



Natural History of Autosomal Recessive Stargardt Disease in Untreated Eyes

A Systematic Review and Meta-analysis of Study- and Individual-Level Data

Liangbo L. Shen, BS,¹ Mengyuan Sun, BS,² Holly K. Grossetta Nardini, MLS,³ Lucian V. Del Priore, MD, PhD¹

Topic: Systematic review and meta-analysis of the natural history of autosomal recessive Stargardt disease (STGD1).

Clinical Relevance: Controversy exists regarding the progression pattern of atrophic lesions secondary to STGD1, and the reported growth rates vary widely among studies.

Methods: We searched in 6 literature databases up through March 15, 2019, to identify studies that monitored atrophy progression by fundus autofluorescence in untreated eyes with STGD1 for 6 months or more. We analyzed both study- and individual-level data from the included studies using 3 models: the area linear model (ALM), radius linear model (RLM), and area exponential model (AEM), in which the area, radius, and natural log-transformed area changes linearly with time, respectively. A horizontal translation factor was added to each dataset to correct for different participants' entry times into the studies. The best model was determined by the predicted age of lesion onset and dependence of growth rates on baseline lesion sizes. The risk of bias was assessed using the Newcastle-Ottawa scale.

Results: Of 3158 articles screened, 7 studies (564 eyes) met our inclusion criteria. Cumulative study- and individual-level datasets fit along a straight line in the RLM after introducing horizontal translation factors to correct for different entry times ($r^2 = 0.99$ and $r^2 = 0.93$, respectively). The growth rate of effective lesion radius was 0.104 mm/year (95% confidence interval, 0.086–0.123 mm/year). The age of atrophy onset predicted by the RLM (22.7 ± 5.0 years) was comparable to the reported age at onset of symptoms (22.1 ± 3.1 years); in contrast, the predictions by the ALM and AEM deviated from this number by more than 5 years. Based on the individual-level data, the effective radius growth rate was independent of the baseline lesion size ($r = 0.06$); in comparison, the growth rates of area and natural log-transformed area were significantly dependent on the baseline lesion size ($r = 0.47$ and $r = -0.33$, respectively).

Conclusions: The progression of STGD1 lesions followed the RLM in both study- and individual-level data. The effective radius growth rate of atrophic lesions could serve as a reliable outcome measure to monitor STGD1 progression. *Ophthalmology* 2019;126:1288–1296 © 2019 by the American Academy of Ophthalmology



Supplemental material available at www.aaojournal.org.

Autosomal recessive Stargardt disease (STGD1) is the most common form of juvenile-onset inherited macular dystrophy.^{1,2} It is associated most commonly with mutations in the *ABCA4* gene¹ and generally is characterized by macular atrophy with or without fundus flecks at the level of the retinal pigment epithelium (RPE).³ Although no major pharmaceutical regulatory agencies in Europe, the United States, or Japan have approved therapies to reverse STGD1, many treatment options are being explored in early phases of clinical trials.^{3,4,5} Therefore, it is important to establish a reliable and sensitive measure to monitor the disease's progression.

One such measure that has been used widely to monitor disease progression is visual acuity.^{6–11} However, this parameter has been found inadequate to capture the

progression of STGD1.⁶ Thus, several studies have chosen the change rate of atrophic lesions as a clinical end point, which can be assessed by several imaging methods including fundus autofluorescence (FAF), color fundus photography, and OCT.^{6–14} However, even using these objective techniques, there is significant disagreement over the progression pattern of atrophic lesions, and lesion growth rates vary widely among different studies. For example, studies using FAF have reported mean growth rates that vary widely from 0.39 to 1.84 mm²/year.^{11,14}

To date, 3 models have been proposed and used in the literature to characterize lesion growth rates (Table S1, available at www.aaojournal.org). The first and most widely used model assumes a linear relationship between

lesion area and elapsed time.^{6–14} If this is the case, the expansion rate of lesion area is the outcome measure because it would always remain constant as the lesion enlarges and would remain independent of baseline lesion size. The second model proposes that the effective radius (square root of [lesion area / π]) of lesions grows linearly with time, and the corresponding outcome measure is the rate of change of the effective radius of the equivalent lesion area.^{9,15} The progression of RPE atrophy secondary to geographic atrophy (GA) in age-related macular degeneration (AMD) has been found to fit this model well.^{16,17} The third model is an exponential model in which lesion area grows exponentially as a function of elapsed time, and the outcome measure is the percent change of lesion area or the change rate of the log-transformed area.^{7,12,18} Although all 3 types of outcome measures have been used in previous studies, evidence and opinions currently are mixed regarding which model best describes lesion progression. A recently published retrospective study suggests that none of the above 3 models is the best and proposes a linear mixed model stratified by initial lesion size with a cutoff of 1.92 mm².¹⁰ Herein, we report the results of a meta-analysis performed of both study- and individual-level data to determine which model best describes the progression pattern of atrophic lesions in STGD1 disease.

Methods

This meta-analysis was reported in accordance with the Meta-analysis of Observational Studies in Epidemiology checklist (Table S2, available at www.aaojournal.org).¹⁹ The study adhered to the tenets of the Declaration of Helsinki. Because this was a systematic review article with meta-analyses of published studies and does not involve human subjects, no informed consent from patients was needed.

Sources and Search Methods

A senior medical librarian (H.K.G.N.) advised on methodology and performed a comprehensive search using controlled vocabulary terms and synonymous free-text words plus the relevant gene name to capture the concepts of *Stargardt* and *natural history*. All databases were searched up through March 15, 2019: MEDLINE, Ovid Embase, Web of Science Core Collection, clinicaltrials.gov, PubMed, and Google Scholar (first 200 hits). We did not restrict the study type, language, or publication date. The search strategy is detailed in Appendix 1 (available at www.aaojournal.org), and a full search strategy for Ovid MEDLINE is included in Appendix 2 (available at www.aaojournal.org). A flowchart per Preferred Reporting Items for Systematic Reviews and Meta-Analyses is presented in Figure S1 (available at www.aaojournal.org).²⁰

Selection Criteria

The inclusion criteria were as follows: (1) a group of patients diagnosed with STGD1 in 1 or both eyes without any treatment, (2) assessed atrophic lesion area by FAF, and (3) reported atrophic lesion size on at least 2 occasions 6 months or more apart. In the present study, the inclusion criteria for the diagnosis of STGD1 were as follows: patients with fundus examination results consistent with STGD1 plus either an autosomal recessive inheritance pattern in the family history or 1 or more *ABCA4* gene mutations shown in genetic testing. The articles with the largest and most

recent datasets were selected in the event of multiple publications derived from an overlapping study population.

Data Collection and Study Quality

Two reviewers (L.L.S. and M.S.) independently screened all records found in the literature search and resolved disagreements through discussion. For each included study, the 2 reviewers independently extracted data regarding study quality, demographic characteristics, best-corrected visual acuity (BCVA; units converted to logarithm of the minimum angle of resolution), and atrophic lesion sizes and growth rates (mean, standard error, and standard deviation). Besides the study-level data, the 2 reviewers also extracted lesion progression data in individual eyes from eligible studies. Extrapolations of lesion sizes were necessary for some studies, as detailed in Table S3 (available www.aaojournal.org). The risk of bias and quality of studies were assessed by the 2 reviewers using the Newcastle-Ottawa scale.²¹ Disputes between the reviewers were resolved through discussion until they reached a consensus.

Data Synthesis and Statistical Analysis

We performed the statistical analysis using MATLAB software (The MathWorks, Inc, Natick, MA) and R software version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria). To determine the pattern of atrophic lesion expansion, we compared 3 progression models using both study- and individual-level data: the area linear model (ALM), the radius linear model (RLM), and the area exponential model (AEM), in which the area, radius, and natural log-transformed area changes linearly with time, respectively. Because most studies did not report the lesion radius, we estimated the effective lesion radius in each study as the square root of (lesion area / π). For the ALM and RLM, the atrophic lesion area was defined as 0 mm² at the onset. Because the value on the vertical axis of an exponential model never reaches 0, we defined the atrophic lesion area at onset as 0.05 mm² for the AEM (similar to the predefined minimum lesion size in previous studies¹⁰). For each model, we first plotted lesion size (area, effective radius, or natural log-transformed area) as a function of time after enrollment for all included studies. To correct for the differences in patients' entry time into the clinical studies, we added a horizontal translation factor (in years) to each dataset, which essentially converts the horizontal axis from *time after enrollment* to *inferred duration of atrophy*, where (inferred duration of atrophy = time after enrollment + translation factor). Time 0 on the inferred duration of atrophy axis represents the time of atrophy onset. To find the optimal translation factor for each dataset, we adjusted each translation factor 1 month at a time within a range of 10 years and repeated this process iteratively for all reasonable combinations of translation factors until we found the combination that maximized r^2 for the trend line of the combined datasets.^{16,22–26}

To determine the predictive performance of each model, we calculated each model's predicted age at onset of atrophic lesion based on study-level data by subtracting the optimized translation factor from the reported mean age in each included study. Then, we performed a paired *t* test to compare the predicted ages of atrophy onset by each model with the reported ages at onset in the included studies (usually reported as the age at onset of visual symptoms). To determine the goodness of fit for each model, we investigated the dependence of growth rate (square millimeters per year, millimeters per year, or log-transformed area per year) on the baseline lesion size using individual-level data using Pearson correlation coefficients (*r* values).

After determining the best model to describe the natural enlargement of atrophic lesions in STGD1, we performed a random-effects meta-analysis using the metafor package²⁷ in R

software to determine the mean and 95% confidence interval (CI) of the growth rate of atrophic lesions. Heterogeneity in meta-analysis refers to the inconsistency of the outcomes between studies and was assessed by the I^2 statistic.²⁸ A low I^2 suggests very little variation in the outcomes between different studies. In addition, we performed a sensitivity analysis by removing one study at a time and repeated the random-effects meta-analysis to assess whether a single study influenced the lesion growth rate significantly. We also investigated the impact of potential confounding factors (study type and inclusion criteria) by comparing the lesion growth rates in different subgroups using unpaired 2-tailed t tests.

Results

Database and Study Quality

The final search retrieved 3158 records after deduplication. The screening comprised 2 stages. The first stage was to screen by title and abstract, and we excluded 3111 records for irrelevance in the first step. The common reasons for the exclusions included wrong types of studies (e.g., review articles, case reports, and animal studies), wrong patient populations (e.g., patients receiving treatment and patients with other diseases, including AMD, retinitis pigmentosa, and infectious eye diseases), no assessment of atrophic lesion size, no follow-up data on lesion size, or lesion size not assessed by FAF. In the second stage, we screened by full text for the remaining articles and excluded another 39 articles (reasons for exclusions are listed in Table S4, available at www.aaojournal.org). In the end, we identified and included 8 articles representing 7 independent studies (564 unique eyes from 428 patients) meeting our inclusion criteria (see the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart in Fig S1). We listed the included 7 studies in Table S3.

We extracted study-level data from all 7 included studies and extracted individual-level data regarding the progression of atrophic lesions in 228 eyes from 5 studies (raw data shown in Fig S2, available at www.aaojournal.org). Among the included 7 studies, the mean follow-up length ranged from 1.0 to 9.1 years. The reported mean age at onset of visual symptoms ranged from 19 to 26.9 years, and the mean age at study baseline ranged from 22.5 to 50 years. The detailed descriptive information of the included studies is shown in Table S3. Newcastle-Ottawa scale scores of the included studies were between 6 and 8 (8 being the highest possible score in our study), with a mean of 7.4 (Table S5, available at www.aaojournal.org), suggesting good qualities of the studies.

The Radius Linear Model Fits the Lesion Progression Based on Study-Level Data

Figure 3A shows the mean $\pm$ standard error of the atrophic lesion area as a function of time in 7 studies. Note that the initial lesion sizes vary widely among different studies and that the slopes (i.e., area growth rates) of datasets appear to increase with increasing baseline lesion sizes (Fig 3A). By converting lesion area to the effective lesion radius in Figure 3B, we found that the datasets still had different initial lesion sizes, but that the lines became more parallel to one another. After introducing a horizontal translation factor (Table 3) to each study, the effective lesion radius fit along a straight line as a function of inferred duration of atrophy (i.e., the RLM) with a very high r^2 value of 0.99 (compare Fig 3B with Fig 3C).

In Figure 4, the age at onset of atrophic lesion predicted by the RLM (22.7 ± 5.0 years) was remarkably similar to the reported age at onset from the studies (22.1 ± 3.1 years; $P = 0.77$). However, the predictions by the ALM (29.3 ± 5.5 years) and AEM (5.6 ± 4.4 years) deviated from the reported values by more than 5 years ($P = 0.02$ and $P < 0.001$, respectively). Thus, the RLM

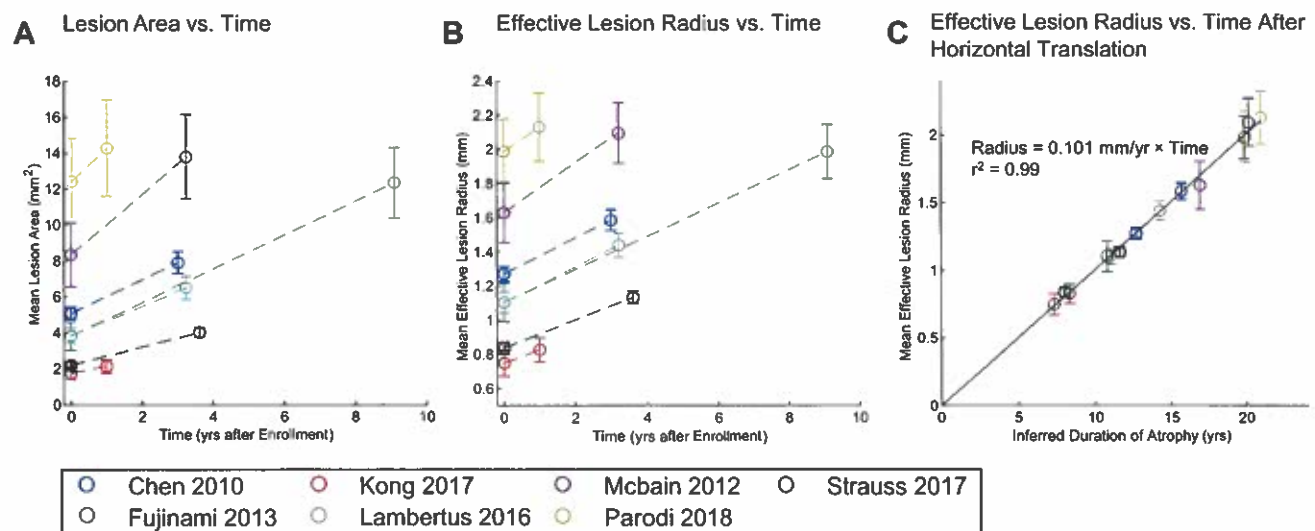


Figure 3. Graphs showing lesion size as a function of time using study-level data. **A**, Reported study-level raw data from prior publications (error bars = standard errors). The plot shows a series of lines for atrophic lesion progression in untreated eyes with Stargardt disease 1; note that the initial size of the lesion (time = 0) varies among different studies and that the slopes (i.e., area growth rates) of datasets appear to increase with increasing baseline lesion sizes (on the y-axis). **B**, Data generated by converting lesion area (in square millimeters) in (A) to effective lesion radius (millimeters) using square root of (lesion area / π); note that the lines appear to be more parallel to one another. **C**, Data generated by adding a horizontal translation factor (expressed in years in Table S3) to each dataset in (B) to correct for different entry times of patients into each study. Horizontal axis now represents duration of disease rather than years after enrollment into trial. After the introduction of horizontal translation factors, datasets from all 7 studies fit along a straight line in the radius linear model with growth in the lesion radius of 0.101 mm/year ($r^2 = 0.99$).

demonstrated the best predictive performance among all 3 models based on the study-level data.

The Radius Linear Model Fits the Lesion Progression Based on Individual-Level Data

Figure 5A shows that the baseline lesion sizes in 228 individual eyes varied widely, suggesting that these represent different time points in the course of the disease. However, after correcting for different baseline lesion sizes by introducing horizontal translation factors to each dataset, the effective lesion radius fit along a straight line versus the inferred duration of atrophy (i.e., the RLM) with a high r^2 value of 0.93 (compare Fig 5A with Fig 5B). In Figure 6B, we found that the radius growth rate did not correlate significantly with the baseline lesion size ($r = 0.06$; $P = 0.37$), further suggesting the good fit of the RLM. However, in the ALM and AEM, the growth rates correlated significantly with the baseline lesion size ($r = 0.47$ and $P < 0.001$ for the ALM; $r = -0.33$ and $P < 0.0001$ for the AEM), suggesting poor fits (Fig 6A, C).

Estimated Growth Rates of Lesions

Based on both study- and individual-level data, we found that the RLM was the best fit to describe the natural progression of atrophic lesions in STGD1. A random-effects meta-analysis using the outcome measure from the RLM (i.e., effective radius growth rate) determined the progression rate of the atrophic lesion as 0.104 mm/year (95% CI, 0.086–0.123 mm/year; Fig S7, available at www.aaojournal.org).

The I^2 value was 65.43%, suggesting some heterogeneity between different studies. Sensitivity analysis showed that the radius growth rate ranged from 0.096 to 0.110 mm/year after removing 1 study repeatedly, suggesting that no single study significantly affected the pooled lesion growth rate. Of note, Fujinami et al⁸ observed a much longer follow-up interval (9.1 years) compared with other studies (range, 1–3.6 years). However, after excluding Fujinami et al in our meta-analysis, the estimated growth rate of effective lesion radius was 0.106 mm/year, which is comparable with the result (0.104 mm/year) using all studies. Thus, the inclusion of Fujinami et al did not alter the study conclusions significantly. In the analysis of confounding factors, we found that study type (prospective vs. retrospective) and *ABCA4* mutations as part of the inclusion criteria did not affect the radius growth rate significantly (Fig S8A, B, available at www.aaojournal.org).

Distribution of Growth Rates of Lesions

Figure 9 shows the histogram of effective radius growth rate of atrophic lesions. Interestingly, the growth rates did not seem to follow a normal distribution. Instead, the distribution was best fit using 2 Gaussian curves with distinct radius growth rates (0.029 ± 0.016 mm/year vs. 0.110 ± 0.052 mm/year).

Discussion

Previous studies on the natural history of atrophic lesions in STGD1 exhibited a wide range of growth rates, ranging from 0.39 to 1.84 mm² per year.^{1,14} In addition, previous authors have suggested different models to describe their own data on lesion progression rates (Table S1). A priori, the reasons for the differences in behavior of atrophic lesions are unknown, but at least 2 possibilities exist. First, it is possible that the eyes within each study represent a unique subpopulation of STGD1. However, a simpler and more attractive hypothesis is that the evolution of STGD1 has a more uniform behavior, with an

underlying pattern of lesion expansion that is the same or very similar across these seemingly disparate studies. If this latter hypothesis is correct, the apparent differences in the behavior of STGD1 lesions may arise from differences in the time of entry of these eyes into clinical studies. Examination of Figures 3A and 5A suggests that this is indeed the case; patients have a wide range of lesion sizes initially, presumably because smaller baseline lesions are present in patients who were entered into the study earlier in the course of their disease. In the present meta-analysis, we specifically tested the hypothesis that the expansion of atrophic lesions in untreated eyes with STGD1 is the same in these studies and that the apparent differences in behavior of these lesions arises mainly because these eyes were entered into studies at different time points in their natural history. The introduction of horizontal translation factors, as proposed in our previous studies,^{16,22–26} corrected for different entry times into clinical studies and resulted in a high correlation between lesion size and elapsed time in both study- and individual-level data (Figs 3C and 5B). In our meta-analysis, we demonstrated that the progression of atrophic lesions in STGD1 follows the RLM, in which effective lesion radius grows linearly with time ($r^2 = 0.99$ and $r^2 = 0.93$ in study- and individual-level data, respectively). The corresponding outcome measure (i.e., growth rate of effective lesion radius) was independent of the baseline lesion size ($r = 0.06$; $P = 0.37$) across a range of 0 to 40.7 mm² (Fig 6B). Moreover, the age at onset of atrophy predicted by the RLM (22.7 ± 5.0 years) was remarkably similar to the reported value in the studies (22.1 ± 3.1 years).

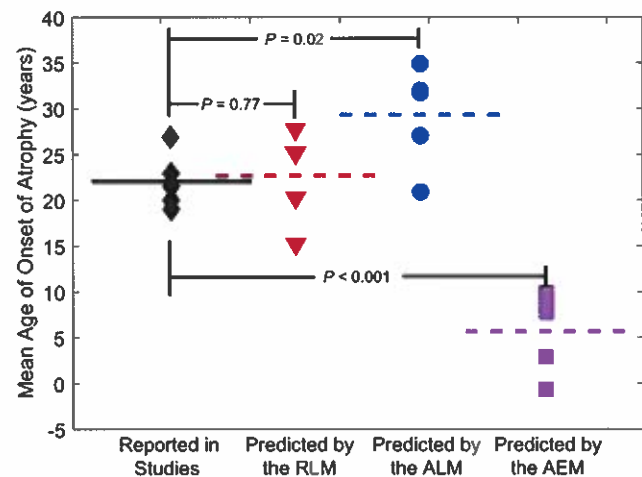


Figure 4. Graph showing the mean age at onset of atrophic lesions reported in prior studies compared with values predicted by the area linear model (ALM), radius linear model (RLM), and area exponential model (AEM). The predicted average age at onset was determined by subtracting the optimized translation factor in each model from the reported average age at the time of enrollment in each study. The horizontal lines represent the averages of the corresponding data points. The age at onset of atrophic lesion predicted by the RLM (mean $\pm$ standard deviation [SD], 22.7 ± 5.0 years) is comparable with the reported average age at onset of symptoms from the studies (mean $\pm$ SD, 22.1 ± 3.1 years; $P = 0.77$). However, the predictions by the ALM (mean $\pm$ SD, 29.3 ± 5.5 years) and AEM (mean $\pm$ SD, 5.6 ± 4.4 years) deviate from the reported ages at onset by more than 5 years ($P = 0.02$ and $P < 0.001$, respectively).

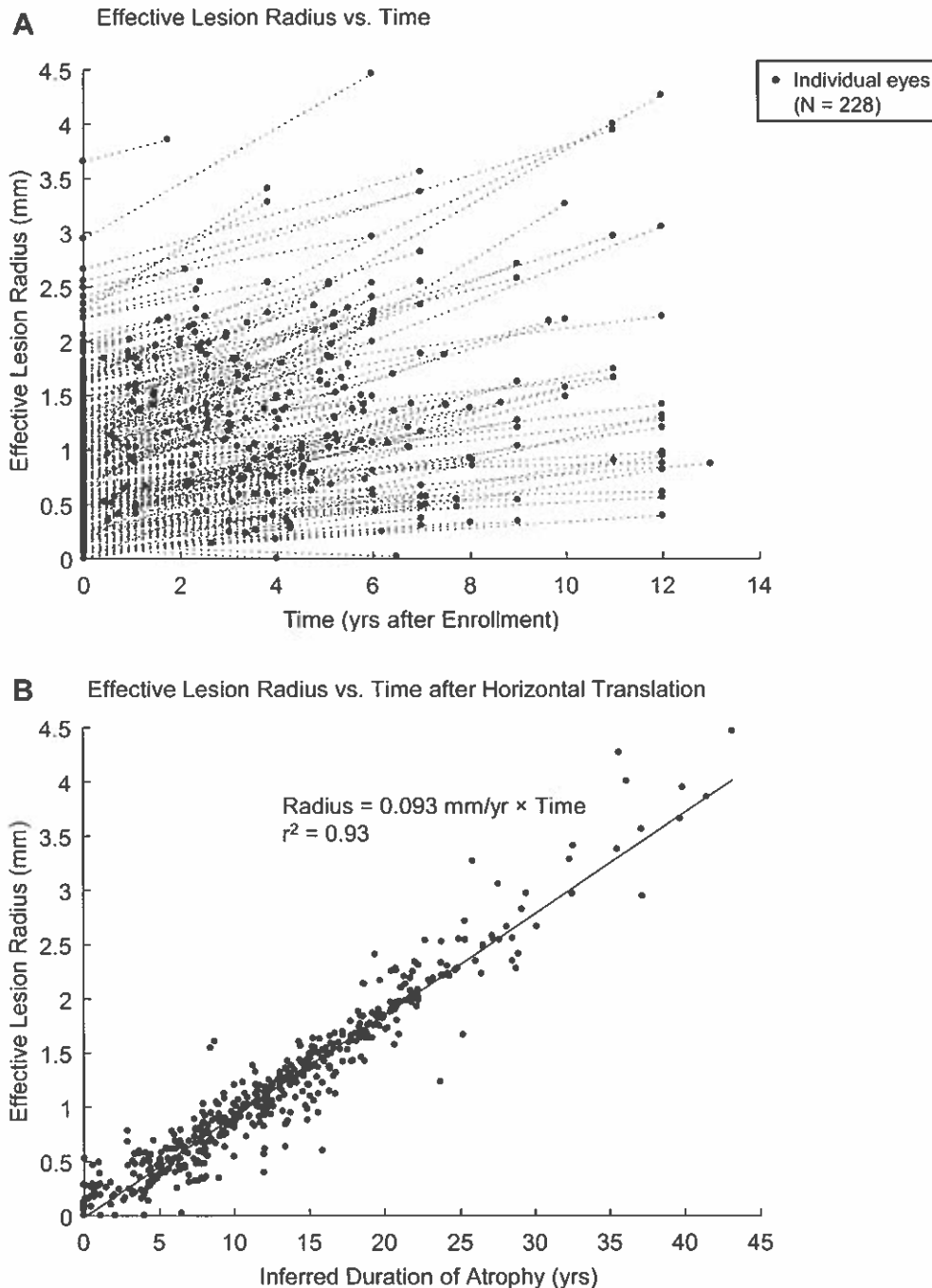


Figure 5. Graphs showing the effective lesion radius as a function of time using individual-level data. **A**, Individual-level raw data from prior publications (the raw data for individual studies are shown in Figure S2, available at www.aaojournal.org). The plot shows a series of 228 lines for atrophic lesion progression in 228 untreated individual eyes with Stargardt disease 1 (STGD1). Each dotted line represents 1 eye with STGD1, and the solid circles on the dotted line represent effective lesion radius at baseline and subsequent follow-up(s). Note that the initial sizes of the lesions vary widely. **B**, Data generated by adding a horizontal translation factor (expressed in years) to each dataset (i.e., each dotted line) in (A) to correct for different entry times of the patients at the time of enrollment. Horizontal axis now represents duration of disease rather than years after enrollment into trial. After the introduction of horizontal translation factors, datasets from all 228 unique eyes now fit along a straight line in the radius linear model with a radius growth rate of 0.093 mm/year ($r^2 = 0.93$). The radius growth rate appears to be constant over the elapsed time.

Several insights can be gained from our analysis. Our previous meta-analysis of 25 studies (2942 eyes) has shown that atrophic lesions in GA secondary to AMD also follow

the RLM.¹⁶ Interestingly, the effective radius growth rate of lesions resulting from GA (0.163 mm/year; 95% CI, 0.158–0.167 mm/year) is approximately 60% higher than

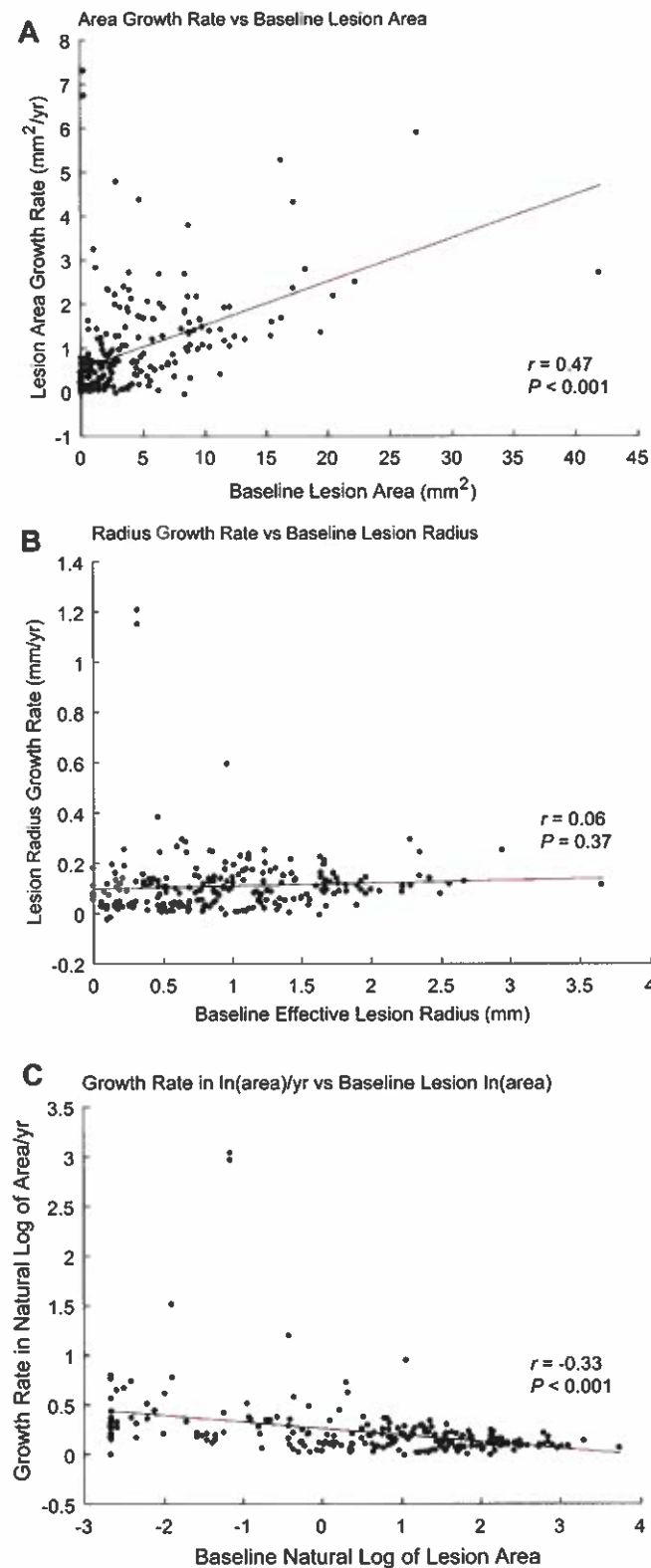


Figure 6. Graphs showing the relationship between the lesion growth rate and baseline lesion size in (A) the area linear model (ALM), (B) the radius linear model (RLM), and (C) the area exponential model (AEM). (A) and (C) show that growth rate depends on the baseline lesion size in the ALM and AEM ($r = 0.47$ and $P < 0.001$ for the ALM; $r = -0.33$ and $P < 0.001$ for the AEM). In contrast, (B) illustrates that the radius growth rate is independent of the baseline lesion radius ($r = 0.06$ and $P = 0.37$) for the RLM. The median radius growth rate is 0.090 mm/year with the first and third quartile as 0.038 mm/year and 0.139 mm/year , respectively.

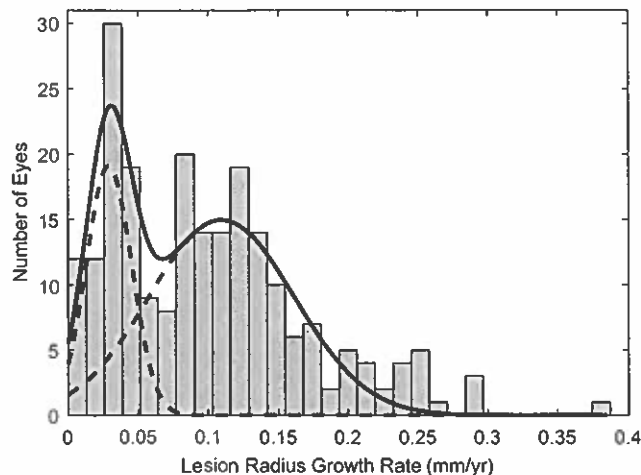


Figure 9. Histogram showing lesion radius growth. Distribution was best fitted using 2 Gaussian curves (dashed lines; mean $\pm$ standard deviation, 0.029 ± 0.016 mm/year and 0.110 ± 0.052 mm/year, respectively), which may indicate at least 2 Stargardt disease 1 subpopulations with distinct lesion growth rates.

that of lesions in STGD1 (0.104 mm/year; 95% CI, 0.086–0.123 mm/year). To compare the loss rate of RPE cells in eyes with GA resulting from AMD with that of eyes with STGD1, the RPE cell densities in the macula for the corresponding patient age groups are required. The loss rate of RPE cells would be RPE cell density in the corresponding age group multiplied by the increase in atrophic lesion area in 1 year. For the sake of our calculations, we can assume the RPE density in patients with STGD1 (age, approximately 20 years) as 5160 cells/mm² and that in patients with GA (age, approximately 70 years) as 4460 cells/mm².²⁹ With an initial lesion size of 1 mm in radius (i.e., 3.14 mm² in area), the macula with GA will lose 4940 cells (corresponding to an area of 1.11 mm²) in 1 year, which is 39% higher than the loss of 3547 RPE cells (corresponding to an area of 0.69 mm²) in patients with STGD1 in 1 year. This suggests that although atrophy in GA starts at a much later age, the rate of RPE cell loss resulting from GA is much faster than that of STGD1 after the atrophy has begun.

It is interesting to note that the histogram of lesion radius growth rates is not a single Gaussian curve, but rather can be represented best as the sum of 2 Gaussian curves (Fig 9). This suggests that there may be 2 subpopulations in STGD1 with roughly a 4-fold difference in lesion growth rate (0.029 mm/year vs. 0.110 mm/year). Because of the lack of individual-level genotype and phenotype information, we are unable to determine the cause for the finding. However, several prognostic factors have been identified previously for STGD1 and may contribute to the apparent different growth rates. One possible explanation is the difference in the genotypes. For example, a recent retrospective study of 157 patients with STGD1 found that patients with 2 alleles harboring likely null variants of *ABCA4* demonstrated larger patches of RPE atrophy (>2.5 mm²) approximately 15 years earlier than patients with only 1 allele

harboring a missense variant.⁷ Another possibility is the different demographic and phenotypic factors among patients with STGD1. For instance, several previous studies suggested that a high lesion growth rate may be associated with late onset of the lesion, multifocal lesions, and the heterogeneous background of FAF.^{8,10,13} However, most studies did not correct for differences in baseline lesion sizes and reported only the area growth rates. Future studies are needed to investigate the relationship between demographic, phenotypic, and genotypic factors and progression rates of STGD1 using the RLM.

Our present study has demonstrated that the atrophic lesion size measured by FAF is a reliable outcome measure to monitor STGD1 progression. Several other outcome measures have been investigated in previous studies. One such measure is the atrophic lesion size measured by OCT.^{7,18} In our literature search, we identified 2 studies (436 eyes)^{7,18} that used en face OCT to monitor atrophic lesion progression in patients with untreated STGD1. To our surprise, the pooled mean effective radius growth rate from the 2 studies (0.016 mm/year; Fig S10, available at www.aaojournal.org) is much smaller than that in our included studies that used FAF (0.104 mm/year; $P < 0.001$). It is possible that there were different characteristics in patient populations between the studies using FAF and those using OCT. A second more likely possibility is that OCT and FAF may look at different parameters; OCT may reflect the presence or absence of cells on the inner aspect of Bruch's membrane, the choriocapillaris, or both, whereas FAF changes are the result of the presence or absence of chromophores, molecules, or both blocking fluorescence. To investigate the potential discrepancies further, future studies are needed to compare OCT with FAF in monitoring the lesion progression in the same STGD1 patient population. Another outcome measure to monitor STGD1 progression is BCVA.^{6–11} However, the rates of change in BCVA vary among studies (–0.06 to +0.08 logarithm of the minimum angle of resolution per year), and the BCVA does not seem to correlate with atrophic lesion sizes ($r = -0.09$; Fig S11, available at www.aaojournal.org). Thus, BCVA may not be a reliable measure to monitor STGD1 progression. Because of the need to establish a sensitive visual function measure to monitor STGD1, other visual function tests including visual field, macular sensitivity, reading speed, and so forth should be investigated in longitudinal studies with a large cohort of patients with STGD1; this will allow a detailed determination of the natural history of visual function in STGD1.^{30–32} Such visual function measures, along with the effective radius of atrophic lesions assessed by FAF, will be particularly important for future clinical trials designed for evaluating the effectiveness of treatment options.

Quality of the Evidence

This study constitutes a thorough literature search and an extensive meta-analysis on the progression of atrophic lesions in patients with STGD1. We analyzed both study-level (7 studies with 564 eyes) and individual-level (228 eyes) raw

data. The included studies have relatively high quality (Newcastle-Ottawa scale score range, 6–8). Because of the relatively small number of included studies (fewer than 10), we did not assess publication bias.³⁸ We found some interstudy heterogeneity among the included studies ($I^2 = 65.43\%$) that may be the result of unbalanced prognostic factors among studies.

Study Limitations

The current study has several limitations, including the relatively small number of studies suitable for analysis. Despite an exhaustive literature search and screening, we were able to identify only 7 studies that met the inclusion criteria and that used FAF to monitor the lesion progression in STGD1. However, these studies contained natural history data on 564 individual eyes. Second, confounding factors might have affected our analysis in the lesion progression pattern. We attempted to minimize the effects by including only studies that used the same imaging method (i.e., FAF). However, other factors such as different characteristics of lesions (e.g., background of FAF, number of lesions, etc.) and different genotypes may not be balanced in individual studies, and thus can affect our estimated lesion growth rates. Finally, most lesions in our meta-analysis ranged from 0 to 19.6 mm², and we do not know if a similar fit is present for lesion sizes outside this range.

Conclusions

This meta-analysis of both study- and individual-level data demonstrated that the effective radius of atrophic lesions secondary to STGD1 enlarges linearly as a function of time. The effective radius growth rate (0.104 mm/year; 95% CI, 0.086–0.123 mm/year) is independent of baseline lesion sizes. Future clinical trials can use the effective radius growth rate of atrophic lesions assessed by FAF as an outcome measure to monitor the progression of STGD1.

Acknowledgments

The authors thank Dr. Vikki A. McBain (Eye Outpatient Department, Aberdeen Royal Infirmary, Aberdeen, Scotland) and Dr. Noemi Lois, Medical Statistics Team, University of Aberdeen, Aberdeen, United Kingdom, for sharing the data of their study and Khadija El-Hazimy and Vermetha Polite, Cushing/Whitney Medical Library, Yale University, New Haven, Connecticut, for technical support.

References

- Allikmets R, Singh N, Sun H, et al. A photoreceptor cell-specific ATP-binding transporter gene (ABCR) is mutated in recessive Stargardt macular dystrophy. *Nat Genet*. 1997;15(3):236–246.
- Tanna P, Strauss RW, Fujinami K, Michaelides M. Stargardt disease: clinical features, molecular genetics, animal models and therapeutic options. *Br J Ophthalmol*. 2017;101(1):25–30.
- Stargardt K. Über familiäre, progressive Degeneration in der Maculagegend des Auges. *Graefes Arch Clin Exp Ophthalmol*. 1909;71(3):534–550.
- Schwartz SD, Hubschman J-P, Heilwell G, et al. Embryonic stem cell trials for macular degeneration: a preliminary report. *Lancet*. 2012;379(9817):713–720.
- Scholl HP, Strauss RW, Singh MS, et al. Emerging therapies for inherited retinal degeneration. *Sci Transl Med*. 2016;8(368):368rv6.
- Kong X, Strauss RW, Michaelides M, et al. Visual acuity loss and associated risk factors in the retrospective Progression of Stargardt Disease Study (ProgStar report no. 2). *Ophthalmology*. 2016;123(9):1887–1897.
- Di Iorio V, Orrico A, Esposito G, et al. Association between genotype and disease progression in Italian Stargardt patients: a retrospective natural history study. *Retina*. 2019;39(7):1399–1409.
- Fujinami K, Lois N, Mukherjee R, et al. A longitudinal study of Stargardt disease: quantitative assessment of fundus autofluorescence, progression, and genotype correlations. *Invest Ophthalmol Vis Sci*. 2013;54(13):8181–8190.
- Lambertus S, Bax NM, Groenewoud JM, et al. Asymmetric inter-eye progression in Stargardt disease. *Invest Ophthalmol Vis Sci*. 2016;57(15):6824–6830.
- Strauss RW, Muñoz B, Ho A, et al. Progression of Stargardt disease as determined by fundus autofluorescence in the retrospective Progression of Stargardt Disease study (ProgStar report no. 9). *JAMA Ophthalmol*. 2017;135(11):1232–1241.
- Parodi MB, Sacconi R, Romano F, Bandello F. Hyper-reflective foci in Stargardt disease: 1-year follow-up. *Graefes Arch Clin Exp Ophthalmol*. 2018;257(1):41–48.
- Chen B, Tosha C, Gorin M, Nusinowitz S. Analysis of autofluorescent retinal images and measurement of atrophic lesion growth in Stargardt disease. *Exp Eye Res*. 2010;91(2):143–152.
- McBain VA, Townend J, Lois N. Progression of retinal pigment epithelial atrophy in Stargardt disease. *Am J Ophthalmol*. 2012;154(1):146–154.
- Kong X, West SK, Strauss RW, et al. Progression of visual acuity and fundus autofluorescence in recent-onset Stargardt disease: ProgStar Study report #4. *Ophthalmol Retina*. 2017;1(6):514–523.
- Lambertus S, Lindner M, Bax NM, et al. Progression of late-onset Stargardt disease. *Invest Ophthalmol Vis Sci*. 2016;57(13):5186–5191.
- Shen L, Liu F, Grossetta Nardini H, Del Priore LV. Natural history of geographic atrophy in untreated eyes with non-exudative age-related macular degeneration: a systematic review and meta-analysis. *Ophthalmol Retina*. 2018;2(9):914–921.
- Feuer WJ, Yehoshua Z, Gregori G, et al. Square root transformation of geographic atrophy area measurements to eliminate dependence of growth rates on baseline lesion measurements: a reanalysis of age-related eye disease study report no. 26. *JAMA Ophthalmol*. 2013;131(1):110–111.
- Melillo P, Testa F, Rossi S, et al. En face spectral-domain optical coherence tomography for the monitoring of lesion area progression in Stargardt disease. *Invest Ophthalmol Vis Sci*. 2016;57(9):OCT247–OCT252.
- Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. *JAMA*. 2000;283(15):2008–2012.
- Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*. 2009;151(4):264–269.

21. Wells G, Shea B, O'Connell D, et al. *The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses*. Ottawa, Ontario: Ottawa Health Research Institute, University of Ottawa; 2001. http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm. Accessed June 11, 2017.
22. Liu TYA, Shah AR, Del Priore LV. Progression of lesion size in untreated eyes with exudative age-related macular degeneration: a meta-analysis using Lineweaver-Burk plots. *JAMA Ophthalmol*. 2013;131(3):335–340.
23. Shah AR, Del Priore LV. Natural history of predominantly classic, minimally classic, and occult subgroups in exudative age-related macular degeneration. *Ophthalmology*. 2009;116(10):1901–1907.
24. Shah AR, Del Priore LV. Progressive visual loss in subfoveal exudation in age-related macular degeneration: a meta-analysis using Lineweaver-Burke plots. *Am J Ophthalmol*. 2007;143(1):83–89.e2.
25. Shen LL, Liu F, Nardini HG, Del Priore LP. Reclassification of fundus autofluorescence patterns surrounding geographic atrophy based on progression rate: a systematic review and meta-analysis. *Retina*; 2019. Feb 28 <https://doi.org/10.1097/IAE.0000000000002480> [Epub ahead of print].
26. Shen LL, Liu F, Grossetta Nardini HK, Del Priore LV. Fellow Eye status is a biomarker for the progression rate of geographic atrophy: a systematic review and meta-analysis. *Ophthalmol Retina*. 2019;3(4):305–315.
27. Viechtbauer W. Conducting meta-analyses in R with the metafor package. *J Stat Softw*. 2010;36(3):1–48.
28. Green S, Higgins J. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0* [updated March 2011]. The Cochrane Collaboration; 2011. Available from <http://handbook.cochrane.org>.
29. Liu Z, Kocaoglu OP, Miller DT. 3D imaging of retinal pigment epithelial cells in the living human retina. *Invest Ophthalmol Vis Sci*. 2016;57(9):OCT533–OCT543.
30. Schönbach EM, Wolfson Y, Strauss RW, et al. Macular sensitivity measured with microperimetry in Stargardt disease in the Progression of Atrophy Secondary to Stargardt Disease (ProgStar) Study: report no. 7. *JAMA Ophthalmol*. 2017;135(7):696–703.
31. Cideciyan AV, Swider M, Aleman TS, et al. Macular function in macular degenerations: repeatability of microperimetry as a potential outcome measure for ABCA4-associated retinopathy trials. *Invest Ophthalmol Vis Sci*. 2012;53(2):841–852.
32. Murro V, Sodì A, Giacomelli G, et al. Reading ability and quality of life in Stargardt disease. *Eur J Ophthalmol*. 2017;27(6):740–745.

Footnotes and Financial Disclosures

Originally received: January 25, 2019.

Final revision: March 28, 2019.

Accepted: May 8, 2019.

Available online: May 16, 2019.

Manuscript no. 2019-179.

¹ Department of Ophthalmology and Visual Science, Yale University School of Medicine, New Haven, Connecticut.

² Department of Molecular Biophysics and Biochemistry, Yale University, New Haven, Connecticut.

³ Harvey Cushing/John Hay Whitney Medical Library, Yale University, New Haven, Connecticut.

Financial Disclosure(s):

The author(s) have made the following disclosure(s): L.V.D.P.: Consultant – Astellas Institute for Regenerative Medicine.

This study is not supported by any sponsor or funding organization.

HUMAN SUBJECTS: No human subjects were included in this study. IRB approval was not required. All research adhered to the tenets of the Declaration of Helsinki. This is a systematic review article using previously published data in the literature.

No animal subjects were included in this study.

Author Contributions:

Conception and design: Shen, Del Priore

Analysis and interpretation: Shen, Del Priore

Data collection: Shen, Sun, Grossetta Nardini

Obtained funding: Del Priore

Overall responsibility: Shen, Del Priore

Abbreviations and Acronyms:

AEM = area exponential model; ALM = area linear model; AMD = age-related macular degeneration; BCVA = best-corrected visual acuity; CI = confidence interval; FAF = fundus autofluorescence; GA = geographic atrophy; RLM = radius linear model; RPE = retinal pigment epithelium; STGD1 = autosomal recessive Stargardt disease.

Correspondence:

Lucian V. Del Priore, MD, PhD, Department of Ophthalmology and Visual Science, Yale University School of Medicine, 40 Temple Street, Suite 1B, New Haven, CT 06510. E-mail: lucian.delpriore@yale.edu