AI Meets the Eye: A Multimodal Artificial Intelligence Approach for the Detection of Ocular and Systemic Diseases

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Abstract

Background: Artificial intelligence (AI) is increasingly playing an important role in the detection and diagnosis of various ocular and systemic diseases. Multimodal retinal imaging together with AI has enabled early identification of disease with potential for earlier management and treatment. The retina represents a non-invasive window through which an examination can be conducted not only of the vascular, neurological, and metabolic condition of the eyes, but also of the body as a whole, thus representing an ideal medium to be screened by AI diagnostic platforms.

Objective: This paper aims to investigate the performance of artificial intelligence for the detection of various ocular diseases and systemic diseases by utilizing multimodal retinal imaging as well as compare AI-based screening against clinician-based screening through a systematic review and meta-analysis.

Methods: The databases searched were the PubMed, Medline, Web of Science, ScienceDirect and CENTRAL. Included studies involved the screening of diabetic retinopathy by artificial intelligence and deep learning applications to fundus images, and OCT scans. Meta-analysis was conducted of the sensitivity and specificity derived from the studies utilizing Meta Disc software. A bivariate random-effects model was applied and analysis was carried out, whilst quality was assessed using
QUADAS-2.

Results: A total of eighteen studies from 2,065 initial articles were included in this review. The overall sensitivity and specificity of AI-based screening for retinopathy were both 0.877 and 0.906 respectively; while for clinicians they were 0.75 and 0.941 respectively. It can be inferred that there is greater sensitivity with AI compared with humans, but a comparable specificity. Deep learning models could diagnose features such as microaneurysms, hemorrhages, exudates, and drusen in the retina with a high diagnostic accuracy. When combining information from

fundus photos, OCT, and patient data a combined model achieved 95.1% diagnostic accuracy. The utility of artificial intelligence via retinal screening in the assessment of a wide range of systemic disease biomarkers was highlighted for cardiovascular disease, stroke risk, chronic kidney disease, and many other neurological disorders.

Conclusion: Artificial intelligence demonstrates high diagnostic accuracy for the identification of various ocular diseases as well as screening for systemic diseases. Combining AI and multimodal imaging offers an accurate, affordable, and scalable means of screening with the ability to significantly reduce the global impact of avoidable blindness.

Keywords: artificial intelligence; deep learning; diabetic retinopathy; age-related macular degeneration; glaucoma; fundus imaging; optical coherence tomography; multimodal AI; systemic disease detection; retinal screening

Abbreviations: AI = artificial intelligence; AMD = age-related macular degeneration; ANN = artificial neural network; AUC = area under the curve; CNN = convolutional neural network; DL = deep learning; DR = diabetic retinopathy; ERG = electroretinography; FDA = Food and Drug Administration; GCL = ganglion cell layer; ML = machine learning; NLP = natural language processing; OCT = optical coherence tomography; ONH = optic nerve head; QUADAS = Quality Assessment of Diagnostic Accuracy Studies; RNFL = retinal nerve fiber layer; ROP = retinopathy of prematurity; SAP = standard automated perimetry; SVP = superficial vascular plexus; VEGF = vascular endothelial growth factor

Introduction

Artificial intelligence, or AI, refers to computer systems that can carry out tasks that normally need human thinking—such as recognizing images, solving problems, learning from experience, and making decisions. In the field of medicine, AI has the potential to make clinical work much more accurate and efficient by processing enormous amounts of information—both organized data (like numbers in a database) and unorganized data (like doctors' notes)—to diagnose diseases and predict outcomes with very little human input [1,2].

There are three main types of artificial intelligence that matter for medical use:

1. **Artificial Narrow Intelligence (ANI):** This is AI that handles one specific job within a limited area, such as sorting images or screening for a particular disease.

2. **Artificial General Intelligence (AGI):** This is a theoretical concept—AI that could do any intellectual task a human can do.

3. **Artificial Superintelligence (ASI):** This is also theoretical, describing AI that would be smarter than humans in every possible way [3,4].

At this moment, every medical AI application in use today—including all the ones used in eye care—falls under the first category, ANI.

Two major technological approaches drive AI in healthcare. Natural language processing (NLP) is a method that pulls useful information from unstructured text, such as electronic health records, clinical notes, and medical research papers [5]. Machine learning (ML) is a technique that analyzes structured data—such as genetic sequences and medical images—to find patterns and make predictions. Within machine learning, deep learning (DL) uses multiple layers of artificial neural networks to create increasingly detailed and accurate representations of data, which makes it especially good at recognizing images [6,7]. In eye care, the most commonly used deep learning designs are convolutional neural networks (CNNs)—networks built specifically to process grid-like data such as photographs—and massive training artificial neural networks (MTANNs), which are trained to spot and classify specific disease-related features [8,9].

Ophthalmology—the branch of medicine dealing with the eye—is an especially promising area for AI development because of the high-quality, standardized digital images that eye doctors routinely collect. These include color photographs of the back of the eye (fundus photography), optical coherence tomography (OCT) scans, OCT angiography (OCT-A), fundus autofluorescence imaging, and visual field tests. The retina is the only place in the human body where doctors can directly see tiny blood vessels and nerve tissue without surgery, making it a unique window into the health of the body's blood vessels, nerves, and metabolism [10,11].

AI applications in eye care have focused on diseases that cause major vision loss, including diabetic retinopathy (DR), age-related macular degeneration (AMD), glaucoma, retinopathy of prematurity (ROP), and macular holes (MH). These conditions are becoming more common worldwide, and there are not enough eye specialists or screening facilities to keep up—especially in low- and middle-income countries. This shortage has created an urgent need for automated, scalable tools that can diagnose these conditions [12,13].

Artificial Intelligence in Age-Related Macular Degeneration

Age-related macular degeneration is a long-term, progressive, and potentially irreversible condition that affects the central part of the retina. It is one of the leading causes of severe vision loss in older adults around the world. The disease is marked by the buildup of yellow deposits called drusen, changes in the retinal pigment epithelium (RPE)—a layer of cells that nourishes

the retina—and, in its more aggressive "wet" form, the abnormal growth of new blood vessels under the retina. These new vessels can leak fluid and blood, causing swelling and damage [14].

The appearance and classification of drusen—whether they are hard or soft, and whether they sit inside or outside the RPE layer—are central to diagnosing and staging AMD. Using machine and deep learning, AI can detect AMD at earlier stages by automatically spotting drusen, fluid under the retina, and fluid within the retina on OCT scans and color fundus images. AI-based tools have shown improved sensitivity (ability to correctly identify disease) and specificity (ability to correctly rule out disease), which gives doctors more confidence in their diagnoses and allows treatment to begin sooner [15,16].

Burlina and colleagues showed that automated AMD assessment using deep learning algorithms matches the grading done by human retinal specialists, highlighting the potential of these systems to lower screening costs and make monitoring more consistent [17]. OCT is one of the most important tests for detecting, staging, and predicting the outcome of AMD, especially the wet form, which requires repeated injections of anti-vascular endothelial growth factor (anti-VEGF) medication into the eye [18].

Antony and collaborators used a specific CNN design called VGG16 to diagnose AMD from OCT scans. This network uses an encoder module to pull out the most important image features and compress them into a feature vector, which is then processed by a fully connected feed-forward neural network (FFNN) to estimate the likelihood of AMD and predict how the patient might fare [19]. Schlegl and colleagues developed a fully automated deep learning algorithm to detect and measure fluid in OCT images caused by AMD. It achieved an average accuracy of 0.94 and performed particularly well at identifying fluid inside the retina [20].

Peng and collaborators created DeepSeeNet, a deep learning tool that evaluates the risk of progression to late AMD by automatically classifying pigment abnormalities and drusen characteristics from color fundus photographs. DeepSeeNet achieved better precision and accuracy than retinal specialists in catching these early warning signs [21]. Together, these studies show that AI-based systems can match or exceed the performance of human experts, and it is expected that these tools will become a routine part of clinical care in the near future.

Artificial Intelligence in Glaucoma

Glaucoma is a progressive disease of the optic nerve—the bundle of nerve fibers that carries visual information from the eye to the brain. It is characterized by structural damage to the optic nerve and corresponding loss of peripheral vision. It is the second leading cause of irreversible blindness worldwide. In many cases, the damage is linked to high pressure inside the eye, which

injures the retinal ganglion cells and their nerve fibers, collectively known as the retinal nerve fiber layer (RNFL) [22].

Currently, doctors evaluate glaucoma by looking at both structural damage and functional loss. Structural damage includes abnormalities in the optic disc and thinning of the RNFL and the ganglion cell layer (GCL), typically measured with OCT scans. Functional damage refers to vision loss, measured with a test called standard automated perimetry (SAP), in which patients respond to lights appearing in their peripheral vision [23]. AI, particularly deep learning, has made significant progress in automating the detection of both types of damage.

AI systems using OCT can automatically measure the thickness of the RNFL and GCL using artificial intelligence segmentation techniques. However, traditional segmentation methods can make mistakes and produce artifacts, especially in eyes with severe disease. Recent studies have shown that deep learning can detect glaucoma and track its progression more accurately and faster than older methods [24,25].

Sigueoka and colleagues conducted a study using SAP and OCT data, applying machine learning algorithms including Radial Basis Function (RBF) networks and feed-forward neural networks (FFNNs) to calculate mean deviation and pattern standard deviation from visual field tests, alongside RNFL thickness measurements. The RBF network, which uses special mathematical functions, proved to be the most powerful model for telling glaucomatous eyes apart from healthy ones [26].

Mariottoni (2020) showed that deep learning algorithms can detect relevant characteristics in OCT cross-sections to predict RNFL thickness without explicitly separating each retinal layer—a "segmentation-free" approach. A downside of this method is that it produces a relatively high number of image artifacts compared to traditional OCT segmentation [27]. Thompson and colleagues addressed this problem by developing a CNN model that uses peripapillary B-scans (cross-sectional images around the optic nerve) to predict the probability of glaucoma. Their model achieved higher diagnostic accuracy and avoided the artifact problem [28].

Jammal and colleagues developed an M2M DL (Machine-to-Machine Deep Learning) algorithm to compare automated estimates of the cup-to-disc ratio and RNFL thickness analysis against manual grading by glaucoma specialists. Looking at 490 fundus photographs, the M2M DL algorithm performed significantly better than conventional SAP-based methods at identifying glaucomatous optic nerve damage [29]. In 2022, Akter and collaborators developed the first integrated technique for glaucoma diagnosis that combines patient risk factors with both functional and structural data. They trained three deep learning models to calculate the cup surface area, showing that this combined approach will be essential for future glaucoma detection [30].

Despite these advances, AI in glaucoma still faces challenges. Deep learning models need large, diverse sets of training images, which take a long time to collect and label. Also, the natural variation in the shape of the optic nerve head across different populations makes it hard for one model to work equally well for everyone. More research is needed to prove that these tools are reliable across different demographic groups [31].

Artificial Intelligence in Diabetic Retinopathy

Diabetic retinopathy is a complication of diabetes that affects the small blood vessels of the retina. It remains the leading cause of preventable blindness among working-age adults. In early stages, the disease causes progressive damage to retinal nerve cells, tiny bulges in blood vessels called microaneurysms, small dot-blot hemorrhages, and hard exudates (deposits of fat and protein)—often without any obvious symptoms. In advanced stages, it causes cotton wool spots (areas of nerve fiber damage), venous beading (irregular swelling of veins), intraretinal microvascular abnormalities (IRMA), and the growth of new, abnormal blood vessels called neovascularization [32,33].

Yearly screening for diabetic retinopathy is essential at every stage of diabetes because early detection and timely treatment—using laser therapy or injections of anti-VEGF medication into the eye—can prevent severe vision loss. The global diabetes epidemic is expected to affect 700 million people by 2045, creating a demand for screening that far exceeds the number of available specialists [34].

In 2018, the U.S. Food and Drug Administration (FDA) approved IDx-DR, the first fully autonomous

AI-based diagnostic system for diabetic retinopathy. It was developed from the Iowa Detection Program (IDP). IDx-DR works with non-mydriatic fundus images—pictures taken without dilating the pupil—using the Topcon NW400 camera. The system requires one image centered on the optic disc and one centered on the macula for each eye; all four images must pass quality checks before the system can produce a diagnosis [35,36].

Earlier versions of the IDP algorithm used separate, hand-crafted algorithms to detect exudates, hemorrhages, neovascularization, cotton wool spots, and other lesions. A validation study conducted on a Caucasian and North African population analyzed 3,640 fundus images and found that the IDP achieved a sensitivity of 86% (correctly identifying 86% of true cases) and a specificity of 70% (correctly ruling out 70% of non-cases), with 334 cases needing image quality improvement [37]. The IDx-DR system improved upon the IDP by integrating deep learning-based features. When tested against the Messidor-2 dataset, specificity improved to 80% (meaning fewer false positives), while sensitivity remained high [38].

In Portugal, software called RetmarkerDR was developed for local diabetic retinopathy screening. Its special feature is the ability to compare older images with new ones to track disease progression. RetmarkerDR calculates a "microaneurysm turnover rate," measuring how many old microaneurysms have disappeared and how many new ones have formed—a dynamic indicator of how active the disease is [39]. Other AI-based systems, including EyeArt and Bosch DR, have shown promising results in screening programs, though more prospective studies are needed to confirm their performance across diverse populations [40].

The combined evidence from multiple meta-analyses shows that AI-based diabetic retinopathy screening systems achieve sensitivity and specificity that match or exceed human graders, making them practical tools for closing the global screening gap [41].

Artificial Intelligence in Retinopathy of Prematurity

Retinopathy of prematurity is a disease involving abnormal blood vessel growth in the retina of premature babies. It is a leading cause of childhood blindness worldwide, especially in middle-income countries. Screening is demanding and resource-intensive because it requires skilled eye doctors to perform indirect ophthalmoscopy (an examination using a handheld lens and light) in neonatal intensive care units [42].

AI offers a way to expand screening capacity and make diagnosis more consistent. Brown and colleagues developed the i-ROP DL system, a deep learning platform for the early diagnosis of ROP. The system analyzes fundus images to produce a numerical severity score, allowing doctors to objectively monitor whether the disease is getting worse, improving, or responding to treatment. By automating the assessment of "plus disease" (abnormal widening and twisting of retinal blood vessels) and retinal vessel tortuosity (excessive twisting of vessels)—two key diagnostic criteria—the i-ROP DL system reduces differences between examiners and helps ensure timely treatment [43].

Adding AI to ROP screening programs is especially promising for regions with limited access to pediatric eye specialists, where the burden of this disease is highest.

Artificial Intelligence in Macular Holes and Other Eye Conditions

The macula is the central part of the retina responsible for sharp, detailed vision. A macular hole (MH) is a full-thickness break in this central area that impairs central vision depending on its size and exact location. Diagnosis requires a thorough dilated eye exam and OCT imaging to evaluate the retinal structure and plan surgery [44].

AI can help analyze OCT images to measure the size of a macular hole, predict how well a patient will see after surgery, and develop personalized surgical plans. Additionally, OCT

angiography (OCT-A) allows analysis of the superficial vascular plexus (SVP) and deep vascular plexus (DVP)—the two main layers of blood vessels in the retina. Changes in the shape and structure of these vessel layers are linked to how well a patient will see after vitrectomy surgery with internal limiting membrane peeling [45].

Beyond these conditions, AI is increasingly being used to detect retinal vein occlusion, screen for keratoconus (a corneal thinning disorder) using corneal topography, grade cataracts using slit-lamp microscope images, and predict the focusing power needed after cataract surgery. The range of AI applications in eye care is growing rapidly.

Multimodal AI and Detection of Systemic Diseases

A groundbreaking development in eye-related AI is the realization that retinal imaging can serve as a non-invasive window into the health of the entire body. The retina shares embryological origins with the brain and provides direct visualization of tiny blood vessels and nerve tissue. As a result, changes in the retina can reflect problems in the body's blood vessels, metabolism, and nervous system [46].

Cardiovascular Disease and Stroke Risk: Deep learning analysis of fundus images can predict cardiovascular risk factors—including age, sex, smoking status, systolic blood pressure, and major adverse cardiac events—directly from the patterns of blood vessels in the retina. Algorithms that segment (trace) blood vessels can measure arterial narrowing, arteriovenous nicking (where arteries press on veins), and vessel tortuosity, all of which are established signs of high blood pressure and hardening of the arteries [47].

Chronic Kidney Disease: The small blood vessels in the retina and the kidney share similar anatomy and function. AI-based detection of microvascular changes in the retina—such as microaneurysm turnover and areas where capillaries have stopped working—has been linked to declining kidney function and the severity of diabetic kidney disease [48].

Neurological Disorders: The optic nerve and retinal nerve fiber layer are part of the central nervous system. Thinning of the RNFL seen on OCT has been associated with Alzheimer's disease, Parkinson's disease, and multiple sclerosis. AI algorithms can detect subtle patterns of nerve degeneration in the retina that appear before the clinical symptoms of brain diseases become obvious, positioning eye imaging as a potential screening tool for early neurodegeneration [49].

Multimodal Integration: The proposed multimodal AI diagnostic framework combines fundus photography, OCT, OCT-A, electrical activity tests of the retina (such as electroretinography), and clinical information (patient history, demographics, and risk factors). Our systematic evaluation found that when these multiple inputs are combined using ensemble deep learning

architectures, the model's accuracy reaches 95.1%. This multi-input approach allows comprehensive coverage of both common and rare eye conditions while simultaneously screening for markers of whole-body diseases [50].

Diagnostic Accuracy: Systematic Review and Meta-Analysis

To ascertain the real-world effectiveness of AI in eye screening, we conducted a systematic review and meta-analysis examining diagnostic accuracy. Twenty-six hundred and five records were searched on PubMed, Medline, Web of Science, ScienceDirect, and CENTRAL. After filtering and quality assessment against the eligibility criteria, a total of eighteen studies were included in the meta-analysis. Sixteen studies used fundus photography, while two used OCT for imaging. While most studies assessed AI screening for diabetic retinopathy, we also extracted data for AMD and glaucoma. Data were pooled using a bivariate random-effects model for diagnosis performance. The resulting sensitivity was 0.877 and specificity was 0.906 with AI screening, while human expert-based screening obtained pooled sensitivity and specificity of 0.75 and 0.941, respectively. In simple terms, AI-based screening methods are able to identify positive cases more effectively (high sensitivity) while missing slightly more cases than human grader (slightly lower specificity than humans) but are not susceptible to the variations of humans. We encountered significant heterogeneity and quality variations between the studies for the AI systems and human experts with I value >99% and >98% respectively, which is common and likely related to different datasets, design of AI algorithms, types of subjects and images and their qualities. We confirmed robustness of pooled results with sensitivity analysis, and quality appraisal through QUADAS-2 framework highlighted patient selection and index test characteristics as the primary sources of potential bias. Applying the Fagan nomogram to estimate post-test probability, we predicted that the post-test probability of having disease after receiving a positive test result from an AI screening tool was 84.92%. The outcome is clinically significant and demonstrates the utility of an AI screening tool in conditions with a certain prevalence. It supports the use of an AI tool as a triage in primary care.

Discussion

The transformation of AI from a hypothetical technology to a validated clinical tool for eye diseases has accelerated dramatically. Deep learning algorithms have demonstrated the ability to detect microaneurysms, haemorrhages, exudates, drusen, and retinal nerve fiber layer thinning with a high degree of accuracy comparable to that of humans [49]. The full autonomy of AI-driven eye screening systems such as IDx-DR approved by the FDA indicates a paradigm shift in screening practices [51].

Advantages of using AI in eye screening include: the rapid, high volume processing of images thereby reducing workload of specialist eye clinicians; cost-effectiveness through enabling point-of-care screening in general practice clinics rather than referring to specialized centers; the ability to scale and expand to remote or under-served areas; and objective and reproducible assessment of retinal images which removes subjective variability inherent in human assessment [52].

Despite its promising applications, a number of significant challenges that need addressing include: data privacy and security concerns due to the sensitive nature of personal health data handled by cloud-based AI systems; interpretability of AI, with current deep learning systems often considered 'black boxes' making it difficult for clinicians to understand the reason for a particular prediction; necessity for explainable AI (XAI) that can provide visualization of factors influencing a prediction and enable clinicians to critically appraise and trust the system's decision. Features like saliency maps showing the regions of the image contributing to a prediction, attention mechanisms focusing the model's attention and visualization of decision trees will be crucial for AI implementation [53]; the issue of data imbalance and lack of diversity in the training data leading to algorithmic bias; necessity for rigorous external testing on populations with different ethnicity and demographics prior to wider adoption and, last but not least, the initial high cost of AI infrastructure and shortage of trained professionals in resource-poor settings [54].

Future Trends

In the future, the role of AI in eye care is anticipated to be guided by several synergistic trends:

Smartphone-based screening: With an increasing number of high-quality smartphone adapters entering the market for fundus imaging, portable and inexpensive screening of remote or resource-limited areas becomes increasingly feasible, circumventing the logistical issues associated with setting up fully integrated imaging suites. This trend will be revolutionized once AI algorithms are adequately tuned for smartphone-acquired images, making eye care accessible to an expanded population [55].

Real-time AI diagnostics: Developments to integrate AI directly into OCT and fundus cameras will be the next crucial step in streamlining workflows. Real-time diagnostic output as the image is taken will improve clinic efficiency and patient experience, diminishing anxiety levels typically associated with a waiting period for analysis results.

Predictive healthcare: Future AI applications will move beyond diagnosis towards predicting the progression of diseases, likely responses to therapy, and prognosis for visual function. In the

case of AMD, such algorithms could predict when further anti-VEGF intervention is warranted, or in glaucoma, estimate the speed of peripheral vision loss [56].

Nationwide screening programs: Large-scale AI-powered screening programs, particularly for diabetic retinopathy, glaucoma and AMD, are projected to become a standard in public health infrastructure across nations. Such initiatives will be critical in regions that lack a sufficient supply of eye care professionals for population-wide screening.

Integration into systemic health: The retina may evolve as a window into entire-body health assessment, as multi-modal AI platforms are developed to simultaneously screen for diseases in other organ systems including cardiovascular disease, neurological conditions and kidney disorders. This may lead to a transformative shift in the responsibilities of eye care practitioners, placing them at the forefront of preventive medicine [57].

Conclusion

Artificial intelligence, far from being merely an incremental advancement, represents a fundamental paradigm shift in how eye diseases are diagnosed. This systematic review and meta-analysis clearly demonstrate the capacity of multimodal AI in retinal imaging to detect eye diseases such as diabetic retinopathy, age-related macular degeneration, glaucoma and retinopathy of prematurity with high diagnostic accuracy. More significantly, they provide the unique capacity for early screening of systemic diseases, including cardiovascular disease, risk of stroke, and neurological disorders, through retinal analysis.

In terms of numerical performance, AI systems consistently exceed human specialists in screening sensitivity and demonstrate comparable specificity in the early detection of these eye diseases, making them ideally suited for mass screening initiatives. When integrated with a deep learning algorithm that clinicians can both trust and interpret, these high-resolution retinal imaging systems truly usher in an era of effective early disease diagnosis, facilitate remote eye care through telemedicine and drive forward preventive medicine.

However, considerable efforts must be made to address data privacy, explainability of AI, and equitability of access. Nonetheless, the future role of AI in ophthalmology is undeniable. Within the next decade, these screening and diagnostic AI systems will become routine in clinical practice, helping to reduce global rates of preventable blindness and establishing the retina as a definitive gateway into overall health.

Conflict of Interest Statement

The authors declare no conflict of interest.

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