# Faster Sensitivity Loss around Dense Scotomas than for Overall Macular Sensitivity in Stargardt Disease: ProgStar Report No. 14

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• PURPOSE: Mean sensitivity (MS) derived from a standard test grid using microperimetry is a sensitive outcome measure in clinical trials investigating new treatments for degenerative retinal diseases. This study hypothesizes that the functional decline is faster at the edge of the dense scotoma (eMS) than by using the overall MS.

• DESIGN: Multicenter, international, prospective cohort study: ProgStar Study.

• METHODS: Stargardt disease type 1 patients (carrying at least 1 mutation in the *ABCA4* gene) were followed over 12 months using microperimetry with a Humphrey 10-2 test grid. Customized software was developed to automatically define and selectively follow the test points directly adjacent to the dense scotoma points and to calculate their mean sensitivity (eMS).

• RESULTS: Among 361 eyes (185 patients), the mean age was 32.9 ± 15.1 years old. At baseline, MS was 10.4 ± 5.2 dB (n = 361), and the eMS was 9.3 ± 3.3 dB (n = 335). The yearly progression rate of MS (1.5 ± 2.1 dB/year) was significantly lower ($\beta = -1.33$; $P < .001$) than that for eMS (2.9 ± 2.9 dB/year). There were no differences between progression rates using automated grading and those using manual grading ($\beta = .09$; $P = .461$).

• CONCLUSIONS: In Stargardt disease type 1, macular sensitivity declines significantly faster at the edge of the dense scotoma than in the overall test grid. An automated, time-efficient approach for extracting and grading eMS is possible and appears valid. Thus, eMS offers a valuable tool and sensitive outcome parameter with which to follow Stargardt patients in clinical trials, allowing clinical trial designs with shorter duration and/or smaller cohorts. (Am J Ophthalmol 2020;216:219–225. © 2020 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).)

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STARGARDT DISEASE IS EXPECTED TO BE THE MOST common phenotype of autosomal recessive inherited retinal degeneration (out of all cases of autosomal recessive inherited retinal degeneration, 23% are expected to be Stargardt disease and 13% are late-onset Stargardt disease).[1] Most recent worldwide genotype analyses expect 1 in 6,578 individuals to be affected by *ABCA4*-related Stargardt disease (STGD1; OMIM entry 248200; Online Mendelian Inheritance in Man, Johns Hopkins University, Baltimore, Maryland) based on their genotypes.[1] *ABCA4* encodes an outwardly directed "flippase" that transports all-trans retinal and *N*-retinylidene-phosphatidylethanolamine (NRPE) to the cytoplasmic side of the photoreceptor disc membrane.[2,3] With the dysfunctional *ABCA4* gene, NRPE and all-trans retinal can react and form toxic metabolites and lead to increased bis-retinoid formation that leads to retinal pigment epithelium cell loss and visible atrophy.[4] Atrophic lesions grow over time with consequent loss of photoreceptors and development of scotomata.[5–8] The area of the dense scotoma has been shown to greatly exceed the visible atrophic lesion in the STGD1.[9,10]

Fundus-controlled microperimetry has been introduced as a psychophysical approach for precise sensitivity analysis of the macula by displaying light stimuli in pre-planned retinal areas and exact correlation of macular pathology with functional defects.[11] Microperimetry can accurately delineate the retinal area not responding to the brightest light stimuli (ie, the dense scotoma).[9] Microperimetry is also a reliable method for testing macular function in

longitudinal treatment studies for STGD1 mutations.[12–15] Using the mean sensitivity (MS) from a standard test grid, the technology has been used to longitudinally follow functional decline in eyes with STGD1.[16]

There is progressive centrifugal (center-to-periphery) expansion of atrophic retina in STGD1 on fundus autofluorescence imaging (FAF),[7,8] using rod- and cone-mediated sensitivity losses[17–19] and on imaging with optical coherence tomography.[15] Therefore, the edge of the deep scotoma is of particular interest as it is likely the area of highest disease activity,[20,21] potentially making the sensitivity loss in this area a useful outcome parameter for clinical trials. This study reports the change of the mean sensitivity at the scotoma edge (eMS) in a large cohort of patients with molecularly confirmed STGD1 by using the MP-1 microperimeter (Nidek, San Jose, California). The hypothesis is that the functional decline is faster using the eMS than the MS.

## SUBJECTS AND METHODS

THIS NATURAL HISTORY STUDY IS PART OF THE INTERNATIONAL, multicenter, prospective ProgStar Study. All administrative and regulatory details of the design and organization of the study, the study centers, ethics committee approval, the Declaration of Helsinki, and the process of written informed consent can be found in ProgStar Report No. 1.[22] Institutional review board (IRB) approval was granted for both the prospective and the retrospective ProgStar Studies by the Western Institutional Review Board and all local IRBs of the involved clinical centers. This study is compliant with the Health Insurance Portability and Accountability Act. The ProgStar Study is registered at Clinicaltrials.gov (NCT01977846).

Patients with molecularly confirmed Stargardt disease type 1 (consisting of at least one mutation in the *ABCA4* gene) were followed over 24 months in intervals of 6 months using the Nidek MP-1 microperimeter. In addition to the inclusion and exclusion criteria specified in ProgStar Report No. 1,[22] only eyes and study visits with at least 12 months of follow-up (and individual study visits 6 months apart) were included. All study visits had to be connected with each other using the MP-1's follow-up function to ensure that all points under investigation were at the same anatomical location during follow-up. The first examination of an eye as part of a succession of at least 12 months was defined as the baseline visit, although this did not necessarily coincide with the patient's actual first study visit in ProgStar. All eligible study images were exported from the Nidek device and analyzed using customized software (Excel template; Microsoft, Redmond, Washington) designed by one of the authors (M.A.I.).

Details of how the MP-1 microperimeter (using NAVIS version 1.7.7 software; Nidek Technologies SRL) was used for sensitivity testing of the macula are described in detail in ProgStar Report No. 7.[23] For the purpose of this analysis, a customized Humphrey field analyzer (Carl Zeiss Meditec, Dublin, California) 10-2 test grid with 68 test locations was used, and the sensitivity in each location was determined on a scale of 0-20 dB. Test locations with 0 dB and an open-square symbol were displayed in NAVIS software (ie, not seeing any stimuli) and were defined as "deep scotomas" (DS).

The custom software automatically identified mean sensitivity points at the edge (ES) of the test locations that are dense scotomas and defined these at the first visit of a succession of consecutive study visits. This is similar to the approach previously described by Chen and associates[24] Points at the edge of the dense scotoma are test locations directly adjacent to DS points (vertically and horizontally but not diagonally). If there were noncontiguous DS loci, the mean of all ES points (eMS) was calculated from the mean of all loci adjacent to the separate scotomata. In other words, we allowed multiple and separate areas of scotoma edge in cases of non-confluent dense scotomata. All remaining points (ie, not DS and not ES points) were defined as seeing retina (SR) (the average sensivitiy in this area is the "peri-scotoma retina" [pMS]). Once defined, the points remained in their respective categories (ie, DS, ES, or SR). The software then automatically calculated the average sensitivity of the full grid (MS) and for all ES and SR test locations for each visit (eMS and pMS, respectively). Figure 1 shows how this was done in the example of 1 eye. For the purpose of quality assurance, 71 randomly selected eyes were graded manually (E.M.S.). Manually calculated results were compared to the those of the fully automated method.

Continuous data were summarized using means and standard deviations; count data were summarized using frequencies and percentages. Generalized estimating equations under the generalized linear model framework were used to compare outcomes while accounting for correlated observations within subjects. Model selection was determined by using the quasilikelihood under the independence model criterion. All results were considered statistically significant when the $P$ value was $<.05$.

## RESULTS

THIS ANALYSIS INCLUDED A TOTAL OF 361 EYES FROM 185 PATIENTS with a mean age of 32.9 ± 15 years. The majority of patients (89 %) were white. Demographic characteristics of study participants are shown in the Table 1.

MS for the overall test grid, the edge of the dense scotoma (eMS), and the peri-scotoma retina (pMS) at each of the 3 time points can be found in Table 2 and plotted

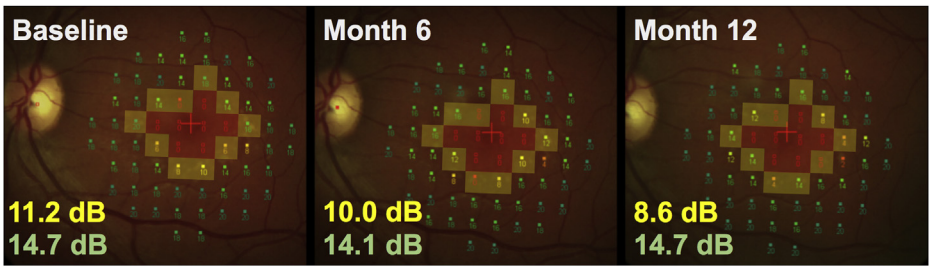


**FIGURE 1. Progression of mean sensitivity derived from a standard test grid using microperimetry over 12 months (MS in dB bottom left in green) in the left eye of a patient with molecularly confirmed Stargardt disease type 1. Test locations where the brightest possible light stimulus could not be detected were defined as a dense scotoma and defined once for each enrolled eye at baseline (red overlay). Points in the edge of the dense scotoma are overlaid in light yellow. Customized software automatically identified these test locations and calculated the average sensitivity in these locations (eMS in dB, indicated in the bottom right in yellow). In the presented example, the MS did not show functional decline after 12 months, whereas the eMS decreased by 2.6 dB after 12 months. dB = decibel; eMS = sensitivity at the scotoma edge.**

**TABLE 1.** Patient Demographics

| | Mean ± SD | Range |
|---|---|---|
| Mean ± SD age, y | 32.93 ± 15.08 | 7-69 |
| Mean ± SD age of onset, y | 22.30 ± 13.17 | 4-64 |
| Mean ± SD disease duration, y | 12.45 ± 10.29 | 0-59 |
| Females (%) | 99 (54) | |
| Race (%) | | |
| White | 164 (89) | |
| African American | 13 (7) | |
| Asian | 6 (3) | |
| Unknown ethnicity | 2 (1) | |

N = 361 eyes from 185 patients.

in Figure 2. Across all time points, MS was significantly higher than eMS ($\beta = 1.80$; $P < .001$). Mean pMS was significantly higher than that of both MS ($\beta = 3.01$; $P < .001$) and eMS ($\beta = 5.12$; $P < .001$). Mean sensitivities did not differ between automated and manual scoring methods for either eMS ($\beta = .09$; $P = .461$) or pMS ($\beta = .001$; $P = .99$).

Of primary interest, differences in sensitivities were calculated between day 0 and 12 months to assess the rate at which sensitivity declined. The 1-year progression rate was significantly lower for MS than for eMS ($\beta = -1.33$; $P < .001$) (Table 2). The 1-year progression rate was also significantly lower for MS than for pMS ($\beta = -.60$; $P < .001$). Finally, the progression rate at 12 months was higher for eMS than for pMS ($\beta = .66$; $P < .001$). Of note, a smaller relative standard deviation (or coefficient of variation [ie, SD/mean]) was also calculated at the scotoma edge. It was 1.02 for eMS but 1.34 for pMS and 1.38 for MS.

The variables of age, age of onset, disease duration, sex, and race were each investigated in univariate models to assess relationships between demographic characteristics and the rate at which sensitivity declined after 12 months (while accounting for repeated measures). Progression rates after 12 months were not associated with age ($\beta = .003$; $P = .909$), age of onset ($\beta = .010$; $P = .733$), disease duration ($\beta = -.007$; $P = .793$), or sex ($\beta = .106$; $P = .844$).

## DISCUSSION

THE MAJOR CLINICAL TRIALS INVESTIGATING THERAPEUtic interventions for age-related macular degeneration (AMD) or diabetic retinopathy used best-corrected visual acuity (BCVA) as the primary outcome measurement. In STGD1, however, it was recently demonstrated that BCVA is not a useful endpoint due to its slow rate of progression[25] and its poor correlation with overall macular function.[23] In fact, some eyes demonstrated improvement of BCVA over time, which is likely secondary to improved fixation stability and neuronal adaptation processes. Microperimetry may be the test of choice as it reflects a more comprehensive assessment of macular function. A cross-sectional analysis of microperimetry data in STGD1 demonstrated that macular function is worst in the center.[23] The simplest way to report microperimetric sensitivity is by using the average of all test locations (ie, the MS). Testa and associates[16] demonstrated a yearly loss of 1.19 dB/year using the MS. The ProgStar Study found a yearly decline of 0.68 dB/year using this approach. These progression rates are low and, given a relatively high test-retest variability, many cases may not exceed the threshold of repeatability. Alternatively, microperimetry may be performed under scotopic conditions to focus on rod photoreceptor function. This was done in the SMART (Scotopic

**TABLE 2.** Mean Sensitivities For the Overall Test Grid, the Edge of the Dense Scotoma, and the Remaining Periphery Across Time

| | Mean Overall (MS) | | | Mean Edge (eMS) | | | Mean Peri-Scotoma (pMS) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Number of eyes | Mean ± SD | 95% CI | Number of eyes | Mean ± SD | 95% CI | Number of eyes | Mean ± SD | 95% CI |
| Visit | | | | | | | | | |
| Day 0 | 361 | 10.43 ± 5.23 | 9.89-10.97 | 335 | 9.34 ± 3.31 | 8.98-9.69 | 346 | 14.28 ± 3.36 | 13.92-14.63 |
| 6 months | 326 | 9.51 ± 5.07 | 8.95-10.06 | 304 | 7.28 ± 3.79 | 6.85-7.71 | 316 | 12.88 ± 3.68 | 12.47-13.29 |
| 12 months | 346 | 9.03 ± 5.13 | 8.48-9.57 | 324 | 6.54 ± 3.95 | 6.11-6.97 | 335 | 12.09 ± 4.34 | 11.61-12.55 |
| Progression Rate | | | | | | | | | |
| 1 year | 341 | 1.51 ± 2.09 | 1.28-1.73 | 319 | 2.86 ± 2.93 | 2.54-3.19 | 330 | 2.19 ± 2.94 | 1.87, 2.50 |

CI = confidence interval around the mean. SD = standard deviation of the mean.
Progression rates: mean overall vs. mean edge, $P < .001$; mean overall vs. mean periphery, $P < .001$.

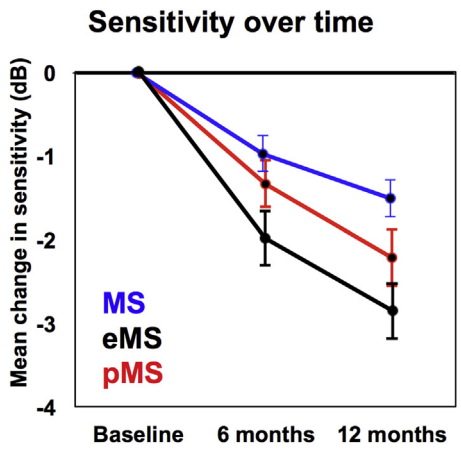


**FIGURE 2. Mean change in microperimetric sensitivities from baseline to month 12 as measured in the entire test grid (MS, in blue), in only the edge of the dense scotoma (eMS, in black), and in only the peri-scotoma retina (pMS, in red). The slope is steepest for the change observed in the edge of the dense scotoma and flattest when looking at the overall change in sensitivity.**

Microperimetric Assessment of Rod Function in Stargardt Disease) study, and a yearly loss of 1.42 dB/year was reported, which was more than double the change resulting from using the photopic test in the same eyes.[12] All these methods suffer from a floor effect: as soon as a test location becomes a dense scotoma, its function cannot decline any more.

Use of the follow-up function is an important aspect of this research that requires additional discussion. The number of eyes in this report is different than that in other ProgStar reports because we decided to include only eyes in which the MP-1 could guarantee exact anatomical follow-up. This is especially important when investigating the scotoma edge as prior research in glaucoma and retinitis pigmentosa has shown how the retest variability in those anatomical areas with a steep slope of the hill of vision worsens.[26,27] The follow-up function minimizes errors from slight adjustment in stimulus position that would result in a different measurement of function. The MP-1 has previously been recommended for testing in exactly such regions with point-by-point test-retest limits of ±4.2 dB (95% confidence intervals).[13]

We tested sensitivity in the pattern of a specified Humphrey 10-2 grid (grid threshold testing). As an alternative to the present approach, a perimetrist could place stimuli manually to define the DS.[9,10] This approach may have a higher resolution for defining the DS and allowing denser sampling specifically in regions of interest, but it is much less standardized and therefore not suitable for a clinical trial.

Defining and selectively following points at the edge of the dense scotoma is a method first described by Chen and associates.[24] The edge of the dense scotoma has presumably the highest disease activity. With conventional perimetry, variability increases at transition zones,[20,21] which are exactly the retinal regions expected to show the greatest rate of disease progression in STGD1.[24] Therefore, only eyes that were followed using the MP-1's follow-up functions were included, allowing for point-to-point comparisons over time and ensuring high reproducibility among visits and among patients. One theory for the centrifugal disease progression in STGD1 is the deposition of

lipofuscin at the lesion edge. The authors previously investigated the disease progression using FAF imaging. However, increased FAF signal at the lesion edge was not associated with a statistically significantly different progression rate of the area of definitely decreased autofluorescence.[7,8]

Our results are in line with those from previous studies of patients with AMD that found the highest functional decline in perilesional areas.[28] Specifically eMS progressed faster than pMS or MS. Overall, the reported MS declines faster in the present analysis than in prior reports (Schönbach EM, and associates, Invest. Ophthalmol. Vis. Sci. 2017; 58(8):4635:ARVO E-Abstract 4635). Possible explanations include the fact that the cohort of eyes is slightly different (ie, the current analysis is a subset of the full population with full follow-up capabilities for this specific type of analysis). However, the difference may also indicate the influence of the follow-up function, suggesting that its use may be associated with more pronounced changes in sensitivity.

Regarding the peri-scotoma retina, the present results show that the progression of disease demonstrated by using pMS is faster (2.19 ± 2.94 dB/year) than using the MS (1.51 ± 2.09 dB/year). This is an expected observation as the method measures the peri-scotoma retina without the small edge area and the dense scotoma, which is expected to be stable ("floor effect"). The result also confirms prior observations that the entire retina is affected in STGD1, as opposed to nonexudative AMD, whose functional deficit is mainly confined to the area of geographic atrophy. Most importantly, retinal sensitivity measured outside of the deep scotoma lesion was generally lower than in equivalent areas of healthy individuals, and the decline in function was faster than in healthy eyes. Using the MP-1, healthy young individuals have an MS that is approximately 1 dB higher than those of healthy people in their seventies.[29] This contrasts with a yearly loss of 2.19 dB in pMS in the present analysis. In addition, the rate of disease progression using eMS in this report of 2.86 ± 2.93 dB/year is comparable to the results by Chen and associates.[24] Although that study analyzed eyes with AMD, a similar progression rate of 2.82 dB/year was found.

STGD1 is a disease with a very high allelic heterogeneity in *ABCA4* with more than 1,000 sequence variations reported to date. A previous study by our group provided the detailed genetic characteristics of the patients enrolled in ProgStar.[30] We identified the 3 most prevalent variants found among all enrolled individuals, which were p.G1961E (15%), p.G863A (7%), and c.5461-10 T>C (5%). Because the present analysis of the scotoma edge required stricter inclusion criteria, further divisions into genetic groups would stretch the cohort very thin and would likely not allow conclusions of different progression rates based on the genotype.

This work represents the first longitudinal and functional analysis of the scotoma edge in a large, prospectively followed cohort of molecularly confirmed individuals with *ABCA4*-related STGD1. Results show that macular sensitivity declines significantly faster at the edge of the dense scotoma than in the overall test grid. The extraction of edge scotoma points and the grading can be performed in an automated, time-efficient way. Comparisons with manual grading demonstrated the validity of the results. Therefore, selectively following test locations directly adjacent to dense scotoma points appears to be a valuable tool and sensitive outcome parameter with which to follow STGD1 in interventional clinical trials. The smaller relative standard deviations for measurements in the edge of the dense scotoma may allow clinical trial designs with shorter duration and/or smaller cohorts.

## CRediT AUTHORSHIP CONTRIBUTION STATEMENT

**ETIENNE M. SCHÖNBACH:** CONCEPTUALIZATION, DATA curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing - original draft. **Rupert W. Strauss:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Writing - review & editing. **Mohamed A. Ibrahim:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Writing - review & editing. **Jessica L. Janes:** Formal analysis, Methodology, Project administration, Software, Visualization, Writing - review & editing. **David G. Birch:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Writing - review & editing. **Artur V. Cideciyan:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Writing - review & editing. **Janet S. Sunness:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Writing - review & editing. **Beatriz Muñoz:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Writing - review & editing. **Michael S. Ip:** Funding acquisition, Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing - review & editing. **SriniVas R. Sadda:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Writing - review & editing. **Hendrik P.N. Scholl:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing - review & editing.

ALL AUTHORS HAVE COMPLETED AND SUBMITTED THE ICMJE FORM FOR DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST and none were reported.

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