Diagnostic Ability and Repeatability of a New Suprathreshold Glaucoma Screening Program in Standard Automated Perimetry

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Purpose: We assess the diagnostic ability and repeatability of a new suprathreshold glaucoma screening test (GST) comprising 28 test points and a 1-of-3 sampling strategy at 95% of the normal limit for standard automated perimetry (SAP) in early to advanced glaucoma.

Methods: This prospective cross-sectional study included 96 eyes of patients with early, moderate, or advanced glaucoma and 37 eyes of normal controls. Participants were evaluated by the G-Dynamic threshold test once and the GST twice, in random order, using the Octopus 600 perimeter. The diagnostic ability of GST was assessed by comparison with the G-Dynamic threshold obtained by receiver operating characteristic analysis. Repeatability was assessed by κ statistics for agreement on glaucoma diagnosis and each test point.

Results: Although the G-Dynamic test exhibited significantly higher areas under the curve (AUC) than the GST (P = 0.009) in early glaucoma, there were no significant differences in any other AUCs between the two methods. The κ values for repeatability of glaucoma diagnosis and each test point were 0.747 to 1.0 and 0.537 to 1.0, respectively. The duration of the GST in the control and early glaucoma groups was less than a minute, while that in the moderate and advanced glaucoma groups was within 1.5 minutes.

Conclusion: The diagnostic ability of the new suprathreshold GST for early to advanced glaucoma was high, with moderate to strong repeatability and short test duration.

Translational Relevance: There currently are no prominent suprathreshold screening strategies using SAP. The GST would be an effective clinical method for glaucoma screening.

Introduction

Standard automated perimetry (SAP) generally is performed using a 30-2 (or 32) or 24-2 test program arranged in a 6x6 grid pattern and the G program following the course of the nerve fiber layer, using a threshold strategy to detect and monitor visual field (VF) defects. Although the threshold strategy helps measure retinal sensitivity at each test point more accurately, it also requires greater time for measurement — 5 to 10 minutes with the Swedish Interactive Threshold Algorithm (SITA)-Standard and 3 to 5 minutes with the SITA-Fast, using the Humphrey Field Analyzer (HFA),¹ 4 to 7 minutes with the Dynamic strategy,²,³ and 2 to 4 minutes with the Tendency Oriented Perimetry strategy⁴,⁵ using the Octopus perimeter.

The suprathreshold strategy generally is used for screening of VF defects.⁶–¹⁰ In the Frequency Doubling Technology (FDT) screener, normal or abnormal VF defects are measured in the presence of stimuli administered at intensities corresponding to...
1% or 5% of the normal limit. In addition, the suprathreshold four-zone probability strategy also is used for screening by Flicker perimetry. Because they are used with specific perimetry methods, these screening strategies exhibit high diagnostic abilities; however, to our knowledge there are no reports on screening for early glaucoma by SAP using these strategies.

The glaucoma screening test (GST) was developed recently for use with the Octopus perimeter (Haag-Streit, Koeniz, Switzerland). The GST comprises 28 test points based on those points of the G program that exhibit decreased sensitivity at high spatial frequencies, as demonstrated by the results of a G program-based large-population screening in patients with glaucoma (Fig. 1). The GST administers stimuli at intensities <5% of the normal limit of a large population; in the absence of response, the same stimulus is administered up to a maximum of three times.

Although the diagnostic ability of SAP in early glaucoma is lower than those of specific perimetry methods, its test–retest variability is better than that of specific perimetry. In addition, the GST has been developed only recently, and no clinical data have been reported regarding its efficacy. We assess the diagnostic ability and repeatability of the newly developed GST with SAP in patients with early to advanced glaucoma.

Methods

Study Design

This prospective cross-sectional study was reviewed and approved by the Kitasato University Hospital Ethics Committee (no. B14-129). All procedures adhered to the tenets of the Declaration of Helsinki, and all study subjects provided written informed consent.

This study included 103 glaucomatous eyes of 103 patients with reliable data from previous HFA 30-2 or 24-2 SITA-Standard tests, who visited the Kitasato University Hospital Glaucoma Service between October 2015 and August 2016. The control group consisted of 38 eyes of 38 healthy volunteers recruited from among the staff members of Kitasato University Hospital and Kitasato University between October 2015 and June 2016; these control subjects had undergone HFA 24-2 or 30-2 SITA-Standard evaluation at least two times within a year. The findings of HFA were considered reliable if the fixation loss and false-positive rate were <20% and <15%, respectively; false-negative rate was not considered for determining the reliability of HFA findings. Glaucoma was diagnosed by one of three glaucoma specialists (MK, KM, or NS) by fundus examination using a slit-lamp indirect ophthalmoscope and 90-diopter (D) lens, on the basis of previously reported SAP results in accordance with the Anderson criteria. Patients with glaucoma as well as the control subjects were administered a comprehensive ophthalmic examination, including noncycloplegic refraction testing, visual acuity testing at 5 m using a Landolt ring chart, intraocular pressure measurement, and slit-lamp and fundus examinations, by a glaucoma specialist (MK, KM, or NS). Patients with glaucoma were included if they exhibited corrected visual acuities ≥20/20, cylindrical power ≤1.50 D, spherical equivalent of −8.00 to +5.00 D, and cataracts of Grade II or lower according to the Emery–Little criteria. The same criteria were applied for selection of control subjects, along with the additional criteria of intraocular pressure ≤21 mm Hg, normal optic disc appearance, and absence of ophthalmic diseases besides errors.

Visual field measurement was performed with an Octopus 600 perimeter (Haag-Streit). The threshold test was performed in accordance with the G-
Dynamic strategy, and the suprathreshold screening test was performed with the GST. The Octopus 600 perimeter is based on thin-film transistor liquid crystal display (LCD). Conventional Octopus perimeters can present stimuli at a maximum intensity of 4000 apostilb. However, because of the limitations of the LCD monitor, the Octopus 600 does not have the ability to present stimuli at intensities more than 400 (10 dB) and less than 15 (24 dB) apostilb using only a size III Goldmann stimulus. To address this limitation, the size of high-intensity stimuli >10 dB was increased to maintain a stimulus intensity of 10 dB, and the size of low-intensity stimuli <24 dB was decreased to maintain an intensity of 24 dB. The size modulation formula has been described previously.2,19 The perimeter uses the size modulation technique for SAP; thus, maintaining the spatial summation of the stimuli within a dynamic range of 0 to 35 dB. The background luminance and maximum stimulus intensity of the Octopus 600 perimeter are 31.4 and 417 apostilb, respectively.

The GST comprises 28 test points, including 19 test points of the G program that tend to exhibit decreased sensitivity at high spatial frequencies and 9 test points that have been reported by previous studies as exhibiting decreased sensitivity at high spatial frequencies (Fig. 1).11–14 At each test point, stimulus is presented at an intensity of 5% of the normal limit; in the absence of any response, the same stimulus intensity is presented up to a maximum of three times. A response to stimulus must be observed at one of the three presentations for the diagnosis to be considered normal (1-of-3 sampling strategy). In the GST, test points considered normal (response to one of three presentations) are indicated by “+”, while those considered abnormal (no response to any of the three presentations) are indicated by “■”, as detailed in a previous study.11

Patients with glaucoma were divided into the early (HFA mean deviation [MD], >–3 dB), moderate (HFA MD, –3 to –6 dB), and advanced (HFA MD, <–6 dB) glaucoma groups. All participants were evaluated once by the Octopus G-Dynamic threshold test and two times by the Octopus GST (GST1st and GST2nd), in random order. Before evaluation, all participants were required to undergo correction for the distance refractive error. This was achieved using the +3.25 D corrective lens for far-distance correction, built into the perimeter eyepiece. In subjects with spherical errors between +4.00 and −8.00 D and cylindrical errors <−1.50 D, refractive errors were corrected by inserting trial lenses with the spherical equivalent correction into the eyepiece. The exclusion criteria were as follows: fixation loss >20% and false-positive rate >15% in HFA measurement and reliability factor (RF) >15%, which is the average of the false-positive and negative rates in Octopus perimetry. Figure 2 presents a flow diagram of the study design.

The diagnostic abilities of the G-Dynamic threshold test and GST were assessed on the basis of number of abnormal points. Abnormal points of both tests were determined on the basis of number of points with $P \leq 5\%$ in the probability map. Repeatability was assessed on the basis of agreement on glaucoma diagnosis and each test point.

**Statistical Analysis**

All data were analyzed using MedCalc version 16.1 (MedCalc Software, Ostend, Belgium). The demographic and ocular data of participants were compared by analysis of variance. The best cutoff value for the number of points with $P \leq 5\%$ was derived from the maximum value of the Youden Index,20 which was calculated by receiver operating characteristic (ROC) analysis. The diagnostic abilities of the G-Dynamic test and GST were compared on the basis of the area under the curve (AUC) of the best cutoff value by the DeLong method. The criteria for glaucoma diagnosis were based on the best cutoff value of the number of points with $P \leq 5\%$ determined by ROC analysis. The $\kappa$ values were calculated to evaluate the agreement between GST1st and GST2nd with regard to the number of points with $P \leq 5\%$. 

**Figure 2.** Flow diagram of study design.
Results

After exclusion of 8 eyes of 8 participants (7 patients with glaucoma; 1 normal control) based on the exclusion criteria, 96 eyes of 96 patients with glaucoma and 37 eyes of 37 normal controls were included in this study. Table 1 and Figure 3 summarize the demographic and ocular data of all participants. Table 2 presents the results of the G-Dynamic test and GST of all participants. The durations of the GST in the control group and the early, moderate, and advanced glaucoma groups were approximately 40, 55, 77, and 95 seconds, respectively.

The AUCs of the G-Dynamic test, GST1st, and GST2nd were 0.967, 0.864, and 0.889 for early glaucoma; 1.000, 0.970, and 0.968 for moderate glaucoma; and 1.000, all, for advanced glaucoma, respectively. Although the AUC of the G-Dynamic test was significantly higher than that of the GST1st (P = 0.009) in the early glaucoma group, there were no significant differences in AUC at other glaucoma stages among the three tests (Fig. 4). Table 3 presents the results of ROC analysis.

The \( \kappa \) values for repeatability of the GST with regard to glaucoma diagnosis and each test point in the control and glaucoma groups are presented in Table 4. With regard to glaucoma diagnosis, the control and advanced glaucoma groups exhibited complete repeatability, while the early and moderate glaucoma groups exhibited strong repeatability. With regard to each test point, the control group exhibited complete repeatability, while the early to advanced glaucoma groups exhibited moderate to strong repeatability.

The results of the G-Dynamic test, GST1st, and GST2nd in representative participants are presented in Figure 5.

Discussion

The GST was developed by Turpin et al.\(^1\) with the aim of enabling detection of VF abnormalities in less than a minute, with high sensitivity and specificity towards glaucoma diagnosis. Although the GST was developed by computer simulation on the basis of VF data of a large population comprising subjects with glaucoma and normal controls, it has yet to be validated in a prospective clinical study. The present findings demonstrated that the duration of the GST in normal controls and patients with early glaucoma was less than a minute, while that in patients with moderate and advanced glaucoma was between 1 and 1.5 minutes. The sensitivity and specificity of the GST were 73\% to 100\% and 98\% to 100\%, respectively. These findings support the results obtained by computer simulation in the previous study.\(^1\) In addition, in the present study, evaluation of diagnostic ability and repeatability of the GST relative to the G-Dynamic threshold revealed that, while the AUC of the GST1st in the early glaucoma group was significantly lower than that of the G-Dynamic test,

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**Table 1.** Demographic Data and Ocular Characteristics of Participants with Glaucoma and Normal Controls

| Parameter                  | Normal Controls | Glaucoma | P Value     |
|----------------------------|-----------------|----------|-------------|
| n eyes                     | 37              | 33       | 33          |
| Age, y                     | 52.6 ± 8.0      | 64.5 ± 11.3 | 64.7 ± 12.8 | 62.2 ± 10.9 | <0.001    |
| Visual acuity, logMAR      | -0.21 ± 0.08    | -0.14 ± 0.08 | -0.10 ± 0.11 | -0.15 ± 0.08 | <0.001    |
| Spherical equivalent, D    | -1.98 ± 2.32    | -1.52 ± 2.60 | -2.62 ± 2.68 | -2.86 ± 2.37 | 0.128      |
| Intraocular pressure, mm Hg| 14.2 ± 3.2      | 14.2 ± 3.8 | 14.4 ± 3.0 | 13.3 ± 3.8 | 0.572      |
| Mean deviation, dB         | 0.81 ± 0.90     | -1.41 ± 0.98 | -4.43 ± 0.96 | -9.65 ± 3.08 | <0.001    |

Data are presented as mean ± SD. P values are calculated by 1-way analysis of variance.
there were no significant differences in AUC at any other glaucoma stage among the three tests. In the early glaucoma group (MD $\geq -3$ dB), the AUC and sensitivity (at 90% specificity) values of the GST1st and GST2nd measured by SAP were 0.864 to 0.889 and 72.7% to 78.8%, respectively; the corresponding values in the moderate glaucoma group (MD, $-6$ to $-3$ dB) were 0.968 to 0.970 and 93.9%, respectively. Previous studies on diagnosis of early glaucoma (MD $> -6$ dB) by specific perimetry — which involves stimulation of the magnocellular or koniocellular layer of the lateral geniculate body — reported AUC and sensitivity (at 90% specificity) values of 0.690 to 0.9909,21–24 and 32.1% to 97.0%, respectively.

### Table 2. Results of the G-Dynamic Test and GST in All Participants

| Parameter                        | Normal Controls, $n = 37$ | Early, $n = 33$ | Moderate, $n = 33$ | Advanced, $n = 33$ | $P$ Value |
|----------------------------------|---------------------------|-----------------|-------------------|-------------------|-----------|
| **G-Dynamic**                    |                           |                 |                   |                   |           |
| Mean defect, dB                  | $-0.7 \pm 1.0$            | $1.8 \pm 1.3$   | $4.8 \pm 2.0$     | $9.0 \pm 2.4$     | $<0.001$  |
| Square loss variance, dB         | $2.1 \pm 0.6$             | $4.1 \pm 1.5$   | $6.5 \pm 2.8$     | $8.8 \pm 1.9$     | $<0.001$  |
| Reliability factor, %            | $3.2 \pm 4.3$             | $3.0 \pm 3.5$   | $2.9 \pm 3.6$     | $5.3 \pm 4.8$     | 0.062     |
| Test duration, s                 | $282.2 \pm 29.3$          | $284.1 \pm 63.5$| $291.1 \pm 27.7$  | $319.2 \pm 45.2$  | 0.003     |
| Number of stimulus presentations | $144.1 \pm 12.6$          | $164.8 \pm 33.4$| $156.3 \pm 12.5$  | $164.5 \pm 32.8$  | 0.001     |
| Number of abnormal points        | $1.1 \pm 1.6$             | $9.4 \pm 4.9$   | $21.1 \pm 8.1$    | $32.6 \pm 7.8$    | $<0.001$  |
| **GST1st**                       |                           |                 |                   |                   |           |
| Reliability factor, %            | $1.3 \pm 4.6$             | $0$             | $0.7 \pm 2.7$     | $0.3 \pm 1.5$     | 0.234     |
| Test duration, s                 | $40.5 \pm 4.0$            | $55.1 \pm 11.3$ | $76.0 \pm 16.9$   | $93.9 \pm 19.3$   | $<0.001$  |
| Number of stimulus presentations | $29.9 \pm 2.6$            | $36.8 \pm 5.9$  | $48.9 \pm 8.8$    | $58.2 \pm 7.5$    | $<0.001$  |
| Number of abnormal points        | $0$                       | $2.4 \pm 2.1$   | $7.1 \pm 4.0$     | $11.8 \pm 3.8$    | $<0.001$  |
| **GST2nd**                       |                           |                 |                   |                   |           |
| Reliability factor, %            | $1.3 \pm 4.6$             | $1.1 \pm 3.4$   | $0.6 \pm 2.2$     | $0.7 \pm 2.5$     | 0.759     |
| Test duration, s                 | $41.7 \pm 5.9$            | $56.5 \pm 13.7$ | $77.7 \pm 24.1$   | $95.8 \pm 19.8$   | $<0.001$  |
| Number of stimulus presentations | $30.5 \pm 2.7$            | $39.3 \pm 7.4$  | $48.5 \pm 9.8$    | $58.6 \pm 8.8$    | $<0.001$  |
| Number of abnormal points        | $0.0 \pm 0.2$             | $2.7 \pm 2.2$   | $7.3 \pm 4.0$     | $12.6 \pm 4.0$    | $<0.001$  |

Data are presented as mean ± SD. Abnormal points are enumerated on the basis of number of points with $P < 5%$. $P$ values are calculated by 1-way analysis of variance.

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**Figure 4.** ROC curves of the G-Dynamic test and GST in the early, moderate, and advanced stages. AUCs were compared by the DeLong method. **$P < 1%$.**
respectively.\textsuperscript{9,23,24} Previous studies on diagnosis of early glaucoma (MD $\leq -6$ dB) on the basis of total and quadrant thicknesses of the retinal nerve fiber layer observed on OCT images reported AUC and sensitivity (at 90\% specificity) values of 0.610 to 0.947\textsuperscript{25–28} and 22.0\% to 86.8\%, respectively.\textsuperscript{25–28} Thus, the values of AUC and sensitivity at 90\% specificity of the GST obtained by SAP in the present study are equivalent to or higher than those obtained by specific perimetry and OCT in previous studies. Because specific perimetry measures the neural pathway of retinal ganglion cells with low redundancy, the variability of specific perimetry findings have been reported to be higher than those of SAP findings not only in patients with glaucoma but also in normal controls.\textsuperscript{15–17} Nevertheless, because of its high specificity and good repeatability, the GST still is able to discriminate between normal presentation and early glaucoma as well as the threshold strategy, specific perimetry, or optical coherence tomography (OCT).

In the present study, the GST exhibited moderate to complete repeatability for glaucoma diagnosis and each test point. However, the repeatability of each test point was slightly lower than that of glaucoma diagnosis, especially in the early and moderate glaucoma groups. The best cutoff criterion for diagnostic decision with GST in early to advanced stages of glaucoma was the presence of 1 or 2 abnormal points. The diagnostic decision became easier with the progression of glaucoma, and its repeatability was high even when each abnormal point did not completely correspond with GST\textsubscript{1st} and GST\textsubscript{2nd}. In contrast, upon evaluating the repeatability of each test point to determine if it indicated normal or abnormal VF, the $\kappa$ value of each test point was lower than that of the diagnostic decision. Additionally, in early and moderate glaucoma, patients exhibit

### Table 3. Results of Receiver Operating Characteristic Analysis of the G-Dynamic Test and GST at Each Glaucoma Stage

| Parameters | AUC (SE) | P Value | Best Cutoff Point | Se/Sp, % | Se at 90\% Sp, % | Se at 95\% Sp, % | PPV, % | NPV, % |
|------------|---------|---------|-------------------|---------|----------------|----------------|--------|--------|
| Early G-Dynamic | 0.967 (0.017) | <0.001 | > 3 | 90.9/89.2 | Upon | 83.5 | 88.2 | 91.7 |
| GST\textsubscript{1st} | 0.864 (0.039) | <0.001 | > 0 | 72.7/100 | 72.7 | 72.7 | 100 | 80.4 |
| GST\textsubscript{2nd} | 0.889 (0.037) | <0.001 | > 0 | 78.8/97.3 | 78.8 | 78.8 | 96.3 | 83.7 |
| Moderate G-Dynamic | 1.000 (0) | <0.001 | > 6 | 100/100 | 100 | 100 | 100 | 100 |
| GST\textsubscript{1st} | 0.970 (0.021) | <0.001 | > 0 | 93.9/100 | 93.9 | 93.9 | 100 | 94.9 |
| GST\textsubscript{2nd} | 0.968 (0.021) | <0.001 | > 0 | 93.9/97.3 | 93.9 | 93.9 | 96.8 | 92.3 |
| Advanced G-Dynamic | 1.000 (0) | <0.001 | > 6 | 100/100 | 100 | 100 | 100 | 100 |
| GST\textsubscript{1st} | 1.000 (0) | <0.001 | > 0 | 100/100 | 100 | 100 | 100 | 100 |
| GST\textsubscript{2nd} | 1.000 (0) | <0.001 | > 1 | 100/100 | 100 | 100 | 97.1 | 100 |

Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value.

### Table 4. Repeatability of the Glaucoma Screening Test

| Parameters           | Repeatability               |
|----------------------|-----------------------------|
|                      | Decision                    | Each Test Point |
| Control              | Complete agreement          | Complete agreement |
| Early glaucoma       | 0.747 (0.117)               | 0.550 (0.003) |
| Moderate glaucoma    | 0.784 (0.207)               | 0.537 (0.004) |
| Advanced glaucoma    | Complete agreement          | 0.671 (0.006) |

Data are presented as $\kappa$ values (standard deviation). The criterion for glaucoma diagnosis is based on the best cutoff value obtained by ROC analysis.
normally sensitive as well as relatively defective areas rather than absolutely defective areas. A previous study on the test–retest variability of each test point reported high variability not only at the relatively defective points but also at the normal points. A previous study on the test–retest variability of each test point reported high variability not only at the relatively defective points but also at the normal points. In addition, other studies have reported fixation behavior of 0.43° to 2.9° during SAP. It is thought that fixation behavior during VF measurement affects the repeatability of each test point in patients with early and moderate glaucoma, who exhibit normal and relatively defective areas.

In the present study, the sensitivity and specificity of the optimal cutoff value for the number of abnormal points for differentiating between normal and abnormal VF were the highest when one or two locations remained unseen. For conventional SAP measurement with the HFA, the optimal cutoff value for the number of abnormal points on the pattern deviation probability plot for differentiating between normal and abnormal VF was defined by the number of points on the pattern deviation probability plot with \( P < 5\% \), with more than three of the points being contiguous and one point having \(<1\% \) probability. Additionally, the optimal cutoff values at the highest sensitivity and specificity were determined to be one or two points in the FDT N-30 test, two points in
the FDT Matrix 30-2 test, and five points in the Pulsar T30W test. Despite the discrepancy in number of test points between the present and previous studies, the present findings indicating an optimal cutoff value of one or two points are closest to those obtained with FDT in terms of number of test points. In a computer simulation, the sensitivity and specificity were reported to be the highest when three locations remained unseen in the HFA and the Wills dataset. The slight difference between the present and previous findings might be attributable to the GST points being based on the G program. In addition, the control subjects in the present study were slightly younger than the patients in each of the glaucoma groups. Therefore, the present method likely is better to discriminate between normal and glaucomatous VF defects than the previous method.

The present study has a few limitations. First, subjects with cataract were excluded from the glaucoma and control groups. The GST was administered at a stimulus intensity <5% of the age-corrected normal limit, because of which, participants with overall decreased sensitivity due to ocular media opacity might have a received false-positive diagnosis. Second, to avoid the learning effect of perimetry, which is a well-established phenomenon in clinical practice, perimetric novices were not included in the present study. Third, the present study had a small sample size. Although the sample size was adequate for ROC analysis, it was far too small for comparison of AUC. These limitations must be corrected for evaluation of consecutive participants.

In conclusion, in the present study, the duration of the GST in the control and early glaucoma groups was less than 1 minute, while that in the moderate and advanced glaucoma groups was within 1.5 minutes. The sensitivity and specificity of the GST were 73% to 100% and 98% to 100%, respectively. The present findings support the previously reported results of computer simulation. The newly developed supra-threshold GST for early to advanced glaucoma exhibits high diagnostic ability and moderate to strong repeatability, indicating that it would be an effective clinical method for glaucoma screening by SAP.

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