Nerve Fibre Bundle Shift and Glaucoma Misdiagnosis Risk in a Small Nonconsecutive Series of African American Patients

Alex Hynes, OD FAAO,
Assistant Professor

Alaina Short, OD FAAO,
Assistant Professor

Nova Southeastern University, College of Optometry, Fort Lauderdale, Florida, United States

Abstract

Purpose

To share preliminary observations of how some African American patients may have anatomically shifted superior-temporal and inferior-temporal retinal nerve fibre layer (RNFL) bundle peaks compared with the Cirrus Optical Coherence Tomography (OCT) normative database majority. This discrepancy may yield false-positive thinning on RNFL deviation maps, thereby appearing glaucomatous. Three nonconsecutive African American patients with mild myopia (<2.12 dioptre spherical equivalent) were selected to illustrate this bundle shift. Despite the very limited sample size, our case study may spur more rigorous study with larger cohorts of diverse patients.

Observations

Three patients of African descent presented with cup-to-disc ratios of 0.6 or higher and were flagged with symmetrical bilateral RNFL thinning in superior-temporal and/or inferior-temporal RNFL sectors compared with the Cirrus OCT normative database. All six eyes had discs without significant peripapillary atrophy nor tilt, either of which could be associated with non-glaucomatous OCT defects. Thinning on RNFL deviation maps in each patient showed symmetrical wedge defects toward the superior-temporal and inferior-temporal vulnerability zones of the disc. However, each patient demonstrated robust macular ganglion cell thicknesses and had automated fields inconsistent with glaucoma. On closer inspection, the principal superior-temporal and inferior-temporal RNFL bundle peaks in these patients appeared shifted more vertically (or nasally).

Conclusions

The RNFL anatomy of African American patients may differ from the OCT normative database majority. Each patient in our series had high-risk, yet symmetrically appearing superior-temporal and/or inferior-temporal RNFL thinning, largely attributable to anatomical shifting of these bundle peaks. Ignoring bundle shift has the potential to result in improper glaucoma diagnoses. This is particularly relevant as clinicians are trained to pay particular attention to the superior-temporal and inferior-temporal RNFL sectors as known vulnerabilities to early glaucoma. Correlation of RNFL findings with macular ganglion cell analysis and fields with careful optic nerve assessment is therefore important.

Keywords

retinal nerve fibre layer (RNFL), optical coherence tomography (OCT), normative database, African American, glaucoma suspect, glaucoma

While identification of glaucomatous optic neuropathy in advanced cases is often clinically apparent on fundoscopy, distinguishing between preperimetric or mild (single hemifield of loss without central defects and mean deviation better than 6 dB) stage glaucoma and glaucoma suspects can be more difficult.[1] To aid in diagnosis, optical coherence tomography (OCT) imaging use has increased significantly in recent years.[2] OCT compares a patient's retinal nerve fibre layer (RNFL) and ganglion cell thickness against an age-matched normative database. People with glaucoma should theoretically have RNFL sector(s) flagged as thin relative to the healthy normative database population. Sectors between the first and fifth percentiles are coded as yellow and those below the first percentile are coded as red.[3] Sectors in preperimetric glaucoma or mild glaucoma that are flagged relative to the normative population with the highest frequency are where the principal superior-temporal and inferior-temporal RNFL bundles enter the disc after arcing around the macula.[4,5] These typically equate to the 6 and 7, and 11 and 12 clock hour locations in the right eye and the 1 and 12, and 5 and 6 in the left eye.[5-8] Looking for thinning in these sectors relative to the normative database can be useful when progression analysis is not yet available for a patient.

Unfortunately, the OCT imaging of individuals possessing normal anatomical variation not well represented in the normative data can be flagged despite the absence of true disease.[4] Hood et al. point out these anatomical variations in healthy eyes can produce apparent abnormalities in the location of the arcuate nerve fibre bundles, which can lead to false-positives.[4] To lower the risk of these false-positives leading to misdiagnoses, research by Mwanza et al.[1] and Hood et al.[4] both advocate for combining multiple individual parameters and test results to improve diagnostic sensitivity and specificity. Hood et al. advocate for using two primary rules or features for diagnosing glaucoma based off OCT deviation maps. The first glaucomatous feature is an arcuate or wedge-like defect (shown as red or yellow on the deviation map) extending toward the superior, inferior, or both disc region(s).[4] These defects are most likely to be on the temporal half of these disc regions, paralleling the high-risk clock hour sectors of the inferior and superior vulnerability zones.[5] The second glaucomatous feature is when the ganglion cell and RNFL deviation maps are simultaneously inspected and the abnormal flagged region crosses the vertical midline, preferably in an arcuate pattern.[4] Ganglion cell defects associated with glaucoma often appear in an arcuate to crescent shape and correlate topographically with peripapillary RNFL defects in the same hemisphere.[4-6]

The three patients presented in this case series were assessed at an urban teaching clinic. No identifiable health information is included in this case report. All patients were African American and had mild myopia (<2.12 D spherical equivalent). All six eyes had intraocular pressures (IOP) less than 22 mmHg without any IOP-lowering therapies or procedures. No anterior segment nor gonioscopy findings were indicative of secondary glaucoma. All six eyes had discs without significant peripapillary atrophy nor disc tilt that could be associated with nonglaucomatous OCT defects.[9]

OCT images were acquired with a Zeiss Cirrus, while automated 24-2 threshold visual fields were conducted on a Zeiss Humphrey Field Analyzer. To illustrate the importance of recognizing the limitations of current normative database comparisons in glaucoma diagnosis, the RNFLs of these patients

Suggested citation

Hynes A, Short A. Nerve fibre bundle shift and glaucoma misdiagnosis risk in a small nonconsecutive series of African American patients. *Can J Optom.* 2025;88(1):45-58. https://doi.org/10.15353/cjo.v88i1.6569

Table 1. Ocular findings in Patients 1 through 3

Patient	Patient 1	Patient 2	Patient 3
Refraction/BCVA	-1.25-0.75 x 70 20/20 OD -1.25-1.25 x 70 20/20 OS	-1.50 SPH 20/20 OD -1.75 SPH 20/20 OS	-1.25 SPH 20/20 OD -1.50 SPH 20/20 OS
Lens status	1+ NS OU	1+ NS OU	1+ NS OD; PCIOL OS
Maximum untreated Goldmann IOP	21 mmHg OD 21 mmHg OS	19 mmHg OD 18 mmHg OS	21 mmHg OD 21 mmHg OS
Central corneal thickness	536 μm OD 532 μm OS	527 μm OD 522 μm OS	541 μm OD 543 μm OS
Clinical cup-to-disc ratio	0.6 round OU	0.65 round OD 0.7V/0.6H OS	0.65 round OD 0.50 round OS
RNFL thinning on OCT deviation maps	ST & IT OU	ST OU	IT greater than ST OU
High-risk RNFL clock hour sectors flagged	11 & 7 OD; 1 & 5 OS	1 OD; 11 OS	7 OD and 1 & 5 OS

The following applies to all three cases.

Anterior segment findings: No corneal endothelial pigmentation nor iris transillumination defects OU.

Gonioscopy: Open to CBB 360 with 2+ pigmentation of PTM OU.

GCA (Cirrus): Healthy and robust; no thinning relative to normative database OU.

24-2 visual field: No glaucomatous defects OU.

Abbreviations: BCVA, best corrected visual acuity; CBB, ciliary body band; GCA, ganglion cell complex; H, horizontal; IOP, Intraocular pressure; IT, inferior-temporal; NS, nuclear sclerosis; OCT, optical coherence tomography; OD, right eye; OS, left eye; OU, both eyes; PCIOL, posterior chamber intraocular lens; PTM, posterior trabecular meshwork; RNFL, retinal nerve fibre layer; SPH, spherical; ST, superior-temporal; V, vertical.

were flagged in high-risk areas, satisfying Hood et al.'s first rule. As multiple studies have demonstrated that RNFL scans with greater signal strength measure higher RNFL thickness, we did our best to only include RNFL scans with very high strength (at least 9/10 strength). This was important for our purposes because signal strength reduction is related to reduced RNFL thickness, which may be incorrectly diagnosed as glaucomatous defects.[10]

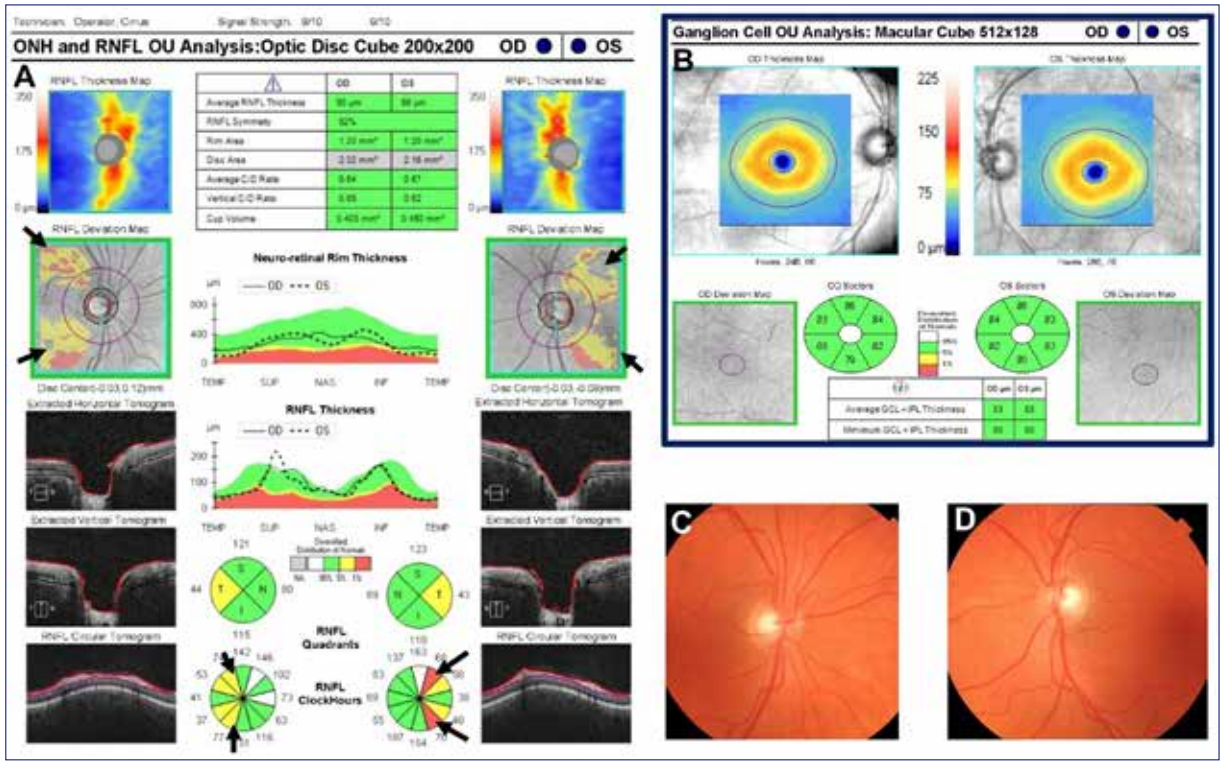
Case Series

The findings in all three patients are summarized in Table 1.

Patient 1

A 59-year-old African American male with no family history of glaucoma presented for a comprehensive eye exam. Best corrected visual acuities measured 20/20 in each eye with the following refractions: -1.25-0.75 x 070 OD and -1.25-1.25 x 070 OS. Goldmann tonometry measured 21 mmHg in each eye at 9 a.m. Central corneal thickness measured 536 μm OD and 532 μm OS. Gonioscopy revealed a flat iris approach with angles open 360° to ciliary body with 2+ pigmentation of the posterior trabecular meshwork of both eyes. There was no peripheral anterior synechiae, neovascularization, nor angle recession noted in either eye. Pupils were equal, round, and reactive without a relative afferent pupillary defect. Slit lamp exam showed no endothelial pigmentation nor iris transillumination defects; 1+ nuclear sclerosis was observed bilaterally. Dilated fundus exam showed stereoscopic cup-to-disc ratios of 0.6 round in each eye with no

Figure 1. Patient 1



(A) Zeiss Cirrus optic nerve head and RNFL analysis of right and left eyes. Black arrows highlight RNFL thinning on deviation maps and RNFL clock hour sectors relative to the normative database.

(B) Cirrus ganglion cell analysis of right and left eyes.

(C) Fundus photo of right eye.

(D) Fundus photo of left eye.

Note the superior-temporal and inferior-temporal major blood vessel branches in C and D exit the disc more superiorly and inferiorly, respectively.

Abbreviation: RNFL, retinal nerve fibre layer.

focal rim notching. The posterior pole and peripheral retina were healthy and otherwise unremarkable (Figures 1C and 1D).

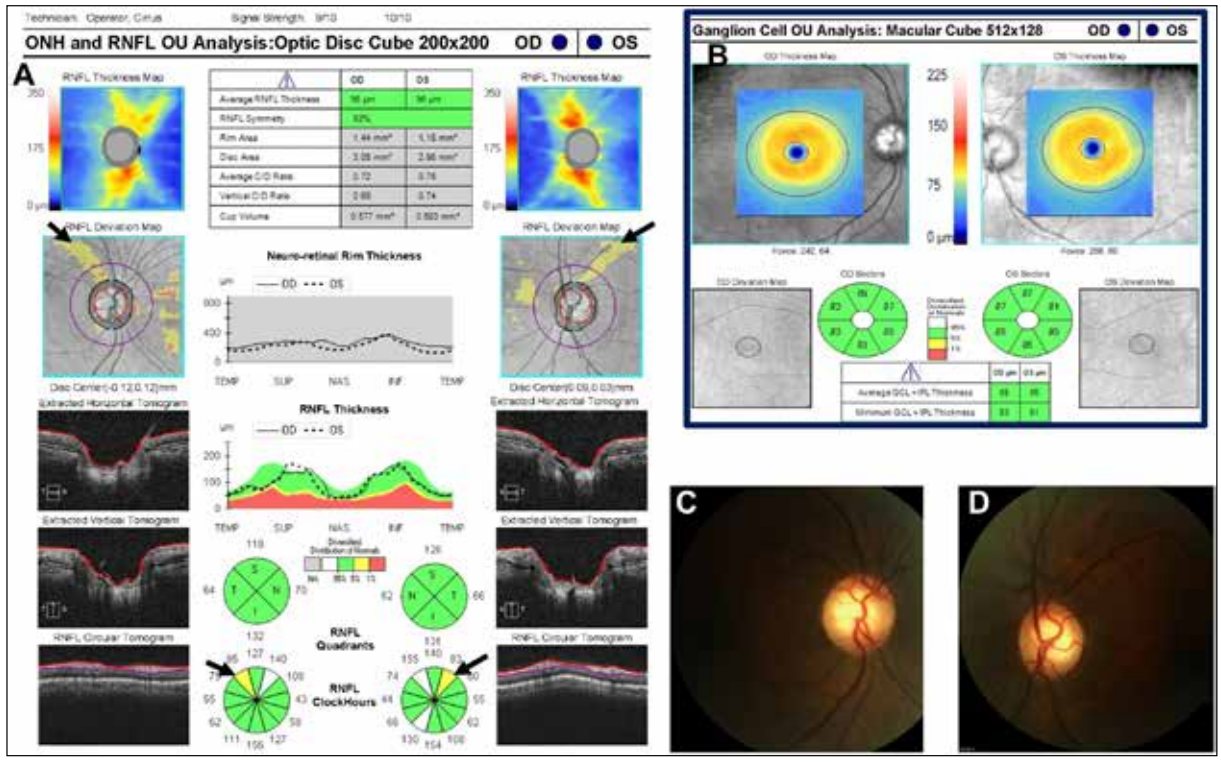
Cirrus OCT showed bilateral superior-temporal and inferior-temporal arcuate defects on the RNFL deviation map (Figure 1A). The following high glaucoma risk clock hours were flagged relative to the normative database: 7 and 11 OD and 1 and 5 OS. Cirrus ganglion cell analysis did not show any ganglion cell-inner plexiform layer (GCIPL) thinning relative to the normative database on deviation map (Figure 1B). Automated visual fields did not show any glaucomatous defects in either eye.

A discussion of the importance of long-term glaucoma risk monitoring with the patient occurred. He agreed to return in a year for a comprehensive exam with the possibility of repeat imaging within two years.

Patient 2

A 63-year-old African American male with a non–first-degree family history of glaucoma (maternal

Figure 2. Patient 2



(A) Zeiss Cirrus optic nerve head and RNFL analysis of right and left eyes. Black arrows highlight RNFL thinning on deviation maps and RNFL clock hour sectors relative to the normative database.

(B) Cirrus ganglion cell analysis of right and left eyes.

(C) Fundus photo of right eye.

(D) Fundus photo of left eye.

Abbreviation: RNFL, retinal nerve fibre layer.

grandmother) presented for a comprehensive eye exam. Best corrected visual acuities measured 20/20 in each eye with the following refractions: -1.50 D OD and -1.75 D OS. Goldmann measured 19 mmHg OD and 18 mmHg OS at 9 a.m. Central corneal thickness measured 527 μm OD and 522 μm OS. Gonioscopy revealed a flat iris approach with angles open 360° to ciliary body with 2+ pigmentation of the posterior trabecular meshwork of both eyes. There was no peripheral anterior synechiae, neovascularization, nor angle recession noted in either eye. Pupils were equal, round, and reactive without a relative afferent pupillary defect. Slit lamp exam showed no endothelial pigmentation nor iris transillumination defects; 1+ nuclear sclerosis was observed bilaterally. Dilated fundus exam showed stereoscopic cup-to-disc ratios of 0.65 round in the right eye and 0.7 vertically/0.6 horizontally in the left eye with no focal rim notching bilaterally. The posterior pole and peripheral retina were unremarkable in both eyes (Figures 2C and 2D).

Cirrus OCT showed bilateral superior-temporal arcuate defects on the RNFL deviation map (Figure 2A). The following high-risk clock hours were flagged relative to the normative database: 1 OD and 11 OS. Ganglion cell analysis did not show any thinning relative to the deviation map (Figure 2B). Automated visual fields did not show any glaucomatous defects in either eye (shown later in Figures 5D and 5E).

A discussion of the importance of long-term glaucoma risk monitoring with the patient occurred. He agreed to return in a year for a comprehensive exam with the possibility of repeat imaging within two years.

Patient 3

A 55-year-old African American female with a first-degree family history of glaucoma (mother) presented for their annual comprehensive eye exam. This patient was established and had been monitored closely with visual fields for 10 years (by a recently retired provider) because of cup-to-disc asymmetry. Maximum untreated IOP was 21 mmHg OD and 21 mmHg OS. Central corneal thickness had previously measured 541 μm OD and 543 μm OS. Gonioscopy had revealed a flat iris approach with angles open 360° to ciliary body with 1-2+ pigmentation of the posterior trabecular meshwork of both eyes. There was no peripheral anterior synechiae, neovascularization, nor angle recession noted in either eye. Automated visual fields had been stable on guided progression analysis in each eye (Figures 3C to 3E).

Best corrected visual acuity measured 20/20 with the following refractions: -1.25 D OD and -1.50 D OS. Pupils were equal, round, and reactive without a relative afferent pupillary defect. Slit lamp exam showed no endothelial pigmentation nor iris transillumination defects; 1+ nuclear sclerosis was observed in the right eye, and a clear posterior chamber intraocular implant was observed in the left eye. Goldmann measured 16 mmHg bilaterally at 10:30 a.m. Dilated fundus exam showed stereoscopic cup-to-disc ratios of 0.65 round OD and 0.5 round OS. Baseline OCT showed bilateral thinning relative to the normative database inferior-temporally more so than superior-temporally (Figure 3A). Ganglion cell thickness was not flagged and robust in each eye (Figure 3B). Repeat automated visual fields were clean; no evidence of progression was noted in either eye (Figures 3D and 3F).

A discussion of the importance of long-term glaucoma risk monitoring with the patient occurred. She agreed to return in a year for a comprehensive exam with the possibility of repeat imaging within two years if exam findings suggested glaucomatous changes.

Discussion

Evidence Against Glaucoma Diagnosis in our Series

All three patients exhibited thinning on the RNFL deviation map as well as clock hour sectors in superior-temporal or inferior-temporal locations, which are vulnerable in preperimetric glaucoma or mild (single hemifield of loss without central defects) stage glaucoma. All six eyes thereby meet the criteria of Hood et al.'s first rule for glaucoma diagnosis via OCT (Figures 1A, 2B, and 3A).

However, we believe these patients do not show sufficient evidence for preperimetric glaucoma or mild stage glaucoma for three reasons.

First, there is no macular ganglion cell thinning on Cirrus GCIPL maps. It follows that there is no thinning on deviation maps that crosses the vertical midline (Hood et al.'s second rule), nor is there GCIPL thinning that correlates with the trajectory of RNFL thinning (Figures 1B, 2B, and 3B).[4]

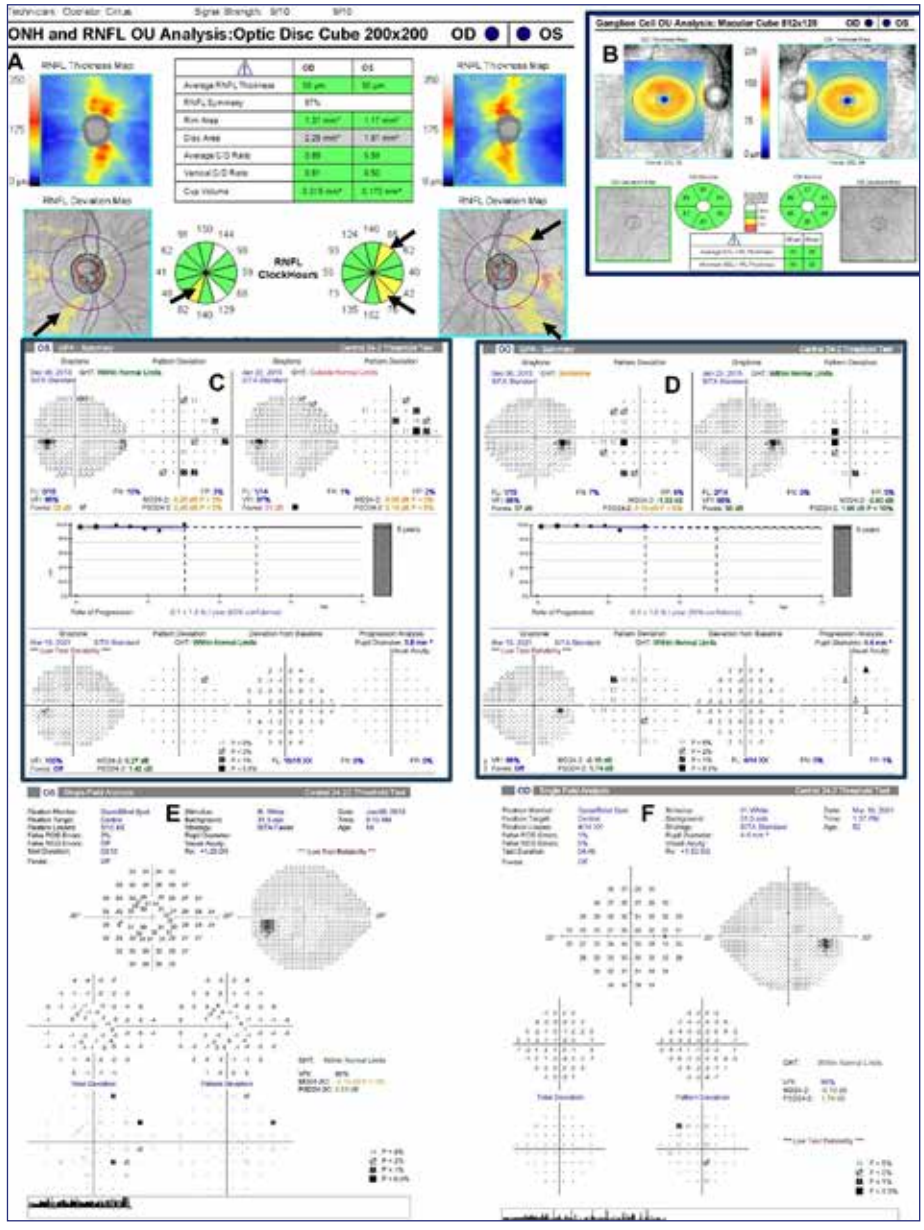
Second, glaucoma usually onsets (at least somewhat) asymmetrically between both eyes.[12] Therefore, the symmetry of the RNFL thinning between the right and left eyes in each patient also suggests a more likely anatomical discrepancy compared with the normative database.[11]

Third, clinically healthy superior and inferior neuroretinal rims with focal notching, circumlinear bearing, or bayonetting of vessels would be expected in glaucoma. Robust neuroretinal rims were seen in all three patients including as shown on the fundus photos of Patients 1 and 2 (Figures 1C, D; 2C, and 2D).[11] While we do not have fundus photos to attach for Patient 3, the Humphrey automated visual field guided progression analysis shows no evidence of progressive field loss over many years (Figures 3C to 3F).

Race: Anatomical Considerations and Database Limitations

Disc area tends to be larger in people of African descent, compared with European descent. However, even after adjusting for the effect of disc area, Knight et al. noted statistically significant differences between races for all Cirrus-measured optic nerve head and RNFL parameters (except for rim

Figure 3. Patient 3



(A) Zeiss Cirrus optic nerve head and RNFL analysis of right and left eyes. Black arrows highlight RNFL thinning on deviation maps and RNFL clock hour sectors relative to the normative database.

(B) Cirrus ganglion cell analysis of right and left eyes.

(C) Zeiss Humphrey GPA summary of left eye showing stability on trend and event-based analysis.

(D) Zeiss Humphrey single field analysis of left eye showing GHT within normal limits and no glaucomatous defects nor progression from baselines.

(E) Zeiss Humphrey GPA summary of right eye showing stability on trend and event-based analysis.

(F) Zeiss Humphrey single field analysis of right eye showing GHT within normal limits and no glaucomatous defects nor progression from baselines.

Abbreviations: GPA, guided progression analysis; GHT, glaucoma hemifield test; RNFL, retinal nerve fibre layer.

area).[13] The same was true for Girkin et al., who found that residual optic disc structural differences still persisted following adjustment of disc area size via confocal scanning laser ophthalmoscopy.[14]

These anatomical differences point to the importance of considering that utilizing normative database colour codes in Black patients may result in glaucoma over-diagnosis in some and under-diagnosis in others.[3] Commercially available OCT devices include only a minority of patients of African descent in their normative database.[15] For example, the Zeiss Cirrus database of 282 healthy subjects is made up of only 18% Black patients.[3] As a result of these databases' limitations, it is unsurprising that both KhalafAllah et al.[16] and Moghimi et al.[17] separately reported that RNFL thickness in Black patients has lower diagnostic performance in glaucoma compared with patients of European descent. These findings were found to be consistent on the Spectralis (Heidelberg) and Cirrus (Zeiss) per KhalafAllah et al.[16] as well as the Avanti (Optovue) per Moghimi et al.[17] This is unfortunate as glaucoma disproportionately impacts individuals of African ancestry; both in incidence and risk of resulting blindness.[18] Black patients may also develop glaucoma earlier in life.[17]

Anatomic variation with race as it relates to the Cirrus normative database is supported by studies completed by Addis et al.[3] and Nousome et al.[19] For example, we noted from Addis et al.'s data that 8.2% of African American eyes had a temporal quadrant flagged, while only 1.3% had a nasal quadrant flagged by Cirrus OCT.[3] In a study of minority populations under-represented in the Cirrus normative database, Nousome et al. reviewed high-quality Cirrus data from healthy patients. This participant group included 2,843 Chinese Americans, 1,979 Mexican Americans, and 1,311 African Americans.

Bundle Shift Illustration

The diversity among participants coupled with the large sample size allowed us to draw the following conclusions about RNFL bundle distributions from their RNFL thickness plots. First, Chinese Americans had statistically significant greater overall RNFL thicknesses than African Americans and Mexican Americans. The next three points are very important to our series' preliminary observations.

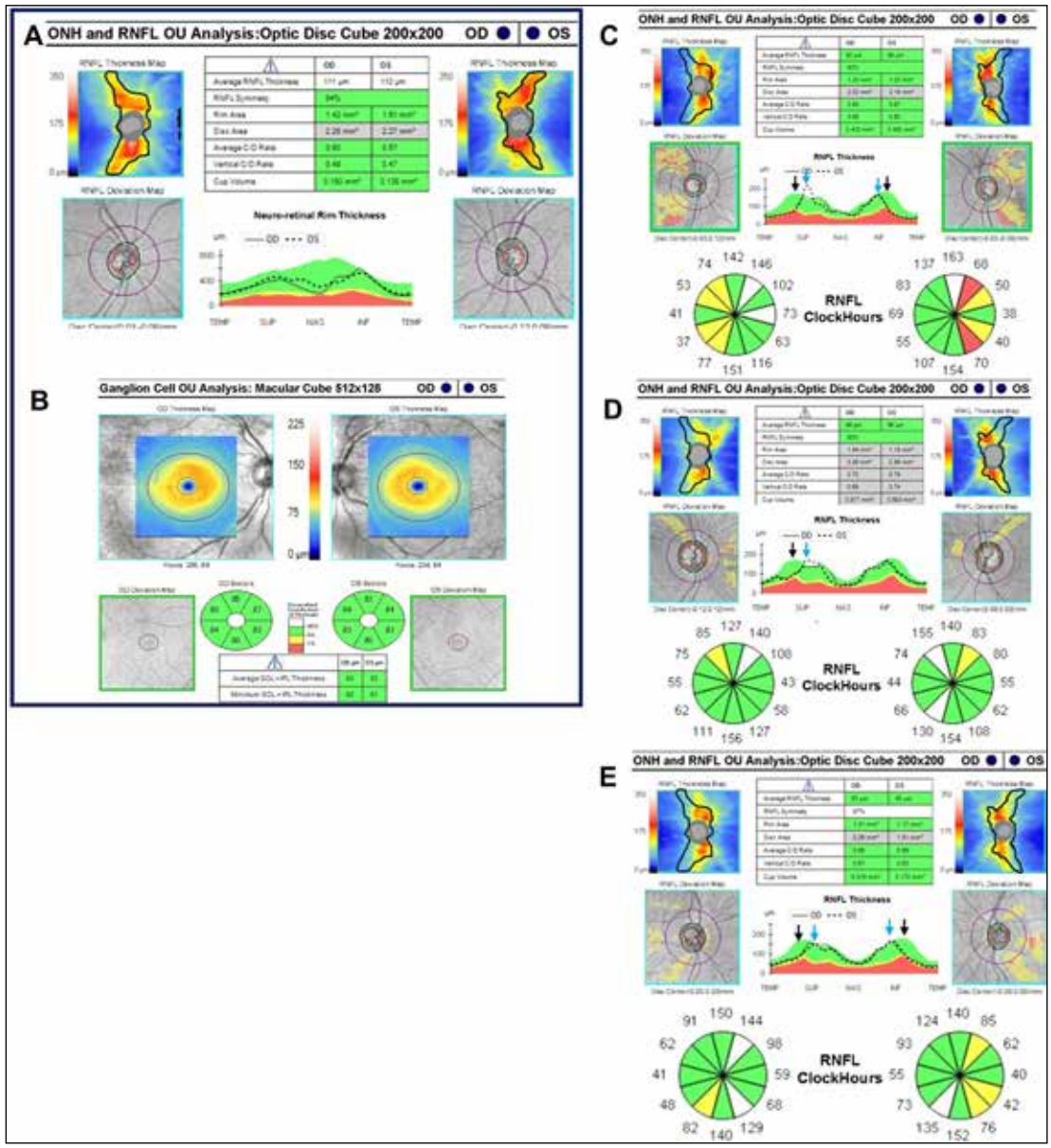
- African Americans had statistically significant thinner temporal quadrants than Mexican Americans (and even more so Chinese Americans).
- African Americans had greater RNFL thickness than Mexican Americans at superior-nasal and inferior-nasal clock hour sectors.
- African Americans had nonstatistically significantly greater RNFL thickness than Chinese Americans at 12 o'clock.[19]

The separate studies by Addis et al.[3] and Nousome et al.[19] are consistent with our preliminary observations that the principal superior-temporal and inferior-temporal arcuate bundle peaks in Black patients commonly enter the disc more vertically (or less temporally), resulting in a greater interarterial angle compared with other races (including Europeans and East-Asians). If further validated, the possible implication of our case series is that existing RNFL thicknesses coded by Cirrus OCT are likely to over-diagnose peripapillary thinning in sectors in or adjacent to the temporal quadrant in Black patients. These adjacent sectors include the superior-temporal and inferior-temporal areas commonly associated with preperimetric, mild stage glaucomatous thinning, or both.[5]

To illustrate our bundle shift hypothesis, we outlined the peak RNFL thickness bundles of one of the author's RNFL thickness maps. This author is of European descent, has healthy appearing discs, roughly average axial lengths, and has an RNFL and ganglion cell analysis that was not flagged as thin anywhere relative to the Cirrus database (Figures 4A and 4B). The thickest points (warmest colours) of this author's RNFL bundles (or wings) in each eye were outlined to serve as a demonstration of an expected RNFL thickness profile relative to the normative database.

The outline was then copied and pasted onto the corresponding eyes of Patients 1 through 3 (Figures 4C to 4E). In Figures 4C to 4E, areas in the outline that do not contain the expected warm colours of the principal superior-temporal and inferior-temporal bundle peaks appear flagged on the underlying deviation maps. This helps illustrate that the eyes of the African American patients in

Figure 4. Vertical bundle shift relative to the expected distribution



(A) Cirrus RNFL analysis of one of the authors (European descent) representing an average RNFL bundle peak distribution and location. The principle superior-temporal and inferior-temporal RNFL bundle peaks or wings were outlined in navy-blue.

(B) Cirrus ganglion cell analysis of the author showing a robust ganglion cell complex within normal limits.

(C, D, and E) The navy-blue outline from (A) is pasted on to the corresponding eyes' RNFL thickness maps in Patient 1 (C), Patient 2 (D) and Patient 3 (E). The outline illustrates how the African American patients' superior-temporal or inferior-temporal RNFL bundle peaks are shifted more vertically (nasally) relative to the author's, resulting in flagging on the underlying deviation maps and RNFL clock hours. On the temporal-superior-nasal-inferior-temporal RNFL thickness plot, the principle RNFL peaks of the normative database (black arrows) are shown to be more temporal relative to the superior peaks of the Black patients (C), (D), and (E) as well as the inferior peaks (D) and (E).

Note that all three patients' eyes in (C), (D), and (E) have at least one superior-nasal or inferior-nasal RNFL sector above the 95th percentile of thickness relative to the database.

Abbreviation: RNFL, retinal nerve fibre layer.

this case series had principal bundle peaks that extended more superior-nasally and inferior-nasally compared with the author's eyes and the normative database by extension. In other words, the superior-temporal and inferior-temporal peaks of these three Black patients appeared more verticalized.

These principal RNFL peaks roughly coincide with the locations of the major superior-temporal and inferior-temporal vessel branches at the optic disc. While these vessels do contribute some thickness to the RNFL measurement, they are thought to form along the points of highest axonal distribution during development.[20] If blood vessel distribution, and by extension RNFL bundles, are located at a different retinal position than expected by the OCT machine, retinal locations in healthy eyes that are thinner due to anatomy alone might be flagged as abnormal.[21] This has already been established in axial myopes where disc vessels and RNFL bundle peaks commonly emerge from the disc more temporally. This thereby yields false-positive thinning in nontemporal sectors in healthy eyes.[20-22]

The African American patients in our series had RNFL bundle shifted in the vertical (or nasal) direction as evidenced by their superior-temporal and inferior-temporal major vessel branches arising from the disc more superiorly and inferiorly. This is seen most prominently in the fundus photos of Patient 1 (Figures 1C and 1D) as well as all three patients' RNFL deviation maps, which helpfully feature blood vessel outlines (Figures 1A, 2A, and 3A). The more verticalized principle bundle peaks may be expected to yield (or compensate) with thicker RNFL in nontemporal sectors. This is shown in Figures 4C to 4E where there is at least one superior-nasal or inferior-nasal nerve fibre layer sector that is above the 95th percentile of thickness relative to the normative database.

Limitations of this Series

To our knowledge, this possible anatomical difference in peak bundle location in Black patients relative to the white majority normative database has not been specifically addressed or questioned in the literature yet. Because this is a small nonrandomly selected series, the true extent of this bundle shift in this population subset is unknown and requires further study. Our series of three nonconsecutively selected African American patients is simply too small to draw evidence-based conclusions. Further, even if our hypothesis is confirmed for African Americans, further study is required for other populations of African descent.

Because our patients all had low myopia (in which case, if anything a mild temporal bundle shift may be expected), we suspect the vertical or nasal bundle shift in our series is not related to refractive error. Nonetheless, future studies should rigorously account for axial length and refractive error. We did not measure axial length in our patients.

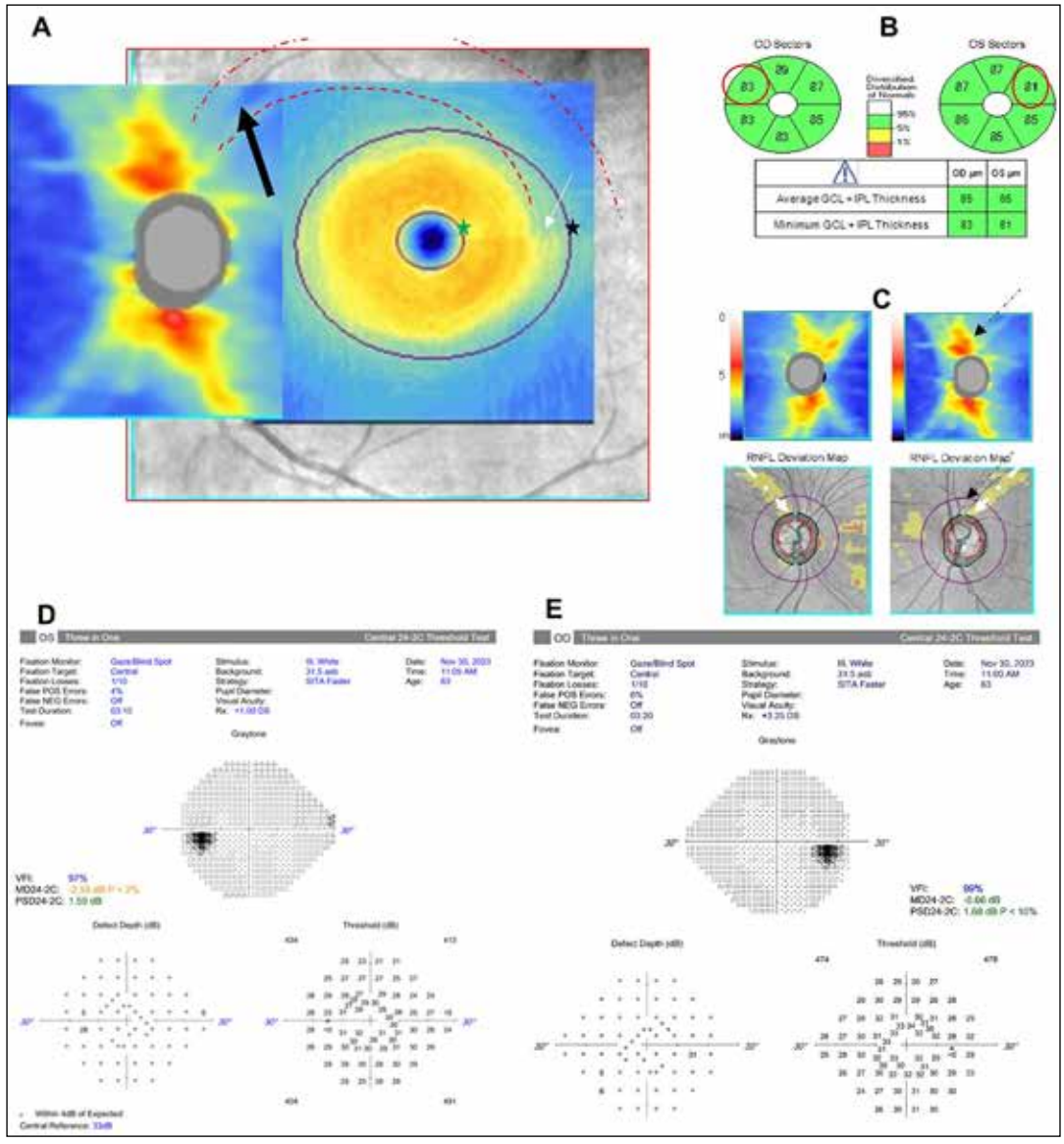
The fields for Patient 3 were also of slightly reduced reliability due to fixation losses (Figure 3). A high rate of unreliability, despite well-trained technician instruction, is an issue in visual field testing.[23]

Lack of widefield RNFL and ganglion cell imaging is another limitation. Kim and Park have shown that the superior-temporal vulnerability zone of the disc is not well represented by the traditional spectral domain 6 x 6 mm–sized RNFL and macular ganglion cell maps.[24] Conversely, 12 x 9 mm swept source maps can better show RNFL wedge defects and correlating ganglion cell loss, particularly in the superior hemisphere.

We note the superior hemisphere because Hood et al. showed that much of the superior macula within the 6 x 6 mm–sized macular ganglion cell map inserts within the less vulnerable temporal disc quadrant (due to anatomy and in part fovea-disc angle).[25] This means the superior GCIPL on traditional-sized maps may be less likely to show significant loss in early glaucoma with superior RNFL loss compared with the inferior GCIPL with equivalent inferior RNFL loss. This may be particularly relevant and require further examination of the left eye of Patient 2 in our series (originally shown in Figure 2).

Figure 5A further examining Patient 2 shows a possible early superior-temporal RNFL wedge defect (white arrow). If real, the defect is still peripheral (has not yet reached the nerve). The red hashed arrows show that this thinning would likely correlate to a GCIPL trajectory outside the traditional macular GCIPL thickness measures, superiorly. Note that an early, correlating (but so far, incomplete)[26] temporal raphe sign may be forming on the GCIPL thickness

Figure 5. Further evaluation of the left eye in Patient 2



(A) The RNFL thickness map shows a possible early wedge defect (black arrow) on RNFL thickness map. Superimposing the RNFL and GCIPL thickness map shows a possible correlation with unconfirmed early GCIPL loss superior-temporally (red hashed lines). The white arrow shows the possible beginning of a temporal raphe sign. It is not yet formed as it does not (at least yet) stretch halfway from the outer annulus (black star) toward the inner annulus (green star).

(B) While still above the fifth percentile in terms of colouring, the superior-temporal GCIPL sector OS is a little (2 μm) thinner than the corresponding sector of the right eye.

(C) The angle of this wedge defect (black arrowhead) does not correlate with the exact location of the symmetrical RNFL deviation map thinning relative to the normative database (white arrows).

(D) Reliable 24-2C Sita Faster HVF does not show any correlating inferior-nasal loss nor any other overt glaucomatous field defects.

(E) Reliable 24-2C Sita Faster HVF of the contralateral right eye again showing no overt glaucomatous defects.

Abbreviations: C, central; GCIPL, ganglion cell-inner plexiform layer thickness; HVF, Humphrey Visual Field; RNFL, retinal nerve fibre layer; μm, microns.

map. The superior-temporal GCIPL sector of the left eye is also thinner than the corresponding sector of the right eye (Figures 5A and 5B). Compared with the right eye (1.44 mm^2), the OCT measured rim area is also thinner on the left (1.18 mm^2) (Figure 2A). Thus, it would have been useful to have acquired a PanoMap printout, a 12 x 9 mm swept source wide field RNFL/ganglion cell thickness scan, or both in this case.[24] While this eye shows the most compelling evidence for possible preperimetric glaucoma in this series, note how Figure 5C shows this possible early peripheral wedge defect on RNFL thickness map does not exactly correlate with the location of the symmetrical superior-temporal deviation map thinning in both eyes due to vertically shifted RNFL bundles (the theme of the paper). Again, reassuringly, reliable fields were obtained for Patient 2 without evidence of early glaucomatous field loss (Figures 5D and 5E). This can also be monitored over time. When using nonwidefield imaging, less overlap is expected between potential macular GCIPL defects and more vertically oriented RNFL bundles. Further study with of this patient population with widefield swept source OCT is thus important.

A final limitation of this series is the lack of serial analysis over time. This would ultimately allow confirmation whether these eyes, such as Patient 2's left eye, are indeed glaucomatous or just physiological cupping with normal anatomical nerve fibre layer variants relative to the normative database. Note that the final verdict may be a combination for some of these eyes, namely the left eye in Patient 2 with the symmetrical RNFL deviation map thinning likely not correlate to the possible superior-temporal RNFL wedge defect and GCIPL loss (Figures 5A to 5C).

Clinical Implications and Future Directions

This discussion regarding variation in RNFL anatomy and parameters has triggered interest in race-specific normative databases.[14-15] Per Realini et al., consideration of ethnic origin in construction of RNFL normative limits may be helpful for diagnosis and management of glaucoma.[27] However, they also note that it is "unclear how best to define ethnic groups in practical and useful ways that support everyday clinical practice."[27] For example, does "African descent" encompass Africans, African Caribbeans, North Africans, African Americans, and the increasing number of multiracial patients with some African descent?[27] These questions illustrate the complexity in appropriately addressing this problem.

One possible way to improve generalizability may be to expand a given normative database with improved ethnic sampling. Nakayama et al. note that diversity is critical for promoting generalizability of results.[15] Further, it would be more equitable and accessible to not have to upgrade to an expanded database (more relevant to a given patient) at additional cost.[16]

For now, clinicians should be aware that normative databases have limitations concerning numbers of healthy anatomical variants due in part to poorly represented patients with significant refractive errors, tilted discs, and non-European ethnicities (particularly African descendants as discussed). This may put these patients at risk of false-positive red disease.[11] It follows that utilization of ganglion cell analysis, visual fields, and accurate clinical inspection of the optic nerve rim tissue are all crucial.[4,5,11] Digital fundus photos also offer a static opportunity to rule out focal neuroretinal rim thinning, circumlinear vessel bearing, vessel bayoneting, and RNFL wedge defects suggestive of true glaucoma.[12] These photos can also be compared over time, even if a different machine is used. These best practices for glaucoma diagnosis are even more vital in patients of African descent given the prevalence of physiological cupping that can easily be misdiagnosed as glaucoma if all the clinical and imaging information is not comprehensively utilized.[14,18]

Conclusion

As preperimetric glaucoma detection becomes more common with the use of OCT, clinicians may need to recognize that the nerve fibre anatomy of some Black patients potentially differs relative to the normative database majority. All three of the selected African American patients in our series had high-risk appearing superior-temporal and/or inferior-temporal, thinning on nerve fibre deviation maps attributable to shifting of the superior-temporal and inferior-temporal bundle peaks. This resulted in flagging of sectors known to be vulnerable in early

glaucoma. This bundle shift may increase the likelihood of glaucoma misdiagnosis. Because this is a small, nonrandomized case series, the extent of this bundle shift in the Black population is unknown and requires further study.

For now, caution against an automatic glaucoma diagnosis may be recommended if a patient of African descent with intraocular pressure of less than 22 mmHg displays roughly symmetrical superior-temporal or inferior-temporal nerve fibre thinning on deviation maps in the absence of correlating ganglion cell thinning, visual field defects, and focal rim thinning or notching on fundoscopy. The RNFL temporal-superior-nasal-inferior-temporal and nasal-superior-temporal-inferior-nasal and blood vessel trajectory out of the nerve may be qualitatively inspected to evaluate if the patient's RNFL bundle profile may be anatomically shifted compared with the normative database average. Whenever unsure, we recommend serial monitoring over time to rule out progressive thinning. Swept source widefield RNFL and ganglion cell OCT mapping may allow earlier and more accurate diagnosis as OCT becomes more commonly utilized while well-trained fundoscopic examination of the nerve head also remains vital.

Disclosures

Contributors: All authors contributed to the conception or design of the work and the acquisition, analysis, or interpretation of the data. All authors were involved in drafting and commenting on the paper and have approved the final version.

Funding: This study did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Competing interests: All authors have completed the International Committee of Medical Journal Editors uniform disclosure form and declare no conflicts of interest.

Ethical approval: Ethical approval is not required for this article type. Patients provided informed, written consent to have their images and clinical data discussed in this article.

Artifical Intelligence Statement: The authors confirm no generative AI or AI-assisted technology was used to generate content.

Corresponding author: Alex Hynes
hynesa17@gmail.com

References

1. Mwanza JC, Warren JL, Budenz DL. Utility of combining spectral domain optical coherence tomography structural parameters for the diagnosis of early glaucoma: A mini-review. Eye Vis. 2018 Apr 15;5:9. https://doi.org/10.1186/s40662-018-0101-6
2. Bussel II, Wollstein G, Schuman JS. OCT for glaucoma diagnosis, screening and detection of glaucoma progression. Br J Ophthalmol. 2014;98 Suppl 2:ii15-ii19. https://doi.org/10.1136/bjophthalmol-2013-304326
3. Addis V, Chan L, Chen J, et al. Evaluation of the cirrus high-definition OCT normative database probability codes in a Black American population. Ophthalmol Glaucoma. 2022;5(1):110-118. https://doi.org/10.1016/j.ogla.2021.05.002
4. Hood DC, La Bruna S, Tsamis E, et al. Detecting glaucoma with only OCT: Implications for the clinic, research, screening, and AI development. Prog Retin Eye Res. 2022;90:101052. https://doi.org/10.1016/j.preteyeres.2022.101052
5. Hood DC. Improving our understanding, and detection, of glaucomatous damage: An approach based upon optical coherence tomography (OCT). Prog Retin Eye Res. 2017;57:46-75. https://doi.org/10.1016/j.preteyeres.2016.12.002
6. Tanna AP. Retinal nerve fiber layer analysis in glaucoma. In: Budenz, DL, ed. Atlas of Optical Coherence Tomography for Glaucoma. Springer Cham. 2020: 31-35. https://doi.org/10.1007/978-3-030-46792-0
7. Mwanza JC, Oakley JD, Budenz DL, Anderson DR. Cirrus Optical Coherence Tomography Normative Database Study Group. Ability of cirrus HD-OCT optic nerve head parameters to discriminate normal from glaucomatous eyes. Ophthalmology. 2011;118(2):241-8.e1. https://doi.org/10.1016/j.ophtha.2010.06.036
8. Hwang YH, Kim YY. Glaucoma diagnostic ability of quadrant and clock-hour neuroretinal rim assessment using cirrus HD optical coherence tomography. Invest Ophthalmol Vis Sci.

2012;53(4):2226-2234. https://doi.org/10.1167/iovs.11-8689

9. Chen JJ, Kardon RH. Avoiding clinical misinterpretation and artifacts of optical coherence tomography analysis of the optic nerve, retinal nerve fiber layer, and ganglion cell layer. J Neuroophthalmol. 2016;36(4):417-438. https://doi.org/10.1097/WNO.0000000000000422
10. Hardin JS, Taibbi G, Nelson SC, Chao D, Vizzeri G. Factors affecting cirrus-HD OCT optic disc scan quality: A review with case examples. J Ophthalmol. 2015; 2015:746150. https://doi.org/10.1155/2015/746150
11. Chong GT, Lee RK. Glaucoma versus red disease: Imaging and glaucoma diagnosis. Curr Opin Ophthalmol. 2012;23(2):79-88. https://doi.org/10.1097/ICU.0b013e32834ff431
12. Susanna R Jr, Vessani RM. New findings in the evaluation of the optic disc in glaucoma diagnosis. Curr Opin Ophthalmol. 2007;18(2):122-28. https://doi.org/10.1097/ICU.0b013e328040bfe0
13. Knight OJ, Girkin CA, Budenz DL, Durbin MK, Feuer WJ; Cirrus OCT Normative Database Study Group. Cirrus OCT normative database study group. Effect of race, age, and axial length on optic nerve head parameters and retinal nerve fiber layer thickness measured by Cirrus HD-OCT. Arch Ophthalmol. 2012;130(3):312-318. https://doi.org/10.1001/archopthalmol.2011.1576
14. 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(8):3382-3387. https://doi.org/10.1167/iovs.02-0792
15. Nakayama LF, Zago Ribeiro L, de Oliveira JAE, et al. Fairness and generalizability of OCT normative databases: A comparative analysis. Int J Retina Vitreous. 2023;9(1):48. https://doi.org/10.1186/s40942-023-00459-8
16. KhalafAllah MT, Zangwill LM, Proudfoot J, et al. Racial differences in diagnostic accuracy of retinal nerve fiber layer thickness in primary open-angle glaucoma. Am J Ophthalmol. 2024;259:7-14. https://doi.org/10.1016/j.ajo.2023.10.012
17. Moghimi S, Zangwill LM, Hou H, et al. Comparison of peripapillary capillary density in glaucoma patients of African and European descent. Ophthalmol Glaucoma. 2021;4(1):51-62. https://doi.org/10.1016/j.ogla.2020.07.005
18. Girkin CA. Differences in optic nerve structure between individuals of predominantly African and European ancestry: Implications for disease detection and pathogenesis. Clin Ophthalmol. 2008;2(1):65-69. https://doi.org/10.2147/opth.s1628
19. 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. 2021;128(7):1005-1015. https://doi.org/10.1016/j.ophtha.2020.11.015
20. Hood DC, Fortune B, Arthur SN, et al. Blood vessel contributions to retinal nerve fiber layer thickness profiles measured with optical coherence tomography. J Glaucoma. 2008;17(7):519-528. https://doi.org/10.1097/IJG.0b013e3181629a02
21. Wang M, Jin Q, Wang H, et al. The interrelationship between refractive error, blood vessel anatomy, and glaucomatous visual field loss. Transl Vis Sci Technol. 2018;7(1):4. https://doi.org/10.1167/tvst.7.1.4
22. Leung CK, Yu M, Weinreb RN, et al. Retinal nerve fiber layer imaging with spectral-domain optical coherence tomography: A prospective analysis of age-related loss. Ophthalmology. 2012;119(4):731-737. https://doi.org/10.1016/j.ophtha.2011.10.010
23. Mendieta N, Suárez J, Barriga N, Herrero R, Barrios B, Guarro M. How do patients feel about visual field testing? Analysis of subjective perception of standard automated perimetry. Semin Ophthalmol. 2021;36(1-2):35-40. https://doi.org/10.1080/08820538.2021.1884270
24. Kim YW, Park KH. Macular parameters For Glaucoma. In: Budenz, DL, ed. Atlas of Optical Coherence Tomography for Glaucoma. Springer Cham. 2020: 77-95. https://doi.org/10.1007/978-3-030-46792-0
25. Hood DC, Raza AS, de Moraes CG, Liebmann JM, Ritch R. Glaucomatous damage of the macula. Prog Retin Eye Res. 2013;32:1-21. https://doi.org/10.1016/j.preteyeres.2012.08.003
26. Lee J, Kim YK, Ha A, et al. Temporal raphe sign for discrimination of glaucoma from optic neuropathy in eyes with macular ganglion cell-inner plexiform layer thinning. Ophthalmology. 2019;126(8):1131-1139. https://doi.org/10.1016/j.ophtha.2018.12.031
27. Realini T, Zangwill LM, Flanagan JG, et al. Normative databases for imaging instrumentation. J Glaucoma. 2015;24(6):480-483. https://doi.org/10.1097/IJG.0000000000000152