.04%, 98.58%, 98.64%	0.9821, 0.9905, 0.9855
Liu et al. [70]	Densely connected CNN	DRIVE	95%			
Lepetit-Aimon et al. [74]	FCNN with large receptive field	MESSIDOR, STARE, DRIVE	95.9%			
Chudzik et al. [77]	CNN	DRIVE, STARE		0.7881, 0.8269	0.9741, 0.9804	0.9646, 0.9837

CNN and conventional machine learning (hybrid models): Similar to [75] Hu et al. [76] proposed an image-to-image deep learning vessel detection model using the CNN combined with conditional random field (CRF). The main contribution of this work was to combine features from each of the convolutional layers and to incorporate class-balanced cross-entropy loss to improve detection accuracy. VGG-16 model was used. Chudzik et al. [77] gave a two stage architecture combining visual codebook framework with CNN. The different approaches for retinal blood vessel segmentation are compared in Table 4.

3.1.4. AMD classification

Recent results on AMD disease classification from fundus images are discussed below.

CNN and conventional machine learning (hybrid model): One of the very first publications in this domain was done by Burlina et al. [78] where they used OverFeat features from DCNN (pretrained in ImageNet database) and used Support Vector Machine to classify between early and intermediate stages of AMD. Later Based upon the work of Burlina et al. [78], Horta et al. [79] reported a hybrid method employing deep image features and random forest to combine different patient non-visual data, e.g. lifestyle, cataract, demographics with the image for AMD classification. To extract deep image features, the CNN (pre-trained with 1.2 million image data) was used. The deep features combined with the non-medical, non-visual information of the patients were used to train a Random Forest Classifier to perform binary classification for higher severity AMD and lower severity of AMD. The combined features were found to achieve higher accuracy than individual feature set. Grassmann et al. [80] proposed a deep learning based classification architecture to predict the severity of AMD. In this study, an ensemble of several convolutional neural networks was used to classify among 13 different classes of AMD [81]. Six different neural networks (AlexNet, GoogLeNet, VGG, ResNet, Inception-v3, 1-ResNet-v2) were used independently to train the model. With the result obtained from each of the individual neural networks, a random forest ensemble model was developed.

CNN based methods: Burlina et al. [82] used a completely data-driven approach using deep CNN (DCNN-A) to perform a binary classification between early-stage AMD and advanced stage AMD using the same AREDS database implemented on AlexNet model [11]. This method was compared with the previous methods combining both deep features and transfer learning. Govindaiah et al. [83] reported an extended study of [84] with a modified deeper VGG16 architecture. The macula was chosen as a Region of Interest and images were resized to a common reference level. For comparison with the VGG16, a 50 layer Keras implementation of residual neural network was used. Matsuba et al. [85] published a new approach for detecting AMD disease from ultra wide-range Optos ophthalmoscope color fundus images. Three convolutional layers, with ReLU unit and max-pooling layers were used to perform this experiment on pre-processed fundus images. The accuracy of DCNN using images was compared with human grading by six ophthalmologists. Tan et al. [86] used a 14 layer CNN to detect AMD. Three fully-connected layers, 4 max-pooling layers, and 7 convolutional layers were implemented in this work. Adam optimization [87] was used for tuning CNN model's parameters. Govindaiah et al. [88] used an ensemble network consisting of state of the art network architectures thereby reaching a satisfactory performance level in AMD classification. The different techniques for AMD detection are compared in Table 5.

3.1.5. Glaucoma classification

CNN based methods: One of the early publications in glaucoma classification using deep learning was by Chen et al. [89]. They implemented a CNN with dropout and data augmentation. A six layers deep CNN with 4 convolutional layers of progressively decreasing filter size (11, 5, 3, 3) followed by 2 dense layers was used. Improving their previous work, Chen et al. [89,90] presented a model using Contextualized CNN (C-CNN) architecture. It combined the output of

Table 5
Summary of AMD detection results.

Reference	Architecture	Dataset	Acc	SN	SP	AUC
Burlina et al. [78]	Deep features with SVM	AREDS	95%	96.4%	95.6%	
Burlina et al. [82]	DCNN using AlexNet	AREDS	91.6%			0.96
Horta et al. [79]	DCNN	AREDS	79.04%	66.34%	88.95%	0.8476
Govindaiah et al. [83]	VGG16	AREDS dataset	92.5%			
Matsuba et al. [85]	DCNN	Tsukazaki Hospital				99.76%
Tan et al. [86]	CNN	Kasturba Medical College	95.45%	96.43%	93.45%	
Grassmann et al. [80]	Ensemble (AlexNet, GoogleNet, VGG, ResNet, Inception-v3, 1-ResNet-v2)	AREDS and KORA		94.3%	84.2%	
Govindaiah et al. [88]	Ensemble network (Inception-ResNet-V2 &Xception)	AREDS	86.13%			

convolutional layers of multiple CNN to a final dense layer to obtain the softmax probabilities. The 5 C-CNN model which was a concatenation of outputs of last convolutional layers of 5 CNNs each of depth 6 (5 convolutional layers + 1 MLP). Chakravarty [91] was first to propose a method for joint segmentation of OD, OC and glaucoma prediction. In this method CNN feature sharing for different tasks ensured better learning and over-fitting prevention. The parts of the model that were shared with U-net contained 8 times fewer number of CNN filters than the conventional U-net. It used an encoder network to downsample the feature and then a decoder network to restore the image size. Two different convolutional layers were applied on the decoder network's output for OC and OD segmentation. The OC and OD segmentation masks were merged into separate channels and CNN was applied to it. The outputs of the CNN and encoder output were combined and fed to a single neuron to predict glaucoma. With a lower number of parameters this method achieved comparable performance with existing architecture, e.g. [92]. Zhixi et al. [93] used the Inception-v3 architecture to detect glaucomatous optic neuropathy. Here researchers graded the images by trained ophthalmologists before applying the algorithm. Local space average color subtraction was applied in pre-processing to accommodate for varying illumination. Chai et al. [94] presented a framework on a dataset of fundus images obtained from various hospitals by incorporating both domain knowledge and features learned from a deep learning model. This method was also used in other applications [63]. The disk image provided local CNN features, the whole image provided global CNN features whereas domain knowledge features were obtained from diagnostic reports. It used a total of 25 features including 3 numerical features: intraocular pressure, age, and visual acuity as well as 22 binary features such as swollen eye, headache, blurred vision and failing visual acuity. The disk and whole images were fed to two separate CNN while domain knowledge features were fed to a third branch consisting of a fully connected neural network. These three branches were concatenated by a merge layer followed by two dense layers and a logistic regression classifier. Perdomo et al. [95] used curriculum learning [96] in DCNN's to achieve better results using a reduced set of training examples.

Feed forward neural network: Asaoka et al. [97] used a 3 layer deep feed-forward neural network (FNN) on a private dataset of 171 glaucoma images.

Autoencoder: Pal et al. [98] introduced the G-EyeNet architecture which proved to be more robust given its results on low quality images. The comparison of different studies for glaucoma detection is provided in Table 6.

3.1.6. Diabetic retinopathy classification

In this section different applications of deep learning algorithms for diabetic retinopathy detection are described briefly.

CNN based methods: Abrámoff et al [99] described DR detection using a device called IDx-DR X2.1. Here retinal images were used in a CNN based on AlexNet to classify different types of DR. The main classes of diseases were referable DR (rDR), vision-threatning DR (vtDR) and proliferative DR (pDR). The CNN-based architectures were designed to characterize and detect optic disc, fovea and lesion characteristics. Using a retinal fundus image dataset consisting of 70,000 images, Colas et al. [100] proposed a DR grading method. There were 4 different classes of DR images in the dataset- no DR, mild DR, moderate DR and acute DR. Gulshan et al. [101] used deep learning algorithms to identify the presence of diabetic retinopathy. Five different types of DR and the presence of macular edema were graded by expert clinicians. Inception v-3 model was used, stochastic gradient descent method for optimization was used and batch normalization was done with a pre-trained model with ImageNet data. Gargeya et al. [102] reported a deep learning architecture to classify between normal and DR fundus images and also reported heatmap visualization of the result. Using the principle of deep residual learning, the CNN model was built to learn deep discriminative features for detecting DR. From average pooling layer of CNN, 1024 features were obtained. Metadata features related to 3 metadata variables, i.e. pixel height, pixel width and field of view of the image were appended to form a final feature vector with 1027 features. A second level tree-based gradient boosting classifier was designed. Quellec et al. [103] discussed a method to detect referable DR as well as lesions with ConvNet architecure using o_O Solution [28]. Unlike the previous studies this method attempted to classify between normal and DR on both image level and pixel level. This proposed model was mainly based on visualization methods of CNN. Heatmap generation modifications were proposed for this purpose to jointly improve the quality of DR and lesion detection. Takahashi et al. [104] graded different stages of the presence of DR using GoogleNet architecture. Unlike in other previously published literature the authors graded the images manually on their own to test the accuracy of the methodology. The model was designed using two different ways, first with manual staging of three color photographs (AI1) and second with manual staging of only one color photograph (AI2). From the GoogleNet model – 5 top layers were deleted, the crop size was expanded and the batch size was reduced. 20-Fold cross-validation was used and for comparison AI1 was also trained with ResNet model. Garcıa et al. [105] applied different architectures of CNN for DR detection. As a pre-processing step, images were subtracted from color mean and rescaled to 256 × 256. Data augmentation by flipping the images was done to increase the robustness. In this work several neural network architectures using various learning rates and different number of layers were used to compare different architectures to calculate the highest accuracy among all. Lin et al. [106] used entropy images instead of original fundus images and showed that the feature maps are generated faster and competently. Table 7 compares the different DR detection methods described in this subsection.

4. Conclusion and discussions

This review addressed different applications of deep learning methodologies in ophthalmic diagnosis.

Table 10 gives a brief overview of state-of-the-art deep learning approach and traditional methods for computer-aided diagnosis. It can be noticed that in most of the cases deep learning methods outperformed traditional methodologies.

From a clinical perspective, the automated diagnosis methods can

Table 6
Summary of glaucoma detection results.

Reference	Architecture	Segmentation	Dataset	Acc	SN	SP	AUC	F-score
Chen et al. [89]	6 layer CNN	NA	ORIGA, SCES				0.831, 0.887	
Asaoka et al. [97]	3 layer FNN	NA	Private: 171				0.926	
Chakravarty et al. [91]	Multi-task CNN	OD segmentation by U-Net	REFUGE				0.9456	
Zhixi et al. [93]	Inception-v3	NA	Private:48000+		95.6%	92.0%	0.986	
Chai et al. [94]	MB-NN	OC and OD, using CNN	Private: 2554	91.51%				
Chen et al. [90]	C-CNN	OD, using Hough transform	ORIGA, SCES				0.838, 0.898	
Perdomo et al. [95]	DCNN	OD and OC, using CNN	RIM-ONE-v1, RIM-ONE-v3, DRISHTI-GS1	89.4%(RIM-ONE-v1)			0.82 (DRISHTI-GS)	
Pal et al. [98]	Autoencoder with CNN classifier	OD segmentation using U-Net	DRIONS-DB				0.923	

be used as a support tool for the clinicians. Clinicians can also diagnose more accurately after performing segmentation of some specific sections of the image for disease detection. Certain robust implementations, e.g. IDx [99] have been FDA approved for automated diabetic retinopathy detection. These automated methods are useful in areas where there is a scarcity of trained specialists.

In Tables 8 and 9, the papers are divided according to the various deep learning architectures and training strategies. As evident from Tables 2–7, for a particular task different authors have used different datasets, different approaches and different performance indicators. Though there are no generalized criteria to discuss drawbacks or advantages of different methods, we offer a few insights encompassing the relation of different architectures' efficacy in performing a task. In Table 2, different OD, OC, ONH segmentation tasks have been discussed. For this particular task Messidor and RIM-ONE are the most popular datasets and U-Net (in general a fully convolutional network) seems to perform pretty well as demonstrated by Feng [42] and Edugupanti et al. [49]. In Table 3 results from the literature of lesion segmentation have been summarized. It should be noted that with the increasing complexity of a given task, the complexity of the model is also increased. For example, authors used 5 layer CNN, 10 layer CNN and GoogleNet architecture respectively for MA detection, MA + HE + exudates detection and MA + HE + exudates + retinal neovascularization works respectively [53,52,57]. For the blood vessel segmentation task in Table 4, DRIVE and STARE are the most popularly used datasets. Here, as in OD detection papers, U-Net like FCN architectures achieved better performance. In general, the segmentation tasks suffer from a huge class imbalance problem, hence accuracy alone is not a good measure. Both sensitivity, specificity should be considered as important factors before concluding the effectiveness of a method. In several retinal diagnosis approaches, the segmentation task is often closely related to disease classification tasks. For example, OD & OC segmentation is frequently performed for glaucoma diagnosis as shown in Table 6 [90,91,94,95,98] since cup to disk ratio is an important clinical measure. Similarly Tables 3 and 7 are related as lesion detection can be also be viewed as a DR detection task from pixel level annotations instead of image level grading. In both classification and segmentation tasks CNNs with different state-of-the-art architectures are frequently used. However, since the advent of U-Net, similar fully convolutional encoder-decoder architectures are getting more prevalent in segmentation tasks as can be observed from Tables 8 and 9. Pre-training or transfer learning has an important role, especially in classification problems [112]. In DR detection (Table 7), Gulshan et al. [101] outperformed other DR detection tasks with a model pre-trained with the ImageNet dataset. Pre-training not only reduces the number of trainable parameters but also helps to reduce the chances of overfitting by initializing weights in a meaningful way. However, it is worth noting that in AMD detection (Table 5) the state-of-the-art result was achieved without pre-training as shown in Table 5. Tan et al. [86] trained from scratch and achieved better results than with pre-training network. Hence it is difficult to conclude if pre-training plays a pivotal role or not but intuitively it can be said that a model is largely dependent on the type of tasks, number of annotated training examples and how the architecture is built. A number of factors contribute simultaneously to make a model more suitable for a given task.

The previous reviews published in this domain empphasized clinical aspects or traditional machine learning algorithms or focused on hardware implementation of artificial intelligence in ophthalmic diagnosis [113–117]. None of them dealt with detailed reviews of different state-of-the-art deep learning algorithms used in ophthalmic diagnosis with retinal fundus images. Hence, to the best of our knowledge, this is the first review article of deep learning algorithms and performance outcomes for ophthalmic diagnosis using retinal fundus images. Deep learning applications in retinal images are quite useful and effective. They reduce the need of manual feature extraction as the methodologies are mainly data-driven.

5. Future research

However, there are still some limitations which need to be addressed. Some of these and also some possible solutions are discussed below:

- Unlike computer vision problems, large datasets are not available.

Table 7
Summary of diabetic retinopathy detection results.

Reference	Architecture	Dataset	Acc	SN	SP	AUC
Abrámoff et al. [99]	CNN AlexNet	Messidor-2		96.8%	87.0%	
Colas et al. [100]	CNN	EyePACS		96.2%	66.6%	0.946
Gulshan et al. [101]	CNN Inception v-3	EyePACS-1, Messidor-2		90.3%, 87%	98.1%, 98.5%	0.991, 0.99
Gargeya et al. [102]	CNN deep residual learning	EyePACS, MESSIDOR e-Optha2		94%	98%	0.97
Quellec et al. [103]	ConvNet	EyePACS, e-optha, DiaretDB1				0.954, 0.949, 0.955
Takahashi et al. [104]	CNN GoogleNet, ResNet	9939 images	80%			
Garcia et al. [105]	CNN AlexNet	EyePACS	83.68%			
Lin et al. [106]	CNN	EyePACS	86.10%	73.24%	93.81%	0.92

Table 8
Architecture information for segmentation.

Reference	Synopsis	Way of training	Application
Convolutional neural network			
Lim et al. [38]	CNN to calculate cup-to-disc ratio instead of ML algorithms	Training from scratch	OD segmentation
Maninis et al. [41]	VGG model with a few modifications of the layers	Training from scratch	OD segmentation
Al-Bander et al. [43]	Segmented grayscale images using dropout layers	Training from scratch	OD segmentation
Mitra et al. [44]	Batch normalization added in CNN to avoid data loss	Training from scratch	OD segmentation
Liu et al. [45]	Used fundus images &output layer classified normal and glaucoma images	Pre-trained model on ImageNet (transfer learning)	OD segmentation
Haloi [53]	Used a 5 layer pixel based DNN	Training from scratch	MA detection
Grinven et al.[54]	CNN with selective sampling algorithm for dynamic selection of misclassified training samples	Training from scratch	Lesion detection
Tan et al. [52]	10-layer CNN for segmentation using a single framework	Training from scratch	EX, MA &HE segmentation
Lam et al. [57]	CNN trained using LeNet architecture with the introduction of a sliding image during testing to give a multi-class outcome probability	Training from scratch	Lesion detection
Son et al. [58]	Used regional annotation of findings thereby improving precision	Training from scratch	Lesion detection
Khojasteh et al. [59]	Used a pre-processing layer before CNN	Training from scratch	HE &MA segmentation
Chudzik et al. [60]	Used a CNN &codebook structure	Training from scratch	HE &MA segmentation
Liskowski et al. [65]	Patch-wise deep learning based approach	Trained from scratch	Blood vessel segmentation
Melinscak et al. [66]	Deep neural network as pixel classifier	Trained from scratch	Blood vessel segmentation
Maji et al. [68]	Ensemble of 12 CNNs trained on 3X31X31 patches	Trained from scratch	Blood vessel segmentation
Leopold et al. [69]	Gabor filter and deep neural network with Adam Optimizer	Trained from scratch	Blood vessel segmentation
Liu et al. [70]	17 layer dense CNN architecture	Trained from Scratch	Blood vessel segmentation
Fully convolutional neural networks			
Feng et al. [42]	Segmentation using FCN	Training from scratch	OD &exudate segmentation
Sevastopolsky [48]	Used U-Net architecture with lesser convolutional filters	Training from scratch	OD &OC segmentation
Edupuganti et al. [49]	Implemented a one-shot segmentation pipeline	ImageNet for initializing FCN encoder	OD &OC segmentation
Sun et al. [50]	Used a faster R-CNN architecture	Training from scratch	OD segmentation
Fu et al. [71]	multi-scale, multi-level CNN with conditional random field (CRF) as RNN	Trained from scratch	Blood vessel segmentation
Zhang et al. [72]	Modified U-Net with stochastic optimization	Trained from scratch	Blood vessel segmentation
Oliveira et al. [73]	stationary wavelet transform followed by a FCN to generate feature maps	Trained from scratch	Blood vessel segmentation
Lepetit-Aimon et al [74]	FCN based architecture LRFFCN	Trained from scratch	Blood vessel segmentation
Self organizing maps (unsupervised learning)			
Ghassabi et al. [51]	Unified approach for ONH &cup segmentation for glaucoma assessment	Training from scratch	ONH &cup segmentation
Autoencoder			
Shan et al. [55]	Used stacked sparse autoencoder to obtain features and softmax layer was used to classify labels	Training from scratch	MA classification
Badar et al. [62]	Used an encoder-decoder based FCN	Training from scratch	EX, HE &cotton wool spots segmentation
Maji et al. [64]	Sparse denoised autoencoders based unsupervised learning of vessel dictionaries	Trained from scratch	Blood vessel segmentation
Hybrid model			
Orlando et al. [63]	Combined hand-crafted features &deep features learned using CNN	Training from scratch	MA &HE segmentation
Hu et al. [76]	Combining CNN features and conditional random field (CRF)	Training from scratch	Blood vessel segmentation

Also there is a scarcity of manual annotation of data. Deep learning equated large amounts of data since the model mainly learns from the inherent pattern of the data. Hence this is a major problem in this field. Generative models proposed by Goodfellow et al. can be an important and useful solution to mitigate this problem. This is a very state-of-the-art area of this research and very few efforts have been made so far [118,119] to explore the possibilities of generative modeling to synthesize new fundus images with annotations and with proper clinical relevance. Generative adversarial network, variational auto-encoders are some very popular architecture for image generation. Successful application of these can be used to generate large amounts of clinically relevant synthetic data. It will not only help to increase the amount of available data but also it will help to avoid the privacy issues.

- A major problem is the unavailability of standardized KPIs (Key Performance Indicators) for measuring the performance of a particular model. Different researchers use different indices to measure their work. Due to this variability one cannot easily compare different deep learning architectures for a given disease state. For example, in lesion detection, Lam et al. [57] achieved an accuracy of 98% which is higher than most of the other state-of-the-art methods, whereas in terms of AUC Haloi [53] achieved 0.982 which is higher than other reported AUC. Leopold et al. [12] took this into consideration and also suggested more generalized metrics such as G-mean and MCC to measure a model's effectiveness.
- Due to the difference in the camera settings, there is a possibility of domain shift problem. In most of the literature, training and test data come from same image distribution. But in real life this is not always the case. Hence this domain shift can cause a major damage in real life application if not taken care of beforehand. Transfer learning has been used for different applications in this area [49,82,120,121]. Domain Adaptation is a sub-domain of Transfer Learning where data for both training and testing are extracted from different distributions. In real world, it is not always possible to get test data and training data from the same distribution. Hence the model should be robust enough to deal with data from a different distribution for test purpose. Often it is found that accuracy decreases due to this domain shift problem. More emphasis should be given to deep domain adaptation approaches in order to create robust models which can be implemented for real world ophthalmic diagnosis. Wang et al. [122] have discussed different deep domain adaptation algorithms which can be used to address this problem. A

Table 9
Architecture information for classification.

Reference	Synopsis	Way of training	Application
Convolutional neural network			
Burlina et al. [82]	Deep CNN with AlexNet model	Trained from scratch	AMD classification
Govindaiah et al.[83]	Modified VGG16 architecture	Trained from scratch	AMD classification
Matsuba et al. [85]	Three convolutional layers, with ReLU unit and max-pooling layers	Trained from scratch	AMD classification
Tan et al. [86]	14 layer CNN	Trained from scratch	AMD classification
Govindaiah et al. [88]	Ensemble of several CNN models	Trained from scratch	AMD classification
Chen et al. [89]	CNN with 6 layers and dropout	Training from scratch	Glaucoma classification
Chen et al. [90]	Combined output from multiple convolutional channels at dense layer	Training from scratch	Glaucoma classification
Chakravarty et al. [91]	Joint segmentation of OD, OC and glaucoma prediction	Training from scratch	Glaucoma classification
Zhixi et al. [93]	Inception-v3 to detect glaucomatous optic neuropathy	Training from scratch	Glaucoma classification
Chai et al. [94]	Neural network on domain knowledge and image features	Training from scratch	Glaucoma classification
Perdomo et al. [95]	Curriculum learning and deep morphometric features	Training from scratch	Glaucoma classification
Abramoff et al. [99]	AlexNet based CNN for DR classification	Training from scratch	DR classification
Colas et al. [100]	DR grading into 4 classes	Pre-trained model on ImageNet (Transfer Learning)	DR classification
Gulshan et al. [101]	Identified presence of 5 types of DR and macular edema	Pre-trained model on ImageNet (Transfer Learning)	DR classification
Gargeya et al. [102]	DR classification using deep residual learning	Training from scratch	DR classification
Quellec et al. [103]	Detecting referable DR using ConvNet with o_O solution	Training from scratch	DR classification
Takahashi et al. [104]	Grading DR stages using modified GoogleNet	Training from scratch	DR classification
García et al. [105]	Compared various CNN architectures for DR detection	Training from scratch	DR classification
Lin et al. [106]	Used entropy images to generate faster and competent feature maps	Training from scratch	DR classification
Feed forward neural network			
Asaoka et al. [97]	3 layer Feed forward neural network	Training from scratch	Glaucoma classification
Hybrid models			
Burlina et al. [78]	CNN features and support vector machines to classify between different stages	Pre-trained on ImageNet (transfer learning)	AMD classification
Horta et al. [79]	Deep image features and random forest to combine different patient non-visual data, e.g. lifestyle, cataract, demographics	Pre-trained on ImageNet (transfer learning)	AMD classification
Grassmann et al. [80]	an ensemble of several convolutional neural networks and random forest	Trained from scratch	AMD classification
Autoencoder			
Pal et al. [98]	G-EyeNet – combination of encoder decoder and traditional CNN	Training from scratch	Glaucoma classification

Table 10
Deep learning vs traditional methods

Application	Reference	Method	Dataset	Acc	SN	SP	AUC	F1 score
OD segmentation	Maninis et al. [41]	CNN DRIU	DRIVE, STARE					0.822, 0.831
	Soares et al. [107]	Wavelets	DRIVE, STARE					0.762, 0.774
Lesion detection	Haloi et al. [53]	5-layer CNN	Messidor	96%	97%	96%	0.988	
	Antal et al. [108]	Ensemble model	Messidor	90%	90%	91%	0.989	
Retinal vessel segmentation	Leopold et al. [69]	FCN using RETSEG13	DRIVE	94.78%				
	Staal et al. [34]	kNN Classifier	DRIVE	94.22%				
AMD classification	Burlina et al. [78]	AREDS	Deep features with SVM	95%	96.4%	95.6%		
	Kankanahalli et al. [109]	AREDS	SURF features with random forest	91.8%	91.3%	92.3%		
Glaucoma classification	Perdomo et al. [95]	DCNN	RIM-ONE-v1, RIM-ONE-v3, DRISHTI-GS1	89.4%				
	Gajbhiye et al. [110]	KNN		89%				
DR classification	Gargeya et al. [102]	CNN Deep Residual learning	EyePACS, MESSIDOR e-Optha2		94%	98%	0.97	
	Roychowdhury et al. [111]	kNN (DREAM)	MESSIDOR		98.88%	48.72%		

recent paper explored adversarial domain adaptation technique to segment blood vessels of STARE dataset with a model trained on DRIVE dataset and it outperformed other works in terms of F score [123]. In the context of ophthalmic diagnosis, it can be an important and necessary direction for future research.

Conflict of interest

The authors declare no conflict of interest.

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