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CANADIAN EYE CARE TODAY

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EDITOR'S WELCOME

Dear Canadian Eye Care Community,

It was wonderful to see so many of you at AAO in Chicago a few weeks ago! It has been a tremendous inaugural year for this journal. Thanks to all our authors, advertising partners and, most of all, to our readers who have provided tremendous feedback and encouragement about both the quality of the journal and its place in helping to spread practical knowledge about the Canadian approach to eye care and the management of eye disease.

Our current issue contains some great articles around the theme of imaging. We have one article on the clinical utility of OCTA and another on the clinical applications of OCT in glaucoma. Additionally, we have two articles on anterior segment OCT for the comprehensive ophthalmologist and a review of the options and the decision-making process for refractive surgery in myopes.

We hope you find these articles illuminating and we thank you for your continued readership. Feel free to share our registration link at catalytichealth.com/cect/ with your peers so that they, too, can subscribe to future issues! And if you ever want to read an archived article, please visit the journal website at www.canadianeyecaretoday.com.

And, of course, at this time of the year, we want to take an opportunity to wish all of you and your families a wonderful and peaceful holiday season.

Be safe and see you in 2023!

Best wishes,

Clara C. Chan,
MD, FRCSC, FACS

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Clinical utility of OCTA

Samantha Orr, MD, BMSc, Mohammad Ali Khan, MSc,

## Netan Choudhry, MD, FRCSC, DABO

INTRODUCTION

Optical coherence tomography angiography (OCTA) is a novel technology that can produce images of blood flow with unprecedented resolution of all the vascular layers of the retina and choroid in a rapid, non-invasive fashion. The technology dates back to 2005, when researchers demonstrated that blood flow could be visualized using swept-source OCT (SS-OCT) based on properties of the Doppler signal.[1] Since then, advancements have led to the technology becoming widely available for the clinical community, aiding in patient diagnosis and monitoring. This review article will highlight examples of ophthalmic diseases where OCTA has important clinical utility; specifically, diabetic retinopathy, age-related macular degeneration, retinal vein occlusions, white-dot syndromes, and early research into neurodegenerative diseases.

DIABETIC RETINOPATHY

In diabetic retinopathy (DR), OCTA allows for diagnosis, monitoring, and may even aid in the early detection of retinal changes in patients with diabetes.[2-4] A study from 2019 used OCTA to compare perfused capillary density (PCD) in diabetic patients with healthy controls. In this study, diabetic patients were further sub-categorized as having non-proliferative DR (NPDR), proliferative DR (PDR), or no DR.[2] Diabetic patients with no clinical signs of DR had a significantly higher PCD compared to the control group, providing objective measurement of preclinical retinal vascular changes. The researchers hypothesized that this increase in PCD may have been related to the increased recruitment of capillaries and capillary dilatation.[2] The NPDR and PDR groups demonstrated progressively decreasing PCD. OCTA also provides notable advantages over the current standard of fluorescein angiography (FA). PDR is characterized by retinal ischemia and the development of neovascularization (NV) at the vitreoretinal interface.[2] OCTA can measure these retinal NVs via observation of supra-retinal flow signals above the internal limiting membrane (ILM) or with outpouching of the ILM. A study in 2020 compared widefield OCTA to ultra-wide-field FA (UWF-FA) and ultra-wide-field colour fundus photography (UWF-CF) to detect retinal NV in eyes with PDR.[3] The study demonstrated that widefield OCTA can identify NV not yet evident on UWF-CF and represents a faster and safer alternative to UWF-FA for surveillance of PDR with comparable diagnostic accuracy. OCTA can also allow for differentiation of subtle NVs from

microaneurysms, which may appear similar on FA.[4] Another study demonstrated the utility of widefield OCTA through flow overlay on cross-sectional B scans in the staging and prognostication of DR.[5] Intraretinal microvascular abnormalities (IRMA) are seen on OCTA as collateral vessels within the retina.[5] As the presence of IRMAs denotes the transition to severe NPDR, widefield OCTA can aid in identifying high-risk DR eyes (**Figure 1**).
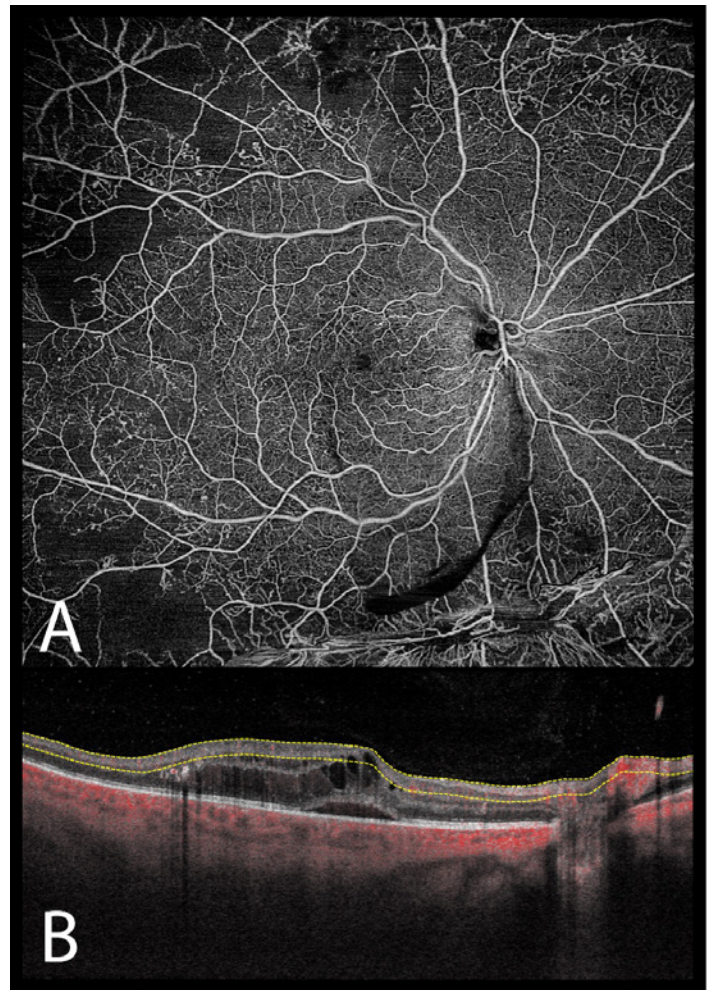
Figure 1: *Widefield OCTA imaging of diabetic retinopathy seen on OCTA (Zeiss Plex Elite 9000, Oberkochen, Germany). Widefield OCTA of the superior vascular plexus (A) showing areas of non-perfusion, vessel pruning, pre-retinal heme, and development of neovascularization. Corresponding flow B scan (B) showing subretinal and intraretinal fluid.*
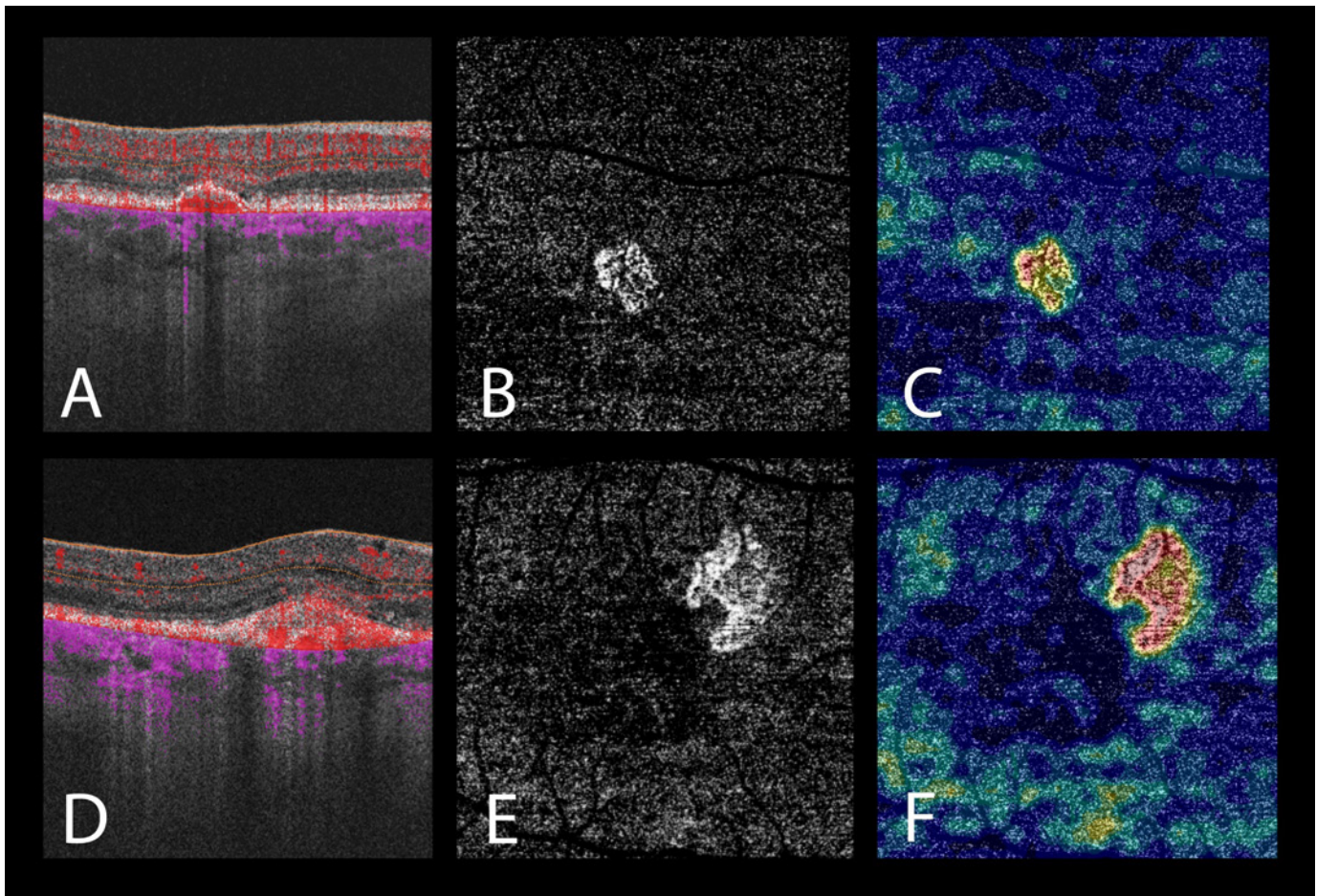
NONEXUDATIVE NEOVASCULAR AGE-RELATED MACULAR DEGENERATION

In recent years, widespread clinical use of OCTA has allowed further exploration into age-related macular degeneration (AMD) presenting with macular neovascularization (MNV) without macular fluid or leakage on FA (**Figure 2**).[6,7] This condition, originally described in the 1970s, is termed non-exudative neovascular AMD.[6,7] Using en-face OCTA correlated with B scan flow overlay, MNV can be reliably detected and monitored (**Figure 2**).[6] These eyes are at an increased risk of exudation compared to eyes with non-neovascular AMD.[6,8-10] The estimated incidence of new onset exudation where the fellow eye had exudative AMD was approximately 25% over different follow-up periods ranging from 6–20 months.[7] Growth of the MNV has been proposed as a possible biomarker to predict conversion to exudative AMD.[7] However, further longitudinal research is required, as this finding has not been consistently elucidated across all studies.[7] Although no randomized clinical trials have been conducted regarding the management of nonexudative neovascular AMD, the consensus is that it should not be treated, but rather monitored.[6,7] Some studies have proposed that this neovascularization may have a protective effect against geographic atrophy (GA), with results from some demonstrating a lower rate of GA lesion growth and surviving retinal pigment epithelium over areas of MNV with adjacent atrophy.[6,7,9] OCT and OCTA technology allows ophthalmologists to closely monitor these patients for the onset of exudation requiring early initiation of treatment.

RETINAL VEIN OCCLUSIONS

In retinal vein occlusions (RVO), OCTA has become particularly valuable in its ability to delineate specific microvascular details in the superficial and deep retinal plexuses and to provide depth-resolved measurements of the foveal avascular zone (FAZ). The size of FAZ measured separately in the superficial and deep vascular plexuses are significantly larger in eyes with RVO compared to fellow eyes, a measurement not possible with the clinical standard using FA.[11] Increased FAZ area in the superficial vascular plexus (SVP) has been shown to correlate with poorer visual acuity in RVO.[11] Both OCTA and FA can evaluate areas of central and peripheral non-perfusion. However, using OCTA to improve determination of the extent and severity of non-perfusion has important prognostic

Figure 2: Nonexudative neovascular age-related macular degeneration seen on OCTA (Topcon DRI Triton, Tokyo, Japan). Cross-sectional B scan with flow overlay (A) showing pigment epithelial detachment without subretinal or intraretinal fluid. OCTA of the outer retina (B) reveals choroidal neovascularization. Perfusion density mapping of the outer retina (C) highlights area of neovascularization. Follow up images after development of exudation and treatment, including B scan with flow overlay (D), OCTA of outer retina (E), and perfusion density map (F).

implications. Although macular edema is often responsible for vision loss in RVO, photoreceptor damage from non-perfusion can cause persistently poor vision.[12] Specifically, grade 4 macular ischemia, according to the Bradley classification, is correlated with poor visual outcomes.[12] However, grades 2 and 3 macular ischemia show no such significant correlation.[12] OCTA also allows for visualization of microvascular changes including vascular tortuosity, telangiectasia, and collateral vessel development.[13]

WHITE DOT SYNDROMES

The use of OCTA in white dot syndromes has provided insight into disease pathophysiology, diagnosis, and management.[14-17] Although these syndromes are rare and can be clinically similar, OCTA has allowed further characterization and differentiation of these pathologies. Lesions in multiple evanescent white dot syndrome (MEWDS) and acute posterior multifocal placoid pigment epitheliopathy (APMPPE) have clinically similar features.[14-18] Use of OCT and OCTA technology demonstrates distinct pathophysiologic processes for these conditions. Normal OCTA of the choriocapillaris in MEWDS has shown that this is likely not a choriocapillaris pathology, but rather a primary photoreceptor inflammatory process.[15] In APMPPE, OCTA reveals patchy flow deficits in the choriocapillaris (**Figure 3**) co-localized with inflammatory lesions, suggesting primary choriocapillaris ischemia with a secondary effect on the outer retinal layers and the retinal pigment epithelium.[16] Although both MEWDS and APMPPE are generally self-limiting, it is important to distinguish between these conditions. MEWDS can be a masquerade for multifocal choroiditis, syphilis, and vitreoretinal lymphoma.[14] Rarely, APMPPE can be complicated by central nervous system vasculitis.[14] The utility of OCTA in detecting choroidal neovascularization is well known.[17] This is useful in white dot syndromes such as birdshot chorioretinopathy and idiopathic multifocal chorditis (iMFC) with panuveitis, which can develop neovascularization secondary to ischemia, requiring treatment.[14,17] Choriocapillaris flow deficits or reduced flow are seen on OCTA in other white dot syndromes, such as acute idiopathic maculopathy (AIM) and serpiginous or serpiginous-like chorditis.[14,17] Conversely, acute macular neuroretinopathy (AMN) is associated with deep capillary plexus ischemia.[14]
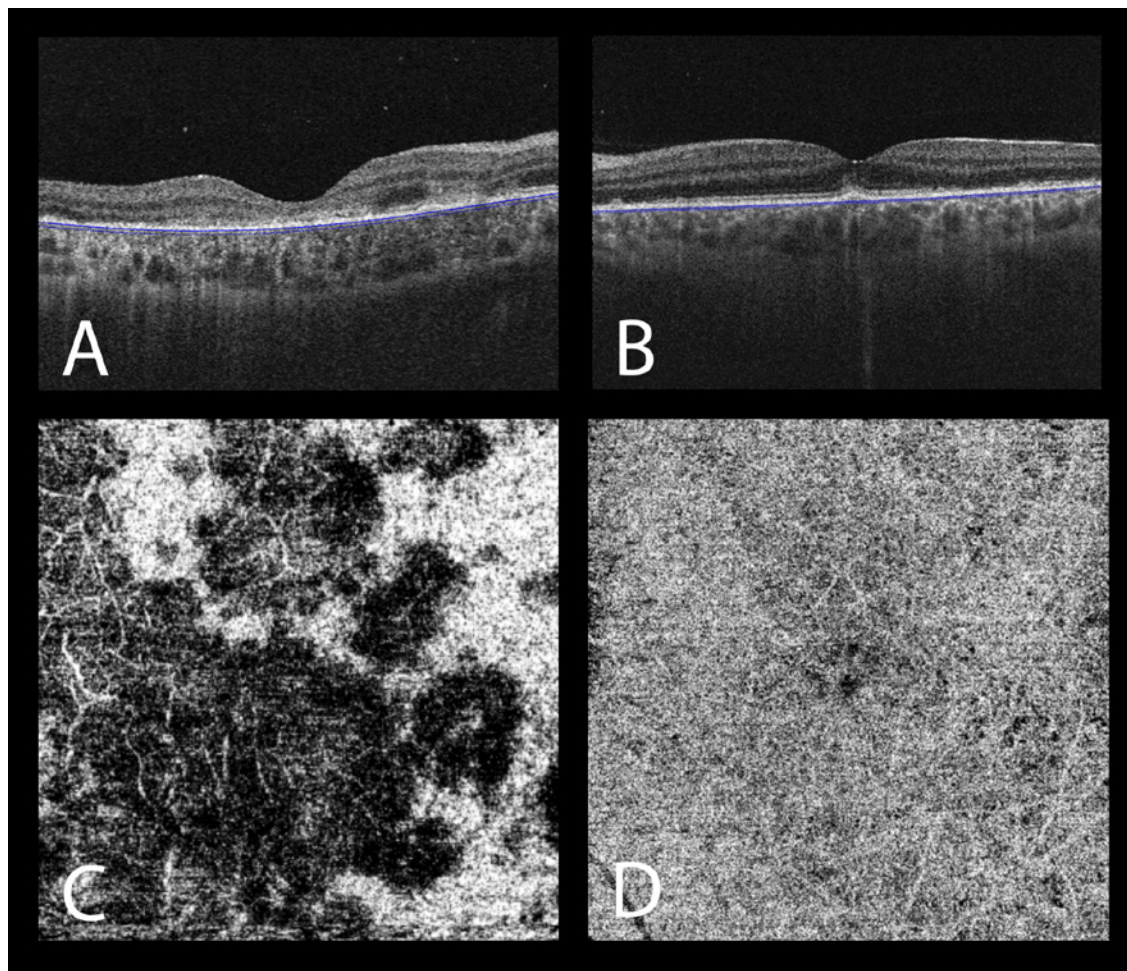
Figure 3: Acute posterior multifocal placoid pigment epitheliopathy and multiple evanescent white dot syndrome seen on OCTA (Topcon DRI Triton, Tokyo, Japan). APMPPE: Single cross-sectional B scan through the fovea (A) demonstrates increased hyperreflectivity in the outer nuclear layer and RPE mottling. 6x6 OCTA of the choriocapillaris (C) shows patchy areas of non-perfusion. MEWDS: Single cross-sectional B scan through the fovea (B) shows focal areas with disruption of the ellipsoid zone. 6x6 OCTA of the choriocapillaris (D) shows normal vasculature with no patchy areas of non-perfusion.

NEURODEGENERATIVE DISEASES

The use of OCTA in patients with neurodegenerative conditions such as Alzheimer's dementia (AD) is an evolving area of research.[19-23] Given the similarities between the microvasculature in the retina and brain, retinal vascular findings on OCTA may provide diagnostic or predictive value for neurodegenerative conditions.[19] In patients with AD, some studies have reported statistically significant OCTA findings compared with control groups and others have found correlations between OCTA measurements and cognitive scores measured by tests such as the Montreal Cognitive Assessment (MoCA).[20,22,24,25] In the eyes of these patients, significantly decreased vessel density in the SVP has been reported.[20] Some studies have also reported a significant decrease in the deep vascular plexus (DVP) density and radial peripapillary capillary level as well, although this has not been reliably replicated.[20-22] A machine learning algorithm used multimodal retinal imaging and patient information to detect AD with reasonable success (AUC of 0.841 in the best-performing model).[25] The algorithm paid particular attention to FAZ size along with SVP density to help make the differentiation.[25] In patients with no diagnosis of cognitive impairment or dementia, density in the SVP was found to correlate with cognitive test scores.[19] These findings could play a role in early detection of cognitive changes.[19] Further research with standardized OCTA acquisition and longitudinal approaches is required to elucidate the full potential of OCTA in the field of cognitive decline.[20,22]

CONCLUSION

OCTA is establishing itself as a valuable tool which provides clinicians with useful diagnostic information in many retinal diseases alongside information that can aid disease management. Furthermore, its use extends beyond the retina and provides potential insights into other ocular conditions and even systemic disease. The evidence for OCTA in clinical practice is growing, with new studies published each year, revealing important insights into the nature and treatment of disease. OCTA provides advantages over the current standard of ophthalmic vascular imaging, allowing for rapid acquisition of non-invasive and reproducible images. Despite these advantages, OCTA-based clinical evidence is still in the early stages of development and further clinical trials are needed to allow for the implementation of this imaging modality into guidelines for various ophthalmic diseases. The standardization of imaging protocols and artifact management will be central to a more widespread adoption of this emerging technology.

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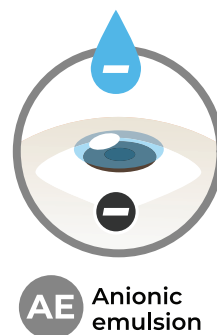
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Refractive surgery for myopia: review of options and the decision-making process

Cristina Bostan, MD, MSc, FRCSC, DABO, Julia Talajic, MD, MPH, FRCSC, Johanna Choremis, MD, FRCSC

Many options now exist for patients seeking surgical correction of myopia. The challenge lies in selecting the right procedure for the right patient. This article provides an overview of current refractive surgery options and discusses the clinical and imaging considerations in decision-making.

CURRENT REFRACTIVE SURGERY OPTIONS FOR MYOPIA
Of the currently used refractive procedures for myopia (**Figure 1**), *photorefractive keratectomy* (**PRK**) is the oldest. In PRK, the corneal epithelium is removed, and the excimer laser ablates the stroma starting at the Bowman's layer. *Laser in situ keratomileusis* (**LASIK**), popularized in the 1990s, has since replaced PRK as the gold standard for the correction of myopia. Comparative studies show no difference in outcomes between the two (**Table 1**), but LASIK is preferred due to minimal patient discomfort and faster visual recovery.[1-3] Without removing the epithelium, the surgeon creates and lifts an anterior corneal flap and applies the excimer laser directly to the stroma. Improvements to the technique now allow for highly predictable outcomes. These include the use of the femtosecond laser to fashion the flap, elliptical shapes to enhance flap fit, and iris registration to ensure centration. The advent of wavefront-optimized and customized (wavefront-guided and topography-guided) ablation profiles has increased tissue preservation and treatment accuracy.[4-6]

In *small incision lenticule extraction* (**SMILE**), a femtosecond laser sculpts a stromal convex lenticule corresponding to the myopic correction and a 2–4 mm incision through which the surgeon extracts the lenticule. SMILE has similar efficacy outcomes compared with femtosecond-LASIK.[7-10] It eliminates flap-creation issues but has its own potential complications, namely a higher risk of decentered ablation and incomplete lenticule extraction.[10] Purported advantages are increased biomechanical stability[11] and corneal nerve preservation;[12] however, a corresponding decrease in the incidence of postoperative dry eye[13] and keratectasia has not been replicated across clinical studies.[14,15] Furthermore, SMILE does not have customized profiles and has shown poorer and slower visual recovery compared to customized LASIK.[16-18] Combined with the less well-studied post-SMILE enhancement options,[19] these limitations have slowed its adoption in Canada.

Intrastromal corneal ring segments (**ICRS**) are indicated in low myopia and keratoconus. Inserted intrastromally at two-thirds of corneal depth, they add "tissue" to the midperiphery, with an arc-shortening and flattening effect on the central cornea.[20] Since "tissue" is added, biomechanical stability is enhanced. More flattening and myopia correction is obtained with proportionally thicker and smaller-diameter devices.[21] Intacs® (Addition Technology Inc.), is the only ICRS approved in Canada and can be obtained in thicknesses ranging from 0.21 to 0.45 mm.[22] Given the excellent results obtained with LASIK in low myopia, surgeons reserve ICRS for patients with keratoconus.

Current *phakic intraocular lenses* (**p-IOLs**) are designed for iris-fixation in the anterior chamber (Verisyse/Artisan, Ophtec B.V.) or for posterior chamber placement (Visian Implantable Collamer Lens, STAAR Surgical). The Visian requires a 3.2 mm corneal incision for intraocular insertion and has a central aperture to prevent pupillary block and avoid iridotomies. P-IOLs are contraindicated in shallow anterior chambers, narrow angles, and low corneal endothelial counts and have good efficacy, predictability, and safety.[23] Although results are less favourable in high myopia compared to lower refractive errors, p-IOLs provide better outcomes in these eyes than subtractive cornea-based procedures.[23]

Refractive lens exchange (**RLE**) is an off-label procedure involving the replacement of the clear crystalline lens with an IOL to correct spherical or astigmatic errors of all ranges. Although the approach is similar to cataract surgery, a discussion concerning simultaneous presbyopic correction and efforts to minimize intraoperative manipulation are of heightened importance in this purely refractive procedure. Of significance in this patient group, the risk of retinal detachment with current techniques is 0–4%–similar to the general myopic population,[24]–but is higher in younger patients, higher myopia/axial length, or lattice degeneration.[24,25]

CHOOSING THE BEST OPTION
In the absence of contraindications–such as pregnancy, monocular status, and risk factors for poor healing[26]–the main considerations in identifying good candidates for laser cornea-based surgery are corneal shape and thickness, manifest and target refraction, estimated residual stromal

bed thickness (RSBT), age, lens, and accommodative status. The surgeon must distinguish good candidates from patients who (1) need a lens-based procedure for an optimal visual outcome, (2) are at risk of developing keratectasia postoperatively, or (3) have frank corneal ectasia preoperatively (**Figure 2**). Tissue removal during laser refractive surgery compromises biomechanical stability and, in a susceptible cornea, can trigger or exacerbate an ectatic process.

Good candidates for cornea-based surgery
Young patients with healthy corneas of normal shape and with an estimated RSBT >275-300 μm are ideal candidates for LASIK (**Figure 3**). PRK is a superior option when LASIK may be less safe from a biomechanical standpoint. This occurs in cases that combine a higher refractive error with a thin cornea, resulting in RSBT <275 μm with LASIK (**Figure 4**). Below this threshold, the risk of postoperative keratectasia is greater even in the absence of ectasia preoperatively. Without a flap, PRK allows for a thicker RSBT for the same corneal thickness and manifest refraction compared to LASIK.[27]

PRK is also a better choice in anterior corneal pathologies, such as anterior basement membrane dystrophy, anterior stromal dystrophies, or scars. Unaddressed, these pathologies may limit the visual outcome following LASIK and cause epithelial defects or incomplete interface cuts during flap creation.[27] PRK eliminates flap-related issues in these cases and may also offer therapeutic value. Anterior-segment optical coherence tomography is useful to assess the depth and extent of stromal scars or dystrophies (**Figure 5**), and the likelihood of interference with flap creation during LASIK or of successful removal with PRK.[27] Other cases in which PRK is preferred include (1) patients with occupational risk of traumatic flap dislocations, (2) irregular corneas following radial keratotomy or corneal grafts, and (3) corneas at risk of free cap or buttonhole during flap creation.[27]

SMILE has the same contraindications as LASIK.[28] In most cases, the choice between the two comes down to patient preference and surgeon experience. Since it involves no flap and less postoperative discomfort than PRK, SMILE may be prioritised in patients at risk of traumatic flap dislocation.[28] LASIK may be preferred over SMILE in cases with greater astigmatism, significant higher order aberrations or irregularities on topography, as iris registration and customized ablation may then be employed to enhance outcomes.[16-18,28]

Older patients with presbyopia or early lens changes
RLE may be best in older patients with presbyopia or early lens changes even in the absence of contraindications to cornea-based procedures. It has the advantage of permanence because it addresses the unstable variable– the lens–whereas cornea-based procedures offer only a temporary solution. Nonetheless, certain patients choose a cornea-based procedure with the understanding that a cataract surgery may be needed soon thereafter. Monovision can be employed to address the presbyopia in

these patients if a cornea-based procedure is elected.

"Borderline" corneas at risk of postoperative keratectasia
Risk factors include younger age, high refractive errors, thinner pachymetry, low RSBT (<275 μm) even with PRK, family history of keratoconus, and personal history of eye rubbing.[29] The surgeon may attempt to decrease the risk with prophylactic corneal collagen crosslinking (**CXL**) during primary LASIK, PRK or SMILE – a combination called "Xtra". "Xtra" procedures promise to preserve corneal rigidity and decrease the likelihood of postoperative keratectasia and myopic regression.[30] More studies are needed to justify their routine use in high risk patients, however.[30] More frequently, these patients undergo a lens-based procedure to avoid weakening the cornea. While p-IOLs are preferred in younger patients, RLE is a better option for those >40 years old. The surgeon may also choose to observe the patient for progression of suspect characteristics before proceeding with surgery.

Patients with ectasia
Corneal topography, epithelial thickness mapping, and the Belin-Ambrosio Enhanced Ectasia Display (Pentacam, Oculus) are essential to reliably identify preoperative corneal ectasia. When facing suspicious topographical features (**Figure 6**), the first step is to rule out pseudo-keratoconus due to inadequate image acquisition, dry eye, anterior basement membrane dystrophy, corneal warpage, trauma, or scars.[31] Repeat topography, careful slit-lamp examination, and inspection of keratoscopy mires can help the process. Epithelial thickness mapping is especially useful (**Figure 7**). In cases of warpage, trauma, scars, and anterior basement membrane dystrophy, epithelial mapping reveals hyperplasia corresponding to affected areas. In true keratoconus, however, it displays epithelial thinning over the cone with surrounding thickening, even in early cases.[32] This is due to a compensatory remodelling of the epithelium to minimize changes to the anterior corneal curvature as the stroma gradually protrudes.[32]

With the advent of CXL, there is renewed interest in the role of cornea-based refractive procedures in the visual rehabilitation of patients with keratectasias. Procedures termed CXL-"Plus",[33] combining therapeutic CXL with phototherapeutic keratectomy (**PTK**), topography-guided-PRK, or ICRS, have emerged as promising approaches to reduce corneal irregularity, visual aberrations, and contact-lens intolerance in these patients.

Epithelial removal using transepithelial PTK to a 50 μm depth during CXL yields better visual outcomes in keratoconus than mechanical debridement.[34,35] This has been attributed to the excimer laser breaking through the epithelium to Bowman's layer in areas where the epithelium is thinnest.[34] The result is differential removal of 10 μm of Bowman's at the cone apex that improves anterior corneal regularity.[33] With CXL-topography-guided-PRK, the goal is to flatten the steepest (usually inferior) zone of the cornea using myopic ablation and to steepen the flattest (superior) zone with hyperopic ablation.[36] This "evens out" the surface. Although results with CXL-topography-guided-PRK

are encouraging, there is controversy surrounding its benefit over CXL alone with respect to, predictability, timing, use of mitomycin C, and long-term safety.[33,37] ICRS have been used for a long time in keratoconus to displace the cone towards the center of the cornea and flatten it. The optimal timing and protocol of ICRS implantation as an adjunct to CXL is still debated. Simultaneous ICRS and CXL seem to provide the greatest benefit.[33]

In deciding among the CXL-"Plus" procedures, the degree of astigmatism and visual acuity are important considerations.[38] PTK-CXL can be considered in mild astigmatism where superficial ablation is judged to be sufficient to regularize the anterior cornea. A recent study suggested CXL-ICRS was more effective at reducing astigmatism and improving vision than CXL-topography-guided-PRK and recommended that it be used in eyes with significant astigmatism and poorer corrected vision.[38] For CXL-topography-guided-PRK, the best candidates are considered to be patients with preserved corrected vision and <10D difference in curvature across the cornea, i.e. between the steepest and flattest areas (**Figure 8**).[36,38]

CONCLUSION

Various options are now available to surgically correct myopia, even for corneas traditionally considered ineligible for cornea-based refractive interventions. Although longer-term studies are needed, "Xtra" and CXL-"Plus" procedures have shown promise for the visual rehabilitation of at-risk and ectatic corneas, respectively. Innovations in diagnostic imaging, such as epithelial thickness mapping, are a valuable addition in guiding the choice of the best surgical approach.
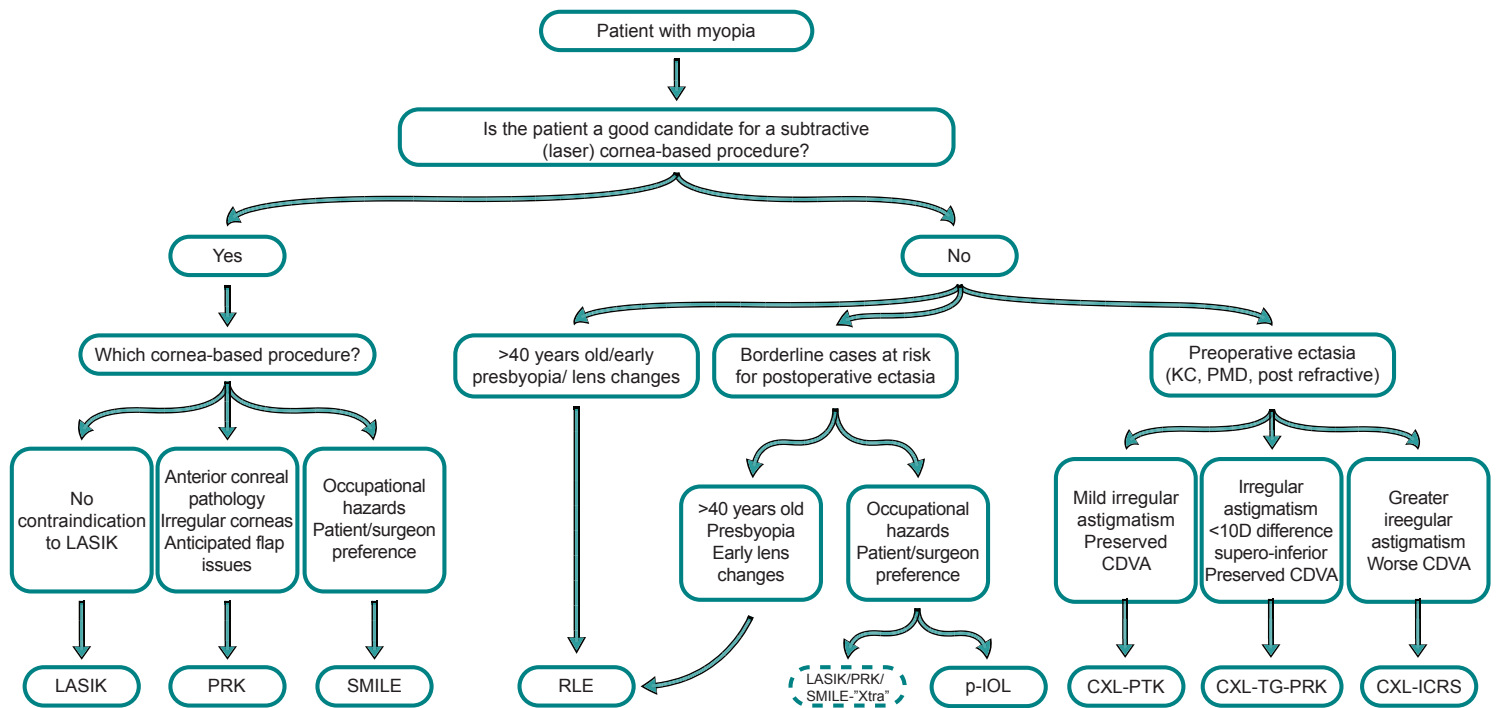
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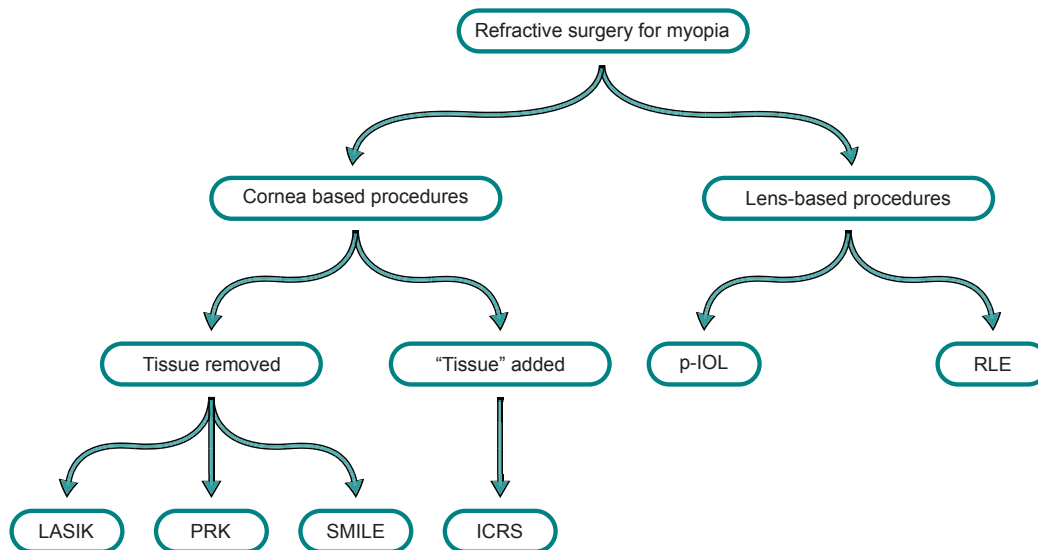
Figure 1: *Classification of refractive surgery options for myopia. LASIK, laser in situ keratomileusis; PRK, photorefractive keratectomy; SMILE, small incision lenticule extraction; ICRS, intracorneal ring segments; p-IOL, phakic intraocular lens; RLE, refractive lens exchange.*

| Procedure	Sphere range	Cylinder range	Efficacy (UCVA)	Predictability (achieved vs. target SE)
LASIK	≤-10.00D	≤4.00D	84-94% ≥20/20[4-6]	76-95% ≤0.50D[4-6]
PRK	≤-10.00D	≤4.00D	82-94% ≥20/20[39, 40]	83-98% ≤0.50D[39, 40]
SMILE	≤-10.00D	≤3.00D	50-96% ≥20/20[7-10]	80-100% ≤0.50D[7-10]
ICRS (Intacs®)	≤-3.00D	-	69% ≥20/20, 96% ≥20/40[41]	69% ≤0.5D[41]
P-IOL Artisan/Verisyse® Visian ICL®	≤-20.00D	≤6.00D	 31% ≥20/20; 84% ≥20/40[42] ≤-7D: 72.4% ≥20/20; 98.3% ≥20/40[43] -7D to -10D: 62.7% ≥20/20; 92.8% ≥20/40[43] >-10D to -20D: 37.5% ≥20/20; 93.8% ≥20/40[43]	 76.7 ≤0.5D[42] 84.7 ≤0.5D[43] 71% ≤0.5D[43] 56.9% ≤0.5D[43]
RLE	All ranges	≤3.00D	71.4-83.7% with vision better than pre-operatively[25]	70.8-86.5% ≤1.0D[25]

Table 1: *Summary of sphere and cylinder correction range, efficacy, and predictability of refractive surgery options for myopia.*

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Figure 2: Simplified diagram of the decision-making process in the refractive correction of myopia. KC, keratoconus; PMD, pellucid marginal degeneration; CDVA, corrected distance visual acuity; LASIK, laser in situ keratomileusis; PRK, photorefractive keratectomy; SMILE, small incision lenticule extraction; RLE, refractive lens exchange; p-IOL, phakic intraocular lens; CXL, corneal collagen crosslinking; PTK, phototherapeutic keratectomy; TG, topography-guided; ICRS, intracorneal ring segments.
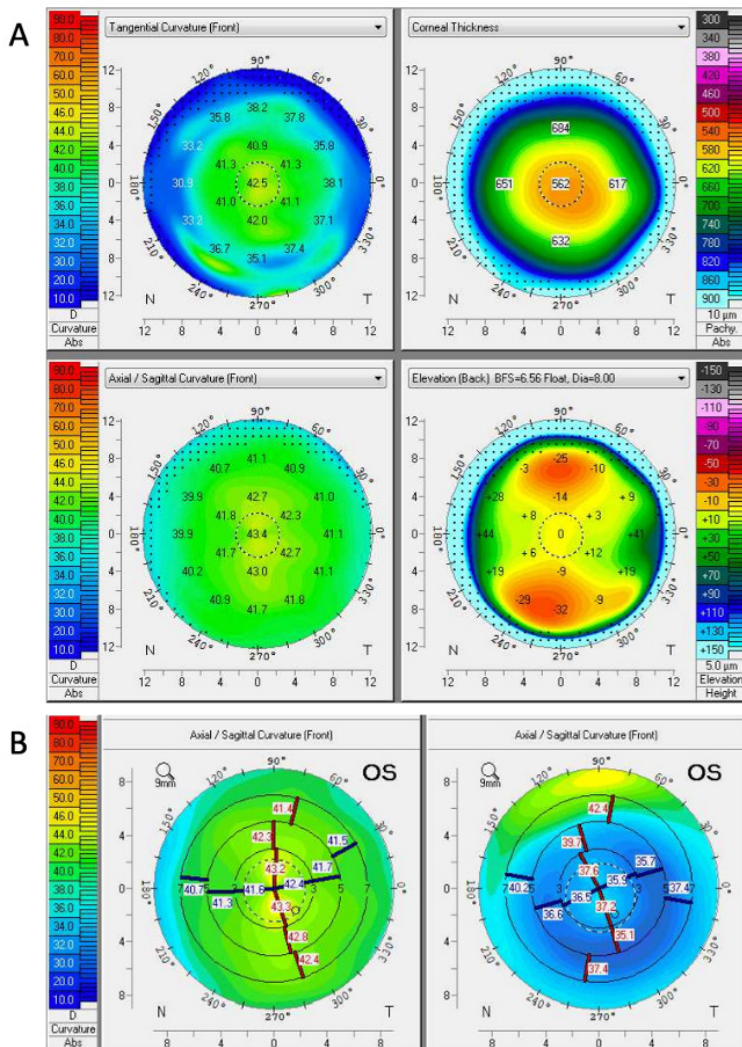
Figure 3: (A) Four-map composite Pentacam image of the normal left cornea of a 24-year-old male with a manifest refraction of -5.75 +0.50 x 95. The Pentacam shows normal corneal thickness and no signs of corneal ectasia on the anterior curvature and posterior elevation maps. With an estimated residual stromal bed of 322 µm and no other contraindications, this patient was a good candidate for LASIK. (B) Preoperative (left) and postoperative (right) curvature maps show central anterior surface flattening following myopic LASIK.
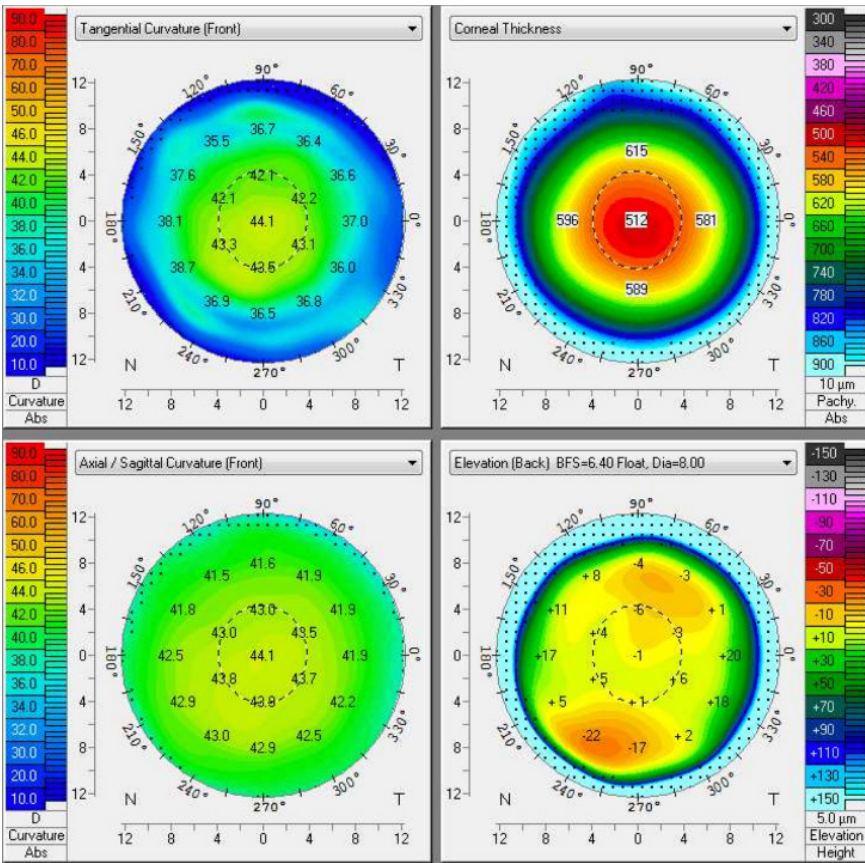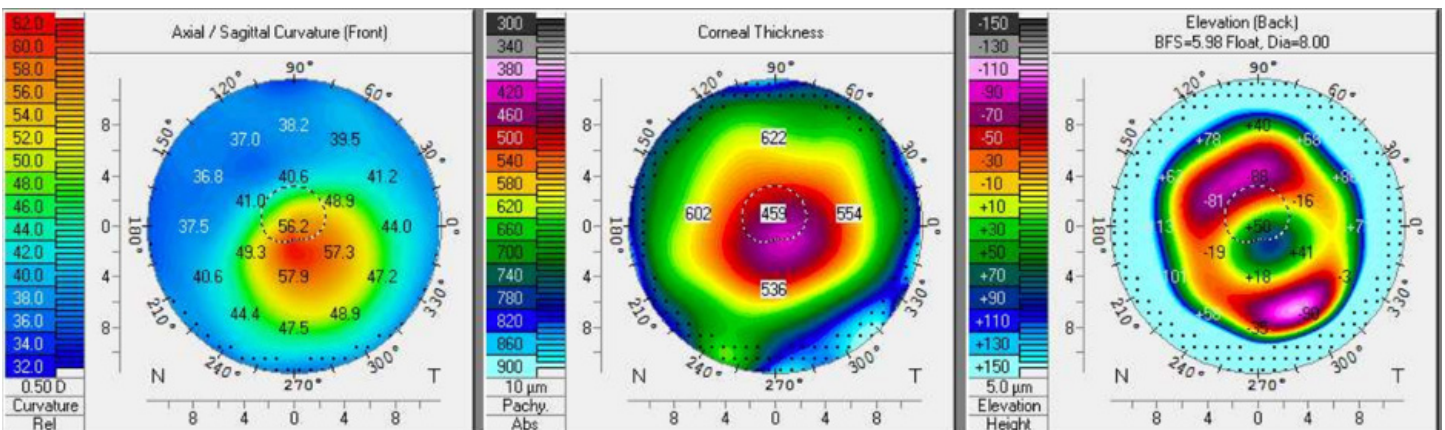
Figure 4: Four-map composite Pentacam image of the left cornea of a 22-year-old female with a manifest refraction of -10.75 +1.00 x15. There are no signs of ectasia, but the cornea is on the thin side, with a central thickness of 512 µm. Given the high refractive error and the thin cornea, the estimated residual stromal bed for LASIK was below 250 µm. PRK allowed a RSBT of 313 µm and was a better option.
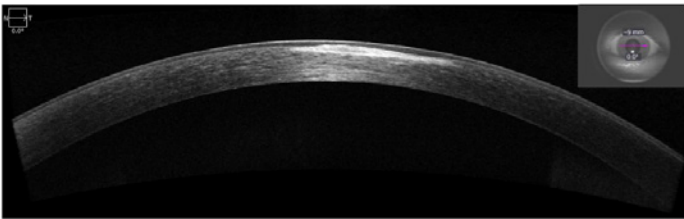
Figure 5: Anterior segment optical coherence tomography showing focal hyperreflectivity at the level of an anterior stromal scar secondary to a contact lens-related ulcer. Note the compensatory overlying epithelial hyperplasia. Considering its depth and location, this scar would interfere with LASIK flap creation. PRK was more suited in this case and allowed both to avoid flap-related issues and to fully remove the scar for a better visual outcome.

Figure 6: Three-map composite Pentacam image of a left keratoconic cornea. The curvature map (left) displays infero-temporal steepening up to 57.9D and superior flattening. Certain cases may display asymmetric astigmatism with skewing of radial axes and a "lobster-claw" pattern. The pachymetry map (middle) shows corneal thinning, with the thinnest point slightly eccentric and corresponding to the location of the maximum steepening. The posterior elevation map (right) demonstrates an eccentric island of protrusion of the posterior surface, coincident with the points of maximum steepening and thinning.
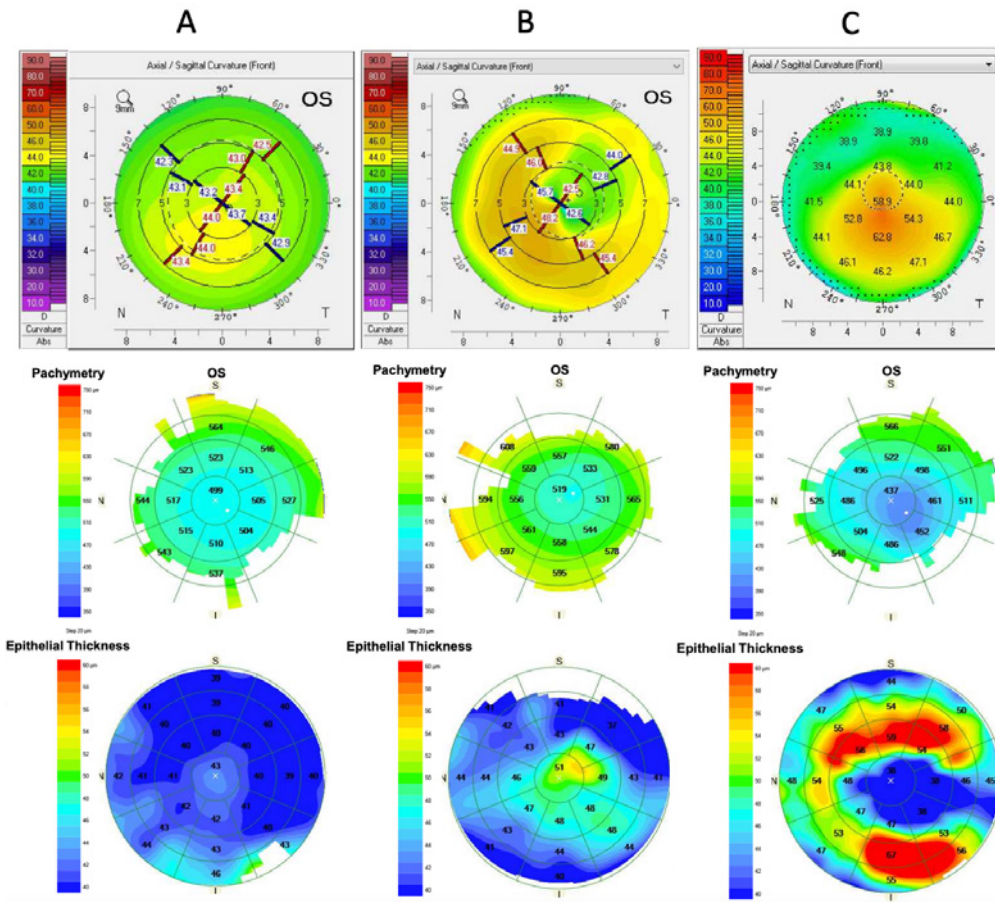
Figure 7: *Composite image of Pentacam sagittal curvature maps (top row) and anterior segment optical coherence tomography pachymetry (middle row) and epithelial thicknes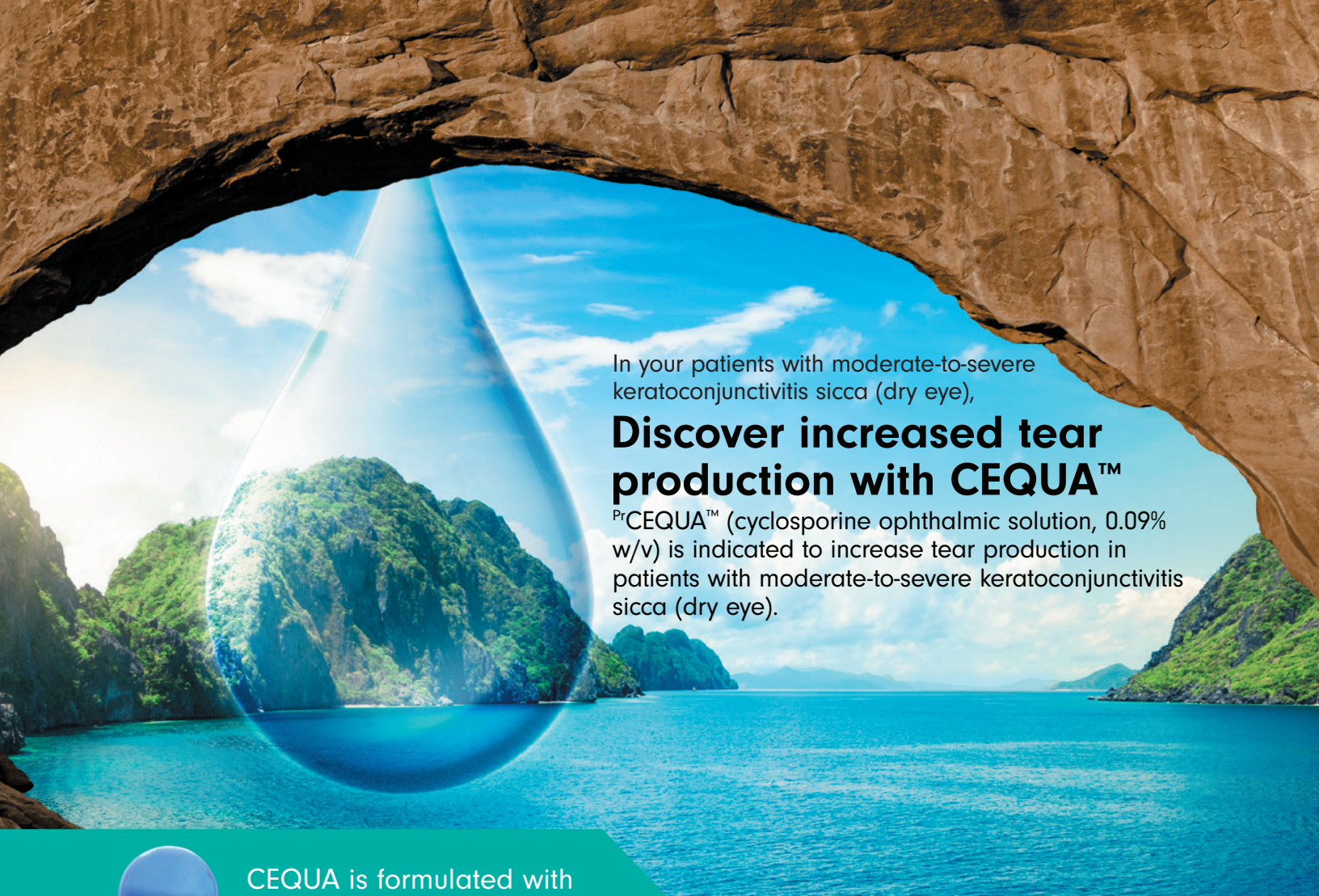s maps (bottom row). (A) The curvature map shows mild inferior steepening. The epithelial thickness map is normal, however, with 43 μm in the central cornea and +/- 2-3 μm in the corneal periphery, showing no thinning over the slightly steeper area. This is not an ectatic cornea. (B) The curvature map displays asymmetric astigmatism with supero-temporal flattening and adjacent infero-nasal steepening. The epithelial thickness map shows focal epithelial thickening reaching 55 μm that overlies the flattened area. This is the same patient as in Figure 3; the flattening and compensatory epithelial thickening overlie the anterior stromal scar. (C) The curvature map shows marked irregular astigmatism with inferior steepening up to 62.8D. The epithelial thickness map shows epithelial thinning to 32 μm over the protruded zone and thickening up to 66 μm surrounding the cone in a "doughnut-shaped pattern", consistent with keratoconus.*
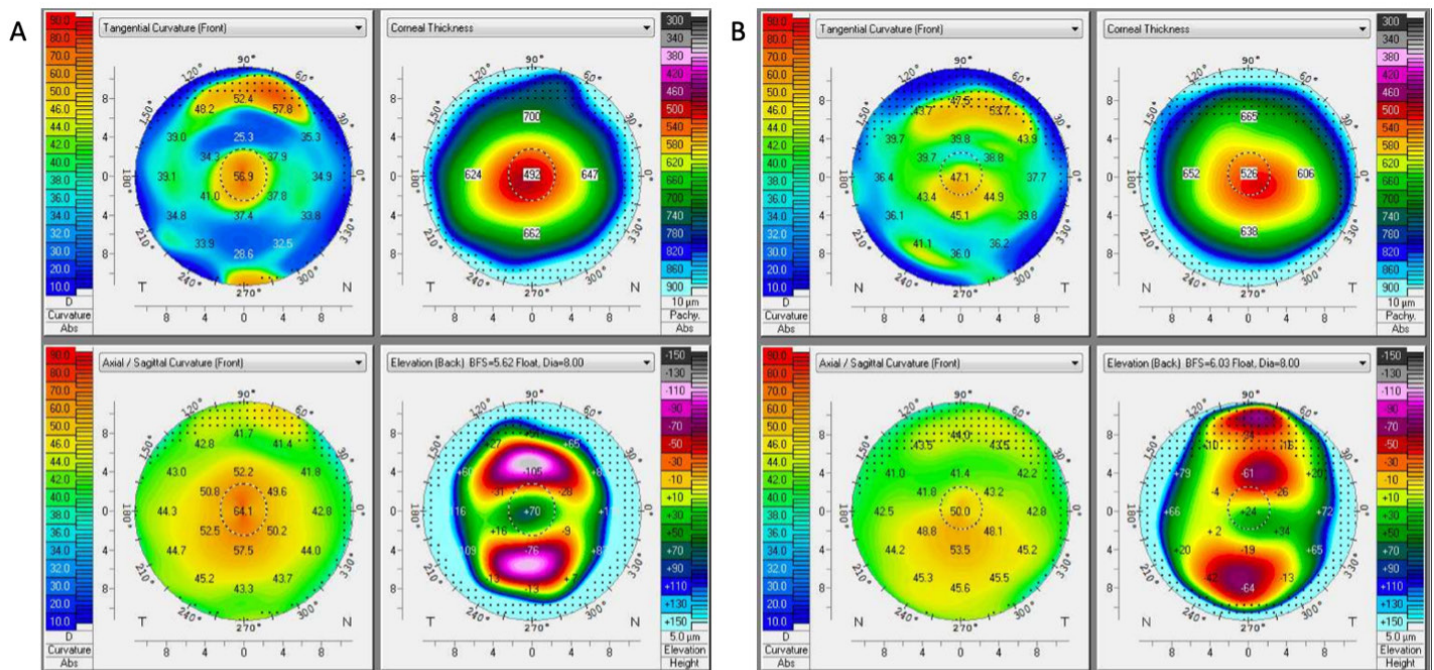
Figure 8: *20-year-old man with keratoconus. Manifest refraction was of -10.25D with a best corrected distance acuity of 20/100 OD, and of -5.25 +6.00 x 35 yielding 20/25 OS. Four-map composite Pentacam images of OD (A) and OS (B) are shown. OD images show presence of a prominent central cone with significant surrounding flattening and a difference in curvature from center to periphery of over 20D. Although combined CXL-PRK could be considered in this eye, better results are likely to be obtained with a combined CXL-ICRS procedure. OS images display superior-inferior asymmetry, with relative inferior steepening and around 10D difference in curvature across the cornea. Considering the preserved visual acuity, combined CXL-PRK could be a good option to stop keratoconus progression and increase corneal regularity in this eye.*

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Clinical applications of optical coherence tomography (OCT) in glaucoma

Hady Saheb, MD, MPH, FRCSC and Ali Salimi, MD, MSc

Visual field (VF) testing has been the mainstay for diagnosing and monitoring glaucoma. However, relying solely on VF can delay the patient's diagnosis in the early stages of the disease, as the structural changes are known to precede the functional changes and VF defects may not be clinically detectable until at least 25-35% of retinal ganglion cells (RGCs) are lost. This concept highlights the importance of alternative diagnostic modalities such as optical coherence tomography (OCT). OCT's ability to reliably segregate and quantify the thickness of retinal layers has allowed earlier detection of glaucoma, up to 6 years before the onset of any detectable VF loss.[1] Compared to VF, OCT is less time-consuming and is less dependent on the patient's cooperation and test-taking ability. There are a few commercially available spectral domain OCT (SD-OCT) machines that are routinely used in glaucoma clinics. These devices are fundamentally similar with comparable performance, but their scanning protocols and segmentation algorithms are not analogous; thus, the measured parameters may not necessarily be interchangeable between devices and the values should be interpreted relative to the normative databases specific to each machine (**Table 1**). In this review, we present the clinical applications of OCT imaging in glaucoma and share some clinical pearls and pitfalls.

OCT circumpapillary retinal nerve fiber layer (cpRNFL, commonly referred to as RNFL) and ganglion cell analysis (GCA) are the two most commonly used OCT-derived markers for the detection and monitoring of glaucoma. The clinical implications of each marker in different disease stages remain a topic of research, as the RNFL or GCA thinning may not necessarily occur simultaneously during the course of RGC degeneration. GCA is shown to outperform RNFL in the detection of glaucoma in the very early stages,[2] in keeping with the theory that RGC anomalies precede axonal loss.[3] However, some researchers have published evidence of a comparable diagnostic ability for both measures. With disease progression toward more advanced stages, it has been suggested that the diagnostic value of RNFL is superior to that of GCA, likely because only 50% of the RGCs occupy the macular region compared to nearly all of the RGCs assessed in peripapillary RNFL analysis.[3,4]

In addition to their diagnostic ability, RNFL and GCA are useful in monitoring disease progression. However, in longitudinal analyses, the pathological change should be discerned from the physiological age-related change. Both parameters exhibit some variation in the age-related rate of thinning, (0.14-0.82 µm/year for RNFL and 0.11-0.32 µm/year for GCA), depending on the patient population being studied and the OCT machine being used. However, the rate of thinning associated with glaucoma is notably greater (0.86-3.30 µm/year for RNFL and 0.49-1.46 µm/year for GCA). Moreover, faster RNFL thinning has been associated with faster disease progression; according to the Duke Glaucoma Registry Study, in those with slow disease progression, RNFL thinning occurred at <1 µm/year compared to >2 µm/year in fast progressors.[5] Currently, there exists no consensus on a cut-off value signifying a clinically significant rate of progression. Nevertheless, in earlier stages of glaucoma, RNFL loss occurs at a faster rate compared to the GCA. As the disease progresses, the RNFL loss slows down and eventually plateaus to a floor, while GCA exhibits a comparatively faster rate of thinning in advanced glaucoma cases. This notion supports the use of RNFL in monitoring disease progression through RNFL at earlier stages of the disease and through GCA in more advanced cases,[6-8] although our clinic still uses both measures throughout the disease spectrum (**Figure 1A–C**).

Current published guidelines from the American Academy of Ophthalmology and the European Glaucoma Society do not endorse a recommended frequency for OCT imaging of glaucoma patients.[9,10] Nonetheless, evidence from multiple studies suggests that best practice includes semi-annual testing intervals using OCT for following glaucoma patients.[11,12] A more recent study found that increasing the OCT testing frequency from twice yearly to three times per year did not reduce the time to detect glaucoma progression.[11]

The clinical applications of RNFL and GCA may not necessarily be generalizable to all eyes and should be individualized in the context of specific pathologies. For instance, in the case of eyes with pathological myopia and tilted disc, RNFL is more significantly affected than GCA,[13-15] rendering GCA a better diagnostic parameter irrespective of glaucoma severity. Similarly, larger disc diameter has been linked to greater RNFL thickness but not ganglion cell thickness;[14,16] thus, GCA is superior to RNFL, as the latter can lead to false negatives in eyes with larger disc diameters. Conversely, in eyes with macular pathology, ganglion cell measures can be artifactually abnormal, thereby rendering RNFL a more reliable diagnostic tool for these cases.

		Cirrus HD-OCT (Carl Zeiss Meditec, Dublin, CA, USA)	Spectralis (Heidelberg Engineering, Germany)	3D OCT 1000 (Topcon, Paramus, NJ, USA)	RTVue-100 (Optovue, Fremont, CA, USA)
Pupil size requirement (mm)		≥ 2.0	≥ 2.0	≥ 2.5	≥ 3.0
Scan speed (a-scans/second)		27,000	40,000	18,000	26,000
Axial resolution (microns)		5	7	5	5
Recommended signal quality		Called "Signal Strength" ≥ 6 [0–10]	Called "Signal Strength Index (SSI)" ≥ 15 [0–40]	Called "Quality factor (Q-factor)" 45 [0–160]	Called "Quality (Q)" 30 for macular [0–100]
RNFL	scanning protocol	Optic Disc cube 200×200 protocol (6×6 mm^2 area)	Peripapillary scan circle spanning 12° of arc	Optic Disc cube 200×200 protocol (6×6 mm^2 area)	combination of radial scans and circular scans
	thickness measurement	3.46 mm diameter circle centered over ONH	Circle diameter depends on the axial length of the eye	3.4 mm diameter circle centered over ONH	3.45 mm diameter circle centered over ONH
Ganglion cell	scanning protocol	Macular Cube 200×200 protocol or 512×128 protocol	30°×25° volume scan of retinal thickness	Macular Cube 512×128 protocol	7×7 mm square area centered 0.75-1 mm temporal to the fovea (thickness calculated within a 6 mm diameter circular macular area)
	thickness measurement	GC-IPL = GCL + IPL GCC = RNFL + GCL + IPL	Posterior pole asymmetry analysis	GCL + IPL RNFL + GCL + IPL	6-mm diameter circular macular area GCC = RNFL + GCL + IPL
Thickness measurement reference plane		Reference-plane dependent (200 μm above the RPE)	Reference-plane independent	Reference-plane dependent (120 μm above the RPE)	Reference-plane dependent (150 μm above the RPE)
Normative Database	Sample size (n)	284 individuals (284 eyes) for RNFL 282 individuals (282 eyes) for macular scan	330 individuals (330 eyes)	399 individuals (399 eyes)	480 individuals (640 eyes)
	Average age [range] (years)	46.5 [19–84]	49.7 [20–90]	46.3 [18–88]	50.7 [19–82]
	Gender (M:F)	134 : 150 for RNFL 133 : 149 for macular scan	146 : 184	173 : 226	N/A
	Ethnicity, (%) • White / Caucasian • Hispanic • Black / African American • Asian • Indian • Other / mixed	43 12 18 24 1 6	66 14 12 7 - 1	49 18 20 13 - -	18 11 10 47 14 -
	Scan values are adjusted for	Age	Age, and Bruch's membrane opening area	Age	Age, signal strength, disc area, ethnicity
	Scan values are NOT adjusted for	Axial length, refraction, optic disc area, signal strength, ethnicity	Axial length, refraction, optic disc area, signal strength, ethnicity	Axial length, refraction, optic disc area, signal strength, ethnicity	Axial length, refraction

Table 1: Characteristics of four commercially available spectral domain optical coherence tomography devices.[28-37]
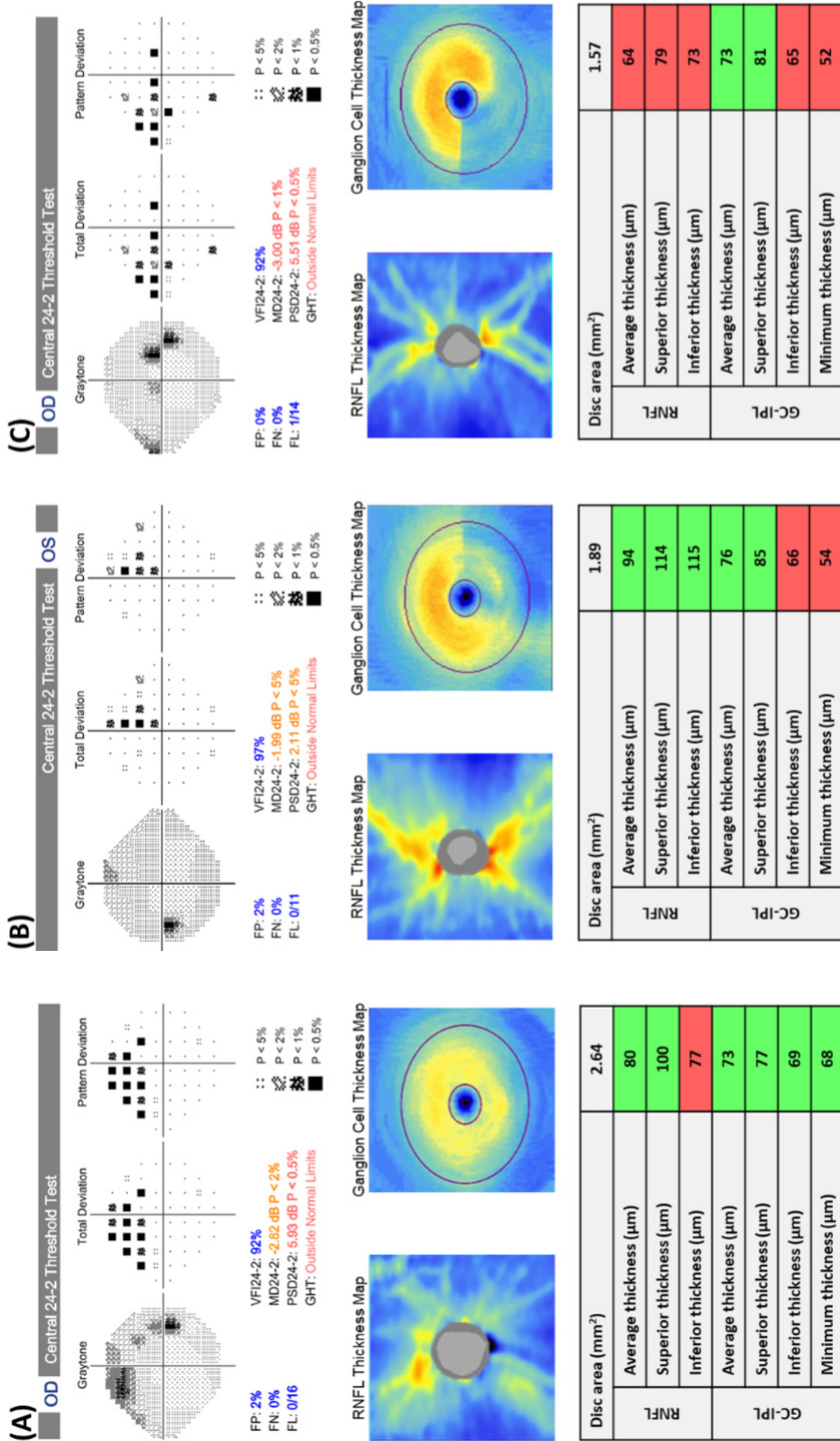
Figure 1: Clinical examples of glaucomatous eyes with structural abnormalities detected through optical coherence tomography. (A) abnormal retinal nerve fiber layer thickness (RNFL) and normal ganglion cell-inner plexiform layer thickness (GC-IPL); (B) normal RNFL thickness and abnormal GC-IPL thickness; (C) Abnormal RNFL and GC-IPL thickness.

Automatic color-coding of RNFL and GCA values according to the age-matched normative database can facilitate and expedite data interpretation; however, clinicians should remain cognizant that the current normative databases offered by the OCT machines' glaucoma modules are established in healthy populations with no retinal or neuro-ophthalmic pathologies. In addition, statistically normal tests are not always indicative of clinically normal measurements. Thus, relying solely on automatic color-coding can lead to false-negative or false-positive interpretations. In cases where the values seem to be within the normal limits of the normative database, attention should be paid to any asymmetry between the two eyes. For instance, on scans performed by Cirrus HD-OCT, an asymmetry greater than 9 μm in average RNFL thickness or 5 μm in GCA should raise suspicion of glaucoma.[17-19] Also, the RNFL temporal-superior-nasal-inferior-temporal (TSNIT) graph is a valuable indicator of subtle RNFL abnormalities that can be missed by the averaged global indices–a pitfall known as green disease. In contrast, the RNFL in highly myopic eyes tends to be thinner and can therefore be color-coded in red, even in absence of glaucoma.[13] In such cases, assessing the interocular RNFL symmetry and the GCA parameters as well as looking for focal defects can help avoid the "red disease" pitfall.

OCT imaging remains prone to errors and the absence of clinically significant artifacts should be ensured before any clinical interpretation. Each manufacturer provides a threshold for signal strength below which the automatic segmentation algorithms may not be reliable (**Table 1**). Misalignment of the optic nerve head (ONH) circle can result in measurement variations,[20] as the RNFL thickness is the highest in the circumpapillary area and decreases away from the ONH.[21] Blinking, saccadic eye movements, the presence of media opacity, and optical focus can all lead to erroneous segmentation, limiting the validity and reliability of the scans.[22] Lastly, in the absence of a normative database for longitudinal age-related changes in RNFL and GCA, the trend-based analysis fails to differentiate the glaucomatous changes from the age-related ones. Thus, statistical significance in the slope of trend-based analysis should be interpreted with caution, given its susceptibility to yield high false positive rates.[23]

More recently, swept-source OCT (SS-OCT) has shown clinical utility in glaucoma clinics thanks to its speed, longer wavelength, deeper penetration, and ability to concurrently capture the ONH and the macula in a single scan.[24] By extending the RNFL measurements beyond the circumpapillary region and the GCA beyond the macular region, this new technique allows simultaneous RNFL and GCA analysis as a single layer. SS-OCT has comparable performance to SD-OCT in detecting glaucoma and monitoring progression,[24] yet it outperforms SD-OCT in myopic eyes[25]–a population in which detection and monitoring of glaucoma are particularly challenging. As SS-OCT gains popularity in glaucoma clinics, clinicians should keep in mind that the RNFL and GCA values obtained via SD-OCT and SS-OCT are not interchangeable.[26]

OCT-angiography (OCTA) constitutes another area of innovation in OCT imaging, with a potential role in glaucoma clinics. This non-invasive dye-free imaging modality allows qualitative and quantitative assessment of retinal vasculature. Flow index and vessel density are two of the OCTA parameters that are affected in glaucomatous patients. Although the evidence at this time is limited, the macular vessel density is not limited by the floor effect, which allows OCTA to overcome one of the main limitations of OCT imaging, making it a potentially superior test for eyes with high myopia or advanced glaucoma.[27] OCTA remains a relatively new technique, but has the potential of leading to a paradigm shift in the detection and monitoring of glaucoma. However, until more evidence uncovers its full applications and limitations, clinicians should remain cautious in interpreting the OCTA results.

The future holds much promise for the prompt detection and monitoring of glaucoma. The continuous technological advancements in imaging modalities have led to a surge in the availability of data on glaucoma. Artificial intelligence and machine learning algorithms continue to unlock the mysteries of glaucoma diagnostics by combining the data from a variety of functional and imaging modalities such as VFs, fundus photos, OCT, and OCTA. A validated and widely accepted integrative algorithm capable of combining functional and structural measures to detect glaucoma or monitor its progression is of paramount clinical importance but has yet to be developed and commercialized.

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Anterior segment ocular coherence tomography: A practical tool for the comprehensive ophthalmologist

Matthew Bujak, MD, FRCSC and Arshdeep Marwaha, BSc.

INTRODUCTION

Ocular coherence tomography (OCT) provides non-invasive and rapid in vivo imaging of ocular structures using low coherence interferometry. It first appeared in 1991 for imaging of the posterior segment of the eye; shortly thereafter, the utility of OCT was expanded to the anterior segment (AS-OCT).[1] With improvements in technology including higher resolution and rapid capture speed of images, AS-OCT has become an integral tool for current-day cornea specialists in the clinical evaluation of the cornea and anterior segment. AS-OCT pachymetry is often used to analyze corneal thickness while cross-sectional images assist with the visualization and morphometric analysis of the anterior segment.[1] These features are commonly used to assess endothelial graft attachment and corneal graft health. Though AS-OCT has been used predominately by cornea specialists, it does have wide-spread application for the comprehensive ophthalmology practice. Moreover, the advent of affordable imaging attachment lenses has also made AS-OCT a more practical tool to have in the clinic.

A comprehensive ophthalmologist can use AS-OCT to monitor pathologies such as recurrent corneal erosions, Salzmann Nodular Degeneration, depth of scarring and endotheliitis.[2–5] It can also be used in the pre- and post-operative assessment for cataract surgery. For example, AS-OCT can be used to help assess the likelihood of whether a patient with Fuchs' dystrophy may develop corneal decompensation following cataract surgery. This information can in turn help navigate shared clinical decision making by informing the patient about the risks and benefits of surgery pre-operatively. In the post-operative setting, mild corneal edema is common and expected. However, if there is edema which is out of proportion to either the surgeon's expectations or the amount of energy from the surgery, a closer look to find the etiology of the edema is warranted. AS-OCT can be used to help delineate common causes of corneal decompensation following cataract surgery including Descemet's membrane (DM) detachment, retained lens fragments, or infectious causes.[6,7] We present four clinical scenarios, one of which is the use of AS-OCT in pre-operative assessment and three cases in which AS-OCT is used to identify post-operative complications.

CASE 1: FUCHS' DYSTROPHY AND CATARACT SURGERY

Patients with Fuchs' dystrophy have progressive deterioration of endothelial cell density which leads to corneal edema, scarring, and decreased visual acuity. This is of particular concern when considering cataract surgery, as intraocular surgeries can accelerate loss of endothelial cell count. Preoperative assessment and suitability for cataract surgery of patients with Fuchs' is therefore imperative in screening for ideal candidates and to avoid causing worsening of edema and corneal decompensation in high-risk patients. AS-OCT pachymetry of the cornea is an excellent tool to quantify edema or corneal haze in patients both pre- and post-operatively, which serves as a surrogate marker for endothelial cell health.[8] AS-OCT can be utilized to determine whether cataract surgery alone (i.e. without DMEK/CE/PCIOL) will suffice for correcting vision. We applied this imaging modality for pre-operative screening to an 80-year-old female with Fuchs' dystrophy who was referred to our clinic for cataract surgery. Her OCT showed slight epithelial thickening from borderline edema (**Figure 1A**). We were able to utilize our OCT image to discuss the risks and benefits of performing cataract surgery without corneal transplant, while also addressing the risk of post-operative corneal edema with the patient. The patient ultimately decided on cataract surgery alone, but the pre-operative assessment utilizing OCT enabled us to provide the patient with realistic expectations following surgery and a good understanding of the inherent risks of endothelial decompensation.

CASE 2: DESCEMET'S MEMBRANE (DM) DETACHMENT POST CATARACT SURGERY

DM detachment typically occurs during cataract surgery but may not be evident until the post-operative visit. It leads to edema which if not treated promptly may lead to corneal scarring and decreased vision. We assessed a 62-year-old female who had an otherwise unremarkable routine cataract surgery. She was referred to our clinic three months after surgery with persistent corneal edema and 20/100 visual acuity OS. The extent and length of the period over which the edema persisted were considered abnormal. AS-OCT pachymetry demonstrated significant corneal thickening (**Figure 2A**). Cross-section AS-OCT revealed a focal detachment of the DM at the site of the corneal incision made during surgery (**Figure 2B**). An injection of air into the anterior chamber (i.e. descemetopexy) was performed as a tamponade to
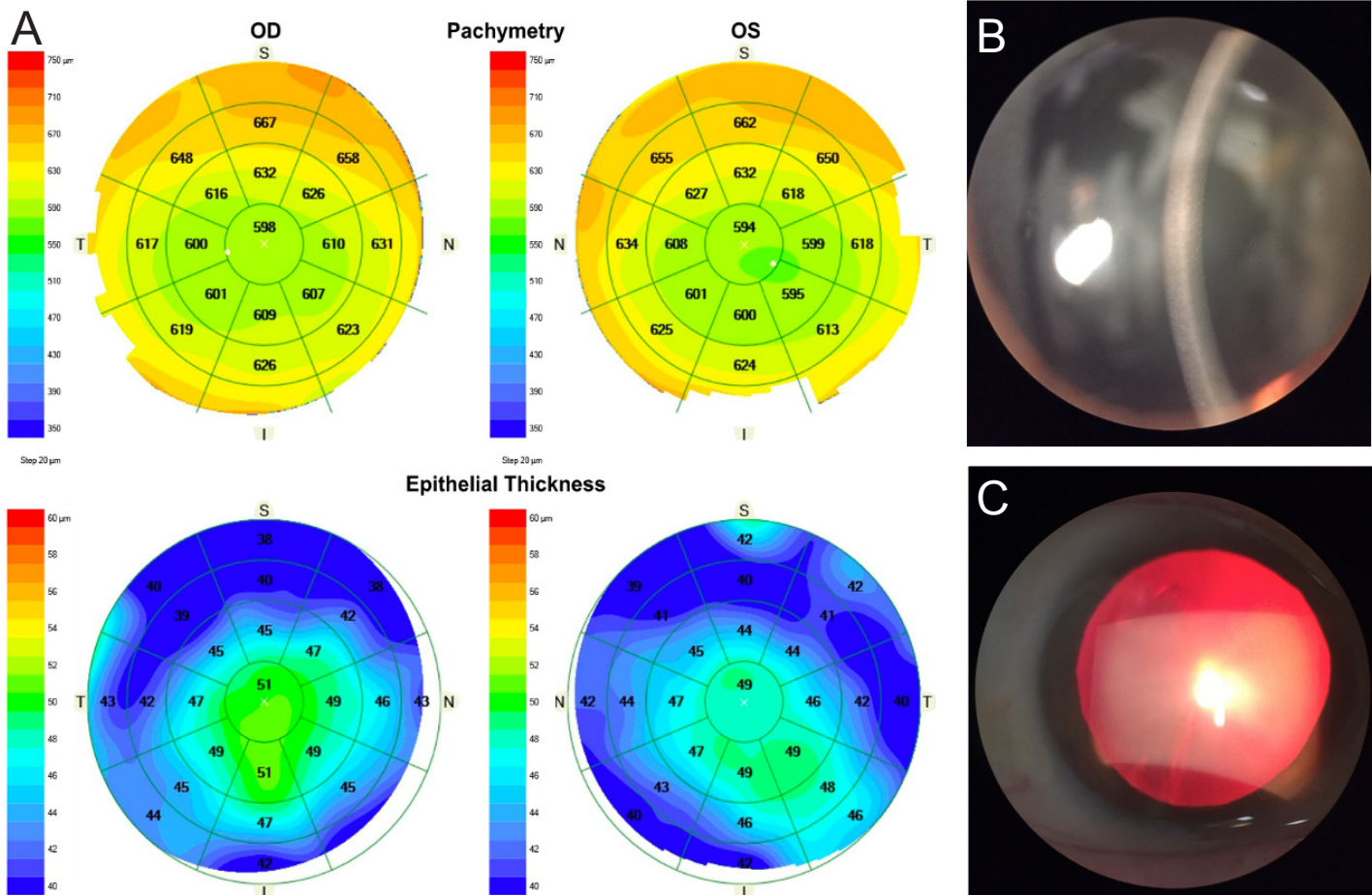
Figure 1: Fuchs' Dystrophy and cataract surgery. (A) AS-OCT pachymetry showing diffusely increased corneal thickness OU. (B) Cornea photograph displaying 1+ guttata. (C) Clear-appearing cornea under direct light.

promote adherence of the Descemet membrane against the stroma. This procedure transiently cleared the edema but ultimately did not result in reattachment of the DM, necessitating further surgical intervention. A DMEK was done, which failed to re-attach the endothelium, likely because of the chronic fibrosis on the posterior corneal interface. A DSAEK was subsequently performed but unfortunately only moderate improvement in visual acuity was observed as substantial interface corneal scarring and fibrosis had already occurred.

DM detachment can be missed during cataract surgery. Furthermore, post-operative corneal edema can be difficult to quantify on slit-lamp examination alone. This case illustrates how early postoperative use of AS-OCT could have identified the cause of the corneal edema and led to a prompt solution without corneal transplantation and the possibility of an improved visual outcome.

CASE 3: RETAINED LENS FRAGMENT POST CATARACT SURGERY

A retained lens fragment is a potential serious complication of cataract surgery. Patients can develop elevated intraocular pressures, eye pain, and blurry vision from corneal edema. In keeping with these symptoms, a 70-year-old female initially presented with good vision after cataract surgery but two weeks thereafter, she complained of right eye discomfort and blurry vision. Clinically, the

patient's anterior segment on slit-lamp examination showed subtle inferior corneal edema (**Figure 3B–C**); however, AS-OCT pachymetry demonstrated stromal and epithelial thickening at the inferior aspect (**Figure 3A**). This imaging modality confirmed clinical corneal edema which was missed on routine examination. The inferior location of the edema prompted a gonioscopic exam which identified a retained nuclear lens fragment. This fragment was promptly removed the following day via surgery prior to the development of any complications. The patient was subsequently monitored for resolution of her corneal edema using AS-OCT pachymetry (**Figure 3D–F**). Fortunately, the retained fragment was retrieved in a timely manner before any significant endothelial decompensation had occurred, allowing our patient to regain 20/20 uncorrected vision after surgery.

CASE 4: HERPES SIMPLEX VIRUS (HSV) AFTER CATARACT SURGERY

Surgical trauma in addition to topical corticosteroid use which is routinely prescribed after cataract surgery can lead to development of HSV keratitis in rare cases. A 57-year-old male presented in our clinic four months after femtosecond laser cataract surgery with worsening vision and focal corneal edema at the wound margin and keratic precipitates. There were no retained fragments on gonioscopy. The AS-OCT showed no DM detachment but pachymetry did reveal corneal edema (**Figure 4A-B**). His clinical picture was unclear, but consistent with a possible
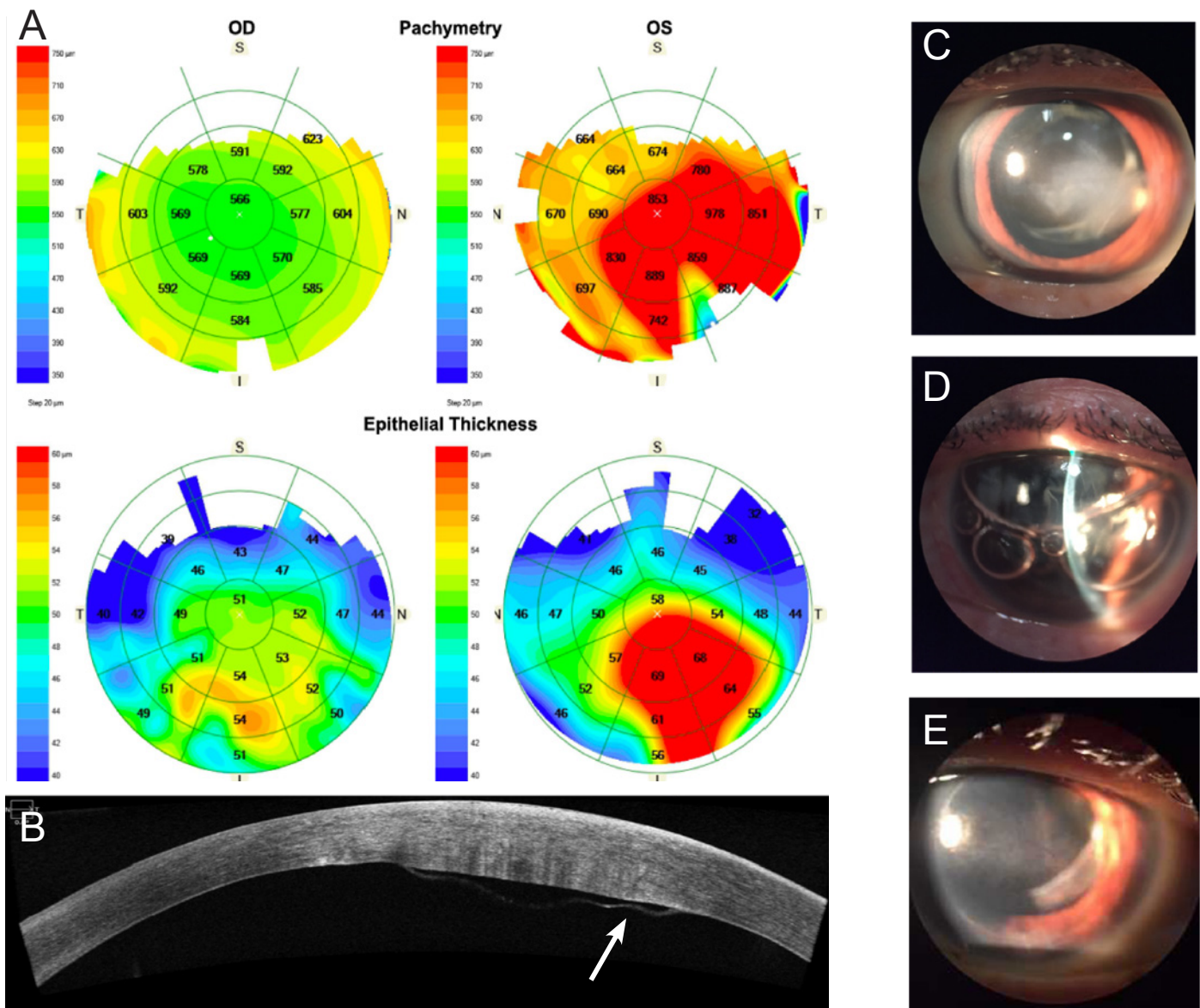
Figure 2: Descemet's Membrane Detachment post cataract surgery. (A) AS-OCT pachymetry showing increased corneal and epithelial thickness inferotemporally OS. (B) AS-OCT image of cornea. White arrow indicates Descemet's Membrane detachment. (C) Cornea photograph at initial presentation, (D) following descemetopexy, and (E) after DSAEK.

avulsion of DM or with an unresolved HSV infection. We elected to treat for the presumed HSV infection with steroids, valacyclovir 500 mg oral tablets three times daily for 10 days and then once daily for several weeks thereafter. We closely monitored the patient with AS-OCT pachymetry. Repeat imaging at 4 weeks post-valacyclovir initiation (**Figure 4C–D**) showed that the patient's corneal edema had resolved with secondary stromal vascularization and decreased corneal sensation, supporting our working diagnosis. This case illustrates the use of AS-OCT cross-section imaging and pachymetry in ruling out certain pathologies (i.e. DM detachment) whilst also providing a quantitative measure to follow the progress of a patient's treatment course and effectiveness of the treatment plan.

CONCLUSION

AS-OCT is an excellent non-contact tool that provides high resolution imaging of structures extending from the corneal epithelium to the ciliary body, facilitating the diagnosis and management of various anterior segment pathologies. Currently, this imaging modality is underutilized in the general ophthalmology clinic. However, given its broad application, the incorporation of AS-OCT has the potential to improve diagnostic certainty, decrease the need for referral to ophthalmology subspecialists, and enhance overall patient care.
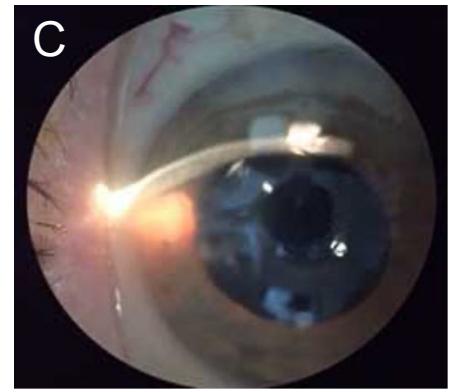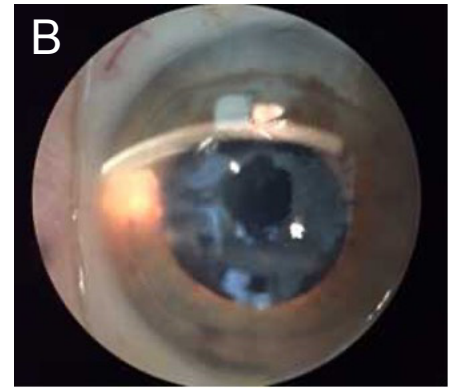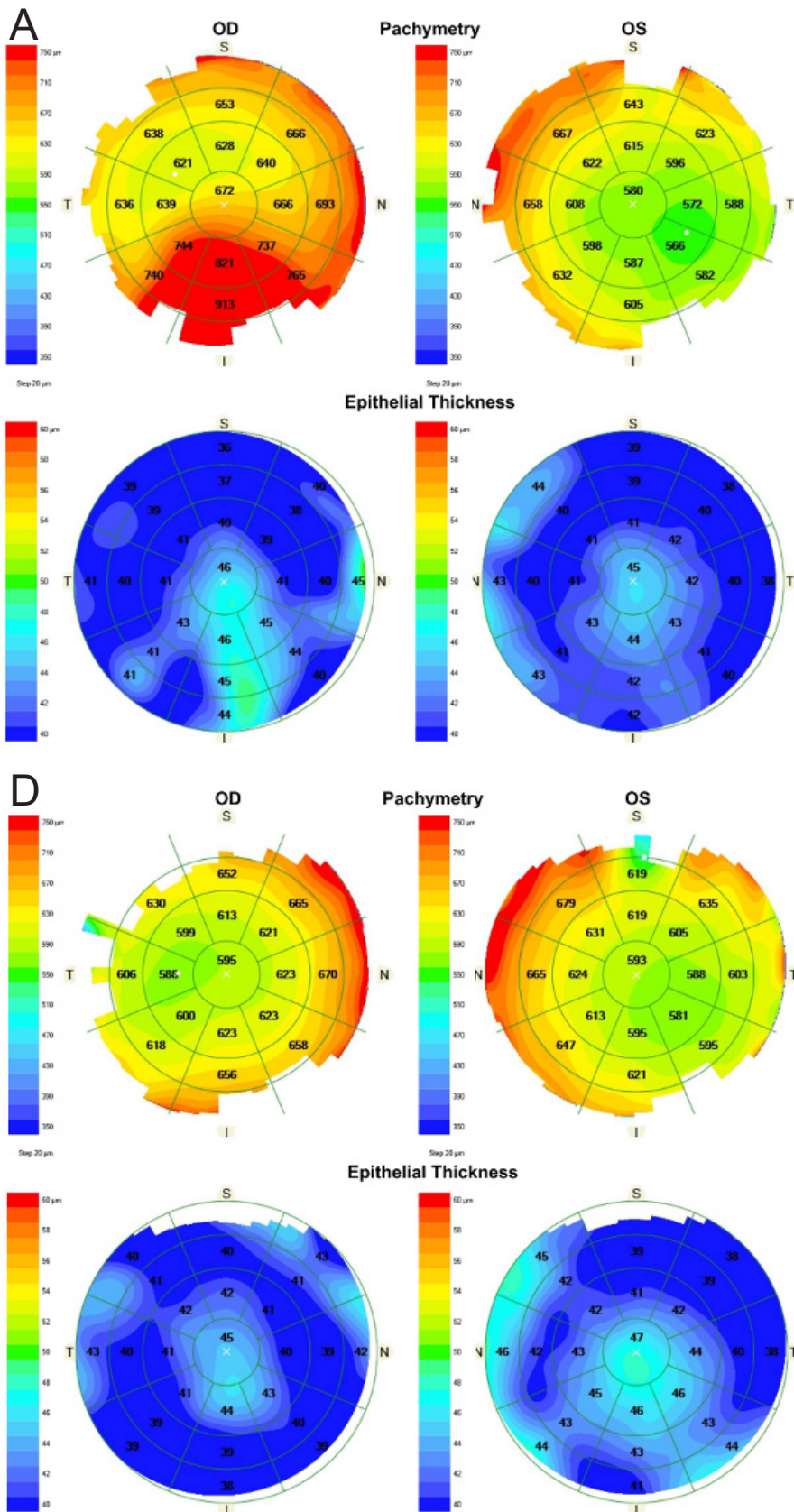
Figure 3: *Retained nuclear fragment following cataract surgery. (A) AS-OCT pachymetry showing increased corneal thickness inferiorly OD 2 weeks after cataract surgery. (B) and (C) Cornea photographs displaying mild corneal edema at initial presentation. (D) Resolved corneal edema 3 weeks after surgical removal of retained nuclear fragment.*

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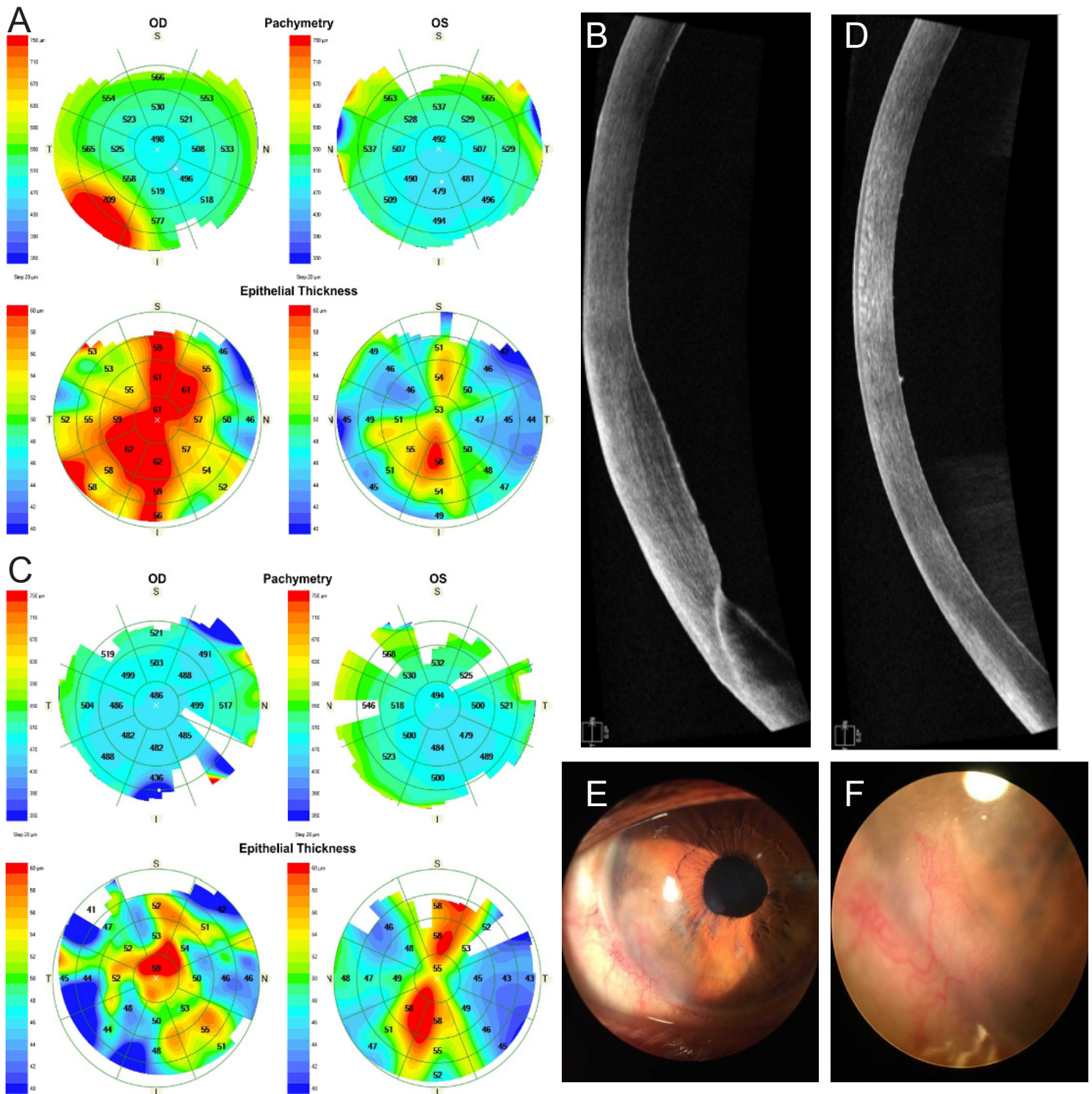
Figure 4: Herpes Simplex Virus infection following femtolaser cataract surgery. (A) AS-OCT pachymetry anterior segment imaging (B) showing increased corneal thickness in the inferotemporal cornea OD, (C) and (D) thickness resolved following steroid and anti-viral therapy. (E) Residual stromal scarring and vascularization adjacent to wound margin and (F) neovascularization of cornea.

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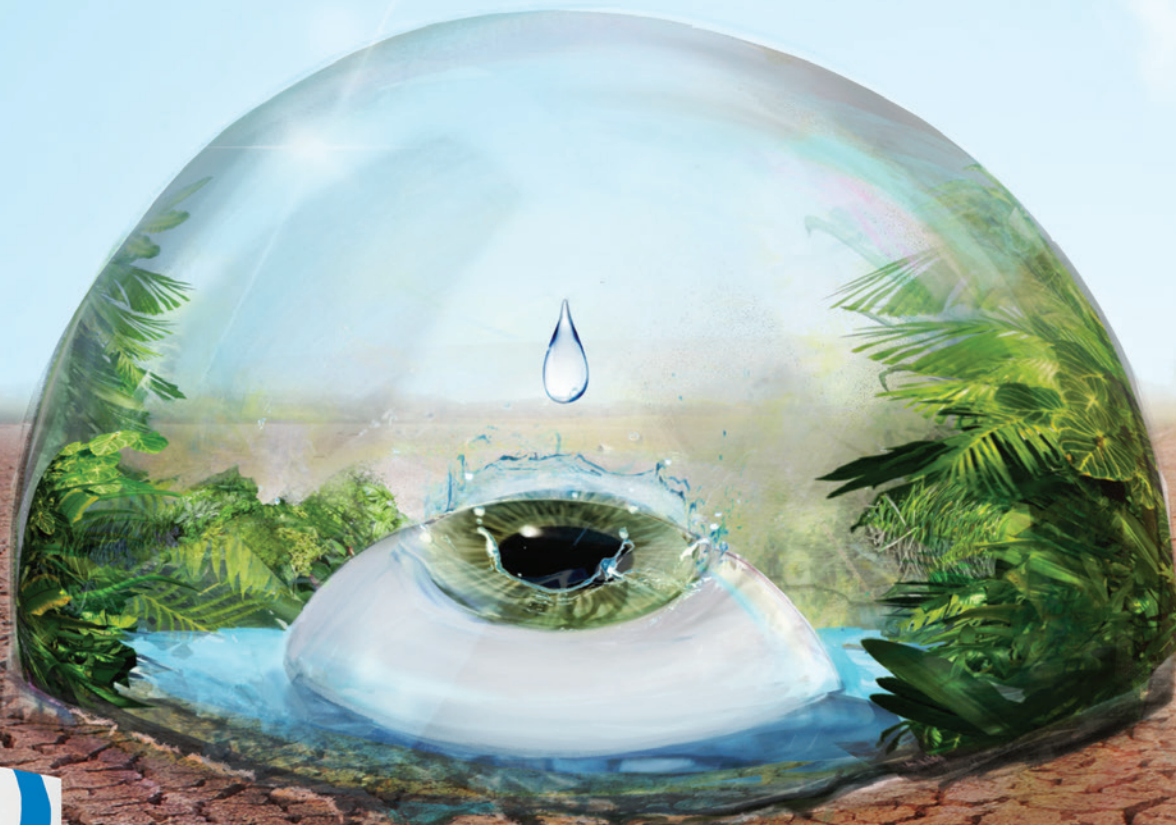
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