Age-Related Macular Degeneration: Pathophysiology, Management, and Future Perspectives

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Abstract
Among older adults, age-related macular degeneration (AMD) is a prevalent disabling condition that begins as subtle visual disturbances and can progress to permanent loss of central vision. In its late neovascular form, AMD is treatable with inhibitors of vascular endothelial growth factor, the key driver of exudative disease. In the atrophic form, treatment remains elusive. This review addresses the natural history of AMD – through early, intermediate, and advanced disease stages – and concentrates on diagnosis and risk stratification, deficiencies of current treatments, and the promising findings of emerging therapies.

Introduction
Age-related macular degeneration (AMD) is a progressive, vision-threatening disease that affects older adults and is a leading cause of irreversible blindness in Western countries. AMD-associated visual loss predominantly occurs in later stages of the disease and manifests as deterioration of high-resolution central vision owing to several processes.

Until the early 2000s, no effective treatment was available for the dry or wet form of advanced AMD. Treatment of AMD with intravitreally injected inhibitors of vascular endothelial growth factor (VEGF) has transformed patient care, restoring or stabilizing vision in those with the neovascular form of disease. However, treatment of wet AMD involves frequent intravitreal injections and follow-up visits that pose significant burdens. For patients with the still-un treatable dry form, slowly worsening vision remains the norm. In this review, AMD management is addressed with an emphasis on stalling disease progression and on therapeutics in the pipeline.

Prevalence and Risk Factors

Global and Local Prevalence
As populations age globally, diseases of older patients are becoming more prevalent. Based on projections from a 2014 systematic review, the estimated 2020 global prevalence of AMD was 196 million and was expected to reach...
288 million by 2040 [1]. In 2015, AMD was a leading cause of moderate or severe vision impairment, affecting 8.4 million individuals globally [2, 3].

Early and late AMDs in Europe were estimated in a meta-analysis of 42,080 patients aged 40 years or older in the European Eye Epidemiology (E3) consortium [4]. The prevalence of early AMD increased with age from 3.5% in those aged 55–59 years to 17.7% in patients aged >85 years; for late AMD, these values were 0.1 and 9.8%, respectively. Regarding neovascular AMD (nAMD), the authors identified a decrease in the prevalence simultaneous with an increase in visual acuity, which could be attributed to the effects of anti-VEGF therapy [4]. The incidence of early or late AMD is projected to stabilize or decrease in Europe by 2040 with the adoption of healthier lifestyles, particularly avoidance of smoking, but the aging population is expected to yield a modest increase in AMD prevalence [4].

Joachim et al. [3] showed that the 15-year incidence of pure geographic atrophy (GA) (i.e., without co-occurring neovascular lesions) was 3.6% among 2,503 at-risk patients in the Blue Mountains Eye study, which took place west of Sydney, Australia. The long-term incidence of GA was associated with common AMD risk factors, such as age, smoking, high-risk CHF (i.e., complement factor H), and ARMS2 genotypes and frequent fish intake. However, characteristics of early AMD lesions – including type and location – also were predictive of GA risk, independent of these common risk factors [3].

Results of numerous population-based studies of AMD worldwide have indicated racial and ethnic differences in disease prevalence, including greater prevalence of early AMD in Europe than in Asia, but similar prevalence of late AMD on these continents [1]. AMD prevalence among those of Asian or African descent has been found to be similar. Some data suggested that Asian individuals were more likely to develop exudative or nAMD than Caucasians, but this association was not preserved in subgroup analyses. In population-based studies, investigators generally have been able to distinguish polypoidal choroidal vasculopathy (PCV), which often masquerades as exudative AMD [1]. Because PCV occurs at a higher prevalence in Asians than in Europeans, data on late AMD in Asians may be overestimating the true prevalence [1].

In the Comparison of AMD Treatments Trials (CATT), investigators found that reticular pseudodrusen (RPD) was associated with incident late AMD (i.e., nAMD or GA); hence, they concluded that RPD represented a risk factor for AMD progression [5]. This relationship varies with the type of RPD; dot lesions are associated with nAMD, whereas confluent RPD are associated with GA [5].

In the Coimbra Eye Study of AMD, prevalence in a coastal town in Portugal was as follows: 15.5% of individuals aged 55 years or older had early AMD, and 0.7% had late-stage AMD, including 0.4% with nAMD and 0.3% with GA [6]. In a subsequent report, the age- and gender-adjusted prevalence of any AMD was 12.5% (late AMD, 1.2%) and included individuals from a coastal town and an inland town. The AMD rate was higher in the inland population by multivariate analysis [7]. Investigators then evaluated the 6.5-year incidence and progression of AMD in a coastal region in Portugal and determined the cumulative incidence to be 10.7% for early AMD and 0.8% for late AMD [8]. Disease progression occurred in 17.2% of patients [8].

It should be noted that epidemiologic estimates of AMD must be interpreted with caution. Inter-study comparability is limited for several reasons, including different AMD classification systems, the age range of the patient population, and the technology applied to evaluate disease (e.g., color fundus photography [CFP] or optical coherence tomography [OCT]) [9].

Risk Factors

AMD is a complex, multifactorial disease for which numerous modifiable and nonmodifiable risk factors have been identified. The main modifiable risk factor of advanced AMD development is smoking; smokers are 2–4 times more likely to experience AMD [10]. Older age (≥65 years), northern European ancestry, and family history are nonmodifiable risk factors for advanced AMD [11]. Additionally, AMD in 1 eye increases the likelihood that AMD will develop in the fellow eye. Generally, men and women experience AMD at similar rates [2]. Hyperlipidemia and hypertension also may be risk factors, but the level of evidence for these is lower [12].

Genetics

In a study of elderly twin men, genetic factors were found to explain 46–71% of the variance in AMD severity [13]. AMD-associated genes are likely to be involved in complement system modulation, the extracellular matrix, and lipid metabolism. Investigators leading a large genome-wide association study identified 52 coding variants, distributed in 34 loci that occurred more frequently in patients with AMD [14], as shown in Table 1.

In a genome-wide association study of >12 million variants, authors identified 52 common and rare variants
Table 1. Identification of 52 independent AMD risk variants in 34 loci [14]

<table>
<thead>
<tr>
<th>Signal number</th>
<th>Locus name</th>
<th>Index variant</th>
<th>Chr:position</th>
<th>Major/minor allele</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>CFH</td>
<td>rs10922109</td>
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<td>C/A</td>
</tr>
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<td>C/T</td>
</tr>
<tr>
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</tr>
<tr>
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<tr>
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<tr>
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<tr>
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<td>C9</td>
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<td>7</td>
<td>PRLR/SPEF2</td>
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<tr>
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<tr>
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<td>1:196,958,651</td>
<td>C/G</td>
</tr>
<tr>
<td>13</td>
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</tr>
<tr>
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<td>C/G</td>
</tr>
<tr>
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<td>SYN3/TIMP3</td>
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<td>1:196,958,651</td>
<td>C/G</td>
</tr>
<tr>
<td>17</td>
<td>SLC16A8</td>
<td>rs8135665</td>
<td>1:196,958,651</td>
<td>C/G</td>
</tr>
</tbody>
</table>

* a Independent signals within loci. b Nearest gene. c Analysis per 10-Mb region.
AMD-associated CFH and C3 variants are regarded as strong genetic risk factors, constituting an estimated 50 and 22%, respectively, of the attributing disease risk [22]. Certain polymorphisms in ARMS2 and HTRA1 also are considered to confer risk of AMD [22]. Compared with control patients awaiting cataract surgery, patients with nAMD were significantly more likely to have certain polymorphisms in CFH (CC genotype), ARMS2 (TT), HTRA1 (AA), and C3 (CG), and these associations were stronger among women than among men [16]. Other investigators found that fewer than half of CFH variants were associated with AMD visual outcomes on anti-VEGF agents [19]. Moreover, efforts to slow enlargement of GA area by systemically inhibiting complement component 5 [15] or complement factor D [23] have been unsuccessful. Researchers recently applied a knowledge-driven pathway analysis to search for driver genes in the largest available database of advanced AMD cases [24]. They found that only PLCG2, which encodes the signaling enzyme phospholipase C gamma 2, was a key player in pathways from the KEGG, Reactome, GO, and NetPath databases and remained significant in sensitivity analyses [24]. Functional studies are underway to better characterize PLCG2 as a candidate AMD gene.

**Pathophysiology and Disease Progression**

Aging of the eye is accompanied by the buildup of unclared cellular debris that originates from the retinal pigment epithelium (RPE) and accumulates where the RPE interfaces with Bruch’s membrane and the neurosensory retina. These deposits, known as drusen, typically are the first ophthalmoscopic sign of AMD, appearing before visual function is appreciably affected. Drusen are comosite structures, primarily consisting of lipids as well as proteins and carbohydrates that can be visualized as small white or yellowish deposits on the macula. Drusen deposition in Bruch’s membrane concomitant with other structural and biochemical changes associated with AMD pathogenesis (including persistent activation of the complement cascade and inflammation) lead to thickening and decreased permeability of the membrane [25]. This obstructs both nutrient transport to the retina and waste exchange to the choroid and is accompanied by thinning of the choroidal vasculature. These steps, combined with neurodegenerative changes within the photoreceptor-RPE complex, result in pigmentary abnormalities of the RPE, including hypo or hyperpigmentation, in early or
intermediate stages of disease [26]. This combination of factors results in impaired RPE and photoreceptor function [25].

**Dry AMD**

Dry AMD is characterized by a slowly progressive loss of visual function, owing to deterioration of the choriocapillaris, atrophic loss of the outer retina, and disruption and eventually death of the photoreceptor layer. GA is the advanced form of dry AMD [26]. In a study of patients with GA and 20/50 vision or better at baseline, the cumulative risk of legal blindness was 27% by 4 years [27].

Drusen aggregate and undergo morphologic changes during AMD progression. Small, well-defined drusen particles, referred to as hard drusen, are common in younger individuals and are not a sign of AMD risk [28]. Soft drusen are less demarcated and grow over time, coalescing into confluent drusen, and co-occurring with AMD. Eventually, soft drusen mature to a crystalline form, which is predictive of GA [28].

RPD, also known as subretinal drusenoid deposits, are structurally comparable to soft drusen but are found in a different location (above the RPE) and have a distinct biochemistry, as shown in Figure 1. RPD occur frequently in dry AMD, and unlike soft drusen, RPD are associated with central choroidal thinning and with decreases in choriocapillaris vascular flow area and vessel volume [29, 30]. RPD also tend to be associated with dysfunction of the RPE and a worse prognosis [31].

In the natural history of dry AMD, drusen accumulate and then regress concurrent with the transition from intermediate to advanced disease [32]. Several additional structures have been recognized recently on spectral-domain (SD)-OCT, but these are only beginning to be understood. SD-OCT-reflective drusen substructures (ODS) (Fig. 2) exist transiently, arising beneath the RPE, rather than from within the RPE, as drusen do [32]. Authors have identified 4 phenotypic subtypes of ODS: low-reflective cores, high-reflective cores, conical debris, and split drusen [32]. Over time, ODS evolve through these forms in a characteristic pattern, from low-reflective and split drusen particles to high-reflective particles and finally conical debris. Investigators found that all forms of ODS, but especially conical debris, were associated with 3-year progression to macular GA but not with progression to choroidal neovascularization (CNV) [32].

Another SD-OCT imaging finding, hyper-reflective foci (HRF), are believed to be distinct from ODS, as depicted in Figure 2. HRF are more persistent than ODS, lasting 2 years or more, and are possibly indicative of migratory RPE cells or microglia [32]. Christenbury et al. [33] showed that the distribution of intraretinal HRF in the macula increased in quantity and migrated from the outer to the inner retinal layers during 2 years of disease progression.

Multimodal imaging data are beginning to reveal the intricacies of drusen evolution in AMD and may ultimately yield more precise biomarkers of disease progression. In a recent imaging study that included patients with intermediate AMD, drusen autofluorescence characteristics were found to be weakly correlated with HRF and with morphology of the outer retinal layers [34].
Dry AMD is characterized by unrelenting expansion of atrophic areas. Investigators in the global Proxima trials demonstrated a 2-year mean increase in GA lesion size of 3.87 mm² among patients with bilateral GA at baseline [35]. One-third of patients with unilateral GA at baseline had bilateral GA by year 1 of follow-up [35]. In 2018, an international group of experts described criteria for classifying dry AMD based on OCT findings; 4 stages of atrophic progression were recognized as follows: (1) incomplete outer retinal atrophy, (2) complete outer retinal atrophy, (3) incomplete RPE + outer retinal atrophy, and (4) complete RPE + outer retinal atrophy (cRORA) [36]. The last stage, cRORA, is equivalent to the traditional terminology of GA.

**Wet AMD**

Although neovascular disease affects only about 20% of patients with AMD, this clinical form is responsible for approximately 90% of severe central vision loss caused by AMD [11]. The pathogenesis of wet AMD involves recruitment of immune cells to the damaged macula and secretion of proinflammatory and proangiogenic cytokines, particularly VEGF. Several retinal cell types, including RPE cells, also can express and secrete VEGF [37]. VEGF stimulates endothelial cell proliferation and migration and leads to angiogenesis and increased vascular permeability [38, 39]. The newly growing blood vessels leak fluid, disrupting and damaging the layer of photoreceptors and impairing vision. Although the abnormal vessels of wet AMD typically arise from the choroidal circulation, neovascularization and leakage also can emanate from the retinal vasculature [40]. Left untreated, this subretinal exudation leads to fibrosis and atrophy of the macula and irreversible loss of central vision in as little as a few months.

In AMD, neovascularization may start in the outer retina or in the choroid; therefore, the term CNV is not always appropriate, although it is widely accepted [41]. Recently, a group of experts convened to address nAMD nomenclature and proposed the term macular neovascularization (MNV) to denote neovascular disease of the macula, independent of origin or location [41]. Type 1 MNV was defined as ingrowth of vessels initially from the choriocapillaris into and within the sub-RPE space, type 2 MNV denoted neovascularization originating from the choroid that traverses Bruch’s membrane and the RPE monolayer and then proliferates in the subretinal space, and type 3 MNV entailed neovascularization originating from the retinal circulation (typically the deep capillary plexus) and extending toward the outer retina and choroid [41].

MNV can occur without exudation [42]. Eyes with nonexudative or pre-exudative nAMD do not have substantial visual loss and do not respond to anti-VEGF treatment. Investigators have hypothesized that this seemingly quiescent neovascularization may afford eyes some protection against atrophy [43]; however, these eyes remain at risk of progressing to exudative AMD and should be monitored closely [42]. Subclinical nonexudative MNV does not appear to contribute to deterioration of visual function and has no indication for anti-VEGF treatment [42].

PCV, which typically involves serosanguineous pigment epithelial detachments (PEDs), exudation, bleeding, and subretinal fibrosis, has been posited as a specific phenotype of nAMD [44]. Classical nAMD and PCV can be distinguished on the basis of clinical presentation and multimodal imaging; between-group genotypic differences have been identified in Asian and Caucasian patients with PCV, but the phenotypes do share some genetic polymorphisms [45].

**Diagnosis and Classification**

**Early, Intermediate, and Advanced Disease**

The diagnostic signs of early and intermediate AMD are drusen and pigmented changes. Patients with early or intermediate AMD constitute 85–90% of all patients with AMD [11]. Staging of AMD disease traditionally is determined from CFP images of the macula. There are several classification schemes that utilize drusen characteristics and pigmentation to differentiate early and intermediate AMD. These include the Rotterdam system [46]; the 9-step severity scale based on drusen and pigmentary abnormalities, reported in the Age-Related Eye Disease Study (AREDS) [47]; and the simplified AREDS severity scale [48]. More recently, the evidence-based clinical classification system was described by Ferris et al. [40] (Table 2). Each step in the Ferris classification corresponds to an incremental increase in risk of 5-year progression to late AMD in patients 55 and older: from 0.5% for eyes classified as normal aging to 50% for the intermediate risk group [40].

In AMD, staging of earlier disease states relies on specific sizes, types, and locations of drusen and pigmented changes, and criteria vary among classification systems. In contrast, diagnosis and staging of late AMD is more straightforward and consistent. The 2 clinical forms of advanced disease are GA and nAMD.
**Imaging Findings**

OCT is a noninvasive test that enables visualization of retinal and choroidal structures in cross section. OCT is more sensitive than CFP, from which most epidemiologic data on AMD are derived. AMD diagnosis and disease staging by means of OCT represents an emerging paradigm shift [49].

OCT findings in early AMD include thinning of the retinal layers with submacular choriocapillaris dropout [50, 51]. Time-domain OCT imaging has largely been supplanted by SD-OCT, which has higher resolution and faster image acquisition. In early AMD, SD-OCT allows for precise visualization and measurement of drusen. In advanced disease, SD-OCT enables detection and volume measurements of fluid exudates in retinal compartments, including intraretinal fluid and subretinal fluid. Longitudinal SD-OCT images allow investigators to monitor gradual thinning or thickening of the RPE – indicating progression of GA or drusen, respectively [52]. Automatic segmentation in SD-OCT allows for reproducible thickness measurements of the retina, the retinal nerve fiber layer, and the choroidal vessels.

Previous to the introduction of OCT, fluorescein angiography (FA) was the accepted standard for ascertaining vascular pathologies of the eye, and CNV lesions were classified as classic or occult [53]. Classic lesions comprise bright well-delineated regions of hyperfluorescence that appear early in the test and progressively leak. Occult lesions span a variety of presentations, including fibrovascular PED and late leakage of uncertain source. Classic neovascular lesions are more active and have a more aggressive natural history than do occult lesions. In patients on anti-VEGF treatment, fluid persistence at 1 year was greatest among those with occult lesions at baseline (20%) and was lowest among those with predominantly classic lesions (12%), suggesting that anti-VEGF agents perform better in the setting of classic-type angiogenesis [53].

A consensus system for staging AMD-associated atrophy was developed recently by an international group of experts, with OCT used as the reference method [36]. The group identified the following stages of atrophic progression on the basis of involvement of specific retinal layers: cRORA (encompassing GA), incomplete RPE and outer retinal atrophy, complete outer retinal atrophy, and incomplete outer retinal atrophy. In addition, the authors set forth criteria for diagnosis of cRORA, including hypertransmission diameter of ≥250 μm, attenuation or disruption of the RPE spanning ≥250 μm in diameter, degeneration of the photoreceptor layer, and scrolled RPE or RPE tear [36].

The E3 consortium has sought to establish a new classification system for macular diseases based on SD-OCT. The authors have proposed standardized terminology and a grading scheme for structural evaluations of macular diseases, to be applied in future epidemiologic studies [54]. OCT is crucial in the diagnosis and monitoring of AMD patients and may be combined with other retinal studies in a multimodal approach, especially in cases of differential diagnosis, unusual disease evolution, or poor response to treatment [55, 56]. These other modalities include CFP, fundus autofluorescence, FA, and indocyanine green angiography.

Patients with phenotypically intermediate AMD subtyped as nonexudative (subclinical or quiescent) nAMD have an increased risk of conversion to exudative disease. Whereas, presence of fluid accumulation is an unequivocal sign of exudative nAMD that is readily diagnosed on traditional OCT; FA and ICGA enable detection of non-exudative neovascularization [55]. OCT angiography (OCTA) is a newer technology that permits rapid, noninvasive visualization of retinal vasculature and is expected to become a mainstay in the diagnosis and monitoring of patients with nAMD [57]. Until data on the natural history of the disease become available, eyes with evidence

<table>
<thead>
<tr>
<th>Stage</th>
<th>Clinical characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>No AMD</td>
<td>No visible drusen or pigmentary abnormalities</td>
</tr>
<tr>
<td>Normal aging</td>
<td>Only small drusen (≤63 μm)</td>
</tr>
<tr>
<td>Early AMD</td>
<td>Medium drusen (&gt;63 and ≤125 μm)</td>
</tr>
<tr>
<td>Intermediate AMD</td>
<td>Large drusen (&gt;125 μm) and/or pigmentary abnormalities</td>
</tr>
<tr>
<td>Late AMD</td>
<td>Lesions from nAMD and/or GA</td>
</tr>
</tbody>
</table>

GA, geographic atrophy; nAMD, neovascular age-related macular degeneration; AMD, age-related macular degeneration.
of subclinical MNV should be followed closely because of the presumed increased risk of exudation and vision loss [55, 56]. Early detection of MNV before leakage occurs should allow for improved monitoring of these at-risk patients [55]. However, anti-VEGF treatment is not recommended until signs of exudative activity occur [55].

The presence of subclinical or quiescent neovascularization in the context of drusenoid elevation is a diagnostic challenge. Growth and regression of drusen are influenced by opposing forces of material deposition and macrophage activity [55–57]. Regressing drusen, evident as multilaminar sub-RPE hyper-reflectivity, are difficult to distinguish from subclinical or quiescent neovascularization [55]. Vascularized tissue also can occur in the context of drusenoid deposits, and its identification is not straightforward with OCT alone [55]. Quiescent neovascularization grows in length (horizontally), and vascularized drusen enlarge in height (vertically and in a multilaminar pattern) [55]. This represents another instance in which multimodal evaluation and natural history data can improve the accuracy of differential diagnosis. Neovascularization also can be considered inactive, meaning that exudative activity has ceased (no fluid on OCT) but had previously occurred and was managed with anti-VEGF treatment [55]. This setting differs from naive neovascularization (i.e., subclinical or quiescent nAMD) and is evident on OCTA as a skeletonized net [55–57]. Inclusion of OCTA imaging at baseline and at follow-up should be considered for cases of intermediate AMD – if not in daily practice, at least in trials enrolling patients with non-exudative AMD [55–57].

**Biomarkers of Disease Progression**

Approximately 10–15% of patients with AMD will experience progression to advanced exudative disease [58]. In eyes with intermediate AMD, early detection and routine monitoring are crucial. Patients lose an estimated 3 to 5 lines of visual acuity in the interrim from onset of nAMD to its diagnosis [17]. CNV lesions have been found to grow more rapidly at lesion onset than in advanced disease [17], potentially resulting in substantial unrecoverable vision loss before nAMD is diagnosed. Additionally, visual acuity at pretreatment baseline has been shown to modify the amount of improvement that is possible on VEGF inhibitors. Patients with better visual function at baseline have higher on-treatment visual acuity, even if they gain fewer letters than do patients with worse visual function at baseline [17].

The 5-year risk of progressing from intermediate to advanced/late AMD ranges from 0.4 to 53% (mean, 18%) [48]. This wide range illustrates the heterogeneity of the patient population and emphasizes the need for AMD progression-related biomarkers. In studies addressing the natural history of AMD, certain features have been identified as most associated with disease-progression risk. These include advanced AMD in the fellow eye; large, soft, and confluent drusen; and AMD-related pigmentary abnormalities [48]. Several risk calculation strategies have followed from these findings [48, 59]. In the AREDS simplified scoring system [48], 1 risk factor is assigned per eye for 1 or more large (≥125 μm) drusen, and 1 risk factor is assigned per eye for any pigment abnormality; these factors are summed to yield a 5-step severity scale (0–4) [48]. On this scale, the 5-year risk of developing advanced AMD in at least 1 eye is estimated as follows: 0 factors, 0.5%; 1 factor, 3%; 2 factors, 12%; 3 factors, 25%; and 4 factors, 50%. For eyes with no large drusen, the presence of medium-sized drusen in both eyes is counted as 1 risk factor (Fig. 3) [48].

Conventional tests of visual function, such as BCVA under high-luminance and high-contrast conditions, are not sensitive enough to detect the subtle deficits in visual function that embody early and intermediate AMD, in part because of the predominant loss of rods versus cones [60]. In a study of visual function tests, Ponderfer et al. [61] found that many widely utilized tests, including BCVA, have inadequate performance in intermediate AMD, even after controlling for age and gender. The authors found that 2-test combinations – contrast sensitivity coupled with either low-luminance visual acuity or Moorfields Vanishing Optotypes Acuity Charts-Visual Acuity – allowed for the best discrimination between patients with intermediate AMD and controls [61]. Work is ongoing by the MACUSTAR consortium to validate a study protocol and statistical test based on predictive modeling to follow disease progression in AMD [62]. These investigators demonstrated that visual function assessments in a low-contrast and low-luminance setting enabled discrimination of AMD severities within the intermediate stage and of progression to exudative late disease.

Evaluation of drusen in CFP represents the current clinical practice standard for assessing patients with intermediate AMD. Employing CFP, researchers have found that the number, area, and extent of drusen are positively correlated with risk of progression in >2 years [63]. However, this strategy has limited predictive value for AMD progression risk because it is relatively crude
and unreliable in the short term. Other authors have proposed a more advanced predictive approach that incorporates the aforementioned CFP-based drusen classification with genetic, demographic, and environmental factors, such as age, smoking, family history, genetic variants, and diet; the risk assessment tool is available as a web application [59].

As a prerequisite to reliably identifying intermediate AMD before it progresses, the bounds of disease severity that constitute the intermediate stage must be standardized [62]. Farsiu et al. [52] proposed an SD-OCT-based classification system for distinguishing intermediate AMD by means of semi-automated thickness mapping of the retinal structures. The authors developed a regression model based on total retina volume, RPE-drusen complex (DC) volume, and RPE-DC thickened or thinned volume and showed that they could discern intermediate AMD-affected eyes from control eyes with 99% precision [52].

Sitnilska et al. [64] aimed to define a phenotypic profile of eyes with early or intermediate disease at increased risk of progression to late AMD. They found that patient age, CFP variant rs1061170, pigment abnormalities, drusenoid PED, and HRF were associated with progression to late AMD in 5.9 years in a multivariable model [64]. Another research group demonstrated that eyes with HRF at baseline, especially copious HRF or HRF tending toward the inner retinal layers, were more likely to have GA at 2 years [33].

Topographic and sensitivity disruptions that occur in intermediate AMD could potentially be used to categorize disease severity. Researchers applied mesopic and scotopic fundus-controlled perimetry in combination with SD-OCT in a series of eyes with intermediate AMD [65]. They found significantly reduced sensitivity levels within the central 4° of the macula in eyes with intermediate AMD versus unaffected controls and a correlation between decreased sensitivity and localized structural changes, including increasing RPE-DC thickness and decreasing outer nuclear layer and photoreceptor layer thicknesses [65].

In recent years, progress has been made on characterizing biomarkers that portend advanced AMD. The widespread use of noninvasive approaches (OCT, OCTA, and fundus autofluorescence) in the diagnosis and monitoring of intermediate AMD has resulted in the identification of numerous imaging biomarkers of disease progression [60, 64]. With the aid of such retinal imaging modalities, an array of previously under recognized risk factors are being further investigated (Fig. 2).

Drusen load, drusen regression, HRF, and RPD are biomarkers that are encountered relatively frequently in eyes with intermediate AMD and are predictive of higher risk of advanced disease [60]. These biomarkers are observable by high-resolution OCT, fundus autofluorescence, or infrared reflectance imaging [60, 66]. A summary of common AMD progression biomarkers is presented in Table 3.

Fundus autofluorescence imaging findings of drusen during disease progression show a relatively predictable pattern of drusen accumulation and regression [60]. Certain fundus autofluorescence features on SD-OCT are highly predictive of GA and include regression of the outer plexiform layer and inner nuclear layer and a wedge-shaped band of hyporeflectivity in the outer plexiform layer [66]. These findings were a harbinger of GA within approximately 1 year and were considered to be signs of nascent GA. Analogously, narrow columns of hyperreflectivity seen under the RPE suggest deficiencies in the RPE layer and precede onset of exudative changes or GA by at least 3 months (Fig. 2). Confluent large drusen with accompanying fluid-filled subretinal spaces beneath the neurosensory retina on SD-OCT have been posited as nascent or subclinical CNV but also could be a product of mechanical strain posed by drusen [67]. Ultrastructural
features of soft drusen on OCT that deviate from the norm of convex shape and medium reflectivity with internal homogeneity also may have applications as prognostic biomarkers [60]. These atypical drusen were named ODS (OCT-reflective drusen substructures) in the AREDS2 ancillary imaging study, as shown in Figure 2 [32].

Waldstein et al. [68] performed SD-OCT-based volume measurements of drusen and HRF using 3-dimensional automatic segmentation driven by artificial intelligence algorithms. In a study population of 1,097 patients with early or intermediate AMD who received monthly imaging for 2 years, the results revealed characteristic topographic patterns of drusen and HRF in eyes that progressed versus those that did not. The authors noted that eyes with mean foveal drusen thickness of 30 μm progressed to nAMD, whereas those with mean thickness of 17 μm progressed to GA or did not progress. Mean HRF thickness at the foveal center was 0.07, 0.06 and 0.04 μm for eyes with progression to nAMD, progression to GA, or no progression [68]. These differences among groups, resolvable with high-precision OCT, may have clinical utility for risk stratification in AMD.

Certain findings in the fellow eye also are predictive of AMD progression risk. Cachulo et al. [69] demonstrated that in patients with unilateral exudative AMD, abnormalities on fundus autofluorescence in the fellow eye were predictive of CNV development in that eye with 93% sensitivity and 37% specificity, although no specific autofluorescence abnormality was associated with disease progression. In eyes with early or intermediate AMD, progression to GA is more common in patients with late AMD in the fellow eye [70]. In AREDS, 26.4% of eyes with medium drusen progressed to advanced AMD by 10 years when the fellow eye had advanced AMD [71].

No single biomarker or set of biomarkers has been found to provide a reliable, sensitive, and specific measure of whether disease progression will occur in an eye with AMD [60]. Although >100 potential AMD biomarker compounds have been considered in the scientific literature, few are consistently associated with disease progression, and few are currently used in the clinic [72]. Results of a comprehensive review of nongenetic molecules implicated in AMD progression indicated that those involved in the oxidative stress pathway, the complement system, and lipid metabolism appear to show the greatest utility as biomarker candidates [72]. Hypothesis-free studies on proteomics, metabolomics, and microRNA profiling may yield promising biomarker candidates, but this work is still in the early stages for AMD screening purposes [22].

Table 4 explores prognostic biomarkers for progression in intermediate AMD, organized by strength of the association with risk and by extent of supporting evidence [73]. Ly et al. [60] reviewed under recognized clinical risk factors that can help practitioners monitor AMD for progression, increase follow-up frequency when risk of progression increases, and intervene when needed. These include presence of late AMD in the fellow eye, large drusen, and pigmentary abnormalities [60].

### Table 3. Disease progression biomarkers in AMD (adapted from Ly et al. [60])

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Imaging findings</th>
<th>Mechanism(s) represented</th>
<th>Prevalence</th>
<th>Expected progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drusen load</td>
<td>Increasing area, volume, or height of drusen</td>
<td>Displacement or deterioration of photoreceptor layer</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Drusen regression</td>
<td>Decreased drusen volume; lessening intensity of foci on fundus autofluorescence</td>
<td>Under investigation</td>
<td>50% (2-year prevalence in intermediate AMD)</td>
<td>May be a necessary precursor for advanced disease (CNV or GA)</td>
</tr>
<tr>
<td>HRF</td>
<td>Punctate lesions atop drusen; accompany pigmentary abnormalities</td>
<td>Degeneration of RPE cells, inflammatory cell migration, intraretinal hemorrhage, cell debris, and calcification</td>
<td>41%</td>
<td>5-fold higher risk of 2-year progression to GA</td>
</tr>
<tr>
<td>Pseudodrusen or RPD</td>
<td>Yellow or white deposits; most commonly reticular, ribbon-like, and interdigitated</td>
<td>Dysfunctional cholesterol homeostasis</td>
<td>9–58% (for reticular form)</td>
<td>2- to 6-fold increased risk of progression to advanced disease (for reticular form)</td>
</tr>
<tr>
<td>Drusen substructures</td>
<td>Varied internal reflectivity</td>
<td>ND</td>
<td>24%</td>
<td>ND</td>
</tr>
</tbody>
</table>

AMD, age-related macular degeneration; CNV, choroidal neovascularization; GA, geographic atrophy; ND, not yet determined; RPD, reticular pseudodrusen; RPE, retinal pigment epithelium; HRF, hyper-reflective foci.
Interventions that stop or delay the transition from intermediate to late AMD are acutely needed. For intermediate stages of disease, the AREDS2 formulation of high-dose antioxidant vitamins and minerals has been found to forestall progression to nAMD [74]. The success of supplementation is attributed, at least in part, to the involvement of oxidative stress in the pathogenesis of AMD. AREDS2 supplementation has not been shown to halt progression of early disease, prevent progression to GA, or avert disease onset in individuals with a family history of AMD.

Macuprev is an oral daily supplement containing carotenoids and antioxidants, including lutein and zeaxanthin. Investigators evaluated the effect of Macuprev on macular function and structure in patients with intermediate AMD [50]. Using multifocal electroretinography and SD-OCT, they found that Macuprev supplementation improved the function of photoreceptors and bipolar cells, as shown by an increased multifocal electroretinography response amplitude density from the central macula. However, structural findings on SD-OCT were similar to those in the placebo arm [50].

### Table 4. Prognostic biomarkers for progression in intermediate AMD [73]

<table>
<thead>
<tr>
<th>Strength of evidence</th>
<th>Strength of risk</th>
<th>Drusen load (volume and area)</th>
<th>Drusen regression</th>
<th>HRF</th>
<th>RPD</th>
<th>Nascent atrophy</th>
<th>Sub-RPE hyper-reflective columns</th>
<th>Small pockets of SRF</th>
<th>ODS</th>
</tr>
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<tbody>
<tr>
<td>high</td>
<td>High</td>
<td></td>
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<tr>
<td></td>
<td>Low</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Inconclusive</td>
<td>Drusen height</td>
<td></td>
<td></td>
<td></td>
<td>Patchy, linear, or reticular FAF patterns</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

AMD, age-related macular degeneration; SRF, subretinal fluid; HRF, hyper-reflective foci; ODS, optical coherence tomography-reflective drusen substructures; RPE, retinal pigment epithelium; RPD, reticular pseudodrusen.

**AMD Treatments: Past, Current, and Pipeline**

**Therapies in the Clinic**

Before the introduction of effective anti-VEGF therapeutics to ophthalmic care, a diagnosis of wet AMD meant certain, irreversible central vision loss. In the late 20th century, nAMD accounted for just 10% of cases but 90% of AMD-associated legal blindness [75]. In the first generation of treatment modalities for nAMD – including laser photocoagulation, photodynamic therapy, radiotherapy, and angiostatic steroids – success generally was defined as prevention of moderate or severe visual acuity loss from nAMD but not improvement in visual function [37, 76]. The findings that VEGF drives CNV and that inhibition of VEGF activity can interfere with this process stand among the most significant advances in ophthalmology in the past 50 years [77]. Anti-VEGF agents function by interacting directly with VEGF or with VEGF receptors. This class of drugs has outperformed all prior treatment modalities – enabling BCVA gains from baseline and maintenance of visual function – and is now the mainstay for wet AMD [78]. Approximately 1 million patients receive VEGF inhibitors annually, including those with nAMD as well as other angiogenic retinal diseases [77]. By comparison, dry AMD is far more common, accounts for only a quarter of AMD-associated cases of severe vision loss [79], and has no preventive or therapeutic options.

To maintain the benefits of anti-VEGF treatments, consistent, frequent follow-up and retreatment are necessary. Currently available VEGF inhibitors delivered by intravitreal injection include ranibizumab, bevacizumab, aflibercept, and brolucizumab. Recommended dosing schedules are every 4–8 weeks for ranibizumab and bevacizumab, every 12 weeks for aflibercept, and every 8–12 weeks for brolucizumab [11]. Alternative anti-VEGF dosing protocols include pro re nata (PRN) or treat-and-extend. These protocols are initiated with an induction phase – usually 3 months – of fixed monthly dosing. PRN dosing involves monthly evaluations during which injec-
mize inflammation-inducing impurities in the formulation [89, 90]. The results demonstrated a 1.6% incidence of severe IOI and no reported cases of endophthalmitis or retinal vasculitis [90].

Recombinant Adeno-Associated Virus Gene Therapy

Adeno-associated virus (AAV) is a nonenveloped virus that commonly is used as a vector to introduce DNA into target cells. Injection of AAV vectors and subsequent expression of VEGF-inhibitory molecules by recipient cells is an attractive strategy for prolonged management of AMD. AAV vectors transduce nondividing cells, enabling long-term expression of a transgene product, and the eye is an immune-privileged site with ease of surgical access. A single subretinal injection of a recombinant AAV2 particle containing the FLT1 transcript, which encodes a naturally occurring VEGF inhibitor, was found to be safe in a phase 1 trial for nAMD [91], with rAAV.sFLT-1 being mostly contained within the target tissue and no serious ocular or systemic adverse effects [92].

Data from a 52-week phase 2 clinical trial involving 32 patients allocated to receive ranibizumab PRN with or without subretinal rAAV.sFLT-1 gene therapy showed no significant between-group difference in BCVA or center-point thickness [92]. In the 3-year follow-up of the phase 1/2b study [93], the authors found limited efficacy in terms of BCVA gains and fluid reduction. They pointed out that the study was small, initially designed to assess safety, and included non-treatment-naïve patients, so the effects of rAAV.sFLT-1 could have been obscured.

In a separate phase 1 study, an AAV2 vector expressing the same therapeutic protein (sFLT01) was delivered by intravitreal, rather than subretinal, injection [94]. The investigators evaluated 1-year safety and tolerability outcomes and determined the level of transgene expression. Although the intervention was safe and well-tolerated, the transgene was expressed at variable levels among patients, possibly because of differences in baseline anti-AAV2 serum antibodies [94].

Thermal Laser Photocoagulation

Decades before anti-VEGF therapies became available for nAMD, investigators found that continuous-wave thermal laser photocoagulation could reduce drusen deposits in the outer retinal layers; however, subsequent clinical trial results showed that laser-induced drusen elimination did not prevent progression to advanced AMD [31]. In addition, laser photocoagulation often was associated with worsening of BCVA, CNV recurrence, and scarring [95]. More recently, researchers have develop-
oped a short-pulse laser therapy that delivers energy sufficient to ablate drusen but not strong enough to induce a thermal burn and subsequent retinal necrosis [31]. In a 3-year randomized trial of subthreshold nanosecond laser treatment, the therapeutic group and the sham group had similar time to late AMD occurrence [31].

Clustered Regularly Interspaced Short Palindromic Repeats-CRISPR-Associated Protein 9

Unlike conventional gene therapy, which serves to add a copy of a healthy gene, clustered regularly interspaced short palindromic repeats (CRISPR) enables actual modification or editing of existing genes by one of several mechanisms, including cut and revise, cut and remove, or cut and replace. The enzyme CRISPR-associated protein 9 (Cas9) functions like a pair of molecular scissors, cutting strands of DNA [96]. Currently, investigators are evaluating the feasibility of a CRISPR-Cas9-based genome editing approach, delivered with an AAV vector, to permanently suppress VEGF in the RPE layer of eyes with nAMD [97], thereby reducing angiogenesis. Avoidance of the need for frequent anti-VEGF injections is an enticing possibility. In a mouse model of laser-induced CNV, this strategy achieved 26% reduction of VEGF-A and 31% suppression of CNV [97]. Given the likelihood that some homeostatic level of circulating VEGF is desirable, this approach may be viable. CRISPR technology has been investigated for hereditary retinal disorders primarily; however, genome editing also may be adapted for treatment of multifactorial conditions, such as nAMD [97]. Compared to intravitreal therapeutic interventions, CRISPR can be genetically encoded to target particular cell types and minimize adverse systemic effects. Although the CRISPR strategy shows promise as a cure for nAMD, extreme care must be exercised in evaluating this possibility because CRISPR-based genome manipulation is vulnerable to off-target effects and is irreversible [97].

Brimonidine

Brimonidine is an alpha 2 adrenergic agonist with cytoprotective and neuroprotective properties in cultured cells and animal models [98]. In a 24-month phase 2 trial, investigators tested the efficacy of the Brimonidine Drug Delivery System (Brimo DDS), a biodegradable intravitreal implant, in preventing GA progression [98]. Patients received 2 doses of brimonidine (132 or 264 μg) versus sham. By 12 months, GA growth was reduced by 28% in the higher dose implanted group, compared with the sham group. Brimo DDS reduced the GA progression rate at month 12 and yielded additional benefits in patients with GA lesions 6 mm² or larger at study entry [98]. The safety profile was favorable, and Brimo DDS was well-tolerated over 24 months [98]. In the phase 2b BEACON study, patients received intravitreal injection of 400 μg brimonidine in the study eye every 3 months from baseline to month 21, and the effect on GA lesion area was assessed at month 24 [99]. The results showed 7 and 11% decreases in GA lesion size at month 24 and 30, respectively [100].

RPE Inhibition for Dry AMD

Choi et al. [101] described a novel dry AMD drug candidate, CK41016, which can inhibit RPE cell death. The authors administered CK41016 in rat and rabbit models by eye drop and intravenous routes. They found that pharmacokinetic and tissue-distribution patterns differed by species. Upon eye drop administration, the tissue-to-plasma partition coefficient was highest in the vitreous humor of rats but the cornea of rabbits. Given the species disparity, the properties of this molecule will need to be evaluated further before clinical trials can be undertaken. In particular, it is vital that topically administered drugs for dry AMD be delivered to the back of the eye, which is difficult to achieve with eye drop formulations [102]. Therefore, the feasibility of CK41016 will be dependent on whether it reaches the back of the eye on delivery.

Regenerative Therapies

Many approaches are being investigated for patients who have progressed to advanced AMD. Gene therapies and optogenetic strategies are under evaluation, but these are years from clinical application and are unlikely to enable restoration of high-resolution vision [103]. Another option is cellular regenerative therapy. Because the inner retina remains intact in advanced AMD, the possibility of replacing the degenerated outer retina with functioning tissue is an attractive one. RPE transplantation could conceptually restore function of this cell layer and rescue dying photoreceptors; this has been demonstrated in select clinical cases in which photoreceptor degeneration had not yet occurred [103]. In advanced AMD with significant photoreceptor loss, it may ultimately be possible to transplant healthy photoreceptor cells in suspension or as part of a retinal sheet. Numerous cell sources have been considered as candidates, with pluripotent stem cell-derived cells regarded as the most promising [103]. Recent primordial and early phase clinical trials in which these cells are employed for RPE replacement have yielded acceptable safety profiles and po-
tential efficacy. Moreover, data from preclinical studies have suggested that photoreceptor replacement may enable restoration of visual function, even in a fully degenerated outer retina [103]. The utility of regenerative treatments still is far from guaranteed; a key barrier to circumvent is immune rejection, which would limit the duration of the effect.

Conclusions

AMD is a vision-threatening disabling disease that is growing more prevalent as life expectancies increase globally. Multimodal imaging of the ultrastructure of the retina has allowed retinal specialists to diagnose AMD earlier and determine disease severity more precisely. Anti-VEGF therapies have revolutionized treatment of nAMD; however, despite remarkable visual benefits, there remain considerable gaps in efficacy. Not all patients respond to anti-VEGF therapy; these treatments tend to wane in the long term, and the frequent injections required pose a significant burden on the health-care system, patients, and caregivers. Research efforts are underway to maximize the benefit of VEGF suppression while mitigating the burden and to develop novel treatment modalities, such as gene therapy. Work is ongoing to expand our understanding of all forms of GA and ultimately to bring about an effective treatment for the ever enlarging population of patients with dry AMD.

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Conflict of Interest Statement

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Author Contributions

R.F. conceived, drafted, and wrote the article. A.C., M.V., S.T., and M.C.S. performed critical revisions of the article. R.F., A.C., M.V., S.T., and M.C.S. approved the final version of the manuscript.

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