• **Review Article** •

Oculomics: advances and perspectives from traditional Chinese medicine to modern multimodal biomarkers

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Abstract
● Oculomics, the study of the relationship between ophthalmic biomarkers (changes or abnormalities in the eye) and systemic health or disease states, posits that the eye can serve as a window into the overall health of the body. This concept aligns closely with the ideas of traditional Chinese medicine (TCM) ocular diagnosis, which similarly emphasizes the eye as a reflective indicator of systemic conditions. As a burgeoning field, oculomics extends beyond traditional imaging-based approaches to encompass a broader spectrum of ocular biomarkers, including biochemical and electrophysiological data. While retinal imaging has been a cornerstone in identifying structural biomarkers from eyes, the integration of biochemical omics (*e.g.*, metabolomics, proteomics, transcriptomics) and electrophysiological assessments offers a more comprehensive and multidimensional approach to understanding the association of systemic health between disease states. By integrating TCM ocular diagnosis with artificial intelligence, oculomics may offer a more cost-effective diagnostic option due to its non-invasive and economically efficient characteristics. In this review, we proposed a research framework for integrating ocular multimodal biomarkers from the perspectives of ocular imaging, biochemical testing, and electrophysiological assessment, further clarifying the new concept of oculomics. This multimodal approach exhibits significant potential for advancing precision medicine, ultimately improving patient outcomes through early detection and personalized treatment strategies.
● **KEYWORDS:** oculomics; traditional Chinese medicine; ocular diagnosis; biomarkers; integrative medicine
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INTRODUCTION

The eyes, as external orifices of the human body with highly intricate structures, can perceive diverse objects and subtle color changes in the environment, serving as a primary channel for external information acquisition. Unlike other organs, the eyes contain abundant neurons (*e.g.*, the optic nerve), vascular tissues (*e.g.*, the retinal vessels and choroid), and connective tissues (*e.g.*, the cornea and ciliary body). Pathological changes in these structures often indicate the presence of systemic diseases. Traditional Chinese medicine (TCM) ocular diagnosis is based on this concept, holding that "the eyes are a microcosm of the viscera". By observing changes in the appearance, color, shape, and posture of various parts of the eyes, practitioners infer the functions of internal organs and the state of disease. However, TCM ocular diagnosis primarily relies on the physician's clinical experience and visual judgment, making it prone to subjectivity and uncertainty. With advances in modern diagnostic technologies, oculomics has emerged as a new field that applies innovative techniques to detect abnormal ocular changes and screen for systemic diseases[1-3]. The term "oculomics" originates from the combination of "oculus" (Latin for "eye") and "omics" (referring to the comprehensive study of a set of biological molecules)[4], and it is used to describe clinical insights that link ocular biomarkers with systemic health status. An increasing number of studies demonstrate that oculomics may provide potential biomarkers for predicting extraocular diseases, such as diabetes[5], cardiovascular diseases[6], and neurodegenerative diseases[7]. Biomarkers, as objective and quantifiable indicators[8], complement the macroscopic observation of TCM ocular diagnosis, and provide new microscopic evidence to supports disease diagnosis, prognosis assessment, and personalized treatment strategies.

Currently, research in oculomics is mainly based on ocular imaging technologies with promising results. Li *et al*[9] found that retinal vascular characteristics are closely related to the incidence of aortic aneurysms and adverse aortic events, confirming the value of oculomics derived from retinal fundus images in the prediction and diagnosis of aortic aneurysms and their adverse outcomes. Wagner *et al*[10] found that patients with schizophrenia had measurable differences in neural and vascular integrity of the retina, suggesting retinal imaging may provide insight into the development of schizophrenia. In fact, beyond traditional imaging-based approaches, the integration of biochemical omics (*e.g.*, metabolomics, proteomics, transcriptomics) and electrophysiological assessments offers a more comprehensive and multidimensional approach to understanding systemic health and disease states[11-13]. Clinically, it is difficult to fully reveal the complex relationship between the eyes and overall health using a single detection method. For example, ocular imaging can directly visualize the structure and morphological features of ocular tissues, but it cannot reflect molecular-level changes. Biochemical testing can accurately identify the molecular markers related to diseases, yet it lacks information regarding functional status. Visual electrophysiological examinations enable comprehensive evaluation of the functional status of various ocular regions, but they cannot precisely localize abnormalities in specific structures. These techniques reveal diverse ocular phenotypes from multiple dimensions such as structure, molecule, and function. Although each method has limitations, they complement one another and collectively form the oculomics system. In this review, we integrate oculomics with TCM ocular diagnosis to discuss recent advancements in ocular biomarkers. On this basis, we further proposed that oculomics theory should encompass ocular imaging, biochemical omics, and electrophysiological assessments (Figure 1). This multimodal approach not only provides a unique perspective for the non-invasive visualization of microvascular circulation and the central nervous system within the human body, but also offers a systematic foundation for correlating ocular phenotypes with the pathological features of systemic diseases. Ultimately, it promotes the development of TCM diagnosis toward greater objectivity and internationalization.

CLINICAL IMPLICATIONS AND LIMITATIONS OF TCM OCULAR DIAGNOSIS

TCM diagnoses diseases through four methods: observation, olfaction, inquiry, and palpation. Among these, visual observation is a key component, providing an important clinical basis for disease diagnosis and prediction. *The Yellow Emperor's Inner Canon* recorded that the eyes are the place where the essence and energy of the body's internal organs converge. Based on this principle, physicians would inspect the eyes to identify disorders of internal organs. This approach aligns closely with the modern concept of oculomics, as both reflect the idea of "local reflection of the whole". Ocular diagnosis is characterized by its convenience and non-invasiveness, and it holds significant clinical value, especially in assisting the diagnosis and prognosis of neurological diseases as well as mental and psychological disorders, where it demonstrates obvious advantages. Mild cognitive impairment represents a transitional state between normal aging and dementia, characterized by abnormal results in objective cognitive tests[14]. Early screening and diagnosis of mild cognitive impairment are critical steps in preventing its progression to dementia. Observing dynamic ocular changes, including pupil responses and eye movements, can provide indicators for auxiliary disease diagnosis[15]. Depression is a common emotional disorder that typically characterized by persistent low mood and slow reaction speed. Studies have shown that ocular features in patients with depression differ significantly from those of healthy individuals[16-18]. Therefore, ocular diagnosis offers important evidence of disease progression by capturing ocular changes, without requiring sophisticated instrumentation. This makes it particularly valuable in the context of grassroots medical settings.

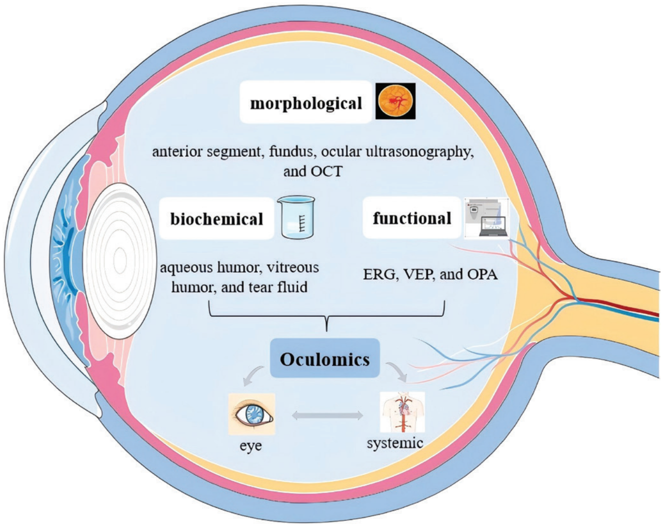

Figure 1 Framework of the oculomics system created by Microsoft PowerPoint. OCT: Optical coherence tomography; ERG: Electroretinogram; VEP: Visual evoked potentials; OPA: Ocular pulsatile amplitude.

However, TCM ocular diagnosis also has certain limitations. First, a systematic theoretical framework has not yet been established for ocular diagnosis, and unified standards are lacking for the collection and analysis of ocular diagnostic information. The diagnostic results depend on the visual

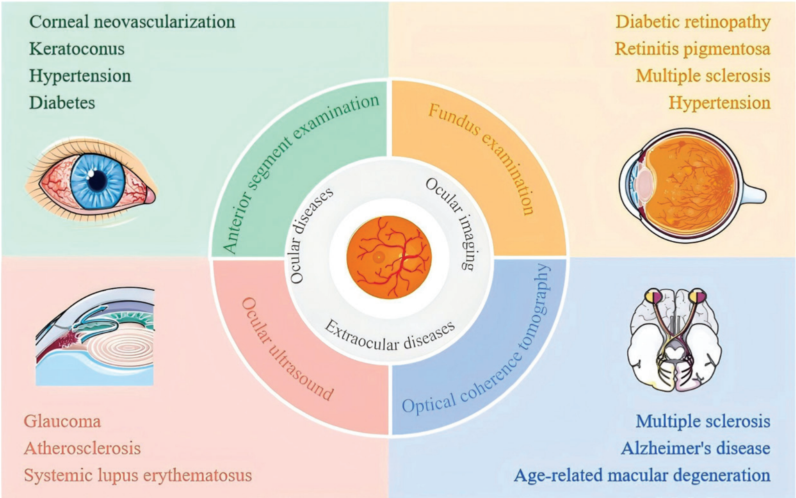

Figure 2 Overview of ocular imaging created by Microsoft PowerPoint.

observation and accumulated experience of the physicians, leading to potential differences in interpreting ocular features among practitioners with different educational backgrounds. Second, the relationship between ocular features and disease status is not one of simple correspondence. For example, abnormal ocular blood vessels may indicate local eye lesions, but they may also result from chronic systemic diseases such as hypertension and diabetes. This complexity increases the risk of both missed diagnoses and misdiagnoses. Third, ocular diagnosis mainly focuses on observable changes on the surface of the eyes and lacks specificity in identifying fundus lesions. Its diagnosis results must be combined with other clinical examination methods to improve accuracy. Modern diagnostic techniques provide a quantifiable scientific basis for TCM ocular diagnosis through quantitative detection and analysis of intraocular tissues, further expanding its clinical application. Therefore, to promote the development of precision medicine, the integration of macroscopic observation from TCM ocular diagnosis with biomarkers derived from modern diagnostic methods, together with the establishment of links between macroscopic phenotypes and molecular mechanisms, represents a key pathway for improving diagnostic precision.

ADVANCES IN OCULAR MULTIMODAL BIOMARKERS RESEARCH

Ocular Imaging As the core foundation of oculomics, ocular imaging has reached unprecedented levels of capability in the assessment of both ocular and extraocular diseases, including anterior segment imaging, fundus imaging, ocular ultrasonography, and optical coherence tomography (OCT; Figure 2). These technologies not only play a critical role in the diagnosis and monitoring of ocular diseases but also hold considerable potential for evaluating the ocular manifestations of systemic diseases, such as diabetic retinopathy and hypertensive retinopathy. Consequently, these technologies provide powerful tools for the early detection, classification, and prognostic evaluation of various diseases.

Anterior segment examination The slit-lamp microscope[19] is an indispensable equipment in ophthalmic examinations. Through high-resolution optical imaging, it enables visual observation of anterior segment tissues, including the cornea, anterior chamber, iris, lens, and vitreous body. Slit-lamp examination can provide excellent illumination of the eyelid and ocular surface. By adjusting the focus and the width of the light source, it not only facilitates observation of superficial structural lesions but also allows for the clear visualization of deeper tissue abnormalities. Corneal neovascularization is a common sign of anterior segment diseases[20]. The abnormal proliferation or regression of corneal vessels is of great significance for evaluating disease progression. Wu *et al*[21] revealed that slit-lamp examination can conduct a preliminary quantitative assessment of corneal neovascularization, effectively monitoring of corneal lesions. Further studies have shown that anterior segment findings also reveal signs of diseases affecting the posterior segment of the eye or systemic health[22]. For instance, keratoconus is a disorder characterized by the central thinning and protrusion of the cornea, presenting a conical shape. It can affect the thickness of the posterior retina, leading to retinal disorders[23]. Moreover, tortuous dilation of conjunctival blood vessels, alterations in pupil size, and other structural changes have been shown to reflect systemic conditions such as hypertension and diabetes[24-26]. Overall, anterior segment imaging technology, through both visual presentation and quantitative analysis, provides an objective tool for disease screening and diagnosis. However, further research is required to evaluate its sensitivity and specificity, as well as to assess its clinical application.

Fundus examination Fundus examination is a non-invasive technique that allows physicians to inspect the posterior ocular structures, including the retina, optic disc, and central retinal arteries and veins. Ophthalmologists can observe the morphological characteristics of the fundus as well as subtle changes in the optic nerve and blood vessels through an ophthalmoscope. These changes may be early signs of diseases. In diabetic retinopathy[27], early pathological changes include thickening of the basal membrane, dilation of blood vessels, and narrowing of capillary lumens. Fundus examination can reveal clinical manifestations such as microaneurysms, retinal hemorrhages, hard exudates, and macular edema, all of which are crucial for diagnosis. Retinitis pigmentosa[28] is a hereditary eye disease that mainly affects the photoreceptor cells of the retina. Fundus examination can find characteristic changes such as osteocyte-like pigmentation in the equatorial retina, narrowed retinal vessels, and a pale yellow optic disc, which are of great diagnostic significance for retinitis pigmentosa. Beyond ocular diseases, fundus examination is also useful in detecting systemic diseases such as multiple sclerosis (MS) and hypertension. MS is an autoimmune disease characterized by inflammatory demyelination of central nervous system white matter, with clinical manifestations including decreased vision, orbital pain, and color vision deficits. Optic neuritis[29] is one of the most common and often initial symptoms of MS. Using an ophthalmoscope, characteristic manifestations of optic neuritis such as congestion of the optic disc and blurred edges can be observed[30], which is beneficial for early identification of MS. Long-term persistent hypertension may also cause fundus changes, such as retinal artery narrowing or retinal edema, hemorrhage, and hard exudative spots. Fundus examination provides direct evidence of these pathological changes[31], making it highly valuable for assessing the severity of hypertension. Overall, the non-invasive nature of fundus examination makes it an indispensable tool in ophthalmology. However, its application also has certain limitations. It may miss diagnoses for complex lesions, which requires the combination of other examination methods to improve accuracy.

Ocular ultrasound examination Ocular ultrasound is a non-invasive, safe, and rapid diagnostic technique that provides pathological information about anterior segment structures of the eye, including the anterior chamber, posterior chamber, cornea, iris, ciliary body, and lens[32]. It is of great value in evaluating the dynamics behind diseases. Currently, ocular ultrasound examination is widely used to observe various conditions, such as retinal detachment, vitreous opacity, hemorrhage, ocular tumors, inflammation, and intraocular foreign bodies. In the diagnosis of glaucoma, ocular ultrasound serves as an important screening tool[33]. It can clearly display intricate intraocular structures, including the anterior chamber angle and ciliary body, as well as detect the position and thickness of the lens, assisting clinicians in understanding the pathogenesis of glaucoma. Furthermore, ocular ultrasound contributes to the diagnosis of diseases related to arteriosclerosis and systemic lupus erythematosus. In arteriosclerosis, ocular blood vessels may be affected in parallel with systemic vascular. Ocular ultrasound can observe changes in the central retinal artery and vein, such as intimal thickening and reduced elasticity. These findings reflect the systemic state of arteriosclerosis and provide reference value for diagnosing arteriosclerotic diseases caused by hypertension and hyperlipidemia. Systemic lupus erythematosus (SLE)[34] is a chronic inflammatory disease affecting multiple systems. Clinical manifestations include fever, photophobia, rash, enlarged lymph nodes, muscle and joint pain. Some patients may develop ocular lesions, such as conjunctivitis, iritis, uveitis, which can cause blurred vision or visual field defects. Ocular ultrasound can be used to assess the location and extent of lesions as well as ocular inflammatory status, thereby aiding in the evaluation of SLE and in monitoring therapeutic efficacy.

Optical coherence tomography OCT is a non-invasive, non-contact optical scanning technique[35]. It enables visualization of the internal structure and physiological functions of the eye by imaging tissues such as the retina, optic nerve, and choroid. In the diagnosis of age-related macular degeneration, OCT can detect characteristic structures including basal lamellar deposits, drusen, and subretinal drusenoid deposits[36]. These features serve as early indicators of age-related macular degeneration and highly valuable for early detection and timely intervention. OCT also plays a significant role in monitoring neurological disorders. For example, in Alzheimer's disease and MS, OCT can detect pathological changes, including thinning of the retinal nerve fiber layer (indicating retinal ganglion cell loss), reduction of the retinal vascular system, and increased neuronal plaque formation along the visual pathway[37-39]. By detecting these anatomical changes, OCT assists clinicians in assessing optic nerve health and improving the accuracy of disease diagnosis. Overall, as a rapid and non-invasive diagnostic tool, OCT provide a more comprehensive understanding of the microscopic structure of the eye. It is expected to further improve our understanding, diagnosis, monitoring, and treatment for various diseases. However, it should be emphasized that OCT is a sensitive but nonspecific tool for retinal pathology. Its results should be combined with a complete ophthalmic examination and visual field assessment to guide clinical decision-making.

Biochemical Testing As illustrated in Figure 3, biochemical testing of the eye encompasses both intraocular and extraocular fluids, such as aqueous humor, vitreous humor, and tear fluid. Disruption of the blood-retinal barrier in diseases affecting the retina or uveal tract (comprising the iris, ciliary body, or choroid) can lead to alterations in the biochemical composition of ocular tissues. Consequently, biochemical testing may provide essential information for the early diagnosis of ocular and systemic diseases, the assessment of therapeutic efficacy, and the monitoring of disease progression.

Tear detection Tears are an extracellular fluid secreted by the lacrimal glands that contain trace components such as proteins, lipids, metabolites, and electrolytes. They serve multiple functions, including nutrient delivery, waste excretion, and maintenance of ocular moisture. The lacrimal functional unit comprises the ocular surface (cornea, conjunctiva, and meibomian glands), the lacrimal glands, and the neural network connecting them. It regulates the secretion of tears through a regulatory mechanism. When ocular surface tissues undergo inflammatory responses, the lacrimal functional unit' function is impaired, resulting in changes in the composition and properties of tears. Abnormalities in tear composition can also reflect the health status of the ocular surface or the presence of systemic diseases. Dry eye is a chronic ocular surface disorder caused by multiple factors. The expression levels of tear proteins and cytokines can be determined through tear fluid testing[40-45], thereby assisting in the diagnosis of the disease. Diabetic retinopathy is one of the early microvascular complications of diabetes. Tears contain vascular endothelial growth factor, and its metabolome can provide relevant pathological information for diabetic retinopathy[43]. Sjögren's syndrome is a chronic inflammatory autoimmune disease characterized by reduced secretion of the lacrimal and salivary glands. Versura *et al*[44] conducted proteomic analysis of tear fluid and found that lactoferrin concentrations were significantly reduced in patients with Sjögren's syndrome, underscoring the diagnostic value of tear proteins for this condition. Alzheimer's disease is the most common neurodegenerative disorder, symptoms include cognitive decline and behavioral disorders[45]. Research has shown that amyloid-beta and tau proteins levels in tears correlate with Alzheimer's disease pathology[46-48]. Breast cancer is a common malignant tumor among women. Studies have reported that tear fluid testing can reveal the expression of Mammaglobin B[49], exosomal protein[50], and Galectin-3 binding protein[51]. This provides new insights into breast cancer screening. Overall, current research has confirmed that tears can serve as potential biomarkers for disease diagnosis. However, further studies are crucial for determining their specificity and reliability in disease screening[1]. Since the specificity of most biomarkers remains limited and many exhibit overlapping characteristics, future research should aim to improve the tear biomarker profile, explore their correlation with disease progression, and assess their potential as non-invasive diagnostic tools for systemic diseases.

Intraocular fluid detection Intraocular fluid refers to the aqueous humor and vitreous body within the eye. The aqueous humor is a colorless and transparent liquid secreted by the epithelial cells of the ciliary body. It contains proteins, vitamin C, sodium chloride, and inorganic salts, and plays an essential role in nourishing the cornea, lens, and trabecular meshwork. The vitreous is a colorless, transparent, gel-like substance located behind the lens that functions in light refraction and retinal stabilization. Due to the unique microenvironment of the eye, blood index tests often fail to accurately reflect intraocular conditions. However, detecting trace cytokines in intraocular fluid can more directly reveal the internal ocular environment and improve the accuracy of clinical diagnosis. Intraocular fluid testing provides important reference value for disease assessment. Glaucoma is a complex neurodegenerative eye disease. The aqueous humor is the key site of direct contact with the onset of glaucoma. The detection of aqueous humor is helpful for understanding the pathological state of glaucoma and for assisting in diagnosis[52]. In addition, Vig *et al*[53] found that postmortem vitreous humor levels of total tau were significantly associated with neuropathological diagnoses of Alzheimer's disease and chronic traumatic encephalopathy in postmortem brains, further confirming the potential role of vitreous biomarkers in the diagnosis of neurodegenerative diseases. Marfan syndrome (MFS) is an autosomal dominant genetic connective tissue disorder[54]. Its clinical manifestations include cardiovascular, skeletal, and ocular lesions, and it may present various serious complications such as aortic aneurysm, aortic dissection, and aortic rupture. Lens ectopia is a typical manifestation of MFS. Shi *et al*[55] conducted a quantitative proteomics study based on high-precision mass spectrometry and found that aqueous humor, as an important intraocular fluid, contains a large number of unidentified proteins. These proteins may serve as biomarkers for ectopic lenses in MFS. Therefore, intraocular fluid detection provides a potential indicator of the disease, thereby facilitating early screening and diagnosis.

Electrophysiological Assessments Changes in visual performance may serve as early indicators of both ocular and systemic diseases. Assessing visual performance plays a crucial role in the early diagnosis and management of these conditions. Electroretinography (ERG), visual evoked potential (VEP), and ocular pulse amplitude (OPA) are three key electrophysiological assessments techniques (Figure 4). These methods record the eye's electrical response to light stimuli, the brain's electrical response to visual stimuli, and variations in intraocular pressure during the cardiac cycle. Together, they provide valuable information for diagnosing and managing both ocular and systemic diseases. The development and application of these technologies enable clinicians to achieve more accurate diagnoses, evaluate treatment efficacy, and offer personalized treatment plans for patients.

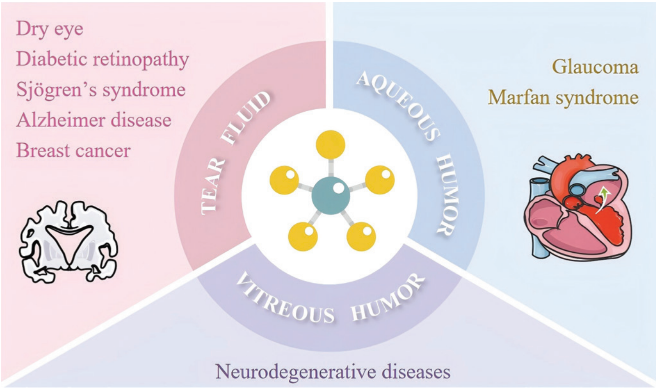

Figure 3 Biochemical testing of ocular tissues created by Microsoft PowerPoint.

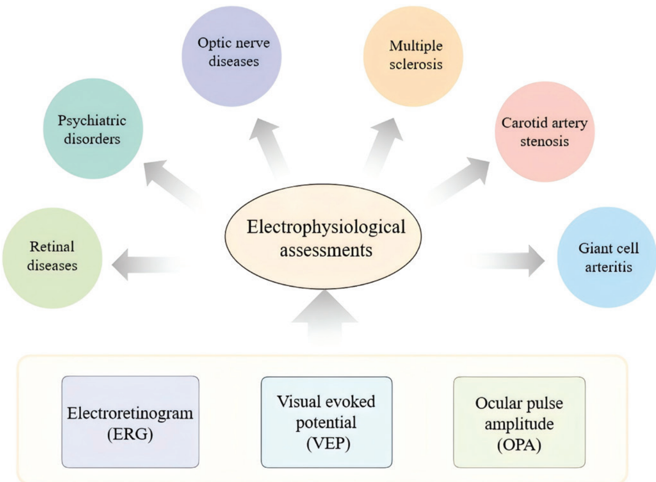

Figure 4 Three key electrophysiological assessments techniques created by Microsoft PowerPoint.

Electroretinogram ERG is a method that uses light or images to stimulate the electrical activity of the retina, enabling accurate, rapid, and objective recording of the functions of multiple small areas at the posterior pole of the retina. Clinically, ERG is mainly used for diagnosing primary retinal diseases (*e.g.*, retinitis pigmentosa, retinal detachment), but studies have found that abnormal manifestations of ERG are also closely related to various extraretinal diseases. For example, some mental disorders, including bipolar disorder, schizophrenia, or autism spectrum disorder, may affect retinal function through alterations in central dopamine and serotonin neurotransmission, resulting in changes in the ERG waveform[56-58]. Additionally, systemic diseases such as hypertension and diabetes can damage the retinal microvasculature, thereby affecting retinal electrophysiological activity[59-60]. In these cases, abnormal ERG patterns provide important reference for both diagnosis and monitoring disease progression.

Visual evoked potentials VEP is an objective method for evaluating visual functions. It measures the electrical activity generated by the brain in response to visual stimuli to detect the integrity of the visual pathways from the retina to the visual cortices[61]. VEP testing is commonly used for diagnosing of optic nerve disorders, such as optic neuritis[62] and ischemic optic neuropathy[63]. Extensive research has confirmed that the application of VEP is not limited to ophthalmology, but also extensively involves the potential impact of multiple systemic diseases on the visual pathway. For example, in patients with MS, VEP can assist in early diagnosis by detecting visual nerve conduction delays (*e.g.*, prolonged latency of the P100 wave), even suggesting subclinical optic nerve damage before obvious visual impairment occurs[64-65]. The characteristic changes of VEP, such as significant reduction in amplitude, can reflect optic nerve microvascular lesions caused by abnormal blood glucose levels, providing an objective basis for the screening diabetic nerve complications[66]. Therefore, VEP offers multi-dimensional functional evidence for disease diagnosis and achieve early intervention.

Ocular pulsatile amplitude OPA is an ophthalmic measurement parameter that describes the range of intraocular pressure variation during the cardiac cycle, typically between 1 and 3 mm Hg. Studies have shown that OPA is a novel method for reflecting retinal blood flow, and its measurement can provide insights into ocular hemodynamic status and mechanisms of intraocular pressure regulation, which is beneficial for diagnosing eye diseases such as diabetic macular edema and glaucoma[67-69]. OPA is an intuitive reflection of the periodic impact of the heart's pumping on intraocular blood flow. Abnormal fluctuations in OPA are significantly associated with various systemic diseases. For example, carotid artery stenosis is a common vascular disorder that can lead to serious consequences such as cerebral ischemia and stroke. A study comparing patients with severe carotid artery stenosis and those without carotid artery stenosis reported significant differences in OPA measurements, suggesting that OPA can serve as a potential non-invasive assessment indicator for carotid artery stenosis[70]. Giant cell arteritis is a systemic vasculitis characterized by symptoms including headache, scalp tenderness, myalgia, or diplopia. Existing studies have confirmed that reduced OPA levels are strongly correlated with giant cell arteritis[71], highlighting its potential value in early diagnosis. With the advancement of interdisciplinary research, OPA is expected to transform from a single intraocular pressure monitoring parameter into a dynamic monitoring window for systemic diseases.

DISCUSSION

Core Challenges and Solutions in Oculomics Research

Although the application of oculomics in disease diagnosis has made significant progress, several challenges remain to be solved urgently. First, the acquisition of ocular samples is characterized by particular complexity and specificity. Differences in collection methods and standards across

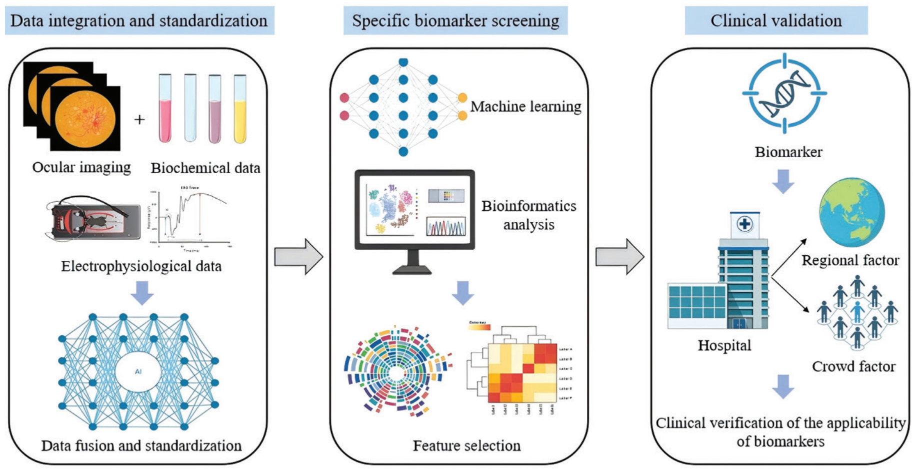

Figure 5 The research framework for integrating ocular multimodal biomarkers created by Microsoft PowerPoint.

medical institutions and regions not only lead to a scarcity of high-quality data but also make it difficult to achieve adequate sample sizes for research. Establishing unified data standards and constructing a high-quality ocular sample biobank will lay a solid foundation for oculomics research. Second, ocular tissues are influenced by special structures such as the blood-retina barrier[72] and the blood-aqueous barrier[73], which may lead to more complex release and detection of biomarkers, and non-specific signals may be amplified, increasing the difficulty of data analysis and validation. How to screen out highly specific biomarkers from the complex omics data has become a key issue in disease diagnosis. As a rapidly developing research field, oculomics needs to be combined with more emerging omics technologies, such as single-cell omics and spatial transcriptomics, in order to enhance the specificity and accuracy of diagnosis. Finally, the existing diagnostic markers lack direct correlation with clinical phenotype. Although certain marker abnormalities may indicate the presence of disease, they often fail to precisely correspond to disease subtype or stage, thereby limiting their clinical diagnostic and prognostic value. Therefore, research in oculomics must be guided by the goal of addressing clinical needs. By standardizing experimental procedures (*e.g.*, detection methods, sample processing), the differences between experiments and clinical practice can be bridged. Moreover, multi-center and large-sample clinical studies are essential to systematically verify the universality of associations between biomarkers and specific disease phenotypes.

Trends in the Development of AI-Enabled Oculomics The rapid development of artificial intelligence (AI) technology has created new opportunities for ophthalmology research. Deep learning, as a key branch of machine learning, can automatically learn multi-level and complex image features from ocular imaging data by constructing intricate neural network models, thereby assisting in clinical diagnosis. Applying deep learning to ocular images has significantly improved the speed of biomarker identification, as well as their sensitivity and specificity, which helps reduce diagnostic and therapeutic errors and promotes personalized medicine[74-76]. Studies have confirmed that AI technology has unique advantages in identifying disease-specific patterns and discovering new correlations, and it can reach the same level as expert clinicians. Li *et al*[77] using retinal images to predict the incidence and progression of glaucoma, the results showed that the deep learning models for predicting the incidence and progression of glaucoma achieved receiver operating characteristic area under the curve values of 0.90 and 0.91, respectively, demonstrating the feasibility of the deep learning algorithm in the early detection and prediction of glaucoma. Lin *et al*[78] trained a clinically applicable deep learning system for ocular fundus diseases using data from the real world. The results showed that the deep learning system demonstrated satisfactory performance in screening multiple retinal abnormalities in the real environment using prospectively collected fundus photographs, further confirming the potential advantages of deep learning in the field of retinopathy. Xiao *et al*[79] used deep learning algorithms to establish a qualitative correlation between ocular features and major liver and gallbladder diseases, achieving automatic screening and identification of liver and gallbladder diseases from ocular images, providing a non-invasive, convenient, and complementary method for the screening and identification of liver and gallbladder diseases. In general, deep learning provides a powerful tool for disease diagnosis. With the continuous development of AI technology, its application in oculomics research will be more extensive and in-depth.

Integrating Ocular Multimodal Biomarkers: a New Paradigm in Oculomics Research Given that a single biomarker may not be sufficient to comprehensively reflect the complex relationship between ocular and systemic diseases, we proposed a framework for integrating ocular multimodal biomarkers (Figure 5). By combining multidimensional data such as ocular imaging, biochemical testing, and electrophysiology, we introduced the new concept of oculomics, which employs various non-invasive and relatively rapid screening methods to detect structural, molecular, and functional changes in the eyes, thereby achieving early disease diagnosis. Its essence is to construct a new paradigm for studying association between ocular characteristics and systemic diseases through the integration of multimodal information. This framework consists of three major components: data integration and standardization, screening of specific biomarkers, and clinical validation. During the data integration and standardization stage, it is essential to merge data from different sources and formats while developing robust algorithms and models for comprehensive analysis. Deep neural networks can play a pivotal role in processing and interpreting complex datasets[80-82]. Additionally, the establishment of standardized protocols for sample collection, data acquisition, and analysis ensures consistency and reproducibility across studies. In the biomarkers screening stage, the focus is on identifying synergistic features from multimodal data. Machine learning algorithms or bioinformatics analysis methods can be applied to select feature combinations that show strong correlations with disease. In the clinical validation stage, multi-center, large-sample, and prospective cohort studies are required to verify the stability and applicability of the selected biomarkers under diverse geographical and population conditions. Such endeavors would facilitate the efficiency of early screening and diagnosis of diseases, thereby improving the long-term prognosis and quality of life of patients.

In conclusion, the development of oculomics technology provides clinicians with precise, objective, and means to observe subtle changes within the eyes. This approach not only complements traditional macroscopic medical observation but also enhances our ability to predict systemic diseases. It even enables the detection of human changes earlier than clinical manifestations for early intervention. With the increasing availability of large imaging datasets, deep learning models can be integrated with ocular biomarkers to provide scientific insights into disease-specific patterns and associated features. In the future, research that integrates multiple modalities of ocular biomarkers is expected to demonstrate significant potential in medical fields beyond ophthalmology, including neurodegenerative, cardiovascular, and metabolic diseases. Such advancements will provide clinicians with efficient and reliable screening tools while promoting the objectification and standardization of TCM diagnosis.

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