HHS Public Access

Author manuscript

Am J Ophthalmol. Author manuscript; available in PMC 2025 April 01.

Published in final edited form as:

Am J Ophthalmol. 2024 April ; 260: 60–69. doi:10.1016/j.ajo.2023.12.002.

Time to Glaucoma Progression Detection by Optical Coherence Tomography in Individuals of African and European Descents

Jo-Hsuan Wu, MD[1,*], **Sasan Moghimi, MD**[1,*], **Evan Walker, MS**[1], **Takashi Nishida, MD, PhD**[1], **Nicole Brye, MS**[1], **Golnoush Mahmoudinezhad, MD, MPH**[1], **Jeffrey M. Liebmann, MD**[2], **Massimo Fazio, PhD**[3], **Christopher A. Girkin, MD**[3], **Linda M. Zangwill, PhD**[1], **Robert N. Weinreb, MD**[1]

[1]Hamilton Glaucoma Center, Shiley Eye Institute, Viterbi Family Department of Ophthalmology, University of California, San Diego, La Jolla, CA, United States.

[2]Bernard and Shirlee Brown Glaucoma Research Laboratory, Department of Ophthalmology, Edward S. Harkness Eye Institute, Columbia University Medical Center, New York, New York.

[3]Department of Ophthalmology and Vision Sciences, Heersink School of Medicine, University of Alabama-Birmingham, Birmingham.

Abstract

Purpose: To examine time to detectable retinal nerve fiber layer thickness (RNFLT) progression by optical coherence tomography (OCT) among glaucoma patients of African (AD) and European descent (ED).

Design: Retrospective cohort study.

Methods: AD and ED glaucoma eyes from DIGS/ADAGES with ≥2-years/4-visits of optic nerve head RNFLT measurements were included after homogenization on age, diagnosis and baseline visual field (VF) measurement. RNFLT variability estimates based on linear mixed-effects models were used to simulate longitudinal RNFLT data for both races. Time to trend-based RNFLT progression detection were calculated under standardized scenarios (same RNFLT baseline/thinning rates for both races) and real-world scenarios (AD and ED cohort-specific RNFLT baseline/thinning rates).

Results: We included 332 and 542 eyes (216 and 317 participants) of AD and ED, respectively. In standardized scenarios, the time to detect RNFLT progression appeared similar (difference <0.2years) for AD and ED across different assumed RNFLT thinning rates/baseline. In real-world scenarios, compared to ED, AD had a faster RNFLT thinning rate (−0.8 vs.−0.6um/year) and thicker baseline RNFLT (84.6 vs.81.8um). With a faster thinning rate, the mean(SD) time to progression detection was shorter in AD (4.8[2.0] vs.ED:5.4[2.4] years), and the 5-year progression rate appeared higher (AD:59% vs.ED:47%).

Corresponding Author/Address for Reprints: Robert N. Weinreb, MD, Shiley Eye Institute, University of California, San Diego, 9415 Campus Point Drive, La Jolla, CA, 92093-0946, rweinreb@ucsd.edu.

*These authors contributed equally as co-first authors

Supplemental Material available at AJO.com

Conclusions: Time to progression detection was similar for both races when assuming identical RNFLT baseline/thinning rates, and shorter in AD eyes under real-world simulation when AD had faster RNFLT thinning. In contrast to prior results on VF, which detected progression later in AD eyes than in ED eyes, OCT may detect progression more consistently across these races.

Keywords

glaucoma; OCT; RNFL thickness; glaucoma progression; African descents

INTRODUCTION

Glaucoma is a treatable and irreversible condition with a chronic and progressive course.[1] Periodic structural and functional assessments of the optic nerve head during clinical follow-up are imperative to detect progressive glaucomatous damage in order to provide intervention before permanent vision loss develops or worsens.

While functional progression of glaucoma is evaluated with visual field (VF) testing, assessment of optical coherence tomography (OCT) is increasingly important for the assessment of glaucoma and the detection of structural progression.[2] As compared to VF, OCT is more objective and has a smaller measurement variability,[3, 4] which may provide more reliable quantification of changes over time. Structural loss of retinal nerve fiber layer thickness (RNFLT) measured by OCT may precede detectable functional deficits in some patients, and may even predict impending VF loss.[5, 6]

Prior studies have investigated the potential presence of racial differences in the structural and functional assessment of the optic nerve head (ONH) and retina to detect glaucoma and glaucomatous changes.[7–12] A few studies have shown these differences may impact detection of glaucoma worsening using the VF.[10–12] We have previously demonstrated that patients of African descents (AD) have greater VF variability in comparison to those of European descents (ED), which was associated with a 3-year delay in the detection of progression.[11]

Given the known racial differences in retinal thickness[7–9] and the higher risk of delayed progression detection for glaucoma patients of AD when assessed only by VF, the current study examined if the performance of OCT-based measurements of progression are also impacted by racial differences in retinal and/or ONH structural measurements. Specifically, we compared the power and time required to detect glaucoma progression by OCT-measured RNFLT in glaucoma patients of AD and ED.

METHODS

This retrospective cohort study was approved by the University of California San Diego (UCSD) Human Research Protection Program (NCT00221897) and the institution review boards of the participating ADAGES centers (University of Alabama at Birmingham and Columbia University) and adhered to the tenets of the Declaration of Helsinki and the Health Insurance Portability and Accountability Act. Written informed consent was obtained from all DIGS/ADAGES participants.

Participants

Primary open angle glaucoma (POAG) and glaucoma suspect participants/eyes of AD and ED from the Diagnostic Innovations in Glaucoma Study (DIGS) / The African Descent and Glaucoma Evaluation Study (ADAGES)[13, 14] were considered eligible if they had a minimum of 2-years and 4-visits of OCT testing data. Random sampling was then performed to identify AD and ED eyes meeting the study criteria to create a final cohort where the two races were homogenized on baseline age-, diagnosis- and VF severity.

Inclusion criteria for DIGS/ADAGES were: (1) age ≥ 18 years; (2) open angles on gonioscopy; (3) baseline best-corrected visual acuity (BCVA) of 20/40 or better. Exclusion criteria were: (1) non-glaucomatous optic neuropathy; (2) history of trauma; (3) axial length ≥ 27mm; (4) coexisting retinal disease; (5) uveitis; (6) history of clinical dementia, Parkinson's disease, and/or stroke. All DIGS/ADAGES participants underwent the following evaluations: (1) At study entry: ultrasound pachymetry and gonioscopy; (2) Annual ophthalmic examination: best-corrected visual acuity, slit-lamp biomicroscopy, dilated fundus examination and stereoscopic optic disc photography; (3) Semi-annual examination: VF, intraocular pressure (IOP) measurement by Goldmann applanation tonometry and OCT imaging; (4) Clinical information and systemic medical history.

Glaucoma suspect was defined as having IOP elevation of ≥ 22 mm Hg or a suspicious-looking optic disc without repeatable glaucomatous VF damage. For inclusion in the study, POAG patients required repeatable and reliable (fixation losses and false negatives ≤ 33%; false positives ≤ 15%) VF damage using the 24–2 Swedish Interactive Thresholding Algorithm (SITA) with a pattern standard deviation > 95% normal limits or a glaucoma hemifield test result outside normal limits. Considering the potential floor effect of OCT,[15] this study excluded eyes with a baseline VF mean deviation (MD) worse than −14 dB.

OCT imaging and simulations of progression detection

The Spectralis spectral domain-OCT (Heidelberg Engineering, GmbH, Heidelberg, Germany) optic nerve head (ONH)-centered retinal nerve fiber layer (RNFL) circle scans (diameter~3.4mm) were used to obtain the mean global RNFLT. Computer simulation was performed in both AD and ED to evaluate the time needed to detect trend-based glaucomatous structural progression by RNFLT using the methods reported in prior study as described below.[16, 17]

RNFLT variability of the AD and ED groups were defined as the residuals from the longitudinal clinical data estimated by fitting separate linear mixed-effects regression models to RNFLT measurements over time with a random slope across follow-up time and random intercepts to account for within-subject and within-subject eye variability. The RNFLT measurements was then grouped into 5μm bins separately by race, and for each sequence of simulations, the RNFLT variability (residuals) was sampled randomly from the appropriate RNFLT bins and added to the simulation, thus providing a reconstruction of how longitudinal RNFLT measurements would appear in clinical practice. For both AD and ED, the assumed OCT testing frequency was set as twice per year (~every 6 months), and the simulated follow-up period for glaucoma progression detection was set to up to 12

years. Trend-based glaucomatous structural progression was defined on per-eye basis using ordinary least squares linear regression (a negative RNFLT thinning rate with a significant P-value).

Simulation protocol and scenarios

We evaluated the simulation protocol specificity with a baseline scenario assuming a RNFLT thinning rate of 0 μm/year, which simulated glaucoma eyes that remain stable throughout follow-up. For subsequent simulations, such simulation protocol was applied to sequences under both (1) standardized scenarios and (2) real-world scenarios, as explained below:

1. Standardized scenarios: In this scenario, we performed a head-to-head comparison between AD and ED on the time to RNFLT progression detection under a variety of conditions using a range of RNFLT thinning rates (−0.5, −1.0, −1.5, and −2.0 μm/year) and baseline RNFLT (70, 80 and 90 μm). For each comparison, the same RNFLT baseline and RNFLT thinning rate were assumed for AD and ED. For example: In standardized scenario, progression detection was compared between AD and ED under the assumption of a baseline RNFLT of 70 μm and thinning rate of −0.5 μm/year for both races.
2. Real-world scenarios: In this scenario, to mimic patient presentation at real-world clinical settings, where AD and ED eyes usually possess different baseline RNFLT and RNFLT thinning rates, the assumed RNFLT thinning rates and baseline used in the simulation were derived directly from our AD and ED cohorts by race. For example, the true RNFLT thinning rate of AD eyes is faster than that of ED eyes in our cohort, and we used these race-specific values to create the simulations in the real-world scenario.

A total of 200,000 simulated sequences were generated for each assumed rate of RNFLT thinning and baseline RNFLT. We then recorded the time required to detect RNFLT progression in the simulated eyes, as well as the required time to detect RNFLT progression when 80% and 90% of eyes show progression (significantly negative RNFLT slope) with an alpha level of 5%, for both AD and ED. The percentages of simulated eyes detected as progressors after 2 and 5 years of OCT follow-up were also calculated by race based on these simulations.

Statistical analysis and sensitivity analysis

Demographic and clinical characteristics of AD and ED were presented as count (%) for categorical variables and as mean (95% confidence interval [CI]) for continuous variables. Statistical analyses were performed using the R programming language version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria) with the packages “lme4”, “nlme”, “lmerTest”, and “performance”. A P-value < 0.05 indicates statistical significance.

Since the sample size is determined by the simulation specification and there is no consensus on how to calculate P-values for simulated data, as in our previous work,[18] we do not include p-values when comparing the progression detection performance of RNFLT by race. Additionally, there has not been an agreed-on statistical approach to calculating long-term RNFLT variability for the construction of longitudinal simulation data. To further

validate our findings, we also performed a sensitivity analysis using ordinary least square regression for variability calculation to examine the time to progression detection under both standardized and real-world scenarios.

RESULTS

Demographic and clinical characteristics of the subjects and eyes are shown in Table 1. After homogenizing the baseline age, diagnosis, and VF severity, we included 332 eyes (216 participants) and 542 eyes (317 participants) of AD and ED, respectively. AD participants reported higher rates of hypertension and diabetes ($P<0.05$ for all). AD eyes also had thinner mean (95% CI) baseline CCT (533.5 [527.9, 539.3] μm vs. ED: 551.6 [547.0, 556.2] μm), faster RNFLT thinning rate (−0.8 [−1.0, −0.7] μm/year vs. ED: −0.6 [−0.7, −0.5] μm/year), and longer follow-up duration AD (7.0 [6.7, 7.4] years vs. ED: 6.3 [6.0, 6.6] years) ($P<0.05$). The mean (95% CI) variability of the longitudinal RNFLT were 1.6 (1.5, 1.7) μm for AD and 1.5 (1.4, 1.5) μm for ED ($P=0.018$). The distribution of RNFLT thinning rates and longitudinal RNFLT residuals by races is shown in Supplemental Figure 1.

As mentioned in the methods, the specificity of the current analysis protocol was evaluated on simulated stable glaucoma eyes with a RNFLT thinning rate of 0 μm/year. As shown in Supplemental Table 1, the percentages of stable glaucoma eyes detected with RNFLT progression in AD and in ED at 2 and 5 years was comparable when simulated with a baseline RNFLT of 70 and 90 μm and the mean baseline RNFLT derived from the whole cohort (82.9 um), suggesting similar specificity for both races.

Standardized scenarios

Table 2 summarizes the simulated time to detect RNFLT progression in AD and ED eyes under the standardized scenarios, where the same RNFLT thinning rates and baseline RNFLT were assumed for both races. Overall, the mean time required to detect RNFLT progression are very similar for both races across different RNFLT thinning rates and baseline RNFLT (range of difference: 0.0–0.2 years). For instance, with an assumed baseline RNFLT of 80 um and thinning rate of −1.0 um/year, the mean (SD) time to detect progression in AD and ED was 4.0 (1.6) and 4.0 (1.6) years, respectively, and 80% of AD and ED eyes would be detected with progression after 5.7 and 5.8 years, respectively. Under the same scenario, the 2- and 5-year rate of RNFLT progression detection was 15.5% and 78.0% in AD, and 14.9% and 77.7% in ED, respectively. Figure 1 shows the time required to detect RNFLT progression across different assumed rates of RNFLT thinning with an assumed baseline of 80 um. Within each race, the time to detection was shorter when the thinning rate was faster.

Results of the standardized scenario sensitivity analysis based on ordinary least square regression analysis are shown in Supplemental Table 2. Consistent with results using linear mixed-effects model, the time to detectable RNFLT progression in AD and ED was similar across various assumed baseline RNFLT and RNFLT thinning rates, with the difference in mean time ranging from 0.0–0.1 years. The time to detecting progression in 80%/90% of eyes, as well as the percentage of eyes detected with progression at 2- and 5-year follow-up, were also similar between AD and ED.

Real-world scenarios

Table 3 summarizes the simulated time to detect RNFLT progression in AD and ED eyes under the real-world scenarios using main method (linear mixed-effects models), which mimicked clinical settings and reflected our ADAGES data, in which AD and ED patients have different baseline RNFLT and rates of thinning. The cohort-derived mean baseline RNFLT was 84.6 um and 81.8 um (P=0.033), and the mean RNFLT thinning rate was −0.82 and −0.59 um/year (P=0.016) for AD and ED, respectively. With a faster thinning rate, the mean (SD) time to detect RNFLT progression in AD (4.8 [2.0] years) was 0.6 years shorter than that in ED (5.4 [2.4] years). Similar findings were observed for the time required to detect RNFLT progression in 80% (AD: 6.9 years vs. ED: 7.7 years) and 90% (AD: 7.8 years vs. ED: 8.6 years) of eyes (difference ~0.8 years). The 2- and 5-year rate of RNFLT progression detection was 11.9% and 58.9% in AD, and 10.5% and 47.0% in ED, respectively.

Results of the real-world scenario sensitivity analysis based on ordinary least square regression analysis are shown in Supplemental Table 3. The findings are consistent with the results using linear mixed-effects model, although the time to RNFLT progression detection in ED eyes increased. Using the regression approach, the difference in mean (SD) time to detect RNFLT progression in AD (5.0 [2.0] years) and ED (6.3 [2.7] years) was 1.3 years, supporting the faster detection of RNFLT progression in AD when a faster RNFLT thinning rate is present. The time required to detect RNFLT progression in 80% and 90% of eyes was approximately 2 years shorter for AD in comparison to ED, and the 5-year rate of RNFLT progression detection was 52.9% in AD and 34.3% in ED.

Supplemental analysis

As shown in our prior work, in addition to race, a few other clinical factors may also affect RNFLT variability, particularly intervening cataract extraction (CE), which has demonstrated the strongest effect on higher RNFLT variabiltiy.[4] Although not significantly different, more AD than ED eyes in this cohort had intervening CE (25.9% vs 20.5%, P=0.067, Table 1), which might have contributed to the racial difference in long-term RNFLT variability and thus affected the time to progression detection. To determine whether the time to RNFLT progression observed was influenced by this factor, we completed a supplemental analysis on subgroup of eyes without intervening CE (Supplemental Table 4–5). In this subgroup, minimal differences in the mean time to progression detection were found between AD and ED under standardized scenario (difference <0.1 year). Under the real-world scenario, the mean time to detect progression was 0.8 year faster in AD, consistent with the main analyses.

DISCUSSION

This study compared the time required to detect glaucoma progression by OCT-measured RNFLT in glaucoma patients of AD and ED. In standardized scenarios, the time to detect RNFLT progression, as well as the percentages of eyes progressing detected within a defined follow-up period, were similar for AD and ED. In real-world scenarios, where AD eyes have a faster RNFLT thinning rate than ED eyes, the time to RNFLT progression detection was

shorter for AD than ED eyes. These findings suggest that, in contrast to previous studies of VF progression,[11, 19] the time to detect RNFLT progression was similar in AD and ED eyes (generally < 3 months) when the same thinning rates and baseline RNFLT were assumed, despite the small but statistically significant difference in RNFLT variability (AD: 1.6 um, ED 1.5 um, P=0.018). Additionally, OCT should allow the timely progression detection in AD, which usually present with a faster RNFLT thinning in clinical settings. Our results may have implications in establishing clinical testing strategies to optimize the detection of glaucoma structural progression in this at-risk minority population.

Individuals of AD are disproportionately affected by glaucoma, with a higher risk of visual impairment and faster disease progression.[20–22] Although the VF is widely utilized to determine glaucoma progression, the greater fluctuation of VF measurement in AD individuals can lead to inaccurate and, even more concerning, delayed or missed progression detection.[18, 19, 23, 24] In the study by Gracitelli et al., the long-term VF variability of AD individuals was 30% higher (~0.33 dB) than that of ED ones, leading to a 3.1-year delay in progression detection at 80% power.[11] Stagg et al. also reported a 22% greater VF variability (~0.27 dB) of AD compared to ED individuals, which corresponded to a 2.9-year delay.[19] Defining the ability of OCT to detect structural progression is especially relevant considering VF alone may be less adequate to identify progressive glaucoma in AD individuals.

Based on the standardized scenarios results, OCT performed similarly in detecting RNFLT progression in individuals of AD and ED when the same baseline and rates of RNFLT thinning are assumed. Notably, we performed simulations under different assumed rates of RNFLT thinning (−0.5 ~ −2.0 μm/year) and baseline RNFLT (70–90 μm). We selected the baseline RNFLT based on the most common range of RNFLT measurements observed at baseline visits for glaucomatous eyes with and without initial VF loss.[5, 25, 26] As for the rate of RNFLT thinning, prior studies generally reported the mean to range from −0.5 to −1.5 μm/year in glaucoma eyes, regardless of disease severity.[27–30] Although there is no consensus on how to define fast RNFLT thinning, rates of moderate (75th percentile) and rapid (90th percentile) RNFLT worsening was −1.1 μm/year and −2.4 μm/year, respectively, based on a large glaucoma cohort.[31] Since the standardized scenarios covered the common range of baseline RNFLT and RNFLT thinning rates encountered in clinical settings, the similar time to progression detection between AD and ED under this scenario support the possible clinical applicability of our results. Moreover, different from prior findings for VF,[18, 19, 24] our findings suggest OCT-measured RNFLT may not cause delayed glaucoma progression detection in individuals of AD, as compared to ED. This might be explained by the small RNFLT variability of both races, as well as the likely clinically insignificant racial difference between them (~0.1 μm).

To simulate the time to progression detection in real-world settings, where AD and ED patients often present with different baseline RNFLT and thinning rates, our real-world simulations used measurements derived directly from our AD and ED cohorts. If OCT indeed performs similarly across the two races, a shorter time to progression detection should be observed for AD, who demonstrated faster RNFLT thinning. Consistent with our hypothesis, the real-world scenarios showed that OCT could detect RNFLT progression

earlier in AD when their thinning rate was faster than that of ED, with the lead time ranging from 0.6–1.3 years. The larger lead time observed in the sensitivity analysis based on linear regression model was also anticipated, given the mixed-effect modeling tends to result in lower estimated variability. Most importantly, with the assumed testing frequency of twice per year, the observed difference in time to detection would allow the clinicians to identify progressing AD eyes 1–2 visits earlier, or even sooner, if more frequent testing is arranged.[17, 31] Overall, findings from both scenarios suggest a consistent performance of OCT-measured RNFLT across the two races and its potential to optimize clinical progression detection in fast-progressing AD eyes.

A limited number of clinical factors other than race have been reported to affect RNFLT variability, which can potentially affect the time to detect progression. As described above, we completed a supplemental analysis excluding eyes with intervening CE, which was performed more in AD group and has been reported as the strongest factor contributing to RNFLT variability.[4] The results were consistent with the main findings, showing similar time to RNFLT progression in standardized scenarios, and faster time to detect progression in AD eyes in the real-world scenarios. While other predictors of RNFLT variability were also identified,[4] we did not perform further sub-analysis given the similar distribution of these factors across the two racial cohorts.

Past studies have shown the time to progression detection is usually shorter with a worse disease and faster measurement change,[16, 17, 31] which was supported by our results in both real-world and standardized scenarios. Of note, under simulation assuming the most common rates of RNFLT thinning, we found the approximate time to detect RNFLT progression by OCT ranged from 3 to 6 years in both AD and ED. As the majority of patients included in this analysis had mild glaucoma at baseline, this suggests administrating OCT twice per year (the assumed testing frequency in our simulations) is likely sufficient to detect structural progression in the early course of disease across different races.[17] Based on previous literature, a longer time might be needed to detect functional progression on VF when the same testing frequency was adopted.[11, 16, 32] The average rates of VF MD worsening in glaucoma mostly ranged from −0.0 to −0.5 dB/year.[25, 33–35] In the study by Wu et al., which also included mainly mild glaucoma eyes, it would take approximately 5–7 years to capture VF progression with assumed VF MD worsening rates of −0.25~−0.50 dB/year, regardless of patient race.[16] Whereas assuming a VF testing frequency of once per year, the race-stratified study by Gracitelli et al. further revealed the time to detect VF progression was significantly longer in AD (7.6–11.2 years) than in ED (6.5–9.5 years).[11] Although we did not directly compare OCT to VF, these results support both OCT and VF should be performed when assessing progression in AD eyes..

While some may question the clinical relevance of structural progression, prior studies have shown structural progression detected by OCT may precede VF progression,[5, 6] and patients demonstrating faster structural thinning on OCT had a higher risk of subsequent VF worsening.[36–38] Furthermore, in a recent simulation study, RNFLT outperformed VF MD (5–15% more accurate) in detecting glaucoma eyes with moderate and rapid worsening over a 2-year period,[31]. Although none of these studies evaluated racial differences, our results show that OCT is likely to perform similarly in AD and ED eyes.[39] It should be noted

that studies have also suggested that a multimodal approach incorporating both OCT and VF,[31] as well as a higher OCT/VF testing frequency and/or a clustered testing approach, may further improve the ability and sensitivity to detect more subtle progression.[16, 17, 31] These strategies can also be applied clinically to enhance progression assessment in high-risk groups, including AD patients. Additionally, since OCT examination is efficient, reproducible and less time consuming than VF, it might be suitable for individuals of AD when more frequent or additional testing is desired to detect changes more quickly.

While we assumed the same testing frequency for both races, studies have suggested a lower real-world visit/testing frequency of AD,[40–42] which could potentially delay progression detection.[4, 17, 31] In fact, our additional analysis on empirical data from the subset of AD and ED eyes that have converted to RNFL progression during their follow-up period supported this point. Among this empirical eye subset, AD eyes showed a longer mean time to progression detection compared to ED eyes, despite the similar rates of RNFLT change; this was mainly due to the skewed distribution of progression detection time (to the longer end) in AD eyes with widely spaced visits. Nonetheless, when including only eyes with a testing frequency of ≥ twice per year, we found comparable time to progression detection between the two races with similar RNFLT thinning rates, which is consistent with our simulation results. These findings based on empirical data suggest that a similar sensitivity of progression detection may be achieved if the same testing frequency can be ensured for AD and ED, as shown in the simulation, and that regular OCT imaging for AD patients may be beneficial. Most importantly, they also highlight the importance to investigate the clinical impacts of racial differences in practice patterns.

This study is not without limitations. First, we assessed only Spectralis OCT measurements. Since the simulation was performed based on measurement variability, the results might differ slightly when other OCT devices are used.[3, 43, 44] Second, patients with baseline VF worse than −14 dB were excluded. Considering the OCT floor effect, how OCT performs on progression detection in AD patients of advanced stage remains to be examined. It is also possible that progression detection by RNFLT may not be more consistent than VF in this scenario. Third, although the trend-based progression definition is commonly used in research setting, it might still falsely identify aging effect as progression.[27, 45, 46] Fourth, as aforementioned, while the same OCT testing frequency was assumed for AD and ED in the simulation, the presence of racial difference under real-world testing patterns and its impact on progression detection needs further investigation. Last, it is important to note that OCT and VF assess different aspects of glaucomatous damage. Therefore, the optimal way to compare results obtained from the two modalities remains to be explored.

In conclusion, when identical baseline RNFLT and thinning rate are assumed in simulation, there is no clinically relevant racial difference in the performance of OCT-measured RNFLT on progression detection across glaucoma individuals of AD and ED. Furthermore, when AD eyes demonstrate a faster RNFLT thinning than their ED counterparts, OCT would allow a sufficient lead time to capture these fast-progressing AD eyes for timely intervention. These results are in contrast to prior results of progression detection with VF,[11, 19] which found detection of progression later in AD individuals than in ED individuals, and suggest

that OCT measurements may help to reliably and consistently detect glaucoma progression across patients of different races.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements and Financial Disclosure

Funding:

This work is supported by National Institutes of Health/National Eye Institute Grants R01EY029058, R01EY011008, R01EY019869, R01EY027510, R01EY026574, R01EY018926, R01EY034148, and Core grant P30EY022589; University of California Tobacco Related Disease Research Program (T31IP1511), and an unrestricted grant from Research to Prevent Blindness (New York, NY). The sponsor or funding organization had no role in the design or conduct of this research.

Financial Disclosure:

Sasan Moghimi reported grants from the National Eye Institute. Takashi Nishida is a consultant for Topcon. Jeffrey M. Liebmann is a consultant to Alcon, Allergan, Thea, Genetech, AdvanceSight, and Carl Zeiss Meditech. Massimo A. Fazio reported grants from the National Eye Institute; grants from Heidelberg Engineering and Topcon; nonfinancial support from Wolfram Research. Christopher A. Girkin reported research support from Heidelberg Engineering and Topcon. Linda Zangwill reported grants from the National Eye Institute; grants from Heidelberg Engineering and nonfinancial support from Carl Zeiss Meditec, Optovue, Heidelberg Engineering, and Topcon; and patents from Carl Zeiss Meditec and AiSight Health. Linda Zangwill is a consultant of Abbvie and Topcon. Robert N. Weinreb is a consultant of Abbvie, Alcon, Allergan, Amydis, Editas, Equinox, Eyenovia, Iantrek, IOPtic, Implandata, iSTAR Medical, Nicox, Santen, Ten Point and Topcon. Robert N. Weinreb reported nonfinancial support from Heidelberg Engineering, Carl Zeiss Meditec, Optovue, Centervue, and Topcon; grants from the National Eye Institute, National Institute of Minority Health and Health Disparities, and Research to Prevent Blindness, patents from Toromedes, Carl Zeiss Meditec to UCSD; all outside the submitted work. No other disclosures were reported.

REFERENCES

1. Weinreb RN, Leung CK, Crowston JG, et al. Primary open-angle glaucoma. Nat Rev Dis Primers. Sep 22 2016;2:16067. doi:10.1038/nrdp.2016.67 [PubMed: 27654570]
2. Tatham AJ, Medeiros FA. Detecting structural progression in glaucoma with optical coherence tomography. Ophthalmology. Dec 2017;124(12s):S57–s65. doi:10.1016/j.ophtha.2017.07.015 [PubMed: 29157363]
3. Wu J-H, Moghimi S, Nishida T, et al. Evaluation of the long-term variability of macular OCT/OCTA and visual field parameters. British Journal of Ophthalmology. 2022:bjo-2022–322470. doi:10.1136/bjo-2022-322470
4. Wu J-H, Moghimi S, Walker E, et al. Clinical factors associated with long-term OCT variability in glaucoma. American Journal of Ophthalmology. 2023/07/16/ 2023;doi:10.1016/j.ajo.2023.07.011
5. Miki A, Medeiros FA, Weinreb RN, et al. Rates of retinal nerve fiber layer thinning in glaucoma suspect eyes. Ophthalmology. Jul 2014;121(7):1350–8. doi:10.1016/j.ophtha.2014.01.017 [PubMed: 24629619]
6. Yu M, Lin C, Weinreb RN, Lai G, Chiu V, Leung CK. Risk of visual field progression in glaucoma patients with progressive retinal nerve fiber layer thinning: a 5-year prospective study. Ophthalmology. Jun 2016;123(6):1201–10. doi:10.1016/j.ophtha.2016.02.017 [PubMed: 27001534]
7. Nousome D, McKean-Cowdin R, Richter GM, et al. Retinal nerve fiber layer thickness in healthy eyes of Black, Chinese, and Latino Americans: A population-based multiethnic study. Ophthalmology. Jul 2021;128(7):1005–1015. doi:10.1016/j.ophtha.2020.11.015 [PubMed: 33217471]

8. Kashani AH, Zimmer-Galler IE, Shah SM, et al. Retinal thickness analysis by race, gender, and age using Stratus OCT. Am J Ophthalmol. Mar 2010;149(3):496–502.e1. doi:10.1016/j.ajo.2009.09.025 [PubMed: 20042179]
9. Girkin CA, Sample PA, Liebmann JM, et al. African Descent and Glaucoma Evaluation Study (ADAGES): II. Ancestry differences in optic disc, retinal nerve fiber layer, and macular structure in healthy subjects. Archives of Ophthalmology. 2010;128(5):541–550. doi:10.1001/archophthalmol.2010.49 [PubMed: 20457974]
10. Girkin CA, Liebmann J, Fingeret M, Greenfield DS, Medeiros F. The effects of race, optic disc area, age, and disease severity on the diagnostic performance of spectral-domain optical coherence tomography. Investigative Ophthalmology & Visual Science. 2011;52(9):6148–6153. doi:10.1167/iovs.10-6698 [PubMed: 21421879]
11. Gracitelli CP, Zangwill LM, Diniz-Filho A, et al. Detection of glaucoma progression in individuals of African descent compared with those of European descent. JAMA ophthalmology. 2018;136(4):329–335. [PubMed: 29450497]
12. Bowd C, Zangwill LM, Weinreb RN, et al. Racial differences in rate of change of spectral-domain optical coherence tomography-measured minimum rim width and retinal nerve fiber layer thickness. Am J Ophthalmol. Dec 2018;196:154–164. doi:10.1016/j.ajo.2018.08.050 [PubMed: 30195890]
13. Sample PA, Girkin CA, Zangwill LM, et al. The African Descent and Glaucoma Evaluation Study (ADAGES): design and baseline data. Arch Ophthalmol. Sep 2009;127(9):1136–45. doi:10.1001/archophthalmol.2009.187 [PubMed: 19752422]
14. Girkin CA, Sample PA, Liebmann JM, et al. African Descent and Glaucoma Evaluation Study (ADAGES): II. Ancestry differences in optic disc, retinal nerve fiber layer, and macular structure in healthy subjects. Arch Ophthalmol. May 2010;128(5):541–50. doi:10.1001/archophthalmol.2010.49 [PubMed: 20457974]
15. Moghimi S, Bowd C, Zangwill LM, et al. Measurement floors and dynamic ranges of oct and oct angiography in glaucoma. Ophthalmology. Jul 2019;126(7):980–988. doi:10.1016/j.ophtha.2019.03.003 [PubMed: 30858023]
16. Wu Z, Saunders LJ, Daga FB, Diniz-Filho A, Medeiros FA. Frequency of testing to detect visual field progression derived using a longitudinal cohort of glaucoma patients. Ophthalmology. 2017/06/01/ 2017;124(6):786–792. doi:10.1016/j.ophtha.2017.01.027 [PubMed: 28268099]
17. Mahmoudinezhad G, Moghimi S, Proudfoot JA, et al. Effect of testing frequency on the time to detect glaucoma progression with optical coherence tomography (OCT) and OCT angiography. American Journal of Ophthalmology. 2023/01/01/ 2023;245:184–192. doi:10.1016/j.ajo.2022.08.030 [PubMed: 36096181]
18. Gracitelli CPB, Zangwill LM, Diniz-Filho A, et al. Detection of glaucoma progression in individuals of African descent compared with those of European descent. JAMA Ophthalmology. 2018;136(4):329–335. doi:10.1001/jamaophthalmol.2017.6836 [PubMed: 29450497]
19. Stagg B, Mariottoni E, Berchuck S, et al. The association between race and longitudinal visual field variability. Investigative Ophthalmology & Visual Science. 2020;61(7):4045–4045.
20. Rudnicka AR, Mt-Isa S, Owen CG, Cook DG, Ashby D. Variations in primary open-angle glaucoma prevalence by age, gender, and race: A bayesian meta-analysis. Investigative Ophthalmology & Visual Science. October 1, 2006 2006;47(10):4254–4261. doi:10.1167/iovs.06-0299 [PubMed: 17003413]
21. Wilson R, Richardson TM, Hertzmark E, Grant WM. Race as a risk factor for progressive glaucomatous damage. Ann Ophthalmol. Oct 1985;17(10):653–9. [PubMed: 4073724]
22. Halawa OA, Jin Q, Pasquale LR, et al. Race and ethnicity differences in disease severity and visual field progression among glaucoma patients. Am J Ophthalmol. Oct 2022;242:69–76. doi:10.1016/j.ajo.2022.05.023 [PubMed: 35654121]
23. Turpin A, McKendrick AM. What reduction in standard automated perimetry variability would improve the detection of visual field progression? Invest Ophthalmol Vis Sci. May 17 2011;52(6):3237–45. doi:10.1167/iovs.10-6255 [PubMed: 21357405]

24. Stagg B, Mariottoni EB, Berchuck S, et al. Longitudinal visual field variability and the ability to detect glaucoma progression in black and white individuals. Br J Ophthalmol. Aug 2022;106(8):1115–1120. doi:10.1136/bjophthalmol-2020-318104 [PubMed: 33985963]
25. Natural history of normal-tension glaucoma. Ophthalmology. 2001/02/01/ 2001;108(2):247–253. doi:10.1016/S0161-6420(00)00518-2 [PubMed: 11158794]
26. Bowd C, Weinreb RN, Williams JM, Zangwill LM. The Retinal nerve fiber layer thickness in ocular hypertensive, normal, and glaucomatous eyes with optical coherence tomography. Archives of Ophthalmology. 2000;118(1):22–26. doi:10.1001/archopht.118.1.22 [PubMed: 10636409]
27. Leung CKS, Ye C, Weinreb RN, Yu M, Lai G, Lam DS. Impact of age-related change of retinal nerve fiber layer and macular thicknesses on evaluation of glaucoma progression. Ophthalmology. 2013/12/01/ 2013;120(12):2485–2492. doi:10.1016/j.ophtha.2013.07.021 [PubMed: 23993360]
28. Medeiros FA, Zangwill LM, Alencar LM, et al. Detection of glaucoma progression with stratus OCT retinal nerve fiber layer, optic nerve head, and macular thickness measurements. Invest Ophthalmol Vis Sci. Dec 2009;50(12):5741–8. doi:10.1167/iovs.09-3715 [PubMed: 19815731]
29. Liu T, Tatham AJ, Gracitelli CP, Zangwill LM, Weinreb RN, Medeiros FA. Rates of retinal nerve fiber layer loss in contralateral eyes of glaucoma patients with unilateral progression by conventional methods. Ophthalmology. Nov 2015;122(11):2243–51. doi:10.1016/j.ophtha.2015.07.027 [PubMed: 26383993]
30. Tatham AJ, Medeiros FA. Detecting Structural Progression in glaucoma with optical coherence tomography. Ophthalmology. 2017/12/01/ 2017;124(12, Supplement):S57–S65. doi:10.1016/j.ophtha.2017.07.015 [PubMed: 29157363]
31. Bradley C, Hou K, Herbert P, et al. Evidence-based guidelines for the number of peripapillary OCT scans needed to detect glaucoma worsening. Ophthalmology. 2023/01/01/ 2023;130(1):39–47. doi:10.1016/j.ophtha.2022.07.025 [PubMed: 35932839]
32. Zhang X, Dastiridou A, Francis BA, et al. Comparison of glaucoma progression detection by optical coherence tomography and visual field. Am J Ophthalmol. Dec 2017;184:63–74. doi:10.1016/j.ajo.2017.09.020 [PubMed: 28964806]
33. Chauhan BC, Malik R, Shuba LM, Rafuse PE, Nicolela MT, Artes PH. Rates of glaucomatous visual field change in a large clinical population. Invest Ophthalmol Vis Sci. Jun 10 2014;55(7):4135–43. doi:10.1167/iovs.14-14643 [PubMed: 24917147]
34. Saunders LJ, Russell RA, Kirwan JF, McNaught AI, Crabb DP. Examining visual field loss in patients in glaucoma clinics during their predicted remaining lifetime. Investigative Ophthalmology & Visual Science. 2014;55(1):102–109. doi:10.1167/iovs.13-13006 [PubMed: 24282228]
35. Kirwan JF, Hustler A, Bobat H, Toms L, Crabb DP, McNaught AI. Portsmouth visual field database: an audit of glaucoma progression. Eye. 2014/08/01 2014;28(8):974–979. doi:10.1038/eye.2013.294 [PubMed: 24875227]
36. Mahmoudinezhad G, Moghimi S, Nishida T, et al. Association between rate of ganglion cell complex thinning and rate of central visual field loss. JAMA Ophthalmology. 2023;141(1):33–39. doi:10.1001/jamaophthalmol.2022.4973 [PubMed: 36416837]
37. Mohammadzadeh V, Moghimi S, Nishida T, et al. Association of rates of ganglion cell and inner plexiform thinning with development of glaucoma in eyes with suspected glaucoma. JAMA Ophthalmology. 2023;doi:10.1001/jamaophthalmol.2023.0005
38. Hou HW, Lin C, Leung CK. Integrating macular ganglion cell inner plexiform layer and parapapillary retinal nerve fiber layer measurements to detect glaucoma progression. Ophthalmology. Jun 2018;125(6):822–831. doi:10.1016/j.ophtha.2017.12.027 [PubMed: 29433852]
39. Nouri-Mahdavi K, Mohammadzadeh V, Rabiolo A, Edalati K, Caprioli J, Yousefi S. Prediction of visual field progression from OCT structural measures in moderate to advanced glaucoma. American Journal of Ophthalmology. 2021/06/01/ 2021;226:172–181. doi:10.1016/j.ajo.2021.01.023 [PubMed: 33529590]
40. Wang F, Javitt JC, Tielsch JM. Racial variations in treatment for glaucoma and cataract among Medicare recipients. Ophthalmic Epidemiol. Jun 1997;4(2):89–100. doi:10.3109/09286589709057101 [PubMed: 9243653]

41. Ostermann J, Sloan FA, Herndon L, Lee PP. Racial differences in glaucoma care: the longitudinal pattern of care. Arch Ophthalmol. Dec 2005;123(12):1693–8. doi:10.1001/archopht.123.12.1693 [PubMed: 16344441]

42. Wu J-H, Varkhedi V, Radha Saseendrakumar B, Acuff K, Weinreb RN, Baxter SL. Social and healthcare utilization factors associated with ophthalmic visit non-adherence in glaucoma: an All of Us study. Journal of Glaucoma. 9900:10.1097/IJG.0000000000002300. doi:10.1097/ijg.0000000000002300

43. Nishida T, Moghimi S, Hou H, et al. Long-term reproducibility of optical coherence tomography angiography in healthy and stable glaucomatous eyes. Br J Ophthalmol. Dec 21 2021;doi:10.1136/bjophthalmol-2021-320034

44. Tan BB, Natividad M, Chua KC, Yip LW. Comparison of retinal nerve fiber layer measurement between 2 spectral domain OCT instruments. J Glaucoma. Apr–May 2012;21(4):266–73. doi:10.1097/IJG.0b013e3182071cdd [PubMed: 21637116]

45. Wu Z, Saunders LJ, Zangwill LM, Daga FB, Crowston JG, Medeiros FA. Impact of normal aging and progression definitions on the specificity of detecting retinal nerve fiber layer thinning. Am J Ophthalmol. Sep 2017;181:106–113. doi:10.1016/j.ajo.2017.06.017 [PubMed: 28669780]

46. Hammel N, Belghith A, Weinreb RN, Medeiros FA, Mendoza N, Zangwill LM. Comparing the rates of retinal nerve fiber layer and ganglion cell-inner plexiform layer loss in healthy eyes and in glaucoma eyes. Am J Ophthalmol. Jun 2017;178:38–50. doi:10.1016/j.ajo.2017.03.008 [PubMed: 28315655]

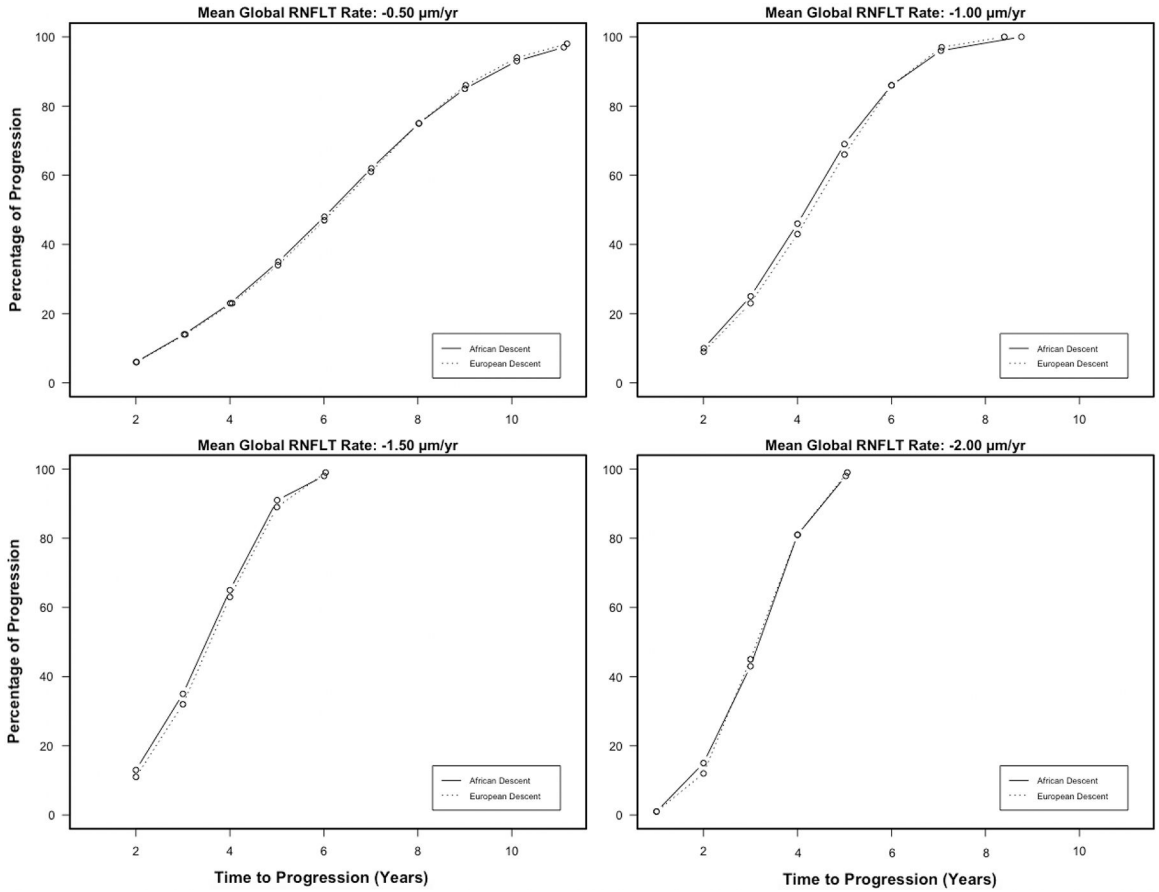

Figure 1.

The time required to detect retinal nerve fiber layer thickness (RNFLT) progression in African (solid line) and European descents (dotted line) with an assumed baseline RNFLT of 80 µm.

Table 1:
Demographic and clinical characteristics of included eyes

	AD (332 eyes, 216 participants)	ED (542 eyes, 317 participants)	
	Mean (95% CI)	**Mean (95% CI)**	**P-value**
Patient-level characteristics			
Age at baseline (years)	64.3 (63.0, 65.6)	65.2 (64.2, 66.2)	0.250
Sex (Female, n)	132 (61.1%)	169 (53.3%)	0.076
Diabetes (Diabetic, n)	48 (22.2%)	22 (6.9%)	**<0.001**
Hypertension (Hypertensive, n)	144 (66.7%)	124 (39.1%)	**<0.001**
Eye-level characteristics			
Diagnosis (n)			0.486
Glaucoma suspect	157 (47.3%)	270 (49.8%)	
POAG	175 (52.7%)	272 (50.2%)	
Baseline axial length (mm)	23.9 (23.8, 24.1)	24.1 (23.9, 24.2)	0.239
Baseline CCT (μm)	533.6 (527.9, 539.3)	551.6 (547.0, 556.2)	**<0.001**
Baseline 24–2 VF MD (dB)	−2.4 (−2.9, −2.0)	−2.1 (−2.4, −1.8)	0.208
Baseline 24–2 VF PSD (dB)	3.2 (2.9, 3.6)	3.4 (3.1, 3.7)	0.467
Baseline RNFLT (μm)	84.6 (82.6, 86.5)	81.8 (80.2, 83.4)	**0.033**
Rate of RNFLT thinning (μm/year)	−0.8 (−1.0, −0.7)	−0.6 (−0.7, −0.5)	**0.016**
RNFLT variability (μm)	1.6 (1.5, 1.7)	1.5 (1.4, 1.5)	**0.018**
Intervening cataract surgery (yes, n)	86 (25.9%)	111 (20.5%)	0.067
Intervening glaucoma surgery (yes, n)	67 (20.2%)	105 (19.4%)	0.793
Mean IOP during follow up (mmHg)	15.5 (15.0, 16.0)	15.7 (15.3, 16.1)	0.470
Maximum follow-up visits	10.2 (9.6, 10.9)	10.1 (9.6, 10.7)	0.813
Follow-up time (years)	7.0 (6.7, 7.4)	6.3 (6.0, 6.6)	**0.005**
Scan quality	28.0 (27.7, 28.4)	28.0 (27.8, 28.3)	0.975

Values are shown in mean (95% CI) and median (range), unless otherwise indicated.

Abbreviations: CCT = central corneal thickness; IOP = intraocular pressure; MD = mean deviation; RNFLT= RNFL thickness; POAG = primary open angle glaucoma; PSD = pattern standard deviation, VF = visual field

Table 2.

Required time and power to detect progression in African and European descents: standardized scenarios

Baseline RNFLT	Races	Rates of RNFLT thinning (μm/year)	Time to detect progression (years)				Percentages of progression (%)	
			Mean	SD	80% progression	90% progression	2 years	5 years
70 um	African descents	−0.5	6.0	2.7	8.8	10.0	9.2	38.2
		−1.0	4.1	1.7	6.0	6.6	14.4	75.0
		−1.5	3.3	1.3	4.7	5.0	21.5	93.1
		−2.0	2.8	1.0	4.0	4.3	30.0	98.4
	European descents	−0.5	5.8	2.6	8.5	9.7	9.8	41.0
		−1.0	4.0	1.6	5.7	6.3	15.7	78.2
		−1.5	3.2	1.2	4.3	5.0	23.6	94.6
		−2.0	2.7	1.0	4.0	4.0	33.0	98.7
80 um	African descents	−0.5	5.9	2.6	8.5	9.7	9.6	40.6
		−1.0	4.0	1.6	5.7	6.2	15.5	78.0
		−1.5	3.2	1.2	4.3	5.0	23.2	94.9
		−2.0	2.8	1.0	4.0	4.0	32.2	99.1
	European descents	−0.5	5.9	2.6	8.4	9.5	9.5	40.0
		−1.0	4.0	1.6	5.8	6.1	14.9	77.7
		−1.5	3.2	1.2	4.4	5.0	22.1	95.9
		−2.0	2.8	1.0	4.0	4.0	30.8	99.5
90 um	African descents	−0.5	6.0	2.7	8.8	10.1	9.4	38.7
		−1.0	4.1	1.7	5.9	6.6	14.6	75.3
		−1.5	3.3	1.3	4.7	5.1	21.6	92.9
		−2.0	2.8	1.1	4.0	4.2	30.0	97.5
	European descents	−0.5	6.0	2.6	8.6	9.8	9.2	39.0
		−1.0	4.1	1.6	5.8	6.3	14.4	77.2
		−1.5	3.2	1.2	4.4	5.0	21.3	94.4
		−2.0	2.8	1.0	4.0	4.1	29.9	98.8

Abbreviation: RNFLT= retinal nerve fiber layer thickness, SD = standard deviation

Table 3.

Required time and power to detect progression in African and European descents: real-world scenarios (linear mixed model)

Races	Mean baseline RNFLT (μm)	Mean RNFLT thinning rates (μm/year)	Time to detect progression (years)				Percentages of progression (%)	
			Mean	SD	80% progression	90% progression	2 years	5 years
African descents	84.6	−0.82	4.8	2.0	6.9	7.8	11.9	58.9
European descents	81.8	−0.59	5.4	2.3	7.7	8.6	10.5	47.0

Abbreviation: RNFLT= retinal nerve fiber layer thickness, SD = standard deviation