

# The Effects of Race, Optic Disc Area, Age, and Disease Severity on the Diagnostic Performance of Spectral-Domain Optical Coherence Tomography

Christopher A. Girkin,<sup>1</sup> Jeffery Liebmann,<sup>2,3</sup> Murray Fingeret,<sup>4</sup> David S. Greenfield,<sup>4</sup> and Felipe Medeiros<sup>5</sup>

**PURPOSE.** To evaluate the effect of race (African or European descent), age, disc area, and severity of disease on the diagnostic ability of spectral-domain optical coherence tomography (SDOCT) imaging of the optic nerve, macula, and retinal nerve fiber layer (RNFL) in the detection of glaucomatous injury.

**METHODS.** In this cross-sectional observational study, data from SDOCT images of 312 eyes of 167 subjects without ocular disease and 233 eyes of 163 patients with open-angle glaucoma. A receiver operating characteristic (ROC) regression modeling technique was used to evaluate the influence of race on the diagnostic accuracy of the ONH, RNFL, and macular parameters in SDOCT in glaucoma, while adjusting and evaluating the possible confounding effects of age, disease severity, and size of the optic disc.

**RESULTS.** The optimal performing measurements of the RNFL and macula were more effective than optic nerve ( $aROC_{RNFL} = 0.87$ ,  $aROC_{inner\ macula} = 0.88$ , and  $aROC_{rim\ area} = 0.81$ ) for the overall group. No variation was noted in the diagnostic performance of SDOCT between racial groups nor was there any association of race with differences in disc area for structural parameters of the optic nerve, RNFL, and macula. Advanced disease severity was associated with increased diagnostic accuracy, with improved performance in eyes with more severe visual field loss.

**CONCLUSIONS.** The diagnostic ability of ONH, RNFL, and macular measurements in the detection of glaucoma was similar across racial groups, and disc area had a minimal effect on the overall diagnostic efficacy of SDOCT. No significant differences were seen in the diagnostic performance of the SDOCT between these groups when generalized or race-specific normative data were used. (*Invest Ophthalmol Vis Sci.* 2011;52:6148–6153) DOI:10.1167/iovs.10-6698

Racial differences in optic nerve structure have been well described Girkin CA, et al. *IOVS* 2004;45:ARVO E-Abstract 5502<sup>1-10</sup> and may have an important role in the variation in

the predilection to develop glaucoma between various ancestral groups.<sup>11-16</sup> In addition, variation in optic nerve structure may affect the ability to detect glaucoma and potentially to detect progressive glaucomatous injury.<sup>17</sup> Specifically, differences in optic disc area that have been demonstrated across racial strata may have an effect on the diagnostic ability of optic nerve imaging.<sup>4,18-20</sup>

Although several studies have demonstrated variations in optic disc anatomy between individuals of African (AD) and European (ED) descent<sup>1-8</sup> and the potential effect of these differences on the diagnostic ability of glaucoma imaging devices,<sup>4,18-20</sup> the effect of racial variation on optic nerve structure has not been determined with the newer spectral-domain OCT (SDOCT) techniques. SDOCT has provided an increased resolution of the RNFL, optic nerve, and macular regions over time-domain approaches. The purpose of this study was to evaluate the effect of racial differences in optic nerve structure between groups of AD and ED patients on the diagnostic ability of SDOCT imaging of the optic nerve, macula, and RNFL in the detection of glaucomatous injury, along with evaluating the effects of age, disc area, and severity of disease in these groups.

## METHODS

Patients of either AD or ED descent with open-angle glaucoma were recruited from the University of Alabama at Birmingham Optic Disc Imaging Center's glaucoma database, which consists of glaucoma patients and normal subjects who have undergone optic disc imaging. Normal controls of AD or ED were recruited from four sites that were participating in a study to obtain normative data for the RTVue (Optovue Inc., Fremont, CA) instrument using identical protocols (University of Alabama at Birmingham, New York Eye and Ear Infirmary, Brooklyn Veteran Administration Hospital, Bascom Palmer Eye Institute). Included in the analysis were 312 eyes of 167 normal subjects and 233 eyes of 163 glaucoma patients. Racial groups were defined by self-description.

All subjects had a complete ophthalmic examination, including slit lamp biomicroscopy, intraocular pressure (IOP) measurement, stereoscopic fundus examination, simultaneous stereoscopic photographs of both optic discs, bilateral 24-2 Swedish Interactive Thresholding Algorithm (SITA) standard visual field testing (Humphrey Field Analyzer II; Carl Zeiss Meditec, Dublin, CA), and bilateral SDOCT imaging with the RTVue. All visual field testing and SDOCT imaging was completed within 3 months. Informed consent was obtained from all participants, and the Human Subjects Committee approved the methodology for all participating sites. The protocol complied with the guidelines set forth in the Declaration of Helsinki.

Glaucoma patients enrolled in this study were selected according to visual field characteristics alone, to avoid bias in the study population by including patients on the basis of subjective abnormalities of the optic disc. Glaucomatous visual field loss was defined as a corrected pattern SD outside the 95% normal limits or a glaucoma hemi-

From the <sup>1</sup>Department of Ophthalmology, School of Medicine, University of Alabama at Birmingham, Birmingham, Alabama; <sup>2</sup>Veterans Administration Harbor Healthcare System, Brooklyn, New York; the <sup>3</sup>New York Eye and Ear Infirmary, New York, New York; <sup>4</sup>Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami, Florida; and the <sup>5</sup>Department of Ophthalmology, University of California San Diego, La Jolla, CA.

Supported by the Eyesight Foundation of Alabama. SDOCT instruments supplied to study sites by Optovue Inc.

Submitted for publication October 8, 2010; revised December 15, 2010, and February 4, 2011; accepted February 6, 2011.

Disclosure: C.A. Girkin, Optovue (F); J. Liebmann, Optovue (F); M. Fingeret, Optovue (F); D.S. Greenfield, Optovue (F); F. Medeiros, Optovue (F)

Corresponding author: Christopher A. Girkin, UAB Department of Ophthalmology, 700 South 18th Street, Suite 601, Birmingham, AL 35233; cgirkin@uab.edu.

field test outside the 99% normal limits confirmed on follow-up examination and a cluster of at least three points flagged as significant on the pattern deviation plot consistent with glaucoma as judged by a fellowship-trained glaucoma specialist. Only patients with repeatable visual field defects were enrolled. Patients with best corrected visual acuity worse than 20/40, visually significant cataracts (nuclear sclerotic or posterior subcapsular cataract, with visual acuity worse than 20/40), spherical refraction outside  $\pm 5.0$  or cylinder correction outside  $\pm 2.5$ , confounding neurologic or ophthalmic conditions, or use of medication known to affect visual sensitivity at the time of visual field testing were excluded.

Normal subjects had a highest documented IOP of less than 22 mm Hg and normal visual field results defined as a corrected pattern SD within the 95% normal limits and a glaucoma hemifield test result within normal limits. Subjects with a best corrected visual acuity of worse than 20/40, spherical refraction outside  $\pm 5.0$  or cylinder correction outside  $\pm 2.5$  were excluded. Those using medications known to affect visual sensitivity at the time of visual field testing and those with ophthalmic or neurologic surgery or disease were also excluded.

The SDOCT examination was performed with the RTVue (software ver. 2.0 during data collection, software ver. 4.5.39 for final data analysis). The RTVue is a spectral-domain or Fourier-domain OCT that scans at a speed of 26,000 A scans per second and has an axial resolution of 5  $\mu\text{m}$ . It uses a scanning laser diode with a wavelength of  $840 \pm 10$  nm, to provide images of ocular microstructures. The scan patterns used in this study were the ONH scan (optic nerve head, formerly called NHM4), the GCC (ganglion cell complex) scan and 3-D scans of the macula and optic disc.

The ONH scan pattern was used to obtain parapapillary RNFL and optic disc measurements. It consists of 12 radial scans 3.4 mm in length (452 A scans each) and 6 concentric ring scans ranging from 2.5 to 4.0 mm in diameter (587–775 A scans each), all centered on the optic disc by the operator. This scan protocol provides 9510 A scans in 0.39 seconds. After the image is acquired, the software automatically demarcates the optic disc margin using the 3-D disc scan. The software uses the ends of the RPE-choroid layer to identify the disc border. The optic disc border is displayed to the user and can be manually adjusted if necessary, which was required in approximately a quarter of the images. The software also detects the RPE-choroid end on the ONH scan in a similar manner. The software then registers the optic disc margin drawing from the 3-D disc scan to the ONH scan to calculate the optic disc parameters (using the disc margin drawing). This registration is performed based on aligning the center of the optic disc drawing from the 3-D scan to the center of the RPE-choroid tips on the ONH scan.

The ONH scan calculates various parameters that describe the optic disc and parapapillary RNFL. The optic cup is automatically defined by the RTVue software as the intersection points of the nerve head's inner boundary and a parallel line that is 150  $\mu\text{m}$  above the connecting line of the RPE tips. ONH parameters measured by the software are optic disc area, optic cup area, neuroretinal rim area, nerve head volume, cup volume, rim volume, cup-disc area ratio, horizontal cup-disc ratio and vertical cup-disc ratio.

The parapapillary RNFL thicknesses are also calculated from the ONH scan. An RNFL thickness map is generated from the optic disc margin out to a 4-mm diameter circle with data interpolated between the B scans. A 3.45-mm diameter circle is then resampled from the RNFL thickness map after it is centered on the optic disc. This resampling ensures that the 3.45-mm circle, the TSNIT circle, is always centered on the optic disc. The TSNIT circle is displayed to the user, and all RNFL thickness measurements are derived from the TSNIT circle. The RNFL parameters include the average RNFL thickness, superior and inferior hemisphere averages, quadrant averages, and eight sectors around the optic disc.

The GCC scan was used to obtain inner retinal thickness measurements (from the internal limiting membrane to the bottom of the inner plexiform layer) in the macula. This scan pattern consists of one horizontal line scan 7 mm in length (467 A scans) followed by 15

vertical line scans 7 mm in length (each 400 A scans) and at 0.5-mm intervals centered 1 mm temporal to the fovea. This scan configuration provides 14,810 A scans in 0.58 seconds. The GCC scan measures the inner retinal thickness which includes the nerve fiber layer, ganglion cell layer, and inner plexiform layer, collectively called the ganglion cell complex, or GCC. The parameters generated by the GCC analysis are the average inner retinal thickness, superior inner retinal thickness, inferior inner retinal thickness, and superior minus inferior inner retinal thickness.

Good-quality images were determined on the basis of the software-provided signal strength index (SSI), as well as a careful qualitative review of the images according to specific guidelines. Scans were excluded that had SSI values below 30, if all or part of the OCT data were outside the OCT scan window boundary, if the fovea for the GCC or ONH scans was not positioned near the center, if the automated optic disc boundary circle was not accurately placed by the software, or if there were segmentation errors on inspection of the retinal cross-sectional images.

## Statistical Analysis

The receiver operating characteristic (ROC) regression-modeling technique was used to evaluate the influence of race on the diagnostic accuracies of the ONH, RNFL, and macular parameters with RTVue in glaucoma, with adjustment and evaluation of the possible confounding effects of age, disease severity, and size of the optic disc. This modeling approach was used previously by Medeiros et al.<sup>20</sup> for evaluation of the effect of covariates on the performance of diagnostic tests in glaucoma. The methodology allows the evaluation of the influence of covariates on the diagnostic performance of the test, so that ROC curves for specific values of the covariate of interest can be obtained. Also, it allows adjustment for the possible confounding effects of other covariates. Details of the modeling procedure have been described previously.<sup>20</sup> In brief, the  $\text{ROC}_{X, X_D}(q)$  is the probability that a diseased individual with disease-specific covariates  $X_D$  (that is, covariates specific to diseased subjects, such as disease severity) and common covariates  $X$  (covariates common to both diseased and healthy subjects, such as race and optic disc size) has test results  $Y_D$  that are greater than or equal to the  $q$ th quantile of the distribution of test results from nondiseased individuals. That is, when the specificity of the test is  $1 - q$ , the sensitivity is  $\text{ROC}_{X, X_D}(q)$ . The general ROC regression model can be written as:

$$\text{ROC}_{X, X_D}(q) = [\alpha_1 + \alpha_2 \Phi^{-1}(q) + \beta X + \beta_D X_D]$$

where the coefficients  $\alpha_1$  and  $\alpha_2$  are the intercept and slope of the ROC curve, respectively,  $\Phi$  is the normal cumulative distribution function (cdf), and  $\Phi^{-1}(q)$  is the inverse normal cdf of the false-positive rate (FPR). If the coefficient for a specific variable  $X$  (say  $\beta$ ) is greater than 0, then the discrimination between diseased and nondiseased subjects increases with increasing values of this covariate. Similarly, if the coefficient for the disease-specific covariate  $X_D$  (say  $\beta_D$ ) is greater than 0, then diseased subjects with higher values of this covariate are more distinct from nondiseased subjects than are diseased subjects with lower values of  $X_D$ . In the present study, the following ROC regression model was fit to assess the influence of race, age, disease severity, and optic disc size on the diagnostic performance of the ONH, RNFL, and macular parameters of the RTVue.

$$\text{ROC}_{X, X_D}(q) = \Phi[\alpha_1 + \alpha_2 \Phi^{-1}(q) + \beta_1 \text{race} + \beta_2 \text{age} + \beta_3 \text{disease severity} + \beta_4 \text{disc size}]$$

where severity is a continuous variable, as determined by the Visual Field Index (VFI). Interaction terms between the variables and  $\Phi^{-1}(q)$  can be included to allow the effects of the covariates to differ by various amounts, depending on the FPR  $q$  (or specificity  $1 - q$ )—that is, to influence the shape of the curve.

TABLE 1. Ocular and Demographic Characteristics

	Glaucoma		Normal		P*
	AD	ED	AD	ED	
Age, y	65.9	68.3	47.3	54.8	<0.0001
Spherical equivalent, D	0.56	0.40	-0.56	-0.52	0.069
Disc area, mm	2.5	2.1	2.1	1.8	<0.0001
Vertical CDR	0.8	0.8	0.5	0.5	<0.0001
RNFL thickness, $\mu\text{m}$	81.5	81.7	105.5	102.4	<0.0001
Inner macular thickness, $\mu\text{m}$	76.9	79.8	94.8	95.7	<0.0001
Intraocular Pressure, mm Hg	14.6	15.4	14.5	14.3	0.052
Mean Defect, dB	-9.7	-7.2	0.06	0.38	<0.0001

\* Glaucoma vs. normal.

Coefficients from the ROC regression method were initially estimated in a full multivariate model. Subsequently, statistically significant coefficients were retained in a final reduced multivariate model and AUCs for arbitrary values of the significant variables were obtained with the formula

$$\text{AUC} = \int_0^1 \text{ROC}_{X, X_D}(q) dt = \Phi\left(\frac{\alpha_1 + \beta X + \beta_D X_D}{\sqrt{1 + \alpha_2^2}}\right).$$

Parameters were estimated by probit regression. To obtain confidence intervals (CI) for regression parameters, we used a bootstrap resampling procedure ( $n = 1000$  resamples).<sup>20</sup> As measurements from both eyes of the same subject are likely to correlate, the standard statistical methods for parameter estimation lead to underestimation of standard errors. Therefore, the cluster of data for the study subject was considered as the unit of resampling when calculating standard errors.<sup>20</sup>

To determine whether the inclusion of race-specific normative databases improved diagnostic efficacy, we compared the aROC adjusted for age and intraocular correlation for the best-performing diagnostic parameters (highest aROC) for the ONH, RNFL, and macula in each racial group, while restricting the normative database to AD or ED individuals. Statistical analyses were performed with commercial software (Stata ver. 10.0; StataCorp, College Station, TX).

## RESULTS

The study included 312 eyes of 167 normal subjects and 233 eyes of 163 glaucoma patients. Age, race distribution, optic

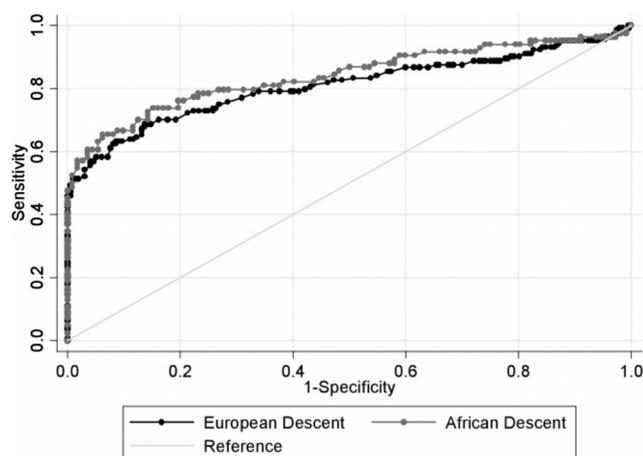


FIGURE 1. Areas under the ROC curves to differentiate glaucomatous from normal eyes using rim area across racial strata.

disc size, and visual field parameters of the two groups of participants are shown in Table 1. One hundred one glaucoma patients were ED and 58 were AD. From the control group, 62 were AD and 105 were ED.

For the ONH parameter rim area, the unadjusted, pooled areas under the ROC curves that differentiated glaucomatous from normal eyes were 0.81 (95% confidence interval [CI], 0.76-0.86) and 0.84 (95% CI, 0.78-0.90) for ED and AD groups, respectively (Fig. 1). Table 2 shows the estimates of the coefficients of the ROC regression model for the ONH rim area. There was no difference in the diagnostic performance of the rim area in AD versus ED subjects, as indicated by the non-statistically significant coefficient associated with race (0.08; 95% CI, -0.36 to 0.57). The diagnostic performance of the rim area increased as the VFI decreased (i.e., disease severity increased) as evidenced by the statistically significant negative coefficient associated with disease severity (-0.03; 95% CI, -0.05 to -0.02). Disc size (-0.43; 95% CI, -0.80 to 0.06) and age (-0.01; 95% CI, -0.02 to 0.01) did not affect the discriminating performance of rim area. The AUCs calculated at arbitrary VFI values of 99%, 90%, 80%, and 70% according to the ROC regression model were 0.75, 0.82, 0.88, and 0.92, respectively.

For the average RNFL thickness, the unadjusted, pooled areas under the ROC curves necessary to differentiate glaucomatous from normal eyes were 0.88 (95% CI, 0.84-0.92) and 0.89 (95% CI, 0.85-0.94) for ED and AD, respectively (Fig. 2). Table 3 shows the estimates of the coefficients of the ROC regression model for this parameter. There was no significant difference in the diagnostic performance of average RNFL thickness in AD versus ED, as indicated by the non-statistically significant coefficient associated with race (0.05; 95% CI, -0.45 to 0.70). The diagnostic performance of average RNFL thickness increased as the VFI decreased (-0.032; 95% CI, -0.07 to -0.02). The nonsignificant coefficient associated with disc size indicated that disc size did not influence the diagnostic accuracy of this parameter (0.05; 95% CI, -0.34 to

TABLE 2. Results of the ROC Regression Model Evaluating the Influence of Race on Diagnostic Accuracy of Optic Disc Rim Area

Parameter	Coefficient	Estimate	95% CI
Intercept	$\alpha_1$	<b>5.48</b>	3.80 to 7.49
$\Phi^{-1}(q)$	$\alpha_2$	<b>0.65</b>	0.50 to 0.80
Race	$\beta_1$	0.08	-0.36 to 0.57
Severity	$\beta_2$	<b>-0.03</b>	-0.05 to -0.02
Disc size	$\beta_3$	-0.43	-0.80 to 0.06
Age	$\beta_4$	-0.01	-0.02 to 0.01

$\Phi^{-1}(q)$ , inverse normal cumulative distribution function of FPR. Significant results are bold ( $P < 0.05$ ).

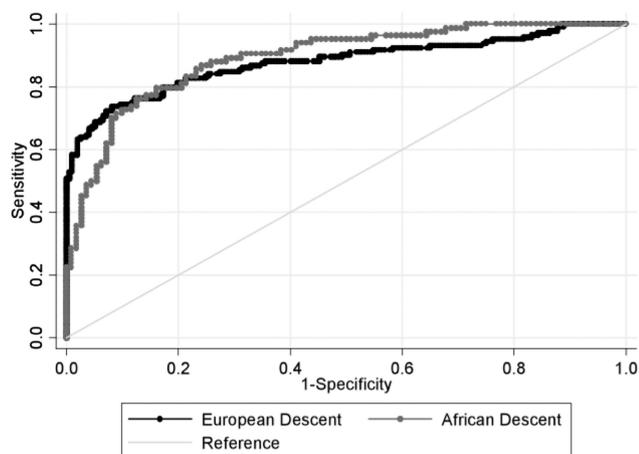


FIGURE 2. Areas under the ROC curves to differentiate glaucomatous from normal eyes using retinal nerve fiber layer thickness across racial strata.

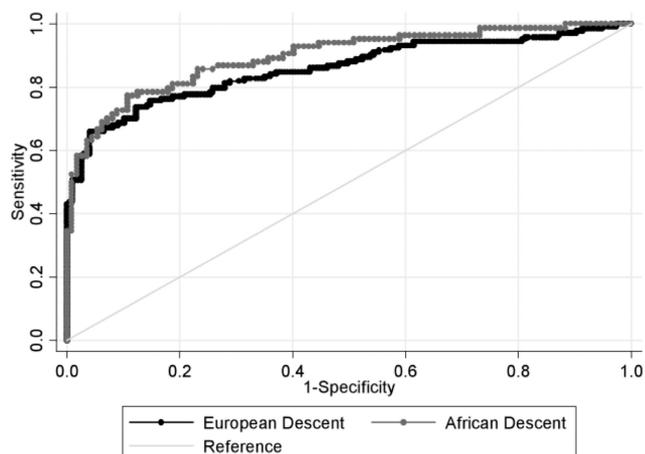


FIGURE 3. Areas under the ROC curves to differentiate glaucomatous from normal eyes using inner macular thickness across racial strata.

0.53). The AUCs calculated at arbitrary VFI values of 99%, 90%, 80%, and 70% according to the ROC regression model were 0.79, 0.86, 0.91, and 0.95, respectively.

For the inner average macular thickness, the unadjusted pooled areas under the ROC curves to differentiate glaucomatous from normal eyes were 0.86 (95% CI, 0.81–0.90) and 0.90 (95% CI, 0.85–0.94) for ED and AD, respectively (Fig. 3). Table 4 shows the estimates of the coefficients of the ROC regression model for this parameter. There was no significant difference in the diagnostic performance between the AD and ED groups, as indicated by the nonstatistically significant coefficient associated with race (0.25; 95% CI, –0.30 to 0.73). The diagnostic performance increased as the VFI decreased (–0.02; 95% CI, –0.03 to –0.01). Disc size (–0.08; 95% CI, –0.45 to 0.31) and age (0.01; 95% CI, –0.01 to 0.02) did not influence the discriminating power of inner average macular thickness. The AUCs calculated at arbitrary VFI values of 99%, 90%, 80%, and 70% according to the ROC regression model were 0.79, 0.83, 0.87, and 0.90, respectively.

Race did not affect the diagnostic performance of any of the other RTVue parameters (*P* values associated with race coefficient in all models >0.05). In addition, restricting the normative databases to reflect only ED or AD individuals did not have a significant impact on the diagnostic ability of the best-performing parameters with SDOCT in either the AD or ED group. For example, for the average RNFL thickness parameter, the area under the ROC curve needed discriminate ED glaucoma patients from ED normal subjects was 0.88 (95% CI, 0.84–0.92). When ED glaucoma patients were compared to AD normal subjects, the aROC curve area was 0.89 (95% CI, 0.86–0.93). For AD glaucoma patients, the aROC curves necessary discriminate them

from AD and ED normal subjects were 0.89 (95% CI, 0.85–0.94) and 0.87 (95% CI, 0.82–0.92), respectively.

### DISCUSSION

The present study showed no variation in the diagnostic performance of SDOCT between the AD and ED groups and none that was associated with differences in disc area for structural parameters of the optic nerve, RNFL, and macula. As expected, increasing disease severity was associated with increasing diagnostic accuracy, with improved performance in eyes with more severe visual field loss. The optimal performing measurements of the RNFL and macula performed better than did optic nerve measurements (aROC<sub>RNFL</sub> = 0.87, aROC<sub>GCC</sub> = 0.88, aROC<sub>rim area</sub> = 0.81) for the overall group.

The lack of a difference in diagnostic performance of the SDOCT between racial groups is interesting given the difference in disc area between the AD and ED groups (Girkin CA, et al. *IOVS* 2004;45:ARVO E-Abstract 5502)<sup>1–9</sup> and that prior studies using the CSLO have shown differences in the diagnostic efficacy of imaging in subjects with various disc areas.<sup>17–20</sup> However, in the present study, using SDOCT, we found no association between disc area and diagnostic performance when we considered ONH, RNFL, and macular measurements. Whereas one prior study using the CSLO demonstrated variation in the association between optic nerve structural changes and visual function in glaucoma between AD and ED individuals,<sup>4</sup> our study agrees with more recent work using the CLSO, which did not show differences in the performance of these techniques in the diagnosis of glaucoma between AD and ED individuals when disc area was taken into account.<sup>3,10</sup>

TABLE 3. Results of the ROC Regression Model Evaluating the Influence of Race on Diagnostic Accuracy of Average RNFL Thickness

Parameter	Coefficient	Estimate	95% CI
Intercept	$\alpha_1$	<b>4.02</b>	1.40 to 7.93
$\Phi^{-1}(q)$	$\alpha_2$	<b>0.70</b>	0.49 to 0.86
Race	$\beta_1$	0.05	–0.45 to 0.69
Severity	$\beta_2$	<b>–0.03</b>	–0.07 to –0.02
Disc size	$\beta_3$	0.05	–0.34 to 0.53
Age	$\beta_4$	0.001	–0.02 to 0.02

$\Phi^{-1}(q)$ , inverse normal cumulative distribution function of FPR. Significant results are bold (*P* < 0.05).

TABLE 4. Results of the ROC Regression Model Evaluating the Influence of Race on Diagnostic Accuracy of Average Inner Macular Thickness

Parameter	Coefficient	Estimate	95% CI
Intercept	$\alpha_1$	<b>2.36</b>	0.29 to 4.42
$\Phi^{-1}(q)$	$\alpha_2$	<b>0.65</b>	0.47 to 0.84
Race	$\beta_1$	0.25	–0.30 to 0.76
Severity	$\beta_2$	<b>–0.02</b>	–0.03 to –0.01
Disc size	$\beta_3$	–0.08	–0.45 to 0.31
Age	$\beta_4$	0.01	–0.01 to 0.02

$\Phi^{-1}(q)$ , inverse normal cumulative distribution function of FPR. Significant results are bold (*P* < 0.05).

In the aROC models, we used normal controls from a group of individuals with similar racial classification, which may explain the lack of effect of race on diagnostic performance. We conclude that, as long as a general normative database contains sufficient individuals of various racial groups to adequately define normal interindividual variation in optic nerve and retina structure both within and between racial strata, no race-specific datasets or detection models are needed to achieve optimal diagnostic performance in specific racial groups from SDOCT measurements of the ONH, RNFL, and macula. However, we did not see any significant difference in diagnostic performance when normal controls were restricted in either AD or ED individuals in either racial group. This result also calls into question the need for race-specific normative databases, as long as normative data contains an adequate sample to reflect the wide range of interindividual variability seen within and across racial strata.

A study published by Medeiros et al.<sup>20</sup> with Stratus OCT did find differences in sensitivity at fixed specificity with changes in disc area.<sup>20</sup> However, the differences in sensitivity with disc area seen when considering optic disc parameters such as retinal nerve fiber layer thickness or rim area for Stratus OCT<sup>20</sup> or HRT<sup>3,18-19</sup> in previous publications occurred at the expense of decreased specificity and therefore does not represent a true change in the overall diagnostic accuracy of the instrument. In their study, Medeiros et al. used a logistic regression model for evaluation of the influence of covariates on the sensitivities of different tests. For inclusion in the logistic model, the results of diagnostic tests (i.e., average RNFL) were dichotomized by using a single cutoff so that their sensitivities could be compared at the same level of *overall* specificity, since disc area varies with both sensitivity and specificity. Their conclusions are still correct with regard to sensitivities, but only when using a fixed cutoff, such as, for example, when analyzing the sensitivity of a classification produced by comparison to a normative database without correcting for disc size. Our current methodology evaluates the effect of disc area on the ROC curve area, which represents the overall diagnostic accuracy and takes into consideration both sensitivity and specificity. Therefore, an improvement in sensitivity occurring along a decrease in specificity does not improve the ROC curve area and explains why we did not find any significant effect of disc area in our models.

Furthermore, the measurement of disc area with SDOCT is not corrected for corneal curvature, as is the case with CSLO. Since this lack of adjustment may create some variation in the measurement of true disc area, it should be considered in interpreting these results and is in disagreement with the prior literature, showing a more significant effect of disc area using other methods. The SDOCT also determines the disc margin automatically as the edge of the retinal pigment epithelium, which may lead to an erroneous estimate of disc size in cases of peripapillary atrophy or algorithm failure. Although manual correction of the disc boundary, which was needed in approximately a quarter of eyes, probably compensated for this problem, it does not reflect common practice in the clinical use of this instrument.

An additional limitation of this study, common to most clinical studies exploring racial differences in disease characteristics, is categorization according to self description of "race," a term that represents an amalgam of cultural, geographic, socioeconomic, and biological characteristics. Self-described race is at best a poor summary of human biodiversity that cannot be interpreted in the strict biological sense. However, this factor has demonstrated dependent and independent

associations in several diseases,<sup>11-16</sup> and thus it is an important risk factor. Its effects are lessened, however, as long as the information is obtained in a standardized manner. The longitudinal study from which this dataset was obtained used a standardized questionnaire given by an interviewer to define race as AD, ED, or other. In addition, self-described race has demonstrated a high correlation with more sophisticated measures of racial classification using genetic admixture techniques and thus is probably an adequate surrogate measure.<sup>21</sup>

In summary, race and disc area had minimal effects on the diagnostic ability of ONH, RNFL, and macular measurements when SDOCT was used for detection of glaucoma between ED and AD groups. No significant differences were seen in the performance of the SDOCT when generalized or race-specific normative databases were used. Race-specific normative data are largely unnecessary, at least for AD and ED groups as long as these data adequately reflect the normal variations in optic nerve structure seen within and across individuals of African and European descent, at least for the RTVue SDOCT.

## References

1. Beck RW, Messner DK, Musch DC, Martonyi CL, Lichter PR. Is there a racial difference in physiologic cup size? *Ophthalmology*. 1985; 92:873-876.
2. Chi T, Ritch R, Stickler D, Pitman B, Tsai C, Hsieh FY. Racial differences in optic nerve head parameters. *Arch Ophthalmol*. 1989;107:836-839.
3. Girkin CA, DeLeon-Ortega JE, Xie A, McGwin G, Arthur SN, Monheit BE. Comparison of the Moorfields classification using confocal scanning laser ophthalmoscopy and subjective optic disc classification in detecting glaucoma in blacks and whites. *Ophthalmology*. 2006;113:2144-2149.
4. Girkin CA, McGwin G, Jr., McNeal SF, DeLeon-Ortega J. Racial differences in the association between optic disc topography and early glaucoma. *Invest Ophthalmol Vis Sci*. 2003;44:3382-3387.
5. Girkin CA, McGwin G, Xie A, DeLeon-Ortega JE. Differences in optic disc topography between black and white normal subjects. *Ophthalmology*. 2005;112:33-39.
6. Tsai C, Zangwill L, Gonzalez C, Weinreb R. Ethnic Differences in optic nerve head topography. *J Glaucoma*. 1995;4:248-257.
7. Varma R, Tielsch JM, Quigley HA, et al. Race-, age-, gender-, and refractive error-related differences in the normal optic disc. *Arch Ophthalmol*. 1994;112:1068-1076.
8. Zangwill LM, Weinreb RN, Berry CC, et al. The confocal scanning laser ophthalmoscopy ancillary study to the ocular hypertension treatment study: study design and baseline factors. *Am J Ophthalmol*. 2004;137:219-227.
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. *Arch Ophthalmol*. 128:541-550.
10. Girkin CA, McGwin G, Jr., Long C, DeLeon-Ortega J, Graf CM, Everett AW. Subjective and objective optic nerve assessment in African Americans and whites. *Invest Ophthalmol Vis Sci*. 2004; 45:2272-2278.
11. Seddon JM. The differential burden of blindness in the United States. *N Engl J Med*. 1991;325:1440-1442.
12. Sommer A. Glaucoma risk factors observed in the Baltimore Eye Survey. *Curr Opin Ophthalmol*. 1996;7:93-98.
13. Sommer A. Epidemiology, ethnicity, race, and risk. *Arch Ophthalmol*. 2003;121:1194.
14. Tielsch JM, Katz J, Quigley HA, Javitt JC, Sommer A. Diabetes, intraocular pressure, and primary open-angle glaucoma in the Baltimore Eye Survey. *Ophthalmology*. 1995;102:48-53.
15. Munoz B, West SK, Rubin GS, et al. Causes of blindness and visual impairment in a population of older Americans: The Salisbury Eye Evaluation Study. *Arch Ophthalmol*. 2000;118:819-25.

16. Tielsch JM, Sommer A, Katz J, Royall RM, Quigley HA, Javitt J. Racial variations in the prevalence of primary open-angle glaucoma. The Baltimore Eye Survey. *Jama*. 1991;266:369-374.
17. Broadway DC, Drance SM, Parfitt CM, Mikelberg FS. The ability of scanning laser ophthalmoscopy to identify various glaucomatous optic disk appearances. *Am J Ophthalmol*. 1998;125:593-604.
18. Iester M, Mikelberg FS, Drance SM. The effect of optic disc size on diagnostic precision with the Heidelberg retina tomograph. *Ophthalmology*. 1997;104:545-548.
19. Mardin CY, Horn FK. Influence of optic disc size on the sensitivity of the Heidelberg Retina Tomograph. *Graefes Arch Clin Exp Ophthalmol*. 1998;236:641-645.
20. Medeiros FA, Zangwill LM, Bowd C, Sample PA, Weinreb RN. Influence of disease severity and optic disc size on the diagnostic performance of imaging instruments in glaucoma. *Invest Ophthalmol Vis Sci*. 2006;47:1008-1015.
21. Rosenberg NA, Pritchard JK, Weber JL, et al. Genetic structure of human populations. *Science*. 2002;298:2381-2385.