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Artificial intelligence for retinal disease management

Umetna inteligenca v obravnavi bolnika z boleznijo mrežnice

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Abstract

Image recognition artificial intelligence represents a new milestone in modern medical technology since it has become a helpful tool in identifying suspicious changes and diseases, patient monitoring, and predicting treatment outcomes. Especially through the implementation of convolutional neural networks in the modelling of computer-based artificial intelligence systems, its clinical applicability has recently increased dramatically. Ophthalmology, particularly retinology, where diagnosis almost entirely relies on imaging, is highly technology-driven and as such uniquely positioned to bring AI innovations into clinical use. However, the integration of AI in the screening, diagnosis and treatment of ophthalmic diseases is however still limited, mainly due to the over-generalisation of lesion detection and the poor ability to identify different clinical entities simultaneously. This articleis focused on recent artificial intelligence algorithms and software, which are primarily aimed to support the detection of the most common retinal diseases and have been, or will be - with improved specificity and sensibility, introduced into clinical practice.

Izvleček

Umetna inteligenca predstavlja zaradi možnosti podpore pri odkrivanju in spremljanju bolezni ter napovedovanju izida novi mejnik v sodobni medicinski tehnologiji. Njena klinična uporabnost se je v zadnjih letih dramatično povečala predvsem na račun uvedbe konvolucijskih nevronskih mrež v modeliranje računalniško podprtih sistemov umetne inteligence. Celotna oftalmologija, zlasti pa področje bolezni mrežnice, pri kateri diagnosticiranje sloni na slikovnih preiskavah, se vodi izrazito tehnološko. Zato je edinstvena stroka pri vpeljavi novosti s področja umetne inteligence v klinično uporabo. Kljub temu pa je integracija umetne inteligence v presejanje, diagnosticiranje in zdravljenje oftalmoloških bolezni predvsem zaradi prevelikega posploševanja pri zaznavanju sprememb in slabih zmožnosti sočasnega prepoznavanja različnih kliničnih entitet zaenkrat še omejena. V članku se osredinjamo na nedavno predstavljene algoritme umetne inteligence, ki so prvenstveno namenjeni odkrivanju najpogostejših bolezni mrežnice in so, ali se še bodo, z morebitnimi izboljšavami, pridobljeno višjo občutljivostjo in specifičnostjo, vendarle uvedli v klinično prakso.

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Ključne besede: umetna inteligenca; strojno učenje; starostna degeneracija makule; diabetična retinopatija; optična koherentna tomografija

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1 Introduction

Artificial intelligence (AI) means the ability of a computer system to mimic the human mind while acting independently of a human. This type of intelligence encompasses the ability to connect and process data, learn, and infer based on algorithms (1,2).

Machine learning is a branch of artificial intelligence that is based on the principles of deep learning or convolutional neural networks (3,4). It is a concept that allows the creation of mathematical models based on input data, and the use of these algorithms to identify and search for complex patterns in the large amounts of data (5-7). For the system to reliably analyze a specific problem, a large enough data set is needed on the basis of which the system practices and learns. In the medical profession, AI is most often used in diagnostic imaging, which, due to its prevalence and standardized use, enables the analysis and interpretation of imaging data samples (8,9). Modern software, based on the principles of AI, can already independently identify deviations and irregularities in the images, compare them with each other, and even give a clinical interpretation of the identified changes (3,5,7,10).

Ophthalmology is one of the branches of medicine in which imaging examinations are part of the basic medical treatment of the patient. As we encounter a huge amount (several terabytes) of imaging data every day in ophthalmology, this field of medicine is unique for introducing artificial intelligence systems into clinical practice. Based on retinal images and optical coherence tomography (OCT) imaging of individual layers of the retina or optic papilla, deep learning algorithms can recognize diabetic retinopathy (DR), age-related macular degeneration (AMD), retinopathy of prematurity (ROP), and glaucoma (Table 1) (4,11-18).

2 Early detection of diabetic retinopathy

Diabetic retinopathy (DR) is the most common chronic complication of diabetes and a cause of blindness in the working age population (19). About one-third of diabetics have DR, and in 10% of patients, the progressive disease poses a serious threat to vision (20,21). The disease may not show any symptoms for a long time; therefore, timely or early detection of changes is essential to prevent complications, including permanent vision loss. The introduction of a screening program for

Table 1: Summary and review of AI systems for retinal disease recognition.

Study	Software	Imaging exams	Usability	AUC
Abramoff (11)	IDx-DR	fundus image	identification of moderate DR	0.98
Chakravarthy (12)	Notal OCT Analyser	OCT	home monitoring for neovascular AMD	0.87
Schmidt-Erfurth (13)	/	OCT	prediction of the probability of AMD progression	0.68
Russakoff (14)	AMDnet	OCT	prediction of the probability of AMD progression	0.78
Rogers (15)	Pegasus	OCT, fundus image	recognition of pathognomonic changes for glaucoma, AMD, DR	0.89–0.94
De Fauw (16)	DeepMind Health	OCT	identification of 50 different retinal pathologies	0.99
Brown (4)	I-ROP DL	fundus image	detection of PLUS disease in preterm infants	0.98
Redd (17)	I-ROP DL	fundus image	identification of individual ROP stages	0.96
Yildiz (18)	I-ROP Assist	fundus image	detection of PLUS disease in preterm infants	0.99

Legend: DR – diabetic retinopathy; fundus image – retinal image; OCT – optical coherence tomography; AUC – area under the curve; ROP – retinopathy of prematurity; AMD – age-related macular degeneration; AI – artificial intelligence; / – no data.

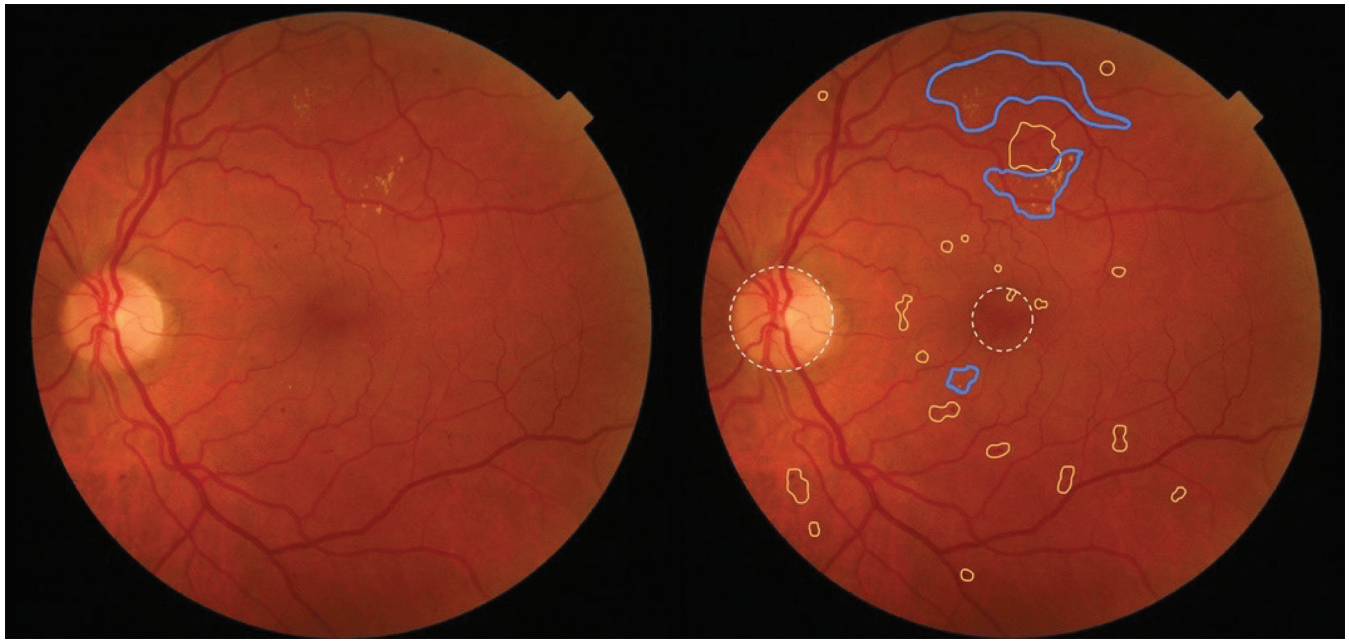

Figure 1: Moderate non-proliferative diabetic retinopathy (DR), retinal image.
Schematic representation of possible automated recognition of optic papilla and macula (dashed), bleeding and/or aneurysm (yellow), soft exudates (blue), as provided by IDx-DR. The image is the source owned by the Department of Ophthalmology, University Medical Centre Ljubljana.

early detection of DR has significantly reduced the incidence of blindness among diabetic patients. However, the implementation of the program in its current form additionally burdens the health care system. The number of patients with diabetes in the world, as well as in our country, is growing rapidly. According to statistics from the National Institute of Public Health (NIJZ), the incidence increases by 3% every year (22). Due to the growing trend of morbidity and the limited availability of qualified specialists, the medical staff is overburdened, and access to appropriate ophthalmology treatment is therefore already difficult in some places (23).

Due to the established standard international classification of individual stages of the disease, retinal involvement in DR is highly suitable for the use of AI in image analysis. AI systems can easily identify patterns of retinal involvement and thus help in screening and diagnosing DR (11,16,29). AI algorithms that detect clinically-significant macular oedema and advanced stages of DR are particularly effective (11,23).

In April 2018, the US Federal Food and Drug Administration (FDA) approved an artificial intelligence system that is capable of self-diagnosing DR without the results having to be interpreted by an ophthalmologist (24). Developed by Abramoff et al., IDx-DR software (Digital Diagnostics, Coralville, Iowa, USA, formerly known as IDx) is based on machine learning and a computer algorithm that acts as a screening program for DR detection in patients with pre-existing diabetes based on standardized retinal images (11). The program detects microaneurysms, hard exudates, retinal haemorrhages, venous malformations, and soft exudates (micro infarctions of the nerve fibre layer, the cotton-wool spots) on retina images taken with a non-mydriatic camera (Topcon TRC NW 400) (Figure 1). The images at the Department of Ophthalmology of the University Medical Centre contain a schematic representation (Figures 1, 2 and 3) with program analysis simulation prepared using the MacOS Preview software.

If the program detects moderate non-proliferative DR (stage of DR > 35 according to the ETDRS [Early Treatment for Diabetic Retinopathy Study] severity scale) or oedema > 300 μm in the wider area of the macula on at least one of the four retinal images, further treatment of the patient at the ophthalmologist is recommended (23,25). The test result is given in binary form, 0 or 1, where the value 0 indicates the absence of significant DR and the value 1 indicates the presence of DR that needs further treatment (11). In a clinical study in 900 volunteers, IDx-DR achieved a sensitivity of 87% and a specificity of 91% (23).

The program is not suitable for the treatment of patients with confirmed DR, pre-existing retinal vascular pathology such as radiation retinopathy or retinal vein

occlusion, and patients who have already received intraocular injection or have undergone eye surgery. The program is also not intended for the blind, cataract patients, children, and pregnant women with rapidly progressive DR (11,24).

The equipment is intended exclusively for use at the primary health care level, as it only identifies patients who need further treatment by an ophthalmologist due to advanced DR. However, the system does not provide information on the general eye condition of the individual or the absence of DR (23,25). The main drawback of such a system is that among patients with an earlier stage of DR, it does not recognize those with a higher risk of disease progression. Due to hormonal imbalance, diabetes is one of the known risk factors for cataract development, age-related macular degeneration, and glaucoma optic neuropathy (26-28). As the system does not recognise other pathologies that need to be examined by an ophthalmologist and may need treatment, it may give patients a false sense of safety due to a negative test result.

The IDx-DR program has been commercially available in the United States since 2018 (24). Although the program was CE certified in 2013, it is not yet available for marketing in most European countries, as the independent research to demonstrate the effectiveness and comparability of software with clinical ophthalmology treatment is still ongoing (29).

3 Monitoring age-related macular degeneration

Age-related macular degeneration (AMD) is the leading cause of functional blindness after the age of 55 in the developed world (30,25). It is a progressive disease that affects the central vision needed for daily tasks such as reading, driving, and face recognition. The disease is initially asymptomatic; only with its progression does it manifest itself with deterioration of vision, metamorphopsia, and later with a central scotoma. In approximately 10–15% of patients with AMD, the disease progresses into a neovascular form, characterized by the growth of new vessels in the macula (macular neovascularisation; MNV) and rapid deterioration of central visual acuity (31). Today, the deterioration of vision and the development of functional blindness due to neovascular AMD can be successfully prevented with biological drugs against vascular endothelial growth factor (VEGF), the anti-VEGF drugs. This treatment is effective only in the initial stages when the newly formed pathological vessels are not yet scarred. Identification of at-risk groups of patients in whom disease progression and early detection of neovascular AMD can be expected is crucial for successful treatment.

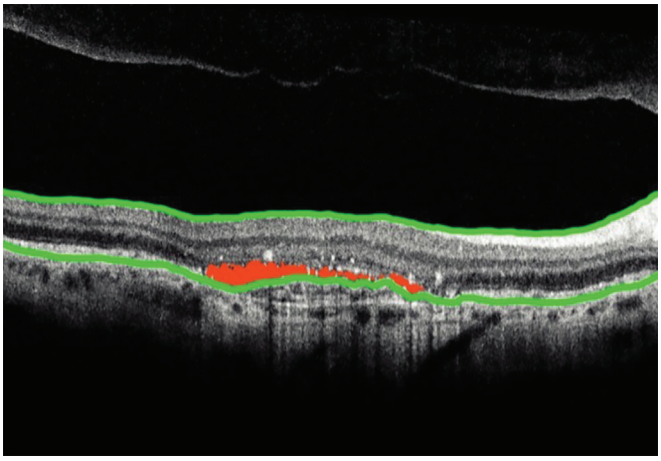

Figure 2: Schematic representation of the analysis of the optical coherence tomography (OCT) image of the macula. Identification of the inner limiting membrane and the layer of pigment epithelium (green), the location of the subretinal fluid (red), as provided by the proprietary algorithm NOA. The image is the source owned by the Department of Ophthalmology, University Medical Centre Ljubljana.

In addition to regular ophthalmic examinations, self-monitoring of vision with the Amsler grid is recommended in the treatment of patients with AMD, through which patients themselves detect visual impairment. Despite adequate patient participation, the subjective perception of changes in visual acuity is often a late indicator of disease progression (32). If the treatment is started with poorer visual acuity, the functional effect of the treatment or the visual acuity after treatment is also poor and vice versa: the better the visual acuity at the beginning of treatment, the better it will be after treatment (33,34). Early detection of the disease can significantly improve the prognosis for vision.

For early detection of the progression of dry AMD into neovascular form, Notal Vision (Notal Vision, Manassas, Virginia, USA) has developed an OCT for home use. The Home OCT combines the research technology of optical coherence tomography and the principles of machine learning and neural networks (12). The device records a macular tomography, which is automatically analyzed by NOA™ (Notal OCT Analyzer). If in the central 10 degrees of the retina, in the macula, it detects fluid in or under the retina, it immediately notifies the chosen ophthalmologist (Figure 2). If it does not detect fluid, it transmits monthly reports to the cloud, which can be accessed by the chosen physician (12). The device thus enables continuous monitoring of macular

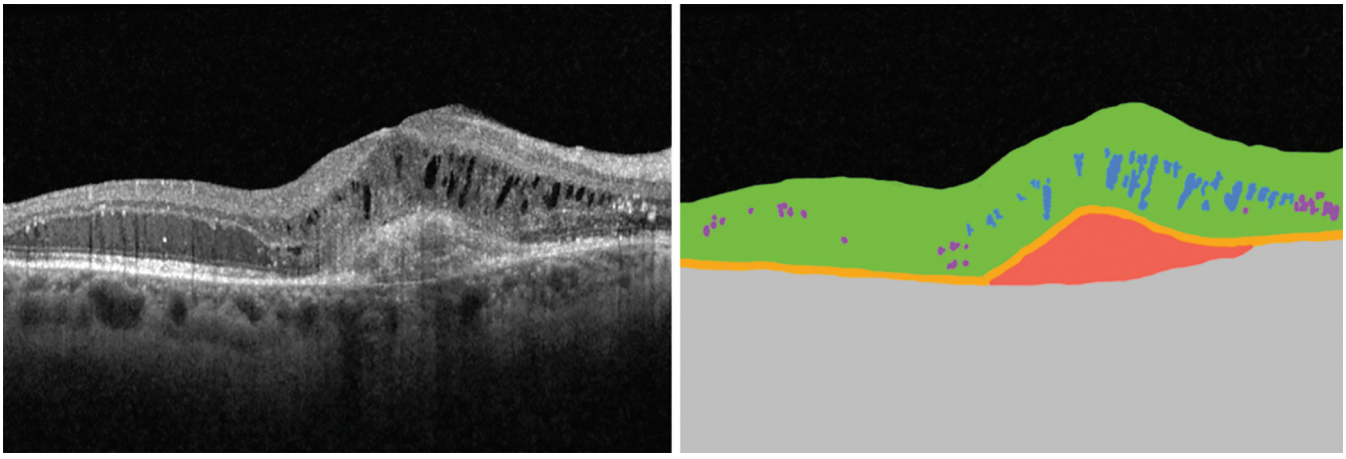

Figure 3: Neovascular age-related macular degeneration (AMD), optical coherence tomography (OCT) image (right), and possible schematic representation of automated image analysis with DeepMind software (left).
Anatomical segmentation of the retina (green), the layer of pigment epithelium (orange) and the choroid (grey). Identification of intraretinal fluid (blue), hyperreflective foci (purple), and neovascularization (red). The image is the source owned by the Department of Ophthalmology, University Medical Centre Ljubljana.

disease in high-risk patients, contributing to the rapid identification of disease progression, thus shortening the time from disease exacerbation to the start of treatment (12). It is known that the results of treating AMD with anti-VEGF drugs in clinical practice are not as good as in clinical trials (12,35). The reason is the high burden of treatment, which requires regular monitoring and treatment at appropriate intervals. Therefore, monitoring of patients with macular changes that pose a high risk of progression into neovascular disease is not regular. The Home OCT device detects pathological events in the macula even before the changes significantly affect vision, when the initial visual acuity is still good. If treatment is timely, intervention is more effective and treatment outcomes are better. The Home OCT device is intended for self-testing at home between regularly scheduled clinical examinations and is not a substitute for regular examinations in the retinal disease clinic, as it is insufficiently accurate compared to professional OCT devices routinely used in specialist clinics (12). The arrival of Home OCT on the market has already been announced for this year. The device would be mainly available to patients at high risk for disease progression (12).

Recently, an AI model has been developed at the University of Vienna that can evaluate the likelihood of progression into neovascular AMD based on demographics, genetic polymorphisms, and image data analysis (13). Using automated segmentation in individual retinal layers, the system detects drusen, pseudodrusen, hyperreflective foci, and other abnormalities in the pigment epithelium that indirectly indicate a high risk of developing neovascular AMD (13). A similar pre-processing algorithm for the analysis of OCT images was also used by Russakoff et al. as the basis of their own AI model (AMDnet). The basic analysis of the retinal layers is followed by automated recognition of pathognomonic retinal abnormalities according to structural parameters such as thickness and volume (14).

4 Software for simultaneous detection of multiple retinal diseases

The British company Visulytix (London, United Kingdom) has developed a series of advanced algorithms that simultaneously identify various retinal pathologies. Their Pegasus software interprets and analyses OCT images in a detailed way: retinal images and stereoscopic images of the optic papilla. It provides immediate support in deciding on the further treatment of patients with DR, AMD and glaucoma (15,36,37). In OCT images, Pegasus detects drusen, atrophic areas of the retina, and intraretinal fluid (IRF) or accumulation of fluid under the retina and thus assesses the presence of macular oedema, and dry, atrophic, and neovascular AMD (36). It detects microaneurysms, retinal haemorrhages, and exudates in retinal images, also recognizes optic papilla anomalies, and accurately measures the vertical cup to disk ratio (CDR) (15,37,38). The company completed its sales in 2019.

Pegasus was designed to unburden ophthalmologists in the tertiary health care, who interpret vast amounts of imaging data taken daily in outpatient clinics where basic screening tests for eye diseases are performed. The program automatically analyses image data, which is

either accessed directly from a device connected to the OCT or with a fundus camera, or captures information from the cloud, where data can also be uploaded by external imaging providers (15,37). In specialist clinics, the program can be used to assist in triage and treatment of patients, and outside clinical centres, Pegasus allows for earlier detection of the disease and thus ensures that emergencies are treated in a timely manner (15,37). In clinical studies, the Pegasus software has achieved the accuracy of a specialist in the detection of glaucoma neuropathy and retinal pathology (40).

In 2016, Google's DeepMind (London, UK), in collaboration with the Moorfields Eye Hospital in London, developed an AI system that successfully detects more than 50 pathological changes on OCT images (16). The system is one of the most advanced in this field, combining the functions of two neural networks and allowing two-stage analysis of OCT images. In the first stage it detects changes in the retina (drusen, geographical atrophy, epiretinal membrane, MNV, macular oedema, macular foramen, vitreomacular traction, and central serous retinopathy), which it then interprets in the second stage and concludes the diagnosis (Figure 3) (16). Depending on the severity of retinal pathology, it also proposes a recommendation for further treatment of the patient, so this software is primarily intended for technological support in specialized ophthalmological clinics.

5 The use of artificial intelligence to guide and determine the effect of treatment

Today, treatment with anti-VEGF drugs (aflibercept, bevacizumab, brolucizumab, ranibizumab) is considered the gold standard in the treatment of patients with neovascular AMD, proliferative DR, and diabetic macular oedema (DME), as by binding to VEGF receptors these drugs prevent endothelial cell proliferation and neovascularization, reduce increased vascular permeability and thus prevent the accumulation of intraretinal fluid (IRF) and subretinal fluid (SRF). Today, measurements of central retinal thickness (CRT) on the OCT image help us to quantify the fluid in the macula.

Rasti et al. have developed the CADNet (Convolutional Attention-to-DME Network) software to help predict the response to anti-VEGF treatment in DME patients (40). Assuming the effectiveness of the drug used and based on the measured CRT on OCT images obtained before the start of intravitreal treatment, the algorithm automatically estimates the predicted reduction in retinal thickness, or the effect of treatment after three months (40). Compared to similar algorithms (Extra Trees, Inception V3, ResNet50, Visual Geometry Group 16, Xception), which require the input of longitudinal OCT images to assess the effect of treatment, the CADNet algorithm has proven to be a more accurate tool for predicting disease outcome (39,40).

In recent years, there is growing evidence that retinal thickness is by no means an ideal method for capturing morphological changes in the retina. CRT should certainly not be the only parameter for deciding on further treatment of the patient (42-45). In addition to retinal fluid, the effect of anti-VEGF treatment is also influenced by structural changes in the retina, such as pigment epithelial atrophy, changes in the photoreceptor layer and vitreoretinal interface, the IRF pattern distribution, cystic degeneration, hyperreflective foci, disorganization of retinal inner layers (DRIL), and vascular thickness (46). The presence of IRF is the most important risk factor for visual acuity deterioration in patients with neovascular AMD due to retinotoxicity (47,48). Since IRF volume and area are directly related to visual function, the predicted treatment outcome can be determined by measuring the amount and distribution of IRF (48). Based on these findings, the University of Vienna has developed a complex algorithm that automatically detects the presence of IRF, SRF, and pigment epithelial detachment on a three-dimensional OCT image (49). The algorithm also reliably detects and spatially evaluates diffusely distributed IRF and IRF with multilocular cysts, which is otherwise clinically difficult to assess (49). In the study, the algorithm proved to be a promising tool for deciding on the intravitreal therapy regimen of patients with neovascular AMD (49).

6 Automated screening for retinopathy of prematurity

Over the last decade, survival of highly immature preterm infants has increased significantly due to advances in perinatal care which means that in neonatology we are facing the problem of higher morbidity of surviving preterm infants. Due to retinal immaturity, preterm infants with very low gestational age are at particular risk of developing retinopathy of prematurity (ROP). ROP is a relatively rare vasoproliferative retinal disease in our geographical area, but it is nevertheless one of the most common causes of irreversible vision loss in premature infants (50). In Ljubljana, on average, 20% of preterm infants meeting the criteria for ROP screening developed the disease in the last 5 years, and 15–35% of preterm infants with ROP required treatment

(51). With a timely diagnosis, most of the sight threatening ROPs can be successfully treated, so in Slovenia, all preterm infants born before the 31st week of gestation and/or with a birth weight of less than 1500 g are included in the ROP screening program (51).

Screening of preterm infants for ROP involves eye examination with an indirect ophthalmoscope at one- to two-week intervals, mostly between the ages of 30 and 37 weeks of gestational age. The number of examinations, the age at the start of the screening, and the completion of screening depend on the stage of ROP and the associated systemic conditions of the preterm infant. The degree of ROP is determined according to the size of the avascular area, the appearance of the border (ridge) between the vascularized and avascular region of the retina, and according to the dilatation and tortuosity of the vessels of the already vascularized retina (52). To more closely monitor the state of retinal vascular development, most institutions use wide-angle cameras to document the appearance of the retina at each screening examination. Comparing a large number of images showing a normal appearance of the retina at different gestational ages of preterm infants with those showing different forms of ROP is the foundation of all software programs that incorporate AI elements. Most existing computer aided ROP detection systems, e.g. Vessel finder (53), RISA (54), RIVERS (55), CAIAR (56), are semi-automated and do not yet achieve the ability of a conventional ophthalmic examination.

The analytical procedures of more advanced automated algorithms for determining the degree of ROP are mostly based on the evaluation of retinal vessel dilatation and tortuosity, the PLUS disease. Such AI systems provide greater objectivity and repeatability, making the accuracy of PLUS disease detection comparable to the conventional clinical examination. Brown et al. devised a fully automated screening program system for ROP based on deep learning and neural networks. It recognizes the PLUS disease in retina images with a specificity of 94% and a sensitivity of 93% (4). The automated computer system has even surpassed the experienced paediatric ophthalmologists involved in clinical research in identifying the disease (4). By upgrading the same AI system, Redd et al. (17) enabled differentiation and quantification of stages of ROP while maintaining the efficiency and accuracy of the program.

E. Ataer-Cansizoglu and V. M. Yildiz developed a similar model of artificial intelligence. It automatically detects clinically significant changes in the retinal vessels in retinal images of preterm infants at risk of developing ROP, thus providing a specific recognition of individual stages of ROP (18,57).

Software programs supported by AI, which are already installed in some wide-angle cameras for documenting the retina of preterm infants, can already be of great help today to a paediatric ophthalmologist during the examination. For the time being, they distinguish only between present and absent PLUS disease, and perform less well at assessing the degree of (pre-)PLUS disease and at other parameters for assessing ROP, such as extension of vasculature, presence and height of the ridge between avascular and vascular retina, in recognizing individual vessels passing over the ridge (and representing a good predictor of continued vascularisation), etc. The development of image processing technology, growing databases, more accurate images, and added information provided by Doppler ultrasonography of the retinal vessels will undoubtedly significantly facilitate screening work in many institutions around the world in the future.

7 Conclusion

With the advancement of information and cognitive science, AI in the medical profession has experienced a rise. Software based on the principles of deep learning and convolutional neural networks has proven to be an effective tool in ophthalmology due to its high performance in image data processing and analysis, especially in the treatment of patients with retinal diseases. The most common diseases of the retina, diabetic retinopathy and age-related macular degeneration, are the leading causes of permanent vision loss, and at the same time their early detection allows for effective treatment and thus significantly increases the chances of maintaining functional vision. The prevalence of DR and AMD in the developed world is rising sharply, and the economic burden of these diseases is increasing at the expense of permanent vision loss. With early detection and treatment of retinal diseases, blindness can be largely prevented and functional vision in patients maintained for a longer period of time. The first AI algorithms in ophthalmology were therefore developed with the aim of early recognition of preclinical signs. Due to the accuracy in recognizing retinal pathology, they can also be used to support decision-making on further treatment of ophthalmic patients.

Conflict of interest

None declared.

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