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## Glaucoma care optimised in an ageing population

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*Document Version*

Publisher's PDF, also known as Version of record

*Publication date:*  
2017

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*

Wesselink, C. (2017). *Glaucoma care optimised in an ageing population*. [Thesis fully internal (DIV), University of Groningen]. Rijksuniversiteit Groningen.

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# CHAPTER 2

## **Glaucoma Monitoring in a Clinical Setting: Glaucoma Progression Analysis vs Nonparametric Progression Analysis in the Groningen Longitudinal Glaucoma Study**

*Archives of Ophthalmology 2009;127:270-274*

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## Abstract

**Objective** To compare prospectively 2 perimetric progression detection algorithms for glaucoma, the Early Manifest Glaucoma Trial algorithm (glaucoma progression analysis [GPA]) and a nonparametric algorithm applied to the mean deviation (MD) (nonparametric progression analysis [NPA]).

**Methods** Patients with a reproducible glaucomatous visual field defect at baseline in at least 1 eye were followed up prospectively using perimetry (Humphrey field analyzer 30-2 Swedish interactive thresholding algorithm). Classifications by GPA and by NPA at the end of the follow-up period were compared.

**Results** Two hundred twenty-one patients met the inclusion criteria; 1 eye per patient was analyzed. On average, 7.1 reliable fields were available after a mean follow-up period of 5.3 years. The mean MD at baseline was  $-9.4$  dB; the mean MD slope during the follow-up period was  $-0.25$  dB/y. Fifty-six eyes showed progression by GPA and 89 eyes by NPA ( $P < .001$ ); 42 eyes showed progression by both techniques ( $\kappa = 0.39$ ). In eyes with progression detected by NPA only, baseline MD was worse than that in eyes with progression detected by GPA ( $-12.5$  vs  $-8.2$  dB,  $P = .002$ ), and GPA more often gave a reading of “baseline MD out of range” ( $P < .001$ ). After exclusion of eyes with baseline MD out of range, the measure of agreement was  $\kappa = 0.50$ .

**Conclusions** Nonparametric progression analysis had fairly good agreement with GPA. Especially in cases of more advanced disease, NPA labeled more eyes as having progression than GPA.

## Introduction

Glaucoma is a chronic progressive disease that may cause irreversible blindness. Because its treatment, the lowering of the intraocular pressure,<sup>1</sup> is not free of adverse effects and risks, treatment intensity should be balanced by disease stage, life expectancy, and rate of progression. Hence, techniques that allow for reliable monitoring are of great importance. Standard automated perimetry is the most widely used technique for this.<sup>2</sup>

Several algorithms for progression detection have been developed, often as part of glaucoma trials.<sup>3-7</sup> A standard criterion for glaucoma progression is lacking, but at least some of these algorithms (eg, the Advanced Glaucoma Intervention Study<sup>8</sup> and Early Manifest Glaucoma Trial<sup>9</sup> [EMGT] algorithms) have proven to be useful tools for progression detection, because they have allowed for the demonstration of the beneficial effect of even a modest lowering of intraocular pressure within a few years. Of these 2 algorithms, software for the EMGT algorithm only is commercially available (Humphrey glaucoma progression analysis [GPA]; Carl Zeiss Meditec Inc, Dublin, California).

Unlike its precursor glaucoma change probability,<sup>5</sup> GPA is based on the pattern deviation plot.<sup>10</sup> As a consequence, GPA is less affected by changes in the overall sensitivity as caused by, for example, cataract or refractive errors.<sup>11</sup> However, GPA has some disadvantages: it cannot be used in advanced glaucoma (the pattern deviation plot returns to normal in end-stage disease), and it may overlook diffuse loss due to glaucoma.<sup>12</sup> Other drawbacks of GPA are that additional software is needed, all visual fields involved must be stored in a single perimeter (which is often challenging), and it is only available for more recent versions of the Humphrey field analyzer (Carl Zeiss Meditec Inc).

For these reasons, a subjective evaluation of a series of fields is still the most widely used approach today. However, interobserver agreement for this approach is moderate at best.<sup>13,14</sup> Therefore, we introduce herein a new approach that is (1) simple to use and understand, (2) objective, (3) not dependent on software, (4) applicable for all (static automated) perimeters, and (5) applicable to all disease stages. This method applies nonparametric ranking<sup>15</sup> to the global index mean

deviation (MD). We named this approach “nonparametric progression analysis” (NPA).

The first aim of the present study was to contrast NPA and GPA by comparing longitudinally the number of eyes that progressed according to either technique. For this purpose, we used data from the Groningen Longitudinal Glaucoma Study,<sup>16</sup> an observational study in a clinical setting begun in 2000 and 2001. The second aim was to determine progression rates (change in MD over time) in this cohort.

## Methods

### *The Groningen Longitudinal Glaucoma Study*

Details of the Groningen Longitudinal Glaucoma Study<sup>16</sup> have been described elsewhere. In short, the main objectives were (1) to study the predictive value of baseline frequency-doubling perimetry (Carl Zeiss Meditec Inc) and nerve fiber analysis (GDx; Laser Diagnostic Technologies, San Diego, California) test results for the development of glaucomatous visual field loss as assessed by conventional perimetry in patients with suspected glaucoma, (2) to study the outcomes of patients with glaucomatous visual field loss already present at baseline (the topic of the present study), and (3) to study the ability of frequency-doubling perimetry and nerve fiber analysis to detect glaucomatous deterioration as assessed by conventional perimetry in the same group of patients with glaucomatous visual field loss at baseline. All patients who visited our glaucoma service between July 1, 2000, and June 30, 2001, and who provided informed consent were included in an institutional review board-approved prospective follow-up study using conventional perimetry, frequency-doubling perimetry, and nerve fiber analysis.

### *Patients*

Of 875 patients included in the study, 452 were classified as having glaucoma. Of 452 patients, the disease in 372 was classified using standard automated perimetry (Humphrey field analyzer). Goldmann perimetry (Haag Streit AG, Bern, Switzerland) was used in 80 patients, who were excluded from the current analysis. Of 372 patients classified using the Humphrey field analyzer, patients who had a follow-up period as measured from the last baseline test of at least 3 years (including  $\geq 2$  reliable follow-up fields) were included in the present study.

### ***Perimetry***

Perimetry was performed using the Humphrey field analyzer 30-2 Swedish interactive thresholding algorithm (SITA) fast strategy. An abnormal test result was defined as any 1 of the following: (1) glaucoma hemifield test result outside of normal limits, (2) pattern standard deviation with  $P < .05$ , or (3) 3 adjacent nonedge points with  $P < .05$  in the pattern deviation probability plot, of which at least 1 point reached  $P < .01$ , with all points being on the same side of the horizontal meridian (ie, the criterion from the Low Tension Glaucoma Study applied to the pattern deviation probability plot).<sup>17</sup> A test result was considered unreliable if false-positive classifications exceeded 10% or if both false-negative classifications and fixation losses exceeded 10% and 20%, respectively.

For glaucoma at baseline, 2 consecutive reliable test results had to be abnormal in at least 1 eye. Defects had to be in the same hemifield, and at least 1 depressed test point of these defects had to have exactly the same location on both fields. Moreover, defects had to be compatible with glaucoma without any other explanation. The first test result was discarded because of a learning effect. Therefore, at least 3 tests had to be performed at baseline before glaucoma could be diagnosed.

During the follow-up period, perimetry was performed at a frequency of 1 test per year. In case of suspected progression or unreliable test results, clinicians were allowed to increase the frequency of testing. This was a subjective decision; no formal tools or rules were given.

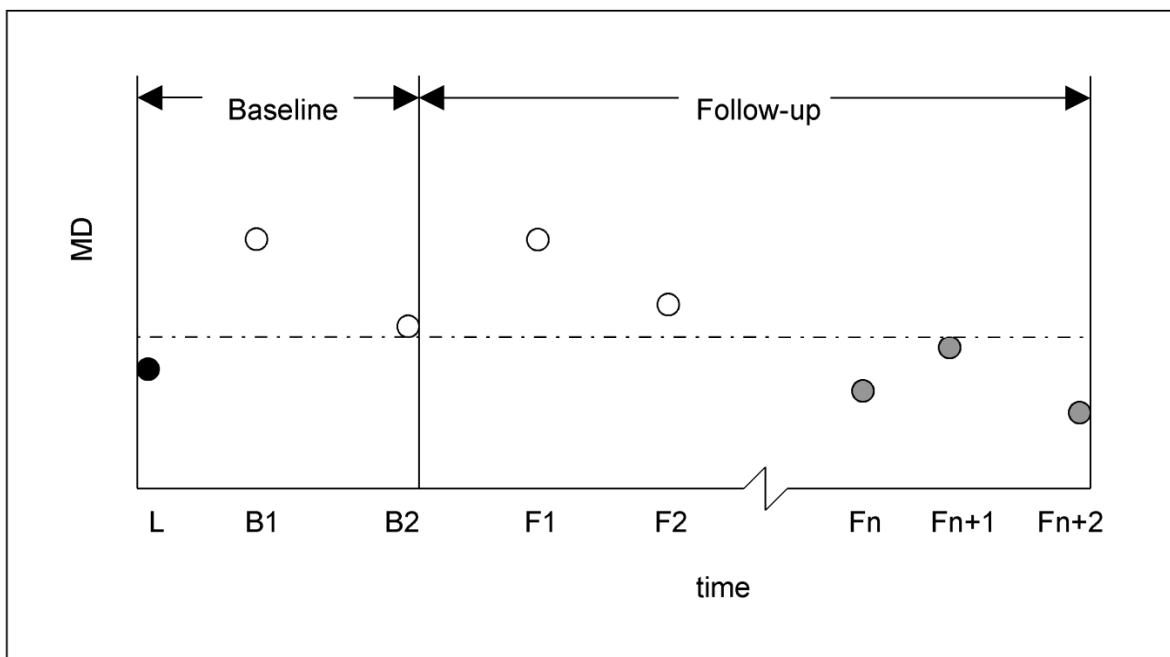
### ***Progression Detection***

Two different methods were used to identify progression, namely, GPA<sup>18</sup> and NPA.<sup>15</sup> In both methods, reliable follow-up test results are compared with 2 reliable baseline test results.

For GPA, visual field progression was based on glaucoma change probability maps.<sup>5</sup> In glaucoma change probability maps, the threshold value of each test point location in every follow-up field is compared with a mean of the values from the same test point in 2 baseline fields. Points that have changed more than might be expected from random variability at  $P < .05$  are flagged as significantly changing. To limit the effect of increasing media opacities, GPA uses pattern deviation

probability plots.<sup>10</sup> Likely progression is reached when 3 or more test point locations at any location in the field, not necessarily contiguous, show significant deterioration in 3 consecutive tests. Possible progression occurs when 3 or more such locations have been identified in 2 consecutive tests.<sup>18,19</sup>

Nonparametric progression analysis is based on nonparametric ranking<sup>15</sup> of MD values. This ranking can be performed directly from the printouts, without additional software. **Figure 2.1** shows the components of NPA.



**Figure 2.1.** Nonparametric ranking is applied to the mean deviation (MD) in nonparametric progression analysis. The learning field (L) is excluded from the analysis. Two baseline fields (B1 and B2) are established, and the MD of all subsequent follow-up fields (F1 through Fn+2) is compared with the MD of the worse baseline field (B2). F1 and F2 are better than B2. Fn through Fn+2 are worse than B2, resulting in suspected progression at Fn, possible progression at Fn+1, and likely progression at Fn+2.

The MD values of follow-up fields are compared with the MD of the worse (B2) of 2 baseline fields (B1 and B2). If the MD of a follow-up field is better than or equal to the MD of the worse baseline field, the field is considered stable (F1 and F2). If the MD of a follow-up field is worse than the MD of the worse baseline field, the change is considered outside of normal variation (ie, suspected progression [Fn]). Possible progression is diagnosed if this change is confirmed once (Fn+1 [deterioration in 2 consecutive fields]), and likely progression is diagnosed if

confirmed more than once ( $F_{n+2}$  [deterioration in  $\geq 3$  consecutive fields]). Following a reading of apparent possible or likely progression, MD readings better than the worse baseline MD are disallowed; in that case, the patient's condition is considered stable.

### ***Statistical Analysis***

One eye per patient was analyzed. If a patient met the inclusion criteria in 1 eye, that eye was selected; if a patient met the criteria in both eyes, a randomly chosen eye was included. The MD slopes and corresponding residuals (a measure of intertest variability within a subject) were calculated using linear regression analysis. The proportion of eyes that progressed using GPA or NPA was compared using the McNemar test;  $\kappa$  statistic was used as a measure of agreement. Continuous variables were compared using t test and proportions using  $\chi^2$  statistic. Statistical analyses were performed using commercially available statistical software (SPSS, version 14.0; SPSS Inc, Chicago, Illinois).  $P \leq .05$  was considered statistically significant.

## **Results**

Two hundred twenty-one patients met the inclusion criteria in at least 1 eye; 113 of these patients met the criteria in both eyes. **Table 2.1** gives the baseline characteristics. The mean MD was -9.4 dB. **Table 2.2** gives the follow-up data. The mean follow-up period (as measured from the last baseline field) was 5.3 years; on average, 5.1 reliable follow-up fields were available (7.1 fields including baseline). The mean MD slope was -0.25 dB/y. The same mean MD slope was found after exclusion of patients who underwent cataract surgery during the follow-up period.

**Figure 2.2A** shows the number of eyes with and without progression according to GPA and NPA. According to GPA, 56 of 221 eyes showed at least possible progression at the end of the follow-up period (4.8% per year). According to NPA, 89 of 221 eyes showed progression (7.6% per year). This difference was significant ( $P < .001$ ). Forty-two eyes showed progression according to both criteria yielding a  $\kappa$  of 0.39. In these eyes, NPA detected progression earlier than GPA (3.5 years for NPA and 4.3 years for GPA,  $P < .001$ ), with  $\kappa = 0.39$  for the measure of agreement. The mean (SD) MD at baseline was -12.5 (7.5) dB for eyes showing



progression according to NPA only and  $-8.1$  ( $5.8$ ) dB for eyes showing progression according to GPA regardless of NPA reading ( $P = .002$ ). Glaucoma progression analysis gave a reading of “baseline MD out of range” significantly more often in eyes with progression according to NPA only compared with eyes with progression according to GPA (20 of 47 vs 5 of 56,  $P < .001$ ). On average, there were slightly more fields available in progressing eyes than in nonprogressing eyes ( $7.7$  vs  $7.0$ ,  $P = .004$  for GPA and  $7.6$  vs  $6.9$ ,  $P = .03$  for NPA).

**Table 2.1. Baseline Patient Characteristics**

Baseline patient characteristics	Mean (SD) or %
Age (yr)	66.4 (12.3)
Sex (% male)	55.2
Family history of glaucoma (%)	16.9
Myopia (%)	18.1
Cataract surgery before baseline (%)	26.7
HFA Mean Deviation (dB)	-9.4 (7.6)
Visual acuity	0.78 (0.28)
IOP at baseline (mmHg)	16.1 (4.7)
Highest IOP ever recorded (mmHg)	30.3 (9.5)

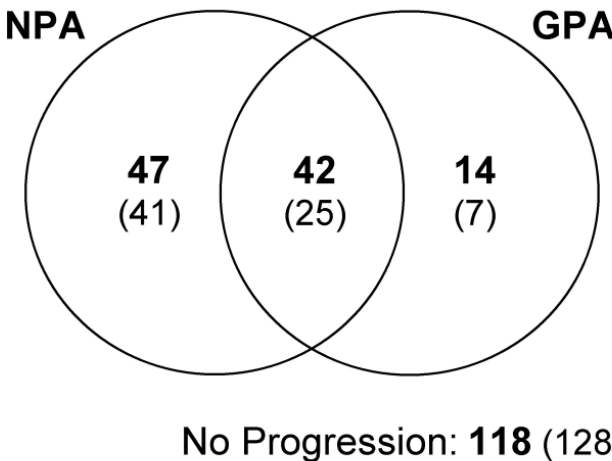
*HFA = Humphrey Field Analyzer; IOP = intraocular pressure; SD = Standard Deviation.*

**Table 2.2. Patient Characteristics During the Follow-up Period**

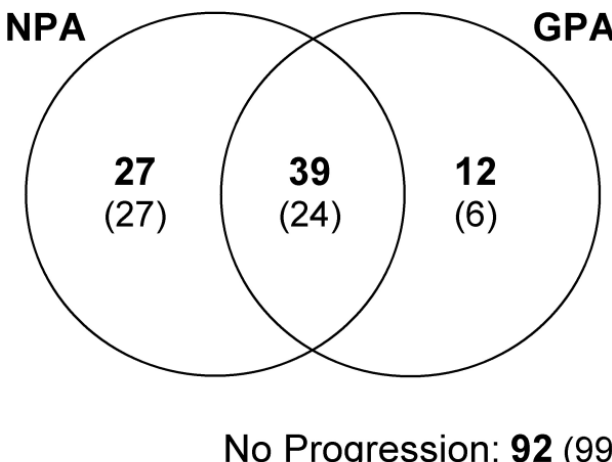
Follow-up patient characteristics	Mean (SD) or %
Follow-up duration (years)	5.3 (1.1)
Number of visual field examinations	5.1 (1.9)
HFA Mean Deviation slope (dB/years)	-0.25 (0.56)
SD of residuals of Mean Deviation (dB)	1.3 (1.2)
Average IOP during follow-up (mmHg)	14.9 (2.9)
SD of IOP during follow-up (mmHg)	2.8 (1.8)
Cataract surgery during follow-up (%)	18.1

*HFA = Humphrey Field Analyzer; IOP = intraocular pressure; SD = Standard Deviation.*

A

All Eyes	Mean MD slope (SD) dB/yr
 <p><b>NPA</b>                      <b>GPA</b></p> <p><b>47</b> (41)                      <b>42</b> (25)                      <b>14</b> (7)</p> <p>No Progression: <b>118</b> (128)</p>	<p>GPA progression: -0.67 (0.64)</p> <p>NPA progression: -0.69 (0.55)</p> <p>No progression: +0.06 (0.28)</p>

B

Eyes with "Baseline MD out of range" excluded	Mean MD slope (SD) dB/yr
 <p><b>NPA</b>                      <b>GPA</b></p> <p><b>27</b> (27)                      <b>39</b> (24)                      <b>12</b> (6)</p> <p>No Progression: <b>92</b> (99)</p>	<p>GPA progression: -0.69 (0.65)</p> <p>NPA progression: -0.69 (0.52)</p> <p>No progression: +0.05 (0.28)</p>

**Figure 2.2.** Results according to glaucoma progression analysis (GPA) and nonparametric progression analysis (NPA) during the follow-up period. The number of eyes with at least possible progression at the end of the follow-up period (with the number with likely progression only in parentheses) is given on the left. The corresponding mean deviation (MD) slopes during the follow-up period are given on the right. A, Among all eyes. B, After exclusion of eyes with baseline MD out of range according to GPA.

After exclusion of eyes with baseline MD out of range (**Figure 2.2B**), 51 of 170 eyes showed at least possible progression at the end of the follow-up period according to GPA, 66 according to NPA, and 39 eyes according to both criteria. The difference between GPA and NPA was still significant ( $P = .02$ ), but, because the exclusion criteria mainly reduced the number of eyes that were flagged by NPA only, agreement between NPA and GPA increased from  $\kappa = 0.39$  to  $\kappa = 0.50$ . In Figure 2.2, the numbers in parentheses on the left refer to likely progression only; these numbers were based on 201 of 221 eyes (Figure 2.2A) and 156 of 170 eyes (Figure 2.2B) with at least 3 follow-up fields. Of 66 eyes with likely progression according to NPA at the end of the follow-up period, 21 were confirmed twice, 16 thrice, and 29 at least 4 times.

If an eye is flagged as showing possible progression at the end of the follow-up period, this is by definition based on the last 2 MD values for NPA and the last printout for GPA. Among all eyes that showed possible progression at any time during the follow-up period, about 40% returned to stability (39% for NPA and 44% for GPA).

## Discussion

In this article, we describe the outcomes of 221 patients with glaucoma who were followed up prospectively using standard automated perimetry in an observational study. We compared a nonparametric ranking method applied to the MD (NPA) with GPA. Most eyes flagged as showing progression by GPA were detected by NPA as well. In addition, some eyes were flagged as showing progression by NPA but not by GPA.

There are several possible explanations for the surplus of eyes flagged as showing progression by NPA. First, as explained in the introduction, GPA cannot be used in advanced stages of glaucoma. Glaucoma progression analysis labels test locations that are already severely affected at baseline with an “X” on the printout. These locations are not further addressed by GPA because it is unable to determine whether any change from baseline is significant (ie, any further deterioration lies within the range expected from long-term fluctuation). Nonparametric progression analysis may perform better because it includes these points out of range in GPA.

Likewise, in eyes with a substantial number of severely affected locations, GPA gives a reading of baseline MD out of range, which occurs when the mean MD of the 2 baseline fields is worse than  $-15$  dB. Nonparametric progression analysis can still assess these eyes. Indeed, in eyes flagged by NPA only, a worse MD was found on average, and GPA more often gave a reading of baseline MD out of range, compared with eyes flagged by GPA. After excluding eyes with baseline MD out of range, agreement between NPA and GPA improved. Second, because of its design, GPA is insensitive to a general decrease in sensitivity. Development of cataract presumably is a common cause of a general decrease in sensitivity. Insensitivity to cataract obviously is an advantage in a glaucoma trial. However, in a clinical setting, patients may benefit from the fact that a clinician has to evaluate the lens before he or she can interpret perimetry results. Third, glaucoma causes diffuse loss in addition to localized deterioration.<sup>12</sup> Glaucoma progression analysis will not detect such diffuse loss. Some eyes flagged by NPA only might have diffuse loss, but because a standard criterion for progression is lacking, it is impossible to determine how many. Fourth, some eyes flagged by NPA only could represent false-positive classifications. The specificity of NPA has been calculated to be 0.83 for possible progression, 0.90 for likely progression with 2 confirmations, 0.93 with 3 confirmations, and 0.95 with 4 confirmations.<sup>15</sup> If we assume a specificity of 0.83, then 27 of 89 eyes flagged by NPA would represent false-positive classifications (estimated from  $TP + [221 - TP] \times [1 - \text{specificity}] = 89$ , where TP is the number of true-positive classifications). Obviously, this number of false-positive classifications is an upper estimate because most eyes flagged by NPA were confirmed more than once. Hence, even without knowing the false-positive classification rate of GPA in this study, it can be concluded that false-positive classification alone cannot explain the number of eyes flagged as showing progression by NPA but not by GPA.

Some eyes were flagged by GPA without being flagged by NPA. This is not an unexpected finding because agreement between different progression detection algorithms has been shown to be less than perfect.<sup>19- 23</sup> The agreement in this study ( $\kappa = 0.39$  and  $\kappa = 0.50$ ) is in line with previously published values ( $\kappa = 0.37$  for the EMGT vs subjective assessment<sup>20</sup> and  $\kappa = 0.40$  for the Advanced Glaucoma Intervention Study vs glaucoma change probability<sup>22</sup>). Eyes flagged by GPA only had a mean rate of progression close to 0 dB/y ( $-0.1$  dB/y).

For GPA and NPA, slightly more fields were available in eyes labeled as showing progression than in eyes labeled as showing nonprogression. This is presumably because clinicians were allowed to increase the frequency of testing if they suspected progression based on their subjective assessment. Because these differences were similar for GPA and NPA, it is unlikely that this affected our comparison of GPA and NPA.

In the Groningen Longitudinal Glaucoma Study, the SITA fast strategy for perimetry was used. The SITA strategies (fast and standard) were introduced as time-saving alternatives for full-threshold testing shortly before the outset of our study. At that time, the apparently more efficient SITA fast strategy was selected and was used during the entire study (a change of strategy during a longitudinal study would have been unwise). Subsequent studies were published suggesting differences between the 2 SITA strategies. Two studies<sup>24,25</sup> reported a slightly higher sensitivity for SITA standard compared with SITA fast; another study<sup>26</sup> reported higher sensitivity for SITA fast. The most obvious difference between the 2 strategies seems to be a higher test-retest variability of SITA fast in areas of low sensitivity.<sup>27</sup> Hence, a comparison of NPA and GPA using data obtained using SITA standard could have different results.

The mean rate of progression in our cohort,  $-0.25$  dB/y, is in good agreement with the rate of progression in the treated arm of the EMGT ( $-0.36$  dB/y).<sup>9</sup> This rate of progression was reached with a mean intraocular pressure of  $14.9$  mmHg during our follow-up period, similar to the intraocular pressure values in the treated arm of the EMGT ( $15.1$  mmHg at the first follow-up visit).<sup>9</sup> Disease stage (mean MD) at baseline was worse in our cohort ( $-9.4$  dB) than in the EMGT ( $-4.7$  dB).<sup>5</sup>

Among eyes that showed possible progression at any time during the follow-up period according to NPA or GPA, about 40% returned to stability. Similar percentages were found by Lee et al.<sup>21</sup> Hence, unless the prior probability of progression is high (because of poor regulation or a long intertest interval),<sup>15</sup> a clinician should not rely on a single confirmation of suspected progression. Especially among patients in whom a change in therapy might have a large effect, 2 confirmations should be recorded before progression is diagnosed to avoid false-positive classification. After diagnosing progression (with or without a subsequent

change in therapy), a new baseline should be defined. The last 2 reliable fields are the obvious candidates for this new baseline.

Neither GPA nor NPA provides information regarding the speed of deterioration. Hence, after progression has been diagnosed using either technique, the amount of deterioration and its localization (toward fixation or not) should be evaluated. Rather than telling the whole story, the algorithms warn the clinician that something is going wrong.

When a new diagnostic tool is developed using experimental data, it has to be tested on an independent data set.<sup>28</sup> It must be stressed that NPA was developed without the use of data from the present cohort. Instead, it was developed theoretically<sup>15</sup> using data from other studies to make estimates of relevant variables.

In conclusion, NPA as evaluated in this study is an easy tool for detecting progression in glaucoma. It can be used with any perimeter and at any disease stage, without the need for additional software. Nonparametric progression analysis seems to flag more eyes as showing progression than GPA. In eyes detected by NPA, clinicians should carefully consider cataract in the differential diagnosis before attributing the observed change to glaucoma. When progression is suspected, this suspicion should be confirmed twice before progression is diagnosed, especially in patients for whom a change in therapy might have a large effect.

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