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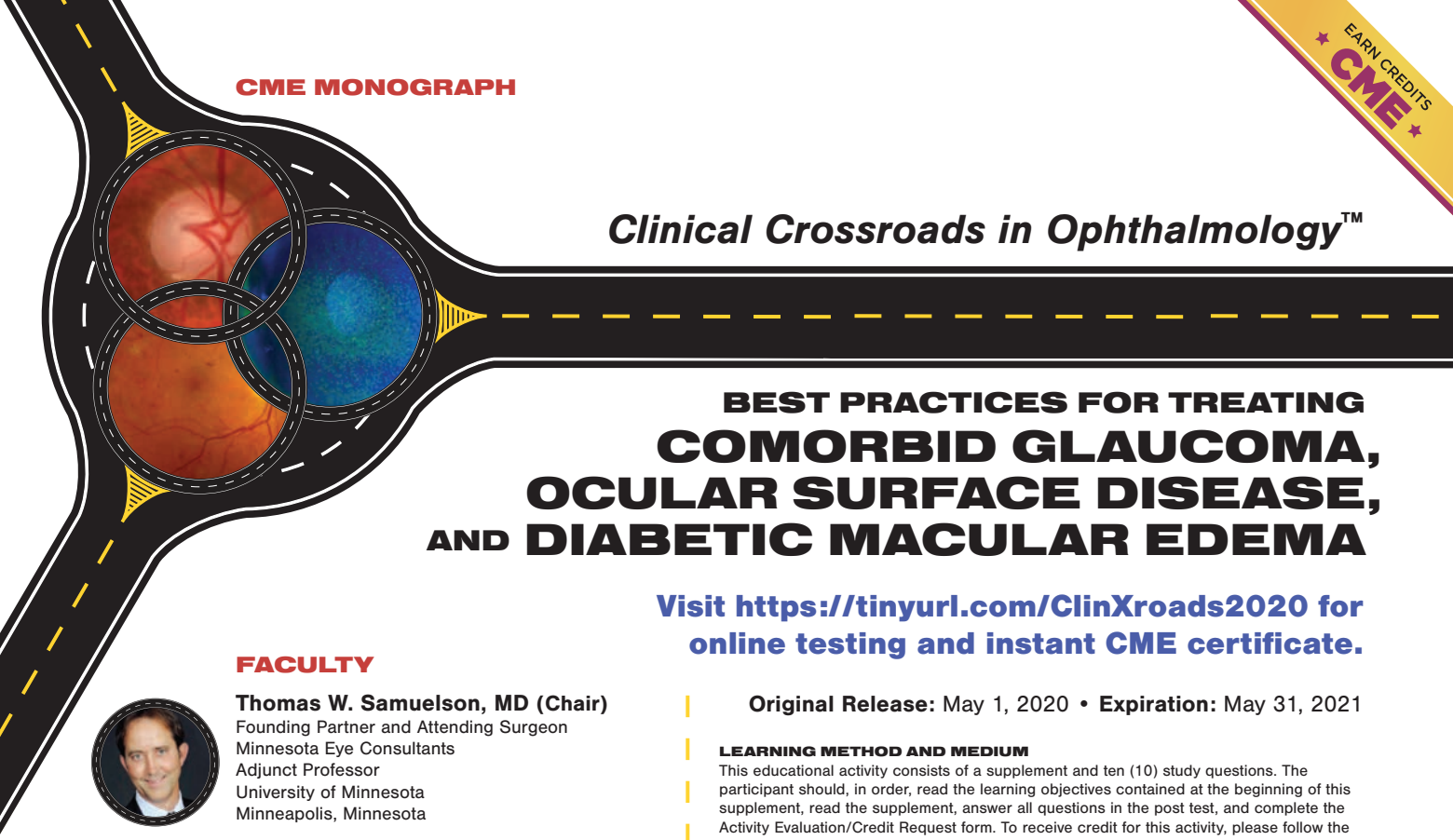

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ACTIVITY DESCRIPTION

The prevalence of common ocular diseases, including ocular surface disease, glaucoma, and diabetic macular edema, continues to rise, as does the number of patients presenting with 2 or more of these conditions. Management of ocular surface disease, glaucoma, and diabetic macular edema must take a holistic approach because these diseases and their treatment might exacerbate one another. Individualizing treatment to each patient's specific needs and disease severity is also critical for optimal outcomes. This monograph captures the proceedings of a live CME symposium held during the 2019 Annual Meeting of the American Academy of Ophthalmology. The desired results of this educational activity are to improve ophthalmologists' confidence and skill in treating standalone or comorbid ocular surface disease, glaucoma, and diabetic macular edema.

TARGET AUDIENCE

This educational activity is intended for ophthalmologists.

LEARNING OBJECTIVES

Upon completion of this activity, participants will be better able to:

- Discuss the epidemiology of ocular surface disease
- Design evidence-based treatment strategies for ocular surface disease according to individual patient factors
- Apply the latest evidence to the management of individual patients with glaucoma to achieve optimal vision outcomes
- Compare the safety and efficacy of intravitreal corticosteroids used to treat diabetic macular edema that is refractory to anti–vascular endothelial growth factor therapy

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INTRODUCTION

Ocular surface disease (OSD) (also known as dry eye disease [DED]), open-angle glaucoma (OAG), and diabetic macular edema (DME) are all common ophthalmic conditions, and they frequently coexist in many patients **(Figure 1)**.[1-11] Each condition has its own distinct signs and symptoms, and each can contribute to significant vision loss. Not only are there frequent interactions among DED, OAG, and DME, but the treatments for each disease can aggravate these comorbid conditions.[1-7] Developing individualized treatment strategies for patients with multiple interacting ocular conditions represents a significant clinical challenge. In this educational activity, a panel of expert ophthalmologists representing the corneal, glaucoma, and retina specialties will discuss 3 cases of patients with multiple ocular issues, highlighting the considerations that must be taken into account when treating them.

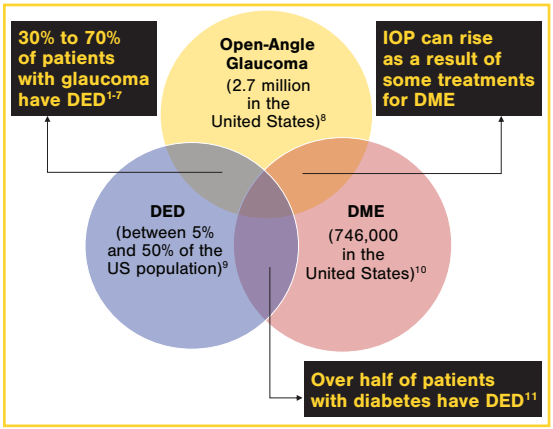

Figure 1. Epidemiology and overlap of common eye diseases
Abbreviations: DED, dry eye disease; DME, diabetic macular edema; IOP, intraocular pressure.

EVOLVING LANDSCAPE OF DED TREATMENT

Dry eye disease is one of the most common ocular conditions, and can produce significant ocular symptoms of discomfort as well as loss of vision. There are an estimated 55 million Americans with DED,[12] of whom up to 38 million may be undiagnosed and untreated.[13] Dry eye disease is more common in women than in men, and its prevalence increases with age, reaching nearly 8% in men aged ≥ 80 years and 10% in women aged ≥ 75 years.[14,15] In patients with glaucoma or diabetes, the prevalence of DED is much higher. As many as 30% to 70% of patients with glaucoma have signs and/or symptoms of DED,[1-7] and comorbid DED is associated with poorer glaucoma-related quality of life.[6,7] Approximately 50% of patients with diabetes have concomitant DED,[11,16,17] often with abnormal tear breakup time and/or tear secretion.[11] Dry eye disease is more prevalent in type 2 diabetes than in type 1 diabetes,[16] is significantly associated with the duration of diabetes,[11] and, as does glaucoma, adversely affects quality of life.[16]

During the past decade, the significance of DED has been recognized by all ophthalmic specialties as a major factor in the outcomes of eye diseases treated both medically and surgically. Dry eye disease is the cause of postoperative dissatisfaction in 28% of patients undergoing LASIK (laser-assisted in situ keratomileusis)[18] and in 15% of patients undergoing multifocal intraocular lens (IOL) implantation.[19]

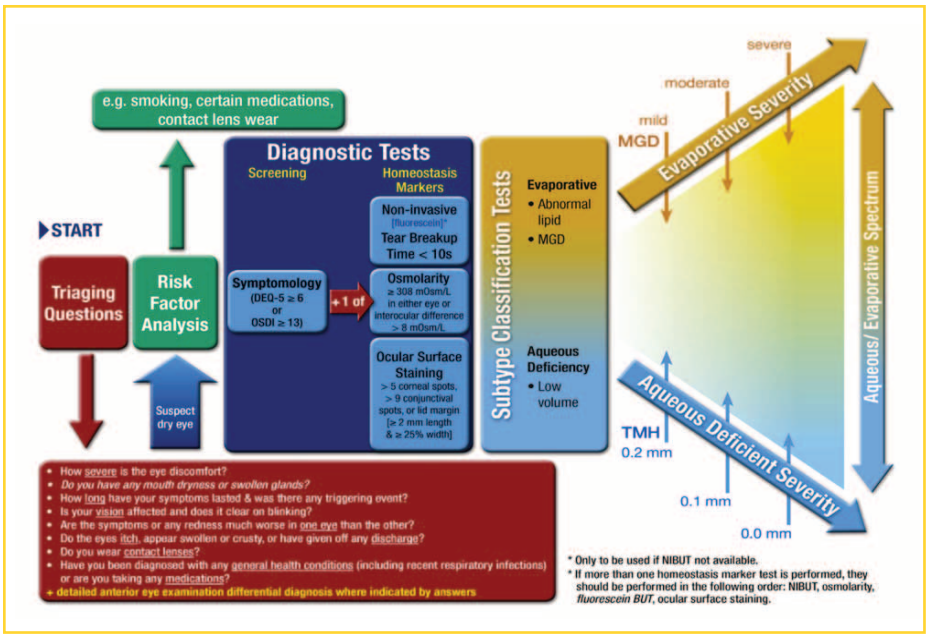

Figure 2. Diagnostic process for dry eye disease[20]

Abbreviations: BUT, breakup time; DEQ-5, 5-Item Dry Eye Questionnaire; MGD, meibomian gland dysfunction; NIBUT, noninvasive breakup time; OSDI, Ocular Surface Disease Index; TMH, tear meniscus height.

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DIAGNOSING DED

The process of diagnosing DED has been systematically described by the Tear Film & Ocular Surface Society at its second Dry Eye WorkShop and is outlined in **Figure 2**.[20]

Once diagnosed, DED can be classified into 2 subtypes: evaporative or aqueous deficiency DED; staging is dependent on the severity of meibomian gland dysfunction (MGD) and/or aqueous deficiency.[20] Evaporative DED arises most commonly in the presence of MGD and can also occur in patients with abnormal lipid profiles. MGD is characterized by hyperkeratinization of the ductal epithelium and increased meibum viscosity.[17] Reduced meibum in the tear film creates an unstable lipid layer, allowing evaporative loss of the aqueous layer. This in turn concentrates electrolytes and inflammatory mediators in the tear film, resulting in loss of conjunctival goblet cells, further perpetuating the DED process. MGD is seen in approximately 50% of DED cases.[21]

Aqueous-deficient DED is the result of low aqueous tear volume due to inadequate tear production in the lacrimal gland[17] and accounts for 10% to 15% of DED cases.[21] Aqueous-deficient DED is most commonly age related and may be caused in part by ductal obstruction promoting lacrimal gland dysfunction combined with chronic inflammation of the gland.[17] The DEQ-5 (5-Item Dry Eye Questionnaire) (available for download at https://www.tfosdewsreport.org/public/images/DEQ5.png) is a short, 5-item, patient self-assessment of DED symptoms.[22] Aqueous-deficient DED should raise suspicion for Sjögren syndrome, especially if the DEQ-5 score exceeds 12 and if the patient reports dry mouth.[17,22] Both DED subtypes may be present to varying degrees within the same patient, and is the case approximately 35% of the time.[21]

INTERPLAY OF DED AND GLAUCOMA

As mentioned previously, patients with glaucoma are particularly at risk for DED. These are typically older patients with higher baseline risk for DED to begin with. Their glaucoma is usually managed with topical intraocular pressure (IOP)-lowering therapy, often multiple drops per day. This represents a high exposure to medications, of which their excipient ingredients—specifically the preservative benzalkonium chloride (BAK)—have been linked to the DED process.[23] A study of more than 4000 patients demonstrated that ocular surface changes were twice as high in patients using preserved IOP medications vs unpreserved medications, and the signs and symptoms of DED were correlated with the number of drops instilled per day.[24] A second study confirmed a 2-fold higher prevalence of DED in patients with glaucoma using preserved vs unpreserved medications and also demonstrated that the coexistence of DED and the use of BAK-containing IOP medications adversely affected vision-related quality of life.[4]

TREATMENT OF DED

Therapy for DED is ideally directed at the primary underlying pathophysiology.[25] Aqueous-deficient DED is best managed with tear replacement, with nonpreserved formulations recommended for frequent use and with gels or ointments for nighttime use. Punctal plugs can be used to potentiate both natural and replacement tears. The inflammatory component of DED can be addressed with immune-modulating agents, such as cyclosporine or lifitegrast, and with topical steroids reserved for more recalcitrant cases or for short-term use to quell inflammatory flares. Patients who are prescribed topical steroids to treat their DED should be monitored for steroid-induced IOP elevation. Autologous serum tears share several key attributes with natural tears, including pH, nutrient content, vitamins, fibronectin, and growth factors, making this a reasonable therapy for cases unresponsive to other topical therapies.

MGD is managed most conservatively with topical lipid-based lubricants.[25] Warm compresses to liquify meibum and facilitate its expression is effective but time consuming. Macrolide therapy with topical azithromycin or oral doxycycline can increase the cellular collection and release of lipids, decrease the bioactivity of inflammatory cytokines, decrease the bacterial lid flora, and reduce the activity of lipolytic enzymes. Low-dose regimens (eg, doxycycline 50 mg daily) are recommended by the Tear Film & Ocular Surface Society second Dry Eye WorkShop guideline committee. Omega-3 fatty acid supplementation may also be beneficial in select patients to exogenously increase lipids in the tear film to prevent evaporative aqueous tear loss.

A number of devices provide mechanical manipulation of the lids, with the goal of expressing meibum and increasing tear lipids.[25] These include thermal treatments that heat the posterior lid and compress the lid to express meibum, microblepharoexfoliation of the eyelid margin to unroof obstructed meibomian gland (MG) orifices, probing of MG ductal orifices, and intense pulsed light treatment to improve meibum flow.

Stimulation of the natural tearing reflex is another approach to DED therapy. An approved neurostimulation device consists of 2 tips that are inserted into the nostrils and which deliver a low-grade electrical stimulation that promotes tear production.[26] In a randomized clinical trial, compared with sham therapy, neurostimulation more effectively promoted mucus secretion via goblet cell degranulation.[26] Neurostimulation also increased aqueous tear secretion as evidenced by increased Schirmer scores.[27,28] Research into other devices and pharmacologic approaches that stimulate lacrimal secretion is under way.[29]

CASE 1: COEXISTING DED AND GLAUCOMA

From the Files of Edward J. Holland, MD

As discussed, OSD is common among patients with glaucoma because of adverse effects sometimes seen with ocular IOP-lowering medication. A common first-line approach is to evaluate whether the topical medication regimen can be adjusted. A 65-year-old man reported chronic decreased vision, burning, and itching in both eyes. He had chronic open-angle glaucoma treated with topical latanoprost, timolol, and brimonidine for many years. On a dry eye questionnaire, he reported fluctuating

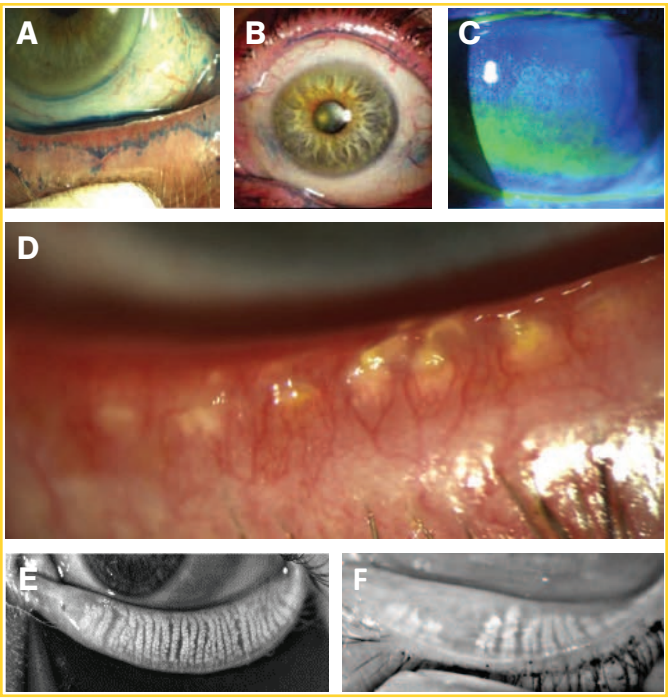

Figure 3. Clinical findings of the patient presented in Case 1. Lissamine green staining of the conjunctiva (A and B). Fluorescein staining of the cornea (C). Meibomian gland inspissation evident upon expression (D). Meibography image of a normal lid (E) and that of the patient presented in Case 1 (F).

visual acuity (VA), chronically red eyes, and frequent watering of the eyes. On examination, his best-corrected VA (BCVA) was 20/40 in both eyes, with 2 D of corneal astigmatism, IOP was 17 mm Hg OU, and he had 3+ nuclear sclerotic cataracts. His ocular surface examination revealed MGD with inspissated MGs, 2+ lissamine green staining of the conjunctiva, and 4+ inferior fluorescein staining of the cornea ***(Figures 3A-3D)****. His tear film osmolarity was 310 mOsm/L OD and 328 mOsm/L OS, Schirmer test was 12 mm OD and 15 mm OS, and tear breakup time was 4 seconds OD and 4 seconds OS. Meibography images revealed truncation and dropout of MGs* ***(Figures 3E and 3F)****.*

Dr Holland: This patient was diagnosed with visually significant cataract, chronic OAG, and moderate-to-severe MGD. To what extent is his glaucoma therapy exacerbating his ocular surface status?

Dr Radcliffe: First, we must consider if he is frankly allergic to any of the component drugs. The timing of onset or worsening of symptoms relative to the initiation of therapy with each drug can help clarify this. Second, we should consider cumulative exposure to preservatives. Latanoprost is a once-daily drug, timolol can be dosed once or twice daily, and brimonidine can be dosed 2 or 3 times daily. He could be receiving up to 6 drops a day. That is a significant BAK load.

Dr Samuelson: Often, BAK intolerance manifests with the second or third medication added. The patient's OSD will worsen, and we have to distinguish between an allergy to the recently added medication and a threshold effect in which the cumulative daily dose of BAK is now enough to become symptomatic.

Dr Holland: The patient is motivated to undergo cataract surgery for visual rehabilitation. What should we consider first?

Dr Samuelson: I would wait to perform cataract surgery until after his MGD has been treated. I would be reluctant to trust IOL calculations—particularly keratometry—obtained while his ocular surface is so irregular. This could affect the surgeon's ability to achieve a selected refractive target.

Dr Radcliffe: Once his OSD is under control, cataract surgery has the potential not only to correct his vision, but the added effect of lowering his IOP and reducing his medication burden.[30] I would also consider a minimally invasive glaucoma surgery (MIGS) procedure at the time of cataract extraction, with the goal of reducing his future reliance on topical IOP-lowering therapy.[31] Selective laser trabeculoplasty (SLT) may also help reduce his medication burden.[32]

Dr Holland: Agreed. We treated his MGD with omega-3 supplementation, doxycycline 50 mg daily, microblepharoexfoliation and thermal therapy, along with a brief course of loteprednol twice daily to address underlying inflammation. Once the ocular surface was healthier, we proceeded with cataract surgery. We implanted a toric IOL to address his corneal astigmatism. I considered a multifocal toric IOL to address his presbyopia as well, but I recommend multifocal IOLs only when the ocular surface is completely normal at the time of IOL calculations to ensure optimal power selection and postoperatively so the patient will achieve excellent visual acuity. We were concerned that his surface was not at that level, and did not recommend a multifocal IOL. We also needed his surface to be healthy enough to achieve an accurate assessment of the corneal astigmatism to be able to recommend a toric IOL. We were confident of his astigmatism measurements and I therefore placed a toric IOL. I added a MIGS procedure to give him the best chance at reducing his medication burden. At last follow-up, his uncorrected distance VA was 20/20 in both eyes, his ocular comfort was improved, and his IOP was well maintained using only daily prostaglandin therapy.

GLAUCOMA: BEYOND MEDICAL THERAPY

Topical medical therapy remains the preferred first-line therapy for the reduction of IOP in eyes with OAG and high-risk ocular hypertension. Although efficacy and safety of modern medical therapy for glaucoma are excellent, the chief drawback is poor adherence.[33] In recent years, new laser and surgical innovations have challenged the historical medications-first approach to glaucoma management. Even though medications will always play a key role in glaucoma therapy, SLT and MIGS procedures are being used far earlier in the treatment paradigm than ever before.

Selective Laser Trabeculoplasty

SLT was introduced 2 decades ago as a lower-energy form of trabeculoplasty compared with its predecessor, argon laser trabeculoplasty.[34] With lower energy and little or no thermal damage imparted to the trabecular meshwork (TM),[34] SLT—unlike argon laser trabeculoplasty[35-40]—is safely repeatable and offers the potential for long-term glaucoma management when repeated as needed given that its effect wanes with time.[41-49]

Recently, the LiGHT study evaluated SLT's role as primary therapy in newly diagnosed and treatment-naïve patients with primary OAG (POAG) or high-risk ocular hypertension.[49] In this landmark study, 718 subjects were randomized to initial SLT (n = 356) or initial medical therapy (n = 362) and followed for 3 years. A disease- and severity-specific target IOP was established for each eye at enrollment, and therapy was advanced (repeat SLT or additional medications, respectively) when IOP consistently exceeded target IOP. After 3 years, 74.2% of SLT eyes were at target IOP and medication free; most of these eyes (76.6%) required only a single SLT treatment. Glaucoma progression was less common in the SLT group than in the medication group (3.8% vs 5.8%, respectively), cataract surgery was less common in the SLT group than in the medication group (13 vs 25 eyes, respectively), and trabeculectomy was required only in medication-treated eyes (0 vs 11 eyes, respectively). Quality of life was comparable between groups. In the long term, SLT was found to be more cost effective than medical therapy, confirming similar previous reports.[49-51]

Minimally Invasive Glaucoma Surgery

On the surgical front, MIGS has transformed the surgical management of glaucoma. A wide array of MIGS procedures are available that shunt aqueous humor into Schlemm canal, the suprachoroidal space, or the subconjunctival space **(Table)**. Collectively, these are generally safer procedures than traditional trabeculectomy or tube-shunt procedures, are easier to perform than filtering surgeries, and offer faster visual rehabilitation.[52,53]

The 2 TM stents—iStent/iStent Inject and Hydrus—bypass the diseased TM using novel implantable devices and are approved for IOP reduction in eyes with mild-to-moderate POAG at the time of cataract surgery.[54,55]

Table. Array of MIGS Procedures, Their Approval Status, and Select Attributes

Procedure	Device	Approved in the United States	Bleb Forming
Schlemm canal	Trabectome	Yes	No
	iStent/iStent Inject	Yes*	No
	Hydrus	Yes*	No
	Kahook Dual Blade	Yes	No
	iTrack (for GATT and ABiC)	Yes	No
	OMNI/VISCO360	Yes	No
Suprachoroidal	iStent Supra	No	No
	Gold shunt	No	No
Subconjunctival	EX-PRESS	Yes	Yes
	XEN Gel Stent	Yes	Yes
	PreserFlo/MicroShunt	No†	Yes

* Approved in the United States only in combination with cataract surgery

† Currently in phase 3 clinical trials

Abbreviations: ABiC, ab interno canaloplasty; GATT, gonioscopy-assisted transluminal trabeculotomy.

The iStent Inject—360 µm long and 230 µm wide, with an 80-µm central lumen—is implanted via an ab interno approach and straddles the TM, facilitating the flow of aqueous humor through the stent into Schlemm canal.[56] In a 2-year phase 3 clinical trial, 75.8% of 380 eyes undergoing cataract surgery with the implant achieved a ≥ 20% reduction in mean diurnal IOP compared with 61.9% of 118 eyes undergoing cataract surgery alone ($P = .005$).[56] Mean IOP reductions from unmedicated baseline were also greater with the combined procedure than with cataract surgery alone (7.0 vs 5.4 mm Hg; $P < .001$). Stent obstruction occurred in 6.2% of 386 eyes receiving the combined procedure; otherwise, rates of postoperative inflammation, secondary surgical interventions, and posterior vitreous detachments were similar between groups.

The Hydrus is a flexible, 8-mm-long stent that is also implanted via an ab interno approach to deliver aqueous humor into Schlemm canal.[57] A 12-month prospective randomized trial (COMPARE) compared the Hydrus with 2 first-generation iStents as standalone procedures in phakic and pseudophakic eyes with mild-to-moderate POAG.[58] The complete surgical success rate (IOP ≤ 18 mm Hg on no medications with no reoperations) was 35.6% with Hydrus and 10.5% with iStents ($P < .001$) **(Figure 4)**. IOP reductions were similar between groups, but Hydrus eyes had greater medication reductions (by 0.6 medications per eye; $P = .004$) and 46.6% of 73 Hydrus eyes were medication free at 12 months vs 24% of 75 eyes receiving iStents ($P = .004$). Device obstruction occurred at similar rates in the Hydrus (n = 74) and iStent groups (n = 76) (12.2% with Hydrus and 13.2% with iStents), but the rate of BCVA loss ≥ 2 lines was greater with Hydrus (2.7% with Hydrus vs 1.3% with iStents). IOP spikes occurred with comparable frequency between groups. Through 24 months of follow-up, secondary glaucoma surgical interventions were performed in 11% of iStent eyes and in 0% of Hydrus eyes.[59] The mean IOP at 24 months was 17.5 mm Hg in the Hydrus group and 18.8 mm Hg in the iStents group, whereas mean medication reduction was 1.31 in the Hydrus group and 0.77 in the iStents group ($P = .006$).[59]

Bleb-based transscleral MIGS procedures have been developed with the goal of achieving greater IOP reductions than have emerged from MIGS procedures that do not rely on bleb formation. The XEN gel stent is a 6-mm-long tube made of crosslinked porcine gelatin that swells upon implantation to facilitate anchoring of the device within the sclera.[60] The device was implanted ab interno in its pivotal trial, with sponge-based scleral application of mitomycin C (MMC).[60] Some clinicians have performed this procedure using an ab externo approach, which might result in a lower rate of needling while maintaining good efficacy.[61,62] Also, the transition from direct application of MMC-soaked sponges to the sclera to the subconjunctival/sub-Tenon delivery of MMC via injection[63] has been shown to result in better bleb morphology and outcomes.[63-66]

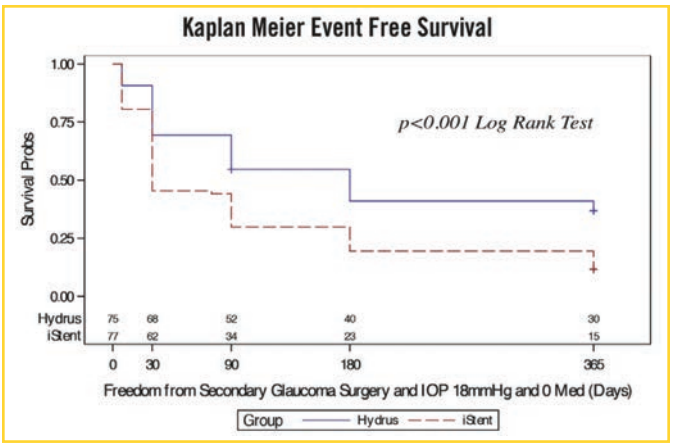

Figure 4. Twelve-month success rates for Hydrus vs 2 first-generation iStents in the COMPARE trial[58]

Abbreviation: IOP, intraocular pressure.

Note: Off-label use of both Hydrus and iStent devices.

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In the XEN pivotal trial, conducted in 65 eyes with glaucoma refractory to medical therapy, mean IOP reduction was 9.1 mm Hg at 12 months, with a 75% success rate at 12 months (success defined as IOP reduction ≥ 20% on the same or fewer medications vs baseline and no additional glaucoma surgery).[60] Transient hypotony was seen in 24.6% of eyes, IOP spikes ≥ 10 mm Hg occurred in 21.5% of eyes, and bleb needling was required in 32.3% of eyes. To demonstrate outcomes beyond 12 months, a recent 24-month study with ab interno implantation of XEN (n = 202 eyes), as either a standalone procedure or in combination with cataract surgery, revealed mean IOP reductions of 6.5 and 6.2 mm Hg at 12 and 24 months, respectively, mean medication reductions of 1.7 and 1.5 medications/eye, respectively, and success rates (using the same criteria as the pivotal trial) of 67.6% and 65.8%, respectively.[67] In this study, the rate of secondary glaucoma surgery was 6.4% through 2 years in 218 eyes. In a more recent prospective study (n = 64), at 4 years, mean IOP was reduced 40% and medications were reduced 50%, with an annual 10% rate of surgical failure.[68]

CASE 2: PATIENT WITH PROGRESSING GLAUCOMA, DED, AND DIABETES

From the Files of Nathan M. Radcliffe, MD

A 70-year-old man with type 2 diabetes presented initially with IOP of 28 mm Hg and central corneal thickness of 525 µm in both eyes. IOP was lowered successfully to a range of 18 to 23 mm Hg using a prostaglandin and a fixed-combination drop. He also had DED, and the glaucoma medications made this worse. Three years later, his left eye demonstrated progression on both the visual field and optical coherence tomography (OCT) images of the retinal nerve fiber layer (RNFL) ***(Figure 5)****. His diabetes was poorly controlled, with* Hb_{A1c} *increasing from 8.3% to 9.4% over the preceding year.*

Dr Radcliffe: This man has 3 significant problems: (1) progressive glaucoma, (2) DED that is being aggravated by his glaucoma therapy, and (3) uncontrolled type 2 diabetes.

Dr Samuelson: You diagnosed his glaucoma at an early stage, when his visual field was essentially full. His RNFL OCT image was also full in the left eye at that time, but the asymmetry compared with the right eye is striking and his IOP strongly supported the diagnosis. Now, clearly both the visual field and the OCT images demonstrate change over time in the left eye, although the change in the visual field is modest. This is despite a significant IOP reduction. The poorly controlled diabetes suggests nonadherence with his diabetes therapy, which may also indicate poor adherence with his glaucoma therapy.

Dr Radcliffe: Yes, and his drops also make his DED worse, which is a further reason for potential nonadherence.

Dr Holekamp: His Hb_{A1c} indicates very poor long-term control of his blood glucose. It is worrisome that it is increasing over time. Every

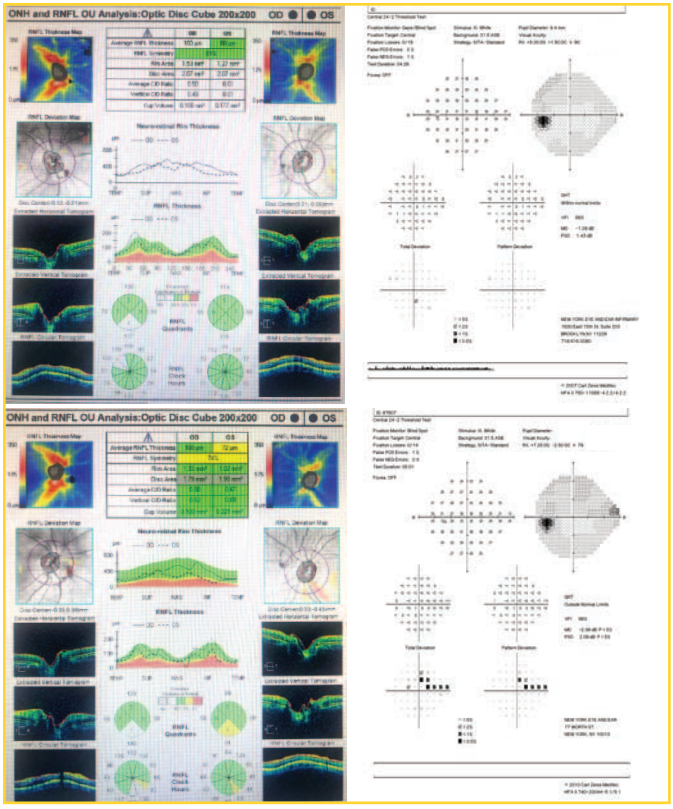

Figure 5. Visual fields and optical coherence tomography images of the retinal nerve fiber layer at baseline (top) and 3 years later (bottom) of the patient presented in Case 2

1% increase in Hb_{A1c} confers an approximately 10-fold greater risk of developing retinopathy.[69] I agree with Dr Samuelson that poor adherence with diabetes medications may suggest poor adherence with his glaucoma medications as well.

Dr Holland: What is his VA, and does he have cataracts? This might indicate a role for MIGS, both to lower his IOP and to reduce his medication burden. This might improve both his DED and his adherence.

Dr Radcliffe: He does have early cataracts, but his BCVA is 20/25. You make a great point—the availability of MIGS leads us to consider surgery far earlier than we used to in glaucoma. Patients who may not warrant a trabeculectomy are often great candidates for a MIGS procedure at the time of elective cataract surgery. But this patient does not need cataract surgery yet.

Dr Samuelson: There are several potential options before we have to consider surgery. SLT might lower his IOP and/or help reduce his medication burden. This could help his adherence and his DED, as Dr Holland pointed out. Also, we may soon have a sustained-release prostaglandin,[70] which might address both his adherence and his DED.

Dr Radcliffe: Prostaglandins are known to be proinflammatory, and cases of cystoid macular edema following prostaglandin treatment have been reported.[71] Given the insights into the pathophysiology of both DED and DME, would you avoid prostaglandins in eyes with DED or DME?

Dr Holekamp: No. The pathophysiology of DME is driven in large part by vascular endothelial growth factor (VEGF), and is likely distinct from that of cystoid macular edema secondary to prostaglandin treatment. If he does develop DME, we have effective therapies such as anti-VEGF intravitreal injections and corticosteroid intravitreal implants. Cystoid macular edema can be treated with topical, injected, or oral corticosteroids. Occasionally, anti-VEGF injections or laser treatment are warranted.

Dr Holland: Likewise, with DED, there is no reason to deprive the patient of the best IOP-lowering medication. As we have discussed, we have many options for treating DED.

Dr Radcliffe: Our patient chose to undergo SLT and experienced both IOP reduction and medication reduction. However, 1 year following SLT, his IOP began to creep back up. His dry eye did improve after medication cessation and SLT, and he did not want to go back on drops. The patient is interested in receiving an intracameral sustained-release medication.

DME: CHALLENGES AND PROGRESS IN INDIVIDUALIZED MANAGEMENT

Inhibition of VEGF is a highly effective therapy for DME. Clinical trials have demonstrated the VA gains associated with monthly intravitreal injections of ranibizumab[72] and monthly or every-other-monthly injections of aflibercept.[73] The results of these robust studies do not always translate into clinical practice, where the burden of therapy often results in significant undertreatment. Diabetes is a disease of working-aged people, and the burden of diabetes-related health care can be difficult to bear, especially by the full-time employed.[74] A recent real-world study (n = 110) found that the mean number of intravitreal injections of ranibizumab or bevacizumab given in the first year of anti-VEGF therapy for DME was 3.1 injections, with most eyes (69%) receiving ≤ 3 injections.[75] Other studies have confirmed these suboptimal injection rates.[76,77]

Not surprisingly, the outcomes in these real-world cohorts generally fall short of the VA improvements achieved with therapy administered repeatedly at set intervals in the clinical trials.[76,77] This is significant because previously undertreated DME is more difficult to treat with subsequent anti-VEGF injections. In the VIVID and VISTA phase 3 trials, eyes with DME were randomized to either aflibercept or laser therapy.[78] The aflibercept group saw a significant improvement in VA, but the laser group did not. After 2 years, the laser group crossed over and began receiving aflibercept, but VA in those eyes never improved as much as that in the eyes treated with aflibercept from the start. The same was true in the RISE and RIDE phase 3 trials of ranibizumab for DME—control eyes that crossed over to anti-VEGF therapy after 2 years never caught up in VA gains or macular drying on OCT images.[72]

Even with robust adherence to recommended dosing schedules, a significant number of eyes manifest suboptimal responses to treatment. In the Diabetic Retinopathy Clinical Research Network (DRCRnet) Protocol I, 40% of eyes had persistent DME after > 6 monthly ranibizumab injections, and 32% had associated reduced VA (20/32 or worse).[79,80] In Protocol T, the percentages of eyes treated with aflibercept, ranibizumab, and bevacizumab that had persistent DME after > 6 monthly injections were 32%, 41%, and 66%, respectively; of these, 16%, 27%, and 39%, respectively, had associated reduced VA.[80-82] In fact, in the Protocol I study, the response to anti-VEGF therapy at 3 months was predictive of long-term (3-year) improvement in VA **(Figure 6)**.[79]

Eyes with suboptimal initial responses to anti-VEGF therapy should be considered candidates for alternative therapies. Although the definition

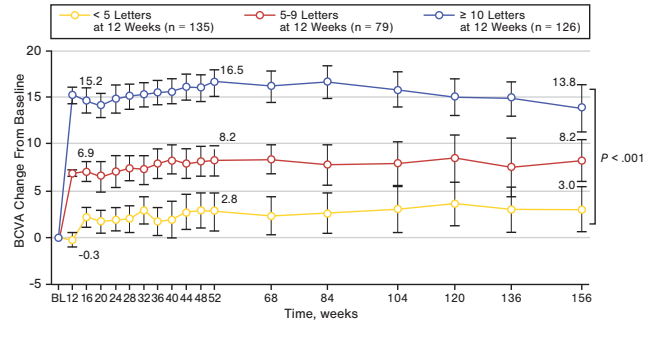

Figure 6. Response to anti–vascular endothelial growth factor therapy at month 3 was predictive of long-term improvement in visual acuity in the Diabetic Retinopathy Clinical Research Network Protocol I study[79]

Abbreviations: BCVA, best-corrected visual acuity; BL, baseline.

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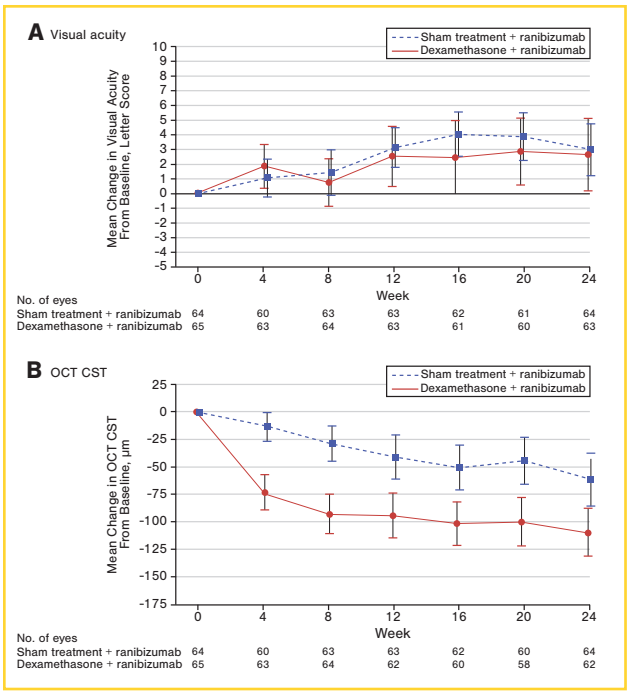

Figure 7. Visual acuity and central subfield thickness outcomes in the Diabetic Retinopathy Clinical Research Network Protocol U study. Visual acuity outcomes were similar between groups (A), whereas greater macular drying was seen in the combined ranibizumab and dexamethasone group than in the ranibizumab monotherapy group (B).[87]

Abbreviations: CST, central subfield thickness; OCT, optical coherence tomography.

of a suboptimal response remains controversial, a panel of expert retina specialists prepared a consensus document on the topic that described a suboptimal response as follows: BCVA worse than 20/40 due to edema after 3 to 6 monthly anti-VEGF injections OR < 50% reduction in excess macular thickness after 3 to 4 monthly anti-VEGF injections.[83] In such eyes, switching to intravitreal corticosteroid therapy is recommended; if the edema fails to improve on corticosteroid therapy, combined anti-VEGF and corticosteroid therapy should be given.[83]

There are 2 options for intravitreal corticosteroid therapy, the dexamethasone implant and the fluocinolone acetonide (FA) implant. The dexamethasone implant is typically effective for approximately 3 months, whereas the FA implant lasts for 1 year or longer.[84,85] Both effectively improve VA vs sham therapy in clinical trials, but these therapies come with serious potential adverse effects.[84,85] Cataract developed in 60% to 80% of eyes in these studies. Elevated IOP was also common in these studies, occurring in 25% to 45.5% of eyes; approximately 40% to 45% of these eyes required IOP-lowering medical therapy. Although glaucoma surgery was uncommon in 347 eyes receiving dexamethasone 0.35 mg and 343 eyes receiving dexamethasone 0.7 mg (0.3% and 0.6%, respectively), it was necessary in 4.8% of 235 eyes receiving FA 0.2 µg/d. The absence of a steroid-related IOP elevation must be assessed prior to implantation of these products, and the FA implant should be reserved for eyes that tolerate steroids but require frequent retreatment.[83]

For eyes that fail to respond adequately to monotherapy with either anti-VEGF agents or steroids, combination therapy is an option. The effectiveness of combined anti-VEGF and corticosteroid therapy has been less well characterized than that with these agents alone. In the DRCRnet Protocol I study, triamcinolone plus laser was as effective in improving VA at 12 months as was ranibizumab in pseudophakic eyes with DME.[86] DRCRnet Protocol U sought to build on this observation by evaluating combined therapy with ranibizumab and dexamethasone in pseudophakic eyes, but, ultimately, suboptimal study enrollment required that phakic eyes also be included.[87] The study demonstrated better macular drying but not better VA outcomes in eyes treated with both ranibizumab and dexamethasone than in eyes treated with ranibizumab alone **(Figure 7)**.

CASE 3: TREATMENT-REFRACTORY DME COMPLICATED BY GLAUCOMA

From the Files of Nancy M. Holekamp, MD

A 59-year-old woman with type 2 diabetes of at least 3 years' duration presented reporting blurry vision. She also had hypertension, cardiac disease, and high cholesterol; her medications included metformin, hydrochlorothiazide, and amiodarone. In the prior 2 years, she had received multiple injections of both bevacizumab and ranibizumab from 4 different physicians, the most recent being 6 weeks ago. On examination, her BCVA was 20/50 OD and 20/30 OS. Her IOP was 14 mm Hg OD and 13 mm Hg OS. She had early nuclear sclerosis without posterior subcapsular changes. Her fundus examination revealed moderately severe nonproliferative diabetic retinopathy, with bilateral DME worse in the right eye. ***Figure 8A*** *shows her OCT images at the time of presentation.*

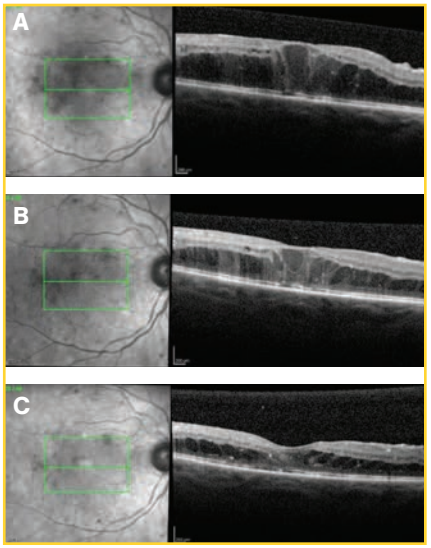

Figure 8. Macular ocular coherence tomography images revealing diabetic macular edema in the right eye of the patient presented in Case 3. Baseline (A), following 4 monthly bevacizumab injections (B), and 1 month following dexamethasone implant (C).

Dr Holekamp: Because her follow-up intervals had been erratic before she came to me, and because she had not had a proper trial of monthly injections, I started with 4 monthly bevacizumab injections, which had no significant impact on her VA or the appearance of her macula **(Figure 8B)**. I injected a dexamethasone implant in her right eye, and within a month, her macula and VA improved **(Figure 8C)**. These gains were maintained with reinjection every 3 months for a year before she developed bilateral cataracts and her BCVA dropped to 20/50 in both eyes. Do you have any considerations when planning cataract surgery in an eye with DME and a steroid implant?

Dr Radcliffe: I have operated on similar eyes. The implant itself does not affect the procedure. When operating on patients with DME who do not already have steroid therapy on board, I will often add an intravitreal triamcinolone injection at the end of the operation to prevent postoperative worsening of the edema.

Dr Samuelson: These eyes tend to heal well, with minimal postoperative inflammation because of the intraocular steroid depot. One key point—if the posterior capsule is ruptured and the implant migrates anteriorly during the procedure, it should be removed at that time to prevent corneal edema.[88]

Dr Holekamp: The patient's surgeries were uneventful, and she attained BCVA of 20/32 OD and 20/20 OS. Then, 3 months postoperatively, her previously normal IOP began to rise. It was 17 mm Hg OD and 25 mm Hg OS, so I brought her back a week later to reassess, and her IOP was then 24 mm Hg OD and 45 mm Hg OS. The risk of adverse effects such as these are why I start with the dexamethasone implant—it has a shorter duration of action than the FA implant.[89,90] If an eye tolerates a series of dexamethasone implants but needs frequent retreatments, I will often then consider switching to the longer-acting FA implant to reduce the frequency of retreatment.[83] How should we manage steroid-related IOP spikes in eyes with implants?

Dr Samuelson: There are many factors to consider. How high is the IOP? Does the patient have preexisting glaucoma? If so, how advanced is it? What is the central corneal thickness and how might it be affecting IOP measurement? These factors help us determine an individual patient's ability to tolerate modest IOP elevations. An interdisciplinary approach can be invaluable to navigate this complex scenario.

Dr Holekamp: The expert panel of retina specialists mentioned previously also provided consensus guidance for retina specialists on the management of steroid-related IOP elevations.[83] These guidelines suggest that if treatment is deemed warranted, a single agent is usually adequate for IOP elevations of 25 mm Hg or less; a combination agent is preferred for IOP ranging from 26 to 30 mm Hg; and when IOP exceeds 30 mm Hg, a fixed combination and a referral to the glaucoma specialist should be considered.

Dr Radcliffe: These are reasonable guidelines and generally mirror what I do in clinical practice.

Dr Samuelson: It is also advisable to get baseline visual fields and RNFL OCT testing at the time of initial medical therapy.

Dr Holekamp: I prescribed topical medications for this patient, and her IOP normalized. We were able to stop the medications as the steroid response dissipated. Four months later, after an additional dexamethasone implant for the DME, her IOP rose again. A visual field test at that time indicated some early glaucomatous damage, so she was referred to a glaucoma specialist. Had her visual field not progressed and had her IOP remained < 30 mm Hg, I would have kept treating her with a single or fixed-combination topical agent. As seen in the MEAD study, IOP increases are not cumulative over time and tend to decrease in magnitude with subsequent dexamethasone implants.[91]

KEY TAKE-HOME POINTS

- **Treating complex ocular disease can be a challenge, but careful consideration of common comorbidities can help guide your decision making**
- **OSD is very common, particularly among patients with diabetes and those who use topical glaucoma therapies**
- **DED treatment should take into consideration causative factors and subtype**
- **Treatment options for glaucoma can now include SLT and MIGS earlier in the treatment paradigm**
- **DME that is unresponsive to anti-VEGF therapy should be addressed promptly to avoid vision loss. Evidence-based strategies such as the use of corticosteroids should be explored.**

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