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Performance of Optic Disc Optical Coherence Tomography Normative Database in a Large, Diverse, Real-World Cohort

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Abstract

Purpose: To compare optic nerve head (ONH) measurements between published values from an optical coherence tomography (OCT) normative database and a more diverse cohort of healthy individuals.

Patients and Methods: ONH parameters from healthy participants of the Michigan Screening and Intervention for Glaucoma and Eye Health through Telemedicine (MI-SIGHT) program and the Topcon Maestro-1 normative cohort were compared. Chi-square tests compared MI-SIGHT retinal nerve fiber layer (RNFL) quadrant color-code labels with the expected distribution and multinomial logistic regression identified factors associated with label classifications.

Results: 1084 MI-SIGHT and 399 Topcon eyes were evaluated. The MI-SIGHT cohort was older (54 v 46 years), with more individuals identifying as Black (61% v 20%), less as Hispanic (4% v 18%), and spherical equivalents closer to plano (−0.6 v −1.2 diopters) compared to the Topcon cohort (all $p < 0.001$). Black/African American MI-SIGHT participants had larger cup-to-disc ratios and cup volumes, while White MI-SIGHT participants had smaller ONH values, except for rim area and rim volume, compared to Topcon participants (all $p < 0.001$). The MI-SIGHT cohort's RNFL color codes did not follow the expected distribution ($p < 0.05$); more MI-SIGHT RNFL

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quadrant measurements were assigned as white (10.6% and 6.3% MI-SIGHT v 5% Topcon) and red codes (2.2% and 1.8% MI-SIGHT v <1% Topcon) than expected in the superior and inferior quadrants respectively.

Conclusion: OCT normative databases should accurately reflect diverse populations to avoid misclassification by RNFL thickness color codes. Larger datasets should be leveraged to encompass the full spectrum of healthy optic nerve anatomy.

Precis:

Current optical coherence tomography normative sample data may not represent diverse human optic nerve anatomy to accurately classify all individuals with true glaucomatous optic neuropathy.

Keywords

Optical Coherence Tomography (OCT); glaucoma; screening; normative data; big data; bias; diversity

Introduction

In 2011, 2.71 million people carried a diagnosis of Primary Open Angle Glaucoma (POAG) in the United States alone.¹ The percentage of individuals with POAG was significantly higher amongst individuals between 70 and 79 years, females, and non-Hispanic Whites.¹ By the year 2050, the number of individuals carrying a diagnosis of POAG is projected to rise to 7.32 million — indicating a rise in prevalence of 28% every decade.¹ The largest increases are expected among Hispanic Americans, indicating a shift towards an increased burden of glaucoma among minority communities. This trend is not new as several studies have historically shown that racial and ethnic minority communities have the highest rates of glaucoma when compared to White communities. The Baltimore Eye Survey was the first to reveal that Black Americans had an age-adjusted glaucoma prevalence 4–5 times higher than White Americans.² A study in Salisbury, Maryland found White participants over age 75 had a glaucoma prevalence of 9.4% while Black participants in the same age group had a much higher glaucoma prevalence rate of 23.2%.³ Moreover, after adjusting for race and medical co-morbidities, people with lower income had a higher incidence of glaucoma compared to those with higher income.⁴ There is a compelling need to better understand the social, cultural, institutional, and environmental factors that lead to such stark inequities in glaucoma diagnosis in the United States.

As glaucoma can be asymptomatic in its earliest stages, without screening, glaucoma often remains undetected until late stages when central vision is affected, and people seek care. It is estimated that 10–33% of individuals with glaucoma already have significant visual field loss upon first presentation to an ophthalmologist.⁵ One approach to mitigate disparities in the diagnosis of glaucoma involves early identification of the disease through screening programs targeted at communities at high-risk of disease, such as communities with large proportions of people living in poverty, or large proportions of minorities. Identifying disease earlier opens the pathway towards earlier initiation of treatment. Optical Coherence Tomography (OCT) offers substantial potential as a screening tool for such

community screening initiatives. OCT is a noninvasive, high-resolution imaging technique that enables real-time measurement of tissue thickness in the posterior pole. Unlike other diagnostic tools, such as visual fields or fundus photography, OCT is fast to administer, is less demanding of patients, and has good reproducibility.^{6–9} Automated assessment of retinal thickness not only provides a reliable method to track disease progression, but also facilitates a comparison with healthy individuals for disease identification. Optic nerve head (ONH) parameters and retinal thicknesses are contrasted with healthy normative values in the OCT device's proprietary software to generate a color-coded label for identification of “normal” versus “abnormal values”. This color-coding system provides a simple heuristic aid for glaucoma decision-making, promoting more streamlined and consistent medical care.¹⁰

Before OCT can be implemented into large community-based screening protocols, it is critical to assess the existing reference databases that define the distinction between “normal” and “abnormal” eyes. These databases need to be appropriate for a diverse range of populations. There are many manufacturers of OCT machines, and each configures their software with their own proprietary normative dataset. For instance, the reference databases for the Spectralis (Heidelberg Engineering, Inc., Germany) and Cirrus (Carl Zeiss Meditec, Inc., Dublin, CA) machines, two of the most commonly used machines in the United States, include subjects with no known eye disease and specifically exclude those with visual field damage, high intraocular pressure (IOP), and severe myopia (−7 diopters or more for Spectralis, and −10 diopters for Cirrus).¹¹ Further, the Spectralis normative database predominantly includes White individuals (79%), and White individuals make up 43% of the Cirrus normative database. The Spectralis cohort excludes those with a family history of glaucoma, and Cirrus excludes those with systemic hypertension and diabetes. Most notably, only 284 and 330 eyes are included in the Cirrus and Spectralis databases, respectively.¹¹ Thus, while the number and demographic composition of the individuals in these reference databases vary, OCT normative cohorts typically consist of small, racially and ethnically homogenous samples, that are often without systemic conditions.^{11,12}

To better understand the applicability of OCT technology to distinguish healthy individuals from those with glaucomatous disease in real-world community contexts, this study aims to investigate differences in ONH parameters and retinal thicknesses between healthy individuals from the Topcon 3D OCT-1 Maestro normative database and healthy individuals from a population with a higher proportion of people identifying as Black or African American and a higher proportion of people with low socio-economic status. These individuals were part of a cohort enrolled in a free eye disease screening program in Southeastern Michigan.

Materials and Methods

MI-SIGHT Participants

This study was reviewed and approved by the University of Michigan (UM) Institutional Review Board (HUM00169371) and adhered to the tenets of the Declaration of Helsinki. The clinical trial portion of this study, not discussed herein, is registered at [Clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT04274764) (NCT04274764). In brief, the Michigan Screening and Intervention for Glaucoma and

Eye Health through Telemedicine (MI-SIGHT) program included community residents 18 years or older who were interested in undergoing a free eye health exam. Participants were recruited from two community-based health care facilities, a free clinic in Ypsilanti, Michigan (Hope Clinic), and a Federally Qualified Health Center in Flint, Michigan (Hamilton Community Health Network). Study coordinators directly recruited patients referred for eye care by their primary care providers at the community clinics and patients with diabetes who had not had an eye exam in over two years. Participants were also recruited from the wider community via outreach guided by the MI-SIGHT Community Advisory Board. Community outreach strategies included placing 11,000 flyers in the community clinics, neighborhood food banks, low-income senior housing buildings, barbershops, and churches. Participants were given extra flyers to share with friends and family. Advertising was done on local buses, local radio, local health fairs, and community access television. Verbal consent to participate in the study was obtained prior to scheduling the study visit. Exclusion criteria to participate in the MI-SIGHT program, as determined by an initial screening intake, included: 1) significant eye pain; 2) sudden decrease in vision in the past week; 3) binocular diplopia; 4) cognitive impairment; 5) pregnancy; 6) current incarceration; or 7) plans to move outside of driving distance to the clinic within the next 6 months.

During the initial MI-SIGHT visit, participants completed numerous health and demographic questionnaires. The ophthalmic technician then completed an ophthalmic examination comprised of: 1. visual acuity assessment at distance (Snellen acuity with current correction, if any); 2. refraction measurements (ARK- Autorefractor & Keratometer, Marco Ophthalmic, Jacksonville, FL) and refinement with subjective refraction using a table-clamped phoropter; 3. contrast sensitivity (Pelli-Robson Letter Sensitivity Chart); 4. pupillary response; 5. anterior chamber angle assessment by penlight; 6. extraocular motility and alignment; 7. IOP measurement (iCare tonometer, Raleigh, NC); 8. dilated mydriatic imaging of the posterior pole by fundus photography; 9. OCT images of the ONH and the macula (Maestro, Topcon Healthcare, Tokyo, Japan). Examination data and images were directly entered into the participant's Electronic Health Record (EHR) (EPIC, Verona, WI) and reviewed by a remote ophthalmologist at the University of Michigan for presence of refractive error, cataract, macular degeneration, diabetic retinopathy, and glaucoma. Participants screened positive for suspected glaucoma if either eye met one of the diagnostic criteria and were judged as positive by the physician using their clinical judgement: 1. Narrow angles by penlight exam; 2. Cup to disc ratio (c/d) ≥ 0.7 ; 3. IOP ≥ 21 mmHg with c/d > 0.3 ; 4. Asymmetric c/d ≥ 0.2 where the larger cup is ≥ 0.6 ; 5. Disc hemorrhage; 6. Focal notch on fundus photography; 7. Self-reported previous glaucoma diagnosis; 8. Abnormal OCT (overall retinal nerve fiber layer (RNFL) thickness < 80 microns or thinning at $< 1\%$ certainty in the inferior or superior quadrants).

For this study, MI-SIGHT program participants enrolled during the first year of recruitment (between July 2020–2021 for the free clinic and between January 2021–2022 for the FQHC) were included if they self-reported being Black/African American or White race, had best-corrected visual acuity of 20/40 or better, IOP < 21 mmHg or IOP between 21–25 with c/d < 0.3 , OCT of sufficient quality as determined by the reading ophthalmologist, and screened negative for ocular disease. Individuals with suspected glaucoma based only on abnormal

OCT, but meeting no other glaucoma criteria, were included. Individuals who self-reported being Asian or of Other race (which included those who were American Indian, Alaska Native, Native Hawaiian, or Other Pacific Islander) were excluded because of small sample sizes. Presence of a cataract, but no other ocular pathology, was not considered an exclusion criteria if OCT was of sufficient quality. If both eyes met inclusion criteria, one eye was randomly selected for each participant to be included in the study.

Topcon Normative Database Participants

Demographic and OCT information regarding the Topcon 3D OCT-1 Maestro normative study sample was obtained from a published report by Chaglasian et al.¹³ The Topcon 3D OCT-1 Maestro normative cohort was comprised of participants recruited from seven study sites: Illinois College of Optometry, Marshall B. Ketchum University, State University of New York College of Optometry, Western University, Valley Eye Care Center Medical Associates, University of Alabama School of Optometry, and New York Harbor Health Care System. Between May and October 2015, 504 participants were enrolled. Recruitment was performed in accordance with Good Clinical Practices, the Code of Federal Regulations, the ethical principles in the Declaration of Helsinki, Health Insurance Portability and Accountability Act regulations, and other applicable local regulations. The study was registered at the US National Institutes of Health ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02447120) Identifier: [NCT02447120](https://clinicaltrials.gov/ct2/show/study/NCT02447120)).¹³ Subjects were eligible for inclusion in the Topcon normative database if both eyes were free of eye disease, had an IOP of < 21 mmHg bilaterally, and a best-corrected visual acuity of 20/40 or better in each eye.¹³ Exclusion criteria for the Topcon Maestro normative database included subjects exhibiting field defects on the Humphrey Visual Field Analyzer (HFA; Carl Zeiss Meditech, Inc., Dublin, CA, USA) using the Swedish Interactive Threshold Algorithm (SITA) 24-2 test strategy.¹³ Participants were also excluded if they were unable to tolerate ophthalmic imaging, had media opacities, had any ocular pathology except for cataract, had narrow angles on gonioscopy, had a history of leukemia, dementia, or multiple sclerosis, or were using hydroxychloroquine and chloroquine.

OCT parameters

Mydriatic OCT images of 3D disc scans and 6×6mm macular scans were retrieved for all MI-SIGHT participants from the database of a single 3D OCT-1 Maestro[®] machine (Topcon Healthcare., Tokyo, Japan) at each of the two sites. The Topcon Maestro[®] OCT machine is a fully automated spectral domain-OCT-based system that has automatic pupil alignment. Scans showing well-demarcated optic discs, centered appropriately, without segmentation errors, missing parts, or motion artifacts were eligible. For participants with multiple OCT scans taken on the date of enrollment, the scan with the highest quality score was used. If there were multiple scans with the same highest quality score for a given eye, the first scan collected was used. Scans deemed insufficient quality by the reading eye care specialist or with quality score <45 were excluded.¹⁴ One of four trained ophthalmic technicians obtained all the scans.

Several OCT parameters were extracted from the Topcon software after acquisition. The following ONH parameters were collected based on the Maestro-1 software output: 1.

Vertical c/d and c/d area, 2. Disc, cup and rim area, and 3. Cup and rim volume. Additionally, global and quadrant RNFL thicknesses and assigned color probability codes were collected from the disc scan along with global retinal ganglion cell + inner plexiform layer (RGC+IPL) thickness from the macula scan. In brief, individual RNFL thickness color probability codes signify where a measurement is relative to the distribution of values within the Topcon proprietary normative dataset such that red labels indicate measurements that fall in the lowest 1% of normative values, or are less than 1st percentile of the normative values (<1%); yellow labels indicate measurements that fall between 1st and 5th percentiles of the normative values (4%); green labels indicate measurements that fall between the 5th and 95th percentiles of the normative values (90%); and white labels indicate measurements that fall in the top 5% of normative values or, in other words, exceed the 95th percentile of normative values (5%).

Statistical Analysis

Demographic characteristics, ocular histories, ONH parameters, and retinal thicknesses of the MI-SIGHT healthy cohort were summarized with descriptive statistics (mean, standard deviation [SD], frequency, and percentage) for the overall sample and stratified by self-identified race. Differences in participant characteristics, ONH parameters, and retinal thicknesses between the MI-SIGHT healthy cohort and Topcon normative cohort were compared using one-sample t-tests for continuous variables and one-sample proportion tests for categorical variables. Within the MI-SIGHT healthy cohort, comparisons between Black/African American participants and White participants were performed using two-sample t-tests for continuous variables and chi-square or Fisher's exact tests for categorical variables. P-values were adjusted for multiple comparisons with Holm's procedure.¹⁵ The percentage and distribution of MI-SIGHT healthy eyes that were labeled with each of the RNFL thickness color codes were examined for each RNFL quadrant. Chi-square tests were used to assess whether the distribution of RNFL thickness in the MI-SIGHT healthy cohort, overall and stratified by self-identified race, fell within the expected 4-color distribution of normal values. Multivariable multinomial logistic regression was performed to investigate predictors of RNFL thickness color code labels by quadrant where each quadrant was in a separate regression model. Model results were reported with odds ratio (OR) and 95% confidence intervals (CIs). Confidence interval precision around a 1% RNFL thickness red color code label was estimated with varying sample sizes using properties of the binomial distribution. All statistical analyses were performed with R version 4.2.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Demographic and Ocular Characteristics

1084 eyes of 1084 participants from the MI-SIGHT healthy cohort and 399 eyes of 399 participants from the Topcon normative cohort were analyzed. The MI-SIGHT cohort was on average 53.9 years old (9% between 18–30 years), 62.8% identified as female, 3.5% as Hispanic or Latino, 60.5% as Black or African American, and 39.5% as White (Table 1). Compared to the Topcon cohort, the MI-SIGHT cohort was significantly older (53.9 v 46.3 years), more female (62.8% v 57%), less Hispanic (3.5% v 18%), and had more individuals

identifying as Black or African American (60.5% v 20%). The best corrected visual acuity of the MI-SIGHT cohort was on average -0.06 logMAR units, but no data on visual acuity were published for the Topcon normative cohort precluding statistical comparison. Spherical equivalent (SE) was closer to plano in the MI-SIGHT healthy cohort compared to the Topcon cohort (-0.63 v -1.16 diopters). The IOP in the MI-SIGHT cohort was on average 14.29 mmHg and the clinical vertical c/d ratio was on average 0.34 .

There were some differences in demographic and ocular characteristics between Black/African American participants and White participants in the MI-SIGHT healthy cohort (Supplemental table 1). Black/African American participants had slightly lower IOP (14.05 mmHg vs. 14.67 , $p=0.0011$) but larger clinical c/d ratio (0.36 vs 0.30 , $p<0.0001$) than White participants.

OCT measures: ONH Parameters and Retinal Thicknesses

The average quality score for the disc scans in the MI-SIGHT healthy cohort was 55.83 . Comparison of ONH parameters and retinal thicknesses between the MI-SIGHT healthy cohort and Topcon normative cohort are highlighted here and summarized in Table 2. Disc area was slightly smaller in the MI-SIGHT healthy cohort compared to Topcon normative cohort (2.06 mm² vs 2.10 , $p=0.0083$). However, no other significant differences were observed in the remaining ONH parameters and retinal thicknesses between the MI-SIGHT healthy cohort and Topcon normative cohort. Specifically, OCT parameter measures were similar between cohorts for vertical c/d (mean $\pm$ SD for MI-SIGHT v Topcon: 0.48 ± 0.20 v 0.48 ± 0.19), RGC+IPL thickness (71.59 ± 0.64 μ m v 71.72 ± 5.88), c/d area (0.29 ± 0.17 mm² v 0.28 ± 0.17 mm²), cup area (0.61 ± 0.41 mm² v 0.61 ± 0.41 mm²), rim area (1.45 ± 0.44 mm² v 1.49 ± 0.38 mm²), cup volume (0.12 ± 0.13 mm³ v 0.13 ± 0.14 mm³), rim volume (0.27 ± 0.18 mm³ v 0.26 ± 0.14 mm³), and global RNFL thickness (103.30 ± 13.00 μ m v 104.04 ± 11.34 μ m) (all $p > 0.05$). The average RNFL thickness by quadrant for the MI-SIGHT healthy cohort followed the predicted ISNT rule and was as follows: 134.97 μ m (SD= 20.41) for inferior, 127.62 μ m (SD= 21.32) for superior, 81.53 μ m (SD= 16.63) for nasal, and 68.97 μ m (SD= 11.83) for temporal. Topcon did not publish RNFL thickness values by quadrant and therefore no statistical comparisons could be made.

By contrast, significant differences in ONH parameters and retinal thicknesses were observed between Black/African American participants and White participants within the MI-SIGHT cohort (Table 2). Specifically, Black/African American participants, versus White participants, had larger vertical c/d ratio (mean $\pm$ SD 0.51 ± 0.19 vs. 0.44 ± 0.21 , $p<0.0001$), larger c/d area (0.32 ± 0.17 mm² vs. 0.24 ± 0.17 , $p<0.0001$), larger disc area (2.12 ± 0.43 mm² vs. 1.96 ± 0.37 , $p<0.0001$), larger cup area (0.68 ± 0.42 mm² vs. 0.48 ± 0.37 , $p<0.0001$), and larger cup volume (0.15 ± 0.14 mm³ vs. 0.08 ± 0.09 , $p<0.0001$). In addition, Black/African American participants had thicker global RNFL (104.39 ± 13.35 μ m vs. 101.56 ± 12.24 , $p=0.0037$), thicker superior quadrant (130.00 ± 22.04 μ m vs. 123.85 ± 19.56 , $p<0.0001$), and thicker inferior quadrant (137.03 ± 21.06 μ m vs 131.70 ± 18.89 , $p=0.0002$) compared to White participants. Black/African American participants also trended towards having thinner temporal quadrants (68.22 ± 11.89 μ m vs 70.17 ± 11.64 , $p=0.0574$).

Further, significant differences in ONH parameters were observed when comparing Black/African American participants and White participants from the MI-SIGHT healthy cohort, respectively, to the Topcon normative cohort (Table 2). Black/African American participants from the MI-SIGHT healthy cohort had larger values in several ONH parameters, including vertical c/d ratio (mean $\pm$ SD, 0.51 $\pm$ 0.18 vs. 0.48 $\pm$ 0.19, $p=0.0002$), c/d area (0.32 $\pm$ 0.17 mm² vs. 0.28 $\pm$ 0.17, $p<0.0001$), cup area (0.68 $\pm$ 0.42 mm² vs. 0.61 $\pm$ 0.43, $p=0.0002$), and cup volume (0.15 $\pm$ 0.14 mm³ vs. 0.13 $\pm$ 0.14, $p<0.0001$), and smaller rim area compared to Topcon normative cohort (1.44 $\pm$ 0.46 mm² vs. 1.49 $\pm$ 0.38, $p=0.0219$). On the contrary, White participants from the MI-SIGHT healthy cohort had smaller values in the majority of ONH parameters which include vertical c/d ratio (mean $\pm$ SD, 0.44 $\pm$ 0.21 vs. 0.48 $\pm$ 0.19, $p=0.0005$), c/d area (0.24 $\pm$ 0.17 mm² vs. 0.28 $\pm$ 0.17, $p<0.0001$), disc area (1.96 $\pm$ 0.37 mm² vs. 2.10 $\pm$ 0.41, $p<0.0001$), cup area (0.48 $\pm$ 0.37 mm² vs. 0.61 $\pm$ 0.43, $p<0.0001$), and cup volume (0.08 $\pm$ 0.09 mm³ vs. 0.13 $\pm$ 0.14, $p<0.0001$) compared to the Topcon normative cohort. There was no significant difference in global RNFL thickness between Black/African American participants from the MI-SIGHT healthy cohort and the Topcon normative cohort. However, White participants from the MI-SIGHT healthy cohort had thinner global RNFL than the Topcon normative cohort (101.56 $\pm$ 12.24 μ m vs. 104.04 $\pm$ 11.34, $p=0.0003$). RGC+IPL thickness was similar across all cohorts and sub-cohorts evaluated.

RNFL Color Code Distributions

The distribution of RNFL color codes by quadrant in the MI-SIGHT healthy cohort is presented in Table 3 and Figure 1. The distribution of the RNFL values coded by the Topcon algorithm for the MI-SIGHT healthy sample did not fall within the expected 5%–90%–4%–<1% color code distribution ($p<0.05$). White labels were over-represented in the superior, inferior, and nasal quadrants for the overall MI-SIGHT healthy cohort and when stratified by self-identified race (5.4% to 13.1% versus 5% expected). Red labels were over-represented in all four quadrants for the overall MI-SIGHT healthy cohort and when stratified by race (1.4% to 4.0% versus <1% expected), except for Black/African American participants in the nasal quadrant (0.9%). On the other hand, the yellow labels were under-represented in the superior and nasal quadrants in the overall MI-SIGHT healthy cohort and when stratified by race (1.2% to 2.4% versus 4% expected). Green labels were also under-represented in all four quadrants for the overall MI-SIGHT healthy cohort and when stratified by self-identified race (83.4% to 89.5% versus 90% expected).

Multinomial Logistic Regression Results

Multinomial logistic regression models were conducted to assess factors associated with the probability of obtaining each of the RNFL thickness color labels, compared to green, adjusting for race. Results from all multinomial logistic regression models are shown in Table 4, but the most clinically meaningful results, namely for the superior and inferior quadrants, are presented here. In the superior quadrant, older age (OR=1.65 for a 10-year increase in age, 95%CI=1.13–2.42, $p=0.0095$) and manifest SEs further from plano (OR=0.79 for a 1 diopter increase, 95%CI=0.65–0.95, $p=0.0132$) was associated with increased odds of a red label compared to green. Similarly, older age (OR=1.18 for 10-year increase in age, 95% CI=1.01–1.38, $p=0.0323$), manifest SE closer to plano (OR=1.13 for a 1 diopter increase, 95% CI=1.01–1.25, $p=0.0296$), and White race (OR=0.41 compared

to Black race, 95% CI=0.25–0.66, $p=0.0003$) was associated with increased odds of a white label compared to green. In the inferior quadrant, larger disc area was associated with a decreased odds of a red label compared to a green (OR=0.27 for 1mm² increase, 95%CI=0.07–0.99, $p=0.0497$).

Discussion

The aim of this study was to compare optic nerve head (ONH) parameters and retinal thickness measurements between participants in the Topcon Maestro normative cohort database and a large, diverse group of participants from a community screening program, MI-SIGHT. The average age of the Topcon cohort was 46.3 years, with 22% of the individuals aged between 18–30 years. In comparison, only 9% of our MI-SIGHT dataset was within this age bracket, with an average age of 53.9 years. There were also significant differences in the racial and ethnic makeup of the two cohorts. In the Topcon normative dataset, 59% of the participants identified as White and 20% identified as Black or African American. In the MI-SIGHT dataset, 40% of participants identified as White and 61% as Black or African American. The Topcon normative dataset included participants with manifest spherical equivalents varying from –11.00 to +4.50D, whereas our dataset featured a broader array of refractive error, ranging from –11.5 to +9.5D. The MI-SIGHT healthy cohort did not exclude individuals based on family history of eye disease, current medication use, or systemic conditions, while the Topcon normative cohort excluded those with a history of leukemia, dementia, or multiple sclerosis, or who were using hydroxychloroquine or chloroquine. Lastly, the Topcon normative cohort participants were recruited from academic and optometric centers across the United States, while the MI-SIGHT healthy cohort was recruited from two community clinics who provide care to medically underserved, economically disadvantaged communities in Southeastern Michigan. Considering these differences, we sought to understand how results from the Topcon software could still be applied to the MI-SIGHT healthy older, majority Black/African American cohort.

When comparing OCT parameters between the Topcon normative cohort and the MI-SIGHT healthy cohort, we found almost all ONH parameters did not differ between the two cohorts. However, when stratifying by self-identified race, we found statistically significant differences in all included ONH parameters between MI-SIGHT Black/African American and MI-SIGHT White participants and the predominantly White Topcon normative cohort. Both the White MI-SIGHT participants and the Black/African American MI-SIGHT participants had significantly different vertical cup to disc ratios, cup to disc areas, cup areas, and cup volumes from the Topcon normative cohort. These differences were masked within the overall cohort comparisons, as the Topcon cohort typically fell in between the average values of MI-SIGHT White participants and MI-SIGHT Black/African American participants. For example, while the mean c/d areas were 0.32mm² and 0.24mm² for the Black/African American MI-SIGHT participants and White MI-SIGHT participants respectively, the Topcon normative dataset had a mean c/d area of 0.28mm². These findings are consistent with results from numerous studies utilizing other imaging modalities including Heidelberg Retinal Tomography II, confocal scanning laser ophthalmoscopy, and stereoscopic fundus photographs that have similarly identified larger disc and cup

areas in Black individuals compared to White individuals.^{16–20} Notably, there appears to be less variation in retinal ganglion cell thickness values between White and Black individuals based on our cohort data and others and RGC thickness perhaps should be further investigated as a diagnostic marker in glaucoma screening.^{21–23}

Our results also coincide with previously published literature demonstrating significantly thicker RNFL values in the superior and inferior quadrants and thinner temporal quadrants in African American individuals compared to White individuals.^{24–29} Accordingly, Black/African American MI-SIGHT participants more frequently exhibited RNFL thicknesses with white and red color labels in the superior and inferior quadrants and less frequently exhibited yellow and green color labels in these quadrants than expected if thickness values were to follow the expected normative distribution, even when compared to White MI-SIGHT participants. Similar results were found by Addis and colleagues when evaluating color code label distributions for 466 healthy eyes from Black/African American participants in the Primary Open-Angle Black American Glaucoma Genetics (POAAGG) study using the Cirrus HD-OCT device.²⁴ They found that more RNFL measurements were assigned as white (9.5%) and red labels (1.7%) than expected and fewer measurements were assigned as green (85.3%) and yellow (3.5%) labels than expected. Unlike the Addis study, we utilized the Topcon Maestro machine, which is more often used in community screening programs than the Cirrus machine, given its more affordable pricing. We also investigated how both individuals self-identifying as Black and/or African American and those self-identifying as White compared to the normative dataset. Systematic over-classification of white and red labels in certain populations is clinically important. Populations with RNFL measurements frequently overclassified with white labels may need to have a larger decrement in RNFL before disease becomes clinically detectable. Conversely, a higher than expected percentage of red labels in certain populations can cause overdiagnosis of disease due to a systemic bias towards classifying these individuals as having unhealthy RNFL.

The discussion around normative databases being race or ethnicity-specific has been ongoing.²¹ Hong et al. evaluated 295 eyes of 166 healthy Korean people and found that the kappa agreement between the original and adjusted color labels for RNFL thickness was between 0.500–0.806. When they applied a Korean-person specific normative database to their cohort, they found that more than 10% of labels were judged differently and the percent of eyes that had yellow or red labels increased from 0.3% to 3.7%, or closer to the expected 5%.³⁰ Perez et al. also found that after applying a White-person specific normative database for the RT-Vue scan, whose normative database is comprised of only 18% White participants, the percent of RNFL abnormal color labels decreased significantly for the overall average thickness in the White participants.²¹ Zelefsky et al. investigated whether a race-specific database would increase the ability of confocal scanning laser ophthalmoscopy to differentiate normal from glaucomatous eyes and found that for White participants, the race specific database increased sensitivity with a comparable level of specificity, but for African-American participants, sensitivity increased but specificity decreased.³¹ In addition, some researchers have looked into adjusting for disc size as a proxy for the variability associated with race. In eyes with larger discs, a constant diameter scan would theoretically measure RNFL locations closer to the disc, and capture thicker RNFL values.³² However, Silverman et al. found that the predominantly White Spectralis reference database performed

similar to the more racially and ethnically heterogeneous Cirrus reference database in differentiating normal versus early glaucoma eyes, even without adjustment for disc size.¹² Results from our multivariable multinomial logistic regression similarly shows the variable influence disc area has on predicting RNFL color-code labels.

A novel contribution of this study is the results of our multinomial logistic regression analysis, which demonstrates that RNFL thickness color code classification is influenced by many factors beyond self-identified race or even disc size, two of the most frequently studied predictors of RNFL thickness. Even after controlling for self-identified race and disc area in our analysis, age and SE were predictive of having either a red or white label, compared to green, in the superior quadrant, but neither were predictive in the inferior quadrant. We found that identifying as White race decreased the odds of having a white compared to green color label in the superior quadrant and increased the odds of having a yellow compared to green color label in the inferior quadrant, but otherwise did not significantly affect the probability of having a particular color label. We did not identify an association between having a white color label and having a larger disc in any quadrant except for the temporal quadrant. These results suggest that there is likely a complex interaction between numerous factors, beyond race, that influence RNFL thickness and classification, including refractive error, axial length, corneal astigmatism, systemic conditions such as diabetes and hypertension, retinal vascular density, and optic nerve size and orientation.^{24,33} Researchers have even found associations between RNFL thickness measures and unique factors such as having polycystic ovary syndrome, being exposed to ambient air pollution, and mountaineering in high altitude areas.^{34–36} The diversity of the human experience extends far beyond the classifications of race and ethnicity and this is reflected in the diverse factors that impact RNFL values.

There are several inherent problems to creating race/ethnicity-specific databases.^{37,38} First, there exists significant differences when it comes to broad racial groupings based on American categorizations of “Asian” or “African” or “Other,” as these categories are arbitrary and do not take into consideration country of origin or ancestry and make it difficult when people’s families come from more than one category.^{31,39–44} The percentage of people identifying as multi-racial is growing faster than any other racial group per the United States census, increasing from 2.9% in 2010 to 10.2% of the population in 2020.⁴⁵ It hardly seems feasible to provide ethnicity-specific normative databases for every single race or ethnicity or combination thereof. Some have even posited that a correction factor should be included when predicting probability of RNFL thickness labels, as is done with age, to take into account ethnic diversity. Again, this tends to be a narrow view of biologic race as it necessitates categorizing people into pre-specified groups that do not capture the diversity of the human experience. In other medical specialties, race correction factors have historically been incorporated into medical calculations, such as for estimating lung capacity in pulmonology and estimating kidney function in nephrology. These factors have not only been disputed and discredited for being founded on inaccurate assumptions about race, but have resulted in worse outcomes and widening health disparities for African Americans. Race and ethnicity, as social constructs, reflect a complex mix of genetic, socioeconomic, political, and cultural factors. These result in heterogeneous phenotypic presentations where inter-group diversity often exceeds intra-group diversity. Ignoring this

variability compromises the diagnostic ability of tests like the OCT, underscoring the need for a more holistic, nuanced approach to developing normative databases.

Instead of limiting the number of individuals included in our normative databases to those who meet strict inclusion criteria, we need to focus on expanding our normative datasets to be more broadly representative of those who will use the test. To be clinically useful as a screening tool, the OCT needs to have high sensitivity and specificity and the confidence interval around classifying an optic nerve as “red” needs to be very narrow. Currently, for example, in the Topcon Maestro normative dataset, the 1% (red) threshold is based on values from 9 eyes and has a confidence interval of 0.4% to 2.5%.¹³ While this sample size was chosen to ensure that the confidence intervals between the different color codes did not overlap, the width of the confidence interval was not pre-specified as part of the power calculation in estimating the sample size needed to create a normative database.¹³ Alternately, to have a truly narrow confidence interval where no fewer than 0.9% and no more than 1.1% of healthy people would be classified as “red” – where “red” is supposed to identify healthy participants whose measured RNFL thickness is the lowest 1 percentile – a sample size of 50,000 patients would be needed in the normative database (Supplemental Table 2).

As we move towards the use of automated analyses of ophthalmic imaging, training and validation of algorithms on multitudes of heterogeneous participant data is essential. In a global review of publicly available datasets that include ophthalmological imaging for the development of machine learning algorithms to detect ocular disease, 18 of 94 datasets included OCT.⁴⁶ Of these, datasets that included both healthy eyes and eyes with ocular diseases from anywhere between 10 to 5319 individuals were included.⁴⁶ To obtain really large normative datasets, on the order of 50,000 participants, we will need to leverage large national and multinational registries such as The American Academy of Ophthalmology IRIS[®] Registry (Intelligent Research in Sight)⁴⁷, the Sight Outcomes Research Collaborative (SOURCE) registry⁴⁸, the IMVISUAL consortium⁴⁹, the UK BioBank⁵⁰, the Million Veteran Program⁵¹, and the *All of Us* Research program⁵². Currently the IRIS registry, UK BioBank, SOURCE, IMVISUAL, and All of Us all include ophthalmic imaging. Such large datasets inform biomedical research and intervention by enabling clinicians and researchers to generalize findings across populations with greater confidence, ensuring that a wider range of individual differences are represented, and providing greater statistical power to detect significant differences. At the very least, further transparency about the characteristics of a reference database is imperative for informed clinical decision making. Clinicians also need to be aware of the limitations of making predictions based on an overreliance of the quadrant maps. Rather, careful scrutiny of B-scans for segmentation defects and thin, focal areas of loss, as well as longitudinal changes within an individual is crucial.

There are several limitations to this study. First, all healthy subjects in the Topcon normative database were required to have a normal visual field. Healthy individuals attending our community screening program, on the other hand, were not obligated to undergo an additional visual field test. Other studies comparing color code labels in healthy cohorts also did not necessarily require visual function testing and found similar discrepancies

in the actual versus expected color code distributions.^{21,24,30,40} While having a visual field for all participants would be ideal, this is not practical in a community screening setting. In addition, because all glaucoma assessments were made without a visual field test, we purposefully included participants who had abnormal OCT if they met no other criteria for glaucoma based on a tele-ophthalmology model of screening for eye disease (normal fundus, normotensive intraocular pressure, no self-reported diagnosis of glaucoma) and therefore may have included individuals who were otherwise considered glaucoma suspects or had pre-perimetric disease. Second, we broadly categorized individuals as White or Black/African American based on self-report from initial intake forms. As acknowledged previously, this is a heterogeneous category. We also did not include individual self-identifying as other races due to small sample sizes. Third, we could not differentiate RNFL thickness measurements with white labels due to thicknesses in the top 95th percentile from those with white labels due to undefined age or disc area. Finally, we did not investigate the suspected interaction effects between the various ocular parameters and sociodemographic factors in predicting RNFL color labels as our study was not powered to do so.

In this study, we compared OCT parameters between the Topcon normative cohort and a large, diverse, real-world cohort of healthy participants from the MI-SIGHT program. Although there were no differences in the mean ONH parameters and retinal thickness measures, significant differences emerged when comparing the Topcon normative cohort to the MI-SIGHT healthy cohort when stratified by self-identified race. Furthermore, the distribution of RNFL thickness color labels in the MI-SIGHT cohort deviated from the expected distributions, despite being a healthy cohort. While color label distributions across various ethnically homogeneous cohorts have been previously studied, this study explores the application of the OCT normative database in a real-world community setting in both White and Black/African American individuals. Additionally, we used a multivariable model to gain deeper insights into predictors of color label classifications. Our findings reveal that factors influencing color labels extend beyond the commonly cited influences of self-identified race and disc area. Our study's results support the argument that to accurately differentiate between normal and glaucomatous eyes in real-world populations with OCT, larger datasets that include individuals with a broad range of ocular parameters and sociodemographic backgrounds are necessary. Only then can the full potential of OCT be utilized for screening, particularly in communities at high risk for blindness from glaucoma.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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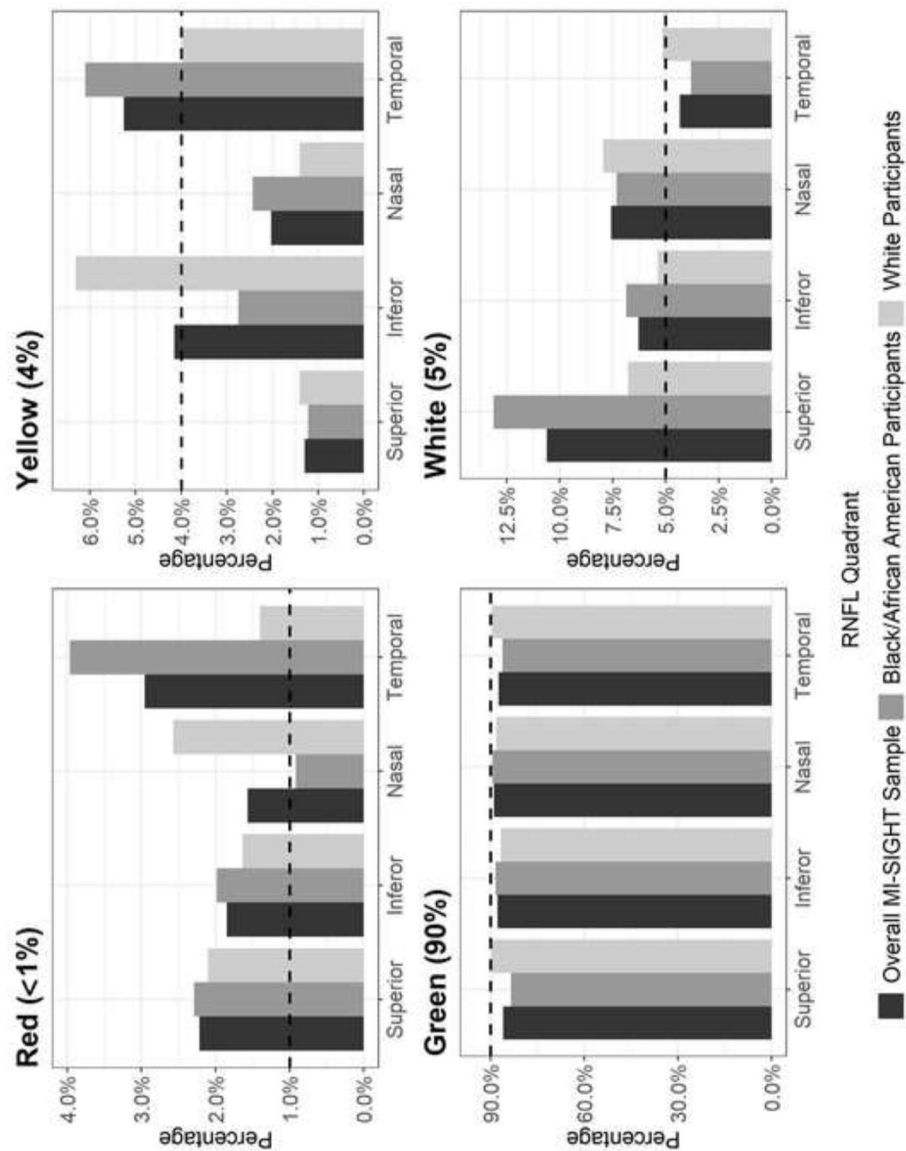


Figure 1. Percentages of RNFL color codes by quadrant in the MI-SIGHT healthy cohort. RNFL, retinal nerve fiber layer. MI-SIGHT, Michigan Screening and Intervention for Glaucoma and Eye Health through Telemedicine. Color code labels derived from software output and is based on a comparison of individual measurements with the Topcon normative dataset, as outlined in the text for further details.

Table 1.

Demographic and ocular characteristics of Black/African American and White participants in the MI-SIGHT healthy cohort compared to Topcon 3D OCT-1 Maestro normative cohort.

Demographics	MI-SIGHT (n _{patient} =1084)		Topcon (n _{patient} =504*)		
Continuous Variable	Mean (SD)	Min, Max	Mean (SD)	Min, Max	P-value [†]
Age (years)	53.9 (14.8)	18.0, 90.0	46.3 (16.3)	18.0, 88.0	<0.0001
Categorical Variable	Frequency (%)		Frequency (%)		P-value [†]
Sex					
Female	678 (62.8)		226 (57%)		0.0001
Male	401 (37.2)		-		
Ethnicity					
Hispanic/Latino	32 (3.5)		71 (18%)		<0.0001
Non-Hispanic/Non-Latino	882 (96.5)		-		
Race					
Black/African American	656 (60.5)		20%		<0.0001
White	428 (39.5)		59%		<0.0001
Asian	-		13%		-
Native Hawaiian/Pacific Islander	-		2%		-
American Indian/Alaskan Native	-		1%		-
Other	-		6%		-
Ocular Characteristics	MI-SIGHT (n _{eye} =1084)		Topcon (n _{eye} =399)		
Continuous Variable	Mean (SD)	Min, Max	Mean (SD)	Min, Max	P-value [†]
LogMAR BCVA	-0.06 (0.10)	-0.30, 0.30	-	-	-
IOP (mmHg)	14.29 (3.08)	6.00, 20.00	-	-	-
Clinical vertical cup to disc ratio	0.34 (0.14)	0.00, 0.65	-	-	-
Manifest Refractive SE (diopters)	-0.63 (2.27)	-11.38, 9.50	-1.16 (2.42)	-11.0, 4.5	<0.0001
Categorical Variable	Frequency (%)		Frequency (%)		P-value
Refractive Error					
High Myopia (SE ≤ -5)					
Moderate Myopia (-5 < SE ≤ -3)	61 (5.7)		-	-	
Mild Myopia (-3 < SE ≤ -1)	81 (7.5)		-	-	
No Myopia/Hyperopia (SE ± 0.99)	227 (21.1)		-	-	-
Mild Hyperopia (1 ≤ SE < 3)	486 (45.2)		-	-	
Moderate Hyperopia (3 ≤ SE < 5)	184 (17.1)		-	-	
High Hyperopia (SE ≥ 5)	28 (2.6)		-	-	
	8 (0.7)		-	-	

MI-SIGHT, Michigan Screening and Intervention for Glaucoma and Eye Health through Telemedicine. LogMAR, Logarithm of the Minimum Angle of Resolution. BCVA, best-corrected visual acuity. IOP, intraocular pressure. mmHg, millimeters of mercury. SE, Spherical Equivalent. SD, standard deviation. Min, minimum. Max, maximum.

[†]One-sample t-tests for continuous variables and one-sample proportion tests for categorical variables.

*Topcon enrolled 504 patients, 102 did not meet the criteria and 3 did not have scans. This reduced the patients that meet the inclusion criteria to 399. However, it is unclear if they reported the patient demographics for 504 patients or 399 patients.

Table 2. Comparison of ONH Parameters and RNFL Thicknesses of MI-SIGHT Healthy Cohort by Self-Identified Race and to the Topcon Normative Cohort.

Continuous Variables	N	MI-SIGHT Overall (n _{eye} =1084)	MI-SIGHT Black/African American (n _{eye} =656)	MI-SIGHT White (n _{eye} =428)	MI-SIGHT Black/African American vs MI-SIGHT White P-value [†]	Topcon (n _{eye} =399)	MI-SIGHT Overall vs Topcon P-value [*]	MI-SIGHT Black/African American vs Topcon P-value [*]	MI-SIGHT White vs Topcon P-value [*]
Disc Scan Quality Score	1027	55.83 (4.30)	56.06 (4.30)	55.47 (4.28)	0.1594	-	-	-	-
C/D Vertical	1023	0.48 (0.20)	0.51 (0.19)	0.44 (0.21)	<0.0001	0.48 (0.19)	1.0000	0.0002	0.0005
C/D Area (mm ²)	1023	0.29 (0.17)	0.32 (0.17)	0.24 (0.17)	<0.0001	0.28 (0.17)	1.0000	<0.0001	<0.0001
Disc area (mm ²)	1023	2.06 (0.42)	2.12 (0.43)	1.96 (0.37)	<0.0001	2.10 (0.41)	0.0083	0.9892	<0.0001
Cup area (mm ²)	1023	0.61 (0.41)	0.68 (0.42)	0.48 (0.37)	<0.0001	0.61 (0.43)	1.0000	0.0002	<0.0001
Rim area (mm ²)	1023	1.45 (0.44)	1.44 (0.46)	1.48 (0.40)	0.3567	1.49 (0.38)	0.0722	0.0219	1.0000
Cup volume (mm ³)	1023	0.12 (0.13)	0.15 (0.14)	0.08 (0.09)	<0.0001	0.13 (0.14)	1.0000	<0.0001	<0.0001
Rim volume (mm ³)	1023	0.27 (0.18)	0.26 (0.20)	0.28 (0.15)	0.3567	0.26 (0.14)	1.0000	1.0000	0.1589
RGC + IPL (μm)	1021	71.59 (6.40)	71.51 (6.57)	71.70 (6.12)	0.6928	71.73 (5.88)	1.0000	1.0000	1.0000
RNFL thickness (μm)	1027	103.30 (13.00)	104.39 (13.35)	101.56 (12.24)	0.0037	104.04 (11.34)	0.4854	1.0000	0.0003
RNFL thicknesses by Quadrant									
Superior	1027	127.62 (21.32)	130.00 (22.04)	123.85 (19.56)	<0.0001	-	-	-	-
Inferior	1027	134.97 (20.41)	137.03 (21.06)	131.70 (18.89)	0.0002	-	-	-	-
Nasal	1026	81.53 (16.63)	82.10 (16.95)	80.62 (16.09)	0.3567	-	-	-	-
Temporal	1027	68.97 (11.83)	68.22 (11.89)	70.17 (11.64)	0.0574	-	-	-	-

ONH, optic nerve head. RNFL, retinal nerve fiber layer. MI-SIGHT, Michigan Screening and Intervention for Glaucoma and Eye Health through Telemedicine. C/D, cup-to-disc. RGC, retinal ganglion cell. IPL, inner plexiform layer. RNFL, retinal nerve fiber layer. N, number of scans after excluding missing values and poor quality scans. SD, standard deviation. Min, minimum. Max, maximum.

^{*} One-sample t-tests. P-values was adjusted for multiple comparisons using Holm's procedure.

[†] Two-sample t-tests. P-values was adjusted for multiple comparisons using Holm's procedure

Table 3.

Distribution of RNFL thickness color labels stratified by quadrant and race in the MI-SIGHT healthy cohort.

Quadrant	Color (Expected %)				P-value*
	White (5%)	Green (90%)	Yellow (4%)	Red (1%)	
Superior	Observed distribution of RNFL thickness color labels (%)				
Overall	10.60%	85.90%	1.30%	2.20%	0.0005
Black/African American	13.10%	83.40%	1.20%	2.30%	0.0005
White	6.80%	89.70%	1.40%	2.10%	0.0035
Inferior					
Overall	6.30%	87.70%	4.20%	1.80%	0.0110
Black/African American	6.90%	88.40%	2.70%	2.00%	0.0065
White	5.40%	86.70%	6.30%	1.60%	0.0465
Nasal					
Overall	7.60%	88.80%	2.00%	1.60%	0.0005
Black/African American	7.30%	89.30%	2.40%	0.90%	0.0110
White	7.90%	88.10%	1.40%	2.60%	0.0005
Temporal					
Overall	4.30%	87.50%	5.30%	3.00%	0.0005
Black/African American	3.80%	86.10%	6.10%	4.00%	0.0005
White	5.10%	89.50%	4.00%	1.40%	0.8496

MI-SIGHT, Michigan Screening and Intervention for Glaucoma and Eye Health through Telemedicine. RNFL, retinal nerve fiber layer.

* Chi-square tests.

Table 4.

Odds ratio for associations between pre-selected variables and RNFL color labels categorized through the Topcon Maestro® OCT machine for each quadrant. Separate multinomial logistic regression models were used for each quadrant. Green is the reference group.

Superior Quadrant	Red (n=24, 2.2%)			Yellow (n=14, 1.3%)			White (n=115, 10.6%)		
	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Age (per 10 year)	1.65	1.13–2.42	0.0095	1.13	0.76–1.69	0.5530	1.18	1.01–1.38	0.0323
Disc Area (per 1mm ²)	0.39	0.11–1.38	0.1453	1.94	0.68–5.53	0.2148	0.89	0.53–1.51	0.6710
Manifest Refractive SE (per 1 diopter)	0.79	0.65–0.95	0.0132	0.77	0.61–0.96	0.0198	1.13	1.01–1.25	0.0296
White vs Black/African American	0.67	0.26–1.75	0.4159	1.04	0.33–3.29	0.9483	0.41	0.25–0.66	0.0003
Inferior Quadrant	Red (n=20, 1.8%)			Yellow (n=45, 4.2%)			White (n=68, 6.3%)		
	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Age (per 10 year)	1.05	0.74–1.50	0.7922	1.19	0.94–1.52	0.1559	0.97	0.81–1.17	0.7622
Disc Area (per 1mm ²)	0.27	0.07–0.99	0.0497	0.85	0.36–2.00	0.7149	1.07	0.58–1.97	0.8373
Manifest Refractive SE (per 1 diopter)	1.19	0.93–1.52	0.1688	0.95	0.81–1.10	0.4693	1.09	0.96–1.24	0.2056
White vs Black/African American	0.69	0.25–1.92	0.4717	2.21	1.15–4.24	0.0173	0.77	0.44–1.33	0.3393
Nasal Quadrant	Red (n=17, 1.6%)			Yellow (n=22, 2.0%)			White (n=82, 7.6%)		
	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Age (per 10 year)	1.66	1.07–2.57	0.0243	1.18	0.84–1.66	0.3500	0.81	0.69–0.96	0.0124
Disc Area (per 1mm ²)	0.48	0.12–1.94	0.3031	1.49	0.54–4.10	0.4448	0.98	0.55–1.73	0.9329
Manifest Refractive SE (per 1 diopter)	0.98	0.76–1.25	0.8500	0.93	0.74–1.16	0.5267	1.13	1.01–1.27	0.0414
White vs Black/African American	2.28	0.79–6.56	0.1253	0.46	0.15–1.41	0.1720	1.07	0.66–1.74	0.7840
Temporal Quadrant	Red (n=32, 3.0%)			Yellow (n=57, 5.3%)			White (n=47, 4.3%)		
	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Age (per 10 year)	1.02	0.78–1.35	0.8606	1.04	0.85–1.26	0.7084	1.41	1.08–1.83	0.0117
Disc Area (per 1mm ²)	0.90	0.33–2.43	0.8278	0.61	0.29–1.27	0.1842	4.92	2.33–10.38	<0.0001
Manifest Refractive SE (per 1 diopter)	1.11	0.92–1.35	0.2777	1.05	0.91–1.20	0.5000	0.88	0.74–1.04	0.1220
White vs Black/African American	0.40	0.16–1.01	0.0530	0.61	0.33–1.11	0.1038	1.71	0.86–3.39	0.1250

RNFL, retinal nerve fiber layer. OCT, optical coherence tomography. OR, odds ratio. CI, confidence interval. SE, spherical equivalent