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Clinical decision making based on data from GDx: One year observations

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CLINICAL DECISION MAKING BASED ON DATA FROM GDx: ONE-YEAR OBSERVATIONS

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ABSTRACT

Purpose: To determine whether information derived from the GDx scanning laser polarimeter aids in the clinical decision-making process for patients with various types of glaucoma.

Methods: Over a 4-month period, 342 consecutive patients with primary open-angle glaucoma, ocular hypertension, angle-closure glaucoma, or secondary glaucomas or in whom the diagnosis of glaucoma was uncertain were evaluated with the GDx scanning laser. After 1 year, 153 patients with glaucoma underwent GDx analysis again. Chart review revealed that 42 of the 153 patients had a change in therapy as a result of the GDx evaluation combined with analysis of visual fields, optic disc cupping, and intraocular pressure (IOP). Outcomes were then compared.

Results: The group who had a change in therapy had a higher average GDx number (51.5 ± 26.1 vs 37.0 ± 23.5 [*P*=.001]) at the initial visit and higher IOP (18.2 ± 4.6 vs 16.0 ± 3.2 mm Hg [*P*=.005]). In spite of a change in therapy, at an average of 344 days later, IOP was unchanged (18.3 ± 5.3 vs 15.7 ± 3.2 mm Hg [*P*=.001]) and GDx values in the altered therapy group were higher than at baseline (57.3 ± 27.9 vs 36.7 ± 23.4 [*P*=.001]), although the differences within each group did not achieve statistical significance.

Conclusion: GDx analysis may be helpful in determining patients at risk for damage from glaucoma, even in eyes in which cup-disc ratio and field loss have not progressed. Changing medications without significantly reducing IOP may be insufficient to halt increases in GDx numbers and may indicate a need for more aggressive therapy.

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INTRODUCTION

Attempts to find an objective discriminant function to separate patients with glaucoma from those without glaucoma have been thwarted by the redundancy of the visual system and the crudeness of the measurement techniques that have been used. Subjective testing has also suffered from individual variation in attention, comprehension, and motor function. Finally, intraocular pressure (IOP) has proved to be of uncertain value in many patients.

The final common pathway for visual loss in the glaucomas is reduction of the competency and number of nerve fibers carrying information to the processing centers in the lateral geniculate body and visual cortex. Thus, when devices purporting to measure the thickness of these layers were introduced, investigators studied the ability of these devices to discriminate between glaucomatous and nonglaucomatous eyes. The result has been a spate of studies defining the specificity and sensitivity of each system to separate the affected eyes from normal eyes.

A more practical question now awaits the ophthalmologist who seeks to use advanced methods such as nerve fiber layer analysis: How does the information gained affect clinical decision making? In an office setting in which some patients are already receiving therapy for glaucoma, others are being followed without medication because of a disparate spectrum of abnormal findings, and still others are discovered to have abnormal findings for the first time, it would be helpful to know how the addition of measurements from a nerve fiber layer analyzer affects the decision-making process and whether these decisions preserve visual function.

Since glaucoma disturbs vision in most cases in a stealthy and slow manner, the conclusions from a 1-year study may be preliminary at best; however, before colleagues are encouraged to invest in expensive equipment, it would be helpful to prove some benefit or demonstrate an additional degree of confidence in judgment corroborated by this added information.

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METHODS

The author's office acquired a GDx nerve fiber layer analyzer (Laser Diagnostic Technologies, San Diego, California) in the fall of 2000. After a 2-month break-in period with instruction and training of the technical staff, reproducibility and reliability were tested on a series of normal

subjects. Results indicated that values of the "number," an age-, sex-, and race-determined derivative of the area under the receiver operating characteristic (ROC) curve, were consistent. Data collection began in December 2000. Since the study is retrospective, the decision was made in December 2001 to analyze the first 342 consecutive patients who had GDx measurements made between December 20, 2000, and April 13, 2001. Patient records were then reviewed to determine whether changes in medications, laser procedures, or surgeries were advised and what part the additional information from the GDx measurement played in the decision to alter therapy. Follow-up has continued until April 10, 2002, and includes analysis of subsequent GDx measurements when available.

Complete ophthalmologic evaluation was obtained, including refraction, slit-lamp biomicroscopy, applanation tonometry, dilated fundus examination, stereo disc photography, and Humphrey visual field evaluation using the Swedish Interactive Threshold Algorithm (SITA) and 30-2 program. Scanning laser polarimetry using the GDx was performed in all patients able to cooperate for the test and in whom the test was indicated for the diagnosis of glaucoma or to follow patients in whom the diagnosis had already been established. The data were obtained from the study population, consisting of a series of 342 consecutive patients examined between December 20, 2000, and April 13, 2001. An attempt was made to reexamine as many patients as possible about 1 year after their original enrollment. Of these individuals, 153 patients with a variety of glaucomas also underwent a second GDx analysis about 1 year following their original examination.

All data were tabulated and transferred to Epiinfo 6.04d. Statistical analysis using analysis of variance (ANOVA) methodology was performed, and results were considered statistically significant when *P* values were <.05.

RESULTS

Table I shows the demographic characteristics of the study population. The age, sex, and racial distribution were indicative of the office population from which the study subjects were drawn. A positive family history of glaucoma was elicited in 94 (27.4%) of all patients. The types of glaucoma treated are shown in Table II. Studies were performed on patients with a spectrum of findings. In some cases, the GDx measurement was taken to establish the diagnosis, in some to differentiate ocular hypertension from glaucoma, and in others to determine whether therapy was adequate to prevent further damage. Of the 153 glaucoma patients who had a second GDx analysis, 70 eyes of 42 patients were found to require a change in therapy initiated at the time of the first visit.

Table III includes the types of glaucoma represented in the 153 patients who underwent a second GDx examination. The decision to change therapy was made on the basis of IOP, visual field findings, and examination of the optic disc; but the GDx data informed the clinical decision-making process. Table IV lists the other variables measured that, taken with the GDx readings, resulted in a change in therapy.

Table V includes the data at baseline for the factors tabulated for each patient. The average IOP is consistent with a population well controlled with therapy. Visual acuities ranged from 20/15 to 20/200, since GDx measurements were found to be difficult in patients with visual acuity reduced to less than 20/400, one-eyed patients, and those unable to fixate well enough for the 300 to 400 msec necessary to obtain reliable means from three scans. In all patients for all examinations, the reliability of the GDx averaged 87% ± 6%. Low-reliability scans (<75%) were considered unreadable and were not included in the study. The overall failure rate gradually improved over the course of the first year but averaged less than 3% for the entire 17-month period.

Among the patients receiving therapy, the average

TABLE I: DEMOGRAPHICS OF STUDY POPULATION

Age	69.2 ± 15.6 yr
Male-female ratio	127:215
White vs nonwhite	91.9% vs 8.1%
Family history of glaucoma	27.4%

TABLE II: TYPES OF GLAUCOMA IN STUDY POPULATION

TYPE OF GLAUCOMA	NO. OF PATIENTS	NO. OF EYES
Primary open-angle	182	360
Secondary	14	26
Low-pressure	28	55
Angle-closure	20	39
Ocular hypertension	67	133
Pigmentary	18	36
Congenital	3	5
Diagnostic testing	10	20
Total	342	674

TABLE III: TYPES OF GLAUCOMA IN PATIENTS WHO UNDERWENT A SECOND GDX MEASUREMENT AT 1 YEAR

TYPE OF GLAUCOMA	NO. OF PATIENTS
Primary open-angle	101
Secondary	6
Low-tension	20
Angle-closure	12
Pigmentary	12
Congenital	2
Total	153

TABLE IV: FACTORS OTHER THAN GDX NUMBER THAT INFLUENCED A CHANGE IN THERAPY

FACTOR	NO. OF PATIENTS*
Intraocular pressure	24
Field loss	13
Increased cup-disc ratio	15

*42 patients required a change in therapy, but total is greater than 42 because some patients had multiple factors.

number of medications used was 1.5 ± 0.7. No patient in this study required surgery for uncontrolled glaucoma during the year of observation, and only one eye was treated with laser trabeculoplasty for uncontrolled IOP.

Table V also depicts the statistically significant differences noted between the eyes in which therapy was changed and those in whom the current regimen was continued, including: (1) higher GDx number, (2) higher initial IOP, and (3) number of medications at the second examination.

DISCUSSION

In an abstract presented at the 2002 annual meeting of the Association for Research in Vision and Ophthalmology, Choi and associates[1] demonstrated that longitudinal analysis over 25.9 months of retinal nerve fiber layer thickness as measured with a scanning laser polarimeter reveals that even when field loss has not progressed, the rate of thinning of the nerve fiber layer is greater in patients with open-angle glaucoma than in normal subjects.

Prior to this study, most of the published literature focused on several other issues. At first, investigators concentrated on the reliability and reproducibility of the various machines designed to measure nerve fiber layer thickness. Zangwill and colleagues[2] tried to distinguish among the Heidelberg retina tomograph (HRT), the GDx nerve fiber analyzer, and the optical coherence tomograph (OCT). They found that, although the areas under the ROC curves were similar, the OCT and HRT had greater sensitivity. Colen and colleagues[3] reported that no significant differences appeared when both normal and glaucomatous patients were studied with the three instruments.

The next phase in studying this equipment has been to determine whether glaucoma patients may be discriminated from normal patients or those with ocular hypertension. Weinreb and coworkers[4] used a variety of the parameters from the GDx to study the detection of glaucoma. They found an overall difference between the normals and patients with glaucoma but also considerable overlap in parameters. Using three variables (average thickness, ellipse modulation, and average ellipse thickness), they generated a specificity of 92% and a sensitivity of 74%. They felt that the software supplied with the GDx did not perform as well as their selected parameters. Lauande-Pimentel and associates[5] performed a case-control study of GDx and visual field examinations together to detect glaucoma. They found the information from the GDx to be useful when added to other functional data.

Paczka and colleagues[6] compared various psychophysical tests to the GDx and concluded that nerve fiber layer photographs had high sensitivity values and frequency-doubling perimetry had high specificity values, but that GDx neural network parameters were almost as sensitive and required less patient cooperation. Poinoosawmy and coworkers[7] tried to separate normal

TABLE V: DIFFERENCES BETWEEN EYES WITH AND EYES WITHOUT A CHANGE IN THERAPY*

VARIABLE	INITIAL VISIT			SECOND VISIT		
	NO CHANGE	CHANGE	*P* VALUE	NO CHANGE	CHANGE	*P* VALUE
GDx No.	37.0 ± 23.5	51.5 ± 26.1	**.001**	36.7 ± 23.4	57.3 ± 23.9	**.001**
Reliability (%)	88.6 ± 5.2	86.3 ± 5.5	.68	87.3 ± 5.6	88.7 ± 6.0	.56
IOP	16.0 ± 3.2	18.2 ± 4.6	**.005**	15.7 ± 3.1	18.3 ± 5.3	**.001**
Cup-disc ratio	0.51 ± 0.17	0.50 ± 0.19	.36	0.50 ± 0.18	0.52 ± 0.19	.54
Visual acuity (20/)	29.1 ± 17.4	38.9 ± 35.4	.08	28.1 ± 18.5	34.4 ± 27.8	.24
No. of medications	1.5 ± 0.6	1.5 ± 0.7	.88	1.5 ± 0.8	2.2 ± 0.7	**.01**
Days to second GDx				347 ± 66	341 ± 60	.42

IOP, intraocular pressure.
*Significant values are in bold type.

patients from those with ocular hypertension and low-pressure glaucoma by using the GDx. They found that the number value determined by the intrinsic software separated the low-tension glaucoma patients from the other groups extremely well. They concluded that a close relationship exists between the parameters measured by scanning laser polarimetry and disease severity. Sanchez-Galeana and coworkers[8] matched the various devices measuring nerve fiber layer thickness against judgments by two ophthalmologists and a vision scientist. They found that no instrument alone was able to provide definitive screening. Finally, Yamada and associates[9] used the GDx as a screening device and found that the GDx, when compared to Humphrey perimetry (Fastpac 24-2 program), separated normal patients from those with ocular hypertension and glaucoma as well and could be performed effectively on 98.5% of patients.

The practitioner who purchases a scanning laser polarimeter or other device to measure nerve fiber layer thickness has to rely on the data derived from examinations and translated by the manufacturer into a user-friendly format. This study has attempted to use just the simplest parameter—the number, extrapolated from the ROC curve and ratios of thickness of the superior and inferior nerve rim—to follow two groups of patients: (1) those in whom a change in therapy appeared to be indicated from the GDx measurement and the other clinical parameters accumulated at the time of the first examination and (2) those who seemed to be well controlled with their then-current regimen. The number was chosen as the parameter to follow in these patients because the manufacturer has communicated to prospective purchasers that with this information, the examiner should be able to distinguish those individuals with nerve fiber layer loss from those with normal nerve thicknesses.[10] As with all new technologies, the specific measurements that are most reliable have yet to be determined for this instrument. In addition, the problem of corneal birefringence and its effect on the repeatability and reliability of the GDx readings has been called into question.[11,12] It may be resolved by newer technology that, according to the manufacturer, will be available in late 2002 (personal communication, Laser Diagnostic Technologies, May 2002).

The study has definite limitations because of its retrospective nature; however, the intention to discriminate between patients who needed a change in therapy and those who did not might have affected the decision-making process. The retrospective perspective may have simulated the "in the trenches" mentality of the clinician who evaluates each patient individually.

All clinical data were collected by a single ophthalmologist and his staff experienced in obtaining IOPs and visual fields. Since the GDx number is free from subjective interpretation except by the technician creating the ellipse from which the nerve fiber layer thickness is calculated, and since each technician was similarly trained with excellent interobserver agreement, this parameter should not be subject to significant error. The cup-disc ratio is subjective, but all patients had optic nerve stereophotography that the author reviewed for consistency.

The decision to alter therapy, armed with the data available, represents the most subjective parameter. Factors such as the patient's ability to comprehend, comply, and cooperate, as well as the establishment of an appropriate "target pressure" for control of glaucoma, are subjective at best. The fact that the groups differed in both their initial data and their subsequent follow-up information suggests that most of the poorly controlled patients were detected and that the patients who continued with their current regimen were well enough controlled, consistent with the interpretation that the GDx may be both sensitive and specific. The groups differ in that those who required a change in therapy had higher GDx numbers and higher IOP. Thus, the GDx either supported or confirmed that a change in therapy was indicated. In addition, the data demonstrate that the group in whom therapy was changed did not have an increase in IOP, an increase in cup-disc ratio, or further visual field loss in the 341-day interval between examinations. The difference in the mean GDx number (51.5 ± 26.1 initially and 57.3 ± 23.9 at the second visit) for this group, although averaging 5.8 points higher, was not statistically significant.

None of the 42 patients whose medications were changed had significant enough alterations in clinical parameters during the 1-year interval to warrant additional changes in therapy, laser procedure, or surgical intervention. Longer follow-up will be necessary to accumulate measurements sufficient to perfect this hypothesis, and during that interval, the equipment will improve to enable viewing the nerve fiber layer in greater detail with improvements especially to minimize corneal birefringence. The fact that only 58% of glaucoma patients had second GDx measurements within the time limits established reduces the power of the data to distinguish between the groups; however, the demographic characteristics of the group who had second GDx analyses are not statistically different from those of the total group, including approximately the same distribution in sex, race, age, and type of glaucoma.

CONCLUSION

The GDx can be used clinically in association with the other time-honored measurements of glaucoma—visual field loss, IOP, and cup-disc ratio—to separate controlled from uncontrolled glaucoma. The inclusion of GDx data may result in increased sensitivity to subtle changes in optic nerve fiber layer deterioration prior to changes in

the other parameters and prevention of subsequent functional loss of vision. The GDx machine reduces dependence on tests that require longer periods of concentration and attention. Finally, normative data may be less helpful than serial data in a single eye acting as its own control.

REFERENCES

1. Choi K-R, Lee H-J, Moon J-I. Nerve fiber layer thickness change in open angle glaucoma. (Abstract) Presented at the 2002 annual meeting of the Association for Research in Vision and Ophthalmology, May 6-10, 2002, Fort Lauderdale, Fla.
2. Zangwill LM, Bow C, Berry CC, et al. Discriminating between normal and glaucomatous eyes using the Heidelberg Retina Tomograph, GDx Nerve Fiber Analyzer, and Optical Coherence Tomograph. *Arch Ophthalmol* 2001;119(7):985-993.
3. Colen TP, Tjon-Fo-sang MJ, Mulder PG, et al. Reproducibility of measurements with the nerve fiber analyzer (NfA/GDx). *J Glaucoma* 2000;9(5):363-370.
4. Weinreb RN, Zangwill L, Berry CC, et al. Detection of glaucoma with scanning laser polarimetry. *Arch Ophthalmol* 1998;116(12):1583-1589.
5. Lauande-Pimentel R, Carvalho RA, Oliveira HC, et al. Discrimination between normal and glaucomatous eyes with visual field and scanning laser polarimetry measurements. *Br J Ophthalmol* 2001;85(5):586-591.
6. Paczka JA, Friedman DS, Quigley HA, et al. Diagnostic capabilities of frequency-doubling technology, scanning laser polarimetry, and nerve fiber layer photographs to distinguish glaucomatous damage. *Am J Ophthalmol* 2001;131(2):188-197.
7. Poinoosawmy D, Tan JC, Bunce C, et al. The ability of the GDx nerve fibre analyser neural network to diagnose glaucoma. *Graefes Arch Clin Exp Ophthalmol* 2001;239(2):122-127.
8. Sanchez-Galeana C, Bowd C, Blumenthal EZ, et al. Using optical imaging summary data to detect glaucoma. *Ophthalmology* 2001;108(10):1812-1818.
9. Yamada N, Chen PP, Mills RP, et al. Glaucoma screening using the scanning laser polarimeter. *J Glaucoma* 2000;9(3):254-261.
10. Laser Diagnostics Technologies Web site. GDx product information. Available at: www.laserdiagnostic.com/products/reading/default.asp. Accessed June 10, 2002.
11. Greenfield DS, Knighton RW, Huang XR. Effect of corneal polarization axis on assessment of retinal nerve fiber layer thickness by scanning laser polarimetry. *Am J Ophthalmol* 2000;129(6):715-722.
12. Greenfield DS, Knighton RW. Stability of corneal polarization axis measurements for scanning laser polarimetry. *Ophthalmology* 2001;108(6):1065-1069.

DISCUSSION

DR ROBERT RITCH. Dr Bobrow has performed a retrospective chart review using the GDx nerve fiber layer analyzer on 342 consecutive patients, 153 of whom underwent a second GDx examination approximately 1 year after the first one. The purpose was to determine if the information acquired influenced patient care by affecting the decision-making process and whether these decisions preserved visual function. Patient records were reviewed to determine whether changes in medications, laser procedures, or surgeries were advised and what part the additional information from the GDx played in the decision to alter therapy. Parameters in addition to the GDx taken into account in changing therapy included intraocular pressure, visual field loss, and an increase in cupping. The eyes in which therapy was changed had a higher mean GDx number, a higher mean initial pressure, and were receiving a greater mean number of medications. Each of these factors is associated with more severe disease, which could make it more likely that a patient would require a change in treatment.

The problem with a retrospective study is the difficulty in determining the consistency of the criteria on which decisions were based. It is not clear what relative role the GDx played in decision making nor whether any decisions were based solely on GDx data. We do not know how much weight was given to the GDx number in the decision-making. The optimal GDx criteria to establish the diagnosis of glaucoma or to determine whether therapy is adequate to prevent further damage have yet to be determined. Thus, the conclusion that the GDx can be used clinically in association with other measures to separate controlled from uncontrolled glaucoma still remains unsubstantiated.

A serious problem with the GDx is the effect of corneal birefringence on the retinal nerve fiber layer thickness assessment.[1-4] The wide distribution of corneal birefringence values observed in normal and glaucomatous eyes suggests that the narrow-band corneal compensator employed by the GDx is inappropriately compensating for anterior segment birefringence in most eyes and limits the discriminating power of the device. Many GDx parameters are heavily biased by the presence of corneal birefringence artifact, particularly integral and average measurements. Dr Bobrow has taken the first step in understanding the utility of this new technology in clinical practice.

A study to evaluate a device like the GDx requires a prospective design with specific well-defined end points, such as criteria for scan quality, definitions of normal or abnormal scans, repeated imaging to validate results, and defined hypotheses on which to base decisions. The recent development of a variable corneal compensator could prove to be a significant advance, allowing diagnosis of early disease and tracking of glaucoma progression.[5]

REFERENCES

1. Greenfield DS, Knighton RW. Stability of corneal polarization axis measurements for scanning laser polarimetry. *Ophthalmology* 2001;108:1065-1069.

2. Greenfield DS, Knighton RW, Huang XR. Effect of corneal polarization axis on assessment of retinal nerve fiber layer thickness by scanning laser polarimetry. *Am J Ophthalmol* 2000;129:715-722.
3. Greenfield DS, Knighton RW, Feuer WJ, et al. Correction for corneal polarization axis improves the discriminating power of scanning laser polarimetry. *Am J Ophthalmol* 2002; in press.
4. Weinreb RN, Bowd C, Greenfield DS, et al. Measurement of the magnitude and axis of corneal polarization with scanning laser polarimetry. *Arch Ophthalmol* 2002; in press.
5. Zhou Q, Weinreb RN. Individualized compensation of anterior segment birefringence during scanning laser polarimetry. *Invest Ophthalmol Vis Sci* 2002; in press.

DR DOUGLAS R. ANDERSON. The hypothesis put to the test with this review is "Which of these various factors–intraocular pressure, increased cupping, and GDx–were used by the clinicians in reaching the decision to alter therapy"? A multivariant analysis rather than single analyses might have answered the question. Once IOP, for example, has been taken into account, what additional variables added to the decision to add therapy or not? Did the GDx number come up with a statistically significant coefficient?

DR JAMES C. BOBROW. In response to Dr Ritch's comments, this novel piece of equipment has become available commercial only recently. The scientific underpinnings may have faults; but I felt that it would be helpful to look retrospectively at my own decision making experience, not on a multivariable or quantitative basis, but to see my "gut-level" results. No patient had a change in therapy unless another parameter plus the GDx was altered in some way, as you can see from the results I presented. The weight given to the GDx, therefore, was confirmatory. I think the value in the study, is simply that, one year later, the changes in the GDx reflected the level of control of the patient's glaucoma. Since I had previously demonstrated that the test was reliable in each individual when repeated, I felt that the changes were significant even if the compensator for corneal birefringence was not utilized (and it has been promised for late 2002 for those who already own the machines.

As far as the need for a prospective study, I agree. I will be following these patients in a prospective fashion for at least another year. In glaucoma, as we all know, trends emerge slowly. Lastly, I want to comment that, just as certain parameters such as Mean Deviation scores from Humphrey Field Analyzer (Zeiss: San Leandro, CA) have been shown to be significant after clinical use, I think that we will find that some of the individual ratios and intermediate calculations in the GDx algorithm will be much more helpful than the "number" that has been commercially derived.