Enhanced Glaucoma Staging System (GSS 2) for Classifying Functional Damage in Glaucoma

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Purpose: To introduce a new method, derived from the Glaucoma Staging System (GSS), for classifying glaucomatous visual field defects.

Patients and Methods: Four sample groups composed respectively of 471 (sample #1), 128 (sample #2), 185 (sample #3), and 131 (sample #4) patients with either ocular hypertension or chronic glaucoma were considered. The GSS 2 uses both the MD and CPSD/CLV or PSD/LV perimetric indices to classify visual field defect in 6 stages and in 3 types (generalized, localized, and mixed). The formulas were determined using sample #1. A new borderline stage was created, on the basis of sample #2. The relationship between the PSD/LV and CPSD/CLV values was studied on sample #3 to verify the possibility of using the uncorrected indices instead of the CPSD/CLV. The relationship with other classification methods was studied on sample #4.

Results: The GSS 2 showed a strong level of association with the AGIS and the Hodapp-Parrish-Anderson methods in staging defect severity. A good correlation was also found with a classification based on the Bebie curve.

Conclusions: The GSS 2 was able to correctly classify both damage severity and perimetric defect type in the sample studied, using either the corrected or uncorrected visual field indices. It is a quick and easy method, and its formulas can be introduced in any software.

Key Words: chronic open-angle glaucoma, staging methods, standard automated perimetry, visual field defects

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Chronic open-angle glaucoma is a slow and progressive disease, in which patients must carefully be observed for their entire lives. Standard automated perimetry (SAP) is still the accepted technique for quantifying functional damage in these patients. A number of different classification methods have been proposed in the past,[1–5] but one has yet to obtain a widespread use because of the following reasons: need for complex mathematical calculations; time-consuming procedures; and subjective interpretation.

In 1996, the Glaucoma Staging System (GSS) was introduced with the intention of providing a standardized classification of perimetric results.[6] It is based on the two main perimetric global indices (Mean Deviation [MD] and Corrected Pattern Standard Deviation [CPSD], or Corrected Loss Variance [CLV]), plotted on an X-Y coordinate diagram (Fig. 1).

The GSS, which can be easily used both with the Humphrey and Octopus threshold tests, has been and continues to be used in the clinical and scientific fields of glaucoma,[7–9] however, some drawbacks can be found: an abrupt normal-abnormal separation between stage 0 (normal tests) and stage 1 (early defects); the need to recalculate the PSD (or LV) values, if corrected indices are not available; the lack of mathematical formulas that define the various GSS stages, which prevents automatically using the system in a PC software.

In attempting to overcome these problems, we modified this classification system based upon 9 years of clinical experience.

The aim of this study was to determine formulas that mathematically define the separation borders between the different stages and defect types; directly use the PSD or LV values when the corrected CPSD and CLV indices are not available; and compare the new GSS version with other classification methods currently used.

MATERIALS AND METHODS

The mathematical formulas, which define the curvilinear lines that separate the stages, were derived using the former Glaucoma Staging System. The GSS, as previously described,[6] was created on the basis of 500 automated visual fields (332 Humphrey 30-2 full threshold tests and 168 Octopus G1/G1X tests, normal strategy, three phases) from 471 patients with primary open-angle glaucoma at various stages of severity (sample #1). The same sample was used to define the GSS 2 mathematical formulas. A new intermediate stage between Stage 0 and Stage 1 has been added in the GSS 2 to include borderline cases. One hundred and twenty-eight automated visual field tests performed with the Humphrey Field Analyzer 30-2 full threshold test (Carl Zeiss Meditec, Inc, Dublin, CA) (sample #2) were analyzed to define the two lines that separate this new borderline stage from both Stage 0 and Stage 1, respectively. This sample included 44 eyes of 44 normal subjects (mean age 56.8 ± 13.2; min. 35–max. 69), and 84 eyes of

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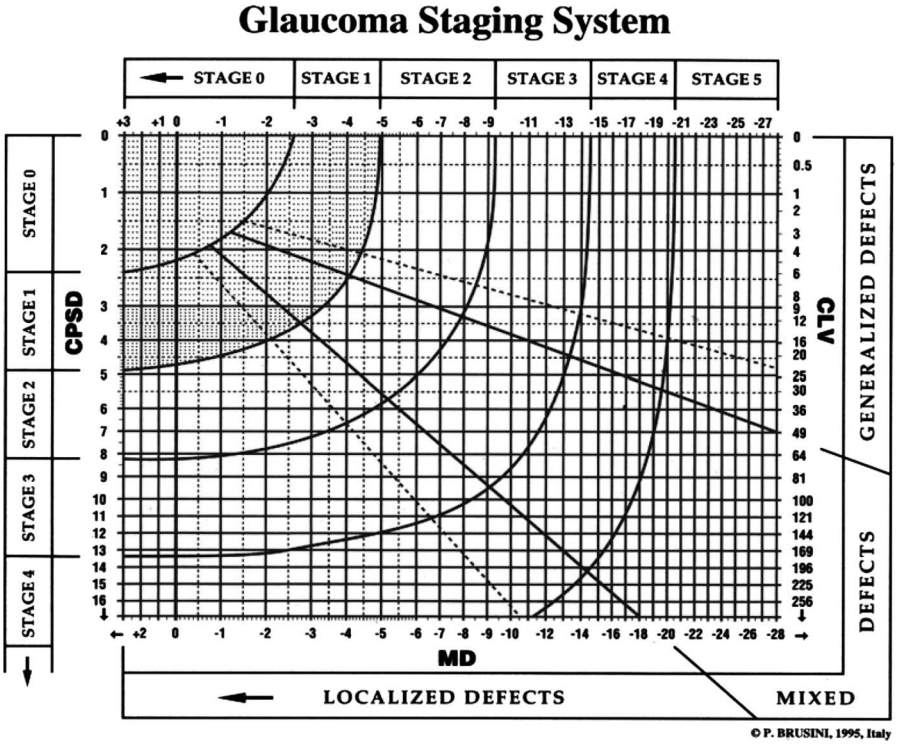

FIGURE 1. The Glaucoma Staging System (GSS). The intersection of the MD and CPSD (or CLV) values defines both the stage and type of defect.

84 patients (mean age 59.7 ± 11.2; min. 37–max. 76), diagnosed with either ocular hypertension or early glaucoma with very subtle defects, and familiar with automated perimetry. In 31 cases, these defects were not significant according to both the Glaucoma Hemifield Test and the Hodapp et al[4] classification. The defects were, however, located along the nerve fiber layer, reproducible and clinically significant.

The relationship between the PSD/LV and CPSD/CLV values was studied on another sample of 185 automated visual fields from 185 patients with different glaucomatous visual field defects (sample #3; mean age 63.7 ± 13.4; min. 42–max. 78) to verify the possibility of using the PSD/LV value instead of the corrected indices (proc reg, SAS, 1988[10]).

An additional 131 automated visual fields from 131 patients with primary open-angle glaucoma at various stages of damage, all tested with the Humphrey 30-2 full threshold test (sample #4), were used in the comparison between the GSS 2 and other methods of classification. The mean age of these patients was 63.5 ± 13.4 (min. 39–max. 84). Only reliable tests (fixation losses <20% and a false positive and negative rate <33%) were considered. Exclusion criteria included patients with at least one of the following conditions: ocular diseases other than glaucoma and mild cataract; poor reliability; a refractive defect higher than 5 diopters; a corrected visual acuity lower than 20/30; any previous ocular surgery or laser treatment; a severe systemic disease; and defects not likely to be related to glaucoma.

The study abided by the principles of the Declaration of Helsinki, and informed consent was obtained from all the patients after having provided an explanation regarding the nature and possible consequences of this study. No subject refused to give his or her consent.

This article is based upon an observational study and no patient identifiable data was used; thus the approval from Ethics Committee was not required.

Mathematical Definition of the GSS 2 Stages

This section briefly explains the mathematical formulas that describe the curves and lines used in the GSS 2. The definition of these formulas allow the system to be inserted in PC software and have the classification be done in an automated fashion. One may choose to overlook this section if this is not applicable.

The general equations used to describe the relationship between the MD and CPSD indices, derived from previous studies[6,11,12] are as follows:

$$\text{if MD} = <0 \text{ then CPSDe} = \alpha\text{MD} + \beta\text{MD}^2 + \gamma \quad (1a);$$

$$\text{if MD} = >0 \text{ then CPSDe} = \gamma \quad (1b)$$

where CPSDe = estimated CPSD.

For each curve that divides the different severity stages, the parameters α, β, and γ were estimated.[10] The new GSS 2 stages were automatically obtained by applying a series of logical equations, and using the observed CPSD value along with the 6 estimated values in the equation reported above. Two regression lines are used to divide the stages in 3 different classes of defects (generalized, localized, and mixed), with exception to the stage 0 and the borderline stage (Fig. 2):

$$\text{MDe} = (-\text{CPSD} + 1.41)/0.225 \quad (2a);$$

$$\text{MDe} = (-\text{CPSD} + 1.1)/0.931 \quad (2b)$$

where MDe = estimated MD.

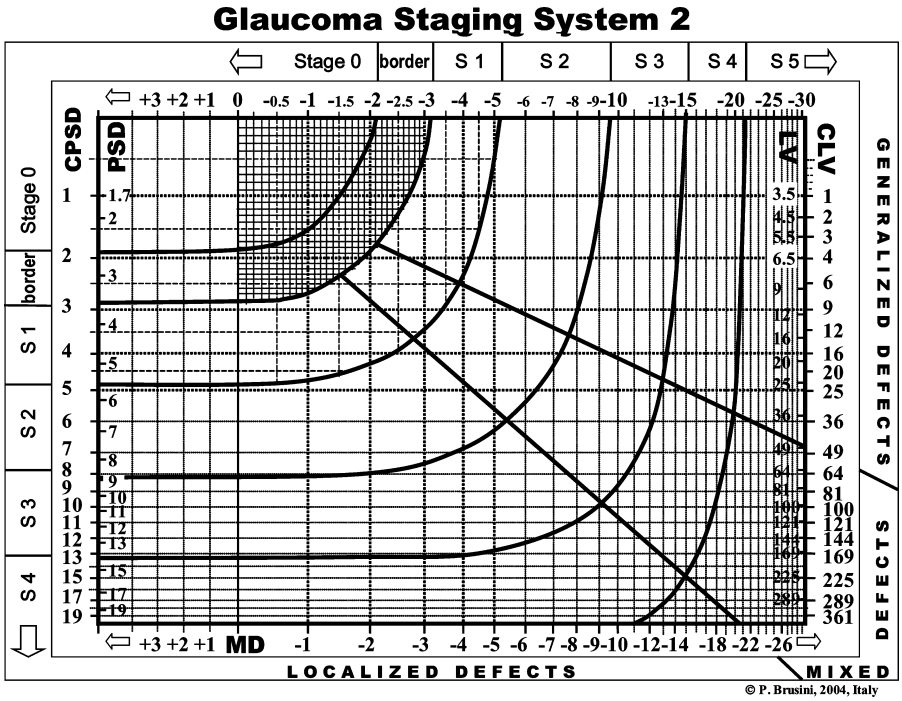

FIGURE 2. The new GSS 2 chart.

The first regression line (2a) separates the generalized defects from the mixed defects, positioned in the central portion of the graph. The second line (2b) separates the localized defects, located in the lower left area, from the mixed defects. The classification of defect type with the GSS is based upon the following assumptions: if the observed MD is lower than the MDe by applying the formula "2a", then the defect is labeled as generalized; if it is higher than the MDe calculated using the formula "2a" but lower than the value estimated using the formula "2b", then the defect is classified as mixed; if it is higher than the MDe obtained using the formula "2b", then the defect is considered to be localized.

Considering that most modern automated visual field tests are performed with programs that do not calculate the short-term fluctuation (SF) (eg, Swedish Interactive Threshold Algorithm, SITA) and thus provide only uncorrected indices, we decided to use the PSD (or LV) values instead of the CPSD (or CLV) values, when estimating the corrected indices in these cases (as reported in Appendix).

Comparison with Other Classification Methods

The capability of the GSS 2 to correctly stage the severity of a defect using PSD (equations 3a or 3b), CPSD (equation 1a or 1b), CLV (equations 4a or 4b), and LV (equations 5a or 5b) values was compared with the old GSS on sample #3.

A comparison was made between the GSS 2 results obtained using the uncorrected PSD values with the Hodapp-Parrish-Anderson[4] and the AGIS[5] classification methods on the sample #4. The correlations (proc corr, SAS[10]) and level of associations between ordinal variables were then calculated (proc freq/chisq measures; SAS[10]).

A previously published classification based on the cumulative defect curve or "Bebie curve"[13] was taken as the gold standard, to assess the GSS 2 reliability in classifying the type of damage (diffuse, localized or mixed), using the same patient sample #4 (regressions 6a, 6b).

The level of association between the qualitative classes was calculated (proc freq/chisq measures; SAS[10]). The agreement between these two classification methods was also measured, by transforming the 4 classes (null, generalized, mixed, and localized defect type) into ordinal values, ranging from 0 to 3, respectively.

RESULTS

Mathematical Definition of the Glaucoma Staging System

The parameters used to estimate the CPSD values are listed in Table 1.

The regression between PSD and CPSD is: PSD = 0.7058 (se = 0.0549) + CPSD (R^2 = 0.9659, n = 185). The following formula was derived from the latter: $\delta = 0.7058$.

The association between values obtained with the GSS and the GSS 2 using the Kendall's tau-b non-parametric measure of association and the Spearman correlation value derived from the contingency table was excellent, varying between 0.940 and 0.985. Some small classification discrepancies were found in 9 cases (4.9%).

The transitional area between stage 0 and 1 incorporates a large number of cases that were classified with some difficulty. Ten of 16 cases, previously classified as stage 0 with the old GSS, were included in the new stage 0 on the sample #2. The borderline stage was made up of 6 cases that were previously classified as stage 0, and 11 cases that were previously labeled as stage 1.

TABLE 1. Separation Lines Among GSS 2 Stages: Results of the Non-Linear Equation Estimate (the Asymptotic Standard Deviations are Shown in Brackets)

Separation Lines Among GSS 2 Stages	α	β	γ	RMSE Sum of the Corrected Total Squared
From Stage 0 to border	−0.225 (0.142)	−0.541 (0.071)	1.934 (0.041)	0.010/7.551
From border to Stage 1	−0.029 (0.219)	−0.276 (0.062)	2.965 (0.141)	0.044/18.565
From Stage 1 to Stage 2	−0.080 (0.199)	−0.184 (0.040)	4.775 (0.181)	0.109/36.260
From Stage 2 to Stage 3	−0.129 (0.118)	−0.100 (0.012)	8.084 (0.191)	0.198/210.143
From Stage 3 to Stage 4	−0.280 (0.108)	−0.074 (0.007)	13.147 (0.256)	0.427/645.901
From Stage 4 to Stage 5	−0.283 (0.114)	−0.067 (0.005)	24.372 (0.444)	1.095/2382.960

RMSE, root mean square error.
Asymptotic standard deviations are shown in parentheses.

Comparison with Other Classification Methods

The relationship between the GSS 2 stages and the AGIS categories, the AGIS score, and the Hodapp-Parrish-Anderson classification are all reported in Table 2.

The level of association between the type of damage estimated with the GSS 2 and the Bebie classification is also listed in Table 2.

The comparison between the GSS 2 and the AGIS categories is shown in Figure 3.

The comparison made with the Hodapp-Parrish-Anderson classification method is listed in Figure 4.

The comparison between the GSS 2 and the classification based upon the Bebie curve is shown in Figure 5.

DISCUSSION

The quantification of functional loss in glaucoma is essential for many reasons, which include: to distinguish between healthy and diseased individuals; to have homogeneous grouping criteria in research in which perimetry is used to define the severity of glaucoma; to adjust therapy on the basis of disease severity; to describe visual field conditions in a short and simple format; to better follow the progression of the disease; and in short, to speak a common language in both a clinical and research setting.

An ideal method for classifying functional damage in glaucoma should have the following essential characteristics:

1. Standardized
2. Objective and reproducible, obviously bearing in mind that perimetry is a subjective psycho-physical test with short- and long-term-fluctuation, which prevents a perfect reproducibility of results
3. User friendly: it should be quick and easy to use, and should not require mathematical calculations or special software, etc.
4. Supported by scientific and clinical evidence, which continually grows and adds to present day knowledge
5. Adaptable for data obtained from different models of perimeters
6. Supply information on the characteristics of visual field defects (shape, type, location, and depth); this can be of clinical use, however, may not be so important when only a simple classification of severity is required
7. Able to provide a classification that may be consistent with structural damage data, even if the correlation between anatomic and functional loss has yet to be further clarified, and may be based upon estimations[14]
8. Widely accepted and used, so that users can compare results
9. Able to monitor even relatively small changes in functional loss over time (3 to 4 stages are not enough, but too many may be meaningless), even if this task could be better accomplished by other specifically designed systems
10. Have the possibility of being inserted in a PC software for day-to-day clinical use (for recording visual field data on the patient chart, for clinical reports, etc.).

The traditional 5-stage Aulhorn and Karmeyer's classification[1] is still considered to be a fundamental reference point

TABLE 2. Association Between GSS 2 (with MD and PSD values), AGIS Categories, AGIS Score, Hodapp-Parrish-Anderson Method, and Bebie Curve Classification

	GSS 2	
	Stage of Damage	
	Kendalls tau-b	Spearman Test
AGIS categories	0.830 (0.020)	0.895 (0.019)
AGIS score	0.855 (0.016)	0.935 (0.011)
H-P-A	0.821 (0.018)	0.900 (0.012)
	Type of Damage	
Bebie curve classification	0.744 (0.044)	0.775 (0.044)

AGIS, Advanced Glaucoma Intervention Study; H-P-A, Hodapp-Parrish-Anderson method; MD, mean deviation; PSD, pattern standard deviation.

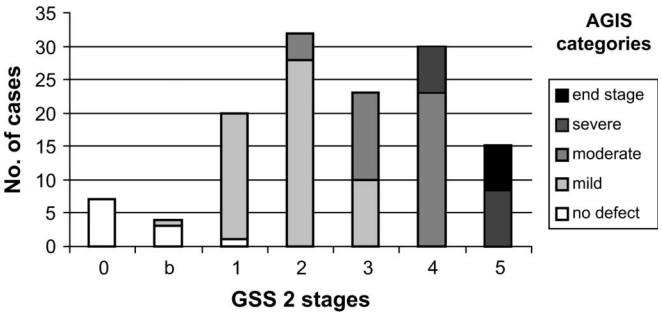

FIGURE 3. Comparison between the GSS 2 stages and the AGIS defect categories.

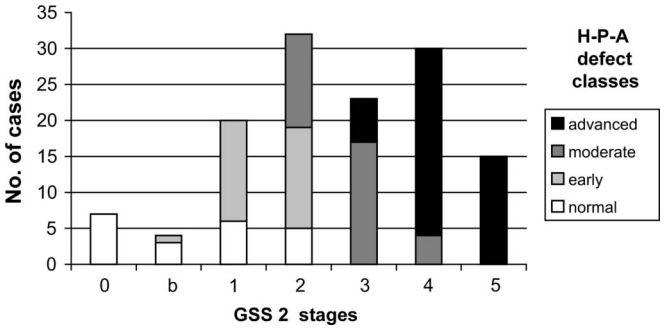

FIGURE 4. Comparison between the GSS 2 stages and the Hodapp-Parrish-Anderson (H-P-A) classification.

in glaucoma research; however, it is subjective and is based upon a testing procedure that is no longer used.

Nowadays, one of the most commonly used methods to stage glaucomatous visual field loss severity is the classification proposed by Hodapp, Parrish, and Anderson in 1993.[4] This method is based upon 2 criteria: the overall extent of damage, which is calculated by using the MD value and the number of defective points in the Statpac-2 pattern deviation probability map; and secondly, on the defect proximity to the fixation point. The defect is classified in 3 classes: early, moderate, and severe defect. The disadvantages of this interesting method include the fact that this 3-stage subdivision may be inappropriate for a fine categorization of visual field defects. Moreover, it requires an accurate and time-consuming analysis of every single visual field result.

The Advanced Glaucoma Intervention Study Investigators (AGIS) proposed a new classification method in 1994,[5] which could later be found in several studies, even though it was not originally designed to be applied in clinical practice. The AGIS score is based on the number and depth of adjacent depressed test locations. This score ranges from 0 to 20, and it can be used to classify the defect into 5 severity categories. This scoring system is analytical and accurate, however, time-consuming and not very simple to use, especially for beginners. The same criticisms can be applied to the Collaborative Initial Glaucoma Treatment Trial (CIGTS) classification method,[15] which is similar to AGIS method. Moreover, the

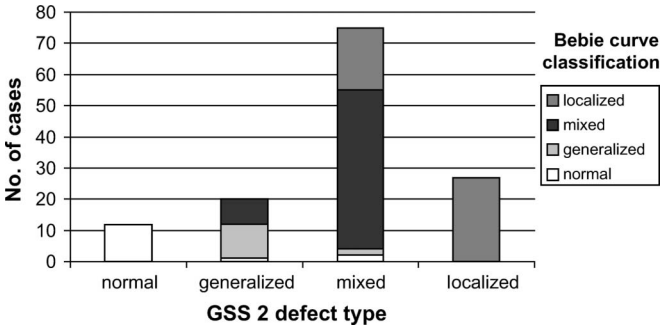

FIGURE 5. Correlation and association between the GSS 2 and the classification obtained using the Bebie curve.

Hodapp-Parrish-Anderson and the AGIS methods have been specifically designed to be used with the 30-2 and 24-2 respectively programs of the early Humphrey perimeters (now Zeiss-Meditec). To obtain information regarding the characteristic of the defect, other methods must be used. The cumulative defect curve proposed by Bebie, for example, is very useful for a quick classification, regarding the quality of the visual field defect.[16] The classification criteria based upon this curve, however, are subjective, and often debatable. A generalized loss of sensitivity is usually properly shown, but very small localized defects can be missed.[17] The AGIS and the Hodapp-Parrish-Anderson methods, on the other hand, are both accurate with regards to localized defects but fail to take into consideration slight diffuse sensitivity depressions, which may at times be due to an early glaucomatous damage.[18,19]

The visual field indices, created by Flammer and coworkers,[20] summarize the distribution of sensitivity within the visual field in a few numbers, and give useful information on the functional loss. They can also be used in staging visual field defects. An approach such as this one can have several theoretical problems, which include: short- and long-term fluctuation and a variety of artifacts can influence the classification; information regarding the spatial distribution of the defect is not provided; different defects can be classified in the same manner; pathologies other than glaucoma can affect visual field indices, etc. Our experience and that of other researchers,[11,13] however, seem to demonstrate that the MD, considered together with the CPSD (or PSD, CLV, or LV) indices, may be useful in the staging of functional damage in glaucoma.

To the best of our knowledge, the GSS is currently the only method that provides the user with an immediate and reliable classification of both the severity and type of visual field defects, using either the 30-2/24-2 Zeiss-Humphrey tests or the G1/G1X/G2 Octopus programs. Moreover, the GSS can be used to analyze automated tests from any other instruments that supply comparable statistical indices. Various studies have demonstrated that it is useful in both clinical practice and in research,[21–24] and may prove to aid in monitoring defect progression over time.[8] With regard to this latter point, the GSS can give useful at-a-glance information on the trend of a defect over time, but should not be used as a statistical method for following progression (eg, the crossing between one stage to another should not be automatically considered as a significant progression). Preliminary research seems to suggest that the GSS can also be used to estimate the amount of structural damage in glaucoma.[25] Further controlled studies are definitely needed to clarify this important point. The creation of a narrow band between stage 0 and stage 1, in which borderline defects can be found, entails that cases grouped in stage 0 are very likely to be normal, whereas those classified as stage 1 have small, yet statistically significant defects, and thus any possible misclassification is kept to a minimum.

The GSS 2 can also be used in cases in which the SF is not calculated (SF off, SITA strategy, G1-G2 program with only first phase performed). The use of the SITA strategy may pose a theoretical problem: because the inter-individual variability is smaller, the normal limits for MD and PSD indices tend to be narrower and some defects that are not statistically

significant with the old full-threshold strategy may become significant, thus making the GSS 2 less sensitive for classifying early defects. Previous studies have demonstrated, however, that the differences in visual field indices between SITA and full threshold strategy, if any, are very small.[26,27]

The GSS 2, by definition, classifies defects in a manner very similar to the previous GSS. A very high correlation rate was also found with both the Hodapp-Parrish-Anderson and AGIS methods, which are much more time consuming.

The capability of the new GSS 2 in correctly classifying the type of defects also proved to be quite good, when compared with a classification based upon the Bebie curve. The GSS 2 correctly classified all localized defects. The few tests that were misclassified, had for the most part, very early and subtle defects. This differentiation may not be of great importance in a clinical setting in cases in which the ophthalmologist is primarily interested in quantifying the severity of a defect.

It should be stressed that the GSS 2, like other classification systems, is not specific for glaucoma, and does not portray any sort of spatial information or any information about the shape of perimetric defects. In order to fully define the location and morphology of the field defect, it is imperative to look at the visual field printout.

In summary, the new GSS 2 has several characteristics of an ideal glaucoma classification method. Moreover it can be used on a regular basis in providing a quick, reliable, and standardized classification of functional damage in patients with glaucoma. The GSS 2 shows good correlations with other classification methods currently used, and offers the advantages of being faster and easier to use. The formulas used to calculate the separation lines can easily be introduced in any software program, thus making the staging procedure automatic and even easier, without manually having to use the GSS charts. Used in conjunction with other functional and structural test results, the GSS 2 can prove to be a useful tool in glaucoma management.

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APPENDIX

Using the Humphrey 30-2 test, the corrected indices were estimated as follows: PSD = δ + CPSD. On the basis of the previous regressions, the formulas used in estimating the damage were modified as follows: $\varepsilon = \gamma - \delta$.

Thus,

$$\text{if MD} = <0 \text{ then PSDe} = \alpha\text{MD} + \beta\text{MD}^2 + \varepsilon \quad (3a);$$

$$\text{if MD} = >0 \text{ then PSDe} = \varepsilon \quad (3b),$$

where PSDe = estimated PSD.

The following formulas were created when Octopus perimeters are used:

$$\text{if MD} = <0 \text{ then } \sqrt{(\text{CLVe})} = \alpha\text{MD} + \beta\text{MD}^2 + \gamma \quad (4a);$$

$$\text{if MD} = >0 \text{ then } \sqrt{(\text{CLVe})} = \gamma \quad (4b),$$

where CLVe = estimated CLV,

and

$$\text{if MD} = <0 \text{ then } \sqrt{(\text{LVe})} = \alpha\text{MD} + \beta\text{MD}^2 + \varepsilon \quad (5a);$$

$$\text{if MD} = >0 \text{ then } \sqrt{(\text{LVe})} = \varepsilon \quad (5b)$$

where LVe = estimated LV.

In the classification of defect type, CPSD was substituted with PSD as follows:

$$\text{MDe} = (-\text{PSD} + \phi)/0.225 \quad (6a);$$

$$\text{MDe} = (-\text{PSD} + \chi)/0.931 \quad (6b).$$

The formulas below can be applied when an Octopus instrument is used:

$$\text{MDe} = (-\sqrt{\text{CLV}} + 1.41)/0.225 \quad (7a);$$

$$\text{MDe} = (-\sqrt{\text{CLV}} + 1.1)/0.931 \quad (7b).$$

The following formulas should be used when only the LV is available:

$$\text{MDe} = (-\sqrt{\text{LV}} + \phi)/0.225 \quad (8a);$$

$$\text{MDe} = (-\sqrt{\text{LV}} + \chi)/0.931 \quad (8b).$$