Artificial intelligence for geographic atrophy: pearls and pitfalls

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Purpose of review
This review aims to address the recent advances of artificial intelligence (AI) in the context of clinical management of geographic atrophy (GA), a vision-impairing late-stage manifestation of age-related macular degeneration (AMD).

Recent findings
Recent literature shows substantial advancements in the development of AI systems to segment GA lesions on multimodal retinal images, including color fundus photography (CFP), fundus autofluorescence (FAF) and optical coherence tomography (OCT), providing innovative solutions to screening and early diagnosis. Especially, the high resolution and 3D-nature of OCT has provided an optimal source of data for the training and validation of novel algorithms. The use of AI to measure progression in the context of newly approved GA therapies, has shown that AI methods may soon be indispensable for patient management. To date, while many AI models have been reported on, their implementation in the real-world has only just started. The aim is to make the benefits of AI-based personalized treatment accessible and far-reaching.

Summary
The most recent advances (pearls) and challenges (pitfalls) associated with AI methods and their clinical implementation in the context of GA will be discussed.

Keywords
artificial intelligence, deep learning, ellipsoid zone, geographic atrophy, optical coherence tomography, segmentation

INTRODUCTION

The application of artificial intelligence (AI) in ophthalmology has developed rapidly due to the availability of large datasets from retinal imaging. Significant advances have been made in the context of age-related macular degeneration (AMD), a leading cause of severe vision loss affecting around 200 million people worldwide [1]. With the continuous growth in AMD prevalence, a result of the world's ageing population, AI provides a potential solution to the need for optimized screening in order to detect AMD-related changes in time for early treatment and prior to the vision-threatening stages of the disease. The focus of this review is on geographic atrophy (GA), an advanced form of AMD characterized by the degeneration of photoreceptors and retinal pigment epithelium (RPE). GA is a slowly progressing disease, which over time moves towards the fovea, where it can lead to irreversible vision loss. Recently the first two treatments for GA, pegcetacoplan (Syfovre) and avacincaptad pegol (Izervay), have been approved by the US Food and Drug Administration (FDA). This represents a breakthrough for GA management [2▪,3▪]. In event of this, a better understanding of the pathomechanisms of GA progression is required, especially on the level of the individual patient, to best understand when and what dose of treatment is needed to obtain optimal treatment effects. The precision of AI-algorithms has shown high utility by providing the means for reliable quantification of disease-specific biomarkers and predicting disease progression. They can thus serve as tools to assist treatment decisions in clinical routine and may represent a novel horizon of personalized medicine. This review will provide an overview of recent advances (pearls) and challenges

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KEY POINTS

- There is a need for efficient methods to optimize screening and monitoring of geographic atrophy (GA) in clinical routine and the real world. This is especially relevant, with the recent breakthrough approvals for the first two GA treatments.
- The use of artificial intelligence (AI) for the automation of GA segmentation on different imaging modalities provides an objective and reliable method for the detection of subclinical disease-specific features.
- Optical coherence tomography (OCT) is a noninvasive imaging modality that provides pixel-level resolution representation of retinal morphology. Combining OCT with AI algorithms can be considered a breakthrough for monitoring the integrity of retinal layers associated with GA.
- The measurement of ellipsoid zone (EZ) integrity using high-precision algorithms has proven a valuable biomarker for monitoring and predicting GA progression. This is underlined by its recent FDA recognition as a clinical outcome measure for GA treatment trials. However current algorithms for measuring EZ integrity are still OCT device-dependent, making it challenging to achieve equal precision due to different levels of signal-to-noise ratio.
- Recently the first algorithm for monitoring GA has been approved in Europe, representing a major advancement in bringing precision medicine into real-world patient management.

(pitfalls) of AI implementation in the context of GA diagnosis and management.

AUTOMATED SEGMENTATION USING ARTIFICIAL INTELLIGENCE: A PEARL FOR GEOGRAPHIC ATROPHY MANAGEMENT

Before the introduction of AI tools, a binary approach was used to assess the presence or absence of GA and associated biomarkers, such as drusen, on different imaging modalities. However, this approach does not account for the dynamics and intricate nature of the disease, making monitoring of atrophy progression difficult. A breakthrough for GA management lies in the advancements of automatic image segmentation. The term *semantic segmentation* refers to the automated detection and delineation of an object of interest, allowing for the extraction of quantitative measurements from images. As a result, through semantic segmentation, AI can provide accurate measurements of disease-specific features from images, which if done manually would be very time-consuming and in-efficient for clinical routine. In the context of retinal imaging, deep learning (DL), a data-driven type of AI based on large artificial neural networks, dominates. Convolutional neural networks (CNN) and in particular a subform of CNN, U-net, have become the most commonly used architecture for image segmentation, also within the context of GA [4,5].

The success of CNN architectures lies in the fact that they are able to effectively exploit the correlation of adjacent pixel values in images. As a result, CNNs can be trained with annotated data sets to learn and detect relevant local features from retinal images that can be used to automatically carry out diverse tasks, including performing automated imaging biomarker segmentation and image interpretation. Recent advances in the segmentation of retinal images show high accuracy and comparable performance between algorithms and human graders.

ARTIFICIAL INTELLIGENCE FOR GEOGRAPHIC ATROPHY DETECTION AND QUANTIFICATION

Historically, color fundus photography (CFP) was used for the detection and monitoring of GA lesions, due to its accessibility and ease of interpretation. On CFP, GA lesions are visualized as sharply demarcated areas and visible choroidal vessels due to an absence of retinal pigment epithelium (RPE) [6]. Multiple studies have shown the utility of DL approaches to automate GA segmentation on CFP [7–10]. While these technologies prove successful in detecting biomarkers such as drusen and pigment abnormalities, their real-world applicability is limited as GA delineation is often challenging on CFP due to poorer contrast and variability in GA presentation, especially from a machine learning perspective [7].

A better delineation of GA lesions is possible with fundus autofluorescence (FAF) imaging, which is based on intrinsic fluorophores in the retina. As GA lesions are associated with retinal pigment epithelium (RPE) degeneration, lesions show up as hypofluorescent areas. Consequently, GA growth rate as measured on FAF is commonly a primary outcome measure in clinical trials [11]. The RegionFinder software by Heidelberg Engineering [12,13] provides a semiautomated segmentation method for GA area measurement on FAF, which is available to any clinic using Heidelberg Engineering FAF devices. However, as this tool still requires manual input, it is subjective and prone to inter-observer variability. Independent work by Treder *et al.* and Spaide *et al.* demonstrate the utility of CNN architectures for automated segmentation of GA on FAF [14,15▪].

In GA clinical trials, FAF is still the dominant modality due to its FDA approval, however OCT has become a gold standard in clinical routine due to its

wide availability and noninvasive nature. Furthermore, in contrast to 2D imaging modalities, OCT provides a 3D cross-sectional image of the macula, providing insight into morphological changes on the level of the neurosensory layers [16]. On OCT, GA is characterized by a loss of RPE and overlying photoreceptors (PR), as well as resulting hypertransmission into the choroid [17]. However, due to the vast amount of information available in a single OCT volume, manual segmentation is time consuming and often limited by interreader variability. These challenges can be mitigated by automated segmentation methods, making them critical for an accurate diagnosis and measurement of GA on OCT, as well as for extracting anatomical structures of interest. Especially relevant is the use of segmentation tools for identifying photoreceptor degeneration, most commonly at the level of the ellipsoid zone (EZ), as well as RPE layer loss. While multiple segmentation approaches have been developed for OCT [18,19,20▪,21–23], a major advancement lies in the full automation of the process, reducing the subjective nature of analysis, and increasing the accuracy of measurements and efficiency in the clinical space.

The difficulty of automated segmentation in the context of GA, lies in the fact that the disease presents as a lack of retinal tissue and is thus not straightforward to annotate on OCT. Approaches have been developed for both *en-face* and 3D volume segmentation. One of the earliest approaches, reported by Pfau *et al.*, uses 2D *en-face* OCT projections and layer thickness maps as an input for a CNN architecture specialized for image segmentation (DeepLabv3) [22]. While reporting a high performance in an independent test set, this approach fails to exploit the full information present in an OCT scan.

An approach to automatically segment and quantify photoreceptor alterations was developed by Orlando *et al.* in 2020 using an ensemble of four different types of CNNs [24]. The segmentation approach was clinically validated in a posthoc analysis of the phase II pegcetacoplan FILLY trial, proving its utility for interpreting photoreceptor condition in a clinical setting [25▪].

Automated detection and pixel-level segmentation of GA lesions using two DL-based approaches on a large dataset of 900 OCT volumes has been described by Kalra *et al.* High-performing DL algorithms were trained on B-scan level and *en-face* level to detect areas of EZ and RPE attenuation, proving a detection accuracy of 91% and 82%, respectively [20▪]. A hybrid approach that combines the strengths of both models would enhance the segmentation performance and its clinical utility.

Pramil *et al.* presented an extensive clinical validation of an AI approach described by Chu *et al.* in 2022 [18,26▪]. For this model, an optical attenuation coefficient (OAC) volume was calculated from the raw swept source (SS)-OCT data which was then used to correctly differentiate areas of RPE disruption from healthy RPE. Additionally, the input of pseudocolor images into a CNN architecture allowed for the generation of *en-face* GA segmentation masks. The automated algorithm was found to have excellent reproducibility and similar accuracy to manual grading [26▪].

Lachinov *et al.* demonstrated that fully automated segmentation on OCT is achieved through a setup with a 3D volume as an input and a 2D en-face map of atrophy as an output. This 3D-to-2D segmentation setup uses projective skip-connections to enhance the U-net architecture [27]. The approach has recently been clinically validated using a large data set from the Phase II FILLY study, as well as OCT images from a real-world cohort [28▪].

The development of AI algorithms for OCT has allowed for the identification of novel biomarkers of subclinical nature. Algorithms have successfully been developed for quantifying features that aid in predicting GA progression, such as hyper-reflective foci (HRF) [29–31]. Schmidt-Erfurth *et al.* have revealed the significance of HRF in the junctional zone and their utility in predicting the progression of the disease [31]. This was confirmed in more recent work analyzing topographic GA progression in the context of treatment [32▪▪]. Subretinal drusenoid deposits (SDD) are another marker shown to strongly correlate with GA progression. Their small size and location underneath the RPE, makes the training of algorithms for segmentation difficult. A recent advancement has been reported by Schwartz *et al.* where an algorithm based on a U-net framework was shown to accurately segment SDD on OCT images from 1284 AMD patients [33].

ARTIFICIAL INTELLIGENCE FOR PREDICTING GEOGRAPHIC ATROPHY PROGRESSION

Precise forecasting of GA progression is critical for identifying patients who will benefit the most from approved therapies and for motivating patients to continue treatment. As GA progresses slowly and growth rates vary among individuals, models to topographically predict GA lesion growth rely on accurate segmentation techniques. Several attempts have been made to predict future GA growth from CFP, from FAF [34–36] and from single OCT volumes [37▪,38,39▪,40]. As early as 2016, Niu *et al.* developed a predictive model to estimate local GA growth by

extracting quantitative features, including retinal layer thickness and reflectivity, from OCT A-scan locations [40]. Gigon *et al.* was the first to describe an approach that takes the spatial and temporal context of GA progression into account using 2D feature maps of retinal layer thickness and reflectance as an input for a U-net model [38].

More recently, Anegondi *et al.* demonstrated the feasibility of three multitask deep learning models to predict concurrent GA area and growth rate from FAF-only, OCT-only and combined FAF and OCT [37▪]. An alternative approach described by Kalra *et al.* uses a U-net to segment the EZ-to-RPE region on a B-scan. Thresholds were determined for EZ that were at risk at baseline ($\leq$10 μm). The strength of this method lies in the large dataset that was used for its development. It was also tested in an independent dataset with 120 patients [41▪]. Lachinov *et al.* make use of the full information given by 3D-OCT images by extending a 3D-to-2D segmentation model with a NeuralODE framework. Using a single baseline scan, this method allows for prediction of GA lesion size at an arbitrary future time point [42▪]. The method was further clinically validated on an independent data set of 184 eyes [39▪].

An unmet need not yet addressed through existing models, lies in predicting the time point at which GA becomes sub-foveal, resulting in substantial vision loss for the patient. This is especially relevant in the context of treatment timing, as it would allow to identify those patients who are of greatest risk for complete vision loss.

ARTIFICIAL INTELLIGENCE IN THE CONTEXT OF GEOGRAPHIC ATROPHY TREATMENT TRIALS

In clinical trials, anatomic endpoints, such as GA lesion growth, are used to evaluate and monitor treatment efficacy. The importance of AI tools is highlighted by the recent recognition of EZ attenuation, an OCT biomarker for photoreceptor (PR) integrity, as a primary outcome measure by the FDA [43▪]. This has been officially announced after a positive end-of-phase 2 meeting for the development of elamipretide, a novel treatment of GA [44]. Already the Phase I study, demonstrated a strong correlation between EZ loss and visual acuity outcomes, where patients with higher EZ integrity values showed better visual function [45].

Multiple studies have shown a consistent correlation between RPE and PR integrity measured on OCT with GA progression, underlining the importance of reliable segmentation of retinal layers [22,46,47,48▪]. For monitoring GA progression in the context of treatment trials, posthoc analysis of data from the phase 2 FILLY trial for pegcetacoplan using high-precision algorithms revealed the superior maintenance of retinal layer integrity as a result of treatment [28▪].

Therapeutic effects at the level of the photoreceptor layer, also outside active GA lesions, were demonstrated by three separate groups using data from the FILLY trial of pegcetacoplan [25▪,32▪▪,49,50]. The precision of AI-driven analysis has furthermore revealed that PR integrity loss precedes RPE atrophy [25▪]. Work by Vogl *et al.* demonstrated the utility of automated segmentation of GA features and a spatial generalized additive mixed-effect model, including treatment as an explanatory variable, to predict future progression rates at the local and global level. Results highlighted the differences in GA progression in patients with and without treatment proving that personalized management of GA is essential [32▪▪]. Analysis of data from the phase 3 OAKS and DERBY trials of pegcetacoplan further validated the utility of AI-derived EZ attenuation measurements to show the effects of treatment on GA progression [51▪▪,52▪▪].

Furthermore, AI-derived quantification of EZ attenuation has resulted in the determination of an objective prognostic biomarker, which may serve as an imperative method for identifying 'fast progressors'. Separate analysis by Riedl *et al.* and Schmidt-Erfurth *et al.* were able to highlight the prognostic value of the EZ/RPE integrity loss ratio in predicting GA progression [25▪,52▪▪]. Their results indicated that individual patients with a larger ratio will need more intensive treatment to slow down progression of GA [25▪,52▪▪]. This identification of 'fast progressors' is imperative for both clinical trial inclusion and real-world patient management. An example of two geographic atrophy lesions with different ellipsoid zone (EZ) / retinal pigment epithelium (RPE) ratios and their change between baseline and month 12 is shown in Fig. 1.

Additionally, a merit in AI-based analysis or PR integrity lies in its spatial correlation with visual function, also contributing to its utility as an outcome measure in clinical trials [53]. Using a machine learning-enabled tool, a retrospective analysis by the Cleveland Clinic found significant correlations between EZ integrity metrics and visual acuity (VA), revealing that eyes with excellent VA had higher EZ integrity compared to those with poorer VA. Additionally, the findings showed that baseline EZ integrity metrics can predict future VA loss, highlighting the potential of quantitative SD-OCT measurements in detecting early changes in dry AMD and their value in clinical trial screenings [54▪▪]. Currently, various groups are implementing microperimetry for point-to-point correlations of PR and RPE

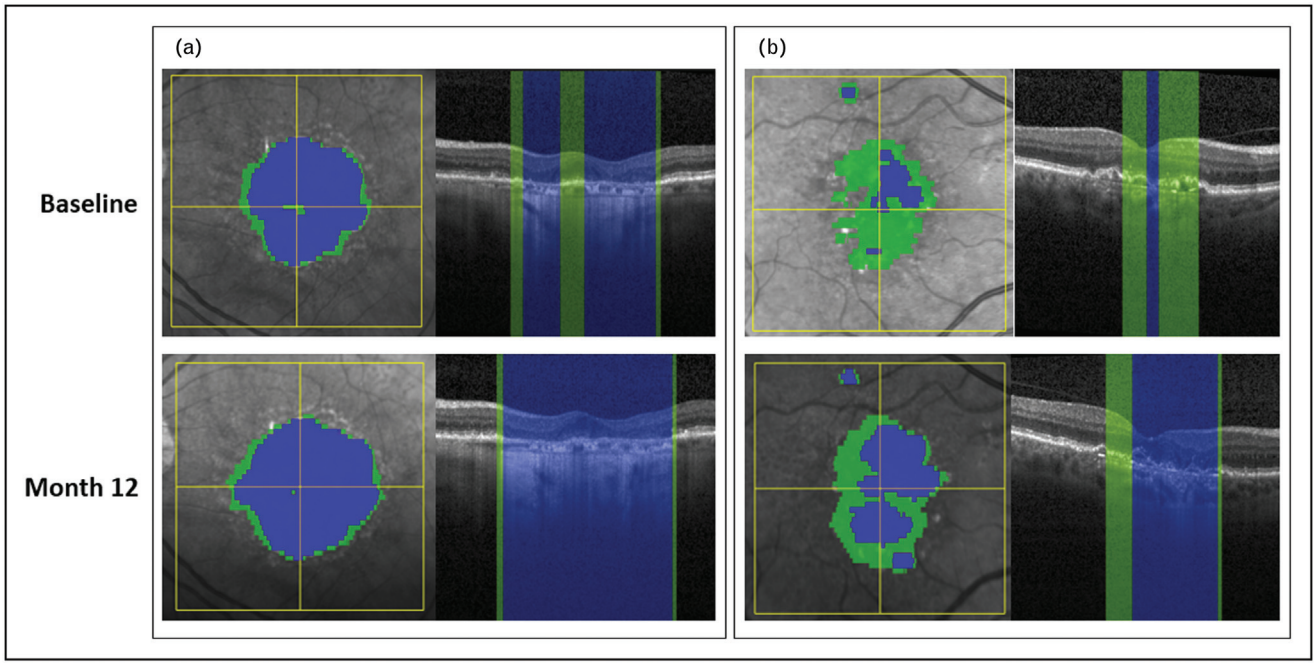

FIGURE 1. Example of two geographic atrophy lesions with different ellipsoid zone (EZ)/retinal pigment epithelium (RPE) ratios and their change between baseline and month 12. Segmentation of areas of RPE atrophy (blue) and EZ atrophy (green) was carried out using the MDR-certified GA monitor (RetInSight; Vienna, Austria). The en-face visualizations show RPE and EZ atrophy overlap and highlight that EZ loss precedes RPE loss. (a) A geographic atrophy lesion with low EZ/RPE ratio. (b) A lesion with high EZ/RPE ratio. The OCT from month 12 shows a faster growth than for the lesion with a lower ratio (a).

damage with retinal sensitivity. This is reviewed in detail in a recent paper by Vujosevic *et al.* [43▪].

Especially the ability of algorithms to assess morphological endpoints in real time, providing high image quality, makes them pivotal for future clinical trials. While most studies use AI algorithms retrospectively, AI also provides an opportunity for prospective on-site treatment monitoring. By demonstrating a slowing in GA progression, these tools can aid in motivating patients to continue treatment more long-term. For a continuous evaluation of the progressive loss or maintenance of the EZ layer, it has to be assured that the active lesion including RPE as well as EZ area are included into the field of view at each visit by the operator. Large lesions are often cut off at their edges. Only the real-time fully automated analysis can provide such a vital image acquisition standard.

ARTIFICIAL INTELLIGENCE IN THE REAL-WORLD MANAGEMENT OF GEOGRAPHIC ATROPHY

Application of AI in the real-world management of GA has recently seen a breakthrough with the first Medical Device Regulation (MDR)-certified GA Monitor (RetInSight; Vienna, Austria) being approved in Europe and approved for investigational use in the United States. This clinical decision support system consists of a composite algorithm which quantifies RPE and PR integrity on OCT volumes in a fully automated procedure. The tool provides a report consisting of numerical data and *en-face* topographical maps, which can be used to identify high-risk patients and monitor their disease progression. The algorithm has been validated clinically on large data sets and is accessible to ophthalmologists globally by uploading OCT images to the Heidelberg Engineering SPECTRALIS AppWay [28▪,52▪▪].

However, a pitfall for the real-world application lies in the fact that existing AI tools, including the approved GA Monitor, are adjusted to high resolution OCT devices. Images from different OCT devices show significant variability and lack of precision, not offering good enough data acquisition. The current literature shows that most advanced algorithms used for GA management, are developed for use on SPECTRALIS (Heidelberg Engineering) OCT devices, as these are more commonly used in clinical sites and have a higher signal-to-noise ratio than other devices, facilitating the visualization of different retinal layers such as the most relevant EZ layer. This is especially relevant for measurements of EZ attenuation as the band is often hard to distinguish

under strong speckle noise, typical of OCT imaging. A potential approach for dealing with image variability across different OCT devices is through image domain adaptation where the covariate shift can be reduced through unsupervised unpaired translational models [55]. Improving algorithms for their use on low-cost OCT devices is imperative for extending the use of AI to screening of patients in the real-world, identifying individuals at risk of GA directly in the primary care setting of ophthalmologist, optometrist and optician offices.

Validating AI tools with real-world data is crucial for the integration of the technology and for the transition from the experimental stage to their application as clinical decision support tools. For AI tools to be able to contribute to precision medicine in an equitable way, they need to be tailored to the complexities of more diverse patient populations. Evaluating AI tools on large-scale datasets from more diverse populations is thus the next step required. However, often large data sets are not integrated or standardized making accurate evaluation challenging.

A further challenge to date lies in the heterogeneity of regulation processes in Europe and the rest of the world. Especially between Europe and United States, the approval and regulation of medical devices are handled differently, with no specific regulatory pathway for AI-based medical devices yet available [56]. Questions regarding data confidentiality and privacy protection are particularly sensitive and crucial to find solutions to prior to device approval.

CONCLUSION

AI tools have shown great advancements over the last years and may soon become crucial to support clinical management of GA and a successful shift towards personalized healthcare. Studies from various groups around the world have shown the utility of CNN architectures to develop AI-based methods for the analysis of large data sets, aiding in the screening and management of GA patients. Furthermore, the use of AI for the analysis of clinical trial data sets has demonstrated its utility in generating invaluable information for monitoring and predicting disease progression. This is especially relevant with the recent FDA approvals of the first two treatments for GA. Future work needs to be directed towards real-world applications of AI algorithms, making them useful for everyday clinical routine and community-based eye-care settings.

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