

Advances in Artificial Intelligence-Based Ocular Imaging for the Detection of Systemic Diseases

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Abstract: Traditional screening for systemic diseases often relies on laboratory tests, imaging evaluations, and specialist consultations, with limited value in applications related to cardiovascular diseases, diabetes and metabolic abnormalities, kidney diseases, hepatobiliary system diseases, neurodegenerative diseases, and certain autoimmune diseases. Extensive research demonstrates that deep learning models perform exceptionally well in these tasks, with multiple studies reporting an Area Under the Curve (AUC) exceeding 0.90. However, the field still faces challenges, such as significant data heterogeneity, insufficient external validation, limitations which are frequently associated with high costs, invasiveness, and limited accessibility in primary care settings. The eye is one of the few organs in the human body that allows for the non-invasive, direct observation of microvessels, neural tissues, and the microstructures of semi-transparent tissues, offering a unique advantage in reflecting systemic health status. In recent years, with the development of deep learning technology and high-resolution ocular imaging, the scope of eye image analysis has gradually expanded from traditional ophthalmic diseases to the screening, risk prediction, and long-term monitoring of systemic diseases. The primary ocular imaging modalities currently available for systemic disease research include color fundus photography (CFP), optical coherence tomography (OCT), optical coherence tomography angiography (OCTA), corneal confocal microscopy (CCM/IVCM), and anterior segment imaging. Existing studies indicate that multimodal ocular imaging holds potential interpretability, low levels of research design, and difficulties in real-world clinical translation. This review focuses on the theoretical basis, methodological framework of deep learning, major disease applications, current challenges, and future directions for identifying systemic diseases using multimodal ocular imaging, with the aim of providing a reference for subsequent research design and clinical translation.

Keywords: Artificial Intelligence, Retinal Images, Deep Learning, Systemic Diseases

1. Introduction

Systemic diseases are disorders that affect the entire body or multiple organ systems rather than being confined to a single organ or anatomical region. These diseases are typically associated with widespread pathophysiological alterations and may impair bodily function through diverse mechanisms, including immune dysregulation, metabolic abnormalities, inflammation, disseminated infection, and genetic factors. Common systemic diseases include cardiovascular disease, kidney disease, systemic lupus erythematosus, and neurodegenerative disorders [1].

According to the Global Burden of Disease Study, both the prevalence and burden of systemic diseases continue to increase. Cardiovascular disease alone caused approximately 18.6 million deaths worldwide in 2019, accounting for 32% of all deaths [2]. The diagnosis and management of these diseases generally require an integrated assessment of multisystem manifestations, supported by laboratory testing, imaging, pathological analysis, and specialist clinical judgment to establish a definitive diagnosis, stratify risk, and guide long-term follow-up. However, shortages of specialized equipment and healthcare professionals constrain early screening in remote and resource-limited settings, while high testing costs impose an additional financial burden on low-income populations and further delay diagnosis.

Collectively, these factors exacerbate the public health burden of systemic diseases and underscore the urgent need for convenient, noninvasive, low-cost adjunctive diagnostic approaches suitable for large-scale population screening.

As the only tissue in which the microvasculature and an extension of the central nervous system can be visualized directly and noninvasively, the retina is not merely a site of ocular pathology but also a unique window into systemic health [3]. Retinal vascular morphology—including caliber, tortuosity, and arteriovenous nicking—provides a microcosm of the systemic circulation and is strongly associated with the severity of vascular disorders such as hypertension and atherosclerosis; degenerative changes in the retinal nerve fiber layer and optic disc are likewise closely linked to neurodegenerative diseases, including Alzheimer's and Parkinson's diseases [4].

Although the concept of inferring systemic health from retinal signs dates back to Marcus Gunn's classic descriptions more than a century ago, conventional diagnostic paradigms have long relied on costly, complex, and invasive clinical examinations [5]. The emergence of ophthalmics in recent years has marked a paradigm shift in this field. Wagner et al. [6] formally defined this interdisciplinary frontier in 2020 as the comprehensive analysis of multidimensional ocular-imaging features associated with systemic disease—at macroscopic, microscopic, and molecular levels—to enable noninvasive assessment of cardiovascular, neurological, metabolic, and immune disorders.

The rapid emergence of ophthalmics has been driven largely by transformative advances in artificial intelligence (AI) and deep learning. The widespread use of advanced algorithms, including convolutional neural networks (CNNs) and vision transformers (ViTs), in medical-image analysis has overcome the feature-extraction bottleneck inherent in manual image interpretation [7]. Their capacity for high-dimensional, high-precision pattern recognition has made it feasible to use a single fundus image for early screening, risk stratification, and longitudinal prediction of systemic diseases.

Nevertheless, despite the considerable potential of AI-assisted retinal imaging for predicting systemic disease, model operation—the “black-box” effect—and the biological basis of extracted features remain insufficiently understood [7].

Recent reviews generally define this research paradigm as ophthalmics, an interdisciplinary field that uses ocular structural, functional, and imaging biomarkers to understand, detect, predict, and monitor systemic disease [8–9]. Whereas early studies focused primarily on color fundus photography and retinal vascular phenotypes, the field has expanded to ultra-widefield fundus imaging, OCT, OCTA, corneal confocal microscopy, and anterior-segment imaging [10]. Accordingly, ocular-imaging-based identification of systemic disease has progressed from single-modality feasibility studies to multimodal integration and evaluation for clinical translation [11].

Existing reviews have two major limitations: some remain centered on retinal images and do not systematically incorporate evidence from corneal nerves and the anterior segment, whereas others cover multiple modalities but remain largely conceptual and provide insufficient analysis of the systemic information offered by each modality, the role of deep learning, and the proximity of current research to real-world clinical application [8–9]. This review therefore systematically examines the imaging foundations, methodological framework, applications, challenges, and future directions of multimodal ocular imaging for systemic-disease detection.

2. Overview of Ocular Imaging

Ocular imaging is a fundamental component of ophthalmics research. Unlike conventional approaches focused solely on local ocular disease, multimodal ocular imaging captures systemic-disease phenotypes at complementary levels: color and ultra-widefield fundus imaging depict the overall posterior segment and retinal vasculature; OCT provides layer-resolved information on the retina and optic nerve [12]; OCTA characterizes microcirculation and perfusion [13]; corneal confocal microscopy reveals corneal nerves and cellular microstructure [14]; and anterior-segment imaging extends observation to low-cost, highly accessible settings [19]. Because these modalities differ in informational depth and pathological emphasis, they are complementary rather than interchangeable sources of multidimensional ocular phenotypes in deep-learning studies of systemic-disease detection.

2.1 Color Fundus Photography

Color fundus photography (CFP), a conventional clinical tool for documenting fundus morphology,

has traditionally been used alongside invasive dynamic imaging techniques such as fluorescein angiography (FA) ^[15]. With advances in nonmydriatic imaging and optical hardware, CFP can now provide comprehensive, noninvasive visualization of posterior-pole structures, including the retina, macula, and optic disc ^[16]. In particular, red–green–blue (RGB) multispectral-channel imaging exploits wavelength-dependent differences in tissue penetration to improve visualization of retinal layers. Owing to its noninvasiveness, affordability, and operational convenience, CFP has become a core imaging modality for assessing baseline fundus vascular status.

At the hardware level, fundus-imaging systems are evolving from conventional tabletop instruments to handheld devices while incorporating advanced functions such as ultra-widefield imaging and automated pupil tracking. As Panwar et al. ^[17] noted, although the low cost of portable devices suits population-scale screening, high-resolution tabletop systems remain the preferred data source for high-quality clinical trials and deep-learning research because of their superior signal-to-noise ratio and image quality. Using such high-quality imaging data, Poplin et al. ^[18] reported landmark work in 2018 on predicting systemic characteristics from fundus images. This Google AI-led study first demonstrated that deep-learning computer-vision models could extract high-dimensional features from CFP images and accurately predict systemic biomarkers—including age, sex, blood pressure, and cardiovascular risk—challenging the conventional view that fundus imaging is useful only for ophthalmic diagnosis.

2.2 Optical Coherence Tomography

Optical coherence tomography (OCT) is a noncontact, noninvasive optical tomographic technique that reconstructs tissue cross-sections from low-coherence interference signals and visualizes the layered structures of the retina and optic nerve at high axial resolution ^[12]. Unlike CFP, which primarily depicts two-dimensional surface morphology, OCT enables objective, quantitative assessment of microstructural changes in the retinal nerve fiber layer, macula, ganglion cell layer, and peripapillary tissues and can generate complex three-dimensional datasets. OCT is therefore particularly suitable for capturing neural structural injury, changes in retinal thickness, and brain–eye-axis phenotypes in systemic-disease research, especially in neurodegenerative diseases, multiple sclerosis, and other conditions involving microstructural alterations. OCT is a major high-resolution ophthalmic imaging technology because it is quantitative and reproducible; however, equipment cost, complex image formats, and limited cross-platform consistency may impair the generalizability of deep-learning models.

In deep-learning research, OCT supports not only disease classification but also fine-grained phenotyping and longitudinal change analysis. Nevertheless, complex data formats, high equipment costs, and limited cross-platform consistency may compromise model generalizability. OCT is therefore best positioned as an important modality for mechanistic interpretation and structural phenotyping.

2.3 Optical Coherence Tomography Angiography

Optical coherence tomography angiography (OCTA) is a noninvasive vascular-imaging technique derived from OCT. By comparing signal differences between repeated OCT B-scans acquired at the same location, OCTA detects blood-flow signals generated by erythrocyte motion and reconstructs retinal and choroidal microvascular networks without contrast-agent injection ^[13]. Unlike conventional OCT, which primarily depicts tissue structure, OCTA provides both structural and blood-flow information and enables layer-specific visualization of the superficial and deep capillary plexuses, radial peripapillary capillary plexus, and choriocapillaris. OCTA is therefore well suited to assessing microcirculatory abnormalities and subtle vascular phenotypes—such as vessel density, nonperfusion areas, and the foveal avascular zone—in studies of diabetic microangiopathy, cerebrovascular disease, neurodegenerative disease, and systemic vascular dysfunction. Its advantages include noninvasiveness, speed, layer-specific imaging, and quantification, whereas its limitations include a relatively narrow field of view, inability to visualize leakage, motion artifacts, and missed detection of slow flow.

Building on OCT, OCTA provides additional information on retinal and choroidal microcirculation and enables noninvasive assessment of capillary density, nonperfusion areas, and perfusion status. Whereas CFP primarily depicts vascular morphology, OCTA emphasizes microcirculatory function and is therefore valuable for research on diabetic microangiopathy, cerebrovascular and neurodegenerative diseases, and systemic vascular dysfunction.

For deep-learning models, OCTA provides fine-grained vascular-network patterns and perfusion

abnormalities that facilitate the discovery of complex microcirculatory phenotypes. However, its stringent image-quality requirements and susceptibility to motion artifacts, segmentation errors, and device-related variation limit comparability across studies. Overall, OCTA is particularly valuable for investigating systemic-disease mechanisms and discovering early biomarkers.

2.4 Corneal Confocal Microscopy (CCM/IVCM)

Corneal confocal microscopy, which primarily visualizes corneal nerve fibers, epithelial cells, and other microstructures, is a distinctive modality within multimodal ocular imaging^[14]. Unlike posterior-segment imaging, which mainly reflects retinal vascular and neural status, CCM more directly characterizes small-fiber nerves and therefore offers unique advantages in studies of diabetic peripheral neuropathy, Parkinson's disease, multiple system atrophy, and other systemic neurological injuries.

From a deep-learning perspective, CCM images are well suited to automated nerve-fiber segmentation, microstructural recognition, and quantitative phenotyping and may become an important tool for noninvasive neuropathological assessment. At present, however, this modality is constrained by limited dataset sizes, demanding acquisition and annotation requirements, and insufficient standardization. CCM is therefore better regarded as a distinctive, highly specific complement within multimodal systems than as a mature primary modality. Table 1 summarizes the principal imaging targets, systemic information, advantages for deep-learning applications, and major limitations of the ocular imaging modalities discussed above.

Table 1. Overview of Ocular Imaging Modalities

Imaging modality	principal imaging target/information	systemic information reflected	advantages for deep-learning applications	major limitations.
Color fundus photography	retinal vessels, optic disc, macula, and overall posterior-segment structure	microvascular status, global posterior-segment phenotypes, and vascular risk features	convenient acquisition, large datasets, and suitability for large-scale training and external validation	two-dimensional imaging without tomographic structure or detailed microcirculatory information.
OCT	retinal-layer thickness, macular structure, nerve fiber layer, and peripapillary tissue	neurodegeneration, microstructural abnormalities, and brain-eye-axis changes	fine-grained structural analysis suitable for phenotype extraction and longitudinal assessment	complex data formats, limited cross-device consistency, and high cost.
OCTA	retinal and choroidal microcirculation, capillary density, and nonperfusion areas	microcirculatory perfusion and vascular dysfunction	discovery of complex flow and microcirculatory phenotypes suitable for mechanistic research	susceptibility to motion artifacts and segmentation errors and stringent image-quality requirements.
Corneal confocal microscopy (CCM/IVCM)	corneal nerve fibers, epithelial cells, and microstructure	small-fiber nerve injury and neural microstructural changes	nerve-fiber segmentation, microstructural recognition, and quantitative analysis	generally small samples, demanding acquisition and annotation, and insufficient standardization.
Anterior-segment/ocular-surface imaging	the cornea, conjunctiva, iris, anterior chamber, and other anterior-segment structures	externally visible phenotypes, ocular-surface vessels, and visible anterior-segment features	low acquisition barriers and compatibility with mobile health and telemedicine	few high-quality studies, fragmented evidence, and nonuniform annotation

3. Theoretical Basis for Detecting Systemic Disease from Ocular Images

The theoretical basis for detecting systemic disease from ocular images extends beyond the general proposition that “the eyes reflect systemic health” and rests on multilevel links between local ocular anatomy and systemic pathological states. Retinal vessels reflect systemic microcirculation and

vascular function; retinal neural structures share developmental and pathological links with the central nervous system; corneal nerves provide a visual window into small-fiber neuropathy; and anterior-segment and ocular-surface structures may exhibit externally visible phenotypes associated with hematologic, hepatobiliary, immune, and metabolic abnormalities. Ocular imaging thus provides a pathway for biomarker discovery that connects locally visible structures with systemic-disease phenotypes.

Compared with conventional morphometric methods, the principal advantage of deep learning lies not merely in improving measurement efficiency but in automatically learning high-dimensional phenotypic features beyond predefined human-derived metrics. Whereas conventional studies typically rely on a limited set of measures—such as vessel caliber, thickness, density, length, and branching angle—deep learning can integrate local texture, spatial distribution, structural relationships, cross-regional patterns, and multimodal information to enable feature discovery approaching deep phenotyping. This transition is transforming ocular imaging from a diagnostic tool for eye disease into an important data source for systemic-disease screening, risk stratification, and progression prediction.

3.1 Retinal Microvascular Phenotypes

The retina is one of the few human tissues in which the microvascular network can be observed directly and noninvasively, and its vessel caliber, branching pattern, course, tortuosity, arteriovenous-crossing changes, and perfusion status are closely associated with systemic microcirculatory function and macrovascular disease ^[1]. This property makes retinal imaging an important entry point for assessing cardiovascular risk factors, abnormal glucose metabolism, chronic kidney disease, and other forms of systemic vascular dysfunction ^[7].

Conventional retinal vascular analysis relies mainly on manual or semiautomated extraction of a limited number of morphological indices, including central retinal arteriolar and venular equivalents, the arteriovenous ratio, vessel density, and tortuosity. Although these indices are readily interpretable, they describe only predefined vascular features and cannot adequately capture complex spatial patterns or subtle textural changes. By contrast, deep-learning models can automatically integrate vascular morphology, peripapillary structure, macular texture, and global spatial distribution without requiring every feature to be manually defined, thereby identifying high-dimensional microvascular phenotypes beyond conventional morphometric analysis. Retinal microvascular phenotypes consequently constitute a core theoretical basis for predicting systemic diseases such as cardiovascular disease, diabetes, and chronic kidney disease from ocular images.

3.2 Retinal Neural Phenotypes

Beyond its microvasculature, the retina is an extension of the central nervous system, and changes in the nerve fiber layer, ganglion cell layer, macula, and optic disc may reflect pathological processes underlying neurodegenerative and cerebrovascular disorders. OCT and OCTA have consequently attracted interest in studies of Alzheimer's disease, Parkinson's disease, multiple sclerosis, and cerebral small-vessel disease because they depict retinal layers, neural-tissue integrity, and microvascular perfusion more precisely than two-dimensional fundus photographs ^[12–13].

This dimension extends the role of ocular imaging in systemic-disease detection beyond the vasculature to neural tissue and brain–eye relationships. Whereas conventional OCT studies focus on quantifiable parameters such as RNFL thickness, GC–IPL thickness, and macular volume, deep learning can additionally identify interlaminar relationships, regional atrophy patterns, textural heterogeneity, and flow–structure coupling. This shift from individual thickness measures to multidimensional neural phenotypes establishes retinal neural structure as an important imaging basis for early screening and risk assessment of neurodegenerative disease.

3.3 Corneal Neural Phenotypes

When ocular-imaging research is extended from the retina to the entire eye, the corneal neural morphology visualized by corneal confocal microscopy provides unique information. Corneal nerve fibers form part of the peripheral small-fiber nervous system, and their length, density, branching pattern, and tortuosity are increasingly regarded as potential noninvasive surrogate markers of systemic small-fiber neuropathy. Systematic reviews indicate that IVCN/CCM has been used to assess corneal nerve alterations in diverse systemic disorders, including diabetic peripheral neuropathy, metabolic

abnormalities, neurodegenerative diseases, and other systemic conditions ^[14].

Unlike retinal imaging, which primarily reflects central neural and microvascular status, corneal confocal microscopy more directly interrogates peripheral nerve injury. Conventional analysis relies on measures such as corneal nerve-fiber length, density, and branch count, whereas deep learning can further identify spatial organization, patterns of fiber disruption, focal rarefaction, and microstructural complexity. Corneal nerve imaging therefore complements retinal vascular and neural imaging within oculomics and is particularly suitable for phenotyping diabetic peripheral neuropathy and other systemic neurological injuries^[15].

3.4 Anterior-Segment and Ocular-Surface Phenotypes

Anterior-segment and ocular-surface imaging extends the scope of ocular-imaging-based systemic-disease detection. Whereas conventional oculomics has centered on posterior-segment structures—particularly the retinal vasculature, optic disc, and macula—anterior-segment imaging expands the field to readily observable structures such as the cornea, conjunctiva, sclera, iris, palpebral conjunctiva, and lens. Recent narrative reviews suggest that anterior-segment imaging may reflect autoimmune, cardiovascular, hematologic, neurological, and psychiatric conditions and, because it offers high visibility and relatively low acquisition barriers, can readily be integrated into mobile-health and telemedicine settings ^[16].

The theoretical value of anterior-segment and ocular-surface phenotypes lies primarily in capturing externally visible pathological information. For example, palpebral-conjunctival color can inform anemia assessment; changes in scleral and conjunctival color may indicate hepatobiliary abnormalities; corneal Kayser–Fleischer rings are an important ocular sign of Wilson disease; and ocular-surface inflammation and corneal alterations may be associated with immune or metabolic dysfunction. Although evidence for anterior-segment imaging in systemic-disease detection remains less extensive than that for retinal and corneal nerve imaging, it represents an important shift from a posterior-segment-centered paradigm toward visible phenotyping of the entire eye. Deep learning may extract externally visible features from color, texture, morphology, and spatial distribution that cannot be quantified reliably by human observation, creating new opportunities for low-cost and highly accessible systemic-disease screening^[17-20].

4. Artificial Intelligence

Artificial intelligence (AI) comprises technologies that enable machines to perceive, learn, reason, and make decisions. Machine learning (ML), a major branch of AI, uses mathematical models to learn features and patterns automatically from data and perform tasks such as classification, regression, clustering, and prediction ^[21]. Deep learning (DL) is the class of machine-learning methods most suited to medical-image analysis. Multilayer neural networks hierarchically extract features from raw images, progressing from low-level edges, textures, and colors to higher-level morphology, spatial relationships, and disease-related phenotypic representations. Deep learning is therefore particularly well suited to high-dimensional ocular images, including fundus photographs, OCT, OCTA, anterior-segment images, and corneal confocal micrographs.

Convolutional neural networks (CNNs) are among the most widely used deep-learning architectures for identifying systemic disease from ocular images. CNNs extract local spatial features through convolutional layers and reduce redundant information while enhancing feature stability through pooling, thereby preserving image structure and capturing disease-relevant visual patterns. Unlike conventional handcrafted feature engineering, CNNs do not depend on a limited set of prespecified measures—such as vessel caliber, thickness, density, or color—but can automatically learn more complex, high-dimensional phenotypic features from the entire image. This capacity enables deep learning not only to recognize overt lesions but also to detect latent imaging signals associated with systemic disease that are difficult to identify consistently by eye ^[22].

Depending on the learning paradigm, machine-learning and deep-learning models can be categorized as supervised, unsupervised, or semisupervised. Supervised learning is currently the most common approach in oculomics and is used primarily for labeled disease classification and risk identification, such as determining whether an individual has diabetes, chronic kidney disease, anemia, or Alzheimer’s disease. Unsupervised learning is more suitable for discovering latent disease subtypes or clusters of imaging phenotypes when explicit labels are unavailable and can help characterize

heterogeneous ocular manifestations of systemic disease. Tasks can also be categorized as classification or regression according to their output. Classification models are commonly used for diagnosis, grading, and screening, whereas regression models predict continuous systemic measures such as blood pressure, glucose, HbA1c, eGFR, hemoglobin concentration, coronary artery calcium score, and retinal age.

From a clinical perspective, AI applications in ophthalmics fall into three principal categories: disease identification from ocular images, biomarker prediction to estimate laboratory or systemic physiological measures, and longitudinal risk prediction that combines follow-up data to forecast disease onset, progression, or prognosis. The first two tasks are usually based on cross-sectional data and are relatively common, whereas longitudinal prediction requires long-term follow-up and reliable labels and is therefore more difficult and less frequently studied. From the perspective of clinical translation, however, longitudinal prediction more clearly demonstrates the value of ocular imaging for early warning, risk stratification, and health management.

AI not only enables automated, scalable ocular-image analysis but also shifts research from conventional morphometric quantification toward high-dimensional phenotype discovery. As multimodal fusion, longitudinal cohorts, and interpretability methods advance, deep learning may reveal increasingly complex links between ocular images and systemic pathological states. Table 2 summarizes representative AI models and the ocular-imaging tasks for which they are best suited.

Table 2. Overview of Representative Artificial-Intelligence Models.

Model category	representative models	core characteristics	principal advantages	major limitations	suitable ocular-imaging tasks.
Conventional machine learning	SVM, random forest (RF), decision tree, KNN, and naïve Bayes	classification or regression after handcrafted feature extraction	relative stability and interpretability in small-sample settings	strong dependence on feature engineering and limited capacity to exploit complex high-dimensional images	small-sample studies, handcrafted vascular-parameter analysis, and early baseline models.
Classical CNN	LeNet, AlexNet, VGG, and GoogLeNet	hierarchical extraction of local textures and structural features through convolution and pooling	mature foundational framework for image classification and routine fundus and OCT tasks	emphasis on local receptive fields with limited modeling of long-range dependencies	fundus-image classification, OCT classification, and basic disease recognition.
Residual/densely connected CNN	ResNet, DenseNet, and EfficientNet	residual connections or feature reuse to improve deep-network training and parameter efficiency	stable training and strong generalization as a common medical-imaging baseline	predominantly local convolutional inductive bias and limited global-pattern integration	multidisease classification, risk stratification, and multicenter baseline experiments.
Channel-attention model	SENet, SKNet, and ECA-Net	amplification of salient feature channels by learning channel importance	improved representation of fine-grained task-relevant structures	limited use of spatial location because the model emphasizes what features to attend to	retinal-vessel segmentation, lesion detection, and enhancement of small structures.
Spatial-attention model	Non-Local networks, Attention Gate, and ViT	weighting of spatial locations or modeling of global spatial dependencies	effective highlighting of vessels, the macula, and optic disc while capturing long-range relationships	high computational cost, particularly for high-resolution images	vessel segmentation, small-object detection, and global phenotypic modeling.
Hybrid-attention	CBAM, scSE,	joint channel-	concurrent	greater	fine

Model category	representative models	core characteristics	principal advantages	major limitations	suitable ocular-imaging tasks.
model	and DANet	and spatial-dimension weighting	modeling of what and where to attend to, often yielding more robust performance	architectural complexity, parameter count, and training cost	segmentation, multiscale phenotype extraction, and analysis of images with complex backgrounds.
Transformer model	Vision Transformer (ViT) and Swin Transformer	self-attention modeling of long-range dependencies and global relationships	integration of global patterns spanning the optic disc, macula, major vessels, and peripheral retina	demanding data and computational requirements and reduced stability relative to CNNs in small datasets	multiregional analysis, global risk modeling, and multimodal representation.
Foundation/self-supervised pretrained model	RETFound and related models	pretraining on large-scale unlabeled ophthalmic images followed by transfer to downstream tasks	mitigation of label scarcity and improved cross-task and cross-center generalization	unresolved issues in fine-tuning, failure detection, interpretability, and standardization	multidisease transfer learning, low-label tasks, and unified representation learning before real-world deployment.

5. Applications of Multimodal Ocular Imaging in Systemic Disease

5.1 Cardiovascular Disease and Vascular Risk Factors

Cardiovascular disease is a leading cause of death worldwide, and early detection and risk stratification are essential for reducing disability and mortality ^[23]. Because retinal vessels constitute one of the few microvascular networks that can be observed directly and noninvasively, hypertensive retinopathy has long been regarded as an important ocular marker of systemic vascular injury, and retinal vascular measures—including caliber, density, branching morphology, and tortuosity—are widely used in cardiovascular research ^[24,25]. The introduction of AI has further expanded the use of ocular imaging in cardiovascular risk assessment. Deep-learning models based on retinal images can identify conventional cardiovascular risk factors, including age, sex, blood pressure, and smoking status ^[26], and can also detect subclinical cardiovascular phenotypes such as atherosclerosis, hypertension, and coronary artery calcification.

In an early study, Poplin et al. ^[27] showed that deep-learning models could predict multiple cardiovascular risk factors from retinal photographs—including age, sex, smoking status, systolic blood pressure, and major adverse cardiovascular events—with an AUC of approximately 0.73. These findings indicate that fundus images contain cardiovascular-risk information not fully discernible by human observation, although the study was limited by dataset size, imaging field, and the completeness of clinical variables. Chang et al. ^[28] subsequently developed a CFP-based deep-learning model to predict carotid atherosclerosis and introduced the deep learning fundusoscopic atherosclerosis score (DL-FAS). The model predicted carotid atherosclerosis with an AUROC of 0.713, and DL-FAS independently predicted cardiovascular mortality; when combined with the Framingham Risk Score, it particularly improved prediction among individuals at moderate-to-high risk. However, because the study was based primarily on a single-center Korean population, the model requires further validation for generalizability.

For coronary-calcification risk assessment, Rim et al. ^[29] proposed RetiCAC, a deep-learning algorithm that predicts coronary artery calcium (CAC) from retinal photographs. The model outperformed individual clinical variables, including age, blood glucose, and smoking status, in predicting the presence of CAC, achieving an AUROC of 0.742. Combining RetiCAC with the pooled cohort equation (PCE) improved cardiovascular risk stratification in borderline- and intermediate-risk groups, suggesting that it may provide an alternative or adjunctive approach to CAC assessment in

resource-limited settings. Tseng et al. [30] subsequently validated Reti-CVD, a RetiCAC-related retinal AI risk-scoring system, showing that it could identify individuals with a 10-year CVD risk of at least 10% and improve the assessment of borderline-risk individuals by conventional models such as QRISK3.

Beyond direct risk prediction, several studies have attempted to infer cardiac structure and function from fundus images. Diaz-Pinto et al. [31] combined retinal photographs with demographic data to train a multichannel variational autoencoder and deep-regression models that estimated cardiac indices—including left ventricular mass and end-diastolic volume—and predicted future myocardial-infarction risk. In UK Biobank, models incorporating only age and sex predicted future myocardial infarction with sensitivity, specificity, and positive predictive value of approximately 0.74, 0.72, and 0.68, respectively; after excluding AMD cases from the AREDS dataset, the corresponding values were approximately 0.70, 0.67, and 0.67. These findings suggest that routine ophthalmic images may help identify individuals at high risk of future myocardial infarction.

For multimodal risk prediction, Lee et al. [32] integrated color fundus images with clinical risk factors in 2023 to develop machine- and deep-learning models for predicting future CVD risk. The study compared unimodal and multimodal models across different CVD latency periods, combinations of clinical risk factors, and external validation datasets. Multimodal models significantly outperformed image-only models, and AUROC remained stable whether conventional or noninvasive risk factors were used, demonstrating the complementary value of fundus images and clinical variables. However, the retrospective design requires confirmation in prospective studies.

With the development of self-supervised learning, Zhou et al. [33] introduced the ophthalmic foundation model RETFound. The model was pretrained on unlabeled CFP and OCT images and then fine-tuned for tasks including ischemic stroke, myocardial infarction, and heart failure. Comparisons of self-supervised strategies—including MAE, SimCLR, SwAV, DINO, and MoCo-v3—showed that the MAE encoder performed best. Subgroup analysis indicated better performance in White populations, possibly because the training data were drawn predominantly from the United Kingdom. RETFound reduces dependence on large-scale manual annotation and advances ocular-imaging AI from task-specific models toward general-purpose foundation models, although the study did not fully investigate fusion of CFP and OCT information. In an interpretable study of retinal vascular quantification, Cheung et al. [34] developed a deep-learning model for automated measurement of retinal vessel caliber. The model showed strong agreement with expert measurements, with intraclass correlation coefficients of 0.82–0.95, and predicted CVD-related risk factors—including blood pressure, BMI, total cholesterol, and glycated hemoglobin—from vessel caliber with performance comparable or superior to that of experts. Rudnicka et al. [35] subsequently developed QUARTZ to automatically quantify retinal arteriolar and venular width, tortuosity, and area and to predict circulatory mortality, stroke, and myocardial infarction in cohorts including UK Biobank. Although predictive performance did not improve significantly, a parsimonious model combining retinal vascular measures with age, smoking status, and medical history performed comparably or better than the FRS, supporting retinal vascular parameters as noninvasive biomarkers of vascular health.

For cross-modal fusion and device translation, Al-Absi et al. [36] combined retinal images with dual-energy X-ray absorptiometry (DXA) data for CVD diagnosis. Accuracy was 75.6% with retinal images alone, 77.4% with DXA alone, and 78.3% after fusion, indicating that fundus images can complement other medical data in early screening. Yi et al. [37] developed the Reti-CVD device to identify individuals at moderate-to-high CVD risk from retinal images using PCE- and QRISK3-defined strata as references; its negative predictive value reached 96.6%, supporting its use to rule out low-risk individuals and prioritize intervention. Other studies have predicted coronary calcium scores from retinal images, with AUC increasing at higher diagnostic thresholds; diagnosed CVD in patients with type 1 diabetes with an AUC of approximately 0.77; and detected peripheral arterial disease from fundus images with AUCs as high as 0.89. In 2025, Muthupalaniaptiaa et al. [38] developed a computer-based diagnostic framework for scanning retinal fundus images to detect potential indicators of cardiovascular disease. The system focuses on extracting the arteriovenous ratio (AVR), a clinically informative measure of vascular structural health. It estimates cardiovascular risk from segmented vessels and AVR values derived noninvasively from retinal images without additional instrumentation.

Despite its promise, the field remains limited by predominantly retrospective studies, ethnic bias in samples, inconsistent endpoints, insufficient model interpretability, and limited multimodal fusion. Future retinal AI systems combining multicenter prospective cohorts, self-supervised foundation models, and multimodal data fusion may improve early CVD screening and individualized risk management.

5.2 Diabetes

Diabetes and related metabolic abnormalities are among the earliest and most extensively studied systemic conditions in ocular-imaging research. Whereas early research focused primarily on diabetic retinopathy, recent work has expanded toward detecting diabetes more broadly, screening for dysglycemia, and predicting future disease risk. The pathophysiological rationale is that chronic hyperglycemia affects ocular tissues through oxidative stress, inflammation, and metabolic dysregulation and induces early structural and functional changes in the retinal microvasculature even before diabetic retinopathy becomes clinically apparent [39]. Studies have shown that AI models can identify hyperglycemia and type 2 diabetes effectively from fundus images. In 2020, Zhang et al. [40] developed a hyperglycemia-detection model from 1,222 fundus photographs of rural Chinese residents, achieving an AUC of 0.880, although the small sample limited generalizability. Zhang et al. subsequently developed a deep-learning model from more than 100,000 fundus images that both screened for prevalent type 2 diabetes and stratified five-year incidence risk using metadata such as age, sex, height, weight, BMI, and blood pressure; in external datasets, the detection model achieved an AUC above 0.80 and the prediction model an AUC of 0.824, while smartphone- and cloud-based implementation showed favorable scalability. Using retinal images from 50,077 UK Biobank participants for training and 12,185 for testing, Yun et al. [41] reported an AUC of 0.731 for type 2 diabetes prediction from fundus images alone versus 0.810 for a model based on conventional noninvasive risk factors, indicating that retinal images have independent predictive value but perform better when combined with conventional clinical factors.

OCT emphasizes quantitative analysis of retinal layers and tissue thickness; using OCT data from 2,824 UK participants, Al Younis et al. developed a machine-learning model that noninvasively classified heart-failure subtypes with an AUC of 0.70, suggesting that retinal structural features may reflect cardiac dysfunction and its heterogeneity. OCTA additionally captures retinal microvascular perfusion; using k-nearest neighbors, naïve Bayes, and SVM models to analyze OCTA microvascular parameters from 120 participants in France and Luxembourg, Rusu et al. predicted coronary-artery-disease risk with accuracy up to 86%, exceeding conventional models and suggesting incremental value for risk stratification. Multimodal studies further overcome the informational constraints of individual image sources; Guo et al. fused CFP with carotid intima-media thickness and related data in an SE-ResNeXt model that predicted CVD risk with an AUC-ROC of 90.41%, highlighting the potential of combining fundus images with vascular imaging or clinical indices for early CVD screening.

5.3 Kidney Disease

The kidney and eye share similarities in structure, development, physiology, and pathogenic pathways [42]. Ocular manifestations, including retinal microvascular parameters, have been shown to predict CKD progression [43]. Kidney disease may also be associated with ocular abnormalities, as exemplified by tubulointerstitial nephritis and uveitis syndrome (TINU syndrome). In children, TINU syndrome presents with fever, pain, photophobia, and acute bilateral nongranulomatous anterior uveitis in association with interstitial nephritis, with ocular symptoms typically preceding or coinciding with the renal diagnosis. A study of the association between age-related macular degeneration (AMD) and CKD found that early AMD without geographic atrophy or choroidal neovascularization was three times as prevalent in patients with moderate CKD as in those with mild or no CKD [44].

In an early fundus-image study of CKD screening, Wong et al. [45] trained three models in 2019: an image-only model using optic-disc- and macula-centered images from each eye, a clinical-data model using age, sex, ethnicity, smoking status, diabetes, and hypertension, and a fusion model combining both data types. The image-only and clinical-data models achieved AUCs of 0.9473 and 0.9317, respectively, whereas the fusion model improved the AUC to 0.9549. The study demonstrated the feasibility of population-level CKD screening from retinal images and laid a foundation for community-screening and public-health applications.

Building on this work, Sabanayagam et al. [46] developed, validated, and externally tested a retinal AI model for CKD in 2020 using three population-based, multiethnic cross-sectional studies from Singapore and China: the Singapore Epidemiology of Eye Diseases study (SEED), Singapore Prospective Study Program (SP2), and Beijing Eye Study (BES). The findings further supported Wong et al.'s algorithm and indicated that retinal images could serve as an adjunctive or opportunistic CKD-screening tool, particularly in community and primary-care settings.

Betzler et al. [47] subsequently extended this approach to the detection of diabetic nephropathy (DN).

The model was developed with fivefold cross-validation using Singapore Integrated Diabetic Retinopathy Program (SiDRP) data, externally validated in two independent datasets, and additionally tested in two predominantly White cohorts: the Australian Eye and Heart Study (AHES) and Northern Ireland Cohort for the Longitudinal Study of Ageing (NICOLA). In internal validation, the fusion model achieved an AUROC of 0.866, suggesting that retinal-image deep learning may provide an adjunctive DN-screening tool for people with diabetes.

To identify early renal impairment, Kang ^[48] developed and evaluated a fundus-image-based deep-learning model in 2020. The model achieved an AUROC of 0.81 for detecting early renal impairment in the overall population. When stratified by HbA1c, AUROCs were 0.81, 0.84, 0.85, and 0.87 among participants with HbA1c $\leq 6.5\%$, $>6.5\%$, $>7.5\%$, and $>10\%$, respectively, indicating stronger predictive performance in those with poorer glycemic control or more pronounced metabolic abnormalities. This finding also suggests that disordered glucose metabolism may strengthen the imaging association between retinal microvascular abnormalities and renal dysfunction.

In a study by Zhang et al. ^[49], an AI model trained on approximately 120,000 fundus images identified CKD-related features from CFP, clinical data, or their combination. Beyond early CKD detection, the model quantified eGFR and blood-glucose levels, demonstrating potential as a digital biomarker. Zhang et al. further conducted a five-year longitudinal cohort study and developed Cox survival models combining fundus-image risk scores with clinical data to predict incident major chronic diseases. The fusion model outperformed either clinical data or fundus images alone, indicating that fundus images complement conventional clinical indices and improve CKD risk assessment.

Joo et al. ^[50] developed Reti-CKD, a noninvasive CKD risk-stratification tool. The tool combined deep-learning features from retinal images with clinical factors and was validated in two longitudinal cohorts: UK Biobank and a Korean diabetes cohort. Compared with a conventional eGFR-based approach, Reti-CKD yielded superior ROC and net reclassification index (NRI) results, particularly for identifying individuals at high future CKD risk despite preserved renal function. These findings suggest that retinal AI risk scores may outperform methods based solely on eGFR and provide a new tool for early CKD risk prediction and stratified management. Nevertheless, external validation was constrained by population characteristics, and further validation across additional disease groups and ethnically diverse populations is required.

For DN detection, Shi et al. ^[51] proposed an AI algorithm in 2023 that combined retinal vascular parameters with readily available clinical variables and achieved a maximum AUROC of 0.914. The study demonstrated the complementary value of retinal vascular morphology and routine clinical measures and showed that joint modeling can improve detection of diabetes-related kidney injury.

Xie et al. ^[52] used AI-assisted ultra-widefield swept-source optical coherence tomography angiography (UWF-SS-OCTA) to identify reliable biomarkers for DN screening. Their analysis combined statistical methods, tenfold cross-validation, and random forests and focused on microvascular perfusion density in patients with diabetic retinopathy. UWF-SS-OCTA-derived microvascular perfusion density was strongly associated with DN, suggesting that AI-assisted ultra-widefield OCTA perfusion parameters may serve as novel imaging biomarkers for DN screening.

Other studies have reported AUCs as high as 0.938 for deep-learning detection of CKD from retinal images in multiethnic populations, with performance comparable—and in some settings superior—to that of physicians. These findings suggest that AI algorithms could be integrated into fundus cameras for adjunctive CKD screening in community or primary-care settings, complementing conventional screening based on serum creatinine and eGFR. AI analysis of retinal images has also accurately predicted CKD-related risk factors—including age, sex, smoking status, and blood pressure—and smartphone-based diagnostic systems may expand healthcare access and facilitate self-monitoring. More broadly, deep learning can identify biomarkers associated with multiple systemic diseases from structural features such as retinal vessels and optic-disc morphology, providing information relevant to the early diagnosis of CKD and other chronic diseases.

5.4 Hepatobiliary Diseases

Hepatobiliary disease is a distinctive but still developing area of ocular-imaging-based systemic-disease detection. Traditionally, clear ocular associations have been established for only a few hepatobiliary disorders, most notably the Kayser–Fleischer (K–F) ring in Wilson disease (hepatolenticular degeneration) ^[53]. The K–F ring is one of the most common and diagnostically informative ocular manifestations of Wilson disease and an important component of clinical diagnosis.

Researchers have recently applied deep learning to automated K–F-ring detection and grading. Using a database of 1,850 images from 399 patients with Wilson disease, Song et al. [54] found that several pretrained CNNs achieved high accuracy, with ResNet34 among the best-performing models, indicating that AI applied to corneal or slit-lamp images may support early screening and severity grading [54]. Because the ocular sign is relatively specific and clinically meaningful, this application represents one of the better-supported areas of ocular AI research in hepatobiliary disease.

Beyond Wilson disease, ocular-imaging research on hepatobiliary disorders more broadly has also made important advances. In a multicenter prospective study, Xiao et al. [55] developed hepatobiliary-disease screening and identification models using slit-lamp and fundus images. For overall hepatobiliary-disease screening, the slit-lamp model outperformed the fundus model; AI identified liver cancer and cirrhosis relatively well but performed less effectively for chronic viral hepatitis, nonalcoholic fatty liver disease, cholelithiasis, and hepatic cysts [55]. Ocular images therefore do not offer equal diagnostic value across hepatobiliary diseases and appear more sensitive to conditions with severe pathological changes and pronounced systemic effects. Visualization analyses further suggested that, in addition to the conventionally emphasized conjunctiva and sclera, the iris and fundus may contribute to model decisions, indicating that hepatobiliary ocular phenotypes may involve a broader range of tissues than external-eye changes alone.

In 2023, Babenko et al. [56] used deep-learning models trained on external-eye photographs to predict laboratory values and found that subtle periocular color and pattern cues identified individuals with abnormal liver-related measures, such as elevated AST or low serum albumin, with accuracy 5%–20% higher than that of nonimage models. Their findings suggest that chronic liver disease may produce subtle changes in conjunctival or scleral coloration that are small but visually detectable. Similarly, Mariakakis et al. [57] developed the early proof-of-concept BiliScreen system in 2017 to estimate bilirubin levels from smartphone photographs of the sclera. In a preliminary study of 70 participants, quantitative analysis of scleral color successfully flagged subclinical jaundice with approximately 90% sensitivity and 97% specificity. These examples illustrate how AI can transform widely available devices into screening tools for hepatic dysfunction by quantifying ocular biomarkers such as scleral icterus.

5.5 Neurodegenerative Diseases and Peripheral Neuropathy

The eye, particularly the retina, is regarded as an anatomical extension of the central nervous system and is therefore closely linked to the brain and spinal cord in both physiological and pathological states [58]. A growing body of evidence indicates that many neurological disorders are accompanied by ocular structural and functional changes. For example, patients with Parkinson's disease (PD) may exhibit visual dysfunction, retinal ganglion-cell loss, and thinning of the retinal nerve fiber layer (RNFL) [59], whereas patients with Alzheimer's disease (AD) may show retinal structural and functional abnormalities and retinal deposition of pathogenic proteins such as amyloid- β and phosphorylated tau [60]. On the basis of this well-established neuro-ocular relationship, researchers are using AI to extract neurological-disease phenotypes from ocular images for convenient, noninvasive early screening.

In a prospective study of cognitive decline and dementia risk, Cheung et al. [61] used deep learning to measure retinal vessel caliber automatically and found that narrower baseline retinal arterioles were associated with subsequent cognitive decline and increased dementia risk, supporting retinal vascular parameters as noninvasive risk markers. Using the CLSA database, Corbin et al. [62] combined retinal images with predicted cognitive scores and showed that fundus images and associated clinical information could assess cognitive status, suggesting a potential approach to screening for mild cognitive impairment and preclinical AD.

Cheung et al. [61] retrospectively pooled fundus images from patients with AD and healthy controls across 11 studies and used an EfficientNet-B2-based deep-learning model with unsupervised domain adaptation to perform binary AD classification from CFP and clinical risk factors. The study included 12,949 retinal images and achieved an internal-validation accuracy of 83.6%, sensitivity of 93.2%, specificity of 82.0%, and AUROC of 0.93; AUROCs in external test sets ranged from 0.73 to 0.91. The model also distinguished amyloid- β -positive from amyloid- β -negative individuals, suggesting that fundus images may reflect AD-related molecular pathology. However, the study was limited by a modest training sample, potentially inaccurate clinical labels, and substantial performance variation across test cohorts.

Multimodal ocular imaging may further improve the potential for AD screening. Although retinal images alone showed limited performance for predicting cognitive status, combining ultra-widefield imaging (UWF), OCTA, and fundus autofluorescence (FAF) yielded an AUC of 0.74 for AD detection [63]. Wisely et al. [64] developed AD-detection models combining OCT, OCTA, ultra-widefield scanning laser ophthalmoscopy, and clinical data; ganglion cell-inner plexiform layer (GC-IPL) thickness maps and multimodal fusion models performed particularly well, with AUCs above 0.80. AI models based on OCT texture features have likewise detected AD with an AUC of 0.795.

In 2024, Slootweg et al. [65] combined multimodal retinal imaging with generative AI to predict amyloid-PET status. The study used a CNN for classification and a denoising diffusion probabilistic model to generate synthetic multimodal retinal images for data augmentation. Synthetic images supported model pretraining and improved CNN-based diagnosis of amyloid-PET status, suggesting that generative AI may alleviate sample scarcity in neurodegenerative-disease research.

AlzEye [66] links longitudinal retinal images from Moorfields Eye Hospital NHS Foundation Trust with systemic-disease data from hospital admission records, focusing on CVD and dementia to identify latent retinal signals for early detection and risk management. However, its reliance on hospital records may lead to incomplete variables and limited population representativeness, while the predominance of patients with ocular disease may introduce selection bias.

For PD prediction, some studies have used deep learning to calculate the retinal age gap, defined as the difference between model-predicted retinal age and chronological age. Each one-year increase in retinal age gap was associated with an approximately 10% increase in PD risk, suggesting a potential noninvasive biomarker for screening high-risk populations [67]. However, the UK Biobank cohort was relatively healthy and young, included few incident PD events, and lacked longitudinal ocular data. In 2024, Tran et al. [68] systematically evaluated conventional machine-learning and deep-learning approaches for distinguishing patients with PD from healthy controls using UK Biobank fundus images, achieving 68% accuracy and improving interpretability and robustness through attribution maps and data-perturbation analyses. In the same year, Richardson et al. [69] developed a CNN to distinguish PD from controls using multimodal retinal images, including OCT-derived GC-IPL thickness maps and macular OCTA images of the superficial capillary plexus. Using pretrained VGG-19 as a shared feature extractor, the model achieved a maximum AUROC of 0.918, indicating that multimodal retinal imaging captures PD-related alterations more effectively than fundus photography alone.

Ocular-imaging AI has also been applied to neurological disorders beyond AD and PD. White-matter hyperintensities (WMHs), a major manifestation of cerebral small-vessel disease, can be predicted from fundus photographs with an AUC of approximately 0.70; Lau et al. [70] further linked retinal images with MRI findings to detect WMHs in healthy individuals with both sensitivity and specificity above 0.90. In neuropsychiatric disease, retinal-image models have identified autism spectrum disorder and schizophrenia with AUCs above 0.97, although these results may partly reflect cross-validation procedures and require independent external validation. Other studies have used AI to extract retinal vascular trajectories for identifying schizophrenia and bipolar disorder. The reported accuracies were 0.86 and 0.73, respectively.

Axial spondyloarthritis has also been distinguished from retinal images with an AUC of 0.74 [71]. For diabetic peripheral neuropathy, a CFP-based AI system has enabled simultaneous neuropathy-risk assessment during diabetic retinal screening and achieved an AUC above 0.85 among patients with diabetic retinopathy.

5.6 Autoimmune, Hematologic, and Other Systemic Diseases

Among hematologic disorders, ocular-imaging AI research has focused primarily on anemia detection. Anemia is generally defined by a reduced hemoglobin (Hb) concentration, and early detection is important for timely clinical intervention [72]. Although venous blood testing remains the gold standard for assessing Hb, it is invasive, causes discomfort, and carries exposure and contamination risks for healthcare workers, motivating the development of more convenient, noninvasive methods [72]. In routine physical examination, pallor of the palpebral conjunctiva, lips, and other mucocutaneous tissues is an important clue to anemia and provides a clear visual basis for AI detection from ocular images. The association between retinal imaging and anemia has also attracted increasing attention. Because retinal structure and vascular manifestations have been associated with anemia [73], researchers have begun investigating anemia detection from fundus images. Using UK Biobank data, Mitani et al. [74] developed a deep-learning model combining fundus images with

metadata to predict Hb and detect anemia; the combined model outperformed the image-only model and performed particularly well for monitoring anemia in people with diabetes, achieving an AUROC of 0.89. With the widespread adoption of OCT in ophthalmology, Wei et al. [75] were the first to predict anemia from retinal OCT images using deep learning and achieved high classification accuracy.

Conjunctival and scleral color and peripapillary morphological and vascular features are among the ocular indicators most frequently used by current models. Ocular-imaging AI may enable not only anemia classification but also noninvasive estimation of continuous Hb levels; integrating retinal images with metadata such as age, sex, ethnicity, and blood pressure substantially reduced the mean absolute error of Hb prediction and enhanced clinical-monitoring utility [73].

Ocular-imaging studies of hematologic conditions other than anemia remain limited. Some evidence suggests that blood groups may be associated with ocular disease—for example, group O with an increased risk of retinal pigment epithelial degeneration and groups A and B with glaucoma or age-related macular degeneration. Because blood group is also associated with systemic conditions such as infection and diabetes, AI analysis of ocular parameters could theoretically provide new insights into genetic background and disease risk. However, no mature AI system currently identifies blood group directly from ocular images or supports related clinical management, and this direction requires further investigation. Overall, AI applications of ocular imaging in hematology remain centered on anemia and offer noninvasive, convenient, and repeatable assessment, but external validation, environmental robustness, and cross-population generalizability require improvement.

6. Current Issues and Challenges

6.1 Data Heterogeneity and Insufficient Standardization

One of the principal technical barriers is the marked heterogeneity across modalities, devices, and acquisition protocols. Even within CFP, differences in camera type, field of view, illumination, and image compression affect model learning, while the greater variation in imaging principles and data structures across OCT, OCTA, CCM, and anterior-segment imaging further impedes cross-center generalization. Standardized acquisition and quality-control procedures across modalities and devices are therefore prerequisites for continued progress.

6.2 Limited Interpretability and Uncertain Biological Mechanisms

Although many models achieve strong discriminative performance, the structures and phenotypes underlying their decisions often remain unclear. Existing heatmaps and attention maps provide some visual explanation but fall short of mechanistic interpretation. For multimodal ocular imaging to achieve clinical translation, model discoveries must be linked to verifiable biological features, including vascular characteristics, retinal-layer thickness, corneal nerves, and anterior-segment phenotypes.

6.3 Multimodal Fusion Remains at an Early Stage

Although whole-eye imaging combined with clinical data is widely regarded as a future direction, few mature multimodal models currently exist. Most studies still focus on a single imaging modality or merely concatenate structured clinical variables with image features, leaving a substantial gap before robust and generalizable multimodal clinical systems can be realized.

7. Conclusion

Artificial intelligence-based multimodal ocular imaging has emerged as a promising noninvasive strategy for detecting and monitoring systemic diseases. The eye provides a unique window into systemic health, and modalities such as CFP, OCT, OCTA, CCM, and anterior-segment imaging offer complementary structural, vascular, and neural information. Deep learning can extract high-dimensional features beyond conventional morphometrics, with encouraging performance in cardiovascular disease, diabetes, kidney disease, hepatobiliary disorders, neurodegenerative diseases, and selected autoimmune and hematologic conditions. However, clinical translation remains limited by data heterogeneity, insufficient external validation, weak interpretability, and immature multimodal fusion. Future work should therefore prioritize standardized multicenter prospective studies,

explainable and generalizable models, and integration of ocular imaging with clinical and laboratory data. With these advances, oculomics may become a scalable, low-cost adjunct for early screening and risk stratification, particularly in primary-care and resource-limited settings.

8. Future Directions

First, the research paradigm will continue to shift from unimodal to multimodal approaches. Future systems are likely to derive greater value from combining multiple ocular-imaging modalities with age, blood pressure, laboratory indices, and medical history than from relying on fundus imaging, OCT, or CCM alone, thereby achieving more robust risk prediction.

Second, research objectives will shift from identifying prevalent disease to predicting future risk. This transition is already emerging in cardiovascular and kidney-disease research. Predicting future events, disease progression, or treatment response is more closely aligned with precision medicine and long-term management than simply determining whether disease is currently present.

Third, ocular-imaging AI will evolve from black-box prediction toward interpretable oculomics. Influential future studies should relate model outputs to quantifiable biomarkers—such as retinal vessel caliber, retinal microvascular parameters, retinal-layer thickness, and corneal nerve-fiber indices—rather than reporting performance metrics alone.

Finally, anterior-segment imaging and mobile health may broaden the reach of the field. Compared with approaches requiring dedicated posterior-segment devices, anterior-segment and ocular-surface imaging can be more readily integrated into primary care, telemedicine, and continuous health-monitoring settings. Although evidence remains limited, this direction may provide a crucial route for extending oculomics to broad populations because of its high accessibility.

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