Artificial intelligence for diabetic retinopathy

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Abstract

Diabetic retinopathy (DR) is an important cause of blindness globally, and its prevalence is increasing. Early detection and intervention can help change the outcomes of the disease. The rapid development of artificial intelligence (AI) in recent years has led to new possibilities for the screening and diagnosis of DR. An AI-based diagnostic system for the detection of DR has significant advantages, such as high efficiency, high accuracy, and lower demand for human resources. At the same time, there are shortcomings, such as the lack of standards for development and evaluation and the limited scope of application. This article demonstrates the current applications of AI in the field of DR, existing problems, and possible future development directions.

Keywords: Artificial intelligence; Deep learning; Diabetic retinopathy

Introduction

Diabetes is a chronic disease with a high prevalence globally. In 2019, there were approximately 463 million adults aged 20 to 79 years with diabetes,[1] and the prevalence is still increasing.[2] By 2040, approximately 600 million people are expected to be diabetic.[3,4] The prevalence of diabetes in Chinese adults has gradually increased from 9.7% in 2010[5] to 10.9% in 2013[6] and 12.8% in 2018.[7] Diabetes can cause damage to the nerves, blood vessels, and multiple systems in the body. Diabetic retinopathy (DR) is one of the main complications of diabetes. Among diabetic patients globally, it is estimated that 34.6% suffer from DR, among which 10.2% have impaired vision.[8] In China, 18.45% of the population with diabetes have DR, and a longer course of diabetes is associated with a higher prevalence of DR.[9] Respectively, 17.6%[10] and 33.2%[11] of diabetic patients in India and the United States have developed DR. DR is progressive and it is associated with the risk of vision loss and even blindness. It is the main cause of blindness among people of the working age.[4] DR is asymptomatic during the early stages. Therefore, quite a lot of diabetic patients do not undergo regular fundus screening until the DR is severe enough to impair visual acuity. By this time, visual function is often difficult to recover.[12] Therefore, early detection and timely treatment are particularly important to prevent visual impairment caused by DR.

The characteristic pathology of DR is retinal vascular abnormalities, including microaneurysms, intraretinal hemorrhages, venous beading, exudates, and neovascularization.[12] Based on severity, DR can be divided into no apparent DR, mild non-proliferative DR (NPDR), moderate NPDR, severe NPDR, and proliferative DR (PDR). Diabetic macular edema (DME) is characterized by the destruction of the blood–retinal barrier and accumulation of fluid in the macular area.[13] It can occur at any stage of DR and threaten vision. Therefore, DME is independently graded[4] and divided into mild, moderate, and severe DME according to the severity. The diagnoses of DR and DME are generally based on the findings of direct and indirect ophthalmoscopy, slit-lamp biomicroscopy with front lenses, fundus photography (FP), optical coherence tomography (OCT), OCT angiography, fluorescein angiography, and B-ultrasound.[14] The ophthalmoscope and slit lamp with front lenses are now widely used because of their low price and accessibility in areas with limited medical resources. FP is currently internationally recognized for DR screening and diagnosis. Owing to its

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relatively high price, OCT is currently not available for screening in some areas, but it is increasingly valued.

Current status of DR screening

The American Academy of Ophthalmology recommends that individuals with type 1 diabetes should undergo annual eye examinations 5 years after the onset of diabetes. Individuals with type 2 diabetes should undergo annual eye examinations at the time of diagnosis.[14] Screening refers to the assessment of the existence or risk of a particular disease in asymptomatic individuals. With early detection and treatment, the outcomes can be improved.[15] Diabetic eye screening in the United Kingdom[16] began in 2003 and covered the entire United Kingdom in 2008. From 2015 to 2016, the program carried out DR screening of 82.8% of the 2,590,082 diabetic patients nationwide. Currently, DR is no longer the main cause of blindness for people aged 16 to 64 years in the United Kingdom. Therefore, extensive screening is believed to help prevent and treat blindness caused by DR.[17] However, compliance with DR screening is generally poor. A U.S. study showed that among the 298,393 patients diagnosed with type 2 diabetes but not DR, nearly half had never undergone an eye examination within the past 5 years; only 15.3% followed the American Academy of Ophthalmology recommendation of having an eye examination once every 2 years. For the patients with type 1 diabetes, one-third did not undergo eye examinations, and only 26.3% of patients followed the American Diabetes Association recommendations for screening.[18] In another previous study, more than one-third of the respondents did not undergo fundus screening regularly.[19] The reasons for the poor compliance of diabetic patients with regular fundus screening recommendations include the lack of understanding of the disease,[20] poor accessibility of medical resources, and insufficient medical insurance coverage.[21] The study by Murchison *et al*[22] found that patients with more severe DR, impaired vision, and poor blood sugar control had better compliance, which showed that most patients without visual impairment did not realize the importance of regular follow-up. Studies have revealed that 73% of DR patients do not realize that they have DR.[23] In addition, the availability of ophthalmologic screening services affects the compliance of diabetic patients with fundus screening recommendations.[24,25] One of the ways to enhance the accessibility of fundus screening is telemedicine, which enables patients to undergo fundus examination nearby, and even anytime and anywhere, instead of going to distant hospitals with ophthalmologists. The Singapore Integrated Diabetic Retinopathy Program (SiDRP) obtains fundus images remotely and gets them evaluated by ophthalmologic professionals, which significantly reduces the medical costs.[26] Studies have found that telemedicine is cost effective in a large-scale population of >3500 people under 80 years of age.[27] However, traditional telemedicine still relies on human resources to grade the fundus images of patients. In recent years, the development of artificial intelligence (AI) has provided a good alternative for both patients and ophthalmologists to improve the compliance of patients and the efficiency of telemedicine in DR.

AI in DR screening

McCarthy *et al*[28] first proposed the concept of AI in 1956. Soon afterward, Arthur Samuel proposed the concept of machine learning (ML) in 1959 and pointed out that ML should have the ability to learn statistical techniques without explicit programming.[29] Deep learning (DL) is a branch of ML that is mainly implemented using multi-layer neural networks. A convolutional neural network (CNN) is a DL model suitable for processing images, and it is mainly composed of convolutional layers, pooling layers, and fully connected layers. Commonly used CNN architectures include AlexNet, VGGNet, Inception V1–V4, ResNet, and DenseNet. The CNN model was trained end-to-end on the datasets of labeled images. It achieves higher accuracy by modifying parameters through an error backpropagation algorithm based on the set objective function. Transfer learning is another ML method. In transfer learning, the model is trained in the source domain and transferred to the target domain and fine-tuned, which helps the model to effectively learn and has a good generalization ability from the target domain with a relatively small sample. Compared with traditional ML, an important advantage of DL is that it can automatically learn different levels of effective semantic feature representations of large-scale datasets.

AI has been applied to image-based medical fields, such as radiology,[30] dermatology,[31] pathology,[32] and ophthalmology because it is suitable for processing complex images. In the field of ophthalmology, AI can assist in the diagnosis of DR, glaucoma, age-related macular degeneration, and retinopathy of prematurity. Early AI software was developed to identify specific image features.[33] With the development of technology, AI software can learn by itself from datasets with a large number of artificially labeled images. In 2018, the Food and Drug Administration approved the first AI software for DR (IDx-DR). IDx-DR (Digital Diagnostics Inc., Coralville, USA) uses Topcon NW400 to capture fundus images, and the doctor uploads the images to the cloud server. The software provides results according to the images: if the image quality is high enough, and mild or severe DR is detected, the doctor will be prompted to refer the patient to an ophthalmologist; if the severity is not higher than mild DR, it will prompt the patient to retest in 12 months.[34] IDx-DR has shown good sensitivity and specificity in several studies [Table 1]. EyeArt (Eyenuk Inc., Los Angeles, USA) was approved by the Food and Drug Administration in August 2020.[35] Retmarker DR (Retmarker, Coimbra, Portugal) has been certified as a Class IIa medical device in Europe[36] and has been used in the DR screening project in Portugal since 2011.[37] In China, AI-based screening software for DR by Shenzhen SiBionics Co. Ltd. (Shenzhen, China) and the AI-based analysis software for DR by Airdoc (Beijing, China) were also approved in August 2020.[38]Table 1 lists the details of the representative AI systems in the present study, including the training, validation, testing set, as well as sensitivity, specificity, and area under curve (AUC). According to current studies, AI-based diagnosis systems for DR have the advantages of high efficiency, high accuracy, and low demand for human resources. An Australian study found that the AI-based screening system

Table 1: Summary of representative AI systems and algorithms in detection of DR.

Authors	AI system	Algorithm	Year	Training set	Validation set	Testing set	Classification of DR	AUC	Sensitivity (%)	Specificity (%)
IDP										
Abràmoff *et al*[40]	IDP	Non-DL	2013	N/A	N/A	Messidor-2	ICDR	0.937	96.80	59.40
Hansen *et al*[42]	IDP	Non-DL	2015	N/A	N/A	Nakuru Eye Disease Study: 6788	ICDR	0.878	86.70	70.00
IDx-DR										
Abràmoff *et al*[43]	IDx-DR	CNN	2018	N/A	N/A	819 patients from US	FPRC	N/A	87.20	90.70
Van der Heijden *et al*[44]	IDx-DR 2.0	AlexNet, VGGNet	2018	10,000–1,250,000	N/A	898 patients from Netherlands	EURODIAB/ICDR	0.94/0.87	91/68	84/86
Abràmoff *et al*[45]	IDx-DR X2.1	CNN	2016	10,000–1,250,000	N/A	Messidor-2	Combination of ICDR and ME	0.980	96.80	87.00
EyeArt										
Solanki *et al*[46]	EyeArt	Image analysis technology	2015	EyePACS: 78685		Messidor-2	ICDR	0.941	93.80	72.20
Rajalakshmi *et al*[47]	EyeArt	Image analysis technology	2018	EyePACS: 78685		296 patients from India	ICDR	N/A	99.30	68.80
Bhaskaranand *et al*[48]	EyeArt v1.2	Image analysis technology	2016	EyePACS: 78685		EyePACS: 40542	ICDR	0.879	90.00	63.20
Bhaskaranand *et al*[49]	EyeArt v2.0	Image analysis technology	2019	EyePACS: 78685		850908	ICDR	0.965	91.30	91.10
Google										
Gulshan *et al*[50]	Google	Inception-v3	2016	128175		EyePACS-1, Messidor-2	ICDR	0.990–0.991	87.00–97.50	93.9–98.5
Gulshan *et al*[51]	Google	Inception-v4	2019	103634	40790	Aravind Eye Hospital: 1983	ICDR	0.963–0.980	88.90–92.10	92.20–95.20
Others										
Krause *et al*[52]	N/A	Inception-v3	2018	1662646	3737	EyePACS-2: 1958	ICDR	0.986	97.10	92.30
Oliveira *et al*[53]	RetmarkerSR	Recognition of characteristic lesions	2011	N/A	N/A	21,544 (5386 patients from Portugal)	No DR or NPDR/NPDR with DME/PDR	0.849	95.80	63.20
He *et al*[54]	Airdoc	Inception-v4	2019	ImageNet dataset: 1200000000		3556 (889 patients from China)	ICDR	0.950	91.80	98.79
Huang *et al*[55]	Airdoc	Inception-v3, SVM	2018	Kaggle: 60000	N/A	34100	ICDR	0.940	95.30	79.50
Zhang *et al*[56]	VoxelCloud Retina	Inception-ResNet v2	2020	143626; 1184	31498	APTOS 2019 Blindness Detection Dataset	ICDR	N/A	83.30	92.50
Hsieh *et al*[41]	VeriSee	Inception-v4, ResNet	2020	5649; EyePACS	1875	N/A	ICDR	0.950	89.20	90.10
Keel *et al*[39]	EyeGrader	Inception-v3	2018	Labelme: 58790	Labelme: 8000	96 patients from Australia	Scale based on ETDRS	0.937–0.989	92.30	93.70
Malerbi *et al*[57]	PhelcomNet	CNN	2021	10569	824 patients from Brazil	ICDR		0.890	97.80	61.40
Ting *et al*[58]	N/A	VGGNet	2017	2010–2013 SIDRP	2014–2015 SIDRP	10 datasets ($n = 1052$–$15,798$)	ICDR	0.889–0.983	94.4–100.00	73.3–92.20
Li *et al*[59]	N/A	Inception-v3	2018	LabelMe: 71043		NIEHS, SIMES, AusDiab: 35201	NHS diabetic eye screening guidelines	0.955	92.50	98.50
Cao *et al*[60]	N/A	Bayesian model	2019	1000 patients from Beijing		N/A	N/A	0.938	94.90	92.80
Gargeya and Leng[61]	N/A	Data-driven DL algorithm	2017	EyePACS		Messidor 2, E-Ophtha	N/A	0.970	94	98
Li *et al*[62]	ZOC-DR-V1	Transfer learning, NASNet	2019	4465	952	1000	ICDR	0.994	96.89	93.57
Sahlsten *et al*[63]	N/A	Inception-v3	2019	28512	7118	N/A	ICDR	0.987	89.60	97.40

AI: Artificial intelligence; AUC: Area under curve; CNN: Convolutional neural network; DL: Deep learning; DME: Diabetic macular edema; DR: Diabetic retinopathy; ETDRS: Early treatment diabetic retinopathy study; ICDR: International Clinical Diabetic Retinopathy Severity Scale; IDP: Iowa Detection Program; N/A: Not available; NPDR: Non-proliferative diabetic retinopathy; PDR: Proliferative diabetic retinopathy; SIDRP: Singapore Integrated Diabetic Retinopathy Program; FPRC: Wisconsin Fundus Photograph Reading Center; ICDR: the International clinical diabetic retinopathy severity scale; ME: Macular edema; SVM: Support vector machine; APTOS: Asia Pacific Tele-Ophalmology Society.

for DR only takes about 7 minutes to assess a patient in an endocrinology clinic and shows a higher accuracy as well as higher popularity among patients than manual screening by ophthalmologists.[39] In a study by Abràmoff *et al*,[40] the sensitivity of the software used in the Iowa Detection Program (IDP) exceeded that of ophthalmologists specializing in retinopathy. Compared with manual work, AI systems are more sensitive and less specific for the diagnosis of DR.[41] Several studies have also shown that AI systems can greatly reduce the workload of manual grading of DR. For example, RetMarker can reduce the workload of manual grading images by 48.42%.[37] Instead of going to specialized hospitals with ophthalmologists, AI systems enable patients to collect fundus photographs or OCT images at a relatively close primary health care clinic, can be used to directly perform grading, and receive further suggestions for follow-up or referral. This characteristic makes it more convenient and efficient for diabetic patients to undergo fundus screening and greatly reduces the workload of ophthalmologists, which can significantly improve the compliance of diabetic patients for fundus screening.

Development of an AI-based diagnostic system for DR

During the development of AI-based diagnostic systems for DR, the dataset used should be divided into training, validation, and test sets, and they should not overlap. The training set is used to train the algorithm. The validation set is used for parameter selection and tuning. The testing set is used to evaluate the actual performance of the AI system in clinical settings.[72] Both the training and validation sets are used to develop and optimize the algorithm, while the testing set must be independent of the training and validation sets and cannot be reused; otherwise, it may lead to deviations during the performance evaluation of the algorithm. Owing to the characteristics of DL, the training set should have abundant and high-quality images, which should be evaluated and labeled by ophthalmologists for algorithm development. According to the Chinese guidelines,[73] the training set should consist of FP images from at least two medical institutions for AI systems based on FP. According to the DR clinical diagnosis and treatment guidelines (2014), the training set should include at least 1000 single-field FP images or 1000 pairs of two-field FP images, 500 images (or image pairs) of non-readable FP images, and 500 images (or image pairs) of other fundus diseases in addition to DR for positive DR stages (I, II, III, and IV). At least three graders with at least an intermediate professional title in ophthalmology and relevant grading qualifications should have the majority opinion in grading each photo. The standard testing set should include 5000 FP images (or image pairs); of these, there should be no <2500 images (or image pairs) for DR stage I and above and 500 images (or image pairs) for other fundus diseases. When testing AI systems, 2000 images (or image pairs) were randomly extracted for the DR stages.[73] Among the current studies that describe the composition of the training set in detail, none have included images of other fundus diseases other than DR. Moreover, the training set of the AI system of Krause *et al*[52] and that sponsored by Google[50,51] meet the rest of the requirements. The remaining problems associated with the training sets of the existing AI systems include the use of FPs from only a single source[60,62] and the inclusion of fewer than 500 non-readable images (or image pairs).[55,56,58,63] Some studies use online datasets as training sets,[59] but with online datasets, it is impossible to have access to the basic information of the patient, such as gender and age.

Efficacy of existing AI-based diagnostic systems for DR

IDP is an early AI system that has been applied to Caucasian and African populations. It mainly grades FP images by identifying characteristic lesions with no DL techniques. Despite its relatively high sensitivity, IDP has a low specificity.[42] IDx-DR adds a CNN based on IDP, which significantly improves the specificity of detection. In prospective clinical studies, the sensitivity of IDx-DR in real clinical settings was lower than that in the testing set, but it still showed satisfactory sensitivity and specificity.[43] EyeArt was the first AI system to detect DR on smartphones. Among 296 patients with type 2 diabetes in India, the sensitivity for referable DR was 99.3% and the specificity was 68.8%, verifying that it is feasible for the system on the smartphone to perform remote DR detection.[47] Referring to the Google algorithm, the threshold can be adjusted to achieve the required sensitivity or specificity. When used for screening, AI and manual work can be combined, as the threshold can be adjusted to a higher sensitivity, and screening can be completed manually. It would be helpful to improve efficiency while ensuring that as few patients with referable DR as possible are missed. Daniel *et al* used VGGNet to train the algorithm and tested it using an external testing set in ten different countries with an AUC of 0.889 to 0.983, which demonstrated good results for each country.[59]

Most current AI-based diagnostic systems for DR are based on FP. FP can only detect DME based on the recognition of hard exudates in the posterior pole, which is limited by the two-dimensional characteristics of FP. Thus, AI systems based on FP may probably miss cases although they cover DME. Compared with FP, OCT has a higher detection rate for DME.[13,43] Various diagnostic systems currently combine OCT and AI techniques to identify DME [as listed in Table 2], and, overall, they have good sensitivity, specificity, and AUC. Hwang *et al*[66] developed an AI system based on OCT that can be used on smartphones, but the system needs to import OCT images into the phone in the first place, which still requires OCT equipment and does not solve the problem of accessibility, which is faced by patients in areas with limited medical resources.

Limitations in clinical application

Although a large number of AI-based diagnostic systems for DR have been developed, there are still problems to be solved.

1. Many AI systems use online datasets, including Messidor and EyePACS, to train their algorithms. The present online datasets have the shortcomings of having the same source of images and similar image quality and covering a single type of disease. It may not be compatible with fundus images of patients in the real world when directly applied in real clinical settings, which may lead to misdiagnosis. In addition, in the

Table 2: Summary of representative AI systems and algorithms in detection of DME.

Authors	Algorithm	Year	Training set	Validation set	Testing set	AUC	Sensitivity (%)	Specificity (%)
Varadarajan *et al*[64]	Inception-v3	2020	6039 (4035 patients from Thailand)	1033	EyePACS	0.890	85.00	80.00
Kermany *et al*[65]	Inception-v3	2018	11349	250	1000	0.999	97.80	97.40
Hwang *et al*[66]	MobileNet	2020	2768 (173 patients)	365	362	0.960	92.51	85.93
Hwang *et al*[67]	Inception-V3	2020	2768 (173 patients)	365	362	N/A	95.15	89.63
Singh and Gorantla[68]	DMENet (HE-CNN)	2020	516 (IDRiD), 1200 (MESSIDOR)	N/A	N/A	0.949–0.965	96.32	95.84
Wu *et al*[69]	VGG-16	2021	12365		656	0.970–0.997	80.10–94.90	96.50–97.60
De Fauw *et al*[70]	3D U-Net	2018	UK: 14884 (7621 patients)	993	997	0.992	N/A	N/A
Li *et al*[71]	VGG-16, Transfer learning	2019	108312	1000	N/A	1	97.80	99.40

AI: Artificial intelligence; AUC: Area under curve; CNN: Convolutional neural network; DME: Diabetic macular edema; HE-CNN: Hierarchical Ensemble of Convolutional Neural Networks; IDRiD: Indian Diabetic Retinopathy Image Dataset; N/A: Not available.

emerging field of AI-based diagnosis, a unified standard has not yet been established. The datasets used in various studies are quite different in sample size, composition, image quality, and other factors. Moreover, most of the studies used online datasets or data collected from previous studies. With the lack of multicenter prospective clinical research, the precision of trained algorithms in assessing patients in the real world is still doubtful.

2. The International Clinical Diabetic Retinopathy Severity Scale (ICDR) is the classification standard used in most studies. According to the ICDR standard, retinopathy is further classified into referable (moderate NPDR, severe NPDR, PDR, DME, and ungradable) and non-referable (no apparent DR and mild NPDR) DR, and vision-threatening (severe NPDR and PDR) and non-vision-threatening DR. However, it has not been determined if ICDR is the most suitable classification standard. Li *et al*[59] believe that since the progression of milder DR is slower than that of severe DR, classification based on ICDR will lead to excessive recommendations for referrals, and early treatment DR study may be a more suitable classification standard. Presently, different studies often use different classification standards, while the different classification standards greatly affect the validity of the algorithm[44] and the evaluation of each algorithm.
3. To date, there is no unified standard for evaluating the validity of AI algorithms. The testing sets of various studies differ significantly. Some studies did not use independent external testing sets, but they used internal validation sets to test the sensitivity, specificity, and AUC of the algorithm. The sensitivity, specificity, AUC, and other indicators reported by different studies were not comparable. Therefore, a standard testing set should be established to evaluate each algorithm.
4. The AI technique has a major unsolvable problem, which is the "black box" phenomenon. This refers to the situation in which the self-learning characteristics of the AI technique make the specific process of assessment by the AI systems unknown, leading to inexplicability. The inexplicability means that people only know the results but cannot judge whether the process of assessment by AI is reasonable or not, let alone intervention.
5. Regarding the misdiagnoses by AI systems, responsibility attribution is another problem that needs to be solved. It seems that neither algorithm developers nor medical staff who use these systems are qualified to assume responsibility alone. Therefore, most AI systems are only used for DR screening. For DR complicated by cataracts and other diseases leading to unclear media or cases where image quality is low due to poor cooperation of the patient, the applicability and reliability of AI-based diagnostic systems are greatly limited, and the only solution is turning to an ophthalmologist.
6. Information security is an issue that cannot be ignored when evaluating AI systems. If AI systems are used to conduct extensive screening of patients with diabetes, a large amount of personal information of patients is likely to be involved. How to ensure that patient information is only used for medical purposes and how to prevent information leakage is a problem that needs to be solved during the development of AI techniques.
7. For most current studies, one AI system can only detect one disease, which means that a patient can only be assessed for a single problem during a fundus examination. If an AI system can detect multiple diseases, the eye examination process will be greatly simplified. Studies have reported detecting other ophthalmic diseases during the screening of DR, which can simultaneously detect age-related macular degeneration and other diseases.[58]

Conclusions and prospects

AI is of great prospects in screening and diagnosis of DR with several potential future directions. More AI systems will be developed based on portable devices such as smartphones enabling patients to complete DR screening with their own devices at home without the aid of medical workers, which leads to a great reduction in the require-

ments of trained medical workers and medical equipment, resulting in improved accessibility of DR screening. Under the pandemic of the coronavirus disease 2019 (COVID-19), such telemedicine is of growing importance and would bring considerable benefits and convenience to both patients and medical workers. Currently, most AI-assisted DR screening systems are based on traditional fundus imaging. With the development of novel examination techniques, AI-based systems may cover more varieties of examinations, including multispectral fundus imaging and OCT, and the accuracy could also be improved by the combination of different examinations. In addition to the existing AI-assisted screening systems, this technology will also take an essential role in the diagnosis of DR. In current studies, AI-based systems show better sensitivity than ophthalmologists[40] and have the potential to exceed ophthalmologists in accuracy. Therefore, the AI-assisted diagnosis systems can support ophthalmologists to make diagnoses more accurately and efficiently.

In conclusion, for countries with existing DR screening programs, the proper use of AI-based diagnostic systems is expected to greatly reduce the burden of human resources and improve efficiency. In general, the application of AI techniques to DR has great prospects. However, the current datasets used to develop AI algorithms are relatively limited. To apply AI-based diagnostic systems for DR more widely in clinical practice, it is necessary to make full use of clinical resources, establish more heterogeneous datasets, and improve the standards for image quality and labeling. AI systems are more normative and effective. The conditions for replacing ophthalmologists with AI systems are still immature. Therefore, combining the AI techniques with manual work is more realistic and beneficial at the initial stage of applying AI to clinical practice.

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Conflicts of interest

None.

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