

# ABOUT THE AUTHORS



**CINDY HUTNIK, MD** is a full professor in the Departments of Ophthalmology and Pathology at the Schulich School of Medicine and Dentistry, at Western University, London, Ontario, Canada. Currently she is the President of the Canadian Glaucoma Society, Chair of the Governing Committee of the Academic Medical Organization of Southwestern Ontario and a member of the Board of Glaucoma Research Society of Canada. She has a keen interest in the development of novel and/or optimization of existing treatments for patients with glaucoma.



**MICHAEL KRYSHTALSKYJ, MD** is a resident physician in ophthalmology at the University of Calgary's Cumming School of Medicine. He completed his medical studies at the University of Toronto, where he was awarded a longitudinal research studentship in Glaucoma and Advanced Anterior Segment Surgery with Dr. Ike Ahmed. Dr. Kryshtalskyj maintains an active interest in ophthalmologic research and has served as a reviewer for the Canadian Journals of Ophthalmology and Neurology. He is also active in global and rural health initiatives.



**KIAN MADJEDI, MD** is an ophthalmology resident at the University of Calgary. He completed his medical training at the Northern Ontario School of Medicine. As a Rotary Scholar, he earned a Master's degree in Epidemiology at the University of Cambridge (Clare College), where his dissertation examined genetic associations with glaucoma. He is an active member of several international research collaborations investigating polygenic risk scores and gene-environment associations in glaucoma using data from international biobanking efforts. He is interested in all aspects of glaucoma and in improving access to glaucoma screening and management for underserved populations.



**ANDREW CRICHTON, MD** is Chief of Ophthalmology for Calgary and Clinical Professor at the University of Calgary. After graduating from medical school at the University of British Columbia, he did his ophthalmology residency in Toronto and his glaucoma fellowship in Vancouver with Dr. Stephen Drance and Dr. Gordon Douglas. Dr. Crichton has previously served as President of the Canadian Glaucoma Society, Secretary of the Canadian Ophthalmologic Society, and President of the Ophthalmology Society of Alberta.

# Spot the differences: challenges in detecting glaucoma in the myopic patient

Cindy M.L. Hutnik, MD, PhD, FRCSC and Michael T. Kryshtalskyj, MD

Kian M. Madjedi, MD, MPhil

Andrew C.S. Crichton, MD, FRCSC

## Clinical Case Conundrum:

A 53-year-old male was referred for glaucoma consultation regarding paracentral visual field defects in the right eye. Prior to phacoemulsification and intraocular ocular lens (IOL) implantation his refraction was -10.50 D and -11.00 D in the right and left eyes, respectively. Axial length was 28 mm in both eyes (OU). He was medically healthy. Visual acuities were 20/25 OU. Intraocular pressures (IOPs) were 16 mmHg OU. Central corneal thicknesses were 652  $\mu$ m OU. Anterior segment, gonioscopy, and fundus findings are indicated in **Figure 1**. Optical coherence tomography (OCT) analysis of the retinal nerve fibre layer (RNFL) is shown in **Figure 2**. This patient's visual fields and structure-function correlations are highlighted in **Figure 3**.

Asymptomatic myopic patients often present with normal intraocular pressures, anomalous nerves, and visual field defects that are challenging to interpret in the context of one another. This is further complicated by myopia being a known risk factor for glaucomatous progression. Decisions regarding diagnosis and management in this patient population remain challenging.

## Epidemiology:

Myopia is a growing epidemic. By 2050, it is predicted that 5 billion people (50% of the global population), will have myopia. Of these, 1 billion are projected to incur vision-threatening complications of high myopia.<sup>1</sup> High, or pathologic, myopia is defined as a spherical equivalent > -6.00 D or an axial length > 26.5 mm.<sup>2</sup> Patients with high myopia are at higher risk for several conditions believed to arise from excessive axial stretching of the globe, including retinal atrophy and degenerations predisposing to detachments. Myopic patients can lose central vision from a host of macular conditions including choroidal neovascularization, chorioretinal atrophy, peripapillary crescents, Bruch's membrane dehiscences, and a thin macular choroid, thereby limiting visual potential.<sup>3,4</sup>

Several landmark trials have identified myopia as an important risk factor for developing primary open angle glaucoma (POAG).<sup>5</sup> Glaucoma represents a group of disorders culminating in optic neuropathy with stereotypic optic nerve changes, loss of retinal ganglion cells, and corresponding visual field defects.<sup>6</sup> High myopia may increase the risk of POAG by as much as six-fold<sup>7</sup> and make patients more susceptible to incurring POAG at an earlier age.<sup>8</sup> POAG often presents despite "normal" pressures, and several studies have found plausible associations between myopia and normal-tension glaucoma.<sup>5</sup> In high myopes, it has been hypothesized that axial stretching or torsional forces at the lamina cribrosa may induce glaucoma through axonal strain.<sup>9,10</sup> Notwithstanding their frequent coexistence, glaucoma may be challenging to diagnose in high myopia. Due to departures from normative data for eyes with myopia and glaucoma, management of the coexisting conditions remains a common clinical conundrum.

## Optic Nerve Analysis:

Glaucomatous optic nerve changes are often difficult to detect in myopic nerves for several reasons. With increasing axial length, the position of the optic disc can be displaced nasally in relation to the fovea, resulting in a rotation or 'tilt' of the disc with an associated shift in the Bruchs' Membrane opening and affording only an oblique view of the optic nerve head (ONH).<sup>11,12</sup> The ONH may be more pallid, reducing contrast between the pink neuroretinal rim and the optic cup. Distinguishing zones of peripapillary atrophy (PPA), with the increase in the beta zone having been linked to glaucoma, may be difficult. The lamina cribrosa can stretch and become thin. Further, choroidal thinning and subsequent retinal pigment epithelium (RPE) atrophy can make it difficult to detect peripapillary RNFL changes.<sup>12</sup> However, in myopes, RNFL defects may be an early sign of glaucoma, especially if they involve the papillomacular bundles.<sup>13</sup>

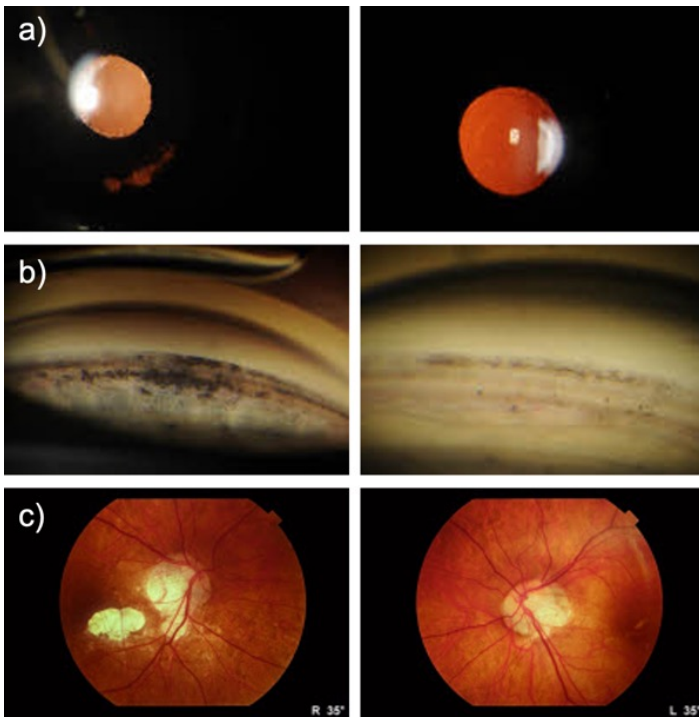


Figure 1: Clinical photograph compilation of salient exam findings including a) transillumination defects OD, b) pigment deposition OD on gonioscopy, c) fundus photographs of the optic nerve heads and peripapillary retina; courtesy of Cindy Hutnik et al.

Interpreting OCT measurements of the RNFL can also be nuanced in myopic patients. The normative database for the Cirrus® (Zeiss, Dublin, California) HD-OCT contains data from only 284 individuals, with limited representation from high myopes and hyperopes.<sup>14</sup> The lack of a myopic reference often biases clinicians towards “red disease” in which the OCT suggests abnormal thinning when the patient in fact has a healthy RNFL (a false positive).<sup>15,16</sup> Indeed, the disc-margin definition algorithm on HD-OCT can be influenced by myopic changes such as tilt, magnification or media artefact and scan circle misalignment from peripapillary atrophy. The superotemporal and inferotemporal RNFL bundles can be temporally displaced. Symmetry, correlation of other clinical parameters, and serial observations are essential, in the evaluation of a myopic patient who is considered at risk for glaucoma.<sup>14,17</sup>

#### Visual Fields:

Visual fields may also be difficult to interpret in myopic patients. Significant PPA can cause visual field defects. Macular pathology, including choroidal neovascularization or atrophy, can cause paracentral scotomas mimicking glaucomatous field loss, especially the paracentral changes seen in normal-tension glaucoma (NTG).

Sub-foveal choroidal thickness has been shown to be the most significant predictor of visual acuity in highly myopic eyes,<sup>3</sup> and choroidal and outer retinal thinning has been

implicated in early visual field defects in myopes.<sup>18</sup> High myopes can have higher mean deviations<sup>19</sup> and lower threshold sensitivities than emmetropes.<sup>20</sup> Therefore, even at a microarchitectural level, myopic macular degenerations can confound visual fields in glaucoma evaluations. It is interesting to note that choroidal thinning has also been linked to the progression of visual field damage in a cohort of NTG patients, possibly implicating choroidal thinning in NTG pathogenesis.<sup>21</sup>

#### Structural Imaging: New Frontiers and New Management Considerations:

A host of novel imaging techniques may enhance our ability to detect glaucoma in myopic patients. For instance, new sd-OCT imaging strategies may more accurately detect the neuro-retinal rim (NRR). The Bruchs’ membrane opening minimal rim width (BMO-MRW) is the minimum distance from the BMO to the internal limiting membrane. Measuring the NRR using the BMO-MRW has been shown to reduce rates of false positive errors in healthy myopic eyes with tilted ONHs, yielding more accurate RNFL analyses.<sup>11,22</sup>

Other imaging approaches have been introduced to better differentiate between glaucomatous optic neuropathy and myopia. Ganglion cell analysis in sd-OCT relies largely on the fact that retinal ganglion cells in the peripapillary RNFL (ppRNFL) are mainly located within the macula. Given the artefactual OCT changes that can confound analysis in myopic eyes, OCT of the ganglion cell-inner plexiform layer (GC-IPL) may aid in the differential diagnosis between glaucoma and myopia, especially in myopic eyes where the optic disc structure may introduce inaccuracies in ppRNFL measurements. Compared to RNFL analyses, macular ganglion cell complex parameters may be less susceptible to artefacts from refractive error or ONH morphology.<sup>23</sup>

Various scoring systems for identifying glaucoma in myopic eyes have been proposed. One study involving 195 highly myopic eyes identified that the GC-IPL hemifield test has an especially high sensitivity for discriminating between myopia and glaucoma. This test measures GC-IPL thickness differences across the horizontal temporal raphe on an OCT macula. The presence of temporal hemifield asymmetry on OCT GC-IPL thickness maps (“raphe sign”) can be a particularly useful parameter for detecting glaucomatous changes in high myopes.<sup>22</sup>

In recent years, many clinicians have advocated for the development of an OCT normative database of myopic eyes as a more meaningful reference group for clinical decision making. Several small myopic normative databases have been developed for these purposes and have shown promise in improving the specificity and sensitivity for detecting RNFL abnormalities in eyes with

OD OS

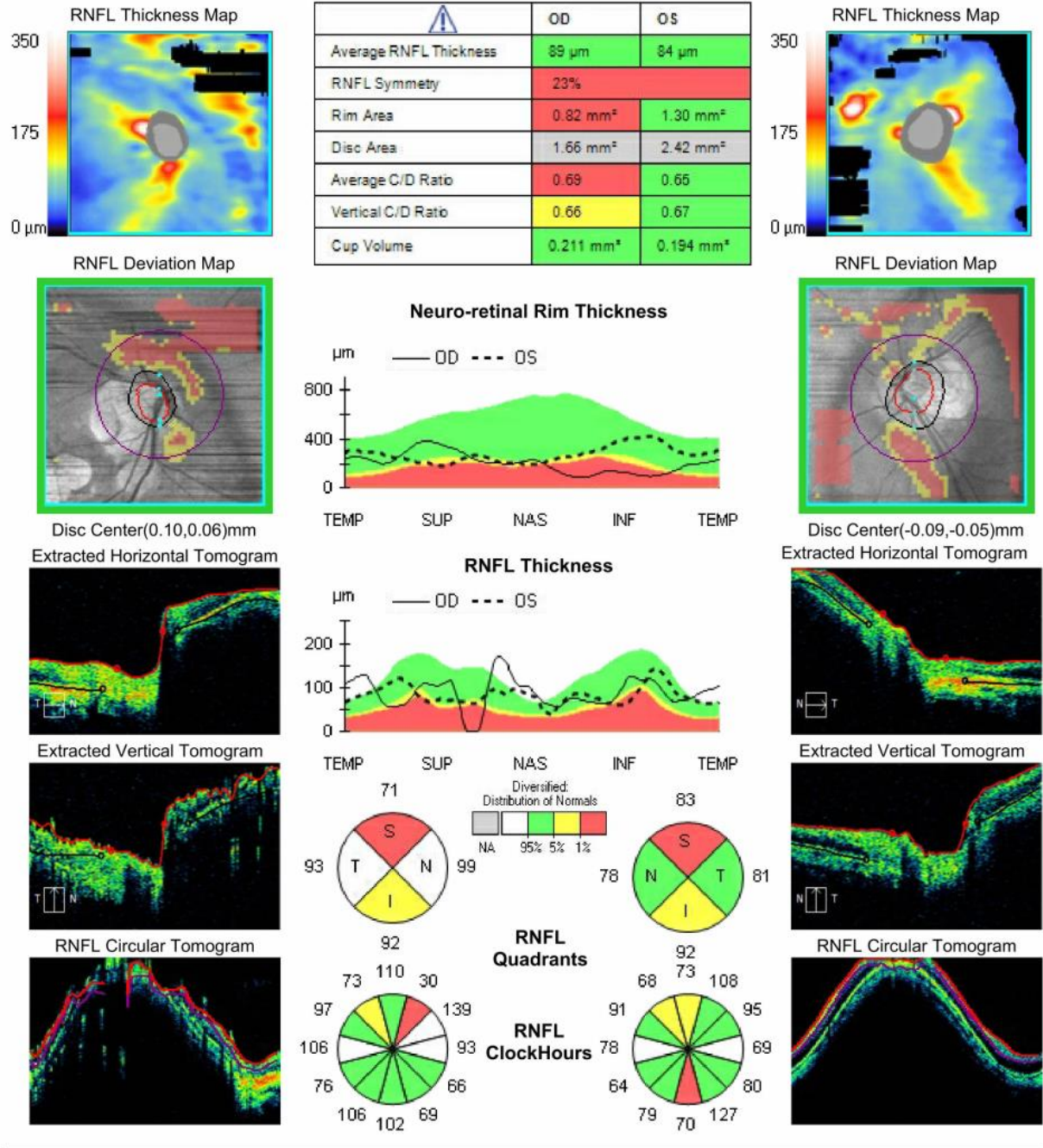


DOB: 7/10/1968  
Gender: Male  
Technician: Operator, Cirrus

Exam Date: 1/27/2022 1/27/2022  
Exam Time: 9:06 AM 9:07 AM  
Serial Number: 6000-10923 6000-10923  
Signal Strength: 8/10 7/10

St. Joseph's Health Care Lond

### ONH and RNFL OU Analysis: Optic Disc Cube 200x200 OD OS



Comments  
Analysis Edited: 1/27/2022 9:09 AM

Doctor's Signature

CIRRUS1  
SW Ver: 11.5.2.54532  
Copyright 2020  
Carl Zeiss Meditec, Inc  
All Rights Reserved  
Page 1 of 1

Figure 2: Zeiss Cirrus® HD-OCT analysis of the retinal nerve fibre layer queried superior thinning OU and inferior thinning OS; courtesy of Cindy Hutnik et al.

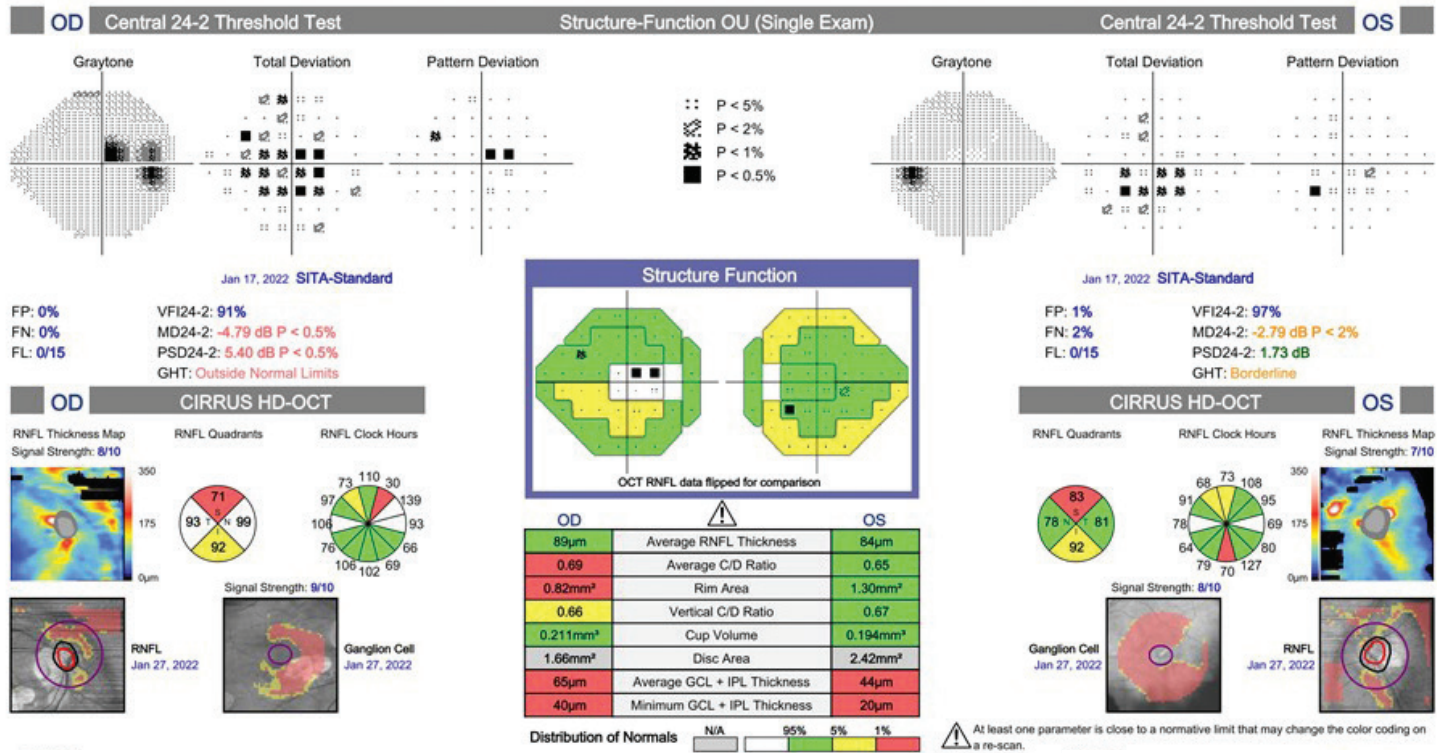


Figure 3: Structure-Function Maps (Zeiss Cirrus® HD-OCT), containing 24-2 visual field data and querying glaucoma OU; courtesy of Cindy Hutnik et al.

high myopia.<sup>24,25</sup> One study found that integrating a myopic normative database for RNFL thickness analyses can lead to a substantial improvement in reduction of false positive errors in myopic eyes compared to the emmetropic normative database contained in the Zeiss Cirrus® HD-OCT.<sup>25</sup> Myopic normative databases have proven challenging to develop for recruitment and proprietary reasons. Further, the considerable diversity of ONH configurations and refractive errors seen in myopia make it challenging to identify a 'standard normal' as a reference group.

### Artificial Intelligence:

The application of artificial intelligence (AI) approaches to identifying glaucoma in the setting of myopia remains an exciting prospect. Current research efforts in this area have largely focused on disease classification and prediction for both glaucoma and myopia. Machine learning models (a branch of AI) have been shown to identify both glaucoma and myopia from OCT printouts and may predict glaucomatous progression.<sup>26</sup> AI approaches have made significant inroads in detecting glaucomatous disc damage from fundus photographs and OCTs. Other algorithms may successfully predict progression of glaucoma in eyes with myopia.<sup>27,28</sup> Since machine learning models in glaucoma

rely heavily on ONH morphology in making decisions, many of the developments in AI in this field are still limited by excluding highly myopic eyes from training datasets. AI remains an exciting frontier and may become an additional clinical tool in distinguishing between glaucoma and myopia. The incorporation of AI platforms into routinely used electronic medical records may be very helpful in deciphering the complexities posed by managing glaucoma in the setting of myopia.

### Conclusion

The growing public health burden associated with high or pathologic myopia is of concern as these patients are at higher risk for other related conditions including POAG. Optic nerve analysis in high myope patients with glaucomatous optic nerve changes may be difficult to detect. In myopes, RNFL changes may be predictive of glaucoma but OCT measurements of the RNFL are hampered by the lack of a myopic reference group which may lead to false positives. Visual fields can also be difficult to interpret with many variables contributing to visual field defects and/or mimicking glaucomatous field loss. The emergence of new imaging techniques and the prospect of AI hold much promise in helping clinicians differentiate between glaucoma and myopia.

## References:

1. Holden BA, Fricke TR, Wilson DA, et al. Global Prevalence of Myopia and High Myopia and Temporal Trends from 2000 through 2050. *Ophthalmology*. 2016;123(5):1036-1042. doi:10.1016/j.ophttha.2016.01.006
2. The impact of myopia and high myopia: report of the Joint World Health Organization–Brien Holden Vision Institute Global Scientific Meeting on Myopia, University of New South Wales, Sydney, Australia, 16–18 March 2015. Geneva: World Health Organization; 2.
3. Nishida Y, Fujiwara T, Imamura Y, Lima LH, Kurosaka D, Spaide RF. Choroidal thickness and visual acuity in highly myopic eyes. *Retina*. 2012;32(7):1229-1236. doi:10.1097/IAE.0B013E318242B990
4. Ohno-Matsui K. Pathologic Myopia. *Asia-Pacific J Ophthalmol (Philadelphia, Pa)*. 2016;5(6):415-423. doi:10.1097/APO.0000000000000230
5. Hsu CH, Chen RI, Lin SC. Myopia and glaucoma: sorting out the difference. *Curr Opin Ophthalmol*. 2015;26(2):90-95. doi:10.1097/ICU.0000000000000124
6. Casson RJ, Chidlow G, Wood JPM, Crowston JG, Goldberg I. Definition of glaucoma: clinical and experimental concepts. *Clin Experiment Ophthalmol*. 2012;40(4):341-349. doi:10.1111/J.1442-9071.2012.02773.X
7. Pan CW, Cheung CY, Aung T, et al. Differential associations of myopia with major age-related eye diseases: the Singapore Indian Eye Study. *Ophthalmology*. 2013;120(2):284-291. doi:10.1016/j.ophttha.2012.07.065
8. Shim SH, Sung KR, Kim JM, et al. The Prevalence of Open-Angle Glaucoma by Age in Myopia: The Korea National Health and Nutrition Examination Survey. *Curr Eye Res*. 2017;42(1):65-71. doi:10.3109/02713683.2016.1151053
9. Lee KS, Lee JR, Kook MS. Optic disc torsion presenting as unilateral glaucomatous-appearing visual field defect in young myopic Korean eyes. *Ophthalmology*. 2014;121(5):1013-1019. doi:10.1016/j.ophttha.2013.11.014
10. Park HYL, Choi S II, Choi JA, Park CK. Disc Torsion and Vertical Disc Tilt Are Related to Subfoveal Scleral Thickness in Open-Angle Glaucoma Patients With Myopia. *Invest Ophthalmol Vis Sci*. 2015;56(8):4927-4935. doi:10.1167/IOVS.14-15819
11. Malik R, Belliveau AC, Sharpe GP, Shuba LM, Chauhan BC, Nicoleta MT. Diagnostic Accuracy of Optical Coherence Tomography and Scanning Laser Tomography for Identifying Glaucoma in Myopic Eyes. *Ophthalmology*. 2016;123(6):1181-1189. doi:10.1016/j.ophttha.2016.01.052
12. Tan NYQ, Sng CCA, Jonas JB, Wong TY, Jansonius NM, Ang M. Glaucoma in myopia: diagnostic dilemmas. *Br J Ophthalmol*. 2019;103(10):1347-1355. doi:10.1136/BJOPHTHALMOL-2018-313530
13. Kimura Y, Hangai M, Morooka S, et al. Retinal Nerve Fiber Layer Defects in Highly Myopic Eyes with Early Glaucoma. *Invest Ophthalmol Vis Sci*. 2012;53(10):6472-6478. doi:10.1167/IOVS.12-10319
14. Chang RT, Singh K. Myopia and glaucoma: diagnostic and therapeutic challenges. *Curr Opin Ophthalmol*. 2013;24(2):96-101. doi:10.1097/ICU.0B013E32835CEF31
15. Chong GT, Lee RK. Glaucoma versus red disease: imaging and glaucoma diagnosis. *Curr Opin Ophthalmol*. 2012;23(2):79-88. doi:10.1097/ICU.0B013E32834FF431
16. Park EA, Budenz DL, Lee RK, Chen TC. Red and Green Disease in Glaucoma. *Atlas Opt Coherence Tomogr Glaucoma*. Published online 2020:127-174. doi:10.1007/978-3-030-46792-0\_8
17. Leung CKS, Yu M, Weinreb RN, et al. Retinal Nerve Fiber Layer Imaging with Spectral-Domain Optical Coherence Tomography: Interpreting the RNFL Maps in Healthy Myopic Eyes. *Invest Ophthalmol Vis Sci*. 2012;53(11):7194-7200. doi:10.1167/IOVS.12-9726
18. Wu Q, Chen Q, Lin B, et al. Relationships among retinal/choroidal thickness, retinal microvascular network and visual field in high myopia. *Acta Ophthalmol*. 2020;98(6):e709-e714. doi:10.1111/AOS.14372
19. Tay E, Seah SK, Chan SP, et al. Optic disk ovality as an index of tilt and its relationship to myopia and perimetry. *Am J Ophthalmol*. 2005;139(2):247-252. doi:10.1016/j.ajao.2004.08.076
20. Aung T, Foster PJ, Seah SK, et al. Automated static perimetry: the influence of myopia and its method of correction. *Ophthalmology*. 2001;108(2):290-295. doi:10.1016/S0161-6420(00)00497-8
21. Hirooka K, Fujiwara A, Shiragami C, Baba T, Shiraga F. Relationship between progression of visual field damage and choroidal thickness in eyes with normal-tension glaucoma. *Clin Experiment Ophthalmol*. 2012;40(6):576-582. doi:10.1111/J.1442-9071.2012.02762.X
22. Kim YK, Yoo BW, Jeoung JW, Kim HC, Kim HJ, Park KH. Glaucoma-Diagnostic Ability of Ganglion Cell-Inner Plexiform Layer Thickness Difference Across Temporal Raphe in Highly Myopic Eyes. *Invest Ophthalmol Vis Sci*. 2016;57(14):5856-5863. doi:10.1167/IOVS.16-20116
23. Shoji T, Sato H, Ishida M, Takeuchi M, Chihara E. Assessment of Glaucomatous Changes in Subjects with High Myopia Using Spectral Domain Optical Coherence Tomography. *Invest Ophthalmol Vis Sci*. 2011;52(2):1098-1102. doi:10.1167/IOVS.10-5922
24. Akashi A, Kanamori A, Ueda K, Inoue Y, Yamada Y, Nakamura M. The Ability of SD-OCT to Differentiate Early Glaucoma With High Myopia From Highly Myopic Controls and Nonhighly Myopic Controls. *Invest Ophthalmol Vis Sci*. 2015;56(11):6573-6580. doi:10.1167/IOVS.15-17635
25. Biswas S, Lin C, Leung CKS. Evaluation of a Myopic Normative Database for Analysis of Retinal Nerve Fiber Layer Thickness. *JAMA Ophthalmol*. 2016;134(9):1032-1039. doi:10.1001/JAMAOPHTHALMOL.2016.2343
26. Foo LL, Ng WY, Lim GYS, Tan TE, Ang M, Ting DSW. Artificial intelligence in myopia: current and future trends. *Curr Opin Ophthalmol*. 2021;32(5):413-424. doi:10.1097/ICU.0000000000000791
27. Leite D, Campelos M, Fernandes A, et al. Machine Learning automatic assessment for glaucoma and myopia based on Corvis ST data. *Procedia Comput Sci*. 2022;196:454-460. doi:10.1016/j.procs.2021.12.036
28. Lee J, Kim YK, Jeoung JW, Ha A, Kim YW, Park KH. Machine learning classifiers-based prediction of normal-tension glaucoma progression in young myopic patients. *Japanese J Ophthalmol* 2019 641. 2019;64(1):68-76. doi:10.1007/S10384-019-00706-2