AI in Research and Ophthalmology

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Introduction: The concept of Artificial intelligence (AI) was first introduced by Dartmouth scholar John McCarthy in 1956 which refers to hardware or software that exhibits behavior that appears intelligent. It has been highlighted recently because of new algorithms, specialized hardware, cloud-based services, and big data development. Machine learning (ML) and Deep learning (DL) are subsets of AI. Machine learning (ML) is a set of methods that automatically detect patterns in data and incorporate information to predict future data under uncertain conditions in the 1980s. Deep learning is rapidly increasing technology of ML which has revolutionized the world of AI[1]. These technologies have powered many aspects of modern society like object recognition in images, translation of real-time languages, and device manipulation via speech such as Apple's Siri, Amazon Alexa, Microsoft Cortana, etc. It has been used for diagnosing and treating common vision-threatening diseases like diabetic retinopathy (DR), glaucoma, age-related macular degeneration, cataracts, etc.

AI tools have increased in rate since the last 10 years which could transform eye health ranging from facilitating and increasing access to eye care to supporting clinical decision making with an objective, data-driven ach.[2,3]

Highlights of Research from 2010 to 2023 and their clinical applications

Table 1: Summary of current AI systems with regulatory approval for retinal disease management.[4-10]

AI system	Company	Year Approved	Regulatory authority	Exam analysed	Target	Impact on prognosis	Cloud-based?
Retmarker DR Biomarker [4]	Retmarker, SA, Taveiro, Portugal	2010	CE, TGA (Australia)	Color fundus images	DR	Identification of the risk of complications	No
Notal Home OCT [5]	Notal Vision, Inc., Manassas, VA, USA	2018	FDA (Breakthrough Device Designation)	OCT	Neovascular AMD	Early detection of fluid	Yes
Notal OCT Analyzer [6]	Notal Vision, Inc., Manassas, VA, USA	2018	FDA (Breakthrough Device Designation)	OCT	Neovascular AMD, DME, RVO	Automated detection of fluid	Yes
RetinAI Discovery [7]	RetinAI Medical AG, Bern, Switzerland	2020	CE, FDA	OCT, color fundus images	AMD, DR, epiretinal membranes, other	Strict follow-up	Yes
VUNO Med-Fundus AI [8]	VUNO Inc., Seoul, Korea	2020	CE, MFDS (Korea), HAS (Singapore)	Color fundus images	AMD, DR, epiretinal membranes, other	Strict follow-up	No
iPredict [9]	iHealth-Screen Inc., Richmond Hill, NY, USA	2021 and 2022	CE, TGA (Australia)	OCT, color fundus images	AMD, DR	Prediction of progression	Yes
RetInSight Fluid Monitor [10]	RetInSight GmbH, Vienna, Austria	2022	CE	OCT	AMD, DME	Automated detection of fluid	Yes

CE=Conformite Europeenne, MFDS=Ministry of Food and Drug Safety of the Republic of Korea, HAS= Hospital Administration Software, TGA=Therapeutic Goods Administration, OCT=Optical Coherence Tomography, AMD=Age-Related Macular Degeneration, DME=Diabetic Macular Edema, DR=Diabetic Retinopathy, FDA=Food and Drug Administration, RVO=Retinal Vein Occlusions

Table 2: Summary of representative works of AI in ophthalmology[1]

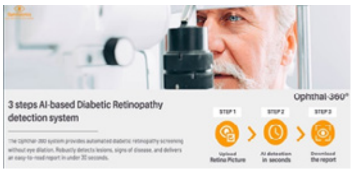
Year	Reference	Topic	Dataset	AUC	SE	SP
2016	Abramoff MD et al.	DR	CFPs, 1748 images	0.98	96.80%	87.00%
2017	Gargeya R et al.	DR	CFPs, 75,137 images	0.97	94%	98%
2017	Ting DSW et al.	DR, glaucoma, and AMD	CFPs, 494,661 images	0.931-0.958	90.5%-100%	87.2%-91.6%
2020	Pan X et al.	DR lesions classification	FFAs, 4067 images	0.870-0.965	79.7%-98.0%	82.7%-99.5%
2022	Gao Z et al.	DR grading	FFAs, 11,214 images	0.922-0.994	/	/
2020	Varadarajan AV et al.	DME OCT-grading	CFPs, 7072 images	0.89	85%	80%
2019	Liu H et al.	Glaucoma	CFPs, 274,413 images	0.996	96.20%	97.70%
2021	Sun S et al.	Glaucoma	OCTs, 777 sets	0.957	89.60%	95.20%
2020	Thompson AC et al.	Glaucoma	OCTs, 20,806 images	0.96	81%	95%
2019	Phene S et al.	Glaucoma	CFPs, 86,618 images	0.945	80.00%	90.20%
2019	Asaoka R et al.	Glaucoma	OCTs, 4316 images	0.937	82.50%	93.90%
2019	Wen JC et al.	Forecast future Visual Fields	VFs, 32,443 VFs	/	/	/
2022	Huang X et al.	Glaucoma visual field grading	VFs, 16,356 VFs	0.93	/	/
2017	Burlina PM et al.	AMD	CFPs, 213,997 iamges	0.96	88.40%	94.10%
2019	Peng Y et al.	AMD grading	CFPs, 59,302 images	0.94	59.00%	93.00%
2020	Yan Q et al.	AMD progression prediction	CFPs, 31,262 images	0.85	/	/
2018	Kermany DS et al.	AMD	OCTs, 207,130 images	0.999	97.80%	97.40%
2020	Schmidt-Erfurth U et al.	Quantification of Fluid Volumes to AMD	OCTs, 24,362 images	/	/	/
2021	Yan Y et al.	AMD	OCTs, 56,091 images	0.940-0.992	80.0%-96.5%	/
2021	Zhang G et al.	Detect and quantify geographic atrophy	OCTs, 5049 images	/	/	/
2021	Xu Z et al.	AMD, PCV	CFPs and OCTs, 1099 CFPs, 821 OCTs	0.939	88.80%	95.60%

2022	Jin K et al.	Identification of choroidal neovascularization activity in AMD	OCTs and OCTAs, 462 image pairs	0.98	89.60%	95.60%
2011	Cheung CY et al.	Cataract	Slit-lamp photographs, 5547 images	/	/	/
2021	Li Z et al.	Keratitis	Slit-lamp photographs, 6567 images	0.998	97.70%	98.20%
2021	Ye X et al.	Myopic maculopathy	OCTs, 2342 images	0.927-0.974	73.9%-92.8%	84.8%-94.0%
2019	Yoo TK et al.	Identify candidate patients for corneal refractive surgery	Multi-instrument data, 13,201 subjects	0.983	/	/
2020	Wang L et al.	Eyelid malignant melanoma	Pathological patches, 225,230 images	0.989	94.70%	95.30%

Table 3: Description and notification of current AI systems[13]

AI system	Description and notification
IRIS (Intelligent Retinal Imaging Systems, Pensacola, FL, USA)	IRIS is an FDA class II cleared medical system that has a moderate risk to consumers and must demonstrate that it is 'substantially equivalent' to similar products. The IRIS program is a cloud-based platform to screen for vision-threatening DR, with sensitivity and specificity of 66.4% and 72.8%, respectively.
ARDA (Google LLC, Mountain View, CA, USA)	ARDA is a DL algorithm developed by Google Health from >128 000 retinal photographs of patients from the United States and India and validated in >10 000 photographs from the UK to detect referable and sight-threatening DR. The validation study of ARDA was the first showing robust performance of DL to detect referable DR with >95% of both sensitivity and specificity. Later, ARDA was prospectively validated in India and a nationwide screening program in Thailand.
	

AI system	Description and notification
SELENA+ (EyRIS Pte Ltd, Singapore)	The Singapore Eye Research Institute and Singapore National Eye Center has developed a DL-based algorithm, SELENA+, to screen for referable DR, vision-threatening DR, DR-related vascular risk factors, suspected glaucoma, and late-stage AMD. It is a multicenter collaborative research effort with half a million retinal images from people of different ethnicities such as Caucasians from Australia and the United States, and Singapore Chinese, Malayans, Indians, Chinese, individuals from Hong Kong, Mexicans, Hispanics, and African Americans. Real-world application and clinical translation of SELENA+ has been integrated into the Singapore Integrated Diabetic Retinopathy Programme in recent years. SELENA+ has significant diagnostic performance in DR, with sensitivity of 91%, specificity of 90%, and area under the curve of 0.93.
IDx-DR (Digital Diagnostics Inc., Coralville, IA, USA)	IDx-DR was the first FDA-approved ophthalmic device to autonomously detect DR, including DME. It can analyze retinal images, detect vision-threatening DR, and provide referral recommendations. The external validation to detect referable DR showed sensitivity and specificity of 91% and 84%, respectively.
	
Medios AI (Remidio Innovative Solutions Pvt Ltd., Karnataka, India)	Medios AI is an integrated offline system with a Remidio smartphone-based, nonmydriatic retinal camera to detect referable DR. The fundus images can be captured by minimally trained healthcare providers. The sensitivity and specificity of diagnosing referable DR were 100% and 88.4%, respectively.
RetCAD (Thirona Retina BV, Nijmegen, Netherlands)	This commercially available DL algorithm can determine referable DR and AMD based on a dataset of CFPs to reduce the workload of screening programs by up to 96%, with sensitivity of 90.53% and specificity of 97.13%. Patients' CFPs can be captured by camera and then transferred to the Thirona server for analysis. The examination report will provide referable suggestions and visualization of heatmaps.
EyeArt (Eyenuk, Inc., Woodland Hills, CA, USA)	This cloud-based autonomous AI system can detect more-than-mild DR and vision-threatening DR by submitting fundus photography to the platform. It is designed to work with various types of retinal cameras. It assesses the quality of uploaded images and explains the reasons behind grading. This algorithm can provide the grading of DR and report the results for each eye based on the UK National Health Service diabetic eye screening program scale. The sensitivity and specificity showed 96% and 98%, respectively.

AI system	Description and notification
	
VUNO Med-Fundus AI (VUNO Inc., Seoul, Korea)	The AI-based VUNO Med-Fundus AI analyzes CFP to detect multiple retinal lesions (areas under receiver operating characteristic curves for all findings were at 96.2%). The area under the receiver operating characteristic curves for DR-related findings was 95%. It was approved as a class III medical device by the Ministry of Food and Drug Safety in Korea.
THEIA (Toku Eyes, Auckland, New Zealand)	The New Zealand company Toku Eyes developed THEIA, an AI platform for cloud-based multimodal image analysis of referable DR and AMD. The THEIA system was developed from two of the largest screening data sets in Auckland, New Zealand: the Auckland District Health Board and the Counties Manukau District Health Board. It can analyze color fundus images, OCT, and OCT-A to provide results about referable DR (sensitivity of 93% and specificity of 63%) and intermediate dry AMD (accuracy of 96%). This AI system is considered to be useful in reducing the workload in the New Zealand National Diabetic Retinopathy Screening Program.
iPredict (iHealthScreen Inc., Richmond Hill, NY, USA)	The iPredict AI Eye Screening System offers fully automated diagnosis of referable DR (maculopathy and/or proliferative DR) (sensitivity of 97.0% and specificity of 96.3%) and AMD (sensitivity of 86.6% and specificity of 92.1%) by analyzing CFPs.
Notal Home OCT (Notal Vision, Inc., Manassas, VA, USA)	Notal Home OCT, the first FDA-cleared in-home OCT device, which includes an AI algorithm and monitoring center, is designed to detect AMD. The imaging quality showed great correlation with in-office OCT for detecting the presence of fluid in 95% agreement with human graders. A patient's ability to use an in-home setting for self-imaging without training demonstrated good capacity with a 95% success rate.
OphtAI (Evolucare/ADCIS, Villers-Bretonneux, France)	OphtAI DR is a semiautomatic AI algorithm that assesses the pathologic lesions and grading of DR and detects AMD and glaucoma. In a multicenter, head-to-head, real-world validation study to compare different algorithms in detecting DR, the OphtAI DR algorithm provided better results (sensitivity of 80.47% and specificity of 81.28%) than an ophthalmologist. It is also deemed clinically safe and economically efficient in reducing the costs by more than U.S. $15 per patient.
	
Retmarker (Retmarker, SA, Taveiro, Portugal)	This AI technology can provide screening for DR and AMD by annotating pathologic lesions, such as microaneurysms, drusen, hypopigmentation, hyperpigmentation, and geographic atrophy. The sensitivity in classifying DR is 73.0% for any DR, 85.0% for referable DR, and 97.9% for proliferative DR. The screening performance of Retmarker appeared to vary with patients' age, ethnicity, and camera type. In economic analysis, the Retmarker was more cost effective than manual grading.

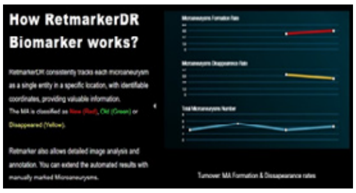
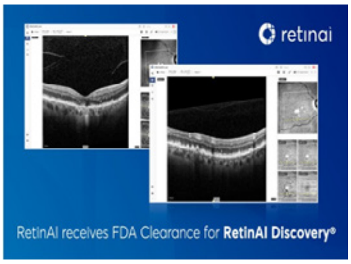
AI system	Description and notification
	
RetinaLyze (RetinaLyze System A/S, Hellerup, Denmark)	The RetinaLyze system is a screening software that can detect DR on nonmydriatic CFPs (sensitivity of 89.9% and specificity of 85.7%). It can detect DR lesions, including microaneurysms and minor hemorrhages (specificity of 71.4%). It can also evaluate biological aging and hemoglobin on optic disc photographs.
RetinAI Discovery (RetinAI Medical AG, Bern, Switzerland)	The Discovery platform can analyze medical data and ophthalmic images such as OCT scans and CFP from a variety of devices. It can help automatically detect the location of the fovea (mean total location error of 0.101 mm), the quantification of pathologic fluid, and the segmentation of atrophic retina on OCT in patients with geographic atrophy. It can detect and quantify fluid from DR, DME, AMD, and RVO. The performance of the AI system showed that the accuracy, specificity, and sensitivity for intraretinal fluid was 0.87, 0.88, 0.84 and 0.93, 0.95, 0.93 and for subretinal fluid was 0.93, 0.93, 0.93 and 0.95, 0.95, 0.95 in the AMD and DME cohorts, respectively.
	

Table 4: Comparison of features in ophthalmologic datasets[11]

DATASET	EYEPACS	ODIR	APTOS	DR 1 & 2	IDRiD	JICHI	ROD Rep	Messidor 2	Tsukazaki	PALM
Images	88702	8000	5590	1597	516	9939	1120	1748	13047	1200
Country	USA	China	India	Brazil	India	Japan	Netherland	France	Japan	China
Grading	ICDR	ICDR	ICDR	None	ICDR	Mod Davis	Non Specified	ICDR	None	Non-applicable
Sex	No	No	No	No	No	No	Yes	No	Yes	No
Age	No	Yes	No	No	No	No	Yes	No	Yes	No
Quality Control	No	No	No	No	No	No	No	Yes	No	No
Social	No	No	No	No	No	No	No	No	No	No
Ethnicity	No	No	No	No	No	No	No	No	No	No

The above mentioned software's are commercially available diabetic retinopathy screening AI platforms.

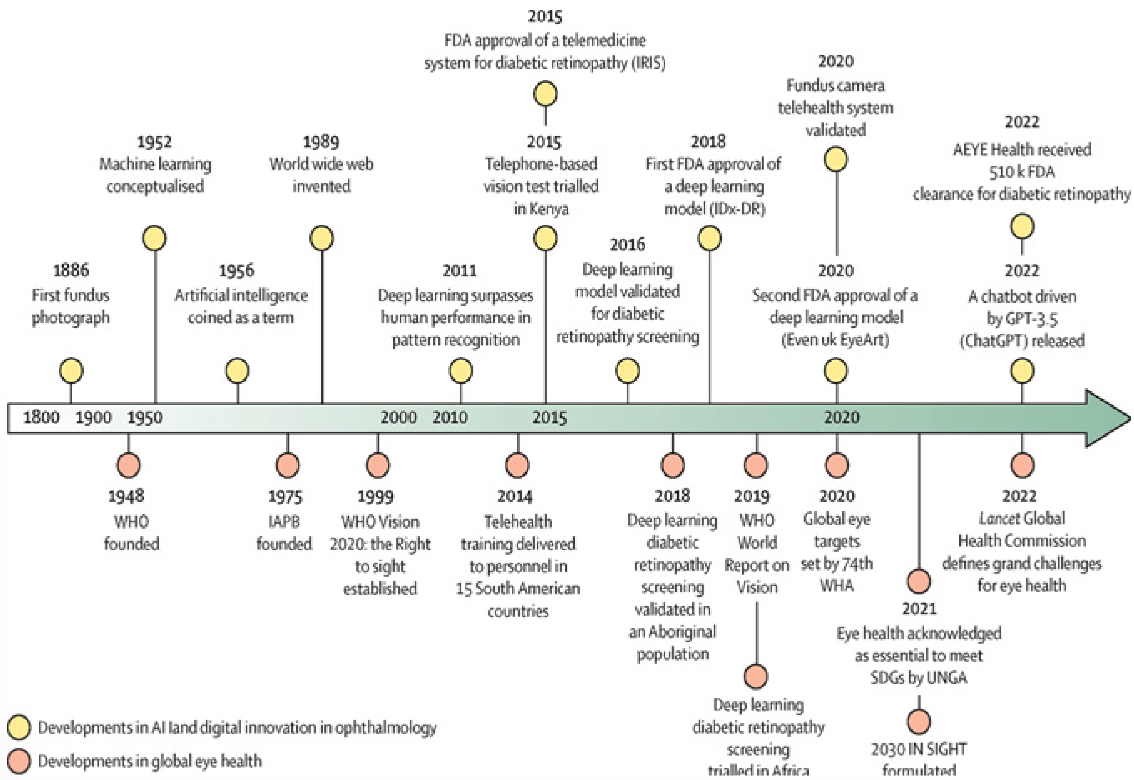


Figure 1: Timeline of the progress of global eye health initiatives (bottom, orange circles), compared with the development of digital health and artificial intelligence applications in eye health (top, yellow circles).[12]

AI=artificial intelligence. GPT=generative pre-trained transformer. IAPB=International Agency for the Prevention of Blindness. IRIS=International Repository for Information Sharing. SDG=Sustainable Development Goal. WHA=World Health Assembly.

Originally from link: *https://www.sciencedirect.com/science/article/pii/S2214109X23003236*

AI disruption in ophthalmology is revolutionizing the field especially in primary care and remote areas. Early detection tools like Artelus India founded in 2015 helps in screening diabetic retinopathy patients making eye health care more accessible.

Remidio has integrated AI with smartphones for eye screening. Their non mydriatic fundus tool captures eye images and generates automatic reports on the phone. It enhances accessibility and convenience for screening, particularly for conditions like referable diabetic retinopathy.

The AlzEye research study by Professor Pearse Keane suggests that the human eye, which human eye, which can be used as a window to see the rest of the body, has been supercharged by the combination of big data, latest advances in AI software and hardware and advances in retinal imaging technology such as optical coherence tomography (OCT). Signs of retinal degeration in the retinal tissue may be seen in patients with dementia tia. We hope to show changes in the inner layers of the retina that may detect early signs of neurodegeneration.

The artificial retina is surgically implanted into the eye of patients who have lost their sight due to conditions like age-related macular degeneration (ARMD) or retinitis pigmentosa (RP). The artificial retina has a tiny camera mounted on glasses worn by the patient, which captures visual information from the surroundings and further transmits the images to a microprocessor. It interprets the visual data and converts it into signals that can stimulate the microelectrodes on the artificial retina. The purpose of implanting an artificial retina into the eye is to restore restricted vision by allowing people to read when moving (walking, running or sitting in a moving car or other vehicle), improve one's vision and help recognize individuals.

Challenges and future directions of AI in research:

AI algorithms require vast amounts of high quality data to train effectively, and obtaining these well-annotated datasets can be challenging. The AI algorithms need clinical validation to prove their safety and effectiveness. Integration of AI systems into present clinical workflows and Electronic Health Record (EHR) systems can be complex where seamless interoperability is crucial. Data biases can be present in the existing training data which can lead to biased AI algorithms. Gaining approval for AI-based medical devices is a complex process, for which strict regulations are being developed to ensure safety and efficacy of patient data. Data transfers between research collaborators, especially for international collaborators are often limited because of patient privacy and data security. Ensuring patients' trust in clinicians and support staff and clinical pathways and procedures is also essential.

Tailoring interventions for diseases like glaucoma and age-related macular degeneration can enable more personalized treatment plans based on each patients unique profile. Telemedicine is an important tool which helps to enhance early detection of disease and remote monitoring of patients who come from areas. Integration of multimodal imaging likes optical coherence tomography, (OCT), fundus photography and angiography can provide a comprehensive view of eye health which includes the tools to predict disease progression and assess the risk of developing certain eye and systemic conditionss.[1,2] AI algorithms can be useful to accelerate drug discovery for retinal diseases by analyzing large datasets to identify potential therapeutic targetss.[1,2] Establishing a global digital eye health task force with country-level representatives from every region in the world could facilitate organised coordination of efforts and progress toward integrating these digital health tools into eye health systems. The financing of eye health services is a critical aspect of healthcare planning striking a balance between operational costs and reimbursements. Present, research on economic analysis of digital health tools and AI in ophthalmology is scarce and mostly restricted to diabetic retinopathy screening in high income countries, though many other eye and related systemic diseases exert a higher burden of disease around the world. There is utmost requirement for greater understanding of cost effectiveness and resources required for new digital health tools, in the unique settings of different countries with varying resource capacities.[12]

AI is tremendously helpful to the scientific research community, but there are some concerns about the application of such technology, ranging from plagiarism, ethical issues, replicating human biases or spreading wrong information.[13] To make sure AI is used in the right way, researchers and other teams need to work together to guarantee that AI driven research systems are constructed in a responsible way and used 14. Also a study by AAO in journal Ophthalmology found that the doctor-AI team is more effective than work that struggles to separate the two [15].

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