Machine Learning Algorithms for the Analysis of Age-Related Macular Degeneration Based on Optical Coherence Tomography: a Systematic Review

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Abstract. Age-related macular degeneration (AMD) is one of the leading causes of irreversible blindness. Every year, there is an increase in the number of patients with AMD worldwide. To date, the primary method in diagnosing AMD is optical coherence tomography (OCT), which provides the most visual data for identifying disease biomarkers. However, a growing volume of research requires optimizing the work of an ophthalmologist to minimize diagnostic errors. In this regard, the study aimed at integrating computer vision applications into the OCT image processing system is gaining popularity since it allows not only to identify images with the most likely presence of AMD but also to determine the stages of this disease, localize biomarkers and obtain a prognosis for the dynamics of its development. The variety of such approaches is expressed in the application of various machine learning algorithms, metrics for evaluating their effectiveness, sources of input information, and work verification. This statistical review analyzes examples of works devoted to computer vision algorithms in the study of OCT images for diagnosing, staging, or predicting the dynamics of AMD and highlights the features and trends within this area.

Keywords: optical coherence tomography; age-related macular degeneration; machine learning; deep learning.

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1 Introduction

Age-related macular degeneration (AMD) is a multifactorial disease, one of the leading causes of irreversible blindness worldwide [1]. According to the massive Beaver Dam Eye Study, over ten years of follow-up, the incidence of AMD in individuals aged 43–54 years increased by an average of 4.2%, and in those aged 75 years and older, by 46.2% [2]. Rising morbidity leads to decreased working capacity and disability of the population, which is a medical and social problem [3–5].

The disappointing dynamics of the disease's spread have generated many reviews on various aspects. Thus, an analysis of the AMD prevalence shows risk groups and the epidemiological situation over time [6–8], while the study of risk factors and pathogenesis provides the trend in the distribution of the patients, possible preventive measures, and method to slow down the progression [9–13]. Finally, many studies are devoted to modern advances in treating AMD [14–19].

The timely detection and staging of AMD based on already explored pathogenetic reactions is the leading assurance of successful therapy, which is the aim of various diagnostic methods.

To date, the predominant approaches for diagnosing AMD and other retinal diseases are methods of visualization of the retinal layers. These include autofluorescence photography, dilated eye examination, fundoscopy or ophthalmoscopy, visual acuity eye testing, fundus photography, fluorescein angiography, tonometry, and optical coherence tomography (OCT). The most recognized and frequently used are the non-invasive Color fundus photography (CFP) and OCT methods [20].

The advantages of the CFP are high data acquisition speed, reproducibility, high resolution, and simple image acquisition. Thanks to that, CFP is a widely used method for digital imaging of the retina. However, the quality of CFP images in the presence of macular edema without stereoscopic visualization is limited and time-consuming [21].

In turn, OCT provides three-dimensional cross-sectional *in vivo* visualization of the retina to assess the layers' thickness and the presence or absence of pathologies. Moreover, it helps monitor treatment effectiveness, necessity, and expected response [22–24]. In 1991, OCT was first described as a possible retinal imaging tool [25]. Since then, OCT has become of great importance in diagnosing diseases of the macular area, particularly AMD [26]. Drusen, hypopigmentation or hyperpigmentation of the retinal pigment epithelium, atrophy of the pigment epithelium and choriocapillaris, neovascularization, detachment of the pigment epithelium and retinal neuroepithelium, intraretinal deposits, cystic edema of the neuroepithelium, subretinal scarring are typical retinal changes that are detected using spectral domain OCT (SD-OCT) method in patients with AMD [27, 28]. Thus, in diagnosing and monitoring AMD, OCT methods are the most effective and promising for further development [29].

The possibility of storing and processing digitized archives of diagnostic images opens up vast opportunities for the development of methods for their automatic processing. Intelligent data processing methods have been widely used [30–32]. A sufficient amount of information presented in digital form makes it possible to carry out statistical analysis and intelligent data processing [33]. Modern computer vision methods based on machine learning (ML) algorithms allow the most efficient visual information processing [34]. Recent studies in integrating recommender systems based on ML algorithms into ophthalmology demonstrate impressive results in reducing the time for diagnosis and the impact of the human factor [35, 36].

There are many reviews on using ML algorithms to analyze visual information from retinal scans. CFP data analysis is represented by a rather extensive range of studies, primarily due to the prevalence of devices [37, 38]. After the introduction of SD-OCT devices with high scanning speed and sufficient visualization accuracy, an increase in the number of reviews of the use of ML for OCT data analysis [39] and both OCT and CFP began [40–42]. However, these reviews do not provide detailed information about all articles on the number of images in the dataset [39], the use of image preprocessing [39, 40], validation to assess the generalizing ability of algorithms, which demonstrates the stability of the algorithm [39–41], and the use of ML in image biomarker segmentation tasks [42]. Due to insufficient research features under consideration, it is not always possible to assess the factors that increase the likelihood of developing an effective application for analyzing OCT images with AMD. In turn, analyzing the dynamics of these research traits over time can demonstrate their "natural selection", which identifies the most viable ones.

The increase in the incidence of AMD determines the need for the introduction of productive tools for the intelligent analysis of medical images to improve the effectiveness of patient treatment, including dynamic monitoring. A convenient tool for specialists who assume the use of machine learning methods in diagnosing and treating AMD with the help of OCT would be the complete review of the proposed solutions, considering their effectiveness and maturity. To date, there is no such review to our knowledge. Therefore, the task of this work is a systematic review that aims to analyze the evolution of the ML application for diagnosing, staging, and predicting the dynamics of AMD by OCT, as well as searching and isolating biomarkers on OCT images, substantiating the specifics and conclusions that will be useful to ML users in ophthalmology.

2 Materials and Methods

2.1 Selecting Publications

In the research, we systematically reviewed papers in the international databases Pubmed, Scopus, Nature, and The Lancet, and the Russian database eLibrary. The search was focused on methods for extracting data from OCT images using ML, aimed at identifying predictors for the presence of AMD, its stage, and dynamics. To show the variety of approaches and their performance, we added to the selection studies, in which OCT data was processed with other information about the patient and, in addition to AMD, diagnosed other retinal diseases.

Thus, the search criterion was the presence in the title, abstract, and/or keywords of the terms: "optical coherence tomography", "age-related macular degeneration", "machine learning", "deep learning", "neural network", "artificial intelligence". The logical relationships of these terms were built in such a way that the first two of the above always appeared in queries with the "AND" operator, the rest with "OR": term No. 1 & term No. 2 & (term No. 3 | term No. 4 | term No. 5). Another limitation was the publication in the period from 2017 to 2022 inclusive. A link to the database or a digital DOI uploaded the full text.

After gathering the search results, we subsequently filtered them in several steps. The first step excluded duplications between databases and non-full-text articles,

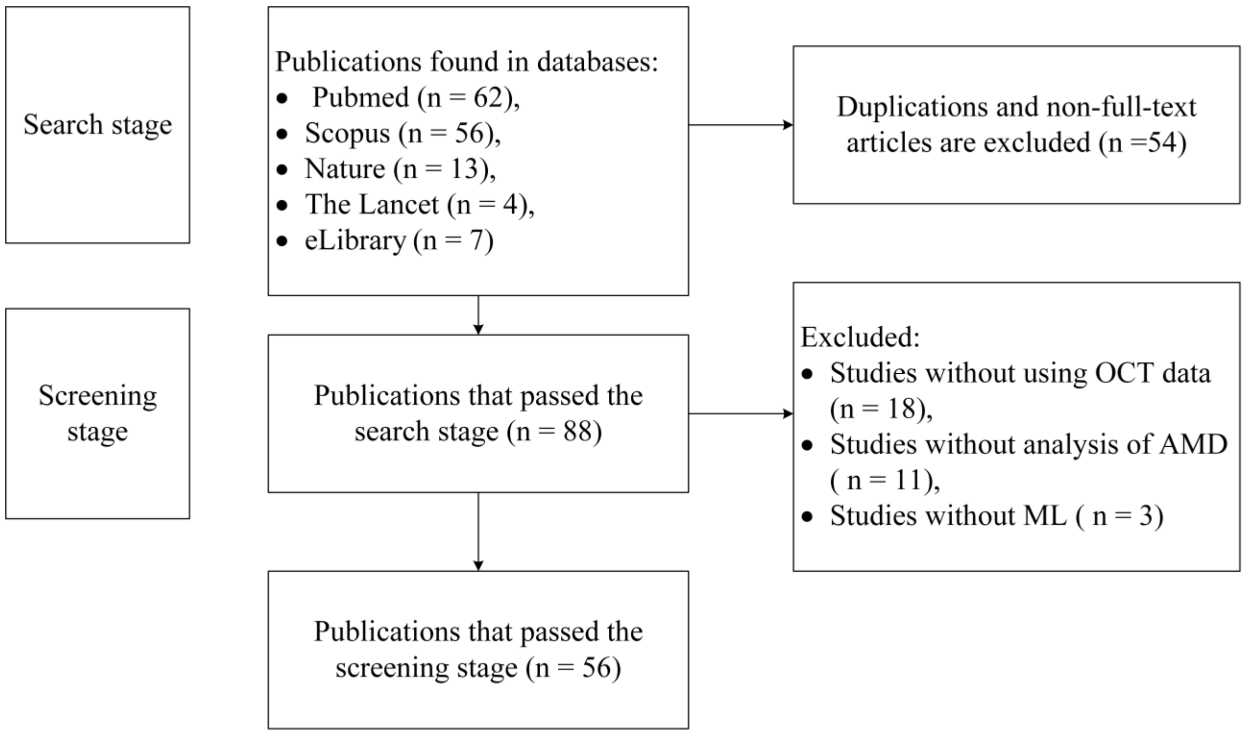

Fig. 1 Flowchart for systematic review.

and the screening step evaluated the relevance of the content to the search goal. We excluded the papers of three categories: where the retina analysis did not rely on OCT data, AMD or related pathologies were not included in the list of detected objects, or ML methods were not implied (Fig. 1). Thus, 142 studies were found, of which 54 were screened out at the search stage, including 42 duplications and 13 non-full-text articles. At the screening stage, 32 papers were removed, i.e., 18 relied on data from the fundus camera, 11 without the AMD diagnosing, and three without ML, after which 56 papers remained for inclusion in the study.

2.1 The Analysis of Publications

For the analysis, the following points were identified that characterize the features of ML performance in diagnosing AMD and other retinal diseases:

1. Date of publication, providing to track the time trend of this topic.
2. Data sources, including the existing databases of OCT images, without specifying the tomograph or other specific equipment.
3. Number of OCT images included in the dataset.
4. Tasks to be solved regarding the application of the ML algorithm:

a) classification as the problem solution for direct diagnostics;

b) segmentation to allocate the pathologies markers of a particular disease, which are the desired features of this type of image since they most fully characterize the state of the retina in the OCT image;

c) a multimodal approach using multiple sources of patient data;

d) a recommender system based on the patient data analysis and designed to accompany the diagnostician's decision.

5. Validation of the algorithm, demonstrating the degree of its generalization and the scope of its relevance.
6. The Technology Readiness Level of the proposed algorithm.

The indicators in feature 4 are not mutually exclusive since they can include each other as intermediate steps, comparable to classifying/diagnosing a disease by analyzing the selected form of pathologies achieved using segmentation. In turn, feature 5 directly influenced the assessment of feature 6, both for cross-validation of the solutions with the defined application and for solutions operating with new data aiming to increase the application area.

At the same time, the following features were identified for greater detail of the methods used:

1. pre-processing of images to facilitate the operation of the ML algorithm or extract the initial parameters;
2. research methods indicating the type of algorithm used;
3. the software for the algorithm implementation;
4. metrics used to evaluate the algorithms performance;
5. distinguished classes/features during the operation of the algorithm.

It is worth noting that features 2 and 4 were not indicated in some studies, which was especially common for those with TRL3.

3 Results

3.1 Initial Data

The papers in the final list included 11 Pubmed articles, 31 in Scopus, 10 in Nature, 2 in The Lancet, and 2 in eLibrary. Of all the papers, one was in Russian, and all the rest were in English. We used only Russian and English for the search, allowing for unaccounted articles published in other languages (Japanese, Chinese, etc.).

For a systematic analysis, the results were detailed according to the main features presented in Section 2.2 (Table 1). The detailed methods are given in the Table 2.

The trend of the publications' distribution over time makes it evident that the popularity of computer vision in AMD diagnosing by OCT images has risen dramatically.

Table 1 Initial data of research detailing.

Feature	Number	%	References
Publication year			
2017	4	7.14	[43, 49, 55, 59]
2018	5	8.93	[45, 46, 50, 53, 64]
2019	12	21.43	[44, 48, 60, 65–73]
2020	10	17.86	[47, 58, 62, 74–80]
2021	14	25.00	[51, 61, 63, 81–90]
2022	11	19.64	[52, 56, 57, 91–98]
Data sources			
Database	15	27.00	[43, 45, 48, 58, 59, 63, 65, 70, 71, 73, 76, 77, 85, 90]
Tomographs	41	73.00	[12, 20, 32, 34–36, 38–41, 44, 22, 45, 46, 48, 49, 58–63, 23, 64–73, 24, 74, 75, 25–28, 30]
Tasks to be solved			
Multimodality-classification	9	16.07	[49, 65, 68, 70, 84, 86, 89, 93, 96]
Classification	29	51.79	[43, 45, 48, 49, 55–61, 63, 67, 71–73, 79–81, 85–87, 90, 94–96, 99]
Segmentation	33	58.93	[44–47, 49–53, 57–66, 68–70, 74–77, 83, 88, 89, 91–93, 97]
Recommender system	11	19.64	[46, 49, 59, 69, 76, 78, 81, 82, 88, 93, 98]
Technology readiness level			
TRL3	26	46.43	[43–48, 55, 56, 62, 65, 66, 70, 72–74, 79, 81, 83, 85, 90, 94, 95, 99]
TRL4	25	44.64	[48–50, 53, 55, 57, 58, 61, 63, 67, 68, 75–78, 80–82, 84, 86–89, 91, 95]
TRL5	5	8.93	[51, 52, 59, 60, 97]
Number of OCT images in the dataset			
hundreds	11	19.6	[15, 44, 49, 57, 68–70, 92, 93, 96, 98]
thousands	23	41.07	[43, 47, 50–53, 55, 56, 61, 65, 66, 75, 77, 81, 83, 84, 86–89, 94, 95, 97]
tens of thousands	16	28.6	[46, 60, 63, 64, 67, 71–74, 78–80, 85, 90, 91, 99]
hundreds of thousands	5	9	[48, 58, 59, 76, 82]

Table 2 Detailing of research methods.

Characteristics of methods	Number	%	References
Image pre-processing			
Without pre-processing	36	64.29	[46, 47, 50–52, 55, 57, 61, 66, 67, 69, 70, 72–74, 77–83, 85–91, 93–99]
Normalization	8	14.29	[45, 58, 59, 63, 64, 71, 75, 76]
Augmentation	11	19.64	[21, 53, 56, 60, 63, 65, 71, 76, 79, 90, 92]
Noise suppression	4	7.14	[45, 48, 62, 84]
Salient Patch Detection	6	10.71	[43–45, 49, 62, 68]
Research methods			
Conventional ML methods	7	12.50	[43–46, 48, 49, 51]
Deep learning models	49	87.50	[46, 47, 50, 52, 53, 55, 56, 58–99]
Software			
Not specified	36	64.29	[43, 45, 46, 48, 49, 51, 53, 60–63, 67–69, 71, 72, 74, 75, 78–85, 87–89, 91, 92, 94–98]
MATLAB	4	7.14	[44, 52, 65, 76]
Python	16	28.57	[47, 50, 55–59, 64, 66, 70, 73, 77, 86, 90, 93, 99]
Metrics			
Kappa parameter	5	8.93	[60, 86, 89, 95, 96]
Intraclass correlation coefficient (ICC)	6	10.71	[53, 61, 64, 70, 83, 92]
Pearson's correlation coefficient (PCC)	2	3.57	[52, 74]
Jaccard index (IOU)	2	3.57	[62, 66]
Determination coefficient (R^2)	3	5.36	[47, 74, 82]
Dice similarity coefficient (DSC)	12	21.43	[44, 45, 53, 61, 62, 64, 68, 83, 88, 89, 91, 97]
F1-score	11	19.64	[51, 55, 61, 79, 80, 84–86, 93, 99]
Quadratic error (RMSE)	1	1,79	[44]
Point of interest (POI)	1	1.79	[57]
CAMs	6	10.71	[57, 58, 85, 87, 90, 95]
AUS	21	37.50	[43, 46, 48, 49, 57, 58, 65, 67–69, 75, 76, 78, 80–83, 85, 87, 96, 98]
precision/recall	12	21.43	[48, 57, 62, 65, 67, 68, 79, 81, 85, 91, 97, 99]
Regression coefficient	3	5.36	[51, 59, 82]
Sensitivity/specificity	21	37.50	[43, 49, 51, 55, 57, 59, 61, 63, 65, 67, 71–73, 77, 79, 81, 86, 87, 89, 93, 98]
Accuracy, %	25	44.64	[48, 50, 51, 55–57, 59–61, 63, 65, 67, 71–73, 81, 84, 85, 87, 90, 93–95, 98, 99]
Validation	31	55.36	[46, 48–50, 52, 55, 57–59, 61, 63, 65, 67–69, 73, 75, 76, 78–82, 86, 89, 91, 92, 95, 96, 99]
Distinguishable classes/features			
Binary classification (absence/presence of AMD)	4	7.14	[55, 62, 73, 87]
AMD and other diseases	12	21.43	[45, 56, 60, 63, 72, 76, 87, 90, 92, 95, 96, 99]
Stages of AMD	15	26.79	[43, 46, 48, 57, 65, 67, 69, 71, 77–79, 84, 86, 93, 94]
AMD biomarkers	28	50.00	[44, 47, 49–53, 58, 61–64, 66, 68–70, 74, 75, 83–85, 88, 89, 91–93, 97]
Prognosis of the disease dynamics	11	19.64	[49, 51, 59, 67, 69, 75, 77, 78, 81, 82, 98]

ML algorithms used in computer vision can be divided into standard (without using multilayer neural networks) and deep learning methods. The standard ML methods include classification based on the visual dictionary [43], pathology detection based on clustering of retinal layers [44, 45], layer and pathology segmentation based on graphs [46, 47] and disease markers identification based on support vectors for finding clusters of superpixels extracted with a shallow autoencoder [48] and voxel clusters for 3D-OCT [49]. Also, standard methods are used in ophthalmological devices' software for automatic retinal layers segmentation, where graph-based methods have become very popular [50–52].

Over the past few years, deep learning methods have become more prevalent than standard ML methods. Firstly, the reason is that standard methods have a greater tendency to operate on the "ad-hoc" principle, which, on average, increases their performance with the data sources considered in the study, however limiting their generalizing abilities [53, 54]. Secondly, the evolution of deep learning possibilities is promoted by accumulating a large amount of OCT data and improving its quality by enhancing the visualizing mechanisms of optical equipment [55–57]. As part of the growing popularity of deep learning in diagnosing/classifying AMD and other retinal diseases, there is a trend towards using segmented biomarkers on OCT images as predictors [45, 49, 57–63]. That is due to the previously stated conclusions, coupled with improving the elaborateness of deep learning methods without a high risk of overfitting.

Many studies have demonstrated the high efficiency of OCT image analysis. However, the results can significantly change in natural experiments with data from sources not represented in the training set. Therefore, in the application's design, it is essential to understand the generalizing ability of the algorithm, carrying out verification using cross-validation and other data sets from different sources, e.g., ophthalmic equipment from various manufacturers and/or various patient samples.

The division of the proposed solutions by TRL relied on the results' maturity, the size of the training and test datasets, and the procedure of verification. For TRL3, the idea was typically experimentally confirmed with data from the training set provided by a single database or one type of commercial tomograph. TRL4 included the concept validation on data from various sources, while for TRL5, the proposed ideas were tested during the diagnostics in natural conditions. The most significant results with TRL5 have been published over the past year, demonstrated in Table 1, indicating the relevance of these methods in OCT diagnostics.

The algorithm's generalizing ability strongly depends on the training dataset's size when operating with actual data. At the same time, the relevance of performance indicators for the entire variety of input data depends on the test dataset. In studies using several hundred examples obtained from one or two brands of tomographs, the applicability of the results is severely limited. However, such an approach can be practical for testing the concepts of AMD data processing at low dataset costs [44, 45, 69, 70, 92, 93, 96, 98].

In most papers, a dataset contained thousands of OCT image examples obtained by the collaboration of several institutions that provided their databases of OCT images, which made it possible to bring more hardware and racial diversity into the dataset. In addition to direct data collection, many studies use publicly available datasets to generate tens of thousands of images, including the most popular OCT2017 [100]. For example, this dataset was used both for training and testing the algorithm [71, 72, 90] and only for training in Refs. [63, 79], while for testing, researchers assembled a separate small set (hundreds of images).

The most extensive datasets of hundreds of thousands of OCT images were created by using large databases accumulated over a long period [59, 76, 82], or by merging several databases into one dataset [48, 58]. The ML algorithm trained on such a dataset will potentially have the highest generalizing ability, as well as adequate behavior on the entire variety of input data. It should be noted that regardless of the size of the dataset, the distribution of standard and non-standard ML algorithms applied in the studies has minimal differences.

Finally, several papers on the analysis of the AMD progression over time do not indicate the exact number of images in the dataset [49, 52, 67, 69, 70, 73, 75]. In such cases, we calculated the number of samples based on the provided information on the study's duration, the number of eyes examined, and the frequency of scanning patients.

Several studies have used image augmentation and Generative Adversarial Networks (GAN) [60, 64, 68, 70], synthesizing OCT images with AMD to move up to the larger category regarding the number of scans. However, in the case of GAN, the generated dataset must be peer-reviewed to filter out the most outliers from the real picture, in addition to using methods to measure the similarity between two images like the Structural Similarity Index Measure (SSIM) [70]. The usefulness of augmentation, in turn, is limited by the fact that the images obtained on its basis have a certain tilt of the retina. However, in most modern tomographs, the presentation of OCT images of the retina occurs with layer alignment.

Regarding the sources of OCT data, the public databases were typical for studies of image classification with TRL3 [43, 45, 48, 56, 58, 65, 70, 71, 73, 90]. At the same time, studies identified as TRL4 [63, 76, 77, 87] indicated the data on institutions and other sources that provided databases for compiling the dataset. However, they did not provide specific equipment brands for obtaining OCT images. In turn, for pathologies segmentation, in which the features of visualization and OCT images' resolution play a significant role, the optical devices were specified in most studies.

Most of the papers that mentioned the brand of the tomograph used SD-OCT technology, as it has become very popular in research and medical institutions due to its high scanning speed. The prevalence of this technology among images in datasets was also noted in a review paper devoted to the direct diagnosis of AMD [42]. Along with SD-OCT, the Swept Source OCT (SS-OCT) technology is employed [52, 66, 81, 92], which allows to achieve of higher scanning speeds with high resolution [101]. All studies based on SS-OCT used convolutional neural networks (CNN) for biomarker extraction [52, 66, 92] and analysis of disease dynamics [81]. At the same time, the performance indicators of the algorithm for SS-OCT are at the level of similar works for SD-OCT. To isolate biomarkers in three dimensions, 3D-OCT is typically used, which potentially provides more information about their actual shape [44, 47, 66, 76, 83, 88, 93] and dynamics of changing [69, 77, 82].

As already noted, the classification primarily relied not only on the preliminary visual data processing when extracting features for ML algorithms [43, 48] or arbitrary parameter selection by deep learning algorithms [43, 48, 55, 56, 67, 71–73, 79–81, 86, 87, 90, 95,96, 99], but rather on selected image segments associated with the pathologies of diseases [45, 49, 58, 61–63, 84, 85]. Such solutions, in some cases, demonstrate a more remarkable generalizing ability and easier verifiability of the algorithm.

The multimodal approach was performed for pathologies segmentation on OCT and images from the fundus camera, where the correlated appearance of disturbances helped to estimate the probability of their presence [49, 65, 70, 84, 86, 89], or when processing images of several OCT modes together [68, 93, 96].

Existing recommender systems use the above methods with the application of risk models based on the information received. Examples of such systems are predictive models for evaluating AMD treatment strategies through intravitreal injection of a blocking vascular endothelial growth factor. That is especially true since such treatment is expensive. Therefore, methods have been proposed to predict the injection response based on an OCT image before the procedure [55, 61, 78, 81, 98] or identify accumulation areas of fluid and its type in the macula [46, 52, 53, 59, 76]. Other forms of recommender systems allowed the prediction of AMD progression by biomarkers [49, 69, 75, 88, 93].

3.2 Research Methods

Since the form of retinal disease biomarkers varies depending on patients' race [102], there is a need to increase the generalizing ability of OCT image analysis algorithms. At the same time, a high generalizing ability is necessary for processing data from several types of tomographs since they have different visualization features of OCT images. A more detailed specification of the methods used showed the predominant advantage of neural network approaches due to the potentially high generalizing ability for various characteristics of input data [54]. Accordingly, using neural network approaches, combined with training on an extensive data set, can significantly increase the efficiency of allocating biomarkers for diseases. [49, 66, 76] and allow you to create an application designed to work with data from several types of tomographs [44, 52, 53].

Another feature of deep learning is the transfer learning ability, which uses neural networks pre-trained on a large data set. That enables efficiently detecting of objects with just a priori data about their boundaries and textures, which in some cases demonstrated a boost in performance indicators in comparison with similar architectures without transfer learning [55, 63, 67, 73, 76, 85, 95]. However, due to the specificity of OCT images and pathologies, as well as the relatively large number of parameters in pre-trained models, some studies deliberately did not use transfer learning [57, 90]. Regarding the last argument, a real-time OCT data analysis based on deep learning methods requires a limited number of free parameters to reduce the computational complexity that affects the maximum system response time [56].

Convolutional neural networks have demonstrated their significance in a variety of computer vision applications and, as expected, have been used in the majority of works that use deep learning for processing OCT images [46, 47, 52, 53, 55–99]. However, in some cases, recurrent neural networks are preferable since they have shown high efficiency in assessing the dynamics of various processes over time. In conjunction with convolutional networks, recurrent neural networks can obtain potentially highly accurate predictions regarding the dynamics of the disease and the likelihood of progression of AMD [78, 80].

Image pre-processing can be used for pre-feature extraction for traditional ML methods [43–45, 49], dataset extension using augmentation [21, 53, 56, 60, 63, 65, 71, 76, 79, 90, 92] and to reduce the shortcomings of visualization and normalization, which in most cases speeds up the training of intelligent algorithms [45, 48, 58, 59, 62–64, 71, 75, 76].

Predominantly, the platform for developing the ML algorithm was not specified. Most of the studies in which this information was provided used Python, which has more flexible functionality than Matlab.

The applicability of the metrics depended mainly on the nature of the output information and the task at hand. To assess the classification efficiency, it is essential to evaluate the errors of the "first" and "second" kinds for each distinguished class is essential. From the given compilation devoted to classification, the following were used as metrics:

– accuracy in terms of the percentage of correct answers, which was most often used in research;
– F1 is a harmonic mean of accuracy and recall;
– sensitivity and specificity, reflecting the proportion of positive and negative results, respectively;
– AUC-ROC (Area Under Curve-Receiver Operating Characteristic) representing the area under the curve of errors, which is more resistant to class imbalance, which is relevant for stages and pathologies of AMD with a varying frequency of detection during an examination of patients.

An additional verifying method for the classifier is the visualization of the attention areas on the image, relying on which it is possible to understand which information supports the decision. For this purpose, several works used class activation maps [57, 58, 90, 95] and the selection of points of interest [57].

In the problems of pathologies segmentation, the rules for evaluating the result are more manageable. To assess the accuracy of area selection, it is possible to represent the sets of segmented pixels of the example and the impact of the algorithm as two compared sets. That enables using the Pearson correlation coefficient, representing a measure of the correlation between two data sets [52, 74]. By limiting the selected areas as an image segment, it is also possible to estimate the overlap area of the original mask, chosen by experts, and the image segmented by the algorithm based on the Jaccard index [66]. The Dice similarity coefficient is a more commonly used analog for the Jaccard index applicable in cases with significant class imbalance [44, 53, 61, 88].

It is also essential to evaluate the degree of consistency between the experts and the ML algorithm, especially when developing a recommender system. Examples of metrics suitable for this assessment are Cohen's Kappa coefficient when measuring interregional agreement, which is more typical for classification/diagnosing problems [60, 95]. An expert's activity in analyzing AMD data is based on background information about the shape and size of biomarkers and professional experience. Therefore, the generally accepted statistical approach is to correlate the found form of pathology with tabular data. The ability of an intelligent algorithm to reproduce this activity can be assessed by parallel testing of experts unfamiliar with the test dataset and the algorithm itself. Numerically, the results of the comparative test are evaluated using the intraclass correlation coefficient (ICC) [53, 61, 64, 83, 92].

Distinguished classes or features represent the results of the algorithm operation. Classes in most works personified the diagnoses of either the presence or absence of AMD in the case of binary classification, the stages of AMD, or various retinal diseases. For the OCT image segmentation tasks, the algorithm's output data was the selected biomarkers, which act either as the final goal or as an intermediate one, based on which a diagnosis, recommendation, or prediction of the disease dynamics was made. Such approaches most reliably reflect an expert's diagnosing process and are easier to analyze the decision-making process using deep learning algorithms.

With a dataset size of hundreds of examples, Unet architectures showed the highest ICC, primarily due to the mechanism for refining the edges of an object based on the concatenation of parallel layers. In turn, Resnet networks showed an accuracy of 86% on average. At the same time, the OptiNet architecture [57], whose structure consists of serial convolution instead of parallel convolution in Resnet, demonstrated an accuracy of 98% that the highest binary classification accuracy.

For datasets of thousands of examples, the VGG network has become the most commonly used model. She also presented the highest numerical performance indicators values, up to 97.7% accuracy. The sensitivity and specificity of the model reach 0.91 and 0.896, respectively [65]. However, Unet networks showed the best specificity at 0.98 [61]. In addition, VGG has demonstrated its potential in optimizing its structure for real-time operation.

For datasets of tens of thousands of images, the highest performance indicators of deep algorithms were demonstrated by pre-trained Resnet networks, where parallel convolutions of different sizes helped to highlight standard features of the same biomarkers that are displayed with differences depending on different tomographs and augmentations. The achieved values of accuracy of 99% and sensitivity and specificity of 0.99 were performed on test data obtained from tomographs not included in the training set [63]. The results obtained on a reasonably large data set show the prospects for pre-training the model on a data bank like the OCT2017.

For several hundred thousand OCT images, parallel network convolutions in the GoogLeNet structure have also shown their effectiveness. Thanks to them, an accuracy of up to 95.5% was obtained, with specificity and sensitivity of 0.9 and 0.96, respectively [59].

4 Discussions

According to the collected data, the application of ML methods for OCT data analysis in diagnostics, staging, search and isolation of biomarkers, and prediction of AMD dynamics, is gaining more and more popularity. An increasing number of publications over the past five years confirm this conclusion. This trend (Fig. 2) is primarily due to the transition from standard ML to deep learning. One of the prerequisites for this transition is extending capabilities to generate large datasets from hundreds to hundreds of thousands of OCT scan samples, which directly affects the efficiency of deep neural network models [40]. The importance of this requirement for datasets in ophthalmology is consistent with the review's conclusions [39]. The availability of large datasets is due to the increasing spread of OCT devices, a collaboration between research and medical institutions, and the improvement of algorithms for the synthetic generation of OCT images. However, synthetic generation, along with augmentation, requires additional expert guidance. In all the analyzed works, ML methods were applied correctly concerning the processed information and methods for evaluating the results obtained.

It is worth noting that at the time of writing the systematic review, not all studies conducted in 2022 have been published, affecting the shape of the bar graphs that display the indicators mentioned below.

The efficiency of deep learning is due to the potentially high generalization ability compared to ML methods and the ability to extract algorithm predictors automatically, simplifying application development.

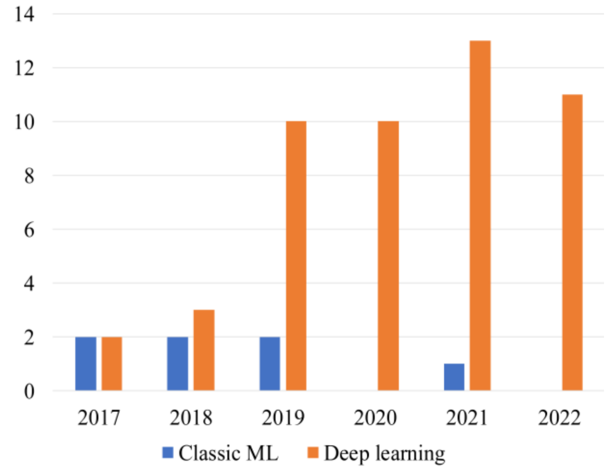

Fig. 2 Distribution of standard and deep ML approaches by years.

The approach to working with AMD data is also changing. Advanced intelligent systems make it possible to bring the classification of OCT images, similar to direct diagnostics requiring additional sufficiency verification of computer vision logic, to the progressive level equal to an expert's visual assessment. The latter relates to segmentation algorithms for retinal pathologies, based on the analysis of which the doctor and an additional classification algorithm carry out diagnostics or staging. Methods for analyzing pathologies and biomarkers have also found wide application in recommender systems and multimodal diagnostic techniques.

This transition from direct diagnosis to the analysis of the retina's segmented areas influenced the quality metrics of ML algorithms used. For direct classification (classic for medical diagnostic mechanisms), the parameters of accuracy, sensitivity, and specificity, i.e., AUS and F1, are evaluated. In turn, various studies differ in the methods used to assess the accuracy of segment boundary detection for segmentation mechanisms. However, recent studies show a greater preference for DSC and IOU due to the calculation simplicity and the relative accuracy of matching with natural segment boundaries.

The specifics of the transition from classical ML to deep learning also influenced the need for pre-processing of images since primary processing, which is extremely important for the self-selection of predictors, does not always make a significant contribution to processing by deep neural networks.

Among the structures used in deep neural network approaches, in connection with the above trends, auto-encoders are distinguished by type: Unet, Resnet, VGG, and a specially designed structure OptiNet. They are applied as the basis for classifiers, clusterers, and predictive models of diseases. Each dimension category of the dataset contains a different variety of data on the nationality of patients. Consistent with the conclusions in Ref. [41], the analysis confirmed the influence of nationality on the shape of biomarkers with the same diagnosis, which imposes additional requirements on the generalizing ability of intelligent algorithms for applications positioned as universal.

Since the dataset's size significantly affects the algorithm's relevance limitations, different deep learning architectures and numerical indicators of their effectiveness should be compared only within the same category It should also be noted that it is difficult to compare research results in many cases due to using different indicators. Therefore, examples of comparisons with only the same indicators are presented below.

Fig. 3 shows the average accuracy of deep learning models. On the given histogram, they are arranged in descending order of their use in the OCT data analysis. The selected most effective deep learning models are included in the selection of basic models for classifiers and segmenters given in Ref. [37] which is devoted to working with CFP data.

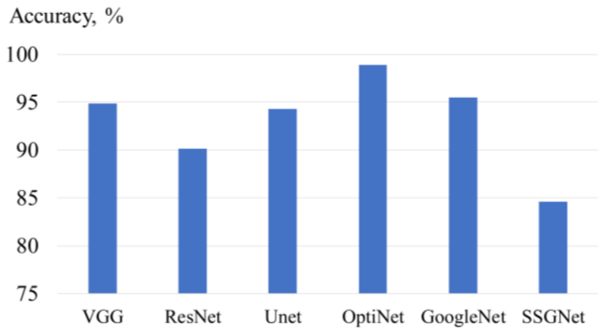

Fig. 3 Average achievable accuracy of deep learning models in disease classification tasks.

According to the results of the metrics used, such as AUS, F1, and sensitivity and specificity, for direct diagnostic methods, the highest indicators were demonstrated by: VGG and ResNet. The same and GoogLeNet with a sufficient data set for segmentation of pathologies.

Based on the papers reviewed in this work and paying particular attention to those studies in which the greatest TRL was obtained, it is possible to identify the key components that characterize the most effective approaches. These approaches included a data set of at least a thousand images, deep learning methods, and operations of both cross-validation and validation on data from other sources (different brands of tomographs or groups of people with different parameters). When solving the problem of diagnosing and staging AMD, approaches with the allocation of biomarkers have the greatest informativeness and explainability, which most clearly reflects the visual analysis of the expert. These circumstances may increase the likelihood of successfully developing an OCT image processing application with a high generalization capability.

5 Conclusions

Due to the trend of increasing the number of integrations of intelligent systems in ophthalmology, the dynamics of the use of various ML applications to solve problems in this area will inevitably correlate with the dynamics of the development of intelligent technologies. This statistical review evaluated this correlation by analyzing 56 studies on the use of ML methods in OCT image analysis tasks with AMD, according to a variety of features. Among the highlighted features were: Publication year, Data sources, Tasks to be solved, Technology readiness level, Number of OCT images in the dataset, Image pre-processing, Research methods, Software, Metrics, Validation, and Distinguishable classes/features. Analyzing feature data in the time domain allowed us to identify the most important and viable factors for creating an up-to-date intelligent OCT image analysis application with AMD. These effective artificial intelligence programs provide us with a unique opportunity to analyze visual information about the state of the retina and help make clinical decisions in the field of ophthalmology, in particular, in diagnosing the disease, automatically identifying biomarkers, and forming and correcting treatment strategies.

Disclosures

The authors declare that they have no conflict of interest.

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References

1. World Health Organisation, “World report on vision,” World Health Organisation, Switzerland (2019) (accessed 14 November 2022). [https://www.who.int/publications-detail/world-report-on-vision]. ISBN 978-92-4-151657-0.
2. R. Klein, B. E. K. Klein, S. C. Tomany, S. M. Meuer, and G.-H. Huang, “Ten-year incidence and progression of age-related maculopathy: The Beaver Dam eye study,” Ophthalmology 109(10), 1767–1779 (2002).
3. T. A. C. D. Guimaraes, M. D. Varela, M. Georgiou, and M. Michaelides, “Treatments for dry age-related macular degeneration: therapeutic avenues, clinical trials and future directions,” British Journal of Ophthalmology 106(3), 297–304 (2021).
4. N. M. Schultz, S. Bhardwaj, C. Barclay, L. Gaspar, and J. Schwartz, “Global Burden of Dry Age-Related Macular Degeneration: A Targeted Literature Review,” Clinical Therapeutics 43(10), 1792–1818 (2021).
5. B. Swenor, V. Varadaraj, M. J. Lee, H. Whitson, and P. Ramulu, “World Health Report on Vision: Aging Implications for Global Vision and Eye Health,” Innovation in Aging 4(1), 807–808 (2020).
6. L. S. Lim, P. Mitchell, J. M. Seddon, F. G. Holz, and T. Y. Wong, “Age-related macular degeneration,” The Lancet 379(9827), 1728–1738 (2012).
7. N. M. Bressler, S. B. Bressler, and S. L. Fine, “Age-related macular degeneration,” Survey of Ophthalmology 32(6), 375–413 (1988).
8. J. R. Evans, “Risk Factors for Age-related Macular Degeneration,” Progress in Retinal and Eye Research 20(2), 227–253 (2001).
9. P. Mitchell, G. Liew, B. Gopinath, and T. Y. Wong, “Age-related macular degeneration,” The Lancet 392(10153), 1147–1159 (2018).
10. J. Ambati, B. J. Fowler, “Mechanisms of Age-Related Macular Degeneration,” Neuron 75(1), 26–39 (2012).
11. R. Klein, T. Peto, A. Bird, and M. R. Vannewkirk, “The epidemiology of age-related macular degeneration,” American Journal of Ophthalmology 137(3), 486–495 (2004).
12. T. J. Heesterbeek, L. Lorés-Motta, C. B. Hoyng, Y. T. E. Lechanteur, and A. I. den Hollander, “Risk factors for progression of age-related macular degeneration,” Ophthalmic and Physiological Optics 40(2), 140–170 (2020).
13. M. P. Rozing, J. A. Durhuus, M. K. Nielsen, Y. Subhi, T. B. Kirkwood, R. G. Westendorp, and T. L. Sorensen, “Age-related macular degeneration: A two-level model hypothesis,” Progress in Retinal and Eye Research 76, 100825 (2020).
14. C. T. Supuran, “Agents for the prevention and treatment of age-related macular degeneration and macular edema: a literature and patent review,” Expert Opinion on Therapeutic Patents 29(10), 761–767 (2019).
15. D. W. Lem, P. G. Davey, D. L. Gierhart, and R. B. Rosen, “A Systematic Review of Carotenoids in the Management of Age-Related Macular Degeneration,” Antioxidants 10(8), 1255 (2021).
16. M. Gil-Martínez, P. Santos-Ramos, M. Fernández-Rodríguez, M. J. Abraldes, M. J. Rodríguez-Cid, M. Santiago-Varela, A. Fernández-Ferreiro, and F. Gómez-Ulla, “Pharmacological advances in the treatment of age-related macular degeneration,” Current Medicinal Chemistry 27(4), 583–598(2020).

17. S. K. Dubey, R. Pradhan, S. Hejmady, G. Singhvi, H. Choudhury, B. Gorain, and P. Kesharwani, "Emerging innovations in nano-enabled therapy against age-related macular degeneration: A paradigm shift," International Journal of Pharmaceutics 600, 120499 (2021).
18. Y. P. Yang, Y. J. Hsiao, K. J. Chang, S. Foustine, Y. K. Ko, Y. C. Tsai, H. Y. Tai, Y. C. Ko, S. H. Chiou, T. C. Lin, S. J. Chen, Y. Chien, and D. K.Hwang, "Pluripotent Stem Cells in Clinical Cell Transplantation: Focusing on Induced Pluripotent Stem Cell-Derived RPE Cell Therapy in Age-Related Macular Degeneration," International Journal of Molecular Sciences 23(22), 13794 (2022).
19. T. A. C. De Guimaraes, M. V. Daich, M. Georgiou, and M. Michaelides, "Treatments for dry age-related macular degeneration: therapeutic avenues, clinical trials and future directions," British Journal of Ophthalmology 106(3), 297–304 (2022).
20. A. Sarkar, S. Dyawanapelly, "Nanodiagnostics and Nanotherapeutics for age-related macular degeneration," Journal of Controlled Release 329, 1262–1282 (2021).
21. K. W. Graham, U. Chakravarthy, R. E. Hogg, K. A. Muldrew, I. S. Young, and F. Kee, "Identifying features of early and late age-related macular degeneration: A comparison of multicolor versus traditional color fundus photography," Retina 38(9), 1751–1758 (2018).
22. B. Lumbroso and M. Rispoli, Practical handbook of OCT (Retina, Choroid, Glaucoma), Jaypee Brothers Medical Publishers, New Delhi, India (2012). ISBN: 978-93-5025-758-6.
23. B. M. Aznabaev, T. R. Mukhamadeev, and T. I. Dibaev, Optical coherence tomoghraphy + angiography of the eye in the diagnosis, therapy and surgery of eye diseases, August Borg, Moscow (2019). [in Russian]. ISBN: 978-5-901053-71-3.
24. A. V. Arus, "The Role of Imaging in Age-Related Macular Degeneration," in Visual Impairment and Blindness-What We Know and What We Have to Know, G. L. Giudice, A. Catalá(Eds.), IntechOpen, UK (2020).
25. D. Huang, E. A. Swanson, C. P. Lin, J. S. Schuman, W. G. Stinson, W. Chang, M. R. Hee, T. Flotte, K. Gregory, C. A. Puliafito, and J. G. Fujimoto, "Optical coherence tomography," Science 254(5035), 1178–1181 (1991).
26. C. V. Regatieri, L. Branchini, and J. S. Duker, "The role of spectral-domain OCT in the diagnosis and management of neovascular age-related macular degeneration," Ophthalmic Surgery, Lasers and Imaging Retina 42(4), S56–S66 (2011).
27. E. H. Lim, J. I. Han, C. G. Kim, S. W. Cho, and T. G. Lee, "Characteristic Findings of Optical Coherence Tomography in Retinal Angiomatous Proliferation," Korean Journal of Ophthalmology 27(5), 351–360 (2013).
28. E. Corbelli, R. Sacconi, A. Rabiolo, S. Mercuri, A. Carnevali, L. Querques, F. Bandello, and G. Querques, "Optical Coherence Tomography Angiography in the Evaluation of Geographic Atrophy Area Extension," Investigative Ophthalmology and Visual 58(12), 5201–5208 (2017).
29. J. Walther, M. Gaertner, P. Cimalla, A. Burkhardt, L. Kirsten, S. Meissner, and E. Koch, "Optical coherence tomography in biomedical research," Analytical and Bioanalytical Chemistry 400, 2721–2743 (2011).
30. L. Rampasek, A. Goldenberg, "TensorFlow: Biology's Gateway to Deep Learning?" Cell Systems 2(1), 12–14 (2016).
31. M. M. Najafabadi, F. Villanustre, T. M. Khoshgoftaar, N. Seliya, R. Wald, and E. Muharemagic, "Deep learning applications and challenges in big data analytics," Journal of Big Data 2(1), 1–21 (2015).
32. D. Shen, G. Wu, and H. I. Suk, "Deep Learning in Medical Image Analysis," Annual Review of Biomedical Engineering 19, 221–248 (2017).
33. B. Juba, H. S. Le, "Precision-Recall versus accuracy and the role of large data sets," Proceedings of the AAAI Conference on Artificial Intelligence 33(1), 4039–4048 (2019).
34. J. Latif, C. Xiao, A. Imran, and S. Tu, "Medical imaging using machine learning and deep learning algorithms: A review," in 2019 2nd International Conference on Computing, Mathematics and Engineering Technologies (iCoMET), 1–5 (2019).
35. B. Lee, M. D'Souza, E. L. Singman, J. Wang, F. A. Woreta, M. V. Boland, and D. Srikumaran, "Integration of a Physician Assistant Into an Ophthalmology Consult Service in an Academic Setting," American Journal of Ophthalmology 190, 125–133 (2018).
36. S. Pandey, V. Sharma, "Robotics and ophthalmology: Are we there yet?" Indian Journal of Ophthalmology 67(7), 988 (2019).
37. B. Goutam, M. F. Hashmi, Z. W. Geem, and N. D. Bokde, "A Comprehensive Review of Deep Learning Strategies in Retinal Disease Diagnosis Using Fundus Images," IEEE Access 10, 57796–57823 (2022).
38. L. Dong, Q. Yang, R. H. Zhang, and W. B. Wei, "Artificial intelligence for the detection of age-related macular degeneration in color fundus photographs: A systematic review and meta-analysis," EclinicalMedicine 35, 100875 (2021).
39. R. Kapoor, B. T. Whigham, and L. A. Al-Aswad, "Artificial Intelligence and Optical Coherence Tomography Imaging," The Asia-Pacific Journal of Ophthalmology 8(2), 187–194 (2019).
40. K. Jin, J. Ye, "Artificial intelligence and deep learning in ophthalmology: Current status and future perspectives," Advances in Ophthalmology Practice and Research 100078, (2022).

41. M. H. Sarhan, M. A. Nasseri, and D. Zapp, "Machine Learning Techniques for Ophthalmic Data Processing: A Review," IEEE Journal of Biomedical and Health Informatics 24(12), 3338–3350 (2020).
42. R. Cheung, J. Chun, T. Sheidow, M. Motolko, and M. S. Malvankar-Mehta, "Diagnostic accuracy of current machine learning classifiers for age-related macular degeneration: a systematic review and meta-analysis," Eye 36(5), 994–1004 (2022).
43. F. G. Venhuizen, B.V. Ginneken, F. V. Asten, M. J. J. P. V. Grinsven, S. Fauser, C. B. Hoyng, T. Theelen, and C. I. Sánchez, "Automated staging of age-related macular degeneration using optical coherence tomography," Investigative Ophthalmology and Visual Science 58(4), 2318–2328 (2017).
44. B. I. Dodo, Y. Li, D. Kaba, and X. Liu, "Retinal Layer Segmentation in Optical Coherence Tomography Images," IEEE Access 7, 152388–152398 (2019).
45. A. Chakravarty, J. Sivaswamy, "A supervised joint multi-layer segmentation framework for retinal optical coherence tomography images using conditional random field," Computer Methods and Programs in Biomedicine 165, 235–250 (2018).
46. U. Schmidt-Erfurth, S. M. Waldstein, S. Klimscha, A. Sadeghipour, X. Hu, B. S. Gerendas, A. Osborne, and H. Bogunović, "Prediction of Individual Disease Conversion in Early AMD Using Artificial Intelligence," Investigative Ophthalmology Visual Science 59(8), 3199–3208 (2018).
47. G. Moraes, D. J. Fu, M. Wilson, H. Khalid, S. K. Wagner, E. Korot, D. Ferraz, L. Faes, C. J. Kelly, T. Spitz, P. J. Patel, K. Balaskas, T. D. L. Keenan, P. A. Keane, and R. Chopra,"Quantitative Analysis of OCT for Neovascular Age-Related Macular Degeneration Using Deep Learning," Ophthalmology 128(5), 693–705 (2021).
48. P. Seeböck, S. M. Waldstein, S. Klimscha, H. Bogunovic, T. Schlegl, B. S. Gerendas, R. Donner, U. Schmidt-Erfurth, and G. Langs, "Unsupervised Identification of Disease Marker Candidates in Retinal OCT Imaging Data," IEEE Transactions on Medical Imaging 38(4), 1037–1047 (2019).
49. H. Bogunović, A. Montuoro, M. Baratsits, M. G. Karantonis, S. M. Waldstein, F. Schlanitz, and U. Schmidt-Erfurth, "Machine Learning of the Progression of Intermediate Age-Related Macular Degeneration Based on OCT Imaging," Investigative Ophthalmology & Visual Science 58(6), BIO141-BIO150 (2017).
50. J. Kugelman, D. Alonso-Caneiro, S. A. Read, S. J. Vincent, and M. J. Collins, "Automatic segmentation of OCT retinal boundaries using recurrent neural networks and graph search," Biomedical Optics Express 9(11), 5759–5777 (2018).
51. T. D. L. Keenan, T. E. Clemons, A. Domalpally, M. J. Elman, M. Havilio, E. Agrón, G. Benyamini, and E .Y. Chew, "Retinal specialist versus artificial intelligence detection of retinal fluid from OCT: age-related eye disease study 2: 10-year follow-on study," Ophthalmology 128(1), 100–109 (2021).
52. S. K. Sodhi, A. Pereira, J. D. Oakley, J. Golding, C. Trimboli, D. B. Russakoff, and N. Choudhry, "Utilization of deep learning to quantify fluid volume of neovascular age-related macular degeneration patients based on swept-source OCT imaging: The ONTARIO study," PLoS One 17(2), e0262111 (2022).
53. F. G. Venhuizen, B. V. Ginneken, B. Liefers, F. V. Asten, V. Schreur, S. Fauser, C. Hoyng, T. Theelen, and C. I. Sánchez, "Deep learning approach for the detection and quantification of intraretinal cystoid fluid in multivendor optical coherence tomography," Biomedical Optics Express 9(4), 1545–1569 (2018).
54. Z. Akkus, A. Galimzianova, A. Hoogi, D. L. Rubin, and B. J. Erickson, "Deep Learning for Brain MRI Segmentation: State of the Art and Future Directions," Journal of Digital Imaging 30, 449–459 (2017).
55. M. Treder, J. L. Lauermann, and N. Eter, "Automated detection of exudative age-related macular degeneration in spectral domain optical coherence tomography using deep learning," Graefe's Archive for Clinical and Experimental Ophthalmology 260(6), 1941–1946 (2017).
56. P. K. Upadhyay, S. Rastogi, and K. V. Kumar, "Coherent convolution neural network based retinal disease detection using optical coherence tomographic images," Journal of King Saud University-Computer and Information Sciences 34(10), 9688–9695 (2022).
57. A. O. Tvenning, S. R. Hanssen, D. Austeng, and T. S. Morken, "Deep learning identify retinal nerve fibre and choroid layers as markers of age-related macular degeneration in the classification of macular spectral-domain optical coherence tomography volumes," Acta Ophthalmologica 100(8), 937–945 (2022).
58. T. H. Rim, A. Y. Lee, D. S. Ting, K. Teo, B. K. Berzler, Z. L. Teo, T. K. Yoo, G. Lee, Y. Kim, A. C. Lin, S. E. Kim, Y. C. Tham, S. S. Kim, C. Cheng, T. Y. Wong, and C. M. G. Cheung, "Detection of features associated with neovascular age-related macular degeneration in ethnically distinct data sets by an optical coherence tomography: trained deep learning algorithm," British Journal of Ophthalmology 105(8), 1133–1139 (2020).
59. P. Prahs, V. Radeck, C. Mayer, Y. Cvetkov, N. Cvetkova, H. Helbig, and D. Märker, "OCT-based deep learning algorithm for the evaluation of treatment indication with anti-vascular endothelial growth factor medications," Graefe's Archive for Clinical and Experimental Ophthalmology 256(1), 91–98 (2017).
60. S. Kuwayama, Y. Ayatsuka, D. Yanagisono, T. Uta, H. Usui, A. Kato, N. Takase, Y. Ogura, and T. Yasukawa, "Automated Detection of Macular Diseases by Optical Coherence Tomography and Artificial Intelligence Machine Learning of Optical Coherence Tomography Images," Journal of Ophthalmology 2019, 6319581 (2019).
61. G. Zhang, D. J. Fu, B. Liefers, L. Faes, S. Glinton, S. Wagner, R. Struyven, N. Pontikos, P. A. Keane, and K. Balaskas, "Clinically relevant deep learning for detection and quantification of geographic atrophy from optical coherence

tomography: a model development and external validation study," The Lancet Digital Health 3(10), e665–e675 (2021).
62. Z. Chen, D. Li, H. Shen, H. Mo, Z. Zeng, and H. Wei, "Automated segmentation of fluid regions in optical coherence tomography B-scan images of age-related macular degeneration," Optics and Laser Technology 122, 105830 (2020).
63. A. Haq, A. Fariza, and N. Ramadijanti, "Development of vulnerable web application based on owasp api security risks," in 2021 International Electronics Symposium (IES), Surabaya, Indonesia, 343–348 (2021).
64. H. Lee, K. E. Kang, H. Chung, and H. C. Kim, "Automated Segmentation of Lesions Including Subretinal Hyperreflective Material in Neovascular Age-related Macular Degeneration," American Journal of Ophthalmology 191, 64–75 (2018).
65. T. K. Yoo, J. Y. Choi, J. G. Seo, B. Ramasubramanian, S. Selvaperumal, and D. W. Kim, "The possibility of the combination of OCT and fundus images for improving the diagnostic accuracy of deep learning for age-related macular degeneration: a preliminary experiment," Medical and Biological Engineering and Computing 57, 677–687 (2018).
66. P. M. Maloca, A. Y. Lee, E. R. de Carvalho, M. Okada, K. Fasler, I. Leung, B. Hormann, P. Kaiser, S. Suter, P. W. Hasler, J. Zarranz-Ventura, C. Egan, T. C. Heeren, and H. P. N. Scholl, "Validation of automated artificial intelligence segmentation of optical coherence tomography images," PLoS One 14(8), e0220063 (2019).
67. S. Saha, M. Nassisi, M. Wang, S. Lindenberg, Y. kanagasingam, S. Sadda, and Z. J. Hu, "Automated detection and classification of early AMD biomarkers using deep learning," Scientific Reports 9(1), 10990 (2019).
68. L. Varga, A. Kovács, T. Grósz, G. Thury, F. Hadarits, R. Dégi, and J. Dombi, "Automatic segmentation of hyperreflective foci in OCT images," Computer Methods and Programs in Biomedicine 178, 91–103 (2019).
69. D. B. Russakoff, A. Lamin, J. D. Oakley, A. M. Dubis, and S. Sivaprasad, "Deep Learning for Prediction of AMD Progression: A Pilot Study," Investigative Ophthalmology and Visual Science 60(2), 712–722 (2019).
70. M. Wu, X. Cai, Q. Chen, Z. Ji, S. Niu, T. Leng, D. L. Rubin, and H. Park, "Geographic atrophy segmentation in SD-OCT images using synthesized fundus autofluorescence imaging," Computer Methods and Programs in Biomedicine 182, 105101 (2019).
71. V. Das, S. Dandapat, and P. K. Bora, "Multi-scale deep feature fusion for automated classification of macular pathologies from OCT images," Biomedical Signal Processing and Control 54, 101605 (2019).
72. L. Fang, Y. Jin, L. Huang, S. Guo, G. Zhao, and X. Chen, "Iterative fusion convolutional neural networks for classification of optical coherence tomography images," Journal of Visual Communication and Image Representation 59, 327–333 (2019).
73. J. Qiu, Y. Sun, "Self-supervised iterative refinement learning for macular OCT volumetric data classification," Computers in Biology and Medicine 111, 103327 (2019).
74. U. Schmidt-Erfurth, W. D. Vogl, L. M. Jampol, and H. Bogunović, "Application of Automated Quantification of Fluid Volumes to Anti-VEGF Therapy of Neovascular Age-Related Macular Degeneration," Ophthalmology 127(9), 1211–1219 (2020).
75. S. M. Waldstein, W. D. Vogl, H. Bogunovic, A. Sadeghipour, S. Riedl, and U. Schmidt-Erfurth, "Characterization of Drusen and Hyperreflective Foci as Biomarkers for Disease Progression in Age-Related Macular Degeneration Using Artificial Intelligence in Optical Coherence Tomography," JAMA Ophthalmology 138(7), 740–747 (2020).
76. K. K. Bhatia, M. S. Graham, L. Terry, A. Wood, P. Tranos, S. Trikha, and N. Jaccard, "Disease classification of macular Optical Coherence Tomography scans using deep learning software: validation on independent, multi-centre data," Retina 40(8), 1549–1557 (2019).
77. J. Yim, R. Chopra, T. Spitz, J. Winkens, A. Obika, C. Kelly, H. Askham, M. Lukic, J. Huemer, K. Fasler, G. Moraes, C. Meyer, M. Wilson, J. Dixon, C. Hughes, G. Rees, P. T. Khaw, A. Karthikesalingam, D. King, D. Hassabis, M. Suleyman, T. Back, J. R. Ledsam, P. A. Keane, and J. D. Fauw,"Predicting conversion to wet age-related macular degeneration using deep learning," Nature Medicine 26(6), 892–899 (2020).
78. I. Banerjee, L. de Sisternes, J. A. Hallak, T. Leng, A. Osborne, P. J. Rosenfeld, G. Gregori, M. Durbin, and D. Rubin, "Prediction of age-related macular degeneration disease using a sequential deep learning approach on longitudinal SD-OCT imaging biomarkers," Scientific Reports 10(1), 15434 (2020).
79. X. He, L. Fang, H. Rabbani, X. Chen, and Z. Liu, "Retinal optical coherence tomography image classification with label smoothing generative adversarial network," Neurocomputing 405, 37–47 (2020).
80. X. Wang, F. Tang, H. Chen, L. Luo, Z. Tang, An-Ran Ran, C. Y. Cheung, and P. A. Heng, "UD-MIL: Uncertainty-Driven Deep Multiple Instance Learning for OCT Image Classification," IEEE Journal of Biomedical and Health Informatics 24(12), 3431–3442 (2020).
81. X. Zhao, X. Zhang, B. Lv, L. Meng, C. Zhang, Y. Liu, C. Lv, G. Xie, and Y. Chen, "Optical coherence tomography-based short-term effect prediction of anti-vascular endothelial growth factor treatment in neovascular age-related macular degeneration using sensitive structure guided network," Graefe's Archive for Clinical and Experimental Ophthalmology 259(11), 3261–3269 (2021).
82. D. J. Fu, L. Faes, S. K. Wagner, G. Moraes, R. Chopra, P. J. Patel, K. Balaskas, T. D. L. Keenan, L. M. Bachmann, and P. A. Keane,"Predicting Incremental and Future Visual Change in Neovascular Age-Related Macular Degeneration Using Deep Learning," Ophthalmology Retina 5(11), 1074–1084 (2021).

83. B. Liefers, P. Taylor, A. Alsaedi, C. Bailey, K. Balaskas, N. Dhingra, C. A. Egan, F. G. Rodrigues, C. G. Gonzalo, T. F. C. Heeren, A. Lotery, P. L. Müller, A. Olvera-Barrios, B. Paul, R. Schwartz, D. S. Thomas, A. N. Warwick, A. Tufail, and C. I. Sánchez, "Quantification of Key Retinal Features in Early and Late Age-Related Macular Degeneration Using Deep Learning," American Journal of Ophthalmology 226, 1–12 (2021).
84. A. Szeskin, R. Yehuda, O. Shmueli, J. Levy, and L. Joskowicz, "A column-based deep learning method for the detection and quantification of atrophy associated with AMD in OCT scans," Medical Image Analysis 63, 101693 (2021).
85. Y. Yan, K. Jin, Z. Gao, X. Huang, F. Wang, Y. Wang, and J. Ye, "Attention Based Deep Learning System for Automated Diagnoses of Age-Related Macular Degeneration in Optical Coherence Tomography Images," Medical Physics 48(9), 4926–4934 (2021).
86. Z. Xu, W. Wang, J. Yang, J. Zhao, D. Ding, D. Chen, Z. Yang, X. Li,W. Yu, and Y. Chen, "Automated diagnoses of age-related macular degeneration and polypoidal choroidal vasculopathy using bi-modal deep convolutional neural networks," British Journal of Ophthalmology 105(4), 561–566 (2021).
87. D. D. J. Hwang, S. Choi, J. Ko, J. Yoon, J. I. Park, J. S. Hwang, J. M. Han, H. J. Lee, J. Sohn, K. H. Park, and J. Han, "Distinguishing retinal angiomatous proliferation from polypoidal choroidal vasculopathy with a deep neural network based on optical coherence tomography," Scientific Reports 11(1), 9275 (2021).
88. F. G. Holz, R. Abreu-Gonzalez, F. Bandello, R. Duval, L. O'toole, D. Pauleikhoff, G. Staurenghi, A. Wolf, D. Lorand, A. Clemens, and B. Gmeiner, "Does real-time artificial intelligence-based visual pathology enhancement of three-dimensional optical coherence tomography scans optimise treatment decision in patients with nAMD? Rationale and design of the RAZORBILL study," British Journal of Ophthalmology 107(1), 96–101 (2021).
89. Y. Derradji, A. Mosinska, S. Apostolopoulos, C. Ciller, S. De Zanet, and I. Mantel, "Fully-automated atrophy segmentation in dry age-related macular degeneration in optical coherence tomography," Scientific Reports 11(1), 21893 (2021).
90. Sunija, S. Kar, Gayathri, V. P. Gopi, and P. Palanisamy, "OctNET: A Lightweight CNN for Retinal Disease Classification from Optical Coherence Tomography Images," Computer Methods and Programs in Biomedicine 200, 105877 (2021).
91. S. Riedl, V. Wolf-Dieter, J. Mai, G. S. Reiter, D. Lachinov, C. Grechenig, A. McKeown, L. Scheibler, H. Bogunović, and U. Schmidt-Erfurth, "The Effect of Pegcetacoplan Treatment on Photoreceptor Maintenance in Geographic Atrophy Monitored by Artificial Intelligence–Based OCT Analysis," Ophthalmology Retina 6(11), 1009–1018 (2022).
92. V. Pramil, L. de Sisternes, L. Omlor, W. Lewis, H. Sheikh, Z. Chu, N. Manivannan, M. Durbin, R. Wang, P. Rosenfeld, M. Shen, R. Guymer, M. Liang, G. Gregori, and N. K Waheed, "A Deep Learning Model for Automated Segmentation of Geographic Atrophy Imaged Using Swept-Source OCT," Ophthalmology Retina 7(2), 127–141 (2022).
93. K. A. Thakoor, J. Yao, D. Bordbar, O. Moussa, W. Lin, P. Sajda, and R. W. S. Chen, "A multimodal deep learning system to distinguish late stages of AMD and to compare expert vs. AI ocular biomarkers," Scientific Reports 12(1), 2585 (2022).
94. T. G. Kamenskikh, O. N. Dolinina, I. O. Kolbenev, and E. V. Veselova, "An intelligent decision-making system for early diagnosis of macular pathology," Rossiiskii Oftal'mologicheskii Zhurnal 15(2), 69–74 (2022). [in Russian].
95. J. Han, S. Choi, J. I. Park, J. S. Hwang, J. M. Han, H. J. Lee, J. Ko, J. Yoon, and D. Duck-Jin Hwang, "Classifying neovascular age-related macular degeneration with a deep convolutional neural network based on optical coherence tomography images," Scientific Reports 12(1), 1–10 (2022).
96. P. Zang, T. T. Hormel, T. S. Hwang, S. T. Bailey, D. Huang, and Y. Jia, "Deep-learning-aided Diagnosis of DR, AMD, and Glaucoma based on Structural and Angiographic Optical Coherence Tomography," Ophthalmology Science 3(1), 100245 (2022).
97. E. Parra-Mora, L. A. da Silva Cruz, "LOCTseg: A lightweight fully convolutional network for end-to-end optical coherence tomography segmentation," Computers in Biology and Medicine 150, 106174 (2022).
98. T. C. Yeh, A.C. Luo, Y. S. Deng, Y. H. Lee, S. J. Chen, P. H. Chang, C. J. Lin, M. C. Tai, and Y. B. Chou, "Prediction of treatment outcome in neovascular age-related macular degeneration using a novel convolutional neural network," Scientific Reports 12(1), 5871 (2022).
99. A. Thomas, P. M. Harikrishnan, R. Ramachandran, S. Ramachandran, R. Manoj, P. Palanisamy, and V. P. Gopi, "A novel multiscale and multipath convolutional neural network based age-related macular degeneration detection using OCT images," Computer Methods and Programs in Biomedicine 209, 106294 (2021).
100. D. S. Kermany, M. Goldbaum, W. Cai, C. C. S. Valentim, H. Liang, S. L. Baxter, A. McKeown, G. Yang, X. Wu, F. Yan, J. Dong, M. K. Prasadha, J. Pei, M. Y. L. Ting, J. Zhu, C. Li, S. Hewett, J. Dong, I. Ziyar, A. Shi, and K. Zhang, "Identifying Medical Diagnoses and Treatable Diseases by Image-Based Deep Learning," Cell 172(5), 1122–1113 (2018).
101. M. Adhi, J. S. Duker, "Optical coherence tomography-current and future applications," Current Opinion in Ophthalmology 24(3), 213 (2013).

102. S. Laotaweerungsawat, C. Psaras, Z. Haq, X. Liu, and J. M. Stewart, "Racial and ethnic differences in foveal avascular zone in diabetic and nondiabetic eyes revealed by optical coherence tomography angiography," PLoS One 16(10), e0258848 (2021).