REFRAME GA

A manifesto for change in geographic atrophy

This white paper is intended for healthcare professionals, patient advocacy groups, and other relevant decision makers such as payers, regulators, and policy makers.

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Prof. Anat Loewenstein,
Tel Aviv Medical Center, Tel Aviv, Israel

Dr David Wong,
St. Michael's Hospital, University of Toronto, Toronto, Canada

Prof. Giovanni Staurenghi,
Department of Biomedical and Clinical Science, University of Milan, Milan, Italy

Dr Imadeddin Abu Ishkheidem,
Sahlgrenska University Hospital, Gothenburg, Sweden

Dr Jordi Monés,
Institut de la Màcula, Barcelona, Spain; John A. Moran Eye Center, University of Utah Health, Salt Lake City, USA; Barcelona Macula Foundation: Research for Vision, Barcelona, Spain; Perceive Biotherapeutics, San Francisco, USA

Prof. Michael Larsen,
Department of Ophthalmology, Rigshospitalet, and University of Copenhagen, Copenhagen, Denmark

Prof. Nicole Eter,
Universitätsklinikum Münster, Münster, Germany

Prof. Paulo-Eduardo Stanga,
The Retina Clinic London, London, United Kingdom

Prof. Sobha Sivaprasad,
NIHR Moorfields Biomedical Research Centre, Moorfields Eye Hospital, London,United Kingdom

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Executive summary

Geographic atrophy (GA) is one of the leading causes of irreversible vision loss and blindness making it an important health issue.[1,2] Unlike wet age-related macular degeneration (AMD; also known as exudative neovascular AMD [nAMD]),[3] treatment options for GA are limited, leaving patients with a significant disease burden.[4–6] Moreover, nascent or small areas of GA are often underdiagnosed[5–7] so that patients may only be identified after they become symptomatic following foveal involvement.[2,4,7]

Recent consensus papers have addressed key issues in GA management, concerning diagnosis, prognostication and treatment options.[1,8] However, consensus was either not achieved or not assessed for several elements that continue to confer frustration across the GA community, including proposals on how we can effectively map the complex structural features of GA to the changes in visual function and variable prognoses of patients with GA.[1,8]

Given the challenges of achieving consensus, we adopted a pragmatic approach. Pulling together our expertise in a roundtable discussion, we aimed to look beyond consensus to characterise what we believe are key challenges that continue to prevent the effective management of GA. Our goals were to identify ways in which we could engage the whole GA community to reframe thinking and effect change. Our discussions focused on four key areas that are summarised in this white paper.

1. **Refined definition and classification of GA are urgently needed –** How can we effectively diagnose and refer patients, or design clinical trials without acknowledging the heterogeneity of the disease?

2. **There is a lack of detailed understanding and experience of GA and its management –** If few of those working in regulatory approval, health commissioning and policy development, or even retina specialists, have sufficient hands-on experience and understanding of GA, how can we as a community optimise care for our patients?

3. **There are no effective, validated tools to measure loss of visual function in GA –** Visual acuity is the gold standard measure of visual function for other disease states that has been erroneously adopted for GA.[9–11] However, in GA the preservation of visual acuity until late in the disease course means functional deficits experienced by patients earlier in the disease fail to be captured.[9,11] Given this limitation, which functional assessment tools can better reflect both lesion progression and the real-world impact of GA on patients' daily lives? How can we identify those patients who might benefit most from clinical management?

4. **Early diagnosis and referral for specialist intervention is needed in GA –** We need to be able to diagnose, refer and manage patients with GA earlier,[1,12] to catch fast-progressing, extrafoveal lesions before patients suffer from the devastating symptoms of irreversible vision loss. How can we make sure this happens in practice?

1.

Refined definition and classification of GA are urgently needed

Despite over 10 years of imaging innovation since the Beckman classification,[13] the eyecare community continues to classify GA as a single entity. How can we appropriately diagnose and refer patients or effectively study potential treatments if we have not classified the distinct patient phenotypes in GA?

Historically, colour fundus photography (CFP) has been the primary imaging modality for classification of AMD.[3,14,15] CFP was used to define GA (Box 1 , page 6) and identify features such as drusen and pigmentary changes, which have become hallmark precursor features of GA (Table 1).[3,13,16]

Table 1. Five-stage clinical classification of AMD as developed by the Beckman Initiative for Macular Research Classification Committee[13]

AMD stage	Drusen (size)	Pigmentary changes*
No ageing	None	None
Normal ageing	Druplets / small drusen (≤63 µm)	None
Early AMD	Medium drusen (between >63 µm and ≤125 µm)	None
Intermediate AMD	Large drusen (>125 µm)	And/or
Late AMD	GA and/or nAMD	

*AMD pigmentary abnormalities = any definite hyper- or hypopigmentary abnormalities associated with medium or large drusen but not associated with known disease entities.

Table adapted from Ferris FL, *et al.* 2013.[13]

Since these early findings, imaging technologies have progressed significantly. Modalities such as fundus autofluorescence (FAF), infrared reflectance (IR) and various forms of optical coherence tomography (OCT) have advanced our understanding of the structural features and progression of atrophy in AMD to reveal the complexity of the disease.[11,14,15,17,18]

The five-stage Beckman clinical classification of AMD and its terminology of early, intermediate and late (Table 1) remain important for the management of AMD.[19] However, mounting evidence from the array of imaging modalities now available suggest that we need to add more granularity to this approach. The progression of intermediate AMD to atrophy and/or neovascularisation is far more complex and nuanced than simply the accumulation of drusen and pigmentary changes.[16,20]

Likewise, GA encompasses a diverse range of anatomical features that can have significant implications for the individual's likely rate of progression and their functional experience of disease.[14,21,22] Moreover, this classification completely neglects reticular pseudodrusen (RPD),[13] an important biomarker for progression, and as such severity.[23,24]

Characteristics of the GA lesion such as size and focality, location relative to the fovea and fellow eye involvement can all confer different experiences of vision loss and rates of progression, including time to foveal involvement.[14,25–29] Similarly, specific border patterns of hyperautofluorescence visible with FAF and key structural features revealed with OCT such as, RPD, hyperreflective foci, loss of thickness in specific retinal bands such as the outer nuclear layer, retinal pigment epithelium (RPE) and ellipsoid zone (EZ) have all been associated with risk for, or rate of, atrophy progression.[14,17,30,31] Such is the significance of these biomarkers that we now have the potential to re-visit previous GA phenotype proposals to support individual treatment decisions and inform future clinical trials (see sections 3.1 and 3.2 for further information).[18,32,33]

Given the inherent complexity and heterogeneity of atrophy in the setting of AMD,[14,22,29] we believe the term GA alone is too simple and needs to be considered as an entity with further subclassifications that take structure and function into account. Is it right that we continue to adopt a single entity classification approach for every patient with GA when we know that each patient can have such inherent differences in their rate of atrophy progression and experience of vision loss?[14,21,22]

> **"The heterogeneous nature of GA remains a significant challenge for both researchers and clinicians"**
>
> Prof. Jordi Monés

Consistent with a need for more accuracy in our stratification of patients is the need, where possible, to move away from using the term 'dry AMD'. We recognise both wet AMD and dry AMD are well established in our vernacular[13] so moving away from these terms may be difficult. However, like GA, dry AMD lacks clarity on the prognosis of the patient. Furthermore, dry AMD can be prone to misuse, or at least regional differences that can lead to confusion in clinic. We have encountered use of dry AMD as both equivalent to GA, the standard within Europe,[13,34] and to describe any AMD that is 'not nAMD', a nomenclature frequently used in the US that is just not true.[35–37]

> **"There is no common agreement on how to define what is GA and what is not GA"**
>
> Prof. Nicole Eter

Recognising the need to evolve our definition of atrophy in AMD, the Classification of Atrophy Meetings (CAM) Group was convened to devise a new classification approach that would support an earlier and more precise estimation of atrophy in AMD using the high-resolution capabilities of OCT.[15,16] The resulting definition, complete RPE and outer retinal atrophy (cRORA) represents a well thought-through and evolved approach to defining atrophy in the AMD setting (Box 1).[1,15,38] cRORA can be applied in the presence or absence of choroidal neovascularisation (CNV) so supports a more accurate diagnostic approach that allows for both manifestations of late AMD to be present in the same eye (defined in Box 1).[15] The term incomplete RORA (iRORA) was also introduced to describe a stage of AMD where the OCT signs were present but did not fulfil the dimension criteria for cRORA, creating a more nuanced description of atrophy that recognises the complexity of the transition from intermediate to late AMD (Box 1).[15,16]

cRORA and iRORA are now both well-established as diagnostic methods for atrophy in AMD.[1] However, the CAM group classification was not set up to categorise a patient's progression or phenotype. cRORA is a descriptive, OCT-based morphological classification that lacks any information on relative speed of progression,[15,16] and, in our experience, can look completely different from one case to another. While cRORA was formalised in the context of AMD and GA, similar structural features can be seen in several other retinal diseases.[15,39] In that sense, cRORA may have limitations as a precise disease-specific definition. The diversity of features, artefacts and variable quality of OCT images can also make cRORA features challenging to ascertain, even among retina-trained ophthalmologists and experienced OCT readers.[38,40]

A revised GA classification approach is therefore needed to educate a broad spectrum of users on the heterogeneity of GA and the implications of any imaging markers on an individual's prognosis. By using a multimodal approach, perhaps with functional inputs, we may be able to develop a refined classification that can speak to the granularity of GA.

Crucially, any new classification must balance the requirement for detail with the need for clarity and consistency. We need to keep the guidance as simple as possible, clearly outlining who and when to refer or treat such that the guidance can support timely referral to specialist care and improved patient outcomes in a way that works for the whole GA community.

> **"We've got to keep the classification consistent and simple, such that it does trickle down to the right people effectively"**
>
> Dr David Wong

Box 1: Existing definitions of atrophy in AMD do not recognise the structural heterogeneity of a patient's GA and the implications this can have for an individual's prognosis.

CFP definition of GA[3,16]

- A sharply delineated round or oval area of RPE hypopigmentation or depigmentation of varying diameter through which choroid vessels are visible

OCT definition of atrophy in the setting of AMD[15,16]

cRORA

- A region of hypertransmission into the choroid at least 250 µm in diameter
- A zone of attenuation or disruption of the RPE at least 250 µm in diameter
- Evidence of overlying photoreceptor (PR) degeneration characterised by features that include loss of the interdigitation zone, EZ, and external limiting membrane and thinning of the outer nuclear layer
- Absence of scrolled RPE or other signs of an RPE tear

iRORA

- For iRORA, the above OCT features are required to be present and vertically aligned but the included features may be smaller than 250 µm in diameter

2.

There is a lack of detailed understanding and experience of GA and its management

Understanding the heterogeneity of GA and how it differs from nAMD is critical for the appropriate counselling of patients and interpretation of clinical trial results.[14] If few eyecare professionals (ECPs), regulators or payers have guidance on, or experience of GA, how can we as a community optimise care for our patients?

As specialists privileged to be able to work in GA, we frequently find ourselves re-educating patients who have received a diagnosis of dry AMD or GA despite presenting with just a few drusen. This unsatisfactory ability to accurately assess GA in practice may speak to some of the limitations of AMD classification just described. However, we also believe the lack of understanding could stem from the recent focus of ECPs, payers and regulators on nAMD.

Many state healthcare systems, strained by cost and capacity pressures, and an ageing population, will allocate time and resources where they can have the greatest impact. The historical absence of any approved treatments for GA has meant the focus for many has been on managing the treatable, neovascular form of late-stage AMD.[41] As a result, monitoring of GA through specialist eye services is often not supported and patients with GA are directed to wider care services,[41] or even completely discharged from care. ECPs, including retina specialists, are therefore rarely involved in the long-term follow-up of patients with GA,[4] giving few the opportunity to see the complexity of GA's natural history in their clinical practice.

Not only is effective management of patients with GA then restricted to a small number of specialists with specific expertise in the condition, but a crucial opportunity to further understanding of GA is missed. Were we to consistently follow GA in routine clinical practice, we could create a database of both anatomical and functional data across a large, standardised pool of natural history patients, helping us to understand, measure and perhaps validate key instruments for assessing both the anatomical and functional progression of GA.

However, our greatest concern is the impact any lack of understanding or experience in GA has on the patient. Not only does the unsatisfactory assessment and misunderstanding seen in practice create confusion in clinic, but it can also confer a potentially unwarranted sense of fear and lack of hope for the patient.

> **"It's important that we can have an accurate discussion with the patient about their future prognosis"**
>
> Prof. Paulo-Eduardo Stanga

Ill-informed patients are confused, unaware of research into new treatments, and, if reliant on their own research into a diagnosis of 'dry AMD', sometimes unnecessarily fearful of the future.[42] While we acknowledge this is understandable, we also ask if this is acceptable, particularly as research in GA is ongoing.[32]

As a community we need to recognise that there is something we can do for patients living with GA. Where appropriate, couldn't we provide information to patients about ongoing management options and/or research available in other parts of the world? Even if patients are not able to access treatment, surely the emotional and quality of life impact of GA[4,42] means that we could continue to support our patients through the offer of regular monitoring.

> **"We need to create a conscience in the public that they need to be screened, that they need an early and accurate diagnosis, and that they need to be monitored"**
>
> Prof. Paulo-Eduardo Stanga

The focus on nAMD has not only affected the capacity of ECPs to build experience and understanding in GA, but it has impacted expectations regarding potential treatments across the entire medical retina landscape.

The development of vascular endothelial growth factor (VEGF) inhibitors for the treatment of nAMD transformed functional efficacy evaluation in retinal disease. Before the advent of anti-VEGF therapy, no treatment had so effectively stabilised or restored visual acuity in AMD.[43,44] When the US Food and Drug Administration (FDA) adopted a 15-letter change in best-corrected visual acuity (BCVA) as a clinically significant definition in the landmark MARINA and ANCHOR trials,[45–49] it was seen as an ambitious target for research in the disease area.[10,45] Ranibizumab's success in meeting the responder target validated the benchmark, cementing it as a standard in nAMD.[46,47]

> **"With nAMD treatment, one third of patients will gain vision, one third will be stabilised, and one third will continue to lose vision, but not as dramatically as they would have done, had they not been treated"**
>
> Prof. Michael Larsen

In GA however, we believe there is a mismatch between BCVA and the characteristics of its anatomical progression and so question whether continued use of a mean ≥15-letter change as the visual acuity benchmark in GA[9,10,29] is aligned with the anatomical or clinical realities of the disease.

In nAMD, CNV and subsequent subretinal haemorrhage frequently affects the fovea, resulting in early loss of visual acuity and severe vision loss within weeks or months.[50,51] In contrast, GA is often foveal sparing until a late stage, with slow, highly variable progression to foveal involvement.[11,29,32] Once the fovea is involved, fluctuations in visual acuity persist as patients compensate for their central vision loss by using any islands of viable retinal tissue, the variability in BCVA increasing as baseline visual acuity worsens.[52]

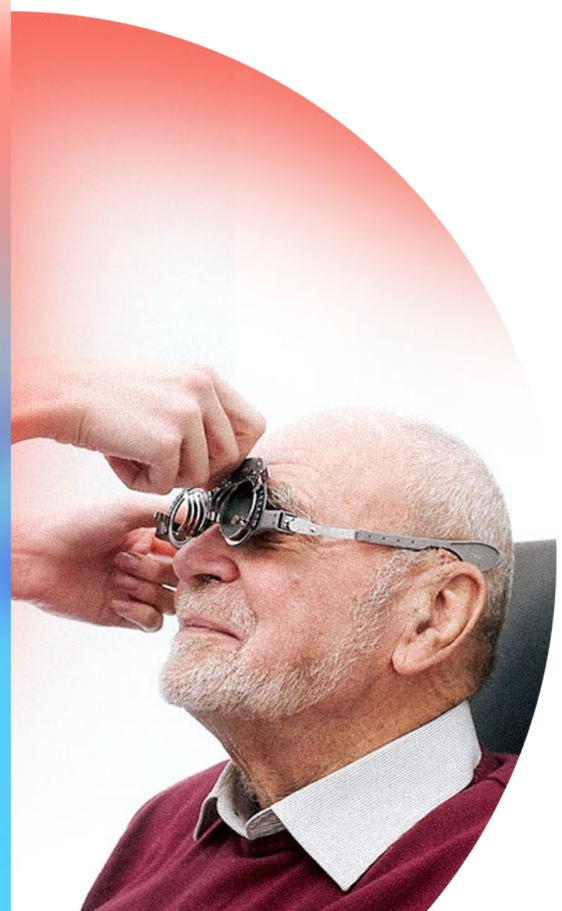
As a result of the gradual and heterogenous loss of vision over the course of GA, mean change in BCVA can be insensitive to changes in visual function over the time course of most clinical trials, with small changes in BCVA potentially masked by noise.[25,49,53] Furthermore, the irreversibility of the disease means the recovery of visual function that can increase the strength of the efficacy signal in nAMD, will never be achieved.[21,46,47] Responder analyses based on a ≥15-BCVA-letter change have their own drawbacks. A large sample size is required for robustness and categorical measures based on a single point of time may be affected by BCVA fluctuations or potential floor effects as baseline visual acuity worsens.[52]

> **"After the first eye is affected, patients say, "let's do something so it won't happen in the other eye" and then no-one is doing anything. Patients are miserable"**
>
> Prof. Anat Loewenstein

We therefore need to recognise that the current BCVA threshold is not a viable metric with the present therapies. While we hope this may change with regenerative and cell-based therapies, right now we need to work with regulators and payers to reframe and reset expectations in GA. Rather than aiming for recovery or complete stabilisation of visual acuity as has been our experience in nAMD,[46,47] we need to focus on slowing the expansion of atrophy and set standards for preservation of visual function that reflect the baseline visual function of the patients under study.[10] There is a need for experienced specialists who understand the complexities of GA and can contribute to the interpretation of clinical trial data, including the nuanced considerations involved in endpoint selection.[14,32] But how can this be achieved when understanding of GA is so compromised within the ECP community?

3.

There are no effective, validated tools to measure loss of visual function in GA



One of the key challenges in the approval and reimbursement of treatments in GA has been our inability to detect a change in visual function with BCVA.[32,54] Without a validated and reliable visual function measure that can work within the constraints of real-world practice, how are we to measure change in the patient's experience of GA to balance against any safety considerations?[10,54]

Research has been conducted to explore the underlying pathophysiology of GA.[32,55] However, several phase 2 and 3 trials, including the large Chroma and Spectri trials, each with more than 900 patients with GA, have failed to demonstrate a functional treatment benefit.[32,56,57]

Clinical trials, some planned over 10 years ago were not designed with the understanding of GA we have now and were never powered to detect a change in visual function.[56] However, given regulators and payers require clear demonstration of a visual function benefit to weigh against any potential safety issues, the challenge of measuring visual function is likely to continue to be a significant obstacle to the development of therapeutic agents in GA.[10,54,58]

Some authors believe this is an opportunity for us to take a more ambitious approach[12] – collaborating with regulators to define clinically meaningful endpoints for AMD, with and without GA, to be assessed in longer-duration clinical trials. However, by necessity clinical trials need to be run over a relatively short period of time to control cost and provide timely results. So is there a way we can effectively assess visual function over the course of a 12–24-month trial?

With the hope that we can help regulators, payers and the research community, we identified three key approaches to address the functional benefit challenge that exists in GA:

1. Improve outcome measures, particularly those assessing visual function in GA

2. Focus on patient subgroups

3. Make better use of the data we already have

1. Improve outcome measures, particularly those assessing visual function in GA

Both the GA research community and regulators are aware of the need for novel functional endpoints to show how any differences in the anatomic progression of GA translate into a functional benefit.[10,11]

> **"We need to recognise that in GA the link between anatomical progression and functional impact is complicated"**
>
> Prof. Giovanni Staurenghi

Challenges for most visual function instruments are that they are not validated for assessment of GA progression;[32] many take time and are technician-dependent,[11,59] and psychophysical endpoints can be subjective and rely on the patient's understanding and cooperation.[58] Clinics may also not have the expertise or resources to perform these assessments. Despite these considerations, we believe there are possible avenues to explore to support future assessment of visual function.

Visual function tests

Best-corrected visual acuity (BCVA)

BCVA is a standard visual acuity assessment where a patient is permitted the use of corrective lenses.[60] Visual acuity estimates the finest level of detail that can be identified by a patient using acuity charts composed of high contrast black targets (such as letters) presented on a white background. The Early Treatment of Diabetic Retinopathy Study (ETDRS) chart is the current chart of choice.[61] Mentions of 'BCVA' in this white paper assume use of the ETDRS chart.

As mentioned, BCVA has recognised shortfalls for the measurement of visual function in GA, particularly in terms of its relationship with the anatomical progression of GA.[9,10] The heterogeneity and fluctuations in visual acuity seen over the time course of clinical trials can make mean change in BCVA ≥15-letters insensitive to any treatment differences in GA, particularly if assessed in a broad patient population with heterogenous or low baseline visual acuity.[10,49,53]

Despite these challenges, we believe BCVA remains a valuable measure of visual function. BCVA is tangible for the patient, available to all ECPs and easy to administer. Furthermore, all patients with GA will eventually experience a significant and irreversible decline in visual acuity.[62] Indeed, in a recent retrospective analysis of the Chroma, Spectri and Proxima A trials (ClinicalTrials.gov identifiers: NCT02247479, NCT02247531 and NCT02479386 respectively), Chakravarthy and colleagues determined that even patients with sub-foveal, unifocal lesions had a high risk of BCVA loss over time.[28]

Categorical and time-to-event analyses that measure the incidence of clinically significant persistent vision loss, measured over at least two visits to mitigate the impact of BCVA variability, may therefore prove to be better measures of visual acuity treatment effect than mean change from baseline.

A small change in mean BCVA for an entire clinical trial cohort can translate into a large clinically meaningful change in responder analysis at the subject level[63] and the metric can be more intuitive for the patient.

Reinforcing the potential value of responder or categorical analyses of BCVA in GA, a trial underway in GA (ClinicalTrials.gov study identifier: NCT06510816) has been designed with a primary endpoint of protection against a persistent ≥15-letter loss from baseline at two consecutive visits at no earlier than 12 months and no later than 18 months.[64,65]

Even if we are able to address some of the shortfalls of BCVA for visual function assessment in GA, there is a concern that BCVA relies on patients reaching the end stage of GA to determine a treatment effect. Is there a functional test we can therefore use to assess benefit before most patients risk central vision loss and that is effective within the time constraints of a clinical trial?

Low luminance visual acuity (LLVA)

LLVA estimates visual acuity in low light conditions, equivalent to moonlight and standard indoor lighting[66] by placing a neutral density filter over the eye under examination. The difference between BCVA and LLVA represents the low luminance deficit (LLD).

LLVA is an outcome of interest for patients with GA as these patients often experience poor visual function in low light conditions before central vision loss in a way that is consistent with the reduction of PR function seen in the dark-adapted state in AMD.[66,67] LLD is an important predictor of future vision loss in GA[11,67] and LLVA is significantly associated with patient-reported visual quality of life, especially in patients with foveal-sparing GA in the inner left and inner lower subfields of the better eye.[58,66,68] While these and other findings suggest LLVA may be a promising measure of visual acuity for both intermediate AMD and early GA in the research setting, LLVA is not a practical assessment for the

real-world clinic; LLVA is associated with a slower rate of GA decline than BCVA and its reliability and sensitivity in GA needs to be determined.[11,66,69] The influence of GA location[68] and association with the presence of RPD may mean targeting LLVA assessment to patients with these anatomical features could maximise the efficacy signal.[32]

Microperimetry

Microperimetry is a visual field test that combines localisation of retinal images with retinal sensitivity information (responses to varying intensities of light stimuli) to allow for spatially-resolved mapping of visual sensitivity.[11,70]

Microperimetry is considered a sophisticated visual field test that differs from standard perimetry by its ability to lock into specific fundus features to characterise regions of interest such as partial or complete loss of sensitivity (scotomas) and link them to underlying retinal pathologies including borders of GA, loss of PRs, RPE and/or choriocapillaris. This provides insightful information on functional disease progression, particularly where the fovea is spared as is the case for the early stages of GA.[11,70,71]

The drawbacks of microperimetry are that it is highly operator dependent, rarely used outside of research, and relies on patients to be able to sustain fixation and concentration for the duration of the test, which in cases of good fixation can take 10–15 minutes but for patients with poor vision can be longer.[11]

Standard microperimetry uses 68 stimulus points usually spaced approximately 290–580 µm apart. This method is not only time intensive and tiring for the patient but may result in stimuli that are too sparse to detect losses of retinal sensitivity in GA.[11,71] Recent data from Chakravarthy *et al* (2025)[71] suggest that if microperimetry is targeted to areas of GA growth to assess time to absolute scotoma, fewer points are needed to determine a visual function effect, and the results may be more likely to reveal a possible functional benefit over the span of a 2-year clinical trial. By using a smaller grid, the time patients need to sustain attention may also be reduced.[11] However, it may still be logistically cumbersome to establish the ideal pattern or patterns of microperimetry versus use of standard grids.

Reading speed

Reading speed is assessed by recording the time taken to read sentences across different print sizes. Recent analyses suggest that the mean reading speed of the 10 print sizes found in everyday life and the mean reading speed of the fastest 3 sentences read outperform other commonly used measures.[72]

Loss of reading ability is important to patients and a frequent complaint among patients with GA.[42,73] The association of reading acuity and speed with patient reports of visual function and structural biomarkers supports the validity of reading performance as a meaningful endpoint in GA clinical trials, particularly within a foveal-sparing population with preserved BCVA.[2,74] However, the FDA currently does not accept this endpoint.[32] The reliability and sensitivity of reading performance in foveal sparing patients can be affected by the location of the lesion, function of the fellow eye, and the language in which the patient reads relative to the location of the lesion.[32,74] With consideration of these parameters, we believe reading speed may be used to assess time to loss of visual performance, providing a potentially useful measure of visual function in patients with foveal-sparing lesions.

Contrast sensitivity

Contrast sensitivity measures the ability to detect targets of equal size as they decrease in contrast. Historically, contrast sensitivity has been most frequently measured with charts like the Pelli-Robson Chart.[61,75] Recently a quantitative contrast sensitivity function (qCSF) that employs active learning has been developed.[75,76]

Like LLVA, contrast sensitivity can be used as an indirect measure of PR function.[77] Compared with BCVA, contrast sensitivity correlates better with visual impairment and vision-related quality of life in GA than visual acuity tests. Contrast sensitivity may be able to detect deficits in visual function at an earlier stage than visual acuity tests and is thought to be of potential value for patients with foveal-sparing lesions.[75,78]

Full contrast sensitivity tests are time consuming to assess in clinic and often difficult for patients to understand.[78] The Pelli-Robson chart uses a single spatial frequency so while being quick, easily applied and inexpensive to perform, is considered a coarse estimate of contrast sensitivity function with poor reliability.[75]

More recently, qCSF, which employs an active learning algorithm (Box 2) to optimise testing with a large set of stimuli, has been developed.[75] Recent evidence in GA suggests that longitudinal change in qCSF is associated with change in the size of the GA lesion.[76] These results, together with the relatively short time to carry out the test (2–5 minutes per eye), and the robust test-retest reliability of qCSF, suggests the measure may be of value as a potential endpoint in GA.[75,76]

Quality of life and patient-reported outcome measures (PROMs)

GA has a profound impact on quality of life, often before BCVA is affected.[5,79] Despite this, the impact of GA on daily activities and quality of life is rarely assessed in clinic.

In the research setting, the quality-of-life burden of GA is often assessed using the 25-Item National Eye Institute Visual Function Questionnaire (NEI VFQ-25). The NEI VFQ-25 has undergone preliminary validation,[79] but a minimum clinically important difference in score change is not yet available[5] and other PROMs such as the Functional Reading Index, are required in addition to the NEI VFQ-25 to fully characterise a patient's visual disability in GA.[79] NEI VFQ-25 is also unable to capture small progressions in GA[68] and is markedly influenced by the choice of better eye versus worse eye as the test eye.[80]

The advent of new technologies such as virtual reality offer exciting opportunities to be able to assess patients' abilities to perform daily activities in a controlled setting.[61] VR-based assessments are in development but will require testing of their validity and reliability prior to use in clinical trials or general practice. There is a growing need to better understand, measure and support the functional burden patients experience in living with GA.

> **"What is important at the end of the day is the patient's voice. We need to find a way to translate the patient's voice into an acceptable data point for authorities"**
>
> Dr David Wong

Surrogate markers

While we await the validation of visual function and functional vision endpoints for GA, the urgent need for therapeutic innovation underscores the importance of advancing how we assess disease progression. In this context, exploring whether additional anatomical endpoints could serve as surrogate markers may help support future clinical research and inform regulatory and health technology assessment frameworks.[32]

Evidence suggests that EZ attenuation may serve as a biomarker and endpoint for GA in both clinical trials and clinical practice.[81] The integrity and reflectance of the EZ is considered an important indicator of PR health[82,83] with loss of EZ integrity adjacent to GA margins as well as within the central subfield important prognostic indicators associated with GA progression and future loss of visual acuity.[81,84,85]

With potential to reduce reading time and human error, deep learning- or artificial intelligence (AI)-based quantitative analysis of EZ integrity has the potential to make close monitoring of patients and early detection of PR loss in patients a reality (Box 2).[84,85] Using deep learning (Box 2) to support with identification, analysis and quantification of PR and RPE degeneration on OCT, Schmidt-Erfurth and colleagues (2025)[86] recently demonstrated that PR thinning due to EZ loss consistently precedes and exceeds RPE loss. They further showed that GA growth – and the ability to detect treatment differences – was strongly influenced by the baseline difference between EZ and RPE integrity. Quantification of EZ metrics using AI may therefore serve as a useful marker of GA progression in clinical trials and prove invaluable in justifying treatment intervention.[85,86]

In 2023, the FDA confirmed total EZ attenuation as an approved endpoint in GA studies[87] and EZ attenuation is set to be used either as a primary or secondary endpoint in two ongoing clinical trials (ClinicalTrials.gov study identifiers: NCT06373731 and NCT06510816).[64,65,89] While reimbursement of GA treatments solely on the basis of EZ attenuation is unlikely in Europe, structural parameters like EZ integrity may prove significant for futility testing, supporting clinical management decisions in GA patients if and when treatments are approved.

The endpoints explored in this white paper do not come without their own challenges, and all need to be validated for use,[11,32,58,59] however, we believe there is potential for measurement of visual function in GA. Given the technological advances gained with AI (Box 2), perhaps we now finally have the capability to identify and validate effective visual function endpoints in GA.

2. Focus on patient subgroups

"GA is not well defined and is not a uniform disease. We need good patient selection. If the study group is too broad, then the signal will disappear in the overall analysis"

Dr Imadeddin Abu Ishkheidem

The slow progression of GA means that any heterogeneity across the population when combined with variability in measurement or error reduces the strength of the signal that can be measured.[29] Consistent with this, a recent in-depth analysis of the criteria used in GA trials highlighted the major need to refine and improve patient selection.[32]
Given the constraints of public health healthcare systems in Europe, broad early treatment of all GA patients may not be immediately feasible.[7,35] In this context, clinical trials focused on specific patient subgroups could support more targeted therapeutic approaches[88] and inform payer decision-making – helping ensure that treatments reach the right patients at the right time.

Patients with lesion characteristics associated with faster GA progression, such as extrafoveal location,[26] multifocal lesions,[27] or diffuse-trickling FAF patterns,[14,17,90] may benefit more from treatment. As such, it is critical that they be considered as part of any new classification or GA staging approach.

> **We need to impress on regulators that if you see a geographic atrophy just extrafoveally to the centre, in two years that patient is at risk of losing his/her vision"**
>
> Prof. Sobha Sivaprasad

Indeed, if we were to refine and improve our patient selection to reflect a fast progressor subgroup of patients, perhaps BCVA would be sensitive enough to reveal an efficacy signal in GA.[32] The 'Reframe GA' initiative is currently embarking on a separate initiative to identify patient subsets for further analysis and research.

> **This is the type of patient where there may be a rescuing potential. Hard to find, but worth looking for"**
>
> Prof. Michael Larsen

3. Make better use of the data we already have

In the past there has been a total reliance on the primary endpoint from prospective clinical trials for regulatory approval. As a result, trial outcomes are often distilled into the statistical significance of the primary endpoint for regulators, while payers interpret this same endpoint through the lens of cost-effectiveness and real-world value. However, the clinical trials for GA were designed years before we accrued the knowledge we have now[12,56] and the completed GA trials were never designed to detect visual function as the primary endpoint.[56,57] So what can we do with the data we have to facilitate access to treatments for those GA patients who need it most?

> **These trials were not beautifully designed for 2025. They were designed 10 years ago ...we need to read between the lines..."**
>
> Dr Jordi Monés

Given the continuing unmet need in GA,[32] the significant advances made in our understanding of the disease,[33,86,90,91] and the recent findings coming out of the *post-hoc* and retrospective analyses of patient subgroups or pooled data from existing clinical trials,[28,71] is there scope for similar analyses of existing clinical trial data to be carried out and submitted for approval?

While we accept that functional testing is more relevant to patients and preferred by regulatory agencies,[54] can a purely anatomical approach be accepted by regulators as a short-term surrogate marker of efficacy in clinical trials as it has been to assess disease progression in clinical practice?[32,59] Drug approvals based solely on anatomic outcomes in ophthalmology and other disease areas like oncology are not unprecedented.[92]

Can alternative metrics of relevance to the patient, such as the concept of 'time to visual loss', be explored? Such a metric could help patients understand how their vision might change over time, offering a clearer understanding and awareness of how the condition is likely to progress. This would result in more informed treatment decisions and outcomes, each of which have the potential to improve the quality of life for those affected by GA.

Given the significant unmet need in GA, is there a way in which regulators may reconsider the interpretation of existing data, potentially to support provisional approval? Or might payers consider a reimbursement programme that would be subject to re-evaluation through real-world evidence (RWE) or prospective clinical trials?

Box 2: The potential for deep learning and AI

Offering rapid and objective analysis of FAF and OCT features[86,93] or optimisation of test stimuli in functional assessments,[75] AI, active or deep learning software has the potential to become standard in future clinical practice. However, a few considerations need to be addressed before its widespread use.

The opportunity of AI

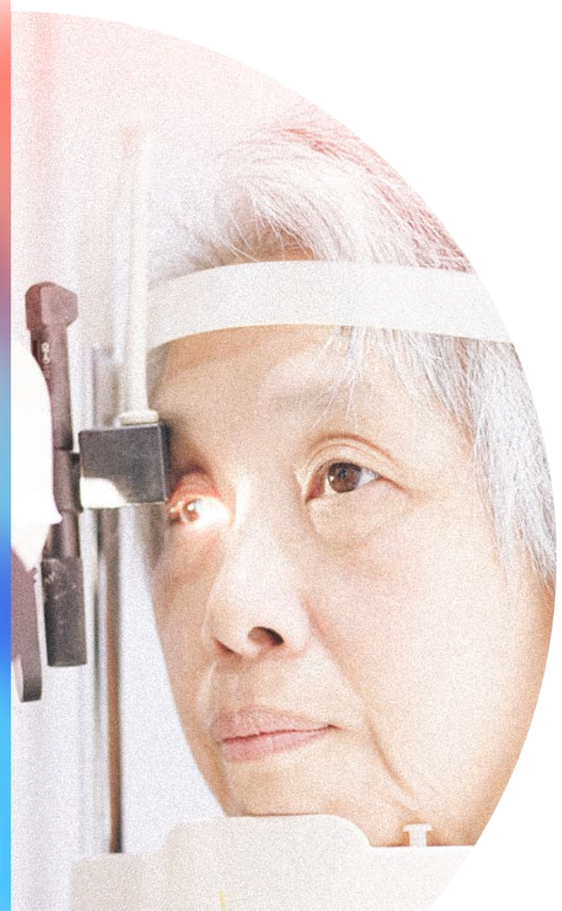
- Optimise information extraction from structure and visual function stimuli from more complex assessments[75,93]
- Rapidly analyse OCT and FAF imagery to the micron level
  - Monitor PR and RPE level changes or the growth pattern of the GA[86]
  - Make predictions about the progress of the lesion based on key imaging biomarkers[93]
  - Make predictions of future visual function loss from images[86]
- Review large population databases to identify additional risk factors for progression and how progression of GA translates into the patient experience of the disease[86]
- Rapidly identify high-risk patients[86] over 1 or 2 scans in a 4–6-month period, with minimal impact on capacity

Considerations for use in practice

- Physician knowledge of patient history must be applied to ensure context
- Real-world validation is still required
- A robust and 'open box' algorithm must be used

4.

There is a need for earlier referral and specialist intervention in GA



A key component of the proposals we have set forward in this white paper is the need to recognise the heterogeneity of GA. However, if we are to identify specific patient subgroups, including those with fast-progressing lesions, we need to diagnose and refer patients with GA to specialist care earlier, before the devastating impact of vision loss.

There is a generalised belief among the elderly population that losing vision is a 'normal' part of old age.[7,42] As many patients with early GA are also asymptomatic,[1] it is not surprising that patients frequently do not present until late in the disease course.

However, if we are to identify subsets of patients, such as those with extrafoveal lesions,[26] this late presentation of patients with GA presents a challenge. How can we hope to design clinical trials in discrete subsets of patients if we are not identifying most patients until they have experienced the profound symptoms of central vision loss? How can we work to include these patients in clinical trials if they are not referred to the specialists leading those trials in the first place?

It is therefore critical that we work to support early identification, diagnosis and referral of patients with GA to specialist care to optimise management and treatment outcomes before significant loss of vision occurs.

Reframing thinking in GA

The clinical landscape of GA is undergoing a significant shift, with emerging therapeutic approaches signalling the transition from an historically untreatable condition to one with potential for intervention.[32,57] However, key challenges remain in how we diagnose, monitor, and manage GA effectively. We suggest that by adopting a pragmatic approach based on the following six proposals, we can reframe thinking and make a meaningful difference in GA.

We call upon the GA community to support this manifesto to improve patient care in GA.

1. Update GA classification to simplify identification of patient subgroups, guide appropriate diagnosis, referral and clinical management, and effectively study potential treatments

2. Ensure better education and resource allocation to improve understanding of GA, the differences between GA and nAMD, and the implications these differences have for patients and their care

3. Work with the wider global research community to identify and validate better endpoints, particularly those related to visual function

4. Identify and validate patient subgroups where stronger signals of functional benefit might be detected or where disease is likely to progress rapidly to life-altering vision loss, to enable the development of more effective solutions

5. Invite regulators and payers to work more closely with us as experts to better interpret existing data and to translate lessons learned in other disease states

6. Support prompt referral of patients diagnosed with intermediate AMD to a retina specialist with expertise in GA and clinical trials, to rule out extrafoveal asymptomatic GA and advise on clinical trial availability

Abbreviations

AI	Artificial intelligence
AMD	Age-related macular degeneration
ARMD	Age-related macular degeneration
BCVA	Best-corrected visual acuity
CAM	Classification of Atrophy Meetings
CFP	Colour fundus photography
CNV	Choroidal neovascularisation
CNV-AMD	Choroidal neovascular age-related macular degeneration
cRORA	Complete retinal pigment epithelium and outer atrophy
ECP	Eyecare professional
EMA	European Medicines Agency
ETDRS	Early Treatment of Diabetic Retinopathy Study
EZ	Ellipsoid zone
EZ-RPE	Ellipsoid zone – retinal pigment epithelium
FAF	Fundus autofluorescence
FDA	Food and Drug Administration
GA	Geographic atrophy
IR	Infrared reflectance
iRORA	Incomplete retinal pigment epithelium and outer atrophy
LLD	Low luminance deficit
LLVA	Low luminance visual acuity
nAMD*	Neovascular age-related macular degeneration
NICE	National Institute for Health and Care Excellence
NEI	National Eye Institute
NEI-VFQ-25	National Eye Institute Visual Function Questionnaire-25
NIH	National Institutes for Health
OCT	Optical coherence tomography
PR	Photoreceptor
PROM	Patient-reported outcome measure
qCSF	Quantitative contrast sensitivity function
RPD	Reticular pseudodrusen
RPE	Retinal pigment epithelium
RWE	Real-world evidence
VEGF	Vascular endothelial growth factor

Active exudative AMD[94]	Often used when disease activity is ongoing and treated
Advanced neovascular AMD[95]	Highlights the progression of the disease
Choroidal neovascular AMD (or CNV-AMD)[96]	Specifies involvement of choroidal neovascularisation
Disciform macular degeneration[97]	Older term, refers to a late stage of wet AMD with scarring
Exudative AMD[98]	Refers to leakage from abnormal blood vessels
Exudative age-related macular degeneration (ARMD)[13,98]	Another variant emphasising fluid leakage using 'ARMD' instead of 'AMD'
Late-stage AMD (neovascular type)[13]	Describes the advanced, vision-threatening neovascular form of AMD
Neovascular ARMD[13]	Alternative abbreviation ('ARMD')
Wet AMD[13]	Wet age-related macular degeneration
Wet ARMD[13]	Another variant using 'ARMD' instead of 'AMD'

*Multiple terms are or have been used to describe nAMD.

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