Artificial Intelligence in Retinal Medicine: A Visionary Revolution

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ABSTRACT Artificial intelligence (AI) has emerged as a powerful technology in medicine, with a potential to revolutionize various aspects of disease management. In recent years, substantial progress has been made in the development and implementation of AI algorithms and models for the diagnosis, screening, and monitoring of retinal diseases. We present a brief update on recent advancements in the implementation of AI in the field of retinal medicine, with a focus on age-related macular degeneration, diabetic retinopathy, and retinopathy of prematurity. AI algorithms have demonstrated remarkable capabilities in automating image analysis tasks, thus enabling accurate segmentation and classification of retinal pathologies. AI-based screening programs hold great promise in cost-effective identification of individuals at risk, thereby facilitating early intervention and prevention. Future integration of multimodal imaging data including optical coherence tomography with additional clinical parameters, will further enhance the diagnostic accuracy and support the development of personalized medicine, thus aiding in treatment selection and optimizing therapeutic outcomes. Further research and collaboration will drive the transformation of AI into an indispensable tool for improving patient outcomes and enhancing the field of retinal medicine.

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Artificial intelligence (AI) is an advanced field of computer science that focuses on the development of sophisticated computational systems and algorithms. These tools enable machines to perform complex tasks that were previously exclusive to human capabilities, including learning, drawing conclusions, and thinking. The field of AI deals with the development and application of techniques and processes based on the analysis and understanding of complex data by artificial neural networks that mimic the structure of nerve cell networks in the human brain.

VARIOUS ASPECTS OF AI MAKE IT HIGHLY SUITABLE AND ADVANTAGEOUS FOR MEDICAL APPLICATIONS.

Machine learning focuses on the development and use of algorithms that allow a machine to learn from data and predict and understand patterns automatically. Deep learning is a more advanced subfield of AI that focuses on the development of methods for deep analysis of data, which gives computers the ability to autonomously learn from the data and make intelligent decisions. By using a multi-layer network model (convolutional neural networks [CNN]), deep learning enables the machine not only to understand the data but also to generate new content from it [1].

Computer vision is another branch of AI that deals with the understanding and segmentation of visual information. Computer vision includes object recognition, characterization of visual patterns, and motion analysis [2]. A combination of diverse approaches coupled with the capacity for sophisticated processing and rapid analysis of huge datasets, identification of subtle patterns, and complex decision making, has led to widespread applications of AI across varied fields, including health and medicine. AI can improve the accuracy, efficiency, and accessibility of medical treatment, and holds promise for the advancement of personalized medicine.

Ophthalmology stands at the forefront of the implementation of AI into medical practices. In recent years, AI has emerged as a transformative technology that can revolutionize the way in which common eye conditions are diagnosed, monitored, and managed. In this context, retinal medicine takes a leading role in the development and application of AI approaches to clinical needs. First, retinal medicine extensively relies on a variety of high-resolution imaging techniques such as color photography, fluorescein angiography, and optical coherence tomography (OCT), which is a prominent non-invasive imaging method based on the principle of reflecting a light beam onto the tissue to obtain a series of high-resolution two-dimensional cross-sectional images, primarily of the retina [3]. These tests often generate complex datasets whose interpretation requires expertise and experience, making them particularly suitable for analysis by sophisticated algorithms. CNNs in image analysis enable the identification of specific characteristics and pinpointing of subtle patterns within the image (segmentation). They can also offer a categorical diagnosis by extracting relevant information (classification) and tracking changes in the image over time to identify characteristics that predict the progression of the disease (prediction) [4]. The performance of such systems is usually much faster compared to the assessments performed by human experts. Moreover, they enable identification of uncommon occurrences, contributing to an informed prioritization of tasks and effective determination of levels of urgency. Furthermore, the availability and abundance of universal retinal imaging tests provide substantial volumes of high-quality data, which is essential for constructing and training models for image recognition and classification. Last, the incidence of retinal diseases, and especially of age-dependent conditions, is constantly rising with the aging population, which increases the critical need to develop tools for remote diagnosis and monitoring, especially in areas where the availability of retinal specialists and ophthalmology services is limited. Integration of AI-based review models into remote imaging systems (telemedicine) can facilitate consultation and guidance to patients who do not have direct access to medical services, thereby minimizing geographic and demographic barriers.

ARTIFICIAL INTELLIGENCE IS DRIVING SIGNIFICANT ADVANCES IN RESEARCH AND INNOVATION IN OPHTHALMOLOGY, WITH TREMENDOUS POTENTIAL TO IMPROVE THE EFFICIENCY AND ACCURACY OF DIAGNOSIS, MANAGEMENT, AND TREATMENT OF COMMON EYE DISEASES.

To date, the development of applications of AI in retinal medicine has focused on several main areas [5]: overview of diseases (automated screening), automated diagnosis, and remote monitoring. Another avenue involves the development of support systems for surgical processes and medical robotics. In terms of diagnostic capabilities,

Deep-learning models are developed for the analysis of color or OCT images. The retinal diseases most studied so far in this context are age-related macular degeneration (AMD) and diabetic retinopathy (DR). Several devices utilizing advanced imaging technologies with AI algorithms are already commercially available. These devices enable efficient and accurate identification, characterization, and monitoring of AMD and DR and thus can promote early diagnosis, intervention, and improve the management of these sight-threatening conditions. Of note, these systems demonstrated performance equal to the capabilities of human experts. In 2018, the U.S. Food and Drug Administration (FDA) approved the first AI-based system for the review of DR, which is the first autonomous system approved for use in medicine [6].

Our review provides information about selected developments of AI dealing with AMD, DR, and retinopathy of prematurity (ROP).

AGE-RELATED MACULAR DEGENERATION

AMD is the leading cause of severe vision loss among the elderly in developed countries, affecting millions worldwide [7]. AMD is characterized by a gradual neurodegenerative process affecting the macula, the central region of the retina responsible for detailed vision. Despite its high prevalence and extensive research efforts, the pathophysiology of the disease remains poorly understood. Nevertheless, several morphological features facilitate the establishment of diagnosis, disease staging, and determination of treatment strategies [8]. In advanced stages, progression to the *wet* form can occur, marked by abnormal growth of new blood vessels beneath the macular center. These vessels may leak and cause irreversible damage characterized by the accumulation of fluid, proteins, and lipids in the retinal tissue, accompanied by the degeneration of its normal cellular structure and subsequent vision loss. In such cases, treatment involving intravitreal injections of vascular endothelial growth factor (VEGF) inhibitors has proven efficacious in preventing further macular deterioration and significantly enhancing visual outcomes. In contrast, the *dry* state, marked by progressive atrophy of the retinal pigment epithelial cells (RPE), the photoreceptors and the choriocapillaris in the

ARTIFICIAL INTELLIGENCE ALGORITHMS CAN RAPIDLY ANALYZE LARGE AMOUNTS OF RETINAL IMAGING DATA, FACILITATE THE DEVELOPMENT OF PERSONALIZED TREATMENT PLANS, AND IMPROVE THE ACCURACY OF MANAGING COMPLEX RETINAL DISEASES.

macular center, accounts for nearly 90% of advanced AMD cases. Encouragingly, recent advancements have been made in the treatment of the dry state as well.

Researchers have described the development of models aimed at the diagnosis of AMD by classifying color photographs of the macula for the purpose of identifying cases necessitating prompt specialist care. Yet, the prevalent diagnostic test for AMD is an OCT scan, and therefore the majority of ongoing efforts center around the analysis of OCT data using CNNs models to efficiently and promptly identify specific findings indicative of treatable stages of the disease.

The Geographic Atrophy Intelligent Analytics algorithm is based on the analysis of OCT scans of patients with dry AMD who develop geographic atrophy of the macula. This model involves automated image segmentation and quantitative analysis of the outer retinal layers structure to monitor the progression of the degeneration according to the clinical disease classifications. Remarkably, the system exhibited performance comparable to manual evaluation conducted by experts in the field [9].

COLLABORATION AMONG OPHTHALMOLOGISTS, ARTIFICIAL INTELLIGENCE EXPERTS, AND REGULATORY BODIES IS ESSENTIAL TO ESTABLISH GUIDELINES AND FRAMEWORKS PROMOTING TRANSPARENCY, SAFETY, AND PERSONALIZED PATIENT CARE.

DIABETIC RETINOPATHY

DR represents a significant complication of diabetes mellitus. It affects tens of millions of patients worldwide and is the primary cause of vision loss among working-age diabetic patients [10]. DR is caused by microangiopathy in the retina and without appropriate ophthalmic and systemic treatment, severe and irreversible vision loss may occur. Diabetic macular edema (DME) is a potential manifestation of DR in which vascular hyperpermeability leads to fluid leakage into the retinal tissue, which results in the formation of macular thickening. The standard treatment for DME typically involves intravitreal administration of VEGF-inhibiting drugs or steroidal agents, which usually facilitates the absorption of the edema and an improvement in vision. Early diagnosis and treatment are of utmost importance to reduce the risk of irreversible vision loss and enhance the likelihood of preserving functional vision. AI-based tools have the potential to improve access to DR screening and facilitate early detection. Current developments in this field primarily focus on computerized analysis of color photographs of the retina. Several studies have detailed the performance of such systems, demonstrating equivalence to expert capabilities and offering a more cost-effective and efficient alternative compared to traditional review systems [11].

IDx-DR (Digital Diagnostics, USA) is an autonomous AI system that has received FDA approval for DR detection. Operating by analyzing color images of the retina captured by an onboard camera, it provides a diagnostic assessment within minutes. This technology aids healthcare providers in conducting broad patient screening for detection of DR in primary care settings, facilitating early intervention. Another FDA-approved system, EyeArt® (Eyenuk, Inc., USA), offers real-time diagnosis during imaging for patients, while the EyRIS SELENA+ system (EyRIS, Singapore) has gained approval for use in Europe and Singapore [12].

More recently, various research systems have been introduced that not only detect the presence of DR but also offer a more precise diagnosis of the disease stage through the analysis of color photographs of the retina [13]. Other studies focused on the analysis of OCT scan datasets for the computerized detection of DME, including predicting response to treatment. An example of this progress is the Maestro2 system (Topcon, Japan), which integrates AI algorithms. This platform provides high-resolution cross-sectional images of the retina. The integrated AI algorithms assist in analyzing the images to identify specific disease characteristics. While such advancements have not yet reached the stage of routine application in patient care, they hold considerable promise for ongoing research and potential implementation in the future.

RETINOPATHY OF PREMATURITY

Retinopathy of prematurity (ROP) is a vascular retinal disease affecting premature infants worldwide. Several initiatives have been undertaken to develop systems for segmenting and characterizing the structure of the blood capillaries in the retina based on color fundus photographs in premature infants. The objective is to identify situations that constitute a threshold for treatment [14]. An example is the i-ROP Deep Learning system developed by i-Optics, was specially designed to identify ROP in premature infants. The system reached a specificity of 94% and a sensitivity of 93% for the diagnosis of ROP-plus and a specificity of 94% and a sensitivity of 100% for the diagnosis of the ROP pre-plus stage [15]. Such systems may play a crucial role in situations where access to specialists in pediatric retina is limited.

APPLICATIONS OF AI

In the developing field of AI and retinal medicine, several applications extend beyond diagnosis. One notable development involves image enhancement, utilizing deep-learning systems to refine images by removing artifacts and increasing the signal-to-noise ratio. This process broadens the scope of visual information and enhance its accuracy [16]. In addition, ongoing research and development are focused on AI applications for retinal surgeries. These systems enhance intraoperative imaging, offer real-time guidance, improve diagnostic capabilities, and assist surgeons in making informed decisions throughout different stages of surgery [17].

AI also plays a crucial role in telemedicine, facilitating the identification, classification, and monitoring of conditions such as DR and AMD. This technology aids in the examination of cases, accurately identifying urgent situations that require immediate treatment and reducing unnecessary referrals, thereby optimizing resource allocation. ForeseeHome, a remote eye monitoring technology developed by Notal Vision, Ltd. (Tel Aviv, Israel), is a home OCT system that leverages AI for the early detection of wet AMD through patient self-monitoring [18]. This system, approved by the FDA, is designed to preserve vision in at-risk patients by enabling treatment at an earlier stage. It is currently available for use in the United States.

The global population is aging, leading to a rise in the prevalence of sight-threatening eye diseases, particularly retinal conditions [19]. AI addresses these concerns with current applications focusing on the early detection and computerized identification of disease through retinal imaging data. However, it is evident that AI will soon become an integral part of daily medical practice, playing a substantial role in patient treatment. Anticipated future developments include the integration of various additional indicators into AI decision-making processes, such as clinical, genetic, and laboratory parameters. This integration enhances treatment precision and enables personalized adaptation for each patient. Nevertheless, it is crucial to acknowledge the current limitations of technology. The algorithms are often considered a *black box*, making it challenging to understand the logic behind the decisions made by AI systems. This lack of transparency may pose challenges in fully integrating technology into daily medical practice and might create hesitancy among healthcare professionals and patients alike in fully trusting the decisions made by AI systems.

Another challenge in the application of AI in retinal medicine arises from the necessity for large and diverse datasets to train models, ensuring reliable and universally applicable results. Acquiring such datasets can be particularly challenging for rare eye diseases or specific patient populations, which may lead to reduced accuracy and generalizability of the algorithms. In addition, ethical and regulatory considerations are crucial.

Ensuring the safety, privacy, and authentication of patient data used by AI requires careful attention and compliance with strict regulations. To address these challenges, continuous research is essential, necessitating universal and mandatory collaboration between clinicians and AI experts. Standardization efforts and the formation of clear ethical guidelines are also crucial steps in navigating the complex landscape of AI in ophthalmology.

CONCLUSIONS

AI holds great potential to revolutionize the field of ophthalmology and retinal medicine by improving early detection of sight-threatening diseases, diagnostic accuracy, operational efficiency, and personalized treatment. By harnessing its power, healthcare professionals will be able to improve access to care, enhance patient outcomes, and deepen our understanding of both healthy and diseased retinal conditions. However, it is important to acknowledge that AI is a tool that complements the human expertise of ophthalmologists. The human touch, connection, and intuition remain indispensable and will always remain the cornerstone of the relationship between retina patients and their doctors. While AI brings transformative benefits, it is the combination of technological advancements and human care that ensures comprehensive and compassionate patient-centered approaches in the realm of retina healthcare.

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Capsule

Targeting the fusion peptide

The fusion peptide (FP) on the HIV-1 envelope protein is a conserved site that can be targeted by neutralizing antibodies. However, the extent of protection conferred by FP-directed antibodies in the context of mucosal infection is unclear. **Pegu** et al. tested three different anti-FP antibodies, including one human antibody and two rhesus macaque antibodies, for their ability to neutralize HIV-1 in vitro and confer protection against simian-human immunodeficiency virus (SHIV) challenge of rhesus macaques in vivo. All three antibodies conferred protection against mucosal challenge with SHIV at clinically meaningful titers, supporting the further development of both anti-FP antibody therapies and vaccines designed to elicit anti- FP humoral responses.

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Capsule

Microbiota-reactive T cells trigger colitis

Cancer immunotherapy with immune checkpoint inhibitors blocks negative signals of T cell activation to mount an immune response against tumors but can also lead to immunopathologies. Colitis is a frequent and severe adverse event in patients treated with antibodies targeting the checkpoint inhibitor cytotoxic T-lymphocyte protein 4 (CTLA-4), but the underlying mechanisms leading to this reaction remain unclear. **Lo** et al. demonstrated that CTLA-4 blockade-induced colitis in mice is dependent on gut microbiota composition and is driven by the unrestrained activation of T cells and the concurrent depletion of a subset of regulatory T cells in the gut by receptors recognizing the Fc domain of the anti-CTLA-4 antibodies. Anti-CTLA-4 nanobodies lacking the Fc domain were found to stimulate antitumor immunity without inducing colitis. These findings may support the development of next-generation CTLA-4 inhibitors with reduced inflammatory toxicities.

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