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Oculomics: Current concepts and evidence

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ABSTRACT

The eye provides novel insights into general health, as well as pathogenesis and development of systemic diseases. In the past decade, growing evidence has demonstrated that the eye's structure and function mirror multiple systemic health conditions, especially in cardiovascular diseases, neurodegenerative disorders, and kidney impairments. This has given rise to the field of oculomics-the application of ophthalmic biomarkers to understand mechanisms, detect and predict disease. The development of this field has been accelerated by three major advances: 1) the availability and widespread clinical adoption of high-resolution and non-invasive ophthalmic imaging ("hardware"); 2) the availability of large studies to interrogate associations ("big data"); 3) the development of novel analytical methods, including artificial intelligence (AI) ("software"). Oculomics offers an opportunity to enhance our understanding of the interplay between the eye and the body, while supporting development of innovative diagnostic, prognostic, and therapeutic tools. These advances have been further accelerated by developments in AI, coupled with large-scale linkage datasets linking ocular imaging data with systemic health data. Oculomics also enables the detection, screening, diagnosis, and monitoring of many systemic health conditions. Furthermore, oculomics with AI allows prediction of the risk of systemic diseases, enabling risk stratification, opening up new avenues for prevention or individualized risk prediction and prevention, facilitating personalized medicine. In this review, we summarise current concepts and evidence in the field of oculomics, highlighting the progress that has been made, remaining challenges, and the opportunities for future research.

1. Introduction

1.1. The eye as a window to systemic health

The eye, often described as the "unique window to health," provides invaluable insights into systemic conditions (Fig. 1). Disorders of almost all vital organs can have manifestations in the eye, affecting structures from the external eye to the inner retina (Duh et al., 2017; Glover et al., 2021; Goyal et al., 2023; Mortensen et al., 2022; Pirani et al., 2019; Vitiello et al., 2020; Woo, 2019). For example, the presence of the external lid lesion xanthelasma indicates the possibility of hyperlipidemia, while severe dry eyes can suggest rheumatoid arthritis, and scleral yellowing, a sign of jaundice, indicates liver disease. Specifically, the retina provides direct, in vivo visualization of two critical organ systems - the microvasculature and the nervous system - that are largely inaccessible elsewhere in the body (Mortensen et al., 2022; Pirani et al., 2019; Woo, 2019). This allows the evaluation of a wide range of systemic diseases through observable end-organ damage (Dehghani et al., 2018; Flammer et al., 2013; Tong et al., 2014).

The biological foundation for viewing the eye as the window to health has roots in its similarities to other organs concerning embryological origin, anatomical features, and physiological properties (Edward and Kaufman, 2003). Embryologically, the retina arises from the diencephalon, extending from the central nervous system (London et al., 2013), suggesting that changes in retinal vessels may mirror those occurring in cerebral vessels (Baker et al., 2008). Anatomically, retinal vessels resemble brain circulation, and retinal neuron axons connect to the visual cortex via the optic nerve and central visual pathways (Flammer et al., 2002; London et al., 2013). Physiologically, the renin-angiotensin-aldosterone cascade in the kidney, which contributes to vascular endothelial dysfunction, is also active in the eye (Fletcher et al., 2010). Intriguingly, the eye's relative immune privilege, with its blood-retina barrier and downregulated immune response, protects it from inflammation (Zhou and Caspi, 2010). However, systemic diseases can disrupt these barriers, leading to ocular problems. For example, Behçet's disease and other forms of uveitis can breach this privilege, causing intraocular inflammation (Murakami et al., 2020). Studies have also revealed the presence of liver-derived proteins in people with retinopathy and gut-derived immune cells inducing ganglion cell damage in glaucoma, pointing to shared pathophysiology of ocular and systemic disease changes (He et al., 2023; Wolf et al., 2023).

1.2. The evolution of the concept - the eye as a window to systemic health

1.2.1. Mid-19th century: invention of the ophthalmoscope

The concept of the eye as a window to general health dates back to the mid-19th century (Fig. 2). The invention of the ophthalmoscope enabled direct visualization of the retina. Early observations linked retinal microvascular characteristics to hypertension, renal and cerebrovascular diseases (Gunn, 1892, 1898). In 1939, Keith et al. confirmed that the severity of retinal microvascular abnormalities could predict mortality in hypertensive patients (Keith et al., 1939). Subsequent research further explored the correlations between retinal pathology and systemic conditions such as hypertension, renal disease, cardiovascular and cerebrovascular disease, Alzheimer's disease (AD), stroke, and mortality (Cheung et al., 2012, 2021a; Goto et al., 1975; Hinton et al., 1986; Lindley et al., 2009; McGeechan et al., 2009; Rim et al., 2020b; Wong et al., 2001c, 2014).

1.2.2. Late 1990s to early 2000s: digital fundus photography and optical coherence tomography

The subsequent phase was between the late 1990s and early 2000s, with the development of digital fundus photography, transitioning retinal assessments from subjective qualitative assessments to objective quantitative evaluations (Lin et al., 2002; Massin et al., 2003).

This advanced technology was swiftly integrated into large population cohort studies. In the United States, the Atherosclerosis Risk in Communities Study (ARIC) (Wong et al., 2001b, 2002b), the Cardiovascular Health Study (CHS) (Wong et al., 2002a, 2003b), the Multi-Ethnic Study of Atherosclerosis (MESA) (Wong et al., 2006), and the Beaver Dam Eye Study (Klein et al., 2000), all employed the novel fundus photography. Similarly, the Blue Mountains Eye Study in Australia (Attebo et al., 1996) and the Rotterdam Study in the Netherlands (Ikram et al., 2006a, 2006b), utilized fundus photography to examine associations between retinal changes and a range of systemic diseases. These large cohort studies not only validated the feasibility of digital fundus photography at the population level but also provided valuable data for exploring the relationship between the retina and systemic health. The emergence of optical coherence tomography (OCT) further enabled depth-resolved visualization of retinal structure, setting the stage for interrogation of associations between retinal neurodegeneration and systemic diseases (Huang et al., 1991; Puliafito et al., 1995).

1.2.3. 2000s-2015: semi-automated computer-aided measurement and diagnosis

From the 2000s, ophthalmic imaging transitioned from manual assessment to semi-automated, computer-aided measurements. Software like IVAN (Integrative Vessel Analysis) (Klein et al., 2012; Wong et al., 2006) and SIVA (Singapore I Vessel Assessment) (Cheung et al., 2011; Cheung et al., 2010; Lau et al., 2014) was developed, enabling more efficient and standardized evaluation of retinal microvascular characteristics. For instance, IVAN was used in the Beaver Dam Eye Study (Myers et al., 2012) and the Singapore Malay Eye Study (Sun et al., 2008), linking retinal microvascular characteristics and systemic diseases such as hypertension and cardiovascular disease (CVD). However, these semi-automated software systems relied on time-consuming input from expert human retinal image graders, which emphasized the need for fully automated, AI-driven retinal image analysis technologies.

1.2.4. 2015-Now: application of artificial intelligence to retinal image analysis

Around 2015, a transformative fourth phase emerged with the application of artificial intelligence (AI) to retinal image analysis (Gulshan et al., 2016; Schmidt-Erfurth et al., 2018b; Wong and Bressler, 2016). The emergence of powerful computational capabilities, evolving models, and large datasets has enabled AI, particularly deep learning (DL) techniques, to achieve significant performance in retinal image analysis, with the potential to revolutionize the way eye diseases are screened, diagnosed, and managed (Ting et al., 2019a, 2019b). This era has garnered significant scientific and popular media attention, as AI analysis of large sets of retinal image data has enabled the identification of image features and disease associations that are beyond human perception. The focus of the current review is on the progress made in this field using AI technology.

1.3. Retinal imaging techniques ("hardware")

Rapid advances in retinal imaging technology have improved image resolution and accessibility. These innovations have enabled exploration of ocular structure with ease and speed at scale. Commonly used retinal imaging modalities include ocular fundus photography, OCT, and OCT angiography (OCTA) (Aumann et al., 2019; Bernardes et al., 2011; Spaide et al., 2018). A multimodal example of these imaging techniques is shown in Fig. 3.

1.3.1. Color fundus photography (CFP)

CFP, the most used imaging technique, captures color photographs of the retina (Bernardes et al., 2011) (Fig. 3A). Optical design of typical fundus cameras is based on the principle of monocular indirect ophthalmoscopy using pupil for illumination and imaging light rays. It can be used to capture both qualitative (e.g., retinopathy) and quantitative (e.g., caliber, tortuosity) retinal vascular features and serves as the input for image analysis computer software such as SIVA, IVAN, VAMPIRE, AutoMorph (Mautuit et al., 2022).

1.3.2. Optical coherence tomography (OCT)

OCT, is a high-resolution imaging based on low-coherence interferometry that serves as a non-invasive in vivo optical biopsy of the retina (Aumann et al., 2019) (Fig. 3B). The emergence of OCT has enabled remarkable advances in assessing retinal micro-structure both in quantitative features (e.g., retina sublayer thickness) and qualitative features (e.g., reflectance). More recently, the evolution from time-domain OCT to spectral-domain OCT (SD-OCT) has allowed a higher scan speed, higher axial resolution, and lower measurement variability (Geevarghese et al., 2021). Importantly, with improved image processing technology and normative databases, detailed specialized neuron cell analysis is now possible (Pazos et al., 2021). Built-in segmentation algorithms facilitate the extraction of information on retinal thickness from OCT scans.

1.3.3. Optical coherence tomography angiography (OCTA)

As a functional extension of OCT, OCTA has provided valuable information on the retinal vasculature in a more detailed, depth-resolved manner (Spaide et al., 2018) (Fig. 3C). By comparing repeated structural images throughout the retina, OCTA can detect areas of motion that

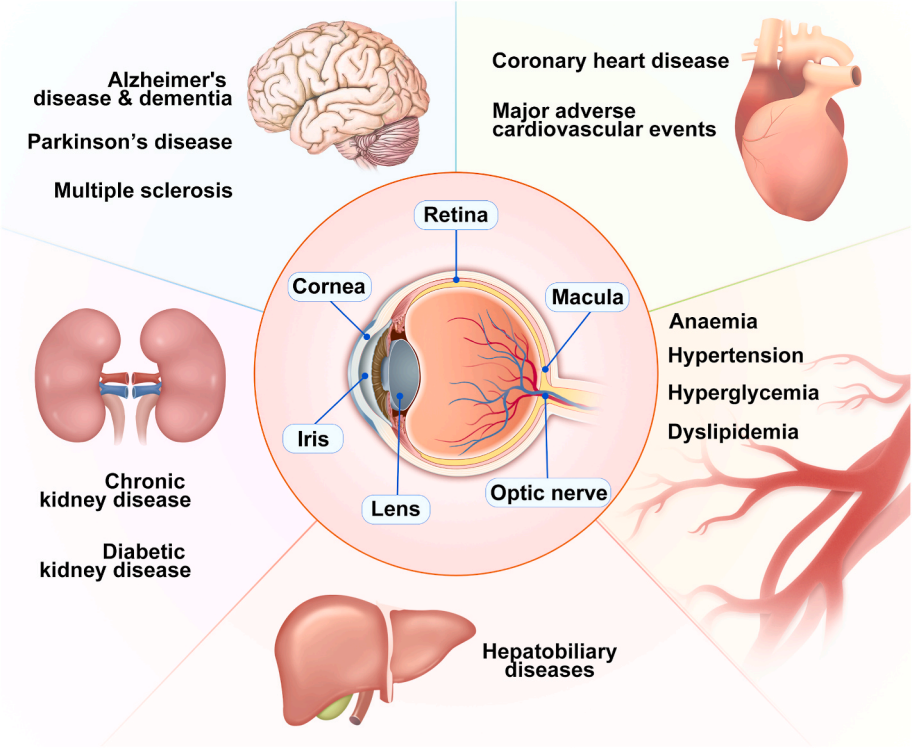

Fig. 1. Schematic figure illustrating the eye as a window to systemic health.

reflect the movement of red blood cells, and subsequently generate high-resolution flow maps that approximate angiograms.

The development of OCT and OCTA revolutionized retinal research, providing microscopic resolution with imaging of distinct cellular layers in the retina and microvasculature down to the level of the capillaries.

1.4. Large datasets that include eye-systemic health ("big data")

Most healthcare institutions possess retinal imaging data at scales ranging from tens of thousands to tens of millions of scans. However, these data are often inaccessible to researchers, even when there is an intention to make them available for research, due to barriers related to access and usability (Khan et al., 2021). Advances in ocular imaging technology have facilitated the creation of large-scale, real-world datasets that integrate retinal images with clinical data, offering invaluable resources for exploring the connections between eye health and systemic diseases.

The high-quality, large datasets, particularly those with richly labeled data, have driven the development of advanced statistical and computational methods, including deep learning, large language models, and generative models (Brown et al., 2024; Zhou et al., 2023a). Furthermore, they have enabled the application of AI in ophthalmology and related systemic diseases, including tasks such as image segmentation, automated diagnosis, disease prediction, and prognostication (Lamb, 1986; Rim et al., 2020a). These innovations hold the potential to significantly enhance diagnostic accuracy, improve patient outcomes, and offer novel insights into the interplay between ocular and systemic health.

These datasets include the UK Biobank, which encompasses a range of ocular data such as eye disease diagnoses, refractive error, habitual visual acuity, spectacle wear status, retinal color photographs, OCT imaging, and a broad array of systemic health indicators and diagnoses (Collins, 2012). Ocular measurements from the U.S. ARIC Study include assessments of distance and near visual acuity, contrast sensitivity, and retinal photographs from one randomly selected eye (Chambless et al., 2002). The Singapore Epidemiology of Eye Diseases (SEED) Study includes a comprehensive range of ocular assessments, such as slit-lamp examination, intraocular pressure measurement, retinal fundus photography, OCT, and OCTA, alongside a thorough systemic examination. This study provides valuable insights into eye health across a multi-ethnic population in Singapore, enabling the exploration of both ocular and systemic disease associations in diverse demographic groups (Majithia et al., 2021). Other studies that include both ocular and systemic health data are CHS (Wong et al., 2002a), MESA (Bild et al., 2002), Blue Mountains Eye Study (Attebo et al., 1996), Rotterdam Study (Ikram et al., 2017), Beaver Dam Eye Study (Klein et al., 1991), the Gutenberg Health Study (GHS) (Korb et al., 2023; Wild et al., 2012), the Beijing Eye Study (Jonas et al., 2009), the Age, Gene/Environment Susceptibility–Reykjavik Study (Jonasson et al., 2014) (Table 1).

Publicly available oculomics datasets are increasingly being utilized by a diverse range of researchers, from epidemiologists to computer scientists. From a global perspective, these datasets hold great potential to drive research advancements; however, as with any data source, it is crucial to consider both the provenance and limitations of the dataset. One key consideration is ensuring adequate representation of diverse populations. An AI algorithm trained exclusively on a single population group may not generalize well to other groups, potentially limiting its applicability and accuracy in broader clinical settings (Kelly et al., 2019). This underscores the critical importance of incorporating diverse and inclusive datasets during the development phase of AI models. By ensuring representation across varied demographic, ethnic, and clinical contexts, researchers can enhance the robustness and applicability of AI systems, ultimately fostering their successful deployment in real-world healthcare scenarios. Similarly, differences in imaging protocols, such as scan depth, field of view, and image preprocessing, can introduce inconsistencies that affect model performance. Standardization of imaging protocols and the development of hardware-agnostic algorithms will be essential to ensure robust performance across diverse clinical environments.

Furthermore, to advance the understanding of oculomic features and their relationship with systemic physiological and pathological changes, larger-scale studies with extended follow-up periods are essential. Such studies would not only provide valuable insights into the associations between oculomic markers and systemic conditions but could also elucidate the underlying mechanisms driving these relationships. This knowledge is crucial for translating oculomic research into clinically actionable tools that can improve patient outcomes.

In summary, the successful implementation of oculomics-based AI models in clinical practice—as the ultimate goal—relies fundamentally on the availability of high-quality, large-scale datasets. The pathway to achieving this goal involves several critical components: the development of diverse and representative datasets to ensure generalizability across populations, the establishment of rigorous benchmark validation standards to assess model performance and reliability, and the execution of randomized controlled trials to evaluate clinical efficacy and safety, both with and without the integration of AI algorithms (Chew et al., 2025). Each of these steps is essential to bridge the gap between research and real-world clinical application, ensuring that oculomics-based AI models can deliver accurate, reliable, and actionable insights in healthcare settings.

1.5. Artificial intelligence ("software")

1.5.1. Understanding artificial intelligence

AI, a branch of computer science, aims to create intelligent machines capable of simulating human cognitive functions such as learning, reasoning, and problem-solving (Schmidt-Erfurth et al., 2018b). In oculomics, AI primarily utilizes machine learning (ML) and its subset, DL, to analyze ocular imaging data (Fig. 4). ML learns patterns from data and makes predictions or decisions, while DL uses artificial neural

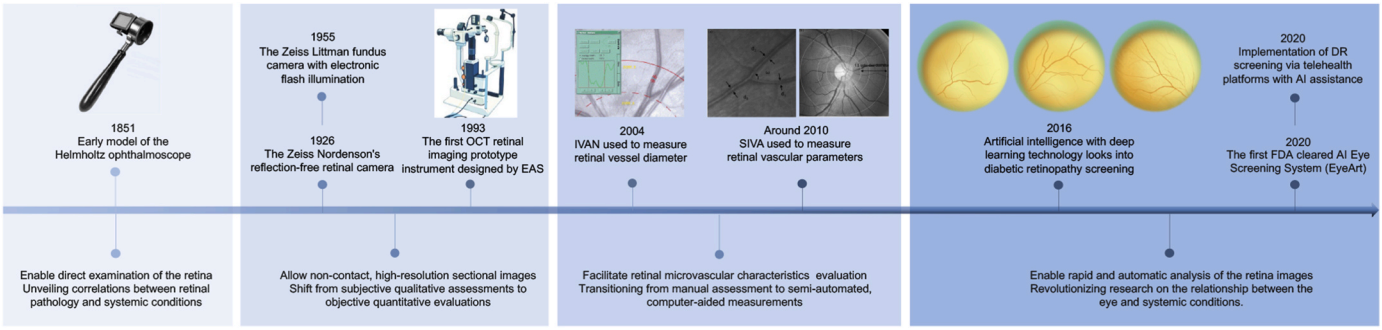

Fig. 2. The evolution of the concept - the eye as a window to systemic health
Images of IVAN from Tien Yin Wong, images of SIVA from Carol Y. Cheung.

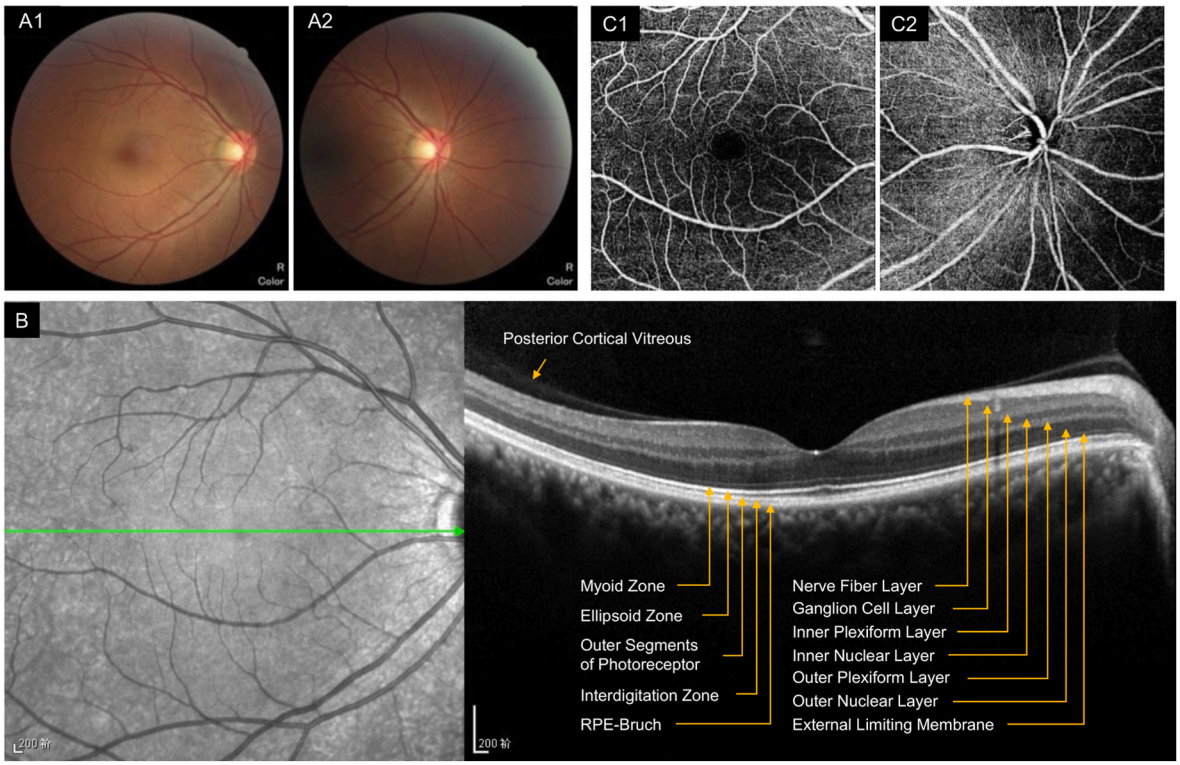

Fig. 3. Multimodal retinal imaging in a healthy 48-year-old female. Color fundus photograph centered on the macula (A1) and optic disc (A2). Cross-sectional optical coherence tomography (OCT) scan, illustrating clear delineation of individual retinal layers (B). OCT angiography (OCTA) image of the macula, showing the foveal avascular zone (C1), and OCTA image centered on the optic disc (C2). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 1
Key studies linking retinal imaging with systemic health.

Dataset	Nation	Population	Retinal Imaging Techniques	Systemic Diseases Explored	References
UK Biobank	UK	Over 500,000	CFP, OCT	CVD, neurodegeneration et al.	(Collins, 2012; Zhu et al., 2023)
Atherosclerosis Risk in Communities (ARIC)	U.S.	15,792	CFP	Atherosclerosi, CVD	(Chambless et al., 2002; Lin et al., 2025)
Cardiovascular Health Study (CHS)	U.S.	Over 2000	CFP	CVD	(Sun et al., 2007; Wong et al., 2002a)
Multi-Ethnic Study of Atherosclerosis (MESA)	U.S.	6814	CFP	CVD	(Bild et al., 2002; El Husseini et al., 2024)
Blue Mountains Eye Study	Australia	3647	CFP	Hypertension, cardiovascular and metabolic diseases	(Attebo et al., 1996; Guo et al., 2023)
Rotterdam Study	Netherlands	over 15,000	CFP, OCT, FA	Cardiovascular, endocrine, hepatic, neurological, psychiatric, dermatological, otolaryngological, locomotor, and respiratory diseases.	(Ikram et al., 2017; Vergroesen et al., 2024)
Beaver Dam Eye Study	U.S.	4926	CFP	CVD	(Chew, 2020; Klein et al., 1991)
The Gutenberg Health Study (GHS)	Germany	Over 15,000	CFP	CVD, cancer, metabolic diseases, diseases of the immune system and mental illness.	(Korb et al., 2023; Wild et al., 2012)
The Beijing Eye Study	China	4439	CFP, OCT	Diabetes mellitus, hypertension	(Jonas et al., 2009; Xie et al., 2023)
Singapore Epidemiology of Eye Diseases (SEED) Study	Singapore	10,033	CFP, OCT, OCTA	Diabetes mellitus, hypertension, lipid profile, creatinine, CVD, chronic kidney disease	(Majithia et al., 2021; Nusinovici et al., 2024)
The Age, Gene/Environment Susceptibility–Reykjavik Study	Iceland	2868	CFP	CVD	(Fisher et al., 2016; Jonasson et al., 2014)

CFP = colour fundus photograph, CVD = Cardiovascular diseases, OCT = optical coherence tomography, OCTA = OCT angiography, FA = Fluorescein Angiography, UK = United Kingdom, U.S. = United States of America.

networks to model complex patterns in data (Janiesch et al., 2021). Convolutional neural networks (CNNs), a class of DL models, are designed to automatically and hierarchically extract features from images, mimicking the way the human visual system processes information (LeCun et al., 2015). These models consist of multiple layers of interconnected nodes that learn to recognize patterns, such as retinal vascular changes, from large datasets of labeled images (Ting et al., 2019b).

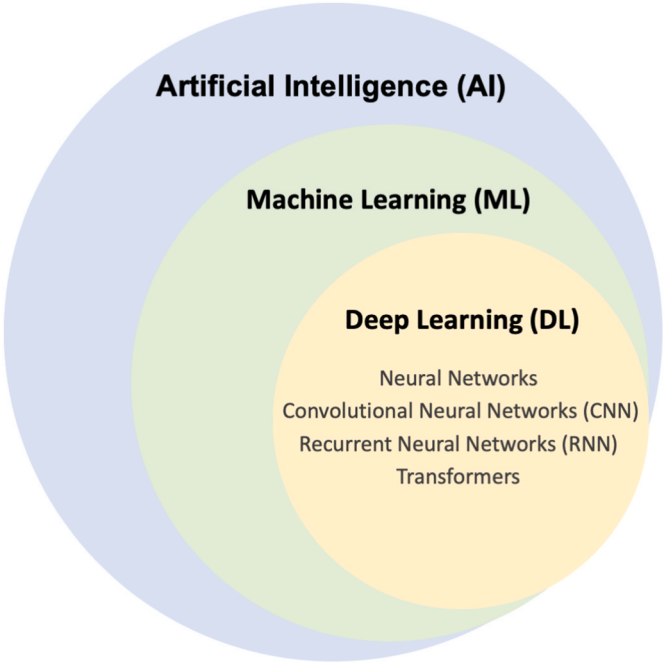

Fig. 4. Hierarchical relationship of artificial intelligence, machine learning, and deep learning.

1.5.2. *Development of deep learning models*

The implementation of DL involves several key steps including multimodal data inputs, preprocessing, model training, and clinically relevant outputs. The process begins with data input, combining ocular imaging modalities with systemic health data. Then, raw ocular images undergo normalization to standardize brightness/contrast, followed by automated segmentation of regions of interest (ROIs) to isolate disease-relevant features (Schlegl et al., 2018). Data augmentation techniques are applied to expand limited training datasets (Plompen et al., 2020).

During model training, a deep neural network (e.g., a CNN) learns to map preprocessed data to clinical outcomes. The network's weights are iteratively updated via forward and backward propagation, followed by parameter updates. A validation set helps monitor performance and tune hyperparameters, reducing overfitting and improving generalization (Yamashita et al., 2018). In the final output phase, model predictions are translated into actionable insights, such as binary classifications, continuous risk scores, or interpretability maps. Techniques like Grad-CAM (Gradient-weighted Class Activation Mapping) enhance interpretability by visualizing regions of interest most relevant to the AI's decision-making process (Selvaraju et al., 2017).

To evaluate the performance of DL models across diverse clinical tasks, researchers rely on standardized metrics tailored to the prediction type (e.g., binary classification vs. continuous risk estimation). Table 2 summarizes key evaluation metrics, their definitions, and clinical interpretations. For instance, while the area under the receiver operating characteristic curve (AUC) provides a global assessment of binary classifiers, precision and recall balance the trade-off between false positives and false negatives in disease screening. In regression tasks, metrics like mean absolute error (MAE) and root mean squared error (RMSE) quantify prediction errors.

While DL-driven analysis offers substantial advancements, limitations persist. Data variability across populations and imaging devices affects model generalizability, necessitating external validation on diverse datasets. Model interpretability remains a challenge, as deep learning models function as "black boxes," making it difficult to explain individual predictions (Qamar and Bawany, 2023). Furthermore, bias in training data can lead to disparities in disease detection across different demographic groups.

1.5.3. *Development of large language models (LLM), foundational models and reasoning-based models*

Subsequently, several major developments in AI occurred in and around 2022, extending beyond DL frameworks. First, inspired by the Transformer architecture proposed in Attention Is All You Need

Table 2
Key model evaluation metrics in deep learning.

Task Type	Metric	Definition	Interpretation	Application Example
Classification	AUC	Measures overall classification performance across all thresholds.	AUC ranges from 0.5 (random guessing) to 1.0 (perfect discrimination). Higher AUC indicates better model performance in classifying diseases.	Diabetic retinopathy screening (distinguishing diseased vs. healthy cases) (Gulshan et al., 2016)
	Sensitivity (Recall)	Proportion of true positives correctly identified (TP/[TP + FN]).	Measures the model's ability to detect positive cases. High sensitivity is critical for disease screening to minimize false negatives.	Glaucoma screening (minimizing missed cases) (Liu et al., 2019)
	Specificity	Proportion of true negatives correctly identified (TN/[TN + FP]).	Measures the model's ability to correctly identify negative cases. High specificity is important for confirming healthy status.	Healthy population screening (reducing false referrals).
	Precision	Proportion of true positives among predicted positives (TP/[TP + FP]).	Measures the model's ability to avoid false positives. High precision is critical when false positives are costly.	Prioritizing accurate diagnoses (e.g., reducing unnecessary treatments)
	F1 Score	Harmonic mean of precision and recall.	Balances precision and recall, especially useful for imbalanced datasets.	Retinal disease grading (balancing false positives and false negatives) (Qian et al., 2024).
	MCC	Comprehensive metric evaluating the confusion matrix (range: −1 to 1).	MCC ranges from −1 (total disagreement) to 1 (perfect prediction). Values > 0.5 indicate good performance in imbalanced datasets.	Rare disease classification(Kauer-Bonin et al., 2022)
Regression	MAE	Mean of absolute differences between predicted and true values.	Measures average prediction error. Lower MAE indicates better model performance. Robust to outliers.	Predicting a continuous variable (e.g., spherical equivalent and bone age) (Suh et al., 2023b; Varadarajan et al., 2018)
	R^2	Proportion of variance in the target variable explained by the model.	Ranges from 0 (no explanatory power) to 1 (perfect prediction). Higher R^2 indicates better model fit.	
	MSE	Mean of squared differences between predicted and true values.	Penalizes larger errors more heavily. Lower MSE indicates better performance. Sensitive to outliers.	
	RMSE	Square root of MSE, in the same units as the target variable.	Similar to MSE but in the original units of the target variable. Lower RMSE indicates better performance.	

AUC=Area Under the Receiver Operating Characteristic Curve; MCC = Matthews Correlation Coefficient; MAE = Mean Absolute Error; R^2=Coefficient of Determination; RMSE = Root Mean Squared Error; MSE = Mean Squared Error.

(Vaswani et al., 2017), Vision Transformer (ViT) architecture shifted DL from CNNs to attention-based architectures, ViTs have different inductive biases, training stability, and data efficiency (Dosovitskiy et al., 2020). ViTs process entire images as sequences of smaller patches, allowing them to capture global contextual relationships rather than relying on localized feature extraction. ViTs have demonstrated improved performance in retinal imaging, particularly in image classification tasks (Yu et al., 2021).

Second, the emergence of Large Language Models (LLMs) such as ChatGPT (OpenAI, 2021) leverage massive text-based datasets to generate human-like responses (Brown et al., 2020). While originally designed for natural language processing, LLMs have increasingly been explored for multimodal tasks, integrating textual and image-based inputs (Luo et al., 2024). In ophthalmology, these models present opportunities for AI-assisted clinical decision-making, automated medical report generation, and enhancing physician-patient communication (Betzler et al., 2023). For example, ChatZOC, a retrieval-augmented LLM framework, was developed by enhancing a baseline LLM with a comprehensive ophthalmic dataset and evaluation framework (Luo et al., 2024). This model has been deployed clinically and is undergoing pilot testing across multiple sites.

Third, foundational models are pre-trained on large-scale multimodal datasets and then fine-tuned for specific medical tasks (Betzler et al., 2023). A notable example is RETFound, a foundation model pretrained on 1.6 million retinal images (Zhou et al., 2023a). Unlike traditional supervised learning approaches that rely on extensive labeled data, RETFound achieved performance comparable to fully supervised models when fine-tuned with minimal labeled data. This capability has been demonstrated in predicting systemic conditions such as heart failure. Additionally, generalist medical AI (GMAI) exhibit the ability to perform diverse medical tasks without task-specific training (Moor et al., 2023). For example, VisionFM, a multimodal multitask vision foundation model, has demonstrated accuracy in detecting up to ten common ophthalmic diseases, including DR, glaucoma, and AMD (Qiu et al., 2024).

Most recently, reasoning-based LLMs have gained attention, addressing a critical limitation of traditional AI—the "black-box" problem. Reasoning-based LLMs, such as DeepSeek, OpenAI's o1 and o3-mini, and Google's Gemini 2.0, incorporate chain-of-thought prompting and step-by-step reasoning to improve transparency in medical decision-making (Liu et al., 2024; Xu et al., 2025). This advancement is particularly important in healthcare, where physician and patient concerns about opaque decision-making processes limit the acceptance of LLMs.

1.6. Oculomics

1.6.1. Definition and scope

The concept of "omics" reflects a comprehensive, integrated understanding in various fields of biology (Hasin et al., 2017). Much like "genome" signifies a holistic exploration of genetic information, the term "oculome" indicates a comprehensive understanding of the macroscopic, microscopic, and molecular features associated with health and disease within the eye.

The term "Oculomics" was first introduced in a 2020 publication entitled "Insights into Systemic Disease through Retinal Imaging-Based Oculomics" (Wagner et al., 2020). The authors suggested the eye could serve as a comprehensive "window into the health of the whole body" by analysing ocular changes that could be indicative of diseases or conditions elsewhere in the body. With advances in technology and research, oculomics has extended beyond observation, diving deep into the combination of big data and AI. The current review focuses on a narrow definition of oculomics - the combination of big data, AI and ocular imaging to identify retinal biomarkers for systemic disease.

1.6.2. Value of oculomics in the context of other "omics"

Oculomics shares similarities with other 'Omics' fields such as genomics, proteomics, transcriptomics, epigenomics, and metabolomics, all of which use high-throughput technologies to identify potential disease biomarkers (Table 3). Oculomics merges big data and AI with ocular imaging to identify subtle retinal biomarkers even prior to the clinical presentation of systemic conditions. In contrast, genomics focuses on the complete set of deoxyribonucleic acid (DNA) in an organism, offering insights into genetic predispositions to disease (Sakaue et al., 2021). Proteomics involves the large-scale study of protein structures, functions, and interactions within cells, tissues, or organisms (Aslam et al., 2017). Transcriptomics, which focuses on ribonucleic acid (RNA) transcripts, provides insights into gene expression and regulation in specific diseases (Jain and Eadon, 2024). Epigenomics, encompassing DNA methylation, histone modifications, and RNA-mediated processes, examines how these modifications influence cellular function and biological processes (Stricker et al., 2017). Metabolomics analyzes small molecule metabolites in biological samples, providing a deep understanding of metabolic pathways and offering critical insights into both the physiological and pathophysiological states of systemic health (Liu and Locasale, 2017).

As an emerging field, oculomics offers clinical benefits that extend far beyond traditional healthcare paradigms (Wu and Liu, 2022) (Fig. 5). First, it offers a non-invasive, simple and rapid approach for the early screening, grading, monitoring, and risk stratifying a range of diseases (Huang et al., 2023; Kim et al., 2022a; Silverstein et al., 2021; Suh et al., 2023a), thereby facilitating timely prevention and interventions. Second, oculomics can help address health disparities and optimize resource allocation. The accessibility of retinal imaging devices and AI-based oculomics software could simplify disease detection, potentially eliminating the need for multiple payments and complex staffing models. Coupled with timely intervention this technology could reduce disease burden and save healthcare costs (Liu et al., 2023a; Tan et al., 2023). Third, the integration of AI-based oculomics into clinical practice may empower healthcare professionals to adopt more precise and individualized care, considering patient-specific needs (Kim et al., 2022a; Lin et al., 2021; Schmidt-Erfurth et al., 2018b), leading to enhance quality of outcomes. Lastly, beyond meeting clinical needs, oculomics contributes to the broader scientific understanding of systemic diseases. This is exemplified by recent studies that have identified proteomic and metabolomic markers in the aqueous humor and tears, which are indicative of the pathogenesis of Parkinson's disease (PD) (Wolf et al., 2023). Similarly, significant differences in tear lipid and metabolite profiles have been observed in patients with multiple sclerosis and AD (Kaštelan et al., 2023; Khanna et al., 2022). These findings underscore the potential of oculomics and other omics technologies, especially with their rapid advancement, in uncovering novel biomarkers for systemic disorders.

1.7. Aim of the review

This review aims to summarise the current concepts and evidence in oculomics and to highlight opportunities it presents for future study.

2. Current evidence

Representative work on oculomics has been proposed since 2018, when Poplin et al. used CFP from nearly 300,000 participants from two independent datasets with validation to predict cardiovascular risk factors including age, sex, smoking status, etc. and major adverse cardiac events, showing comparable performance to currently used clinical risk scores (Poplin et al., 2018). The capability of oculomics to estimate traditional risk factors was further strengthened and validated in Rim et al.'s following study with over 200,000 fundus photographs from seven diverse Asian and European cohorts, where 47 systemic biomarkers indicating different organ functions were predicted as outcome variables (Rim et al., 2020a). It was further proved in a multicenter study across 11 clinical sites that external eye photographs also contain

Table 3
Comparison among oculomics, genomics, proteomics, and metabolomics.

	Similarities	Differences	Potential Applications	References
Oculomics	1) All aim to identify biomarkers for disease detection and management. 2) Use of high-throughput technologies.	Based on retinal imaging; Integrates AI	Early detection of systemic diseases; Risk stratification	Wagner et al., 2020
Genomics		Based on genetic material; Includes inherited traits	Disease prediction; Personalized medicine	(Lander et al., 2001; Sakaue et al., 2021)
Proteomics		Based on protein expression; Reflects functional state	Disease detection; Drug development	(Aslam et al., 2017; Sun et al., 2023)
Transcriptomics		Based on RNA transcripts; Reflects gene expression and regulation	Disease detection; Subtype classification; Risk stratification	Jain and Eadon, 2024
Epigenomics		Including DNA methylation, histone modifications, and RNA-mediated processes; Reflects modifications influence cellular function and biological processes	Disease detection; Disease progression; Drug development	Stricker et al., 2017
Metabolomics		Based on metabolic pathways and small molecules; Reflects physiological and pathophysiological state	Metabolic disease detection; Nutritional assessment	(Liu and Locasale, 2017; Li et al., 2024a)

AI = artificial intelligence.

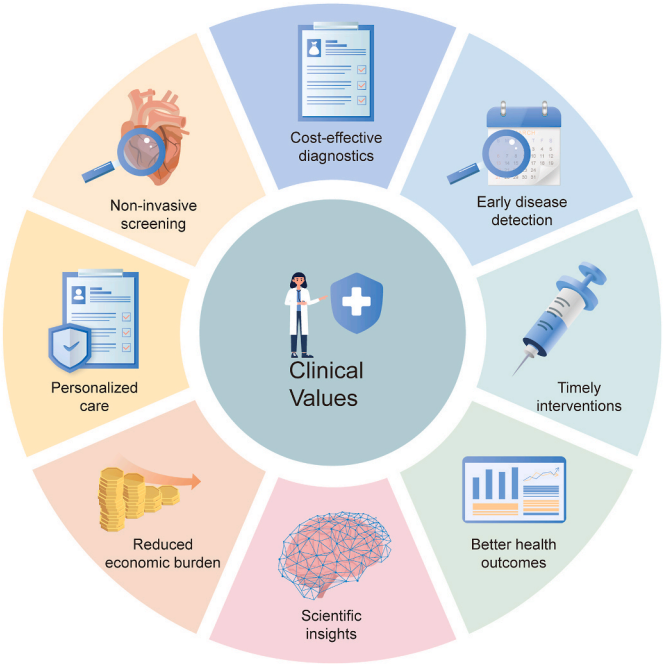

Fig. 5. Schematic of the clinical value of Oculomics.

critical information on systemic biomarkers spanning multiple organ systems (Babenko et al., 2023).

CVD, the leading cause of death globally, has become a major focus of oculomics research due to the close relationship between the eye and the heart. Large-scale studies, using over 200,000 retinal photographs from multiethnic and multi-country datasets, have shown that retinal images can be used by DL algorithms to predict coronary artery calcium (CAC) scores and myocardial infarction. These predictions were comparable to traditional CVD risk biomarkers, such as heart CT scan-measured CAC and the Pooled Cohort Equations (PCE) (Diaz-Pinto et al., 2022; Rim et al., 2021). As oculomics continues to expand, its application now extends to multiple systemic diseases including neurological diseases (Cheung et al., 2022), chronic kidney disease (CKD) (Sabanayagam et al., 2020; Zhang et al., 2021a), hepatobiliary diseases (Xiao et al., 2021), and anemia (Mitani et al., 2020). A DL model trained on over 10,000 retinal photographs from 11 studies across different countries can accurately detect pathological changes in AD and dementia (Cheung et al., 2022). Another representative study by Zhang et al. developed a DL model for CKD detection using CFP from two independent cohorts. This study is particularly noteworthy for its inclusion of images captured with a smartphone camera, showing the feasibility of non-invasive CKD and diabetes prediction across diverse clinical settings (Zhang et al., 2021a).

These studies were conducted in multiple population-based, multi-ethnic data, showing the generalizability of oculomics in different clinical settings, yet each model was usually designed for only one disease detection task. In 2023, Zhou et al. developed a foundation model of retinal images for generalizable downstream tasks on multiple systemic disease detection (Zhou et al., 2023a), starting the era of the combination of large foundation models and oculomics. Another foundational model provided an efficient platform for diagnosing and predicting multiple diseases using diverse imaging modalities. Its open-sourced model weights and codebase make it highly scalable, allowing for the incorporation of additional data, modalities, and applications (Qiu et al., 2024). With such effort accumulating in these landmark studies that represent the current state of the field, we are getting closer to the full potential of oculomics.

Overall, leveraging AI ("software") in oculomics can be structured into three primary frameworks. The first framework involves estimating traditional risk factors such as age, sex, and blood pressure, which are general risk factors for multiple diseases (Table 4). The second framework focuses on replacing systemic biomarkers, such as CAC scores for atherosclerosis (Table 5). The third approach involves detecting specific diseases, particularly those affecting the heart, brain, and kidney (Table 6).

2.1. AI in estimating traditional risk factors

2.1.1. Demographic factors

2.1.1.1. Age. The accuracy of age prediction from CFP is impressive, with a coefficient of determination (R^2) or AUC values over 0.9 and MAE of about 3 years (Gerrits et al., 2020; Khan et al., 2022; Kim et al., 2020; Poplin et al., 2018; Ting and Wong, 2018). One representative study of Poplin et al. with over 200,000 participants achieved MAE within 3.26 years (Poplin et al., 2018). Key retinal features, such as retinal vessels and the optic disc, are instrumental in predicting demographic information (Rim et al., 2020a). While internal performances of these algorithms were usually excellent (R^2 over 0.8), these values drop to 0.5–0.6 (close to random guess) in large external datasets with diverse populations spanning Singapore, Korea, China, and UK (Rim et al., 2020a). Confounding factors like hypertension, diabetes, smoking, and older age can also affect the accuracy of age predictions (Kim et al., 2020).

In addition to CFP, age can be predicted from OCT images using AI, with an acceptable MAE of approximately 5–6 years, indicating such age estimates reliable with moderate margin of error (Mendoza et al., 2021; Shigueoka et al., 2021). Similarly, external eye photographs hold

Table 4
Summary of AI in estimating traditional risk factors.

Target of Oculomics	Ocular modality	AI application	Limitations	Future insights	References
Demographic factors	• CFP • OCT • External eye image	1) Age	• Performance variability across external datasets and health conditions. • Small sample sizes.	• Adjustments for diverse populations. • Larger, more varied datasets for broader validation.	• (Bobrov et al., 2018; Chueh et al., 2022; Gerrits et al., 2020; Khan et al., 2022; Kim et al., 2020; Ma et al., 2021; Mendoza et al., 2021; Poplin et al., 2018; Rim et al., 2020a; Shigueoka et al., 2021; Ting and Wong, 2018)
	• CFP • Iris texture	2) Sex	• Variations in image quality, preprocessing techniques, and neural network architecture. • Confounders such as age-related changes and dataset biases.	• Useful for security, detecting errors and forensic applications.	• (Khalifa et al., 2019; Kim et al., 2020; Lang et al., 2024; Poplin et al., 2018; Wagner et al., 2020; Yamashita et al., 2020)
Body composition measurements	• CFP	1) BMI and body composition[a]	• Poor performance in predicting continuous variables. • Not reliable for clinical use.	• Targeting a better prediction accuracy.	• (Betzler et al., 2022; Poplin et al., 2018; Rim et al., 2020a, 2020b; Zhang et al., 2020b)
Blood pressure	• CFP	1) Hypertension 2) SBP and DBP	• Bias in different ethnicities. • Accuracy variation across subgroups[b]. • Limited explainability for DBP prediction.	• Thorough testing and recalibration across diverse populations. • Optimize BP predictions for specific age groups.	• (White et al., 2024) • (Gerrits et al., 2020; Poplin et al., 2018; White et al., 2024)
Hematological, glycemic and lipid parameters	• External eye image • CFP • OCT • CFP • External eye image • External eye image	1) Haemoglobin, white blood cell, platelets 2) Hemoglobin, anemia levels, red blood cell 3) Blood glucose 4) Cholesterol levels	• Poor performance in predicting continuous parameters. • Variations in image quality and preprocessing.	• Non-invasive method for early detection and lifestyle modifications. • Improvements in accuracy for broader clinical applications. • Mechanisms for prediction via external eye images need further investigation.	• (Babenko et al., 2023; Banowati et al., 2019; Mitani et al., 2020; Wei et al., 2021; Zhang et al., 2020b, 2021a)
Biochemical measures	External eye image	1) Hypocalcemia	• Excluding color reduces accuracy significantly. • Further investigation on specific mechanisms.	• Capturing effective biochemical information from external eye appearance. • Non-invasive biochemical monitoring.	• (Babenko et al., 2023; Rim et al., 2020a)

CFP = colour fundus photograph, OCT = optical coherence tomography, BP = blood pressure, SBP = systolic blood pressure, DBP = diastolic blood pressure.
[a] Such as body fat percentage, muscle mass, height, weight, waist-hip ratio, etc.
[b] For example, poor sensitivity for high SBP and poor specificity for high DBP.

valuable information for predicting chronological age. DL models trained on images of eye corners and ocular anterior segment have exhibited high accuracy, with MAE of 2.3 years and 2.8 years in previous studies (Bobrov et al., 2018; Ma et al., 2021). However, the relatively small sample size used for validation may limit the clinical utility of these models in broader populations. To address the challenges of inaccurate age prediction in external datasets with diverse populations, as well as the scarcity of datasets that include both OCT and external eye photographs, there is a pressing need for the development of more publicly accessible datasets. These datasets should encompass a wider spectrum of oculomic features and ensure equitable global representation. Additionally, they should adhere to principles of fairness, privacy protection, and compliance with regulatory norms, thereby fostering trust and reliability in oculomics research and clinical applications (Chew et al., 2025).

2.1.1.2. Sex. AI algorithms trained to predict sex using CFP have demonstrated consistently high accuracy. The earliest prediction on sex using CFP reported a high AUC of 0.97 (Poplin et al., 2018). Recently, researchers have attempted to identify explainable features associated with sex, such as papillomacular angle, tessellation fundus index, retinal vessel angles, and retinal artery trajectory (Yamashita et al., 2020). While foveal morphology is suggested to play an important role in the identification of sex by some of these algorithms (Wagner et al., 2020), other studies found high AUCs for sex prediction even in fovea-erased images and underscored the significance of the nearby vascular region and choroidal vasculature (Kim et al., 2020; Lang et al., 2024). The disparity in results could be attributed to variations in image quality, differences in image preprocessing techniques, and the specific neural network architecture used. Additionally, confounding factors and potential dataset biases should be carefully evaluated in future research.

There are also efforts for sex prediction using other modalities such as ocular anterior segment images with iris texture (Khalifa et al., 2019). Efforts should ensure the accuracy and applicability of oculomics-based sex prediction models for future security surveillance systems and forensic applications. This includes ensuring that the models are reliable and can be generalized across diverse populations and demographic groups (Betzler et al., 2021, 2022).

2.1.2. Body composition measurements

The measurement of body mass index (BMI) and body composition is important due to its association with obesity-related health risks, clinical outcomes, and side effects from immunological treatments. Oculomics has also been applied to predict body composition measurements, but existing algorithms generally perform poorly in predicting these continuous variables. For instance, even in two representative studies with large datasets such as the UK Biobank, predicting percentage body fat and BMI from CFP yields poor R^2 values of less than 0.2 (Poplin et al., 2018; Rim et al., 2020a). Recently, other body composition measurements, such as body muscle mass, and waist-hip ratio (WHR), are

Table 5
Summary of AI in replacing systemic biomarkers.

Target of Oculomics	Ocular modality	AI prediction	Limitations	Implications	References
Heart function	• CFP	1) Coronary artery calcium scores 2) Carotid atherosclerosis measured by carotid ultrasound	• Limited data from patients who have both retinal images and cardiac imaging. • Providing only a specific aspect of heart function.	• Potential as a more accessible proxy for expensive and invasive cardiovascular imaging.	• (Barriada et al., 2022; Chang et al., 2020; Diaz-Pinto et al., 2022; Gong et al., 2024; Rim et al., 2021; Son et al., 2020)
	• CFP + demographic data	3) Left ventricular function measured by cardiovascular MRI[a]			
Brain function	• CFP/CFP + clinical metadata	1) White matter changes[b]	• Not able to reflect aspects of brain function beyond cognition. • Insufficient description on brain regions and states.	• Predicting future neurodegenerative diseases. • Technological advancements.	(Arevalo-Rodriguez et al., 2021; Hua et al., 2022; Kim et al., 2022b; Shu et al., 2023; Zee et al., 2021)
	• CFP	2) MMSE 3) CAIDE dementia risk score			
Kidney function	• CFP	1) Renal impairment[c] 2) Serum creatinine concentration	• Difficult to predict eGFR values. • Only able to detect non-specific changes. • Limited training data.	• Distinguishing specific ocular changes in renal impairment.	• (Kang et al., 2020; Liu et al., 2023b; Rauscher et al., 2021; Rim et al., 2020a)
	• OCT	3) Cystatin C and eGFR			
Liver function	• External eye image	1) Low albumin levels	• Not effective in predicting certain liver biomarkers (e.g., γ-glutamyl transferase and alanine aminotransferase).	• Exploring certain liver biomarkers that are predictable through oculomics.	• (Babenko et al., 2023; Rim et al., 2020a)
Thyroid function	• External eye image	1) Elevated thyroid stimulating hormone levels	• Limited research.	• Understanding how TSH and thyroid hormones impact oculomics.	• (Babenko et al., 2023)
Retinal vessel parameters	• CFP • OCT • OCTA	1) Retinal vessel calibre[d]	• Many of the retinal parameters lack clinical implication. • Some of the parameters lack standardized definition.	• Use of advanced analytical methods and combination of multiple retinal parameters to understand the whole network.	• (Daien et al., 2013; Günthner et al., 2019; Liew et al., 2011, 2012; Lim et al., 2013; Owen et al., 2019; Witt et al., 2006; Wong et al., 2001b, 2003a, 2003b)
	• CFP	2) Retinal vessel tortuosity[e]			
Risk calculators	• CFP	1) Cardiovascular risk score[f]	• Limited generalizability across populations.	• Validation across diverse populations. • Combination with clinical metadata to improve effectiveness.	• (Lee et al., 2023; Ma et al., 2022; Tseng et al., 2023; Yi et al., 2023)
		2) Ageing score[g]	• No ground truth of biological age. • Hard to identify prediction error. • Methodology heterogeneity.	• Enhancing compatibility and generalizability of current aging oculomics.	• (Li et al., 2023c; Nusinovici et al., 2022, 2024; Zhu et al., 2023)

CFP = colour fundus photograph, OCT = optical coherence tomography, OCTA = OCT angiography, MRI = magnetic resonance imaging, MMSE = Mini-Mental State Examination, CAIDE = Cardiovascular Risk Factors, Aging, and Incidence of Dementia, eGFR = estimated glomerular filtration rate, TSH = thyroid-stimulating hormone, AVR = arterio-venous ratio, PCE = Pooled Cohort Equations, FRS = Framingham risk score, ASCVD = astherosclerotic cardiovascular disease, CVD = cardiovascular disease.

[a] Defined as left ventricular end-diastolic volume and left ventricular mass.
[b] Defined as global age-related white matter changes score ≥2 based on MRI.
[c] Defined as eGFR <90 ml/min/1.73 m^2.
[d] Including central artery calibre, vein calibre, AVR.
[e] Including fractal dimension, vascular density, vessel segments, anatomical factors, and tortuosity values.
[f] Including PCE, FRS, QRISK3, WHO-CVD risk, ASCVD, 10-year ischemic CVD risk scores.
[g] Including RetiAGE, Retinal age gap, LensAge.

Table 6
Summary of AI in detecting specific diseases.

Target of Oculomics	Ocular modality	AI application	Limitations	Implications	References
Neurological diseases	• CFP/CFP + demographic factors • OCT • UWF + FAF + OCT/ OCTA + clinical factors • Ocular movement	1) Alzheimer's disease, dementia and cognitive impairment	• Expensive eye movement trackers. • Limited sample size on high quality ocular data.	• Develop low-cost equipment for high-quality data collection.	(Cheung et al., 2022; Maleki et al., 2024; Nunes et al., 2019; Tian et al., 2021; Wisely et al., 2022; Yoon et al., 2024; Zhang et al., 2021b; Zuo et al., 2024; Sim et al., 2025)
	• CFP/CFP + demographic factors • OCT • Ocular movement	2) Parkinson's disease	• Limited clinically viable accuracy and high-quality ocular data.	• Requirement of datasets with enough retinal imaging data and clinical outcomes. • Develop low-cost equipment for high-quality data collection.	(Ahn et al., 2023; Hu et al., 2022; Nunes et al., 2019)
	• OCT	3) Multiple sclerosis	• Reliance on OCT-derived data as an intermediate variable.	• High-speed OCT image processing algorithms • Direct prediction from retinal images.	(López-Dorado et al., 2021; Montolío et al., 2021; Zhang et al., 2020a)
CVD	• CFP + clinical factors a/CFP + DXA • OCTA + ECG + clinical factors	1) Coronary heart diseases	• Limited incident cases. • Limited studies on predicting incident CVD events directly.	• Requirement of longitudinal data. • Improving algorithm performance in predicting CVD event solely from retinal images.	(Al-Absi et al., 2022; Khan et al., 2022; Mellor et al., 2023; Zhong et al., 2022)
	• CFP/CFP + genomics	2) Major adverse cardiovascular events[b]			(Mordi et al., 2022; Poplin et al., 2018; Rudnicka et al., 2022)
Kidney diseases	• CFP/CFP + clinical factors	1) Chronic kidney disease	• Low specificity. • Limited kidney failure patients and longitudinal follow-up data.	• Improvement on model performance and clinical applicability.	(Joo et al., 2023; Tan et al., 2024)
Anemia	• UWF + FFA + OCTA	1) Sickle cell hemoglobinopathy	• Lacking large-sample, high-quality images.	• Simplify or standardize the imaging modalities to enhance applicability. • Telemedicine-based screening models.	(Alam et al., 2017; Cai et al., 2021b; Sevgi et al., 2022)
	• Palpebral conjunctiva images	2) Anemia and hemoglobin levels	• Limited research on different imaging modalities.		Chen et al. (2016)
Diabetes	• CFP/CFP + traditional risk factors; external eye images	1) Prevalent and incident diabetes	• Segmentation of external eye images replies on human labelling.	• Balanced large-scale datasets. • Additional training on diverse cohorts.	(Aslam et al., 2020; Yun et al., 2022; Zhang et al., 2021a)
	• OCTA • Corneal confocal microscopy images	2) Complication of diabetes, e.g., diabetic peripheral neuropathy	• Limited specificity using conjunctival images.	• Automatic segmentation of external eye images. • Hardware advancements for remote healthcare improvement.	Preston et al. (2022)

CVD = cardiovascular disease, CFP = colour fundus photograph, OCT = optical coherence tomography, DXA = dual-energy X-ray absorptiometry, OCTA = OCT angiography, ECG = electrocardiogram, UWF = ultra-widefield, FAF = fundus autofluorescence, FFA = fundus fluorescein angiography.
[a] Clinical factors include traditional risk factors for systemic diseases such as demographic factors (e.g., age, sex), health conditions (e.g., diabetes, hypertension), lifestyle (smoking, alcohol drinking) etc.
[b] Incident myocardial infarction, stroke or CVD mortality.
[c] Kidney failure and diabetic kidney disease.

considered more reliable indicators of cardiometabolic risk and nutritional status than BMI (Zhang et al., 2020b). However, predictions for these biomarkers also show moderate accuracy, with R^2 values lower than 0.5 (Rim et al., 2020a).

Still, model generalizability across ethnically diverse datasets remains an area that requires further improvement (Betzler et al., 2022). Attention heat maps revealed that AI models' focus is non-specific, suggesting that the predictive signals for body composition may be diffusely distributed throughout the retinal image (Poplin et al., 2018). These findings suggest that current DL models for body composition prediction are not yet capable of identifying specific retinal regions containing body composition information, or such signals are a composite of multiple factors and difficult to isolate.

2.1.3. Blood pressure

Based on hypertension-related changes in retinal vessels, such as narrowing arterioles and arteriovenous nicking, AI models have demonstrated varying performance in the prediction of blood pressure. For the prediction of systolic blood pressure (SBP) and diastolic blood pressure (DBP), model performances were found acceptable (R^2 of 0.24–0.4) but varying across subgroup populations (Gerrits et al., 2020). For high SBP predictions (over 140 mmHg), AI model exhibited high specificity but poor sensitivity, whereas the opposite was true for high DBP predictions (over 80 mmHg), suggesting the model intends to underestimate SBP and overestimate DBP (White et al., 2024). Attention maps from a different AI model indicated that retinal vessels were the primary focus when predicting SBP, but no specific features were highlighted for DBP (Poplin et al., 2018). Another major concern is the reduced accuracy when applying AI models beyond the ethnic group they were trained on. For example, an AI model trained using data from the UK Biobank may perform poorly in the Kenya population, particularly for long-term follow-up data (White et al., 2024).

2.1.4. Hematological, glycemic and lipid parameters

Oculomics has shown potential in predicting various hematological indicators such as anemia classification, hemoglobin levels, red and

white blood cell (WBC) counts, platelet count, and hematocrit. Leveraging external eye photographs, Babenko et al. trained a DL-based model using images from 145,832 diabetic patients from over 300 clinical sites, and externally validated it on four validation datasets including 48,644 patients from 198 additional screening sites (Babenko et al., 2023). The model demonstrated reasonable detection accuracies ranging from 73.8% to 82.5% for haemoglobin<11.0 g/dL, 64.5%–71.5% for WBC<4.0 × 10^3/μL, and 58.9%–71.0% for platelets<150.0 × 10^3/μL.

Generally, AI models show better performance in classifying binary tasks (e.g., hyperglycemia and dyslipidemia detection) than predicting continuous hematological parameters (Wei et al., 2021; Zhang et al., 2020b). The Google Health team found that CFP-only models predicted hemoglobin concentration and anemia levels better than metadata-only models, achieving a good accuracy of 0.87 for anemia prediction (Mitani et al., 2020).

Analyzing ocular images for blood glucose levels can help detect vascular changes and nerve damage. One milestone development is from Zhang et al.'s study, which utilized CFP to predict blood-glucose levels, as indicators of severity and progression of diabetes (Zhang et al., 2021a). The model were trained and validated with a total of 115,344 CFPs from 57,672 patients, showing solid results across internal and external test sets (MAE 0.65–1.1 mmol/L) and high agreement between HbA1c and random blood glucose. Good prediction performance (AUC of 70.2%) also presented by another AI model trained by external eye images from the EyePACS/LACDHS datasets, further strengthen the value of oculomics across image types (Babenko et al., 2023).

There are also efforts to predict high cholesterol levels using retinal or iris images, which could serve as indicators of heart diseases and stroke risk. While this approach holds promise for non-invasive lipid testing, current research is largely limited to small sample sizes (Babenko et al., 2023; Banowati et al., 2019; Zhang et al., 2020b). Further validation is necessary before these methods can be implemented clinically.

2.1.5. Biochemical measures

Attempts to predict blood biochemical parameters such as electrolyte levels using CFP via DL have shown poor performance, with R^2 values for these parameters falling below 0.15 (Rim et al., 2020a). However, there has been some success in predicting hypocalcemia (blood calcium<8.6 mg/dL) using external eye photographs, with one model achieving an AUC of over 0.7 for this task (Babenko et al., 2023). Notably, eliminating the pupil and iris from the external eye photographs did not affect the model's accuracy, while excluding color resulted in AUC decrease by approximately 10%. This suggests that biochemical information may be more effectively captured through the appearance of the external eye, particularly the sclera and eyelid.

2.2. AI in replacing systemic biomarkers

2.2.1. Cardiac diseases

2.2.1.1. Coronary artery calcium (CAC). CAC, a tool endorsed by international guidelines for atherosclerotic CVD risk stratification, is usually evaluated using non-contrast multi-detector computed tomography (CT) scanning (Arnett et al., 2019a; Nasir and Cainzos-Achirica, 2021). However, Medicare does not cover CAC measurement in the US due to costs and radiation exposure. Retinal imaging holds potential as an inexpensive, radiation-free screening tool for discriminating CAC status in patients at risk of CVD. Rim et al. developed a DL system for predicting CAC, utilizing a large dataset comprised of 216,152 CFPs from South Korea, Singapore, and the UK. This DL system outperformed all alternative single clinical parameter models, with an AUC of 0.742, demonstrating comparable performance to CT scan-measured CAC in CVD risk stratification (Rim et al., 2021).

Other studies have explored methods to enhance the accuracy of CAC score predictions, including the integration of clinical data with CFP and the use of bilateral retinal imaging (Barriada et al., 2022; Son et al., 2020). Retinal vasculature and the fovea were considered important in such predictions, as they contained the majority of recognizable patterns of the retina (Son et al., 2020).

2.2.1.2. Carotid ultrasound and other cardiovascular imaging-based biomarkers. Carotid ultrasound assesses carotid intima-media thickness (CIMT) and identifies carotid artery plaque characteristics, is crucial for predicting carotid atherosclerosis progression and incident CVD (Ray et al., 2015). The DL-FAS model, trained on 15,408 CFPs from Korea, predicts carotid atherosclerosis measured by carotid ultrasound with an AUC of 0.713, outperforming the traditional Framingham risk score (FRS) (Chang et al., 2020). In healthy controls, carotid atherosclerosis-related information predominantly clustered around the optic disc vascular area, though this pattern diminished in disease groups (Gong et al., 2024).

Another study developed an AI model to predict cardiovascular magnetic resonance (MR) metrics, such as left ventricular end-diastolic volume and left ventricular mass, using CFP and demographic data (Diaz-Pinto et al., 2022). The model was able to predict the risk of myocardial infarction with a high AUC of 0.8, indicating retinal imaging's potential as a more accessible alternative to magnetic resonance imaging (MRI).

However, collecting data from patients who have both retinal images and cardiac imaging results, such as CAC scores, is challenging. This difficulty limits the number of studies in this area and hinders further longitudinal predictions of future cardiac events. Additionally, each cardiac examination provides insight into only a specific aspect of heart function. As a result, predictions based on cardiac examination results are ultimately indirect and do not fully capture the comprehensive status of heart health.

2.2.2. Neurological diseases

The retina has some similarities with the brain in vascular anatomy, blood barriers, neuroanatomy and pathophysiology (Erskine and Herrera, 2014; London et al., 2013). These similarities enable ocular images to serve as a promising proxy for certain brain functions and for the identification of several neurological conditions. For instance, early detection of age-related white matter changes (e.g., white matter hyperintensity [WMH]) via retinal images could be useful for population screening, allowing for early intervention for cognitive decline (Zee et al., 2021). It was reported that DL models primarily focused on the macula and retinal vasculature to detect WMH, indicating these regions may be critical for predicting white matter changes (Shu et al., 2023).

Moreover, AI systems trained to predict cognitive function have demonstrated performances comparable to traditional cognitive function tests, such as the Mini-Mental State Examination (MMSE) and the Cardiovascular Risk Factors, Aging, and Incidence of Dementia (CAIDE) dementia risk score. These AI models offer simpler and more standardized clinical workflows than traditional cognitive tests, as they only require CFP as the only input (Arevalo-Rodriguez et al., 2021; Hua et al., 2022; Kim et al., 2022b).

Brain function is highly complex, and current oculomics methodologies primarily reflect impairments in cognitive function. For example, fundus-driven microperimetry, which assesses not only the functional status of the retina but also the entire visual system, has revealed that retinal sensitivity correlates with topographical parameters of brain tissue loss (such as total grey matter volume, cortical thickness, and hippocampal volume) and brain hypometabolism in type 2 diabetes mellitus (T2DM) patients with cognitive impairment (Ciudin et al., 2017, 2024). However, these methodologies are not yet capable of linking to aspects such as motor function, behavior, and emotions. Additionally, AI techniques still need to be paired with more detailed

and wider-field imaging for comprehensively characterizing and predicting various human brain states. This integration could provide deeper insights into different brain regions and their functions.

2.2.3. Kidney function

DL applications exploring the potential to assess kidney function via retinal images, such as detection of renal impairment (indicated as estimated glomerular filtration rate [eGFR] < 90 ml/min/1.73 m^2), have yielded mixed results (Kang et al., 2020). False positives were mostly observed in cases with retinal scarring, subretinal fluid, or optic disc swelling, potentially restricting the clinical utility of this approach. Another DL model predicting serum creatinine concentration from CFP displayed an R^2 of 0.38 in validation, indicating a moderate predictive performance while majority variance remained unexplained (Rim et al., 2020a). While DL shows some capability for predicting kidney function from CFP, these findings indicate limited clinical applicability in identification of specific renal parameters.

Several cross-sectional studies have highlighted associations between abnormal kidney function and OCT parameters. The LIFE-Adult Study involving 8952 individuals revealed that thinner circumpapillary retinal nerve fiber layer thickness was associated with worse renal function (assessed by cystatin C and eGFR) (Rauscher et al., 2021). In other studies, thinning of the choroid was associated with changes in biomarkers of altered microvascular structure and function. Several studies found that the choroid was thinner in those with lower eGFR and higher proteinuria, independent of clinical risk factors, strongly indicating at microvascular dysfunction (Balmforth et al., 2016; Stehouwer et al., 2004; Thambyrajah et al., 2000). However, predicting kidney function though OCT remains challenging. Retinal and choroidal thickness changes in patients with impaired kidney function are non-specific, and training data is limited (Liu et al., 2023b).

2.2.4. Liver function

The liver secretes polypeptides into the bloodstream, including hepcidin, which regulates iron levels in the body. Elevated plasma iron levels can result in iron accumulation within the retina, even in the presence of an intact blood-retinal barrier (Baumann et al., 2019). However, DL analysis of CFP has shown limited effectiveness in predicting certain liver biomarkers, such as γ-glutamyl transferase and alanine aminotransferase ([ALT], $R^2 \leq 0.10$ in external test sets) (Rim et al., 2020a). External eye photographs have demonstrated moderate accuracy in predicting abnormal ALT levels, with AUCs around 61.7% and AUC for low albumin levels of 77.0% (Babenko et al., 2023). More research is necessary to elucidate why certain liver biomarkers are predictable through oculomics, while others are not, and to establish a scientific foundation for predicting liver diseases based on oculomics.

2.2.5. Thyroid function

Thyroid-associated ophthalmopathy (TAO) is an autoimmune condition prevalent among patients with Graves' disease and other thyroid disorders. Radiomics models have been developed to assist in diagnosing, staging, grading, and making treatment decisions for TAO (Zhang et al., 2024). However, research exploring oculomics-based AI for detecting thyroid function or thyroid-associated antibodies remains limited. In a study by Babenko et al., an AI model trained using external eye photographs predicted elevated levels of thyroid stimulating hormone (TSH) with a moderate accuracy of 62.5%, slightly higher than the baseline performance of 60.5% (Babenko et al., 2023). Future research should delve into how TSH and thyroid hormones impact oculomics, paving the way for advancements in using AI-driven diagnosis and treatment strategies for TAO.

2.2.6. Retinal vessel parameters

Historically, measuring retinal parameters relied on semi-automated segmentation and manual correction, which required human involvement and introduced inconsistencies. The introduction of AI has streamlined this process, enabling rapid and reliable automatic measurement of retinal vessel parameters, including retinal vessel caliber and tortuosity features. Through detailed assessments of retinal vascular architecture, researchers can discern specific oculomics for systemic diseases, including CVD, stroke, cognitive impairment, and renal diseases (Daien et al., 2013; Günthner et al., 2019; Liew et al., 2011, 2012; Lim et al., 2013; Owen et al., 2019; Witt et al., 2006; Wong et al., 2001a, 2003a, 2003c).

2.2.6.1. Retinal vessel caliber. Retinal vessel caliber is an important parameter for evaluating systemic vascular characteristics. Initially, the idea for measuring retinal vessel caliber involved using AI for accurate vessel segmentation in CFP and OCT/OCTA, followed by measurements based on the segmented vessels (Gao et al., 2022; Maderuelo-Fernandez et al., 2020; Yan et al., 2024). Methods for retinal vessel segmentation include both supervised (e.g., Bayesian methods, support vector machine, random forest) and unsupervised (e.g., Gaussian mixture model, fuzzy c-means, k-means clustering) techniques (Mookiah et al., 2021). Recent advances in DL have significantly improved the accuracy of vessel segmentation and measurement (Du et al., 2023). For example, fully CNNs and Three-Stage Deep Learning Models (Jiang et al., 2018; Yan et al., 2019) and Generative Adversarial Networks, enhance segmentation effectiveness by generating synthetic retinal images, particularly those with retinal lesions (Zhao et al., 2018). Researchers have developed and validated the SIVA deep-learning system to automatically measure retinal vessel caliber without the requirement for segmentation. Using this approach, the research team linked narrower baseline retinal arteriolar caliber to increased risk of developing dementia (Cheung et al., 2021b).

2.2.6.2. Retinal vessel tortuosity. The assessment of retinal vascular tortuosity reflects geometric complexity and self-similarity of the vascular network, which is important for understanding vascular changes across a broad spectrum of diseases. However, there is currently no standardized definition of retinal vascular tortuosity (Gao et al., 2023). Manual or semi-automated measurement of vascular tortuosity from CFP is complicated and time-consuming, requiring meticulous measurements on multiple retinal topological features.

Fractal dimension (FD) is a biomarker that reflects the overall branching pattern of retinal vessels, that has been shown to be valuable for detecting subclinical systemic conditions. DL models have been developed to segment retinal microvasculature and measure FD from CFP (Engelmann et al., 2024; Zekavat et al., 2022). DL models have also demonstrated excellent performance in analyzing various retinal topological features such as vascular density, vessel segments, anatomical factors, and tortuosity values, achieving accuracy comparable to clinical experts (Delavari et al., 2023; Hervella Á et al., 2024; Hormel et al., 2021). While hundreds of retinal parameters can be extracted from a single CFP, linking these parameters to clinical outcomes remains challenging. Advanced analytical methods and integrative approaches are necessary to harness the full potential of these retinal parameters in clinical practice.

2.2.7. Risk calculators

2.2.7.1. Cardiovascular risk score. Accurate risk stratification is crucial for identifying and managing individuals at risk of CVD. Currently, various risk calculators, such as the PCE and FRS, have been developed to estimate future CVD risk (Wilson et al., 1998; Yi et al., 2023). However, these methods can be challenging in resource-limited areas due to the need for invasive tests and multiple inputs (Abràmoff et al., 2010). Oculomics offers an automatic, rapid, and non-invasive means to estimate CVD risk (Chang et al., 2020; Cheung et al., 2021b; Rim et al., 2021; Son et al., 2020; Vaghefi et al., 2024; Xu et al., 2019; Zhu et al., 2022a).

Reti-CVD is a tool developed from a CAC prediction model (RetiCAC) using CFP to identify individuals with intermediate and high CVD risk from CFP. This tool has been validated in multi-ethnic populations, including those from the UK and Korea, showing high comparability with conventional risk scores (Lee et al., 2023; Tseng et al., 2023; Yi et al., 2023). Additionally, other information on vascular health, including factors like carotid artery atherosclerosis, CAC levels, arterial stiffness, and retinal vessel calibre, can enhance individualized CVD risk prediction. Population background should be considered when training algorithms against existing CVD risk calculators due to variations across ethnic groups (Ma et al., 2022). Recent studies have further provided real-world evidence regarding the implementation of AI-based retinal CVD risk assessment system in primary care settings. Hu et al. demonstrated through a pragmatic trial that an automated AI-assisted system was successful in generating a real-time rpCVD risk score in more than 90% of the primary care patients, with a comparable predictive performance to the World Health Organization (WHO) CVD risk score, and high level of patient and physician acceptability (Hu et al., 2025). These findings supported the potential of translating oculomics technologies from the "code" to "practice".

2.2.7.2. Ageing score. The gap between chronological and biological age underscores the importance of effective biological ageing indicators. DL has shown potential in predicting both chronological age and well as biological age, with a deviation of 3–5 years. Nusinovici et al. developed 'RetiAGE', a DL model based on retinal photographs to predict the probability of individuals being ≥65 years old. RetiAGE scores, indicative of biological aging, were associated with higher risks of mortality and morbidities (Nusinovici et al., 2022; Peng et al., 2025) Building on this, Nusinovici et al. introduced a DL-based marker, 'RetiPhenoAge,' which integrated retinal images and phenotypic age biomarkers to predict morbidity and mortality. RetiPhenoAge demonstrated robust associations with all-cause mortality (hazard ratio [HR] 1.92), cardiovascular disease mortality (HR 1.97), cancer mortality (HR 2.07), and CVD events (HR 1.70), outperforming other aging markers such as hand grip strength, telomere length, and physical activity (Nusinovici et al., 2024). Furthermore, in a Singapore cohort with 5-year follow-up and the UK Biobank cohort with 12-year follow up, RetiPhenoAge was proved as having a high predictive value for future cognitive decline and dementia (Sim et al., 2025).

Zhu's research group proposed the "retinal age gap" as a measure of biological ageing based on CFP. Each 1-year increase in the retinal age gap correlated with a 2% rise in all-cause mortality risk and a 3% increase in cause-specific mortality from non-cardiovascular and non-cancer diseases (Zhu et al., 2023). In addition, a larger retinal age gap was significantly associated with leading causes of morbidities, including CVD, stroke, metabolic disease, PD, and end-stage of renal disease (Zhu et al., 2022a, 2022b; Zhang et al., 2023; Hu et al., 2022). Beyond the retina, Li et al. utilized cumulative age-related changes in the lens to develop a DL-based model predicting chronological age from lens photos, introducing the 'LensAge index' (Li et al., 2023c).

Notably, there is no standard way of defining biological age, making the ground truth of aging score predictions uncertain. The black-box nature of AI further complicates the identification of prediction errors. Although current oculomics methods have demonstrated the potential for aging prediction using eye images, the heterogeneity of methodologies can lead to significant variations among different tools (Chen et al., 2023). Thus, the compatibility and generalizability of current aging oculomics remain significant challenges and call for methodological innovation.

2.3. AI for disease detection

2.3.1. Neurological diseases

Retinal photography can serve as a non-invasive tool for qualitative analysis of neurological diseases (Wong, 2004). OCT and OCTA technology enable the detection of subtle changes in retinal layers and microvasculature that may herald the onset of neurological diseases (Baker et al., 2008; Cheung et al., 2017; Zhang et al., 2021c). AI emerges as a promising solution to integrate ocular biomarkers spanning retinal lesions, thickness of retinal and choroidal layers, vascular parameters, and electroretinogram (ERG) indices for effective early detection of neurological diseases.

2.3.1.1. Alzheimer's disease & dementia. Oculomics, utilizing various ocular diagnostic tools such as retinal photography, OCT, OCTA, microperimetry, ERG, and eye trackers, has been increasingly associated with AD and all-cause dementia (Asanad et al., 2021; Ciudin et al., 2017; Nam et al., 2020; Nunes et al., 2019; Tian et al., 2021; Wisely et al., 2022). These techniques enable the assessment of retinal and visual system biomarkers that may reflect underlying brain changes, offering potential for early detection and monitoring of cognitive decline (Cheung et al., 2017). In recent years, AI-based algorithms have been developed to analyze retinal features such as vascular changes, retinal nerve fiber layer (RNFL) thickness, and eye movements, which correlate with specific brain regions affected by neurodegeneration.

Supervised ML facilitates clinical diagnosis of AD by leveraging comprehensive retinal parameters (Tian et al., 2021). Notably, Cheung et al. leveraged 12,949 CFPs from 648 AD patients, to develop a DL model for AD detection, achieving an overall good diagnostic performance (accuracy ranging from 0.796 to 0.921) (Cheung et al., 2022). The model successfully differentiated between amyloid β positive and negative participants. However, common comorbidities slightly compromised model performance in patients without eye diseases or diabetes, reducing accuracy by approximately 10%.

Specific retinal features, including small retinal vessels and OCT features (such as area, solidity, retinal texture etc.) also showed strong predictive value in detecting cognitive impairment (Zhang et al., 2021b; Nunes et al., 2019; Yoon et al., 2024). While it looks promising to integrate multiple data to enhance model performance in dementia prediction, a multi-modality study involving OCT, OCTA parameters and ultra-widefield (UWF) fundus images did not show significantly higher accuracy (ranging from 0.67 to 0.84) compared to those using only CFP (Wisely et al., 2022).

An emerging approach involves using eye movement features for early and non-invasive detection of dementia. Ocular assessments of AD patients have demonstrated saccadic dysfunctions, particularly simultaneous vertical movements of the face and eyes (Nam et al., 2020). Participants were given visual stimuli for data collection, with their eye movements recorded to create an eye-tracking dataset (Sun et al., 2022). ML approaches analyzing characteristics like fixations, saccades, and refixations can achieve reasonable performance (AUCs ranging from 0.73 to 0.93), while deep neural networks may enhance the capability in distinguishing visual attention disparities (Maleki et al., 2024; Miles et al., 2024; Zuo et al., 2024). However, challenges in collecting high-quality eye movement data and the cost of eye trackers have restricted these models to small sample sizes. Future research may aim to develop low-cost and wearable sensor-based glasses to enable broader and high-quality data collection.

2.3.1.2. Parkinson's disease (PD). AI has also been used to explore the links between oculomics and clinical manifestations in PD. However, detecting PD from CFP remains challenging. A study combining fundus images with demographic data suggested the potential for non-invasive PD monitoring but did not achieve clinically viable accuracy (Ahn et al., 2023). Zhu et al. investigated the retinal age gap and found that each 1-year increase in this metric increased the risk of developing PD by 10% (Hu et al., 2022). Retinal texture assessed via OCT offers insights into distinguishing between healthy individuals and those with PD (Nunes et al., 2019). Furthermore, ocular movement deteriorates as PD

progresses, characterized by prolonged saccadic latency and reduced response accuracy (Reiner et al., 2023).

2.3.1.3. Multiple sclerosis (MS). Current MS diagnosis through oculomics relies on OCT parameters as an intermediary step. Various ML algorithms including Support Vector Machines, ensemble classifiers, and Recurrent Neural Networks, demonstrated effectiveness in MS diagnosis and prediction, achieving AUCs between 0.82 and 0.88 (Montolío et al., 2021; Zhang et al., 2020a). AI has also identified crucial ocular parameters for MS diagnosis, such as OCT-measured ganglion cell layer (GCL) and whole retinal thickness (López-Dorado et al., 2021). However, studies differ in their findings regarding the diagnostic value of RNFL thickness loss versus GCL, or even advocate using choroidal thickness data instead of retinal thickness for diagnosis (Cavaliere et al., 2019; Pérez Del Palomar et al., 2019). This variation could result from the application of different McDonald criteria versions for diagnosing MS (Filippi et al., 2022). Currently, DL significantly enhances 3D OCT image segmentation, enabling rapid extraction of subtle retinal changes within a rapid 10-s timeframe (He et al., 2019). Future research might pivot toward directly identifying MS and predicting its onset and progression from retinal images, aiming for a simpler and more direct diagnostic strategy.

2.3.2. Cardiovascular diseases

2.3.2.1. Coronary artery disease (CAD). Since the early 21st century, clinicians have observed a significant association between retinal microvascular abnormalities and the risk of CVD (Duncan et al., 2002). Researchers have discerned specific biomarkers such as heightened vessel tortuosity linked with CVD mortality and incidents (Liew et al., 2011; Owen et al., 2019; Witt et al., 2006). AI technology offers the potential for automatic unsupervised analysis, revealing novel retinal biomarkers and pathways previously unexplored.

Multimodal approaches combining prediction outputs from CFP with traditional CVD risk factors have demonstrated improvements in diagnostic performance of CVDs. In addition to traditional risk factors, dual-energy X-ray absorptiometry and retinal images as inputs can enhance accuracy by 2–3% (Al-Absi et al., 2022; Mellor et al., 2023). OCTA-based retinal vascular network parameters were also applied as additional input for identifying CAD (Zhong et al., 2022). While previous findings demonstrated the potential of OCTA in CAD diagnosis, the added value of OCTA over clinical parameters was minimal and only applicable for patients without hypertensive or diabetic retinopathy (DR) changes. To better highlight the potential of oculomics, further studies, including those with longitudinal images and broader patient populations, are needed.

2.3.2.2. Major adverse cardiovascular events. Rudnicka et al. developed a DL model that utilized retinal vascular features to predict adverse events including circulatory mortality, myocardial infarction and stroke, achieving C-statistic of 0.75–0.77 comparable to FRS (Rudnicka et al., 2022). Similarly, Poplin et al. developed models to predict adverse cardiovascular events within the next 5 years and achieved an AUC of 0.70 using CFP alone-a performance comparable to that of the composite SCORE risk calculator (Poplin et al., 2018). In patients with diabetes, retinal parameters, both alone and in combination with polygenic risk scores for coronary heart diseases, have shown incremental prognostic value at major adverse cardiovascular events over 10 years (Mordi et al., 2022). Additionally, the concept of 'retinal age gap,' has proven to be an effective predictive biomarker for CVD mortality (Nusinovici et al., 2022; Zhu et al., 2022a, 2023).

2.3.3. Kidney diseases

AI has shown promise in directly predicting renal events such as CKD and diabetic kidney diseases (DKD), potentially surpassing models relying on traditional risk factors. Several DL algorithms have emerged for screening CKD in primary care settings, providing a non-invasive alternative to blood test-based methods (Sabanayagam et al., 2020; Zhang et al., 2021a). It has been reported that subtle changes in retinal vasculature not only indicate prevalent CKD but also predict future CKD development, with C-statistic values ranging from 0.638 to 0.703, reflecting moderate accuracy (Joo et al., 2023). A recent meta-analysis focusing on CFP for CKD prediction reported a fair performance, with pooled sensitivity of 87.8%, specificity of 62.4%, and an AUC of 0.864 (Tan et al., 2024). However, the diagnostic efficacy of DL for CKD detection varies significantly due to DL methods, type of fundus camera, and sample size of images and datasets.

By analysing the retinal age gap derived from CFP, Zhu's team revealed that each additional year of the retinal age gap at baseline was associated with a 10% higher risk of incident kidney failure over a decade (Zhang et al., 2023). These efforts underscore the added value of incorporating retinal images in renal disease prediction. Nevertheless, the low specificity of current models suggests a potential for high misdiagnosis rates, underscoring the critical need for further refinement and validation of these models.

2.3.4. Miscellaneous conditions

2.3.4.1. Anemia. Ocular manifestations such as the color of palpebral conjunctiva offer a quick and non-invasive method for anemia diagnosis without the need for invasive blood test (Goldberg, 1971; Moriarty et al., 1988). AI has helped advance this field, surpassing human experts' performance in the screening and early detection for hematological diseases (Chen et al., 2016). AI-based screening systems could help detect sickle cell retinopathy and automate the detection and quantification of pathologic vascular changes from multi-modality retinal images, including UWF fundus photographs, fundus fluorescein angiography (FFA), and OCTA (Alam et al., 2017; Cai et al., 2021b; Sevgi et al., 2022). Furthermore, researchers integrated a DL detection system into regular CFP to estimate blood-haemoglobin levels and anemia status (Mitani et al., 2020). Telemedicine AI-based methods could predict risks of future vision loss and identify patients with hematological diseases requiring ophthalmic treatment, thereby reducing reliance on retinal specialists and improving patient adherence (Cai et al., 2021a).

2.3.4.2. Diabetes. Beyond predicting blood glycemic parameters, studies have employed DL approaches to detect diabetes directly from retinal images including CFP and OCTA images (Yun et al., 2022; Aslam et al., 2020). The model developed by Zhang et al. not only accurately detected prevalent diabetes but also predicted future onsetof T2DM within five years (Zhang et al., 2021a). With methods such as adaptive optics (AO) providing higher image resolution than traditional imaging modalities, early signs of arteriolar dysfunction, prior to the progression of impaired glucose tolerance to diabetes, have shown promise for detection through noninvasive measurements, even in individuals with prediabetes (Lai et al., 2024; Zaleska-Żmijewska et al., 2017). Therefore, instruments offering a wider field of view, more detailed microscopic techniques, and additional training on more diverse clinical and demographic cohorts could further enhance diagnostic accuracy and clinical utility. These advancements also hold significant potential for lowering the current diagnostic threshold for diabetes.

AI-derived diagnostic capabilities are applicable not only to retinal images obtained using professional cameras but also to external eye images captured using smartphones. Using iris patterns, colors, tissue weakness, breakage, and other characteristics, oculomics can also achieve high accuracy in diabetes detection (Samant and Agarwal, 2018). However, due to limited automated segmentation for external eye images, reliance on manual labeling in this method highlights the need for further improvements. Complications of diabetes, such as diabetic

peripheral neuropathy, can also be detected from corneal confocal microscopy images, without the need for complicated nerve segmentation (Preston et al., 2022). These approaches provide the basis for the development of a remote mobile screening tool for diabetes in the future.

3. Challenges

3.1. Lack of real-world prospective research

Although numerous tools/algorithms have been developed for systemic health evaluation using ocular images as mentioned previously, there remains a significant gap in real-world application on this technology. Real-world evidence is critical for addressing this gap. First, the performance of algorithms might be compromised in real-world settings due to variations in imaging devices and population characteristics (Li et al., 2023b). Moreover, translating these technologies into clinical practice requires more than the robustness of technical performance; it also depends on the adaptability of the technology within clinical environments, workflow integration, and the acceptability among end-users. Prospective studies could provide essential data for regulatory approval and the successful integration of these tools into routine medical practice (Ruamviboonsuk et al., 2022).

To date, only a limited number of oculomics-related algorithms have undergone external validation and received approval as clinical tools. Notably, the Reti-CVD algorithm, which predicts the likelihood of CAC presence from the retinal images, has been validated through a pivotal regulated trial in Korea, demonstrating robust CVD risk stratification capability comparable to the established biomarkers, including CAC score, carotid intima-media thickness and brachial-ankle pulse wave velocity (Lee et al., 2023). Despite the nascent stage of oculomics in real-world application, its potential for clinical translation is promising, particularly following the approval of several AI-powered clinical devices for diabetic eye disease detection from retinal images, such as the IDx-DR and EyeArt (FDA, 2018) (American Academy of Ophthalmology, 2020). Specifically, the IDx-DR (Digital Diagnostics Inc) has been successfully implemented outside ophthalmology clinics, demonstrating accuracy and safety in real-world populations (Abràmoff et al., 2013; Hansen et al., 2015). Both automated grading with the IDx-DR device and the AI-Human Hybrid Workflow have proven effective in detecting referable and vision-threatening DR (Dow et al., 2023b; van der Heijden et al., 2018). Oculomics-based AI systems hold significant promise for achieving transformative breakthroughs in screening, referral, and diagnosis for one or more diseases. However, to fully realize their potential in revolutionizing eye and systemic healthcare, these systems must undergo rigorous validation in diverse real-world settings. Such validation is essential to demonstrate their robustness, generalizability, and clinical utility across varied populations and healthcare environments.

As early in 2018, Google Health has conducted a prospective interventional study in Thailand to validate the real-time performance of AI-based DR detection. The findings suggested a comparable performance of AI and retinal specialists (Ruamviboonsuk et al., 2022). A concurrent clinical field study of the system further identified several socio-environmental factors and logistical facilitators and barriers of implementing such systems (Beede et al., 2020). Utilizing advanced 3D OCT images, Nguyen et al. prospectively validated a DL algorithm for diabetic macular edema (DME) detection in Vietnam with high accuracy similar to human experts in the real-time (Nguyen et al., 2024). In addition, a recent pragmatic trial conducted in Australia first validated the real-world feasibility, accuracy and end-user acceptance of an automated AI system that assesses CVD risk in the real-time (Hu et al., 2025).

The limited number of real-world prospective studies in oculomics can be attributed to several challenges. Firstly, for algorithms that predicts future systemic diseases, validation of the performance requires long-term follow-up to capture the onset of outcomes, necessitating large cohorts with sufficient incident cases. Second, unlike the detection of eye disease, labeling retinal images in oculomics studies often demands expertise beyond ophthalmology. Diagnosing certain systemic diseases requires a combination of different tests and examinations to establish the diagnosis. For example, Alzheimer's disease diagnosis needs clinical-criteria-based diagnostic tools, amyloid-positron emission tomography (PET) scans, cerebrospinal fluid assessments, or plasma assays (Cheung et al., 2022). The prospective documentation of information to form the gold standard can be costly and resource-demanding, as well as requires interdisciplinary collaboration. Thirdly, obtaining ethics approval for real-world interventional studies could be challenging, particularly when the AI is incorporated within the clinical workflow and may provide additional information to the clinicians (Khera et al., 2023). These potential risks may also hinder the engagement of clinicians and participants. Therefore, meticulous study design and a robust risk mitigation strategy are essential to ensure smooth execution. Lastly, the real-world studies cannot be initiated without essential infrastructure, such as software interface, imaging devices, and secure data management solutions (Bizzo et al., 2023). Establishing supportive infrastructure for clinical research would build a solid foundation to carry out real-world prospective studies.

3.2. Regulatory approvals for oculomics-related medical devices

The rapid development of AI technologies and related devices presents a challenge for transforming regulatory approval tailored for these medical devices. Regulatory bodies worldwide have acknowledged these challenges and are working to develop frameworks for AI/ML-based devices. The US Food & Drugs Administration (FDA) published "Artificial Intelligence and Machine Learning Software as a Medical Device Action Plan" which highlighted the need for tailored regulatory framework for AI/ML-based software as medical devices (SaMD) (FDA, 2021a). Similarly, the European Medicines Agency (EMA) and the Heads of Medicines Agencies (HMAs) have published an AI workplan in 2018 (EMA, 2023), and China's National Medical Products Administration (NMPA) launched the 'Principles for the Classification Defining of AI-Based Medical Software Products' to strengthen oversight of these innovations (NMPA, 2021).

The level of evidence for the regulatory approval of AI-based algorithms, or SaMD, differ from traditional medical devices or drugs, where randomized controlled trials (RCTs) are typically mandatory. This difference arises primarily due to the unique, dynamic, and adaptive nature of AI algorithms, which evolve over time through real-world learning and updates (Benjamens et al., 2020). Traditional regulatory frameworks, designed for static devices, face challenges in keeping pace with the rapid advancements in AI technologies. Recognizing this, the FDA is exploring a total product lifecycle-based regulatory framework to address the safety and effectiveness of adaptive algorithms, as current guidelines are insufficient to manage their unique characteristics (Benjamens et al., 2020).

While RCTs are not explicitly required for all AI/ML-based SaMDs, rigorous clinical validation is still critical. Regulatory bodies like the FDA emphasize the importance of demonstrating clinical utility through appropriate study designs, with representative clinical study participants for the patient population, device performance test in clinically relevant conditions, and model monitoring after deployment and retraining risk management are required for SaMD deployment (FDA, 2021b). For instance, the iDx-DR system for DR detection was approved upon a prospective pivotal trial in primary care settings that demonstrates higher sensitivity and specificity than the pre-specified values (Abràmoff et al., 2018). In addition, Singapore Eye Lesion Analyzer (SELENA+) was approved by Singapore's Health Science Authority in 2019, following comprehensive and extensive validation in multi-ethnic populations from the existing Singapore Integrated Diabetic Retinopathy Program (SiDRP) as well as global datasets from China, Australia,

the US, and Mexico (Ting et al., 2017). For oculomics-oriented SaMDs, only one software, RetiCVD, has received regulatory approval. It obtained CE certification as a Class IIa medical device in the European Union and authorization from the Korean Ministry of Food and Drug Safety (K-MFDS) based on clinical evidence from a pivotal trial that retrospectively assessed its performance against established cardiac biomarkers (Lee et al., 2023).

3.3. Scalability of AI, potential biases and ethical implications

The effective application of AI in oculomics faces several scaling challenges. Oculomics involves processing complex multimodal data from various eye imaging techniques and medical records across diverse populations and healthcare settings. To address these challenges, researchers have developed several key solutions. Cloud computing infrastructure provides the necessary computational power to process large volumes of healthcare data efficiently (Yadav et al., 2021). Advanced AI approaches like RETFound demonstrate how foundation models, trained on large datasets of retinal and OCT images through self-supervised learning, can adapt to new tasks with minimal additional labeled data (Zhou et al., 2023a). Recent work by Lin et al. shows how AI systems can be adapted to work across different devices, enabling algorithms trained on high-end fundus cameras to maintain performance when using images from portable, low-cost devices. This helps expand access to oculomics technology across different healthcare settings (Lin et al., 2022).

Data bias and representation issues pose significant challenges in the deployment of AI models for oculomics. Domain shifts between the development set and the test set, arising from differences in demographic factor distributions, can compromise AI performance on specific test datasets. For instance, an oculomics model trained on a Korean population for biological aging exhibited lower performance when externally validated on the UK Biobank dataset, which comprises individuals predominantly of Caucasian ethnicity (Nusinovici et al., 2022). Extensive validation across diverse cohorts is one of the most important approaches to address this issue (Ntoutsi et al., 2020). Recent developments in mitigating data bias include efforts to create balanced datasets for algorithm training. The National Institutes of Health has funded a project called AI Ready and Equitable Atlas for Diabetes Insights (AI-READI), which aims to construct a dataset with an equal representation of individuals across sex, ethnicity, and diabetes status (AI-READI, 2025). Researchers have also explored various bias-mitigation techniques that can be applied throughout the algorithm processing pipeline (Ntoutsi et al., 2020).

The clinical deployment of oculomics technology requires careful consideration of ethical issues such as data privacy and accountability. Developing AI algorithms requires large amounts of real-world data, and concerns like data breaches, misuse, and unauthorized access could lead to significant ethical problems. Recent research has explored techniques to enhance data security in healthcare, such as federated learning, which allows multiple collaborators to train models without sharing confidential data (Nguyen et al., 2022). Techniques such as blockchain has also been discussed for its potential role through authorized-only data access (Tagde et al., 2021). In addition, clear legal and regulatory frameworks are needed to address questions of liability and accountability for AI systems. If an AI makes a misdiagnosis that harms a patient, it may be unclear whether responsibility lies with the developer, the hospital, or the clinician who used the AI. Establishing processes for continuous monitoring and upgrading of AI systems after deployment is also critical, as it is unrealistic to expect all safety considerations to be fully resolved before real-world use begins (Habli et al., 2020). Proactively addressing these ethical challenges around privacy, security, and accountability will be essential for responsibly integrating oculomics technology into clinical practice (Wang et al., 2024d).

3.4. Who will use oculomics?

Given previous research evidence on the capability of retinal imaging and AI in detecting or predicting demographic factors, systemic biomarkers and systemic diseases, oculomics is positioned to be a valuable clinical tool that extends beyond eye care professionals. It enables broader usage across various healthcare sectors, such as general practitioners (GPs), cardiologists, neurologists and other specialists to assess not only ocular health but also systemic conditions, driving the multidisciplinary approach to improving patient care (Fig. 6).

3.4.1. Ophthalmologists, optometrists

Eye care professionals, including optometrists for primary eye care and ophthalmologists for advanced eye care, are most likely to be the primary users of oculomics. Given the office-based ocular imaging facilities are standard tools in eye care settings, the infrastructure for implementing oculomics tests is largely in place (Goetz et al., 2024). Moreover, there is growing acceptance of AI among eye care professionals. A recent survey reveals that 72% of the optometrists believe AI would enhance their practice, and up to 88.1% of the ophthalmologists are open to using AI as a clinical aid (Gunasekeran et al., 2022; Scanzera et al., 2022). Particularly, the COVID-19 pandemic has further accelerated the adoption of digital health solutions, increasing willingness to incorporate AI into routine practice (Gunasekeran et al., 2022; Scanzera et al., 2022).

AI has demonstrated value in the eye diseases management by enhancing diagnostic accuracy, enabling early disease detection, prediction of disease progression, and streamlining patient management (Dai et al., 2024; Li et al., 2024b; Ruamviboonsuk et al., 2022; Ting et al., 2017). The use of AI could assist both the diagnostic accuracy and efficiency of ophthalmologists. For instance, Guo et al. have proposed a diagnostic intelligent decision support system using natural language processing to extract key diagnostic information of retinal diseases from electronic medical records (EMRs), improving diagnostic efficiency for ophthalmologists (Guo et al., 2024). AI could also assist eye care providers in providing individualized and patient-centered care. For example, the recently developed DeepDR Plus system enables the prediction of the progression timeline of DR, allowing personalized screening interval recommendations on the baseline DR status, rather than adhering to a fixed one-year cycle (Dai et al., 2024). Similarly, the prognosis of neovascular age-related macular degeneration (AMD) after receiving anti-vascular endothelial growth factor (VEGF) therapy using could also be predicted using patient's baseline clinical information through machine learning (Schmidt-Erfurth et al., 2018a).

Beyond ocular diseases, oculomics has the potential to involve eye care professionals in the management of systemic conditions. By analyzing subtle changes in the eye—such as retinal vascular alterations or structural variations—oculomics can reveal early signs of diseases like diabetes, cardiovascular issues, and neurodegenerative disorders. This enables ophthalmologists and optometrists to play a key role in identifying systemic health risks, guiding patients to appropriate care pathways, and collaborating with other healthcare providers for comprehensive disease management, thus extending their impact beyond traditional eye care. For example, during DR screenings, integrated algorithms that predict risk for diabetes, hypertension or CVD could enable optometrists to offer additional referral recommendations. This would maximize the benefit of a single eye exam, contributing to more comprehensive patient care. However, there has been limited research on this model of care to date and future studies are required to explore the feasibility and effectiveness of this care pathway.

3.4.2. GPs, cardiologists, neurologists, diabetologists, and other specialists

Oculomics presents vast potential beyond eye care, offering transformative opportunities for integration across various medical specialties, and enhancing disease prevention and management. GPs, as the most accessible healthcare professionals who serve the greatest number

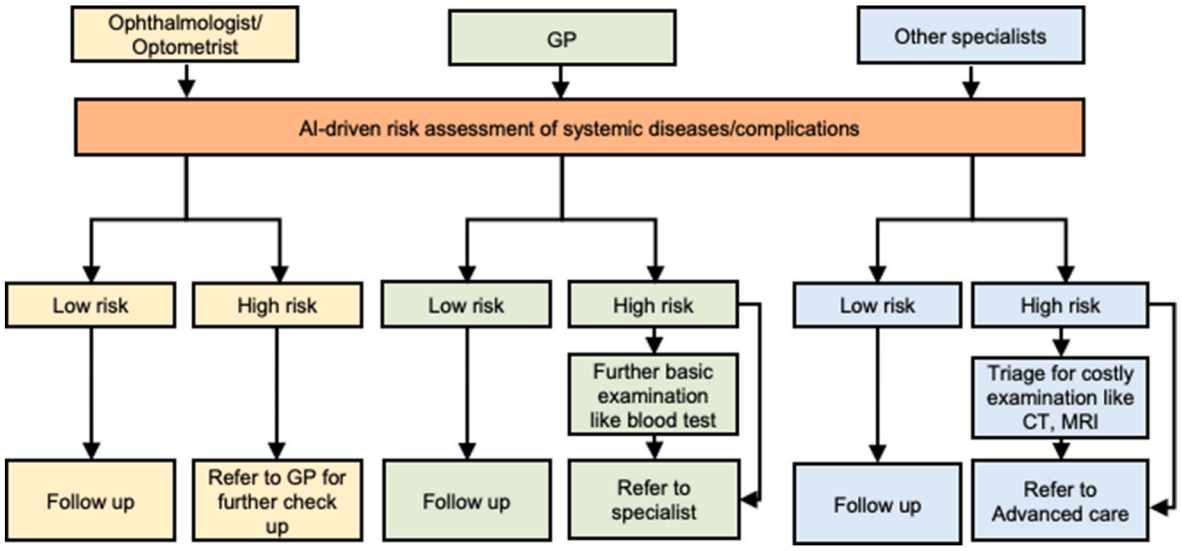

Fig. 6. Potential users of oculomics across healthcare disciplines.

of patients in the community, can be the key players in adopting oculomics. It will potentially help GPs address the key challenges in their practice, such as time constraints in conducting comprehensive risk assessment for common conditions like CVD and CKD (George et al., 2016; Sperati et al., 2019). AI-based tools like oculomics could streamline triage by simply using retinal images to assess the risk (Tseng et al., 2023), thereby enhancing prevention efforts for high-burden diseases like CKD and diabetes (Sabanayagam et al., 2020; Zhang et al., 2021a). Therefore, integrating of oculomics-based screening in general practice will enhance GPs' role in early detection and prevention, ultimately improving the public health outcome. Additionally, oculomics could bridge the skill gaps in GPs and improve diagnostic accuracy. For example, GPs often report difficulties interpreting fundus photography (Watson et al., 2021), but oculomics-assisted DR screening enables them to be actively involved in DR screening, offer timely referrals, and coordinate diabetes care with endocrinologists.

Cardiologists can also leverage oculomics for CVD risk assessments, particularly for triaging before sending patients for costly advanced tests, such as CAC, computerized tomography coronary angiogram (CTCA) and cardiovascular MR (Hamilton-Craig and Chan, 2016; Hecht, 2015). For example, the adoption of tools like Reti-CVD, which predicts CAC from retinal imaging could serve as a cost-effective method that optimizes resource use (Lee et al., 2023; Tseng et al., 2023).

Moreover, oculomics has the potential for the early detection of neurological conditions such as stroke, which may present as central retinal artery occlusion (CRAO), or signs of intracranial tumours or hemorrhages that increase intraocular pressure, presenting as papilledema (Avery et al., 2019; Rigi et al., 2015). Since traditional ophthalmoscopy is challenging for neurologists to use (He et al., 2022), oculomics can assist in identifying these life-threatening neurological signs. This could be extended to emergency doctors as well, serving as an assistive tool for patients presenting with sudden visual impairment or headache.

In the comprehensive management of diabetes and its various complications, oculomics holds significant promise in assisting diabetologists with early detection, progression prediction, and other critical aspects of diabetic care (Bynoe et al., 2024; Katsuyama et al., 2020; Keel et al., 2018). Diabetes complications, including both microvascular and macrovascular outcomes as well as other systemic conditions, are among the leading causes of morbidity and mortality. For instance, DR is the primary cause of visual impairment and blindness in working-aged individuals, while cardiovascular events and diabetic nephropathy are major contributors to mortality (Ting et al., 2017; Gerstein et al., 2013; Tan et al., 2017). Traditional methods for assessing systemic complications of diabetes, such as CAC scans, blood tests, and eGFR evaluations, are often invasive and costly, making them relatively inaccessible for the global diabetic population. In contrast, artificial intelligence-driven early and non-invasive detection of these systemic complications using retinal imaging has emerged as a promising approach. This method provides an ideal platform for identifying high-risk individuals and enabling more targeted, intensive interventions, thereby reducing the incidence and mortality associated with diabetes and alleviating its societal burden (Yang et al., 2025a). These interventions could include health education, dietary and lifestyle management, as well as symptom-specific treatments, ultimately improving patient outcomes and reducing the burden of diabetes-related morbidity and mortality. Future research should prioritize robust validation across diverse populations, further quantitative studies with a focus on deeper analysis and broader real-world impact, and strengthen clinical translation and policy development, thereby supporting diabetologists in delivering more effective and personalized care.

Other healthcare professionals including allied health professionals could be potential users of the oculomics. Allied health professionals or other primary care practitioners can further use oculomics for tailoring behavioural interventions and improving patient-centered care (Li et al., 2024b). While these applications highlight oculomics' potential, further research is needed to integrate these tools into the workflows of different clinical specialties. Due to the different routines and specific needs of each specialty, customized implementation strategies will be crucial.

3.5. *Do the oculomics AI algorithms meet "screening tests" criteria?*

While oculomics has demonstrated significant promise in detecting and predicting a wide range of ocular and systemic diseases, its large-scale adoption as a valid screening tool hinges on its ability to fulfill the stringent criteria for screening tests (Australian GovernmentDepartment of Health and Aged Care, 2018). Key regulatory challenges must be addressed to ensure its clinical utility and reliability. For instance, what constitutes the ground truth for oculomics, particularly in the context of risk stratification? How can regulatory bodies evaluate the accuracy and clinical utility of oculomics' risk prediction capabilities? These questions underscore the need for robust validation frameworks and clear regulatory guidelines.

To address these challenges, the development and implementation of oculomics-based AI systems necessitate interdisciplinary collaboration. This involves forming multidisciplinary teams that include vision

researchers, internal medicine specialists, data scientists, epidemiologists, and clinical trial experts (Chew et al., 2025). Such collaboration is critical to overcoming the technical, clinical, and regulatory complexities associated with integrating oculomics into mainstream healthcare. By leveraging diverse expertise, these teams can ensure that oculomics-based AI systems are both scientifically robust and clinically applicable.

A key step in this process is the standardization of integration of oculomics into standard clinical workflows. Consistent imaging protocols are essential to ensure high-quality data collection, which is critical for training reliable AI models. Moreover, expanding the use of retinal imaging technology beyond traditional ophthalmic settings—such as into intensive care units, inpatient wards, and primary care facilities—can significantly broaden the scope of oculomics applications, enhancing its role in systemic health monitoring. Standardization is vital not only for advancing the field but also for establishing a reliable ground truth for oculomics. It is also key to ensuring that the accuracy and clinical utility of oculomics' risk prediction capabilities are both reproducible and generalizable.

3.5.1. Prevalence of targeted conditions

The prevalence of targeted conditions is a key component to in determining the viability of oculomics as a screening tool. By analyzing ocular biomarkers through retinal imaging, oculomics is especially effective for detecting widespread conditions with substantial public health impacts, while also offering insights into rarer disorders.

CVD, diabetes and CKD are the major public health concerns, particularly in the ageing population, contributing significantly to global disease burdens. CVD is responsible for nearly 20.5 million deaths annually, making it a critical target for screening (Di Cesare et al., 2024). With 529 million people living with diabetes globally (Collaborators, 2023), early detection through retinal imaging could not only predict diabetes risk but also address DR, diabetic kidney disease, and cardiovascular risk (Fox et al., 2007; Vujosevic et al., 2020; Zhang et al., 2021a). CKD, affecting about 10% of the population (Kidney Disease: and Improving Global Outcomes (KDIGO) CKD Work Group., 2024), is often diagnosed late, but oculomics can help detect CKD at an earlier stage (Zhang et al., 2021a). Given their high prevalence, impact on morbidity and mortality, and the presence of detectable ocular manifestations, these conditions are well-suited for oculomics-based screening. This approach enables earlier diagnosis and helps alleviate healthcare burdens through timely intervention.

Neurodegenerative conditions, such as Alzheimer's, Parkinson's, have been explored as oculomics targets due to retinal changes that may precede clinical symptoms. Despite their lower prevalence compared to CVD or diabetes, these conditions have major implications for quality of life. Oculomics also shows potential in the detection of schizophrenia (Appaji et al., 2022), but the lower global prevalence of these disorders—schizophrenia affects less than 1% of the population (Charlson et al., 2018)-making population-wide screening makes widespread screening less practical. These conditions require more targeted studies to assess the feasibility and may be better suited for screening within high-risk or specialized groups.

The prevalence of a condition directly influences the positive predictive value (PPV) of oculomics-based screening. High-prevalence conditions like diabetes and CVD result in more accurate screening outcomes, justifying their integration into routine programs. In contrast, lower-prevalence conditions have a greater risk of false positives, leading to unnecessary follow-ups and anxiety.

While oculomics has strong potential for high-prevalence conditions like CVD and diabetes, its use in lower-prevalence diseases will require further research and careful consideration of targeted screening strategies to ensure effectiveness.

3.5.2. Targeted population

To maximize the clinical impact of oculomics AI screening, it is essential to define the targeted population, enabling optimized healthcare resource use and improved patient outcomes (Australian GovernmentDepartment of Health and Aged Care, 2018). Key risk factors, including age, medical history, and lifestyle, provide the foundational criteria for screening eligibility. Broad, actionable criteria such as age and sex allow for scalability, while targeting specific high-risk groups—such as patients with hypertension or diabetes—ensures clinical relevance in populations where the benefit of retinal assessment is maximized. The effectiveness of criteria-based screening has been demonstrated in established programs like the NHS Diabetic Eye Screening Programme, which targets all people with diabetes aged 12 and above (England, 2024), and Australia's national cancer screening programs, which employ age as a primary determinant (Australian GovernmentDepartment of Health and Aged Care, 2023). In the case of CVD, age is similarly used as a straightforward criterion in clinical guidelines, enabling targeted outreach and streamlined recruitment of at-risk populations (Arnett et al., 2019b).

Moreover, prioritizing specific groups—such as younger or middle-aged individuals who might experience greater productivity, health, and quality-of-life gains from early disease intervention—can optimize screening impact, compared to screening older adults who may already have advanced disease (Kotwal and Walter, 2020). Epidemiological data can further refine targeting by revealing systemic disease prevalence patterns within local populations, helping align criteria with regional health trends.

By concentrating on these high-risk demographics, oculomics AI algorithms can maximize their potential to improve health outcomes, reduce healthcare costs, and enhance overall quality of life, thus demonstrating their relevance and importance in public health strategies.

3.5.3. Cost-effectiveness

The cost-effectiveness of oculomics is a pivotal consideration when evaluating its potential as a screening tool. Numerous studies have investigated the economic implications of implementing AI-based retinal screening systems across various healthcare settings, highlighting their potential to achieve substantial cost savings by reducing reliance on healthcare professionals, highlighting its promise for substantial cost savings by reducing reliance on healthcare professionals (Hu et al., 2024; Huang et al., 2022; Karabeg et al., 2024; Wolf et al., 2020; Xie et al., 2020). However, the cost-effectiveness of AI-driven screening may be influenced by several factors, which need to be weighed in real-world implementation.

Regional economic conditions and healthcare infrastructure are critical factors influencing the cost-effectiveness of AI-driven screening tools like oculomics. In some low-income regions, studies indicate that AI-driven screening may be less cost-effective than traditional manual screening methods (Gomez Rossi et al., 2022), probably attributed to the relatively low cost of human assessments in these settings. Thus, the economic viability of oculomics is context-dependent, highlighting the need to tailor its implementation to specific regional conditions for optimal value.

Another crucial factor influencing the cost-effectiveness of oculomics is the accuracy of the AI algorithms used in the screening process. Standard screening tests are generally expected to achieve both high sensitivity and specificity (McKay et al., 2021). Wang et al. have validated the cutoff values for sensitivity and specificity in AI-based DR screening, demonstrating a minimum sensitivity of 88.2% and specificity of 80.4% (Wang et al., 2024c). As achieving these standards has become increasingly common in the current landscape of AI technology (Lim et al., 2023; Ruamviboonsuk et al., 2022; Scheetz et al., 2021), it is anticipated that implementing oculomics will very likely be more cost-effective.

Moreover, the long-term effectiveness and cost-effectiveness of oculomics-based screening depend significantly on the coverage and accessibility. Compared to manual screening, the portable and

automated nature of AI-driven screening tools makes them more accessible, particularly in rural, remote, or resource-constrained areas. Hu et al. have demonstrated that increasing screening coverage is directly related to improved health outcomes (Hu et al., 2024). Increasing screening coverage leads to earlier detection and treatment of diseases. Although this may raise treatment costs, it helps prevent more people from progressing to severe stages that require complex and expensive interventions, ultimately saving significant healthcare costs (Hu et al., 2024).

In summary, while the potential for cost savings through oculomics is promising, careful consideration of the local economic context, the accuracy of the AI algorithms, and the accessibility of screening programs will be essential for realizing the full value of oculomics-based screening.

3.5.4. Downstream considerations

Downstream considerations following oculomics-assisted screening are important for evaluating its effectiveness as an eligible screening test. Key factors to assess include patient compliance with follow-up recommendations and rescreening schedules, as well as the availability of treatment options for identified conditions.

The availability and accessibility of follow-up care play a vital role in the overall outcomes of screening programs. For screening tests to be effective, target diseases should have readily available treatments and can be effectively prevented through early intervention. Conditions such as CVD, CKD, and DR exemplify this principle. For instance, effective management of risk factors including simple behavioural interventions can prevent up to 75% of CVD cases (Stewart et al., 2017), highlighting the potential benefits of early detection and management.

In contrast, while oculomics shows promise for certain conditions in experimental settings, such as dementia or schizophrenia (Appaji et al., 2022; Cheung et al., 2022), the prevention and treatment options for these disorders are significantly limited (Brown and McGrath, 2010; Tisher and Salardini, 2019). This limitation raises concerns about whether screening for these conditions might result in emotional distress among participants (Coon et al., 1999). Therefore, it is essential to be cautious when considering the implementation of oculomics-based screening for diseases that currently lack effective treatments.

Furthermore, ensuring accessible follow-up care is crucial for maintaining patients' compliance with downstream management. If patients receive follow-up recommendations but fail to seek further care, the benefits of early detection may be diminished. Although there were a few real-world studies that followed up on the participant compliance rate after AI-powered retinal screening which was shown to be relatively higher than the routine practice arms, compliance rates remained to be improved, with a varied range from 35.5% to 77.78% (Dow et al., 2023a; Li et al., 2024b; Scheetz et al., 2021). More research is needed to investigate the follow-up outcomes of oculomics-based screening and to develop strategies that enhance adherence to follow-up visits and care plans.

3.6. How will clinicians interpret and use oculomics?

Clinicians are increasingly recognizing oculomics-based technology as a valuable tool for decision support, disease monitoring, and optimizing clinical workflows, particularly in the management of systemic diseases, by leveraging non-invasive ocular imaging.

In decision support, recent studies have demonstrated that oculomics, both independently and in conjunction with clinical data, significantly enhances early diagnosis, prevention, and treatment of systemic conditions (Suh et al., 2024; Wagner et al., 2020). Advanced segmentation algorithms for ocular lesions and neurovascular features have facilitated the application of AI in decision support, enabling automated disease reporting, annotation, and explainable clinical decision support (Cen et al., 2021).

As oculomics continues to evolve, its potential integration with EMRs may offer a holistic view of patient health in the future (Cimino, 2013). By synthesizing ocular biomarkers with broader health parameters, clinicians can improve diagnostic precision and make more informed clinical decisions.

For personalized disease monitoring, clinicians can utilize retinal imaging to observe changes in the retinal nerve fiber layer, blood vessels, and optic disc, which serve as key indicators of systemic health issues. The growing accessibility of retinal imaging platforms, including smartphone-based solutions, offers a dynamic approach for tracking disease progression over time, particularly for chronic conditions such as DR and glaucoma (Karakaya and Hacisoftaoglu, 2020; Kim et al., 2018). Oculomics-based tools, utilizing pre-trained models on large datasets, enable real-time monitoring of patients' risk levels for systemic diseases, helping clinicians mitigate the risk of severe outcomes such as blindness or stroke (Zhou et al., 2023a). Furthermore, by integrating omics data (genomics, proteomics, metabolomics) with ocular imaging, oculomics holds the potential to offer precision monitoring and a deeper understanding of disease progression and underlying mechanisms in the future.

For workflow prioritization, including recommendations for interventions and scheduling follow-ups, the use of advanced care models like large language models (LLMs) and intelligent scheduling tools in combination with oculomics is increasingly encouraged to assist clinicians. There is ongoing exploration of how to integrate LLM into EHRs for application in clinical medicine (Eguia et al., 2024). Jiajia et al. provided a compelling example with the development of DeepDR-LLM, an integrated system combining image-based deep learning for DR/DME grading from fundus images with an LLM for personalized diabetes management recommendations. It could support primary care physicians by providing DR/DME diagnostic results and leveraging patient data from EMRs, including medical history, physical exams, and lab results, to automatically generate personalized management recommendations. The real-world prospective study showed that integrating DeepDR-LLM into primary care workflows improved patient self-management, adherence to DR referrals, and enhanced the quality and empathy of clinical recommendations (Li et al., 2024b). Despite being in the early stages, LLMs are already showing potential to enhance patient care and improve physician efficiency.

Still, clinicians must be cautious in recognizing the limitations when interpreting the oculomics and applying new technologies in practice. Many previous models have been primarily trained on structured laboratory data, while clinical environments often involve unstructured information from patient narratives. To optimize reliability, it is essential to standardize phenotypes and integrate data from diverse sources with EMRs (Roger et al., 2020). AI-assisted decisions need to be contextualized with clinicians' expertise and real-world patient circumstances, including family, economic, and social factors. Additionally, new biases-such as the digital divide and disparities in internet access by geography, population groups, and socioeconomic status-must be considered when designing studies and interpreting results of oculomics.

While much of the data from epidemiological studies is not easily translatable to clinical applications, further steps are needed to facilitate this integration. Standardization of protocols for ocular biomarkers, retinal imaging, and improved interoperability across different types of retinal imaging equipment are essential. For instance, the STRIVE Initiative (Standards for Reporting Vascular Changes on Euroimaging, https://www.nichd.nih.gov/about/org/strive) has proposed standard definitions and imaging protocols for retinal biomarkers, particularly in the context of cerebral small-vessel disease (Wardlaw et al., 2013). Developing evidence-based guidelines and best practices is also critical to advancing this field.

Additionally, clinical trials involving diverse populations, representing varied races, ethnicities, and sexes, are necessary to test the implementation of artificial intelligence-assisted algorithms and establish benchmark datasets for validation. However, challenges remain in deploying ophthalmic imaging equipment in non-ophthalmic settings,

unless research funding is secured to support image capture, grading, and interpretation. To eventually transition into clinical practice, a centralized platform for sharing data—including images and clinical information - along with a centralized reading center for grading and interpretation, will be indispensable.

3.6.1. Explainable AI in oculomics

The concept of explainable AI (XAI) is particularly critical in the context of oculomics. Explainability ensures that clinicians can understand and trust the decision-making processes of AI models and ensure a clear communication between clinicians and patients, thereby improving adoption and integration into clinical workflows (Nazar et al., 2021). In addition, XAI aligns with the critical demand of transparency and accountability in medical practice. Healthcare decisions directly impact patient outcomes and safety and therefore require clinicians to understand and validate AI-generated recommendations. When AI systems make errors, demonstrate biases, or limited by external factors, such as retinal image upgradeability, explainability becomes crucial for understanding, correcting and compensating for these limitations (Li et al., 2018).

The "black box" nature of AI models was particularly relevant to the scenarios where retinal images were used to predict systemic diseases or risk factors that could not be visualized through pathologies *in situ*. Researchers have developed a range of techniques to provide intelligible visualization of the AI systems to enhance the validity and trustworthiness of AI deployment. For example, Poplin et al. applied soft attention technique first in oculomics to visualize retinal regions contributing to the AI development that accurately predicts CVD risk factors. The regions were further validated through a blinded approach by ophthalmologists which demonstrated the clinical explainability of the algorithms (Poplin et al., 2018). Novel methods such as SHapley Additive exPlanations (SHAP) values have been recently utilized in oculomics research to further identify the contributing factors to the disease outcome (Dai et al., 2024). These findings marked the important implication of XAI in oculomics beyond trust-building. Results from the XAIs provide additional scientific understanding by highlighting previously unknown relationships between retinal features and systemic conditions, potentially leading to new biomarker discoveries and targeted interventions (Dai et al., 2024; Keel et al., 2019).

In 2025, development of reasoning-based models (e.g., DeepSeek, OpenAI's o1 and o3-mini, Google's Gemini 2.0 Flash Thinkingetc) may be particularly useful for oculomics, where translation of this field has been hampered by poor acceptability of physicians and patients because of the "black-box" limitation of the models (Schwartz et al., 2024). New reasoning models incorporate chain-of-thought and expose intermediate reasoning steps and may provide a key future research direction in oculomics. This interpretable approach could potentially increase the acceptance of the technology by clinicians by providing evidence-based reasoning to elaborate the connection between retinal features and systemic diseases, with increased the trust and clinical adoption.

3.7. Who will pay for oculomics?

In addition to hospitals and clinics investing in oculomics devices and imaging technologies (e.g., OCT, scanning laser ophthalmoscopy [SLO], AO) as part of their diagnostic infrastructure, a diverse range of stakeholders—including patients, innovators, companies, Medicare, and health insurance providers-are poised to support and fund the adoption of emerging oculomics technologies.

3.7.1. Patients

Preventive health and disease management are universal concerns. Patients seeking personalized medicine or early detection of specific conditions may be willing to pay for services, particularly when they offer real-time feedback, as seen with oculomics. A notable example of this trend is the growing use of wearable sensors, such as smartwatches equipped with heart rate monitors and electrocardiograms, which provide continuous health monitoring (Spatz et al., 2024). AI has emerged as a pivotal player in this rapidly expanding field of wearable sensors (Bayoumy et al., 2021). oculomics similarly offers the advantages of non-invasive, real-time data collection. When integrated with LLMs, it has the potential to provide comprehensive, real-time health insights across multiple organs, significantly enhancing the personalization of care.

Moreover, oculomics can draw inspiration from successful commercial models in other omics fields. The rising demand for genomic sequencing services, where individuals willingly pay for personalized insights from saliva samples, serves as a strong precedent (Marshall et al., 2016). Unlike genomic sequencing, which is typically performed only once, oculomics encourages repeated measurements, making its easily accessible technology highly appealing to the broader population.

3.7.2. Innovators and companies

The extensive datasets generated through oculomics are likely to attract interest from commercial entities and data companies, creating a potential revenue stream for healthcare institutions. Processed oculomics data—cleaned, categorized, or preprocessed—can be offered to enhance usability for analysis and training AI models. Additionally, labeled datasets specifically designed for AI training, such as image classification in computer vision or text annotation in natural language processing, are in high demand due to their rarity, quality, applicability, and competitive value (Wang et al., 2021).

Pharmaceutical companies may invest in oculomics-based technologies for clinical trial and drug development processes, leveraging their potential to identify biomarkers, predict patient responses, and monitor disease progression (Vora et al., 2023). Moreover, companies developing oculomics technologies may offset early adoption costs by offering free or low-cost trials to healthcare providers. This strategy not only facilitates market establishment but also showcases the practical value of oculomics technologies before full financial responsibility shifts to healthcare providers or insurance companies.

3.7.3. Medicare

AI-driven healthcare technologies are increasingly being integrated into public health services, demonstrating their potential to enhance clinical outcomes and operational efficiency. For instance, Singapore's Ministry of Health (MOH) has begun incorporating AI into clinical decision support systems and disease prediction tools, such as the Clinical Assessment for Pneumonia Evaluation and adverse drug reaction monitoring systems (https://www.moh.gov.sg/licensing-and-regulation/artificial-intelligence-in-healthcare).

Similarly, the US Centers for Medicare and Medicaid Services launched an AI challenge in 2019 to develop predictive models for unplanned hospital admissions and skilled nursing facility placements, further illustrating the federal commitment to embedding AI into healthcare systems (https://ai.cms.gov/).

In this context, oculomics stands to leverage the vast amount of data generated by these AI initiatives to advance Medicare's mission of promoting health equity, broadening access to care, and improving health outcomes for diverse populations. Medicare may consider investing in oculomics technologies, including imaging devices such as retinal scanners, as essential components of their diagnostic infrastructure to support precision healthcare.

3.7.4. Health insurance

The integration of AI in oculomics significantly enhances the early detection of systemic diseases, which not only improves patient outcomes but also reduces the long-term financial burden associated with advanced disease management (Harris, 2017). By identifying diseases like complications from diabetes and hypertension at an earlier stage, insurers can lower the need for expensive late-stage interventions. Moreover, oculomics-driven tools can optimize treatment plans,

potentially lowering the rate of hospital readmissions and complications. Predictive analytics can identify individuals at high risk for specific conditions, enabling timely preventive measures that help minimize costly emergency care or hospitalizations.

For health insurers, oculomics facilitates the optimization of systemic disease workflows, leading to reduced administrative costs and streamlined claims processing. AI-driven tools can further refine care plans, reducing complications and hospital readmissions, ultimately lowering overall healthcare costs for insurers (Feng et al., 2022; Maleki et al., 2024). Given the potential for cost savings and improved health outcomes, health insurers are increasingly likely to support oculomics-driven preventive services. This approach not only strengthens the financial sustainability of insurance models but also enhances the quality of care delivered to patients.

In summary, patients, innovators, companies, Medicare, and health insurance providers are motivated to invest in oculomics-based healthcare due to its potential to reduce costs, improve patient outcomes, enhance system efficiency, and offer valuable preventive care tools. By enabling early disease detection and facilitating personalized treatment plans, oculomics not only addresses pressing healthcare challenges but also aligns with the financial interests of stakeholders, fostering a more sustainable and effective healthcare ecosystem.

4. Future opportunities

The future of oculomics presents exciting opportunities to reshape healthcare, enhance research capabilities, and deliver advanced diagnostics with wide accessibility. These opportunities are fueled by advancements in ocular imaging technologies, the integration of diverse data sources, and the development of innovative, accessible multimodality-based AI algorithms (Fig. 7).

4.1. Advancements in ocular imaging ("Hardware")

Ocular imaging is a rapidly evolving field, offering new approaches to visualize and diagnose both retina and systemic diseases. The innovative ocular imaging techniques extend beyond the traditional CFP and OCT techniques.

4.1.1. Ps-OCT, Doppler OCT, Vis-OCT, and oximetry

As for advancements in OCT, there have been emerging techniques with various structural and function measurements, including polarization-sensitive OCT (ps-OCT) (Pircher et al, 2011), Doppler OCT (Leitgeb et al., 2014), and visible wavelength OCT (Vis-OCT) (Asghari, 2023). Ps-OCT and its subtype Polarization-diversity OCT (PD-OCT) (Hsu et al., 2020) represent significant innovations. Ps-OCT measures the polarization state of light (Baumann et al., 2012; Pircher et al, 2011; Sakai et al., 2022; Yamanari et al., 2020; Yamanari et al., 2018), enhancing assessment of tissue properties and pathological changes. The degree of polarization uniformity (DOPU) is a metric developed to measure this depolarization (Miao et al., 2023). PD-OCT can obtain DOPU contrast in addition to scattering information attainable by conventional SS-OCT imaging. These technologies are valuable in distinguishing the retinal pigment epithelium (RPE) and other retinal layers through their unique polarization properties, allowing for automated segmentation of the RPE and improved detection of macular and optic nerve head pathologies (Pircher et al, 2011). Doppler OCT allows for quantifying the speed of moving particles with high spatial resolution and sensitivity in addition to structural imaging, holding the promise for investigating retinal vascular health and its relationship to systemic conditions. For instance, Doppler OCT can non-invasively assess blood flow dynamics in DR and glaucoma, revealing the extent of microvascular damage and guiding treatment decisions (Leitgeb et al., 2014). Vis-OCT provides structural information at the sub-micrometer level and functional information about quantitative measurements of endogenous chromophore, enhancing the understanding of ischemia and neurodegeneration in diabetes as well as other ischemic retinopathies and improving quantification of damage in glaucoma and AD, as well as other optic neuropathies (Wang et al., 2024a). Integrating oximetry (Stefánsson et al., 2019) with OCT provides a more comprehensive view of the retina. Because retinal blood flow and oxygenation are physiological indicators of retinal ischemia, often preceding anatomical symptoms, making them early biomarker candidates for disease diagnostics. Compared to invasive approaches such as fluorescein angiography (FA), oximetry measures retinal oxygen levels non-invasively and enhances the understanding of oxygenation-related diseases, such as ischemic heart conditions (Rilvén et al., 2017).

4.1.2. Wide-field digital imaging, hyperspectral imaging and adaptive optics

Further opportunities also lie in other retinal imaging modalities. For instance, wide-field digital imaging (WFDI) (Haefeli et al., 2022) can capture a broad view of the retina, hyperspectral fundus imaging (HFI) (Kaluzny et al., 2017) can detect chemical components by capturing information from multiple wavelengths, and AO technology (Liang et al., 1997) allows for retinal imaging at the cellular level. Specifically, WFDI offers an ultra-wide field view of 180–200° (Witmer and Kiss, 2013), which is particularly useful for examining the peripheral retina in conditions such as DR and neonatal ophthalmic screening (Desurmont et al., 2023; Ji et al., 2022; Olvera-Barrios et al., 2021; Vinekar et al., 2015). Peripheral retinal changes may correlate with systemic vascular complications, making retinal imaging a valuable tool for diagnosing and managing systemic diseases. HFI, by providing spectral information from the retina, facilitates the identification of pathological structures associated with systemic diseases (Hadoux et al., 2019; M'hiri et al., 2017), such as the metabolic status of hemoglobin in the context of retinal blood vessel oxygenation and amyloidopathy related to AD (Douglass and Oden,; Hadoux et al., 2019). It can serve as a non-invasive alternative to FA, allowing real-time, high-resolution visualization of retinal and choroidal structures even in the presence of cataracts, thus enhancing the detection of systemic diseases (Lemmens et al., 2020).

AO technology enhances the resolution of optical systems to 2 μm by correcting optical wave-front aberrations, allowing for accurate

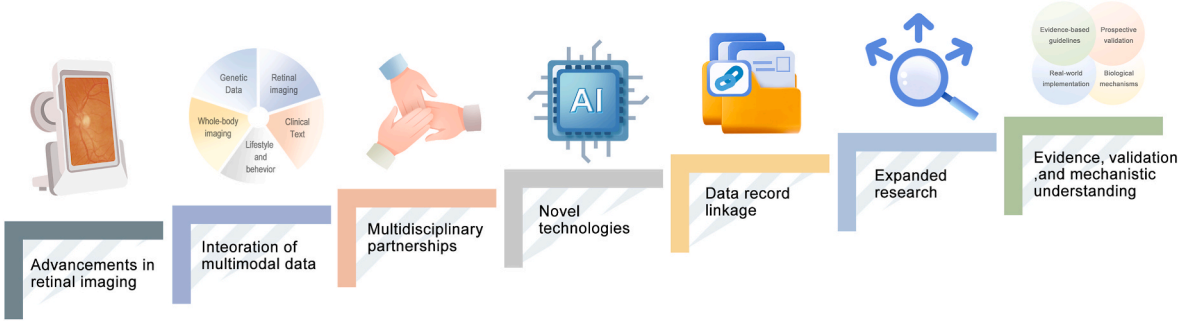

Fig. 7. Schematic illustrating future opportunities of Oculomics.

quantification of cell density and connectivity in vivo (Burns et al., 2019; Miller and Kurokawa, 2020). AO has been applied in imaging structures in healthy eyes and in various ocular diseases to evaluate the retina at the cellular level (Matuszewski et al., 2024; Zhang et al., 2022). Clinically, AO is used to study the progression of inherited retinal diseases such as Stargardt disease, retinitis pigmentosa and achromatopsia (Georgiou et al., 2018; Gill et al., 2019), and cone-rod dystrophy (Wolfing et al., 2006), providing insights into photoreceptor health and function. AO imaging can also reveal microvascular changes associated with hypertension (Koch et al., 2014), linking cellular-level observations in the retina to systemic health. Further application of high-resolution and adaptive imaging in systemic diseases may reveal additional ocular biomarkers.

4.1.3. Portable & cost-effective imaging modalities

One of the most promising future opportunities in oculomics is the enhanced accessibility of ocular imaging, driven by the advancements in smartphone-based fundus imaging and the development of semi-automatic, fully automatic, and portable, cost-effective retinal imaging devices (Iqbal, 2021). The global rise of mobile health (mHealth) industry has facilitated the evolution of home monitoring using mobile or tablet devices (Dicianno et al., 2015; Källander et al., 2013; Steinhubl et al., 2015). Recently, the emergence of ophthalmic home-used devices, such as visual acuity test app, visual field exam and intraocular pressure home-used devices, smartphone-based autorefractor has recently attracted a lot of attention (Amirsolaimani et al., 2017; Anderson et al., 2017; Ciuffreda and Rosenfield, 2015; Gaiser et al., 2013; Ittoop et al., 2016; Kaiser et al., 2013; Loewenstein et al., 2003; Schmid et al., 2019; Wisse et al., 2019). Research is also underway on options for at home self-administered OCT imaging (Ho et al., 2021; Maloca et al., 2018). These innovations will significantly broaden access to retinal assessments. For example, in underserved and resource-limited areas, healthcare workers equipped with smartphone-based fundus cameras can screen for DR, glaucoma, and other conditions (Dolar-Szczasny et al., 2023). Additionally, they enable non-ophthalmic healthcare providers to conduct retinal assessments. By integrating these devices into routine health check-ups, general practitioners can screen for retinal biomarkers indicative of systemic diseases such as diabetes, hypertension, and CVD, enabling timely referrals to specialists. In summary, as retinal imaging becomes more accessible, a broader audience, including non-ophthalmologists, can conduct retinal evaluations.

4.2. Advancement and integration of data ("Big data")

4.2.1. Combining clinical data & metadata

By integrating tabular clinical data and metadata, including multimodal images and structured clinical information from various sources and ethnic groups, oculomics can provide a more comprehensive and precise evaluation of systemic health (Li et al., 2023a; Miao et al., 2024).

With the advancement of omic modalities and open-access resources, such as genomics, proteomics, and metabolomics, developing a single-domain assay to identify individuals at high risk of future events has become feasible for multi-disease and mortality prevention(Meng et al., 2024; Oh et al., 2023; You et al., 2023). Most studies currently focus on a single omic modality, and are unable to conduct quantitative comparisons between different omic domains within the same study cohort, primarily due to limitations in data, with insufficient emphasis on ocular imaging. A few studies have, however, successfully integrated two or more omic modalities. For example, genetically predicted multi-omic traits are facilitating the large-scale generation and application of multi-omics data for broader community use (Xu et al., 2023). Additionally, the metabolic fingerprints of retinal layers have shown promise in improving predictability and clinical utility for stratifying future diseases such as T2DM (Yang et al., 2023, 2025b). Therefore, the future of oculomics is inherently multidimensional, offering opportunities to integrate diverse sources of data, including genomics, proteomics, metabolomics, and even single-cell omics. It is also worth considering the potential of opportunistic screening, where a single omic modality, such as retinal imaging, may be available in resource-constrained settings without traditional blood biomarkers, still offering valuable opportunities for disease screening and prevention.

DL-based multi-omics data integration methods have the potential to elucidate mechanisms of ocular development, discover eye disease biomarkers and identify pathogenic targets. Recently, proteomics of ocular liquid biopsies has been integrated with single-cell transcriptomics to trace the cellular origin of proteins detected in the aqueous humor (Wolf et al., 2023). Additionally, oculomics has uncovered insights into retinal degeneration in PD and identified the cells driving DR as they switch with disease stages, which transforms molecular diagnostics and prognostics while uncovering new cellular disease and aging mechanisms (Wolf et al., 2023). The development of data processing and sharing systems will further empower data-driven AI technologies, facilitating a holistic approach to healthcare and research (Liang et al., 2017). Of note, the integration of multimodal data is also accompanied with technical complexity, necessitating more advanced technology solutions (Johnson et al., 2021).

4.2.2. Multimodal machine learning

As the field advances, algorithms will increasingly combine data from different modalities and disciplines (Li et al., 2021a). Multi-modal ML has the flexibility to evaluate various combinations of imaging modalities and determine the AI algorithm with the best diagnostic or predictive power (Shao et al., 2020). In addition to enhancing screening, diagnosis, and prediction efficiency, the use of multi-modal inputs is crucial for demonstrating the advantages of oculomics (Gaw et al., 2018). For instance, predicting neurological diseases should involve evaluating corresponding changes in brain electroencephalography (EEG), CT, or MRI, and comparing their performance with oculomics. While the development, plasticity, and function of the eyes and parallel visual pathways share similarities with the brain (Olavarria et al., 2022), the utility of oculomics should be reported accurately, robustly, and convincingly, without exaggeration, and should be compared with different modalities.

While multi-modal inputs may help improve the diagnostic and predictive power of AI systems and move closer to simulating the decision-making process of a clinician, their real-world deployment can be challenging. For example, acquisition of a complete set of multi-modal data from real-world clinical practice can be limited (Kelly et al., 2019). Therefore, a balance needs to be achieved between the optimal performance of a multi-model algorithm and the feasibility of acquiring a set of multi-modal data in real-world practice for eligible patients.

4.3. Embracing multidisciplinary partnerships

The full potential of oculomics can only be realized through multidisciplinary collaborative efforts beyond ophthalmology. For example, oculomics is poised to leverage AI for developing innovative tools to address various diseases. For example, for brain disorders, advances in ML now enable the interpretation of human emotional and cognitive states (Elyoseph et al., 2024). This capability holds promise for individuals with brain disorders by facilitating oculomics-based AI applications in neurological healthcare. These applications could enhance patient self-monitoring of symptoms and enable real-time interventions to improve social and psychological functions (Chong et al., 2023). This example highlights the importance of multidisciplinary collaboration in achieving the ultimate goal of oculomics.

Engaging experts from various disciplines, including medicine, biology, digital techniques, computer science, mathematics, and imaging engineering, brings diverse perspectives, technical know-how, and innovative approaches (Zhou et al., 2021). For instance, clinicians and researchers can collaboratively formulate clinical-relevant oculomics

questions and develop innovative solutions. Specialists in digital techniques, computer science, and AI, for example, are well-equipped to tackle complex data within oculomics. Their expertise can streamline the integration of diverse data sources, enhance data processing, improve model accuracy, and facilitate the implementation of the technology. Collaborative efforts from imaging engineering and computer engineering experts can lead to the development of more sophisticated and user-friendly imaging devices, enhancing the quality and accessibility of oculomics data. Furthermore, the involvement of end-user experience research and market access strategies, will further help researchers to understand and translate the technology into real-world implementation.

However, endless integration and complexity are not oculomics research goals. The highly specialized technical expertise necessary to develop AI models is currently limited. Even transfer learning, which leverages existing algorithms, demands ML experience to achieve satisfactory results in clinical tasks. This constraint currently restricts the application of DL to a small but expanding community of computer scientists and engineers (Faes et al., 2019). Multidisciplinary teams can develop user-friendly tools, standardized protocols, and data-sharing platforms that accelerate the translation of oculomics research into clinical practice.

4.4. Need for supporting novel technologies: 6G wireless networks, Internet of Things (IoT), and digital security

Digital innovations including the further development of 5th and 6th generation wireless networks (5G and 6G), the Internet of Things (IoT), LLMs, and digital security capabilities such as blockchain, have created an ecosystem for new opportunities in healthcare and beyond (Ting et al., 2020).

5G wireless communications have the potential to meet the challenges of serving large-scale complex network connections, enabling fast data transmission (Pons et al., 2023). Despite its potential, 5G may be subject to current high expenses, implementation challenges, and potential limitations in security and reliability. The anticipated introduction of 6G in the next decade (Samsung, 2020) may address the limited computational power, security and privacy challenges associated with data collection and sharing, which could be a potential solution for oculomics application in a wider population.

Over the last decade, with the number of mobile devices exceeding the global population figure (Simkó and Mattsson, 2019), device interconnectivity has markedly increased. This has led to the growth of the Internet of Things, a network of physical objects embedded with sensors and the ability to transmit and process data, facilitating communications with other machines or humans, frequently in an automated fashion (Brous et al., 2020; Kumar et al., 2019). This interconnected ecosystem has the potential for transforming healthcare delivery and accelerating the integration of oculomics into everyday clinical practice.

4.5. Need for data record linkage

DL models in oculomics rely on acquiring large and diverse training datasets, often sourced from prospective observational cohort studies or retrospective real-world data. In the former, the data may be available to researchers either through open access (e.g., MESSIDOR) or upon application (e.g., UK Biobank). As for the latter, using retrospective real-world data can be quite challenging due to potential mismatches between the original data capture and specific requirements of oculomics research (e.g., systemic health outcomes). Additionally, ophthalmic healthcare is relatively standalone and may not routinely collect systemic health information. To circumvent these challenges and scale of data collection for DL in oculomics, researchers are turning to link routinely collected healthcare data (i.e., data record linkage). This approach emerges as a possible solution for mining existing healthcare data to uncover valuable insights (Bohensky et al., 2010; Padmanabhan et al., 2019).

4.5.1. AlzEye data linkage

A pioneering example of data record linkage in oculomics is the AlzEye study led by Pearse and Siegfried (Wagner et al., 2022). AlzEye is a longitudinal dataset linking retinal photographs and OCT scans from routinely collected National Health Service (NHS) data with systemic disease data from hospital admissions using a privacy-by-design third--party linkage approach (Zhou et al., 2023b). The study links more than 2 million retinal photos and scans from over 250,000 individuals aged 40 years or older to the NHS database between 1 January 2008 and 1 April 2018. To date, approximately 10,000 of those patients have been documented to have had a stroke, approximately 12,000 had a heart attack, and approximately 13,000 developed dementia.

4.5.2. Australian data linkage

Another successful data linkage project of oculomics is the National Data Linkage Project led by He and Zhu from Centre for Eye Research Australia. This project includes retinal images from participants aged 18 years and older who have attended eye hospitals and optometry stores over the past 20 years linked with data from the Australian Institute of Health and Welfare (AIHW) (Ali et al., 2024). The project has facilitated the integration of extensive ocular data with broader health records, including medical and pharmaceutical prescription data, hospital admission data, and the national death registry, enhancing the potential for comprehensive oculomics research.

4.6. Proposed future research directions

4.6.1. Research into prediction of other systemic conditions

Oculomics has advanced the understanding of the links between ocular health and systemic conditions. Nevertheless, several research areas other than the cardiovascular and neurological systems remain in their infancy.

Papilledema, a pathological ocular change, is a significant indicator frequently observed in intracranial diseases and holds clinical importance. It is closely associated with neurosurgical conditions. The diagnostic work-up for papilledema involves neuroimaging and lumbar puncture, AI model from fundus photos achieved >90% sensitivity at detecting papilledema, superior to human experts (Chang et al., 2024; Milea et al., 2020).

Additionally, thyroid disease is associated with various external eye findings, including conjunctival hyperemia, chemosis, lid retraction, and proptosis. Emerging evidence suggests that AI can be valuable in diagnosing and assessing thyroid eye disease before treatment. AI models have demonstrated high diagnostic accuracy using diagnostic imaging (CT or MRI orbits) and external eye photographs (Bao et al., 2022; Chng et al., 2023; Jiang et al., 2024; Zhang et al., 2024).

Diseases from other systems, such as hepatobiliary diseases, autoimmune diseases and even psychiatric diseases also demonstrated established ocular manifestations (Elder and Court, 2017; Glover et al., 2021; Vitiello et al., 2020). However, research on these topics within the scope of oculomics remains scarce (Xiao et al., 2021).

4.6.2. Research into novel modalities

Incorporating additional imaging modalities, such as external eye photography, could broaden the scope of oculomics (Ringel et al., 2021). External eye imaging is particularly relevant in conditions like thyroid eye disease, where symptoms such as lid retraction, proptosis, and periorbital edema, are externally visible (Karlin et al., 2023). In addition, several ocular manifestations, such as xanthelasma formation associated with elevated cholesterol levels and atherosclerosis (Bergman, 1994), and floppy eyelids associated with obstructive sleep apnea (Cheong et al., 2023), can be observed externally. Google's recent research on external eye images demonstrates the potential of this imaging modality (Babenko et al., 2022, 2023). Google's algorithms

demonstrated that external eye images can readily assess DR, cardiovascular risk factors and biomarkers for multiple organs. More importantly, external eye imaging is easier to capture with a smartphone. This opens the opportunities of using easily accessible devices rather than sophisticated ophthalmic device for oculomics.

Previous research in the oculomics area often overlooks the potential of videos. For disease auto-screening in daily life, recent studies have utilized video and photo features to train neural networks with long short-term memory, achieving results comparable to traditional evaluations (Smagulova and James, 2020; Sun et al., 2018). Eye tracking-based assessments have been well-developed, using video stimuli on monitors to evaluate cognitive impairments such as autism spectrum disorder (ASD) and AD (Eraslan Boz et al., 2024; Xiao et al., 2022). Parameters such as saccades, pupillary response, and blinking rate, detectable through videos, can provide detailed information on human affective states (Li et al., 2021b). Other portable imaging devices, such as handheld OCT, retinal fundus cameras, and portable slit-lamps, can be used in various settings, from remote areas to primary care clinics (DeBuc, 2016; Maamari et al., 2014). These devices facilitate non-invasive monitoring of ocular biomarkers, enabling early detection of both ocular and systemic conditions, particularly in underserved populations. Furthermore, portable imaging devices generate real-time data that can be integrated with AI and machine learning algorithms, enhancing diagnostic accuracy and improving clinical outcomes.

To further explore the clinical significance and everyday applications of oculomics, advancements in other technologies, such as wearable sensors and federated learning for AI model training, will provide valuable support. Innovative wearable technologies, which include on-body and implantable sensors, have greatly improved the quality of life (Jayathilaka et al., 2019; Mukhopadhyay et al., 2022). Notable progress has been made in areas like glucose monitoring, physiological signals, and body motions (Johansson et al., 2018; Sunstrum et al., 2025). The integration of health data with oculomics will further elucidate how oculomics reflects systemic health, enhancing its potential for early detection of diseases that pose significant risks.

Federated learning allows AI models to be trained on decentralized data, meaning sensitive patient information, such as genetic, clinical, and ocular data, stays within local healthcare institutions (Truhn et al., 2024; Zhou and Li, 2023). This is especially important in oculomics, as it ensures data privacy and security while overcoming challenges in multi-center collaborations. By integrating federated learning with oculomics, AI models can learn from diverse global populations, reducing bias and improving representativeness. This approach combines a wide range of ocular datasets (e.g., CFP, OCT, OCTA, and sequencing data of intraocular fluid and tears) with systemic health data (e.g., biomarkers, metabolic data, and genetic information), enhancing the robustness and generalizability of AI models.

4.6.3. Research into future AI applications

Future AI applications in applications could shift from mere diagnosis to the prediction of future risks of systemic conditions, the progression of systemic conditions, and the guidance of treatment (Davenport and Kalakota, 2019). This approach could enhance early prevention and individualized intervention. For instance, AI may be able to predict the response to treatments such as anti-hypertensive medications for hypertension, refining the patient management strategies, and ultimately resulting in better patient outcomes (Hae et al., 2023). Therefore, further research is required to explore the full potential of oculomics application for improved population health.

4.6.4. Research into future AI models – foundational models, large language models, etc

Since the debut of ChatGPT (OpenAI, San Francisco, CA, USA) in November 2022, LLMs have been recognized for their potential to significantly improve the efficiency and efficacy of clinical practice, medical education, and research in ophthalmology (Betzler et al., 2023). Recently, oculomics-based LLMs have emerged as valuable tools for remotely triaging patients by providing information and addressing inquiries about a wide range of ocular symptoms (e.g., blurred vision, ocular pain, redness) and specific eye conditions (e.g., glaucoma, cataract, DR) (Antaki et al., 2023; Pushpanathan et al., 2023). In practical terms, LLMs can integrate with mobile applications via an Application Programming Interface (API) or connect directly to eye hospital websites, benefiting both patients seeking eye care and healthcare providers (Huang et al., 2024).

A pressing concern with the integration of LLMs into clinical settings revolves around cybersecurity and data privacy, especially when the software necessitates training on EMR data or is directly embedded into a live EMR system (Hasal et al., 2021). Not only LLMs but all AI research and open models involve critical attacks and security issues at the data storage and process levels. Digital security capabilities, such as blockchain, are essential to address these concerns. Blockchain is a prevailing technology that produces a data structure with inherent security qualities based on cryptography, decentralization, and consensus principles (Ng et al., 2021). Although research on blockchain in ophthalmology is currently limited, future applications could revolutionize international data collection from various private and government institutes. This advancement could lead to improved patient care, the secure management of epidemiological data, ocular images, and patients' multiomics information (Gurnani et al., 2023).

4.6.5. Research into evidence, validation, mechanistic understanding, policy

To maximize the impact of oculomics research on healthcare, further development is required in key areas, including but not limited to evidence-based guidelines, prospective validation and real-world implementation, and investigation of biological mechanisms between eye and systemic conditions.

The development and implementation of oculomics requires evidence-based guidelines. These should encompass validation against a reference standard, data acquisition and transfer device standards, data analysis protocols, personnel qualifications, quality assurance measures, data protection policies, and clinical integration procedures. Standardized protocols and best practices are essential for consistent and effective application across clinical settings (Ricciardi W. and Cascini F., 2020). Collaboration between ophthalmologists, data scientists, healthcare policymakers, and other stakeholders is crucial in developing these guidelines to ensure standardized data collection, analysis, and clinical integration.

To date, there has been limited research directly comparing state-of-the-art oculomic approaches with proteomic or metabolomic-based methods in the screening, grading, monitoring, and prediction of systemic diseases. Oculomics, offering a non-invasive, simple, and rapid diagnostic strategy, holds significant potential in advancing personalized medicine and improving disease prediction. While existing studies have primarily concentrated on the application of individual omic modalities, the integration of oculomics with other omics, and its comparative analysis with proteomics and metabolomics, remains relatively underexplored. This gap in research presents an opportunity to investigate how combining different omic data, such as genomics, transcriptomics, proteomics, and metabolomics, could offer a more comprehensive understanding of complex diseases, especially in the context of oculomics. Furthermore, there is a need for qualitative studies on the perception and acceptance of oculomics compared to traditional and emerging techniques. Understanding stakeholders' views—ranging from clinicians to patients—could facilitate the adoption of oculomics in clinical settings and help identify barriers to its integration.

The increasing availability of large-scale multi-omic datasets and the rapid advancements in oculomic technologies are expected to drive more comparative studies in the near future (Ali et al., 2024; Wagner et al., 2022). As these technologies evolve, they will enable more refined analyses and offer insights into how oculomics can complement or even

outperform other omic approaches in predicting and diagnosing complex diseases.

Additionally, prospective validation studies are crucial for establishing the reliability and clinical utility of oculomics, which is essential to gain widespread acceptance and trust from healthcare practitioners. Usually, the AI algorithms were tested on images collected through clinical trials with strict inclusion and exclusion criteria (Burlina et al., 2017). The real-world validation of AI algorithms still needs to be tested with large-scale, diverse clinical data beyond controlled trial environments. A flexible yet rigorous and transparent validation framework is needed to navigate this constant evolution field, focusing on reproducibility, reliability, clinical value, usability, and cost-effectiveness in real-world settings (Mathews et al., 2019; Wang et al., 2024b).

Research efforts should also focus on identifying the enablers and barriers to oculomics implementation. Understanding what facilitates or hinders its adoption can inform strategies for overcoming challenges. In addition, further research is needed to delve into the biological mechanisms underlying the connections between ocular and systemic health. Leveraging the state-of-art biotechniques such as genomics, proteomics and metabolomics, future research is required to unravel the intricate biological pathways involved in oculomics. Investigating the pathophysiological processes that link ocular changes to systemic diseases can enhance our understanding of both eye and systemic conditions, and inform targeted interventions.

5. Conclusion

Research on oculomics has significantly advanced over time. Technological innovations, particularly the development of advanced retinal imaging techniques, and AI analysis, have revolutionized our capacity to assess ocular health and its potential links to various systemic conditions. Oculomics holds immense promise for the future of healthcare, offering a novel non-invasive tool for replacing invasive or expensive tests for assessing vital organ health, and enabling early diagnosis and intervention of major systemic diseases. However, substantial opportunities for further exploration remain. Advancements in retinal imaging technologies, multimodal data integration, and multidisciplinary collaborations are crucial for unlocking the full potential of oculomics. Data infrastructure advancements such as 6G networks and data record linkage are also essential steps to broaden research and deployment opportunities. Future research should focus on expanding the scope of disease prediction, exploring additional imaging modalities, and evidence-based validation and mechanistic understanding. The comprehensive approach of oculomics promises to unlock the true potential of the eye as a powerful tool for early disease detection, personalized medicine, and ultimately, improved health outcomes.

CRediT authorship contribution statement

Zhuoting Zhu: Writing – review & editing, Supervision, Project administration, Funding acquisition, Formal analysis, Conceptualization. **Yueye Wang:** Writing – original draft, Visualization, Methodology, Investigation. **Ziyi Qi:** Writing – original draft, Visualization, Methodology, Investigation. **Wenyi Hu:** Writing – original draft, Visualization, Methodology, Investigation. **Xiayin Zhang:** Writing – original draft, Visualization, Investigation. **Siegfried K. Wagner:** Writing – review & editing. **Yujie Wang:** Writing – review & editing. **An Ran Ran:** Writing – review & editing. **Joshua Ong:** Writing – review & editing. **Ethan Waisberg:** Investigation. **Mouayad Masalkhi:** Investigation. **Alex Suh:** Investigation. **Yih Chung Tham:** Writing – review & editing. **Carol Y. Cheung:** Writing – review & editing. **Xiaohong Yang:** Investigation. **Honghua Yu:** Investigation. **Zongyuan Ge:** Writing – review & editing. **Wei Wang:** Writing – review & editing. **Bin Sheng:** Writing – review & editing. **Yun Liu:** Writing – review & editing. **Andrew G. Lee:** Writing – review & editing. **Alastair K. Denniston:** Writing – review & editing. **Peter van Wijngaarden:** Writing – review & editing. **Pearse A. Keane:** Supervision. **Ching-Yu Cheng:** Supervision. **Mingguang He:** Supervision. **Tien Yin Wong:** Writing – review & editing, Supervision, Resources, Project administration, Conceptualization.

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Conflict of interest statement

Dr. Y Liu is an employee of Google and owns Alphabet stock. Dr. AG Lee works as a consultant for NASA but the views expressed here are his own and do not necessarily represent those of NASA or the United States government; he has the following disclosures which are not relevant to the contents of this manuscript: Amgen (speaker), Alexion (speaker), Viridian, Catalys, Ethyreal, Astrazeneca, Bristol Myers Squibb, Stoke. Dr. PA Keane has acted as a consultant for Retina Consultants of America, Topcon, Roche, Boehringer-Ingleheim, and Bitfount and is an equity owner in Big Picture Medical; he has received speaker fees from Zeiss, Novartis, Gyroscope, Boehringer-Ingleheim, Apellis, Roche, Abbvie, Topcon, and Hakim Group; he has received travel support from Bayer, Topcon, and Roche, he has attended advisory boards for Topcon, Bayer, Boehringer-Ingleheim, RetinAI, and Novartis. Dr. CY Cheng is a consultant for Medi-Whale. Dr. TY Wong is a consultant for Bayer, Boehringer-Ingelheim, Genentech, Opthea Limited, Roche; he is an inventor, holds patents and is a co-founder of start-up companies EyRiS and Visre, which have interests in, and develop digital solutions for eye diseases.

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Data availability

No data was used for the research described in the article.

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