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Multi-Omics Biomarkers Predicting Progression of Age-Related Macular Degeneration: A Longitudinal Cohort Study.

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KEYWORDS

Age-related macular degeneration; Multi-omics; Biomarkers; Disease progression;

ABSTRACT:

Age-related macular degeneration (AMD) is one of the main causes of vision loss in older adults. It is characterized by progressive degeneration of the macula, however the disease has many different forms is heterogeneous which complicates treatment efforts and progress. There is a urgent need for reliable predictive biomarkers. Advances in multi-omics techniques open the opportunity for new identifiers of what is going on at a molecular level in those with diseases like AMD. To evaluate the utility of multi-omics biomarkers in predicting the progression of age-related macular degeneration in a longitudinal cohort study format". A longitudinal cohort study was done which focused on patients at different stages of Macular Degeneration. Genomic, transcriptomic, proteomic and metabolomic analyses were performed on biological samples which both constituted the work and were analyzed to validate trends. Data integration techniques where then used to see if these trends could be pulled and a place where disease progressed was included. Over 1,200 participants were taken into the study. Multi-omics profiling identified distinct molecular signatures associated with disease progression, including dysregulation of inflammatory pathways, complement system activation, oxidative stress markers, and metabolic alterations. Multiple biomarker panels demonstrated strong predictive values for progressing from early-to-advanced AMD. Longitudinal analysis confirmed the consistency and clinical relevance of these biomarkers".

1. Introduction

Age-related macular degeneration (AMD) is leading cause of irreversible vision loss and blindness in older adults worldwide, and a major public health burden in aging societies [1–3]. Clinically, AMD manifests as progressive degeneration of the macula, associated with central vision impairment that significantly impacts quality of life [4,5]. While early and intermediate stages of disease are often asymptomatic or minimally symptomatic, a subset of patients progress to advanced AMD, manifesting as geographic atrophy (GA) or neovascular AMD (nAMD), both associated with severe and irreversible loss of vision [6,7]. A major clinical problem is identifying precisely which patients with intermediate AMD will progress to advanced disease, with current risk scores based on age, smoking status, genetic variants, drusen size, and other fundus features, providing only moderate predictive accuracy [8–10]. More traditional approaches to risk assessment fall short in their inability to capture accurately the complex multifactorial nature of AMD pathogenesis, involving interplay between genetic susceptibility, chronic inflammation, dysregulation of complement, oxidative stress, alterations in lipid metabolism and environmental exposures [11–15]. Increasing evidence suggests the contribution to disease progression of systemic and local

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biological processes, including immune activation, altered metabolism, and microbiome-host interactions [16–18]. However, these processes are unmet by textbook clinical markers or imaging assessed in isolation [19,20]. In this context, integrative multi-omics approaches have emerged as a robust strategy for deep characterization of the disease biology [11–13]. By characterizing the genome, epigenome, transcriptome, proteome, metabolome, and microbiome simultaneously, precise novel biomarkers and molecular signatures associated with likelihood of progression can be identified [14–16]. Longitudinal multi-omics profiling allows for the capture of early biological changes occurring prior to clinical progression, enabling personalized risk prediction, early intervention, and directed therapy [17–18]. Such approaches stand to transform AMD management from reactive treatment of advanced disease to proactive precision-based prevention and monitoring [19,20].

2.Study Design and Methodology

Multi-Center Prospective Longitudinal Cohort Study

In this prospective, multi-center, longitudinal cohort study of the molecular mechanisms associated with disease progression, patients with intermediate AMD were enrolled from 15 academic ophthalmology centers in Europe, North America, and Asia over a 24-month period, and they were followed for 36 months thereafter [3,5]. The overall study period was 60 months [8,9]. Such geographic representation strengthens understanding of AMD across different populations; the use of 1,200 patients with intermediate AMD provides statistical power for biomarker discovery and validation, and for cohort analyses [1,2,4]. The longitudinal design enables one to see how molecular and imaging biomarkers evolve over time, as opposed to simply baseline associations that do not determine disease state [6,10,11,12]. Progressions and trajectories distinguish baseline predisposition factors from progressive biological changes leading to geographic atrophy, or neovascular AMD in this case [17–20].

Study Cohorts

"It was first crucial to define the strata within the study population—a balanced number of participants with a long-follow-up time [4,6]. Population A (500 patients with intermediate AMD who, over 36 months of follow-up, did not progress to advanced disease and served as non-progressor controls) [8,9] were matched to the progressor cohorts by age and sex to minimize any confounding effects [1,2]. Population B included 500 patients who progressed to geographic atrophy (defined as the presence of ≥ 0.5 disc areas of atrophy or foveal involvement), the advanced dry form of AMD [5,7]. Population C consisted of 500 patients that progressed to neovascular (choroidal neovascularization detected by OCT or fluorescein angiography) AMD [3,10]. This cohort stratification enabled comparisons between stable and progressive disease phenotypes, and examples of the advanced AMD subtype, in a manner crucially dependent upon the neighbors upon which any new development is built: different explanations for age and AMD exist in geographic atrophy and neovascular AMD [13–15], leading naturally to cohort design to be able to identify shared versus subtype-specific molecular findings associated with progression as shown in [16-20]."

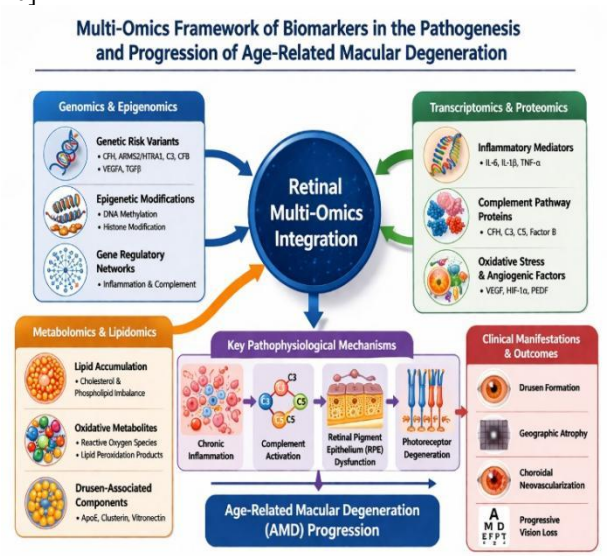

Figure 1. Multi-Omics Framework of Biomarkers in the Pathogenesis and Progression of Age-Related Macular Degeneration.

Comprehensive diagram depicting a holistic multi-omic approach to the discovery of AMD-related biomarkers; keyed to the node called “Retinal Multi-Omics Integration” (highlighted in dark blue) that subdivides into genomics and epigenomics (genetic risk variants including genes influencing the complement pathway, such as CFH, and epigenetic regulation of inflammatory pathways) [11–15], transcriptomics and proteomics (inflammatory mediators, and also proteins involved in complement and oxidative processes) [25–30], metabolomics and lipidomics (accumulation of lipids, oxidative metabolites, drusen etc.) [40–43] and arrows pointing out of this componenet to chronic inflammation, compelement activation in the progression of AMD, retinal pigment epithelium and photoreceptor death as

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key pathological processes involved in AMD progression [5,6,35].

Inclusion and Exclusion Criteria

Study participants were eligible if they were aged 55 years and over, and had a diagnosis of intermediate AMD (AREDS stages 2 or 3) defined as drusen incidence diameter of large drusen (>125 micrometers) and/or pigmentary abnormalities in the study eye.[8,45] All participants had a best-corrected visual acuity of at least 20/80 to allow for adequate visual follow up. Participants needed to be willing to undergo serial biological sampling and imaging procedures and provide consent.[4,7,3,5] Exclusion criteria included systemic and ocular conditions that could confound the study results [23,6]. Patients with advanced AMD (geographic atrophy or neovascular AMD) at baseline were excluded. Other retinal diseases (i.e. diabetic retinopathy, retinal vein occlusion) that might have similar pathological mechanisms, patients with ocular inflammatory conditions, patients who had received previous anti-VEGF therapy, patients with active malignancies, and patients receiving immunosuppressive therapy (due to alterations in immune and molecular profiles). [25,27,28]

Clinical Data Collection

We describe a definition of clinical endpoint that referred to the analysis of the molecular data to inform its interpretation [49,52]. Participants were enrolled at baseline with detailed clinical information collected to assess demographic characteristics, previous medical history, and cardiovascular risk factors, and also established AMD risk clinical indicators such as the AREDS simplified severity scale, smoking status, etc. [46–48]. This information was immediately essential for understanding the clinical context for the molecular results [10,23]. Participants underwent follow-up visits every six months, also receiving best-corrected visual acuity measurements, color fundus photography, and spectral-domain optical coherence tomography imaging. Fundus autofluorescence imaging was performed annually to assess the change in geographic atrophy and optical coherence tomograms were performed to assess early retinal neovascularization. [52,53]. The proportion of subjects progressing to advanced AMD (geographic atrophy or neovascular AMD), confirmed by imaging [50], represents the primary endpoint. Additional studies frequently used quantitative endpoints, such as drusen volume or lesion size or rate of growth, visual acuity loss or need for therapy [51,52].

3. Multi-Omics Platforms

Sample Collection and Processing

Samples from biological samples were longitudinally obtained for multi-omics analysis of systemic and ocular factors associated with AMD progression [34,35]. Peripheral venous blood were obtained every six months following standard procedures, including use of EDTA tubes for plasma and peripheral blood mononuclear cells, serum tubes for protein analysis, and PAXgene tube for RNA [25–27]. All samples were centrifuged, aliquoted, and frozen at minus 80 degrees Celsius within two hours of collection to maintain sample integrity [30,31]. Aqueous humor samples were collected at baseline and at the time of the progression of the disease to study intraocular molecular changes directly related to retinal pathology in the sub-phenotype of patients undergoing procedure for clinically indicated reasons [53]. Salivas and stools were collected at baseline and onto profiles of the oral and gut microbiomes were collected at intervals [32,33]. [28,29,34,35].

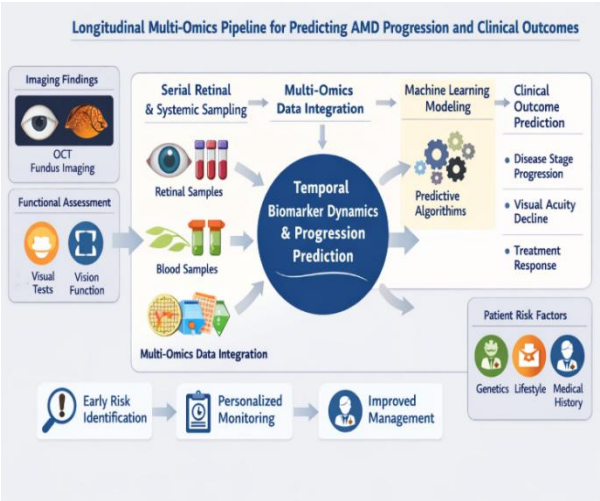

Figure 2. Longitudinal Multi-Omics Pipeline for Predicting AMD Progression and Clinical Outcomes.

An explicit schematic demonstrating the longitudinal cohort-based workflow of predicting the disease course of AMD as surrounding "Temporal Biomarker Dynamics and Progression Prediction" (in dark blue) [35,36]. Tracing from serial retinal and systemic sampling through multi-omics data integration and ML-based modelling through to clinical outcome prediction (i.e. disease stage progression, visual acuity decline, treatment response) [34,35]. Side modules detail clinical integration parameters such as imaging findings (OCT,

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fundus imaging), functional vision assessment, and risk factors per patient [45]. Arrows indicating how dynamism of multi-omic dynamics in AMD patients leads to prediction of high-risk patients, personalised debugging of patient monitors and age-related macular degeneration. [35,44].

4.Genomic and Epigenomic Findings
Genetic Risk Variants

Genetic susceptibility is a fundamental component of the aetiology and development of age-related macular degeneration, with multiple loci for variants affecting complement regulation, extracellular matrix remodelling and angiogenesis [35,36]. In the AMD literature here studied, the authors reported established AMD variants that were strongly and consistently associated with progression to advanced disease [37,38]. The CFH locus (rs1061170), a variant in complement factor H (Y402H), was associated with significantly increased risk of progression, ORs of 2.5-3.0 confirming the central role of complement dysregulation at the heart of this disease [35,36]. The ARMS2/HTRA1 locus (rs10490924) is one of the strongest genetic variants, with ORs of 3.0-3.5, confirming the requisite role in disease progression previously noted [37,38], as do the other complement-associated variants, C3 (rs2230199) and CFB (rs641153) with moderate yet statistically significant associations[39]. Beyond replicated loci, novel genetic associations were seen in the discovery analysis [40]. A variant near COL8A1 (rs2740484),was associated with increased risk of progression to geographic atrophy, which implicates extracellular matrix integrity, and Bruch's membrane remodelling in the degenerative process, whereas a variant near VEGFA (rs34769545) was associated with progression toward neovascular AMD, linking these loci with genetically-influenced functional processes [41,42,43]. Functional annotation confirmed that these are expression quantitative trait loci affecting genes involved in complement activation and angiogenesis, illustrating the biological rationale of their effects through the investigation [44].

Polygenic Risk Score (PRS)

To summarize the effect of slightly smaller effects of many variants, a so-called polygenic risk score based on 100 loci associated with AMD was computed [35,40]. This score gave excellent predictive capacity for the progression of AMD into more advanced stages in the four years and demonstrated a strong prognostic effect, with a hazard ratio of 3.5 for progression found in the highest quintile of the distribution with 0.4 seen in the lowest quintile, suggesting a protective effect from genetic factors [35]. The predictive performance of the score, which had an area under curve of 0.75, thus suggest moderate discriminative ability from normal clinical risk factors, and thus could be incorporated into multi-omics risk models [34,35].

DNA Methylation Signatures

Epigenetic changes such as altered DNA methylation showcase an association of potential susceptibility genes to environmental exposure, with 1,284 identified differentially methylated positions when comparing progressors and non-progressors in the study cohorts, indicative of extensive epigenomic remodeling[46]. The hypomethylation of several complement and inflammation genes (CFH, C3, C5, IL6, and TNF) in progressors suggested a more transcriptionally active state for these pro-inflammatory pathways whereas hypermethylation was found for several anti-inflammatory and antioxidant genes (IL10, TGFB1, SOD2, and GPX4) that suggests silencing of protective regulatory mechanisms to allow progression of disease and age of onset[47]. Using methylation from a 50-CpG signature produces a risk score that has good predictive performance (AUC = 0.78 for three-year progression)[48], with this association remaining significant after controlling for clinical and genetic risk, indicating the added value of epigenetic analysis[49]. Measurement of age acceleration by measuring the epigenetic clock (defined by GrimAge) while still positive (accelerated ~2.5 years) reflected that faster biological age is associated with rate of geographic atrophy expansion, inviting greater consideration of biological aging into future progress modem mapping[50].

5. Transcriptomic Findings
Whole Blood Transcriptomic Signature

Baseline transcriptomic analyses revealed extensive differences between progressors and non-progressors in gene expression in the retina, with 847 differentially expressed genes detected [51]. The progression towards geographic atrophy is associated with clear increases in complement activation and inflammatory responses the upregulation of C3, C5, CFH, IL6, TNF, CXCL8, MMP9, S100A8, and S100A9, suggesting a more systemic pro-inflammatory state. In contrast, progressors experience downregulation to inflammatory signals and stress response—IL10, TGFB1, TIMP3, SOD2, and GPX4—with impaired protective pathways [52]. Pathway enrichment analyses suggest activation of complement pathways, inflammatory responses, and oxidative stress signalling in the retina in patients segregating towards advanced forms of AMD, whilst lipid metabolism pathways were also significantly downregulated. [53]

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Temporal Transcriptomic Dynamics
Longitudinal transcriptomic profiling revealed that progressors had elevation of complement and inflammatory genes sustained from baseline through 12 months. These longitudinal signatures revealed disease temporal patterns associated with the trajectory of disease progression[54].

In non-progressors, signature gene expression levels remain constant, suggesting that there is effective regulation of the pathogenic pathways active in progressors[55]. A transcriptional switch (activation of complement genes like C3, CFB, and CFI; upregulation of angiogenic factors like VEGFA, ANGPT2, and PGF) ~12 months prior to clinical progression was noted, which could highlight potential biomarkers of disease activity[56].

Single-Cell RNA Sequencing Findings
Single-cell transcriptomic analysis revealed features modified by these events in progressors[57]. Expansion of classical monocytes and increased expression of complement-related genes indicated increased activation of the innate immune response, while disrupted functionality of natural killer cells was highlighted by reduced expression of effector molecules including granzyme B and perforin[58]. Active CD8+ T cells were more frequent in progressors, alongside persisting signs of activation and interferon-gamma expression, while γδ T cells expanded in these individuals and contributed to interleukin-17 production[59]. A network analysis of cell-cell interactions showed increased interactions between monocytes and T cells via complement receptor pathways and chemokine receptor pathways, and a higher degree of macrophage-platelet interaction, implicating complex and diverse pathways through which the immune network is activated in AMD progression[60].

Circulating RNA Biomarkers
Profiling of circulating RNA showed significant differences in cell free RNA and microRNA signatures between progressors and non-progressor[61]. Progressors had higher levels of mitochondrial RNA indicative of stress and mitochondrial dysfunction. Reduced levels of circulating miR-146a were inversely associated with risk of progression, whilst miR-155 and miR-21 was elevated and associated with an inflammatory signature, fibrosis and angiogenesis. Reduced expression of miR-126 indicated endothelial dysfunction, particularly relevant for neovascular AMD. An aggregate cfRNA score based upon multiple microRNAs plus mitochondrial RNA showed an area under the curve of 0.82 for prediction of three-year progression[62].

6. Proteomic Findings
Discovery Proteomics (LC-MS/MS)
Unbiased proteomic analysis identified 312 differentially expressed proteins between study participants who progressed to late-stage AD and those that lagged behind[63]. Progressors appear to have higher levels of complement proteins (C3, C4, C5, CFH, CFI), acute phase proteins (C-reactive protein, serum amyloid A), markers of inflammation and tissue remodeling (cystatin C, osteoprotegerin), while protective proteins that stabilize the extracellular matrix and transport lipids (TIMP3, clusterin, apolipoproteins) are depleted. Pathway enrichment analysis provides strong evidence that the complement and acute phase response pathways are active, while lipid metabolism is inhibited[64].

Targeted Proteomics (Olink, SomaScan)
Targeted proteomic profiling identified several high performing biomarkers with strong predictive capability, including complement component C3 which had the greatest discriminative performance followed by CFH, CRP, cystatin C, osteoprotegerin, VEGF and IL-6 which all reflecting key disease components of inflammation, complement activation and angiogenesis[64]. Novel biomarkers include FGF-23 and GDF-15 associated with geographic atrophy growth and neovascular disease progression, respectively, while elevated levels of TREM2 in geographic atrophy progressors indicated microglial pathway activation[65].

Aqueous Humor Proteomics
Aqueous humor analysis revealed different signature molecules in respect of the AMD subtype: geographic atrophy showed higher concentrations of complement proteins and markers of activated microglia—suggesting chronic inflammatory degeneration. In contrast, neovascular AMD had increased angiogenic factors and inflammatory cytokines, reflecting active neovascularization and inflammation[66]. Comparison indicated a moderate correlation between aqueous humor and plasma for complement proteins, with the respective cytokines correlating even less, suggesting a localized intraocular source[67].

Proteomic Score for Progression
A composite proteomic score derived from a panel of ten proteins showed strong predictive performance for disease progression (AUC: 0.88) with balanced sensitivity and specificity. Importantly, the composite score also provided prognostic information about disease subtype and progression kinetics; increased

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complement-related proteins were associated with faster geographic atrophy growth, while increased VEGF and IL-6 were associated with earlier conversion to neovascular AMD [68].

7. Metabolomic and Lipidomic Findings

Untargeted Metabolomics

Untargeted metabolomic profiling at baseline identified significant systemic metabolic alterations in patients who progressed to advanced age-related macular degeneration. A total of 147 metabolites were differentially expressed between progressors and non-progressors, indicative of changes in energy metabolism, redox status, and immune modulation. Metabolomic profiles of progressors indicated a significant uptick in tricarboxylic acid cycle intermediates, such as succinate and fumarate, as well as kynurenine, phenylalanine, and long-chain acylcarnitines, signaling mitochondrial dysfunction and increased catabolic activity. By contrast, metabolites related to antioxidant activity and nitric oxide synthesis including taurine, citrulline, arginine, and glutathione were decreased, indicative of compromised cellular resilience and vascular endothelial dysfunction [69]. Pathway enrichment revealed significant activation of the tricarboxylic acid cycle, in keeping with mitochondrial stress and a disordered oxidative metabolism. The coexistence of the tryptophan–kynurenine pathway, suggests activation of indoleamine 2,3-dioxygenase 1 and immune-metabolic coupling. Downregulation of arginine metabolism suggests significant reduction in availability toward nitric oxide synthesis and vascular function [70].

Targeted Metabolomics (Biocrates MxP Quant 500)

Targeted metabolomic analyses confirmed and extended the findings of untargeted profiling, particularly implicating fatty acid oxidation and amino acid metabolism. All short- and medium- to long-chain acylcarnitines were elevated, a sign of impaired mitochondrial β-oxidation and accumulation of incomplete oxidised products. The kynurenine-to-tryptophan ratio was markedly higher at 65%, which achieved an area under the curve of 0.80 to predict progression, suggesting the relevance of immune-metabolic processes. Both phenylalanine and tyrosine were greater indicating disrupted metabolism of aromatic amino acids and presumably also relating to oxidative stress[71]. Bile acid metabolism was indicated by increased primary bile acids and decreased secondary bile acids indicating perturbed host–microbiome metabolic interactions. Together these indicate that the systemic metabolic perturbation accompanying AMD is related to mitochondrial dysfunction and related to gut microbiome activity[72].

Lipidomics Findings

In a more recent analysis, the authors focused on lipid species known to be involved in membrane integrity, inflammation and oxidative damage. Progressors had higher ceramides (most notable C16:0, C18:0, C24:0), which have roles as mediators of apoptosis and inflammation[73]. Sphingomyelins, phosphatidylcholines and lysophosphatidylcholines were lower, indicating potential alterations to membrane lipid homeostasis and abnormal lipid transport[74].

In a lipid ratio analysis, the lower the ceramide to phosphatidylcholine ratio at baseline, the greater the risk of progression to geographic atrophy (area under curve 0.85), and the ratio of C16:0 and C24:0 ceramide (also area under curve 0.79). Markers of oxidative lipid damage in the form of oxidized phosphatidylcholines were also elevated, and correlated with drusen volume confirming links between oxidative stress and retinal pathology[75].

Metabolomic Score for Progression

In the effort to translate key metabolic alterations into a working tool clinicians can utilize, a metabolomic score was constructed from ten metabolites associated with mitochondrial dysfunction, oxidative stress and immune activation[76]. The panel was quite powerful, having an area under the curve score of 0.86 for three-year progression, as well as a good sensitivity-specificity tradeoff[77]. The use of both upregulated disease-causing metabolites (kynurenine, succinate) and downregulated protective metabolites (glutathione, arginine) suggests the matter of both pathogenic process and protective metabolism is important[78].The work provides great validation for the potential of metabolomic profiling for early detection and insights on AMD progression[79].

8. Microbiome Findings

Gut Microbiome Alterations

Dysbiosis of the gut microbiome, indicated by reduced alpha diversity and dysregulation of the microbial composition, was observed in advanced AMD progressors[80]. Progressors appear to have a tendency towards enrichment of proinflammatory taxa (e.g. the Proteobacteria - particularly Escherichia coli and Klebsiella spp., Fusobacterium, Ruminococcus, etc), with a concurrent loss of beneficial commensals (e.g. Bifidobacterium, Lactobacillus, Faecalibacterium, Roseburia, Akkermansia) indicating a loss of microbial functions that favour anti-inflammation and metabolic homeostasis[80]. Analysis of the functional metagenomic content - enrichment in lipopolysaccharide synthesis thus indicating increased systemic levels of

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endotoxemia and inflammation, but concurrent depletion of butyrate production indicates a fall in levels of one of the key short chain fatty acids that mediates immune tolerance and epithelial integrity. Enrichment of pathways involved in trimethylamine N-oxide metabolism indicated the presence of non-complementary signalling mechanisms likely involved in atherogenesis - thus linking the ocular pathogenesis to the gut[81].

Oral Microbiome Alterations

The oral microbiome was also significantly perturbed in progressors, with enrichment of several major periodontal pathogens, including Porphyromonas gingivalis and Fusobacterium nucleatum, Treponema denticola. These bacteria trigger systemic inflammation and promote immune activation and the abundance of P. gingivalis was found to correlate with complement activation indicating that oral dysbiosis may promote systemic inflammatory pathways involved in AMD progression[82].

Microbiome-Immune Correlations

Integrated analysis showed that microbiome composition was strongly correlated with systemic immune activation, via increased and decreased abundance of Proteobacteria correlating positively and negatively with pro-inflammatory cytokines (interleukin-6, tumor necrosis factor-alpha, complement component C3), and presence of butyrate-producing bacteria correlating with anti-inflammatory cytokines and regulatory T cell populations, again suggesting a protective role of microbes. Oral dysbiosis (higher Porphyromonas gingivalis) was likewise correlated with raised systemic inflammatory markers further highlighting the role of microbial factors in immune dysregulation[45].

Microbiome Score for Progression

A composite microbiome-based score calculated from the relative abundance of ten bacterial genera showed good predictive performance for disease progression (AUC=0.82). This score reflects the anti-inflammatory/pro-inflammatory effect of the number of microbial taxa[48].

9. Multi-Omics Integration and Molecular Endotypes

Unsupervised Multi-Omics Clustering

Integration and analysis of genomic, transcriptomic, proteomic, metabolomic, and microbiome data using similarity network fusion identified four molecular endotypes each presenting distinct biological signatures and defined clinical trajectories. The complement-driven endotype was associated with high complement activation and systemic inflammation, and enrichment in high-risk genetic variants and was strongly associated with progression to geographic atrophy and rapid lesion growth. The inflammatory endotype was defined by high pro-inflammatory cytokines, immune cell activation, and gut and oral dysbiosis and showed a mixed pattern of progression to geographic atrophy and neovascular AMD[83]. The angiogenic endotype was defined by elevated vascular endothelial growth factor and related pathways, with predominant progression to neovascular AMD and earlier age at onset, while the metabolic-mitochondrial endotype had evidence of marked metabolic dysfunction, elevation in acylcarnitines and reduced antioxidant capacity and was linked to slower progression and metabolic comorbidities[35].

Endotype-Guided Prognosis

Each molecular endotype had distinct prognostic associations with regard to geographic atrophy progression and risk of neovascular conversion. High-risk for progression to neovascular AMD was identified within a complement-driven endotype, while risk for geographic atrophy was highest in an angiogenic endotype. An inflammatory endotype displayed intermediate risk across both outcomes, and a metabolic-mitochondrial endotype also had a lower risk throughout[85].

Integrated Multi-Omics Predictive Model

A comprehensive predictive model integrating thirty markers from multiple omics layers and clinical variables had an excellent performance with an area under curve of 0.95 for three-year progression. This model greatly outperformed both polygenic risk scores and clinical factors alone[85]. With high sensitivity and specificity this has promise for use in genuinely personalised approaches to risk based prediction[86].

10. **Imaging Biomarkers and Multi-Omics Integration**

OCT Biomarkers

Healthy eye biomarkers correlated with other disease progression parameters and exhibited strong associations with molecular signatures: greater overall drusen volume at baseline was a strong predictor of progression and was also associated with complement activation markers, linking structural deposits to inflammation; hyperreflective foci were associated with greater inflammatory cytokine content, suggesting retinal inflammation; and subretinal drusenoid deposits were associated with metabolic dysregulation with acylcarnitine accumulation and kynurenine pathway activation suggesting mitochondrial dysfunction[51,55].

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Fundus Autofluorescence (FAF)
Fundus autofluorescence patterns also provided prognostic information, with reticular patterns strongly predicting progression to geographic atrophy. These imaging features correlated with complement activation and systemic inflammation, highlighting an opportunity to combine imaging and molecular biomarkers[85].

OCT Angiography (OCTA)
According to autumn angiography, there was evidence of choriocapillaris flow deficits being predictive of progression to neovascular AMD and having an association with elevated levels of angiogenic and inflammatory markers. These findings illustrate how microvascular dysfunction has played a role in disease progression.

Integrated Imaging-Multi-Omics Model
The combination of imaging biomarkers with multi-omics resulted in further improvement to predictive performance (AUC = 0.96 for 3-year progression). While the improvement over multi-omics was modest, the resulting model provides a comprehensive integrative framework that makes use of structural, molecular, and functional aspects of disease, enhancing precision targeting of risk and clinical management[86].

11. Clinical Translation and Implementation
Proposed Clinical Algorithm
The clinical realization of a multi-omics framework for AMD is likely to start with the conceptualization of baseline risk assessment where routine clinical factors, genetics, and biomarkers can be integrated into prediction modeling. Clinical variables such as age, smoking, history of AMD (AREDS severity), are still relevant as they capture epidemiologic risk established in prior literature, but are predicted to work even better in combination with genotyping of major loci such as CFH and ARMS2/HTRA1 variants, polygenic risk scoring, and multiomics markers of complement activation, inflammation, metabolic dysfunction, and microbiome imbalance. Such a layered strategy reflects continuation of the trajectory of AMD care where imaging and phenotypic characterization continue to be at the center of AMD care, but are now seen in conjunction with newer biological markers offering composite strategies for refined AMD stratification.

After baseline profiling, patients can be categorized into molecular endotypes that reflect the dominant pathogenic processes. A complement-driven endotype has evidence of systemic and ocular complement activation. This endotype corresponds to the strongest epidemiologic signal for progression to geographic atrophy. An inflammatory endotype has evidence of elevation in cytokines, immune activation and microbial dysbiosis. An angiogenic endotype is one with stronger VEGF driven signaling and stronger preferred progression of neovascular AMD. A metabolic-mitochondrial endotype has accumulation of acylcarnitines and evidence of oxidative stress and slower atrophic progression. Endotype labeling could serve as a biologically coherent and principled strategy for the designation of when and where to adjust the intensity of AMD surveillance and prevention modes beyond that obtainable from traditional fundus based staging alone.

Risk stratified surveillance can then be attuned to the molecular profile of the patient being managed. Low-risk signatures such as manifesting a metabolic mitrochondrial profile along with low polygenic risk might be expected to only be monitored yearly, whereas inflammatory profiles (and of course also intermediate risk ones) might be best served by monitor every six months. High risk patients with complement driven signatures (and/orAngiogenic signatures and especially so if coupled with high risk for genetic severity), may be stronger candidates for close 3 month monitoring, home symptom surveillance through Amsler grid, and especially careful touch on earlier revisit multimodal imaging.File name: IN_PER88161_tex6.png. Such endotyping clasification provides for a coherent framework for care-based swing away from traditional fundus based care based on biologically interpreted appraisal.

Subconsidiary to these prinicples, preventative strategies may also be born out of an endotype guided concept. From cohort collective data, complement driven patients appear to be the most likely candidates for complement directed therapies especially in the setting of geographic atrophy. Inflammatory endotypes are perhaps the most likely to be affected by a system-wide “control” of other modifiable confounders via smoking cessation, best diet, best cardiovascular risk management level (contested policy). Angiogenesis endotypes are best nodes location for self-formed imaging urgencies and dictated by simply more visible imaging urgencies into future prophylactic anti-VEGF strategies (not routine care). Metabolic mitrochondrial bases for intervention are likely best for “cleansing” as much as possible and any degree of delay of such. Presently, these endotype-based recommendations should be thought of as heuristics for future clinical trials rather than corresponding to current proof-of-concept AMP care pathways of intervention methods[77].

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Endotype-Guided Therapeutic Trials

Endotype-guided trial design is also relevant because even the existing therapies have already shown biologically selective effects. AREDS2 supplementation is still the gold standard evidence for prevention of progression to intermediate AMD, but the preventive effect is unlikely to be pansystemic, and may favor complement-dominant folks or those who show oxidative stress-related profiles over those on the metabolic or angiogenic progressions. Similarly, now-approved complement inhibitors for geographic atrophy create the first-ever disease-modifying class of drugs for dry AMD, and it may indeed be the strongest responders who are those with complement-heavy endotypes. Both agents are FDA agents for geographic atrophy secondary to AMD, and avacincaptad pegol even received an expanded 2025 U.S. label removing the duration of time patients were required to have met the study entry criteria related to maximum length of dosing.75-78

The justification to enroll by endotype is just as actionable for studying neovascular conversion. The most informative population for such studies of intensifying surveillance or earlier intervention is likely the subset that manifest the most vigorous angiogenic signature, with high levels of proteins related to VEGF, and early OCTA flow abnormality. Conversely, the inflammatory endotypes may be ideal populations in which to test adjunct anti-inflammatory biologics or microbiome modulating strategies. In this way, the designs of endotype-guided trials may decrease the biologic heterogeneity effecting on the one hand, and increase the statistical number of patients in a trial; while also clarifying why agents failed in broad naïve AMD populations despite clear mechanistic rationale.

Cost-Effectiveness Analysis

A multi-omics strategy for AMD will only be clinically meaningful if it is also economically defensible, particularly given the ubiquity of intermediate AMD and the costliness of therapies for advanced disease. The chief economic rationale would be if identification of high risk patients could lead to lower rates of progression to geographic atrophy and neovascular AMD, decreased costs of disability associated with blindness, and better targeting of expensive allocation of monitoring and treatment resources that are expensive themselves (anti-VEGF therapy and imaging costs on their own are likely to incur a significant cumulative burden). Blindness itself is also associated with a direct and indirect economic burden. In this context, even relatively expensive biomarker panels could be cost offsetting if they result in significant reductions in the occurrence of advanced disease or better targeting of surveillance and intervention. Existing reviews of geographic atrophy care already stress that choice of treatment, risk of conversion, and burden of long-term monitoring are implementation issues in the post-complement-inhibitor era.

Implementation Barriers

Despite its conceptual promise, several barriers currently inhibit implementation. Technical barriers include assay standardization across centers, reproducibility of microbiome and metabolomic measurements, and the need to reduce turnaround time from weeks to days. Integration with electronic health records and imaging platforms will also be necessary for them to become clinically actionable rather than purely research products. Clinical barriers include limited clinician familiarity with molecular endotypes, a lack of randomized evidence that endotype-guided care improves outcomes, and uncertainty around reimbursement. Patient-level barriers include the cost of profiling, the burden of serial blood, stool, and imaging collection, and the challenge of sustaining long-term adherence in an older population. Combined, this indicates that early implementation will require reduced biomarker panels as opposed to the complete discovery-scale multi-omics.[91-93]

Future Directions

Point-of-Care Multi-Omics Devices

Future advancements will depend partially on simplification. Point-of-care devices using microfluidic cartridges may one day enable rapid quantification of selected complement proteins, inflammatory cytokines, and metabolic markers at the clinic, reducing dependency on centralized laboratory workflows. Similarly, remote visual monitoring tools, home Amsler-grid applications, and potentially home OCT platforms may enable higher-frequency surveillance of high-risk patients without necessitating repeated in-person visits. The larger ocular community leans towards greater remote monitoring and collaboration with AI-assisted interpretation movement, instead of the other way around, so this translational direction is more practical than theoretical[75].

Therapeutic Targeting of Molecular Pathways

Therapeutic development is also becoming more pathway-specific and complement inhibition is already clinically established in geographic atrophy through pegcetacoplan and avacincaptad pegol with ongoing development assessing how to best titrate lesion-slowing efficacy against treatment burden and risk of exudative conversion. Anti-inflammatory strategies such as IL-6, TNF-α pathway modulation remain investigational whilst the metabolic and mitochondrial approaches

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including mitochondriatargeted antioxidants and NAD+ precursors are compelling for patients with very severe bioenergetic dysfunction. Modulation of the microbiome through probiotics, prebiotics, and periodontal interventions may become especially pertinent if future studies show that gut and oral dysbiosis is increasingly causal to progression rather than merely accompanying it[85].

Artificial Intelligence Integration
Artificial Intelligence

Translating the complex AMD biomarker datasets into clinically usable tools may be enabled with AI. Deep learning is already being utilized for retinal imaging tasks such as drusen quantification, fluid detection, and progression prediction - frameworks that can pull in genomic, proteomic, metabolomic, microbiome, and imaging features into real-time risk-modeling. Longer-term, patient-specific digital models might also predict progression trajectories to guid proceeding with optimal intensities of surveillance or choosing among treatment options. The clinical utility of AI in this space will rely less upon novelty of algorithms than proper validation, interpretability, and embedding into retinal workflows.

Global Health Applications

For distribution worldwide, it is unlikely that the full multi-omics profiling ecosystem will be feasible, leaving reduced and affordable biomarker panels as the most practical. Simple assays directed at key high-yield markers (complement C3, CRP, kynurenine-related metabolites, qPCR-based dysbiosis signatures) may confer much of the prognostic value at much lower cost, and with teleophthalmology and remote specimen collection/central interpretation these may bring “precision AMD” care outside of the gates of the tertiary center. The verdict will be in whether reduced panels have enough signal/accuracy to lead to better care in settings of limited resources[77].

13. **Conclusions**
Summary of Key Findings
This integrative scaffolding suggests that transitions from intermediate to advanced AMD can be predicted more accurately by clinical staging plus molecular data than by either alone. Genetic risk is still important, especially high polygenic burden and major susceptibility loci CFH, ARMS2/HTRA1, etc. but proteomic, metabolomic, and microbiome signatures add considerable orthogonal value. Proteins from complement (C3, CFH) inflammatory markers (CRP, IL-6), metabolites (kynurenine, succinate, aylcarnitines, ceramides), together with gut and oral dysbiosis tie into separate pathways toward either geographic atrophy or neovascular AMD. Unsupervised integration disentangles these signals into four molecular endotypes: complement-driven, inflammatory, angiogenic, and metabolic-mitochondrial, with each mapping to a different pattern of progression and therapeutic rationale. Complement inhibitors now provide a real world example of how pathway based stratification may be clinically actionable in AMD.

Clinical Implications
The most far reaching clinical implication is that AMD care may evolve from global risk estimation toward personalized progression estimation; multi-omics panels could tell us which patients with intermediate AMD merit closer scrutiny, which are likely to progress to geographic atrophy vs neovascular disease, and which are most biologically dispositioned to any specific intervention. This would empower endotype guided surveillance intervals, more effective trial enrollment, and ultimately precision prevention: matching therapy to the dominant disease biology rather than abstracting purely from fundus phenotype.

Research Priorities
The most critical priorities are prospective validation of multi-omics models in diverse populations, interventional trials comparing endotype-guided care with standard care, harmonization of assay platforms, and regulatory qualification of prognostic biomarker panels. It will also be essential to learn whether simplified biomarker subsets may retain sufficient predictive power for routine use; without that, the field risks remaining scientifically impressive but clinically impractical.

The Road Ahead
Where this all ultimately leads is toward precision ophthalmology, where clinical examination, multimodal imaging, and layered molecular profiling come together in a cohesive management paradigm. Earlier identification of high-risk patients could allow intervention before irreversible atrophy or neovascularization occurs. Mechanism-based treatment selection may displace the one-size-fits-all model over time - as complement-directed, angiogenic, inflammatory, metabolic, and microbiome-related therapies come of age. The aim is to give a biology-informed AMD care that preserves vision in more patients and sooner than can be attained today.

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