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Evaluation of Geographic Atrophy from Color Photographs and Fundus Autofluorescence Images: AREDS2 Report Number 11

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Abstract

Purpose—To compare measurements of area of geographic atrophy (GA) and change in GA area from color photographs and fundus autofluorescence (FAF) images.

Design—The Age-Related Eye Disease Study 2 (AREDS2) was a prospective multicenter randomized clinical trial evaluating progression of dry AMD using color photographs at annual visits over a 5 year study period. FAF images were acquired in a subset of participants who joined the FAF ancillary study at any of the annual visits over the study period.

Participants—The AREDS2 FAF ancillary study included 8070 corresponding color and FAF visits of 2202 participants with variable follow-up.

Methods—Corresponding color and FAF images were independently evaluated at a central reading center for GA area measurement, lesion growth, and involvement of the macula center.

Main Outcome Measures—Presence, area, growth rate of GA and involvement of center of macula from color and FAF images.

Results—Autofluorescence images were available for 8070 visits of 2202 participants. Hypoautofluorescence was visible in 2048 visits (25.4%). Agreement for presence of GA between the two modalities had a kappa of 0.79 with 23% of visits with hypoautofluorescence not presenting with GA on color photos. Percentage agreement for GA presence ranged from 43% at baseline to 81% at year 5 with improving agreement over time. The mean difference in GA area between the two modalities was 0.5 mm², with larger areas on FAF. Growth rate of GA was 1.45 mm² from color photos and 1.43 mm² from FAF images. Center of macula was involved in 51% of color photos and 56% with FAF images.

Conclusion—GA may be detected earlier by the use of FAF images but over the course of the study, the two modalities become comparable. Progression of GA area is comparable between color photographs and FAF images, but evaluating involvement of center of macula may differ, probably due to macular pigmentation blocking autofluorescence.

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Introduction

Age-related macular degeneration (AMD) is the primary cause of blindness in the economically developed countries and the third leading cause worldwide.¹ In the United States, AMD affects 1.75 million individuals and the number is predicted to reach 3 million by 2020.² Geographic atrophy (GA), the end stage of dry AMD, is a progressive disease which can cause substantial visual impairment; two year rate of visual acuity loss of 3-or-more lines occurs in 40% of eyes with GA and baseline visual acuity of 20/50 or better.³ The natural history of GA has been studied in detail and currently there is no approved treatment available for GA.⁴⁻¹⁰ Change in GA area has been used as an outcome measure for clinical trials evaluating treatments of the condition.^{6,10-12} Historically, area measurements of GA were performed using stereoscopic color fundus photographs.^{4,13} Fundus autofluorescence (FAF) imaging is a more recent modality from which GA location and extent can be accurately measured; GA is typically visualized as dark areas due to absence of autofluorescence.¹⁴

Several groups have evaluated the rate of GA enlargement, either by color photographs, FAF or optical coherence tomography scans (OCT).^{4,10,12,15,16} Sunness *et al.* reported a mean overall GA enlargement rate of 2.6 mm²/year (median area enlargement rate of 2.1 mm²/year) using film color photographs.⁸ The Age Related Eye Disease Study (AREDS) Research Group evaluated change in GA area over a four year period with images digitized from film color photos; mean change in area was 2.03 mm² in the first year and enlargement rate thereafter was 1.71 mm²/year.¹⁰ Holz *et al.* found a mean growth rate of 1.74 mm²/year (median area 1.52 mm²/year) using FAF images.¹⁷ The Geographic Atrophy Progression study (GAP) reported a growth of 1.85 mm² with FAF and 1.57 mm² with color photographs in one year.¹⁵ FAF offers the advantage of improved contrast resulting in more precise delineation of GA borders which enables semi-automated delineation of GA area and has been more widely used in GA imaging over recent years.¹⁸

The Age Related Eye Disease Study 2 (AREDS2) was a multicenter phase III randomized controlled clinical trial designed to assess the effects of nutritional supplements on the course of AMD in people at moderate-to-high risk of progression to late AMD. Eligibility included participants with bilateral intermediate AMD or advanced AMD in one eye.¹⁹ The primary outcome of the study was development of late AMD, defined as either center-involved GA or neovascularization. Digital color fundus photographs taken at baseline and annual visits were sent to the AREDS2 Reading Center (University of Wisconsin Fundus Photograph Reading Center, Madison, WI) for evaluation. During the second year of the study, an FAF ancillary study was added and FAF images were submitted by a subset of clinical sites at annual visits along with the color photographs. Sites were permitted to join the FAF ancillary study over the course of the study period. This report compares results from the AREDS2 FAF ancillary study with temporally coincident stereoscopic color fundus photographs in eyes with GA. We report findings on cross-sectional and longitudinal comparisons of GA area measurements from color photographs and corresponding FAF images.

Methods

The study design and subject characteristics are detailed in AREDS2 Report number 1.¹⁹ The study was conducted under the Declaration of Helsinki and approved by institutional review boards at all participating clinics. Written informed consent was obtained from all study participants.

Digital stereoscopic color photographs of AREDS2 participants were obtained by certified photographers and sent to the AREDS2 Reading Center for evaluation. Evaluation of color photographs was performed by certified and trained graders with no access to any other visits, imaging modalities including FAF images, visual acuity scores or other medical data. The details of the imaging protocol and evaluation methods using color photographs is described elsewhere.²⁰ In brief, calibrated stereoscopic images were viewed in a standardized digital viewing platform (ImageNet 2000, Topcon Corp) after color contrast and illumination adjustment.²¹ GA from color photographs was defined as a lesion equal to or larger than drusen circle I-2 (diameter 430 μ , area 0.15 mm²) in its widest diameter with at least two of the following features present: circular shape, sharp (well-demarcated) edges, and loss of the retinal pigment epithelium (RPE) (partial or complete depigmentation of the RPE, typically with exposure of underlying choroidal vessels). Planimetry tools were used to demarcate the area of GA within the AREDS grid. If non-central, distance of the proximity of the atrophy border closest to the center was documented.

FAF images were obtained from Heidelberg Retinal Angiograph (HRA, Heidelberg, Germany) instruments or fundus cameras with FAF capability (outfitted with the appropriate excitation and barrier filters) by certified operators. A single image was acquired at 30° centered on the macula (Field 2). The images from HRA were captured in high speed mode (768 $\times$ 768 pixels) using the Automatic Real Time Mean (ART Mean) function set at 14. Colors were taken before FAF images to precipitate photoreceptor pigment bleaching.²² All images were viewed in the same software to standardize the evaluation for color photographs, fundus camera based FAF images and HRA based FAF images. Hypo-autofluorescence was classified as well-defined, homogeneously black areas with a minimum size of drusen circle I-2 in its widest diameter. Areas of hypo-autofluorescence were demarcated using software planimetry tools. Areas were summed for eyes with multifocal GA to yield a single value for analysis. Involvement of macula by the hypo-autofluorescent lesion was also noted. The macula was considered involved if the nearest border of hypo – autofluorescence was within 200 microns of the center of the macula. In Heidelberg images, the macula was assumed to be involved if the hypoautofluorescent patch merged with the darkness of the macula and there was no clear region demarcating the two. Halo was defined as presence of hyperautofluorescence surrounding at least 10% of the perimeter of the area of hypoautofluorescence. Areas of non-uniform autofluorescence surrounding the area of hypoautofluorescence within the grid were also measured using planimetry. Irregular background autofluorescence was identified as a mix of both increased and decreased autofluorescence changes occurring outside the grid. FAF evaluations were performed by the trained and certified graders with no direct comparison of corresponding color photographs and FAF images or data. Figure 1 demonstrates the results for GA area using planimetry in color photographs and FAF images.

Statistical Analysis

For the purpose of this report, the visit at which GA was first evaluated on both color and FAF image was considered the “baseline” visit. Eyes with at least 2 or more annual follow up visits were included for growth rate analysis. Eyes with neovascular AMD and/or poor image quality were excluded. Intergrader variability was assessed using an ongoing masked regrading of 5% of images throughout the study period. All statistical analysis was performed using SAS software (Version 9.3, SAS Institute Inc, Cary, NC).

Results

The AREDS2 included 4203 participants with annual color photos over 5 years. The FAF ancillary study included 5048 eyes (2,524 AREDS2 participants) with follow up varying from 2-6 years. The cumulative FAF images evaluated across all visits for the study were 12,158. After excluding images with neovascular AMD (2954 images) and poor image quality (404 images), corresponding color photographs and FAF images were available for 8070 visits (2202 participants). Abnormal autofluorescence (hyper and/or hypoautofluorescence) was visible in 7620 (94%) FAF images. GA was present on color in 1693 (21%) eyes and hypoautofluorescence was visible in 2048 (25%) eyes, kappa 0.79 (CI 0.78 – 0.81) (table 1). This distribution of presence and absence of GA from color compared to presence/ absence of hypoautofluorescence was similar across all visits. Agreement on presence of GA between the two modalities was 76.8 % with more eyes showing hypoautofluorescence on the FAF images without corresponding GA found on color photographs. When compared across follow-up, agreement of color photographs and FAF images for presence of GA improved from 42.9 % at baseline to 80.9% at year 5 (Figure 2).

In eyes with GA present on both modalities at baseline (n = 860 eyes), mean area of GA on color photographs was 5.5 mm² (SD 6.4) and FAF images 6.0 mm² (SD 6.8). The mean difference in area of GA between the two modalities was 0.5 mm² (SD 2.6) (p 0.97) with FAF area being larger than color. This difference remained consistent through all follow-up visits (Figure 3).

There was no significant difference in the change in area between the two modalities over the follow-up period (Figure 4). Change in area of GA was 1.45mm²/year (SE 0.06) with color photos and 1.43 mm²/ year (SE 0.06) with FAF images. Change in area of GA with square root transformation was 0.30 mm/year for colors and 0.29 mm/ year for FAF images.

Involvement of the center of the macula was compared between the two modalities in 1570 visits with GA present on both modalities. Agreement on involvement of center of macula was substantial between the two modalities (kappa 0.72, 95% CI 0.68, 0.75). Macula was involved in 51% of color photos and 56% of FAF images as shown in table 2. Almost 18% of eyes that had involvement of center of macula on FAF images did not involve the macula on color photos.

Among the 601 eyes regraded for intergrader variability, the mean difference in area of hypoautofluorescence was 0.02 (CI –0.36, 0.32) mm². Intergrader variability for color photos for

measurement of GA has been previously published as a mean difference of 0.02 (CI -1.76, 1.8) mm².²⁰

Discussion

The results from the AREDS2 ancillary study evaluating GA from color photos and corresponding FAF images shows that estimation of area change is not significantly different between the two modalities: 1.45 mm²/year with color images and 1.43 mm²/year with FAF images. These rates are comparable to other published results.^{10,15,16,23}

In AREDS2 data, area measurements between color and FAF measurements are consistent over all visits, with a mean difference of 0.5mm² and FAF measurements being larger than color photograph. Khanifar et al measured GA from colors and FAF images in 72 eyes and found the difference between the two measurements to be close to zero.²⁴ They measured GA areas larger on color photographs than on FAF for larger areas of atrophy and GA areas smaller with color photographs than on FAF for smaller areas of GA. We did not notice this trend in our dataset. In contrast, the GAP study showed that FAF measurements were significantly smaller than GA areas from colors but highly correlated at all visits.¹⁵ The two imaging modalities in the GAP study were assessed by different reading centers, using different display and analysis software. The FAF measurements were performed by a semi automated method compared to manual planimetry used in this study. Algorithm based measurements outline the contours of the atrophic lesion in a precise manner compared to manual planimetry where irregular edges might be rounded off. The methodological differences between the GAP study and the AREDS2 FAF project make direct comparison of the results between studies problematic.

Semi-automated methods have been developed and used for measuring area of hypo-autofluorescence in FAF images.^{25,26} However, semi-automated analysis of FAF areas is commercially available for Heidelberg instruments only. To be inclusive of optical fundus cameras and to standardize the method between all modalities, we employed manual planimetry for all imaging modalities. In this dataset, measurements from FAF images are generally larger than those from color photos at all visits.

Almost 25% of eyes with hypo-autofluorescence did not have corresponding GA. With independent grading, hypo-autofluorescence patches that may not correspond to GA in color are included in the area of hypo-autofluorescence. A sample of images with a difference of >1 mm² in area between color and FAF images at both baseline and year 2 were reexamined to look for reasons for the difference. Reasons for the discrepancy were hypo-autofluorescence not corresponding to GA in color photos (42%), variation in border delineation (38 %), differences due to poor photo quality (7%) and discrepancy in involvement of center of macula(4%). The two modalities appear to reflect related but different phenomena, and are not interchangeable measurements in a clinical trial. A common presentation of GA is that additional foci appear over time. Areas of hypoautofluorescence emerge earlier than GA on colors, thereby increasing the relative area measurement. An additional concern with evaluating FAF images is that hypo-autofluorescence is not specific for GA.^{14,27} Drusen and depigmentation may also present

with changes in FAF images. The term ‘nascent GA’ has been used to characterize these changes on optical coherence tomography.²⁸ Agreement on presence between the two modalities improves over time from 45% at baseline to 75% by year 2, indicating that GA probably presents earlier on FAF images than color photographs. In most clinical trials for GA, the inclusion criteria ensure that there is good agreement on presence of GA between all modalities being used. The AREDS2 study primarily included eyes with intermediate AMD where autofluorescence changes are seen before development of GA. This disagreement can play an important role in clinical trials for early or intermediate AMD where the modality for identifying both inclusion criteria and primary outcomes needs to be clearly identified. No large studies comparing GA by color photographs and hypo-autofluorescence have defined relative sensitivity for clinical outcomes. Figure 5 demonstrates corresponding color and FAF images with discrepant area measurements.

Sunness *et al.* reported difficulties with the evaluation of GA in film color photographs, such as problems identifying the center of the macula for grid placement and defining the borders of GA in lightly pigmented fundi and suggested that measurement of GA employ other imaging modalities in addition to color photos.⁴ While FAF and color photographs were evaluated independently in this study, we agree that having both imaging types evaluated at the same time is likely to produce a more informed and consistent measurement. Even with the use of digital tools, the evaluation of GA remains difficult. Image quality enhancements have helped overcome some of the digital photographic issues seen in prior studies.²¹ Optimizing the tonal balance of digital images improves the definition of borders of GA especially where red over-saturation is an issue. Defining the margins of hypo-autofluorescent patches in good quality FAF images is generally easier than defining GA in color photos due to the high contrast between the area of hypo-autofluorescence and surrounding retina.²⁹ The wide availability of fundus cameras and the vast experience most photographers have with fundus cameras is one of the biggest advantages of stereoscopic color fundus photography. In the AREDS2 FAF ancillary study conducted between 2007 and 2012, less than half the sites had FAF imaging capability; 36 of 90 sites enrolled had a Heidelberg camera and 4 had a fundus camera with FAF capabilities.

Based on natural history studies, GA usually forms at a non-central location, and in many eyes eventually involves the center.^{7,30-32} Central involvement by atrophy significantly impairs central visual acuity, and thus is an important outcome measure for clinical trials.³³ Optical coherence tomography (OCT) scanning is the modality of choice for identifying involvement of fovea.³⁴ The normal marked hypo-autofluorescence seen in SLO FAF images at the center of the macula is sometimes difficult to distinguish from hypo-autofluorescent lesions threatening or at the center due to the merging of the lesion with the dark blocked fluorescence of the macula as shown in Figure 1. In such cases, the AREDS2 reading center methodology for FAF grading assumes that the center of the macula is involved. This is a potential reason for the discrepancies in central involvement between color and FAF images in this dataset, in which more cases (about 20% more) of center involvement were found on FAF images than on color photos. Fundus camera based FAF images do not have blocked autofluorescence at macula making identification of involvement of center of macula more accurate.³⁵

In a digitized color photograph dataset in AREDS, the average difference in GA measurement area between two reading centers was 0.14 mm^2 .¹⁰ The Fundus Autofluorescence in Age related Macular Degeneration (FAM) Study Group has published reproducibility of measurements of hypo-autofluorescence via planimetry, with mean differences of 0.39 mm^2 between graders and of -0.03 mm^2 between two passes of a semi-automated image analysis algorithm.³⁶ In the AREDS2 data set, the mean differences between graders was 0.02 mm^2 for both color and FAF images, but the inter-grader variation was greater with color photographs.

The images acquired in the AREDS2 study are from large clinical centers with experienced and certified photographers. The images were all acquired and graded using a common method. Despite variable follow up, this is a large dataset with at least one follow up visit in more than 300 eyes. Weaknesses of this study include lack of fluorescein angiography or OCT to confirm presence and boundaries of GA and the absence of choroidal neovascular membrane in the study eyes. We included many bilateral cases of GA and did not analyze our data with respect to relatedness between eyes. Since development of GA was a study outcome, the majority of eyes had recent development of GA which accounts for the relatively smaller mean baseline area.

Conclusion

Area measurements by digital planimetry of GA from color photographs and FAF images are very reproducible and highly correlated. Analysis of change in area of GA between the two modalities is also comparable. FAF possibly displays GA earlier than color photos, yielding slightly larger areas, and therefore area measurements of GA from color photos and FAF images are not interchangeable. Evaluation of GA area from FAF images requires a complementary image to confirm the presence and foveal localization of GA. Progression to involvement of center of macula is difficult to assess in SLO based FAF images due to blockage of the autofluorescence signal from luteal pigments.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. Resnikoff S, Pascolini D, Etya'ale D, et al. Global data on visual impairment in the year 2002. Bulletin of the World Health Organization. 2004; 82:844–51. [PubMed: 15640920]
2. The Eye Diseases Prevalence Research Group. Prevalence of Age-Related Macular Degeneration in the United States. Arch Ophthalmol. 2004; 122:564–72. [PubMed: 15078675]
3. Sunness JS, Rubin GS, Broman A, Applegate CA, Bressler NM, Hawkins BS. Low luminance visual dysfunction as a predictor of subsequent visual acuity loss from geographic atrophy in age-related macular degeneration. Ophthalmology. 2008; 115:1480–8. 8.e1–2. [PubMed: 18486216]
4. Sunness J, Bressler N, Tian Y, Alexander J, Applegate C. Measuring geographic atrophy in advanced age-related macular degeneration. Invest Ophthalmol Vis Sci. 1999; 40:1761–9.
5. Sunness JS. The natural history of geographic atrophy, the advanced atrophic form of age-related macular degeneration. Mol Vis. 1999; 5:25. [PubMed: 10562649]

6. Sunness JS, Applegate CA, Bressler NM, Hawkins BS. Designing clinical trials for age-related geographic atrophy of the macula: enrollment data from the geographic atrophy natural history study. *Retina*. 2007; 27:204–10. [PubMed: 17290203]
7. Sunness JS, Gonzalez-Baron J, Applegate CA, et al. Enlargement of atrophy and visual acuity loss in the geographic atrophy form of age-related macular degeneration. *Ophthalmology*. 1999; 106:1768–79. [PubMed: 10485549]
8. Sunness JS, Margalit E, Srikumaran D, et al. The long-term natural history of geographic atrophy from age-related macular degeneration: enlargement of atrophy and implications for interventional clinical trials. *Ophthalmology*. 2007; 114:271–7. [PubMed: 17270676]
9. Klein R, Meuer SM, Knudtson MD, Klein BE. The epidemiology of progression of pure geographic atrophy: the Beaver Dam Eye Study. *Am J Ophthalmol*. 2008; 146:692–9. Epub 2008 Jul 30. [PubMed: 18672224]
10. Lindblad AS, Lloyd PC, Clemons TE, et al. Change in area of geographic atrophy in the Age-Related Eye Disease Study: AREDS report number 26. *Arch Ophthalmol*. 2009; 127:1168–74. [PubMed: 19752426]
11. Petrou PA, Cunningham D, Shimel K, et al. Intravitreal sirolimus for the treatment of geographic atrophy: results of a phase I/II clinical trial. *Invest Ophthalmol Vis Sci*. 2015; 56:330–8.
12. Yehoshua Z, de Amorim Garcia Filho CA, Nunes RP, et al. Comparison of Geographic Atrophy Growth Rates Using Different Imaging Modalities in the COMPLETE Study. *Ophthalmic Surg Lasers Imaging Retina*. 2015; 46:413–22. [PubMed: 25970861]
13. The Age-Related Eye Disease Study Research Group. The Age-Related Eye Disease Study system for classifying age-related macular degeneration from stereoscopic color fundus photographs: the Age-Related Eye Disease Study Report Number 6. *Am J Ophthalmol*. 2001; 132:668–81. [PubMed: 11704028]
14. von Ruckmann A, Fitzke FW, Bird AC. Fundus autofluorescence in age-related macular disease imaged with a laser scanning ophthalmoscope. *Invest Ophthalmol Vis Sci*. 1997; 38:478–86. [PubMed: 9040481]
15. Schmitz-Valckenberg S, Sahel JA, Danis R, et al. Natural History of Geographic Atrophy Progression Secondary to Age-Related Macular Degeneration (Geographic Atrophy Progression Study). *Ophthalmology*. 2015
16. Bearely S, Khanifar AA, Lederer DE, et al. Use of fundus autofluorescence images to predict geographic atrophy progression. *Retina*. 2011; 31:81–6. [PubMed: 20890245]
17. Holz FG, Bindewald-Wittich A, Fleckenstein M, Dreyhaupt J, Scholl HP, Schmitz-Valckenberg S. Progression of geographic atrophy and impact of fundus autofluorescence patterns in age-related macular degeneration. *Am J Ophthalmol*. 2007; 143:463–72. [PubMed: 17239336]
18. Batio lu F, Demirel S, Özmert E. Fundus autofluorescence imaging in age-related macular degeneration. *Semin Ophthalmol*. 2015; 30:65–73. [PubMed: 23952079]
19. Chew EY, Clemons T, SanGiovanni JP, et al. The Age-related Eye Disease Study 2 (AREDS2) Study Design and Baseline Characteristics (AREDS2 Report Number 1). *Ophthalmology*. 2012; 119:2282–9. [PubMed: 22840421]
20. Danis RP, Domalpally A, Chew EY, et al. Methods and Reproducibility of Grading Optimized Digital Color Fundus Photographs in the Age-Related Eye Disease Study 2 (AREDS2 Report Number 2). *Investigative Ophthalmology & Visual Science*. 2013; 54:4548–54. [PubMed: 23620429]
21. Hubbard LD, Danis RP, Neider MW, et al. Brightness, contrast, and color balance of digital versus film retinal images in the age-related eye disease study 2. *Invest Ophthalmol Vis Sci*. 2008; 49:3269–82. [PubMed: 18421079]
22. Delori FC, Dorey CK, Staurengi G, Arend O, Goger DG, Weiter JJ. In vivo fluorescence of the ocular fundus exhibits retinal pigment epithelium lipofuscin characteristics. *Invest Ophthalmol Vis Sci*. 1995; 36:718–29. [PubMed: 7890502]
23. Holz FG, Bindewald-Wittich A, Fleckenstein M, et al. Progression of geographic atrophy and impact of fundus autofluorescence patterns in age-related macular degeneration. *Am J Ophthalmol*. 2007; 143:463–72. [PubMed: 17239336]

24. Khanifar AA, Lederer DE, Ghodasra JH, et al. Comparison of color fundus photographs and fundus autofluorescence images in measuring geographic atrophy area. *Retina*. 2012; 32:1884–91. [PubMed: 22547167]
25. Deckert A, Schmitz-Valckenberg S, Jorzik J, Bindewald A, Holz F, Mansmann U. Automated analysis of digital fundus autofluorescence images of geographic atrophy in advanced age-related macular degeneration using confocal scanning laser ophthalmoscopy (cSLO). *BMC Ophthalmology*. 2005; 5:8. [PubMed: 15813972]
26. Fleckenstein M, Adrion C, Schmitz-Valckenberg S, et al. Concordance of Disease Progression in Bilateral Geographic Atrophy Due to AMD. *Invest Ophthalmol Vis Sci*. 2010; 51:637–42. [PubMed: 19797219]
27. Sunness JS, Ziegler MD, Applegate CA. Issues in quantifying atrophic macular disease using retinal autofluorescence. *Retina*. 2006; 26:666–72. [PubMed: 16829810]
28. Wu Z, Luu CD, Ayton LN, et al. Fundus autofluorescence characteristics of nascent geographic atrophy in age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 2015; 56:1546–52. [PubMed: 25678689]
29. Schmitz-Valckenberg S, Fleckenstein M, Scholl HP, Holz FG. Fundus autofluorescence and progression of age-related macular degeneration. *Surv Ophthalmol*. 2009; 54:96–117. [PubMed: 19171212]
30. Sunness JS, Applegate CA, Haselwood D, Rubin GS. Fixation patterns and reading rates in eyes with central scotomas from advanced atrophic age-related macular degeneration and Stargardt disease. *Ophthalmology*. 1996; 103:1458–66. [PubMed: 8841306]
31. Sunness JS, Bressler NM, Maguire MG. Scanning laser ophthalmoscopic analysis of the pattern of visual loss in age-related geographic atrophy of the macula. *Am J Ophthalmol*. 1995; 119:143–51. [PubMed: 7530408]
32. Maguire P, Vine AK. Geographic atrophy of the retinal pigment epithelium. *Am J Ophthalmol*. 1986; 102:621–5. [PubMed: 3777083]
33. Sunness JS, Rubin GS, Applegate CA, et al. Visual function abnormalities and prognosis in eyes with age-related geographic atrophy of the macula and good visual acuity. *Ophthalmology*. 1997; 104:1677–91. [PubMed: 9331210]
34. Forte R, Querques G, Querques L, Leveziel N, Benhamou N, Souied EH. Multimodal evaluation of foveal sparing in patients with geographic atrophy due to age-related macular degeneration. *Retina*. 2013; 33:482–9. [PubMed: 23400084]
35. Schmitz-Valckenberg S, Fleckenstein M, Gobel AP, et al. Evaluation of autofluorescence imaging with the scanning laser ophthalmoscope and the fundus camera in age-related geographic atrophy. *Am J Ophthalmol*. 2008; 146:183–92. Epub 2008 Jun 2. [PubMed: 18514607]
36. Schmitz-Valckenberg S, Jorzik J, Unnebrink K, Holz FG. Analysis of digital scanning laser ophthalmoscopy fundus autofluorescence images of geographic atrophy in advanced age-related macular degeneration. *Graefes Arch Clin Exp Ophthalmol*. 2002; 240:73–8. [PubMed: 11933894]

Précis

Geographic atrophy (GA) is reliably measured using both color photographs and fundus autofluorescence (FAF) images with comparable measurements and change in area over time. FAF images may detect GA earlier than color photographs.

Figure 1.

Color photograph and corresponding autofluorescence (FAF) image with AREDS grid overlay and planimetry outline of geographic atrophy (GA). The center of the macula is just involved in the color photograph whereas the hypoautofluorescence merges with the darkness of the fovea in the FAF image. The area of GA is 7.43 mm^2 with color photographs and 7.36 mm^2 with FAF image.

Figure 2. Agreement on presence of Geographic Atrophy (GA) between color photographs and autofluorescence (FAF) images at baseline and followup visits.

Figure 3. Mean area of Geographic Atrophy (GA) from color photographs (blue) and FAF images (red) at baseline and followup visits. Error bars represent standard deviation.

Figure 4.
Change in area of Geographic Atrophy (GA) over time as measured from color photographs (blue) and FAF images (red)

Figure 5. Corresponding color photographs and FAF images at baseline (BL) and 4 year follow-up. FAF images show a small area of hypoautofluorescence at BL and no GA visible on corresponding color photograph. GA is present in both modalities from year 1 (Y1) onwards with FAF measuring slightly larger than color photographs.

Table 1

Cross tabulation of evaluation of presence of Geographic Atrophy (GA) from color photographs and autofluorescence images

Geographic Atrophy	Fundus Autofluorescence images				Total	
Color Fundus Photographs	GA absent		GA present			
GA absent	5901	98.0%	476	23.2%	6377	79.1%
GA present	121	2.0%	1572	76.8%	1693	20.9%
Total	6022	74.6%	2048	24.4%	8070	

Table 2

Cross tabulation of evaluation of involvement of center of macula with Geographic Atrophy (GA) from color photographs and fundus autofluorescence images

Fundus Autofluorescence images						
Color Fundus Photographs	GA macula not involved		GA macula involved		Total	
GA macula not involved	621	90.3%	155	17.6%	776	49.4%
GA macula involved	67	9.7%	727	82.4%	794	50.6%
Total	688	43.8%	882	56.2%	1570	