Visual Acuity Loss and Associated Risk Factors in the Retrospective Progression of Stargardt Disease Study (ProgStar Report No. 2)

Xiangrong Kong, PhD,[1,2*]
Rupert W. Strauss, MD,[1,3,4*]
Michel Michaelides, MD,[3]
Artur V. Cideciyan, PhD,[5]
José-Alain Sahel, MD, [6]
Beatriz Muñoz, MS, [1]
Sheila West, PhD,[1]
Hendrik P.N. Scholl, MD, MA,[1**]
for the ProgStar Study Group

[1] Wilmer Eye Institute, Johns Hopkins University, Baltimore, MD, USA.
[2] Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA.
[3] Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology, London, United Kingdom.
[4] Departments of Ophthalmology, Medical University Graz and Johannes Kepler University Linz, Linz, Austria.
[5] Scheie Eye Institute, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA.
[6] Sorbonne Universités, University Pierre et Marie Curie (UPMC) Université de Paris 06, Institut national de la santé et de la recherche médicale (INSERM), Centre national de la recherche scientifique (CNRS), Institut de la Vision, Centre Hospitalier National d'Ophtalmologie (CHNO) des Quinze-Vingts, Paris, France.

*contributed equally and share first authorship

**Corresponding Author:
Hendrik P.N. Scholl, MD, MA,
Wilmer Eye Institute, Johns Hopkins University,
Maumenee 748
600 N. Wolfe Street,
Baltimore, Maryland 21287
Telephone (Office): 1-410-502-2789
Office Fax: 1-443-287-8343
(hscholl1@jhmi.edu)

Financial Disclosure:

Running head: Visual acuity loss in Stargardt disease

Address for reprints: Hendrik P.N. Scholl, MD, MA, Wilmer Eye Institute, Johns Hopkins University, 600 N. Wolfe Street, Baltimore, Maryland 21287, phone: +1 410 614 6908 (hscholl1@jhmi.edu)

Supplemental materials: This article contains additional online-only material. The following should appear online-only: Supplemental text (Statistical anaylsis details), supplemental table 1, supplemental figure 1 and ProgStar study team list (available at http://www.aaojournal.org)

1 **Abstract**

2 **Purpose:** To examine the association between characteristics of Stargardt disease and visual

3 acuity (VA), to estimate the longitudinal rate of VA loss, and identify risk factors for VA loss.

4 **Design:** Retrospective, multi-center cohort study.

5 **Participants:** 176 patients (332 eyes) with molecularly and clinically confirmed Stargardt

6 disease enrolled from the USA and Europe.

7 **Methods:** Standardized data report forms were used to collect retrospective data on

8 participants' characteristics and best-corrected or presenting VA from medical charts. Linear

9 models with generalized estimating equations were used to estimate the cross-sectional

10 associations, and linear mixed effects models were used to estimate the longitudinal VA loss.

11 Main Outcome Measures: Yearly change in visual acuity.

12 **Results:** The median duration of observation was 3.6 years. At baseline, older age of

13 symptom onset was associated with better VA, and a longer duration of symptoms with

14 worse VA. Longitudinal analysis estimated an average of 0.3 lines loss (p<0.0001) per year

15 overall, but the rate varied according to baseline VA: (i) eyes with baseline VA better than or

16 equal to 20/25 (N=53) declined at a rate of ~1.0 line per year; (ii) eyes with VA between

17 20/25 and 20/70 (N=65) declined at a rate of ~0.9 lines per year; (iii) eyes with VA between

18 20/70 and 20/200 (N=163) declined at a rate of 0.2 lines per year; and (iv) eyes with VA

19 worse than 20/200 (n=49), improved at a rate of 0.5 lines per year. Older age of onset was

20 associated with slower VA loss: patients with onset age >30 years showed 0.4 lines slower

21 change of VA per year (p=0.01) compared to patients with onset ≤14 years.

22 **Conclusion**: Given the overall slow rate of VA loss, VA is unlikely to be a sensitive outcome

23 measure for treatment trials of Stargardt disease. However, given the faster decline in

24 younger patients and those with no or mild visual impairment, VA may be a potential

25 outcome measure for trials targeting such subgroups of patients. These observations will

26 need to be assessed in a prospective study bearing in mind the inherent limitations of

27 retrospective datasets.

28

Introduction

Stargardt macular dystrophy (STGD1; OMIM: 248200) is the most common macular dystrophy with a prevalence of 10-12.5 per 100,000 persons,[1] and is inherited as an autosomal recessive trait.[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 atrophic lesions. Patients with STGD1 experience progressive impairment of visual acuity which often begins in the first or second decade of life, but some patients may maintain good VA until the fourth or fifth decade of life.[3] Currently there is no approved treatment for the disease, with on-going phase I/II clinical trials based on gene, stem cell, and pharmacological therapy.

There are limited data documenting the rate of change of visual acuity (VA) in STGD1. Several studies have reported average VA measured at two study visits,[4-6] these analyses however did not take into consideration the variable length of follow-up of the study participants. Rotenstreich et al. estimated the time to reach VA of 20/200 and its association with age among participants with VA of 20/40 or better, or VA between 20/50-20/100, at their first study visit.[7] Oh et. al. compared the time to vision loss of 20/200 VA among different clinical phenotypes.[8] More recently, the longitudinal analysis from Testa et al, [9] estimated the yearly progression rate of best corrected VA in STGD1 patients with an age of onset younger than 30 years.

To better understand visual function loss in STGD1 and to help assess the appropriateness of VA as an outcome measure for future treatment trials, we analyzed data from the retrospective multi-center study on "the natural history of the Progression of Atrophy

5

53   Secondary to <u>Stargardt Disease (ProgStar)</u>". Our specific purposes were to examine the

54   cross-sectional relationship between participant demographic, clinical characteristics and

55   baseline VA, to estimate the yearly rate of VA loss using the longitudinal data, and to identify

56   participant demographic and clinical characteristics associated with yearly VA change rate.

57   We identified that the rate of VA loss in the entire cohort was too slow to be an effective

58   clinical trial outcome measure. However, a faster decline in younger patients and those with

59   no or mild visual impairment at baseline, suggests that VA may be a potential end-point in

60   these patient subgroups, and is worthy of assessment in a prospective study bearing in mind

61   the inherent biases of retrospective data.

62

63   **Participants and Methods**

64   Data for this analysis are derived from the retrospective ProgStar study which has been

65   described in detail elsewhere.[10] In brief, from March of 2013 to December of 2014, eligible

66   participants were identified and enrolled through retrospective review of medical charts at

67   nine participating sites, including six sites from the United States, and one site each from the

68   United Kingdom, France and Germany. Inclusion criteria were:[10] (1) presence of at least one

69   well-demarcated area of atrophy with a minimum diameter of 300 μm, with the total area of

70   all atrophic lesions being less than or equal to 12 mm^2 at the most recent visit; (2) presence

71   of at least two likely disease-causing variants in *ABCA4*, or one likely disease-causing variant

72   associated with at least one eye with flecks at the level of the RPE typical for STGD1; (3)

73   sufficient quality of images and/or psychophysical tests; (4) age at least six years at the most

74   recent visit; (5) follow-up for at least two visits over a period of at least 24 months, up to 60

75   months between single visits, and must have had at least one test of the following

76   completed at each visit for the same eye(s): FAF obtained with a Heidelberg Engineering®

77   instrument (e.g. HRA2) and/or SD-OCT obtained with the Heidelberg® Spectralis and/or MP

78   obtained with the Nidek® MP-1

79   Exclusion criteria were: (1) presence of ocular disease in either eye that may confound

80   assessment of the retina morphologically and functionally; (2) intraocular surgery in the

81   study eye(s) within 90 days prior to any eligible visit; (3) current or previous participation in a

82   clinical trial to treat STGD1; and (4) current participation in, or participation within the last

83   six months in, any drug trial.

84

85   Prior to data collection, site investigators and study coordinators received training from the

86   data coordinating center (DCC) in chart review, reporting of VA, and in data entry using the

87   REDCap (Research Electronic Data Capture) system (http://www.project-

88   redcap.org/cite.php). A standardized clinical report form (CRF), designed by the DCC, was

89   used at all sites to record information on VA, results from the biomicroscopy of the anterior

90   segments and dilated fundus examination, and use of vitamin A supplementation at each

91   study visit. Participant's age at enrollment, gender, race and age of symptom onset were

92   identified from chart review and recorded in a standardized demographic form. For each

93   participant, data of up to four visits were collected.

94

95   Monocular VA was measured using either Snellen or "Early Treatment of Diabetic

96   Retinopathy Study (ETDRS)" charts,[11] and the measurements extracted from chart review

97   were entered into the CRF. A participant may have multiple types of VA captured at a visit,

98   including best or presenting VA with correction (BPC VA), uncorrected (SC), and pinhole VA.

99   Up to two types of VA were recorded in the CRF for each eye at each visit. As BPC VA

100   constituted the major type of VA measurement, all downstream analyses used BPC VA.

101

102   The retrospective ProgStar study was approved by the Western Institutional Review Board

103   (WIRB), the local institutional review boards (IRB), and the Human Research Protection

104   Office (HRPO) of the U.S. Army Medical Research & Materiel Command (USAMRMC). The

105   study was registered at www.clinicaltrials.gov (Identifier NCT01977846). If required by the

106   local IRB, participants' consent was obtained prior to data collection.

107

108   **Statistical analysis**

109   Participant demographic and clinical characteristics at the first study visit (baseline visit)

110   were summarized. Baseline data of study eyes were used to explore the cross-sectional

111   association of VA with demographics including age (<=18, >18-50, 50+ years), gender, and

112   race (white vs. non-white), and clinical characteristics including age at symptom onset (≤14,

113   15-20, 21-30, 30+) and duration of symptoms (0-2, >2-6, >6-11.5 and >11.5-53 years).

114

115   VA measures were converted to LogMAR scale, and univariate linear models with

116   generalized estimating equations (GEE) were used to estimate the unadjusted cross-

117   sectional associations while accounting for between-eye correlation, followed by

118   multivariate linear models with GEE to estimate the adjusted associations adjusting for

119   variables associated with VA in univariate analyses with $p<0.1$. Additionally, the variables of

120   baseline age, and age of onset and duration, were also modeled as continuous variables.

121

122   Linear mixed effects model (LMM) was used on the longitudinal data to estimate the yearly

123   change rate of VA as described in the supplemental material (available at

124   www.aaojournal.org). To further identify baseline variables associated with VA change rate,

125 LMMs were used by including each variable and its interaction with time. Baseline variables

126 examined included the aforementioned demographics and clinical characteristics, with

127 baseline VA also categorized on the basis of WHO's International Classification of Diseases

128 (ICD)-10,[10, 12] as (i) VA better than or equal to 20/25 (LogMAR≤ 0.1) (i.e. no visual impairment

129 [VI]); (ii) worse than 20/25 to 20/70 (LogMAR 0.1-0.54) (i.e. mild VI); (iii) worse than 20/70 to

130 20/200 (LogMAR 0.54-1.0) (i.e. moderate VI); (iv) worse than 20/200 to 20/400 (LogMAR 1.0-

131 1.3) (i.e. severe VI); and (v) worse than 20/400 (LogMAR>1.3) (i.e. blindness). The univariate

132 association of each variable with VA change rate was first estimated. As VA progression rate

133 was shown to differ significantly by baseline VA, adjusted associations were also estimated

134 using multivariate LMMs including variables that were significantly associated with baseline

135 VA at p<0.1.

136

137 All analyses were conducted in SAS 9.3, and two-sided p-values from Wald-tests were

138 reported. For the cross-sectional analysis using GEE models, model fit was assessed using

139 aggregated residuals,[13] and for the longitudinal analysis using LMMs, model fit was assessed

140 using plots of scaled residuals.

141

142 **Results**

143 Among the 251 participants enrolled in the retrospective ProgStar study, 176 participants

144 with 332 study eyes had BPC VA measurements available for at least two visits and thereby

145 constituted the study sample (Figure 1). There were 165 participants (94%) with at least two

146 likely disease-causing variants in *ABCA4* (23/165 had three, and 4/165 had four disease-

147 causing mutations). The remaining 11 participants had one likely disease-causing variant

148 detected. The median duration of observation was 3.6 years (interquartile range [IQR] 2.7-

149   5.1 years), and each participant contributed data for 2 to 4 visits (Figure 1).

150

151   Table 1 summarizes the baseline demographic and clinical characteristics of these

152   participants and the study eyes. There were 109 females (61.9%), and the majority of

153   participants were white (71.6%). At baseline, the median age was 29.5 (IQR 20-42) years.

154   Among participants whose age of symptom onset was available (N=140), median age of

155   onset was 20 (IQR 14-30) years. The median duration from the age of onset to the baseline

156   visit was 6 (IQR 2-11.5) years. The median Snellen VA at baseline was 20/115 and LogMAR

157   was 0.76 (IQR 0.40-1.00), ranging from -0.10 to 1.40. Based on the categorized BPC VA, 53

158   eyes (16.1%) had no impairment, 65 eyes (19.7%) had mild impairment, 163 (49.4%) eyes

159   had moderate impairment, and 49 eyes (14.8%) had severe impairment or were blind (Table

160   1 and Figure 2). Details of the excluded participants and comparisons with the included are

161   provided in supplemental table 1 (available at www.aaojournal.org).

162

163   *Cross-sectional associations of participant characteristics with baseline visual acuity*

164   Table 2 presents the baseline VA in subgroups determined by participant characteristics and

165   the difference of VA between subgroups. When age was modeled as a continuous variable,

166   worsening VA was significantly associated with older age (adjusted VA LogMAR difference

167   with every 5 years older in age: 0.04, 95%CI [0.01, 0.07], p=0.006); suggesting that the

168   observation of worse VA associated with younger age in univariate analysis was mainly

169   explained by earlier symptom onset in younger participants.

170

171   Figures 3A and 3B show the distribution of baseline VA by quartiles of age at onset and

172   duration of symptoms respectively. Later symptom onset was associated with better VA in

173   both univariate and multivariate analyses (Table 2): compared to patients with onset age

174   ≤14 years and after adjusting for duration since symptom onset, both patients with onset

175   age >30 years had ~2.3 lines better VA (LogMAR adjusted difference -0.23, 95%CI -0.39, -

176   0.06, p=0.007), and patients with onset age of 21-30 years had 1.1 lines better VA (LogMAR

177   difference -0.11, 95%CI -0.25, 0.03, p=0.12). Longer duration since symptom onset was

178   associated with worse VA: after adjusting for age of onset, patients who had symptoms for

179   6-11.5 years and patients with symptoms for over 11.5 years both had 1.8 lines worse VA

180   (LogMAR difference 0.18, 95%CI 0.03, 0.33, p=0.002, and difference 0.18, 95%CI 0.02, 0.33,

181   p=0.03, respectively) compared to patients with recent onset (duration ≤2years) (Table 2).

182

183   _Longitudinal analysis of yearly change in visual acuity and associated risk factors_

184   The overall yearly rate of VA change was ~0.3 lines worsening per year; LogMAR change of

185   0.03, 95%CI (0.026, 0.043; p<0.0001) per year. Table 3 shows the yearly VA change rate by

186   subgroups and the differences between subgroups. The baseline VA level was significantly

187   associated with yearly rate of VA change: (i) VA of eyes with no impairment worsened at a

188   rate of ~1.0 line (LogMAR rate 0.096, 95%CI [0.080, 0.112]) per year; (ii) eyes with mild

189   impairment worsened at a rate of ~0.9 lines (LogMAR rate 0.094, 95%CI [0.080, 0.107]) per

190   year; and (iii) VA of eyes with moderate impairment worsened at a rate of 0.2 lines (LogMAR

191   rate 0.019, 95%CI [0.008, 0.029]) per year. For eyes with severe impairment or blindness at

192   baseline, their VA improved at an annual rate of 0.5 lines (LogMAR rate -0.047, 95%CI [-

193   0.064, -0.031]) per year. Figure 4 shows the estimated average rates of change in these

194   subgroups (Spaghetti plots are provided as Supplemental Figure 1, available at

195   http://www.aaojournal.org). When comparing the annual VA change between different

196   baseline VA groups, there were significant differences in both univariate and multivariate

197 analyses: the adjusted LogMAR difference in yearly VA change rate was -0.08 (95%CI [-0.11,-

198 0.06], p<.0001) between eyes with moderate impairment and eyes with no impairment, and

199 was -0.16 (95%CI [-0.19,-0.12], p<.0001) between eyes with severe impairment / blindness

200 and eyes with no impairment. However, the VA loss rate was not significantly different

201 between eyes with mild and no impairment.

202

203 Age of symptom onset was not associated with VA change in univariate analysis (Table 3).

204 However, in the multivariate analysis that adjusted for baseline VA and symptom duration,

205 compared to patients with age of onset ≤14 years, participants with symptom onset age >30

206 years had a significant 0.4 lines slower change of VA per year (LogMAR difference -0.04,

207 95%CI [-0.07, -0.01] per year, p=0.01). When age of onset was modeled as a continuous

208 variable, every 5 years later in symptom onset was also associated with a significantly slower

209 VA loss (i.e. difference in LogMAR VA change rate=-0.006, 95%CI [-0.01, -0.002] per year,

210 p=0.005).

211

212 Longer symptom duration was significantly associated with slower VA worsening in

213 univariate analysis (Table 3). After adjusting for baseline VA and age of onset, duration was

214 no longer associated with VA change (Table 3).

215

216 **Discussion**

217 We have characterized the demographic and clinical characteristics and VA of a cohort of

218 STGD1 patients enrolled from the US and Europe in the ProgStar retrospective study. Half of

219 the participants reported onset of symptoms at age of 30 years or older, i.e. adult-onset

220 STGD1.

221

222 In our study, over 35% of the study eyes had no or mild visual impairment at baseline, with

223 the average BPC VA being better than that of participants enrolled in prior studies.[7, 9, 14]

224 Nevertheless, as reported in these studies, our cross-sectional analysis also showed that a

225 younger age of symptom onset was associated with worse VA. Additionally, as reported in

226 Testa et al., we found that a longer duration of onset was associated with worse VA.[9] Older

227 age groups had better VA, which was also observed in Rotenstreich et al.[7] Considering

228 younger participants have earlier symptom onset, after adjusting for age of onset, our

229 multivariate analysis showed that older age was associated with worse VA, which is

230 compatible with our finding that longer duration since symptom onset was associated with

231 poorer VA.

232

233 Our longitudinal analysis estimated a 0.3 line loss of BPC VA per year overall. A similar rate of

234 VA change can be inferred from the survival analysis by Rotenstreich et al.[7] that reported a

235 median time of 22 years from VA of 20/40 or better to reach VA of 20/200 or worse (i.e. ~7

236 lines loss in 22 years). For the group of participants with symptom onset age <30 years, we

237 estimated the rate of VA loss to be ~ 0. 4 lines per year. The same rate was also reported in

238 the recent study by Testa et al.[9] that focused on patients with age of onset <30 years.

239

240 We found the better the baseline VA, the faster decline over time: VA of eyes starting with

241 no or mild impairment declined one line per year, and VA of eyes with moderate impairment

242 declined at a significantly slower rate. Counterintuitively, eyes that already had VA worse

243 than 20/200 at baseline showed a small but statistically significant improvement in VA over

244 time. This may relate to the poor inherent accuracy of Snellen charts in measuring low

245 vision[15] Other reasons include a lack of standardization in illumination, correction for

246 refractive errors, and contrast in the tests that generated our VA data. However, there is

247 also a biological plausibility for observing improvement in VA, as a result of change of the

248 fixation location of the preferred retinal locus (PRL). [16-19] This phenomenon of eccentric

249 fixation and its better use by the patient over time is currently an area of interest for on-

250 going research, especially in the context with reading rehabilitation.[20] In the case of STGD1,

251 it is also possible for the PRL to move from a superior retinal locus to the peripapillary region

252 as the central scotoma expands with disease progression.[21] Another possible explanation

253 might be the statistical phenomenon of "regression towards the mean" that describes the

254 observation of outliers being more likely to retest closer to their mean values. [22]

255

256 In keeping with previous findings, after controlling for baseline VA level, younger age of

257 symptom onset was associated with faster loss of VA.[7]

258 Our data may have implications on selection of appropriate outcome measures for future

259 STGD1 clinical trials. VA is an important visual function outcome directly related to

260 participants daily activities,[23] and is the most common primary outcome measure for

261 efficacy studies of retinal diseases.[24] Changes of at least 15 ETDRS letters are considered

262 clinically significant.[24] Our study showed that the overall rate of VA decline was slow, thus

263 VA is not sensitive enough to show a clinically relevant change during a treatment trial.

264 However, we found that for the subgroup of participants with no or mild visual impairment

265 (35% of the cohort), the VA loss rate was approximately 1 line per year; suggesting that in a

266 trial with three to four years of follow-up a clinically significant change may be anticipated in

267 such participants. Hence a therapy shown to be efficacious in slowing VA deterioration in

268 this population may potentially benefit a significant number of patients with STGD1. One

269 limitation of this finding is that it only alludes to patients enrolled into this retrospective

270 study who by definition have shown some degree of progression in the past..

271

272 Our study herein has further limitations. First, data were collected through retrospective

273 review of medical records, thus VA was not measured in a standardized way over time

274 within the same clinic and across the different study sites. Second, our longitudinal analysis

275 used repeatedly measured best-corrected or presenting VA. As chart review often could not

276 differentiate between best corrected VA and presenting VA, it was possible that the change

277 observed in a participant was due to change in refraction rather than due to disease

278 progression. Third, BPC VA was not consistently available in all participants, and only 70%

279 had multiple visits with BPC VA data available. Comparison between participants included in

280 and those excluded from this analysis showed comparable distributions of most participant

281 characteristics, but there was difference in race composition and vitamin A use status (see

282 supplemental table 1, available at www.aaojournal.org). However, such differences are

283 unlikely to have biased the results as race and vitamin A use was not found to be associated

284 with VA change. Lastly, information on age of symptom onset could not be retrieved for 18%

285 of participants. However, comparisons between participants with known and those with

286 unknown age of onset did not show significant differences in their demographics and

287 baseline VA distributions (data not shown), thus the results regarding age of onset using

288 available data should not have been biased.

289

290 Strengths of our study include that we assessed the associations of VA with a range of

291 variables on demographics and clinical characteristics, some of which have not been

292 explored previously. Additionally, our study participants were enrolled from multiple sites in

293   the US and Europe, increasing the generalizability of our findings. Lastly, despite being a

294   retrospective study, data abstraction and entry was conducted in a standardized way by

295   trained study coordinators, and the data coordinating center's monitoring visits at the

296   participating sites ensured the data quality.

297   In conclusion, we identified that the rate of VA loss in the entire cohort was too slow to be

298   an effective clinical trial outcome measure. However, a faster decline in younger patients

299   and those with no or mild visual impairment at baseline, suggests that VA may be a potential

300   end-point in these patient subgroups, and is worthy of assessment in the prospective study

301   bearing in mind the inherent biases of retrospective data. It is also important to explore

302   other potentially more sensitive outcome measures based on imaging modalities or

303   psychophysical tests, such as spectral-domain optical coherence tomography[25] or

304   microperimetry.[26]

305

306   **References:**

307   1.   Michaelides M, Hunt DM, Moore AT. The genetics of inherited macular dystrophies. J

308   Med Genet 2003;40:641-50.

309   2.   Allikmets R, Singh N, Sun H, et al. A photoreceptor cell-specific ATP-binding

310   transporter gene (ABCR) is mutated in recessive Stargardt macular dystrophy. Nat Genet

311   1997;15:236-46.

312   3.   Fishman GA, Farber M, Patel BS, Derlacki DJ. Visual acuity loss in patients with

313   Stargardt's macular dystrophy. Ophthalmology 1987;94:809-14.

314   4.   Kim LS, Fishman GA. Comparison of visual acuity loss in patients with different stages

315   of Stargardt's disease. Ophthalmology 2006;113:1748-51.

316   5.   Zahid S, Jayasundera T, Rhoades W, et al. Clinical phenotypes and prognostic full-field

317   electroretinographic findings in Stargardt disease. Am J Ophthalmol 2013;155:465-73 e3.

318   6.   Fujinami K, Lois N, Davidson AE, et al. A longitudinal study of stargardt disease:

319   clinical and electrophysiologic assessment, progression, and genotype correlations. Am J

320   Ophthalmol 2013;155:1075-88 e13.

321   7.   Rotenstreich Y, Fishman GA, Anderson RJ. Visual acuity loss and clinical observations

322   in a large series of patients with Stargardt disease. Ophthalmology 2003;110(6):1151-8.

323   8.   Oh KT, Weleber RG, Oh DM, et al. Clinical phenotype as a prognostic factor in

324   Stargardt disease. Retina 2004;24:254-62.

325   9.   Testa F, Melillo P, Di Iorio V, et al. Macular function and morphologic features in

326   juvenile stargardt disease: longitudinal study. Ophthalmology 2014;121:2399-405.

327   10.   Strauss RW, Ho A, Munoz B, et al. The Natural History of the Progression of Atrophy

328   Secondary to Stargardt Disease (ProgStar) Studies: Design and Baseline Characteristics:

329   ProgStar Report No. 1. Ophthalmology 2016;123:817-28

330   11.   Early Treatment Diabetic Retinopathy Study design and baseline patient

331   characteristics. ETDRS report number 7. Ophthalmology 1991;98(5 Suppl):741-56.

332   12.   Dandona L, Dandona R. Revision of visual impairment definitions in the International

333   Statistical Classification of Diseases. BMC Med 2006;4:7.

334   13.   Lin DY, Wei LJ, Ying Z. Model-checking techniques based on cumulative residuals.

335   Biometrics 2002;58(1):1-12.

336   14.   Miraldi Utz V, Coussa RG, Marino MJ, et al. Predictors of visual acuity and genotype-

337   phenotype correlates in a cohort of patients with Stargardt disease. Br J Ophthalmol

338   2014;98:513-8.

339   15.   Kaiser PK. Prospective evaluation of visual acuity assessment: a comparison of snellen

340   versus ETDRS charts in clinical practice (An AOS Thesis). Trans Am Ophthalmol Soc

341   2009;107:311-24.

342   16.   Sunness JS, Applegate CA, Gonzalez-Baron J. Improvement of visual acuity over time

343   in patients with bilateral geographic atrophy from age-related macular degeneration. Retina

344   2000;20:162-9.

345   17.   Singerman LJ, Wong B, Ai E, Smith S. Spontaneous visual improvement in the first

346   affected eye of patients with bilateral disciform scars. Retina 1985;5:135-43.

347   18.   Ishiko S, van de Velde F, Yoshida A. Paradoxical improvement of visual acuity in

348   macular disease. Curr Eye Res 2010;35:651-6.

349   19.   Sunness JS. Spontaneous improvement in visual acuity in age-related geographic

350   atrophy of the macula. JAMA Ophthalmol 2014;132:356-7.

351   20.   Mishra A, Jackson ML. Translational Vision Rehabilitation: From Eccentric Fixation to

352   Reading Rehabilitation. Semin Ophthalmol 2016;31:169-77.

353   21.   Cideciyan AV, Swider M, Aleman TS, et al. ABCA4-associated retinal degenerations

354   spare structure and function of the human parapapillary retina. Invest Ophthalmol Vis Sci

355   2005;46:4739-46.

356   22.   Stigler SM. Regression towards the mean, historically considered. Stat Methods Med

357   Res 1997;6:103-14.

358   23.   Szlyk JP, Fishman GA, Grover S, et al. Difficulty in performing everyday activities in

359   patients with juvenile macular dystrophies: comparison with patients with retinitis

360   pigmentosa. Br J Ophthalmol 1998;82:1372-6.

361   24.   Beck RW, Maguire MG, Bressler NM, et al. Visual acuity as an outcome measure in

362   clinical trials of retinal diseases. Ophthalmology 2007;114:1804-9.

363   25.   Strauss RW, Munoz B, Wolfson Y, et al. Assessment of estimated retinal atrophy

364   progression in Stargardt macular dystrophy using spectral-domain optical coherence

365   tomography. Br J Ophthalmol 2015. In press

366   26.   Cideciyan AV, Swider M, Aleman TS, et al. Macular function in macular

367   degenerations: repeatability of microperimetry as a potential outcome measure for ABCA4-

368   associated retinopathy trials. Invest Ophthalmol Vis Sci 2012;53:841-52.

369
370

371

372

Figure legends:

Figure 1: Flowchart of the study participants

Figure 2: Illustrative examples of eyes with no impairment (A: best-corrected or presenting visual acuity (BCP-VA 20/16), mild impairment (B: BCP-VA 20/32), moderate impairment (C: BCP-VA 20/120), and severe impairment or blindness (D: 20/400) according to WHO-criteria.

Figure 3A: Best-corrected or presenting visual acuity at baseline by quartiles of age of symptom onset.

Figure 3B: Best-corrected or presenting visual acuity at baseline by quartiles of duration of symptoms.

Figure 4. Estimated average rate of change of visual acuity and its 95% confidence interval, by baseline visual acuity. (VI: visual impairment)