OCT-based applications of artificial intelligence in the management of neovascular and atrophic age-related macular degeneration

Sophie Riedl[1], Ursula Schmidt-Erfurth[1]

[1] Department of Ophthalmology and Optometry, Medical University of Vienna, Vienna, Austria; Laboratory for Ophthalmic Image Analysis

Neovascular AMD

Retina specialists, treating neovascular age-related macular degeneration, are highly dependent on optical coherence tomography (OCT) with respect to the monitoring of treatment response, planning of future treatment intervals, and assessment of disease course.[1] While the underlying progression of outer retinal atrophy as well as fibrotic changes is what ultimately limits vision gains, clinicians' treatment decisions are guided by the "active" disease component: fluid. In the last decade various regimens as well as differing approaches with respect to "tolerable" fluid have been proposed.[2,3] All of them are highly dependent on precise OCT assessment, specifically intra- and subretinal fluid (IRF, SRF). With these being the established, widely agreed upon retreatment criteria, automated localization and quantification of fluid by means of artificial intelligence (AI), has naturally become inevitable. Besides the mere detection of fluid, precise AI-based fluid measurement enables an accurate, quantitative assessment of the treatment response.[4]
The availability of volumetric information of the extent of fluid and, more importantly, fluid change caused by therapy, has several implications. The following paragraphs will discuss the applications of AI-based fluid assessment in the setting of both clinical and scientific challenges in nAMD.

-) In a **cloud-based setting**, due to fast processing a complete report is at the physician's hand when seeing the patient. The report demonstrates all relevant features, i.e. fluid compartments and volumes at one glance. Repetitive scrolling through the entire B-scan fly-through is no longer necessary. The workflow is much facilitated and rapid while also leaving a clear documentation of each visit and each patient on site for the physician's assessment at the next visit. The difference in nanoliters (nl) of fluid indicating increase/decrease objectively represents a robust base for retreatment decisions leading to optimized therapeutic guidelines based on real-world data.[5]

-) AI-based **retinal fluid analysis** enables comparability of treatment efficacy of different therapeutic agents and regimens. In the HARBOR study a clear correlation of fluid resolution with dosing and regimen parameters was shown.[6] Based on the HAWK and HARRIER trials, two phase III, randomized, multi-center studies, in which brolucicumab was tested against aflibercept in treatment-naïve nAMD, superior morphologic efficacy, i.e., the ability to dry the subretinal compartment from fluid was demonstrated for brolucicumab.[7] A systematic comparison of central subfield thickness (CRT) showed that actual fluid volumes are not reflected by CRT values, which should therefore not be used to asses therapeutic efficacy in nAMD.[8] Continuously emerging new therapeutic agents and means of pharmacological delivery require rigorous evaluation, as shown in the aforementioned post-hoc analyses. Besides functional and basic morphologic endpoints commonly applied in pivotal trials, detailed assessment of the morphologic efficacy of treatment has become indispensable, as

it leads toward a more comprehensive characterization of our available therapeutic agents, thereby enhancing the understanding of how we may modify the course of disease in the best functional and socioeconomic manner.

-) Investigation of the relevance of differences in morphologic efficacy is facilitated by the analysis of **structure-function correlation**, which can be conducted far more robustly due to the availability of reproducible and precise quantification of IRF and SRF. In the aforementioned post-hoc analysis of the HAWK and HARRIER trials, an accurate correlation of fluid resolution and macular function was demonstrated, which was reflected in progressive functional loss in patients presenting with more residual fluid.[7] These findings corroborate results from a further AI-based fluid quantification analysis, performed on HARBOR trial data, in which functional improvement was even more substantially correlated with SRF resolution compared to IRF resolution.[9] Moreover, the application of fluid quantification to data of the FLUID trial, in which a SRF-tolerating treat-and-extend regimen was investigated, confirms the relevance of revisiting clinical trial data in order to fully utilize the information provided by these prospective studies. The results showed, that an increase in SRF, following an extension of treatment interval had a negative impact on macular function.[10]

-) Lastly, AI assists our aims to optimize **treatment regimens** not only via AI-based segmentation, but also methodologically. Based on clinical and OCT imaging features an AI-based model was able to predict visual outcomes as well as treatment intervals of a treat-and-extend regimen from data following just one intravitreal treatment administration.[11] These are necessary steps on the way to a reliable and objective AI-based treatment guidance, which is expected to minimize the burden on both patients and caregivers as well as reduce costs.

Geographic Atrophy

In contrast to nAMD, disease “activity” in geographic atrophy does not refer to the presence or absence of a morphologic feature, rather than the continuous – more or less rapid - growth of the atrophic lesion(s).[12] Precision in morphologic assessment is crucial due to the fact that functional parameters are unsuitable for the purpose of disease monitoring. This is because measurements feasibly obtainable in everyday clinical practice reflect central vision which is only affected once the functional loss in irretrievable.[13] Recent therapeutic breakthroughs, predominantly in the field of intravitreal complement inhibitory therapy, are just about to revolutionize management of patients presenting with the atrophic late stage of AMD, geographic atrophy.[14,15] Sight-threatening progression of GA may, therefore, soon be prevented in millions of patients, affected by this chronically progressive disease. With this new era comes an immense burden for caregivers and budgets. In order to streamline patient management there is an urgent need of reliable assessment of disease progression as well as the estimated effect of treatment. There is a clear lack of widely agreed upon benchmarks particularly at the level of OCT which is the main tool in AMD management with respect to progression and management of GA. In practical terms this would mean the establishment of criteria identifying slow and fast progressors as well as high-risk patients, in which progression toward the fovea is expected. Furthermore, quantitative evaluation of treatment success is needed. The use of AI supports the path toward tackling these complex challenges on several levels:

-) AI can ideally be applied to the **segmentation of the atrophic lesion** in order to provide reproducible results, which would otherwise have to be obtained in a highly time-consuming manner by human annotation. In addition to lesion segmentation based on fundus autofluorescence (FAF) imaging, the state-of-the-art and FDA-approved modality to monitor the GA progression in clinical trials, segmentation algorithms have also been developed for OCT imaging, which offers far more detailed assessment of the various tissue layers, affected by GA.[16,17] AI-based tools are most successful in detecting the subclinical biomarkers relevant in GA such as the photoreceptor (PR) layer changes which cannot be perceived in contrast to fluid by the retinal expert.[18]

-) Consequently, assessment of lesion growth presents another suitable task, for which AI may be deployed, especially as **reliable disease monitoring** will be the key for making treatment decisions and repeatedly refining criteria for this purpose. With respect to the aforementioned groundbreaking advances in the treatment of GA, AI-based OCT analysis provides relevant contributions to **understanding disease pathomorphology and investigate treatment effects** in more detail. It enables the quantification of morphologic efficacy, not only on the level of the retinal pigment epithelium (RPE), but also the PR layers which are the most relevant for visual function.[19,20] Correlation of structural OCT with functional microperimetry demonstrated a clear correlation of PR integrity loss on OCT with retinal sensitivity loss on MP with a clear grading by the level of PR thinning. Areas with PR integrity loss demonstrate relative scotomas which expand over time if left untreated.[21] Differentiated information on the various affected layers has revealed ground-breaking insight into the growth patterns of GA, such as primary photoreceptor integrity loss preceding secondary RPE loss.[22] Furthermore, post-hoc investigation of the FILLY trial, in which C3 inhibitory intravitreal pegcetacoplan therapy was administered, confirmed treatment not only to slow RPE loss, but even more importantly the thinning and loss of photoreceptor integrity, as visualized by OCT.[23,24]

-) AI-based lesion delineation of various layers has furthermore spurred on **detailed topographic assessment of GA growth**, which goes hand in hand with the development of reliable **prediction modeling** (Figure 1). This has become increasingly relevant due to emerging therapeutic options. For example, a post-hoc analysis of the aforementioned FILLY trial revealed that particularly fovea-oriented GA growth appeared to be slowed by treatment.[25] AI-based prediction tools, informed by the results of such in-depth analyses, will become indispensable for patient management, specifically identification of patients suitable for therapy, as well as treatment monitoring.

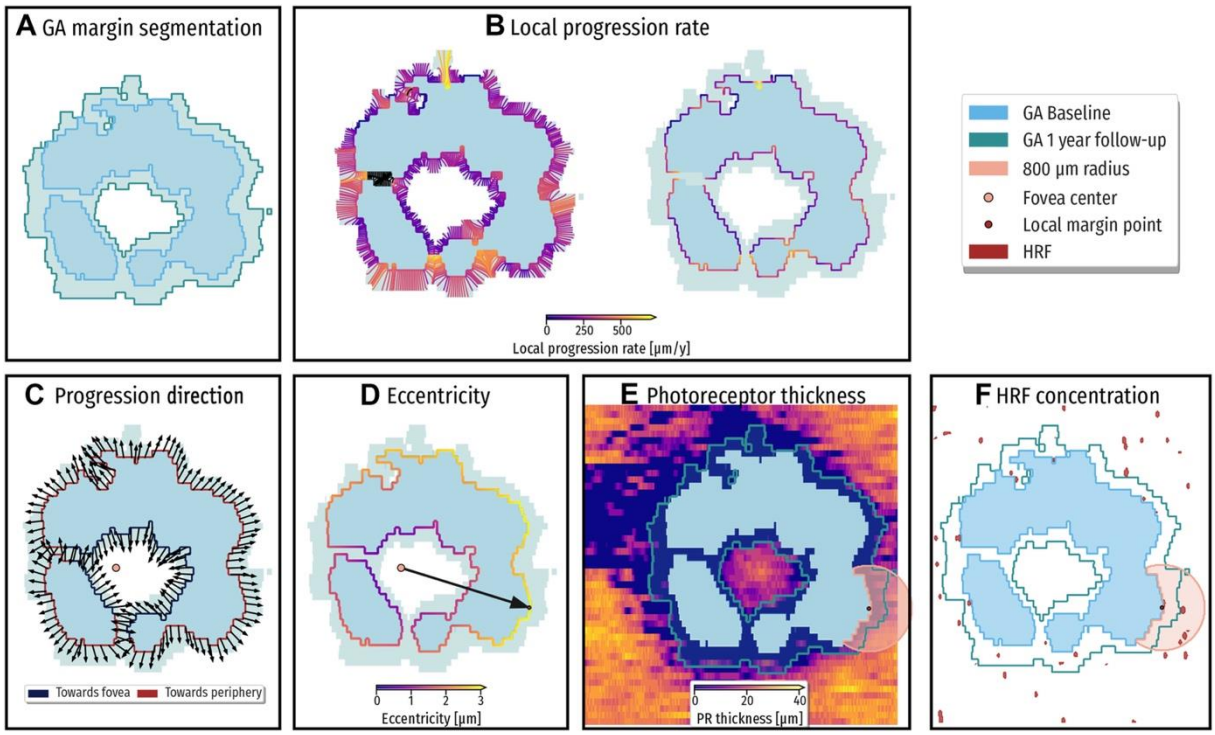

Figure 1: Illustration of morphologic and topographic features, which can be fed into progression models, computed for each margin point of a geographic atrophy lesion. **A**, Automated segmentation of retinal pigment epithelium (RPE) loss determining GA at baseline (blue) and at 1-year (green). **B**, Local progression rate (LPR) visualized as individual growth trajectories (left) and color coded for local progression activity of each margin point (right). **C**, Growth direction toward the fovea (blue margin) or toward the periphery (red margin), determined from the local tangent normal vector, illustrated as black arrows. **D**, Distance to the fovea for each GA margin point. **E**, Color-coded Photoreceptor (PR) thickness map. For progression modeling, mean PR thickness of the junctional zone (exemplarily demonstrated as the orange circle with 800 µm radius) of each margin point is computed. **F**, Similarly, the hyperreflective foci (red dots) concentration is computed.
Figure reproduced from: *Vogl WD, Riedl S, Mai J, Reiter GS, Lachinov D, Bogunović H, Schmidt-Erfurth U. Predicting Topographic Disease Progression and Treatment Response of Pegcetacoplan in Geographic Atrophy Quantified by Deep Learning. Ophthalmol Retina. 2023 Jan;7(1):4-13. doi: 10.1016/j.oret.2022.08.003. Epub 2022 Aug 7.*

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