AMERICAN ACADEMY OF OPHTHALMOLOGY®

Geographic Atrophy in Age-Related Macular Degeneration

A Tale of Two Stages

Tiarnan D.L. Keenan, BM BCh, PhD[1]

Purpose: To examine disease progression in age-related macular degeneration (AMD) at 2 distinct stages, progression to geographic atrophy (GA) versus GA expansion, by comparison of the risk and protective factors at each stage.

Design: Perspective.

Subjects: Individuals at risk of GA or with GA.

Main Outcome Measures: Progression to GA and GA expansion rate.

Methods: Critical synthesis of the literature on risk and protective factors, both environmental and genetic, for progression to GA versus GA expansion in AMD.

Results: Comparison of the risk and protective factors demonstrates partially overlapping but partially distinct risk and protective factors for progression to GA versus GA expansion. Some factors are shared (i.e., operating in the same direction at both stages), others are not shared, and others seem to operate in different directions at each stage. Risk variants at *ARMS2/HTRA1* increase both risk of progression to GA and GA expansion rate, presumably through the same mechanism. By contrast, risk and protective variants at *CFH/CFHR* alter risk of GA but not GA expansion rate. A risk variant at *C3* increases risk of GA but is associated with slower GA expansion. In environmental factors, cigarette smoking is associated with increased risk of GA and faster GA expansion, whereas increased age is associated with the former but not the latter. The Mediterranean diet is associated with decreased progression at both stages, although the food components with the largest contributions seem to differ between the 2 stages. Some phenotypic features, such as reticular pseudodrusen and hyperreflective foci, are associated with increased progression at both stages.

Conclusions: Analysis of the risk and protective factors for progression to GA and GA expansion demonstrates partially overlapping but partially distinct elements at each stage: some are shared, some are relevant to 1 stage only, and some even seem active in opposite directions at each stage. Aside from *ARMS2/HTRA1*, the overlap between the genetic risk factors for the 2 stages is minimal. This suggests that the biologic mechanisms differ at least partially between the 2 disease stages. This has implications for therapeutic approaches and suggests that treatment aimed at the underlying disease processes may need to be tailored by stage.

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> *"I tell thee," said madame …, "that although it is a long time on the road, it is on the road and coming. I tell thee it never retreats, and never stops. I tell thee it is always advancing."*[1]

In age-related macular degeneration (AMD), the development of geographic atrophy (GA) differs partially but fundamentally from its subsequent expansion: in its timecourse, its risk factors, and its underlying mechanisms. Across the life cycle of GA, its conception and gestation differ in notable ways from its infancy and adulthood. Its birth is over 50 years in the making, whereas its expansion across the macula is typically accomplished in less than a decade; the interval from incidence of noncentral GA to central involvement is typically around 3 years.[2]

> *"It does not take a long time to strike a man with Lightning," said Defarge. "How long," demanded madame, composedly, "does it take to make and store the lightning? Tell me."*[1]

Similarities and differences between GA incidence and GA expansion can be evaluated by comparison of genetic and environmental risk factors between the 2 stages (Table 1). This has important implications not only for potential differences in the underlying biological mechanisms but also for whether partially distinct therapeutic approaches may therefore be required at each stage.

Metaphors from other fields may be helpful: in a forest fire, factors that increase the risk of the first ignition may

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Table 1. Partially Distinct and Partially Overlapping Risk and Protective Factors for Progression to GA (Incidence) Versus Progression of GA (Expansion)

	Progression to GA (Incidence)	GA Progression (Expansion)
Shared	*ARMS2/HTRA1* genotype: minor allele at rs10490924 (risk factor)	*ARMS2/HTRA1* genotype: minor allele at rs10490924 (faster progression)
	Cigarette smoking (risk factor)	Cigarette smoking (faster progression)
	Mediterranean dietary pattern (protective factor)	Mediterranean dietary pattern (slower progression)
	Phenotypic characteristics including reticular pseudodrusen and hyperreflective foci (risk factors)	Phenotypic characteristics including reticular pseudodrusen and hyperreflective foci (faster progression)
Not Shared	Age (risk factor)	Age (no association)
	CFH genotype/haplotype (risk or protective factors)	*CFH* genotype/haplotype (no association)
	Multiple other genetic variants, including *C2/CFB* and *CFI* (risk or protective factors)	Multiple other genetic variants, including *C2/CFB* and *CFI* (no association)
	Genetic variants at *PRMT6* and *LSS* (no altered risk at genome-wide significance)	Genetic variants at *PRMT6* and *LSS* (altered progression rate)
	Mediterranean diet food components: - higher fish intake (protective factor; strong interaction with *CFH* genotype) - higher whole grain intake (protective factor)	Mediterranean diet food components: - higher fish intake (no association) - higher whole grain intake (no association)
	Mediterranean diet food components: - higher whole fruit intake (possible protective factor) - lower red meat intake (no association) - moderate alcohol intake (possible protective factor) - higher MUFA: SFA intake ratio (no association)	Mediterranean diet food components (association with slower progression for each): - higher whole fruit intake - lower red meat intake - moderate alcohol intake - higher MUFA: SFA intake ratio
Opposite Direction	*C3* genotype: minor allele at rs2230199 (risk factor)	*C3* genotype: minor allele at rs2230199 (slower progression)
	APOE genotype: minor allele at rs73036519 (protective factor)	*APOE* genotype: minor allele at rs73036519 (faster progression)
Uncertain	AREDS supplements (no significant effect, with outcome as progression to GA or central GA)	AREDS supplements (nominally significant slower progression for antioxidants plus zinc vs. placebo, in post hoc analyses with low power)
	Local complement inhibition at C3 by pegcetacoplan (nominally significant decreased progression from iRORA to cRORA, in post hoc analyses of a phase II trial)	Local complement inhibition at C3 by pegcetacoplan or C5 by avacincaptad pegol (slower progression for each)

AREDS = Age-Related Eye Disease Study; cRORA = complete retinal pigment epithelium and outer retinal atrophy; GA = geographic atrophy; iRORA = incomplete retinal pigment epithelium and outer retinal atrophy; MUFA = monounsaturated fatty acid; SFA = saturated fatty acid.

have some similarities but important differences from those that lead to faster spread of the fire at its leading edges. Related to this, the mechanisms responsible for the first ignition may be quite different from those responsible for subsequent spread. Importantly, therefore, different fire-fighting approaches may be required at each stage. Similarly, in large-scale uprisings like the French Revolution, factors that increase the risk of isolated insurrection may have some similarities but important differences from those that make insurrection spread more quickly.[3–5] Again, therefore, partially distinct approaches may be effective in addressing uprising at each stage.

In some scenarios, as in the spread of revolution, the nature of the inciting event has implications for the rate of subsequent spread because each new unit added must undergo its own conversion to the cause (akin to cell death). Any attempt at treatment must take into account the original event and underlying grievances (perhaps related to AMD genotype and phenotype, for example). In other scenarios, as in a forest fire, the nature of the original event may be largely irrelevant for the purposes of subsequent spread. In these cases, treatments that are agnostic to the original event might still be effective. Knowing whether GA behaves in one or other of these ways, therefore, has important implications for appropriate therapeutic strategies. For example, 1 cross-sectional cluster analysis of patients with GA reported 3 partially distinct GA subtypes: (1) one characterized by higher frequency of soft drusen and GA central involvement and higher complement-based genetic risk score (GRS); (2) another characterized by lower frequency of soft drusen or reticular pseudodrusen (RPD) and low AMD GRS; and (3) a third characterized by higher frequency of RPD, lower frequency of GA central involvement, and higher *ARMS2* GRS and extracellular matrix GRS.[6] However, longitudinal cluster analysis of GA in the Age-Related Eye Disease Study 2 (AREDS2) did not replicate these findings; no strong genotype-phenotype correlations were observed and the results were not consistent with distinct GA subtypes arising from different pathway-based genetic etiologies.[7]

A further distinction is important: some forest fires are triggered by a single ignition event, whereas others may arise from multiple ongoing ignitions at different locations, which gradually spread and merge. A similar distinction is relevant in considering the phenomenon of GA expansion,

although this difference is not captured in most natural history studies or clinical trials.[8,9] Geographic atrophy expansion occurs through a combination of contiguous enlargement at the circumference of established lesions and incidence of new lesions. However, the relative contribution of these 2 factors likely differs widely between individuals (and even between different time points of the same eye). At 1 extreme, some eyes with GA may have only 1 incidence event, followed by contiguous enlargement only, such that the GA remains unifocal throughout its life cycle. At the other extreme, other eyes may have multiple incidence events early on and on an ongoing basis, such that the GA is highly multifocal in early years before lesion confluence leads to fewer foci. Importantly, the risk factors and mechanisms underlying each type of expansion may differ partially; the risk factors for ongoing incidence events seem likely to resemble more closely the risk factors for the first incidence event.[8,9]

The spatiotemporal behavior of these different types will vary and, importantly, the optimum approaches to slowing expansion may vary according to these types. Therefore, models attempting personalized predictions of GA expansion rate (either globally as a mm/year rate or spatially on a pixel-by-pixel basis) should be more accurate if they are trained on data that makes this distinction. Similarly, analysis of risk factors of expansion should be more meaningful if this distinction is considered, such that risk factors are considered separately for contiguous enlargement versus the incidence of additional foci. Most importantly, studying the treatment effect of potential therapies will be more meaningful when this distinction is prespecified in the analyses.

Age

Higher age is an established risk factor for GA incidence. Meta-analysis of multiple studies from different countries has shown that the prevalence of GA increases exponentially with age—from 0.7% at 70 years, to 2.9% at 80 years, to 11.3% at 90 years in populations of European ancestry.[10] By contrast, higher age is not a significant risk factor for faster GA expansion.[2,11,12] In the AREDS2 cohort of 1616 eyes with GA (without previous neovascular AMD), age was not significantly associated with altered GA expansion rate (in multivariable analyses using the square root transformation).[2] By analogy, conception might take longer, on average, to occur with older parental age; however, once this is attained, the subsequent rate of pregnancy does not vary according to parental age.

This may seem surprising: age represents an accumulation of multiple environmental exposures, other age-related biological changes, and even accumulated genetic and epigenetic changes. Therefore, one might imagine GA tending to progress more quickly with advanced age, perhaps owing to increased tendency to inflammation; decreased reserve in the retinal pigment epithelium (RPE), choriocapillaris, and photoreceptors; and to multiple other adverse consequences. One possible explanation is that some of these abnormalities may correlate more closely with AMD stage than with age alone. In this way, the degree of macular aging changes might already be captured by age of GA onset, such that age has no additional capacity to predict GA enlargement rate. We might imagine that GA develops when a particular threshold of macular aging changes is reached. This threshold could be similar between individuals; someone who developed GA at 60 years had a faster rate of macular aging changes, whereas someone who developed GA at 90 years had a slower rate of macular aging changes but to the same threshold. In this way, the degree of macular aging changes would be similar at GA onset between the 2 individuals, despite their age difference, and GA enlargement would therefore proceed at a similar rate, irrespective of age.

However, the contrast might also point to important differences between the mechanisms underlying GA incidence and expansion. If GA tends to progress at similar rates in individuals aged 60 and 90 years, then aging changes (at the molecular, cellular, and genetic/epigenetic levels[13]) might not be centrally implicated in mechanisms of GA expansion. Related to this, previous studies have investigated the potential efficacy of drugs like sirolimus, which have demonstrated anti-aging properties in extending the lifespan of worms, flies, and mice through the mTOR pathway.[14,15] However, clinical studies of subconjunctival or intravitreal sirolimus in GA did not seem to slow GA enlargement.[16,17] Overall, it remains difficult to distinguish between these 2 possible explanations, and further studies are recommended.

Genetic Factors

Genome-wide association studies (GWAS) have been conducted separately for late AMD prevalence and GA expansion.[18,19] Interestingly, the results do not overlap at all. A large GWAS of late AMD identified 52 independently associated genetic variants across 34 loci.[18] These loci relate to genes involved in biological pathways, including the complement system, lipid metabolism and transport, extracellular matrix maintenance and remodeling, angiogenesis, and cell survival.[18,20] By contrast, a GWAS of GA expansion revealed only 2 loci with genome-wide significance (likely related to the genes *PRMT6* and *LSS*), neither of which was observed in the GWAS of late AMD.[19]

For late AMD prevalence, of the 34 loci, the 2 with highest population attributable risk are at *CFH* and *ARMS2/HTRA1*.[18] Of these 2, 1 appears to be associated with faster GA expansion, whereas the other does not. For *ARMS2/HTRA1*, the minor allele at rs10490924, which is highly associated with increased risk of GA incidence, is also highly associated with faster GA expansion in most studies.[2,11,19,21] In multivariable analyses of the AREDS2 cohort of 771 eyes with GA and genetic data, *ARMS2/HTRA1* risk alleles were very strongly associated with faster GA expansion.[21] However, the relative contribution of the 2 types of expansion described earlier is unknown

here. By contrast, for *CFH*, none of the common risk or protective haplotypes appear to confer altered risk of faster or slower GA expansion.[2,11,19] In the AREDS2, *CFH* genotype was not even nominally associated with altered GA expansion rate.[2] Hence, the minor allele at *ARMS2/HTRA1* increases both the risk of GA development and of that GA, once present, expanding faster—presumably through the same mechanism, according to Occam's razor. By contrast, *CFH* haplotypes increase or decrease the risk of developing GA but do not alter the subsequent expansion rate.

According to the revolution metaphor, widespread grievances against the political elite might increase both the likelihood of initial insurgence and speed of subsequent spread, whereas fragmentation of communities might increase the former but not the latter. Similarly, in the case of forest fires, severe heat might increase both the risk of initial ignition and rate of spread, through similar mechanisms, whereas human activity might increase the former but not the latter.

In fact, *CFH* genotype may be less relevant for disease progression at even earlier severity stages. In analyses of the AREDS and AREDS2 cohorts using multivariable models that included baseline AMD severity level and demographic factors, the minor allele at rs10922109 (the lead variant at the *CFH* locus in a large GWAS and a protective variant) was highly associated with altered risk of progression to late AMD in the AREDS,[18] which comprised a wide spectrum of AMD severity at baseline, but not even nominally in the AREDS2, for which the eligibility criterion was at least intermediate AMD.[22] This was also true for progression to GA specifically. By contrast, the minor allele at *ARMS2/HTRA1* was highly associated with progression to late AMD (and GA specifically) in both the AREDS and AREDS2.

In some cases, we observe not only lack of overlap for risk at the 2 disease stages but even associations in opposite directions (Table 1). This is most striking for *C3* (rs2230199); the minor allele at this locus has consistently been associated with increased risk of late AMD, including GA.[18] However, in multivariable analyses of the AREDS2, the same allele was highly associated with slower GA expansion[2]; this finding has been observed elsewhere also.[23] Hence, it appears that *C3* risk alleles, which increase systemic complement activation levels,[24,25] may drive disease pathogenesis over many decades toward the point of GA incidence but, at the point of established GA, encourage slower expansion. This appears paradoxical and difficult to explain. However, by analogy, in a forest fire, low wind conditions may increase the likelihood of initial ignition but lead to slower spread, or a thunderstorm might increase the risk of initial ignition through lightning strike but lead to slower spread through wet timber.

Other important observations have come from recent randomized controlled trials of local complement inhibition, at either the C3 or C5 level, as discussed below. In both cases, local complement inhibition has slowed GA expansion, although the degrees of slowing have been relatively modest, and treatment has led to increased risk of neovascular AMD.[26–29]

It is difficult to reconcile these 3 sets of observations: (1) no difference in GA expansion rates according to *CFH* haplotype; (2) slower GA expansion rates with a *C3* genotype that increases systemic complement activation and increases risk of GA; and (3) slowing of GA expansion with local C3 (or C5) inhibition. From the first observation, we might conclude that the complement system is involved in the risk of progression to GA but not in GA expansion. However, from the other 2 observations, this appears not to be the case; rather, it seems likely that the complement system is involved at both stages but in different ways. One possibility is that the complement system might represent the central process driving disease progression at both stages but in different ways at each stage (perhaps through partially distinct effector mechanisms or targeting different cell types). This might help explain why local C3 inhibition is effective at slowing GA enlargement,[26,30] despite the first observation, as well as why *C3* genotype appears to have different effects at different disease stages. Another possibility is that the complement system might represent the central process driving disease progression up to GA incidence but might be a contributing rather than a central process for GA expansion. This might help explain why the efficacy of local C3 inhibition for slowing GA enlargement is not even greater, as well as the failure of some previous trials of complement inhibitors for GA expansion.[24,26,30,31]

In particular, the complement system has multiple effector mechanisms; the most well-known are the membrane attack complex (which can lead to cell lysis but also sublytic effects), the opsonin C3b and its fragments (which lead to phagocytosis of opsonized material, but also immunomodulation), and the anaphylatoxins C3a and C5a (which lead to chemotaxis, inflammation, and immunomodulation).[32,33] However, C3 and its fragments are thought to play highly multifaceted roles in AMD, even beyond these mechanisms. These have been reviewed in detail and include inflammasome activation, recruitment of microglia/macrophages to the subretinal space, intracellular C3 mechanisms within the RPE (including activation of the mTOR pathway), and aberrant lysosomal turnover.[24,32] Given this complex situation and the lack of animal or other models that fully recapitulate human disease, understanding which of these different roles played by C3 are those most highly implicated in AMD, and whether the dominant mechanisms may differ by disease stage, has not been fully elucidated.[34,35]

It is even possible that a degree of complement signaling may be required to maintain retinal health and homeostasis. Hence, whereas prolonged excess complement activation may lead to chronic local inflammation and contribute to AMD progression,[36] a degree of complement signaling may be required for photoreceptor and neuronal health through noncanonical roles of the complement system in cell survival and immune regulation.[37,38] For the membrane attack complex, in some cells and scenarios, sublytic membrane attack complex levels are thought to activate

transcription factors that favor cell survival and resistance to apoptosis.[39] For C3, there is some evidence from animal models that it has an important role in maintaining retinal integrity and homeostasis during aging,[40] although these observations are complicated by a background of abnormal complement-dependent neuronal pruning during development in C3 knockout mice.[41]

The idea of C3 potentially acting as a survival factor in some situations might help explain the paradoxical findings for *C3* genotype by disease stage. Despite this, it remains difficult to reconcile the observations of slower GA expansion with a high-risk *C3* genotype and slower GA expansion with local C3 inhibition. However, substantial differences may exist between the complement status of an individual through genetic variation versus pharmacologic treatment[32]; in this case, the former is systemic, continuous, and life-long, whereas the latter is local, intermittent, and therefore likely partial. Overall, further research from both the basic science and clinical domains is required to help reveal the precise roles played by the complement system in AMD, both according to patient genotype and to disease stage.

The genetic factors described earlier have been considered in terms of associations with global GA expansion rates. However, 2 additional factors have important influences on visual acuity and prognosis: (1) GA location at the point of incidence and (2) preferential GA expansion locally. The location most commonly affected by GA at incidence is the parafoveal region.[2,21,42] In the AREDS2 cohort of eyes with incident GA, 67% of cases did not involve the central macular zone at the time of incidence, whereas the remaining 33% did.[2] In the same cohort, the mean proximity of GA to the central macula (i.e., the shortest distance from the nearest pixel with GA to the macular center point) was 459 μm. In analyses of potential associations between AMD genotype (specifically 18 single nucleotide polymorphisms at 9 loci strongly associated with risk of late AMD) and risk of central involvement at GA incidence, no significant association was observed.[2] Few other studies have analyzed potential associations between genotype and GA location. Hence, although the location of GA at the point of incidence is important for visual acuity and prognosis, this characteristic does not seem to be strongly genetically determined. The predilection for the parafoveal region may relate more strongly to anatomical factors, such as the presence of high-risk lesions (particularly soft drusen and basal linear deposits) in both the fovea and parafoveal regions, but the relative absence of protective xanthophyll carotenoid pigment and Müller glia cells in the parafoveal area.[42,43] Indeed, dark adaptation studies and histological analyses show that, in AMD, rod photoreceptor degeneration is prominent in a parafoveal ring surrounding the fovea long before GA occurs.[43]

Regarding local GA expansion, GA tends to expand preferentially in some directions more than others. In particular, analyses of an AREDS GA cohort have demonstrated that local GA expansion rates tend to be incrementally higher with increasing eccentricity across the macula, after adjustment for baseline GA area.[44] Hence, expansion into the fovea tends to be slowest, whereas expansion into the peripheral macula tends to be fastest. This likely explains the phenomenon of relative foveal sparing, including the common occurrence of GA configurations (e.g., horseshoe or donut) that tend to wrap around the fovea before the fovea itself finally becomes involved in later years.[2,45,46] Potential mechanisms for faster expansion with increasing macular eccentricity overlap with the anatomic factors discussed above; they may include greater vulnerability of rods than cones to atrophy expansion (with rod concentrations increasing gradually away from the central macula), the effects of decreased macular pigment density away from the fovea, or other potential factors.[43,44]

Overall, the effects of GA on visual acuity and prognosis relate to the interplay of the following: (1) location of GA at incidence, likely related more to anatomic or stochastic factors than to AMD genotype; (2) altered global GA expansion rates, partly explained by genetic and environmental factors; and (3) preferential GA expansion by macular eccentricity, likely related partly to anatomic factors. In analyses of the AREDS2, visual acuity at the time of GA incidence was worse with GA that had central involvement or larger size.[2] The rate of visual acuity decline was numerically faster according to some characteristics (e.g., GA that was central, or had intermediate lesion size, or had a horseshoe/ring configuration).[2] In analyses of the Chroma/Spectri trials, visual acuity decline was faster in unifocal than multifocal GA; faster GA expansion was also associated with faster decline in visual acuity.[47,48]

Environmental Factors

> *"I am not old, but my young way was never the way to age."*[1]

Cigarette smoking has consistently been demonstrated as a strong risk factor for the development of late AMD, including GA.[22,49,50] Evidence for altered GA expansion rate according to smoking status has been less consistent.[11] However, in 1 of the largest studies, multivariable analyses of the AREDS2 cohort of 1616 eyes with GA revealed a nominally significant association between smoking status (current vs. former vs. never) and faster GA expansion.[2] Similarly, in longitudinal phenotypic cluster analyses of the same cohort, positive smoking status and faster GA expansion rate characterized a prominent cluster division.[7] Hence, this factor appears to be active and operating in the same direction at both disease stages, perhaps like heat in the context of forest fire initiation and spread.

> *"La destinée des nations dépend de la manière dont elles se nourrissent"*[51]

Like smoking, dietary pattern has consistently been identified as a strong risk or protective factor for the development of late AMD and particularly GA.[52,53] Comprehensive longitudinal analyses using detailed data on diet, genetics, and AMD status have been conducted in the AREDS and AREDS2.[54] In both cohorts, closer

adherence to a Mediterranean-like dietary pattern was very strongly associated with decreased risk of progression to late AMD; this was particularly true for GA. Similarly, regarding GA expansion, multivariable analyses of an AREDS2 cohort of 1155 eyes with GA showed that closer adherence to a Mediterranean-like dietary pattern was strongly associated with slower GA enlargement.[55] Therefore, like smoking, this environmental factor appears to be active and operating in the same direction at both disease stages (Table 1).

However, further insights into the foods chiefly responsible for these associations can be provided by analyses at the level of the 9 components of the Mediterranean diet index.[56] Importantly, in evaluation of the AREDS and AREDS2, these analyses isolated the contribution of each component by adjusting for the overall dietary pattern excluding the component under study.[54,55] For progression to GA, the dietary component with the strongest protective association was higher fish intake, with weaker protective associations observed for whole grains and possibly whole fruits and moderate alcohol.[54] By contrast, for GA expansion, no meaningful association with faster or slower expansion was observed according to fish intake; instead, the components with the strongest associations for slower GA expansion were higher intake of whole fruits, lower intake of red meat, moderate alcohol intake, and higher healthy-to-unhealthy lipid intake ratio.[55] Hence, a Mediterranean-like dietary pattern is strongly associated with slower progression to GA and slower GA expansion, but for partially distinct reasons at each stage. This in turn suggests that the biologic mechanisms underlying GA development may be partially distinct from those driving GA expansion and emphasizes that some differences in therapeutic approaches may be required at each stage.

Furthermore, a very strong gene−diet interaction has been observed in association with GA development, but not in association with GA expansion.[54,55] In the AREDS, the association between closer adherence to a Mediterranean-like dietary pattern and decreased progression to late AMD was found only in those with a common protective allele at *CFH*.[54] At the food component level, an extremely strong interaction was present; the association between higher fish intake and decreased progression to GA was present only in those with the *CFH* protective allele. By contrast, for GA expansion, in the absence of any significant association between GA expansion and either *CFH* genotype or fish intake, no such interaction is possible.

The relevant foods, together with their constituent nutrients and potential effects on the intestinal microbiome,[57,58] may provide important insights into which biologic mechanisms are most implicated at each disease stage. Overall, the beneficial effects of the Mediterranean diet are thought to include anti-inflammatory properties, anti-oxidative properties, altered lipid metabolism, improved vascular endothelial health, improved mitochondrial energetics, and neural protection.[59] For progression to GA, the strong finding for fish and its powerful interaction with the protective *CFH* genotype suggest that, for many patients, the dominant biologic mechanisms at this stage may include those related to innate immunity and inflammation, as discussed below. For GA expansion, the findings suggest that the dominant mechanisms at this stage may include oxidative stress, lipid metabolism, and perhaps vascular dysfunction. For example, the beneficial effects of higher whole fruit intake on systemic health are thought to relate to flavonoids and other antioxidants decreasing oxidative stress and likely improving vascular health.[60]

For progression to GA, the strong genotype dependence argues that the biological mechanism underlying potential protection from fish intake may be closely related to the complement system. The protective allele at *CFH* is frequently characterized by the *CFHR3/1* deletion.[61] These 2 CFH-related proteins are known to compete with CFH (and its splice variant FHL-1) for binding to important epitopes, such as malondialdehyde (MDA).[62,63] Malondialdehyde is a common lipid peroxidation product that accumulates in many pathophysiological processes, including AMD; it is an important source of oxidative stress and of enhanced complement activation.[62] CFH is a major MDA-binding protein that is thought to block the uptake of MDA-modified proteins by macrophages and MDA-induced proinflammatory effects.[62] Therefore, the deletion means that CFH can bind to its appropriate epitopes, leading to less excess complement activation and less chronic inflammation. However, the food−gene interaction observed suggests that this protective effect is particularly powerful when combined with high dietary intake of fish. Fish flesh is known to contain multiple natural antioxidants, including enzymes (e.g., catalase and superoxide dismutase), carotenoids, peptides, amino acids (e.g., taurine), and phenolic compounds (e.g., tocopherols like vitamin E, and the ubiquinones), as well as omega-3 polyunsaturated fatty acids like docosahexaenoic acid and eicosapentaenoic acid that also have antioxidant capacity.[64,65] Hence, the pairing of high fish intake, with many antioxidants, and a protective *CFH* genotype, with decreased tendency to complement activation and inflammation, may work strongly in combination to decrease risk of progression to GA, by decreasing both the stimulus for and the response to oxidative stress. However, further research to investigate interactions between fish nutrients and complement regulation is appropriate to understand which particular nutrients may be most important.

Genetic and environmental factors have been considered simultaneously in some studies. For example, pooled analysis of 3 population-based studies of AMD led to the development of a prediction model to calculate the risk of progression to late AMD.[66] The model included the factors age, sex, 26 single nucleotide polymorphisms in late AMD risk genes, smoking, body mass index, and baseline AMD phenotype. However, when the same model was applied to GA expansion rate in 2 of the same population-based studies, the correlation was very poor, and not even a nominally significant association was observed (although GA expansion was considered without square root or other transformation).[12]

Clinical and Imaging Factors

A comprehensive review of phenotypic or imaging factors is outside the scope of this review. However, RPD, also known as subretinal drusenoid deposits, and hyperreflective foci are worthy of discussion. In both the AREDS and AREDS2, RPD presence was associated with significantly increased risk of progression to late AMD, despite adjustment for other characteristics of AMD severity.[67] This was particularly true for progression to GA. Similarly, in both the AREDS and AREDS2, RPD presence was also associated with significantly faster GA expansion.[21] This is generally consistent with the results of other smaller studies.[11,68,69] Likewise, hyperreflective foci have been reported as a significant risk factor for both progression to late AMD and faster GA expansion.[68–71] Finally, GA presence in 1 eye is associated in the fellow eye with both increased risk of GA incidence (if GA is absent) and faster GA expansion (if GA is present).[2,11,72,73] Hence, these phenotypic factors have associations operating in the same direction at both disease stages.

According to Occam's razor, this suggests that similar mechanisms are responsible for linking the risk feature to faster progression at both stages. Reticular pseudodrusen, for example, might represent a precursor lesion for GA at the time points of both GA incidence and GA expansion.[21] Geographic atrophy is diagnosed on OCT by a combination of RPE loss and photoreceptor degeneration,[74] and retinal areas affected by RPD typically show decreased RPE cell density and a thin outer retina (particularly in the outer nuclear layer).[75–77] Considering RPD in this way could explain faster progression at both disease stages through local effects. Other explanations might include innate immune cell activity or choroidal abnormalities, with each believed to be involved in the pathogenesis of RPD but also with GA development and GA expansion.[75,78,79]

Potential Treatments

The AREDS oral supplements are commonly used at more severe stages of AMD. For individuals with large drusen in $\geq$ 1 eye or advanced AMD in 1 eye, they decrease the risk of progression to advanced AMD (i.e., neovascular AMD or central GA).[80] However, this treatment effect is weighted strongly toward decreased risk of neovascular AMD. In the AREDS category 3 and 4 participants, the odds ratio (OR) was highly significant for neovascular AMD (OR, 0.62; 99% confidence interval [CI], 0.43−0.90; P = 0.001) but not significant for either central GA (OR, 0.75; 99% CI, 0.45−1.24; P = 0.13) or any GA (OR, 1.08; 99% CI, 0.70−1.65). Regarding a potential treatment effect of the AREDS supplements in slowing GA expansion, post hoc analyses of a subset of AREDS participants with GA have been performed; these included adjustment for baseline GA area but no square root transformation, and power was low, with only 68 participants between the 4 treatment arms.[81] The statistical test for an overall treatment effect was not significant, although the individual test of antioxidants plus zinc versus placebo was nominally significant (P = 0.05), with slower enlargement in participants randomized to antioxidants plus zinc. In the AREDS2, randomization to either lutein/zeaxanthin or docosahexaenoic acid/eicosapentaenoic acid did not lead to significantly slower GA enlargement (in the context of all participants also taking the AREDS supplements).[2] Hence, AREDS supplements seem to have relatively little, if any, effect on decreasing progression to GA and a possible but uncertain effect on slowing GA expansion.

Local complement inhibition has attracted great interest as a potential therapy to slow GA expansion, as discussed earlier.[9] Randomized controlled trials of local inhibition, at both the C3 and C5 level, have observed significantly slower decrease GA expansion, although the treatment effects reported in phase III trials have been relatively modest.[26–29] For progression to GA, in post hoc analyses of 1 phase II trial of a C3 inhibitor, macular lesions > 500 μm beyond GA margins at baseline were analyzed by OCT.[82] Monthly treatment was nominally significant for decreased progression from incomplete to complete RPE and outer retinal atrophy. Hence, it appears that local complement inhibition might be effective and operating in the same direction at both disease stages. However, for progression to GA, the findings were from post hoc analyses of a single phase II trial and relate to a very narrow spectrum of disease progression (when incomplete RPE and outer retinal atrophy is already present, rather than progression from the medium or large drusen stage). In addition, importantly, the 2 sets of findings overlap so should not necessarily be considered additive. If the potential decrease in progression to complete RPE and outer retinal atrophy contributes to lower GA area measurements at later time points in the clinical trial, this effectively downgrades the treatment effect related to slower enlargement at GA margins.[8,9] As discussed above, for any potential treatment, we must consider that decreased ongoing progression to GA will seem to cause slower GA expansion if we do not analyze contiguous enlargement at the circumference of established lesions separately from the addition of new foci.

Conclusions

Analysis of the risk and protective factors for progression to GA and GA expansion demonstrates partially overlapping but partially distinct elements at each stage: (1) some are shared, (2) some are relevant at 1 stage only, and (3) some even seem active in opposite directions at each stage. This indicates that the underlying biologic mechanisms differ at least partially between the 2 stages. This in turn suggests that therapeutic approaches need to be tailored to the stage. Where a risk factor is shared between stages, as for *ARMS2/HTRA1* risk alleles or cigarette smoking, Occam's razor suggests that the factor is increasing risk through the same mechanism throughout. Where a risk factor is relevant at 1 stage only, as for age or *CFH* genotype, it suggests that the mechanism operating during 1 stage is not highly implicated

in pathogenesis at the other stage. Where a factor increases risk at 1 stage but decreases risk at the other, as for *C3* genotype, we must either invoke 2 separate mechanisms or consider 1 mechanism with opposing effects at each stage. Such an integrated view of risk and protective factors operating differentially by stage, including interactions between diet and genotype, will also improve prognostic predictions across the life cycle of GA development and expansion.

Regarding potential therapeutic approaches, these considerations suggest that complement modulation is likely to be more effective at relatively early disease stages, whereas future therapies targeting *ARMS2/HTRA1* might be effective at both decreasing GA development and slowing GA expansion. In addition, complement modulation will presumably be most appropriate in those with a high complement pathway-based polygenic risk score (or other evidence of local or systemic complement dysregulation), whereas *ARMS2/HTRA1* modulation will presumably be most appropriate in those with risk alleles at that locus. In these ways, early therapeutic approaches can be tailored to the underlying disease processes (i.e., by analogy, to the type of ignition event or the underlying grievances). Even after the time point of GA incidence, some of these might need to be continued, either in the case of ongoing relevance (e.g., for *ARMS2/HTRA1*) or to decrease ongoing incidence events (toward multifocality). In addition, after GA incidence, some additional therapeutic approaches that are agnostic to the incident event could also be appropriate.

Importantly, alongside pharmacological interventions, these data indicate that lifestyle modification may be effective at all stages. Smoking cessation may be helpful at any stage. Similarly, the Mediterranean diet is strongly associated with decreased progression to intermediate AMD, decreased progression to GA, and slower GA expansion.[54,55] However, pending further research, dietary recommendations on the most relevant food components for each stage might be tailored in the future to disease stage and *CFH* genotype. Meanwhile, AREDS-style supplements remain appropriate alongside a healthy diet because associations with decreased progression to late AMD seem additive, without redundancy or other interaction.[54,83] The 2 are complementary, because supplements preferentially decrease risk of neovascular AMD, whereas a healthy diet is associated preferentially with decreased risk of GA.

Footnotes and Disclosures

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[1] Division of Epidemiology and Clinical Applications, National Eye Institute, National Institutes of Health, Bethesda, Maryland.

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The author has completed and submitted the ICMJE disclosures form.

The author has made the following disclosure: T.D.L.K.: Employment - National Eye Institute (National Institutes of Health); Patent—Co-inventor on a patent application: Methods and Systems for Predicting Rates of Progression of Age-related Macular Degeneration; Board Member: Voting member of the Safety Monitoring Committee for the APL2-103 interventional study (Apellis Pharmaceuticals), 2020-2021.

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Abbreviations and Acronyms:
AMD = age-related macular degeneration; **AREDS** = Age-Related Eye Disease Study; **GA** = geographic atrophy; **GRS** = genetic risk score; **GWAS** = genome-wide association study; **MDA** = malondialdehyde; **OR** = odds ratio; **RPD** = reticular pseudodrusen; **RPE** = retinal pigment epithelium.

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Correspondence:
Tiarnan D. L. Keenan, BM BCh, PhD, NIH, Building 10, CRC, Room 10D45, 10 Center Dr, MSC 1204, Bethesda, MD 20892-1204. E-mail: tiarnan.keenan@nih.gov.

References

1. Dickens C. *A Tale of Two Cities*. London, United Kingdom: Penguin Classics; 2012.
2. Keenan TD, Agrón E, Domalpally A, et al. Progression of geographic atrophy in age-related macular degeneration: AREDS2 report number 16. *Ophthalmology*. 2018;125:1913–1928.
3. Epstein JM. Modeling civil violence: an agent-based computational approach. *Proc Natl Acad Sci U S A*. 2002;99(Suppl 3):7243–7250.
4. Giabbanelli PJ. Modelling the spatial and social dynamics of insurgency. *Secur Inform*. 2014;3:2.
5. Weyland K. The diffusion of revolution: '1848' in Europe and Latin America. *Int Organ*. 2009;63:391–423.
6. Biarnés M, Colijn JM, Sousa J, et al. Genotype- and phenotype-based subgroups in geographic atrophy secondary to age-related macular degeneration: the EYE-RISK consortium. *Ophthalmol Retina*. 2020;4:1129–1137.

7. Keenan TDL, Oden NL, Agrón E, et al. Cluster analysis and genotype-phenotype assessment of geographic atrophy in age-related macular degeneration: age-Related Eye Disease Study 2 report 25. *Ophthalmol Retina*. 2021;5:1061−1073.
8. Re: Jaffe et al.: C5 inhibitor avacincaptad pegol for geographic atrophy due to age-related macular degeneration: a randomized pivotal phase 2/3 trial (*Ophthalmology*. 2021;128:576-586). *Ophthalmology*. 2021;128:e25−e26.
9. Keenan TDL. Local complement inhibition for geographic atrophy in age-related macular degeneration: prospects, challenges, and unanswered questions. *Ophthalmol Sci*. 2021;1:100057.
10. Rudnicka AR, Jarrar Z, Wormald R, et al. Age and gender variations in age-related macular degeneration prevalence in populations of European ancestry: a meta-analysis. *Ophthalmology*. 2012;119:571−580.
11. Fleckenstein M, Mitchell P, Freund KB, et al. The progression of geographic atrophy secondary to age-related macular degeneration. *Ophthalmology*. 2018;125:369−390.
12. Colijn JM, Liefers B, Joachim N, et al. Enlargement of geographic atrophy from first diagnosis to end of life. *JAMA Ophthalmol*. 2021;139:743−750.
13. Ardeljan D, Chan CC. Aging is not a disease: distinguishing age-related macular degeneration from aging. *Prog Retin Eye Res*. 2013;37:68−89.
14. Selvarani R, Mohammed S, Richardson A. Effect of rapamycin on aging and age-related diseases-past and future. *GeroScience*. 2021;43:1135−1158.
15. Juricic P, Lu YX, Leech T, et al. Long-lasting geroprotection from brief rapamycin treatment in early adulthood by persistently increased intestinal autophagy. *Nat Aging*. 2022;2:824−836.
16. Gensler G, Clemons TE, Domalpally A, et al. Treatment of geographic atrophy with intravitreal sirolimus: the Age-Related Eye Disease Study 2 Ancillary Study. *Ophthalmol Retina*. 2018;2:441−450.
17. Wong WT, Dresner S, Forooghian F, et al. Treatment of geographic atrophy with subconjunctival sirolimus: results of a phase I/II clinical trial. *Invest Ophthalmol Vis Sci*. 2013;54:2941−2950.
18. Fritsche LG, Igl W, Bailey JN, et al. A large genome-wide association study of age-related macular degeneration highlights contributions of rare and common variants. *Nat Genet*. 2016;48:134−143.
19. Grassmann F, Harsch S, Brandl C, et al. Assessment of novel genome-wide significant gene loci and lesion growth in geographic atrophy secondary to age-related macular degeneration. *JAMA Ophthalmol*. 2019;137:867−876.
20. Fritsche LG, Fariss RN, Stambolian D, et al. Age-related macular degeneration: genetics and biology coming together. *Annu Rev Genomics Hum Genet*. 2014;15:151−171.
21. Agrón E, Domalpally A, Cukras CA, et al. Reticular pseudodrusen status, ARMS2/HTRA1 genotype, and geographic atrophy enlargement: Age-Related Eye Disease Study 2 report 32. *Ophthalmology*. Published online December 5, 2022. https://doi.org/10.1016/j.ophtha.2022.11.026.
22. Ding Y, Liu Y, Yan Q, et al. Bivariate analysis of age-related macular degeneration progression using genetic risk scores. *Genetics*. 2017;206:119−133.
23. Grassmann F, Fleckenstein M, Chew EY, et al. Clinical and genetic factors associated with progression of geographic atrophy lesions in age-related macular degeneration. *PLOS ONE*. 2015;10:e0126636.
24. de Jong S, Tang J, Clark SJ. Age-related macular degeneration: a disease of extracellular complement amplification. *Immunol Rev*. 2023;313:279−297.
25. Paun CC, Lechanteur YTE, Groenewoud JMM, et al. A novel complotype combination associates with age-related macular degeneration and high complement activation levels in vivo. *Sci Rep*. 2016;6:26568.
26. Liao DS, Grossi FV, El Mehdi D, et al. Complement C3 inhibitor pegcetacoplan for geographic atrophy secondary to age-related macular degeneration: a randomized phase 2 trial. *Ophthalmology*. 2020;127:186−195.
27. Jaffe GJ, Westby K, Csaky KG, et al. C5 inhibitor avacincaptad pegol for geographic atrophy due to age-related macular degeneration: a randomized pivotal phase 2/3 trial. *Ophthalmology*. 2021;128:576−586.
28. Apellis, Apellis Announces Top-Line Results from Phase 3 DERBY and OAKS Studies in Geographic Atrophy (GA) and Plans to Submit NDA to FDA in the First Half of 2022 https://investors.apellis.com/news-releases/news-release-details/apellis-announces-top-line-results-phase-3-derby-and-oaks. Accessed December 13, 2022.
29. Iveric Bio. Iveric Bio Announces Positive Topline Data from Zimura® GATHER2 Phase 3 Clinical Trial in Geographic Atrophy. https://investors.ivericbio.com/news-releases/news-release-details/iveric-bio-announces-positive-topline-data-zimurar-gather2-phase. Accessed December 30, 2022.
30. Apellis Pharmaceuticals. FDA Approves SYFOVRE (pegcetacoplan injection) as the First and Only Treatment for Geographic Atrophy (GA), a Leading Cause of Blindness. https://investors.apellis.com/news-releases/news-release-details/fda-approves-syfovretm-pegcetacoplan-injection-first-and-only. Accessed February 28, 2023.
31. Halawa OA, Lin JB, Miller JW, Vavvas DG. A review of completed and ongoing complement inhibitor trials for geographic atrophy secondary to age-related macular degeneration. *J Clin Med*. 2021;10:2580.
32. Kim BJ, Liu T, Mastellos DC, Lambris JD. Emerging opportunities for C3 inhibition in the eye. *Semin Immunol*. 2022;59:101633.
33. Zarantonello A, Revel M, Grunenwald A, Roumenina LT. C3-dependent effector functions of complement. *Immunol Rev*. 2023;313:120−138.
34. Bharti K, den Hollander AI, Lakkaraju A, et al. Cell culture models to study retinal pigment epithelium-related pathogenesis in age-related macular degeneration. *Exp Eye Res*. 2022;222:109170.
35. Handa JT, Bowes Rickman C, Dick AD, et al. A systems biology approach towards understanding and treating non-neovascular age-related macular degeneration. *Nat Commun*. 2019;10:3347.
36. Anderson DH, Radeke MJ, Gallo NB, et al. The pivotal role of the complement system in aging and age-related macular degeneration: hypothesis re-visited. *Prog Retin Eye Res*. 2010;29:95−112.
37. Kawa MP, Machalinska A, Roginska D, Machalinski B. Complement system in pathogenesis of AMD: dual player in degeneration and protection of retinal tissue. *J Immunol Res*. 2014;2014:483960.
38. Calippe B, Augustin S, Beguier F, et al. Complement factor H inhibits CD47-mediated resolution of inflammation. *Immunity*. 2017;46:261−272.
39. Rus HG, Niculescu F, Shin ML. Sublytic complement attack induces cell cycle in oligodendrocytes. *J Immunol*. 1996;156:4892−4900.
40. Mukai R, Okunuki Y, Husain D, et al. The complement system is critical in maintaining retinal integrity during aging. *Front Aging Neurosci*. 2018;10:15.

41. Stevens B, Allen NJ, Vazquez LE, et al. The classical complement cascade mediates CNS synapse elimination. *Cell*. 2007;131:1164−1178.
42. Saßmannshausen M, Behning C, Weinz J, et al. Characteristics and spatial distribution of structural features in age-related macular degeneration: a MACUSTAR study report. *Ophthalmol Retina*. Published online December 20, 2022. https://doi.org/10.1016/j.oret.2022.12.007
43. Curcio CA, McGwin Jr G, Sadda SR, et al. Functionally validated imaging endpoints in the Alabama study on early age-related macular degeneration 2 (ALSTAR2): design and methods. *BMC Ophthalmol*. 2020;20:196.
44. Shen LL, Sun M, Ahluwalia A, et al. Local progression kinetics of geographic atrophy depends upon the border location. *Invest Ophthalmol Vis Sci*. 2021;62:28.
45. Sunness JS, Bressler NM, Tian Y, et al. Measuring geographic atrophy in advanced age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 1999;40:1761−1769.
46. Sunness JS, Rubin GS, Zuckerbrod A, Applegate CA. Foveal-sparing scotomas in advanced dry age-related macular degeneration. *J Vis Impair Blind*. 2008;102:600−610.
47. Heier JS, Pieramici D, Chakravarthy U, et al. Visual function decline resulting from geographic atrophy: results from the chroma and spectri phase 3 trials. *Ophthalmol Retina*. 2020;4:673−688.
48. Chakravarthy U, Anegondi N, Steffen V, Ferrara D. Visual functional loss in geographic atrophy (GA): learnings from lampalizumab trial data. Paper presented at: The Macula Society 2023 Annual Meeting; January 15, 2023; Miami, FL. https://medically.gene.com/content/dam/pdmahub/restricted/ophthalmology/macula-society-2023/macula-society-2023-presentation-chakravarthy-visual-function-loss-in-geographic-atrophy.pdf.
49. Woodell A, Rohrer B. A mechanistic review of cigarette smoke and age-related macular degeneration. *Adv Exp Med Biol*. 2014;801:301−307.
50. Chakravarthy U, Wong TY, Fletcher A, et al. Clinical risk factors for age-related macular degeneration: a systematic review and meta-analysis. *BMC Ophthalmol*. 2010;10:31.
51. Brillat-Savarin JA. *Physiologie du goût, ou méditations de gastronomie transcendante*. Paris, France: Sautelet; 1825.
52. Pameijer EM, Heus P, Damen JAA, et al. What did we learn in 35 years of research on nutrition and supplements for age-related macular degeneration: a systematic review. *Acta Ophthalmol*. 2022;100:e1541−e1552.
53. Gastaldello A, Giampieri F, Quiles JL, et al. Adherence to the Mediterranean-style eating pattern and macular degeneration: a systematic review of observational studies. *Nutrients*. 2022;14:2028.
54. Keenan TD, Agrón E, Mares J, et al. Adherence to the Mediterranean diet and progression to late age-related macular degeneration in the Age-Related Eye Disease Studies 1 and 2. *Ophthalmology*. 2020;127:1515−1528.
55. Agrón E, Mares J, Chew EY, et al. Adherence to a Mediterranean diet and geographic atrophy enlargement rate: Age-Related Eye Disease Study 2 Report 29. *Ophthalmol Retina*. 2022;6:762−770.
56. Davis C, Bryan J, Hodgson J, Murphy K. Definition of the Mediterranean diet; a literature review. *Nutrients*. 2015;7:9139−9153.
57. Agrón E, Mares J, Clemons TE, et al. Dietary nutrient intake and progression to late age-related macular degeneration in the Age-Related Eye Disease Studies 1 and 2. *Ophthalmology*. 2021;128:425−442.
58. Grant MB, Bernstein PS, Boesze-Battaglia K, et al. Inside out: relations between the microbiome, nutrition, and eye health. *Exp Eye Res*. 2022;224:109216.
59. Schwingshackl L, Morze J, Hoffmann G. Mediterranean diet and health status: active ingredients and pharmacological mechanisms. *Br J Pharmacol*. 2020;177:1241−1257.
60. Lovegrove JA, Stainer A, Hobbs DA. Role of flavonoids and nitrates in cardiovascular health. Proc Nutr Soc. Published online January 19, 2017:1−13. https://doi.org/10.1017/S0029665116002871
61. Pappas CM, Zouache MA, Matthews S, et al. Protective chromosome 1q32 haplotypes mitigate risk for age-related macular degeneration associated with the CFH-CFHR5 and ARMS2/HTRA1 loci. *Hum Genomics*. 2021;15:60.
62. Weismann D, Hartvigsen K, Lauer N, et al. Complement factor H binds malondialdehyde epitopes and protects from oxidative stress. *Nature*. 2011;478:76−81.
63. Alic L, Papac-Milicevic N, Czamara D, et al. A genome-wide association study identifies key modulators of complement factor H binding to malondialdehyde-epitopes. *Proc Natl Acad Sci U S A*. 2020;117:9942−9951.
64. Awuchi CG, Chukwu CN, Iyiola AO, et al. Bioactive compounds and therapeutics from fish: revisiting their suitability in functional foods to enhance human wellbeing. *BioMed Res Int*. 2022;2022:3661866.
65. Hosseini SF, Rezaei M, McClements DJ. Bioactive functional ingredients from aquatic origin: a review of recent progress in marine-derived nutraceuticals. *Crit Rev Food Sci Nutr*. 2022;62:1242−1269.
66. Buitendijk GHS, Rochtchina E, Myers C, et al. Prediction of age-related macular degeneration in the general population: the Three Continent AMD Consortium. *Ophthalmology*. 2013;120:2644−2655.
67. Agrón E, Domalpally A, Cukras CA, et al. Reticular pseudodrusen: the third macular risk feature for progression to late age-related macular degeneration: Age-Related Eye Disease Study 2 report 30. *Ophthalmology*. 2022;129:1107−1119.
68. Nassisi M, Lei J, Abdelfattah NS, et al. OCT risk factors for development of late age-related macular degeneration in the fellow eyes of patients enrolled in the HARBOR study. *Ophthalmology*. 2019;126:1667−1674.
69. Bui PTA, Reiter GS, Fabianska M, et al. Fundus autofluorescence and optical coherence tomography biomarkers associated with the progression of geographic atrophy secondary to age-related macular degeneration. *Eye*. 2022;36:2013−2019.
70. Lad E, Sleiman K, Banks DL, et al. Machine learning OCT predictors of progression from intermediate age-related macular degeneration to geographic atrophy and vision loss. *Ophthalmol Sci*. 2022;2:100160.
71. Schmidt-Erfurth U, Bogunovic H, Grechenig C, et al. Role of deep learning-quantified hyperreflective foci for the prediction of geographic atrophy progression. *Am J Ophthalmol*. 2020;216:257−270.
72. Chakravarthy U, Bailey CC, Scanlon PH, et al. Progression from early/intermediate to advanced forms of age-related macular degeneration in a large UK cohort: rates and risk factors. *Ophthalmol Retina*. 2020;4:662−672.
73. Klein ML, Francis PJ, Ferris III FL, et al. Risk assessment model for development of advanced age-related macular degeneration. *Arch Ophthalmol*. 2011;129:1543−1550.
74. Sadda SR, Guymer R, Holz FG, et al. Consensus definition for atrophy associated with age-related macular degeneration on OCT: classification of atrophy report 3. *Ophthalmology*. 2018;125:537−548.

75. Wu Z, Fletcher EL, Kumar H, et al. Reticular pseudodrusen: A critical phenotype in age-related macular degeneration. *Prog Retin Eye Res*. 2022;88:101017.
76. Greferath U, Guymer RH, Vessey KA, et al. Correlation of histologic features with in vivo imaging of reticular pseudodrusen. *Ophthalmology*. 2016;123:1320−1331.
77. Chen L, Messinger JD, Kar D, et al. Biometrics, impact, and significance of basal linear deposit and subretinal drusenoid deposit in age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 2021;62:33.
78. Zhang Y, Wong WT. Innate immunity in age-related macular degeneration. *Adv Exp Med Biol*. 2021;1256:121−141.
79. Gelfand BD, Ambati J. A revised hemodynamic theory of age-related macular degeneration. *Trends Mol Med*. 2016;22:656−670.
80. Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. *Arch Ophthalmol*. 2001;119:1417−1436.
81. Lindblad AS, Lloyd PC, Clemons TE, et al. Change in area of geographic atrophy in the Age-Related Eye Disease Study: AREDS report number 26. *Arch Ophthalmol*. 2009;127:1168−1174.
82. Nittala MG, Metlapally R, Ip M, et al. Association of pegcetacoplan with progression of incomplete retinal pigment epithelium and outer retinal atrophy in age-related macular degeneration: a post hoc analysis of the FILLY randomized clinical trial. *JAMA Ophthalmol*. 2022;140:243−249.
83. Keenan TD, Agrón E, Mares JA, et al. Adherence to a Mediterranean diet and cognitive function in the Age-Related Eye Disease Studies 1 & 2. *Alzheimers Dement*. 2020;16:831−842.