Detection of Glaucoma Progression in Individuals of African Descent Compared With Those of European Descent

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IMPORTANCE Individuals of African descent have been reported to be at higher risk for becoming visually impaired from glaucoma compared with individuals of European descent.

OBJECTIVE To investigate racial differences in longitudinal visual field variability and their impact on time to detect visual field progression.

DESIGN, SETTING, AND PARTICIPANTS This multicenter prospective observational cohort study included 236 eyes of 173 individuals of European descent and 235 eyes of 171 individuals of African descent followed up for a mean (SD) time of 7.5 (3.4) years.

MAIN OUTCOMES AND MEASURES Differences in test-retest variability and simulated time to detect progression in individuals of African descent and of European descent with glaucoma. Standard automated perimetry mean deviation values were regressed over time for each eye, and SD of the residuals was used as a measure of variability. Distributions of residuals were used in computer simulations to reconstruct “real-world” standard automated perimetry mean deviation trajectories under different assumptions about rate of change and frequency of testing. Times to detect progression were obtained for the simulated visual fields.

RESULTS Among the 344 patients, the mean (SD) age at baseline was 60.2 (10.0) and 60.6 (9.0) years for individuals of African descent and of European descent, respectively; 94 (52%) and 86 (48%) of individuals of African descent and of European descent were women, respectively. The mean SD of the residuals was larger in eyes of individuals of African descent vs those of European descent (1.45 [0.83] dB vs 1.12 [0.48] dB; mean difference: 0.33 dB; 95% CI of the difference, 0.21-0.46; \( P < .001 \)). The eyes in individuals of African descent had a larger increase in variability with worsening disease (\( P < .001 \)). When simulations were performed assuming common progression scenarios, there was a delay to detect progression in eyes of individuals of African descent compared with those of European descent. For a scenario with baseline mean deviation of –10 dB and rate of change of –0.5 dB/y, detection of progression in individuals of African descent was delayed by 3.1 (95% CI, 2.9-3.2) years, when considered 80% power and annual tests.

CONCLUSIONS AND RELEVANCE Patients of African descent with glaucoma showed increased visual field variability compared with those of European descent, resulting in delayed detection of progression that may contribute to explain higher rates of glaucoma-related visual impairment in individuals of African descent compared with those of European descent with glaucoma.
Glaucoma is a leading cause of irreversible blindness worldwide. Population-based studies have shown that the prevalence of primary open-angle glaucoma is higher in individuals of African descent compared with those of European descent. In addition to being more prevalent, glaucoma may cause a disproportionally higher rate of functional impairment in individuals of African descent.

The reasons for the higher incidence of functional impairment from glaucoma in individuals of African descent have not been well clarified. Previous studies suggest that glaucoma tends to occur at an earlier age and present with more extensive damage at diagnosis in individuals of African descent compared with those of European descent. It has also been suggested that the disease may progress at a faster rate in individuals of African descent, who may have lower adherence rates.

Standard automated perimetry (SAP) remains the reference test for assessment of functional loss in glaucoma and is still the most widely used method to detect progression of visual field damage. However, SAP is disadvantaged from considerable test-retest variability. Such variability can hinder detection of change, as detection of progression depends on the ability to separate true change (the signal) from test-retest variability (the noise). In the presence of large test-retest variability, significant changes can be missed and lead to delayed initiation or escalation of treatment.

If racial differences exist in visual field variability, this could influence the ability to detect progression with SAP in individuals of African descent and of European descent with glaucoma. To our knowledge, differences in visual field variability by race have not been previously investigated. We hypothesized that increased visual field variability in individuals of African descent may result in delayed detection of progression in this group, potentially leading to delayed treatment and offering an additional or alternative explanation for the increased risk for functional impairment previously reported in this group.

The purpose of this study was to investigate differences in test-retest SAP variability in a large cohort of individuals of African descent and of European descent with glaucoma followed up over time. We also investigated the impact of differences in visual field variability in the time to detect progression in the 2 racial groups by use of computer simulation.

Methods

Individuals were enrolled from the Diagnostic Innovations in Glaucoma Study and the African Descent and Glaucoma Evaluation Study. The study collaboration included the Hamilton Glaucoma Center, University of California, San Diego; Edward S. Harkness Eye Institute, Columbia University Medical Center, New York, New York; and Department of Ophthalmology, University of Alabama at Birmingham. Written informed consent was obtained from all participants, and methods adhered to the Declaration of Helsinki. All 3 institutions provided institutional review board approval.

Key Points

**Question** Are there racial differences in visual field variability over time?

**Findings** In a cohort study, individuals of African descent with glaucoma showed a larger variability in standard automated perimetry results, as well as increased times to detect progression on computer simulated analyses, compared with individuals of European descent.

**Meaning** Increased visual field variability in glaucomatous eyes in individuals of African descent may result in delayed detection of progression that could potentially contribute to explain higher rates of glaucoma-related visual impairment in this population.

At each annual visit during follow-up, patients underwent a comprehensive ophthalmologic examination that included review of medical history, best-corrected visual acuity, slitlamp biomicroscopy, Goldmann tonometry, dilated ophthalmoscopic examination, stereoscopic optic disc photograph (Kowa Nonmyd WX3D; Kowa Optimed, Inc), and SAP using the Swedish interactive threshold algorithm standard 24-2 test (Carl Zeiss Meditec, Inc). Individuals were excluded if they had any ocular or systemic disease that could affect the optic nerve or the visual field.

All patients had the diagnosis of primary open-angle glaucoma at baseline based on the presence of repeatable (at least 3 consecutive) abnormal SAP test results with associated glaucomatous appearance of the optic disc. Abnormal SAP was defined as a pattern standard deviation with \( P < .05 \) and/or glaucoma hemifield test results outside normal limits. Optic disc damage was evaluated by masked assessment of stereophotographs. Glaucomatous optic disc appearance was defined based on the presence of neuroretinal rim thinning, excavation, notching, or characteristic retinal nerve fiber layer defects. For inclusion in the analyses, each eye was required to have had at least 5 SAP tests over a follow-up duration of at least 2 years with 6-month intervals between the visits.

**Standard Automated Perimetry** Visual fields were performed using SAP Swedish interactive threshold algorithm 24-2. Visual fields were excluded if they had more than 33% fixation losses or more than 15% false-positive errors. Visual fields were excluded in the presence of the following artifacts: eyelid artifacts, rim artifacts, fatigue effects, inappropriate fixation, evidence that the visual field results were caused by a disease other than glaucoma, or inattention. Visual fields exhibiting a learning effect (ie, initial test results showing consistent improvement on visual field indices) were excluded.

**Socioeconomic Variables** Information on socioeconomic variables was also collected by self-reported questionnaire for all patients. The questionnaire contained degree of education (at least high school degree [yes/no]), marital status (married [yes/no]), health insurance coverage (yes/no), and income (less than $25 000 per year [yes/no]).
Data Analysis

Ordinary least squares linear regression models of SAP mean deviation (MD) over time were fit to the sequence of visual field tests for each eye in individuals of African descent and of European descent. The residuals from the trend lines were calculated, and the SD of the residuals was used as a measure of variability. The SD of the residuals was compared between the 2 racial groups using a Wilcoxon rank sum test. Subsequently, we evaluated the association of race with the SD of the residuals in a multivariable model adjusting for average MD during the follow-up period, age, and duration of follow-up. As the association between variability and visual field sensitivity is nonlinear, it was modeled using restricted cubic splines, with the number of knots determined by cross-validation. We investigated whether the association of race with the SD of the residuals depended on visual field sensitivity by including second-order interaction terms between race and splines representing average MD.

Next, we used computer simulations to estimate time to detect visual field progression in both racial groups. The ordinary least squares residuals of MD trends over time obtained from the original cohort were binned according to the fitted levels of MD. Empirical distributions of residuals were then available for each level of MD, allowing reconstruction of MD trajectories over time by computer simulation, according to expected “true” rates of glaucoma progression. A similar approach has been described previously by Russell et al. Given a “true” MD value, the empirical distributions of MD residuals contain the range of measured values that would be expected for a given test. Longitudinal sequences of visual field tests were then simulated by assuming a “true” baseline MD and a “true” rate of change and then sampling from the empirical distributions of residuals to reconstruct what the test MD would be at each time. For example, assuming a “true” baseline MD of −5 dB and an annual rate of change of −1 dB/y, “true” MD measurements would be −5, −6, −7, −8, and −9 dB in the first 4 years of follow-up. However, visual field data are affected by noise, which in our simulations was added to the “true” values by sampling from the empirical distributions of residuals for each corresponding level of MD. For example, one of the simulated visual fields for this situation had MD values of −5.3, −4.9, −7.5, −8.6, and −7.9 dB for the first 4 years of follow-up. Visual field data were simulated for each racial group, taking into account race-specific empirical distributions of residuals. We simulated 10,000 sequences of visual fields for each racial group, assuming equivalent fixed-test intervals for each racial group. We then obtained the earliest time to detect progression for each sequence of visual fields in each racial group. Progression was defined as a statistically significant negative slope of MD over time with \( P < .05 \). This allowed us to construct cumulative probability functions of time to detect progression for each racial group and estimate differences in time to detect progression under specific visual field scenarios. All statistical analyses were performed with commercially available software (Stata, version 14 [StataCorp] and Matlab, version R2016a [MathWorks]). The \( \alpha \) level (type I error) was set at .05.

Table 1. Demographic and Clinical Characteristics of Study Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (SD) African Descent</th>
<th>Mean (SD) European Descent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total eyes</td>
<td>235</td>
<td>236</td>
</tr>
<tr>
<td>Total patients</td>
<td>171</td>
<td>173</td>
</tr>
<tr>
<td>Age, y</td>
<td>60.0 (10.6)</td>
<td>60.8 (9.1)</td>
</tr>
<tr>
<td>Women, No. (%)</td>
<td>55 (32.2)</td>
<td>50 (28.9)</td>
</tr>
<tr>
<td>Baseline SAP MD 24-2, dB</td>
<td>−6.5 (6.7)</td>
<td>−6.4 (5.5)</td>
</tr>
<tr>
<td>Baseline SAP PSD 24-2, dB</td>
<td>5.5 (3.7)</td>
<td>6.9 (4.0)</td>
</tr>
<tr>
<td>Baseline IOP, mm Hg</td>
<td>17.4 (5.2)</td>
<td>19.4 (7.4)</td>
</tr>
<tr>
<td>Baseline RNFL thickness, μm</td>
<td>78.9 (17.5)</td>
<td>74.1 (15.5)</td>
</tr>
<tr>
<td>Progressing eyes, %</td>
<td>31 (13.2)</td>
<td>40 (16.9)</td>
</tr>
<tr>
<td>Rate of change in progressing eyes, dB/y</td>
<td>−0.6 (0.6)</td>
<td>−0.6 (0.5)</td>
</tr>
<tr>
<td>Follow-up time, y</td>
<td>8.6 (0.2)</td>
<td>6.4 (0.3)</td>
</tr>
<tr>
<td>No. of tests</td>
<td>13.6 (6.1)</td>
<td>13.2 (6.4)</td>
</tr>
<tr>
<td>Education level (at least high school degree), No. (%)</td>
<td>67 (39.2)</td>
<td>83 (48.0)</td>
</tr>
<tr>
<td>Income (&gt; $25 000), No. (%)</td>
<td>69 (40.4)</td>
<td>88 (50.9)</td>
</tr>
<tr>
<td>Marital status (married), No. (%)</td>
<td>33 (19.3)</td>
<td>68 (39.3)</td>
</tr>
<tr>
<td>Insurance (yes), No. (%)</td>
<td>92 (53.8)</td>
<td>92 (53.2)</td>
</tr>
</tbody>
</table>

Abbreviations: IOP, intraocular pressure; MD, mean deviation; PSD, pattern standard deviation; RNFL, retinal nerve fiber layer; SAP, standard automated perimeter.

Results

The study included a total of 471 eyes of 344 patients followed up for a mean (SD) of 7.5 (3.4) years with a mean (SD) number of 13.4 (6.3) visual field tests. From the 471 eyes, 235 eyes (49.9%) were from 171 individuals of African descent, and 236 eyes (50.1%) were from 173 individuals of European descent. Table 1 shows demographic and clinical characteristics of included individuals from the 2 groups. There was no difference between the number of field tests during follow-up in individuals of African descent and of European descent (mean [SD], 13.6 [6.1] vs 13.2 [6.4], respectively; \( P = .91 \)). Seventy-two eyes (3%) were detected as progressing in individuals of African descent vs 95 (40%) in individuals of European descent (\( P = .03 \)). There was no difference in average rate of change in progressing eyes for individuals of African descent and of European descent (mean [SD], −0.60 [0.64] dB/y vs −0.61 [0.54] dB/y, respectively; \( P = .91 \)).

The average SD of the residuals was larger in the individuals of African descent vs those of European descent (mean [SD], 1.45 [0.83] dB vs 1.12 [0.48] dB; mean difference, 0.33 dB; 95% CI, 0.21–0.46; \( P < .001 \)), with greater visual field variability over time in eyes of individuals of African descent. Figure 1 shows a histogram of SD of the residuals for the 2 groups. Table 2 shows the multivariable model investigating the association of race with visual field variability adjusted for disease severity (average MD during follow-up), age, and duration of follow-up. Race was associated with visual field variability (\( P < .001 \), joint Wald test). Worse visual field damage was also associated with increased variability (\( P < .001 \), joint Wald test). The nonlinear association was
modeled by splines (Figure 2). There was an interaction between race and disease severity to determine visual field variability. This can be seen in Table 2 by the coefficients associated with the interaction terms between race and MD splines (P < .001; joint Wald test for interaction terms). The difference in visual field variability between individuals of African descent and of European descent initially increased with worse visual field damage but then decreased as the visual field damage became advanced. The greatest difference between the 2 groups was seen at an MD of approximately –12 dB.

The eTable in the Supplement shows the multivariable model investigating the association of race with visual field variability adjusted for disease severity (average MD during follow-up), age, duration of follow-up, and socioeconomic variables. Race was significantly associated with visual field variability (P < .001) even adjusted for socioeconomic data.

From data on visual field variability of the 2 groups, we simulated a variety of scenarios to estimate the difference in time to detect progression between patients of African descent and of European descent. We assumed baseline MD values of –5 dB and –10 dB and true rates of MD change of –0.25 dB/y (slow), –0.5 dB/y (moderate), and –1 dB/y (fast), with annual testing. Table 3 reports mean predicted times to detect progression as well as predicted times to detect progression to achieve 80% power (when 80% of the progressing eyes would be detected as progressing). Individuals of African descent had longer times to detect progression than those of European descent. For the scenario of a baseline MD of –10 dB, true rate of progression of –0.5 dB/y, and annual testing, it would take 11.4 years to detect 80% of progressing eyes of individuals of African descent vs 8.3 years to detect 80% of progressing eyes of those with European descent, with a mean difference of 3.1 years.

Discussion

In the current study, we demonstrated that patients of African descent with glaucoma show larger visual field variability over time compared with individuals of European descent. To our knowledge, this is the first study to suggest the existence of racial differences in visual field variability, which could potentially affect the ability to detect glaucomatous change over time. Our findings may have significant implications to establish strategies for monitoring disease progression.

Test-retest variability may significantly affect the ability to detect change over time. In our study, test-retest variability was estimated by the SDs of residuals, which were on average approximately 30% larger in individuals of African descent vs those of European descent. A previous study suggested that SAP variability must be reduced by approximately 20% for a clinically appreciable improvement in detection of visual field change. Therefore, using a similar reasoning, an increase of 30% in variability would likely result in a clinically appreciable worsening in the ability to detect visual field change in individuals of African descent. Of note, racial differences in variability were more pronounced for MD values close to –10 dB, which was the result of a significant
The interaction between race and visual field severity in explaining levels of variability (Figure 2). This is an especially important result, as at these levels of damage any further visual field worsening could significantly compromise quality of life.28

We performed computer simulations to investigate the impact of increased variability on the time to detect progression. Assuming a common progression scenario with a baseline MD of −10 dB and rate of change of −0.5 dB/y, there was a difference of 3.1 years in the time to detect progression in eyes of individuals with African descent vs those of European descent, assuming 80% power and annual testing. Even with faster rates of change of −1 dB/y, there was still a 2-year lag in detecting change between the 2 groups. Moreover, previous studies have suggested that patients of African descent actually get less frequent visual field testing in clinical practice.29,30 For example, Ostermann et al30 found that patients of African descent with glaucoma were 32% less likely to undergo an eye examination during the year compared with those of European descent. Wang et al29 showed that Medicare beneficiaries of African descent were only 67% as likely as their counterparts of European descent to use eye care services. Therefore, it is likely that the frequency of visual field examinations in patients of African descent with glaucoma may be lower than in those of European descent, which would magnify the differences in time to detect progression found in our study. Delayed detection of progression could result in late initiation/escalation of treatment and irreversible functional loss. In addition, delayed detection could lead to loss of follow-up by giving a false sense of security to patients that the condition has not been progressing and no follow-up is needed.29,30

Large variability may also result in an increase in the number of visual fields declared as progression when in fact no true change has occurred. These false positives may lead to unnecessary escalation of treatment with potential adverse effects to patients.

The reasons for the larger visual field variability found in individuals of African descent are not clear. We conducted separate analysis by site, and race was still associated with visual field variability for each site: San Diego (1.24 dB; 95% CI, 0.93-1.55; P < .001), Alabama (2.44 dB, 95% CI, 1.74-3.14; P < .001), and New York (0.95 dB; 95% CI, 0.28-1.62; P = .006). Therefore, it is unlikely that our results could be explained by site differences. Differences in socioeconomic or educational background could potentially affect visual field variability. In our sample, individuals of African descent had a lower mean income and lower mean educational level compared with those of European descent. However, the association of race with visual field variability was still present even after adjustment for these factors. It should be noted, however, that socioeconomic variables were obtained by self-reported questionnaires and may be subject to reporting biases. In addition, it is possible that the measured variables might not have fully captured other existing socioeconomic differences between the 2 groups. A 2017 study by Diniz-Filho et al30 concluded that cognitive decline was associated with increased visual field variability over time. Although we were not able to assess overall cognitive status in the individuals enrolled in the current study, the association between cognitive decline and race in the literature has been controversial.32-38 As another potential reason for the differences in variability, it is possible that technician supervision while performing perimetry may have differed between the 2 groups. Although patients were all part of a prospective longitudinal study with a rigorous protocol for testing, differences may still have existed, which would be difficult to quantify.

Regardless of the underlying reason for the increased variability found in individuals of African descent, it is likely that the differences found in our study represent realistic scenarios found in clinical practice. Although the differences in variability found in our study are most likely due to uncontrolled covariates rather than a direct racial effect per se, it is likely that in practice, such scenarios are present at a similar, if not worse, degree. Therefore, clinicians may need to increase the frequency of testing to obtain more precise estimates of indices of change over time or use complementary tests for assessment of progression, such as structural imaging of the optic nerve, nerve fiber layer, or macula. Alternatively, methods combining structural and functional tests may also be helpful.39,40

Limitations
Our study has limitations. Assessment of visual field variability and progression was based solely on investigation of trend analysis of MD over time. There are other methods available to detect visual field changes, which rely on assessment of localized losses and also on event-based approaches. It is possible that the impact of variability on times to detect progression would be different by these methods. However, it is likely that the effects of increased variability would be even higher.
in assessing localized losses compared with a global index such as MD. As another limitation of our study, the classification of race was based on self-reported assessment by the study individuals. The term race is complex and may represent a large biodiversity of cultural, geographic, biological, and socioeconomic characteristics. However, it has been shown that studies using “self-described race” are useful as long as this information can be obtained in a standardized manner. In addition, it has been shown that “self-described race” has a good correlation with measures of racial classification using genetic admixture techniques.

### Conclusions

Our results demonstrated that individuals of African descent with glaucoma have increased longitudinal visual field variability compared with individuals of European descent with the disease. The increased variability may lead to delayed detection of progression and possible delayed intervention, which could explain in part the higher incidence of glaucoma-related visual impairment in individuals of African descent compared with those of European descent.

**REFERENCES**

Visual Field Progression Is More Complicated Than Meets the Eye

Eve J. Higginbotham, SM, MD

In this issue of JAMA Ophthalmology, Gracitelli et al raise more questions than answers, a few of which this Editorial will highlight. To summarize, the authors examined the longitudinal differences in perimetric testing in ancestry groups and determined that patients of African ancestry showed greater variability in visual field testing than individuals of European ancestry. As the authors noted, this finding and its underlying mathematical modeling suggests that delayed detection of progression of visual impairment may occur in patients of African descent. This delay may contribute to greater visual impairment in these patients compared with members of other ethnicities. Although one may draw a direct line between the differences noted between these groups and the conclusions of the authors, missing details beneath the surface raise questions that should be considered before settling on those conclusions.

Clinicians assess the status of a patient’s disease using information that extends beyond functional testing. Thus, Gracitelli et al based their conclusions on a mere fraction of the universe of critical information. There are 3 points that will be underscored in this editorial: (1) the contribution of factors other than genetics to the progression of glaucoma; (2) the absence in this analysis of other clinical tools commonly used to assess progression; and (3) the potential contribution of other comorbidities to progression of disease.

The authors conducted their primary analyses based on the ancestry groups of patients, thus increasing the contribution of genetics to their observations. A recent publication from the National Academy of Medicine noted that genetics is not the dominant contributor to responsiveness to treatment and thus to disease progression because of variations in causal factors across populations. Other factors, such as behavioral choices made by patients, differences in social support, inequities in the delivery of care, and elements of the environment may account for as much as 70% of the variation in disease presentation and responsiveness to treatment. Although Gracitelli et al stated that socioeconomic factors were accounted for in their analysis, the factors, as assessed, may not be sufficiently representative of the totality of factors that should be considered. There are clues to the socioeconomic contributors to the findings in the statistical differences in education level, marital status, and income level between the 2

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