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GLAUCOMA SURGICAL TREATMENTS

Policy Number: CS050.~~MN~~

Effective Date: ~~September 1, 2019~~ **Xx 1, 2020**

[Instructions for Use](#) ⓘ

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Related Community Plan Policy

- [Corneal Hysteresis and Intraocular Pressure Measurement](#)

Commercial Policy

- [Glaucoma Surgical Treatments](#)

Medicare Advantage Coverage Summary

- [Glaucoma Surgical Treatments](#)

APPLICATION

This policy does not apply to the states of **Nebraska, New Jersey and Tennessee**.

- **For the state of Nebraska, refer to the Medical Policy titled Glaucoma Surgical Treatments (for Nebraska Only).**
- **For the state of New Jersey, refer to the Medical Policy titled Glaucoma Surgical Treatments (for New Jersey Only).**
- **For the state of Tennessee, refer to the Medical Policy titled [Glaucoma Surgical Treatments \(for Tennessee Only\)](#).**

COVERAGE RATIONALE

The following are proven and medically necessary:

- **Canaloplasty (ab externo) for treating primary open-angle glaucoma**
- Glaucoma drainage devices for treating refractory glaucoma when medical or surgical treatments have failed or are inappropriate
- iStent®, iStent *inject*®, and the Hydrus® Microstent when used in combination with cataract surgery for treating mild to moderate open-angle glaucoma and a cataract in adults currently being treated with ocular hypotensive medication
- ~~Canaloplasty for treating primary open-angle glaucoma~~

The following are unproven and not medically necessary for treating any type of glaucoma due to insufficient evidence of efficacy and/or safety:

- **Canaloplasty (ab interno)**
- **Glaucoma drainage devices that are not FDA approved**
- **Gonioscopy-Assisted Transluminal Trabeculotomy**
- **Viscocanalostomy**
- **XEN® Glaucoma Treatment System**
- ~~CyPass® Micro-Stent System~~
- ~~XEN® Glaucoma Treatment System~~
- ~~Glaucoma drainage devices that are not FDA approved~~
- ~~Viscocanalostomy~~

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APPLICABLE CODES

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by federal, state or contractual requirements and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Coverage Determination Guidelines may apply.

***Coding Clarification:** Utilize CPT code [66174](#) when reporting viscocanalostomy.

CPT Code	Description
0191T	Insertion of anterior segment aqueous drainage device, without extraocular reservoir, internal approach, into the trabecular meshwork; initial insertion
0253T	Insertion of anterior segment aqueous drainage device, without extraocular reservoir, internal approach, into the suprachoroidal space
0376T	Insertion of anterior segment aqueous drainage device, without extraocular reservoir, internal approach, into the trabecular meshwork; each additional device insertion (List separately in addition to code for primary procedure)
0449T	Insertion of aqueous drainage device, without extraocular reservoir, internal approach, into the subconjunctival space; initial device
0450T	Insertion of aqueous drainage device, without extraocular reservoir, internal approach, into the subconjunctival space; each additional device (List separately in addition to code for primary procedure)
0474T	Insertion of anterior segment aqueous drainage device, with creation of intraocular reservoir, internal approach, into the supraciliary space
66170	Fistulization of sclera for glaucoma; trabeculectomy ab externo in absence of previous surgery
*66174	Transluminal dilation of aqueous outflow canal; without retention of device or stent
66175	Transluminal dilation of aqueous outflow canal; with retention of device or stent
66179	Aqueous shunt to extraocular equatorial plate reservoir, external approach; without graft
66180	Aqueous shunt to extraocular equatorial plate reservoir, external approach; with graft
66183	Insertion of anterior segment aqueous drainage device, without extraocular reservoir, external approach
66184	Revision of aqueous shunt to extraocular equatorial plate reservoir; without graft
<u>66185</u>	<u>Revision of aqueous shunt to extraocular equatorial plate reservoir; with graft</u>

CPT® is a registered trademark of the American Medical Association

HCPCS Code	Description
L8612	Aqueous shunt

DESCRIPTION OF SERVICES

Glaucoma refers to a group of eye diseases in which vision is lost due to damage of the optic nerve. The 2016 American Academy of Ophthalmology (AAO) Preferred Practice Patterns Guidelines on primary open-angle glaucoma (POAG) states that the severity of glaucoma damage can be estimated using the following:

- Mild: Optic nerve abnormalities consistent with glaucoma and a normal visual field as tested with standard automated perimetry (SAP)

- Moderate: Optic nerve abnormalities consistent with glaucoma and visual field abnormalities in one hemifield that are not within 5 degrees of fixation as tested with SAP
- Severe: Optic nerve abnormalities consistent with glaucoma and visual field abnormalities in both hemifields and/or loss within 5 degrees of fixation in at least one hemifield as tested with SAP
- Indeterminate: Optic nerve abnormalities consistent with glaucoma, inability to perform visual field testing, unreliable/uninterpretable visual field test results, or visual fields not yet performed

Trabeculectomy is a surgical procedure that removes part of the eye's trabecular meshwork and adjacent structures to reduce intraocular pressure (IOP) in individuals with glaucoma. For the majority of individuals, it is the most common surgery that allows drainage of aqueous humor from within the eye to underneath the conjunctiva where it is absorbed.

Non-penetrating procedures include canaloplasty and viscocanalostomy. The difference between viscocanalostomy and canaloplasty is that the latter aims at opening the entire length of the canal, not just one section of it.

Canaloplasty is a surgical technique for glaucoma which aims to restore the natural drainage of fluid from the eye (National Institute for Health and Care Excellence (NICE), 2008; updated 2017). It may be performed using an ab externo (from the outside) approach or more recently, an ab interno (from the inside) approach. Both approaches involve viscodilation of Schlemm's canal to restore normal aqueous outflow. With an ab externo approach, the microcatheter is inserted through cuts in the conjunctiva and sclera and then, uses an intracanalicular suture that cinches and stretches the trabecular meshwork inwards while permanently opening the Schlemm's canal. With an ab interno approach, the microcatheter is inserted through either a clear corneal or limbal micro-incision, through the trabecular meshwork and then, into Schlemm's canal. Once in the canal, a viscoelastic gel is used to dilate it.

~~Canaloplasty is a surgical technique for glaucoma which aims to restore the natural drainage of fluid from the eye (National Institute for Health and Care Excellence (NICE), 2008; updated 2017). Canaloplasty involves viscodilation of the Schlemm's canal with an illuminated tipped microcatheter. The microcatheter is used to place an intracanalicular suture that cinches and stretches the trabecular meshwork inwards while permanently opening the Schlemm's canal.~~

Viscocanalostomy is a procedure used to treat glaucoma that involves surgical incisions and injection of a viscous, elastic material into the eye. The goal of this procedure is to reduce IOP by creating a channel that allows excess fluid to drain from the eye.

Gonioscopy-assisted transluminal trabeculotomy (GATT) is a recent refinement of circumferential ab interno trabeculotomy. With GATT, a temporal corneal wound is made and direct gonioscopy is used to visualize the nasal angle structures. A goniotomy is created and microsurgical forceps are used to guide an illuminated microcatheter or suture into Schlemm's canal. The forceps are used to progress the microcatheter or suture circumferentially until the tip is identified at the original goniotomy site and retrieved. Then, traction on the suture or catheter used to create a 360-degree trabeculotomy (Baykara 2019, SooHoo 2015).

Glaucoma drainage devices (also known as aqueous shunts) include the EX-PRESS™ Mini Glaucoma Shunt, the Molteno implant, the Baerveldt tube shunt, and the Ahmed glaucoma valve implant. The EX-PRESS™ Mini Glaucoma Shunt is a small stainless steel device that is placed beneath the scleral flap into the anterior chamber instead of creating a punch or excisional sclerostomy, thereby bypassing the trabecular meshwork and directing aqueous fluid to form a perilimbal conjunctiva-covered bleb. The Molteno, Baerveldt and Ahmed glaucoma implants consist of a length of flexible plastic tubing that is inserted into anterior or posterior chamber and connect to a plastic or silicone plate with a large surface area that is secured to the posterior sclera between 2 of the extraocular muscles, and covered by conjunctiva. The plate acts as a physical barrier to scarring of the conjunctiva to the sclera providing a large surface area bleb posterior to the limbus.

Glaucoma drainage devices such as iStent® and iStent *inject*® Trabecular Micro-Bypass systems, Eyepass, or DeepLight SOLX® Gold Shunt (suprachoroidal shunt) divert aqueous fluid from the anterior chamber directly into Schlemm's canal (Samuelson, 2008). The XEN® Gel Stent is for use in individuals with refractory glaucoma. A gelatin tube is implanted into the subconjunctival space and is proposed as a less traumatic alternative to ab externo

procedures such as trabeculectomy and shunt implantation (AqueSys, Inc., 2017). These stenting/shunting procedures are similar to viscocanalostomy in that they lower IOP without the formation of a filtering bleb.

Micro-invasive or minimally invasive glaucoma surgery (MIGS) refers to a group of newer surgical procedures that are performed via an ab interno approach and involve minimal trauma to ocular tissues. Although less effective in lowering IOP than trabeculectomy and aqueous shunt surgery, MIGS appears to have a more favorable safety profile in the short term and is commonly combined with phacoemulsification. Examples of MIGS are the iStent® *Inject* and the Hydrus® Microstent (AAO, 2016; ~~Hayes, 2018~~).

CLINICAL EVIDENCE

Canaloplasty (ab externo)

Rękas et al. (2015) conducted a prospective, randomized trial comparing safety and efficacy of non-penetrating deep sclerectomy (NPDS) using a viscoelastic compound versus canaloplasty in 29 eyes of individuals with uncontrolled POAG and a cataract. Outcomes measured included corrected distance visual acuity, IOP, and number of medications required postoperatively. Complete and qualified success was an IOP ≤ 18 mmHg. Follow-up examinations were performed on days 1 and 7, and at 1, 3, 6, and 12 months. Both groups had similar IOPs preoperatively. At 12 months, there were no statistical differences identified either in IOP or number of medications utilized. Complete and qualified success rates for the canaloplasty and NPDS groups were 79% and 77%, respectively. With these findings, the authors concluded that neither procedure is superior to the other in providing safe and effective treatment to the glaucoma patient with cataracts. However, over 50% of the NPDS group required intervention for AEs occurring in the postoperative period, while the canaloplasty group required no postoperative management.

Matlach et al. (2015) conducted a prospective, comparative, randomized controlled trial (RCT) known as the TVC study, where participants received trabeculectomy (n=32) or canaloplasty (n=30) and were followed for 2 years. Primary outcomes included complete success (without medication) and qualified success (with or without medication), defined as IOP of ≤ 18 mmHg (definition 1) or IOP ≤ 21 mmHg and $\geq 20\%$ IOP reduction (definition 2), IOP ≥ 5 mmHg, no vision loss and no further glaucoma surgery. Each surgical intervention resulted in significantly reduced IOP. Complete success was achieved in 74% and 39% (definition 1), and 68% and 39% (definition 2) at 2 years in the trabeculectomy and canaloplasty groups, respectively. Mean absolute IOP reduction was slightly better at 2 years with trabeculectomy (10.8 ± 6.9 mmHg) versus canaloplasty (9.3 ± 5.7 mmHg). Adverse events (AEs) were more frequent following trabeculectomy. The authors concluded that trabeculectomy is associated with a better reduction in IOP and less need for medication, but has a higher complication rate. If target IOP is attainable by moderate reduction, canaloplasty may be considered for its ease of postoperative care and lack of complications-(2015).

Koerber et al. (2012) compared the safety and efficacy of canaloplasty in one eye with viscocanalostomy in the contralateral eye in 15 patients (30 eyes) with bilateral primary open-angle glaucoma (POAG). Sixty percent of patients had the canaloplasty procedure first, followed by the viscocanalostomy procedure. At 18-month follow-up, both procedures canaloplasty and viscocanalostomy were successful in reducing IOP. The percentage reduction in IOP was significantly higher in the canaloplasty eyes (approximately 44%), as compared with the viscocanalostomy eyes (approximately 33%), at both 12 and 18 months. Final absolute IOP was not significantly different, although lower, in the canaloplasty group versus the viscocanalostomy group at 18 months. Using the criteria for complete success defined as an IOP of ≤ 18 mm Hg without antiglaucoma medication, and qualified success as an IOP of ≤ 18 mm Hg with 1 or 2 antiglaucoma medications, the canaloplasty cohort achieved complete success in 60.0% of eyes, and complete or qualified success in 87% of eyes. The viscocanalostomy group achieved complete success in 35.7% of eyes, and complete or qualified success in 36% and 50.0% of eyes, respectively. Complications were minimal in both groups. According to the authors, canaloplasty and viscocanalostomy were safe and effective in the surgical management of OAG. The authors also stated that canaloplasty procedures showed superior efficacy to viscocanalostomy in the reduction of IOP.

Lewis et al. (2011) conducted a multicenter clinical trial that included 157 eyes in 157 patients (140 patients with POAG, 17 patients with other glaucoma diagnoses) who underwent canaloplasty or combined cataract-canaloplasty surgery. A total of 121 eyes (77%) had canaloplasty alone, while 36 eyes (23%) with visually significant cataracts had canaloplasty combined with cataract extraction (phacocanaloplasty). Complete success (defined as attaining an IOP of ≤ 18 mm Hg without antiglaucoma

medication) at 3-year follow-up was achieved in 36% of eyes receiving canaloplasty alone with successful suture placement, and 70% of eyes having the combined phacocanaloplasty procedure with successful suture placement. Complete or qualified success (defined as attaining an IOP of ≤ 18 mm Hg with 1 or 2 antiglaucoma medications) was achieved in 77.5% of eyes with canaloplasty alone, and 89% of eyes with phacocanaloplasty. The authors concluded that canaloplasty led to a significant and sustained IOP reduction in adult patients with OAG and had an excellent short- and long-term postoperative safety profile.

Bull et al. (2011) reported 3-year results investigating the safety and efficacy of canaloplasty in a prospective, multi-center, interventional study of 109 eyes of 109 adult OAG patients undergoing canaloplasty or combined cataract-canaloplasty surgery. IOP and medication use results for all study eyes were significantly decreased from baseline. According to the authors, canaloplasty demonstrated significant and sustained IOP reductions accompanied by an excellent short- and long-term safety profile in adult patients with OAG.

Grieshaber et al. (2010b) compared the safety and efficacy of 2 polypropylene (Prolene) sutures for tensioning of the inner wall of Schlemm's canal in patients with POAG undergoing canaloplasty. This prospective RCT included 90 patients. The mean preoperative IOP was 42.7 mm Hg in group 1 and 45.0 mm Hg in group 2. The mean postoperative IOP without medications was 18.4 mm Hg in group 1 and 16.4 mm Hg in group 2 at 1 month. Mean IOP at 15 months for group 1 was 19.2 mm Hg and 16.4 mm Hg in group 2. Pressures equal or less than 21, 18, and 16 mm Hg without medications (complete success) at 12 months were 51%, 34%, and 21% in group 1, and 77%, 69%, and 54% in group 2, respectively. The investigators concluded that IOP reduction was substantial in canaloplasty. Younger age, but not the level of IOP at surgery, had a positive effect on the amount of IOP reduction, thus suggesting that an early surgical intervention to re-establish physiological outflow offers the best prognosis.

Grieshaber et al. (2010a) evaluated the safety and effectiveness of 360° visco-dilation and tensioning of Schlemm canal (canaloplasty) in patients with POAG. Sixty randomly selected eyes of 60 consecutive patients with POAG were included in this prospective study. The mean preoperative IOP was 45.0 mm Hg. The mean follow-up time was 30.6 months. The mean IOP at 12 months was 15.4 mm Hg (n=54), 16.3 mm Hg at 24 months (n = 51), and 13.3 mm Hg at 36 months (n=49). For IOP ≤ 21 mm Hg, complete success rate was 77.5% and qualified success rate was 82% at 36 months. Complication rate was low. The investigators conclude that canaloplasty produced a sustained long-term reduction of IOP in patients with POAG independent of preoperative IOP. As a bleb-independent procedure, canaloplasty may be a true alternative to classic filtering surgery, in particular in patients with enhanced wound healing and scar formation.

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Canaloplasty (ab interno)

A Hayes Health Technology Assessment, Canaloplasty for Open-Angle Glaucoma (2020), states that there is insufficient evidence to assess the effectiveness and safety of ab interno canaloplasty.

Gallardo et al. (2018a) conducted a retrospective single-center case series of patients with uncontrolled primary open-angle glaucoma (POAG) who underwent ABiC as a stand-alone procedure or in conjunction with cataract extraction. The primary outcomes were mean IOP and mean number of glaucoma medications. Secondary outcomes included surgical and postsurgical complications and secondary interventions. A subset analysis was conducted comparing the outcomes of patients who underwent ABiC and phacoemulsification vs. ABiC as a stand-alone procedure. A total of 68 patients (75 eyes) were included with a mean age of 73.7 ± 9.9 years. At baseline, the mean IOP was 20.4 ± 4.7 mmHg and mean medication use was 2.8 ± 0.9 . Twelve months postoperatively, the mean IOP reduced to 13.3 ± 1.9 mmHg ($n=73$) and mean medication use was reduced to 1.1 ± 1.1 medications. At 12 months, 40% of eyes were medication free. In the ABiC/phacoemulsification subgroup ($n=34$ eyes), the mean IOP and medication use decreased from 19.4 ± 3.7 mmHg on 2.6 ± 1.0 medications preoperatively to 13.0 ± 1.8 mmHg on 0.8 ± 0.2 medications at 12 months (both $p<0.001$). In the stand-alone ABiC subgroup ($n=41$), the mean IOP and medication use decreased from 21.2 ± 5.3 mmHg on 3.0 ± 0.7 medications preoperatively to 13.7 ± 1.9 mmHg on 1.3 ± 1.1 medications at 12 months ($p=0.001$ and $p<0.001$, respectively). No serious adverse events were recorded. The authors concluded that their results demonstrate that ABiC was effective at reducing IOP and medication use in eyes with uncontrolled POAG with or without cataract surgery. However, limitations of this study should be noted. For example, all cases are from a single center, the study design, as a retrospective case series, is uncontrolled and subject to selection bias, the combination cataract surgery results are confounded by the IOP-lowering effect of cataract surgery and therefore, the precise mechanism of the ability of ABiC to reduce IOP is unclear, and only 12 months of follow-up. Longer-term, multi-center prospective randomized trials with a larger sample size are still need to assess the safety and efficacy of ABiC.

Gallardo et al. (2018b) conducted a non-randomized, retrospective, single-center paired eye study to assess the efficacy of ab-interno canaloplasty (ABiC) vs. ab-externo canaloplasty (CP) in reducing intraocular pressure (IOP) and glaucoma medication dependence. Patients with primary open-angle glaucoma underwent ABiC in one eye and CP in the other eye, either as stand-alone procedures or combined with cataract extraction. The primary outcomes included mean intraocular pressure (IOP) and number of glaucoma medications at 12 months after surgery. Secondary outcomes included surgical complications and secondary interventions. A total of 12 patients (8 females and 4 males) with a mean age of 73.8 ± 12.6 years were included. In the CP group, the mean preoperative IOP was 18.1 ± 3.9 mmHg on 2.4 ± 0.5 medications, which reduced to 13.5 ± 2.2 mmHg ($p<0.05$) on 0.9 ± 0.9 medications ($p<0.001$). In the ABiC group, the mean preoperative IOP was 18.5 ± 3.4 mmHg on 2.4 ± 0.5 medications and postoperative IOP was 13.8 ± 2.2 mmHg ($p<0.05$) on 0.8 ± 0.8 medications ($p<0.05$). There was no significant difference in IOP and medication use between treatment groups at 12 months after surgery. No serious adverse events were recorded in either group, though two patients in the CP group developed pressure spikes 10 mmHg beyond preoperative IOP. The authors concluded that in this small pilot paired eye study, ABiC was found to have comparable IOP lowering and glaucoma medication reduction to CP in open-angle glaucoma and that ABiC may be a suitable method for improving aqueous outflow via the trabecular pathway. However, larger-scale studies with longer follow-up are needed to confirm these findings.

Gonioscopy-assisted transluminal trabeculotomy (GATT)

Grover et al. (2018) conducted a retrospective chart review of patients with various types of open-angle glaucoma (OAG) who underwent a gonioscopy-assisted transluminal trabeculotomy (GATT). The purpose of the study was to provide 24-month follow-up on surgical success and safety. A total of 198 patients (198 eyes) between 24 to 89 years of age with intraocular pressures of ≥ 18 mmHg underwent GATT. Patients were stratified into 6 groups: 1) primary open-angle glaucoma (POAG) with no prior CE, receiving only GATT; 2) POAG with no prior CE, receiving combined GATT and CE; 3) POAG with prior CE, receiving only GATT; 4) Other glaucoma with no prior CE, receiving only GATT; 5) Other glaucoma with no prior CE, receiving combined GATT and CE; and 6) Other glaucoma with prior CE, receiving only GATT. At 24 months, patients with primary OAG (groups 1 – 3, $n=72$) had an average IOP decrease of 9.2 mmHg and an average decrease of 1.43 glaucoma medications. The mean percentage of IOP decrease in these primary open-angle glaucoma groups at 24 months was 37.3%. In patients with secondary open-angle

glaucoma (groups 4 – 6, n=49), there was an average decrease in IOP of 14.1mmHg and an average of 2.0 fewer medications. The mean percentage of IOP decrease in the secondary open-angle glaucoma groups at 24 months was 49.8%. The cumulative proportion of failure at 24 months ranged from 0.18 to 0.48, depending on the group. In all 6 study groups, at all 5 postoperative time points (3, 6, 12, 18, and 24 months) the mean IOP and reduction in glaucoma medications was significantly reduced from baseline (p<0.001) with the exception of one time point (i.e., the POAG Prior CE group, at 24 months, reduction in glaucoma medication, p=0.059). The authors concluded that the 24-month results demonstrate that GATT is relatively safe and effective in treating various forms of open-angle glaucoma. The long-term results for GATT are relatively equivalent to those previously reported for GATT and ab externo trabeculotomy studies. However, limitations of this study should be noted. For example, all cases are from a single glaucoma center, the decision for this particular surgical intervention was based on the individual surgeon's discretion rather than a randomization scheme, the number of patients who were lost to follow-up or censored after reoperation and the study design which is prone to selection bias, missing data, inaccuracies and lacks a control. Multi-center, randomized controlled trials with longer follow-up are still needed to ensure the safety and efficacy of GATT.

Rahmatnejad et al. (2017) conducted a single-center retrospective chart review of adult patients who underwent GATT due to inadequately controlled intraocular pressure (IOP) or intolerance to medication. Main outcomes included success rate, IOP, and number of glaucoma medications. Success was defined as IOP reduction >20% from baseline or IOP between 5 to 21mmHg, and no need for further glaucoma surgery. When success criteria were not met for any postoperative visit > 3 months after surgery, failure was determined. In total, 66 patients, average age 62.9 ± 14.9 years (50.8% female) were included in the analysis. Average follow-up was 11.9 months (range, 3 to 30) and overall success rate was 63.0%. Mean IOP was 26.1 ± 9.9 mmHg preoperatively and 14.6 ± 4.7 mmHg at 12 months (44% IOP decrease; p<0.001). Mean number of medications decreased from 3.1 ± 1.1 preoperatively to 1.2 ± 0.9 at 12 months (p<0.001). No significant differences between patients with primary open-angle glaucoma and other types of glaucoma were found. The rate of hyphema at 1 week and 1 month postoperatively was 38% and 6%, respectively. Overall GATT success rate among white and black patients was 69% and 42%, respectively, which was statistically significant (p<0.05). The authors concluded the future of GATT as a minimally invasive glaucoma surgery in adults seems promising and that this position is supported by its low rate of long-term complications and the conjunctiva-sparing nature of the surgery. However, limitations of this study should be considered when evaluating these results e.g., all cases are from a single-center, the surgeon's learning curve may have affected the results of early cases, and as a retrospective chart review, there was no randomization scheme or control group as well as, the potential for various biases or the presence of confounding factors that were not documented in patients' medical records. Further research is warranted to better understand who would most benefit from GATT as well as, its long-term safety and efficacy of its IOP-lowering effects.

Grover et al. (2017a) conducted a single-center, retrospective case series of patients who underwent a GATT procedure and had a prior incisional glaucoma surgery. A total of 35 eyes of 35 patients were treated. The mean age was 67.7 years. Nineteen eyes had a prior trabeculectomy, 13 eyes had a prior glaucoma drainage device, 4 eyes had a prior trabectome, and 5 eyes had prior endocyclophotocoagulation. The mean follow-up time was 22.7 months. For all eyes, the mean preoperative IOP was 25.7 ± 6.5 mm Hg on 3.2 ± 1.0 glaucoma medications and at 24 months, the mean IOP was 15.4 ± 4.9 mm Hg on 2.0 ± 1.4 glaucoma medications (both p<0.05). The prior trabeculectomy group had a preoperative IOP of 24.6 ± 6.4 mm Hg on 3.2 ± 1.0 medications and at month 24, the mean IOP was 16.7 ± 5.6 mm Hg (p=0.027) on 2.1 ± 1.4 glaucoma medications (p=0.063). In the prior glaucoma drainage device group, the mean preoperative IOP was 27.0 ± 7.1 mm Hg on 3.4 ± 1.1 glaucoma medications and at 24 months, the mean IOP was 12.9 ± 2.6 mm Hg (p<0.05) on 2.1 ± 1.2 glaucoma medications (p=0.080). At 24 months, the cumulative proportion of failure was 0.4 and the cumulative proportion of reoperation was 0.29. The authors concluded that GATT appears to be safe and successful in treating 60% to 70% of open-angle patients with prior incisional glaucoma surgery. When considering all eyes, there was a significant decrease in IOP and required glaucoma medications at 24 months. Study limitations should be considered when evaluating these results. For example, the retrospective case series design lacks randomization or comparisons to other glaucoma surgical

procedures, the surgeons' may have still been refining their technique since GATT was a relatively new procedure at the time of this study, the small sample sizes at 24 months and limited follow-up period. Randomized controlled trials with larger sample sizes and longer follow-up periods are still needed to better understand the safety and efficacy of GATT in patients with a prior incisional glaucoma surgery.

Viscocanalostomy

A Cochrane review analyzed data from RCTs and quasi-RCTs where surgical techniques were utilized to treat primary congenital glaucoma (PCG). The rationale for the analysis was to compare the efficacy and safety of different surgical techniques in children diagnosed at age one and younger and having surgical therapy before 5 years of age (n=61). Due to the limited sample sizes for all trials (average of 10 children per trial), the evidence as to whether a particular surgical technique is effective and which surgical technique is better still remains uncertain. AEs such as choroidal detachment, shallow anterior chamber and hyphema were reported from 4 trials. None of the trials reported quality of life (QOL) or economic data. These trials were neither designed nor reported well overall. Due to poor study design and reporting, the reliability and applicability of evidence remain unclear. The author states that no conclusions could be drawn from the trials included in this review due to paucity of data, stating that more research is needed to determine which of the many surgeries performed for PCG are effective (Ghate et al., 2015).

Another Cochrane review conducted by Eldaly et al. included relevant RCTs and quasi-RCTs on participants undergoing standard trabeculectomy for OAG compared to non-penetrating glaucoma surgery (NPGS), specifically viscocanalostomy or deep sclerectomy, with or without adjunctive measures. Included were 5 studies with a total of 311 eyes (participants = 247), of which 133 eyes (133 participants) were quasi-randomized. Eyes having trabeculectomy (n=160) were compared to those having NPGS (deep sclerectomy = 101 eyes, and 50 eyes had viscocanalostomy). The authors concluded that this review provided limited evidence that control of IOP is better with trabeculectomy than viscocanalostomy, although there is uncertainty about trabeculectomy versus deep sclerectomy. AEs appeared more common in the trabeculectomy arm, as cataract was more commonly reported in addition to OAG. However, overall AEs were rare. Study limitations identified included absence of QOL measurement, poor quality evidence and high risk of bias. Further RCTs are needed (2015⁴).

Cheng et al. (2011) evaluated the IOP-lowering effects achieved by NPGS in patients with OAG in a systematic review of RCTs. The pooled estimates were calculated using the random effects model. Both deep sclerectomy and viscocanalostomy were less effective than trabeculectomy in lowering IOP, with the percentage IOP reductions at 2 years being 35%, 30%, and 46% for deep sclerectomy, viscocanalostomy, and trabeculectomy, respectively. The complete success rates at 4 years were 35% for deep sclerectomy, and 23% for viscocanalostomy, both lower than that of trabeculectomy (48%). According to the authors, primary deep sclerectomy and primary viscocanalostomy were associated with fewer complications than trabeculectomy. However, trabeculectomy was superior to NPGS in reduction of IOP and overall success.

Chai et al. (2010) conducted a meta-analysis to compare the efficacy and safety profile of viscocanalostomy versus trabeculectomy. Ten RCTs were selected and included in the meta-analysis with a total of 458 eyes of 397 patients with medically uncontrolled glaucoma. Trabeculectomy was found to have a significantly better pressure-lowering outcome. Viscocanalostomy had a significantly higher relative risk of intraoperative perforation of the Descemet membrane, whereas trabeculectomy had significantly more postoperative AEs. The reviewers concluded that trabeculectomy had a greater pressure-lowering effect compared with viscocanalostomy. However, viscocanalostomy had a significantly better risk profile.

A meta-analysis by Hondur et al. (2008) evaluated the efficacy of NPGS for OAG with respect to target IOP and severity of glaucoma. The studies reviewed included deep sclerectomy and viscocanalostomy. With lower set IOP targets, the rates of success varied between 35% and 86% for deep sclerectomy, and between 10% and 67% for viscocanalostomy. Mean follow-up was mostly in the range of 3 years. The authors concluded that NPGS seems to provide IOP reduction into the high teens. Its potential to achieve lower target IOPs seems to be low. Longer-term studies with data related to glaucoma severity and proper target IOPs are required.

~~Cheng et al. (2011) evaluated the IOP-lowering effects achieved by NPGS in patients with OAG in a systematic review of RCTs. The pooled estimates were calculated using the random effects model. Both deep sclerectomy and~~

viscocanalostomy were less effective than trabeculectomy in lowering IOP, with the percentage IOP reductions at 2 years being 35%, 30%, and 46% for deep sclerectomy, viscocanalostomy, and trabeculectomy, respectively. The complete success rates at 4 years were 35% for deep sclerectomy, and 23% for viscocanalostomy, both lower than that of trabeculectomy (48%). According to the authors, primary deep sclerectomy and primary viscocanalostomy were associated with fewer complications than trabeculectomy. However, trabeculectomy was superior to NPGS in reduction of IOP and overall success.

In a guidance on the diagnosis and management of chronic OAG and ocular hypertension, NICE concluded from the evidence (low to moderate quality) that trabeculectomy is more effective than non-penetrating surgery (e.g., viscocanalostomy) in reducing IOP from baseline at 6- and 12-month follow-ups, but the effect size may be too small to be clinically significant. Trabeculectomy is also more effective in reducing the number of eyes with unacceptable IOP at 6- and 12-months (2009, updated 2017).

Glaucoma Drainage Devices Approved by the U.S. Food and Drug Administration (FDA)

EX-PRESS™

A 2017 Hayes report of published literature on the use of the EX-PRESS™ Glaucoma Filtration Device (EGFD) for the treatment of IOP in patients with OAG yielded 7 RCTs reported in 10 publications with participants ranging from 15-120 patients. They concluded that a moderate quality body of evidence suggested that use of the EX-PRESS™ device results in similar outcomes when compared with trabeculectomy (the current standard of care), citing few differences between the 2 procedures relative to reduction of IOP, medication use, and the return of visual acuity in both the short and long term (up to 5 years).

de Jong (2009) conducted a prospective RCT of 78 patients (80 eyes) with primary open angle, pseudoexfoliative, or pigmentary glaucoma to compare the EX-PRESS™ mini glaucoma shunt with trabeculectomy. A total of 84.6% of patients receiving EX-PRESS™ and 60% of patients receiving trabeculectomy achieved complete success (defined as an IOP of >4 mmHg ≤ 18 mmHg without the use of antiglaucoma medications). The respective proportions of patients achieving an IOP >4 mmHg and ≤ 15 mmHg were 76.9% and 50.0%. At 1-year follow-up, complete success rates were 81.8% for EX-PRESS™ and 47.5% for trabeculectomy. The authors concluded that the EX-PRESS™ mini glaucoma shunt implanted under a superficial scleral flap produces significantly higher success rates compared with trabeculectomy.

Sun et al. (2019) conducted an updated meta-analysis of randomized controlled trials to compare the efficacy and safety of trabeculectomy and EX-PRESS implantation in open-angle glaucoma (OAG). The search was conducted using PubMed, Web of Science, Embase, and the Cochrane Library. Articles that met the predetermined search terms and published up to November 2018 were included. IOP reduction and antiglaucoma medication reduction were considered continuous variables with the mean difference (MD) measured. Complication, postoperative success, and intervention were considered dichotomous variables measured as the odds ratio (OR). Complete success was defined as target endpoint IOP without antiglaucoma medication, while qualified success was defined as target endpoint IOP with or without antiglaucoma medication. All outcomes were reported with a 95% confidence interval (CI). Data were pooled using a random effects model. A total of 8 RCTs were included in the final analysis (223 eyes in the EX-PRESS group and 217 eyes in the trabeculectomy group). EX-PRESS device implantation had a better IOPR% at 12 months postoperatively compared with trabeculectomy. There was no difference in the antiglaucoma medication reduction and qualified success between the groups. Complete success at 1 year postoperatively was higher in the EX-PRESS group (OR=3.26, 95% CI=1.24-8.55, p=0.02). EX-PRESS was associated with a lower frequency of increased IOP (OR=0.15, 95% CI=0.03-0.93, p=0.04) and hyphema (OR=0.20, 95% CI=0.05-0.74, p=0.02). Less postoperative intervention was needed in the EX-PRESS group (OR=0.43, 95% CI=0.20-0.94, p=0.04). The authors concluded that for OAG patients, EX-PRESS implantation provided better efficacy in IOP control and complete success at 1 year postoperatively, with fewer patients with increased IOP and hyphema as well as requiring postoperative interventions. The EX-PRESS device and trabeculectomy were similar in the qualified success and antiglaucoma medication reduction.

In follow up to the above study de Jong et al. (2011) reported on outcomes at 4 years, beyond those in the original RCT (i.e., up to 5 years in the patients who received either the EX-PRESS™ device [n=39] or who underwent

trabeculectomy [n=39]). Compared with trabeculectomy, the EX-PRESS™ device controlled IOP more effectively without medication in a higher percentage of patients from year 1 (86.8% versus 61.5%) to year 3 (66.7% versus 41.0%) post-treatment. At 1 year post-treatment, only 12.8% of patients required IOP medication after EX-PRESS™ implantation, compared with 35.9% after trabeculectomy; however, the proportions became closer each year and at 5 years were 41% versus 53.9%, respectively. Up to the end of the third year after surgery, IOP remained better controlled by EX-PRESS™ devices than by trabeculectomy. In the fourth and fifth years, the differences in IOP control between the 2 groups were not significant.

Ates et al. (2010) evaluated IOP control and graft survival after EX-PRESS™ mini glaucoma shunt implantation in 15 patients. IOP decreased from 41.46 mm Hg to 12.06 mm Hg over a mean follow-up of 12.2 months. Neither biomicroscopy nor pachymetry showed worsening of preoperatively opaque grafts. The investigators concluded that the EX-PRESS™ mini glaucoma shunt implantation may be an effective procedure for refractory post-penetrating keratoplasty glaucoma with acceptable graft failure rates in short term.

de Jong (2009) conducted a prospective RCT of 78 patients (80 eyes) with primary open-angle, pseudoexfoliative, or pigmentary glaucoma to compare the EX-PRESS™ mini glaucoma shunt with trabeculectomy. A total of 84.6% of patients receiving EX-PRESS™ and 60% of patients receiving trabeculectomy achieved complete success (defined as an IOP of >4 mmHg <=18 mmHg without the use of antiglaucoma medications). The respective proportions of patients achieving an IOP >4 mmHg and <=15 mmHg were 76.9% and 50.0%. At 1-year follow-up, complete success rates were 81.8% for EX-PRESS™ and 47.5% for trabeculectomy. The authors concluded that the EX-PRESS™ mini glaucoma shunt implanted under a superficial scleral flap produces significantly higher success rates compared with trabeculectomy.

Molteno Implant, Baerveldt Tube Shunt and Ahmed Glaucoma Valve Implant

In a Cochrane Review conducted by Tseng et al. (2017) the objective was to assess the effectiveness and safety of aqueous shunts for reducing IOP in glaucoma. A search was conducted in CENTRAL, MEDLINE Ovid, Embase.com, PubMed, LILACS (Latin American and Caribbean Health Sciences Literature Database), ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) and included randomized controlled trials that compared various types of aqueous shunts with standard surgery or to each other in eyes with glaucoma. The search resulted in 27 relevant trials, which included a total of 2,099 participants. Four trials compared an aqueous shunt (Ahmed or Baerveldt) with trabeculectomy, 2 trials that compared the Ahmed implant with the Baerveldt implant, 1 trial compared the Ahmed implant with the Molteno implant, 2 trials compared the double-plate Molteno implant with the Schocket shunt, and the remaining 18 trials evaluated modifications to aqueous shunts. The authors concluded that information was insufficient to conclude whether there are differences between aqueous shunts and trabeculectomy for glaucoma treatment. While the Baerveldt implant may lower IOP more than the Ahmed implant, the evidence was of moderate-certainty and it is unclear whether the difference in IOP reduction is clinically significant. Overall, methodology and data quality among existing randomized controlled trials was heterogeneous across studies, and there are no well-justified or widely accepted generalizations about the superiority of one surgical procedure or device over another.

Budenz et al. (2011) evaluated the relative efficacy and complications of the Ahmed glaucoma valve (AGV) (New World Medical, Rancho Cucamonga, CA) and the Baerveldt glaucoma implant (BGI) (Abbott Medical Optics, Abbott Park, IL) in refractory glaucoma in a multicenter, RCT. The study included 276 patients (143=AGV group and 133=BGI). Preoperative IOP was 31.2±11.2 mmHg in the AGV group and 31.8±12.5 mmHg in the BGI group. At 1 year, mean±SD IOP was 15.4±5.5 mmHg in the AGV group and 13.2±6.8 mmHg in the BGI group. The mean±SD number of glaucoma medications was 1.8±1.3 in the AGV group and 1.5±1.4 in the BGI group. The cumulative probability of failure in the AGV and BGI groups at 1 year were 16.4% and 14%, respectively. More patients experienced early postoperative complications in the BGI group (58%) compared to 43% in the AGV group. Serious postoperative complications also were more frequent in the BGI group than in the AGV group, at 34% versus 20%, respectively. The investigators concluded that although the average IOP after 1 year was slightly higher in patients who received an AGV, there were fewer early and serious postoperative complications associated with the use of the AGV than the BGI.

~~A Cochrane review compared various aqueous shunts for IOP control and safety (Minkler, 2006). Only RCTs and quasi-RCTs were included. This included 15 trials with a total of 1153 participants with mixed diagnoses. Five studies reported details sufficient to verify the method of randomization but only 2 had adequate allocation concealment. Data collection and follow-up times were variable. Meta-analysis of 2 trials comparing Ahmed implant with trabeculectomy found trabeculectomy resulted in lower mean IOPs 11 to 13 months later. One study concluded there were outcome advantages with a double versus a single-plate Molteno implant and one trial comparing the 350 mm² and 500 mm². Baerveldt shunts found no clinically significant advantage of the larger device, but neither of these trials included all patients randomized. One study comparing endocyclophotocoagulation (ECP) with Ahmed implant in complicated glaucomas found no evidence of better IOP control between the 2 treatments. The authors concluded that there are relatively few randomized trials that have been published on aqueous shunts, therefore methodology and data quality among them is poor. To date there is no evidence of superiority of one shunt over another. This meta-analysis was a review of comparative studies and did not evaluate whether aqueous shunts could lower IOP.~~

Gedde et al. (2009) evaluated the use of the Baerveldt glaucoma implant or trabeculectomy with mitomycin C in a multicenter RCT (known as the Tube versus Trabeculectomy (TVT) Study). A total of 212 eyes of 212 patients with uncontrolled glaucoma were enrolled (tube group =107, and 105 in the trabeculectomy group). At 3 years, IOP was 13.0 mm Hg in the tube group and 13.3 mm Hg in the trabeculectomy group. The number of glaucoma medications in the tube group versus trabeculectomy was 1.3 and 1.0, respectively. The cumulative probability of failure during the first 3 years of follow-up was 15.1% in the tube group and 30.7% in the trabeculectomy group. Postoperative complications developed in 39% and 60% in the tube and trabeculectomy groups, respectively. The investigators concluded that while tube shunt surgery had a higher success rate compared to trabeculectomy during the first 3 years of follow-up, both procedures were nearly equal with regard to IOP reduction and use of supplemental medication therapy at 3 years. While the incidence of postoperative complications was higher following trabeculectomy with MMC relative to tube shunt surgery, most complications were transient and self-limited.

iStent® and iStent inject®

An ECRI review, *iStent Inject Trabecular Microbypass System for Treating Open-angle Glaucoma during Cataract Surgery (2019)*, evaluated 7 studies (5 full text and 2 abstracts) with a total of 1,112 eyes. Those included 1 multi-center RCT, 1 single-center RCT, and 5 non-randomized comparison studies. Evidence from those studies showed that *iStent inject* implantation during cataract surgery reduced IOP (>20%) and use of glaucoma medication for patients with mild-to-moderate primary open-angle glaucoma through two years of follow-up. Serious adverse events did not differ statistically between *iStent inject* plus cataract surgery or cataract surgery alone. Ongoing postmarket trials may provide additional safety and efficacy evidence (www.clinicaltrials.gov).

Samuelson et al. (2019) evaluated the safety and effectiveness of the *iStent inject®* Trabecular Micro-Bypass System (Glaukos Corporation, San Clemente, CA, USA) in combination with cataract surgery in subjects with mild to moderate POAG through a prospective, single-masked, concurrently controlled, multicenter RCT (NCT00323284). After uncomplicated cataract surgery, eyes were randomized 3:1 intraoperatively to ab interno implantation (single or multiple) of *iStent inject®* (Model G2-M-IS; treatment group, n=386) or no stent implantation (control group, n=118). Subjects were followed for 2 years post-implant. At 24 months, 75.8% of treatment eyes versus 61.9% of control eyes experienced $\geq 20\%$ reduction from baseline in unmedicated diurnal IOP (DIOP), and mean reduction in unmedicated DIOP from baseline was greater in treatment eyes (7.0 \pm 4.0 mmHg) than in control eyes (5.4 \pm 3.7 mmHg). Of the subjects who were responders (e.g., 24-month unmedicated mean DIOP reduced by $\geq 20\%$ from baseline in the absence of IOP-affecting surgery during the study), 84% of treatment eyes and 67% of control group eyes were not receiving ocular hypotensive medication at 23 months. In addition, 63% of treatment eyes and 50% of control eyes had medication-free DIOP ≤ 18 mmHg at 2 years. The overall safety profiles were highly favorable and similar in both groups throughout the follow-up period. The researchers concluded that clinically and statistically greater reductions in IOP without medication were achieved after *iStent inject®* implantation with cataract surgery versus cataract surgery alone. Additionally, the pivotal study's findings support the consideration of this second generation trabecular micro-bypass stent system as a safe, durable, and less compliance-dependent treatment modality for additional unmedicated IOP reduction in POAG eyes undergoing cataract surgery.

Clement et al. (2019) conducted a retrospective multi-center study of iStent *inject*[®] trabecular micro-bypass implantation with cataract. Eyes had mild to advanced glaucoma (predominantly primary open-angle, appositional angle-closure, or pseudoexfoliative glaucoma) or ocular hypertension (OHT) and cataract requiring surgery. Patients have been followed for 12 months, and follow-up is ongoing. Of the 290 total eyes that underwent surgery, 165 eyes had 12-month outcomes at the time of data collection and are included in this report. Mean IOP at one year reduced by 23.2%, with 95.8% of eyes achieving IOP of ≤ 18 mmHg vs 60.6% preoperatively. Mean number of medications decreased by 71.5%, with 76.4% of eyes on zero medications at 12 months vs 17.6% preoperatively. 98.2% of eyes maintained or reduced medications vs their preoperative regimen. Safety profile was excellent, with only limited and transient postoperative AEs. The authors concluded that the iStent *inject*[®] combined with cataract surgery significantly and safely reduced medications and IOP in eyes with various types and severities of glaucoma. Future reports may assess longer-term outcomes and larger sample sizes, as well as include subgroup analyses of eyes with different glaucoma types or stratification by history of prior glaucoma surgery.

In a single center, longitudinal, retrospective, comparative study, Guedes et al. performed a side-by-side comparison of the iStent[®] and iStent *inject*[®] trabecular micro-bypass stent systems. The study evaluated performance and safety in consecutive eyes following implantation of either device with concomitant cataract surgery. Performance outcomes included IOP reduction; glaucoma medication reduction; proportions of eyes achieving an IOP of < 18 , < 16 , < 14 , or < 12 mmHg; and proportions of eyes on 0, 1, 2, or ≥ 3 medications. Safety outcomes included AEs, secondary surgeries, and best corrected visual acuity (BCVA). The follow up period was 6 months. A total of 73 eyes with OAG and cataract were included in the study; of these, 38 eyes were implanted with the iStent[®] device and 35 were implanted with the iStent *inject*[®] device. At 6 months post-surgery, mean IOP had fallen in both groups; however the reduction was significantly greater in the iStent *inject*[®] eyes versus the iStent[®] eyes (26.6 vs. 15.8%). All who received the iStent *inject*[®] device achieved an IOP of < 18 mmHg at 6 months compared to 86.8% of the iStent[®] recipients, and $> 70\%$ of eyes in both groups became medication-free by 6 months post implantation. AEs occurred in 2 iStent[®] eyes which resulted in no sequelae; and 2 iStent[®] eyes underwent non-penetrating deep sclerectomy during follow-up. No complications or secondary surgeries occurred in the iStent *inject*[®] group. All eyes in both groups maintained or showed improved BCVA versus baseline. The authors concluded that significant and safe IOP and medication reductions were observed after iStent[®] or iStent *inject*[®] implantation with concomitant cataract surgery. However, compared with the iStent[®], trends toward greater effectiveness and fewer AEs were observed with the iStent *inject*[®]. This advantage may be attributed to device design: each individual iStent *inject*[®] stent has four lateral outflow lumens and uses two stents versus one in the trabecular meshwork which allows for greater IOP-reducing potential. Several limitations to the study include a modest number of eyes in each group, relatively short follow up period and lack of a control group. A prospective study with a larger population and longer follow-up is necessary to validate these findings (2019).

Popovic et al. (2018) conducted a systematic review and meta-analysis on the efficacy and adverse event profile of the iStent in the treatment of open-angle glaucoma. Using predetermined search terms a systematic review was performed using Ovid MEDLINE and Ovid EMBASE. A total of 28 studies were included in the meta-analysis. The main analysis was performed based on whether patients had 1, 2 or 3 iStents implanted and whether they did or did not receive combined phacoemulsification and iStent. The mean age was 71.4 ± 5.4 years, and 44.9% of patients were male. There was a significantly greater IOP reduction after the use of two first-generation stents compared to one, irrespective of phacoemulsification status ($p < 0.001$). Additionally, there was a significantly greater IOP reduction following iStent alone relative to phaco-iStent for the first-generation iStent ($p < 0.001$) and the iStent *inject* ($p < 0.001$). For the first generation stent, combined phaco-iStent provided a greater level of IOP reduction ($p < 0.001$) and reduction in the number of medication classes relative to phacoemulsification alone ($p < 0.001$). In total, 22.5% of eyes that received iStent implantation sustained some type of adverse event. The most common adverse events were intraocular pressure elevation, stent blockage or obstruction, stent malposition and hyphema. The authors concluded that there may be differences in treatment response for the iStent due to varying parameters, including the number of iStents and phaco-iStent compared to either iStent alone or phacoemulsification alone. In their analysis, two stents delivered a greater response in terms of IOP reduction relative to one and iStent alone had a significantly greater IOP reduction compared to phaco-iStent. Combined phaco-iStent was statistically superior relative to phacoemulsification alone in the reduction of IOP and medication classes pre- to post-operatively.

The aim of a prospective, non-randomized, consecutive cohort study by Hengerer et al. (2018) was to assess 36-month outcomes after cataract surgery and implantation of two second-generation trabecular micro-bypass stents (iStent *inject*[®]). Participants (81 eyes of 55 consecutive patients) presented with cataract plus varying types of glaucoma (POAG/n=60, pseudoexfoliative (PEX)/n=5), appositional narrow-angle/n=4, pigmentary/n=1) or neovascular (secondary)/n=1). Following cataract surgery, all eyes underwent ab interno iStent *inject*[®] implantation. Effectiveness endpoints included IOP, number of medications, and proportion of eyes with $\geq 20\%$ IOP reduction, IOP ≤ 18 mmHg, and IOP ≤ 15 mmHg. Safety measures included corrected distance visual acuity, AEs, and secondary surgeries. Outcomes were evaluated for the overall cohort, and for the POAG and PEX subgroups. In the overall cohort, substantial reductions in both IOP and medication use were observed for 36 months postoperatively. With regards to the POAG and PEX subgroups, the outcomes in PEX eyes were similarly favorable to those in POAG eyes, thereby corroborating prior studies showing iStent[®] technology to be a highly suitable and effective treatment option in patients with this condition. The authors concluded that the study demonstrated substantial reductions in both IOP and medication burden along with favorable safety through 36 months following the implantation of iStent *inject*[®]. While there were several limitations in this unmasked, single arm study, these outcomes were interpreted as significant and future studies are encouraged.

A retrospective, intraindividual eye study was conducted on 27 patients (54 eyes) with cataract and OAG to compare the safety and efficacy of combined micro-incision cataract surgery (MICS) in one eye with the ab interno trabeculectomy (Trabectome[®]) versus MIGS with two iStent *inject*[®] devices in the contralateral eye. Patients were followed for 6 weeks, 3, 6, and 12 months post-implantation. The authors concluded that the trabeculectomy and iStent *inject*[®] were both effective in lowering IOP with a favorable and comparable safety profile, citing no significant difference between the 2 approaches. Further research would be necessary to determine long-term outcomes and evaluate significant differences (Gonnermann et al., 2017).

In a prospective, uncontrolled, non randomized interventional case series, Arriola-Villalobos and colleagues evaluated the long-term efficacy and safety of the iStent *inject*[®] device combined with phacoemulsification in 20 patients with coexistent cataract and OAG or OHT. Patients underwent cataract surgery along with the implant of two iStent *inject*[®] devices. Outcome measures were IOP, topical hypotensive medications required, and BCVA. Mean follow-up was 47.4 \pm 18.46 months. Mean end-follow-up IOP demonstrated a decrease of 36.92% from baseline washout IOP. 45% of patients were medication-free by the end of follow-up, and mean BCVA improved significantly. No complications of surgery were observed. The authors concluded that the iStent *inject*[®] device combined with cataract surgery significantly reduces both IOP and medication use in the long term in patients with coexistent OAG or OHT and cataract. Confirmation of these findings via RCTs with large patient cohorts is required (2016).

Arriola-Villalobos et al. (2012) also evaluated the long-term efficacy and safety of combined cataract surgery and Glaukos iStent[®] implantation for coexistent OAG and cataract. This prospective case series included 19 patients. Mean follow-up was 53.68 months. Mean IOP was reduced from 19.42 mm Hg at the end of follow up to 16.26 mm, representing a 16.33% decrease. The mean number of pressure-lowering medications used by the patients fell from 1.32 to 0.84. In 42% of patients, no antiglaucoma medications were used at the end of follow-up. Mean BCVA significantly improved from 0.29 to 0.62. The authors concluded that combined cataract surgery and iStent[®] implantation seems to be an effective and safe procedure to treat coexistent OAG and cataract.

In a prospective case series, Belovay et al. (2012) evaluated the efficacy and safety of multiple trabecular micro-bypass stents in 47 cataract patients (53 eyes) to treat POAG. Either 2 (n=26) or 3 (n=23) stents were implanted along with concurrent cataract surgery. Efficacy measures were IOP and topical ocular hypotensive medication use. Patients were followed for 1 year. The overall mean 1-year postoperative IOP was 14.3 mm Hg, which was significantly lower than preoperative IOP overall and in each group. The target IOP was achieved in a significantly higher proportion of eyes at 1 year versus preoperatively (77% versus 43%). Overall, 83% of eyes had a decrease in topical ocular hypotensive medication at 1 year from preoperatively, with a 74% decrease in the mean number of medications (from 2.7 to 0.7) at 1 year. The 3-stent group was on significantly fewer medications than the 2-stent group at 1 year. The authors concluded that the use of multiple micro-bypass stents with concurrent cataract surgery led to a mean postoperative IOP of less than 15 mm Hg and allowed patients to achieve target pressure control with significantly fewer medications through 1 year.

Samuelson et al. (2011) assessed the safety and efficacy of the iStent® trabecular micro-bypass stent in combination with cataract surgery in a prospective, open-label, multicenter randomized controlled trial (RCT). A total of 240 eyes with mild to moderate OAG with IOP \leq 24 mmHg controlled on 1 to 3 medications were randomized to undergo cataract surgery with iStent® implantation (treatment group) or cataract surgery only (control). Fifty additional patients were enrolled to undergo cataract surgery with iStent® implantation under protocol expansion. The primary efficacy measure was unmedicated IOP \leq 21 mmHg at 1 year. The study met the primary outcome, with 72% of treatment eyes versus 50% of control eyes achieving the criterion. At 1 year, IOP in both treatment groups was significantly lower from baseline values. Sixty-six percent of treatment eyes versus 48% of control eyes achieved 20% or more IOP reduction without medication. The overall incidence of adverse events (AEs) was similar between groups with no unanticipated adverse device effects. The investigators concluded that pressure reduction on fewer medications was clinically and statistically better 1 year after iStent® plus cataract surgery versus cataract surgery alone, with an overall safety profile similar to that of cataract surgery alone.

~~In a prospective case series, Belovay et al. (2012) evaluated the efficacy and safety of multiple trabecular micro-bypass stents in 47 cataract patients (53 eyes) to treat POAG. Either 2 (n=26) or 3 (n=23) stents were implanted along with concurrent cataract surgery. Efficacy measures were IOP and topical ocular hypotensive medication use. Patients were followed for 1 year. The overall mean 1-year postoperative IOP was 14.3 mm Hg, which was significantly lower than preoperative IOP overall and in each group. The target IOP was achieved in a significantly higher proportion of eyes at 1 year versus preoperatively (77% versus 43%). Overall, 83% of eyes had a decrease in topical ocular hypotensive medication at 1 year from preoperatively, with a 74% decrease in the mean number of medications (from 2.7 to 0.7) at 1 year. The 3-stent group was on significantly fewer medications than the 2-stent group at 1 year. The authors concluded that the use of multiple micro-bypass stents with concurrent cataract surgery led to a mean postoperative IOP of less than 15 mm Hg and allowed patients to achieve target pressure control with significantly fewer medications through 1 year.~~

An interventional procedure guidance published by NICE concluded that after systematic review and meta-analysis of multiple clinical studies on almost 3100 participants, current evidence demonstrates that trabecular stent bypass microsurgery for OAG is safe and effective (2017).

~~After examination of 1 systematic review, 6 controlled trials, and 6 case series reporting on more than 3,000 patients, a 2017 ECRI report concluded that the iStent® system implanted during cataract surgery reduces both IOP and postoperative glaucoma medication use. Results are reported as sustained for 1-4 years and AEs have been reported in no more than 12% of study participants. Additional long-term comparative data and more data on vision loss are needed.~~

~~A 2019 ECRI report on the iStent *inject*® stated that evidence from controlled trials and case series shows that this second-generation device implanted during cataract surgery lowered IOP $>$ 20% for most patients with glaucoma and reduced glaucoma medication use in some patients. One large multicenter RCT reported sustained effectiveness at 2-year follow-up, and serious AEs did not differ significantly between groups given iStent® plus cataract surgery or cataract surgery alone. One small retrospective study at high risk of bias reported that iStent *inject*® was as effective as trabeculectomy. Postmarket studies will provide more longer-term data.~~

~~A Hayes report concluded that the iStent® device, when used in combination with cataract surgery, appears to be an efficacious and safe treatment for patients with OAG who do not achieve adequate control of IOP on ocular hypotensive medications, although its effectiveness compared with other minimally invasive surgical procedures is not established (2018).~~

~~Regarding the iStent *inject*® device, a 2019 Hayes report finds there is sufficient published evidence to evaluate this technology, citing that study abstracts present conflicting findings regarding its use in the treatment of POAG in combination with cataract surgery. Pending a full-text review to confirm abstract content, conclusions about the safety and efficacy cannot be made.~~

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Several registered ongoing clinical trials relevant to the iStent® and iStent *inject*® are in progress, including 2 large trials (n=860) assessing 3 to 5-year outcomes with the device. For more information, go to www.clinicaltrials.gov. (Accessed April 30, 2019) ~~January 27, 2020~~)

CyPass®

~~In August 2018, the manufacturer of the CyPass® Micro Stent voluntarily withdrew the device from the global market and surgeons were advised to immediately cease further use. In October 2018, the FDA classified this as a Class I recall, representing "a situation where there is a reasonable chance that the product will cause serious health problems". No new information on this issue has been published.~~

~~A 2017 Hayes search of published peer reviewed literature on the use of the CyPass® Micro Stent (Alcon, Fort Worth, TX) identified 5 abstracts (1 RCT (the COMPASS trial), 1 prospective uncontrolled study, and 3 uncontrolled postmarket registry studies) with a combined total of 825 participants. It was concluded that there is insufficient published evidence to assess the safety and/or impact on health outcomes or patient management of the CyPass® Micro Stent for the treatment of glaucoma in adults.~~

~~In a multicenter interventional RCT, Vold et al. evaluated 2-year safety and efficacy of supraciliary microstenting (CyPass®) for treating mild to moderate POAG in patients undergoing cataract surgery. Subjects had POAG with mean diurnal unmedicated IOP of 21–33 mmHg and were undergoing phacoemulsification cataract surgery. Of 505 subjects, 131 were randomized to the control group and 374 to the microstent group. There was early and sustained IOP reduction, with 60% of controls versus 77% of microstent subjects achieving ≥20% unmedicated IOP lowering versus baseline at 24 months. Mean 24-month medication use was 67% lower in microstent subjects; 59% of control versus 85% of microstent subjects were medication free. No vision-threatening microstent-related AEs occurred. Visual acuity was high in both groups through 24 months; >98% of all subjects achieved 20/40 best-corrected visual acuity or better. The authors concluded that microinterventional surgical treatment for mild to moderate POAG was safe, and the technology's use resulted in a sustained 2-year reduction in IOP and glaucoma medication use (2016).~~

~~A multicenter, single-arm interventional study known as the DUETTE study was conducted by García-Feijoo et al. to evaluate the safety and efficacy of a supraciliary micro-stent (CyPass®) for surgical treatment of glaucoma in patients refractory to topical medications. Patients with OAG (Shaffer Grade 3 and 4) and uncontrolled medicated IOP >21 mm Hg at baseline and candidates for conventional glaucoma surgery were enrolled. CyPass® Micro Stent implantation was completed in all patients using a standard clear corneal approach. AEs, postoperative IOP changes, and need for IOP lowering medications during the first 12 postoperative months (12M) were monitored. Sixty-five eyes were enrolled, and 55 were available at 12M. There were no serious intraoperative events or major AEs. At 12M, mean IOP was reduced by 34.7% and mean medication usage also decreased. In eyes originally indicated for conventional glaucoma surgery, no secondary surgery was performed in 83% (53/64). The authors concluded that supraciliary stenting with the CyPass® effectively lowers IOP as a surgical treatment for glaucoma, precluding the need for more invasive glaucoma surgery in >80% of patients at 1 year, thereby reducing postoperative glaucoma surgical complications (2015).~~

~~There are multiple clinical trials at various stages relating to the CyPass® Micro Stent implantation system. For more information, go to www.clinicaltrials.gov. (Accessed April 30, 2019)~~

XEN® Glaucoma Treatment System

Buffault et al. (2019) conducted a systematic review to analyze the change in intraocular pressure (IOP) and glaucoma medications using the XEN® Gel Stent as a solo procedure or in association with phacoemulsification in patients with chronic open angle glaucoma (OAG). Using predetermined search terms a systematic review was performed using PubMed. A total of 8 case series or cohort studies (6 prospective and 2 retrospective) that were published between 2016 and 2018 were included. There were no randomized controlled trials included. Data was analyzed for 777 patients or 958 eyes. The various studies showed a mean IOP at 12 months between 13 and 16 mmHg, which represented an IOP reduction between 25 and 56% (mean: 42%). This decrease was associated with a reduction in glaucoma medications in all studies. The decrease in IOP was significantly greater in XEN® implantation as a stand-alone procedure (44%) than in combined surgery (32%) (p<0.05). Transient hypotony (< 1 month) (3%), choroidal detachment or choroidal folds (1.5%), hyphema (1.9%), bleb leak (1.1%) and shallow anterior

chamber (1.1%) were the most frequent complications. As for severe complications, four cases of malignant glaucoma (0.4%) and one case of retinal detachment have been reported. In the follow-up period, needling was been required in 32% of cases, and a total of 55 eyes (5.7%) required repeat filtering surgery or cyclodestructive procedure. The authors concluded that the XEN® Gel Stent appears effective for reducing IOP and the number of medications in OAG patients within 1 year postoperatively, and with an acceptable safety profile. However, its use required vigilant postoperative follow-up and frequent postoperative interventions. While these results appear promising, randomized controlled trials are needed to confirm the XEN® Gel Stent's safety and efficacy.

In 2018, De Gregorio and colleagues provided a review of the currently published clinical data to assess the potential role of XEN® gel stent, the only filtering MIGS device that allows the subconjunctival filtration, in the management of glaucoma. Citing the findings of Galal (2017), Schlenker (2017), Grover (2017b), Pérez-Torregrosa (2016) and others, the authors concluded that XEN gel stent is a safe and effective MIGS for controlling IOP in early, moderate, advanced, or refractory glaucoma patients, offering ophthalmologists a new tool to reach the target IOP as a final step in refractory glaucoma, as well as an early surgical treatment for patients intolerant to medical therapy.

Schlenker et al. (2017) conducted an investigator-initiated, international, multicenter, retrospective cohort study of consecutive patients who underwent either standalone microstent insertion with mitomycin C (MMC) or trabeculectomy with MMC. A total of 354 eyes of 293 patients (185 microstent and 169 trabeculectomy) participated in the study that extended between January 1, 2011, and July 31, 2015. Eligibility criteria included patients with multiple types of glaucoma and above-target IOP on maximum medical therapy. Participants were between the ages of 30-90 years with no history of previous incisional surgery for their eye disease. The authors concluded that there was no detectable difference in risk of failure and safety between standalone microstent with MMC and trabeculectomy with MMC. However, further research was believed to be warranted to further investigate these procedures.

Grover et al. evaluated the performance and safety of the XEN® 45 Gel Stent (Allergan, Irvine, CA) for the treatment of refractory glaucoma in a prospective, single-arm, open-label, multicenter clinical study sponsored by the manufacturer. Selection criteria included individuals with refractory glaucoma, defined as prior failure of a filtering or cilioablative procedure and/or uncontrolled IOP on maximally tolerated medical therapy. A total of 65 eyes in patients 45 years of age and older were implanted. No intraoperative complications or unexpected postoperative AEs were reported. During the 1 year of follow up, most AEs were considered mild/moderate and resolved with no sequelae. The authors concluded that the XEN® 45 Gel Stent safely reduced both IOP and medication use and offer a less invasive surgical option for this subset of patients. Potential study limitations include the absence of comparator and open-label study design, which could have impacted the outcomes (2017b).

De Gregorio et al. (2017) conducted a nonrandomized prospective clinical study to assess safety and efficacy of the XEN® 45 Gel Stent when combined with microincisional cataract surgery (MICS). Forty-one eyes of 33 patients with OAG underwent the combination surgery, and there were no major intra- or postoperative complications noted. Complete success was achieved in 80.4% and a qualified success reported in 97.5% after 12 months of follow-up. The authors concluded that the XEN® 45 gel implant is statistically effective in reducing IOP and medication use with minimal complications in glaucoma patients.

~~In 2018, De Gregorio and colleagues provided a review of the currently published clinical data to assess the potential role of XEN® gel stent, the only filtering MIGS device that allows the subconjunctival filtration, in the management of glaucoma. Citing the findings of Galal (2017), Schlenker (2017), Grover (2017), Pérez-Torregrosa (2016) and others, the authors concluded that XEN gel stent is a safe and effective MIGS for controlling IOP in early, moderate, advanced, or refractory glaucoma patients, offering ophthalmologists a new tool to reach the target IOP as a final step in refractory glaucoma, as well as an early surgical treatment for patients intolerant to medical therapy.~~

A review of published literature by Kerr et al. (2017) concluded that a growing body of evidence suggests that primary MIGS (including but not limited to the XEN® Glaucoma Treatment System) may be a viable initial treatment option to non-surgical intervention. However, further investigator-initiated randomized trials of sufficient size and duration are necessary to better evaluate efficacy.

Vinod and Gedde (2017) reviewed published literature from 2015 through 2016, commenting that findings are notable regarding new and emerging glaucoma procedures. While the data on newer techniques (including but not limited to the XEN® Gel Stent) are promising, the opinion of the authors was that further studies by means of RCTs with extended follow-up periods continue to be necessary to better evaluate long-term efficacy.

In a prospective interventional study, 13 eyes with POAG underwent XEN® implantation with subconjunctival mitomycin-C. Of those eyes, 3 were pseudophakic and 10 underwent simultaneous phacoemulsification and XEN. Patients had uncontrolled IOP, intolerance to therapy, or maximal therapy but undergoing cataract extraction. One year of follow-up documentation of IOP, number of medications, visual acuity, and complications. Complete success was defined as IOP reduction $\geq 20\%$ from preoperative baseline at 1 year without any glaucoma medications, while partial success as IOP reduction of $\geq 20\%$ with medications. Results reflected a drop in IOP from 16 ± 4 mmHg pre-op to 9 ± 5 , 11 ± 6 , 12 ± 5 , 12 ± 4 , and 12 ± 3 mmHg at 1 week, 1, 3, 6, and 12 months, respectively. At 1 year, BCVA improved from 0.33 ± 0.34 to 0.13 ± 0.11 ; and mean number of medications decreased from 1.9 ± 1 preoperatively to 0.3 ± 0.49 . 42% of eyes achieved complete success and 66% qualified success. Complications included choroidal detachment in 2 eyes, implant extrusion in 1 eye, and 2 eyes underwent trabeculectomy. The authors concluded that the XEN implant is an effective surgical treatment for POAG, with significant reduction in IOP and glaucoma medications at 1 year, and state that longer follow-up is needed (Galal et al., 2017).

A 2017 ECRI review of peer-reviewed literature assessing the XEN® gel stent implantation system cites the studies of Grover (2017b) and De Gregorio (2017above) as well as 2 other small single center case series (total n=134) published between January 1, 2012, and June 1, 2017. While most patients experienced a reduction in both IOP and glaucoma medication use post-implantation, the reviewers found the evidence in the 4 small case series to be inconclusive for both safety and efficacy. Larger, longer-term, controlled studies comparing XEN® with trabeculectomy are needed (2 of which are currently in progress).

To assess the safety and efficacy of phacoemulsification combined with XEN®45 implant surgery, a prospective study was conducted on 30 eyes of patients with cataract and OAG. Surgery was performed using 2 temporal incisions within 15 minutes of administering subconjunctival mitomycin C. Outcomes measured were BCVA, IOP before and 1 day, 1 month, 3 months, 6 months, 9 months, and 12 months after surgery, number of anti-glaucoma medications, and AEs. BCVA before and 12 months post-surgery was 0.37 ± 0.2 and 0.72 ± 0.15 , respectively. The pre-operative IOP was 21.2 ± 3.4 mmHg, with 3.07 drugs, decreasing by 61.65% on the first day, 37.26% at 1 month, 35.05% at 3 months, 31% at 6 months, 30.6% at 9 months, and 29.34% at 12 months. Anti-glaucoma medication usage decreased by 94.57%. Complications occurred in 3 eyes: 2 of them were excluded because the implantation could not be completed, and 1 developed an encapsulated bleb at 5 months post-surgery. The authors concluded that phacoemulsification combined with XEN45 implant surgery can effectively reduce IOP and the number of drugs in mild-moderate OAG with few complications (Pérez-Torregrosa, et al., 2016).

There are multiple clinical trials in progress relating to the XEN® Glaucoma Treatment System. For more information, go to www.clinicaltrials.gov. (Accessed ~~April 30, 2019~~ **January 27, 2020**)

HYDRUS® Microstent

An ECRI review, Hydrus Microstent for Treating Open-angle Glaucoma during Cataract Surgery (2019), evaluated 2 RCTs and 2 cohort studies. Evidence from those studies showed that Hydrus implantation is safe and effective in normalizing IOP in patients with OAG however, evidence gaps remain. The studies' follow-up periods are limited to two years, which is insufficient to assess changes in visual acuity and vision-related quality of life in most patients with early or mild-to-severe glaucoma. Randomized control trials with 5- to 10- years of follow-up are needed to assess the device's longevity and potential adverse events are needed.

Samuelson et al. (2019) conducted a prospective, multicenter, single-masked RCT to compare cataract surgery with implantation of a Schlemm canal (Hydrus®) microstent versus cataract surgery alone for the reduction of IOP and medication use in individuals with POAG, visually significant cataract, and washed-out modified diurnal IOP (MDIOP). Known as the HORIZON study, participants (556 eyes) were randomized 2:1 following uncomplicated phacoemulsification to receive either the Hydrus® Microstent (HMS/369 eyes) or no microstent (NMS/187 eyes). Follow up comprehensive eye exams occurred 1 day, 1 week, and 1, 3, 6, 12, 18, and 24 months postoperatively.

Medication washout and MDIOP measurement were repeated at 12 and 24 months. Primary and secondary outcome measures were the proportion of subjects demonstrating a 20% or greater reduction in unmedicated MDIOP and change in mean MDIOP from baseline at 24 months, respectively. Hypotensive medication use was tracked throughout the course of follow-up. Safety measures included the frequency of surgical complications and AEs. Randomized subjects completing the full 24 month follow up was 95%. Results showed that at 2 years, unmedicated MDIOP was reduced by $\geq 20\%$ in 77.3% of HMS eyes versus 57.8% of NMS eyes. Seventy eight percent of HMS eyes were medication free compared with 48% in the NMS group at 2 years. Among medication-free eyes, the mean IOP in the HMS group remained within the range 15.5 to 17.0 mmHg and was consistently lower than in the NMS group over the course of follow-up. There were no serious ocular AEs related to the microstent, and no significant differences in safety parameters between the 2 groups. The authors concluded that use of the Hydrus[®] Microstent combined with phacoemulsification demonstrated superior reduction in MDIOP and medication use compared to phacoemulsification alone in subjects with mild-to-moderate POAG.

In their 2019 review of new minimally invasive technologies for treatment of glaucoma, Dick and colleagues cited Pfeiffer's 2015 study, emphasizing that the percentage of patients with a Hydrus[®] Microstent plus cataract surgery who no longer needed additional IOP-lowering medications at month 24 was significantly higher (72.9%) than those who underwent cataract surgery alone (37.8%).

Pfeiffer et al. (2015) conducted a prospective, multicenter, randomized, single-masked, controlled clinical trial known as HYDRUS II to evaluate the safety and efficacy of the Hydrus[®] Microstent with concurrent cataract surgery (CS) for IOP reduction in OAG. One hundred eyes from 100 patients 21-80 years of age with OAG and cataract with IOP of 24 mmHg or less with 4 or fewer hypotensive medications and a washed-out diurnal IOP (DIOP) of 21 to 36 mmHg were included. On the day of surgery, participants were randomized 1:1 to undergo CS with the microstent or CS alone. Postoperative follow-up was at 1 day, 1 week, and 1, 3, 6, 12, 18, and 24 months. Washout of hypotensive medications was repeated at 12 and 24 months. Main outcome measures were a 20% or more decrease in washed out DIOP at 12 and 24 months of follow-up compared with baseline. MDIOP at 12 and 24 months, the proportion of subjects requiring medications at follow-up, and the mean number of medications were also analyzed. Safety measures included change in visual acuity, slit-lamp observations, and AEs. Compared to the CS alone group, the proportion of patients with a 20% reduction in washed out MDIOP was significantly higher in the Hydrus plus CS group at 24 months (80% vs. 46%). Washed out MDIOP in the Hydrus[®] plus CS group was significantly lower at 24 months (16.9 \pm 3.3 mmHg vs. 19.2 \pm 4.7 mmHg), and the proportion of patients using no hypotensive medications was significantly higher at 24 months in the Hydrus[®] plus CS group (73% vs. 38%). There were no differences in follow-up visual acuity between groups. Except for one notable device-related complication, AE frequency was similar in the 2 groups. The authors concluded that implantation of the Hydrus[®] Microstent is both safe and effective in patients undergoing CS, providing a significant reduction in IOP and medication use compared with CS alone for 2 years post-surgery.

Al-Mughairy and colleagues (2017) conducted an observational cohort study to evaluate learning effects with respect to outcomes when the Hydrus[®] Microstent is inserted during cataract surgery in glaucoma patients. Twenty five patients were included with a minimum follow-up of 12 months. A learning curve analysis was performed by assessing hypotensive effect, AEs, and surgical procedure duration, with respect to consecutive case number. Success was defined with respect to various IOP targets (21, 18, 15 mm Hg) and reduction in required antiglaucoma medications. Complete success was defined as achieving target IOP without antiglaucoma therapy. There were no significant AEs or learning effects identified, although surgical time reduced with consecutive case number. The researchers found no significant learning curve effects for a trained surgeon with respect to the MIGS microstent insertion performed at the time of cataract surgery. Adjunctive MIGS surgery using the Hydrus[®] Microstent was successful in lowering IOP and reducing/abolishing the requirement for antiglaucoma medication in eyes with OAG, but less successful at achieving low IOP levels.

Fea et al. (2017a) conducted a prospective interventional case series comparing the reduction of IOP and glaucoma medications following selective laser trabeculoplasty (SLT) versus stand-alone placement of the Hydrus Microstent. Participants with uncontrolled POAG (n=56 eyes/56 patients) received either SLT (n = 25) or Hydrus implantation (n=31) at 2 centers. Patients were evaluated at baseline and 1 day, 7 days, 1, 3, 6 and 12 months post-surgery. Primary outcome measures were IOP and use of glaucoma medications. There were no significant differences at baseline between groups. After 12 months, the Hydrus[®] group had significant decreases in both IOP and medication

use compared with baseline. In the SLT group, while there was a significant decrease in IOP, there was a 3-fold greater reduction in medication use in the Hydrus group compared with SLT. At 12 months, 47% of patients versus 4% were medication-free in the Hydrus® and SLT groups, respectively. In the SLT group, members were complication-free. Three patients in the Hydrus group experienced a temporary reduction of visual acuity post-operatively, and 2 patients had post-operative IOP spikes that resolved within one week. The authors concluded that while both procedures are safe, the use of the Hydrus® implant led to a significant and further reduction in medication dependence at 12 months.

Fea and colleagues also conducted a multi-site retrospective case series, evaluating the safety and efficacy of the Hydrus® Microstent combined with cataract surgery in routine clinical practice. The study included 92 eyes and analyzed outcomes based on IOP, number of glaucoma medications, incidence of complications and baseline and at 2 years post procedure. The researchers concluded that combined phacoemulsification and implantation of the Hydrus® Microstent is an effective surgical treatment option in patients with OAG, including patients with previously failed incisional glaucoma surgeries. The combined surgery led to a significant reduction in IOP and a high medication-free rate 24 months postoperatively (2017b).

Gandolfi et al. (2016) conducted a retrospective, nonrandomized case series at a single institution comparing canaloplasty (CP) (24 patients/24 eyes) to the Hydrus® Microstent (HM) (21 patients/21 eyes) in individuals with primary or secondary OAG. At 2 years post-surgery, the eyes were labelled as "complete" success, "qualified" success, or "failure" if they needed no hypotensive medications, some hypotensive medications, or further glaucoma surgery to attain the target IOP, respectively. Researchers found that both CP and the HM implant allowed significant IOP reductions with comparable rate of clinical success and safety profile. Limitations to this study include small sample size and nonrandomized design.

MIGS

~~To analyze the change in IOP and glaucoma medications using different MIGS devices, as a solo procedure or in association with phacoemulsification, Lavia et al. (2017) conducted a systematic review and meta-analysis (registered on PROSPERO, CRD42016037280). The review included over 3069 studies (9 RCTs and 21 non-randomized case series) with follow up of at least one year on a total of 2928 eyes. The main outcomes were the effects of MIGS devices compared to medical therapy, cataract surgery, other glaucoma surgeries, and other MIGS on both glaucoma medication use and IOP 12 months post-surgery. Outcome measurements were the mean difference in the change of IOP and medication usage compared to baseline at 1 and 2 years, as well as all ocular AEs. Limited evidence was found based on both RCTs and non-RCTs that compared MIGS surgery with medical therapy or other MIGS. MIGS seemed effective in before-after series in lowering both IOP and glaucoma drug use and showed a good safety profile, with IOP spikes being the most frequent complication. No cases of infection or BCVA loss due to glaucoma were reported. The reviewers found that the evidence on the efficacy of MIGS compared to other therapies is still limited and is based on few RCTs of acceptable quality and a larger number of non-randomized studies and uncontrolled before/after case series. Although there is increasing interest on safer, standardized and minimally invasive surgeries, they suggest further comparative and randomized research.~~

~~Agrawal and Bradshaw conducted a systematic review of clinical and economic outcomes of MIGS in POAG. From an economic standpoint, 23 studies were analyzed. Using the Cochrane Risk of Bias tool, clinical outcomes and safety were assessed using RCTs comparing MIGS with trabeculectomy or other therapies, as well as observational studies and other non-RCTs. A total of 9 RCTs (7 iStents®, 1 Hydrus®, and 1 CyPass®), and 7 non-RCTs (3 iStent®, 3 CyPass®, and 1 Hydrus®) were analyzed. The devices described in this review were typically associated with higher postoperative IOP levels, resulting in increased hypotony rates or bleb needling in subconjunctival placed devices. There is limited available evidence on the cost-effectiveness of MIGS, therefore actual cost-savings information remains unclear. The authors concluded that larger randomized trials and 'real-world' observational studies are needed for all MIGS devices to better evaluate clinical and economic effectiveness (2018).~~

~~In a review of MIGS procedures and safety profiles of various devices (iStent, Hydrus® Microstent, CyPass® Microstent, and Xen® Gel Stent), Yook et al. stated that complications associated with MIGS, albeit infrequent and mostly transient, do occur despite a less-invasive approach than trabeculectomy and tube shunt surgery (2018).~~

Glaucoma Drainage Devices Not Approved by the U.S. Food and Drug Administration (FDA)

Eyepass

Wittmann et al. (2018) conducted a prospective case series evaluation of patients with open-angle glaucoma who underwent an implantation of the Y-shaped Eyepass glaucoma implant. The outcomes of interest were IOP, visual acuity, complications and the number of antiglaucomatous medications were during a period of 5 years. A total of 15 patients (16 eyes) primary open-angle glaucoma underwent implantation of the Y-shaped Eyepass glaucoma implant. Mean IOP was reduced from 26.4±8.1 mm Hg (SD) to 16.4±5.3 mm Hg (P=0.032) at the end of the follow-up. Mean number of antiglaucomatous medications dropped from 2.1±1.2 (SD) to 0.9±1.2 (SD). In 5 cases, no pressure-lowering medications were necessary 5 years after surgery. Mean best-corrected visual acuity did not change significantly (P>0.05). In all cases, filtering blebs were observed and sustained using antimetabolites. The most common complication was temporary ocular hypotony. Two patients required a revision surgery due to implant malposition. The authors concluded that the Eyepass glaucoma implant seems to be a safe and effective treatment option for patients with primary open-angle glaucoma. While these results are promising, FDA approval and randomized controlled trials with comparisons to other glaucoma implants are still needed.

Dietlein et al. (2008) conducted a small study to evaluate the safety and pressure-reducing efficacy of the Y-shaped Eyepass glaucoma implant in 12 glaucoma and cataract patients, finding that combined cataract surgery with Eyepass shunt implantation was safe and appeared to be beneficial in glaucomatous eyes with cataract not requiring a low target IOP. Perforation of the trabecular meshwork during Eyepass implantation occurred in 2 eyes requiring explantation. In the remaining 10 eyes, the mean maximum IOP was 30.4 mm Hg preoperatively, 12.0 mm 1 day postoperatively, 17.2 mm Hg at 4 weeks, and 18.3 mm at the end of the preliminary follow-up. **FDA approval of the Eyepass glaucoma implant and randomized controlled studies with long-term results are still needed to determine its safety and efficacy.**

SOLX Gold Shunt

Tanito and Chihara (2017) conducted a case series analysis to assess the safety and effectiveness of the SOLX gold shunt (GS) in reducing intraocular pressure (IOP) in Japanese patients with open angle glaucoma (OAG). Best-corrected visual acuity (BCVA), IOP, corneal endothelial cell density (CECD), anterior chamber (AC) flare, surgical complications, and required interventions were monitored at baseline, and 1 day, 1 week, 1, 3 and 6 months, and 1 year postoperatively. A total of 24 patients (24 eyes) were implanted with the GS either with or without cataract surgery. The mean age was 68.9 ± 12.7 years, 67% were women, 29% were diagnosed with pseudoexfoliation glaucoma and 1 had steroid response glaucoma. Baseline IOP of 21.3 ± 4.1 mmHg and glaucoma medications of 3.5 ± 1.0 were significantly reduced at every follow-up visit. At 1 year postoperatively, IOP was 16.4 ± 5.8 mmHg (23% reduction from baseline, p<0.0001) with use of 2.1 ± 1.1 medications (40% reduction from baseline, p=0.0002). Intraoperative hyphema occurred in 5 (21%) eyes. Transient bleb formation occurred in 20 (83%) eyes, and AC cell was reported in 17 (71%) eyes. Inflammation-related complications such as posterior and anterior synechiae or iritis/keratic precipitates tended to occur during late postoperative periods. At 1 year, BCVA was unchanged or improved in 23 (96%) eyes. AC flare was elevated at 1 week postoperatively and later. CECD declined at 3 months and 1 year postoperatively. The authors concluded that GS is effective in reducing IOP in Japanese patients with OAG and that chronic inflammation in AC might be associated with late onset complications. FDA approval of the SOLX Gold Shunt and randomized controlled trials with long-term follow-up and comparisons to other glaucoma implants are still needed to determine its safety and efficacy.

One Phase III trial has been completed, but no data has yet been published (<http://clinicaltrials.gov/ct2/show/NCT01282346>). (Accessed ~~April 30, 2019~~ **January 28, 2020**)

Professional Societies

American Academy of Ophthalmology (AAO)

The 2016 AAO Preferred Practice Patterns on POAG state that while several other glaucoma surgeries exist as alternatives to trabeculectomy and aqueous shunt implantation (e.g., nonpenetrating procedures, MIGS), the precise role of these procedures in the surgical management of glaucoma remains to be determined.

The CyPass® Micro-Stent System, the XEN® Glaucoma Treatment System, and/or the HYDRUS® Microstent are not specifically addressed by name in the guideline.

On the topic of combining glaucoma and cataract surgery, the guideline states:

- The decision of which procedure(s) to perform first or whether to combine cataract and glaucoma surgery is determined by the ophthalmologist and patient.
- Generally, combined cataract and glaucoma surgery is not as effective as glaucoma surgery alone in lowering IOP, so patients who require filtration surgery who also have mild cataract may be better served by filtration surgery alone and cataract surgery later.
- A systematic review published in 2002 found moderate quality evidence that separating the cataract and glaucoma incisions results in lower IOP than a one-site combined procedure, but the differences in outcomes were small. Subsequent publications have found no difference between the 2 approaches (Prum et al).

An AAO Ophthalmic Technology Assessment by Minckler et al. (2008) provided an evidence-based summary of commercially available aqueous shunts currently used in substantial numbers (Ahmed, Baerveldt, Krupin, and Molteno) that are used to control IOP in various glaucomas. Although the primary indication for aqueous shunts is when prior medical or surgical therapy has failed, they may be used as primary surgical therapy for selected conditions such as trauma, chemical burns, or pemphigoid (level III evidence - case series, case reports, and poor quality cohort and case-control studies). Based on level I evidence, aqueous shunts seem to have benefits (IOP control, duration of benefit) comparable with those of trabeculectomy in the management of complex glaucomas (phakic or pseudophakic eyes after prior failed trabeculectomies). Level I evidence indicates that there are no advantages to the adjunctive use of anti-fibrotic agents or systemic corticosteroids with currently available shunts. Too few high-quality direct comparisons of various available shunts have been published to assess the relative efficacy or complication rates of specific devices beyond the implication that larger-surface-area explants provide more enduring and better IOP control. Long-term follow-up and comparative studies are encouraged.

An AAO Technology Assessment on novel glaucoma procedures (Francis et al, 2011) provided an evidence-based summary of clinically relevant information on novel devices for treating OAG (e.g., iStent®, EX-PRESS™ mini glaucoma shunt, SOLX® Gold Shunt). The authors concluded that the novel glaucoma surgeries studied all showed some promise as alternative treatments to lower IOP in the treatment of OAG. However, their report states that it is not possible to conclude whether these novel procedures are superior, equal to, or inferior to surgery such as trabeculectomy or to one another.

Canadian Ophthalmological Society

~~This society's guidelines for the management of glaucoma in the adult eye lists viscocanalostomy under other strategies for the surgical management of coexisting cataract and glaucoma, but the guideline developers report that there is insufficient scientific evidence comparing these procedures to phaco-trabeculectomy (2009).~~

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Viscocanalostomy and Canaloplasty

Specialized devices used for viscocanalostomy and canaloplasty are regulated by the FDA as Class II devices. Additional information under product codes HMX (cannula, ophthalmic), MPA (endoilluminator), or MRH (pump, infusion, ophthalmic) is available at: <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm>. (Accessed ~~January 27, 2020~~ April 30, 2019)

The Canaloplasty Ophthalmic Microcannula, or iTRACK, is a flexible microcannula designed to allow atraumatic cannulation of spaces in the eye such as the anterior chamber and posterior segment, for infusion and aspiration of fluids during surgery, including saline and viscoelastics. The FDA approved the Ophthalmic Microcannula in August

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2006. Additional information is available at: https://www.accessdata.fda.gov/cdrh_docs/pdf6/k062259.pdf. (Accessed ~~January 27, 2020~~ April 30, 2019)

Glaucoma Drainage Devices

The EX-PRESS™ Mini Glaucoma Shunt, indicated for use in reduction of IOP in patients with glaucoma where medical and conventional surgical treatments have failed, received 501(k) approval on March 13, 2003. Additional information is available at: http://www.accessdata.fda.gov/cdrh_docs/pdf3/K030350.pdf. (Accessed ~~January 27, 2020~~ April 30, 2019)

Predicate devices include the Molteno Implant (K890598 and K902489), the Baerveldt Glaucoma Implant (K905129 and K955455), the Krupin Eye Valve (K885125 and K905703), the Ahmed Glaucoma Valve Implant (K925636) and the XEN® Glaucoma Treatment System (K161457). Additional information under product code KYF (Implant, Eye Valve) is available at: <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm>. (Accessed ~~January 27, 2020~~ April 30, 2019)

iStent® Trabecular Micro-Bypass Stent System, Model GTS100R/L, was approved by the FDA on June 25, 2012. This device is approved for use in combination with cataract surgery to reduce IOP in adult patients with mild to moderate open-angle glaucoma and a cataract who are currently being treated with medication to reduce IOP. The iStent *inject*® Trabecular Micro-Bypass System (Model G2-M-IS) received FDA approval through the Premarket Approval (PMA) process ([P170043](https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm?id=P170043)) on June 21, 2018. The device is approved only for use in conjunction with cataract surgery; use in a standalone procedure would be considered "off-label". Additional information is available at:

- http://www.accessdata.fda.gov/cdrh_docs/pdf8/p080030b.pdf
- <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm?id=P170043>

(Accessed ~~January 27, 2020~~ April 30, 2019)

CyPass® System, Model 241-S, was approved by the FDA on July 29, 2016. This device is approved for microinvasive glaucoma surgery (MIGS) in combination with cataract surgery, and is indicated to reduce IOP in adults with mild-to-moderate POAG. Additional information is available at:

https://www.accessdata.fda.gov/cdrh_docs/pdf15/p150037b.pdf. (Accessed ~~January 27, 2020~~ April 30, 2019)

Hydrus® Microstent was approved by the FDA on August 10, 2018. This device is approved for use in conjunction with cataract surgery for the reduction of IOP in adult patients with mild to moderate POAG. Additional information is available at: <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm?id=P170034>.

(Accessed ~~January 27, 2020~~ April 30, 2019)

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Medicare does not have a National Coverage Determination (NCD) for glaucoma drainage devices used for treating refractory glaucoma when medical or surgical treatments have failed or are inappropriate. Local Coverage Determinations (LCDs) exist; see the LCDs for Category III Codes, Micro-Invasive Glaucoma Surgery (MIGS), Non-Covered Category III CPT Codes and Non-Covered Services.

Medicare does not have an NCD for iStent®, iStent *inject*® Trabecular Micro-Bypass Stent Systems or the Hydrus® Microstent when used in combination with cataract surgery for treating mild to moderate open-angle glaucoma and a cataract in adults currently being treated with ocular hypotensive medication. LCDs exist; see the LCDs for Category III CPT Codes, Micro-Invasive Glaucoma Surgery (MIGS), Non-Covered Category III CPT Codes and Non-Covered Services.

Medicare does not have an NCD for canaloplasty used for treating primary open-angle glaucoma. LCDs do not exist at this time.

Medicare does not have an NCD for the CyPass® Micro-Stent System used in treating any type of glaucoma. LCDs exist; see the LCDs for Category III CPT Codes, Micro-Invasive Glaucoma Surgery (MIGS), Non-Covered Category III CPT Codes and Non-Covered Services.

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Medicare does not have an NCD for the XEN® Glaucoma Treatment System. LCDs exist; see the LCDs for Category III CPT Codes, Micro-Invasive Glaucoma Surgery (MIGS), Non-Covered Category III CPT Codes and Non-Covered Services.

Medicare does not have an NCD for viscocanalostomy procedures used in treating any type of glaucoma. LCDs do not exist at this time.

(Accessed January 28, 2020)

~~Medicare does not have a National Coverage Determination (NCD) for glaucoma drainage devices used for treating refractory glaucoma when medical or surgical treatments have failed or are inappropriate. Local Coverage Determinations (LCDs) exist; see the LCDs for Category III Codes, Micro-Invasive Glaucoma Surgery (MIGS), Non-Covered Category III CPT Codes and Non-Covered Services.~~

~~Medicare does not have an NCD for the insertion of the iStent® or iStent *inject*® Trabecular Micro-Bypass Stent Systems for treating mild to moderate open-angle glaucoma when used in combination with cataract surgery. LCDs exist; see the LCDs for Category III CPT Codes, Services That Are Not Reasonable and Necessary and Micro-Invasive Glaucoma Surgery (MIGS).~~

~~Medicare does not have an NCD for canaloplasty used for treating primary open-angle glaucoma. LCDs do not exist at this time.~~

~~Medicare does not have an NCD for the CyPass® Micro Stent System used in treating any type of glaucoma. LCDs exist; see the LCDs for Category III CPT Codes, Micro-Invasive Glaucoma Surgery (MIGS) and Non-Covered Category III CPT Codes.~~

~~Medicare does not have an NCD for the Xen® Glaucoma Treatment System or Hydrus® Microstent System. LCDs exist; see the LCDs for Category III CPT Codes and Micro-Invasive Glaucoma Surgery (MIGS).~~

~~Medicare does not have an NCD specifically for glaucoma drainage devices that are not FDA approved. LCDs do not exist at this time.~~

~~Medicare does not have an NCD for viscocanalostomy procedures used in treating any type of glaucoma. LCDs do not exist at this time.~~

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POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
<u>Xx/01/2020</u>	<p><u>Application</u></p> <ul style="list-style-type: none"> • <u>Added language to indicate this policy does not apply to the state of Nebraska; refer to the Medical Policy titled Glaucoma Surgical Treatment (for Nebraska Only)</u> • <u>Added language to indicate this policy does not apply to the state of New Jersey; refer to the Medical Policy titled Glaucoma Surgical Treatment (for New Jersey Only)</u> <p><u>Coverage Rationale</u></p> <ul style="list-style-type: none"> • <u>Added "(ab externo)" to Canaloplasty on the proven indication list</u> • <u>Added "Canaloplasty (ab interno)" and "Gonioscopy-Assisted Transluminal Trabeculectomy" to the unproven indication list</u> • <u>Removed "CyPass® Micro-Stent System" from the unproven indication list</u> <p><u>Applicable Codes</u></p> <ul style="list-style-type: none"> • <u>Removed CPT Code 66170</u> • <u>Added CPT Code 66185</u> <p><u>Supporting Information</u></p> <ul style="list-style-type: none"> • <u>Updated Description of Services, Clinical Evidence, FDA, CMS, and</u>

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Date	Action/Description
	<p><u>References sections to reflect the most current information</u></p> <ul style="list-style-type: none"><u>Archived previous policy version CS050.M</u>

INSTRUCTIONS FOR USE

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The UnitedHealthcare Medical Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

DRAFT