

# Comparison between Nonmydriatic Spectral Domain Optical Coherence Tomography and Conventional Ophthalmologic Examination in Detecting Adult Macular Pathology

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## Keywords

Adult population · Correlation · Macula · Nonmydriatic optical coherence tomography · Comprehensive ophthalmic evaluation · Screening · Sensitivity · Specificity

## Abstract

**Objective:** To compare nonmydriatic spectral domain optical coherence tomography (NMOCT) to comprehensive ophthalmologic evaluation (COE) in detecting adult macular abnormalities. **Methods:** This is a single-reader observational pilot study of adults older than 50 years with no known ophthalmologic problems to assess the correlation between NMOCT and COE in detecting macular abnormalities classified as epiretinal, intraretinal, subretinal, or a combination thereof. Subjects underwent NMOCT of the macula followed by COE which included a dilated fundus examination and ancillary tests as needed. **Results:** A total of 771 eyes of 406 patients were included. Cohen's kappa coefficient of agreement between NMOCT and COE for detecting any abnormality was high (0.90,  $p < 0.0001$ ), with NMOCT having an overall sensitivity of 82.65% and specificity of 98.97%. Sensitivities and specificities of NMOCT in detecting each category of

macular abnormalities were as follows: epiretinal (86.36%, 99.73%), intraretinal (80.00%, 99.58%), and subretinal (88.89%, 99.73%), respectively. **Conclusion:** NMOCT is a promising tool for detecting adult macular abnormalities.

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## Introduction

Common adult retinal diseases affecting the macula, such as diabetic maculopathy or age-related maculopathy (ARM), remain the main causes of vision loss in the developed world today [1, 2]. Detecting the pathology early on will lead to more favorable treatment results and better visual outcomes [3, 4]. This, however, still poses a challenge since most changes can often be asymptomatic in their initial stages due to minimal change in vision, or being unilateral and hence masked by the better-seeing contralateral eye. Therefore, early changes may be difficult to detect by patients unless they undergo routine eye examination [4]. While a comprehensive ophthalmologic evaluation (COE) remains the gold standard to uncover these abnormalities, such an endeavor would be unrealistic, fi-

nancially taxing, and time consuming as a cross-sectional screening tool [5]. In parallel, screening methods using fundus photography combined with fluorescein angiography showed excellent potential in early detection of macular abnormalities, but the interventional and invasive nature of such studies as well the duration of testing discouraged their use for evaluation at the community level [5]. Therefore, the need for a fast, noninvasive screening tool that can be integrated into a telemedicine platform is both necessary and important to identify early macular changes representing potential disease. This in turn will allow early referral of patients with macular abnormalities to a specialist for a complete examination and further management.

Spectral domain optical coherence tomography (SD-OCT) lends itself as a noninvasive, detailed imaging modality with fast and dense volumetric scanning capability of the fovea [6]. Cross-sectional images can be acquired easily, rapidly, and with minimal discomfort to the patient. While mostly used on pharmacologically dilated pupils, it has also been studied on nondilated pupils as a nonmydriatic imaging tool [7, 8]. In fact, nonmydriatic spectral domain optical coherence tomography (NMOCT) has gained popularity in fundus evaluation since it was proven to be effective in catching early macular changes in diabetes and early macular degeneration and even subtle non-specific changes [7–9]. However, its use as a sole stand-alone tool for detecting macular diseases has not yet been studied and validated against the benchmark traditional ophthalmologic evaluation comprising a comprehensive eye evaluation followed by ancillary fundus imaging testing when needed, such as MOCT, fundus autofluorescence photography, or fluorescein angiography. Our aim in this paper is to evaluate NMOCT in detecting macular irregularities in an adult population as compared to the COE. If proven adequate, NMOCT would be an ideal telemedicine tool for detection of diseases of the adult macula.

## Methods

### *Patient Recruitment and Examination*

After obtaining approval from the hospital's Institutional Review Board, between March 2011 and June 2013, a prospective single-reader observational pilot study was conducted of subjects with no overt eye complaints who happened to be accompanying patients attending the ophthalmology clinic at the Beirut Military Hospital. These patients were asked to undergo NMOCT imaging using only dark adaptation as a means of pupillary dilatation. Images were stored and sent electronically to a reading center where a masked retina specialist would interpret these images at a later date. Any abnormality was noted and categorized based on the location

vis-à-vis the retina (classification explained below). Subjects afterwards underwent COE including a dilated fundus examination complemented by a dilated SD-OCT, fundus autofluorescence, and fluorescein angiography as needed if the patient had vision loss that could not be corrected by spectacles, or if any retinal changes were noted including, but not limited to, blunted foveal reflex, retinal pigment epithelium changes, drusen, retinal atrophy, exudates, microaneurysms, intraretinal hemorrhages, subretinal hemorrhages, intraretinal microvascular abnormalities, epiretinal abnormalities, and abnormalities of the vitreoretinal interface. Inclusion criteria were age 50 years and above, ability to sign an informed consent form, and willingness to undergo NMOCT followed by a dilated ophthalmologic evaluation and possible imaging afterwards. Exclusion criteria were use of any pupillary constricting agents, history of uveitis or contraindication for pupillary dilatation, and a history of fluorescein hypersensitivity. Subjects were placed in a dark room for 10 min to create mesopic physiologic pupillary dilatation. The Cirrus OCT system (Cirrus HD-OCT, Model 4000; Carl Zeiss Meditec, Zeiss industries, Dublin, CA, USA) was used to acquire OCT images. A  $6 \times 6$  mm macular cube of the central macular area consisting of 128 B-scans with each B-scan consisting of 512 A-scans ( $512 \times 128 \mu\text{m}$  cube) was taken for each eye by a skilled technician with training in nonmydriatic imaging. Briefly, after subjects maintained steady fixation on an internal fixation target, scans were acquired by centering them on the fovea and then improving the quality of the image by optimizing the focusing to correct for the patients' refractive errors. Images were stored and sent electronically to the reading center to be interpreted at a later date. Subjects then underwent a COE including best-corrected visual acuity, anterior segment biomicroscopy, tonometry, a dilated fundus examination, and possible posterior segment imaging when deemed necessary (dilated SD-OCT, fundus autofluorescence, and fluorescein angiography). A fellowship-trained retina specialist (H.S.) performed the ophthalmologic evaluation.

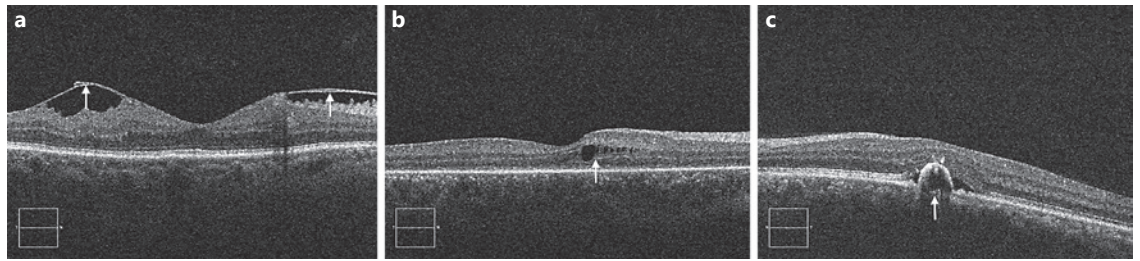
### *NMOCT Interpretation*

All NMOCT interpretation was performed by the same investigator (H.S.) at least 1 month after image acquisition to make sure the investigator was blind to the findings of the ophthalmologic evaluation.

In an effort to simplify OCT analysis, only the automated macular cube printout was utilized for OCT image interpretation. The vertical and horizontal line scans included in the printout were analyzed. No effort was made to analyze the other line scans of the macular cube study or the retinal thickness measurements generated in the macular cube printout. This approach was quick, simple, and efficient, reflecting how a potential screening test should be.

Scan results were classified as follows:

1. Epiretinal abnormalities (Fig. 1a): defined as epiretinal membrane abnormalities varying from a cellophane change to epimacular fibrosis. Macular holes were included in this category. Also, vitreomacular interface changes or any abnormality detected at the surface of the retina were also labeled as epiretinal.
2. Intraretinal abnormalities (Fig. 1b): defined as change in the retinal thickness such as an increase suggestive of edema or a decrease suggestive of retinal atrophy. The abnormality in retinal thickness (increase or decrease) was detected based on a comparison with the Zeiss age-matched normative patient database. In addition, any hyperreflective feature within the retina substance (e.g., hemorrhage, vascular abnormality, or RPE



**Fig. 1.** Nonmydriatic optical coherence tomography images showing typical epiretinal (a), intraretinal (b), and subretinal abnormalities (c) (white arrows).

migration to the retinal layers) or hyporeflective features such as fluid form edema or serous retinal detachment were considered as intraretinal abnormalities. Photoreceptor irregularities were also included in this category.

3. Subretinal abnormalities (Fig. 1c): defined as any change in the choroid or in the retinal pigment epithelium such as thinning, thickening, or pigment epithelial detachment.

OCT images could have changes in more than one category. Unreadable images were defined as having very low signal strength or artifacts from staphylomatous changes or large anteroposterior diameter and were excluded from the analysis.

#### Statistical Analysis

Macular abnormalities (intraretinal, epiretinal, and subretinal) from the NMOCT and from the gold standard COE were recorded and compared. A true-positive result was defined as macular abnormality that was detected on both NMOCT and COE, and a true-negative result as the absence of abnormality on both NMOCT and COE. A false-negative result, or underdetection, is one where there was a macular abnormality on COE that did not show on the NMOCT macular map, whereas a false-positive result is one in which an irregularity appeared on NMOCT but not on the COE. From these values, contingency tables were created and the sensitivity and specificity of the NMOCT in detecting any macular abnormality, or only one category of abnormalities (epiretinal, intraretinal, or subretinal), were calculated. Cohen's kappa coefficient was used to evaluate the overall agreement between the NMOCT and COE in detecting any macular irregularity. Finally, regression and correlation analyses were carried out to determine the relationship between age and the incidence of macular abnormalities detected on the COE and NMOCT. For this, subjects were divided into 5-year interval age groups: 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, and 80 and above.

## Results

Of the 552 patients initially approached, 406 subjects completed both macular evaluation methods. The demographic details of the study population are summarized in Table 1. A total of 771 NMOCT studies were judged as having adequate quality images (94.95%). A

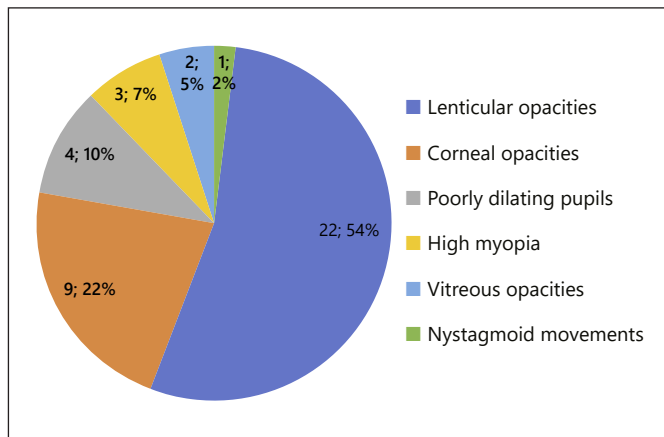
**Table 1.** Demographic characteristics of the study population ( $n = 406$ )

Male gender	184 (45.32)
Age, years	59 (50–88)
Diabetes	47 (11.58)
Hypertension	142 (34.98)
Coronary artery disease	44 (10.84)
Peripheral vascular disease	26 (6.40)
Rheumatologic diseases	55 (13.55)
Current smokers	253 (62.32)

Values are  $n$  (%) or mean (range), as appropriate.

review of the COE of eyes with poor-quality NMOCT images was done to look into possible causes of this difficulty (Fig. 2). Using NMOCT, intraretinal abnormalities were detected in 44 eyes (5.71%) in the adequate-quality images. Epiretinal abnormalities were detected in 19 eyes (2.46%) and subretinal abnormalities were detected in 24 eyes (3.11%). Looking at the same population with the readable images, the COE detected intraretinal abnormalities in 55 eyes (7.13%), epiretinal abnormalities in 22 eyes (2.85%), and subretinal abnormalities in 27 eyes (3.50%) (Table 2).

Cohen's kappa coefficient for overall agreement between NMOCT and COE was 0.90 ( $p < 0.001$ ). Sensitivity and specificity of NMOCT to detect any macular abnormality was 82.65% (95% CI: 73.69–89.56) and 98.97% (95% CI: 97.89–99.59), respectively. When considering each category of macular abnormalities separately, the sensitivities and specificities were 86.36% (95% CI: 65.09–97.09) and 99.73% (95% CI: 99.02–99.97) for epiretinal abnormalities, 80.00% (95% CI: 67.03–89.57) and 99.58% (95% CI 98.77–99.91) for intraretinal abnormalities, and 88.89% (95% CI: 70.84–97.65) and 99.73% (95% CI: 99.01–99.97) for subretinal abnormalities, respectively.



**Fig. 2.** Possible causes of poor-quality nonmydriatic spectral domain optical coherence tomography images.

The incidence of macular abnormalities increases exponentially with age, whether detected on the COE or by NMOCT (Fig. 3). In fact, there was no significant difference in the incidence rates with age between the two modalities ( $p = 0.0625$ ). Furthermore, regression analysis demonstrated a strong nonlinear relationship between age and the percentage of subjects with macular abnormalities  $R^2 = 0.97$ , as well as a strong positive correlation between the two, with a correlation coefficient  $R = 0.86$  ( $p = 0.024$ ).

## Discussion

Macular changes due to diabetic maculopathy from diabetes mellitus and ARM are becoming increasingly common since both diseases are reaching epidemic levels [10]. Data from the USA suggest that baby boomers are at an age of developing ARM and in parallel, diabetes has been recognized as a pandemic condition [11, 12]. Catching macular changes from either disease at an early stage, when eyes are still asymptomatic with minimal change in vision, is important since this is usually associated with a better outcome in terms of treatment and prevention of vision deterioration [3]. Furthermore, other macular findings such as telangiectasia and cysts, albeit less common, represent potential diseases that present with the same challenge of a more favorable outcome if caught and dealt with at an early stage [13]. This would entail routinely examining a large number of subjects without any eye complaints looking for changes that are amenable to treatment. Despite ample efforts campaigning for a baseline eye examination starting at the age of 40 years fol-

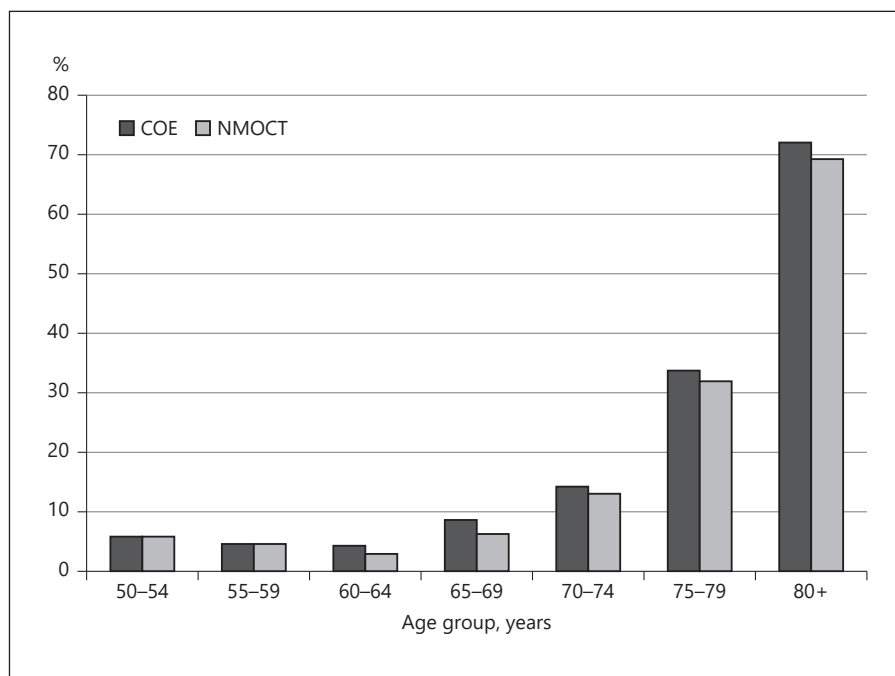
**Table 2.** Changes detected by NMOCT and COE

Location	Abnormality	COE	NMOCT	
Epiretinal	Epiretinal membrane	9	9	
	Thickened ILM	6	6	
	Wrinkling	4	4	
	Mechanical traction	1	1	
Intra-retinal	Nonspecific hypodense lesions	–	2	
	Nonspecific hyperdense lesions	–	6	
	Intraretinal abnormalities	–	18	
	Hemorrhage	9	–	
	Atrophic changes	24	13	
	Telangiectatic vessel	2	0	
	Retinal scar	7	–	
	Cystoid spaces	3	2	
	Exudates	2	0	
	Cotton-wool spots	1	2	
	Microaneurysm	1	0	
	Subretinal	Drusen	17	13
		RPE atrophy	4	4
Subretinal scar		5	4	
Atrophic changes		2	1	
Chorioretinal scar		3	–	
Nonspecific subretinal abnormalities		–	9	

NMOCT, nonmydriatic optical coherence tomography; COE, comprehensive ophthalmologic evaluation; ILM, internal limiting membrane; RPE, retinal pigment epithelium.

lowed by yearly routine examination, such a policy remains difficult to implement financially and is time consuming for the patient and the ophthalmologist. A telemedicine-applicable screening method for adults at risk of macular changes, preceding an evaluation by an ophthalmologist looking for abnormalities in the fovea, is of paramount importance since it would allow catching pathology at an early stage and referring the subject in question for a comprehensive evaluation and further management. Fundus photography combined with fluorescein angiography detects early pathology with great precision; however, such an effort is unrealistic and is associated with rare but serious complications: intravenous fluorescein injection has been reported to cause allergy, anaphylactic shock can lead to possible death [14, 15], and pharmacologic dilatation can result in an acute angle-closure glaucoma attack [16]. A method using modern technology avoiding pupil dilatation and the infusion of systemic dyes would be ideal for screening. Nonmydriatic fundus photography, when introduced, rapidly gained momentum since it relieved patients from dilata-

**Fig. 3.** Incidence (%) of macular abnormalities detected by COE and NMOCT per age group. COE, comprehensive ophthalmologic evaluation; NMOCT, nonmydriatic spectral domain optical coherence tomography.



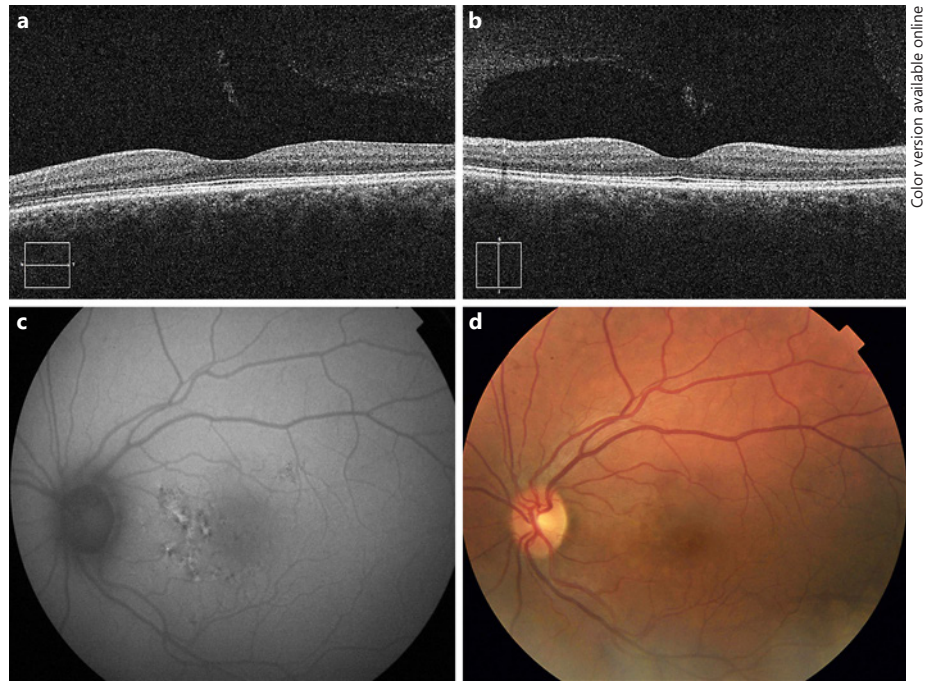
tion. Patients were impressed and comfortable after the image acquisition experience. In a number of studies, however, nonmydriatic fundus photography failed to detect an increase in macular thickening, a hallmark of disease progression requiring intervention, be it diabetic maculopathy or ARM [17, 18]. This was somewhat dealt with at a later stage when the digital imaging era was introduced to fundus photography. Investigators advocated the use of stereo digital imaging to overcome such a shortcoming [19]. These endeavors had limited success since stereo image acquisition using the nonmydriatic fundus camera, and the stereo interpretation of fundus images involved both a learning curve and at times expensive machinery, making this technique adequate only in specific and particular settings [19]. Furthermore, extensive iris shadows in nonmydriatic fundus imaging refuted fundus photo screening in communities of dark-skinned individuals [20]. Our technique using NMOCT was a reliable tool in detecting minor changes, including macular thickening, with a small percentage of underdiagnosed irregularities (Table 3). The majority of the changes missed were of minor consequence; in fact, intraretinal punctate hemorrhages were the most commonly underdetected irregularity by the NMOCT. Without an overt leak and a microaneurysmal transformation, these do not cause any vision loss and do not pose an overt threat to vision. Epiretinal abnormalities were rarely missed be-

**Table 3.** NMOCT underdiagnosed findings compared to COE

Underdetected abnormality	<i>n</i> = 17
Drusen	3
Atrophic changes	3
Wrinkling	2
Hemorrhage	5
Thickened ILM	1
Retinal precipitate	1
Telangiectatic vessel	2

NMOCT, nonmydriatic optical coherence tomography; COE, comprehensive ophthalmologic evaluation; ILM, internal limiting membrane.

cause of the nature of the imaging, which concentrates on the vitreomacular interface. Subretinal abnormalities not detected by NMOCT were mostly due to changes of very small size or present outside the central subfield (Fig. 4). These usually represent hard drusen and are seldom associated with the transformation to the wet form of ARM leading to poor vision. Subretinal atrophy, when subtle, was also missed, especially if not accompanied by a change in thickness. This again, when present, does not cause any visual symptom and does not require treatment. A closer look at the specificity values representing the overreported findings on the NMOCT compared to the COE reveals



Color version available online

**Fig. 4.** Example of a false-negative case of subretinal irregularities: nonmydriatic optical coherence tomography images in horizontal (a) and vertical sections (b) of the macula showing no irregularity, while the corresponding autofluorescence (c) and fundus photographs (d) demonstrate retinal pigment epithelium changes in the nasal juxtafoveal area.

that they were mainly artifactual, relating to the nonmydriatic nature of the imaging technique combined with some mild central media opacities and motion artifact. Thus, these findings were not of clinical significance, but their existence should be acknowledged to avoid overdiagnosis. Lastly, the increasing incidence of macular abnormalities with age could suggest that NMOCT could potentially be instituted as a periodic telemedicine monitoring device for macular abnormalities, should access to an ophthalmologist be difficult.

The findings of this study are by and large a reflection of the OCT image interpretation protocol utilized. As mentioned in Methods, it was our intention to simplify the OCT image analysis so it is most reflective of a true screening tool that should ideally be relatively quick and simple, yet efficient. As such, only qualitative data noted in the vertical and horizontal line scans included in the macular map printout were analyzed. No effort was made to analyze the other line scans of the macular cube study or the retinal thickness measurements generated in the macular cube printout, although this would have likely improved the sensitivity of NMOCT in detecting macular abnormalities. However, such a detailed OCT image analysis would be so time consuming and labor intensive that it would not be adopted as a simple screening methodology.

In conclusion, although the COE remains the gold standard for detecting macular abnormalities, NMOCT

is a promising tool integrating telemedicine to screen for macular diseases. Nevertheless, the method has limitations that ought to be underlined. First, the screening covers the macular area only. Any changes happening outside that area will be missed. For instance, some diabetic patients may present with proliferative diabetic retinopathy in the absence of associated diabetic macular edema or other macular abnormalities, which will be missed using NMOCT as a screening method. Stressing such a scenario is important when the subjects screened happen to suffer from diabetes. This particular group of patients should not be given a false sense of security when the NMOCT capturing the macula is negative. Second, as discussed above, analyzing only the vertical and horizontal line scans included in the macular map printout may have limited the sensitivity of NMOCT imaging in detecting macular abnormalities. Third, the current optics on the OCT machine used in this study do not feature a small pupil adaptation. It is therefore a machine designed for dilated pupils and is heavily taxed by any media opacity. In our analysis, this was the main reason behind unreadable images. Fourth, proper image acquisition on a constricted pupil requires experience and skill in catching the foveal center and proper alignment. However, the recently available eye tracker application (available since 2013) creates ease in detecting the fovea and reproducing images at the same location. In addition, the advent of swept-

source OCT could also provide better means of nonmydriatic macular imaging. Lastly, while this was a pilot study, having only one reader evaluate the clinical setting and the fundus photographs could potentially bring bias that could be avoided by having two or more readers and then evaluating their agreement.

In summary, we presented a potential screening method for macular changes that seems to be promising in detecting early signs of potentially sight-threatening diseases. Perhaps future studies investigating the use of NMOCT in detecting optic nerve abnormalities, including glaucomatous changes, may further prove its use as a screening tool for most of the common causes of vision loss. Sensitivities were high, and agreement coefficients were excellent at all retinal levels. In fact, changes missed were of little importance. However, it should be stressed that this technique does not replace an eye examination or even a retinal evaluation, since the NMOCT is limited to chang-

es in the macular area. A good number of changes such as macular hole were not encountered in our subjects because of the relatively small sample size. In our opinion, a larger study with a wider age range, a bigger subject number, and using newer OCT machines with an eye tracker system is needed to confirm our results. In addition, the OCT interpreter could have access to the electronic image rather than the simple 2D map. Once established as a screening tool, it could be advised as a routine step for middle-aged patients having an evaluation without dilatation, since it does not require any mydriatic eye drops.

### Disclosure Statement

None of the authors have any proprietary interests or conflicts of interest related to this submission. No funding was received for this study.

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