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EDITORIAL

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Precision medicine and glaucoma management: how mathematical modeling and artificial intelligence help in clinical practice

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1. Introduction

Open angle glaucoma (OAG) represents a leading cause of irreversible blindness worldwide [1]. To date, an elevated IOP represents the major risk factor for the onset, incidence, and progression of the disease, and IOP reduction is the cornerstone of glaucoma therapy [2]. However, a significant portion of OAG patients exhibit vision loss despite successful IOP-lowering treatment, and several non-IOP factors have been shown to contribute to OAG risk, including age, family history, race, genetic factors, central corneal thickness, blood pressure (BP) and ocular perfusion pressure, diabetes mellitus, myopia, and cerebrospinal fluid pressure [2,3]. Importantly, glaucoma disproportionately affects persons from African descent, who experience a higher prevalence and more rapid progression of the disease, with less favorable outcomes than persons of European descent [2–4]. In recent years, progress has been made in the discovery and characterization of novel treatment modalities for OAG, including neuroprotective agents and strategies focused on the co-regulation of BP and IOP [3,5]. However, a lack of understanding of the physiological mechanisms behind the relative weight of IOP and non-IOP risk factors in each patient hinders the bench-to-bedside translation of these novel treatments and represents a major obstacle to preventing vision loss and reducing OAG disparities worldwide.

2. Precision medicine in glaucoma: IOP and non-IOP risk factors

Among the non-IOP risk factors, BP has been investigated in multiple large-scale epidemiologic studies [3]. However, contradictory findings on the relationship between BP and OAG have hindered the development of therapeutic approaches based on the coregulation of IOP and BP [3,6]. Quantifying the relative contribution of BP and IOP to OAG for each individual is essential to improve our ability to prevent and manage glaucoma, as this would assist clinicians in directing care to those who need it the most, while avoiding unnecessary treatment for those at lowest risk. Mathematical modeling and artificial intelligence (AI) are innovative methods for analyzing and interpreting these contributions.

3. Access to technology

OAG diagnosis, monitoring and management are dependent on access to technology. In addition to IOP, the most commonly available instruments for data collection in a clinical setting are those related to structural and functional evaluations. This has important implications on the capability to quantify the role of non-IOP risk factors in glaucoma. For example, while BP is easy to measure, its impact on the eye requires evaluations of multiple hemodynamic variables such as volume, velocity and blood flow in relevant vessels and local perfusion of ocular tissues, variables measured with instruments that are found only in selected clinics or clinical research centers (e.g. optical coherence tomography (OCT) angiography, Heidelberg retinal flowmetry, color Doppler imaging, retinal oximetry). Thus, most of the population does not have access to the sophisticated modalities that are required to assess the impact that non-IOP risk factors, such as BP, have on their ocular health and vision. The broad lack of technological access significantly contributes to the disease disparities observed in OAG worldwide. Mathematical modeling and AI provide a platform to leverage the wealth of information available in exclusive research centers and make it accessible to the broader patient population. The transfer of learning from highly specialized research center data to the general public overcomes the challenge of limited technological access and represents an

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important advancement for precision medicine in glaucoma care.

4. Non-commensurate data

Another challenge related to OAG evaluations is that clinical measurements pertaining to the same ocular parameters are not necessarily consistent when performed with different instruments, thereby leading to what data scientists call non-commensurate data. For example, both OCT and Heidelberg retinal tomography (HRT) provide estimates of the optic nerve head (ONH) parameters and retinal nerve fiber layer (RNFL) thickness, but they do so by means of different physical principles. These differences lead to ONH parameters and RNFL estimates that cannot be directly compared between devices, with studies suggesting that parameters acquired via OCT and HRT should not be used interchangeably [7–10]. Thus, the question of how to generalize the relationship between IOP and non-IOP risk factors across studies with non-commensurate data needs to be addressed. Once again, mathematical modeling and AI offer an answer, as we discuss next.

5. Physiology as common denominator across technology and data: role of mathematical modeling and AI

While access to technology and instrument selection may vary among clinics, the fundamental principles of ocular physiology are the same for everyone, everywhere. Let us consider for example the relationship between IOP, BP and blood flow. From physiology we know that blood flow in the eye is driven by BP, impeded by IOP, and modulated by regulatory mechanisms. Physiology principles can be translated into quantifiable metrics by means of mathematical modeling. For example, physiology-based mathematical models can be used to estimate the impact of BP and IOP on hemodynamic variables (e.g. blood flow and pressure) and biomechanical variables (e.g. stresses and strains) [11–14]. Since these model estimates derive from well-established principles of physiology and are based upon widely accessible clinical data (BP and IOP), they can be used for assessing non-IOP factors, especially those related to BP and blood flow, on a large scale without requiring access to advanced technology. However, in order for model-based estimates of physiological variables to be considered effective complements to clinical evaluations, it is imperative to assess their correlation to relevant clinical outcomes, such as glaucomatous structural damage and visual function deterioration. This is where AI can be particularly helpful. AI bridges various disciplines, including statistics, computer science and mathematics, to generate algorithms that can be applied to a vast amount of data collected from individual patients and assist in identifying trends that correspond to the development or progression of a disease.

When used together, mathematical modeling and AI can achieve much more than when used separately. Mathematical modeling transforms readily available data (BP, IOP) into sophisticated markers such as those related to ocular hemodynamics, making them available across clinics despite the heterogeneity in instrument availability. AI can then combine these biomarkers with other patient information (age, race, gender, medical history, medications) to evaluate OAG risk that is patient-specific, meaningful, and immediately useful to clinicians.

6. Communication is the key

The effective communication of the relevance of mathematical modeling and AI in clinical practice is an essential step to connect scientists and medical professionals, bridging the gap between basic science, clinical relevance, and clinical adoption. To this end, we performed a pilot study aimed at evaluating the current climate of AI-informed practice among providers [15]. The study conducted on 18 medical professionals, including ophthalmologists, ophthalmology residents, and fellows, showed that AI informed practice is perceived as vital in ophthalmology, with many participants describing it as the 'future of the profession.' While all participants were able to discuss specific applications of AI to the field, such as diagnosing diabetic retinopathy and glaucoma, very few participants had used AI in their own practice. Identified challenges of an AI-integrated practice included difficulties in balancing between the 'computer and the clinician,' potential human data collection bias affecting AI outcomes, and a lack of 'big data' to help inform AI models.

Physiology informed mathematical modeling and AI can address each other's shortcomings and thus multiply their individual potentials. On one hand, AI algorithms are capable of processing large amounts of data to identify patterns that help us formulate hypotheses concerning the relative contribution of IOP and BP toward OAG. However, these algorithms can also be led astray by missing or discrepant data, as well as implicitly reproduce our own potentially incorrect preconceptions. Mathematical modeling can leverage principles of physiology to establish a common denominator for all people that can help keep AI algorithms rooted in physiological reality. In other words, we can use mathematical modeling to remind our AI algorithms that behind each data point there is a person, and it is the person that we really aim to understand.

In conclusion, AI and mechanistic modeling allow for quantification of the relative weight of IOP and non-IOP risk factors including hemodynamic parameters in glaucoma, in a method that is patient-specific and can be applied consistently across clinics despite the heterogeneity in instrument availability. A combined AI and mathematical modeling approach is a powerful, innovative, and multidisciplinary tool capable of improving OAG diagnosis, advancing precision care, and reducing glaucomatous disease disparities worldwide.

Declaration of interest

G Guidoboni would like to disclose that she received remuneration from Foreside Healthcare, LLC and Qlaris Bio, Inc for serving as a consultant. These relationships are pursuant to the University of Missouri's policy on outside activities. A Harris would like to disclose that he received remuneration from AdOM, Qlaris, Luseed, and Cipla for serving as a consultant, and he serves on the board of AdOM, Qlaris, and Phileas Pharma. A Harris holds an ownership

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Reviewer disclosures

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