

Longitudinal visual field variability and the ability to detect glaucoma progression in black and white individuals

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ABSTRACT

Background/Aims To investigate racial differences in the variability of longitudinal visual field testing in a 'real-world' clinical population, evaluate how these differences are influenced by socioeconomic status, and estimate the impact of differences in variability on the time to detect visual field progression.

Methods This retrospective observational cohort study used data from 1103 eyes from 751 White individuals and 428 eyes from 317 black individuals. Linear regression was performed on the standard automated perimetry mean deviation values for each eye over time. The SD of the residuals from the trend lines was calculated and used as a measure of variability for each eye. The association of race with the SD of the residuals was evaluated using a multivariable generalised estimating equation model with an interaction between race and zip code income. Computer simulations were used to estimate the time to detect visual field progression in the two racial groups.

Results Black patients had larger visual field variability over time compared with white patients, even when adjusting for zip code level socioeconomic variables (SD of residuals for Black patients=1.53 dB (95% CI 1.43 to 1.64); for white patients=1.26 dB (95% CI 1.14 to 1.22); mean difference: 0.28 (95% CI 0.15 to 0.41); $p<0.001$). The difference in visual field variability between black and white patients was greater at lower levels of income and led to a delay in detection of glaucoma progression.

Conclusion Black patients had larger visual field variability compared with white patients. This relationship was strongly influenced by socioeconomic status and may partially explain racial disparities in glaucoma outcomes.

INTRODUCTION

Primary open-angle glaucoma is known to cause more functional impairment in black individuals compared with whites.^{1,2} Though the cause of this disparity is not clear, there are a number of proposed explanations. Black individuals may develop glaucoma at an earlier age, present with more extensive damage, experience faster progression, be less adherent to treatment and have less access to healthcare.^{3,4}

In a recent work, Gracitelli *et al* proposed a novel explanation for this disparity: higher visual field variability in black individuals compared with

whites.⁵ Standard automated perimetry (SAP) is the gold-standard test to measure vision loss from glaucoma and is used routinely to monitor the disease. One of the key limitations of SAP, however, is its high test variability, which can make it difficult to detect true change over time.^{6,7} A high variability can result in missed or delayed identification of glaucomatous progression, delayed interventions and worse visual outcomes.^{7,8} The study by Gracitelli *et al*, however, used data from a relatively small population of patients who were enrolled in a prospective clinical study with a rigid follow-up scheme. It is not known whether racial differences in visual field variability would also be present and have the same magnitude in a large 'real-world' clinical population.

The purpose of this study was to evaluate differences in SAP visual field variability between black and white individuals in a large 'real-world' clinical population and to evaluate how these differences are influenced by socioeconomic status. We then estimated differences in the time to detect glaucoma progression between the two racial groups.

METHODS

This retrospective cohort study used data from the Duke Glaucoma Registry (DGR).

Study population

The DGR is a repository of electronic medical record data for patients who received glaucoma care at the Duke Eye Center from 1998 to 2019. This 'real-world' data registry allows for the evaluation of data from patients under the care of attending physicians in routine clinical practice. For this study, we included patients with primary-open angle glaucoma from the DGR who had performed at least five SAP tests performed during follow-up. All glaucomatous eyes were required to have repeatable visual field defects at baseline, as defined by the first two visual fields with glaucoma hemifield test outside of normal limits or pattern SD with probability $<5\%$. Patients were excluded from this study if they had less than 2 years of follow-up, were younger than 18 or older than 100, had secondary glaucoma, received panretinal photocoagulation, or had other causes of visual field loss (retinal detachment, retinal



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vascular occlusion, optic neuritis, cortical vision loss, intraocular tumours, amblyopia or uveitis).

Standard automated perimetry

Visual fields were performed using the SAP Swedish Interactive Threshold Algorithm 24–2 from the Humphrey Field Analyzer (Carl-Zeiss Meditec, Dublin, California, USA). Visual fields were excluded if they had more than 15% false-positive errors or more than 33% fixation losses.

Sociodemographic variables

Patient age, gender and race were ascertained from the electronic medical record data. Using validated methods,⁹ the zip code of residence for each patient was also extracted and used to derive socioeconomic variables using the 2006–2011 US census. For each patient, the proportion of adults with annual household income larger or equal to US\$25 000 per year in his or her zip code was recorded. This proportion represented the probability that the patient was in the higher income group and followed a distribution that was close to normal. Similarly, the proportion of adults with at least a high school degree in the zip code was recorded. This proportion represented the probability that the patient was in the higher education group. These proportions were treated as continuous variables.⁹

Data analysis

Ordinary least squares (OLS) linear regression was performed on the SAP mean deviation (MD) values for each eye over time. The residuals from the trend lines were calculated. The SD of the residuals was calculated and used as a measure of variability for each eye, using methods previously described.^{5 7 10} Univariable and multivariable generalised estimating equation (GEE) models were used to evaluate differences in the SD of the residuals by race, with SD of the residuals as the dependent variable. Multivariable models adjusted for age, average SAP MD during the follow-up period, duration of follow-up, number of visual fields performed, and income, as indicated by the probability of annual household income larger or equal to US\$25 000 in the zip code of residence. Because the association between visual field variability and sensitivity is nonlinear, average SAP MD was modelled using restricted cubic splines, with the number of knots determined by cross-validation.^{11 12} We included second-order interaction terms between race and the splines representing average MD. To evaluate the influence of socioeconomic status on the relationship of race with visual field variability, we included an interaction between race and income in the model. All continuous and count variables were centred on the mean. The necessity of the interaction terms was verified using a likelihood ratio test showing improved model fit.

We then used computer simulations to reconstruct ‘real-world’ SAP MD trajectories and estimate the time to detect visual field progression in the two racial groups, using methods previously described.^{5 7} In short, the OLS residuals of MD trends over time obtained from the original cohort were binned based on MD values. This provided empirical distributions of residuals for each level of MD, which allowed reconstruction of MD trajectories over time by computer simulation based of expected ‘true’ rates of glaucoma progression. For each ‘true’ MD value, the bin of empirical distributions of MD residuals contain the range of measured values that would be expected for a given test. Computer simulation was then used to create longitudinal sequences of visual field tests by assuming a ‘true’ baseline MD and a ‘true’ rate of change and sampling from the empirical

Table 1 Characteristics of the study population

	Black race	White race
Total eyes	428	1103
Total patients	317	751
Age, years, mean (SD)	62.2 (11.2)	66.7 (11.0)
Women, N (%)	187 (59.0)	420 (55.9)
Follow-up time, year, mean (SD)	8.7 (4.0)	8.1 (3.8)
No of visual fields, mean (SD)	6.9 (2.4)	7.4 (2.9)
Baseline SAP MD 24–2, dB, mean (SD)	−6.0 (6.4)	−5.6 (5.5)
Baseline SAP PSD 24–2, dB, mean (SD)	4.8 (3.4)	5.1 (3.5)
Rate of change, dB/year, mean (SD)	−0.20 (0.85)	−0.25 (0.61)
Proportion of adults in zip code with annual household income ≥ US\$25 000, mean (SD)*	53.8% (19.9)	63.6% (16.9)
Proportion of adults in zip code with at least a high school degree, mean (SD)†	82.6% (13.2)	90.6% (9.4)
False positive percentage, mean (SD)	3.1% (3.4)	2.9% (3.2)
False negative percentage, mean (SD)	4.7% (12.8)	4.0% (10.9)
Fixation loss percentage, mean (SD)	8.4% (9.2)	7.7% (8.6)
Test duration, seconds, mean (SD)	347.9 (96.1)	333.3 (92.8)

*For each patient, the proportion of adults with annual household income larger or equal to US\$25 000 per year in the zip code was recorded. This proportion represents the probability that the patient was in the higher income group.

†For each patient, the proportion of adults with at least a high school degree in the zip code was recorded. This proportion represents the probability that the patient was in the higher education group.
MD, mean deviation; PSD, pattern SD; SAP, standard automated perimetry.

distribution of residuals to reconstruct what the SAP MD would be at each time. The ‘measured’ slopes calculated from these simulated SAP MD points differ from the ‘true’ slopes in that they reflect the measurement variability observed in our cohort and allow us to evaluate how quickly progression would be identified given this variability under different circumstances. Simulations were performed for each racial group, using race-specific empirical distributions of residuals. We simulated 10 000 sequences of visual fields for each racial group. We conducted the simulations first assuming annual testing and then assuming testing every 6 months. We calculated the earliest time to detect progression for each sequence of visual fields. Progression was defined as a statistically significant negative slope of MD over time with $p < 0.05$. We then constructed cumulative probability functions of time to detect progression for each racial group and estimated differences in time to detect progression under specific visual field scenarios. All statistical analyses were performed using commercially available software (Stata, V.16 (StataCorp)). The α level was set at 0.05.

RESULTS

A total of 1531 eyes from 1068 individuals were included in the analysis. Of the total, 1103 (72.0%) eyes were from 751 (70.3%) White individuals and 428 (28.0%) eyes were from 317 (29.7%) black individuals. **Table 1** presents the characteristics of the study population, stratified by the two racial groups. The mean (SD) follow-up time was 8.1 (3.8) years for whites and 8.7 (4.0) years for blacks ($p = 0.424$). The mean (SD) number of visual fields was 7.4 (2.9) for white individuals and 6.9 (2.4) for black individuals ($p < 0.001$). The mean (SD) rate of MD change was -0.25 (0.61) dB/year for white individuals and -0.20 (0.85) dB/year for blacks ($p = 0.443$). The mean (SD) test duration was 347.9 (96.1) for black individuals and 333.3 (92.8) for white individuals ($p = 0.007$).

The mean of the SD of residuals was larger for black individuals (1.53 dB (95% CI 1.43 to 1.64)) than whites (1.26 dB (95% CI 1.14 to 1.22); mean difference: 0.28 (95% CI 0.15 to 0.41); $p < 0.001$ from univariable GEE model), indicating greater visual field variability over time in eyes of black individuals. This is shown in **figure 1**, which presents a histogram of SD of the

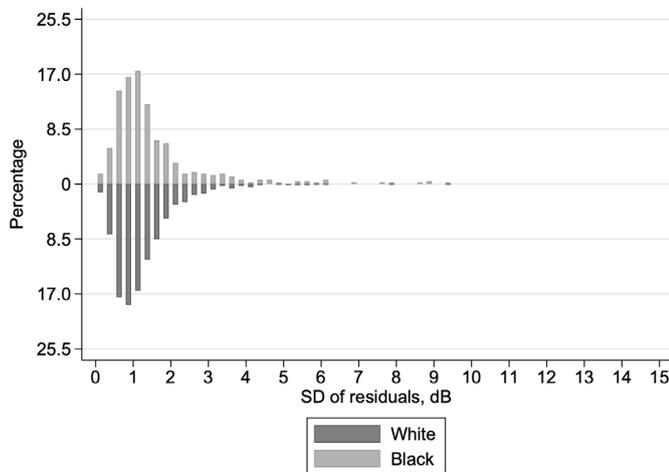


Figure 1 Distribution of the SD of the residuals in black and white individuals.

residuals for the two groups. The results of the multivariable GEE model evaluating the association of race with the SD of the residuals are presented in table 2. Eyes of black individuals had on average 0.22 dB higher SD of residuals compared with eyes of white individuals, even after adjusting for age, average SAP MD during the follow-up period, duration of follow-up, number of visual fields performed and income. Worse visual field damage (lower SAP MD) and longer follow-up duration were also associated with increased variability.

There was a significant interaction between race and disease severity in the association with visual field variability. This interaction is shown in figure 2A and table 2. The difference in visual field variability between black and white individuals was greatest at an MD of approximately -11 dB. Importantly, there was also a significant interaction between race and income in the association with visual field variability, with lower incomes associated with greater differences in visual field variability between the races (shown in table 2, $p=0.002$). The impact of this interaction is illustrated in figure 2. The difference in visual field variability

Table 2 Results of the multivariable generalised estimating equation evaluating the association of race with visual field variability (SD of the residuals)

Parameter	Coefficient	95% CI	P value
Black race	0.216	0.092 to 0.341	<0.001
SAP MD spline 1, per 1 dB lower	0.057	0.033 to 0.081	<0.001
SAP MD spline 2, per 1 dB lower	-0.101	-0.137 to 0.065	<0.001
SAP MD spline 3, per 1 dB lower	0.306	-0.462 to 1.073	0.435
Race x SAP MD spline 1	0.022	-0.025 to 0.068	0.357
Race x SAP MD spline 2	-0.105	-0.175 to 0.035	0.003
Race x SAP MD spline 3	1.777	0.311 to 3.243	0.018
Age, per 10 years	0.041	-0.008 to 0.089	0.099
Follow-up duration, per 1 year	0.022	0.006 to 0.038	0.007
Number of visual fields performed	-0.007	-0.029 to 0.015	0.534
Income*, per 10%	-0.007	-0.044 to 0.030	0.707
Race x income	-0.096	-0.158 to 0.034	0.002

*Income: For each patient, the proportion of adults with annual household income larger or equal to US\$25 000 per year in the zip code was recorded. This proportion represents the probability that the patient was in the higher income group. This value was treated as a continuous variable in the model.
MD, mean deviation; SAP, standard automated perimetry.

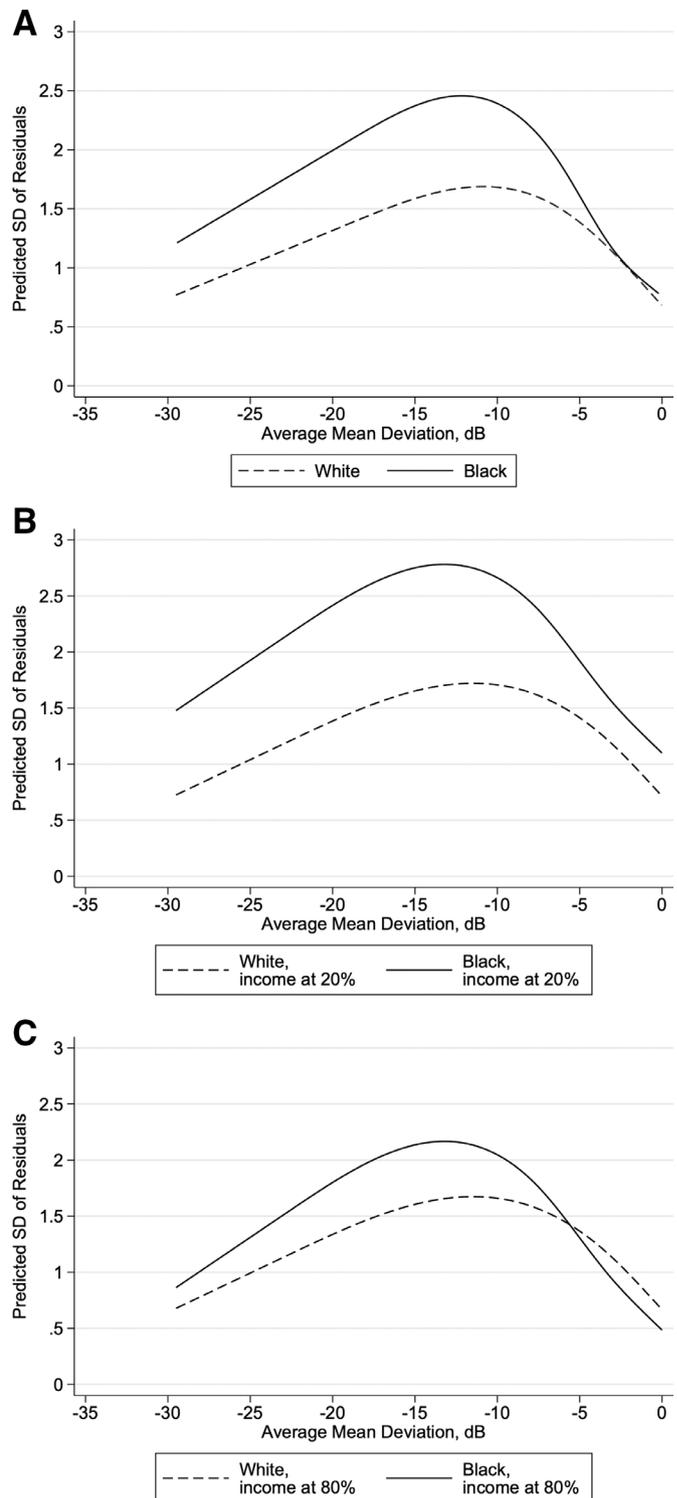


Figure 2 Association between visual field variability and visual field severity, stratified by race. The y-axis is the predicted SD of residuals, calculated from based on the results of the multivariable generalised estimating equation. The relationship between SD of residuals and mean deviation is non-linear and was modelled using splines. (A) shows the overall difference between black and white individuals. The difference between the racial groups was greatest at about -11 dB. (B) shows the SD of residuals for individuals from zip codes with 20% of adults with annual household income larger or equal to US\$25 000 and (C) is for those from zip codes with 80% of adults with annual household income larger or equal to US\$25 000.

Table 3 Simulated time to detect progression with visual field testing every year or every 6 months in varying scenarios of visual loss in black and white individuals

Baseline MD, dB	'true' rate of change, dB/year	Testing every year				Testing every 6 months			
		Mean time to detect progression, mean (SD), year		Time to detect progression in 80% of eyes (80% power), year		Mean time to detect progression, mean (SD), year		Time to detect progression in 80% of eyes (80% power), year	
		White race	Black race	White race	Black race	White race	Black race	White race	Black race
-5	-0.25	9.8 (4.1)	11.6 (5.0)	13.1	15.5	7.1 (3.4)	8.4 (4.1)	9.8	11.6
	-0.5	6.9 (2.5)	7.9 (3.1)	8.9	10.4	4.9 (2.1)	5.8 (2.5)	6.5	7.7
	-1.0	5.0 (1.6)	5.8 (2.0)	6.2	7.4	3.4 (1.3)	4.0 (1.5)	4.4	5.2
-10	-0.25	11.4 (4.6)	15.0 (6.2)	15.1	19.9	8.6 (4.0)	11.2 (5.5)	11.7	15.6
	-0.50	7.7 (2.7)	9.8 (3.6)	9.8	12.7	5.7 (2.3)	7.5 (3.1)	7.5	9.9
	-1.0	5.2 (1.6)	6.5 (2.2)	6.5	8.2	3.8 (1.4)	4.9 (1.8)	4.9	6.4

MD, mean deviation.

between the two races is greater in individuals from zip codes where 20% of adults have annual household income greater than or equal to US\$25 000 per year (figure 2B) compared with those from zip codes where 80% of adults have annual household income greater than or equal to US\$25 000 per year (figure 2C). The models using education alone and both income and education resulted in a similar association of race with variability and had similar model fit.

To estimate the difference in time to detect progression between black and white individuals, we simulated a variety of scenarios using the data on visual field variability from our study population. We assumed annual visual field testing, baseline MD values of -5 dB and -10 dB, and true rates of MD change of -0.25 dB/year (slow progression), -0.5 dB/year (moderate progression) and -1 dB/year (fast progression). Table 3 shows mean predicted times to detect progression and predicted times to detect progression with 80% power (when 80% of progressing eyes would be detected as progressing) for the overall population. For all scenarios, it took longer to detect progression in Black individuals compared with whites. For example, in patients with a baseline MD of -10 dB and moderate progression (-0.5 dB/year) undergoing annual testing, to detect 80% of progressing eyes it would take 12.7 years in black individuals and 9.8 years in white individuals. For testing every 6 months, this time reduced to 9.9 years for Black individuals and 7.5 years for white individuals.

DISCUSSION

In a large 'real-world' clinical population, we found that Black patients had larger visual field variability over time compared with White patients. This difference was present even when adjusting for age, follow-up duration, number of visual fields performed and zip code-level socioeconomic variables. The association of race with visual field variability was influenced by socioeconomic status, with a greater difference in visual field variability between black and white individuals at lower incomes. In simulation modelling of eye trajectories, we identified a delay in identification of progression in blacks caused by the larger values of visual field variability. These findings may contribute to worse clinical outcomes that are often seen in black patients.

Our study confirms the findings of the Gracitelli *et al* publication.⁵ In a large, 'real-world' clinical population, we also found increased visual field variability and delayed identification of glaucomatous progression in black patients compared with white patients, even when adjusting for zip code level socioeconomic variables. However, in our study using 'real-world' clinical data we found more visual field variability and longer times to detect progression in both racial groups compared with the Gracitelli publication, which used data from patients enrolled

in a longitudinal study with rigorous test protocols. In the prior study, the mean of the SD of residuals was for 1.45 dB blacks and 1.12 dB for whites (mean difference: 0.33; $p < 0.001$). In the present study, the mean of the SD of residuals was 1.53 dB for black patients and 1.26 dB for white patients. In the prior study, the authors estimated that it would take 11.4 years in a black patient compared with 8.3 years in a white patient to detect progression with 80% power in patients with a baseline MD of -10 dB and a 'true' rate of -0.5 dB/y with annual testing. In the present study, we estimated corresponding values of 12.7 and 9.8 years, respectively. Overall, our findings also make clear that annual visual field testing is likely not sufficient for detecting glaucoma progression, as previously shown in other investigations.^{8 13} In our simulation, the time to detect progression was considerably less with testing every 6 months rather than testing every year in all patient scenarios (see table 3).

Higher SAP variability makes it more challenging to detect visual field progression because there is more 'noise' (variability) compared with 'signal' (true progression).¹⁴ Worse visual field damage, older age and neurocognitive decline have all been associated with higher SAP variability.^{7 15 16} Our study found an interaction between race and visual field damage in the association with SAP variability. The effect of this interaction is shown in figure 2. The difference between the two racial groups was lowest at MD values greater than approximately -5 dB. The difference between the two races was the greatest at MD levels between -10 and -20 dB. Decreased ability to detect visual field progression in this MD range is particularly dangerous as it could lead to irreversible loss of vision with considerable impact on the patient's quality of life.¹⁷

The simulation models we conducted showed the impact of the difference in SAP variability between the two racial groups. For example, for a baseline MD of -10 dB and assuming a 'true' progression rate of -0.5 dB/year, it would take almost 3 years longer to detect progression in Black individuals. It is also important to note that, in our study, black patients received fewer visual field tests which were spread over a longer follow-up period compared with Whites. Therefore, this would increase even further the difference in time to detect progression between the two groups. This disparity in the frequency of visual field testing is not unique to our study population. Previous research using national claims databases has also shown that Black patients receive visual field testing less frequently than white patients.^{18 19}

The underlying cause of greater visual field variability in black patients compared with whites is not clear. It is likely that socioeconomic disparities play a role in this difference. In our study, the association of race with visual field variability was clearly influenced by socioeconomic status. However, it is likely that other social factors that we were not able to include in our model

could further explain the association of race with visual field variability. For example, sleep quality, anxiety and depression may be associated with decreased visual field performance reliability.^{20–22} Experiencing racism is associated with depression, anxiety and insomnia.^{23 24} It is possible that black patients experience unmeasured social stressors, such as racial discrimination, that lead to worse sleep quality, anxiety and depression and that this explains some of the difference in visual field variability that we observed. It is also possible that black patients receive less support and instruction from the technicians administering the visual field tests.²⁵ No matter the cause of greater visual field variability in Black patients compared with white patients, it is important that clinicians are aware of this difference because it may partially explain why black patients often have worse clinical outcomes from glaucoma. Other factors such as access to care, socioeconomic barriers, adherence to treatments, frequency of testing and disease severity at diagnosis may also be playing a major role.

We did not find a difference in the rate of MD change in black individuals (−0.20 dB/year (0.85)) compared with white individuals (−0.25 dB/year (SD 0.61), $p=0.443$). Some prior publications have found that Black individuals have faster rates of progression than white individuals^{26 27} while others have not,^{28 29} particularly when other factors are adjusted for.³⁰ One possible explanation for why we did not find a difference in progression rate between the racial groups in our study is that all patients in our study had been diagnosed with glaucoma and were receiving ongoing care. The differences in progression between the races found in some studies may be driven by differences in access to care, consistent follow-up and other socioeconomic circumstances.^{4 31} It is possible, for example, that blacks may have received more aggressive treatment by their treating physicians due to the perception that they may be at higher risk for progression.

The participants in this study were seen at the Duke Eye Center in the state of North Carolina in the USA. In North Carolina, 21.4% of the population is black compared with 12.7% for the entire USA.³² Although we expect that our findings would be similar across other parts of the country, it is possible that racial disparities may be different in other regions of the globe, leading to different findings. Further studies should investigate this. Of note, our study evaluated the association of visual field variability with race, not ancestry; ancestry cannot be reliably ascertained from race in the USA.³³

Our study had limitations. It relied on self-reported race recorded in the electronic medical record. Collection of data on race is required as part of meaningful use for electronic medical records. Prior work evaluating the accuracy of the race documented in the electronic medical record has shown that Black race recorded in the electronic medical record has a sensitivity of 70.9% and specificity of 98.8% for self-reported black race.³⁴ This means that most of the patients we considered to be black likely were, but some of the patients we considered to not be black actually were. If anything, we expect this misclassification would have decreased the differences we found between the two racial groups and we would likely find an even greater difference if there existed a more accurate representation of racial background. There is no way to consistently classify race—a social and political construct, rather than a biological process, as it is often considered.³³ Our evaluation of visual field variability and progression used only the global index SAP MD and did not look at point-wise variability and progression in the visual fields. The differences in variability and time to detect progression between the two racial groups may be different when evaluating

localised losses. However, trend-based MD progression is traditionally used to assess progression and previous studies have shown that, for the same specificity, it performs very similarly to pointwise event-based progression.³⁵ Though we adjusted for socioeconomic status in our model, residual confounding may be present as socioeconomic status is closely related to race. We conducted a subanalysis matching black and white individuals based on average SAP MD, zip code income, and zip code education. We identified 221 eyes from 221 black individuals and 221 eyes from 221 White individuals. In this subanalysis, there was still a difference in visual field variability between the races, with an average SD of residuals of 1.42 dB for black individuals and 1.22 dB for white individuals ($p=0.02$, paired t-test).

In conclusion, we found that black patients had larger visual field variability over time compared with white patients in a large ‘real-world’ clinical population. This difference was present even when adjusting for age, follow-up duration, number of visual fields performed and zip code level socioeconomic variables. Simulation modelling showed that this increased variability could lead to a delay in identification of glaucomatous progression in black patients.

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Contributors FAM and BS conceived of the presented idea. FAM, SB, EBM and AJ developed the theory and planned the computations. BS, EBM, SB, AJ, ARE, RH, KK, BH and FAM discussed and revised the analysis plan. EBM performed the computations. FAM, BS, SB, AJ, RH, KK, BH verified the analytical methods. BS, EBM, SB, AJ, ARE, RH, KK, BH and FAM discussed the results and contributed to the final manuscript and revision.

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Patient consent for publication Not required.

Ethics approval The Duke University Institutional Review Board approved this study, which adhered to Health Insurance Portability and Accountability Act (HIPAA) regulations and the Declaration of Helsinki.

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