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# Visual Acuity Change over 12 Months in the Prospective Progression of Atrophy Secondary to Stargardt Disease (ProgStar) Study

## *ProgStar Report Number 6*

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***Purpose:*** To estimate the yearly rate of change of best-corrected visual acuity (BCVA) and the risk of loss 1 line or more over 1 year and to identify risk factors for BCVA loss in patients with Stargardt disease (STGD1).

***Design:*** Multicenter, prospective cohort study.

***Participants:*** Two hundred fifty-nine patients (489 eyes) with molecularly confirmed STGD1 enrolled at 9 centers in the United States and Europe.

***Methods:*** Participants were followed up every 6 months, and data at the baseline and 6- and 12-month visits were analyzed. Best-corrected visual acuity was measured using the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol. Standardized reporting forms were used to collect participants' characteristics and clinical observations. Linear mixed effects models were used to estimate the rate of BCVA loss. Linear models with generalized estimating equations were used to identify risk factors for BCVA loss of 1 line or more over 1 year.

***Main Outcome Measures:*** Change in BCVA over 1 year.

***Results:*** Cross-sectional analysis at baseline showed that earlier symptom onset and longer duration since onset was associated with worse BCVA. Longitudinal analysis showed no overall significant change of BCVA within 12 months, but the rate of BCVA change was significantly different by baseline BCVA ($P < 0.001$). The BCVA of eyes with baseline BCVA of 20/25 or better declined at a rate of 2.8 ETDRS letters per year ($P = 0.10$), eyes with baseline BCVA between 20/25 and 20/70 declined at a rate of 2.3 ETDRS letters per year ($P = 0.002$), eyes with baseline BCVA between 20/70 and 20/200 declined at a rate of 0.8 ETDRS letters per year ($P = 0.08$), and eyes with baseline BCVA worse than 20/200 showed a significant improvement of 2.3 ETDRS letters per year ($P < 0.001$). Overall, 12.9% of eyes lost 1 line or more, and the risk of such BCVA loss was different by baseline BCVA level ($P = 0.016$). Smoking and vitamin A use was not associated significantly with baseline BCVA, nor with rate of BCVA loss over 1 year.

***Conclusions:*** Change in BCVA in STGD1 patients over a 12-month period was small, but varied depending on baseline BCVA. Given the slow change during 1 year, BCVA is unlikely to be a sensitive outcome measure for STGD1 treatment trials with 1 year's duration. *Ophthalmology 2017;124:1640-1651 © 2017 by the American Academy of Ophthalmology*

*Supplemental material available at www.aaojournal.org.

Stargardt disease (STGD1; Online Mendelian Inheritance in Man identifier, 248200) is the most common juvenile macular dystrophy, with a prevalence of 10 to 12.5 per 100 000 persons,[1] and is inherited as an autosomal recessive trait associated with mutations in the *ABCA4* gene.[2] It is characterized by the appearance of yellowish-white lesions called fundus flecks at the level of the retinal pigment epithelium (RPE) and by the development of macular atrophic lesions. Patients with STGD1 are known to experience impairment of visual acuity progressively and at various ages. Currently, there is no approved treatment for the disease. Understanding the natural history of STGD1 and determining the rate of disease progression using multiple functional or structural methods is of great interest for determining appropriate outcome measures in clinical trials of potential treatments.[3–8]



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Prior studies reporting the rate of change of visual acuity (VA) in STGD1[9–15] were based on retrospective review of medical records. In this study, we used data from the prospective international multicenter examination of the natural history of STGD1, the Progression of Atrophy Secondary to Stargardt Disease (ProgStar) study, to assess the rate of VA change and to identify participants' demographic, clinical, and behavioral characteristics associated with VA loss over 1 year.

## Methods

Data for this analysis are from the prospective ProgStar study, which was approved by the Western Institutional Review Board, the local institutional review boards, and the Human Research Protection Office of the United States Army Medical Research and Materiel Command. The study was registered at www.clinicaltrials.gov (identifier, NCT01977846).

Details of the prospective ProgStar study have been described in detail elsewhere.[7] In brief, from September 2014 through March 2015, eligible STGD1 patients were enrolled into the ProgStar study at 9 participating sites in the United States, United Kingdom, France, and Germany. Eligibility of participants included: age 6 years or older; willingness to undergo ocular examinations every 6 months for up to 24 months; and having 2 pathogenic mutations in the *ABCA4* gene, or having 1 pathogenic mutation in the *ABCA4* gene together with a typical STGD1 phenotype such as flecks at the level of the RPE (further inclusion and exclusion criteria are described in ProgStar report no. 1).[7] The particularly relevant inclusion criteria for analysis herein are that study eyes had to have a best-corrected visual acuity (BCVA) of 20 or more Early Treatment Diabetic Retinopathy Study (ETDRS) letters (i.e., 20/400 Snellen equivalent or better), at least 1 well-demarcated area of atrophy on fundus autofluorescence imaging with a diameter of 300 μm or more and the sum of all lesions of 12 $mm^2$ or less, and clear ocular media and adequate pupillary dilation per site investigators' assessment. All participants gave written informed consent before enrollment in the study.

Participants were followed up every 6 months. At each visit, participants underwent detailed ophthalmic examinations; refraction and BCVA were obtained following the ETDRS protocol[16] at all sites. For data collection, a standardized demographic form and clinical report form were used at all sites to record age, gender, race, age at symptom onset and clinical information on BCVA, results from the biomicroscopy of the anterior segments and dilated fundus examination, and behavioral characteristics (use of vitamin supplementation, smoking history) at each study visit. All data were double entered by study coordinators into the Research Electronic Data Capture system (http://www.project-redcap.org/cite.php) and transferred to a data coordinating center for data quality control and management.

### Statistical Analysis

Data from the baseline, 6-month, and 12-month visits were used in this analysis. Participant demographic and clinical characteristics at baseline visit first were summarized. Baseline BCVA also was categorized in referencing the World Health Organization's International Classification of Diseases, 10th revision,[17] and as (1) VA of 20/25 or better (i.e., ≤0.1 logarithm of the minimum angle of resolution [logMAR] or ≥80 ETDRS letters; i.e., no visual impairment [VI]); (2) worse than 20/25 to 20/70 (0.1−0.54 logMAR or 58−80 ETDRS letters; i.e., mild VI); (3) worse than 20/70 to 20/200 (0.54−1.0 logMAR or 35−58 ETDRS letters; i.e., moderate VI); (4) worse than 20/200 to 20/400 (1.0−1.3 logMAR or 20−35 ETDRS letters; i.e., severe VI); and (5) worse than 20/400 (>1.3 logMAR or <20 ETDRS letters; i.e., blindness).

For all analyses, ETDRS letter scores were converted to the logMAR scale. Baseline data of participants and study eyes were used to explore the cross-sectional association of BCVA with participant demographic and behavioral characteristics including age (categorized as ≤18 years, >18−50 years, and ≥50 years), gender, race (white vs. nonwhite), smoking status, and vitamin A use and with clinical characteristics including age at symptom onset (categorized into ≤14 years, 15−20 years, 21−30 years, 30+ years on considering data distribution and prior publications) and duration between symptom onset and baseline (categorized as 0−2 years, >2−6 years, >6−11.5 years, and >11.5−53 years on considering data distribution and prior publications). Age, age at symptom onset, and duration between symptom onset and baseline also were modeled as continuous variables in separate models. Eye-level clinical characteristics included observations from biomicroscopy of the anterior segments and dilated fundus examination. Univariate linear models with generalized estimating equations (GEEs) were used to estimate the unadjusted cross-sectional associations while accounting for between-eye correlation, followed by multivariate linear models with GEEs to estimate the associations adjusting for variables associated with BCVA in univariate analyses with $P < 0.1$.

To estimate the longitudinal change of BCVA, a linear mixed-effects model was used to estimate the yearly change rate: the mean of participants' BCVA was modeled as a linear function of time since baseline visit, with the intercept and slope parameters assumed to be normally distributed random effects. Additionally, BCVA change from baseline to year 1 was dichotomized further regarding whether there was a loss of 1 line or more (i.e., loss of 5 or more ETDRS letters), and the proportion of such loss was estimated. Univariate log-binomial models with GEEs were used to estimate the risk ratios of baseline variables (for the behavioral variable of vitamin A use, the report at year 1 visit was considered) in association with the risk of 1 line or more of BCVA loss during the year. Multivariate log-binomial models with GEEs were used to estimate the adjusted risk ratios for variables associated with risk of BCVA loss of 1 line or more in univariate analysis with $P \leq 0.10$ and for variables associated with baseline BCVA with $P \leq 0.10$.

All analyses were conducted in SAS software version 9.3 (SAS Inc., Cary, NC), and 2-sided $P$ values from Wald tests were reported. For analyses using GEE models, model fit was assessed using aggregated residuals,[18] and for the longitudinal analysis using linear mixed-effects models, model fit was inspected visually and based on plots of scaled residuals.[19]

## Results

Four hundred eighty-nine eyes of 259 participants were enrolled in the prospective ProgStar study. The follow-up rate was 92% at month 6 and 93% at month 12 (Fig 1). Table 1 summarizes characteristics of participants and the study eyes. The median age at baseline was 31 years (interquartile range [IQR], 21−44 years), and 54% (n = 141) were women. Most participants were white (n = 222; 86%), 7.7% were black (n = 20), and 4% were Asian (n = 10). The median self-reported age at symptom onset was 19 years (IQR, 12−29 years), and the median duration between symptom onset and baseline visit was 9 years (IQR, 5−15 years). Vitamin A use was reported by 37 participants (14%; a summary of dosage and frequency is presented in Table S1, available at www.aaojournal.org). Current smoking was reported

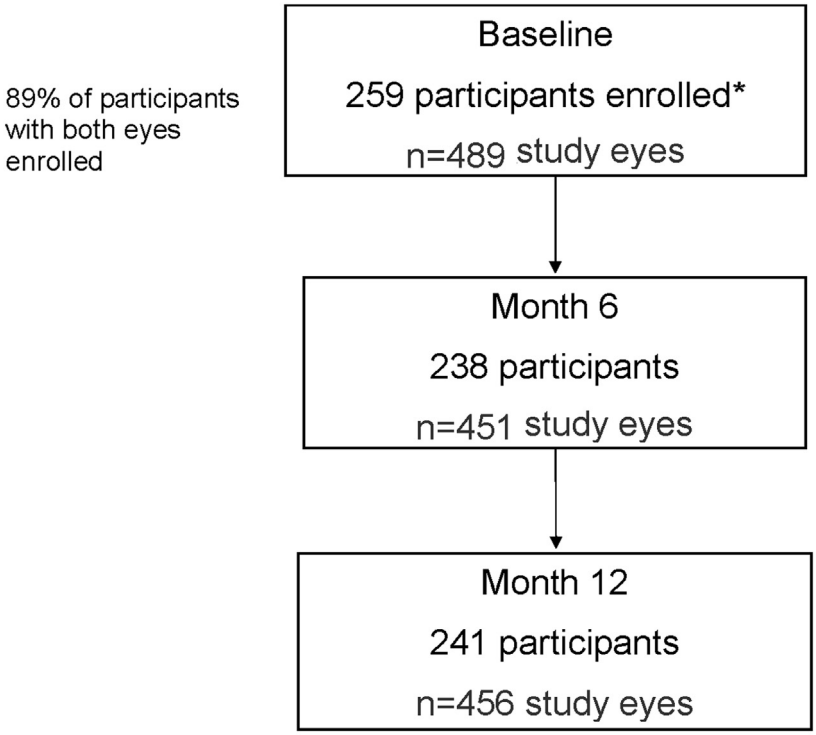


**Figure 1.** Flowchart showing enrollment and follow-up of the prospective Progression of Atrophy Secondary to Stargardt Disease (ProgStar) study.

in 29 participants (11%), and 35 participants (14%) were former smokers.

At baseline, the median BCVA of the study eyes was 41 ETDRS letters (IQR, 35−52 ETDRS letters; range, 20−88 ETDRS letters; median, 0.88 logMAR), and 21% of eyes had no or mild VI, 55% were moderately impaired, and 25% were severely impaired. Lens change or abnormalities of the anterior segment were rare. Clinical examination data showed that 9.5% of eyes had nerve pallor, 93% of eyes had RPE atrophy, and 67% of eyes had RPE pigmentary abnormality (i.e., hypopigmentation, hyperpigmentation, or both at the level of the RPE). Most eyes (92%) had flecks present within the arcades, and 46% of eyes had flecks outside the arcades (Table 1).

## Cross-Sectional Associations of Participant Characteristics with Baseline Best-Corrected Visual Acuity

Table 2 presents the baseline BCVA in subgroups by participant characteristics and the difference in BCVA between subgroups. Compared with participants 18 years of age and younger, the BCVA of those 18 to 50 years of age and those older than 50 years was better by 4.5 and 10.5 ETDRS letters, respectively (i.e., approximately a 0.09- and 0.21-logMAR difference). However, such differences were not significant in adjusted analysis. When age was modeled as a continuous variable, older age was associated with better BCVA in univariate analysis ($P = 0.007$). But in multivariate analysis controlling for age at symptom onset, older age was associated with worse BCVA (adjusted $P = 0.02$). There was no significant difference in BCVA by gender or by race. Older age at symptom onset was associated significantly with better BCVA ($P < 0.001$); for example, compared with participants with onset at 14 years of age or younger, the BCVA of those with onset at older than 30 years was 11.5 ETDRS letters better (i.e., adjusted difference, −0.23 logMAR). Such an association also was significant when age at onset was modeled as a continuous variable (adjusted $P < 0.001$). Longer duration of symptoms was associated significantly with worse BCVA ($P < 0.001$); for example, compared with participants with symptoms of 2 years' duration or less, the BCVA of those with symptoms for more than 11.5 years was 13 ETDRS letters worse (i.e., adjusted difference, 0.26 logMAR). The association also was significant when duration was modeled as a continuous variable (adjusted $P < 0.001$). For behavioral variables, vitamin A use was not associated with BCVA ($P = 0.34$). The BCVA of current smokers was 5 ETDRS letters (i.e., difference of 0.1 logMAR) worse than never smokers, but this difference was not statistically significant ($P = 0.26$)

For eye-level clinical characteristics, having nerve pallor and flecks within the arcades was not associated with worse BCVA. The BCVA of eyes with RPE pigmentary abnormalities was 5 ETDRS letters (i.e., difference of 0.1 logMAR; adjusted $P = 0.003$) worse than eyes without this abnormality; BCVA of eyes with flecks outside the arcades was 6 ETDRS letters (i.e., difference of 0.12 logMAR; adjusted $P < 0.001$) worse than eyes without flecks outside the arcades. Associations of BCVA with other fundus examination variables were not assessed because of the small sample sizes in certain subgroups.

## Longitudinal Analysis of the Yearly Change in Best-Corrected Visual Acuity

Overall, there was no statistically or clinically significant change in mean BCVA over 12 months (Fig 2). The rate of change

Table 1. Baseline Demographic, Behavioral, and Clinical Characteristics of Participants and the Study Eyes in the Prospective Progression of Stargardt Disease Study

| Characteristic | Data |
|---|---|
| Participant characteristics | |
| Total no. of participants | 259 |
| Age at baseline visit (yrs) | |
| Median | 31 |
| IQR | 21–44 |
| Range | 7–69 |
| Gender, no. (%) | |
| Female | 141 (54.4) |
| Male | 118 (45.6) |
| Race, no. (%) | |
| White | 222 (85.7) |
| Black | 20 (7.7) |
| Asian/Indian | 10 (3.9) |
| Other (Pakistan, Near East, or multiple races) | 3 (1.2) |
| Don't know | 4 (1.5) |
| Age at symptom onset, no. (%) | |
| Asymptomatic | 2 (0.8) |
| Unknown | 16 (6.2) |
| Known | 241 (93.0) |
| Age of symptom onset among known (yrs) | |
| Median | 19 |
| IQR | 12–29 |
| Range | 4–64 |
| Duration from symptom onset to baseline visit (yrs) | |
| Median | 9 |
| IQR | 5–15 |
| Range | 0–55 |
| Vitamin A use, no. (%) | |
| No | 222 (85.7) |
| Yes | 37 (14.3) |
| Smoking, no. (%) | |
| Never | 195 (75.3) |
| Former smoker | 35 (13.5) |
| Current smoker | 29 (11.2) |
| Currently living with a smoker, no. (%) | |
| No | 222 (85.7) |
| Yes | 37 (14.3) |
| Eye characteristics | |
| No. of study eyes | 489 |
| Best-corrected visual acuity | |
| VA in ETDRS letter score | |
| Median | 41 |
| IQR | 35–52 |
| Range | 20–88 |
| LogMAR equivalent | |
| Median | 0.88 |
| IQR | 0.66–1.00 |
| Range | −0.06 to 1.30 |
| Categorized VA, no. (%)* | |
| No VI | 17 (3.5) |
| Mild VI | 83 (17.0) |
| Moderate VI | 267 (54.6) |
| Severe VI | 122 (25.0) |
| Blindness | 0 (0) |
| Fundus examination results, no. (%) | |
| Total no. of eyes | 483† |
| Cataract | |
| Intraocular lens (pseudophakic) | 5 (1.0) |
| No cataract | 470 (97.3) |
| Nuclear | 8 (1.7) |
| Cornea | |
| Normal | 480 (99.4) |
| Abnormal | 3 (0.6) |
| Iris | |
| Normal | 483 (100) |
| Anterior chamber | |
| Normal | 481 (99.6) |
| Can't determine | 2 (0.4) |
| Dilated fundus examination results, no. (%) | |
| Total no. of eyes | 483† |
| Nerve pallor | |
| No | 437 (90.5) |
| Yes | 46 (9.5) |
| Nerve cupping | |
| No | 462 (95.7) |
| Yes | 17 (3.5) |
| Can't determine | 4 (0.8) |
| Macular edema | |
| No | 480 (99.4) |
| Yes | 3 (0.6) |
| RPE atrophy | |
| No | 33 (6.8) |
| Yes | 450 (93.2) |
| RPE pigmentary abnormality | |
| No | 159 (32.9) |
| Yes | 324 (67.1) |
| Flecks within arcades | |
| No | 37 (7.7) |
| Yes | 446 (92.3) |
| Flecks outside arcades | |
| No | 262 (54.2) |
| Yes | 220 (45.6) |
| Can't determine | 1 (0.2) |
| Vascular attenuation | |
| No | 465 (96.3) |
| Yes | 18 (3.7) |
| Peripheral abnormalities | |
| No | 479 (99.2) |
| Yes | 1 (0.2) |
| Can't determine | 3 (0.6) |

ETDRS = Early Treatment Diabetic Retinopathy Study; IQR = interquartile range; logMAR = logarithm of the minimum angle of resolution; RPE = retinal pigment epithelium; VA = visual acuity; VI = visual impairment.

*Visual acuity categorization references the World Health Organization's International Classification of Diseases, 10th revision: no VI, VA ≥20/25 (≤0.1 logMAR or ≥80 ETDRS letters); mild VI, VA <20/25 to 20/70 (0.1–0.54 logMAR or 58–80 ETDRS letters); moderate VI, VA <20/70 to 20/200 (0.54–1.0 logMAR or 35–58 ETDRS letters); severe VI, VA <20/200 to 20/400 (1.0–1.3 logMAR or 20–35 ETDRS letters); and blindness, VA <20/400 (>1.3 logMAR or <20 ETDRS letters).

†Fundus examination carried out on 483 eyes.

was −0.36 ETDRS letters (0.007 logMAR) per year (95% confidence interval [CI], −1.18 to 0.46 ETDRS letters; $P$ = 0.38). However, the change was statistically significantly different by baseline BCVA level ($P$ < 0.001; Table 3; Fig 3): eyes with no VI at baseline (n = 17) had a nonsignificant BCVA change of −2.8 ETDRS letters (0.056 logMAR) per year (95% CI, −6.01 to 0.49 ETDRS letters), eyes with mild VI (n = 83) showed a significant BCVA change of −2.3 ETDRS letters

Table 2. Baseline Best-Corrected Visual Acuity and Differences by Participant Characteristics: Cross-sectional Associations of Participant Characteristics with Baseline Visual Acuity

| Characteristic | Mean Visual Acuity (95% Confidence Interval)* | Univariate Model | | Multivariate Model | |
|---|---|---|---|---|---|
| | | *Difference Compared with Reference Group (95% Confidence Interval)* | P *Value*† | *Adjusted Difference Compared with Reference Group (95% Confidence Interval)* | P *Value*† |
| Age at baseline visit (yrs) | | | 0.005 | | 0.32 |
| ≤18 | 0.89 (0.83–0.94) | Reference | | Reference‡ | |
| >18–50 | 0.79 (0.75–0.84) | −0.09 (−0.17 to −0.02) | | 0.06 (−0.02 to 0.14) | |
| 50+ | 0.67 (0.55–0.79) | −0.21 (−0.35 to −0.08) | | 0.08 (−0.07 to 0.23) | |
| Age at baseline modeled as a continuous variable, every 5 yrs older | | | | | |
| VA difference | | −0.02 (−0.03 to −0.005) | 0.007 | | |
| Adjusted VA difference‡ | | | | 0.03 (0.01–0.06) | 0.02 |
| Gender | | | 0.84 | NA | |
| Female | 0.79 (0.74–0.84) | | | | |
| Male | 0.80 (0.74–0.85) | 0.01 (−0.07 to 0.08) | | | |
| Race | | | 0.08 | | 0.14 |
| White | 0.80 (0.76–0.84) | Reference | | Reference§ | |
| Nonwhite | 0.71 (0.62–0.81) | −0.09 (−0.19 to 0.01) | | 0.07 (−0.16 to 0.02) | |
| Age at symptom onset (yrs) | | | < 0.001 | | < 0.001 |
| ≤14 | 0.94 (0.89–0.98) | Reference | | Reference‖ | |
| 15–20 | 0.84 (0.78–0.90) | −0.09 (−0.17 to −0.02) | | −0.00 (−0.13 to 0.13) | |
| 21–30 | 0.73 (0.65–0.81) | −0.20 (−0.29 to −0.11) | | −0.11 (−0.25 to 0.03) | |
| 30+ | 0.59 (0.49–0.69) | −0.35 (−0.46 to −0.24) | | −0.23 (−0.39 to −0.06) | |
| Age at symptom onset modeled as a continuous variable, every 5 yrs later in onset | | | | | |
| VA difference | | −0.05 (−0.07 to −0.03) | < 0.001 | | |
| Adjusted VA difference‖ | | | | −0.08 (−0.11 to −0.04) | < 0.001 |
| Duration since symptom onset at the baseline visit (yrs) | | | < 0.001 | | < 0.001 |
| 0–2 | 0.56 (0.43–0.68) | Reference | | Reference‖ | |
| >2–6 | 0.72 (0.653–0.80) | 0.16 (0.02–0.31) | | 0.10 (−0.03 to 0.22) | |
| >6–11.5 | 0.76 (0.69–0.84) | 0.20 (0.0.05–0.35) | | 0.15 (0.02–0.27) | |
| 11.5+ | 0.90 (0.85–0.95) | 0.34 (0.21–0.48) | | 0.26 (0.15–0.40) | |
| Duration since symptom onset modeled as a continuous variable, every 5 yrs longer in duration | | | | | |
| VA difference | | 0.06 (0.05–0.08) | 0.001 | | |
| Adjusted VA difference‖ | | | | 0.05 (0.04–0.07) | < 0.001 |
| Vitamin A use | | | 0.34 | NA | |
| No | 0.80 (0.76–0.84) | Reference | | | |
| Yes | 0.73 (0.60–0.87) | −0.06 (−0.20 to 0.07) | | | |
| Smoking status | | | 0.26 | NA | |
| Never | 0.78 (0.74–0.82) | Reference | | | |
| Former | 0.79 (0.67–0.91) | 0.01 (−0.11 to 0.14) | | | |
| Current | 0.87 (0.77–0.98) | 0.10 (−0.01 to 0.20) | | | |
| Nerve pallor | | | 0.44 | NA | |
| No | 0.79 (0.75–0.83) | Reference | | | |
| Yes | 0.82 (0.74–0.90) | 0.03 (−0.05 to 0.11) | | | |

Table 2. (Continued.)

| Characteristic | Mean Visual Acuity (95% Confidence Interval)* | Univariate Model | | Multivariate Model | |
|---|---|---|---|---|---|
| | | Difference Compared with Reference Group (95% Confidence Interval) | P Value† | Adjusted Difference Compared with Reference Group (95% Confidence Interval) | P Value† |
| RPE pigmentary abnormality | | | 0.006 | | 0.003 |
| No | 0.72 (0.66–0.78) | Reference | | Reference§ | |
| Yes | 0.83 (0.78–0.87) | 0.10 (0.03–0.18) | | 0.10 (0.04–0.17) | |
| Flecks within arcades | | | 0.27 | NA | |
| No | 0.74 (0.64–0.84) | Reference | | | |
| Yes | 0.80 (0.76–0.84) | 0.06 (−0.05 to 0.17) | | | |
| Flecks outside arcades | | | < 0.001 | | < 0.001 |
| No | 0.71 (0.66–0.76) | Reference | | Reference§ | |
| Yes | 0.89 (0.83–0.94) | 0.18 (0.11–0.25) | | 0.12 (0.05–0.19) | |

NA = not applicable in multivariate model because the variable was not associated with baseline VA in the univariate analysis; RPE = retinal pigment epithelium; VA = visual acuity.
*Logarithm of the minimum angle of resolution units.
†Testing for significant difference in VA compared with the reference group.
‡Because age at baseline was a linear function of age at symptom onset and duration from onset to baseline visit, when estimating adjusted difference by age, the multivariate model included only baseline age and age at symptom onset.
§The multivariate model included categorized baseline age, categorized age at symptom onset, race, RPE pigmentation, and having flecks outside the arcades.
‖The multivariate model included age at symptom onset and duration since symptom onset.

(0.047 logMAR) per year (95% CI, −3.86 to −0.83 ETDRS letters), eyes with moderate VI (n = 267) showed a nonsignificant BCVA change of −0.8 ETDRS letters (0.015 logMAR) per year (95% CI, −1.59 to 0.09 ETDRS letters), and eyes with severe VI (n = 122) had a statistically significant gain of 2.3 ETDRS letters (−0.045 logMAR) per year (95% CI, 1.00−3.52 ETDRS letters). These change rates (Table 3) suggested a dose-response relationship between baseline BCVA level and the rate of BCVA change. Therefore, we modeled baseline BCVA as continuous in the linear mixed-effects model that confirmed that the better the baseline BCVA, the larger the BCVA decline over 1 year ($P < 0.001$).

### Longitudinal Analysis of the Factors Associated with Risk of Loss of 1 Line or More from Baseline to 12-Month Visit

Among the 456 eyes observed at baseline and month 12, the proportion losing 1 line or more of VA was 12.9% (59/456). The risk of such loss was significantly different by baseline BCVA level (adjusted $P = 0.02$): 11.8%, 25%, 12.7%, and 5.5% in eyes without VI, with mild VI, with moderate VI, or with severe VI at baseline, respectively (Table 4). The risk of BCVA loss also was significantly different by age at symptom onset (adjusted $P = 0.03$). In particular, compared with participants with symptom onset at 14 years of age or younger, the risk of BCVA loss was 66% lower in participants with symptom onset of between 15 and 20 years of age (adjusted risk ratio [RR], 0.34; 95% CI, 0.14−0.82). Best-corrected VA loss of 1 line or more at 1 year was not associated with duration of symptoms at baseline, vitamin A use (at year 1), smoking status, or having nerve pallor, RPE pigmentary abnormalities, or flecks within the arcades. Having flecks outside arcades was associated with a lower risk of BCVA loss in univariate analysis, but the association was not significant in adjusted analysis.

## Discussion

We reported the demographic and clinical characteristics and change of BCVA over 1 year for STGD1 patients enrolled in the multicenter ProgStar prospective study. Our longitudinal analysis found that the rate of BCVA change was significantly different by baseline BCVA level, but overall, there was no significant change over 1 year of follow-up (estimated rate, 0.007 logMAR/year). This finding differs from our ProgStar retrospective cohort[20] in which BCVA declined at a small but statistically significant rate of 0.03 logMAR/year. The difference between these 2 findings in part may be the result of the differences in the length of follow-up between our 2 cohorts: The current analysis on the prospective cohort focused on data during 1 year of follow-up, whereas the retrospective study had variable but longer follow-up, with a median of 3.6 years. The difference in the 2 findings also may be because the retrospective cohort had better baseline VA than the prospective cohort, especially considering that both studies found that the rate of VA change was significantly different by baseline VA, with better baseline VA associated with a greater yearly rate of decline. These findings suggest that VA loss in STGD1 is not a linear process, where loss is greatest at an early stage when a degree of foveal vision is still present despite accompanying parafoveal degeneration,[21–23] and then BCVA loss

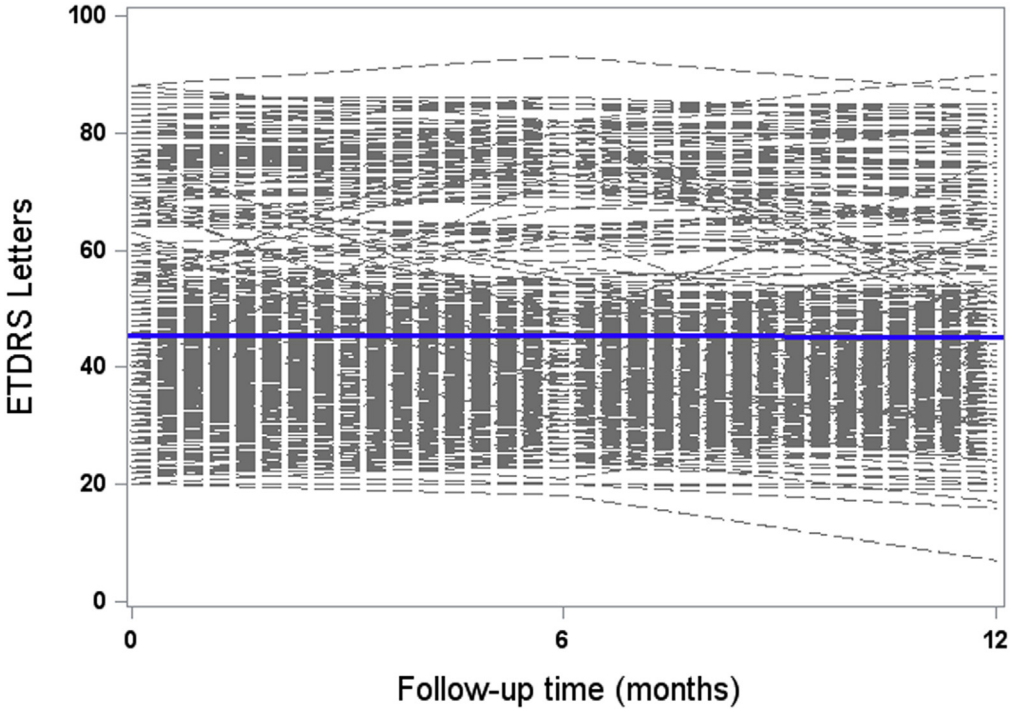


**Figure 2.** Spaghetti plot showing visual acuity of the participants during the 1-year follow-up. Each *gray line* represents data for 1 eye. The *blue line* represents the estimated average visual acuity change: −0.36 letters/year (95% confidence interval, −1.18 to 0.46 letters/year; 0.007 logarithm of the minimum angle of resolution). ETDRS = Early Treatment Diabetic Retinopathy Study.

slows after foveal vision is lost and fixation becomes eccentric.

Eyes without any visual impairment at baseline showed a loss of VA over 1 year, but it was not statistically significant. This may be the result of the small sample size in the group. The estimated rates of change in eyes without impairment (0.056 logMAR/year) and eyes with mild impairment (0.047 logMAR/year) were smaller than the estimates in the ProgStar retrospective cohort (0.096 and 0.094 logMAR/year, respectively).[20] This difference again is most likely because of the difference in length of follow-up and because of the nonlinear process of BCVA loss in STGD1. The rates of change in eyes with moderate or severe impairment at baseline were similar to those estimated in the retrospective study (approximately 0.02 logMAR/year loss and 0.05 logMAR/year gain, respectively), suggesting that VA change may be relatively constant at these stages.

In particular, similar to our findings in the ProgStar retrospective study and in our analysis with ProgStar participants with recent onset of symptoms,[11,20] we found that eyes with severe impairment (VA worse than 20/200) at baseline showed a small (approximately 0.5 lines/year) but statistically significant improvement in VA over time. The improvement may be the result of regression to the mean, where patients with poor vision tested poorly at baseline and tested slightly better at subsequent visits, reflecting normal variation. Additionally, VA is known to vary to a greater extent in patients with more severe visual impairment. However, it is also plausible for VA to improve as a result of

Table 3. Rate of Visual Acuity Change over 12 Months by Baseline Visual Acuity

| Baseline Visual Acuity* | Mean Visual Acuity Change (95% Confidence Interval) | Difference in Change Rate Compared with Reference Group (95% Confidence Interval) | *P* Value |
|---|---|---|---|
| No VI | 0.056 (−0.010 to 0.120) | Reference | **<0.001**† |
| Mild VI | 0.047 (0.017–0.077) | −0.008 (−0.080 to 0.063) | 0.82 |
| Moderate VI | 0.015 (−0.002 to 0.032) | −0.040 (−0.108 to 0.027) | 0.24 |
| Severe VI | −0.045 (−0.070 to −0.020) | −0.101 (−0.170 to −0.031) | 0.005 |

VA = visual acuity; VI = visual impairment.
Data are logarithm of the minimum angle of resolution units per year.
*No VI, VA ≥20/25; mild VI, VA <20/25 to 20/70; moderate VI, VA <20/70 to 20/200; severe VI/blindness, VA <20/200.
†Testing for difference in rate of VA change by baseline VA level.

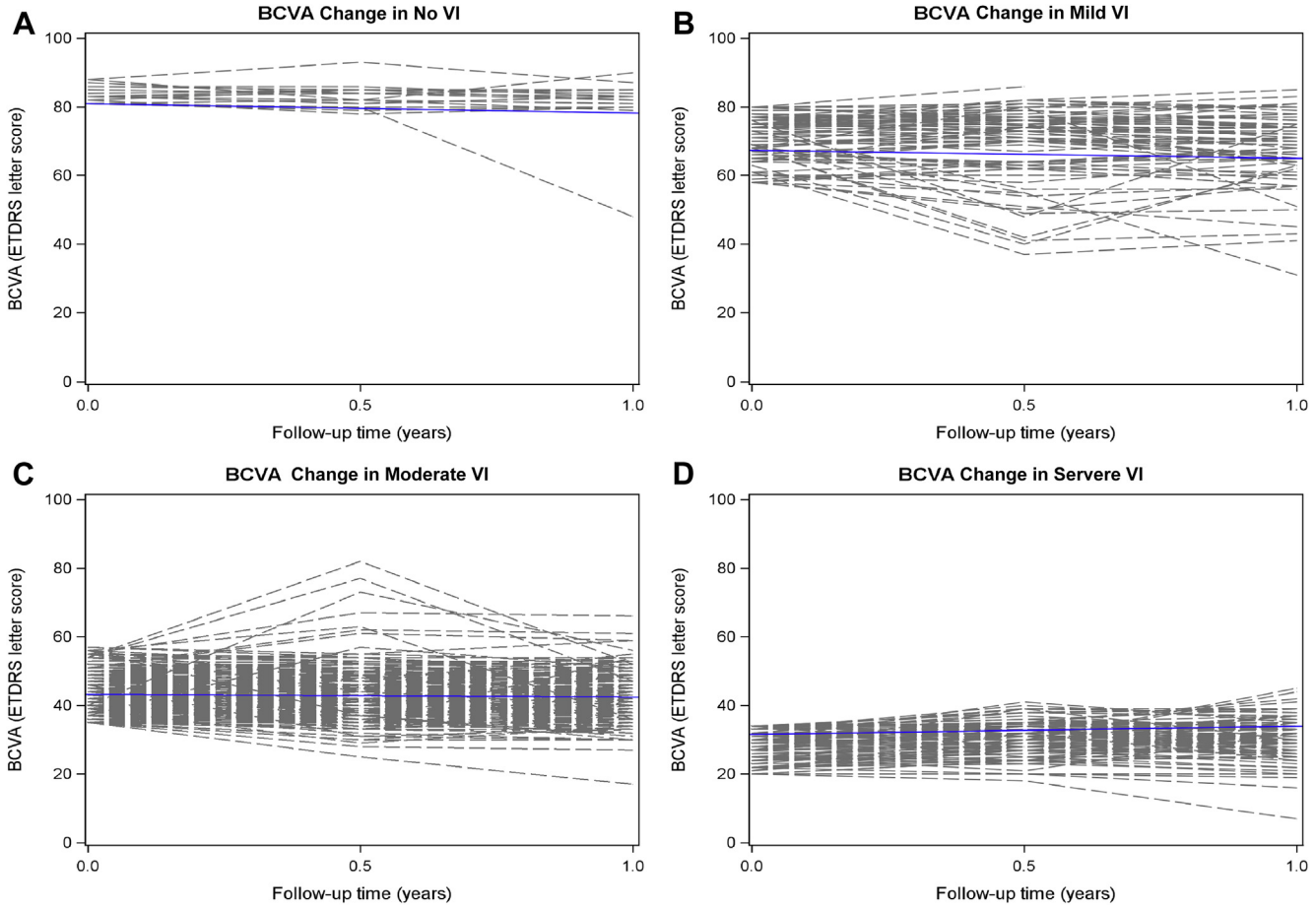


**Figure 3.** Spaghetti plots showing visual acuity change during 1 year of follow-up by baseline best-corrected visual acuity (BCVA) level. Each *gray line* represents data for 1 eye. The *blue line* represents the estimated average BCVA change. **A**, Visual acuity change in eyes with no visual impairment (Snellen equivalent, 20/25 or better) at baseline. Rate of change, −2.77 letters/year (95% confidence interval [CI], −6.02 to 0.49 letters/year; 0.056 logarithm of the minimum angle of resolution [logMAR]/year). **B**, Visual acuity change in eyes with mild visual impairment (Snellen equivalent, 20/25−20/70) at baseline. Rate of change, −2.35 letters/year (95% CI, −3.96 to −0.83 letters/year; 0.047 logMAR/year). **C**, Visual acuity change in eyes with moderate visual impairment (Snellen equivalent, 20/70−20/200) at baseline. Rate of change, −0.75 letters/year (95% CI, −1.59 to 0.09 letters/year; 0.015 logMAR/year). **D**, Visual acuity change in eyes with severe visual impairment (Snellen equivalent, worse than 20/200) at baseline. Rate of change, 2.26 letters/year (95% CI, 1.00−3.52 letters/year; −0.045 logMAR/year). ETDRS = Early Treatment Diabetic Retinopathy Study; VI = visual impairment.

change of the location of the preferred retinal locus, as has been observed in participants with geographic atrophy and inherited macular dystrophies.[24–27] Also, fixation stability may improve over time.[28] In the case of STGD1, it is possible for the preferred retinal locus to move from a superior retinal locus to the parapapillary region as the central scotoma expands with disease progression.[29] This hypothesis will be tested in conjunction with the microperimetry data from the ProgStar prospective study.

In clinical trials, loss of 15 ETDRS letters (equivalent to 3 Snellen lines) or more is considered clinically significant.[30] However, such loss was rare in our cohort during the 12 months: 12 eyes lost 3 lines or more from baseline to year 1, a risk of 2.6%. Clinically, loss of 1 line or more may be concerning for patients and their physicians, and such loss was not rare in our cohort, occurring in 59 eyes (12.9%). Consistent with the findings regarding the yearly rates of BCVA change, baseline BCVA level was the strongest predictor for BCVA loss of 1 line or more, with eyes with severe impairment at baseline having the lowest risk of such loss. For the variable of age at symptom onset, results from the multivariate model were similar to those from our retrospective ProgStar study: older age at symptom onset was associated with lower risk of BCVA loss of 1 line or more during the year. However, in this prospective cohort, the risk of BCVA loss of 1 line or more in the oldest onset age group (>30 years) was not significantly lower than the youngest onset age group (≤14 years). This discrepancy could be the result of the difference in outcomes in the 2 studies: the current analysis considered the dichotomized outcome of BCVA loss of 1 line more over 1 year (which was of clinical relevance), whereas the retrospective study assessed the yearly change rate that used the actual BCVA values (rather than dichotomized values) and that was based on data of variable follow-up lengths among participants.

Table 4. Risk of Best-Corrected Visual Acuity Loss between Baseline and Year 1 Visits and Risk Ratios Associated with Participant Characteristics

| Characteristic | No. of Eyes with Visual Acuity Loss/Total No. of Eyes (%) | Univariate Model | | | Multivariate Model* | | |
|---|---|---|---|---|---|---|---|
| | | *Risk Ratio* | *95% Confidence Interval* | P *Value*† | *Adjusted Risk Ratio* | *95% Confidence Interval* | P *Value*† |
| Baseline VA level | | | | 0.02 | | | 0.02 |
| No VI | 2/17 (11.8) | Reference | | | Reference | | |
| Mild VI | 19/76 (25.0) | 1.95 | 0.56–6.76 | | 2.04 | 0.61–6.84 | |
| Moderate VI | 32/253 (12.7) | 1.09 | 0.29–4.07 | | 1.03 | 0.27–3.92 | |
| Severe VI | 6/110 (5.5) | 0.46 | 0.10–2.08 | | 0.39 | 0.08–1.96 | |
| Age at baseline visit (yrs)‡ | | | | 0.30 | NA | | |
| ≤18 | 10/97 (10.3) | Reference | | | | | |
| >18–50 | 33/284 (11.6) | 1.08 | 0.53–2.21 | | | | |
| 50+ | 16/75 (21.3) | 1.95 | 0.85–4.43 | | | | |
| Gender | | | | 0.30 | NA | | |
| Female | 28/246 (11.4) | Reference | | | | | |
| Male | 31/210 (14.8) | 1.32 | 0.78–2.25 | | | | |
| Race | | | | 0.56 | NA | | |
| White | 50/398 (12.6) | Reference | | | | | |
| Nonwhite | 9/58 (15.5) | 1.22 | 0.62–2.44 | | | | |
| Age at symptom onset (yrs) | | | | 0.05 | | | 0.03 |
| ≤14 | 19/133 (14.3) | Reference | | | Reference | | |
| 15–20 | 6/96 (6.3) | 0.42 | 0.17–1.03 | | 0.34 | 0.14–0.82 | |
| 21–30 | 11/94 (11.7) | 0.80 | 0.38–1.68 | | 0.53 | 0.23–1.19 | |
| 30+ | 19/98 (19.4) | 1.31 | 0.67–2.59 | | 0.90 | 0.47–1.73 | |
| Duration from symptom onset to baseline visit (yrs) | | | | 0.91 | | | 0.68 |
| 0–2 | 9/55 (16.4) | Reference | | | Reference | | |
| >2–6 | 12/103 (11.7) | 0.73 | 0.32–1.66 | | 0.78 | 0.33–1.84 | |
| >6–11.5 | 13/104 (12.5) | 0.78 | 0.35–1.74 | | 0.90 | 0.39–2.06 | |
| 11.5+ | 21/163 (12.9) | 0.78 | 0.35–1.73 | | 1.30 | 0.62–2.73 | |
| Vitamin A use at year 1 | | | | 0.15 | NA | | |
| No | 49/408 (12.0) | | | | | | |
| Yes | 10/48 (20.8) | 1.72 | 0.83–3.57 | | | | |
| Smoking status | | | | 0.31 | NA | | |
| Never | 50/351 (14.3) | Reference | | | | | |
| Former | 5/59 (8.5) | 0.60 | 0.19–1.93 | | | | |
| Current | 4/46 (8.7) | 0.58 | 0.21–1.60 | | | | |
| Nerve pallor | | | | 0.09 | NA | | |
| No | 57/409 (13.9) | Reference | | | | | |
| Yes | 1/41 (2.4) | 0.15 | 0.02–1.32 | | | | |
| RPE pigmentation | | | | 0.49 | | | 0.78 |
| No | 22/152 (14.5) | Reference | | | Reference | | |
| Yes | 36/298 (12.1) | 0.82 | 0.47–1.44 | | 0.92 | 0.53–1.58 | |
| Flecks within arcades | | | | 0.16 | NA | | |
| No | 8/37 (21.6) | Reference | | | | | |
| Yes | 50/413 (12.1) | 0.55 | 0.24–1.27 | | | | |

Table 4. (Continued.)

| Characteristic | No. of Eyes with Visual Acuity Loss/Total No. of Eyes (%) | Univariate Model | | | Multivariate Model* | | |
|---|---|---|---|---|---|---|---|
| | | *Risk Ratio* | *95% Confidence Interval* | P *Value*† | *Adjusted Risk Ratio* | *95% Confidence Interval* | P *Value*† |
| Flecks outside arcades | | | | 0.03 | | | 0.23 |
| No | 41/247 (16.6) | Reference | | | Reference | | |
| Yes | 17/202 (8.4) | 0.51 | 0.29–0.92 | | 0.70 | 0.38–1.29 | |

RPE = retinal pigment epithelium; VA = visual acuity; VI = visual impairment.
*Included continuous baseline VA, age at symptom onset, duration of symptoms, and presence of RPE pigmentation and flecks outside the arcades.
†Testing for difference in risk of VA loss of 1 line or more over the course of 1 year among the subgroups determined by the baseline variable.
‡The multivariate model included categorized baseline VA level, categorized age at symptom onset, categorized duration of symptoms, presence of RPE pigmentation, and presence of flecks outside the arcades. Age at baseline was not included because it was a linear function of age at symptom onset and duration of symptoms.

Similar to the retrospective study, duration of symptoms, presence of RPE pigmentary changes, flecks within the arcades, and flecks outside the arcades were not associated with the 1-year risk of BCVA loss of 1 line or more. We are not aware of prior studies that assessed the effects of smoking and vitamin A use in STGD1 patients. Our longitudinal analysis did not find a higher risk of loss of BCVA during the year associated with smoking and vitamin A use. Because few people used vitamin A (14%) or smoked (11%) in this cohort, it is possible that the study was underpowered to detect small effects.

Examination of the brand names of the supplement showed that the supplementation often was through multivitamin use. The cross-sectional analysis at baseline showed that baseline BCVA was not significantly different by smoking or vitamin A use. Other results from the baseline cross-sectional analysis are similar to prior published studies and to our earlier findings in the retrospective ProgStar cohort[11,13,14,31]: a younger age at symptom onset and a longer duration between symptom onset and baseline visit were associated with worse VA, and older age was associated with worse VA, which is compatible with the finding that the longer the duration between symptom onset and baseline visit, the poorer the VA.

The ProgStar prospective study is a large-scale study and the first to examine STGD1 with prospective data collection under a predesigned standardized study protocol involving multiple sites from both the United States and Europe, greatly increasing generalizability. One limitation of the study herein is that we inferred that the VA loss trajectory was nonlinear in STGD1. However, this inference was not based on directly observing the VA trajectory over many years from the same individuals; rather, it was based on data from multiple participants with different current VA levels and who showed different rates of VA change over 1 year. Nonetheless, considering the small rate of change per year, it is reasonable to use linear models to describe the BCVA change over 1 year.

Stargardt disease patients may show distinct phenotypes at presentation, such as macular atrophy surrounded by flecks, patchy or mottled foveal changes, bull's-eye maculopathy, foveal sparing, and others.[8,32] These phenotypes may be associated with different genetic variants and may have different VA progression patterns[33–35]; for example, the foveal sparing phenotype is known to be on the milder end of the spectrum of the disease, and VA of patients with such a phenotype may be maintained longer.[34,36,37] However, because our clinical data did not record specific phenotype information, we were unable to assess VA change associated with each phenotype in our cohort. Nevertheless, using information from fundus autofluorescence image grading, we will evaluate VA in patients with no foveal involvement at baseline in a subsequent ProgStar report. Another limitation of this report is that at baseline, the study tested participant BCVA only once using the ETDRS protocol, and thus did not control for any potential learning effect associated with the ETDRS chart. However, at least 56% of participants had undergone ETDRS VA testing during routine clinical visits before this study enrollment, and thus a learning effect should be minimal in these participants.

Best-corrected VA is an important visual function outcome directly related to participants' daily activities[38] and is the most common outcome measure for efficacy studies of retinal diseases.[30] However, our data suggested that the change of BCVA in STGD1 was small and not statistically significant over the course of 1 year. Because it will be difficult for trials aiming to prevent or slow VA loss to show a difference over a 1-year period, VA is not sensitive enough to serve as a primary outcome. Nevertheless, we found that the change in BCVA depended on the starting level of BCVA, and faster progression was observed in patients with baseline BCVA better than 20/70. This information may inform planning of future trials that target patients who are most likely to show VA loss at 12 months.

In summary, we found that there was no significant change in BCVA over the course of 1 year, but baseline BCVA level was associated with different rates of subsequent BCVA change. We found that patients with poor vision at baseline showed a small, but statistically significant, gain in VA. Smoking and vitamin A use was not associated with worse BCVA at baseline, nor was it associated with higher risk of BCVA loss during the 1-year follow-up. Best-corrected VA seems to be relatively insensitive to detect changes in a reasonable period. Therefore, it is important to explore other potentially more sensitive outcome measures derived from functional or morphologic analysis, such as microperimetry, optical coherence tomography, adaptive optics, or fundus autofluorescence imaging.

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Abbreviations and Acronyms:
**BCVA** = best-corrected visual acuity; **ETDRS** = Early Treatment Diabetic Retinopathy Study; **GEE** = generalized estimating equation; **IQR** = interquartile range; **logMAR** = logarithm of the minimum angle of resolution; **ProgStar** = Progression of Atrophy Secondary to Stargardt Disease; **RPE** = retinal pigment epithelium; **STGD1** = Stargardt disease; **VA** = visual acuity; **VI** = visual impairment.

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