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Optical Coherence Tomography Measurement of Macular and Nerve Fiber Layer Thickness in Normal and Glaucomatous Human Eyes

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Abstract

Purpose— To evaluate the hypothesis that macular thickness correlates with the diagnosis of glaucoma.

Design— Cross-sectional study.

Participants— We studied 367 subjects (534 eyes), including 166 eyes of 109 normal subjects, 83 eyes of 58 glaucoma suspects, 196 eyes of 132 early glaucoma patients, and 89 eyes of 68 advanced glaucoma patients.

Methods— We used optical coherence tomography (OCT) to measure macular and nerve fiber layer (NFL) thickness and to analyze their correlation with each other and with glaucoma status. We used both the commercial and prototype OCT units and evaluated correspondence between measurements performed on the same eyes on the same days.

Main Outcome Measure— Macular and NFL thickness as measured by OCT.

Results— All NFL parameters both in prototype and commercial OCT units were statistically significantly different comparing normal subjects and either early or advanced glaucoma ($P < 0.001$). Inner ring, outer ring, and mean macular thickness both in prototype and commercial OCT devices were found to be significantly different between normal subjects and advanced glaucomatous eyes ($P < 0.001$). The outer ring was the only macular parameter that could significantly differentiate between normal and early glaucoma with either the prototype or commercial OCT unit ($P = 0.003$, $P = 0.008$, respectively). The area under the receiver operator characteristic (AROC) curves comparing mean NFL thickness between normal and advanced glaucomatous eyes was 1.00 for both the prototype and commercial OCT devices for eyes scanned on both machines on the same day. The

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AROC comparing mean macular thickness in normal and advanced glaucomatous eyes scanned on both machines on the same day was 0.88 for the prototype OCT device and 0.80 for the commercial OCT.

Conclusions— Both macular and NFL thickness as measured by OCT showed statistically significant correlations with glaucoma, although NFL thickness showed a stronger association than macular thickness. There was good correspondence between findings using both the prototype and commercial OCT units. Macular and NFL thickness measurements made with OCT may have usefulness in the clinical assessment of glaucoma.

Glaucoma is a process in which a loss of retinal ganglion cells (RGCs) results in characteristic optic nerve and visual field abnormalities. Detection of glaucomatous damage is typically through observation of the optic nerve head and retinal nerve fiber layer (NFL) and measurement of visual function with perimetry; however, both perimetry and observation of optic disc changes are subjective examinations that are prone to variability. It is for this reason that objective methods are under development to aid in the early diagnosis of glaucoma and to assist in the detection of disease progression.

Defects in the retinal NFL may be an early sign of glaucoma, preceding optic disc and visual field changes.[1–3] The NFL is composed primarily of RGC axons, neuroglia, and astrocytes. The ganglion cells are arranged in layers of four to six cells in the macula; the ganglion cell layer is only one cell thick outside the macula. The ganglion cells along with the NFL constitute 30% to 35% of macular retinal thickness, although the NFL itself is a major component of total retinal thickness close to the optic nerve head. Loss of macular thickness in glaucoma can be attributed mainly to RGC and NFL atrophy.[4,5] It may be useful, therefore, to assess macular thickness, because Zeimer et al[4,6] hypothesized that macular RGC loss may result in significant retinal thinning. They proposed quantitative detection of glaucomatous damage at the posterior pole by retinal thickness mapping. Glovinsky et al,[7] Frishman et al,[8] Wygnanski et al,[9] and Weber et al[10] demonstrated loss of RGCs in the macula in experimentally glaucomatous monkeys.

Through the use of optical coherence tomography (OCT), an imaging technique that allows high-resolution (approximately 10 μm) cross-sectional imaging of the eye based on the principles of low-coherence interferometry, we are able to evaluate and quantify macular and peripapillary NFL thickness and to analyze the effect of glaucoma in these areas. Because we have significant experience with our prototype OCT device, but only the commercial OCT device is available in the community, we analyzed these parameters with both the prototype and commercial OCT and compared the data obtained with the two devices.

Materials and Methods

A total of 367 subjects (534 eyes) examined between October 1998 and July 2000 at the New England Eye Center, Boston, Massachusetts, were enrolled in this cross-sectional study after informed consent approved by the New England Medical Center Human Investigation Review Committee.

All subjects underwent a thorough ophthalmologic examination. This consisted of the following: medical history (including ocular and family histories), visual acuity, refraction, intraocular pressure (IOP) measurement, Humphrey 24-2 visual field testing, undilated and dilated slit-lamp examination with stereoscopic biomicroscopy of the optic nerve head (ONH) and NFL, and indirect ophthalmoscopy. Subjects had OCT testing of both the macula and peripapillary NFL using the prototype OCT unit on the same day. To compare prototype OCT results with measurements from the commercial OCT unit, a subset of subjects underwent

commercial NFL (95 eyes) and macular (126 eyes) OCT on the same day as their prototype OCT scan.

All test eyes had a best-corrected visual acuity of 20/40 or better. Refractive errors were between +3.00 and −6.75 diopters (D). Eyes were excluded that exhibited signs of retinal disease, opaque media, or when the fundus was not visible. Subjects were excluded if they were unwilling or unable to participate in the study.

We divided the eyes according to the following criteria into four diagnostic groups: normal, glaucoma suspect, early, and advanced glaucoma.

Normal eyes served as the control group. Eyes in this group had no history of glaucoma, retinal pathology, laser therapy, or intraocular surgery. IOP was 21 mmHg or lower. Optic nerve heads had a normal appearance. All had normal visual field test results. Normal visual field test results were defined as those having no cluster of three or more adjacent points depressed more than 5 dB or of two adjacent points depressed more than 10 dB.

Glaucoma suspect eyes had no history of retinal pathology, laser therapy, or intraocular surgery. Intraocular pressure was between 22 and 30 mmHg and/or they had asymmetric cupping (difference in vertical cupping greater than 0.2) or abnormal-appearing ONHs. Visual field results were normal as defined previously. Glaucoma suspect eyes were divided into three categories: ocular hypertensive (OHT), increased cupping (vertical cup-to-disc ratio greater than 0.6), or miscellaneous group (e.g., asymmetric cupping, glaucoma family history).

Early glaucomatous eyes exhibited a typical arcuate or para-central scotoma and/or nasal step on their visual field test, with clusters of three or more adjacent points depressed more than 5 dB or two or more adjacent points depressed more than 10 dB. This visual field loss was present only on one side of the horizontal meridian and/or untreated IOP greater than 35 mmHg despite a full visual field. There was no complete loss of the neuroretinal rim to the ONH margin in any quadrant, and their ONH cupping and/or NFL defect on stereo biomicroscopy was in correspondence with their visual field loss.

Advanced glaucomatous eyes possessed all characteristics of the early glaucoma group as described previously. What distinguished the advanced glaucoma group from the early glaucoma group was either a complete loss of the neuroretinal rim to the ONH margin or visual field loss above and below the horizontal meridian as determined by visual field testing.

To create a normative database we included a set of normal eyes with normal perimetry either by standard full threshold Humphrey 24-2 automated perimetry, short wavelength automated perimetry, or Swedish interactive thresholding algorithm. For the other diagnostic groups we used only 24-2 Swedish interactive thresholding algorithm standard visual field examinations.

OCT Technology

OCT is an optical technique for high-resolution measurements and cross-sectional imaging of the human retina.

OCT was performed using prototype and commercial devices. The commercial OCT device (OCT1, Zeiss-Humphrey, Dublin, CA) ran the A-6 software revision. Detailed descriptions of the principles of OCT have already been published; a summary follows.[11–23]

OCT is based on the principles of low coherence interferometry. By directing a low coherence light beam, which is analogous to a series of short pulses of light, onto a partially reflective mirror, two beams are created: reference and measurement beam. The measurement beam is directed onto the subject’s eye, and it is reflected from intraocular microstructures and tissues

according to their distance, thickness, and different reflectivity. The reference beam is reflected from the reference mirror at a known, variable position. Both beams travel back to the partially reflective mirror, recombine, and are transmitted to a photosensitive detector. For the two beams to recombine, their pulses must arrive at nearly the same time. An interference signal is created when path lengths of the reference and measurement arms are closely matched to within the coherence length of the light.

OCT measurements are performed using a fiberoptically integrated Michelson interferometer with a short coherence length superluminescent diode source. Near-infrared illumination (840 nm) is used to minimize subject discomfort. The prototype OCT system was integrated into a slit-lamp biomicroscope, a 78-diopter condensing lens mounted on the slit lamp in front of the subject's eye, and an attached infrared sensitive video camera that provided a view of the scanning beam on the fundus. The commercial OCT was integrated into a fundus camera.

Axial reflectance profiles (A-scans) were measured versus depth. Tomographic images were constructed from a series of A-scans. The scan rate used was 100 lateral pixel retinal tomograms with a depth of 2 to 3 mm. The prototype OCT acquired an image in approximately 2.5 seconds, whereas the commercial unit captured an image in just less than 1 second. OCT showed good reproducibility,[15] and the resolution of the devices used in this study was approximately 10 μm in the eye.

Optical Technique

Each eye was dilated with 1% tropicamide and 2.5% phenylephrine before recording the images. Each subject eye underwent three circular scans around the center of the optic disc using a circle size of 3.4 mm, which have been shown to provide better reproducibility than a single scan.[18,24] Internal fixation was chosen (subject fixated with the eye being studied) because of better reproducibility than external fixation (subject fixated with the fellow eye). Retinal and NFL thickness were reported as averages over each quadrant (superior, inferior, nasal, temporal), as averages for each clock hour, and as averages over the entire cylindrical section.[12,18,24]

Figures 1 through 8 show optic nerves, visual fields, and prototype and commercial peripapillary NFL OCT scans for normal and glaucomatous eyes.

Macular scans consisted of six 100-pixel radial scans centered on the fovea and spaced 30° from one to another. These scans were used to create a macular thickness map that represented either approximately the central 20° of vision (6-mm diameter map, prototype OCT) or approximately 10° of vision (3.45-mm diameter map, commercial OCT). The macular thickness map was divided into nine sections, and it was displayed as three concentric circles, including a central circle, an inner ring, and an outer ring, with each ring divided into four quadrants. The central circle, inner ring, and outer ring in the prototype macular thickness map had diameters of 1 mm, 3 mm, and 6 mm, respectively. Commercial thickness maps showed a smaller area than prototype maps. The central disc, inner ring, and outer ring diameters were 1 mm, 2.22 mm, and 3.45 mm, respectively. Retinal thickness maps were color coded, with brighter colors for thicker retinal areas and darker colors for thinner ones. Figures 5, 6, 9, and 10, show prototype and commercial macular OCT scans for normal and glaucomatous eyes.

OCT Analysis

Raw data obtained by OCT were analyzed using standard processing algorithms that measured total retinal and NFL thickness. In addition, the algorithms corrected for various artifacts, including eye movement, blood vessel shadows, blinks, and media opacities.

The location of the vitreoretinal interface and the retinal pigment epithelium defined the inner and outer boundaries, respectively, of the neurosensory retina. These two boundaries were associated with the sharpest edges in each OCT A-scan because of the high contrast in optical reflectivity between the relatively nonreflective vitreous and the reflective neurosensory retina and between the minimally reflective photoreceptor outer segments and the highly reflective retinal pigment epithelium/choriocapillaris.

The boundaries of the NFL were defined by first determining the thickness of the neurosensory retina as described previously. The posterior boundary of the NFL was determined by evaluating each A-scan for a threshold value chosen to be 15 dB greater than the filtered maximum reflectivity of the adjacent neurosensory retina.

Statistical Analysis

The subject information was entered into a computer database (FileMaker Pro 5, FileMaker, Inc., Santa Clara, CA) and was analyzed using SAS (SAS Institute, Cary, NC). Because most subjects in the study had two eyes, we used linear mixed regression models to compute all means and regression results. Attempts at prediction were done using logistic regression, in which only one observation per subject was used. The receiver operator characteristic curves and the areas under them (AROC) were computed empirically using the c statistic produced by SAS proc logistic.[25]

To compute correlation coefficients, one randomly chosen eye for each subject was used.

Differences between groups were described as mean difference ± standard error. Dispersion within groups was shown by the standard deviation. When multiple comparisons were performed, Bonferroni correction was used.

Results

Subject Basic Characteristics

We performed peripapillary NFL and macula scans using the prototype OCT unit on 534 eyes of 367 subjects. A subset of subjects underwent peripapillary NFL (95 eyes of 61 subjects) and macular (126 eyes of 81 subjects) scanning with the commercial OCT unit on the same day as their prototype OCT scan. Demographic data are summarized in Table 1.

OCT

Effects of Age, Gender, and Race among Normal Eyes—There was an effect of age on mean macular thickness. When measurements were performed with the prototype OCT unit, for which there was a larger population under study, there was a nonsignificant *increase* in the central ring macular thickness of +0.26 μm/year ($P = 0.06$). Inner ring, outer ring, and mean macular thickness showed *decreases* of −0.18 μm/year ($P = 0.09$), −0.03 μm/year ($P = 0.72$), and −0.03 μm/year ($P = 0.73$), respectively; these also did not achieve statistical significance. Men had thicker central rings (by 10.7 ± 4.7 μm, $P = 0.03$), but there were no other statistically significant differences between the genders. Blacks and Asians had thinner macular inner rings compared with whites (−18.4 μm, $P = 0.003$; −3.9 μm, $P = 0.01$, respectively), as well as thinner central rings (−18.2 μm, $P = 0.02$, −19.5 μm, $P = 0.006$, respectively) and thinner 0 to 3 μm rings (−13.8 μm, $P = 0.009$, −17.2 μm, $P = 0.0006$, respectively). The effect of age, gender, and race on NFL thickness was similar to that described previously.[20]

Effects of Glaucoma on Macular and NFL Thickness—Mean macular thickness (± standard deviation) for prototype and commercial OCT units are summarized in Tables 2 and 3 by diagnostic group (normal, glaucoma suspect, early glaucoma, advanced glaucoma).

Glaucoma suspects were further subdivided into three categories (ocular hypertensive, suspicious cupping, miscellaneous) shown in Tables 4 and 5.

Many of the macular parameters showed statistically significant differences in comparing normal and advanced glaucomatous eyes (Tables 2 and 3). Using both the prototype and commercial OCT units, all NFL parameters were found to be significantly different between normal and either early or advanced glaucomatous eyes (Tables 2 and 3).

The outer ring and the mean macula were the only prototype macular parameters that differed between normal subjects and early and advanced glaucoma patients. The commercial macula measurements of the inner ring, the outer ring, and the mean macula also differed between the two types of glaucoma and normal subjects (Tables 2 and 3). The findings were similar after adjusting for age, race, and gender using both prototype and commercial devices.

NFL in all sectors and the mean NFL were significantly different between normal subjects and early and advanced glaucoma patients with both devices (Tables 2 and 3). The only parameter that was found to differ between the normal subjects and the glaucoma suspect group was the prototype device inferior quadrant NFL measurement.

There was a trend toward a reduction in NFL thickness compared with normal subjects in all three categories of glaucoma suspects (Tables 4 and 5), although this finding did not achieve statistical significance. Overall, the suspect group had a mean NFL thickness 6.4 μm (± 3.3, $P = 0.06$) lower than that of normal subjects. The OHT subgroup had a trend toward thicker macular measurements than that of the other suspect groups; this finding was significant for the prototype device in all sectors except the center ring when compared with that of the cupping subgroup, and the mean macular thickness when compared with that of the miscellaneous subgroup. For the commercial device only the inner + outer sector was significantly thicker in the OHT subgroup compared with the cupping subgroup.

AROC

The AROC comparing mean NFL thickness in normal subjects and eyes with advanced glaucoma using the prototype OCT unit was 0.93. When considering only those individuals scanned with both the prototype and commercial OCT devices on the same day, the AROC for both units was 1.00. Comparing mean macular thickness in normal subjects and those with advanced glaucoma scanned with both the prototype and commercial OCT devices on the same day, the AROCs were 0.88 and 0.80, respectively (Table 6).

For the prototype device, measurements without the center ring had higher AROCs than those with the center ring. For the commercial device, this finding was not duplicated.

Prototype and Commercial OCT Correlations—The correlation between prototype and commercial OCT for overall mean NFL thickness was $r = 0.73$. The superior NFL had the best correlation ($r = 0.79$). The best correlation between the macular thickness measurements with the two devices was found with the prototype's inner ring (diameter, 1–3 mm) and commercial inner + outer ring (diameter, 1–3.45 mm) with $r = 0.93$.

Discussion

This study was designed with the major objective of evaluating the association between macular thickness and glaucoma; we found this association to be significant. We also wished to determine whether macular thickness compared favorably with NFL thickness in its association with disease and found that NFL thickness was more closely tied to glaucoma status. Finally, we compared measurements made with our prototype OCT device with those

made with the commercially available device. We found a significant correlation between measurements made with the two devices.

According to Zeimer et al's hypothesis,[4,6] quantitative detection of glaucomatous damage at the posterior pole by retinal thickness mapping may provide a unique method for the detection and monitoring of early glaucomatous tissue loss. The macula is defined anatomically as that region of the retina where the ganglion cell layer is more than one cell thick. Because the photoreceptor layer is not believed to decrease in thickness in glaucoma, this loss of retinal thickness is attributed mainly to the ganglion cell and NFL. The ganglion cells and NFL contribute 30% to 35% of the retina thickness in the macula, where the ganglion cells are known to be most concentrated.[4,5] According to Zeimer et al's hypothesis, it would be logical to expect that glaucoma detection would be most readily accomplished through macular thickness assessment, because the RGC soma is 15 μm or more in size, and its axon is only 1 to 2 μm in size.

When first proposed, the concept that macular thickness decreased in glaucoma was viewed as heretical. It is most unusual to see macular visual field defects early in the disease, but this is because of the redundancy of the macular visual system. Many studies have shown generalized loss of RGCs in glaucoma.[26–28] Ganglion cells are lost in the macular region, as well as in the retinal periphery; however, detection by perimetry requires the loss of twice as many RGCs in the central visual field compared with the more peripheral retina. Each macular cone is subserved by two to three ganglion cells. The consequently greater number of ganglion cells in the macular region allows substantial redundancy in the detection of simple stimuli.[7,27,29]

We looked at our data in a number of ways, most specifically comparing means between groups, performing regression analysis, and analyzing AROCs. With regard to AROCs, we chose this statistical method to facilitate future comparison between studies and because it is a summary statistic for sensitivity and specificity. The disadvantage of the AROC is that it does not describe the shape of the curve, only the area underneath it, so the number alone does not define the relationship between the sensitivity and specificity for the given comparison; actual visual analysis of the curve provides some of this information (Fig 11).

Despite the hypothetical advantages to macular thickness assessment in glaucoma in this study, whereas macular thickness was significantly associated with glaucoma, NFL thickness showed a still stronger relationship with the disease. This finding may be due to undersampling of the tissue at risk, because only approximately 50% of the RGC are present in the macula, yet nearly 100% of the RGC are assessed in a peripapillary OCT NFL scan. Because glaucoma is a diffuse disease, the ability to measure the damage done by glaucoma in the entire eye may give peripapillary NFL assessment a distinct advantage over macular thickness evaluation in detecting glaucoma. Furthermore, the absolute thickness changes are greater when measuring nearly all of the RGCs, even if just their axons, than when measuring just the subpopulation in the macula, despite the greater size of the RGC soma than that of its axon. In addition, the nature of the OCT macular map leaves large areas of the macula unsampled; another configuration of macular sampling might produce results more related to glaucoma. The problem in increasing sampling density is balancing the number of scan points and the length of scan time. As the technology continues to improve, it is possible that reductions in scan time will allow a higher macular transverse scan density.

Another major advantage of NFL over macular thickness assessment is the confounding of macular thickness measures by nonglaucomatous macular disease. Entities such as diabetes and macular degeneration, for example, directly affect macular thickness and could obscure

or exaggerate the abnormalities seen with glaucoma. These are not significant issues in peripapillary NFL assessment.

This is not to say that macular thickness measurement may not be a useful parameter in the evaluation of glaucoma. It is significantly associated with the disease, and there may be fewer technical challenges in its measurement than in the quantitation of peripapillary NFL thickness. Interestingly, we found that the outer ring macular thickness with our prototype OCT device provided better correlation than did the inner ring thickness in comparing normal with glaucomatous. This more peripheral area of the macula showed a stronger association with the disease than did the more central macula, and yet this area was not presented by the commercial OCT software (revision A6). This finding points to the importance of the inclusion of our prototype dataset in this study. Both OCT devices use six 6-mm radial scans in constructing a macular map; however, whereas the prototype device presents the entire 6-mm diameter macular map, only the central 3.45 mm is presented using the commercial OCT software revision A6. Had we not had the prototype data, we would have missed the strength of the macular thickness–glaucoma association. On the basis of these findings, we recommend that future software revisions should include at least the central 6 mm of the macula, data that are *already* acquired in a macular OCT scan.

Outer ring and mean macular thickness using the prototype OCT device distinguished normal subjects from both early and advanced glaucoma patients in this study. With the commercial device, inner ring, outer ring, and mean macula each discriminated between the groups.

Zeimer and coauthors,[4] using the Retinal Thickness Analyzer (RTA, Talia Technologies, Neve-Ilan, Israel), studied 19 eyes of 18 subjects and found losses up to 34% of normal macular thickness in the posterior poles of patients with glaucoma, presumably because of the loss of ganglion cells and NFL. Their data were a stimulus for this investigation, because OCT theoretically offers a significant advantage in macular thickness assessment over the RTA. Specifically, OCT allows 10 μm resolution (versus approximately 50 μm resolution for RTA), providing more precise tissue measurement. OCT also uses near-infrared light, as opposed to visible light used by the RTA; this gives OCT an advantage in patient comfort during scanning. RTA has the advantage of a tighter scan pattern, producing more scan lines per unit area than OCT.

This study showed once again that the inferior NFL was the parameter most strongly associated with glaucoma status. In the prototype OCT data, the inferior NFL was the only parameter that could show a statistically significant difference between normal subjects and the glaucoma suspect group. It is well known that optic nerve defects associated with glaucoma often occur initially at the inferior pole and that visual field defects associated with glaucoma frequently manifest first in the superior visual field, corresponding to the inferior pole defects.[22]

There were other interesting findings in this study. We separated our glaucoma suspects into three groups: ocular hypertensives, suspicious cupping, and miscellaneous (which included family history of glaucoma or asymmetric cupping), in reverse hierarchical order. We were surprised to find that those subjects who were glaucoma suspects by suspicious cupping had a trend toward the thinnest macular and NFL measurements, although this finding achieved statistical significance only for the inferior quadrant NFL with the prototype device ($P = 0.01$; Tables 4 and 5). On more thoughtful reflection, however, it is possible that those individuals who were glaucoma suspects by suspicious cupping might be those most likely to have glaucoma compared with suspects by OHT, family history, or asymmetric cupping. Our data bear out the importance and value of careful clinical examination and suggest that those people with glaucomatous-appearing optic nerves should be the suspects we follow most closely.

Furthermore, these findings confirm the relevance of OCT macular and NFL measurements in correlating with clinical findings and their potential role in helping to guide clinical care.

OHTs had a trend toward the thickest macular measurements of any of the suspect groups, more pronounced with the prototype device where all sectors were found to be significantly thicker, except the center ring when comparing the OHT and cupping subgroups and only the mean macula when comparing the OHT and the miscellaneous subgroups (Table 4). In the commercial device, the OHT was significantly thicker compared with the cupping subgroup for the inner + outer sector only (Table 5). The reason for these findings is unclear, as is the reason for the age-related thickness increase of approximately 0.25 μm/year in this parameter.

It is encouraging to find that measurements made with the prototype and commercial OCT devices were highly correlated and similar. These findings support the ability to extrapolate from the datasets that have been accumulated using the prototype device to clinical patient care with the commercial device. The fact that the findings in the larger dataset with the prototype device were close to the same as those from the smaller commercial OCT dataset suggest that the two devices function in a similar way, despite different delivery systems (slit-lamp based for the prototype, fundus camera based for the commercial unit).

Macular thickness measurement may provide a new tool for the detection of glaucoma. Our study results support Zeimer et al's hypothesis that macular thickness is reduced in glaucoma. Conversely, we found that peripapillary NFL thickness was a more sensitive indicator of the presence or absence of glaucoma than was macular thickness. Nevertheless, macular thickness assessment clearly may have a role in the assessment and care of glaucoma patients. Future goals in this direction include the creation of new algorithms to specifically measure the macular NFL/ganglion cell layer, or ganglion cell layer alone, and the development of ultrahigh-resolution OCT devices (2–3 μm) to actually image and count ganglion cells. Further investigation is necessary to improve the early detection of glaucoma damage. The recognition of the importance and benefits of macular thickness measurements in glaucoma represents a new approach to the evaluation and management of the disease.

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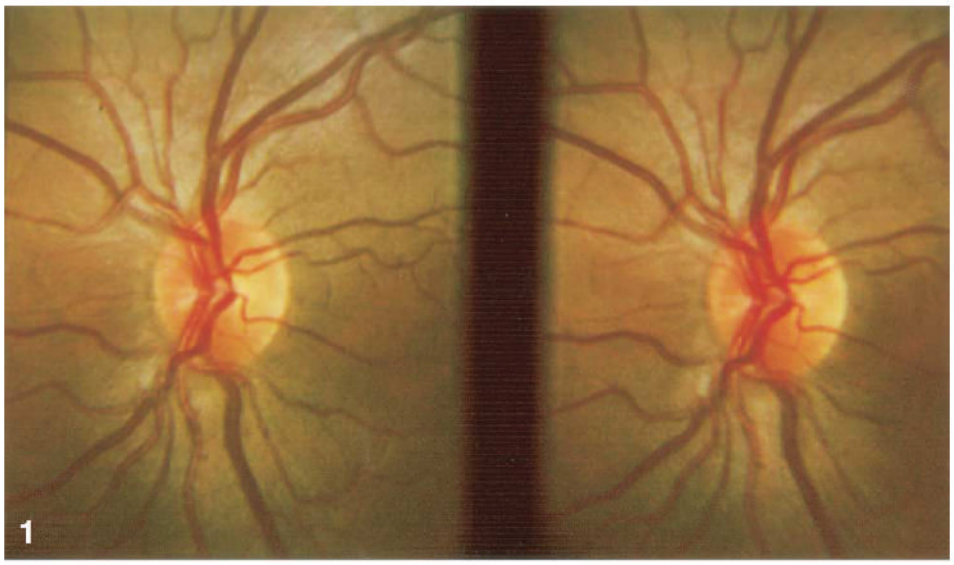

Figure 1.
Stereoscopic photograph of a normal optic nerve head.

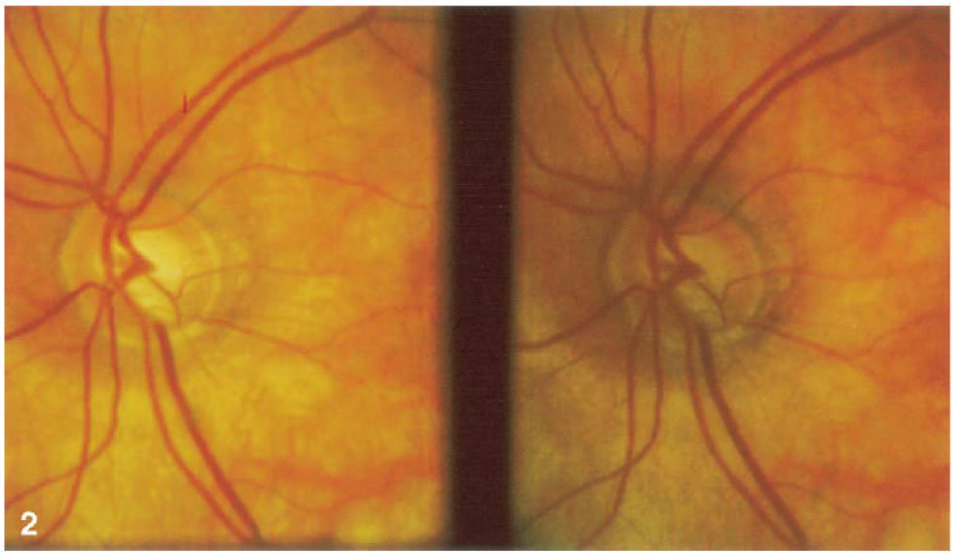

Figure 2.
Stereoscopic photograph of a glaucomatous optic nerve head showing moderate cupping and an inferior notch.

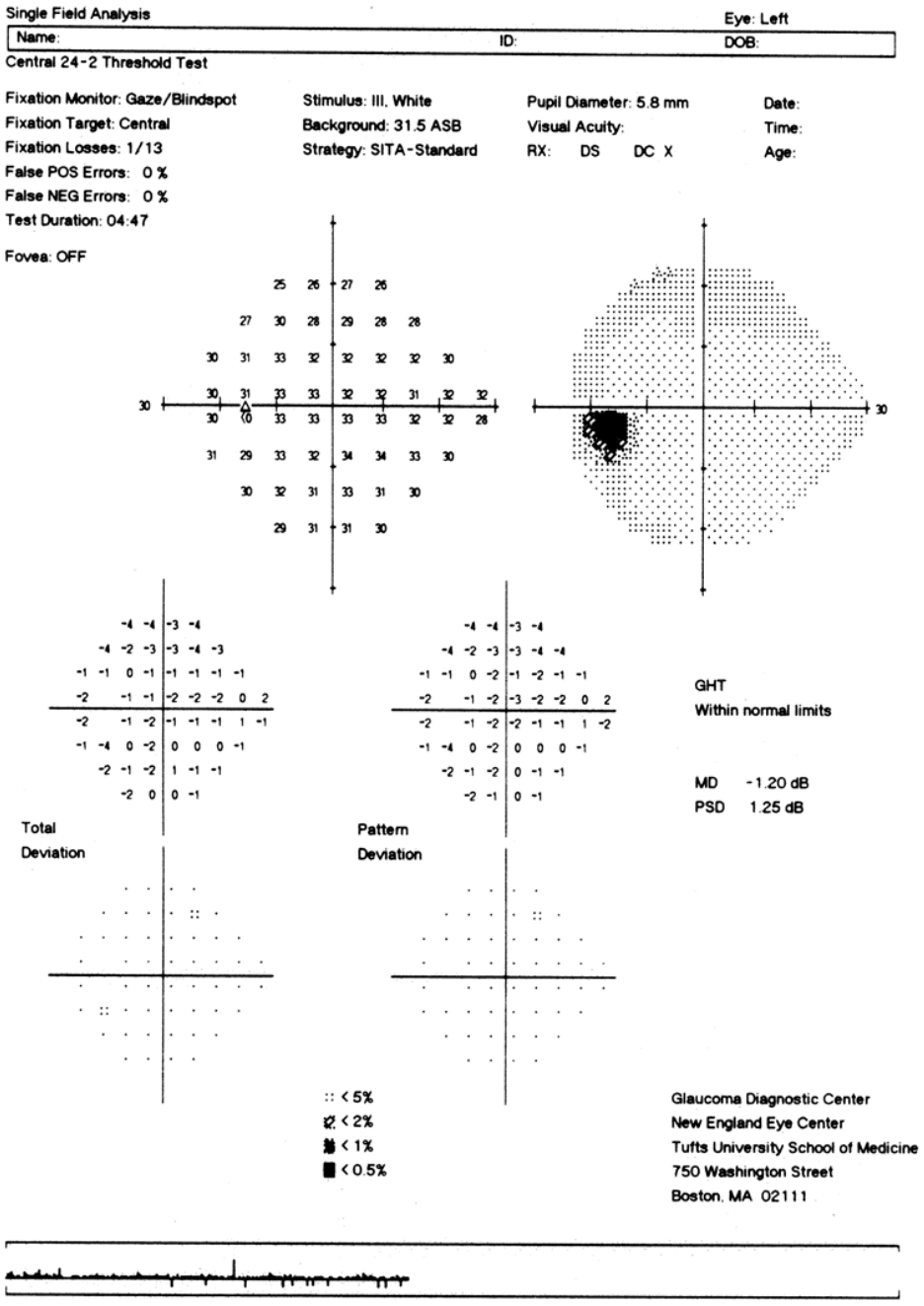

Figure 3.
Normal Humphrey 24-2 Swedish interactive thresholding algorithm standard visual field examination in the normal eye represented in Figure 1.

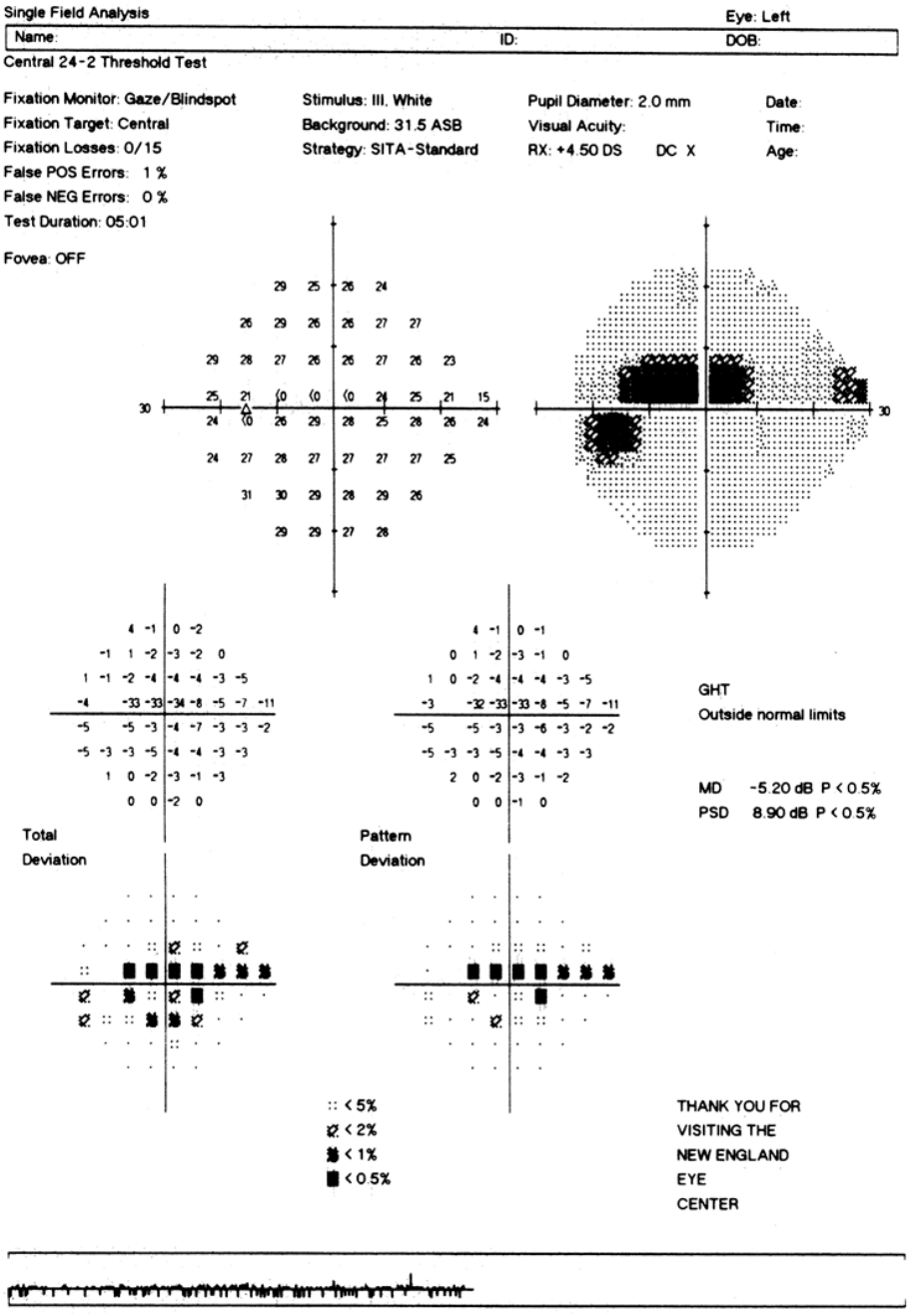

Figure 4.
Humphrey 24-2 Swedish interactive thresholding algorithm standard visual field examination showing a superior defect in the glaucomatous eye represented in Figure 2.

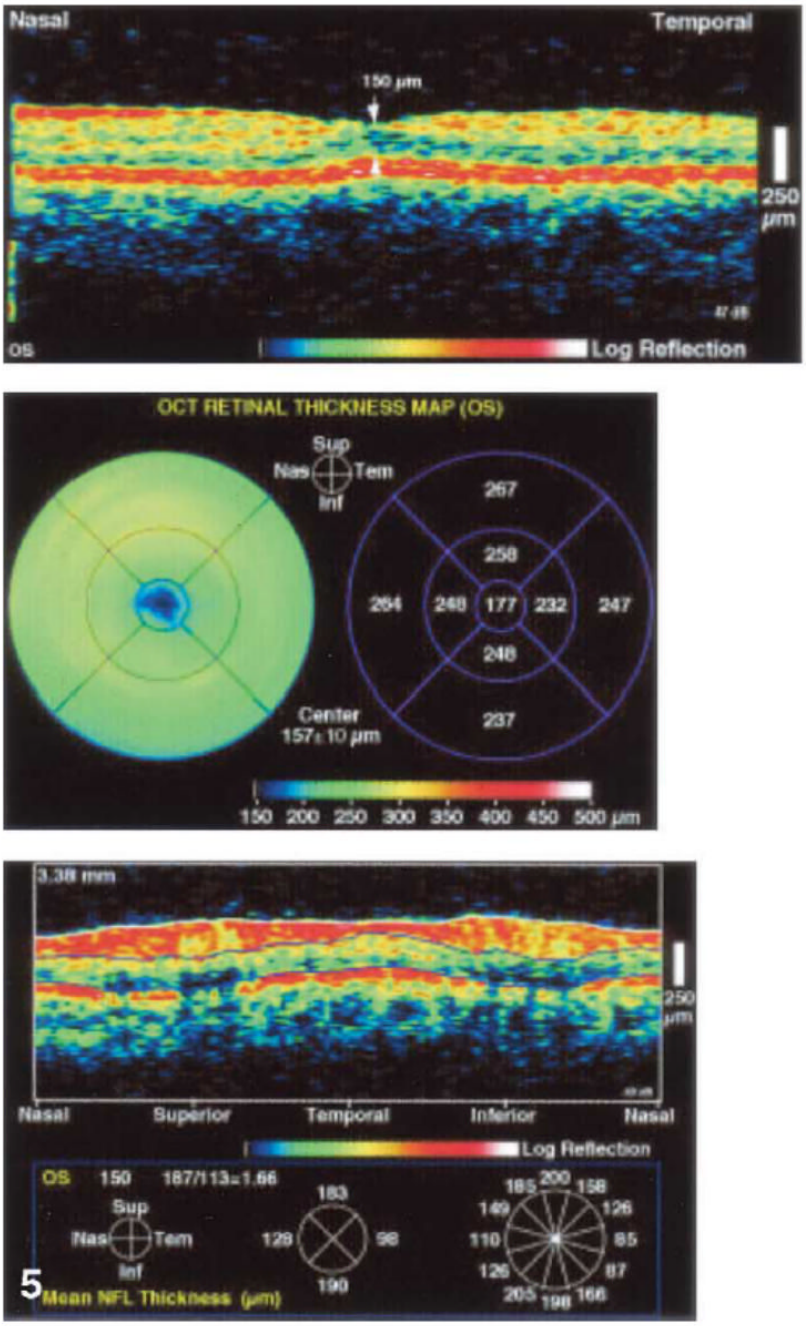

Figure 5.
Prototype optical coherence tomography of eye shown in Figure 1. **A,** Normal macular scan. **B,** Normal macular thickness map. **C,** Normal nerve fiber layer scan.

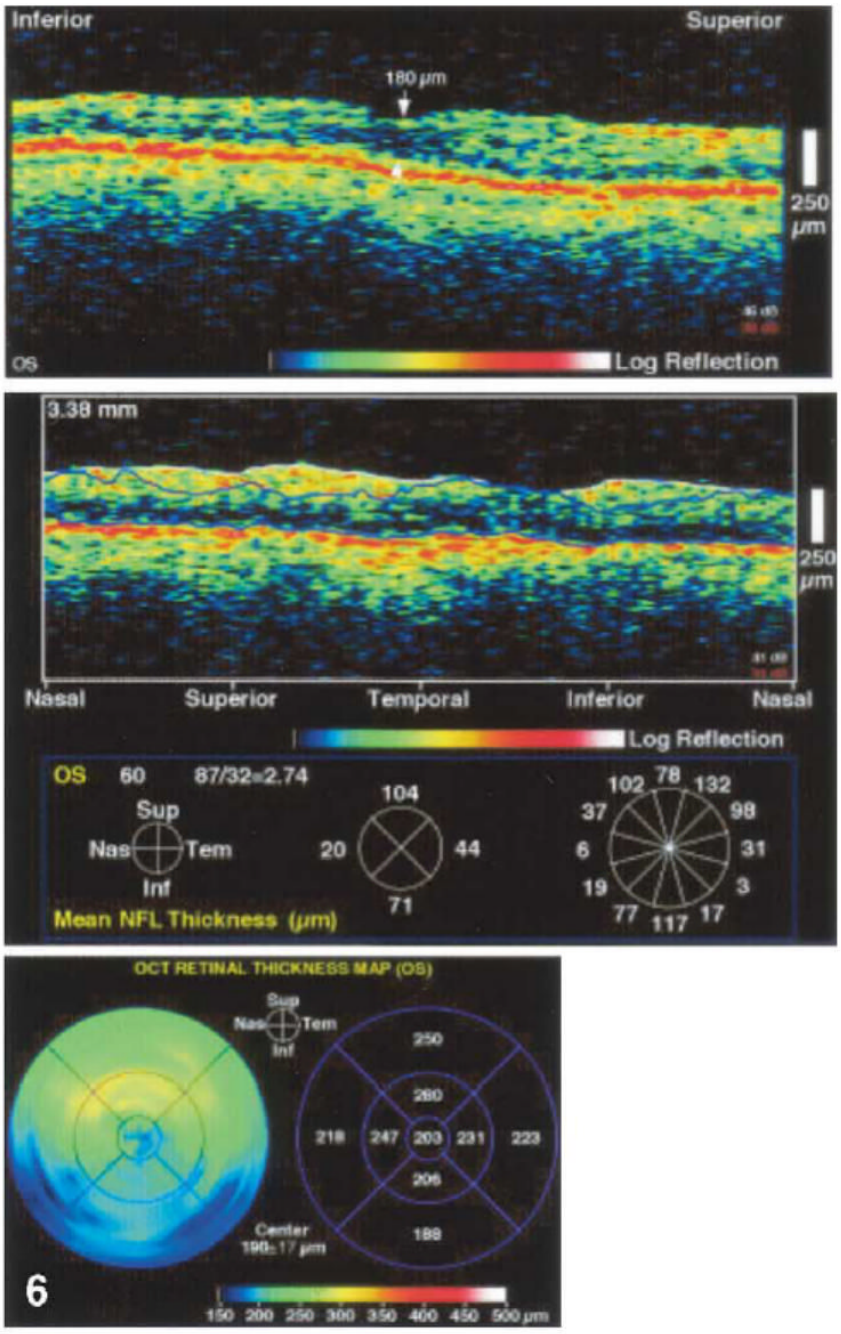

Figure 6.

Prototype optical coherence tomography (OCT) of eye shown in Figure 2. **A,** Glaucomatous macular scan. **B,** OCT showing glaucomatous nerve fiber layer thickness decreased particularly in the inferior quadrant. **C,** Glaucomatous macular thickness map showing decreased macular thickness particularly in the inferior inner ring and outer ring.

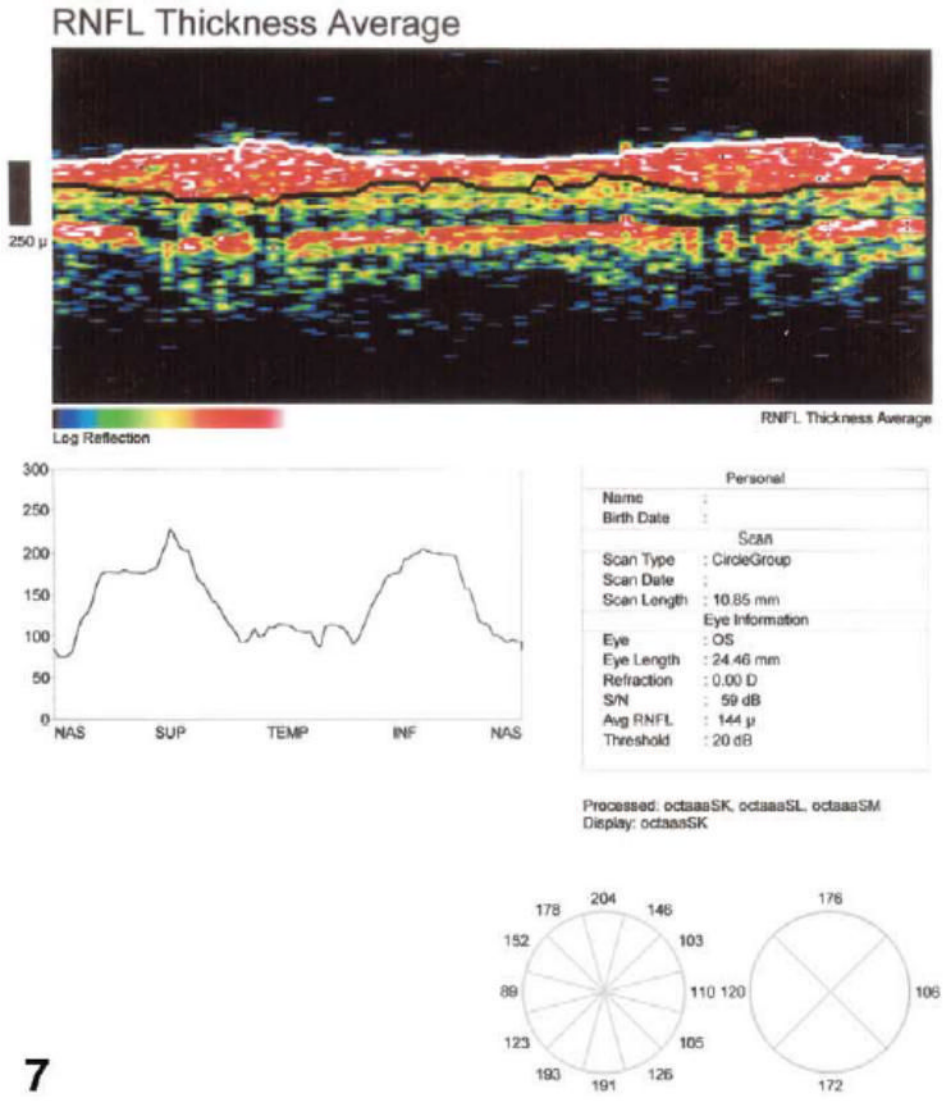

Figure 7.
Commercial optical coherence tomography. Normal nerve fiber layer scan of eye shown in Figure 1.

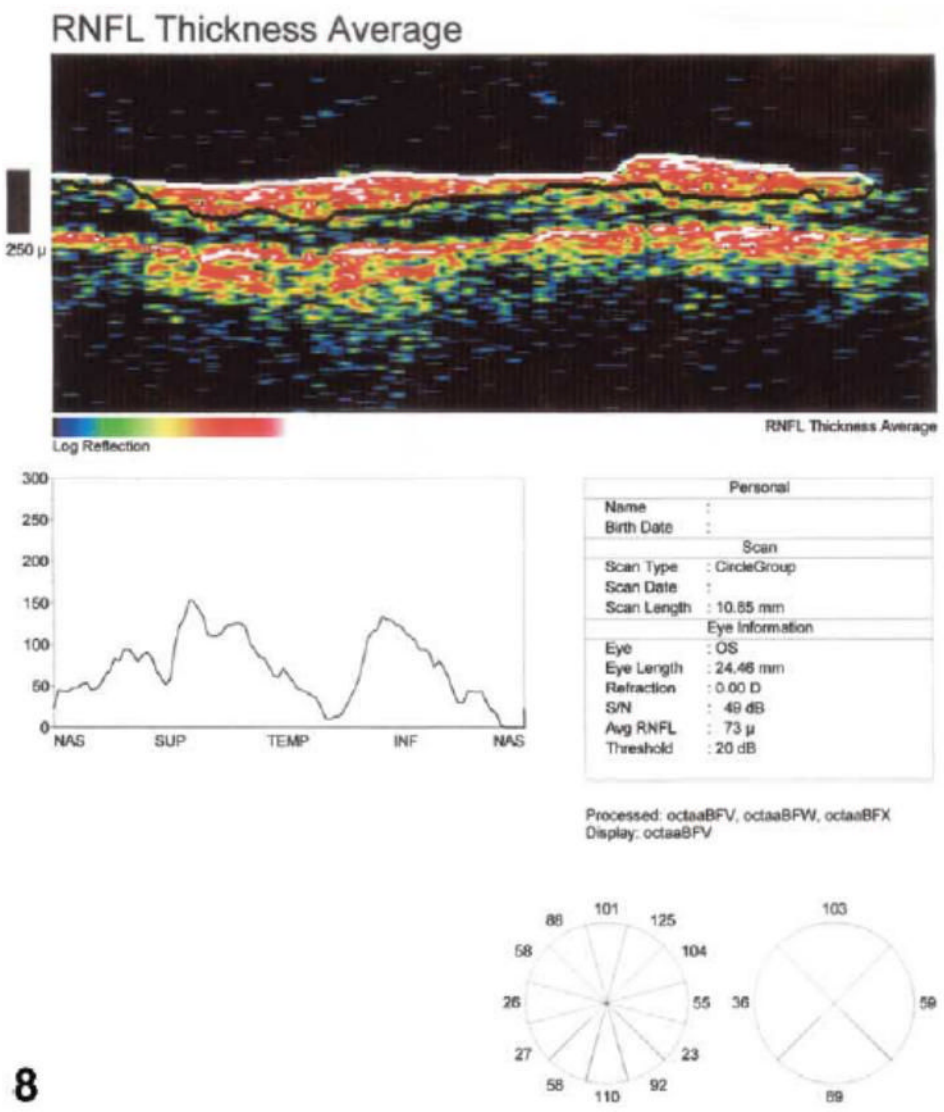

Figure 8.

Commercial optical coherence tomography. Glaucomatous nerve fiber layer scan of eye demonstrated in Figure 2, showing decreased thickness particularly in the inferior quadrant.

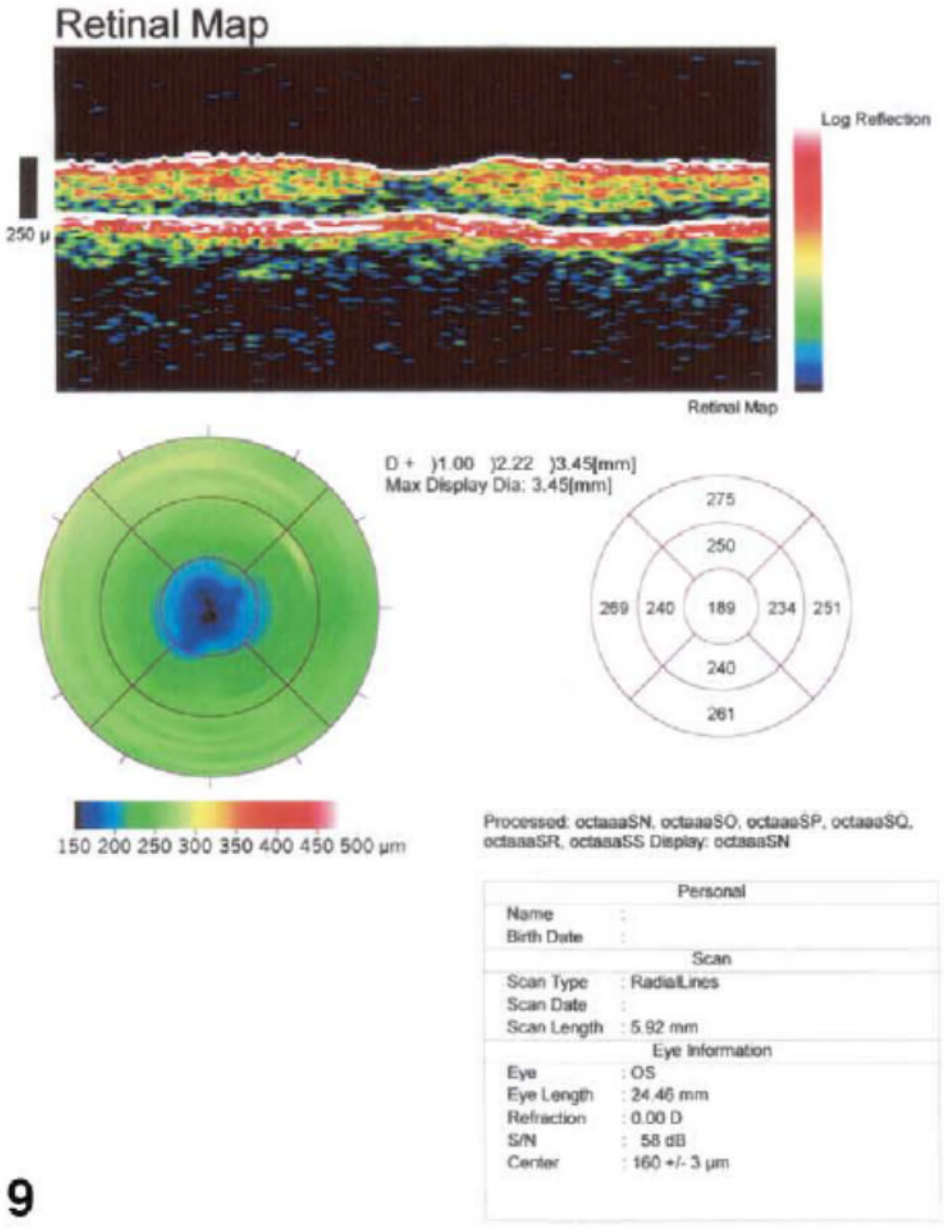

Figure 9.
Commercial optical coherence tomography. Normal macular thickness map of eye shown in Figure 1.

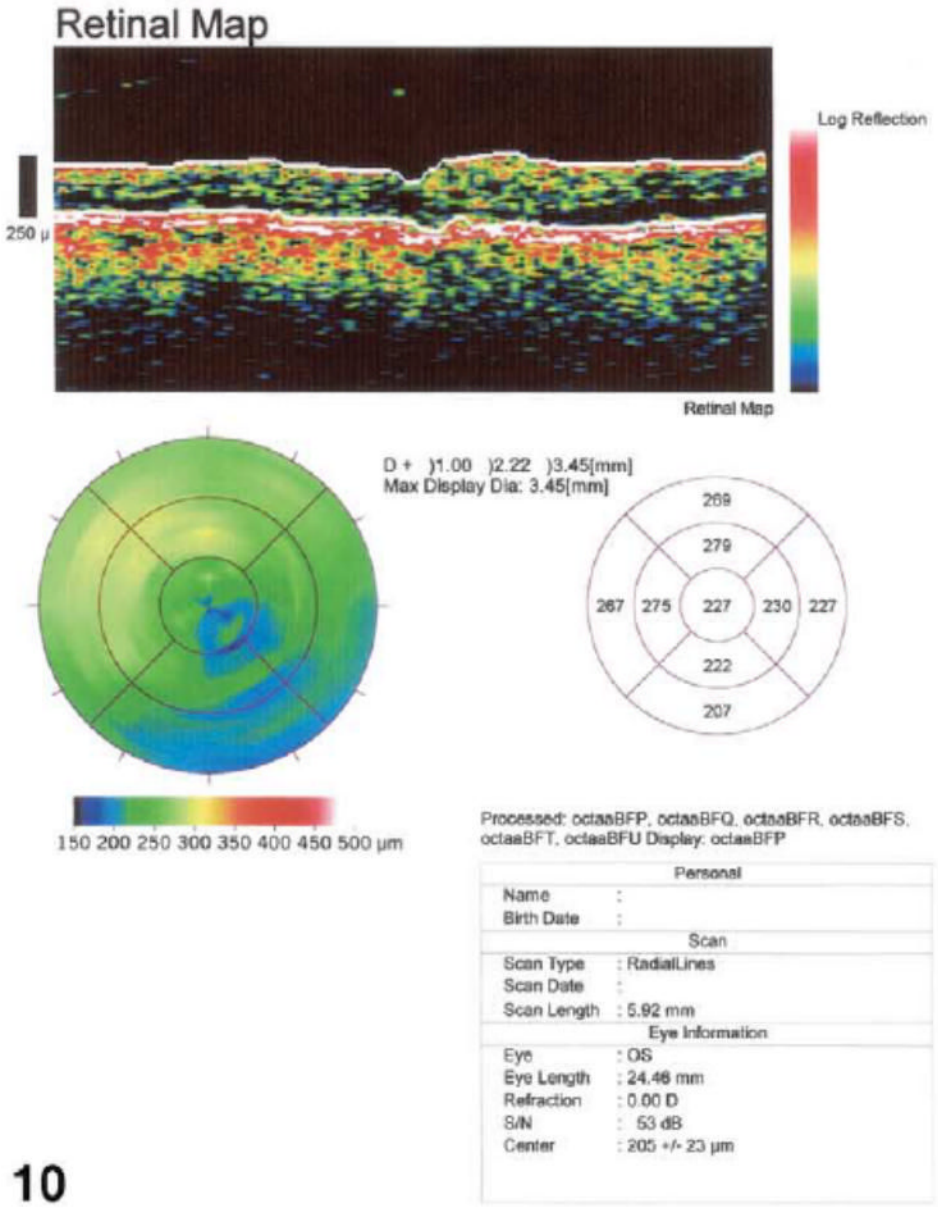

Figure 10.

Commercial optical coherence tomography. Glaucomatous macular thickness map of eye shown in Figure 2, showing decreased macular thickness particularly in the inferior inner ring and outer ring.

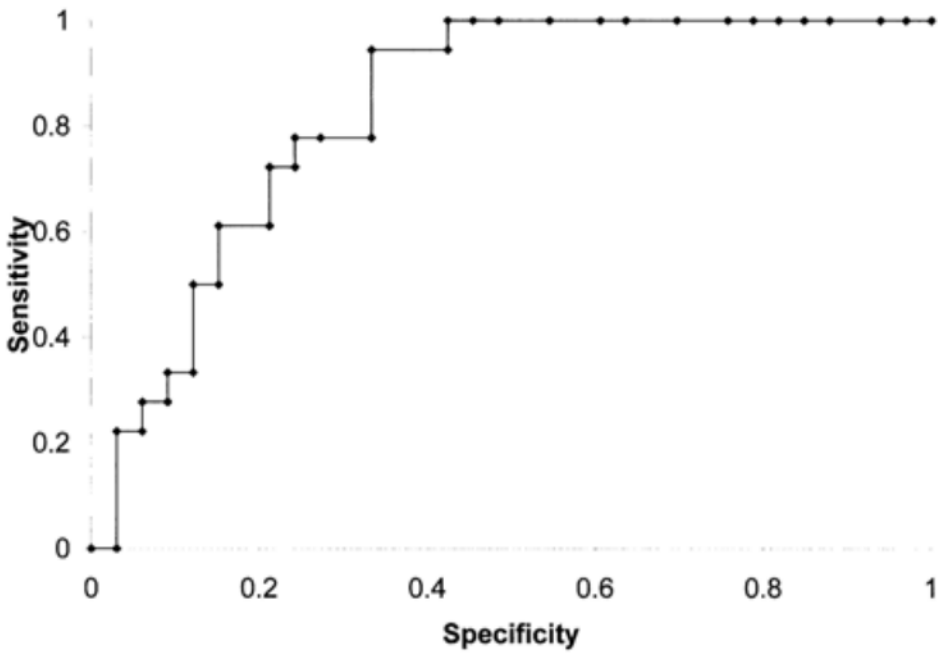

Figure 11.
Receiver operator characteristic (ROC) curve: Overall mean macular thickness comparing normal and advanced glaucoma (prototype optical coherence tomography); area under the curve (AROC) is 0.87. This curve is shown as an example of the ROC curves summarized by AROCs in Table 6 but does not represent the parameter with the best discriminating ability.

Table 1

Demographic Characteristics of Patients Undergoing Optical Coherence Tomography

	Normal	Glaucoma Suspect			Early Glaucoma	Advanced Glaucoma
	(n = 109 Subjects)	Ocular Hypertension (n = 27 Subjects)	By Cupping (n = 21 Subjects)	Miscellaneous (n = 10 Subjects)	(n = 132 Subjects)	(n = 68 Subjects)
Age (SD)	50.1 (17.7)	58.3 (14.9)	56.7 (18.9)	62.8 (10.6)	65.3 (12.8)	65.9 (16.3)
% Male	45.9	48.2	15.8	30.0	39.7	50.8
% Black	10.6	15.4	5.9	0.0	15.5	18.5
% Asian	12.5	11.5	11.8	33.3	9.3	9.2
Mean deviation (SD)	−0.38 (1.22)	−0.64 (1.56)	−1.36 (1.63)	−2.93 (1.97)	−3.01 (2.88)	−12.01 (8.13)
Pattern standard deviation (SD)	1.51 (0.38)	1.88 (0.73)	1.68 (0.28)	2.06 (0.38)	2.90 (1.73)	7.88 (3.38)

No statistically significant differences between groups except for mean deviation and pattern standard deviation ($P = 0.0001$).

* Numbers of subjects do not add to 367, because some subjects have different diagnoses in the two eyes.

SD = standard deviation.

Ophthalmology. Author manuscript; available in PMC 2007 August 15.

Table 2

Macular and Nerve Fiber Layer Thickness: Relation to Diagnosis (Prototype Optical Coherence Tomography Device)

	Normal	Glaucoma Suspect		Early Glaucoma		Advanced Glaucoma	
	(n = 166 Eyes, 109 Subjects)	(n = 83 Eyes, 58 Subjects)		(n = 196 Eyes, 132 Subjects)		(n = 89 Eyes, 68 Subjects)	
	Mean (Standard Deviation)	Mean (Standard Deviation)	P Value	Mean (Standard Deviation)	P Value	Mean (Standard Deviation)	P Value
Center ring	183.5 (24.3)	184.3 (27.4)	0.76	185.1 (22.5)	0.24	190.9 (25.5)	0.06
Inner ring	248.2 (19.5)	245.3 (22.5)	0.61	244.3 (19.3)	0.48	232.7 (22.7)	0.0001*
Outer ring	230.4 (14.9)	227.3 (14.0)	0.34	224.5 (15.8)	0.003	211.5 (19.3)	0.0001*
Center + inner	227.4 (17.5)	223.7 (21.4)	0.41	224.1 (18.2)	0.64	218.1 (19.1)	0.001
Mean macula	229.0 (13.4)	224.9 (16.0)	0.23	224.0 (14.5)	0.04	214.5 (17.0)	0.0001*
NFL superior	134.6 (23.3)	126.9 (21.3)	0.13	112.4 (28.0)	0.0001*	77.9 (31.2)	0.0001*
NFL inferior	138.1 (23.2)	127.1 (23.7)	0.02	114.5 (27.8)	0.0001*	76.3 (37.0)	0.0001*
NFL temporal	89.9 (15.6)	82.9 (19.3)	0.10	75.9 (23.0)	0.0001*	49.4 (23.9)	0.0001*
NFL nasal	91.9 (28.9)	86.2 (32.9)	0.30	76.1 (31.5)	0.0001*	53.0 (36.0)	0.0001*
Mean NFL	113.6 (15.8)	106.0 (18.9)	0.06	94.7 (22.2)	0.0001*	64.3 (27.3)	0.0001*

* Statistically significant after Bonferroni correction.

P value for comparison with normals.

Center ring dimeter, 1 mm; inner ring diameter, 1–3 mm; outer ring diameter, 3–6 mm; center + inner ring diameter, 3 mm; overall mean macula diameter, 6 mm.

NFL = nerve fiber layer.

Table 3

Macular and Nerve Fiber Layer Thickness: Relation to Diagnosis (Commercial Optical Coherence Tomography Device)

	Normal	Glaucoma Suspect		Early Glaucoma		Advanced Glaucoma	
	(n = 33 Eyes, 21 Subjects)	(n = 40 Eyes, 26 Subjects)		(n = 35 Eyes, 22 Subjects)		(n = 18 Eyes, 12 Subjects)	
	Mean (Standard Deviation)	Mean (Standard Deviation)	P Value	Mean (Standard Deviation)	P Value	Mean (Standard Deviation)	P Value
Center ring	209.0 (20.5)	203.1 (26.0)	0.41	195.2 (16.0)	0.05	191.6 (32.9)	0.09
Inner ring	254.8 (16.0)	249.4 (19.5)	0.38	238.0 (20.0)	0.02	219.6 (42.3)	0.0006*
Outer ring	255.2 (15.9)	250.4 (15.5)	0.42	237.9 (21.4)	0.008	212.5 (41.4)	0.0001*
Inner + outer	239.3 (14.7)	236.3 (17.1)	0.44	234.4 (15.7)	0.06	222.1 (20.0)	0.0001*
Mean macula	236.2 (13.9)	230.9 (17.9)	0.36	220.5 (16.7)	0.01	204.0 (37.7)	0.003
	(n = 18 Eyes, 11 Subjects)	*(n = 29 Eyes, 20 Subjects)*		*(n = 33 Eyes, 20 Subjects)*		*(n = 15 Eyes, 10 Subjects)*	
	Mean (Standard Deviation)	*Mean (Standard Deviation)*	*P Value*	*Mean (Standard Deviation)*	*P Value*	*Mean (Standard Deviation)*	*P Value*
NFL superior	142.7 (16.0)	130.1 (17.5)	0.08	104.8 (19.0)	0.0001*	48.9 (23.2)	0.0001*
NFL inferior	138.6 (19.5)	126.4 (21.9)	0.19	103.9 (30.8)	0.0007*	69.0 (21.6)	0.0001*
NFL temporal	86.3 (20.2)	77.8 (17.1)	0.14	60.2 (16.3)	0.0001*	36.9 (16.8)	0.0001*
NFL nasal	91.3 (24.4)	80.9 (25.1)	0.20	60.2 (18.9)	0.0003*	32.4 (12.9)	0.0001*
Mean NFL	114.8 (13.1)	104.9 (14.4)	0.06	83.2 (14.2)	0.0001*	47.2 (14.8)	0.0001*

* Statistically significant after Bonferroni correction.

P values for comparison with normals.

Center ring diameter, 1 mm; inner ring diameter, 1–2.22 mm; outer ring diameter, 2.22–3.45 mm; inner + outer rings diameter, 1–3.45 mm; overall mean macular thickness diameter, 3.45 mm.

NFL = nerve fiber layer.

Table 4

Macular and Nerve Fiber Layer Thickness: Relation to Glaucoma Suspect Group (Prototype Optical Coherence Tomography Device)

	Glaucoma Suspect				
	Ocular Hypertension	By Cupping		Miscellaneous	
	(n = 39 Eyes, 27 Subjects)	(n = 29 Eyes, 21 Subjects)		(n = 15 Eyes, 10 Subjects)	
	Mean (Standard Deviation)	Mean (Standard Deviation)	P Value	Mean (Standard Deviation)	P Value
Center ring	192.4 (29.0)	176.3 (26.7)	0.07	176.5 (16.0)	0.18
Inner ring	252.9 (20.5)	236.9 (22.9)	0.02	242.4 (18.5)	0.21
Outer ring	232.5 (14.6)	222.9 (9.6)	0.02	221.3 (16.8)	0.05
Center + inner	231.8 (19.8)	215.3 (21.9)	0.02	217.5 (16.6)	0.08
Mean macula	231.9 (15.1)	218.3 (13.4)	0.01	218.7 (14.6)	0.04
NFL superior	132.2 (23.5)	120.4 (16.9)	0.06	124.2 (19.8)	0.38
NFL inferior	125.1 (25.3)	126.6 (23.0)	1.00	133.6 (20.2)	0.24
NFL temporal	88.8 (14.7)	72.0 (21.1)	0.0001	88.4 (11.9)	0.97
NFL nasal	81.7 (33.7)	92.8 (37.0)	0.44	86.4 (22.6)	0.75
Mean NFL	107.1 (19.8)	103.5 (19.5)	0.30	108.2 (14.8)	0.78

P value for comparison with ocular hypertension.

Differences between cupping and miscellaneous groups are not statistically significant (except for nerve fiber layer temporal, where $P = 0.01$).

Center circle diameter, 1 mm; inner ring diameter, 1–3 mm; outer ring diameter, 3–6 mm; center + inner ring diameter, 3 mm; overall mean macular diameter, 6 mm.

NFL = nerve fiber layer.

Table 5

Macular and Nerve Fiber Layer Thickness: Relation to Glaucoma Suspect Group (Commercial Optical Coherence Tomography Device)

	Glaucoma Suspect				
	Ocular Hypertension	By Cupping		Miscellaneous	
	(n = 13 Eyes, 9 Subjects)	(n = 16 Eyes, 10 Subjects)		(n = 11 Eyes, 7 Subjects)	
	Mean (Standard Deviation)	Mean (Standard Deviation)	P Value	Mean (Standard Deviation)	P Value
Center ring	205.2 (25.2)	198.1 (32.7)	0.66	206.0 (15.2)	0.92
Inner ring	251.0 (27.3)	247.7 (17.7)	0.68	249.3 (14.9)	0.77
Outer ring	252.6 (20.0)	247.3 (12.4)	0.47	253.3 (12.5)	0.95
Inner + outer	242.7 (16.3)	229.9 (14.7)	0.01	231.8 (17.8)	0.10
Mean macula	232.8 (21.8)	227.9 (18.4)	0.58	232.9 (11.8)	0.89
	(n = 7 Eyes, 5 Subjects)	*(n = 13 Eyes, 9 Subjects)*		*(n = 9 Eyes, 6 Subjects)*	
	Mean (Standard Deviation)	*Mean (Standard Deviation)*	*P Value*	*Mean (Standard Deviation)*	*P Value*
NFL superior	137.4 (13.5)	128.7 (20.1)	0.37	125.5 (14.7)	0.26
NFL inferior	129.9 (18.9)	118.7 (24.7)	0.42	137.5 (14.5)	0.62
NFL temporal	87.4 (16.9)	72.2 (13.1)	0.15	80.8 (20.2)	0.53
NFL nasal	88.0 (31.3)	80.8 (26.5)	0.74	79.0 (17.9)	0.56
Mean NFL	111.8 (15.8)	100.6 (15.8)	0.25	105.7 (8.4)	0.52

P value for comparison with ocular hypertension.

Differences between cupping and miscellaneous groups are not statistically significant.

Center circle diameter, 1 mm; inner ring diameter, 1–2.22 mm; outer ring diameter, 2.22–3.45 mm; inner + outer rings diameter, 1–3.45 mm; overall mean macular thickness diameter, 3.45 mm.

NFL = nerve fiber layer.

Table 6

Areas Under Receiver Operator Characteristic Curves for Prototype and Commercial Optical Coherence Tomography Devices > 0.60 Subjects Scanned with Both Devices

	Prototype Optical Coherence Tomography	Commercial Optical Coherence Tomography
	Normal vs. Advanced Glaucoma	**Normal vs. Advanced Glaucoma**
Macula		
1–3 mm/1–3.45 mm	0.87	0.79
0–3 mm/0–3.45 mm	0.68	0.80
3–6 mm	0.81	N/A
0–6 mm	0.88	N/A
NFL		
Mean NFL	1.00	1.00
Superior NFL	1.00	1.00
Inferior NFL	1.00	0.99
	Normal vs. Early Glaucoma	*Normal vs. Early Glaucoma*
Macula		
1–3 mm/1–3.45 mm	0.69	0.62
0–3 mm/0–3.45 mm	0.68	0.73
3–6 mm	0.63	N/A
0–6 mm	0.77	N/A
NFL		
Mean NFL	0.93	0.94
Superior NFL	0.89	0.90
Inferior NFL	0.90	0.82
	Normal vs. Suspect	*Normal vs. Suspect*
Macula		
0–6 mm	0.64	N/A
NFL		
Mean NFL	0.79	0.69
Superior NFL	0.76	0.67
Inferior NFL	0.82	0.67
	Normal vs. Ocular Hypertension	*Normal vs. Ocular Hypertension*
Mean NFL	0.69	0.64
Superior NFL	0.67	0.60
Inferior NFL	0.79	0.70
	Normal vs. Suspect by Cupping	*Normal vs. Suspect by Cupping*
Macula		
1–3 mm/1–3.45 mm	0.67	0.70
0–3 mm/0–3.45 mm	0.57	0.61
3–6 mm	0.70	N/A
0–6 mm	0.67	N/A
NFL		
Mean NFL	0.86	0.68
Superior NFL	0.84	0.64
Inferior NFL	0.86	0.71

Prototype and commercial optical coherence tomography center circle diameter, 1 mm; prototype optical coherence tomography center circle + inner ring diameter, 3 mm; prototype optical coherence tomography inner ring diameter, 1–3 mm; prototype optical coherence tomography overall mean macular thickness diameter, 6 mm; commercial optical coherence tomography inner + outer ring diameter, 1–3.45 mm; commercial optical coherence tomography overall mean macular thickness diameter, 0–3.45 mm. N/A = Not available for commercial optical coherence tomography; NFL = nerve fiber layer.