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An Approach to Optic Neuropathies

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Optic neuropathies are varied in their clinical presentations, etiologies, recommended diagnostic investigations, and treatments. This article aims to provide a practical framework to guide the evaluation of a patient suspected of an optic neuropathy (**Figure 1**).

One should consider whether there is clear optic nerve dysfunction. Decreased visual acuity, obvious subjective blurring of central or peripheral vision, acquired dyschromatopsia, or a relative afferent pupillary defect (RAPD) in unilateral or asymmetric cases, are clues that suggest an optic neuropathy[1]. Determining whether vision loss is the result of a primary retinal cause (e.g., maculopathy, retinal degeneration, retinal detachment, etc.) or optic nerve damage, can be challenging given the overlapping clinical features[2]. Paying attention to key clinical and optical coherence tomography (OCT) features can be helpful. Clinically, macular disease may produce relative micropsia, macropsia, or metamorphopsia all of which are very uncommon in optic neuropathies unless there is secondary retinal involvement (e.g., spill over edema into the macula in neuroretintis, papilledema, hypertensive or diabetic papillopathies). Careful review of an OCT of the macula can reveal whether there are inner retinal abnormalities (e.g., retinal nerve fiber layer [RNFL], or ganglion cell layer ([GCC]) versus outer retinal (e.g., ellipsoid zone, or retinal pigment epithelium [RPE]) disruption. For a helpful functional assessment, multifocal electroretinography (mfERG) can aid in distinguishing optic neuropathies exhibiting RNFL or GCC dysfunction from maculopathies (usually outer retinal damage) given that maculopathies will usually demonstrate reductions in amplitude and/or increase in latency, whereas optic neuropathies generally yield normal mfERG findings.

If optic nerve function is relatively spared, determine if there are signs or symptoms of raised intracranial pressure (ICP), such as transient visual obscurations, morning

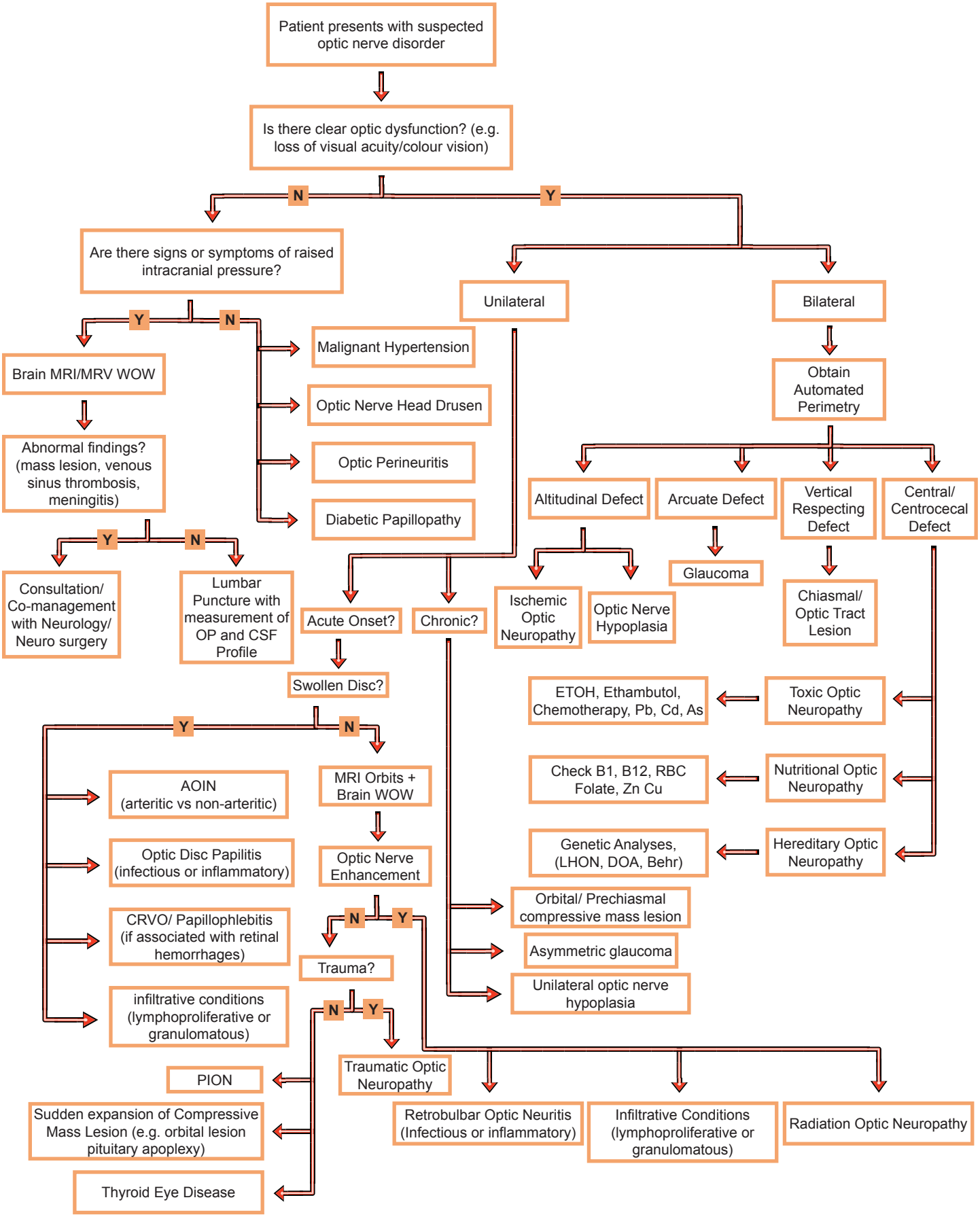

Figure 1. Flow diagram outlining a practical approach for the evaluation of a patient presenting with a potential optic neuropathy.

headaches, pulsatile tinnitus, or new onset abducens palsy. If present, obtain an MRI and magnetic resonance venography (MRV) of the brain with and without contrast (WOW) to look for mass lesions, hydrocephalus, meningitis, or cerebral venous sinus thrombosis[3]. If a structural abnormality is found, coordination and co-management with the relevant service is most appropriate. If neuroimaging does not reveal a structural lesion, obtain a lumbar puncture with opening pressure and cerebrospinal fluid (CSF) profile evaluations to further work up the possibility of idiopathic (IIH) or secondary forms of intracranial hypertension. Even inflammatory etiologies such as meningitis, encephalitis, or autoimmune conditions (e.g., lupus, sarcoidosis) can affect the arachnoid granulations' ability to absorb CSF, leading to elevated intracranial pressure (ICP)[4]. Hence, reviewing the CSF profile is essential before making a diagnosis of IIH. If elevated ICP is not suspected clinically, or a negative work-up as per above, diagnostic possibilities may include malignant hypertension, buried optic nerve head drusen (consider B-scan, fundus autofluorescence or OCT nerve), optic perineuritis where the optic nerve itself is spared but the nerve sheath demonstrates involvement (consider MRI orbits WOW), or diabetic papillopathy[5,6].

In patients presenting with unilateral loss of central acuity or dyschromatopsia, determine whether the condition developed acutely (within hours to days) or rather had a more indolent, chronic course (weeks to months).

In acute cases, if the optic disc appears swollen, anterior ischemic optic neuropathy (AION)[7] and inflammatory optic neuritides[8] should be considered first. Patients >55 years of age should be asked about clinical features of giant cell arteritis (GCA), such as headache, scalp tenderness, jaw claudication, systemic malaise, unintentional loss of weight or appetite, and low grade fevers. Acute non-arteritic AION usually presents unilaterally with up to a 15% chance of contralateral eye involvement within 5 years.[9] Risk factors include a small cup-to-disc ratio, obstructive sleep apnea, erectile-dysfunction medication use, and vascular co-morbidities. The use of amiodarone should be investigated since a similar form of optic neuropathy can occur in patients even after several months of using this medication[10]. Occasionally, infiltrative conditions like leukemia, lymphoma, or granulomatous disease can produce an acute papillitis (**Figure 2**). A thorough retinal examination may reveal posterior pole venous congestion (papillophlebitis) or wide-spread perivenous hemorrhages (CRVO) in addition to disc edema. Infectious papillitis due to syphilis or toxoplasmosis, among others, should be considered, as well as inflammatory etiologies like myelin oligodendrocyte glycoprotein associated disease (MOGAD), and demyelinating optic disc papillitis, which may be associated with painful eye movements. A recent study from 2020 reported that 86% of patients with MOGAD present with disc edema[11], in contrast to the landmark Optic Neuritis Treatment Trial (ONTT) which revealed that approximately only one third of demyelinating optic neuritis presents with disc edema (usually non-hemorrhagic)[12].

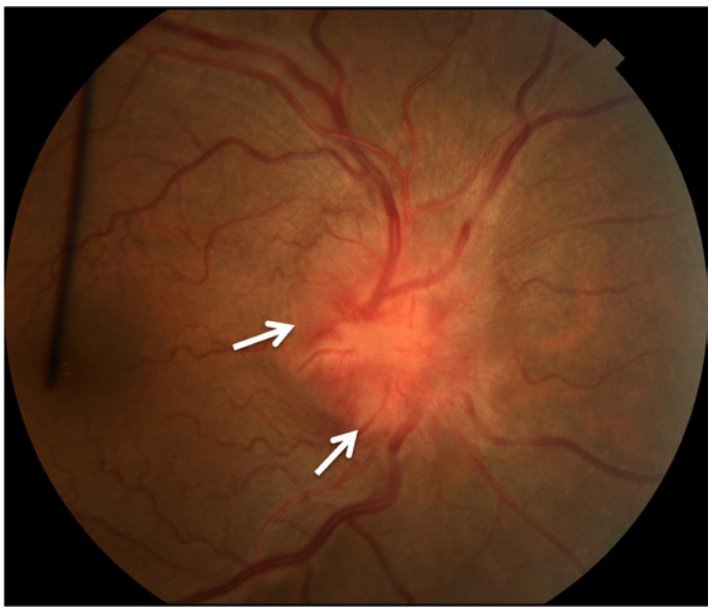

Figure 2. A patient with leukemic infiltration of the right optic nerve. Note the diffuse elevation of the disc with nodular lesions (arrows) within the substance of the infiltrated optic nerve.

In patients with an acute optic neuropathy without disc edema, obtain an MRI orbits and brain WOW to better evaluate the retrobulbar structures, paying close attention to whether the optic nerve enhances post-contrast.

If no enhancement is seen, and there is a history of orbital or head trauma, consider traumatic optic neuropathy (TON). TON eventually (usually several weeks after the trauma) leads to pallor and cupping of the optic disc. Acutely, only decreased visual acuity, dyschromatopsia and varied patterns of visual field loss may be present. If a history of trauma is not present, posterior ischemic optic neuropathy (PION) may be a possibility. PION may be further classified as related to GCA, non-arteritic, or post-surgical (e.g., prolonged surgery, significant blood loss, decreased hematocrit, prone position, etc.). The history should point to a particular PION etiology[13]. A rapidly compressive orbital or parasellar lesion (e.g., thyroid eye disease, hemorrhage, vascular malformation which has bled, pituitary apoplexy, etc.) can produce features of an optic neuropathy without disc edema, given the deep retrobulbar location of optic nerve compression. The causative abnormalities will be evident on neuroimaging; MRI is best in this scenario given greater soft tissue detail and resolution than CT.

If the MRI reveals optic nerve enhancement, retrobulbar optic neuritis -- both inflammatory and infectious forms -- are the most common etiologies (e.g., MOGAD, MS, neuromyelitis optica spectrum disorder [NMOSD], tuberculosis, herpes simplex virus, syphilis, fungal disease, etc.). Radiation optic neuropathy typically demonstrates avid enhancement of the pre-chiasmal region of the optic nerve(s), 12 to 18 months after high

dose radiation treatment (>50 Gy) to the retrobulbar or parasellar regions (**Figure 3**).

Chronic unilateral optic neuropathies warrant consideration of a retrobulbar compressive mass lesion, asymmetric glaucoma, or unilateral optic nerve hypoplasia. Imaging (MRI orbits and brain WOW) is imperative in these cases.

Evaluation of a bilateral optic neuropathy should begin with a careful, thorough history, followed by automated perimetry. The pattern of visual field loss can be very informative and help narrow down the diagnostic possibilities. As mentioned above, approximately 15% of non-arteritic AION may become sequentially bilateral; hence, clinicians should consider this possibility if bilateral altitudinal defects are seen. Central/centrocecal defects are classically associated with toxic/nutritional/metabolic/hereditary optic neuropathies[14]. In such cases, there may be subtle optic disc swelling in the acute or subacute phases, with distinct ganglion cell loss present even in the acute phase, with the latter structural finding correlating better with the clinical picture of central vision and dyschromatopsia than the seemingly "normal" RNFL measurements. There may also be a sharp, distinct demarcation between the preferentially affected papillomacular bundle (higher metabolic demand hence more susceptible) and the adjacent arcuate bundles (**Figure 4**).

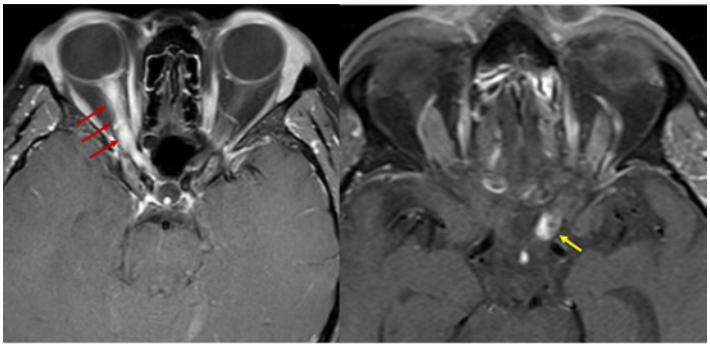

Figure 3. On the left is a T1 post-gadolinium MRI axial image demonstrating avid, homogeneous enhancement of the entire left optic nerve in a patient with MOGAD. On the right is a post-gadolinium MRI axial image of a patient with radiation of optic neuropathy exhibiting focal enhancement (arrow) at the junction of the left optic nerve and chiasm, 18 months following high dose radiation to the parasellar region.

Glaucoma remains the most common bilateral optic neuropathy (e.g., nasal steps, arcuate, nerve-fiber bundle type visual field defects, etc.) with chronic, often subclinical field loss, and superior and inferior RNFL thinning on OCT; however, if the field loss respects the vertical meridian, a chiasmal or optic tract lesion must be considered. Inflammatory optic neuropathies such as MOGAD[15], NMOSD[16], infectious, autoimmune or paraneoplastic optic neuropathies, can also present bilaterally and may have a predilection for the chiasm. MRI brain and orbits WOW can be informative, looking for optic nerve enhancement in inflammatory and infectious forms of optic neuropathies, followed by the relevant serological and systemic evaluations such as bloodwork, chest and abdominal imaging, and CSF analysis.

The evaluation of a patient suspected of having an optic neuropathy requires attention to the major tenets of clinical medicine: thorough yet poignant history-taking, careful clinical examination, and thoughtful, directed use of ancillary investigations. While the optimal approach is far from algorithmic, maintaining a logical, sequential framework from which to evaluate the individual patient, can aid in improving diagnostic accuracy. When determination of a specific diagnosis is not possible, categorization of the condition such as ischemic, infiltrative, inflammatory, etc. can be very helpful in guiding management. Careful follow up is key, allowing the clinician to reassess as necessary.

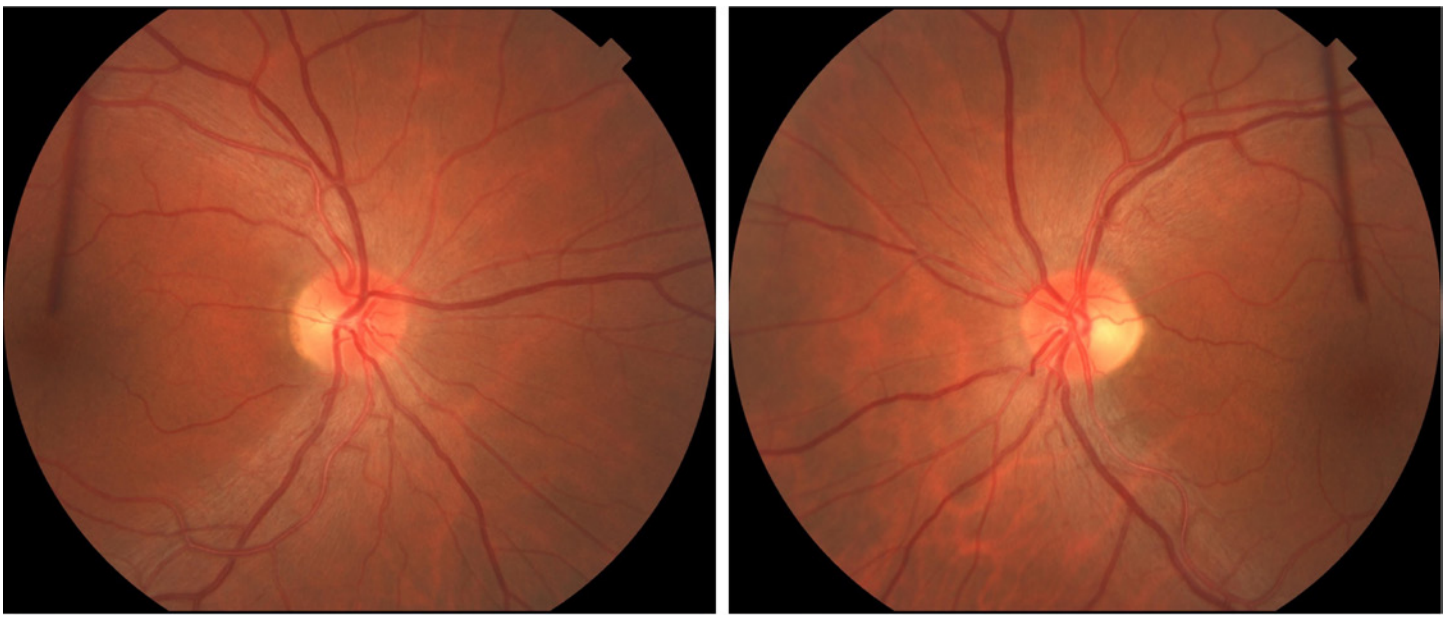

Figure 4. Prominent thickening of the interface between the papillomacular and arcuate bundles bilaterally in a patient with chronic heavy alchohol consumption, leading to a bilateral toxic optic neuropathy.

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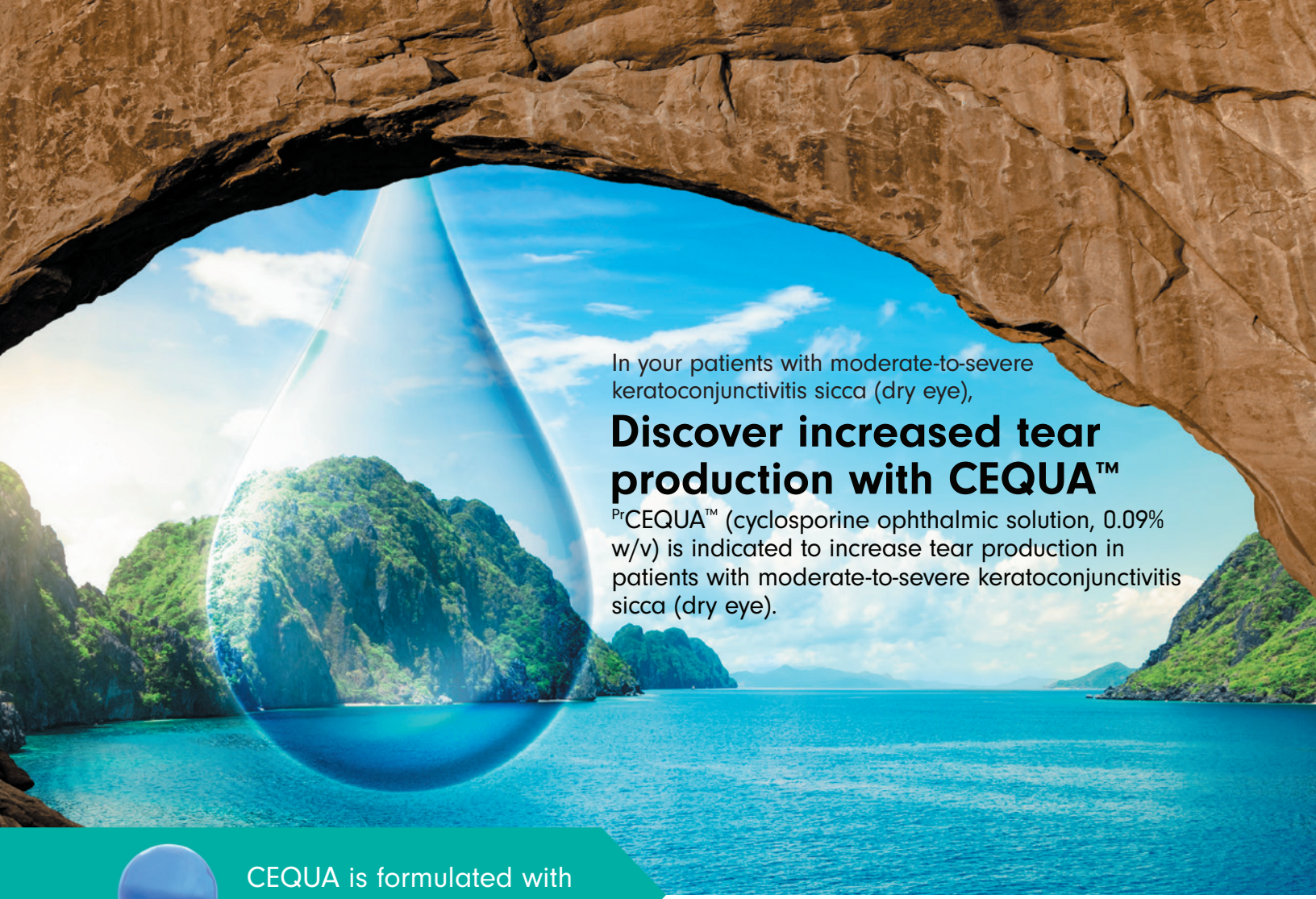

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Strategies for the Management of Ocular Surface Disease in Glaucoma

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INTRODUCTION:
Ocular surface disease (OSD) is a common ophthalmological concern, with a prevalence in the Canadian population estimated at 25%[1]. Amongst glaucoma patients, up to 60% report symptoms of OSD and up to 78% have clinical signs[2]. Surface symptoms significantly reduce glaucoma-related quality-of-life (QOL), and there is emerging evidence to suggest that treatment of OSD may in fact improve intraocular-pressure (IOP) control and contribute to disease stabilization[3,4]. The treatment of OSD in glaucoma has been receiving increasing attention, however specific recommendations remain sparse[5].

Ocular surface disease is known to represent a complex milieu of genetic predisposition, adnexal and periorbital status, environmental factors, systemic diseases, and medications (topical and systemic), amongst other predisposing factors. Effective management of this condition therefore demands that treatment be targeted to the specific clinical context. A 2020 study of Canadian glaucoma specialists found that, although 97% identified optimization of ocular surface disease as important for improving patient QOL, only 22.2% felt this was currently being managed adequately in the subspecialty clinic setting. Moreover, although all participants felt comfortable modifying topical hypotensive regimens to improve surface disease, only 61.1% were confident identifying patients who would benefit from topical steroids, and just 30.5% felt knowledgeable regarding the use and dispensation of autologous serum tears, which are increasingly deployed for treatment-resistant OSD in dry-eye practices[5]. There is, therefore, an unmet need for clarity in the treatment algorithm to optimize OSD in glaucoma patients. Here, we discuss the therapeutic approach to these patients and present a suggested algorithm to guide management.

STANDARDIZED SCORES/ASSESSMENT FORMS
There are many standardized assessment forms and criteria to grade the presence and severity of OSD in diverse populations, but these are currently underutilized in the glaucoma practice[5]. Amongst the most well-known is the Ocular Surface Disease Index (OSDI), but others—such as the Symptom Assessment in Dry Eye (SANDE), and Dry Eye Questionnaire-5 (DEQ-5)—all serve to quantify dry eye signs and symptoms in the clinical setting[6-9]. The chief benefits of these tools are providing consistent, reproducible means to assess disease activity which can be helpful in guiding therapy and gauging response to treatment in a quantifiable manner.

OPTIMIZATION OF ENVIRONMENTAL/PERIORBITAL FACTORS
The ocular surface is influenced by both local environmental and periorbital factors. An ambient humidity of 40-45% has been proposed as a reasonable target, as it has been shown that when humidity falls to 20-25%, evaporative tear loss increases by 99.7%[10].

Lid malposition such as entropion, ectropion, or lagophthalmos, and inflammatory lid disorders (such as blepharitis or rosacea) should be managed carefully in this population. Patients should also be examined for signs of predisposing conditions such as allergic conjunctivitis and contact-lens overwear, which should be managed aggressively.

STEPWISE TREATMENT ALGORITHM

The benefits of a stepwise approach to the management of surface disease include logical progression of care while minimizing both the cost and complexity of treatment. Such an algorithm is outlined below and presented in **Figure 1**. The use of a standardized approach eases clinical integration for the physician, reducing barriers for the initiation of the appropriate treatments, while offering the opportunity to 'step up' or 'step down' therapy based on a patient's symptoms, severity scores, and the tolerability of each treatment.

OPTIMIZATION OF GLAUCOMA THERAPY

It has been well-established that benzalkonium chloride (BAK)--one of the most common ophthalmic preparation preservatives--contributes to aqueous tear deficiency, evaporative tear film loss, and diminished reflex tearing, via decreased corneal sensitivity[11]. Further, there is data to suggest that chronic BAK exposure increases trabeculectomy failure rates[12] and active ingredients themselves impact many anterior segment structures[11]. Every effort should be taken, therefore, to minimize these effects. Various fixed-dose combination drops are available and reduce BAK exposure when compared to multi-drop regimens. Further, there are increasing options for alternatively-preserved or non-preserved formulations, which have fewer surface sequelae than BAK. Where possible, these should be employed, taking into consideration price and convenience factors for each patient.

Early intervention with laser trabeculoplasty as a drop-sparing therapy should be considered for glaucoma patients with OSD. Selective laser trabeculoplasty has been shown in large trials and meta-analyses to be equivalent to topical hypotensive agents as a first-line intraocular pressure (IOP)-lowering therapy, with further advantages in terms of cost-effectiveness and compliance[13]. Minimally invasive glaucoma surgery (MIGS) should be considered at the time of cataract surgery when appropriate to further reduce medication and preservative burden when clinically appropriate. *Ab interno*, conjunctiva-sparing MIGS may be favored, such as gonio-assisted trabeculotomy (GATT), Trabectome, iStent or Hydrus microstent.

While allergy is possible with any topical glaucoma formulation, which may include sensitivity to the active ingredient, preservative, or vehicle, alpha agonists such as apraclonidine and brimonidine have the highest incidence of allergic response. When considering allergic conjunctivitis or contact dermatitis, up to 25.7% of patients on brimonidine may develop a response[14]. If allergy is suspected to a topical formulation, consideration could be given to switching to another class of medication if appropriate, to another topical formulation within the same class of topical active ingredient, or to the same medication with an alternative or unpreserved formulation, if preservative sensitivity is suspected.

Step 1: Promote Ocular Surface Health

The ocular surface should be optimized with drops, punctal occlusion, and supplements. Mainstay therapy consists of artificial tears and ointments, with preference for non-preserved agents where possible. Dosing can be initiated with a frequency between QID and Q1H based on the severity of signs and symptoms. A viscous tear ointment/gel should also be considered for QHS usage, or indeed can be utilized more frequently during the day, however this may be limited by the patient's ability to tolerate the transient blurred vision that these agents often induce.

Punctal occlusion has been shown to decrease standardized OSD severity scores[4], with many options available. Absorbable plugs may allow for a temporary trial

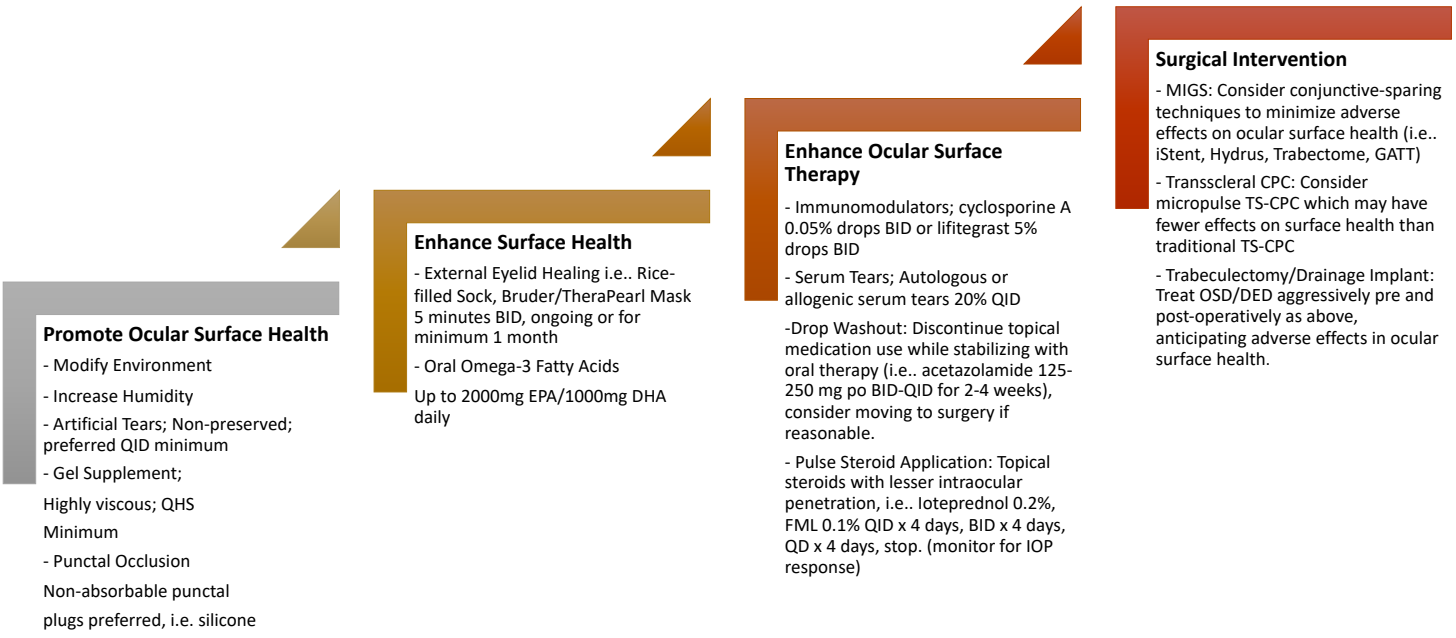

Figure 1. Stepwise approach to ocular surface disease management in glaucoma patients; adapted from Muzychuk et al, 2020

EPA: eicosapentaenoic acid; **DHA:** docosahexaenoic acid; **IOP:** intraocular pressure; **MIGS:** minimally invasive glaucoma surgery ; **GATT:** Gonioscopy-assisted transluminal trabeculotomy; **CPC:** cyclophotocoagulation; **OSD:** ocular surface disease; **DED:** dry eye disease

of punctal occlusion with an absorbable plug and movement to permanent silicone plugging if successful, with punctal ablation available in cases of recurrent extrusion or plug discomfort. As permanent plugs may be more efficacious than temporary plugs, with specific evidence for their use in glaucoma, they may represent a reasonable starting point for punctal occlusion therapy, and moreover are typically reversible[4]. As increasing drop burden is known to impact compliance, punctal occlusion may be particularly compelling for patients already on complex drop regimens. If there is a paradoxical worsening in OSD signs and symptoms, these should be removed as it is theoretically possible that patients with inflammatory dry eye may worsen due to pooling of inflammatory mediators.

External eyelid heating devices are effective in reducing surface staining and improving tear breakup time (TBUT) and meibomian gland secretion quality[15]. Optimally, patients are advised to use BID-TID applications of these devices in a minimum of 5 minute increments. Due to evaporative cooling associated with wet devices, commercially available dry heating devices are preferred.

Omega-3 supplementation has been widely investigated as an OSD therapy. One of the largest randomized-controlled trials, the NIH-funded DREAM study, showed no benefit over placebo[16] while a subsequent large-scale meta-analysis found omega-3 significantly improved OSD symptoms/signs[17]. Doses up to 2000 mg of eicosapentaenoic acid and 1000 mg of docosahexaenoic acid daily were well tolerated. Though possibly of modest effect, omega-3 may be considered for patients with treatment-resistant OSD.

Step 2: Enhance Ocular Surface Health

For refractory disease, escalation of therapy with immune-modulators and serum tears may be necessary. A recent prospective study demonstrated that six months of topical cyclosporine A 0.05% significantly improved TBUT, corneal staining, and OSDI scores in patients on BAK-preserved glaucoma drops[18]. In Canada, topical cyclosporine 0.09% and 0.1% are also commercially available. Lifitegrast 5% modulates T-cell activity implicated in the pathogenesis of OSD, and although yet to be studied in glaucoma, may hold promise for these patients.

Autologous serum tears may also be considered for recalcitrant OSD in this clinical setting. These have been shown to contain growth factors, fibronectin, and vitamin A—integral components in the tear film and surface signaling. These are typically initiated at a concentration of 20% QID-Q2H, and superiority over artificial tears in the setting of severe OSD has been demonstrated[19]. Higher concentrations (30% and 40%) can also be compounded but the excess protein concentration can make the solution thicker which some patients may not prefer. Cost and compounding access limit their use however; allogenic serum tears derived from donor blood products may mitigate these constraints.

Step 3: Enhance Ocular Surface Therapy

When the above steps prove inadequate, topical glaucoma therapy washout should be considered, provided the patient can be maintained on oral agents (such as acetazolamide) alone for a 2-4 week period. This may be performed independently or combined with a short course of topical corticosteroid to interrupt the cycle of surface inflammation. Topical corticosteroids used preoperatively for trabeculectomy have been shown to improve outcomes; it is hypothesized that this occurs by reversing medication-induced conjunctival inflammation, but specific recommendations for their use in glaucoma therapy-induced OSD are lacking[20]. Care should be taken to minimize steroid response when selecting an agent, and careful monitoring of IOPs should be undertaken for the duration of therapy. Preparations such as fluorometholone or loteprednol etabonate may have lesser IOP-raising effects; reasonable choices include fluorometholone 0.1%, loteprednol etabonate 0.2-0.5%, or prednisolone 0.5%. A short course may comprise an initial application QID, reducing the dosage by half every 4-7 days until completion.

Step 4: Surgical Intervention

Finally, if the outlined steps are unsuccessful, drop-sparing surgical intervention may be considered. Ab interno, conjunctiva-sparing MIGS procedures may be favored, such as GATT, Trabectome, iStent, or Hydrus microstent. While the Xen gel implant forms a filtering conjunctival bleb and is often used in conjunction with mitomycin C (MMC), it can obviate the need for conjunctival dissection, which may in theory better preserve ocular surface health. Micropulse cyclophotocoagulation, when appropriate for the targeted IOP reduction, may have fewer adverse effects on the ocular surface than traditional continuous wave due to its “on-and-off” cycle, allowing structures adjacent to the targeted pigmented ciliary epithelium to cool, protecting them from collateral thermal damage[21]. Trabeculectomies and glaucoma drainage devices remain the mainstay for cases necessitating significant IOP reduction, however. In any bleb-forming procedure, the possible implications of the bleb itself for ocular surface health must be considered. Blebs are known to interfere with proper lid function, compromise the precorneal tear film, and elevated/cystic blebs have been implicated in worsening OSD[22]. Further, MMC—a common adjunct in modern filtering procedures—is known to have adverse effects on limbal stem cells and decreases conjunctival goblet cell density[23]. Therefore, it is advisable to optimize all other factors for the ocular surface prior to surgery, anticipating its potential adverse effects on surface health.

ADDITIONAL MODALITIES

Newer therapeutic modalities may be considered on an individualized basis. Among the most studied of these modalities in ocular surface disease are intense pulsed light (IPL) and thermal pulsation (i.e.. LipiFlow, Johnson & Johnson Vision, Jacksonville, FL, USA; iLux, Alcon Laboratories), particularly in the setting of significant meibomian gland disease (MGD). A cross-sectional study found MGD to be present in 80% of patients with glaucoma on topical IOP-lowering agents, however, the presence of MGD did not appear to have an additional detrimental

effect on the ocular surface to those induced by topical glaucoma medication use[24]. In glaucoma patients with OSD, a small, non-comparative series on IPL demonstrated significant improvement in signs and symptoms of OSD[25]. However, a randomized controlled trial evaluating thermal pulsation with lid hygiene versus lid hygiene alone for glaucoma patients with OSD failed to demonstrate an added benefit with thermal pulsation over lid hygiene measures alone[26]. Future studies may better delineate the role for these newer modalities for the treatment of OSD in glaucoma. As with all interventions, cost and availability must be carefully considered.

CONCLUSION

The management of ocular surface disease in glaucoma is multifaceted but may be streamlined through the adoption of a stepwise algorithm. By treating aggravating comorbidities, optimizing the patient's topical glaucoma and dry eye therapy, and considering drop-sparing laser and surgical therapies using techniques that may be less likely to worsen ocular surface disease, physicians may be better able to address this frequently comorbid condition.

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Genetics of retinal degeneration in 2023

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Inherited retinal degenerations (IRDs) are of great interest with the development of novel therapies, thereby allowing this group of conditions to be “actionable” for the first time.

A molecular diagnosis can be obtained in nearly 70% of cases of IRD, with over 300 IRD-linked genes having been identified to date. Numerous animal models of different genetic subtypes of IRDs replicated the human phenotypes enough to develop and test novel therapies to improve outcomes for IRD patients.[1,2] The first gene replacement therapy indicated for IRD, Luxturna (voretigene neparvovec-rzyl), was approved by Health Canada in October 2020 and is now available to patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic *RPE65* mutations. Clinicians from Ontario, Quebec and Alberta can now access this treatment through their province's public health plan.

This article aims to review some basic information and present new knowledge about IRDs to allow clinicians to better understand diagnosis and disease management

DIAGNOSIS

Inheritance
Autosomal recessive (AR) diseases usually affect only one generation unless there is consanguinity or the diseased-allele frequency in the population is unusually high. The latter is the case in Stargardt disease, which has an estimated incidence of 1 in 8,000–10,000 and a reported carrier frequency of 1 in 20.[3,4,5] Parents who happen to both be carriers for a disease-causing gene variant have a 25% risk of having an affected child at each conception. The carriers of AR IRD usually do not manifest any signs or symptoms.

X-linked recessive diseases in principle affect men and are inherited through a female lineage. Occasionally, women can manifest signs and/or symptoms of the disease due to unfavourable inactivation of the X chromosome (lyonization). Examples of this include X-linked retinitis pigmentosa (RP), choroideremia, and X-linked ocular albinism.[6] Most often, carriers of an X-linked retinoschisis variant do not show signs of the disease.

Autosomal dominant (AD) diseases affect both sexes, have variable expressivity and may show incomplete penetrance (skipped generation). AD is characterized by male-to-male transmission, when present. The risk of transmission of the genetic defect from an affected individual is 50% at each conception. Occasionally, an individual with an AR IRD can have an affected child if the other parent is a carrier of an AR variant in the same gene. This is referred to as pseudodominant inheritance and is seen more often in consanguineous populations.

It is necessary to assume a mode of inheritance to effectively interpret the results of genetic testing and to diagnose an IRD, whether you expect to find one or two variants. Specific mutations in approximately 10% of IRD-linked genes can be associated with AR or AD inheritance.

Mitochondrial diseases, which are mainly transmitted through the female to her offspring affect the retina in two distinct ways: retinal dystrophy and optic atrophy. The phenotypic manifestations of mitochondrial diseases are highly heterogenous and depend on the level of heteroplasmy (the amount of mutated mitochondrial DNA within the cell). This will not be reviewed further in this article.

Genotyping

Genetic testing aims to confirm a diagnosis and the inheritance pattern of a condition. It also guides in prognostication and determining eligibility for potential treatment or clinical trial enrolment. Patients with IRDs should be encouraged to seek genetic testing. Genetic testing requires a biological specimen (e.g. blood or saliva) and patient consent. The results must be interpreted in the context of the phenotype and when possible, with segregation analysis (testing of family members) to ensure only the affected individuals carry potential disease-causing variant(s). A diagnosis requires the integration of the phenotyping and genotyping information.

In Canada, genetic testing is supported by provincial health care, though there is an often-lengthy bureaucratic process to access it. Patients may choose to pay out-of-pocket or seek free genetic testing, however, in the case of free testing, data ownership resides with the testing company and genetic counselling is seldom offered by the companies. We recommend that all patients enter their genetic testing results in the National Fighting Blindness Canada patient registry (https://www.fightingblindness.ca), which allows patients to be contacted for the purpose of research or when new treatments become available.

Retinal Degeneration

IRDs are clinically and genetically heterogeneous conditions marked by progressive (though in some cases stationary) malfunction of retinal photoreceptors, retinal pigment epithelial cells, trans-synaptic signalling with bipolar cells, and/or the choriocapillaris complex. They usually present as bilateral and symmetrical. There are numerous classification systems for IRDs, with the most common based on the age of onset, the anatomical distribution of the disease, and/or the predominantly affected photoreceptor system (**Figure 1**). Detailed phenotyping is important, especially at the first visit, to guide the diagnosis and genetic testing. Documenting the natural history of change via yearly or bi-yearly follow-ups is also important to best understand the course of the condition. Based on the clinical understanding of the genotyping of IRDs, some conditions previously believed to be stationary, have shown progression when seen in follow up.

Phenotyping

Workup for a new IRD case often includes retinal electrophysiology tests, fundus imaging, fundus autofluorescence (FAF), optical coherence tomography (OCT), and some type of visual field test, depending on the condition. For a follow-up assessment of photoreceptor dysfunction, OCT and visual field tests are the most useful in determining progression. FAF is very useful for detecting progression of Stargardt disease and chorioretinal conditions, as the ring of autofluorescence often correlates to changes in the visual field and ellipsoid zone (EZ) line.[7] The use of fundus photography should be limited on follow up visits as it is less informative as compared to other modalities. In addition, the use of intravenous fluorescein angiogram (IVFA) testing is typically limited to vascular conditions.

The main elements to look for in phenotyping, are changes in a genotype-specific pattern, the type and cellular level of retinal degeneration, and complications (e.g. CME, macular hole, choroidal neovascular membrane, glaucoma, etc.).

Phenotyping tools

a. **Visual acuity (VA):** Low-vision acuity charts may be used to quantify vision as much as possible. Near vision should also be assessed, as loss of eye accommodation typically presents early in the onset of IRDs.

b. **Assessment of refractive errors:** Some phenotypes, such as congenital stationary night blindness (CSNB) and X-linked RP with myopia, are associated with specific refractive errors. Knowing the natural history of refractive errors in certain dystrophies can aid in management (e.g. using atropine eye drops to halt myopic progression).

c. **Contrast sensitivity (CS):** CS is very useful in understanding subjective vision changes seen in early IRD.

d. **Colour vision:** Colour vision assessments are useful in determining the degree of cone involvement.

e. **Comprehensive eye exam:** Attention must be paid to the entire eye, as some retinal diseases may have anterior segment manifestations. Patients with some forms of Best disease are at risk of angle closure glaucoma. When posterior subcapsular cataracts are present, the field of vision must be taken into consideration.[8] The diagnosis of glaucoma may be challenging in light of the pre-existing field changes but must be investigated.

f. **Enhanced depth imaging optical coherence tomography (EDI-OCT):** the EDI-OCT is the most useful phenotyping tool as it can be used in the very young (4–5 years old) and the very visually impaired, even with nystagmus. In assessing the OCT for retinal degeneration, the key area of interest is the integrity of the outer retina, specifically the ellipsoid zone (the mitochondria-rich photoreceptor inner segments) and the outer nuclear layer (ONL) reflecting the photoreceptor nuclei. Central retinal thickness, maintenance or loss of lamination, and thickness of the inner retina and ganglion cells should also be assessed. EDI-OCT helps to evaluate the choriocapillaris and choroid-sclera junction, and hence it is used in disease grading. North Carolina macular dystrophy is a good example, where macular coloboma-like excavation (grade 3) presents with absent RPE and choriocapillaris and deep chorioretinal posterior bowing. EDI-OCT can also be used to

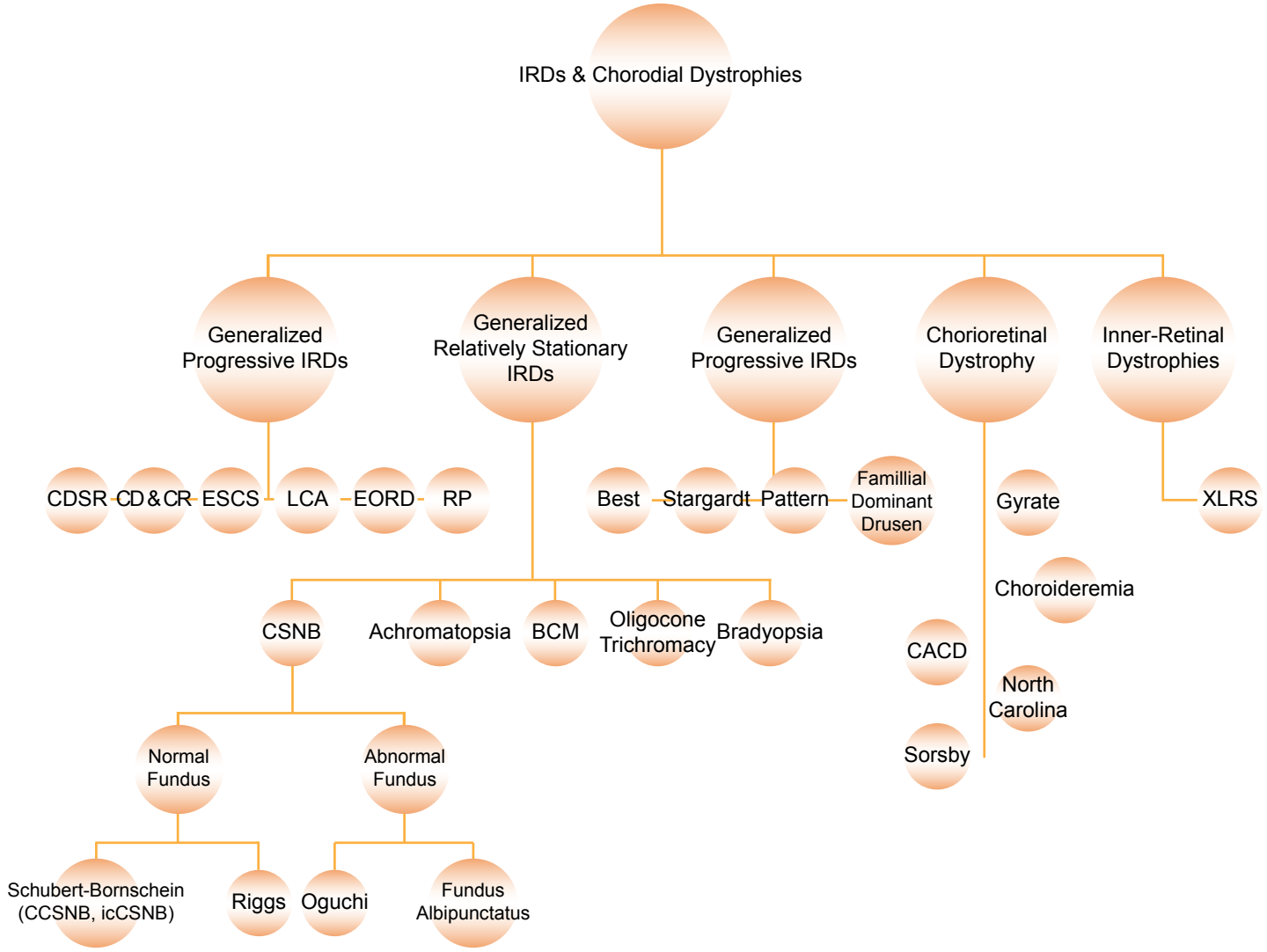

Figure 1: Classification of inherited retinal diseases and choroidal dystrophies.
RP: Retinitis pignmentosa **EORD:** Early-onset retinal dystrophy **LCA:** Leber congenital amaurosis
ESCS: Enhances S-cone syndrome **CD & CR:** Cone dystrophy & cone-rod dystrophy **CDSRR:** Cone dystrophy with supernormal rod response **CSNB:** Congenital stationary night blindness **cCSNB:** Complete form **icCSNB:** Incomplete form **BCM:** Blue cone monochromacy
CACD: Central areolar choroidal dystrophy **XLRS:** X-linked juvinile retinoschisis

document cystoid macular edema, schisis, macular hole, and depth of deposits. The presence or absence of ONL can be used to determine eligibility for gene replacement therapy, as it is indicative of the potential for outer segment revival.

g. **FAF:** FAF is an indirect measure of retinal pigment epithelium (RPE) health and is useful in documenting the stage of disease. FAF can sometimes show early signs of RP (i.e. paramacular annular ring). In Stargardt disease, FAF will show a generalized increase in autofluorescence in the posterior pole with peripapillary sparing. Loss of fluorescence reflects RPE cell death, which is an important measure of disease progression.[7]

h. **Fundus photography:** Fundus photography is most useful as a baseline, and wide-field fundus photography may be used to document a pattern. However, excessive light exposure can be toxic to the retina,[9] which is why fundus photography should be used sparingly and with purpose.

i. **Intravenous fluorescein angiogram (IVFA):** IVFA is only indicated in familial exudative vitreoretinopathy (FEVR), Incontinentia Pigmenti, or on suspicion of a choroidal neovascular membrane as a complication to IRD. Although the “silent choroid” sign on IVFA was previously used as a diagnostic marker of Stargardt disease, FAF and OCT now provide better prognostic capability, and IVFA is not recommended. Excessive light exposure from IVFA can also be toxic to the macula.

j. **Visual field tests:** For generalized retinal degeneration, our center prefers kinetic visual field tests using the I4e, III4e, or V4e stimuli. When the central field is under 20º, microperimetry may be useful as it also assesses the fixation stability.

k. **Electrophysiology:** A battery of electrophysiology tests may be performed to assist in diagnosis and prognosis and to inform disease progression.

1. Retinal function tests:

- Generalized retinal function:
  - Full-field electroretinogram (ffERG)
  - Full-field stimulus testing (FST): measures sensitivity of the entire visual field successfully from a young age and beyond the sensitivity of ERG measurements
- Macular function:
  - Pattern ERG: informs retinal ganglion cell function
  - Multifocal ERG: tests localised cone-driven retinal function.

2. RPE integrity test: The electrooculogram (EOG)

3. Optic nerve and visual pathway tests:

- Visual evoked potential (VEP): assesses the entire visual pathway up to the primary visual cortex.
  - Flash VEP: evaluates the integrity of the visual pathways.
  - Pattern reversal VEP: evaluates macular function, optic nerve function, and chiasmal and retro-chiasmal function.
  - Multi-channel pattern reversal VEP: evaluates intracranial misrouting in albinism, and post-chiasmal visual pathway function.

Phenotype Variability

Approximately 30% of IRD-related gene mutations are associated with more than one phenotype. For example, mutations in the genes *USH2A* (Usher syndrome type 2; RP and hearing loss) and *ABCA4* (Stargardt disease) are the most common causes of non-syndromic autosomal recessive retinitis pigmentosa (ARRP). Depending on the level of impairment of the *ABCA4* protein, mutations in *ABCA4* can lead to fundus flavimaculatus (no maculopathy), Stargardt disease, cone rod dystrophy, or RP (**Figure 2**).[10] Stargardt disease may or may not have flecks but presents with increased autofluorescence.

Monoallelic mutations in *BEST1* can cause AD Best vitelliform macular dystrophy (BVMD), AD adult-onset vitelliform macular dystrophy, or more rarely AD vitreoretinochoroidopathy (ADVIRC) or MRCS (microcornea, rod-cone dystrophy, cataract, and posterior staphyloma).[11] Patients with *BEST1* mutations tend to have narrow anterior chambers and are at risk for closed-angle glaucoma. Biallelic mutations in *BEST1* cause the distinct AR bestrophinopathy (ARB) phenotype (**Figure 3**).[12]

Mutations in *RPE65* usually cause AR Leber congenital amaurosis (LCA) (early onset retinal degeneration) but may also cause ARRP, fundus albipunctatus, and AD RP. The latter group is ineligible for gene replacement therapy proposed for AR LCA, despite being caused by the same mutation. Patients with mutations in *RPE65* usually do not show any autofluorescence.

Retinitis pigmentosa (RP) may or may not show pigment, especially early in disease onset. Some cases, such as those associated with mutations of *RPE65*- and *GUCY2D*, show dissociation of structure-function, meaning the retina can look almost normal, but the function is severely reduced. These are optimal cases for gene replacement therapy. However, RP caused by other genetic variants, such as *TULP1*, *CRB1*, or *CEP290*, can show severe remodelling of the retina with loss of lamination.

DISEASE MANAGEMENT

Patients with visual impairment often benefit from a good refraction, a low vision assessment and should be referred to the Canadian National Institute for the Blind (CNIB). For young patients, the school should be informed of the disability. Patients in the workforce, have the right to be accommodated and may benefit from being connected to a social worker.

Annual or bi-annual follow-up appointments should be arranged to document the natural history of change and to monitor patients for cataracts and glaucoma. IRD patients tend to develop cataracts early, particularly posterior subcapsular cataracts (PSCs) and nuclear sclerotic cataracts. Cataract surgery may be indicated if glare is significant even though the cataract may not be classified as severe. Optimal outcomes of cataract surgery result when the ellipsoid zone is still present, the macula is not too thin (>200 µm), and central retinal function (HVF 10-2) can be documented.[13,14] The better the vision pre-operatively, the greater the likelihood of having better vision post-operatively, as in advanced cases the central retina is prone to phototoxicity.[13] The anterior segment should be examined carefully as some cases may have zonular instability.[15] The vitreous of patients with RP is often cellular, though this is not a vitritis and should not be treated with steroids. That said, cells in the anterior chamber should be managed as per standard of care.

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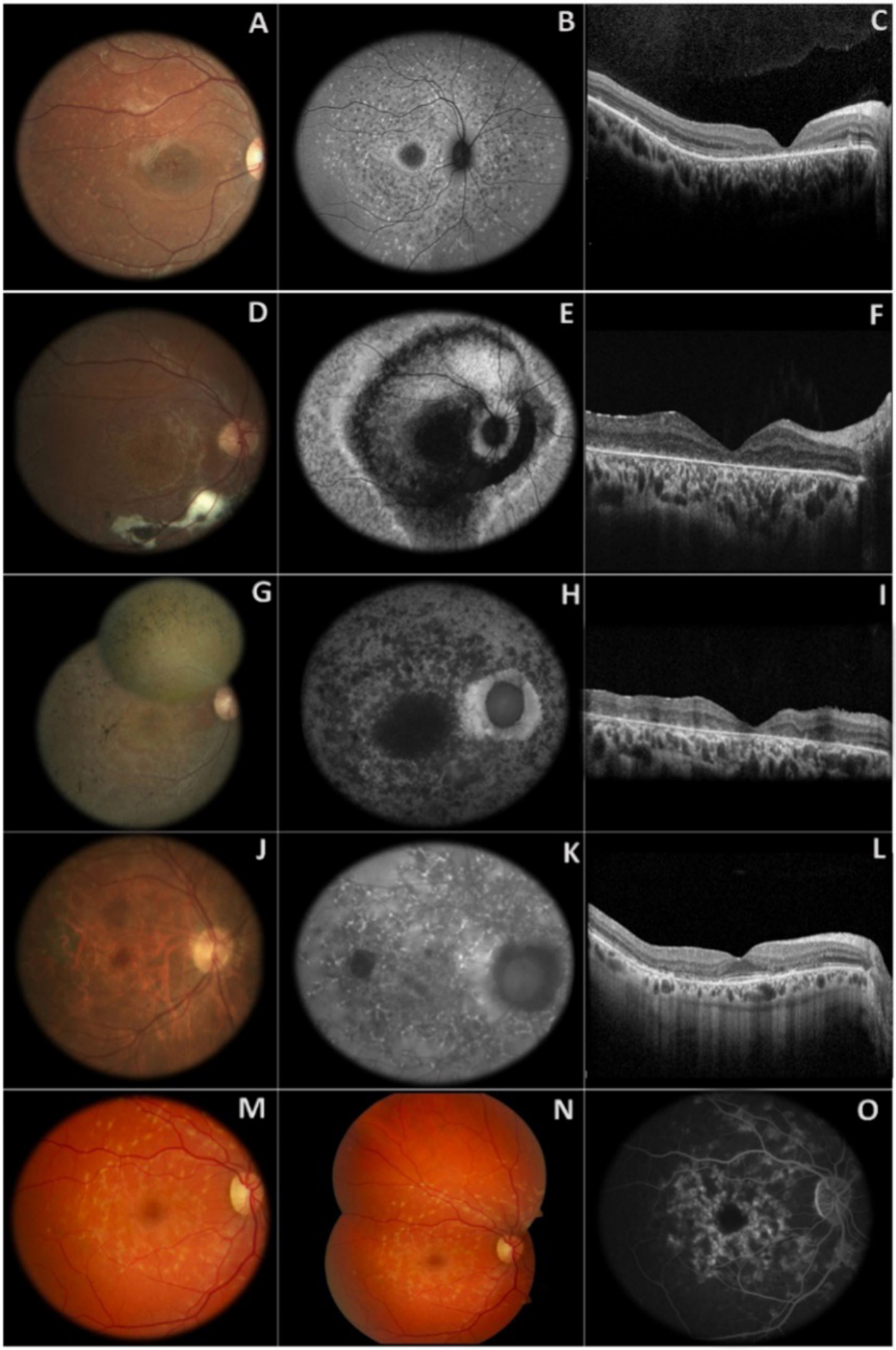
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Figure 2. (A–C) The diagnostic triad of *ABCA4*-related retinal degeneration (maculopathy, retinal flecks, and peripapillary retina and RPE spared from degeneration) seen in the right eye of a 10-year-old male carrying compound heterozygous mutations in the *ABCA4* gene: c.3322C>T (p.Arg1108Cys) and c.4253+5G>A. (A) Fundus photo; (B) FAF showing a hyperautofluorescence background of the macula; (C) OCT. (D–F) Imaging findings in a 14-year-old female with cone-rod dystrophy due to homozygous mutation in the *ABCA4* gene: c.1357G>T (p.D453Y). (E) FAF imaging revealing more extensive abnormalities than fundoscopy, with heterogeneous background autofluorescence and the central macula and crescent area nasal to disc showing definitely decreased autofluorescence, indicating a total loss of RPE in these areas. (F) OCT showing severe loss of ellipsoid zone and outer nuclear layer in the central foveal area. (G–I) Retinal imaging findings of *ABCA4*-associated AR retinitis pigmentosa, in a 20-year-old female carrying homozygous mutation in the *ABCA4* gene: c.885delC. (G) Fundus photo showing classic RP features (mid-peripheral bone spicules pigments migration and mottled RPE, and attenuated retinal vessels). (H) FAF showing mottled hypoautofluorescence extending from the mid-peripheral area to the central macula, with a spared peripapillary area. (I) OCT image of the foveal, parafoveal, and perifoveal areas showing disruption of the outer nuclear layer, external limiting membrane, and ellipsoid zone. (J–L) Retinal imaging revealing reticular pattern dystrophy in a 60-years-old female carrying two heterozygous mutations in the *ABCA4* gene: c.4139C>T (p.Pro1380Leu) and c.5603A>T (p.Asn1868Ile). (J) Fundus photograph showing multiple yellow deposits temporal to the macula and near the arcades, as well as macular pigmentary changes. (K) FAF showing scattered irregular linear areas of hyperautofluorescence with heterogeneous hypoautofluorescence in the posterior pole extending to arcades. (L) OCT of the central foveal area revealing a preserved island of outer retinal layers. (M–O) Fundus flavimaculatus, a milder form of Stargardt disease, in a 41-year-old female carrying heterozygous mutations in the *ABCA4* gene: c.5196+1137G>A - intron variant and (p.S445R). (M) Fundus photograph revealing diffuse flecks that are dispersed throughout the posterior pole and (N) extend to the mid-periphery. (O) Fundus fluorescein angiography confirming less involvement of the central macula, with a silent choroid and dispersed small areas of hyperfluorescence, indicating some RPE atrophy in the posterior pole.

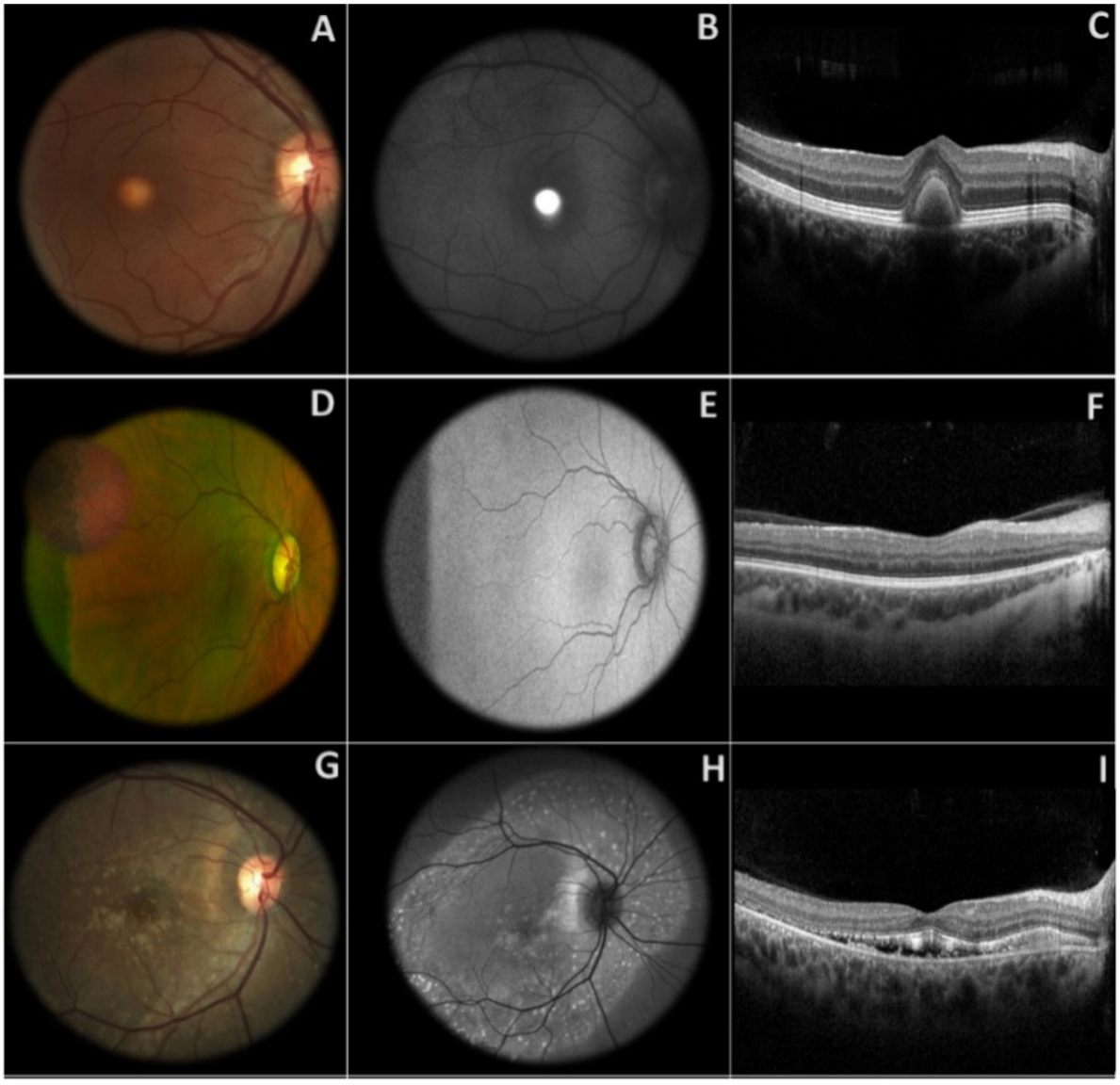

Figure 3. (A–C) Classic features of *BEST1*-associated autosomal dominant BVMD in a 26-year-old male carrying a heterozygous variant in *BEST1* gene: c.652C>T (p.Arg218Cys). (A) Coloured fundus photo showing “egg-yolk-like“ vitelliform macular lesion; (B) FAF with hyperautofluorescence corresponding to lipofuscin-containing subretinal lesion; (C) OCT macular scan showing dome-shaped neurosensory retinal detachment. (D–F) Distinctive peripheral hyperpigmented band, a characteristic sign of ADVIRC, in a 23-year-old female carrying a heterozygous mutation in the *BEST1* gene: c.214T>A (p.Y72N). (F) OCT showing normal central foveal area. (G–I) Autosomal recessive bestrophinopathy (ARB) phenotype in a 45-year-old female carrying two mutations in the *BEST1* gene: c.341T>C (p.V114A) and c.400C>G (p.L134V). (G) A fundus photo showing scattered white-yellow retina lesions; (H) FAF showing presentation as hyperautofluorescence effect; (I) OCT showing neurosensory retinal detachment and irregularity of the ellipsoid zone.

Expert opinions vary with respect to nutritional supplementation, although most agree that antioxidant supplements (e.g., omega-3, lutein, zeaxanthin) can be beneficial for IRD patients.

Patients with Stargardt disease should avoid taking synthetic vitamin A supplements, although there are no side effects associated with vitamin A obtained through a normal diet. Although a 1993 study suggested that taking 15,000 IU/d of vitamin A could slow RP disease progression, this study was significantly flawed.[16] We recommend vitamin A palmitate supplements only in RP cases caused by a rhodopsin mutation or for patients with a rare type of late-onset retinal degeneration due to a mutation in the *C1QTNF5* gene.

Regular exercise, stress management, sleep quality, avoiding smoking, and limiting direct eye exposure to UV rays in sunlight are also important cautionary factors in disease management.[17] Many IRD patients struggle with depressive episodes due to the challenge of adapting to changes in vision, and should be encouraged to consult a psychologist. IRDs can be part of multi-systemic diseases, some as life-threatening as Batten disease,[18] while others such as Refsum disease or abetalipoproteinemia may benefit from early management.[19,20]

NOVEL TREATMENTS

There is no cure for IRDs. Some treatments are being developed for specific gene mutations (e.g., gene replacement therapy, gene editing, or pharmacotherapy.), while other treatments are gene-agnostic (e.g., cell transplants, stem cells, or optogenetics). Numerous clinical trials for IRD treatments are ongoing worldwide, including in Canada (clinicaltrials.gov).

The first-ever gene replacement therapy for AR early-onset retinal degeneration (LCA) caused by two mutations in the *RPE65* gene, Luxturna (voretigene neparvovec-rzyl), was approved by Health Canada in 2020. Reimbursement via provincial formularies is still evolving as the list price to treat both eyes exceeds $1 million dollars. Once the therapy becomes accessible, patients with confirmed biallelic *RPE65* mutations will be able to be treated in Edmonton, Toronto, or Montreal. The results of the phase 3 trial showed improvement in retinal sensitivity (which translates to mobility at reduced light levels) and improved visual fields, but no improvement in visual acuity.[21] For patients to be able to adapt to decreasing light levels is life changing. Minimum eligibility criteria for gene replacement therapy include ≥4 years of age and the presence of a viable retina (**Figure 4**).

Ongoing clinical trials include therapies for Stargardt disease, USH2A, XLRS, XLRP, achromatopsia, and choroideremia, among others. The future is very promising for IRD patients.

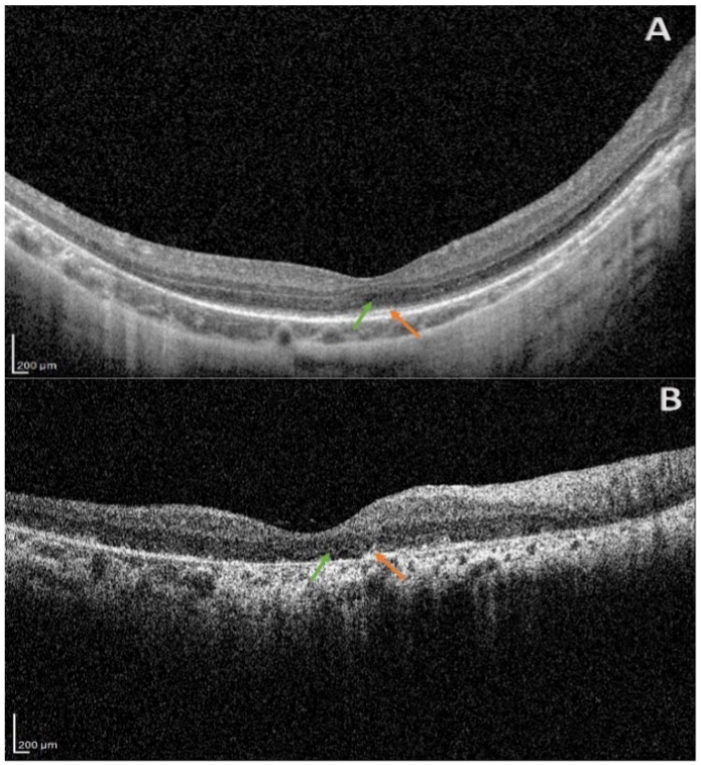

Figure 4: (A) An example of a patient eligible for gene therapy. OCT image of the right macula with the presence of ellipsoid zone (orange arrow) and the outer nuclear layer (green arrow) in the sub-foveal and parafoveal area. (B) An example of a poor candidate for gene therapy. OCT image of the right macula with diffuse loss of the ellipsoid zone except for a minimal remnant in the parafoveal area (orange arrow) and marked atrophy of the outer nuclear layer (green arrow).

COMPLEX RETINAL TRAITS:

Although diabetic retinopathy and age-related macular degeneration (AMD) have been linked to genetic predispositions, these are complex conditions with significant environmental influences and could not be included in this review. Genetic testing for these conditions is not routinely done but can be provided for patients with AMD.[22–24]

SUMMARY

Ocular genetics has become an important part of ophthalmology as conditions that were once considered untreatable are now becoming clinically actionable. As we learn more about IRDs, it is important to use our knowledge of inherited disease, retinal degeneration, genotyping, and phenotyping to aid in making accurate diagnoses. Clinicians will have novel therapeutic options available to treat IRDs which portends a new era for ophthalmologists and patients in terms of improved outcomes and quality of life.

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Keratoconus Management: Navigating Patient Options

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INTRODUCTION

Keratoconus (KC) is a condition which results in progressive corneal thinning. It was first discovered by Dr. John Nottingham in 1854 who described it as "conical cornea" due to the outward bowing appearance caused by the condition.[1] The prevalence of KC is between 0.2 and 4,790 per 100,000 people. KC does not have a gender predilection. It is believed to appear more commonly in South Asian and Middle Eastern populations.

Keratoconus typically begins in the second and third decades of life although it can develop at any time. The clinical symptoms of the condition include blurred and distorted vision. Patients may present with higher-order aberrations (HOA)–the most characteristic of which is coma –resulting in blurred and double vision. The common signs of KC include corneal protrusion and thinning, prominent corneal nerves, Fleischer ring, Vogt's striae, and scissors reflex on retinoscopy[2]. The most frequently encountered phenotype is oval cones in the central cornea. The primary diagnostic tool for KC is corneal topography, although pachymetry, including epithelial mapping and corneal tomography, are often performed in conjunction with each other as they aid with early detection and the monitoring of KC progression.

Advancements in clinicians' knowledge of KC and expertise in its treatment, have led to novel therapies. Stopping disease progression is now possible and improving patients' quality of vision is feasible in many cases.

Preventive measures halting progression and management of mild and moderate forms of KC are reviewed. Treatment of severe KC will also be briefly reviewed.

MANAGEMENT

Current KN management options are based on three pillars: prevention, progression and precision. Treatment should be based on the patient's primary complaint and treatment objectives. It should be specific to the individual and penetrating keratoplasty (PKP) or deep anterior lamellar keratoplasty (DALK) should be considered only in advanced cases due to their surgical risks and the increased risk of corneal graft rejection in young patients.[3] Surgical options should be assessed based on these considerations: i) Does progression of KC need to be arrested? ii) Does the corneal shape need to be significantly modified to improve corrected distance visual acuity (CDVA)? iii) Does the patient's quality of vision need to be enhanced? Various clinical parameters in combination with clinical history are used to answer these questions and provide the optimal case management option.

Scheimpflug imaging and epithelial optical coherence tomography (OCT) mapping are essential in the evaluation and surgical planning of KC eyes. The Pentacam® (Oculus Optikgeraete GmbH [Wetzlar, Germany]) is preferred due to its proven accuracy and repeatability, although various other systems may be used based on surgeon preference[2,4]. In addition to a complete ocular examination, the parameters examined are pachymetry (microns, µm), keratometry (Diopters, D) and corrected distance visual acuity (CDVA). KC is categorized based on severity: mild (>440 µm, <55 D, >20/25 CDVA), moderate (>440 µm, <55 D, >20/50 CDVA) and severe (<440 µm, >55 D, <20/25 CDVA). This classification corresponds approximately to Stages I, II and III of the ABCD parameters on the Pentacam. Progression is monitored using the ABCD progression display and Belin-Ambrosio enhanced ectasia total deviation display (BAD). The Pentacam uses an anterior and posterior curvature 3 mm from the thinnest corneal pachymetry and CDVA.[5] The BAD incorporates anterior and posterior radius of curvature,

as well as corneal thickness at the thinnest point.[4] Both systems offer reliable methods to monitor KC progression.[2,4,5]

PREVENTION

The early detection of KC is challenging as patients may present with non-specific refractive symptoms. Formal corneal measurements may be the only method for early diagnosis. The BAD (D-index) has a high sensitivity and specificity for detecting subclinical and clinical KC.[4] Advances in machine learning have the potential to further improve the accuracy of early KC detection.[6] Early detection of KC may also be improved by knowledge of modifiable and non-modifiable risk factors. KC has a strong hereditary component: there is a 15 to 67 times greater risk of KC in patients with affected relatives.[2] Patients with obstructive sleep apnea are also at increased risk.[7] The primary modifiable risk factor for KC is eye-rubbing, which increases both the likelihood of disease development and its progression (**Table 1**).[8] Atopic conditions such as allergy, asthma and eczema can lead to eye rubbing. Therefore, regular use of antihistamines when indicated, as well as patient counselling to completely avoid eye rubbing is recommended.

PROGRESSION

Corneal collagen cross-linking (CXL) is a proven treatment modality for halting the progression of KC as it alters corneal biomechanics through covalent bonds formation, without impacting corneal translucency.[9] In fact, there are few, if any, conditions in medicine where a treatment has such a dramatic impact on the arresting of a disease. CXL can be used for patients with mild and moderate, and in some cases, advanced, KC (**Table 1**). The Dresden protocol is the standard approach. It utilizes riboflavin 0.1% and ultraviolet-A light.[2] The epi-off protocol is preferred as riboflavin has limited corneal penetration due to its macromolecule structure. Epi-on protocol may be used in pediatric populations as children are more sensitive to the effect of epithelial debridement. CXL slightly improves uncorrected distance visual acuity (UDVA) and CDVA, reduces higher order aberrations, and may improve topographic/tomographic parameters (**Table 2**).[10–12] CXL alone does not significantly impact the mean sphere and magnitude of astigmatism. Corneal pachymetry becomes more compact at 6 months, and reverts to pre-CXL levels by 12 months.[13] CXL is contraindicated in patients with <400 µm central corneal thickness as it may damage the endothelium due to toxicity.[14] However, recent studies dispute this notion.[15] Patient counselling regarding the avoidance of eye rubbing, and the performance of CXL, are crucial in preventing KC progression as it may worsen the condition.[2]

PRECISION

While the objective for the majority of patients with KC is to halt the progression of disease. Fortunately, surgeons are now able to offer patients treatments proven to not only stop, but also improve, UDVA and CDVA, reduce refractive parameters, and allow for better spectacle or contact lens fitting, thus improving the patient's overall visual experience. CXL combined with treatments such as topography and wavefront-guided excimer laser, intracorneal ring segments (ICRS), and toric phakic lenses, have the potential to improve visual acuity, enhance topography/tomography parameters, and reduce higher-order aberrations. Various types of precision treatments can be combined to achieve optimal patient outcomes, depending on KC severity (**Table 1**). It is important to note that, in addition to these treatments, scleral contact lenses still have a role to play.

Wavefront-guided and topography-guided photorefractive keratectomy (WF-PRK and TG-PRK, respectively) can be combined with CXL for the treatment of mild cases of KC with a mild level of astigmatism (**Table 1**). WF-PRK and TG-PRK utilize the excimer laser to modify the shape of the cornea by removing a section of the stroma. It can improve CDVA (more so than UDVA), manifest refraction, amount of astigmatism, and higher order aberrations, primarily coma.[9] It is important to be aware of the risk of corneal haze formation following WF-PRK, although it is reduced with the application of mitomycin C.

Intracorneal ring segments (ICRS) reshape the cornea through polymethacrylate stromal implants. They are a favourable treatment option for moderate KC when combined with CXL and phototherapeutic keratectomy (PTK).[2] The combination of these three methods is effective and safe in improving visual acuity and clinical parameters, and reducing higher-order aberrations (**Table 2**).[16] However, it is important to keep in mind that ICRS can only be applied in transparent corneas with minimal thickness of 450 µm.

Toric intraocular lens (IOL) implants can correct astigmatism in phakic and pseudo-phakic patients. The ideal patient population is those who are intolerant to contact -lenses, and have mild-to-moderate KC and high-levels of regular astigmatism. Toric phakic IOLs can significantly improve visual acuity in KC patients who are stable, either due to their relatively young age or to previous CXL. They are contraindicated in patients with progressive KC or significant irregular astigmatism with poor CDVA.[2]

The treatments cited above focus on mild-to-moderate KC. Approximately 10%-20% of patients with KC have a severe presentation requiring keratoplasty.[2] In such cases, the most common procedures are PKP, where the full thickness cornea is replaced, and DALK, which involves selective transplantation of the anterior corneal stroma. DALK is associated with faster visual recovery, lower rates of graft rejection, and lesser endothelial cell loss, although patients with PKP may achieve better final visual acuity.[2,17] Several novel treatments are being investigated, including Bowman layer transplantation (BLT),[18] intrastromal stem cells transplantation[19] and corneal allogenic intrastromal ring segment (CAIRS).[20] These treatment modalities along with scleral contact lenses offer hope in preventing or delaying the need for invasive cornea surgery in patients with severe KC.

CONCLUSION

Multiple advances in the treatment of keratoconus currently are available and should be individualized to each patient, based on three principles: condition progression, whether or not the shape of cornea needs to be modified and whether or not the quality of vision requires improvement. Patient counselling regarding the avoidance of eye-rubbing, as well as performing corneal cross-linking, can prevent progression. The shape of the cornea can be altered with ICRS and TG-PRK, and combining these treatments can produce positive results for patients with mild and moderate KC. Patients with mild-to-moderate KC and severe correctable "regular-ish" astigmatism who are intolerant of contact lenses may benefit from Toric IOLs. Patients with severe KC having failed a trial of scleral contact lens wear, may require PKP and DALK, although non-invasive therapies that delay invasive treatment may be available in the future.

<table>
<tr><th></th><th>Mild[a]</th><th>Moderate[b]</th><th>Severe[c]</th></tr>
<tr><td>Eye-rubbing</td><td colspan="3">Stops progression</td></tr>
<tr><td>Cross-linking</td><td colspan="2">Stops progression</td><td rowspan="4">Penetrating Keratoplasty
DALK

BLT

Intrastromal stem cells transplantation</td></tr>
<tr><td>WG and TG-PRK/CXL
(Wavefront-guided and topography-guided photorefractive keratectomy)</td><td>Improves UDVA to functional level</td><td></td></tr>
<tr><td>ICRS/PTK/CXL</td><td></td><td>Improves UDVA to functional level</td></tr>
<tr><td>Toric ICL</td><td>Improves UDVA to functional level</td><td></td></tr>
</table>

Table 1. Treatment modalities for patients with mild, moderate and severe keratoconus.

[a]Pachymetry >440 µm, keratometry <55 D, CDVA >20/25
[b]Pachymetry >440 µm, keratometry <55 D, CDVA >20/50
[c]Pachymetry <440 µm microns, keratometry >55 D or CDVA <20/50

WG: wavefront guided, **TG-PRK:** topography guided photorefractive keratectomy, **CXL:** crosslinking, **ICRS:** intrastromal corneal ring segment, **PTK:** phototherapeutic keratectomy, **ICL:** implantable collamer lens, **UCDA:** uncorrected distance acuity, **DALK:** deep anterior lamellar keratoplasty, **BLT:** Bowman's layer transplantation.

	CXL	WG-PRK/CXL	ICRS/PTK/CXL
UDVA/CDVA	↑ ↔	↑↑	↑↑
Topographic/Tomographic parameters	↑↓	↓MR[a] ↓Cylinder Δ cornea	↓MR[a] ↓Cylinder Δ cornea
Higher-order aberrations/ Coma	↓	↓↓	↓↓

Table 2. Utility of corneal crosslinking (**CXL**), wave-front guided (**WG**) and topography-guided photorefractive keratectomy (**TG-PRK**) and intrastromal corneal ring segment (**ICRS**) for various visual parameters in patients with keratoconus.

[a]Mean refractive indices
Δ: Change

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From Social Media to Peer Review: How Can we Evaluate Medical Content for Misinformation and Bias?

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Traditionally, ophthalmologists stay current by referring to peer reviewed papers found on scientific databases, such as PubMed, where rigorous publication standards reduce the potential for bias. We now access medical information from diverse online sources and social media allowing for fast-paced dissemination of content. Access to this rapidly evolving online information has allowed us to be more versed in our specialized knowledge than ever before. However, the rise of social media use in medicine may challenge the traditional methods aimed to limit misinformation and bias. How can we identify and evaluate bias when we access information from multiple disparate online sources in 2023?

EVALUATING BIAS IN PEER REVIEWED LITERATURE

Bias is a systematic error that can be introduced during planning, subject selection, data collection, analysis, and publication phases of studies.[1] Biases can be explicit, within our awareness, or implicit, where an unconscious belief surreptitiously influences judgement and decision making. Thus, when evaluating a study's conclusions, we need to consider sources of bias that might reduce the validity of the findings.

Low-level evidence, such as case reports, case series and expert opinions, are common in peer reviewed literature and are inherently at increased risk of bias.[2,3] Low-level evidence carries major limitations including a lack of ability to generalize, no possibility to establish cause-effect relationship, and a publication bias that heavily favours positive-outcome findings.[4] We should not over-generalize the conclusions of low-level evidence papers. Instead, where possible, we can look for high-level evidence such as well-designed (RCTs), with high internal and external validity. Having high internal validity means being confident that study design, implementation and data analysis have yielded non-biased findings. High external validity also means that study findings can be generalized to other groups or populations.[1,2]

Given the busy nature of our ophthalmology practices, many will seek out review articles to remain up-to-date and access clinical information. Systematic review and meta-analyses are preferred over unstructured reviews since they have formal methodologies for study inclusion and publication bias assessment. These methodologies reduce the risk of studies being selectively excluded to overestimate the effect of a treatment.

In addition to systematic review methodologies, some factors that seem to protect against bias are reviews of clinical interventions and being published in a higher impact factor (IF) journal.[2,5] One study found that higher IF journals may be helpful in bias assessments given that industry sponsorship and reporting positive results were not found to be connected with publishing in these journals.[6] However, we need to be cognizant that IF is vulnerable to self-citation manipulations. These manipulations can over-inflate the importance or impact of a journal, with recent increased rates of self-citations reported across many journals.[7]

Recognizing the risk of bias in peer reviewed literature, we can use tools to critically appraise the information we are accessing. Guyatt and colleagues have developed a GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach for evaluating bias in literature and an open-access user's guide on how to adopt evidence into practice.[2,8] The GRADE system helps readers and organizations grade the quality of evidence and the strength of a study's recommendations.[8]

WHICH DATABASE SHOULD I USE?

Google Scholar is commonly used by physicians due to its intuitive search interface and greater access to free full-text articles than other search engines.[9] However, significant differences exist in how Google Scholar extracts information compared with other academic search engines. One study attempted to reverse-engineer Google Scholar's classified ranking algorithm and raised concerns regarding the accuracy and validity of search results.[10] Google Scholar uses automated robot web crawlers with citation counts as the highest weighted factor, with author and journal name also having meaningful impact.[10,11] Another study found that Google Scholar has a limited search syntax which does not allow for advanced search limits or filters and does not consider variations in search term sequence or spelling.[11] Although it retrieves a large number of hits per search, the results are of low precision and are poorly indexed for topic relevance. Finally, Google Scholar presents challenges for non-English colleagues, as one study concluded there could be bias in multilingual searches with Google Scholar downgrading non-English documents in their search to virtually invisible positions.[12]

ASSESSING FOR BIAS IN SOCIAL MEDIA PUBLICATIONS

Scientific information is often published by Key Opinion Leaders (KOLs) on social media platforms such as Twitter, YouTube, Instagram and Facebook, before publication in peer-reviewed journals. Leigh and colleagues found that academic expertise and seniority are not consistently correlated with digital influence and less established researchers with smaller academic networks can be considered KOLs through self-promotion of their content on social media platforms such as Twitter.[13] Additionally, industry influence of KOLs and sponsored content is a concern, with US pharmaceutical companies spending nearly 70% (20 billion USD) of their promotional budget for medical marketing on KOLs in 2016.[14] KOLs can influence sales through their strong social media following and perceived expertise in the field, and can impact the clinical practices of their colleagues more successfully than traditional industry-sponsored talks and educational materials.[14,15]

Video-heavy social media platforms, such as Instagram and YouTube, are also at risk of influence and the absence of regulations regarding the need for medical content to disclose conflicts of interest (COI) is concerning. The Federal Trade Commission recently provided some guidance to address this situation, stating "a connection that might affect the weight or credibility that consumers give the endorsement – that connection should be clearly and conspicuously disclosed."[16] Non-enforceable recommendations are made on how KOLs are to specifically disclose sponsorships on fast-paced videos and posts.[16] No higher standard is required of medical content which may render FTC guidance insufficient.

Surgical-related videos posted on social media platforms can be powerful tools for educating learners and give procedural exposure to patients. However, videos, especially those posted on YouTube, can also be used by KOLs for self-promotion or industry promotions. YouTube's algorithm can be subverted through top of the page advertisement. It is biased toward popularity instead of quality and accuracy, and several studies of ophthalmology surgery content suggest the YouTube algorithm presents variable-quality educational resources.[17,18]

A recent Canadian study looked at the most popular cataract surgery videos on YouTube and while only 8% of the videos were uploaded by a commercial manufacturer, 21% of the videos had a fundamental commercial focus promoting the surgeon's practice or a specific product.[19] Ophthalmology-specific video-sharing on social media platforms can offer high-quality surgical videos categorized by subspecialty but are likely at risk of similar sources of bias if social media algorithms are used.

Almost all social media platforms have indexing functions using hashtags (#) which permit easy access to posts containing specific keywords.[20] A search of #ophthalmology, creates a filtered list blocking out any other non-hashtagged posts. Users can "tag" other accounts to identify specific people or organizations to boost their posts' exposure. The information shared through the indexing function is non-peer reviewed, with no formal process in place to account for industry sponsorship, COI and publication bias.

One way to access peer-reviewed material through social media is by following respected medical organizations and high IF journals, which tweet out links to published articles.[20] Ophthalmology, American Academy of Ophthalmology (AAO) and Canadian Journal of Ophthalmology (CJO-JCO) use hashtags and social media indexing to make their postings more visible and to disseminate pertinent information.

TAKE-AWAY POINTS

Any type of information presented to us in today's online environment is at risk of bias and we need to develop a personalized approach to evaluating evidence **(Figure 1)**. We can use tools such as GRADE; we can avoid lower levels of evidence; and we can seek out systematic reviews with a formal assessment of publication bias.[2,8]

Social media can disseminate information in a timely fashion, but if left unchecked, potentially biased

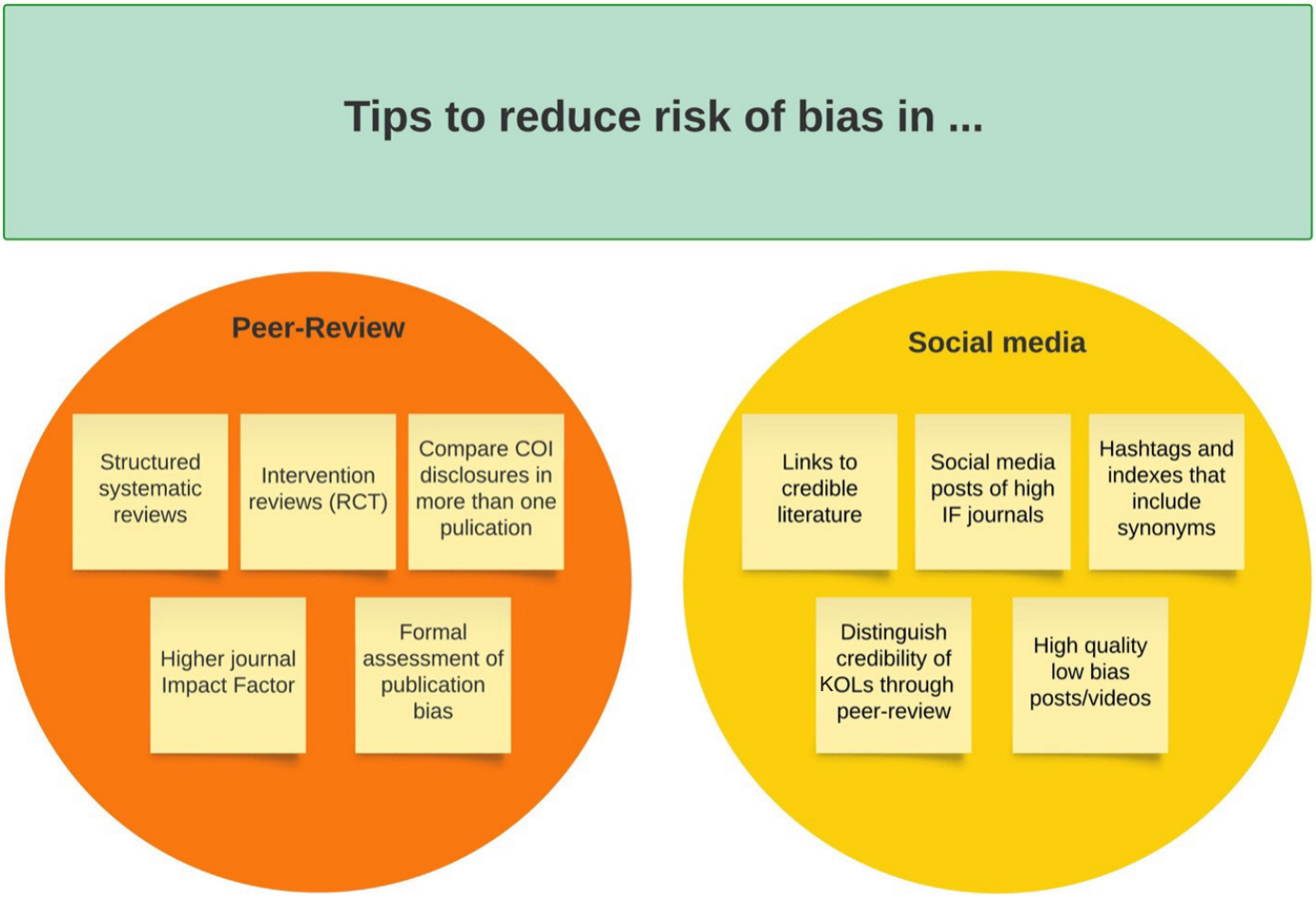

Figure 1. Tips to reduce risk of bias; courtesy of Chryssa McAlister MD, Hannah Chiu MD and Amin Hatamnejad BSc
Legend: Randomized control trial (**RCT**), conflict of interest (**COI**), key opinion leader (**KOL**).

misinformation on social media platforms can have deleterious effects. We need to be thoughtful about the manner in which social media and online content can be manipulated and presented to us based on algorithms that prioritize sponsored content and popularity over relevance and quality. We can reflect on the role of self-promotion, true expertise and COI of KOLs as we engage with content. We can preferentially follow known trustworthy sources with citations from peer reviewed literature and appropriate disclosures that are less susceptible to bias and misinformation. Finally, KOLs active on social media need to be familiar with their respective medical college policies surrounding promotion and advertising on social media, which in Canada prohibit references to drugs, devices or equipment.

Medical organizations and leaders representing the medical community can help encourage social media companies to adjust algorithms in order to reduce bias and improve transparency and relevance. A recent systematic review concluded that YouTube could improve the quality of videos available on their website by incorporating medical- and health-related expert reviews into their algorithm.[18] There also needs to be a call for uniform in-depth COI disclosure policies across all platforms where we access medical information so that we can better evaluate the risk of bias. Until meaningful changes are made, we need to be cautious in how we engage with medical content on social media and be cognizant of how bias and misinformation may impact our clinical judgment.

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