# Glaucoma Surgical Treatments

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Instructions for Use

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## Application

This Medical Policy does not apply to the states listed below; refer to the state-specific policy/guideline, if noted:

| State | Policy/Guideline |
|---|---|
| Indiana | Glaucoma Surgical Treatments (for Indiana Only) |
| Kentucky | Glaucoma Surgical Treatments (for Kentucky Only) |
| Louisiana | Glaucoma Surgical Treatments (for Louisiana Only) |
| Nebraska | Glaucoma Surgical Treatments (for Nebraska Only) |
| New Jersey | Glaucoma Surgical Treatments (for New Jersey Only) |
| Pennsylvania | Glaucoma Surgical Treatments (for Pennsylvania Only) |
| Tennessee | Glaucoma Surgical Treatments (for Tennessee Only) |

## Coverage Rationale

The following are proven and medically necessary:
- Canaloplasty (ab externo) for treating primary open-angle glaucoma
- Some glaucoma drainage devices (specifically: EX-PRESS, Molteno Implant, Baerveldt Tube Shunt, Ahmed Glaucoma Valve Implant and Krupin-Denver Valve Implant) 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
- Gonioscopy-assisted transluminal trabeculotomy for pediatric glaucoma (age 18 years or less)

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 (for all other conditions not included above)

- Viscocanalostomy
- Viscocanalostomy and gonioscopy-assisted transluminal trabeculotomy (e.g., OMNI® Surgical System)
- XEN® Glaucoma Treatment System

## 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 Guidelines may apply.

*Coding Clarification: Utilize CPT code 66174 when reporting viscocanalostomy.

| CPT Code | Description |
|---|---|
| 0253T | Insertion of anterior segment aqueous drainage device, without extraocular reservoir, internal approach, into the suprachoroidal space |
| 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 |
| 0671T | Insertion of anterior segment aqueous drainage device into the trabecular meshwork, without external reservoir, and without concomitant cataract removal, one or more |
| 65820 | Goniotomy |
| *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 |
| 66185 | Revision of aqueous shunt to extraocular equatorial plate reservoir; with graft |
| 66989 | Extracapsular cataract removal with insertion of intraocular lens prosthesis (1-stage procedure), manual or mechanical technique (e.g., irrigation and aspiration or phacoemulsification), complex, requiring devices or techniques not generally used in routine cataract surgery (e.g., iris expansion device, suture support for intraocular lens, or primary posterior capsulorrhexis) or performed on patients in the amblyogenic developmental stage; with insertion of intraocular (e.g., trabecular meshwork, supraciliary, suprachoroidal) anterior segment aqueous drainage device, without extraocular reservoir, internal approach, one or more |
| 66991 | Extracapsular cataract removal with insertion of intraocular lens prosthesis (1 stage procedure), manual or mechanical technique (e.g., irrigation and aspiration or phacoemulsification); with insertion of intraocular (e.g., trabecular meshwork, supraciliary, suprachoroidal) anterior segment aqueous drainage device, without extraocular reservoir, internal approach, one or more |



| HCPCS Code | Description |
|---|---|
| C1889 | Implantable/insertable device, not otherwise classified |
| 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.

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).

Viscocanalostomy (ab interno) and gonioscopy-assisted transluminal trabeculotomy involves the use of two different mechanistic modalities successively to address multiple points of outflow resistance in the conventional outflow pathway, both proximal and distal. First, canaloplasty is performed to open a distal outflow pathway including a collector channel ostia then, trabeculotomy removes the resistance residing in the trabecular meshwork (Vold 2021).

Glaucoma drainage devices (also known as aqueous shunts) include the EX-PRESS™ Mini Glaucoma Shunt, the Molteno implant, the Baerveldt tube shunt, Ahmed glaucoma valve implant and the Krupin-Denver 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.

The Krupin-Denver value implant has a pressure sensitive unidirectional valve to provide filtration restriction and the implant is designed to open when IOP is >11 mmHg (Krupin 1988).

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 may 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).

# 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 adverse events (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 ≥ 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). 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. They also concluded that if target IOP is attainable by moderate reduction, canaloplasty may be considered for its ease of postoperative care and lack of complications.

Lewis et al. (2011) conducted a multicenter case series 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. The study is limited by the lack of comparison group.

Bull et al. (2011) reported 3-year results investigating the safety and efficacy of canaloplasty in a prospective, multi-center, case series 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. The study is limited by the lack of comparison group.

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 case series. 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. The study is limited by the lack of comparison group.

## Canaloplasty (Ab Interno)

There is insufficient quality evidence in the published clinical literature to determine the safety and efficacy of canaloplasty using an ab interno approach for the treatment of glaucoma.

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 needed to assess the safety and efficacy of ABiC.

Gallardo et al. (2018b) conducted a non-randomized, retrospective, single-center paired eye cohort 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. Limitations of this study include lack of randomization and small sample size that may have been insufficient to detect clinically significant differences.

## Gonioscopy-Assisted Transluminal Trabeculotomy for Pediatric Glaucoma (Age 18 Years or Less)

Gagrani et al. (2020) updated a previously conducted systematic review (Ghate, 2015) that aimed to compare the effectiveness and safety of various surgical techniques for primary congenital glaucoma (PCG). A search was conducted using Cochrane Central Register of Controlled Trials (CENTRAL), Ovid MEDLINE, Embase, PubMed, *meta*Register of Controlled Trials (*m*RCT), ClinicalTrials.gov, and the World Health Organization International Clinical Trials Registry Platform (ICTRP). A total of 16 trials (13 RCTs and three quasi-RCTs) with 587 eyes in 446 children were included in the review. Three trials (on 68 children) compared combined trabeculotomy and trabeculectomy (CTT) with trabeculotomy, 2 trials (on 39 children) compared viscotrabeculotomy to conventional trabeculotomy, 2 trials (on 95 children) compared microcatheter-assisted 360-degree circumferential trabeculotomy to conventional trabeculotomy, 1 trial compared CTT versus CTT with sclerectomy; 3 trials compared various suturing techniques and adjuvant use including mitomycin C, collagen implant in CTT; 1 trial compared CTT versus Ahmed valve implant in previously failed surgeries; 1 trial compared CTT with trabeculectomy; 1 trial compared trabeculotomy to goniotomy, and two trials compared different types of goniotomy. The authors concluded that evidence on the comparative benefits and risks of different surgical procedures for PCG is limited however, microcatheter-assisted 360-degree trabeculotomy is probably more beneficial than standard trabeculotomy, but probably causes more unwanted effects. The authors also stated that considering the rarity of the disease, future research would benefit from a multicenter, possibly international trial, involving parents of children with PCG and with a follow-up of at least one year.

Huang et al. (2018) conducted a single-center cohort study to investigate the long-term postoperative outcome of three surgical procedures for childhood glaucoma. The investigators retrospectively reviewed the medical records of patients with various types of childhood glaucoma and based on the initial surgery, categorized patients into goniotomy, trabeculotomy, or filtering surgery groups. The main outcome measure was the probability of success of surgery based on a Kaplan–Meier analysis. Surgical failure was defined as one of the following: 1) when additional glaucoma filtering surgery was performed; 2) visual acuity deteriorated to an absence of light perception; and 3) an IOP greater than or equal to 21 mmHg with ocular hypotensive medications, verified during two consecutive visits. A total of 73 eyes of 43 patients were analyzed. The age at the initial surgery was 4.1 ±6.4 years (mean ± SD; range: 1 month to 17.7 years). The follow-up period was 9.6±6.7 years (range: 2–20 years). Forty eyes of 25 patients, 21 eyes of 15 patients, and 12 eyes of 7 patients underwent initial surgery with goniotomy, trabeculotomy, and filtering surgery, respectively. The probability of success was 65.2% ±7.8% and 65.2% ±7.8% (estimated probability ± standard error) at 10 and 20 years after the initial surgery, respectively, in the goniotomy group. It was 42.2% ±13.6% at 10 years in the trabeculotomy group (no data for 20 years), and 91.7%±8.0% and 80.2%±12.8% at 10 and 20 years after the initial surgery in the filtering surgery group. The authors concluded that all three procedures maintained an IOP of less than 21 mmHg for up to 10 years and therefore, provide valuable options for the treatment of childhood glaucoma.

Yeung and Walton (2010) conducted a retrospective case series study to report outcomes of patients with acquired juvenile open-angle glaucoma (JOAG) who underwent goniotomy surgery. Medical records from 10 patients were reviewed (20 goniotomy procedures, 17 eyes). The investigators reviewed sex, ethnicity, family history, refraction, preoperative gonioscopic findings, surgical outcome, age at initial goniotomy, duration of postoperative observation, preoperative and postoperative IOP, and glaucoma medication used. Complete success was defined as an IOP < or =21 mmHg, qualified success as IOP < or =21 mm Hg with use of glaucoma medications, and failure as IOP >21 mmHg despite medical therapy. The surgical technique used to perform the goniotomy procedures was reviewed and the absence of significant complications noted. Overall surgical success was achieved in 77% (13/17) of the eyes. Average IOP for complete success (9 eyes) was 14.7+/-2.1 mmHg (range: 12 to 18 mmHg), qualified success (4 eyes) 16.5+/-2.4 mmHg (range: 14 to 19 mmHg), and failure (4 eyes) 33.5+/-5.7 mmHg (range: 30 to 42 mmHg). The mean age at surgery was 16.3+/-8.1 years (range: 7.3 to 32 years). Mean follow-up interval was 7.8+/-6.2 years (range: 0.1 to 16.3 years). Gonioscopy demonstrated normal appearing filtration angles in all eyes. No significant surgical complications occurred. Mean refractive error was -3.3+/-2.8 (range: 0.0 to -7.8). Sixty percent of patients

possessed a family history of JOAG. The authors concluded that goniotomy is a potentially effective initial surgical treatment of JOAG and that it can be successfully performed using a standard goniotomy technique. This study is limited by the lack of a comparison group.

Ho et al. (2004) conducted a retrospective case series study to describe the safety and efficacy of goniotomy in medically uncontrolled glaucoma complicating chronic childhood uveitis and the factors affecting its outcome. The main outcome measures were IOP at the last follow-up and time to surgical failure. Success was defined as final IOP of no greater than 21 mm Hg without medications and qualified success as IOP of no greater than 21 mm Hg with medications. The secondary outcome measure was the number of medications needed to achieve an IOP of no greater than 21mmHg after surgery. All goniotomies were performed by a single surgeon. Fifty-four goniotomies were performed in 40 eyes of 31 patients. Juvenile rheumatoid arthritis–associated uveitis was the diagnosis in 30 eyes (75%). Eleven eyes (28%) were aphakic. Mean follow-up was 98.9 months (range, 2 to 324 months). Mean age at surgery was 10.3±4.7 years (range, 4 to 22 years). Mean preoperative IOP was 36.7 ±6.4 mm Hg while receiving a mean of 2.9 ±1.1 medications. Overall surgical success was achieved in 29 eyes (72%), including success in 22 (55%) and qualified success in 7 (18%) while receiving a mean of 1.6 ±1.1 medications. Mean postoperative IOP in the success and qualified-success groups were 14.3 ±2.8 and 15.7 ±3.1 mm Hg, respectively. Kaplan-Meier survival probabilities (95% confidence interval) at 1, 5, and 10 years were 0.92 (0.82 to 1.00), 0.81 (0.65 to 0.97), and 0.71 (0.49 to 0.92), respectively. Phakic eyes, eyes with fewer peripheral anterior synechiae, patients younger than 10 years, and eyes with no prior surgery had significantly better outcomes. Hyphema, typically mild and transient, occurred in 43 procedures (80%). The authors concluded that goniosurgery is low risk and effective for refractory glaucoma complicating chronic childhood uveitis and therefore, it should be considered the surgical procedure of choice for this condition. They also stated that surgical outcome is adversely affected by increased age, peripheral anterior synechiae, prior surgeries, and aphakia. This study is limited by the lack of a comparison group.

Gramer et al. (1997) conducted a single-center, retrospective case series study to obtain information about the development of visual acuity, visual field and cup-disc ratio of patients with primary congenital glaucoma who underwent IOP-regulating goniotomy. A total of 196 patients who underwent goniotomy were contacted. Of those, 92 returned replies and the contact information of the treating ophthalmologists could be ascertained from 77 patients. Sixty of the 77 patients fulfilled the inclusion criteria, which included primary congenital glaucoma and IOP-regulating goniotomy as the last surgery. In 76% of 106 eyes childhood glaucoma was diagnosed during the first year of life. In 72% of 60 eyes/patients with primary congenital glaucoma one goniotomy was sufficient to reach a normal IOP. In 18% a second and in 10% a third goniotomy was necessary, but without influence on the visual outcome. Even in the groups of eyes with a preoperative IOP of more than 40 mmHg, preoperative corneal diameter of more than 13 mm and preoperative severe corneal opacity more than 50% reached a visual acuity of 0.4-1.2 and more than 80% had a normal visual field. Only 9% of the eyes showed a cup-disc ratio of 0.6 or more. The authors concluded that in patients with primary congenital glaucoma, even with high preoperative IOP, large corneal diameters and severe corneal edemas, there was a good prognosis of visual outcome after goniotomy. This study is limited by the lack of a comparison group.

### *Clinical Practice Guidelines*

#### American Academy of Ophthalmology (AAO)

The AAO's report, Pediatric Glaucoma Surgery, states that there are many surgical options for the treatment of the pediatric glaucomas (e.g., primary congenital glaucoma, aphakic glaucoma, and glaucomas associated with other ocular or systemic anomalies) including goniotomy, trabeculotomy, trabeculectomy, combined trabeculotomy and trabeculectomy, tube shunt surgery, cyclodestruction, and deep sclerectomy. The relative efficacy of these various procedures for specific diagnoses and clinical situations should be weighed against the specific risks associated with the procedures for individual patients (Chen, 2014).

## Gonioscopy-Assisted Transluminal Trabeculotomy (GATT) for All Other Conditions not Included Above

There is insufficient quality evidence in the published clinical literature to determine the safety and efficacy of gonioscopy-assisted transluminal trabeculotomy (GATT) for all other glaucoma types except pediatric glaucoma.

Grover et al. (2018) conducted a retrospective chart review case series 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. They noted that 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 case series 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

The evidence in the published clinical literature does not support the safety and efficacy of viscocanalostomy for the treatment of glaucoma. Limited evidence suggests that this approach is inferior to other established approaches.

A 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.

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% and50.0% 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.

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 with 29 randomized clinical trials included in the meta-analysis. 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.

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).

## Viscocanalostomy and Gonioscopy-Assisted Transluminal Trabeculotomy

There is insufficient quality evidence in the published clinical literature to determine the safety and efficacy of combined viscocanalostomy and gonioscopy-assisted transluminal trabeculotomy for treatment of glaucoma e.g., with the OMNI surgical system.

Grabska-Liberek et al. (2021) conducted case series study to characterize clinical outcomes of combined viscodilation of Schlemm's canal and collector channels and 360° trabeculotomy using the OMNI surgical system as a standalone procedure or combined with cataract surgery in eyes with mild to moderate OAG. Eligible participants were adults aged 45 years or older, with either visually significant cataract or pseudophakia, and open-angle glaucoma (including primary, pigmentary, and pseudoexfoliative) with intraocular pressure (IOP) > 21 mmHg using up to three topical IOP-lowering medications. The primary outcome was the proportion of eyes with IOP reduction ≥ 20% from baseline using the same number or fewer IOP-lowering medications compared to baseline at Month 24. Secondary outcomes included the proportion of eyes with IOP ≤18 mmHg and the proportion with IOP ≤15 mmHg (and IOP ≥6 mmHg in both cases) at Month 12; the proportion of eyes that were medication-free or on at least one fewer medication compared to baseline at Month 12; changes from baseline in IOP and the number of IOP-lowering medications at each visit; and the number of secondary surgical interventions performed for IOP control. Safety endpoints included the nature and incidence of ocular adverse events. Participants were re-evaluated at 1 week and 1, 3, 6, 12, and 24 months postoperatively. Among 17 eyes of 15 subjects, mean IOP was reduced from 20.4 mmHg to 12.7–13.7 mmHg through 12 months of follow-up ($p < 0.001$ at every time point) and mean medications reduced from 2.5 to 0.1–0.6 ($p<0.001$ at every time point). IOP reductions in eyes undergoing standalone surgery were approximately 2–4 mmHg greater at each time point compared to eyes undergoing surgery combined with phacoemulsification; this may be related to a higher baseline IOP in the former eyes (22.1 vs. 18.5 mmHg). Six eyes developed hyphema, of which three required washout for elevated IOP on the first postoperative day; six additional eyes had IOP elevations that resolved with medical management. The authors concluded that viscodilation of Schlemm's canal and collector channels paired with ab interno trabeculotomy performed with a single integrated instrument (OMNI), whether as standalone or combined with phacoemulsification, effectively lowers both IOP and the need for IOP-lowering medications through 12 months of follow-up. The authors also mentioned that this study ongoing and 24-month data will be reported when available. Limitations of this study include its design, a case series lacking a contemporaneous comparison group, the small sample size, that all surgeries were performed by the same surgeon, and the unexpectedly high rate of hyphema. Additional randomized studies with larger sample sizes and longer follow-up periods are still needed to clarify efficacy and safety of this technology.

Gallardo et al. (2021) conducted a multi-center case series to report 6-month safety and efficacy outcomes of 360° canaloplasty and 180° trabeculotomy using the OMNI® Surgical System concomitantly with phacoemulsification in patients with open-angle glaucoma (OAG). Eligible patients had cataract and mild-moderate OAG with intraocular pressure (IOP) ≤ 33 mmHg on 1 to 4 hypotensive medications. Effectiveness outcomes included mean IOP and medications. Safety outcomes included AEs, best corrected visual acuity (BCVA) and secondary surgical interventions (SSI). A total of 137 patients were enrolled and treated. Mean diurnal IOP after washout was 23.8 ± 3.1 mmHg at baseline. At month 6, 78% (104/134) of patients were medication free with IOP of 14.2 mmHg, a mean reduction of 9.0 mmHg (38%). One hundred percent (104/104) had a ≥ 20% reduction in IOP and 86% (89/104) had IOP ≥ 6 and ≤ 18 mmHg. The mean number of medications at screening was 1.8 ± 0.9 and 0.6 ± 1.0 at month 6. AE included transient hyphema (4.6%) and IOP elevation ≥10 mmHg (2%). There were no AE for loss of BCVA or recurring hyphema. There were no SSI. The authors concluded that canaloplasty followed with trabeculotomy and performed concomitantly with phacoemulsification has favorable intra and perioperative safety, significantly reduces IOP and anti-glaucoma medications through 6 months in eyes with mild-moderate OAG. Limitations of this study include its design, which lacks a comparison group and short follow-up period. Additional prospective, randomized studies are still needed to determine the efficacy and safety of this technology.

An ECRI review, Omni Surgical System (Sight Sciences, Inc.) for Treating Open-Angle Glaucoma, evaluated 3 studies (4 publications), which reported on a total of 217 patients. Those included case series, three retrospective and 1 prospective. It was concluded that very-low-quality evidence suggest that the OMNI Surgical System is safe and reduces IOP and medication use up to 18 months of follow-up in patients with mild to moderate OAG when performed alone or during cataract surgery. No studies compared OMNI with other OAG treatments. RCTs comparing OMNI with other MIGSs and with long-term (> 12 months) outcomes are still needed to assess its safety and effectiveness (2021).

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

### *EX-PRESS™*

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.

De Jong et al. (2011) published results from a 5-year extension of a prospective RCT conducted to establish the efficacy and safety of the Ex-PRESS mini glaucoma shunt in open-angle glaucoma. In the original study (de Jong 2009), enrolled patients were randomly assigned to either Ex-PRESS implantation under a scleral flap, or trabeculectomy. The main outcome measures included: mean IOP, postoperative medication use, visual acuity, and incidence of complications. Complete success was defined as an IOP of > 4 mmHg and < or = 18 mmHg without the use of antiglaucoma medications. A more stringent target of IOP > 4 mmHg and < or = 15 mmHg was also noted. A total of 78 patients (80 eyes) with primary open-angle, pseudoexfoliative, or pigmentary glaucoma were enrolled. Of those, 84.6% of patients who were randomized to Ex-PRESS and 60.0% of patients who were randomized to trabeculectomy achieved complete success (p=0.0230). Patients who achieved an IOP > 4 mmHg and < or = 15 mmHg were 76.9% and 50.0%, respectively (p = 0.0193). At 1-year of follow-up, complete success rates were 81.8% for Ex-PRESS and 47.5% for trabeculectomy (p = 0.0020), and 71.7% and 37.5% (p=0.0070), respectively, for the more stringent target. There was a similar level of postoperative interventions and complications for each group. In the extension study, risk-benefit data for 78 patients who received either the EX-PRESS glaucoma filtration device or underwent a trabeculectomy were followed for up to an additional four years (five years total) beyond the original study (39 eyes per treatment group). Outcome variables were intraocular pressures and intraocular pressure medications. Complete success was denoted by intraocular pressure values ≤ 18 mmHg without medication. The EX-PRESS glaucoma filtration device controlled intraocular pressure more effectively without medication for more patients from year 1 (86.8% versus 61.5%, p = 0.01) to year 3 (66.7% versus 41.0%, p=0.02) than trabeculectomy. At year 1, only 12.8% of patients required intraocular pressure medication after EX-PRESS implantation, compared with 35.9% after trabeculectomy. The proportions became closer at year 5 (41% versus 53.9%). The responder rate was higher with EX-PRESS and time to failure was longer. In addition, surgical interventions for complications were fewer after EX-PRESS implantation. The authors concluded that the five-year analysis confirmed and extended the results reported after one year, and that compared with trabeculectomy, EX-PRESS provided better intraocular pressure control in the first three years, and patients required fewer intraocular pressure medications and fewer surgical interventions during the five-year study period. They also concluded that for patients with primary open-angle glaucoma, the EX-PRESS glaucoma filtration device produced significantly higher success rates than trabeculectomy, and therefore the EX-PRESS is an effective device for long-term treatment of primary open-angle glaucoma. de Jong (2011) was included in the Sun 2019 study.

Ates et al. (2010) evaluated IOP control and graft survival after EX-PRESS™ mini glaucoma shunt implantation in a case series of 15 patients with refractory post penetrating keratoplasty glaucoma. 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. This study is however, limited by the lack of a comparison group.

### *Molteno Implant, Baerveldt Tube Shunt, Ahmed Glaucoma Implant and Krupin-Denver Value Implants*

Islamaj et al. (2020) conducted an RCT to compare Baerveldt glaucoma implant (BGI) surgery and trabeculectomy (TE) in patients without previous ocular surgery. Inclusion criteria were age 18–75 years, primary open-angle glaucoma, normal-tension glaucoma (NTG), pseudo exfoliative glaucoma or pigmentary glaucoma and the need for intraocular pressure (IOP) lowering surgery. Patients with a history of any ocular surgery, such as TE, strabismus surgery or cataract extraction were excluded from the study. Other exclusion criteria were history of active uveitis or diabetic retinopathy, pregnancy or lactation, anticipated glaucoma surgery combined with other ocular procedures (i.e. cataract surgery), narrow anterior chamber angle

interfering with tube implantation, BCVA <0.1 in the study eye or fellow eye and history of ocular motility disturbances. Primary outcomes were IOP and failure rate. Secondary outcomes were medication, anterior chamber laser flare value and complications. A total of 119 patients with glaucoma were included in the trial (60 patients received TE surgery and 59 received a BGI). After 5 years, an IOP of 12.7 ± 3.9 mmHg (mean ± SD) was achieved in the TE group and 12.9 ± 3.9 mmHg in the BGI group. There was no difference in the failure rate between the groups (p=0.72). More BGI patients needed additional medication to control their IOP (85%; 1.9 ± 1.2 types of glaucoma medication) compared to the TE patients (57%; 0.5 ± 0.9 types of glaucoma medication). Diplopia was significantly more present in the BGI group than in the TE group (27% versus 4%; p<0.001). The self-limiting complication rate was similar in both groups. The authors concluded that, in the long term, the final IOP and failure rate are similar after TE and BGI surgery, and that the need for additional medication after BGI surgery is higher than after TE. They also stated that the increased risk of developing diplopia after BGI surgery must be taken into consideration.

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, Ranchos 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. This study was included in the Tseng (2017) study.

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 (p=0.010; hazard ratio, 2.2; 95% confidence interval, 1.2 to 4.1). Postoperative complications developed in 39% and 60% in the tube and trabeculectomy groups, respectively (p=0.004). 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 mitomycin C (MMC) relative to tube shunt surgery, most complications were transient and self-limited. This study was included in the Tseng (2017) study.

Mastropasqua et al. (1996) conducted a retrospective case series to evaluate long-term outcomes in patients (28 eyes) who underwent implantation of the Krupin-Denver value for neovascular glaucoma. The preoperative IOPs ranged from 28 to 62 mm Hg (mean, 36.8 +/- 5.8 mm Hg). Success was considered an IOP of less than 22 mm Hg and greater than 5 mm Hg without medication (complete success) or with medication (qualified success) without additional glaucoma filtering surgery or

devastating complications. Postoperative success was obtained in 10 of 28 eyes after a mean follow-up period of 58.4 +/- 23.02 months (range: 10-108 months). The 3- and 6- year life table success rates were 66 and 34%, respectively. Early complications included: shallow or flat anterior chamber (15 patients, 53.6%), hypotony (16 patients, 57.1%), hypertony (7 patients, 25%), serous choroidal effusion (7 patients, 25%), fibrinous uveitis (5 patients, 17.9%), blockage of the intracameral portion of the tube by fibrin (5 patients, 17.9%), choroidal hemorrhage (2 patients, 7.1%). Late complications included: external conjunctival bleb failure (12 patients, 42.9%), blockage of the intracameral portion of the tube by fibrovascular tissue (5 patients, 17.9%), cataract (2 patients, 7.1%), bullous keratopathy (2 patients, 7.1%), external erosion of the Silastic valve (2 patients, 7.1%), phthisis bulbi (2 patients, 7.1%). Mortality during long-term follow-up was high, and the complications of an underlying diabetes mellitus were the most common cause of death (15 of 22 patients). The authors concluded that the high mortality of patients subjected to valve implantation makes it difficult to interpret the results of long-term studies however, the valve implant is an alternative surgical procedure for controlling IOP in eyes with neovascular glaucoma that have visual potential. This study is limited by the lack of a comparison group.

Fellenbaum et al. (1994) conducted a single-center case series to evaluate outcomes of the patients who underwent Krupin Eye Valve implantation for complicated glaucomas. Medical records of 25 patients (25 eyes) were retrospectively reviewed. The authors reported that IOP was reduced from a mean of 36.1 +/- 11.5 mmHg to 15.3 +/- 7.5 mmHg at follow-up intervals of 4 to 19 months (mean, 13.2 months). On the first postoperative day, IOPs ranged from 0 to 40 mmHg. In two eyes (8%), the IOP was less than 6 mmHg, and in five eyes (20%) the IOP was more than 21 mmHg. Serous choroidal effusion and/or choroidal hemorrhage occurred in seven patients (28%). Six- and 12-month life-table success rates (6 < or = IOP < or = 21 mmHg) were 84% and 66%, respectively. The authors concluded that the Krupin implant lowers IOP in most patients however, the presence of a slit valve does not eliminate either early postoperative hypotony with its attendant complications or early IOP spikes. This study is limited by the lack of a comparison group.

The Krupin Eye Valve Filtering Surgery Study Group (1994) conducted a case series to evaluate a long posterior tube shunt device with a pressure sensitive valve for filtration surgery in eyes with recalcitrant glaucoma. One-stage implantation without the use of restrictive sutures was performed in 50 eyes with various types of glaucoma unresponsive to prior glaucoma surgery. The mean (+/- standard error of the mean) preoperative IOP of 36.4 +/- 1.6 mmHg was reduced significantly ($p<0.001$) to 8.3 +/- 1.3 mmHg on the first postoperative day. The mean anterior chamber depth (scale, 0-4+) was 3.4 +/- 0.1. The mean IOP 1 month after surgery was 14.1 +/- 1.3 mmHg. The implant was removed from four eyes due to IOP failure (1 eye), external erosion (2 eyes), or endophthalmitis (1 eye). A suprachoroidal hemorrhage occurred in one eye on the first postoperative day. Diplopia developed in one eye after surgery. Mean IOP at last follow-up examination (25.4 +/- 2.4 months; range, 16-36 months) was 13.1 +/- 1.3 mmHg. Intraocular pressure was 19 mmHg or lower in 80% of the eyes, 59% of which were without adjunctive antiglaucoma medications. The authors concluded that this therapeutic device can be effective in the long-term control of IOP in glaucomatous eyes not responsive to prior filtration surgery with adjunctive antimetabolite therapy. This study is limited by the lack of a comparison group.

### *iStent® and iStent inject®*

Healey et al. (2021) conducted a systematic review and meta-analysis to evaluate the efficacy of iStent devices (iStent® and iStent inject®) when performed independently of cataract surgery in patients with open-angle glaucoma. A search was conducted using Embase.com (EMBASE and MEDLINE) as well as the Cochrane Library. All randomized trials were considered as well as non-randomized studies that included at least 6 months of follow-up or more than 10 eyes. Efficacy analyses included post-operative intraocular pressure and medication use, and the proportion of eyes free of ocular medication. Post-operative adverse events were descriptively summarized. The literature search yielded a total of 760 citations and after further review, a total of 13 studies were included in the analysis. Those included 4 RCTs and 9 non-randomized or single-arm studies providing data for 778 eyes. In eyes implanted with iStent devices, a weighted mean intraocular pressure reduction of 31.1% was observed at 6–12 months. In studies reporting longer-term outcomes (36–48 months or 60 months), the weighted mean IOP reduction was 30.4% and 32.9%, respectively. The pooled weighted mean reduction in intraocular pressure from baseline across all studies at 6–12 months and 36–60 months post-stent implantation was 7.01 mmHg (95%CI: 5.91 to 8.11) and 6.59 mmHg (95%CI: 5.55 to 7.63), respectively. Medication burden was reduced by approximately 1.0 medication at 6–18 months and 1.2 medications at 36–60 months. Adverse events reported in more than 5% of participants included progression of pre-existing cataract/cataract surgery and loss of BCVA but these rates were no different to those reported in comparator medical therapy study arms. The authors concluded that these results support the independent effect of the iStent trabecular bypass devices on intraocular pressure and medication burden for up to five years after treatment, and without the potential for confounding from cataract surgery.

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. The authors concluded that the evidence is somewhat favorable.

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 ≥ 20% reduction from baseline in unmedicated diurnal IOP (DIOP), and mean reduction in unmedicated DIOP from baseline was greater in treatment eyes (7.0±4.0 mmHg) than in control eyes (5.4±3.7 mmHg). Of the subjects who were responders (e.g., 24-month unmedicated mean DIOP reduced by ≥ 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. This study was included in the ECRI review.

Clement et al. (2019) conducted a retrospective multi-center case series 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. They also noted that 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. This study is limited by the lack of a comparison group.

In a single center, longitudinal, retrospective, comparative study, Guedes et al. (2019) 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 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 randomization. A prospective study with a larger population and longer follow-up is necessary to validate these findings. This study was included in the ECRI review.

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 case series 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 ≥ 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). This study was included in the ECRI review.

In a prospective, interventional case series, Arriola-Villalobos and colleagues (2016) 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 ± 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). This study is limited by the lack of a comparison group.

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. This study is limited by the lack of a comparison group.

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 ≤ 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 ≤ 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.

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).

Several registered ongoing clinical trials relevant to the iStent® and iStent inject® are in progress. For more information, go to www.clinicaltrials.gov. (Accessed March 29, 2021)

### *XEN® Glaucoma Treatment System*

There is insufficient quality evidence in the published clinical literature to determine the safety and efficacy of the XEN Glaucoma Treatment System for the treatment of glaucoma.

An ECRI review, XEN Gel Stent (Allergan plc.) for Treating Open-angle Glaucoma (2021), evaluated 7 studies (1 systematic review, 2 nonrandomized comparison study, and 4 pre-post studies). It was concluded that the evidence is somewhat favorable in concluding that the XEN gel stent is safe and reduces IOP and the use of glaucoma medication in patients with OAG through 24 months of follow-up. The systematic review and 1 nonrandomized comparison study suggest that XEN works as well as trabeculectomy for reducing medication use and IOP in patients with OAG. One nonrandomized comparison study suggests that XEN reduces IOP and medication more than GATT however, this study has a high risk of bias to be conclusive. Additional RCTs are still needed to validate findings, and RCTs comparing XEN with other OAG microstents would be useful. Two studies included in this review (Hengerer, 2017 and Mansouri, 2018) were also included in the Buffault (2019) systematic review.

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.

Schlenker et al. (2017) conducted an investigator-initiated, international, multicenter, retrospective cohort study of consecutive patients who underwent either standalone microstent insertion (XEN 45 microstent) 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. As with retrospective cohort studies, the risk for bias is elevated. Further research was believed to be warranted to further investigate these procedures. This study was included in the Buffault (2019) study.

Grover et al. (2017b) 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 case series 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.

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. The finding are limited by the lack of a comparison group. This study was included in the Buffault (2019) study.

Galal et al. (2017) conducted in a prospective interventional case series of 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 ≥ 20% from preoperative baseline at 1 year without any glaucoma medications, while partial success as IOP reduction of ≥ 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. The findings are limited by the lack of a comparison group. This study was included in the Buffault (2019) study.

To assess the safety and efficacy of phacoemulsification combined with XEN®45 implant surgery, a prospective case series (Pérez-Torregrosa et al., 2016) 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±3.4mmHg, 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 The findings are limited by the lack of a comparison group. This study was included in the Buffault (2019) study.

There are multiple clinical trials in progress relating to the XEN® Glaucoma Treatment System. For more information, go to www.clinicaltrials.gov. (Accessed March 22, 2021)

### *HYDRUS® Microstent*

Otarola et al. (2020) conducted a systematic review of RCTs to evaluate the efficacy and safety of ab interno trabecular bypass surgery with the Hydrus microstent in treating patients with OAG. A search was conducted using the Cochrane Central Register of Controlled Trials, Ovid MEDLINE, Ovid Embase, the International Standard Research Clinical Trial Number (ISRCTN) registry, the US National Institutes of Health Ongoing Trials Register, and the World Health Organization (WHO) International Clinical Trials Registry Platform. A total of 209 publications were screened, and 3 studies (4 publications, Ahmed 2019, Jones 2018, Samuelson 2018, Pfeiffer 2015), with 808 randomized subjects were included in the review. Two studies compared the Hydrus microstent combined with cataract surgery to cataract surgery alone, in participants with visually significant cataracts and OAG and the other study reported short-term data for the Hydrus microstent compared with the iStent trabecular micro-bypass stent. The authors concluded that in patients with cataracts and mild to moderate OAG, there is moderate-certainty evidence that the Hydrus microstent with cataract surgery compared to cataract surgery alone, likely increases the proportion of participants who do not require IOP lowering medication, and may further reduce IOP at short- and medium-term follow-up. The authors also stated that there is moderate-certainty evidence that the Hydrus microstent is probably more effective than the iStent in lowering IOP of patients with OAG in the short-term, complications may be rare using the Hydrus microstent, as well as the iStent, and that because only a few Hydrus microstent studies exist, additional larger studies are needed to fully investigate its safety.

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 were considered to be somewhat favorable and 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.

Al-Mugheiry and colleagues (2017) conducted a case series 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. The findings are limited by the lack of a comparison group.

Fea et al. (2017a) conducted a prospective interventional cohort study 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. The study is however limited by the lack of randomization.

Fea and colleagues (2017b) 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. The findings are however limited by the lack of a comparison group.

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

There is insufficient quality evidence in the published clinical literature to determine the safety and efficacy of the Eyepass and SOLX Gold Shunt for the treatment of glaucoma.

### *Eyepass*

There is insufficient quality evidence in the published clinical literature to determine the safety and efficacy of the Eyepass and SOLX Gold Shunt for the treatment of glaucoma.

Wittmann et al. (2017) 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 five 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 pilot case series 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 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 March 17, 2021)

### *Clinical Practice Guidelines*

#### American Academy of Ophthalmology (AAO)

The 2020 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 guideline states that iStent, iStent inject and XEN gel stent studies were of insufficient quality (i.e., the estimate of the effect is very uncertain) and therefore, the use of these devices should be left to the discretion of the treating ophthalmologist, in consultation with the individual patient. The guideline also states that Hydrus microstent studies were of moderate quality and that the desirable effects of this device clearly outweigh the undesirable effects.

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 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.

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.

## U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

### Viscocanalostomy, Canaloplasty, and Trabeculotomy

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 March 17, 2021

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 2006. Additional information is available at: https://www.accessdata.fda.gov/cdrh_docs/pdf6/k062259.pdf. (Accessed March 17, 2021)

The OMNI Surgical System is a handheld, manually operated device used by ophthalmologists to access, microcatheterize, and viscodilate Schlemm's canal ("canaloplasty") and to re-access Schlemm's canal and cut trabecular meshwork tissue ("trabeculotomy"). Additional information under product codes MRH (pump, infusion, ophthalmic) and HMZ (trabeculotome) is available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed April 15, 2021)

### 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 March 17, 2021)

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 March 17, 2021)

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) 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 March 17, 2021)

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 March 17, 2021)

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# Policy History/Revision Information

| Date | Summary of Changes |
|---|---|
| 06/01/2022 | Application<br>*Mississippi and North Carolina*<br>• Updated language to indicate this Medical Policy applies to the states of Mississippi and North Carolina (retired state-specific policy versions)<br>Supporting Information<br>• Archived previous policy version CS050.P |

# 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 InterQual® criteria, 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.