SOMATO PUBLICATIONS ISSN: XXXX-XXXX

Annals of Ophthalmology and Eye Disorders

Review Article

Evaluation of fundus photography as a Prognostic Tool in age-related macular degeneration

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Received: 17 April 2025; Accepted: 22 July 2025; Published: 24 October 2025.

Citation of this article: Colombo S, Marino A, Ricci G (2025) Evaluation of fundus photography as a Prognostic Tool in age-related macular degeneration. Ann Ophthalmol Eye Disord, 7(1): 01-06. DOI: 10.5281/zenodo.22812219

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Abstract

Background: Fundus photography has anchored age-related macular degeneration (AMD) staging since the earliest clinicopathological classification systems, and the Age-Related Eye Disease Study (AREDS) severity scales, derived entirely from stereoscopic color fundus photographs, remain the basis for multi-year risk stratification [5,7].

Objective: This review evaluates the evidence that features visible on fundus photographs, including drusen size, pigmentary abnormality, and fundus autofluorescence (FAF) pattern, carry genuine prognostic value for progression to geographic atrophy and conversion to neovascular AMD.

Methods: We synthesized natural-history cohorts, AREDS and AREDS2 ancillary analyses, FAF pattern studies, and deep-learning re-analyses of legacy fundus photograph archives addressing photographic prediction of AMD progression and vision loss.

Findings: AREDS severity scores predict 5-year progression to advanced AMD ranging from roughly 0.5% to 50% across risk categories [6]; FAF pattern predicts geographic atrophy enlargement rate, with banded and diffuse patterns enlarging fastest [12,11]; and convolutional neural networks trained on archived photographs now match or exceed expert grading, in some cases predicting neovascular conversion months before clinical exudation [25,29].

Conclusions: Fundus photography functions as a genuine prognostic instrument in AMD rather than a purely diagnostic record, and automated grading tools are likely to extend, rather than replace, its role as the most widely accessible entry point into individualized AMD risk assessment [27,26].

Keywords: fundus photography; age-related macular degeneration; fundus autofluorescence; AREDS severity scale; deep learning

1. Introduction

Age-related macular degeneration (AMD) remains the leading cause of irreversible central vision loss among older adults in industrialized countries, with global burden projected to reach nearly 288 million by 2040 [1,2]. Long before OCT and OCT angiography became routine, color fundus photography was the primary tool by which clinicians documented, staged, and followed the disease, and it remains indispensable because it is inexpensive, fast, and comparable across decades of legacy data [3]. The question this review addresses is not whether fundus photography can detect AMD, but whether features visible on a standard photograph carry genuine prognostic information: can a photograph taken today predict who will progress to geographic atrophy, who will convert to neovascular disease, and who will lose vision over the following years.

The foundational classification systems that anchor clinical and trial practice were built entirely from fundus photographs. Bird and colleagues' international classification established standardized terminology for drusen, pigmentary change, and atrophy that made cross-study comparison possible [4], and the Age-Related Eye Disease Study (AREDS) built on this with a detailed severity scale derived from masked grading of stereoscopic photographs, culminating in the widely used simplified severity scale that assigns risk points for large drusen and pigment abnormalities [5,6,7]. These systems were designed from inception to stratify risk, which is what makes fundus photography a prognostic tool rather than merely a diagnostic one.

This review synthesizes evidence from natural-history cohorts, trial ancillary analyses, and deep-learning re-analyses of legacy photograph archives on how well photographic features predict progression to geographic atrophy and conversion to neovascular disease, and the vision loss that follows each, including fundus autofluorescence (FAF) and convolutional neural network models that re-derive prognostic signal beyond what human graders reliably achieve.

2. AREDS severity scales and the photographic basis of AMD staging

The AREDS simplified severity scale assigns one risk point for each eye with large (>125 micron) drusen and one additional point for each eye with pigment abnormality, producing a 0-4 scale whose 5-year risk of progression to advanced AMD in at least one eye rises from roughly 0.5% at a score of 0 to approximately 50% at the maximum score, based purely on features read from stereoscopic photographs [7,6]. This scale, along with the more granular 9-step scale used for ancillary grading, demonstrated that photographic drusen size, area, and pigmentary change are graded, quantifiable prognostic variables (Table 1) [5]. Ferris and colleagues later proposed a simplified clinical classification, still photograph-based, dividing AMD into no apparent aging change, normal aging changes, early, intermediate, and late AMD, designed so any examining ophthalmologist grading a photograph could assign a prognostically meaningful category [8].

Population-based cohorts corroborate the trial-derived risk gradients. The Beaver Dam Eye Study followed a community cohort for fifteen years and found cumulative incidence of early and late AMD rising steeply with baseline photographic drusen characteristics, confirming the AREDS-derived risk relationships generalize beyond the referral-biased trial population [9]. Reticular pseudodrusen, a subtler feature not fully captured by the original scale, was later shown by Klein and colleagues to carry independent prognostic weight, prompting revisions to more recent grading protocols [10].

3. Fundus autofluorescence as a prognostic photographic modality

Fundus autofluorescence extends conventional color photography by imaging lipofuscin accumulation in the retinal pigment epithelium, and its prognostic value for

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geographic atrophy has been documented more thoroughly than for any other photographic AMD feature. Bindewald and colleagues classified early AMD eyes into distinct FAF patterns - normal, focal increased, patchy, linear, lacelike, reticular, and speckled - that carry differential risk of progression to atrophy [11]. Holz and colleagues, in a multicenter natural-history study, showed banded and diffuse FAF patterns surrounding atrophy predicted substantially faster enlargement than eyes with no abnormal perilesional autofluorescence, establishing FAF pattern as one of the strongest predictors of atrophy growth rate [12]. Schmitz-Valckenberg and colleagues' review of FAF imaging clarified the biological rationale: hyperautofluorescent junctional zones mark metabolically stressed but still-viable retinal pigment epithelium destined to die at a predictable rate [13].

Table 1: AREDS simplified severity scale risk points and approximate 5-year risk of progression to advanced AMD in at least one eye, derived from photographic grading of drusen size and pigment abnormality [7,6,5].

Risk score (0-4)	Photographic criteria	Approx. 5-year progression risk
0	No large drusen or pigment abnormality in either eye	~0.5%
1	One risk factor present in either eye	~3%
2	Two risk factors, or bilateral single risk factor	~12%
3	Three risk factors present	~25%
4	Risk factors in both eyes at maximum severity	~50%

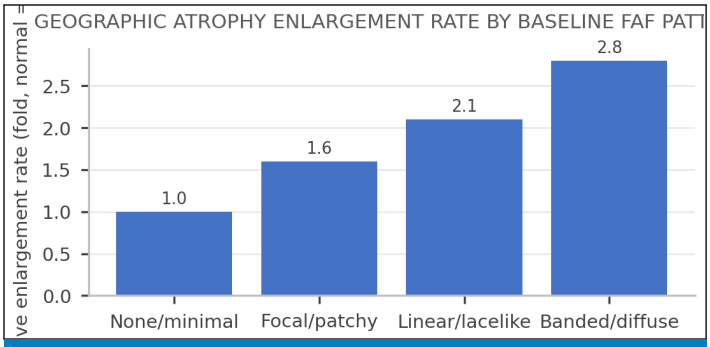


Figure 1: Approximate geographic atrophy enlargement rate by baseline fundus autofluorescence (FAF) pattern, with banded and diffuse perilesional patterns predicting substantially faster enlargement than eyes with no abnormal autofluorescence [12,11,13].

Geographic atrophy, once established, follows a fairly predictable enlargement trajectory trackable longitudinally on photographs and FAF alike. Sunness and colleagues established that atrophy enlarges at a roughly constant rate per eye correlating with visual acuity loss over time [14], a finding extended in longer follow-up tracking eyes for up to ten years [15]. Fleckenstein and colleagues showed enlargement rate in one eye strongly predicts the rate in the fellow eye, evidence that this photographically derived growth-rate phenotype reflects a patient-level trait rather than eye-specific noise, strengthening its use as an individualized marker (Figure 1) [16].

4. Predicting conversion to neovascular AMD from photographic features

Conversion from non-neovascular to neovascular (wet) AMD has likewise been linked to specific photographic features, though with somewhat less precision than atrophy prediction. Cukras and colleagues, analyzing the natural history of drusenoid pigment epithelial detachment in AREDS, found these lesions - visible and measurable on standard photography - carry substantial risk of progression to either atrophy or neovascularization, with size and morphology predicting which pathway a given eye follows [17]. Ying and colleagues identified baseline photographic and imaging features, including lesion size and subtype, that independently predicted one-year visual acuity after ranibizumab therapy, showing photographically derived lesion characteristics retain prognostic value even after conversion and treatment [18]. The pivotal ranibizumab trials, ANCHOR and MARINA, used photographic and angiographic lesion classification at baseline as an eligibility criterion precisely because lesion type predicted both treatment response and untreated natural history [19,20].

Table 2: Photographic and imaging features reported to predict conversion from non-neovascular to neovascular AMD, or subsequent visual outcome after conversion [17,18,23,21].

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Photographic feature	Outcome predicted	Source
Drusenoid pigment epithelial detachment size/morphology	Progression to atrophy or neovascularization	[17]
Baseline lesion size and subtype	1-year visual acuity after anti-VEGF therapy	[18]
Reticular pseudodrusen, pigmentary change	Conversion risk independent of drusen size	[21]
Photographically graded severity + covariates	Individualized multi-year progression risk	[23]

Reticular pseudodrusen and pigmentary abnormalities also predict conversion risk independent of drusen size, and OCT-era studies correlating photographic baseline features with subsequent conversion have generally confirmed the AREDS-era risk ordering, even as OCT angiography adds complementary detail photography alone cannot provide [21,22]. Seddon and Rosner's validated prediction models, built substantially on photographically graded severity together with genetic and demographic covariates, show photographic staging remains a core input even in the most sophisticated contemporary risk tools [23].

5. Deep learning and automated prognostic grading of fundus photographs

The most significant recent development is the demonstration that convolutional neural networks can extract prognostic signal from photographs that meets or exceeds expert grading, directly from archived AREDS-era images. Burlina and colleagues first showed deep networks trained on AREDS photographs could grade AMD severity approaching retinal specialist accuracy [24], then extended this to direct estimation of five-year progression risk from a single baseline photograph, collapsing a multi-step risk calculator into an end-to-end image-based prediction [25]. Grassmann and colleagues, in an independent European cohort, trained a network to reproduce AREDS severity grading with high concordance to human graders, showing this generalizes beyond the original cohort [26] (Table 2).

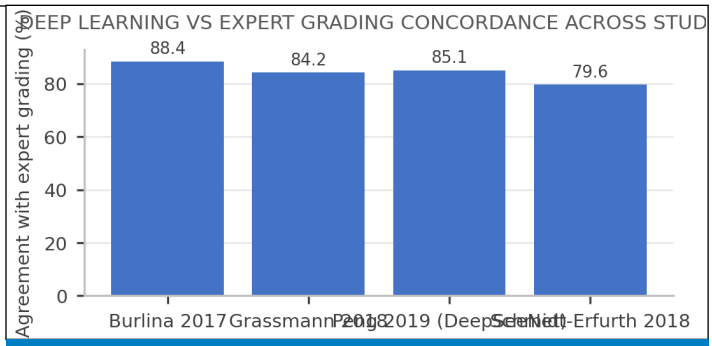


Figure 2: Concordance of automated deep-learning grading with expert human grading of AREDS severity scale category from color fundus photographs across four independent model validations [24,26,27,28].

Peng and colleagues' DeepSeeNet reformulated automated grading at the patient rather than eye level, matching specialist performance for drusen-size and pigmentary-abnormality classification [27]; across these independent validations, agreement with expert grading has consistently exceeded 79-88% (Figure 2). Schmidt-Erfurth and colleagues combined machine learning with quantitative image features to predict individual conversion to late AMD, reporting accuracy meaningfully above chance-level clinical risk scores [28]. Yim and colleagues built a system predicting conversion to neovascular AMD up to six months before clinically apparent exudation, with direct implications for surveillance interval design [29]. Keenan and colleagues extended automated analysis to geographic atrophy detection from color photographs, complementing FAF-based assessment given photography's wider availability [30]. Ting and colleagues' broader review situates these results within image-based prognostic modeling across retinal disease, noting AMD progression prediction is among the more mature applications given the large, well-annotated AREDS/AREDS2 archives [31].

6. Risk factors, supplementation trials, and the role of photographic staging in clinical decision-making

Photographic AMD stage is not merely descriptive; it is the primary criterion for selecting patients for interventions proven to alter prognosis. The AREDS antioxidant and zinc trial enrolled and stratified participants by

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photographically determined severity, and the roughly 25% reduction in five-year progression to advanced AMD was concentrated almost entirely among participants with intermediate or high photographic risk at baseline, with negligible benefit in early disease alone [32,33]. AREDS2 again used photographic severity staging for eligibility and outcome stratification, confirming lutein and zeaxanthin substitution preserved efficacy within the same risk strata [34,35]. AREDS Report No. 3 used baseline photographs to identify smoking, cardiovascular, and dietary risk factors associated with more severe photographic disease category, cementing photography's role as the substrate against which environmental and genetic risk factors are validated [36,37].

This dependence on photographic staging for trial eligibility is itself strong evidence for prognostic validity: a feature predicting differential response to a proven intervention meets a higher evidentiary bar than one merely correlated with outcome. Ferris and Bressler's commentary framed photographic severity grading as the necessary common language for comparing risk and treatment effect across studies, a framing that has held up across two subsequent decades of trial design [38].

7. Discussion

Taken together, the evidence supports fundus photography as a genuinely prognostic tool in AMD, not simply a diagnostic snapshot. Its prognostic value operates through overlapping channels: (1) drusen size, area, and pigmentary abnormality, quantified by the AREDS scales, predict multi-year progression risk with a gradient that is large, reproducible, and generalizable to community cohorts [5,6,9]; (2) FAF pattern predicts the rate of geographic atrophy enlargement, for this outcome perhaps exceeding what color photography alone provides [12,11]; (3) lesion morphology and drusenoid pigment epithelial detachment characteristics predict which late-disease pathway a given eye follows [17,18]; and (4) deep learning models trained on large archives now extract prognostic signal matching or exceeding expert grading, occasionally detecting subclinical change months before conversion becomes apparent [25,29].

Several limitations temper enthusiasm. Photographic grading carries inter-grader variability that AREDS itself controlled for through masked protocols [5]. Reticular pseudodrusen and subtler lesions are imperfectly captured by two-dimensional photography and better resolved on OCT or FAF, so photography-only models likely omit some predictive structural information [10,21]. Deep learning models have mostly been validated on the same AREDS-derived archives used for training, and prospective, multi-ethnic, multi-camera external validation remains comparatively sparse [31,26]. Finally, most photographic prognostic markers were derived in trial or research cohorts that differ systematically from unselected community patients, which can distort risk estimates applied naively in practice [1].

Despite these caveats, the field's trajectory is toward greater reliance on fundus photography for prognosis, since photographs are cheap enough to obtain at every visit, comparable across the multi-decade archives underpinning current risk models, and now amenable to automated analysis extracting more signal than human graders reliably could. A single well-acquired photograph, staged by the AREDS scale and, where available, interpreted alongside FAF pattern, already provides meaningful multi-year prognostic information, and automated grading tools are likely to make this more consistently available at the point of care.

8. Conclusion

Three decades of clinicopathological classification, natural-history follow-up, randomized supplementation trials, and, most recently, deep-learning re-analysis converge on the same conclusion: fundus photography is not merely a diagnostic record of AMD but a genuine prognostic instrument. Drusen size and pigmentary abnormality, quantified through the AREDS scales, and

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autofluorescence pattern each predict multi-year progression risk and, for atrophy, the rate of progression once it begins [5,12]. Lesion morphology predicts which late-disease pathway is more likely, and machine-learning models trained on legacy archives now extract this signal with accuracy and, in some cases, lead time exceeding conventional grading [25,29]. As automated tools mature and are validated across more diverse populations and camera platforms, fundus photography seems likely to remain the most widely accessible entry point into individualized AMD prognosis.

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