



# Artificial intelligence and quantitative retinal imaging: toward biomarker-driven glaucoma care

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Glaucoma remains one of the leading causes of irreversible blindness worldwide and continues to pose substantial challenges for early diagnosis and individualized risk stratification. Despite significant advances in structural and functional imaging, current glaucoma management still relies predominantly on detecting and monitoring established damage, either through structural loss identified via fundus imaging and optical coherence tomography (OCT) or functional impairment detected by visual field testing<sup>(1)</sup>. In routine clinical practice, clinicians primarily monitor disease consequences rather than directly assessing underlying biological activity or accurately predicting disease trajectory.

A major unmet need in glaucoma care is the identification of reliable biomarkers capable of detecting susceptibility, estimating progression risk, and identifying neurodegenerative changes prior to clinically significant functional loss<sup>(2)</sup>. In this context, artificial intelligence (AI) has emerged not only as a diagnostic support tool but also as a promising platform for biomarker discovery<sup>(3)</sup>. By extracting quantitative information from conventional retinal imaging, deep learning algorithms can identify structural patterns that are imperceptible to human observers yet strongly associated with glaucomatous neurodegeneration<sup>(4)</sup>.

In a recent longitudinal study, Samico et al.<sup>(5)</sup> introduced a clinically relevant application of a deep learning-based machine-to-machine (M2M) model capable of estimating retinal nerve fiber layer (RNFL) thickness from color fundus photographs, effectively generating a “virtual OCT” from standard retinal imaging. Using data from the Canadian Longitudinal Study on Aging (CLSA), this work represents one of the first large-scale, population-based longitudinal evaluations of AI-predicted structural glaucomatous damage and its association with incident glaucoma.

The investigators analyzed 30,202 eyes from 18,247 participants over an approximate 3-year follow-up period. The M2M model was initially trained on paired datasets of optic disc photographs and OCT-derived RNFL measurements, enabling quantitative estimation of RNFL thickness directly from fundus photographs. This approach is particularly relevant given the broader global accessibility of fundus photography compared with OCT, especially in large-scale screening programs and teleophthalmology settings.

A major strength of the study is its epidemiological design. Unlike most previous AI studies conducted in tertiary referral centers, the CLSA cohort reflects a real-world aging population. The authors demonstrated that the model identified biologically plausible patterns of neural loss at the population level. Eyes with self-reported glaucoma exhibited significantly faster RNFL thinning than nonglaucomatous eyes ( $-0.46$  vs.  $-0.18$   $\mu\text{m}/\text{year}$ ), supporting the algorithm’s ability to detect clinically meaningful longitudinal structural changes.

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Importantly, the study extended beyond cross-sectional classification by emphasizing disease progression. Accelerated M2M-predicted RNFL loss was independently associated with an increased risk of incident glaucoma during follow-up. Specifically, each additional 1  $\mu\text{m}/\text{year}$  of RNFL loss was associated with a 12.5% increase in the risk of developing glaucoma.

The study also evaluated established glaucoma risk factors. Older age, elevated intraocular pressure (IOP), and reduced corneal hysteresis were independently associated with accelerated RNFL loss. A significant interaction between age and IOP suggested that older individuals experience disproportionately greater structural damage at comparable IOP levels, supporting the concept that aging increases optic nerve vulnerability to pressure-related injury.

Several limitations should be acknowledged. Glaucoma diagnosis relied on self-report rather than standardized ophthalmic examination, and the follow-up duration was relatively short for a chronic disease such as glaucoma. In addition, the analysis focused exclusively on global RNFL thickness rather than sectoral measurements, which may reduce sensitivity for detecting early localized defects.

Overall, this study provides compelling evidence that deep learning models can extract clinically meaningful structural biomarkers from fundus photographs and apply them at an epidemiological scale. Rather than replacing OCT, this approach may expand access to structural glaucoma assessment in underserved populations and large-scale screening programs. Fundus photography remains substantially more accessible and scalable than OCT in many

clinical settings worldwide. More importantly, the ability to longitudinally estimate RNFL thinning from standard fundus photographs introduces the possibility of transforming retinal imaging into a quantitative biomarker platform for glaucoma detection and progression assessment<sup>(5)</sup>.

Future directions will likely involve integrating AI-derived retinal biomarkers into multimodal predictive frameworks incorporating polygenic risk scores, IOP profiles, corneal biomechanics, vascular parameters, and other clinical variables<sup>(5,6)</sup>. Rather than functioning as isolated diagnostic tools, these algorithms may become components of individualized predictive models capable of estimating glaucoma susceptibility, progression rate, and treatment response.

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