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Imaging biomarkers in ophthalmology: hype, hope or game-changer?

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Over the last decade, ophthalmology has undergone a dramatic evolution, mainly driven by the rapid advancement in multimodal imaging and the integration of artificial intelligence (AI). These innovations led to the identification of novel biomarkers as well as to a better understanding of the pathogenesis of several eye diseases.[1 2] In the context of this editorial, a biomarker refers to a specific characteristic, identifiable through various imaging modalities, whose recognition and quantification can carry both diagnostic and therapeutic implications; in addition, AI models can be trained to detect and objectively measure these findings in order to enhance diagnostic accuracy, enable early disease detection, stratify risk and guide personalised management strategies.

In the diagnostic approach to ocular pathologies, the combination of different imaging modalities can lead to the identification of different patterns of signs facilitating the diagnosis of complex or less common pathologies, including genetic conditions, refining our ability to detect and monitor them.[3–6] For instance, outer retinal corrugations have been proposed as a novel diagnostic feature of late-onset retinal degeneration,[4] whereas it has been suggested that retinal nerve fibre layer may have a good specificity to detect optic dysfunction not only in patients affected by Leber hereditary optic neuropathy but also in their asymptomatic relatives.[5] Although both studies were conducted on relatively small cohorts, the rarity of these conditions reinforces the value of these findings, potentially paving the way for future investigations with larger and more diverse populations. In their recent meta-analysis, Yang *et al*[3] highlighted consistent structural and vascular alterations in dysthyroid optic neuropathy, detectable with optical coherence tomography (OCT) and OCT angiography and proposed them as early diagnostic biomarkers.

Imaging biomarkers can also have a crucial role as indicators of the course and/or progression of a certain disease. In this regard, Zhou *et al*[7] reported the association between choroidal thickening and active Graves' ophthalmopathy and the positive correlation between disease activity and both total and stromal choroidal area. The authors also highlighted an important limitation regarding potential discrepancies in data obtained through image binarisation, which may arise from differences in scale bars and the wide range of measurement values. In addition, specific structural biomarkers can predict the response to treatment and the postoperative functional recovery in several pathologies.[8–10] It is also worth to highlight the emerging and promising role of ocular alterations as valuable and often early biomarkers for systemic diseases, such as diabetes, cardiovascular and neurodegenerative diseases, autoimmune disorders or genetic syndromes.[11 12] This growing interdisciplinary link underscores the important role of ophthalmology in broader diagnostic strategies. In this regard, Sakono *et al*[13] proposed the retinal artery sclerosis evaluated on colour scanning laser ophthalmoscopy as a surrogate marker for systemic arterial stiffness and, thus, cardiovascular risk. Notably, specific structural alterations may also serve as indicators of the impact of a certain systemic risk factor, as recently suggested by the positive correlation between entity of choroidal microvasculature dropout and smoking in glaucomatous eyes.[14] It is important to recognise that a significant limitation in the use of imaging biomarkers stems from the variability in image quality and the potential presence of artefacts, which can substantially affect both the accuracy and reproducibility of image interpretation. These technical challenges underscore the need for standardised imaging protocols, rigorous quality control and advanced post-processing techniques to minimise artefacts and enhance the reliability of quantitative imaging data in both clinical and research settings.

In a scenario where the number and complexity of validated biomarkers continue

to grow, the task of considering all these quantitative parameters and integrating this data into coherent clinical decisions can become increasingly challenging. This complexity can be particularly evident in well-known and high-prevalence conditions such as glaucoma, diabetic retinopathy and age-related macular degeneration, where an increasing number of imaging-derived features are being identified and need to be considered, along with patient history and systemic risk factors, to optimise therapeutic management and define a realistic prognosis. In this regard, AI and machine learning algorithms, trained on large high-quality datasets, can emerge not merely as tools for automation but as essential cognitive extensions of clinical practice. The application of AI in real-world screening programmes has demonstrated meaningful clinical relevance. Notably, studies by Shi *et al*[15] and Kemp *et al*[16] have supported AI-driven systems for the detection of glaucoma and diabetic retinopathy, respectively. Indeed, reporting good sensitivity and specificity, both studies suggested that AI-driven screening programmes may be a promising and cost-effective solution for early identification of vision-threatening diseases in large populations. The applications of AI-based algorithms to the analysis of ophthalmic images enable the identification and automated measurement of specific ocular parameters, thereby generating objective, quantitative data. This approach has recently been validated in studies using colour fundus photography in hyperopic children[17] and ultrasound biomicroscopy in patients with primary angle closure.[18] Such advancements hold significant potential to facilitate and improve several phases of patient management, including early diagnosis and the planning of targeted and timely intervention. Furthermore, AI capabilities can be particularly relevant in risk grading, where the goal is not only to identify disease but to anticipate its evolution and guide preventive or individualised interventions.

Finally, in the context of biomarkers in ophthalmology, it is mandatory to mention the increasingly recognised role of serum biomarkers, alongside proteomic and metabolomic profiling, as tools for elucidating pathogenetic mechanisms and identifying novel diagnostic and prognostic indicators as well as new potential therapeutic targets.[19–21] In this view, these systemic approaches may contribute to the development of precision medicine strategies tailored to individual patient profiles.

Overall, growing evidence supported the feasibility and reliability of imaging advanced tools and AI-based algorithms in ophthalmology, demonstrating its ongoing evolution towards a data-driven, technology-enhanced discipline. As imaging modalities become more sophisticated and AI algorithms more accessible, the challenge ahead lies in translating these innovations into routine clinical workflows. However, relevant limitations need also to be taken into account. For instance, regarding OCT-based measurement, it is important to recognise the potential factors that may impact on measuring and interobserver variability and, thus, on the precision of the acquired quantitative parameters.[22] In general, the application of AI also raises important concerns, including bias in training datasets with consequent potential lack of generalisability, issues related to algorithm transparency, the potential for over-reliance on automated decision-making, security of sensitive data and the related legal issues as well as ethical issues, costs and accessibility.[23] It is also crucial to highlight that the meaningful development of reliable algorithms to be integrated in the clinical routine hinges critically on the nature and depth of the data used.[24] Specifically, robust AI models require large-scale, multicentre datasets involving different populations and disease phenotypes, longitudinal data providing information on disease progression and treatment responses, multimodal inputs and expert-labelled annotations and outcome measures for supervised learning.

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