The Journal of Precision Medicine: Health and Disease 4 (2025) 100023

Contents lists available at ScienceDirect

The Journal of Precision Medicine: Health and Disease

journal homepage: www.sciencedirect.com/journal/the-journal-of-precision-medicine-health-and-disease

Review Article

The eye as a window to systemic health: A survey of retinal imaging from classical techniques to oculomics

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ARTICLE INFO

Index Terms:
Retinal imaging
Retinal vasculature
Oculomics
Systemic diseases
Artificial intelligence
Deep learning
Retinal biomarkers
Phenotypes
Genotypes

ABSTRACT

The unique vascularized anatomy of the human eye, encased in the retina, provides an opportunity to act as a window for human health. The retinal structure assists in assessing the early detection, monitoring of disease progression and intervention for both ocular and non-ocular diseases. The advancement in imaging technology leveraging Artificial Intelligence has seized this opportunity to bridge the gap between the eye and human health. This approach facilitates the unveiling of systemic health insights from the ocular system and the identification of non-invasive surrogate markers for timely intervention and detection. The new frontiers of oculomics in ophthalmology cover both ocular and systemic diseases, and are getting more attention to explore them. In this survey paper, we explore the evolution of retinal imaging techniques, the dire need for the integration of AI-driven analysis, and the shift of retinal imaging from classical techniques to oculomics. We also discuss some hurdles that may be faced in the progression of oculomics, highlighting the research gaps and future directions.

1. Introduction

The retina, the crucial light-sensitive tissue at the back of the eye, is a treasure trove of insights for ophthalmologists, clinicians, and technicians. It plays a pivotal role in the early prediction and intervention of both ocular and non-ocular disorders. Retinal imaging, a key interpretation, encompasses a variety of techniques designed to visualise and analyse the retina Zhou et al. (2022). Colour Fundus photography (CFP) captures detailed, subtle changes in the ocular system, while optical coherence tomography (OCT) provides a cross-sectional view, and OCT angiography visualizes blood flow. These modalities, serving as vital diagnostic tools, enable healthcare professionals to examine the intricate structure of the retina, including the macula, optic disc, and retinal vasculature. This non-invasive assessment allows for the early detection and monitoring of ocular diseases like diabetic retinopathy, glaucoma, macular degeneration, and other related diseases that can lead to significant vision impairments if left unattended Ringel et al. (2021).

Beyond ocular health, retinal imaging also provides insight into detecting systemic diseases. The retina's unique accessibility and the visibility of its microvasculature make it a valuable indicator of overall health. For example, changes observed in the blood vessels and layers of the retina can trigger cardiovascular Zekavat et al. (2022), neurodegenerative Bsteh et al. (2024), and cerebrovascular diseases Cheung et al. (2013). That is why the eye serves as a window of overall health in the association of ocular and systemic health Cheung et al. (2012). High-resolution imaging can further reveal fine-grained features and act as a facilitator for timely intervention and personalised care. This contributes to improved patient outcomes and a better understanding of the interrelation between bodily systems Honavar (2022).

Oculomics studies ocular biomarkers, using advanced imaging technologies to probe the eye in relation to other organ systems Wagner et al. (2020) through shared physiological functions, embryological origins, and anatomical structures Cheung et al. (2012). It aims to establish correlations between these markers and systemic diseases Honavar (2022). Growing evidence indicates that oculomics is significant in identifying clinical manifestations in ocular markers, such as retinal vessel patterns and neural layer thickness, which can reveal the presence of systemic diseases such as diabetes, cardiovascular diseases (CVDs), neurological issues, and stress-related disorders Hanssen et al. (2022). This field is driven by three significant advances, including the widespread availability of high-resolution ophthalmic imaging, the emergence of big data, and the development of automated artificial

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https://doi.org/10.1016/j.premed.2025.100023
Received 8 July 2025; Received in revised form 11 September 2025; Accepted 23 September 2025
Available online 26 September 2025

intelligence (AI) software. Together, it has the potential to revolutionise disease management by providing a comprehensive and accessible approach to monitoring and maintaining human health Zhu et al. (2025).

AI is at its peak in the era of big data and parallel processing. The AI model is based on recorded data, and disciplines with data can easily participate in it. In the current epoch, it is hard to conclude that there may be fields in academia and industry that can thrive without data. Therefore, no discipline will be empty-handed when discussing data. AI models are now prevalent and deployed in every aspect of life Lyu et al. (2021). Both intrinsic and extrinsic deployments have positively impacted our society, especially in socioeconomic and socio-health aspects. Renowned computer scientist Dr. Knuth revealed that biology has at least 500 years of exciting problems to explore Bansal et al. (2023, pp. 211–239). This perspective encourages the computing and biomedical research communities to address challenges in life science collaboratively.

AI is transforming retinal imaging and ocular studies by automating and enhancing the analysis of complex visual data. AI algorithms, especially deep learning (DL), excel in identifying subtle patterns and abnormalities within retinal images that human observers might overlook Hassan et al. (2024). This automation significantly speeds up the screening process for ocular and non-ocular diseases, allowing for earlier detection and intervention. In addition, AI can enable the development of predictive models by evaluating the vast data set, encompassing the assessment of the individual patient's risk factors and anticipating disease progression, paving the way for personalised medicine in ophthalmology Schmidt- Erfurth et al. (2018), Ting et al. (2019).

Eye diagnostic research is shifting from its classical origin to the current AI software tools. Now, it's beyond the classical methods, such as preprocessing, model training, and limited clinically relevant output. These limited circumstances hinder the quantification of retinal structures at the minute and micro levels to address the objective measurements, which are crucial for the efficacy of effective treatments and the monitoring of disease progression in the growing field of oculomics. Likewise, for meaningful research, high-quality and large health datasets comprising rich annotated data are crucial, which advances the role of statistical, computational, and AI-driven techniques Brown et al. (2024), Zhou et al. (2023). Furthermore, this framework can be further nourished by integrating retinal imaging with clinical information, namely electronic health records and genetic data, including diverse demographic and ethnic data. However, translating this vision into practice remains a considerable challenge. Existing datasets often lack the necessary integration across epidemiological, clinical, and imaging domains, limiting the development of a unified infrastructure supporting oculomics research and clinical application De Fauw et al. (2018), Poplin et al. (2018), Wagner et al. (2020).

Despite the increasing availability of large-scale datasets, significant limitations impede their practical use in oculomics. Even though there are several Retinal imaging repositories, including those of Moorfields Eye Hospital De Fauw et al. (2017), UK Biobank Collins (2012), and the 10k Cohort Shilo et al. (2021), access to these resources is often restricted to trusted research environments due to anonymisation protocols. Moreover, much of the publicly available data lacks critical demographic and ethnic metadata, with estimates suggesting that approximately 74 % of these datasets do not include such information. As a result, even healthcare providers with extensive retinal image collections, ranging from ten thousand to ten million scans, face challenges in generating truly representative Khan, Liu, et al. (2021), integrative datasets.

More broadly, a substantial gap exists in integrating retinal imaging data with molecular, clinical, and diverse datasets. Such integration is crucial for capturing the multi-dimensional nature of complex diseases Agarwal et al. (2024). However, epidemiological models, such as cohort, longitudinal and population-based studies, have successfully mapped disease trajectories in other domains Pe'rez-Guerrero et al. (2024); their application to oculomics remains onerous Wagner et al. (2020). The combined burden of global communicable and non-communicable diseases has further highlighted the need for such inclusive, multi-modal datasets that account for diversity across ethnicity, age, and geography Vos et al. (2020).

These shortcomings highlight the urgent need for a next-generation framework to unify fragmented data sources and enable deeper clinical insights. This includes robust epidemiological frameworks, large-scale imaging biobanks, and AI- enabled platforms harmonising disparate data types. Unified and multidimensional data frameworks, including molecular signatures, imaging biomarkers, and longitudinal clinical pro-files, have the potential to provide a more holistic understanding of disease onset and progression. These frameworks, already successful in fields such as oncology and cardiology Wang, Liu, et al. (2024), are timely and necessary for their adoption in oculomics Hanssen et al. (2022).

As a result of these converging needs and opportunities, oculomics has emerged as a leading frontier in multimodal healthcare research, with biomarkers to infer both ocular and systemic health Pearson et al. (2022). The retina is uniquely positioned for this purpose due to its rich vascular and neural architecture, which reflects broader physiological states throughout the body. As a transparent and non-invasive window into the vascular and neurobiological environment, retinal imaging allows early detection of systemic conditions. This makes the retina an ideal candidate for multimodal investigation in both research and clinical settings Ran et al. (2024).

Recent developments in automated image analysis tools have further enhanced retinal imaging capabilities. The AutoMorph software developed by Zhou et al. (2022) enables a precise, large-scale extraction of morphological features from the retinal vasculature in a fully automated pipeline. This advancement significantly supports high-throughput oculomics research by offering standardised and scalable morphological analysis of retinal structures.

In recent years, oculomics has emerged as a highly interdisciplinary domain, yet there remains a lack of cohesive literature synthesising its technological, clinical, and methodological advancements. Most existing reviews focus either on specific imaging techniques or isolated systemic diseases, without bridging the broader implications of AI-powered retinal analysis for integrated healthcare Akpinar et al. (2024), Jin and Ye (2022), Lee et al. (2024), Li, Yin, et al. (2024), Zhu et al. (2025). Given the rapid development of retinal image processing tools, dataset accessibility, and AI-driven diagnostic models, a comprehensive review is now both necessary and timely. This survey aims to fill that gap by contextualising classical foundations, highlighting cutting-edge innovations like AutoMorph, and proposing a unified framework for future research. This survey paper presents a structured synthesis of advancements in retinal imaging, AI integration, and multi-modal health data. It highlights key breakthroughs, identifies current gaps in clinical translation, and offers a roadmap for future interdisciplinary collaborations in oculomics. Through this, we aim to support the development of robust, explainable, and scalable tools capable of revolution-ising healthcare delivery across disciplines.

2. Ocular anatomy and physiology & HistoricalPerspective on eye disease research

2.1. Ocular anatomy and physiology

The eye is a living optical system, and its role as a window into systemic health is grounded in its unique anatomy and physiology, where refractive, neuronal, and vascular components interact to enable vision and reflect disease processes. Each element of this system, illustrated in Fig. 1, is not only vital for sight, but is also sensitive to disturbance, which means that localised abnormalities often signal both ocular pathology and broader systemic disease.

At the outer surface, the sclera, iris, and pupil regulate the entry of

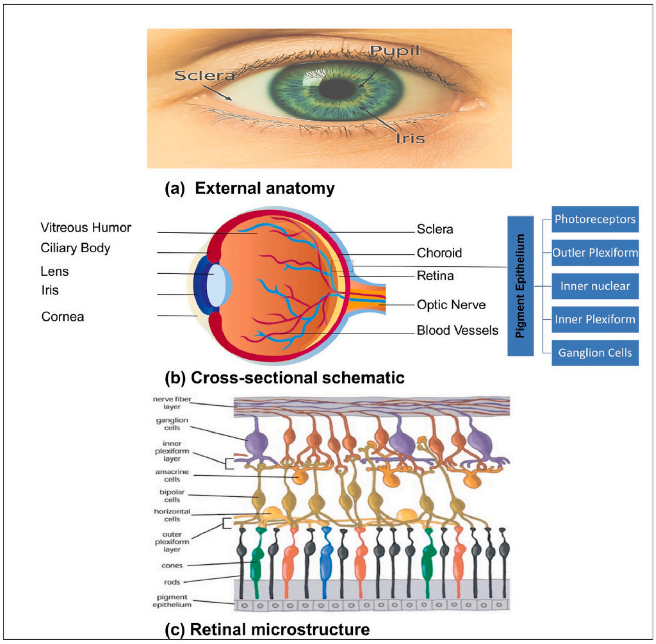


Fig. 1. Structural organization of the human eye at multiple anatomical levels. (a) External anatomy of the eye showing the pupil (central opening), iris (colored ring), and sclera (white outer coat that maintains ocular shape and protection). (b) Cross-sectional schematic illustrating the major internal structures including the cornea, iris, lens, vitreous humor, sclera, choroid, retina, blood vessels, and optic nerve. This orientation highlights the key optical and supportive components of the eye. (c) Retinal microstructure depicting the layered neuronal architecture, including photoreceptors (rods and cones), bipolar, horizontal, and amacrine cells, ganglion cells, and the pigment epithelium.

light and protect the delicate internal structures, as portrayed in Fig. 1a. The cornea, while anatomically part of the external coat of the eye, is transparent and therefore not readily visible in a superficial view. In cross-sectional orientation (Fig. 1b), the cornea is seen as a curved dome that provides nearly three-quarters of the eye's total refractive power. Its highly ordered collagen fibrils maintain curvature and transparency Abràmoff et al. (2010) , but when disrupted, as in keratoconus or corneal scarring, irregular astigmatism and impaired vision result Kreps et al. (2021). Surrounding it, the sclera forms the opaque, fibrous shell that preserves the globe's shape and stability. Excessive thinning and stretching of the sclera underlie high myopia, now a growing global public health concern Jonas et al. (2019). The iris adjusts the pupil aperture to balance light entry: it widens in low-light environments and constricts in bright conditions, safeguarding the retina from excess light exposure.

Behind the iris lies the crystalline lens, a biconvex structure suspended by zonular fibers. The lens fine-tunes focus through accommodation, altering its curvature to shift between near and distant vision. With aging, the lens gradually hardens and its proteins aggregate, producing cataract, the world's leading cause of reversible blindness Wishart et al. (2021). Light then traverses the vitreous humor, a transparent gel that fills the posterior chamber. This medium stabilizes the ocular globe and transmits light without distortion, but it is not static. Over time, the vitreous liquefies and contracts, often detaching from the retina. Such posterior vitreous detachment can predispose to retinal tears and even retinal detachment, both of which pose a serious risk to sight.

The retina lies at the back of the eye and functions as the sensory core of vision. It is a multilayered neural tissue where photons are converted into electrical signals. As shown in Fig. 1c, the retinal microstructure consists of photoreceptors (rods and cones), bipolar, horizontal, and amacrine cells, ganglion cells, and the retinal pigment epithelium. Specialised photoreceptors, rods for dim-light and peripheral vision, and cones for colour perception and fine detail, initiate this process. Their output is integrated by horizontal, bipolar, and amacrine cells, which refine contrast and spatial information. Finally, ganglion cells collect these signals, and their axons converge to form the optic nerve, transmitting information to the brain's visual cortex. Within the retina, the macula supports high-acuity central vision, while the peripheral retina detects movement and supports night vision Cholkar et al. (2013), Liang et al. (2023). Cross-sectional analyses, such as those provided by OCT, reveal this layered architecture in vivo and demonstrate how dysfunction at any level, whether photoreceptor loss in age-related macular degeneration (AMD) or microvascular leakage in DR, directly alters visual capacity. Fig. 1b highlights these internal structures in cross-section, including the cornea, lens, vitreous humor, retina, choroid, and optic nerve.

The retina is sustained by an intricate network of supporting tissues and circulations. The retinal pigment epithelium (RPE) nourishes photoreceptors, regulates waste clearance, and recycles visual pigments. The choroid, a dense vascular layer, supplies approximately 65 % of retinal oxygen and nutrients, while the retinal vasculature provides the remaining 35 % Abràmoff et al. (2010). This dual circulation reflects the enormous metabolic demand for the retina. Because retinal vessels are optically accessible, their geometry, summarised by traits such as vessel caliber, fractal dimension, tortuosity, and vessel density, provides quantifiable endophenotypes. These vascular signatures have been linked not only to local conditions such as DR but also to systemic disease, including hypertension, cardiovascular disease, stroke, and even renal dysfunction Cheung et al. (2013), Ikram et al. (2013).

The optic nerve forms the final bridge between the eye and the brain. Its vulnerability is twofold: localised ocular pathologies, such as glaucoma, that progressively damage retinal ganglion cell axons, while systemic neurodegeneration also manifests here. The thinning of the retinal nerve fiber layer (RNFL) has been observed in both Alzheimer's and Parkinson's disease Snyder et al. (2021), suggesting that the eye can act as a biomarker of central nervous system health. This role, both in transmitting visual signals and in reflecting neurological status, cements its place in the investigation of systemic disease.

Collectively, the eye is not only an organ of sight, but also a mirror of health. Each component, from the cornea that bends light to the retina that transduces it into neural signals to the optic nerve that delivers these signals to the brain, offers unique diagnostic insight. Because these structures are accessible through modern imaging modalities, their disruption reveals both ocular disease and systemic pathology. This foundational understanding of anatomy and physiology has historically guided eye research and now underpins the transition to advanced imaging and oculomics, which will be explored in the following section on the historical development of ophthalmology.

2.2. *Historical perspective of eye diseases research: from ancient techniques to modern AI-driven oculomics*

The study of the eye and associated diseases dates back to ancient civilisations, where early contributions focused on anatomy, diseases, and basic treatments. Over the centuries, the field of ophthalmology has evolved significantly, driven by the pressing need to understand, diagnose, and treat eye diseases. Today, AI integration has revolutionized the field, enabling unprecedented advances in diagnostics, treatment, and research. This section traces the historical journey of eye disease research, from ancient techniques to the era of classical AI and modern deep learning, culminating in the emerging field of oculomics.

1) ***Pioneer surgical and observational techniques:*** The study of the eye dates to ancient civilisations, where early contributions focused on ocular anatomy, diseases, and basic treatments. Cataracts were among the first documented eye diseases, dating back to around 600

BCE. The Sushruta Samhita, an ancient Indian medical text, described a surgical technique called "couching", where the opaque lens was inserted into the vitreous humor to restore some vision Chan (2010). However, insertion often led to complications, for instance infection and blindness, underscoring the limitations of early surgical techniques. Greek scholars Hippocrates (460–375 BCE) and Galen (129–216 CE) founded anatomical descriptions of the choroid, lens, and optic nerve. Their work provided the foundation for understanding ocular anatomy, but their reliance on animal dissection led to inaccuracies Ghadiri (2024). Islamic scholars like Al-Zahrawi and Ibn al-Haytham improved surgical tools and advanced optical studies, connecting anatomy with light refraction. Ibn al-Haytham's Book of Optics emphasised the principles of vision and optics, enabling a framework for understanding refractive errors Reeves and Taylor (2004).

2) ***Early breakthrough in the optical imaging:*** The development of the ophthalmoscope by Hermann von Helmholtz in 1851 was a transformative milestone. This device enabled clinicians to visualise the retina and optic nerve directly, facilitating diagnosing of conditions such as retinal detachment and optic neuritis McMullen (1917). Although initial iterations of the ophthalmoscope required considerable skill to be effective, this limited its wider adoption in clinical practice. The early twentieth century saw significant progress in tackling prevalent eye diseases such as trachoma and cataracts. Trachoma, a bacterial infection caused by *Chlamydia trachomatis*, was a leading cause of blindness in low-income regions. Public health campaigns focusing on hygiene, antibiotic use, and surgical interventions significantly reduced its prevalence. Nevertheless, these efforts were limited to localised outbreaks and lacked global coordination Clare et al. (2024).
3) ***Technological and optical imaging advancement during the mid-20th Century:*** The invention of fundus photography in the 1920s enabled static documentation of the retina, providing a foundation for modern research of retinal disease. Although this innovation allowed for detailed visualization, early cameras suffered from low resolution and were not widely accessible. Cataract extraction methods improved with the introduction of intracapsular cataract extraction. Due to the absence of intraocular lenses, visual outcomes were less than ideal, requiring patients to wear thick corrective lenses after surgery.

The mid-20th century saw rapid advances in imaging and treatment technologies. In the 1960s, fluorescein angiography allowed for dynamic retinal and choroidal vasculature imaging. It became a critical tool for diagnosing retinal vein occlusion and diabetic macular edema. However, the invasive nature of dye injection posed risks to patients with allergies or comorbidities Weiss and Papakostas (2022). Laser treatments became the standard for managing proliferative DR (PDR) and retinal detachment. While effective, these treatments were limited to advanced stages of the disease and could not prevent disease onset. Tonometry was standardised as a reliable method for measuring intraocular pressure, enabling earlier detection of glaucoma. Tonometry alone cannot detect optic nerve damage, highlighting the need for additional diagnostic tools. Garcıa-Feijoo (n.d.), Moutray et al. (2018).

4) ***The emergence of digital era and AI in ophthalmology:*** The digital era introduced technologies that significantly enhanced the precision and accessibility of oph-thalmic diagnostics. Optical coherence tomography, invented in 1991, provided cross-sectional imaging of retinal layers with micrometer resolution. This technology revolutionized the management of macular degeneration, DR, and glaucoma, but early devices were expensive and required significant expertise Aumann et al. (2019). Early computational models automated tasks like vessel segmentation and lesion detection. While these methods were groundbreaking, they were limited by small datasets and reliance on handcrafted features. Digital fundus photography enabled large-scale diabetic retinopathy screening programs. These initiatives demonstrated the feasibility of integrating technology into public health, but faced challenges in reaching rural and underserved populations Abràmoff et al. (2010), Schmidt-Erfurth et al. (2018). The integration of AI into eye disease research began with classical machine learning algorithms, which laid the foundation for automated analysis of retinal images and clinical data.

Early models, such as Support Vector Machines (SVM), Random Forests, and k-Nearest Neighbors, were used for tasks like lesion detection, disease classification, and retinal vessel segmentation. These models relied on hand-crafted features extracted from CFP and OCT images, which limited their generalizability and scalability GeethaRamani and Balasubramanian (2018), Liu et al. (2011), Remeseiro et al. (2014), Veiga et al. (2018) For example, SVMs were employed to classify DR stages based on features, namely microaneurysms (MAs), haemorrhages (HMs), and exudates (EXs). These models faced challenges due to the varying image quality and complex retinal structures. Despite these limitations, classical Machine Learning (ML) algorithms demonstrated the potential of AI in automating ophthalmic diagnostics and reducing the burden on clinicians.

5) ***Early Deep learning models in eyes research:*** The advent of deep learning, particularly Convolutional Neural Networks (CNNs), marked a paradigm shift in the analysis of ophthalmic imaging. Unlike classical ML, CNNs automatically learn hierarchical features from raw images, eliminating the need for manual feature engineering. This capability made CNNs highly effective for tasks like DR detection, glaucoma diagnosis, and age-related macular degeneration classification. One of the earliest breakthroughs in deep learning for ophthalmology was the development of algorithms for the screening of diabetic retinopathy using fundus images. Studies demonstrated that CNNs could achieve a good diagnostic accuracy comparable to that of human experts Gulshan et al. (2016), Ting et al. (2017). For example, InceptionV3 and ResNet architectures were widely adopted for DR classification, achieving high sensitivity and specificity in detecting early-stage disease. Similarly, CNNs were applied to OCT scans for the automated detection of retinal pathologies such as macular edema, choroidal neovascularization, and retinal detachment. These models improved diagnostic accuracy and reduced the time required for image analysis, enabling faster decision-making in clinical settings.
6) ***The Rise of pre-trained AI models and multimodal data integration:*** CNNs revolutionized ophthalmic imaging, but their limitations in capturing long-range dependencies and spatial relationships led to the development of Vision Transformers (ViTs) Dosovitskiy et al. (2021). Inspired by the success of transformers in natural language processing, ViTs introduced self-attention mechanisms to image analysis, enabling better modelling of global context and spatial relationships within medical and optical imaging. ViTs have been applied to tasks like DR grading, age-related macular degeneration classification, and retinal vessel segmentation, outperforming traditional CNNs in many cases. For example, Swin Transformers and Multiple Instance Learning ViTs (MIL-ViTs) have been used to detect subtle retinal changes associated with systemic diseases such as diabetes and hyper-tension Yu et al. (2021).

In addition, integrating multimodal data, which combines imaging, text, and molecular data, or may of the same modal-ities, has opened new frontiers in oculomics. For instance, AI models can now analyse retinal images alongside electronic health records and genomic data to predict disease progression and treatment outcomes. This multimodal approach has been particularly useful in studying complex conditions such as diabetic retinopathy and AMD, where genetic factors play an important role in disease pathogenesis Li, Dong, et al. (2024), Zekavat et al. (2022).

The application of AI extends beyond imaging to the realm of genomics and gene editing. Advances in next-generation sequencing and single-cell RNA sequencing have generated vast amounts of genomic and transcriptomic data, which can be analysed using AI to identify disease-associated genes and pathways. For example, AI-driven genomic analysis has identified key genetic variants associated with AMD, DR and glaucoma Chen et al. (2023), Fritsche et al. (2016), Gharahkhani et al. (2021). These insights have paved the way for gene editing technologies such as CRISPR-Cas9, which hold promise for treating inherited retinal diseases. AI models are also used to optimise gene editing protocols, predict off-target effects, and design personalised therapeutic interventions for individual patients Choi et al. (2023).

7) ***LLMS and future AI in the*** oculomics*:* The emergence of Large Language Models (LLMs) such as GPT- 4 has further expanded the scope of AI in healthcare. LLMs can analyse vast amounts of textual data, including scientific literature, clinical notes, and patient records, to extract insights and generate hypotheses He et al. (2025). Although in the field of oculomics, LLM is in the early stages and requires improvement, some results of the study show Antaki et al. (2023), Betzler et al. (2023) that the knowledge gained by LLM is generally taken by humans. Although LLMS represent a cutting-edge branch of AI with growing potential in oculomics, it is equally important to understand the broader trajectory of AI as it intersects with medical and retinal research. The evolution of Artificial Intelligence, from its early origins to present-day applications, forms the foundation for modern techniques that now reshape retinal imaging.
8) ***Overview on the evolution of AI:*** In a nutshell, the emergence of AI has reshaped the dynamics of almost every field, specifically healthcare. The short description, limitations, evolution, and relevance to medicine are shown in Fig. 4, and some related stuff is discussed here. In 1956, the emergence of AI took its main start from the Dartmouth College conference, which mainly consisted of symbolic AI, in other words, a rule-based system. However, due to the computational limit, the transition of the rule-based system into the classical ML occurred from 1966 to 1970. The wave of back-propagation was another milestone in 1980; despite the emergence of this technique, AI was not getting full attention due to the funding constraints, along with the expected results Perez-Lopez et al. (2024). The era 1980–1990 is considered a winter era for AI, and again, the domain is shifted to statistical and classical ML. The Chronology of LENET Architecture, which spans from 1990 to 2012, laid the foundation for the emergence of the DL model and paved a new horizon for the future of AI LeCun et al. (2015), Rawat and Wang (2017). The DL model is a seismic change that is now non-stop in the current era, and day-to-day, new algorithms and models are emerging. The transition of AI from a theoretical to a practical tool has changed the dynamics of the research, academia and industrial world.

The capabilities of AI now extend from the basic models to the complex, whether supervised or unsupervised, transforming research, clinical practice, and industry alike. Within ophthalmology, this evolution intersects directly with the trajectory of retinal imaging. While classical imaging techniques laid the foundation for retinal diagnostics, they were largely limited to descriptive or handcrafted analyses. These approaches successfully characterised ocular lesions and vascular features but lacked scalability, sensitivity, and integration with systemic health. The rise of artificial intelligence has transformed this landscape, enabling automated segmentation, feature extraction, and predictive modelling at a scale unattainable with manual methods. Section III explores how modern AI-driven methods build upon these classical foundations, translating retinal images into quantitative biomarkers with applications that extend beyond ocular disease to systemic health.

3. Modern techniques: the rise of oculomics

As mentioned earlier, the eye disease is retained in the retina. The same is also connected and affects the important parts of the body, such as the brain, heart, kidneys, etc. This type of disease is called systemic disease, a condition that affects the entire body or several organs, not just one part. The linking of eyes with systemic diseases is coined oculomics Wagner et al. (2020), Zhou et al. (2022). The potential behind oculomics has expanded further by leveraging the existing retinal imaging research with the advancement of multiple data modalities. This can be gained by revealing the medical modalities. The modalities used so far in the field of ophthalmology are OCT, fluorescence angiography (FA), and CFP to reveal structural and functional changes in the ocular system Honavar (2022), Ringel et al. (2021). These modalities help provide enormous retinal imaging data and are widely used in the real world of medical vision. These imaging data emerged as the dataset used to mitigate the burden of eye diseases with respect to monitoring, therapeutic, prognostic, and diagnostic, respectively Ringel et al. (2021). The datasets are used in different case studies individually and combined for monitoring and identifying a variety of eye diseases, such as DR, glaucoma, macular edema, and cataracts, etc. The different retinal datasets are publicly available to detect and classify eye diseases on time. These datasets have been very helpful so far and are used for different objectives of classical ocular diseases.

3.1. Retinal imaging techniques

Retinal imaging technologies have evolved rapidly, transforming our ability to capture both structure and function of the eye at increasing resolution. Among the classical modalities, colour fundus photography remains one of the most widely applied tools in both clinical practice and large-scale epidemiological studies. Its strengths lie in simplicity, low cost, and broad availability, making it indispensable for screening conditions such as diabetic retinopathy, hypertensive retinopathy, and retinal vein occlusion. For decades, CFP has served as the standard tool in population-based studies, enabling quantification of vascular parameters such as caliber, tortuosity, fractal dimension, width, and focal narrowing. The rationale is that the retina, as the only part of the central nervous system visible non-invasively, provides direct access to microvascular and neural health Tan et al. (2022). Modern image analysis platforms now extend their utility: SIVA (Singapore I Vessel Assessment), IVAN (Integrative Vessel Analysis), and VAMPIRE (Vascular Assessment and Measurement Platform for Images of the Retina) offer semi-automated measurements of vascular geometry Mautuit et al. (2022), while AutoMorph provides a fully automated, end-to- end pipeline for vessel segmentation and trait extraction Zhou et al. (2022). The major limitation of CFP remains its two-dimensional nature, which lacks depth resolution and reduces sensitivity to subtle intraretinal changes.

Optical coherence tomography introduced a step change in retinal diagnostics by allowing cross-sectional, micrometer-resolution imaging of the retinal layers. The progression from time-domain to spectral-domain OCT has greatly improved speed, resolution, and reproducibility, supporting the quantitative evaluation of the retinal sublayers Geevarghese et al. (2021), Pazos et al. (2021). OCT is now the gold standard for detecting macular edema, glaucoma-related thinning, and AMD, although its cost and sensitivity to motion artifacts remain challenges. The functional extension, OCT angiography (OCTA), non-invasively visualizes retinal and choroidal microvasculature by detecting red blood cell motion. OCTA generates depth-resolved vascular maps and vessel density metrics that are particularly valuable in ischemic conditions and neovascular disease Greig et al. (2020). Yet, OCTA can miss slow or turbulent flow, is prone to segmentation errors, and typically covers a narrower field than wide-field angiography.

Fluorescein angiography has long been regarded as a core imaging tool for assessing retinal vasculature. By injecting sodium fluorescein dye, FA highlights vascular leakage, non-perfusion, and neovascularization, making it essential in diagnosing diabetic macular edema, retinal vein occlusion, and neovascular AMD Ricardi et al. (2024). Despite its diagnostic utility, FA is invasive, time-consuming, and associated with risks such as nausea and, rarely, anaphylaxis, prompting the development of non-invasive alternatives like OCTA.

Beyond these established modalities, a number of emerging technologies extend the diagnostic horizon. Wide-field digital imaging (WFDI) captures up to 200° Witmer and Kiss (2013) of the retina in a single shot, proving especially useful in identifying peripheral changes in diabetic retinopathy and for neonatal screening Desurmont et al. (2023). Hyperspectral imaging (HFI) provides biochemical and metabolic information by measuring reflectance at multiple wavelengths, revealing signals such as hemoglobin oxygenation and amyloid deposits associated with Alzheimer's disease Hadoux et al. (2019). These tools remain largely research-focused but hold promise for systemic disease characterization.

Adaptive optics (AO) should be understood as an enabling technology rather than a standalone clinical modality. By correcting ocular aberrations, AO achieves near-cellular resolution, and when coupled with imaging platforms such as scanning laser ophthalmoscopy (AO-SLO) or OCT (AO-OCT), it allows direct visualization of photoreceptors, retinal pigment epithelial cells, and fine capillaries in vivo. AO has provided unprecedented insights into inherited retinal diseases, including Stargardt disease, retinitis pigmentosa Georgiou et al. (2018), and cone–rod dystrophy Wong (2004), and also shows potential for functional imaging by enabling the tracking of erythrocyte movement and local blood flow dynamics at the capillary level Tan et al. (2022). However, its technical complexity and limited commercial availability currently confine AO to research laboratories rather than routine clinics. In parallel, confocal scanning laser ophthalmoscopy (cSLO) has enhanced classical retinal imaging, supporting modalities such as FA and fundus autofluorescence, with recent refinements including multicolor and ultra-widefield capabilities Horie et al. (2021). AO and cSLO extend imaging into both cellular and functional domains, complementing OCT and CFP within multimodal frameworks.

Today, the landscape of retinal imaging ranges from classical modalities such as CFP, FA, and OCT, which remain central to clinical care, to newer innovations including OCTA, WFDI, HFI, AO-enabled systems, and cSLO-based platforms that expand the scope of investigation into vascular, bio-chemical, cellular, and functional domains. As illustrated in Fig. 2, this spectrum can be organised into core modalities that underpin current diagnostic practice and emerging approaches that extend capabilities for research and multimodal integration. Each approach contributes unique strengths but also carries limitations, underscoring why multimodal combinations are increasingly applied. These limitations may be further compounded in patients with unstable fixation or ocular motility disorders such as nystagmus, where motion artifacts can compromise image quality and reduce the reliability of quantitative outcomes. Nevertheless, the convergence of classical and emerging technologies has generated an unprecedented volume of high-resolution ocular data, enabling the creation of large-scale repositories. These resources now play a central role in validating AI-driven pipelines and advancing oculomics toward clinical translation, as explored in the next section on retinal datasets.

3.2. Publicly available retinal datasets

In the present day, the data is used as a tool for competing, from small tech companies to giants and from developing to developed countries. Data is valuable and works as a gold mine in the epoch of GEN-AI. In this context, the available data is getting more attention if found in large amounts, specifically in the field of the medical sciences. This data can emerge as a dataset which can be used further in the real world of health research and drive innovations and discoveries Khan et al. (2021). Furthermore, gold-standard imaging techniques provide

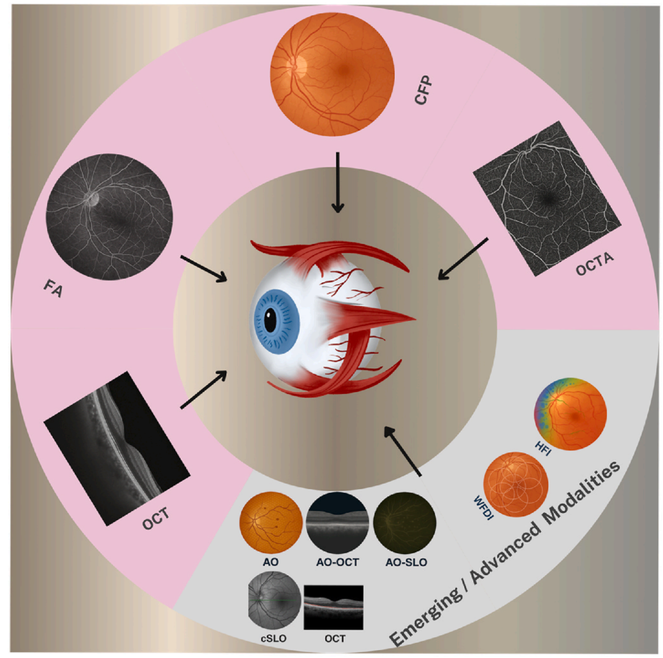


Fig. 2. The schematic illustrates the spectrum of retinal imaging technologies. Modalities shown on a pink background (CFP, OCT, FA, OCTA) represent the core, widely adopted clinical tools that underpin current diagnostic practice. Modalities grouped on a white background (WFDI, HFI, AO, AO-OCT, AO- SLO, cSLO) reflect advanced or emerging approaches that extend the field of view, resolve cellular or biochemical detail, or enhance functional assessment. While these latter techniques remain largely research-focused, they point to the expanding potential of multimodal imaging for linking retinal structure with systemic disease processes.

the opportunity for the creation of a dataset used as a benchmark for the validation and testing of real clinical trials in situ and in vivo. The advancement of retinal imaging techniques has created numerous publicly available datasets, which have become indispensable resources for researchers and physicians. These datasets are widely used for lesion detection, disease classification, and vessel segmentation Li et al. (2021). For example, datasets such as **STARE** Hoover et al. (2000), **DRIVE** Staal et al. (2004), **DIARETDB1** Kauppi et al. (2007), **CHASE DB1**, Owen et al. (2009), **HRF** Budai et al. (2013), **E-ophtha** Decenciere et al. (2013), **MESSIDOR**, **MESSIDOR-2** Decencière et al. (2014), **KAGGLE-EyePACS** Dugas et al. (2015), **IDRiD** Porwal et al. (2018), **KAGGLE- APTOS** Karthik and Dane (2019), and **DDR** Li et al. (2019) have been instrumental in developing algorithms for detecting and classifying diabetic retinopathy, segmenting retinal vessels, and identifying other ocular pathologies.

Collectively, these publicly available datasets have established the foundation for advancements in image-based ophthalmic research, particularly in the automated detection and classification of retinal diseases. However, the diagnostic requirements and imaging targets vary significantly across different ocular conditions. To understand how these datasets contribute to disease-specific model development, it is important to contextualise their relevance across major retinal disorders.

In this survey, therefore, we transition from the dataset overview into a focused discussion of key localized diseases: beginning with glaucoma, where structural deterioration of the optic nerve is a primary concern; followed by age-related macular degeneration, which involves degeneration of the macula; and finally diabetic retinopathy, where vascular abnormalities and lesion characteristics dominate. Each disease presents unique imaging biomarkers and machine learning challenges, necessitating tailored approaches in algorithm design and data representation.

Glaucoma: Glaucoma is a long-term and gradually worsening condition of the optic nerve that results in permanent loss of vision and stands as one of the primary causes of blindness worldwide. It affects an estimated 76 million people as of 2020 and is projected to impact over 111.8 million by 2040 Tham et al. (2014). Elevated intraocular pressure is often linked to the disease, but many patients also experience normal-tension glaucoma, illustrating the condition's complex origins. The disease affects both the structural and functional health of the eye, especially through the degeneration of retinal ganglion cells (GC) and harm to the optic nerve head. Clinically, a key biomarker for diagnosing glaucoma is the cup-to-disc ratio, which quantifies the size of the optic cup relative to the optic disc and reflects the cupping of the optic nerve Sahu (2024), Wagner et al. (2022).

Two primary imaging modalities, CFP and OCT, are widely used to detect and monitor glaucomatous changes. OCT provides high-resolution cross-sectional views of the RNFL and GC complex, enabling the early identification of nerve fiber loss. In contrast, CFP offers a top-down view of the optic nerve head, allowing for disc cupping evaluation and broader topographic interpretation Coan et al. (2023). Mehta et al. (2021) demonstrated that the combination of OCT and CFP scans could improve accuracy in detecting structural glaucomatous damage by assessing the cup-to-disc ratio. In the last decade, deep learning has significantly reshaped the landscape of glaucoma diagnostics. Early ML models often relied on handcrafted features like texture and colour histograms to classify glaucoma cases Bock et al. (2010). These models provided a baseline but lacked scalability and robustness in real-world scenarios.

With the rise of CNNS, researchers shifted to end-to- end learning pipelines capable of automatically extracting hierarchical visual featuresTing et al. (2019). In a study, Li et al. (2018) developed a CNN-based glaucoma detection model trained on fundus images, reporting performance metrics on par with experienced ophthalmologists. The research conducted by Kihara et al. (2022) established a multimodal deep learning framework that integrated Optical Coherence Tomography and visual field data. This approach effectively captured both the structural and functional aspects of the disease. Similarly, Xu et al. (2021) built on this research by employing deep regression models to forecast future visual field deterioration using only baseline OCT scans, providing a useful clinical resource for long-term monitoring.

More recently, attention-based architectures, specifically ViTs, have shown promise in retinal image analysis. Unlike CNNS, which rely on localised filters, transformer models can capture long-range dependencies and global context, making them suitable for capturing subtle glaucomatous patterns across the optic disc and RNFL regions. Playout et al. (2022) applied transformer models to fundus images and reported superior classification performance and generalizability across datasets compared to conventional CNN-based baselines.

Age-Related Macular Degeneration: Age-Related Macular Degeneration is a name that suggests that it can affect the center vision part of the eye, the macula. Eyesight declines with the passage of time and can impact daily routine activities. It is complicated in the early and later stages, as the early stage shows minimal symptoms and can cause vision loss in the former stage Gao et al. (2024). In the case of unattended patients, AMD cases will be projected to be 288 million patients by 2040 Wong et al. (2014). Due to this, it poses an important public health challenge. Different case studies have used an AI-driven retinal diagnostic model to address this ailment. Mark and Andres designed the study van Grinsven et al. (2013),Garc'ıa-Floriano et al. (2019) to quantify and detect the abnormality of the macula in Fundus images using ML. This model helped to assess the risk of progression, along with the prediagnosis of AMD.

A comprehensive study Abd El-Khalek et al. (2024) which leverages the ML algorithm, categorises the age-related macular degeneration stages along with the data-driven technique and develops a Computer-Aided Diagnosis framework. This model is classified into No, Intermediate, Dry, and Wet AMD, and the results are compared with those of the other studies. This model has a better result. Likewise, unlike typical machine learning, a deep learning algorithm is employed in different case studies of AMD patients. Due to their hierarchical, deep structure, the DL model gets an improved result by interacting directly with the hidden parameters and acting as an autonomous model.

A deep learning-AI-driven solution has been developed for automated AMD detection and differential diagnosis, leveraging vision transformers, data augmentation, and Swin transformers to improve accuracy, efficiency, and cost-effectiveness Xu et al. (2023). Likewise, a deep learning model integrates with the local outlier Factor algorithm's goal to classify the age-related macular degeneration from the OCT scans. The generalizations are tested on the unseen dataset, a Duke dataset, which performs very well in the early detection of AMD He et al. (2022).

Diabetic Retinopathy: When insulin production is not enough in the human body, it can raise the glucose level in the blood and lead to diabetes. Type 1 and 2 both have a high socioeconomic effect. However, type 2 requires more attention as it leads to other chronic diseases associated with heart, kidney, nose, nerve and eye diseases Azeem et al. (2022).

DR is one of the complications directly related to the eye. The complication involves swelling of the retinal vasculature, causing blood and fluid to leak, and, at a later stage, it leads to vision loss if left unattended. The pathophysiology of the DR risk is distributed like this: the retinal vascular leakage causes fluid accumulation in the vitreous humor. Similarly, MA and HM are red lesions, and by the same soft and hard EX, a bright lesion disrupts normal vision, and the lesion advances in the shape of Neovascularization, leading to severe vision as portrayed in Fig. 3 Wei et al. (2022). The commonly occurring retinal lesions include MAs, intraretinal HMs, and venous beading (characterised by alternating areas of venous dilation and constriction). Additionally, intraretinal microvascular abnormalities, hard EXs (lipid deposits), and retinal neovascularization are also recognised as common types of lesions Li et al. (2021). Since these DR risks are distributed into binary and multiple classes, in multiple classes, there are often five classes, which are No, mild, moderate, severe and PDR Sarki et al. (2020). In contrast, in the binary, these classes are non-proliferative DR (NPDR), further subdivided into the mild, moderate, and Severe DR. Subsequently, the remaining stages are considered as PDR Khan, Khan, et al. (2021).

Over the past two decades, much research has been conducted to prevent DR from the classical algorithms to the modern ones Yang et al. (2022). A tetragonal local octa pattern method was proposed to represent features of fundus images Nazir et al. (2019). Building on this, Gayathri et al. (2021) applied traditional ML algorithms such as SVM, decision trees, and random forests for classification. Likewise, the study conducted at Washburn et al. (2020) employed the approach of Gabor

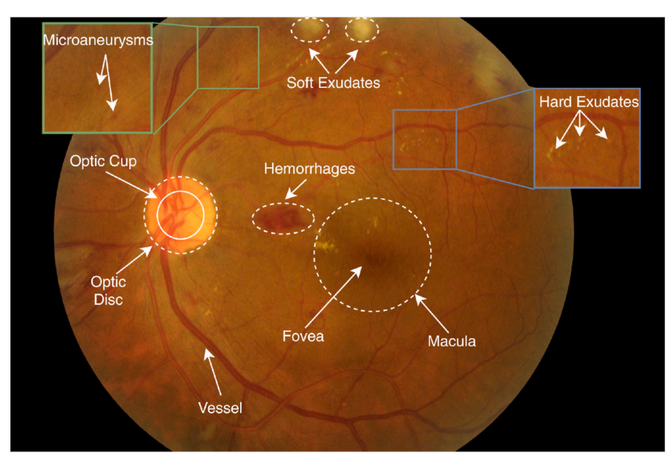


Fig. 3. An annotated fundus image reproduced from Li et al. (2021), showing pathological markers including microaneurysm, haemorrhage, exudates, and anatomical regions like the fovea and optic disc.

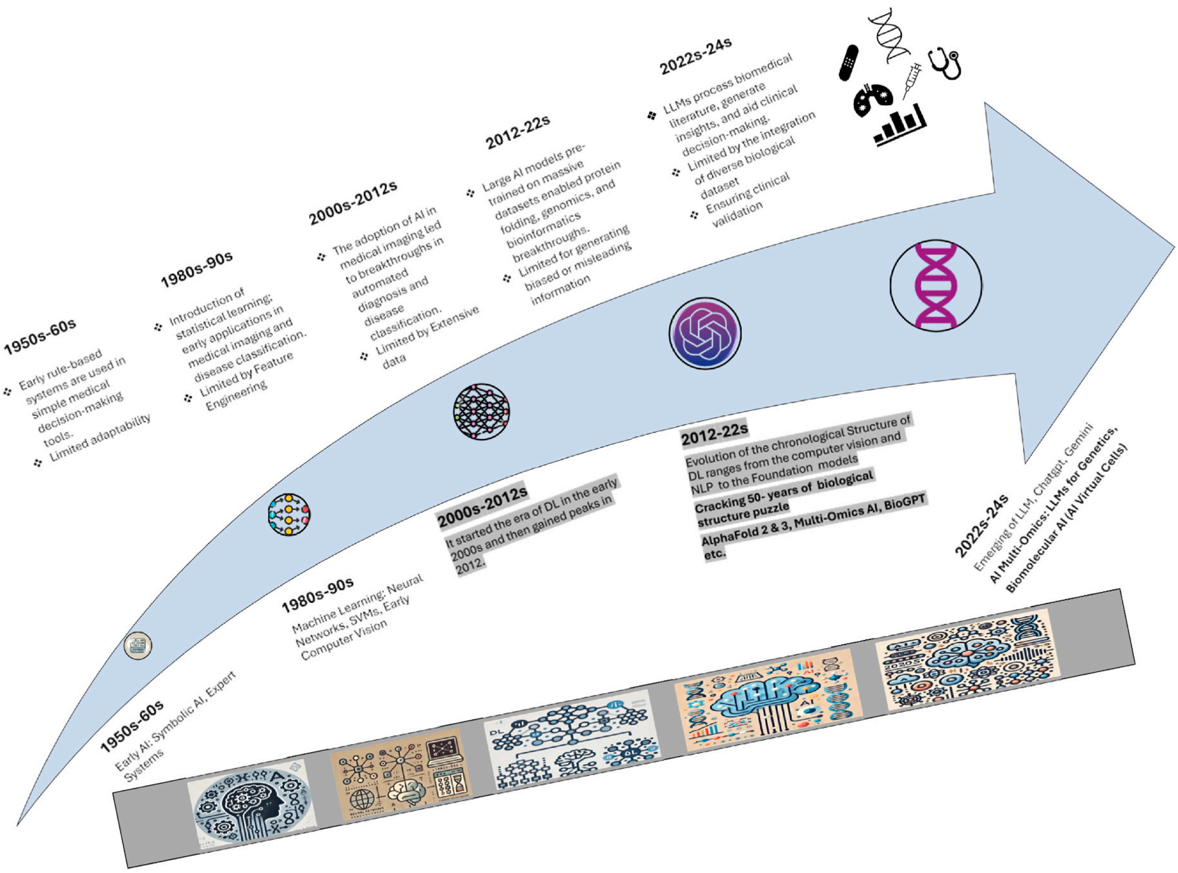


Fig. 4. Illustrates a timeline that outlines the development of artificial intelligence, starting with symbolic rule-based systems in the 1950s and progressing to modern deep learning, foundation models, and large language models. This evolution emphasises important technological changes that have impacted the overall AI field, providing a basis for today's uses in healthcare and biomedical research.

wavelet encased with the Adaboost classifier to classify the DR. For the binary classification of a DR, a range of studies Esfahani et al. (2018), Suriyal et al. (2018), Xu et al. (2017), Zago et al. (2020) has been available using the CNN model, which has gained a significant result.

Furthermore, the binary and multi-classification of DR leveraging the DL model is evidenced in these studies. For instance, in Rêgo et al. (2021), InceptionV3 was employed to detect DR using RGB and texture features. Pamadi et al. (2022) developed binomial and multinomial classification models for fundus images using MobileNetV2, while Saranya et al. (2022) utilised the DenseNet-121 model to identify DR from fundus images. Additionally, various architectures of EfficientNet were explored in Mudaser et al. (2021). Some studies proposed hybrid models that combined DL models for feature extraction with traditional ML models for classifica-tion. For example, Boral and Thorat (2021)used InceptionV3 for representation learning in conjunction with an SVM for DR classification.

Ensemble models (EMs) have long been recognised in medical image analysis as an effective way to improve clas-sification accuracy and robustness by combining the outputs of multiple base learners Hassan et al. (2024). In the case of DR detection, Jiang et al. (2019) demonstrated this approach with an ensemble of three CNNs, where AdaBoost was used to optimise the integrated predictions. More recently, attention has shifted toward transformer-based architectures, which employ self-attention mechanisms to capture long-range spatial relationships that CNNs often miss. The introduction of Vision Transformers Dosovitskiy et al. (2021) marked a turning point, and subsequent studies have highlighted their value in medical imaging applications Amin et al. (2025). Comparative evaluations confirm this advantage: Kumar and Karthikeyan (2021) found that Swin-Transformer and Vision-Transformer consistently outperformed CNN-based models such as EfficientNet and ResNet, as well as MLP-Mixer architectures. Building on this progress, Yu et al. (2021) introduced the Multiple Instance Learning Vision Transformer (MIL-ViT), which was pretrained on large fundus datasets before fine-tuning for DR tasks. When tested in APTOS2019 Karthik and Dane (2019) and RFMiD 2020 Pachade et al. (2020), MIL-ViT achieved superior accuracy compared to conventional CNNs. An ensemble of transformer models was developed that integrates four distinct networks to evaluate the severity of DR Adak et al. (2023). Furthermore, Gu et al. (2023) proposed a DR grading model that combines a vision transformer with residual attention. This model features two primary components: (1) a feature extraction block based on the transformer, which emphasises retinal haemorrhage and exudate areas, and (2) a grading prediction block employing residual attention to capture different spatial regions corresponding to various classes. For further insights into the application of transformers in medical imaging, readers are encouraged to explore recent studies Parvaiz et al. (2023), Ye et al. (2023).

These diseases and their detection are pivotal and are used in vivo and in vitro, and have established a foundation for the field of oculomics. However, diseases covered in the above data sets may not have the potential to provide deep insight into the underlying mechanism of genotype-wide association. These are primarily focused on phenotypic analysis, which limits their utility for genotypic studies. To fully realise the prospective of oculomics, the acquisition of datasets needs to be extended to include cohort-based studies that integrate clinical patient records, high-throughput data, and structural and functional imaging data. Such comprehensive datasets would enable researchers to explore the genetic and molecular underpinnings of ocular and systemic diseases, paving the way for personalised medicine. Importantly, one of the most promising directions for such integration lies in the automated quantification of retinal vascular morphology, as the retinal circulation directly reflects systemic vascular health and provides measurable traits that can bridge imaging, genetics, and multi-omics frameworks.

C. Automated retinal vascular morphology: A pathway to oculomics

The circulatory system plays a critical role in systemic health, and the dysfunction often manifests in the retina's microvascular structures. Retinal circulation, characterised by the unique accessibility and transparency, provides an invaluable opportunity to study vascular health non-invasively. Blood viscosity, vessel length, and vessel diameter are critical determinants of vascular resistance and have been closely examined within the retinal vasculature to uncover systemic disease mechanisms Nguyen and Wong (2006). In connection with these features and parameters, a vascular structure encased in the retinal circulation gained close attention to unveil the mechanism underlying these structures. In recent decades, interest has gone beyond the classical techniques of oculomics due to its relationship with systemic diseases, namely, both types of diabetes, cardiovascular diseases, and dementia Brazionis et al. (2023), Ebuchi et al. (2022).

Automated analysis of retinal vascular morphology provides objective, quantitative measurements of the retinal circulation. Standardized protocols typically focus on the six largest arterioles and venules emerging from the optic disc, measured within predefined concentric regions, most commonly Zone.

B (0.5–1.0 disc diameters from the disc margin) and Zone.

C (1.0–2.0 disc diameters). From these measurements, the central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE) are derived, summarizing average vessel caliber, while their ratio (AVR) reflects the arteriovenous balance Zhou et al. (2022). Additional quantitative traits extend this characterization: fractal dimension describes the geometric complexity of the branching network Avakian et al. (2002); tortuosity quantifies the curvature and deviation of vessels from a straight path Grisan et al. (2008); vessel density captures the proportion of retinal area occupied by vasculature Curcio and Kar (2019); branching angle measures bifurcation geometry; and arteriovenous crossing patterns define vessel interactions Ikram et al. (2013). These retinal vascular traits provide reproducible phenotypes that can be computed at scale, forming the foundation for downstream oculomics and multi-omics integration.

The microvasculature features of the eye in the in vivo assessment of imaging modalities allow a computerized approach to measuring the caliber of the retinal vessels of the arterioles, venules and the relationship between these. These measurements are the gold standard for oculomics, which can be correlated with systemic diseases Zekavat et al. (2022). Studies showed that hypertension and atherosclerosis are associated with narrowing of the arteries Nguyen & Wong (2006),Cheung et al. (2007), and DR is associated with dilation of the retinal veins Wong (2011). In addition, increasing retinal artery tortuosity is interrelated with hypercholesterolemia and hypertension Cheung et al. (2011), Owen et al. (2011).

Initially, retinal calibers were measured manually, a tedious process requiring human computation and traditional formulas. However, manual vessel segmentation often produces sub-optimal results, which can hinder model performance. Over the past few decades, extensive research has been conducted to automate this process and extract retinal vascular features. Significant advancements have been achieved through various approaches, including feature-based methods, unsupervised graph-based techniques, and supervised deep learning models Dashtbozorg et al. (2013), Estrada et al. (2015), Hatamizadeh et al. (2022), Huang et al. (2018), Mirsharif et al. (2013), Ronneberger et al. (2015), Srinidhi et al. (2019). These developments have led to the emergence of multiple software tools for clinical and research applications. However, most of these tools remain semi-automated, necessitating human intervention to correct vessel segmentation and identify features such as bifurcations, tortuosity, branching angles, artery/vein diameters, widths, and Fractal dimension.

To address these limitations, AutoMorph, a fully automated software package, was developed by Zhou et al. (2022), leveraging deep learning models to autonomously measure retinal calibers without human intervention. The AutoMorph pipeline consists of four key components: preprocessing, image quality grading, anatomical segmentation, and morphological feature measurement. The anatomical segmentation and morphological feature extraction stages play a crucial role in advancing oculomics, an emerging field that explores the relationship between retinal and systemic diseases. The third stage of AutoMorph enables precise segmentation of the optic disc/cup, vessels, arteries, and veins. The final stage extracts key vascular morphology metrics, including tortuosity (via distance measurement, squared curvature, and density) for each artery and vein, and fractal dimension to quantify vessel complexity. Additionally, it measures retinal vascular calibers for CRAE and CRVE, AVR, and enables macular region-specific assessments.

With advancements in retinal imaging software, researchers can now efficiently quantify retinal vascular features, segment major arteries and veins, and capture the fine-grained structural details of smaller vessels with high precision. These developments have expanded the potential of retinal imaging beyond ophthalmic disease diagnosis, providing valuable insights into systemic health conditions Hanssen et al. (2022). Increasing evidence suggests that retinal vascular morphology serves as a biomarker for various systemic diseases, including hypertension, diabetes, cardiovascular disease, and neurodegenerative disorders Honavar (2022). By enabling automated high-throughput retinal vascular analysis, AutoMorph and similar technologies contribute to a deeper understanding of the intricate connections between retinal changes and systemic pathophysiology, reinforcing the growing role of oculomics in predictive medicine and disease monitoring.

D. *Evolution of oculomics: From classical to future frame-works*

The field of oculomics is transforming from traditional medical imaging to modern multi-modality and omics data integration. This shift is driven by three current paradigms: Automated AI software tools, big data, and high-resolution ophthalmic imaging.

Fig. 5 represents the classical paradigm of eye research before oculomics emerged. In this era, diagnostic pipelines were built on conventional image preprocessing methods such as contrast enhancement, region-of-interest cropping, and manual noise reduction. Machine learning or early deep learning models were applied to handcrafted features, such as texture patterns, vessel widths, and colour intensity, extracted from fundus photography or optical coherence tomography. The outputs of these pipelines were typically limited to binary or multi-class classification (e.g., disease present or absent), with low interpretability, of localised optometry diseases, and minimal systemic relevance. This approach lacked scalability and failed to capture the full complexity of vascular and neural changes in the retina that could indicate broader systemic health conditions.

Fig. 6 represents the current phase of oculomics, where deep learning automates the entire process of retinal vascular analysis. Starting with quality control, fundus images are either accepted or rejected before progressing through vessel probability mapping, binary segmentation, artery–vein separation, skeletonization, and disc/cup segmentation. Standard epidemiological zones (B and C) are then overlaid around the optic disc to provide consistent reference frames for vascular measurement. From these outputs, quantitative biomarkers such as CRAE, CRVE, AVR, fractal dimension, vessel density, and multiple tortuosity indices are derived in a standardized way. Unlike the handcrafted approaches of earlier decades, these pipelines generate reproducible traits at scale, making them suitable for population cohorts and cross-study comparisons. By translating images into structured, quantitative endophenotypes, automated analysis has transformed the retina into a measurable biomarker source rather than a descriptive image. This stage is crucial in the evolution of oculomics. It bridges classical imaging, which

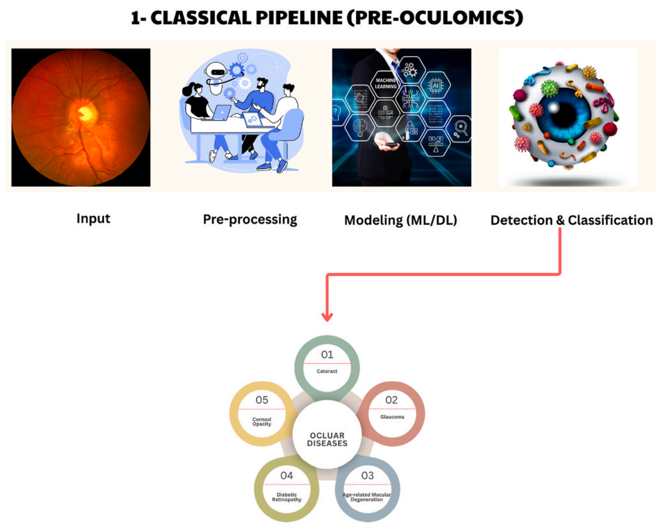


Fig. 5. Before the rise of oculomics, computational pipelines for ophthalmology followed a straightforward path: Images were acquired as input for clarity, processed through pre-processing. The classical method went through feature engineering with a need for manual interpretation, including contrast enhancement, region of interest cropping and segmentation, and noise reduction. Then these were put in the model for training, testing and validating the model for the specific ocular diseases for machine learning and early deep learning modelling. This work is in the classification, detection and prediction of different diseases. These systems focused almost entirely on ocular diseases such as cataract, glaucoma, age-related macular degeneration, diabetic retinopathy, and corneal opacity. While they laid the foundation for computer-assisted diagnosis, they were limited in scope, largely handcrafted, and confined to the eye itself without considering wider systemic health.

remained focused on ocular disease, and future frameworks, where retinal traits are integrated with genetics, proteomics, metabolomics, and digital health data. In other words, Fig. 6 does not just show technical automation; it marks the point where retinal imaging becomes scalable, reproducible, and ready for systemic integration.

Recent studies further illustrate how oculomics is expanding beyond descriptive pipelines into integrative, mechanistic frameworks. For instance, Lu et al. (2025), Zekavat et al. (2022) demonstrated how high-resolution fundus datasets can be combined with clinical records and Mendelian randomization to show that changes in vascular morphology, such as arteriolar narrowing or reduced fractal dimension, are not merely correlates but causally implicated in major vascular events including stroke and myocardial infarction. This move from association to causation provides evidence that retinal traits can function as mechanistic biomarkers rather than statistical surrogates. Deep phenotyping cohorts, such as the UK Biobank Collins (2012) and the 10K Shilo et al. (2021) study, further strengthen this approach by embedding retinal imaging within multi-layered datasets that include lipidomics, metabolomics, immune profiling, body composition, and many more. Complementing these resources, Reicher et al. (2025) has extended deep phenotyping even further by integrating genetics, transcriptomics, metabolomics, immune and microbiome profiling, lifestyle data, continuous physiological monitoring, and imaging into a prospective cohort of more than 28,000 participants, alongside the development of foundation AI models trained for disease prediction. In another study, analysis from the 10K project has shown how deeply phenotyped cohorts can also reveal sex-specific dynamics of biological ageing, with machine learning models generating system-specific biological age scores that predict age-related disease risk beyond chronological age Reicher et al. (2024). These studies reveal that retinal traits can be contextualised within broader biological signatures of health and ageing, providing a richer framework for interpreting systemic variation across populations.

In parallel, plasma proteomic research has highlighted how organ-specific proteomic ages, particularly those of the brain and immune system, are strong predictors of Alzheimer's disease and longevity, with hazard ratios exceeding 3.0 even after adjustment for conventional risk factors Oh et al. (2025). Such findings offer a mechanistic model for how retinal imaging could be linked with proteomic and genomic data to stratify risk for neurodegeneration and systemic aging. Disease-specific pipelines also illustrate the breadth of this vision: Eye2Gene, trained on multimodal retinal imaging, achieved top-five diagnostic accuracy of nearly 84 % across 63 inherited retinal disease genes, demonstrating how foundation-style phenotyping can accelerate genetic diagnosis Pontikos et al. (2025). Similarly, DeepSLE, a deep learning system to detect Systemic lupus erythematosus (SLE), has shown that autoimmune disease, specifically SLE, can be detected from fundus photographs using AI with performance comparable to serological screening, extending oculomics beyond cardiometabolic and neurodegenerative domains into immunology Li et al. (2025).

Together, these examples capture the trajectory summarised in Fig. 7. Current studies are beginning to show how causal inference can elevate retinal biomarkers from correlates to mechanisms, how multimodal concatenation of retinal and clinical data improves prediction, and how foundation-style models like Eye2Gene can compress complex phenotypes into actionable diagnostic outputs. At the same time, multisystem screening models such as DeepSLE preview a future where a single retinal image could support simultaneous risk profiling across cardiovascular, neurological, and immune conditions. Looking forward, the integration of retinal imaging with genomic-wide associations, plasma proteomics, metabolomics, digital devices, and longitudinal clinical data, processed through ensemble and foundation AI models, will define the next-generation framework of oculomics. In this vision, the inputs from genomics and clinical/digital streams (Fig. 7A and C) converge in advanced computational architectures (Fig. 7B) to produce validated biomarkers, risk stratification tools, and decision-support systems that move oculomics firmly into the domain of precision medicine.

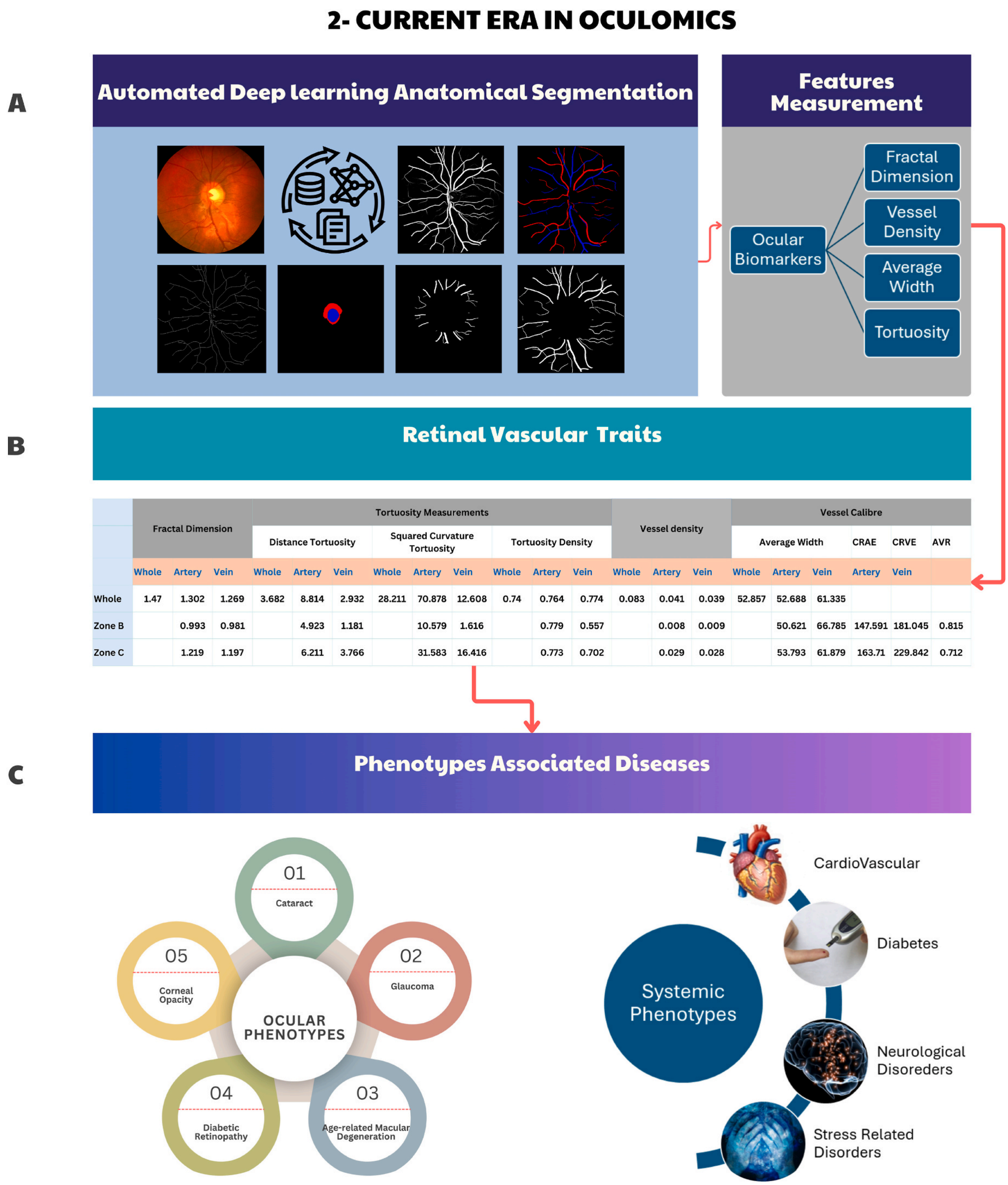
This figure underscores the ambition of oculomics to evolve from a diagnostic subfield of ophthalmology into a central node in precision medicine. Fig. 5 through 7 collectively offer a visual synthesis of this paper's thematic arc. They represent the chronological and conceptual development from basic retinal diagnostics, through current AI-driven phenotyping, and toward a highly integrative, multi-omics-enabled future.

This transition also aligns with the paper's overall structure: beginning with classical foundations, moving through tools like AutoMorph, and culminating in the future of AI-integrated oculomics. By placing these stages adjacent to each other, the infographics demonstrate the evolution of the field from organ-centric diagnostics to a comprehensive approach, where the eye serves as a window to understanding human health at both the cellular and molecular levels. Such a framework supports the central argument of this paper: oculomics is not merely a subfield of ophthalmology, but a rapidly evolving interdisciplinary platform for next-generation healthcare innovation. Building on the current state of AI-enabled retinal imaging, the subsequent section expands into the systemic implications, demonstrating how retinal biomarkers are increasingly used to infer cardiovascular, neurological, and metabolic diseases.

4. Linking eye and systemic diseases

4.1. *The eye as a mirror of systemic health*

The eyes are considered a window for the mirror of the soul of health. What does this mean to us? This means that looking at the eyes of the person can be interpreted, and the other person's concealed attitudes, thoughts, and emotions can be guessed Ph.D (2024). The same is true; the eyes are the only organ in the human body that acts as a window to



	Fractal Dimension			Tortuosity Measurements									Vessel density			Vessel Calibre					
				Distance Tortuosity			Squared Curvature Tortuosity			Tortuosity Density						Average Width			CRAE	CRVE	AVR
	Whole	Artery	Vein	Whole	Artery	Vein	Whole	Artery	Vein	Whole	Artery	Vein	Whole	Artery	Vein	Whole	Artery	Vein	Artery	Vein	
Whole	1.47	1.302	1.269	3.682	8.814	2.932	28.211	70.878	12.608	0.74	0.764	0.774	0.083	0.041	0.039	52.857	52.688	61.335			
Zone B		0.993	0.981		4.923	1.181		10.579	1.616		0.779	0.557		0.008	0.009		50.621	66.785	147.591	181.045	0.815
Zone C		1.219	1.197		6.211	3.766		31.583	16.416		0.773	0.702		0.029	0.028		53.793	61.879	163.71	229.842	0.712

Fig. 6. (A) Left-to-right workflow: Fundus images undergo automated quality assessment, followed by vessel segmentation (binary masking), artery/vein classification, skeletonization, and disc/cup delineation. Peripapillary measurement zones (B & C) are defined as concentric annuli centred on the optic disc for standardized caliber and trait quantification. (B) Vascular Biomarkers: The system extracts quantitative vascular metrics, including dimensions, fractal dimension, vessel density, and tortuosity indices for both arteries and veins. Outputs, generated using AutoMorph on CHASE DB1 (image 007-L) Owen et al. (2009), are reported in micrometres calibrated to the device's field of view. (C) Transition to Systemic Biomarkers: By standardizing and scaling retinal phenotypes, AI facilitates the association of ocular conditions (e.g., diabetic retinopathy, glaucoma, age-related macular degeneration) with systemic diseases (cardiovascular, metabolic, neurodegenerative), transitioning from handcrafted descriptors to traits suitable for population studies and enabling multi-omics integration.

see the world, making them unique organs to care for. In connection with other non-communicable diseases like rheumatic, neurodegenerative, hypertensive and diabetic Mellitus, eyes will help us to detect them in a non-invasive manner and act as biomarkers for these fatal diseases.

The World Health Organisation estimated that 2.2 billion people in the world are suffering from eye diseases and are being prevented to the tune of one billion of them. Therefore, other than an ophthalmologist, researchers and scientists are keenly interested in unveiling the hidden patterns and mechanisms to analyse with the latest research, emulsified with the holistic approach to care for our eye health and save the whole body XLab Health (2024). In addition, a recent study revealed that the eye also manifests a variety of stress diseases in which oxidative stress is crucial. This leads to the onset of different degenerative and chronic disorders such as cancer, atherosclerosis, coronary arteries, kidney, neurological, Respiratory, and Rheumatoid arthritis diseases Honavar (2022), Wei et al. (2022).

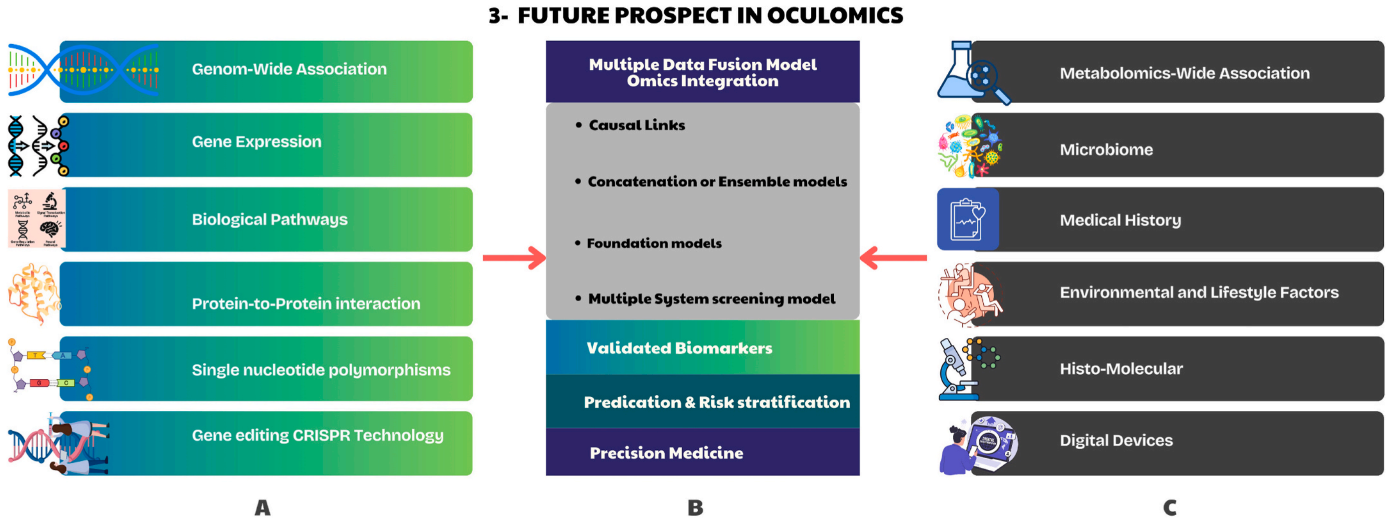


Fig. 7. Future prospects in oculomics, toward validated biomarkers and precision medicine. (A) Genomic & molecular inputs: GWAS, gene expression, pathways, protein–protein interactions, single-nucleotide polymorphisms (SNPs), and gene-editing constraints provide a mechanistic context for retinal traits. (C) Clinical, environmental & digital context: metabolomics, microbiome, medical history, lifestyle and environmental factors, histo-molecular readouts, and data from digital devices. (B) Computational core: multi-modal data fusion supports four complementary strategies, (i) causal inference (e.g., Mendelian randomization) to separate correlation from causation; (ii) multimodal ensembles/concatenation for robust prediction; (iii) foundation/next-generation phenotyping models (e.g., Eye2Gene for IRDs) to learn generalizable retinal representations; and (iv) multi-system screening models that jointly profile ocular and systemic phenotypes. Outputs include validated biomarkers, risk stratification, and decision support for precision medicine. Example systems span automated vascular phenotyping (AutoMorph), phenotypic screening with genetic validation for vascular events, deep learning for systemic autoimmunity (DeepSLE), and IRD gene prioritization (Eye2Gene).

The advancement in retinal imaging technologies, such as fundus photography, OCT, and OCTA, has not only improved the diagnosis of sight-threatening ocular diseases but also opened the door to using ocular markers as indicators of systemic conditions. These biomarkers can anticipate disease onset and serve as non-invasive surrogates for risk stratification and treatment monitoring Wagner et al. (2020). In essence, the eye is both a mirror and a window to systemic health, reflecting numerous chronic disorders. Building on this perspective, the following section reviews systemic diseases where retinal changes are most evident, with a particular emphasis on age-related conditions.

4.2. Systemic diseases linked to retinal changes

1) ***Cardiovascular diseases:*** Blood vessels captured in retinal images can be visualised noninvasively, and subtle differences in their caliber and branching patterns provide valuable insights into systemic vascular health and future cardiovascular risk Hanssen et al. (2022). The ability to stratify risk is central to preventing CVD, which remains a leading cause of mortality worldwide. Current clinical scores, such as the Framingham Risk Score (FRS) and pooled cohort equations, rely on factors like age, smoking, body mass index (BMI), cholesterol, glucose, blood pressure, and sex, often supplemented by blood tests Goff Jr et al. (2014). However, these approaches face practical limitations. For instance, cholesterol values are not always available, with one study noting they were missing for nearly 30 % of patients in a 10-year risk calculation Hira et al. (2015). Alternatives, such as using BMI in place of lipids, have been proposed, but they only partially capture metabolic risk. In this context, the retina offers an attractive non-invasive surrogate, providing a direct view of the microvasculature and its relationship to systemic disease Poplin et al. (2018).

Early population studies consistently reported that narrower arterioles and wider venules were associated with hyper-tension, coronary artery disease, and atherosclerosis Cheung et al. (2012). These cross-sectional observations highlighted the eye's potential as a cardiovascular biomarker but did not establish causality. More definitive evidence came from large-scale longitudinal analyses. A pooled individual-participant meta-analysis of 20,798 people across six cohorts showed that wider venular caliber independently predicted incident stroke, with a hazard ratio of 1.15 (95 % CI: 1.05–1.25) per 20 μm increase, whereas arteriolar caliber was not significantly associated (HR 1.00, 95 % CI: 0.92–1.08) McGeechan et al. (2009). Importantly, incorporating venular caliber into standard risk models reassigned more than 10 % of individuals at intermediate stroke risk, underscoring the added predictive value of retinal vascular traits. Similarly, hypertensive retinopathy, characterised by vessel narrowing, haemorrhages, and exudates, not only reflects chronic blood pressure elevation but also signals a higher likelihood of stroke, heart attack, and heart failure Wang, Feng, et al. (2024). These findings underscore that the vascular features of the retina can serve as validated predictors, not merely correlates, of cardiovascular outcomes.

More recently, advances in artificial intelligence have expanded the predictive scope of retinal imaging. A deep learning model was induced by Rudnicka et al. (2022) leveraging retinal vascular traits to predict major adverse cardiovascular events, including circulatory mortality, myocardial infarction, and stroke, with a C-statistic of 0.75–0.77, comparable to FRS. In a similar study, Poplin et al. (2018) showed that fundus photographs alone could predict 5-year cardiovascular events with an AUC of 0.70, matching the performance of the composite SCORE calculator. In people with diabetes, the addition of retinal parameters to polygenic risk scores for coronary artery disease improved prognostic accuracy over a 10-year period Mordi et al. (2022). Other biomarkers, such as the retinal age gap, a measure comparing biological and chronological age derived from retinal images, have also been shown to predict cardiovascular mortality in multiple cohorts Nusinovici et al. (2022), Zhu et al. (2023).

Integrative approaches further highlight the potential of oculomics. Combining fundus photographs with conventional clinical risk factors or dual-energy X-ray absorptiometry improved CVD risk prediction by 2–3 % Al-Absi et al. (2022), Mellor et al. (2023). Optical coherence tomography angiography-based vascular parameters have also been investigated as markers of coronary artery disease Zhong et al. (2022). Although their additional predictive value over established risk factors remains modest, particularly in patients with advanced diabetic or hypertensive retinopathy, they demonstrate the breadth of retinal imaging modalities that can contribute to cardiovascular risk assessment.

Finally, large-scale AI studies integrating genetics have begun to provide causal insights Zekavat et al. (2022). In the UK Biobank, deep learning models predicted 10-year risks of stroke, myocardial infarction, and chronic kidney disease with AUC values (area under the receiver operating characteristic curve) of 0.74–0.77, performing on par with or better than traditional clinical scores. Importantly, genome-wide association studies and Mendelian randomization analyses confirmed causal links between retinal vascular traits and cardiovascular outcomes, while also identifying reverse effects of chronic kidney disease on retinal microcirculation Lu et al. (2025). These advances mark a shift from descriptive correlations to validated, mechanistic pathways, placing the retina at the forefront of precision cardiovascular medicine.

2) ***Diabetes and diabetic retinopathy:*** Diabetes, or in other words, Diabetes Mellitus, is one of the most pressing challenges in the socio-health scenario of the 21st century. It has experienced a dramatic rise in the incidence rate for the past three decades. The international diabetes Federation estimates that, to the tune of 536.5 million, the adult age group suffered from diabetes in the year 2021. This number could reach 738.2 million by 2045 Sun et al. (2022).

This disease association is characterised by hypercalcemia, which further exacerbates other complications like CVDS, kidney failure, and vision loss and imposes substantial burdens on the economy and healthcare system Azeem et al. (2022). Microvasculature complications damage the small blood vessels linked to the different organs and diseases like Diabetic Nephropathy, Neuropathy and Retinopathy Bereda (2022). Microvasculature plays an important role in maintaining tumorigenesis and organ health, and the human eye, i.e., the retinal fundus, serves as a window for in vivo assessment Zekavat et al. (2022). OCT and OCTA have facilitated the non-invasive assessment of the retinal microvasculature Oliveira et al. (2025).

Studies have shown that individuals with diabetes exhibit alterations in retinal vascular caliber, including wider venular diameters, which are associated with an increased risk of developing diabetes and its complications. A comprehensive analysis with 18,771 participants indicated that a larger retinal venular diameter is linked to a higher risk of developing Type-2 diabetes over a median follow-up duration of 10 years, even when controlling for possible confounding factors Sabanayagam et al. (2015).

Moreover, retinal texture analysis has emerged as a potential tool for the early detection of diabetes-related retinal changes. A recent study utilising OCT-derived texture characteristics found that changes in retinal texture are concurrent with biological retinal changes, suggesting that texture analysis could serve as a biomarker for the early diagnosis of DR Sun et al. (2022). Circulating biomarkers have also been found, which also play a role in predicting diabetic complications. Higher levels of immunocomplexes and immunoglobulin M anti-cardiolipin antibodies have been observed in diabetes patients with vascular complications, suggesting their potential as biomarkers for DR Simo'-Servat et al. (2016).

Similarly, the progression of DR is closely linked to systemic metabolic control, evidenced by some recent studies, which underline the implication of advanced glycation end products (AGEs) and oxidative stress in the development of DR. The accumulation of AGEs in the retinal vasculature triggers the complication of inflammation and endothelial dysfunction; by the same oxidative stress, it worsens the cellular damage Wei et al. (2022), Zhan (2023). These complications, on the one side, contribute to the progression of DR and, on the other side, reflect the systemic disease related to diabetes, like neuropathy and nephropathy. For example, the presence of DR has been associated with a higher risk of diabetic kidney disease, underscoring the interconnectedness of microvascular complications Fang et al. (2023), Yamanouchi et al. (2019).

3) ***Neurodegenerative Diseases:*** The retina, an extension of the central nervous system, offers a unique opportunity to visualise brain health in vivo. Acting as a “window to the brain,” retinal imaging has revealed structural and functional alterations that mirror pathological processes in Alzheimer’s disease (AD), Parkinson’s disease (PD), multiple sclerosis (MS), and even cerebrovascular disease. This dual role, as both a mirror and a biomarker, has increasingly positioned oculomics as a powerful approach to detect early neurodegenerative changes before they manifest clinically Honavar (2022).

In Alzheimer’s disease, thinning of the retinal nerve fiber layer and the loss of the ganglion cell layer (GCL) are among the most consistent findings. Studies have shown that individuals at high genetic risk for AD exhibit reduced macular thickness even before cognitive symptoms emerge Lo’pez- Cuenca et al. (2020). Patients with AD also present with significantly thinner central macula compared with healthy controls Farzinvash et al. (2022). Retinal microvascular abnormalities, such as narrower venules and increased tortuosity, further suggest a vascular contribution to AD-related pathology Cheung et al. (2014), Czako et al. (2020), Ong et al. (2014).

AI-based models analyzing retinal features have achieved promising results: one deep learning study using over 12,949 fundus images from 648 AD patients achieved diagnostic accuracies ranging from 0.80 to 0.92 Cheung et al. (2022). However, while these biomarkers are strongly correlative, their independent predictive value beyond established markers such as amyloid PET or cerebrospinal fluid assays remains to be validated.

In Parkinson’s disease, retinal changes also mirror underlying brain pathology. OCT studies have revealed retinal thinning and dopaminergic cell loss, both correlating with disease severity and progression Elanwar et al. (2023), Satue et al. (2014). Beyond these structural alterations, functional markers are also being explored. Eye-tracking studies have identified prolonged saccadic latency and reduced response accuracy in PD patients, with machine learning models achieving AUC values of 0.73–0.93 in distinguishing patients from healthy controls Maleki et al. (2024), Miles et al. (2024). Although these findings remain largely correlative, they highlight the potential of combining structural retinal imaging with functional eye-movement analysis to improve early, non-invasive monitoring of neurodegenerative disease. In Alzheimer’s disease, deep learning applied to eye-tracking data has likewise shown that visual attention heatmaps can distinguish patients from controls with performance metrics of 0.84 accuracy and 0.90 AUC Zuo et al. (2024). This provides early evidence that non-invasive eye-movement behaviours could serve as functional biomarkers for cognitive decline.

In multiple sclerosis, evidence is stronger and more val idated: Longitudinal OCT studies consistently demonstrate thinning of the retinal RNFL and GCL as biomarkers of disease activity and disability progression Bsteh et al. (2024). These structural markers have been further supported by machine learning approaches: support vector machines, ensemble classifiers, and recurrent neural networks applied to OCT parameters have achieved AUC values ranging from 0.82 to 0.88 for MS diagnosis and prediction of progression Montolío et al. (2021). More recently, Lopez-Dorado et al. (2021) demonstrated that CNNs trained in OCT thickness maps of sweep source, augmented with synthetic data using a deep generative adversarial network, could distinguish newly diagnosed MS patients from controls with near-perfect sensitivity and specificity (both 1.0). The retinal structures contributing most to discrimination included the ganglion cell layer plus inner plexiform layer (GCL+), the extended ganglion cell complex including RNFL and inner plexiform layer (GCL++), and the complete retina. These findings establish retinal imaging as both a structural and a computational biomarker platform to monitor MS, complementing its role in other neurodegenerative disorders.

Finally, cerebrovascular disease links further underscore the eye–-brain connection. Longitudinal population-based studies consistently show that retinal vascular traits are predictive of stroke risk. In the Rotterdam Study, wider venular caliber was independently associated with both cerebral infarction and intracerebral haemorrhage, with hazard ratios of 1.28 (95 % CI: 1.13–1.46) and 1.53 (95 % CI: 1.09–2.15), respectively, while associations with narrower arteriolar caliber were weaker and borderline significant Wieberdink et al. (2010). The Multi-Ethnic Study of Atherosclerosis (MESA) extended these findings to a diverse U.S. cohort, demonstrating that narrower arteriolar caliber (HR = 3.01, 95 % CI: 1.29–6.99) and retinopathy in non-diabetic individuals (HR = 3.07, 95 % CI: 1.17–8.09) were independently associated with incident stroke, even after adjustment for atherosclerotic markers such as carotid intima-media thickness and coronary calcium Kawasaki et al. (2012). In Asian populations, the Singapore Malay Eye Study showed that larger venular caliber (HR = 3.28, 95 % CI: 1.30–8.26) and retinopathy signs predicted stroke events, and that the inclusion of retinal microvascular measures improved risk prediction and reclassification beyond established factors Cheung et al. (2013).

The decrease in retinal fractal dimension was similarly associated with stroke risk, with an odds ratio of 1.80 for the venular and 2.28 for the arteriolar networks Wu et al. (2017). More recently, large-scale AI studies have strengthened these associations. A UK Biobank study of 45, 161 participants reported that each standard-deviation change in vascular traits, including vessel density, caliber, and branching complexity, was associated with a 9.8–19.0 % change in stroke risk. Incorporating these measures into conventional models improved predictive accuracy, increasing the area under the ROC from 0.739 to 0.752 Yusufu et al. (2025). Similarly, the DeepRETStroke framework, trained on hundreds of thousands of retinal photographs across multiple countries, predicted incident stroke with an AUC of 0.901 by detecting silent brain infarctions, outperforming conventional predictors across diverse populations Jiang et al. (2025).

These validated findings illustrate how subtle retinal vascular changes can forecast cerebrovascular accidents years in advance, making them one of the most clinically actionable domains of oculomics. Collectively, these examples show how the retina serves as a biological bridge between the eye and brain. While many associations remain exploratory, validated pathways in multiple sclerosis and stroke demonstrate the clinical promise of oculomics. Ongoing advances in AI, mul-timodal imaging, and wearable eye-tracking technologies are expected to strengthen this bridge, enabling earlier detection, more accurate risk stratification, and deeper insights into the mechanisms of neurodegenerative disease.

5. Future directions in oculomics

Despite advancements in the field of oculomics from the classic to the modern. The emergence of AI models and their multi-faceted functions opens a door for interdisciplinary programs to dive into and solve socioeconomic and sociohealth problems. Many of the studies included in this review paper tackle the localised and associated diseases of the eyes. However, this field still needs more attention to tackle these problems in one go.

Here are future directions to heighten this field: design and develop a robust, monolithic, reliable and reproducible Automatic diagnosis system (ADS) to act as a life-saving tool for clinical and industrial research.

1) It is important to mention that the current retinal imaging datasets mainly focus on phenotypic characteristics, such as lesion segmentation, disease classification, and vascular analysis. However, they lack genetic and molecular data, limiting our understanding of ocular disease progression and systemic correlations. This gap is particularly evident in diseases such as DR, AMD, and glaucoma, where genotypic variations play a critical role in disease progression and treatment response. A major limitation of existing datasets is that they do not capture the progression of gene expression changes at different disease stages. For example, in DR, we currently lack information on:
   a) Gene expression variations associated with early, moderate, and proliferative DR stages.
   b) Patterns of arterial, venous, and capillary alterations and their correlation with gene activity.
   c) Molecular pathways linking DR to cardiovascular risks, including blood pressure, BMI, lipid levels, and systemic inflammation markers.

This cannot be covered by the existing public dataset, such as those used in Budai et al. (2013), Decenciere et al. (2013), Decencière et al. (2014), Dugas et al. (2015), Hoover et al. (2000), Karthik and Dane (2019), Kauppi et al. (2007), Li et al. (2019), Owen et al. (2009), Porwal et al. (2018), Staal et al. (2004). Expanding epidemiological studies, such as cohort and longitudinal approaches, are essential and will cover the genetic sequencing data from the same patients, allowing for cross-comparison of gene expression, imaging biomarkers, and clinical factors. Tracking the same patients over time will help us to understand the underlying mechanism and result in a reliable outcome.

Likewise, this will create retinal imaging datasets that include multi-omics data, such as genomics, transcriptomics, proteomics, and metabolomics, which are crucial to uncovering disease mechanisms at a systems level. This approach will allow researchers to study the genetic inclination to retinal diseases, track disease progression through molecular signatures, and establish links between ocular and systemic health. This chain will be interlinked with fostering interdisciplinary collaboration in areas like ophthalmology, data science, computer science, bioinformatics, molecular biology, and life sciences, opening a door for the success of oculomics. Similarly, the easily accessible multi-dataset (open access) will be a gold mine for institutional and healthcare research. The policymakers engage to ensure the practical implementation of data privacy and security to innovate the advancement in oculomics.

2) Expanding the retinal imaging capabilities to work with a diverse range of imaging, namely OCT, OCTA, AO-OCT, fundus and infrared imaging. The Automorph package still has the same limitation: they are only suitable for the fundus images and cannot be relied on if its modalities are other than this. A diverse range of images should be integrated, which will be suitable for all the modalities of retinal images. This improvement will help us with the subtle retinal changes in the cellular and vasculature network of the eyes and act as ADS for localised and systemic diseases like hypertension, diabetes and neurodegenerative conditions.
3) Foundation model and domain shifting are the future of medical image analysis; these two are scarce in oculomics. Domain shifting is hard to correlate with the CFP as it is well suitable for the OCT, and this can be achieved by shifting histoimaging of different tissues into the domain of eye tissue. However, the question arises as to why this model cannot be applied to all the modalities of optic systems. However, there is promise in this methodology, and it could be a popular approach in the future. Subsequently, the foundation model is trained on the enormous, diverse dataset and, by the same fine-tuning through a large number of tasks, produces reliable models. This model is found rare in the study of the retina and can be quite helpful in promoting ophthalmology. For example, the retina is linked with different diseases, including CVD. Finding the biomarkers for CVD with respect to retinal imaging. Creating a different model outcome like the features of carotid arteries correlates with the retinal imaging, the same for the serum lipidomics, sleep monitoring and oral microbiome dataset. Exploring the dataset directly connected with CVD and is associated with retinal imaging through the statistical model. Once a linkage is found and at the end, we add these models via the foundation model. This mechanism will be another way of contributing to eye research. In addition, this will

maximise the transition of the research setting to routine clinical usage and could be expandable to portable retinal imaging devices to work as an ADS tool, which will also be helpful for the easily accessible remote regions of low- and middle-income countries.

4) The black box experience is the Elephant in the room, which is still challenging; however, the explainable AI solves some parts of it and goes further. This field itself needs attention. However, they have solved real-life puzzles. In connection with this, Explainable AI can also heighten the medical vision domain and help us identify which morphological patterns are responsible for systemic diseases through the DL system.
5) LLM is another buzzword in today's era and is trained on almost the world's puzzle. However, there is still room for oculomics, and we should focus on applications like the NYUTron Jiang et al. (2023), which is trained on 750,000 patients for routine clinical notes. Expanding to eye research can mitigate the burden on health practitioners. Likewise, the LLM medical specialist model Llava-Med Li et al. (2024) and PathChat Lu et al. (2023) demonstrate promising biomedical and histopathology imaging capabilities. There is a dire need for oculomics research communities to design an application specific to retinal systems to uncover complex patterns in one go.
6) Finally, it pertains to mention that despite the inclination of AI in the medical domain and the advancement in AI-based medical and ocular applications, they are still in the translational stage, and their benefits in clinical practice remain challenging. To fully utilise the potential of AI in oculomics medical trials, these key challenges need to be addressed.
   a) The integration of multiple data modalities as discussed earlier
   b) The development of transparent and explainable AI models encased with the code of conduct for data sharing and model validation.
   c) The collaboration between the AI researcher, clinician and healthcare practitioner ensures the care of AI-based tools relevant to the needs of stakeholders of the public health sector.
   d) The oculomics domain expert should be familiar with the rapid advancement of AI technology and tools. This will enable him to navigate the world and solve real-time problems in a routine clinical environment.

6. Conclusion

Our detailed survey presents a broad exploration of the evolution of retinal imaging, tracing its path from classical techniques such as fundus photography and early machine learning approaches to the emerging era of oculomics powered by artificial intelligence. The transition from traditional vision-based diagnostics to deep phenotyping frameworks demonstrates the expanding role of the retina as a non-invasive biomarker for systemic health. Critical gaps remain despite significant advancements, such as the development of automated tools, the rise of multimodal AI frameworks, and the emergence of vision transformers. The disparity of datasets, the integrational paradigm lack between clinical, genetic, and imaging data, and limited demographic diversity constrain real-world deployment. Additionally, AI systems' interpretability and adaptation to heterogeneous clinical environments remain open challenges. As oculomics advances, it offers a unique opportunity to unify molecular, phenotypic, and clinical insights. This field could further nurture early diagnosis, risk prediction, and personalised healthcare by enriching an inclusive, longitudinal, and ethically governed research infrastructure. Sooner or later, the eye may serve not only as a diagnostic tool but as a window into systemic health and human biology at large.

CRediT authorship contribution statement

Inamullah Inamullah: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Imran Razzak:** Writing – review & editing, Formal analysis, Conceptualization. **Shoaib Jameel:** Writing – review & editing, Supervision, Formal analysis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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