



Medical Coverage Policy

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Glaucoma Surgical Procedures

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INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer’s particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer’s benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer’s benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see “Coding Information” below). When billing, providers must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy

will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This Coverage Policy addresses established and emerging surgical procedures for the treatment of glaucoma including aqueous shunts and various proposed surgical interventions.

Coverage Policy

Aqueous Shunts/Aqueous Drainage Devices

Any of the following aqueous shunts/aqueous drainage devices (CPT®/HCPCS Codes 66179, 66180, 66183, C1783, L8612) is considered medically necessary for refractory glaucoma when there is failure, intolerance or contraindication to conventional medical (i.e., topical or oral medication) and surgical (i.e., laser therapy, trabeculectomy) treatment:

- Ahmed™ glaucoma valve
- Baerveldt® glaucoma implant
- ExPRESS™ mini glaucoma shunt
- Krupin eye valve
- Molteno® implant

Insertion of one or two Glaukos iStent® Trabecular Micro Bypass Stent or Glaukos iStent Inject® (CPT®/HCPCS Codes C1783, L8612, 66989, 66991) is considered medically necessary in conjunction with cataract surgery for the reduction of intraocular pressure in an individual with mild to moderate open-angle glaucoma currently treated with ocular hypotensive medication.

Insertion of a single Ivantis Hydrus™ Microstent (CPT®/HCPCS Codes C1783, L8612, 66989, 66991) is considered medically necessary in conjunction with cataract surgery for the reduction of intraocular pressure in an individual with mild to moderate open-angle glaucoma currently treated with ocular hypotensive medication.

Insertion of a single XEN®45 Gel Stent (CPT Codes® 0449T, C1783, L8612, 66183) is considered medically necessary for the management of refractory glaucoma, including ANY of the following:

- primary open angle glaucoma
- failure of previous surgical treatment
- pseudoexfoliative or pigmentary glaucoma with open angles that is unresponsive to maximum tolerated medical therapy

Insertion of iStent Infinite (CPT 0671T) in an individual age 18 years or older with open-angle glaucoma is considered medically necessary when there is failure, intolerance or contraindication to conventional medical and surgical treatment for reduction of intraocular pressure.

Each of the aqueous shunt/aqueous drainage devices listed above is considered not medically necessary for ANY other indication.

EACH of the following devices is considered experimental, investigational or unproven for any indication:

- ab interno suprachoroidal microstent (i.e., ab interno suprachoroidal microstent (i.e., CyPass Micro-Stent) Micro-Stent) (CPT Codes® 0253T; 0474T)
- drug-eluting ocular devices (CPT Codes® 68841, 0444T, 0445T, 0660T, 0661T)

Procedures

Canaloplasty (CPT Code® 66174, 66175), whether performed ab externo or ab interno, is considered medically necessary in an individual age 18 years or older for the treatment of open-angle glaucoma when there is failure, intolerance or contraindication to conventional medical management (i.e., topical or oral medication).

Goniotomy (i.e. trabeculotomy, trabeculotomy ab interno) (CPT Code® 65820) is considered medically necessary for the reduction of intraocular pressure in an individual with glaucoma when performed using an FDA approved device.

EACH of the following procedures is considered experimental, investigational or unproven for ANY indication:

- excimer laser trabeculostomy (ie, ExTra ELT) (CPT Code® 0621T, 0622T, 0730T)
- transcliliary fistulization (transcliliary filtration, Singh filtration) (CPT Code® 66999)
- viscocanalostomy (including phacoviscocanalostomy) (CPT Code® 66999)

Health Equity Considerations

According to the Centers for Disease Control and Prevention (CDC), glaucoma is one of the leading causes of irreversible blindness in the United States (CDC, 2023). More than three million Americans have glaucoma. By 2050, that number is expected to rise to 6.3 million. According to the National Eye Institute (2023), a branch of the National Institute of Health (NIH), and the American Academy of Ophthalmology (AAO) (2020) those at risk for developing glaucoma include:

- Black/African American people at a younger age (age 40 years)
- People over the age of 60 years especially those of Hispanic/Latino descent
- People with diabetes
- People with a family history of glaucoma

General Background

Glaucoma is a group of eye diseases that are depicted by chronic, progressive optic neuropathy. It is characterized by optic nerve damage that results in the progressive loss of retinal ganglion cell axons and is usually associated with increased intraocular pressure (IOP) (Jacobs, 2024). There are several forms of glaucoma with primary open angle glaucoma (POAG) being the most common. If left untreated, glaucoma can result in partial or complete visual impairment or blindness. Currently, intraocular pressure (IOP) is the only treatable risk factor for glaucoma, and lowering IOP has proven beneficial in reducing the progression of loss of vision. Early diagnosis and treatment are essential to prevent visual disability.

In most cases, topical or oral medication is the first treatment of choice. For patients who are unwilling or unable to use medications or are unresponsive to medications, laser therapy or trabeculectomy, may be an option. Although laser therapy reduces IOP initially, its effects diminish over the course of a few years, and repetition of the procedure may not be beneficial.

Trabeculectomy (CPT® 66170 and 66172), an invasive procedure, is the current standard surgical technique for reduction of IOP, but it can result in extremely low IOP, causing ocular damage. Over time, the surgery may fail due to scar formation at the drainage site. Aqueous shunts have been developed as an alternative surgical treatment for patients with inadequately controlled glaucoma. Microstents have also been evaluated in the treatment of mild to moderate glaucoma in patients who are receiving treatment with ocular hypotensive medication.

Minimally invasive or microincisional glaucoma surgery (MIGS) has been proposed to provide a medication-sparing, conjunctival-sparing approach to lower intraocular pressure for patients with mild-to-moderate glaucoma. MIGS is proposed to be safer than traditional incisional glaucoma surgery. The terms goniotomy, trabeculotomy, and trabeculotomy ab interno all describe the same anatomical procedure which is opening of the trabecular meshwork to allow aqueous access to Schlemm's canal to reduce outflow resistance and consequently lower intraocular pressure. The current approaches include: trabecular meshwork bypass by stent placement (e.g., iStent, iStent inject, Hydrus stent); trabecular meshwork bypass by tissue excision (e.g., Kahook Dual Blade Goniotomy, Trabectome, Goinioscopy Assisted Transluminal Trabeculotomy [GATT], TRAB 360/OMNI); enhancing aqueous outflow through Schlemm's canal (e.g., Visco 360/OMNI, Ab Interno Canaloplasty [ABiC]); enhancing aqueous outflow through the suprachoroidal space (e.g., CyPass micro-stent); and shunting aqueous outflow into the subconjunctival space (e.g., XEN gel stent) (American Academy of Ophthalmology [AAO], 2023; Richter, et al., 2016). Alcon has voluntarily withdrawn the CyPass Micro-Stent from the global market based on five-year post-surgery data from the COMPASS-XT long-term safety study. The study demonstrated a clinically and statistically significant increase in corneal endothelial cell loss reported in the CyPass Micro-Stent group compared to the cataract surgery-only control group (FDA, 2018).

Drug-eluting devices

Patient's poor adherence to topical eye medication for the treatment of glaucoma has led to the development of various drug-eluting devices. Several companies are developing sustained-release devices and clinical trials are being conducted to evaluate their safety and effectiveness. Some devices are placed in the eye, while others are placed outside of the eye. Some devices are implanted in the lacrimal canaliculus and others may be inserted under the eyelid without surgical incision. Drug-eluting contacts placed on the sclera, under the upper eyelid are also being investigated. Drug-loaded punctal plugs that are inserted into the tear ducts may be left in place for 2–3 months. Plugs are being made of various polymers (e.g. silicone, hydrogel, biodegradable polycaprolactones). Ocular Therapeutics Inc. (Bedford, MA) is developing a drug-delivery device that is inserted into the lacrimal canaliculus for the delivery of travoprost, a resorbable punctum plug for use after cataract surgery and a dexamethasone punctum plug (OTX-DP). Mati Therapeutics (Austin, TX) is developing a punctal plug for the delivery of latanoprost. A clinical trial is being conducted by Allergan on a bimatoprost sustained-release implant (bimatoprost SR) that is injected into the anterior chamber. Another drug-releasing injected implant that targets the anterior chamber is ENV515 (travoprost XR) by Envisia Therapeutics (Durham, NC). Replenish is developing an ophthalmic MicroPump™, a refillable drug eluting device that is implanted into the sclera and is proposed to deliver a drug for up to 12 months (Myers and Fudember, 2016; Kang-Mieler, et al., 2014; Karmel, 2013). There is insufficient evidence in the published peer-reviewed literature to support the safety and efficacy of these devices nor are any of these devices FDA approved at this time.

Dextenza® (dexamethasone ophthalmic insert) 0.4mg (Ocular Therapeutix™ Inc., Bedford, MA) is an insert placed into the canaliculus to improve pain following ocular surgery. The insert allows for sustained and tapered dexamethasone administration over 30 days, potentially decreasing peaks and troughs in drug concentration. In patients undergoing cataract surgery, Dextenza improved ocular pain and inflammation compared with placebo in four clinical trials. Dextenza is associated with few adverse events. Although there are no head-to-head trials comparing Dextenza with

dexamethasone eye drops or other ocular corticosteroid preparations, the insert may improve compliance and ease of administration in patients unable to adhere to complex corticosteroid eye drop regimens (Ocular Therapeutix, 2024; FDA, 2018). There is insufficient evidence in the published peer-reviewed literature to support the safety and efficacy of Dextenza at this time.

Additional surgical procedures including excimer laser trabeculostomy, transciliary fistulization and viscocanalostomy have been proposed for the treatment of glaucoma. However, there is insufficient evidence in the published medical literature to demonstrate the safety and efficacy of these procedures.

Aqueous Shunts/Aqueous Drainage Devices

Aqueous shunts, also known as aqueous drainage devices, glaucoma drainage devices, setons, tube implants and tube shunts, are drainage devices used to control intraocular pressure (IOP) in the management of glaucoma. First generation shunts in widespread use (e.g., Ahmed [New World Medical, Inc., Rancho Cucamonga CA], Baerveldt [Advanced Medical Optics, Inc. Santa Ana, CA], Krupin [Eagle Vision, Inc., Memphis TN], Molteno [Nova Eye Medical Limited, Fremont CA]) follow the same principles. They include an explant plate that, when encapsulated, creates a potential space into which aqueous humor can drain via a connecting tube. The explant plates are constructed of polypropylene or silicone rubber to which fibroblast cannot tightly adhere. Typically, the tube of a shunt is placed into the anterior chamber of the eye and drains into one or more plates. Shunts differ based on the type of materials used (e.g., silicone, gold, stainless steel); presence or absence of a valve or flow restrictor in the tube; explant surface area; and shape, size, thickness and number of plates. Aqueous shunts are associated with intraoperative and postoperative complications similar to trabeculectomy plus an additional risk related to implantation of a foreign body and erosion of the tube. Diplopia has also been reported. However, the risk of postoperative infection appears less with shunts compared to trabeculectomy. When a single quadrant device is in place and not providing adequate IOP control (i.e., clinical failure), an option is to add a second device in another quadrant (Minckler, et al., 2008; Schwartz, et al., 2006).

The EXPRESS™ Mini Glaucoma Shunt (Optonol, Israel) is a stainless steel non-valved device designed to have more reproducible results with less dependency on surgical skills than other aqueous shunts. The device is placed under a partial thickness scleral flap and transports aqueous fluid from the anterior chamber to the sub-conjunctival space, forming a bleb similar to trabeculectomy. Unlike a standard trabeculectomy, the procedure is noninvasive and does not require a traditional sclerectomy or iridectomy.

U.S. Food and Drug Administration (FDA): Examples of first-generation aqueous drainage devices that received FDA 510(k) clearance between 1988 and 1995 include the following:

- Ahmed™ Glaucoma Valve (New World Medical, Inc., Rancho Cucamonga, CA): management of intractable glaucoma, particularly in cases where previous filtering procedures have failed or are known to have unsatisfactory results
- Baerveldt® Pars Plana Glaucoma Implant (Pharmacia Lovision, Inc., Peapack, NJ): medically uncontrollable glaucoma with poor surgical prognosis
- Krupin eye valve with disk (Hood Laboratories, Pembroke, MA)
- Molteno Valve (Staar Surgical Co., Monrovia, CA)

Modified versions of the Ahmed and Molteno devices received subsequent 510(k) clearance in 2006. The most recent version of the Molten Valve, the Molteno 3, is intended to reduce intraocular pressure in neovascular glaucoma or glaucoma where medical and conventional surgical treatments have not been successful in controlling the progression of disease. The

Ahmed™ Glaucoma Valve (AGV™) Model M4 is intended for use in patients with intractable glaucoma to reduce intraocular pressure where medical and conventional surgical treatments have failed.

The EXPRESS™ Mini Glaucoma Shunt (Optonol, Ltd, Israel), originally received 510(k) clearance in 2002. It was considered to be substantially equivalent to several predicate devices, including the Ahmed and Baerveldt devices, described above. A revised version, the Blunt Tip EXPRESS mini glaucoma shunt, was cleared in 2003, and is indicated for use in reduction of intraocular pressure in patients with glaucoma where medical and conventional surgical treatments have failed.

Literature Review Ahmed, Baerveldt, Krupin, and Molteno: The Ahmed, Baerveldt, Krupin, and Molteno are first generation devices and have become an established treatment option for selected patients with glaucoma. Systematic reviews, meta-analysis, randomized controlled trials and case series with up to ten-year follow-ups have reported that these devices are effective in lowering intraocular pressure (IOP) and improving the visual field. Overall high success rates and/or lower reoperation rates have also been reported. Complications have been transient and self-limiting (Haibo, et al., 2015; Gedde, et al., 2012a; Gedde, et al., 2012b; Budenz, et al., 2011; Christakis, et al., 2011; Molteno, et al., 2011; Wishart, et al., 2010; Gedde, et al., 2009; Woodcock, et al., 2008; Wilson, et al., 2003; Broadway, et al., 2001).

Literature Review Express: Meta-analysis and randomized controlled trials (Chen, et al., 2014; Netland, et al., 2014; Wang, et al., 2013; de Jong, et al., 2011; de Jong, et al., 2009) have evaluated the safety and efficacy of insertion of the EXPRESS™ Mini Glaucoma Shunt to trabeculectomy in the treatment of patients with open-angle glaucoma and uncontrolled glaucoma. Postoperatively, Ex-PRESS patients showed stable IOP or improved IOP and were more likely to achieve complete success. The responder rate was higher, time to failure was longer, ExPRESS was better tolerated and/or surgical interventions for complications were less in the ExPRESS group.

iStent Trabecular Micro-Bypass Stent

The iStent Trabecular Micro-bypass Stent is a heparin-coated titanium L-shaped implant that was developed as a treatment option for patients with mild or moderate open-angle glaucoma. It is intended to improve aqueous outflow and decrease IOP by creating an opening in the trabecular meshwork and allow aqueous humor to drain into Schlemm's canal and exit the eye. The iStent is a one-piece, heparin-coated, titanium L-shaped implant that can be inserted by either an internal or external approach. Unlike the devices described above, the iStent is an ab interno device (entirely within the eye with no communication to the outside) implanted through the trabecular meshwork to target the Schlemm's canal and enhance trabecular outflow. It is used in patients with mild-to-moderate chronic open-angle glaucoma who are also candidates for cataract surgery. A single iStent device was implanted in each eye in randomized controlled trials evaluating the device. Studies evaluating the use of more than one iStent in each eye are lacking.

U.S. Food and Drug Administration (FDA): The Glaukos iStent Trabecular Micro-Bypass Stent (Glaukos Corp., Laguna Hills, CA) received FDA premarket approval (PMA) in June 2012 for use in conjunction with cataract surgery for the reduction of intraocular pressure (IOP) in adult patients with mild to moderate open-angle glaucoma currently treated with ocular hypotensive medication. As a condition of approval, Glaukos was required to submit follow-up of the Investigational Device Exemption (IDE) study cohort extending to five years, a prospective, randomized multicenter parallel study with new enrollment (n=360) to assess long-term safety, and a prospective multicenter registry to include 500 patients.

Literature Review: Randomized controlled trials (RCTs), systematic reviews and meta-analysis support iStent for the treatment of glaucoma. RCTs comparing cataract surgery with Glaukos

iStent Trabecular Micro-Bypass Stent compared to cataract surgery alone have reported significantly better outcomes with insertion of a single iStent. Significant improvement in IOP and decreased medication usage with no increased complications were reported (Popvic, et al., 2018; Malvankar-Mehta, et al., 2015; Craven, et al., 2012; Samuelson et al., 2011; Fernandez-Barrientos et al., 2010; Fea, 2010).

iStent *inject* Trabecular Micro-Bypass System

The iStent *inject* Trabecular Micro-Bypass System (Glaukos, Laguna Hills, CA) contains two preloaded intraocular stents that are manufactured from titanium and are coated with stearylchondroitin sulfate heparin from a porcine source. The stent has a single piece design, is 230 µm in diameter, 360 µm in height, and the central inlet and outlet lumen has a diameter of 80 µm. The head of the stent has four outlets on each side. The iStent *inject* has a rear flange which resides in the anterior chamber, a head that resides in Schlemm's canal and the thorax of the stent is retained by the trabecular meshwork. The two multi-directional stents are placed two to three clock hours apart. The stent is designed to be implanted in either the left or right eye. There are two preloaded intraocular stents in each injector to be loaded one at a time into Schlemm's canal (FDA, 2018; Pillunat, et al., 2017).

The iStent *inject* is a second generation iStent and is much smaller than any other FDA approved implant. Unlike the original iStent, the G2-M-IS iStent *inject* is injected rather than inserted and contains two stents. Because the iStent *inject* is injected it increases the risk of not going into the canal.

U.S. Food and Drug Administration (FDA): The iStent *Inject* was PMA FDA approved in 2018 "for use in conjunction with cataract surgery for the reduction of intraocular pressure (IOP) in adult patients with mild to moderate primary open-angle glaucoma".

Literature Review: Case series with small patient populations (n=20-99 eyes) and short-term follow-ups (12-36 months) have reported postoperative improvement in IOP with or without medication and reduction in ocular hypotension medications required following cataract surgery (Hengerer, et al., 2018; Berdahl, et al., 2017; Arriola-Villalobos, 2016; Lindstrom, et al., 2016) and in standalone procedures (Voskanyan, et al., 2014). A case series by Hooshman et al. (2018) reported on outcomes with iStent (n=145 eyes) and iStent *inject* (n=100 eyes). At 12 months, 56.0% of the iStent and 51.3% of the iStent *inject* eyes had achieved an IOP of ≤ 18mmHg with zero medications and 63.1% and 57.7% an IOP of ≤ 18mmHg with reduced medications.

Samuelson et al. (2019) conducted a multicenter, randomized controlled trial to assess the safety and effectiveness of the iStent *inject* implanted in combination with cataract surgery. Eyes were randomized 3:1 intraoperatively to iStent *inject* (n=387) or no stent implantation (control group, n=118). Inclusion criteria were: (1) diagnosis of mild to moderate POAG; (2) age-related cataract eligible for phacoemulsification, with BSCVA 20/40 or worse in the presence of glare; (3) screening IOP ≤ 24 mmHg on 1-3 ocular hypotensive medications, with a stable dosage regimen for ≥ 2 months; (4) baseline unmedicated (post-wash out) DIOP ≥ 21 mmHg and ≤ 36 mmHg, and at least 3 mmHg higher than medicated screening IOP; (5) screening cup-to-disc (C:D) ratio of 0.8 or less; (6) normal open-angle anatomy (Shaffer grade ≥3) by gonioscopy; and (7) ability to provide an adequate, interpretable visual field. Primary outcome measure was ≥ 20% reduction from baseline in month 24 unmedicated DIOP. The secondary outcome measure was the change in unmedicated DIOP from baseline compared to month 24. Safety measures included best spectacle-corrected visual acuity (BSCVA), slit-lamp and fundus examinations, gonioscopy, pachymetry, specular microscopy, visual fields, complications, and adverse events. In both groups, ocular medications after surgery included 1 week of topical antibiotics and 4 weeks of tapered topical prednisolone acetate 1%. Follow-ups occurred for up to two years. Annual washout of ocular hypotensive medication was performed. In the treatment group 380 eyes were implanted

with two stents. At 24 months, there was a statistically significant difference in the treatment group compared to the control group in the number of eyes that experienced a $\geq 20\%$ reduction from baseline in unmedicated DIOP ($p=0.005$) and mean reduction in unmedicated DIOP ($p<0.001$) from baseline. Of the responders, 84% of iStent eyes and 67% of control eyes were not receiving ocular hypotensive medication and 63.2% of treatment eyes compared to 50.0% of control eyes had medication-free DIOP ≤ 18 mmHg at month 24. The majority of eyes in both groups achieved BSCVA of 20/40 through 24 months. Approximately 79% of eyes in both groups exhibited no change in C:D ratio. At month 24, 12 subjects in the treatment group and six in the control group did not undergo washout. Eleven intraoperative adverse events were reported during stent implantation (2.8%); four eyes were implanted with three stents and two eyes with one stent. One stent was implanted in the ciliary body, and there were three cases of corneal abrasion that resolved by postop day three. A lower proportion of iStent eyes than control eyes experienced adverse events (54.1% vs. 62.2%, respectively). Stent obstruction occurred in 24 eyes. Per the authors the main study limitations were that surgeons were not masked to the treatment groups, and the data include the surgeons' learning curve with the technology. Additional limitations are the short-term follow-up and patients who did not wash out at 24 months.

Fea et al. (2014) conducted a multicenter, randomized controlled trial (Second Line Study) to compare the outcomes of patients with open-angle glaucoma treated with two iStent inject devices ($n=94$) vs medical therapy ($n=98$) (fixed combination of latanoprost/timolol). Included subjects had a baseline post-washout IOP between ≥ 22 mmHg and < 38 mmHg; minimum best corrected visual acuity (BCVA) of 20/200 or better; scleral spur clearly visible by gonioscopy; and able and willing to attend follow-up visits for one year postoperatively. The study was initiated using the first-generation injector, inserting one stent at a time and then the iStent inject which hold two stents was used in the study. Outcome measures included percentage of subjects who achieved an IOP reduction $\geq 20\%$ versus baseline unmedicated IOP; percentage of subjects who achieved an IOP ≤ 18 mmHg, mean IOP at each study visit, and mean reduction in IOP. Safety measures assessed cup-to-disc (CD) ratio, BCVA, and incidence of adverse events. Following implantation of two iStent inject devices, subjects received topical postoperative anti-inflammatory and anti-infective medications for 4 weeks. Follow-up occurred got up to 12 months. At the month 12 visit, 94.7% of eyes (89/94) in the stent group reported an unmedicated intraocular pressure (IOP) reduction of $\geq 20\%$ versus baseline unmedicated IOP compared to 91.8% of eyes (88/98) in the medical therapy group. A statistically significant 17.5% between-group treatment difference in favor of the iStent inject group was recorded ($p=0.02$) at the $\geq 50\%$ level of IOP reduction. An IOP ≤ 18 mmHg was reported in 92.6% of eyes (87/94) in the iStent inject group and 89.8% of eyes (88/98) in the medical therapy group. Mean IOP decreases from screening of 8.1 (2.6) mmHg was reported in the iStent inject group vs. 7.3 (2.2) mmHg in the medical therapy group. The proportion of eyes with BCVA of 20/40 or better was 84% preoperatively vs. 79% at month 12 in the iStent inject group and 87% preoperatively vs. 84% at month 12 in the medication group. In the iStent group one subject experienced an elevated IOP at 48 mmHg, one subject had one stent reported as not visible, one subject reported soreness/discomfort. All events were resolved. Two adverse events were reported in two subjects in the medical therapy group, one was mild burning of the eye, and the other was suspected allergy to medication. Four eyes in the iStent inject group were taking medication at the 12-month follow-up visit. Author-noted limitations of the study include that it was not a blinded study; because of the qualifying IOP requirement, lower dispersion of IOP measurement data or regression to the mean may have occurred; and the patient population was limited to white patients. Additional limitations of the study include the small patient population, short-term follow-up, and change in stent device during the study.

Ab Interno Suprachoroidal Microstent (i.e., CyPass MicroStent): An ab interno suprachoroidal microstent has been proposed for the treatment of glaucoma. The CyPass® Micro-

Stent (Transcend Medical, Inc., Menlo Park, CA), a polyimide (plastic) tube with a fenestrated lumen, is designed for use during cataract surgery to decrease intraocular pressure (IOP) in adult patients with mild to moderate primary open-angle glaucoma (POAG). Using an ab interno approach, the device is placed in the angle of the eye, with the proximal end extending from the angle into the anterior chamber (AC) and the distal end residing in the supraciliary space (supraciliary microstenting). It is proposed to allow outflow of aqueous fluid from the AC of the eye through and around the distal end of the tube (where the device proximal end resides) into the supraciliary and suprachoroidal spaces. The stent is loaded onto the guidewire before insertion into the eye. Once the guidewire has positioned the Micro-Stent at the desired location within the eye, the implant is released from the guidewire (FDA, 2016). There is insufficient evidence to support the safety and efficacy of the CyPass for the treatment of glaucoma.

U.S. Food and Drug Administration (FDA): The CyPass[®] Micro-Stent (Alcon Laboratories, Inc., Fort Worth, TX) was FDA PMA approved in 2016 for “use in conjunction with cataract surgery for the reduction of intraocular pressure (IOP) in adult patients with mild to moderate primary open-angle glaucoma (POAG)”. The CyPass System consists of the CyPass Micro-Stent, which is contained in a loading device (Loader), and the CyPass Applier. In 2019, Alcon voluntarily withdrew the CyPass Micro-Stent from the global market based on five-year post-surgery data from the COMPASS-XT long-term safety study. The study demonstrated a clinically and statistically significant increase in corneal endothelial cell loss reported in the CyPass Micro-Stent group compared to the cataract surgery-only control group (FDA, 2018).

Literature Review: There is insufficient evidence to support the safety and effectiveness of CyPass for the treatment of glaucoma. Studies are primarily in the form of case series with small patient populations (n=65–111) and short-term follow-up (six months to two years). Improvement in IOP was reported and in some cases mean postoperative medication usage was significantly decreased. Early and late postoperative IOP elevations were seen in 1.2%–1.8% of subjects. Up to 8.8% events of microstent obstruction were reported with up to 40% loss to follow-up. In one study 11% of patients required secondary incisional glaucoma surgery (Hoeh, et al., 2016; García-Feijoo, et al., 2015; Hoh, et al., 2014). Studies comparing CyPass to pharmacotherapy and established surgical intervention are lacking.

Vold et al. (2016) conducted a multicenter, randomized controlled trial (n=505) (COMPASS) comparing supraciliary microstenting (CyPass) to surgical treatment (phacoemulsification) for mild-to-moderate primary open-angle glaucoma (POAG). COMPASS was a US Food and Drug Administration clinical trial and according to the authors the first study on nontrabecular stenting. Outcomes were reported for up to two-years. At the conclusion of uncomplicated cataract surgery, 131 patients were randomized to the control group which had cataract surgery alone and 374 patients were randomized to the microstent group (CyPass) which had cataract surgery with microstent implantation. Prior to the study all subjects underwent full glaucoma medication washout for unmedicated baseline evaluation. Inclusion criteria were as follows: 1) age \geq 45 years; 2) diagnosed or confirmed POAG (Shaffer grade 3 in all quadrants of the study eye) within 90 days of screening; 3) screening medicated IOP \leq 25 mmHg or unmedicated IOP between 21–33 mmHg; 4) baseline unmedicated diurnal IOP between 21–33 mmHg, and \geq 3 mmHg higher than screening IOP; and 5) age-related cataract with best-corrected visual acuity (BCVA), or acuity testing with a Brightness Acuity Meter, of 20/40 or worse that was eligible for phacoemulsification cataract surgery with intraocular lens implantation. The primary outcome measure was the proportion of eyes with unmedicated IOP reduction \geq 20% at 24 months vs unmedicated baseline IOP. A total of 480 subjects (mean age 70 years) completed the two-year follow-up. Microstenting with the CyPass plus cataract surgery significantly reduced IOP compared with cataract surgery alone. Significantly more microstent subjects (77%) than controls (60%) achieved a $>$ 20% reduction in unmedicated diurnal IOP at the 24-month follow-up (p=0.001). Postoperative IOP was reduced from baseline significantly more in the microstent group

($p < 0.001$). Microstent vs. control group had significantly reduced hypotensive ocular medication use ($p < 0.001$). Control subjects required a three-fold greater number of IOP-lowering medications than microstent recipients ($p < 0.001$). Compared with baseline values 0% controls and 1.1% of CyPass subjects displayed a BCVA reduction of ≥ 2 lines at the 24-month follow-up. Visual acuity was high in both groups with $> 98\%$ of all subjects achieving $\geq 20/40$ BCVA. Most minor adverse events (e.g., iritis, corneal edema, visual field loss progression, BCVA loss) were transient. Six microstent and three control subjects completed the study with unresolved BCVA loss. Microstent adverse events included eight stent obstructions including two malpositioning and two migration dislodgement events. No vision threatening ocular or serious adverse events related to surgical intervention occurred in either group. Limitations of the study as noted by the authors included lack of equal representation of all ethnic groups and the principal investigator at each study site was not masked to treatment randomization during patient follow-up examinations. Other limitations are the short-term follow-up, 3:1 randomization and number of patients lost to follow-up (10%).

XEN Glaucoma Treatment System: A second device which is an aqueous gel stent also been approved for use in the United States. The XEN Glaucoma Treatment System (Allergan, Inc. Aliso Viejo, CA) consists of the crosslinked XEN Gel Stent preloaded into the XEN Injector. The Stent is composed of a gelatin derived from porcine dermis, formed into a tube, and then cross-linked with glutaraldehyde. The Gel Stent is proposed to create a permanent channel through the sclera allowing an outflow of aqueous humor from the anterior chamber to the subconjunctival space resulting in a conjunctival bleb. The XEN Gel Stent is preloaded into the injector which is designed to place the Gel Stent in the intended position through an ab interno approach. The goal of the XEN is to lower IOP without relying on physiologic outflow pathways. Proposed advantages of the Gel Stent include: 1) the hydrophilic device swells to secure itself into the scleral tissue which is proposed to limit movement without requiring additional surgical fixation; 2) the implant material is proposed to be highly malleable compared to the silicone tubing used in tube shunt surgery which allows the XEN to bend easily and convey less force against the tissue once implanted; 3) since, the XEN is injected, no conjunctival incision is necessary. Chaudhary et al. (2018) noted that a potentially greater degree of postoperative management is needed with the XEN due to formation of a subconjunctival bleb requiring close follow-up. It is not yet been established if this additional workload is made worthwhile by its efficacy and whether the greater simplicity and safety profile outbalance the established efficacy of traditional filtering surgery. The XEN Gel Stent comes in three models that vary in internal lumen diameter (45 μ m, 63 μ m and 140 μ m) (FDA, 2016; Sheybani, 2015; Lewis, 2014). According to the manufacturer's website, the safety and effectiveness of implanting more than one XEN gel stent in an eye has not been studied (Allergan, 2023).

U.S. Food and Drug Administration (FDA): In 2016, the XEN Glaucoma Treatment System (Allergan, Inc. Aliso Viejo, CA) was FDA 510(k) (K161457) approved as a Class II aqueous shunt indicated "for the management of refractory glaucomas, including cases where previous surgical treatment has failed, cases of primary open angle glaucoma, and pseudoexfoliative or pigmentary glaucoma with open angles that are unresponsive to maximum tolerated medical therapy". The XEN Glaucoma Treatment System consists of the XEN45 Gel Stent preloaded into the XEN Injector. The XEN45 Gel Stent is composed of a gelatin derived from porcine dermis, formed into a tube, and then cross-linked with glutaraldehyde. Xen-EX describes the ab externo approach and involves inserting the device externally through the conjunctiva first, then through the sclera and then through the angle into the anterior chamber.

Literature Review: Clinical trials evaluating the safety and effectiveness of the XEN45 system are primarily in the form of retrospective reviews and case series with small patient populations ($n=30-65$) and short-term follow-ups (12 months) (De Gregorio, et al., 2018; Widder, et al., 2018; Grover et al., Nov 2017; Schlenker, et al., 2017; Hengerer, et al., 2017; Pérez-Torregrosa,

et al., 2016;). Case series (n=12–111) reported the six- to 12-month outcomes of Xen implant with (XenPhaco) and without cataract surgery (Hohberger, et al., 2018; Fea, et al., 2017). Studies have also been conducted investigating XEN used with mitomycin C (Galal, et al., 2017). Sng et al. (2018) investigated the use of XEN45 for the treatment of uveitic glaucoma (n=24). Some studies used the XEN140 and/or XEN63 which are no longer recommended by the manufacturer (Colby, et al., 2017; Sheybani, et al., 2016; Sheybani, et al., 2015). According to Chaudhary et al. (2018) these XEN devices are not directly comparable to the currently commercialized devices and techniques. The XEN45 system is inserted via an ab interno or an ab externo approach. The safety and effectiveness of both approaches are supported by the studies (Do, et al., 2021; Tan, et al., 2021; Panarelli, et al., 2020; Vera, et al., 2020).

Tan et al. (2021) conducted a retrospective review to compare the safety and efficacy of two different techniques for implantation of the XEN Gel Stent, ab interno (n=50 eyes) or ab externo (n=30 eyes). All patients had a diagnosis of open-angle glaucoma and had uncontrolled IOP, progressing glaucoma, and/or an intolerance to topical hypotensive drops. In the ab interno group, average age was 71.0±13.4 years, 48% female, 48% Hispanic, 30% white, 16% African American and 6% Asian. For the ab externo group, average age was 67.6±9.3 years, 70% female, 63.3% Hispanic, 13.3% white, 23.3% African American and no Asians. Patients were excluded if they received a glaucoma drainage device concomitant with XEN Gel Stent insertion and those that were lost to follow-up before six months. Mean intraocular pressure (IOP) was 8.4±1.7 mmHg (28.6% decrease) in the ab interno group and 12.8±3.0 mmHg (40.1% decrease) in the ab externo group (p=0.208) at 12 months. The ab interno cohort demonstrated a mean reduction in medication use of 1.81±0.29 medications at 12 months, compared to a mean reduction of 1.86±0.37 in the ab externo group (p=0.913). By 12 months, 5-fluorouracil injection was required in 58% of ab interno eyes versus 36.7% of ab externos (p=0.105). Bleb needling was applied to 42% and 26.7% of the eyes, respectively (p=0.231) and a second glaucoma surgery was necessary for 20% of the ab interno cohort and 10% of the ab externo cohort (p=0.351). Adverse events included numerical hypotony (ab interno 2/50 [4.0%], ab externo 1/30 [3.3%]), choroidal effusion (ab interno 2/50 [4.0%], ab externo 0/30 [0%]), two Snellen lines or more loss of visual acuity (ab interno 5/50 [10%], ab externo 3/50 [10%]). The vision loss was accounted to cataract formation in two cases in the ab interno group and one case in the ab externo group. An advantage of this study is the racial diversity of the patient population. Author noted study limitations included the retrospective study design, small patient populations, short term follow up and the potential impact of the surgeon's increase in technique proficiency over time. Patient outcomes were very similar between ab interno and ab externo placement of the XEN Gel Stent. Both approaches are safe and effective for lowering IOP.

Reitsamer et al. (2019) conducted a case series (n=218 eyes; 200 patients) to evaluate the safety and efficacy of XEN45 implant in the treatment of medically uncontrolled moderate primary open angle glaucoma (POAG). Inclusion criteria were: ≥ 18 years of age, diagnosis of moderate POAG (defined by a mean deviation score between -3 and -12 dB); uncontrolled on topical therapy; medicated IOP ≥ 18 and ≤ 33 mmHg; use of one to four topical IOP-lowering medications; area of healthy, free, and mobile conjunctiva in the target quadrant; Shaffer angle grade ≥ 3 in the target quadrant. Postoperative change in mean IOP and medication usage were the primary outcome measures. Clinical success was defined as achieving ≥ 20% IOP reduction on the same or fewer IOP-lowering medications at month 12 or 24 compared with baseline, without glaucoma-related secondary surgical intervention (SSI) (which did not include needling) or intention to be converted to another procedure during the study. Follow-up occurred intermittently for up to 24 months. Overall, 197/218 (90.4%) eyes completed the 12-month visit; 174/218 (79.8%) completed the 24-month visit, while 44/218 (20.2%) discontinued the study due to conversion to surgical procedure, lost to follow-up, implant malposition, explanations, and other miscellaneous issues. Average age was 71.8 years, 51.4% female, 48.6% male, 96.2% white, 1.6% Black and 2.2% Asian. There was a significant improvement at the 24-month follow-up in mean IOP (p<0.001)

and medication usage ($p < 0.001$) in the Xen alone and Xen plus cataract subjects. The clinical success was 65.8% and 72/161 eyes were medication free. The overall needling rate was 41.1% ($n = 83/202$) with no significant difference between the groups. Ten intraoperative complications included six anterior chamber bleeds. Six eyes/patients had serious ocular adverse events. All cases of hypotony (defined as IOP < 6 mm Hg) were self-limited and self-resolved within one month of surgery. An author noted limitation of the study was the variability in perioperative treatment regimen which was at the investigator's discretion. Additional limitations include the number of patients lost to the study (44/218; 20.2%), lack of an established medical or surgical comparator, and the fact that less than 5% of the study population was of Asian or Black ethnicity.

King et al. (2018) conducted a Cochrane review of randomized controlled trials (RCTs) that compared the Xen gelatin implant or InnFocus MicroShunt to other minimally-invasive glaucoma device techniques, trabeculectomy, laser treatment or medical treatment. The objective of the review was to evaluate the efficacy and safety of subconjunctival draining minimally-invasive glaucoma devices in patients with open angle glaucoma and ocular hypertension that were inadequately controlled with drops. The primary outcome was mean change in IOP. Secondary outcomes included subjects who were drop-free following the intervention; achieved an IOP of 21 mmHg or less, 17 mmHg or less or 14 mmHg or less; and the occurrence of intraoperative and postoperative complications. No RCTs were found that met the inclusion criteria.

Mansouri et al. (2018) conducted a prospective case series to evaluate the safety and efficacy of the XEN45 gel implant in the treatment of glaucoma patients ($n = 149$ eyes; 113 patients) with uncontrolled IOP in combination with a cataract extraction procedure or as a standalone procedure. Based on visual field results, glaucoma severity ranged from mild to moderate disease with the majority of patients being in the mild stage. Subjects were age ≥ 18 years and diagnosed with primary or secondary OAG. Inclusion criteria for XEN surgery were uncontrolled IOP, progressing glaucoma, and/or intolerance to IOP-lowering drops. A total of 109 (73.2%) eyes underwent XEN plus cataract surgery and 40 (26.8%) underwent XEN alone. Data on 87 eyes (58%) were available one year following surgery. A significant reduction (31%) was seen in IOP ($p < 0.01$) and mean medication usage ($p < 0.001$). In total, 62.1% of patients achieved a $\geq 20\%$ IOP reduction which was higher in the XEN alone group. The median IOP reduction was 40% in the XEN alone group and 22.9% in the XEN plus cataract group. Complete success was achieved in 57.5% of the XEN alone group and 64.2% of the XEN plus cataract group using the < 18 mmHg threshold and in 57.5% and 57.8%, respectively, using the < 16 mmHg threshold. At one year, 28.7% of eyes required some antiglaucoma medications for IOP reduction. A total of 55 eyes (37%) required needling – 18 eyes (45%) in the XEN alone eyes versus 37 eyes (34%) in the XEN plus cataract eyes. Adverse effects included bleb revision ($n = 5$ eyes), choroidal detachment ($n = 2$ eyes), and a second glaucoma surgery due to uncontrolled IOP ($n = 9$ eyes). Visual acuity loss was permanent in two eyes. In one eye, a second XEN device was implanted next to the first XEN due to presumed device obstruction. In the XEN plus cataract surgery group, there were two cases of intraoperative posterior capsule rupture. Limitations of the study include the small patient population, short-term follow-up, lack of a comparator, and the number of patients lost to follow-up. Additional author-noted limitations were the lack of washout at baseline which made the unmedicated IOP unknown, two surgeons performed the procedures and the decision to reinstate medications and to perform needling procedure were not standardized, and the homogenous white study population limiting generalizability to other ethnicities.

Hydrus™ Microstent: The Hydrus® Microstent or Hydrus implant (Ivantis, Inc. Irvine, CA) is considered an "intracanalicular scaffold". It is a crescent-shaped, implantable microstent composed of a metal alloy of nickel and titanium (nitinol) pre-loaded onto a hand-held delivery system. Its curvature shape is intended to match the curvature of Schlemm's Canal and occupy 90° (three full clock hours) of the canal. The implant is 8 mm in overall length, is delivered ab

interno into the trabecular meshwork and Schlemm's canal through a clear corneal incision into the canal. The device is proposed to enhance aqueous outflow by providing trabecular meshwork (TM) bypass, dilation of a quadrant of the Schlemm canal (SC), and direct aqueous access to multiple collector channels. After the implantation, the Hydrus micro-stent dilates Schlemm's canal in the complete nasal quadrant, allowing aqueous humor to bypass the trabecular meshwork through multiple collector channels (Samuelson, et al., 2019; FDA, 2018; Pillunat, et al., 2017).

U.S. Food and Drug Administration (FDA): The Hydrus[®] Microstent (Ivantis, Inc. Irvine, CA) was FDA PMA approved in August 2018 "for use in conjunction with cataract surgery for the reduction of intraocular pressure (IOP) in adult patients with mild to moderate primary open-angle glaucoma (POAG)".

Literature Review: Samuelson et al. (2019) conducted a multicenter, randomized controlled trial (HORIZON study) to compare the safety and efficacy of cataract surgery followed by implantation of Hydrus Microstent (HMS) (n=369) to cataract surgery with no microstent (NMS) (n=187). Randomization was 2:1 in favor of the Hydrus. Included patients had age-related cataract and a diagnosis of mild-to-moderate POAG on 1–4 topical hypotensive medications. Patients who were eligible for participation had ophthalmoscopically visible glaucomatous optic neuropathy; mild-to-moderate visual field; best-corrected visual acuity 20/40 or worse with or without brightness acuity testing; Schaffer grade III–IV angle in all four quadrants; and a medicated IOP of ≤ 31 mmHg. Baseline wash out of medications was required to ensure inclusion of subjects within a known range of IOP. After wash out of all hypotensive medications, modified diurnal IOP was required to be 22–34 mmHg at baseline, with an increase of at least 3 mmHg compared to the medicated IOP value recorded at the screening visit. The MDIOP value was obtained by averaging three Goldmann applanation tonometry measurements taken 4 ± 1 hours apart between 8:00 AM and 4:00 PM. All MDIOP values reported in this study were unmedicated. Follow-ups occurred for up to 24 months. The primary outcome measure was the number of subjects demonstrating a 20% or greater reduction in unmedicated modified diurnal IOP (MDIOP). Secondary outcome was the change in mean MDIOP from baseline. At 24 months, there was a significant reduction of MDIOP in the HMS group vs. the NMS group ($p < 0.001$), and in the mean reduction of unmedicated MDIOP ($p < 0.001$). A 30% or greater MDIOP reduction was reached in 53.4% HMS vs. 32.1% NMS eyes ($p < 0.0001$), and a 40% or greater reduction in MDIOP was reached in 24.7% HMS vs. 8.0% NMS eyes ($p < 0.0001$). There was also a significant difference in the reduction in the mean number of medications in the HMS group vs the NMS group ($p < 0.001$). At 24 months, 78% of HMS eyes were medication free vs. 48% in the NMS group ($p < 0.001$). One subject from each group had lost ≥ 2 lines compared to preoperative BCVA. Visual field mean deviation worsened by ≥ 2.5 dB or more in 4.3% of HMS and 5.3% of NMS eyes. There were no serious microstent adverse events and no difference in safety between the groups. Secondary surgical intervention was more common in the NMS group. In the NMS group, four eyes with inadequately controlled IOP required trabeculectomy or tube shunt placement. The most common adverse finding in the HMS group was focal adhesion consisting of peripheral anterior synechiae (PAS) or iris tissue near the device inlet. Author noted limitations of the study included the potential for bias due to inability to mask the surgeon to the treatment group during postoperative examinations. Also, the study excluded patients with secondary open-angle glaucomas and thus the results may not be generalizable to these populations. Another limitation is the short-term follow-up. The 5-year follow up to this study supported the outcomes of the two-year study (Ahmed, et al., 2022).

Pfeiffer et al. (2015) conducted a multicenter, randomized controlled trial to assess the safety and efficacy of cataract surgery with implantation of the Hydrus Microstent (n=50) compared to cataract surgery alone (n=50). Inclusion criteria were: concurrent open-angle glaucoma and cataract; IOP ≤ 24 mmHg with no more than four hypotensive medications; Shaffer grade III or IV chamber angle in all quadrants; visual field changes characteristic of glaucoma or

glaucomatous optic nerve damage; capable of safely undergoing medication washout; and diurnal IOP (DIOP) 12–36 mmHg. Patients underwent wash out to obtain preoperative baseline diurnal IOP (DIOP) value which was obtained by averaging 3 Goldmann tonometry measurements obtained four hours apart between 8:00 AM and 4:00 PM. The primary outcome measure was the proportion of patients with $\leq 20\%$ reduction in mean washed out DIOP. Follow-ups occurred for up to 24 months. At 24 months, the total number of evaluable washout subjects was 78 (87%) of 90. Significantly more subjects in the Hydrus group had $\geq 20\%$ reduction in washed out DIOP compared with baseline ($p=0.0008$). The mean washed out DIOP in the cataract plus Hydrus group was significantly lower compared with the cataract alone group ($p=0.0093$). The mean medicated IOP was 16–17 mmHg in both groups from month three through month 24. There was a significant difference in medication use between the groups ($p=0.0189$) with 0.5 ± 1.0 medication usage in the Hydrus group vs 1.0 ± 1.0 in the cataract only group. At 24 months the number of unmedicated patients was significantly less in the Hydrus group ($p=0.008$), almost 2:1. There were no significant safety issues in either group. In most subjects, adverse events resolved without intervention in 1–3 months. One subject in the Hydrus plus CS group and two from the CS group had secondary glaucoma surgery for elevated IOP despite maximum tolerated medical therapy. Author noted limitations of the study include: surgeons weren't masked to the assigned treatment; several patients did not wash out medications for safety reasons which led to more failures in the cataract only group, and the study population was white making it difficult to generalize the results to other ethnicities. Other limitations include the small patient populations, short-term follow-up and number of patients lost to follow-up.

iStent Infinite® Trabecular Micro-Bypass System, Model iS3: The iStent infinite Trabecular Micro-Bypass System, Model iS3 (Glaukos Corp., Laguna Hills, CA) consists of three micro stents on a single preloaded injector. The stents are implanted via an ab interno approach in three separate areas of the trabecular meshwork. The three stents create a patent bypass through the trabecular meshwork into Schlemm canal to increase physiological aqueous outflow and reduce IOP.

U.S. Food and Drug Administration (FDA): The iStent infinite Trabecular Micro-Bypass System, Model iS3 was 510(k) (K220032) approved on August 2, 2022 “for use in adult patients with primary open-angle glaucoma in whom previous medical and surgical treatment has failed”. It was approved as a standalone procedure.

Literature Review: Sarkisian et al. (2022) conducted a prospective, multicenter, single-arm study to evaluate the efficacy and safety of the iStent Infinite Trabecular Micro-Bypass System in the treatment of open angle glaucoma (OAG) in patients ($n=72$) uncontrolled by prior surgical or medical therapy. Primary outcomes included the proportion of eyes achieving $\geq 20\%$ mean diurnal intraocular pressure (MDIOP) reduction from baseline on the same or fewer intraocular pressure (IOP)-lowering medication classes and mean change in MDIOP from baseline at 12 months. The mean medicated MDIOP was 23.4 ± 2.8 preoperatively and patients were on a mean of 3.1 ± 0.9 IOP-lowering medication classes. A total of 76.1% of patient met the responder endpoint with a mean reduction in MDIOP of 5.6 mmHg at 12 months. At 12 months, medication was reduced to 2.70 ± 1.03 . There were no explants, infection, or device-related interventions or hypotony. The study limitations included a small patient population and short-term follow-up. iStent infinite stand-alone surgery achieved clinically significant IOP reduction and favorable safety in patients with OAG uncontrolled by prior therapy.

Additional devices

Several additional devices are under development/investigation but have not yet received FDA approval. Some of these devices include: EyePass™ Glaucoma Implant (GMP Companies, Inc., Ft. Lauderdale, FL), the SOLX® Gold Shunt (SOLX, Inc., Waltham, MA), iStent Supra® (Glaukos, Laguna Hills, CA), STARflo (iSTAR Medical, Isnes, Belgium), Aquashunt (OPKO Health Inc., Miami,

FL) and PRESERFLO MicroShunt (Santen Pharmaceutical Co., Ltd., Osaka, Japan [previously InnFocus MicroShunt® Innfocus Inc., Miami, FL]).

Technology Assessments

American Academy of Ophthalmology (AAO): The American Academy of Ophthalmology (AAO) (Chopra, et al., 2024) conducted a technology assessment on aqueous shunts with extraocular reservoir for the treatment of open-angle glaucoma (OAG) in adults. Following a systematic review of the literature, AAO made the following conclusion: "Implantation of aqueous shunts with extraocular reservoir, including valved or nonvalved devices, has been shown to be an effective strategy to lower IOP. Strong level I evidence supports the use of aqueous shunts with extraocular reservoir by clinicians for the management of adult OAG."

Procedures

Canaloplasty

Canaloplasty is a nonpenetrating procedure (ab externo or ab interno), similar to viscocanalostomy, aimed at lowering the IOP by permanently stretching the trabecular meshwork and restoring the natural drainage of fluid out of the eye. Conceptually, canaloplasty is an extension of viscocanalostomy with the addition of a flexible microcatheter-aided dilation using the iTRack device, the placement of a permanent suture under tension in Schlemm's canal, and the creation of an intrascleral reservoir (Kim, 2023). Proposed advantages of canaloplasty over trabeculectomy include: no subconjunctival bleb, lack of need for antimetabolites, fewer postoperative complications and simplified follow-up. The surgery is technically challenging with an initial learning curve and is contraindicated in eyes with angle recession, neovascular glaucoma, chronic angle closure, and narrow-angle glaucoma and in patients with previous ocular surgery that would prevent 360° catheterization of the Schlemm's canal. Canaloplasty also has the disadvantage of causing conjunctival scarring, which can make subsequent glaucoma surgery technically more difficult. Studies have shown a significant improvement in IOP and need for antiglaucoma hypotensive medications following canaloplasty.

Literature Review: Systematic reviews, randomized controlled trials and case series support the safety and efficacy of canaloplasty for the treatment of glaucoma. Canaloplasty has also evolved into an accepted treatment option for patients with open-angle glaucoma who have failed established medical management.

Zhang et al. (2017) conducted a systematic review and meta-analysis of canaloplasty (CP) compared to trabeculectomy (TE). Two randomized controlled trials, 11 prospective reviews, and 18 retrospective reviews (n=1498) were included. Twenty-eight studies were included in the quantitative analysis. Selection criteria included studies with the following: diagnosis of glaucoma, canaloplasty with or without phacoemulsification; IOP outcomes; and follow-up of at least six months. The primary outcomes were the changes in IOP and the number of antiglaucoma medications (AGMs). The secondary outcomes were the complete and qualified successful rates and the incidence of adverse events. A complete success was defined as an IOP that was less than a given level without any AGMs. A qualified success rate was defined as a confirmed IOP that was less than a given level with or without AGMs. The reduction of IOP in all subgroups at six months was 10.69. Results of the meta-analysis showed that there was an IOP decrease by 9.94 mmHg with an average antiglaucoma medications reduction of 2.11 at 12 months following canaloplasty. The IOP reduction was significantly higher after trabeculectomy with an average difference of 3.61 mmHg at 12 months. TE was more efficient in IOP control than CP. There was no significant difference in the reduction of AGMs or in the complete or qualified success rates between the two groups (n=3 studies). Regarding adverse events, hyphema was more prevalent in CP. Descemet membrane detachment was only observed in CP with a reported incidence of 3%. Suprachoroidal hemorrhage and bleb needling were only reported in TE with incidences of 2.3% and 10.9%,

respectively. TE had significantly higher incidences in hypotony and choroidal effusion/detachment. No significant difference was found in the incidence of conjunctiva leakage. Limitations of the study include the lack of randomized controlled trials and the high number of retrospective reviews, CP was less effective in IOP reduction, was able to achieve similar postoperative success rates and reduce the number of the AGMs. CP was also associated with lower incidence of complications and was reported with higher patient satisfaction. The author noted that more high-quality studies, especially RCTs, are needed to verify these findings.

Liu et al. (2017) conducted a systematic review of the literature to assess the safety and efficacy of canaloplasty and trabeculectomy for the treatment of glaucoma. Four prospective case studies and four retrospective reviews met inclusion criteria. Pooled intraocular pressure (IOP) of canaloplasty (n=129) and trabeculectomy (n=179) at six and 12 months showed no significant difference in outcome of the two groups, but the postoperative IOP was higher in the canaloplasty group. The success rate of the canaloplasty group was significantly lower than that of the trabeculectomy group (p=0.010). Compared to trabeculectomy, the canaloplasty group had a higher risk of hyphema and a lower risk of hypotony and choroidal detachment. Limitations of the studies include the retrospective study designs, small patient populations, short-term follow-ups, inconsistent outcomes and lack of a comparator group.

Matlach et al. (2015) conducted a randomized controlled trial to compare the safety and efficacy of canaloplasty (CP) (n=30) and trabeculectomy (TE) (n=32) in the treatment of open angle glaucoma. Patients were included who were aged 18 years or older with medically uncontrolled primary or secondary (pseudoexfoliative and pigmentary) open-angle glaucoma. Primary outcomes was success rate which was defined as IOP \leq 18 mmHg or IOP decreased by \geq 20% and to \leq 21 mmHg without medication (complete success) or with medication (qualified success). Secondary endpoints included the absolute reduction of IOP at the two-year follow-up, visual acuity, use of IOP-lowering medication, postoperative complications, further interventions, and early bleb management. Following surgery both groups had a significant reduction in IOP (p<0.001, each) but was not significantly different between the groups (p<0.56). At the two-year follow-up complete success was achieved in 23 TE patients and nine CP patients (p=0.001) and 21 TE patients vs. nine CE patients met success without medications (p=0.04). Complete success was significantly higher in the TE group for both success criteria (p<0.05). Qualified success was not different between the two groups for an IOP \leq 21 mmHg and \geq 20% IOP reduction but was statistically significant for IOP \leq 18 mm HG in the TE group (p=0.01). Twelve CP patients and eight TE patients needed additional IOP-lowering medication postoperatively. The mean number of required medications was significantly lower in the trabeculectomy group following surgery (p=0.01). Visual acuity was not significantly different between the groups during follow-up (p=0.08). Intraoperative complications in the canaloplasty group included microperforation of Descemet membrane in two eyes. There were no intraoperative complications in the TE eyes. The number of postoperative complications and second interventions was higher in the trabeculectomy group including: transient hypotony (37.5%), hypotony-related choroidal detachment (12.5%) and elevated IOP (25.0%). CP complications included elevated IOP (30%) and hyphema (23.3%). None of the trabeculectomy patients and two CP patient underwent further glaucoma surgery. Limitations of the study include the small patient populations and short-term follow-up.

Brusini et al. (2014) reported on the prospective outcomes of 214 eyes of 185 patients who underwent canaloplasty for the treatment of OAG under maximum tolerated medical therapy. Diagnosis included primary open-angle glaucoma (n=189), pseudoexfoliation glaucoma (n=53), juvenile glaucomas (n=10), and pigmentary glaucoma (n=4). Follow-ups occurred for up to five years with mean follow-up ranging from 9.7 months to 30.9 months. All patients underwent postoperative local medical treatment with levofloxacin and dexamethasone drops. The percentages of eyes that obtained postoperative IOP \leq 21mmHg, \leq 18mmHg, and \leq 16mmHg with or without medical therapy after two years were 88.7%, 73.7%, 46.2% and after three years

86.2%, 58.6%, and 37.9%, respectively. Seventeen eyes underwent trabeculectomy. The most frequent reported complications included: hyphema; descemet membrane detachment; IOP spikes; and hypotony. Limitations of the study include: the lack of a comparator; small patient population; and short-term follow-up. Also, the full procedure could not be performed in 42 eyes (16.4%) (39 patients out of the original cohort of 256 eyes). The authors concluded that canaloplasty is a demanding and difficult surgical technique with promising outcomes but is a relatively new procedure. Future studies are needed to establish patient selection criteria; establish instruments and tools to assess whether or not collector channels are functioning; and development of simplification and standardization of the procedure.

Ab Interno Trabeculectomy (Trabectome and ab interno Kahook dual blade trabeculectomy)

Ab interno trabeculectomy is a minimally invasive surgical procedure aimed at selectively removing the trabecular meshwork and the inner wall of Schlemm's canal using an internal approach. One device for this procedure is the Trabectome system (Neomedix Corp., Tustin, CA). Trabectome is proposed as a treatment option for early or moderately advanced glaucoma where a percentage reduction in IOP cannot be achieved with medication alone. The Trabectome system consists of a disposable hand piece tip that will fit through a 1.6 millimeter corneal incision. The hand piece is connected to a console with irrigation and aspiration capabilities and to an electrocautery generator. Using the microcautery tip, the arc of the trabecular meshwork and inner wall of Schlemm's canal are removed in order to open the drainage system in the eye. The targeted tissue is vaporized using bursts of high-frequency electrocautery. The procedure takes about 20 minutes and is performed in an outpatient setting. The proposed advantages of trabectome are that the procedure opens a large pathway for aqueous drainage from the anterior chamber to the collector channels with minimal damage to adjacent structures; the temporal clear cornea approach spares the conjunctiva; there is absence of a filtering bleb; and it allows for further glaucoma surgery if needed. Proposed disadvantages are the lack of circumferential flow in Schlemm's canal limiting outflow; possibility of cleft closure; the limitation of IOP reduction by episcleral venous pressure and Schlemm's canal resistance; and reported postoperative intraocular pressure (IOP) remained, at best, in the mid-teen range making it undesirable in patients with low-target IOP goals. It is proposed to be used in conjunction with cataract surgery (Francis, et al., 2011; Pantcheva and Kahook, 2010; Filippopoulos and Rhee, 2008).

Ab interno trabeculectomy may also be achieved using the Kahook Dual Blade ([KDB]; New World Medical, Rancho Cucamonga, CA) or Goniotome (NeoMedix Corporation, Tustin, CA), and both single-use goniotomy blades may be used with cataract surgery or as a stand-alone procedure. The Kahook Dual Blade is a novel goniotomy blade created to produce a more complete removal of TM through a minimally invasive approach with minimal, if any, surrounding tissue damage. In other ab interno trabeculectomy techniques (Gonioscopy-Assisted Transluminal Trabeculotomy [GATT] and traditional trabeculotomy), the TM is incised which leaves residual TM leaflets that remain post-procedure (Young, et al., 2022).

U.S. Food and Drug Administration (FDA): The Trabectome High Frequency Generator/LP (NeoMedix Corp, Tustin, CA) is FDA 510(k) approved "for use with compatible electrosurgical instruments in low power microsurgical applications for the removal, destruction and coagulation of tissue" (FDA, 2006). The FDA approval did not specifically say that the Trabectome is indicated for the treatment of glaucoma. In 2014, the FDA issued a warning letter to NeoMedix that the device is not FDA approved for the treatment of glaucoma.

The Kahook Dual Blade is an FDA Class I exempt device. A device may be exempt from 510(k) requirements if the FDA determines that a 510(k) is not required to provide reasonable assurance of safety and effectiveness for the device. (FDA, 2019)

Literature Review-Trabectome: Although the evidence is not robust, professional societies (American Academy of Ophthalmology [AAO], American Glaucoma Society [AGS], American Society of Cataract and Refractive Surgery [ASCRS]) support the use of the procedure ab interno trabeculectomy for the treatment of glaucoma (AAO, 2023; Fellman, et al., 2020). Studies on the Trabectome device are primarily in the form of case reports, case series and retrospective reviews with short-term follow-ups (six months to two years). Patient selection criteria have not been established. Current concepts regarding the IOP goal at which a patient would avoid optic nerve damage would not be achieved by trabectome in patients with advanced glaucoma. Some studies have reported that there was no significant difference when trabectome was used (Pahlitzsch, et al., 2018; Wecker, et al., 2016; Mizoguchi, et al., 2015; Jordan, et al., 2013; Jea, et al., 2012; Ting, et al., 2012; Mosaed, et al., 2009; Filippopoulos and Rhee, 2008; Francis, et al., 2008; Minckler, et al., 2008).

To ensure maintenance of the corneal integrity and transparency, the corneal endothelium is essential. Thus, Omatsu et al. (2018) prospectively compared the effect of trabeculectomy (n=60 eyes) and EX-PRESS device implantation (n=50 eyes) on corneal endothelial cell density (CECD). Eyes selected for inclusion in the study were age, gender and lens status matched. Included subjects were aged 20 years or older and had preoperative uncontrolled IOP despite treatment with the maximum tolerated medical therapy. The primary outcome measure was the endothelial cell count as measured by a noncontact specular microscope with an autofocus device. Follow-ups occurred for up to 24 months. There was no significant difference in the number of cataract surgeries performed in the groups (p=0.72). Significant decreases in the IOP and in the number of antiglaucoma medications compared to baseline were observed after the surgery in both procedures. The mean CECD in the trabeculectomy group was 2505 ± 280 cells/mm² at baseline, 2398 ± 274 cells/mm² (p<0.001), 2349 ± 323 cells/mm² (p<0.001), 2293 ± 325 cells/mm² (p<0.001), and 2277 ± 385 cells/mm² (p=0.003) at 6, 12, 18, and 24 months, respectively. The CECD in the EX-PRESS group was 2377 ± 389 cells/mm² at baseline, and 2267 ± 409 cells/mm² (p=0.007), 2292 ± 452 cells/mm² (p=0.043), 2379 ± 375 cells/mm² (p=0.318), and 2317 ± 449 cells/mm² (p=0.274) at 6, 12, 18, and 24 months, respectively. While there was a significant difference from baseline for the CECD at each of the study visits in the trabeculectomy group, the CECD in the EX-PRESS combined cataract surgery group at 12 months no longer exhibited any significant difference from the baseline. Also, in patients undergoing only the EX-PRESS procedure, the CECD did not exhibit any significant difference from baseline at any of the study visits. There were significant decreases observed in the CECD following trabeculectomy. In conclusion, the EX-PRESS device implantation appeared to be a safer procedure with regard to the endothelial cell loss risk. Limitations of the study include the small patient population, short-term follow-up, and heterogeneity of types of glaucoma (primary open-angle glaucoma, normal-tension glaucoma, secondary glaucoma, exfoliation glaucoma).

Islamaj et al. (2018) conducted a randomized controlled trial (n=119) to compare the outcomes of Baerveldt implant (BGI) and trabeculectomy (TE) in glaucomatous patients without previous ocular surgery. Inclusion criteria were: age 18–75 years; diagnosis of primary open-angle glaucoma, normal tension glaucoma (NTG), pseudo exfoliative glaucoma or pigmentary glaucoma; the need for IOP lowering surgery, and Caucasian. Caucasian was selected to make the group homogenous and studies have shown that there is a difference in TE success rates between different races. Primary outcomes were intraocular pressure (IOP) and failure rate at the one-year follow-up. Failure was defined as persistent intraocular hypertension (IOP > 21 mmHg), hypotony (IOP ≤ 5 mmHg), or less than 20% reduction compared to baseline IOP for at least two consecutive examinations. Complete success was defined as no additional medication needed and qualified success was defined as additional medication was needed. One eye of each subject was randomized to either a Baerveldt glaucoma drainage device or trabeculectomy. Both procedures showed a significant reduction in IOP at the one-year follow-up compared to preoperative measurements but the difference between the groups was not significant. Significantly, more

patients in the TE group (85%) than in the BGI group (25%) could maintain a stable IOP without additional pharmacological therapy ($p < 0.001$). Complete success (without medication) was significantly higher in the TE group (75% versus 22%). There was no significant difference in the failure rate between the groups. In the BGI group, three patients failed because of an IOP higher > 21 mmHg compared to no TE patients. Neither visual acuity nor visual field showed significant changes and no statistically significant between group changes were seen. One year postoperatively, 54 (90%) TE patients versus 49 (83%) BGI patients were free of complications. Three BGI patients and one TE patient required cataract extraction one year after surgery. Significantly more patients in the BGI group reported diplopia than in the TE group ($p < 0.001$). Limitations of the study are the small patient population and short-term follow-up.

Hu et al. (2021) conducted a Cochrane Review of randomized controlled trials to evaluate safety and efficacy of ab interno trabecular bypass surgery with Trabectome for open angle glaucoma at two-year follow-ups. Comparators included conventional medical management, laser, or surgical treatment. A secondary objective was to examine the effects of Trabectome surgery in subjects who have concomitant phacoemulsification in comparison to those who do not have concomitant phacoemulsification. No high-quality evidence was found.

Bussel et al. (2015) conducted a prospective case series ($n=73$) to investigate ab interno trabectome (AITs) ($n=59$) and phacoemulsification (phaco-AITs) ($n=17$) following failed trabeculectomy. Subjects had a diagnosis of glaucoma (with or without visually significant cataract), who had failed trabeculectomy at least three months prior to enrollment. The indication for AIT consisted of an IOP above target with worsening glaucoma on maximally tolerated medical or laser therapy. The targeted IOP was determined on a case-by-case basis by the treating physician. The indication for phaco-AIT included a visually significant cataract with at least 20/50 on brightness acuity test and the need to lower IOP or the number of glaucoma medications. At the one year follow-up, mean IOP in the AIT group significantly decreased by 28% from 23.7 ± 5.5 mm Hg, and medication usage reduced from 1.6–4.0 to 0.7–3.3 ($n=58$). In the phaco-AIT group the mean IOP decreased 19% from 20 ± 5.9 mm Hg and medication usage reduced from 1.0–4.0 to 0.2–3.0 ($n=15$). Transient hypotony occurred in 7% of subjects and further surgery was necessary in 18%. For AIT and phaco-AIT, the one-year cumulative probability of success was 81% and 87%, respectively. Author-noted limitations of the study included: potential selection bias towards worse outcomes, small patient population; short-term follow-up. Other limitations include: lack of randomization, unequal number of study group subjects; loss to follow-up in the AIT group (21%) and lack of a defined IOP for inclusion.

Kaplowitz et al. (2016) conducted a systematic review of the literature to evaluate ab-interno trabeculectomy (AIT) using the Trabectome to analyze post-procedure IOP and medication usage. AIT was used in adults primarily with POAG (IOP > 20 mmHg) who were uncontrolled on maximally tolerated medical therapy. The review included 12 case series and five retrospective reviews. Seven studies evaluated AIT alone and 10 included AIT with phacoemulsification (AIT- phaco). Total patients were 5091. The authors noted that no randomized controlled trials have been published to date. Fourteen studies met criteria for meta-analysis. Primary outcomes were change in IOP and anti-glaucoma medications. Secondary outcomes were adverse events. Follow-ups ranged from 6–60 months with nine studies having follow-ups of 6–12 months. The largest data came from the manufacturer's global Trabectome study database ($n=4659$, ATI and ATI-phaco). For AIT the average success rate at one year based on five studies was 44%–78% and 12%–80% based on two studies at two years post-procedure. Based on six studies at one-year follow up success rate for ATI-phaco was 68%–100% and based on two studies at two-year follow-up 78%–92%. Primarily based on the manufacturer's database, success rates at five years were 85% for phaco-AIT and 56% at 7.5 years, overall rate 66%. A total of 7% of cases required reoperation. The definition for success was a final IOP ≤ 21 mm Hg with a 20% decrease from baseline, without reoperation. Meta-analysis of both procedures indicated an overall significant improvement in IOP

from baseline to end point and medication reduction ($p < 0.001$, each). However, the authors noted that the estimates were based on data with high heterogeneity. The most common serious complication was 10 cases of hypotony (IOP < 5 mm Hg) four weeks following surgery (0.09% of all reported cases). Other complications included peripheral anterior Synecchia (adhesions of peripheral iris), corneal injury and transient IOP spike. Limitations of this analysis include: retrospective data; various definitions of success rate; conflicting outcomes; high degree of heterogeneity of data, glaucoma subtypes, follow-up duration and baseline IOP; and overlapping data sets.

Literature Review- ab interno Kahook dual blade trabeculectomy: Although the evidence is not robust, professional societies (American Academy of Ophthalmology [AAO], American Glaucoma Society [AGS], American Society of Cataract and Refractive Surgery [ASCRS]) support the use of the procedure ab interno trabeculectomy for the treatment of glaucoma (AAO, 2023; Fellman, et al., 2020). Studies on the Kahook device are primarily in the form of case series and retrospective reviews with short-term follow-ups (six to 12 months) (Laroche, et al., 2021; ElMallah, et al., 2019; Lee, et al., 2019; Dorairaj, et al., 2018).

Gonioscopy-Assisted Transluminal Trabeculotomy (GATT)

Gonioscopy-assisted transluminal trabeculotomy (GATT) is a minimally invasive ab interno circumferential trabeculotomy. A modification of the standard trabeculotomy, it gives the ability to perform trabeculotomy without conjunctival or scleral incisions. GATT is performed by making a micro-incision in the cornea. After entering the eye and using either an illuminated microcatheter, 5-0 Prolene suture, or TRAB 360 hand piece (Sight Sciences). The suture is then passed through the canal 360 degrees and pulled into the anterior chamber. Sparing the conjunctival tissue is proposed to allow for better outcomes if a traditional glaucoma surgery is needed at a later time. GATT is also proposed to have fewer complications than trabeculotomy. GATT is proposed for the treatment of adult and developmental open-angle glaucomas.

Literature Review: Although the evidence is not robust, professional societies (American Academy of Ophthalmology [AAO], American Glaucoma Society [AGS], American Society of Cataract and Refractive Surgery [ASCRS]) support the use of the procedure gonioscopy-assisted transluminal trabeculotomy for the treatment of glaucoma (AAO, 2023; Fellman, et al., 2020). Studies assessing the safety and efficacy of gonioscopy-assisted transluminal trabeculotomy are primarily in the form of systematic reviews, case series and retrospective reviews (Guo, et al., 2020; Baykara, et al., 2019; Baker-Schena, 2018; Grover, et al., 2018; Smith, et al., 2018; Grover, et al., 2017; Rahmatnejad, et al., 2017; Grover et al., 2015; Grover et al., 2014).

Viscocanaloplasty: Viscocanaloplasty is similar to viscocanalostomy differing with injection of a viscous medication to open Schlemm's canal. The American Academy of Ophthalmology (AAO) (Kim et al., 2024) describes viscocanaloplasty or ab interno canaloplasty (ABiC) as a type of non-implant micro invasive glaucoma surgery (MIGS). The procedure, performed through a single self-sealing clear corneal incision, involves 360-degree viscodilation of the canal using either the iTrack microcatheter (Ellex) or the VISCO360® (Sight Sciences) handpiece and an ophthalmic visco-elastic device inserter. (Baker-Schena, 2018). According to the manufacturer's website, the Visco360 Viscosurgical System (Sight Sciences, Inc., Menlo Park, CA) is a non-implantable micro-invasive glaucoma surgery device indicated for ab interno microcatheterization and viscodilation of Schlemm's canal to reduce intraocular pressure (IOP) in adult patients with primary open-angle glaucoma. The procedure can be completed in conjunction with cataract surgery using the same corneal incision or as a stand-alone procedure. The Visco360 is introduced by way of a single, self-sealing, clear corneal incision (similar to clear corneal cataract surgery). Under gonioscopic visualization, the system's cannula is used to pierce the trabecular meshwork and enter Schlemm's canal. The system's microcatheter is then deployed around the entire 360° circumference of Schlemm's canal. Upon retraction of the microcatheter a small volume of

viscoelastic is automatically dispensed, yielding a controlled and reproducible transluminal canal viscodilation (Sight Sciences, 2020). As of April 30, 2019, the VISCO360 is no longer available for commercial distribution (Access Gudid, 2023).

U.S. Food and Drug Administration (FDA): The Visco360 Viscosurgical System received FDA-approval via the 510(k) process on July 27, 2017 (K171905) The Sight Sciences Visco360 Viscosurgical System is a manually operated device for delivery of small amounts of viscoelastic fluid (e.g., Healon, Amvisc or PROVISC) during ophthalmic surgery. The device consists of the following components and accessories: Cannula; Microcatheter; Internal reservoir; Plunger tube; and Finger wheels (FDA, 2017).

Literature Review – Viscocanaloplasty: Although the evidence is not robust, professional societies (American Academy of Ophthalmology [AAO], American Glaucoma Society [AGS], American Society of Cataract and Refractive Surgery [ASCRS]) support the use of the procedures viscocanaloplasty and ab interno canaloplasty (ABiC) for the treatment of glaucoma (AAO, 2023; Fellman, et al., 2020). Studies are primarily in the form of retrospective reviews (Gillman, et al., 2021; Kazerounian, et al., 2021; Davids, et al., 2019; Gallardo, et al., 2018).

Canaloplasty and trabeculotomy ab interno (OMNI® Surgical System): The OMNI® Surgical System (Sight Sciences, Inc., Menlo Park, CA) is predicated by the iTrack Catheter (Ellex) and the VISCO360 Viscosurgical System (Sight Sciences). It is an ophthalmic surgical tool for the delivery of controlled amounts of viscoelastic fluid into the anterior segment and the cutting of the trabecular meshwork when a trabeculotomy is indicated. A catheter is advanced into Schlemm's canal, where viscoelastic is inserted in order to dilate the canal. The iTrack Microcatheter is an FDA-approved device for the delivery of viscoelastic in 360° procedures but is not a cutting device. The Omni Surgical System is an FDA-approved device that combines the functions of cutting the trabecular meshwork and delivering viscoelastic for 180° (viscocanalostomy) or 360° (canaloplasty) procedures.

U.S. Food and Drug Administration (FDA): The OMNI surgical system received FDA approval via 510(k) process on December 21, 2017 (K173332). The predicate devices were the iTrack Catheter (Ellex) and the VISCO360 Viscosurgical System (Sight Sciences). The OMNI™ Surgical System is a manually operated device for delivery of small amounts of viscoelastic fluid, for example Healon® or Healon GV® from Abbott Medical Optics (AMO), Amvisc® from Bausch & Lomb, or PROVISC® from Alcon, during ophthalmic surgery. It is also indicated to cut trabecular meshwork tissue during trabeculotomy procedures. Sight Sciences received additional 510(k) approvals on July 14, 2020 (K201953) for the OMNI PLUS Surgical System and on January 21, 2021 (K202678) for the OMNI® Surgical System. The OMNI PLUS Surgical System's indications for use were the same as the predicate device the OMNI surgical system. The OMNI® Surgical System is indicated for canaloplasty (microcatheterization and transluminal viscodilation of Schlemm's canal) followed by trabeculotomy (cutting of trabecular meshwork) to reduce intraocular pressure in adult patients with primary open-angle glaucoma.

Literature Review: Although the evidence is not robust, professional societies (American Academy of Ophthalmology [AAO], American Glaucoma Society [AGS], American Society of Cataract and Refractive Surgery [ASCRS]) support the use of the procedures canaloplasty and trabeculotomy ab interno for the treatment of glaucoma (AAO, 2023; Fellman, et al., 2020). Studies are primarily in the form of an observational study, retrospective reviews and a case series (Gallardo et al., 2021; Grabska-Liberek, et al., 2021; Hirsch, et al., 2021; Vold, et al., 2021).

Additional Procedures

In an effort to forego the complications of trabeculectomy, the established surgical treatment for glaucoma, new surgical techniques are being investigated. These proposed procedures include transciliary fistulization, and viscocanalostomy including phacoviscocanalostomy. However, there is insufficient evidence to support the safety and efficacy of these evolving surgical interventions for the treatment of glaucoma.

Excimer laser trabeculostomy (ELT) (ie, ExTra ELT)

Excimer laser trabeculostomy is a microinvasive glaucoma surgery (MIGS) that uses a nonthermal excimer laser to create multiple microscopic channels in the trabecular meshwork and the inner wall of the Schlemm's canal (Durr, et al., 2020; Berlin, et al., 2013). It is proposed that the use of the nonthermal laser prevents scarring allowing fluid to flow through the trabecular meshwork lowering intraocular pressure (Elios Vision, 2024). Although it has received CE Mark approval (2014) and has been used in Europe, it is not FDA approved, and evidence in the peer reviewed scientific literature evaluating clinical effectiveness is lacking.

Trabeculotomy by laser is a minimally invasive technique in which an excimer laser is used to excise tissue from the inner wall of the Schlemm's canal, purportedly opening a canal that allows for improved outflow of intraocular fluids with minimal scarring.

Transciliary Fistulization

Transciliary fistulization, transciliary filtration or Singh filtration uses the Fugo Blade™ (MediSURG Ltd., Norristown, PA), also called the Plasma Blade, for tissue ablation and noncauterizing hemostatic mechanisms to create a nonbleeding micropore which drains aqueous from behind the iris and into subconjunctival lymphatics. The proposed advantages of this procedure are the posterior route of aqueous filtration, lack of use of antifibrotic agents, low relative cost and shorter surgery time relative to trabeculectomy. The disadvantages are that it is an external filtration procedure with bleb formation with a risk of overfiltration and hypotony (Francis, et al., 2011, Singh and Singh, 2002).

U.S. Food and Drug Administration (FDA): The Fugo Blade for glaucoma (MediSURG Ltd., Norristown, PA) is 510(k) approved by the FDA for "sclerostomy for the treatment of primary open-angle glaucoma when maximum tolerated medical therapy and trabeculopasty have failed" (FDA, 2004).

Literature Review: There is insufficient evidence in the peer-reviewed literature to support the safety and efficacy of transciliary fistulization using the Fugo blade. The limited number of studies are primarily in the form of case series and retrospective reviews with small patient populations (n=16-147) and six to 12 months follow-up. Studies lacked specific inclusion and exclusion criteria and paucity of data (Francis, et al., 2011).

Viscocanalostomy and Phacoviscocanalostomy

Viscocanalostomy involves the injection of ophthalmic viscoelastic device (OVD) into the Schlemm's canal (SC) on either side of an external scleral dissection site with a metal cannula. Because the canula was not flexible, it could only be extended in the SC a limited distance. Therefore, it could only dilate a limited portion of the canal on either side of the dissection site. This opening allows passage of fluid from the anterior chamber into the canal which lowers the IOP. Unlike trabeculectomy, viscocanalostomy avoids full-thickness penetration into the anterior chamber of the eye (Goldberg, 2006; Koerber, 2007).

Viscocanalostomy is also proposed for use in conjunction with phacoemulsification (i.e., the removal of lens nucleus within the lens capsule by breaking up the lens into tiny pieces for extraction) during cataract surgery. The combination of cataract surgery and viscocanalostomy is called phacoviscocanalostomy and is proposed for use in the place of phacotrabeculectomy. The

combined surgery is used for patients who require surgical intervention for the treatment of cataract and glaucoma. Compared to cataract surgery alone, phacoviscocanalostomy is proposed to provide better long-term control of IOP, protection from postoperative IOP spikes and prevention of late-failure trabeculectomy (Kobayashi and Kobayashi, 2007; Shoji, et al., 2007; Park, et al., 2006; Wishart, et al., 2006). The evidence in the published peer-reviewed literature does not support viscocanalostomy or phacoviscocanalostomy for the treatment of glaucoma.

Literature Review-Viscocanalostomy: Randomized controlled trials have reported that viscocanalostomy is not clinically comparable to trabeculectomy, the standard surgical procedure for the treatment of glaucoma, in reducing and maintaining lower IOP values. Overall, significantly better reductions in IOP were seen following trabeculectomy and in some cases, with less repeat treatments needed. Eldaly et al. conducted a 2014 Cochrane review of randomized and quasi-randomized controlled trials comparing standard trabeculectomy to viscocanalostomy (n=50) for the treatment of open-angle glaucoma and concluded that limited evidence showed better control of IOP with trabeculectomy.

Chai and Loon (2010) conducted a meta-analysis of ten randomized controlled trials (n=458 eyes/397 patients) to compare the outcomes of viscocanalostomy to trabeculectomy mainly for the treatment of primary (n=371) or secondary (n=75) open-angle glaucoma. The authors compared the postoperative mean intraocular pressure (IOP), mean number of antiglaucomatous medications, as well as adverse events. Follow-ups ranged from six months to four years. At six, 12, and 24 months, a significantly lower mean IOP was reported following trabeculectomy (p<0.00001, p<0.00001, p<0.0001, respectively). Trabeculectomy patients required a significantly less number of postoperative antiglaucomatous medications compared to viscocanalostomy (P<0.00001). Six studies reported that viscocanalostomy had a significantly higher relative risk of perforation of Descemet membrane (p=0.007). The relative risk of hypotony, hyphema, shallow anterior chamber, and cataract formation were significantly less in the viscocanalostomy group (p=0.0005, p=0.008, p=0.0002, p=0.002, respectively). Author-noted limitations of the study included: the studies may not be completely comparable due to various surgical techniques and surgeon experience; two studies lacked data on IOP; and the follow-ups were short-term.

Hondur et al. (2008) performed a meta-analysis of randomized controlled trials and case series that evaluated nonpenetrating glaucoma surgery (NPGS), including deep sclerectomy (n=22) and viscocanalostomy (n=14) for the treatment of OAG. Success was defined as IOP of ≤ 21 millimeters of mercury (mmHg) without the use of antiglaucoma medicine. Because they affect the results of NPGS, data related to postoperative goniopuncture and needling with antimetabolite application were noted. In general, the mean follow-up of the viscocanalostomy studies was 25.6 months. The percentage of cases achieving ≤ 21 mmHg was 51.1% following primary viscocanalostomy (n=9) and 36.8% after viscocanalostomy with antimetabolite or implant (n=3). With lower set IOP targets, the rates of success ranged from 10%–67% following viscocanalostomy. Several factors were identified that may account for the wide variation in the success rates of NPGS including the variations in surgical techniques (i.e., use of implants and antimetabolite application) and post-operative manipulation (e.g., goniopuncture, subconjunctival 5-FU injection), variations in success criteria and targeted IOPs, and differences in follow-up lengths. There was an absence of data regarding the severity of glaucoma in the pre-operative patient populations and a lack of data regarding visual acuity following viscocanalostomy. The authors noted that data regarding the success of NPGS beyond three years was limited. According to the authors, the analysis implied that NPGS can achieve IOP reduction. However, these procedures “may not be suitable surgical options for patients in whom vigorous IOP reduction is required.” Long-term studies with data related to glaucoma severity and proper target IOPs are needed.

Earlier published reports from randomized controlled trials also compared the results of viscocanalostomy to trabeculectomy for the treatment of glaucoma (Gilmour, et al., 2009; Cheng, et al., 2004; O'Brart, et al., 2004; Yalvac, et al., 2004; Yarangümeli, et al., 2004; Carassa, et al., 2003; Kobayashi, et al., 2003; O'Brart, et al., 2002; Lüke, et al., 2002; Jonescu-Cuypers, et al., 2001). Overall, trabeculectomy provided a statistically significant decrease in IOP and an increase in IOP control compared to viscocanalostomy. Reported complications were varied and conflicting. Some studies reported no significant differences in complications while others reported a lower incidence of post-operative cataract formation and hypotony following viscocanalostomy.

Systematic Review of Multiple Procedures: Rulli et al. (2013) conducted a systematic review and meta-analysis of randomized and nonrandomized trials to determine the safety and hypotensive effect of trabeculectomy (TE) vs. nonpenetrating surgeries (NPS) which included canaloplasty vs trabeculectomy (n=79 eyes) and viscocanalostomy (n=315 eyes) for the treatment of open-angle glaucoma. Analysis of the data at six-month follow-ups showed that the pooled estimate of the mean difference between the groups was -2.15 mm in favor of TE with no difference between the NPS groups. TE was more effective in reducing IOP than NPS following surgery. The absolute risk of hypotony, choroidal effusion, cataract, and flat or shallow anterior chamber was higher in the TE group than viscocanalostomy. Evidence was insufficient to assess the safety of TE vs. canaloplasty.

Literature Review-Phacoviscocanalostomy: The evidence in the published peer-reviewed literature does not support the safety and efficacy of phacoviscocanalostomy for the treatment of glaucoma. Published studies include a limited number of case series and retrospective reviews with small patient populations and short-term follow-ups (Awadalla and Hassan, 2011; Kobayashi and Kobayashi, 2007; Wishart, et al., 2006). The effects on postoperative medication usage, as well as the long-term effects of phacoviscocanalostomy are unknown. Studies comparing phacoviscocanalostomy to established treatment modalities are lacking.

Professional Societies/Organizations

American Academy of Ophthalmology (AAO): The AAO published an ophthalmic technology assessment on novel glaucoma procedures (Francis, et al., 2011). The assessment included Fugo blade transcliliary filtration, iStent, Ex-PRESS glaucoma shunt, SOLX Gold Shunt, canaloplasty, and trabectome. AAO concluded that these devices and techniques "are still in the initial stage (≤ 5 years) of clinical experience and lacking widespread use." Clinical trials were limited to "nonrandomized, retrospective or prospective, interventional, clinical case series, generally classified as providing only level III evidence in support of the procedures". Randomized clinical trials are needed to compare these procedures to trabeculectomy and phacoemulsification. AAO concluded "it is possible to state that these novel procedures show potential for the treatment of glaucoma and that they warrant continued support and future studies. It is not possible to conclude if they are superior, equal to, or inferior to surgery such as trabeculectomy or to one another".

The AAO (2018, updated 2023) glaucoma summary benchmarks for the management of primary open-angle glaucoma (OAG) stated that medical therapy is the most common intervention initial intervention to lower intraocular pressure (IOP). Laser trabeculoplasty can be considered as initial therapy in selected patients or an alternative for patients at high risk for nonadherence to medical therapy who cannot or will not use medications reliably.

American Glaucoma Society (AGS): The objective of the American Glaucoma Society Position Paper on Microinvasive Glaucoma Surgery (MIGS) (Fellman, et al., 2020) was to provide an overview of the procedures while dispelling misconceptions. MIGS were designed to lower intraocular pressure (IOP) by improving the physiologic aqueous outflow pathways with minimal disruption to the sclera or conjunctiva with or without an implanted device, or by reducing

aqueous production selectively. The Society states that the advantages of MIGS over traditional glaucoma procedures include being performed with smaller incisions, an enhanced safety profile, limited discomfort, faster recovery, less impact on leisure activities (such as swimming), and reduced risk of damaging other structures in the eye that can necessitate additional ocular surgeries.

Medicare Coverage Determinations

	Contractor	Determination Name/Number	Revision Effective Date
NCD	National	No National Coverage Determinations found.	
LCD	NGS	Microinvasive Glaucoma Surgery (MIGS) (L37244)	12/01/2019
LCD	Palmetto	Microinvasive Glaucoma Surgery (MIGS) (L37531)	6/23/2022
LCD	CGS	Microinvasive Glaucoma Surgery (MIGS) (L37578)	3/23/2023
LCD	Novitas Solutions	Microinvasive Glaucoma Surgery (MIGS) (L38223)	12/30/2019
LCD	First Coast	Microinvasive Glaucoma Surgery (MIGS) (L38233)	12/30/2019
LCD	Wisconsin Physicians	Category III Codes (L35490)	6/12/2022

Note: Please review the current Medicare Policy for the most up-to-date information.
(NCD = National Coverage Determination; LCD = Local Coverage Determination)

Coding Information

Notes:

1. This list of codes may not be all-inclusive since the American Medical Association (AMA) and Centers for Medicare & Medicaid Services (CMS) code updates may occur more frequently than policy updates.
2. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Aqueous Shunts/Aqueous Drainage Devices

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	Description
65820	Goniotomy
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
66989	Extracapsular cataract removal with insertion of intraocular lens prosthesis (1-stage procedure), manual or mechanical technique (eg, irrigation and aspiration or

CPT®* Codes	Description
	phacoemulsification), complex, requiring devices or techniques not generally used in routine cataract surgery (eg, 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 (eg, 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 (eg, irrigation and aspiration or phacoemulsification); with insertion of intraocular (eg, trabecular meshwork, supraciliary, suprachoroidal) anterior segment aqueous drainage device, without extraocular reservoir, internal approach, one or more
0449T	Insertion of aqueous drainage device, without extraocular reservoir, internal approach, into the subconjunctival space; initial device
0671T	Insertion of anterior segment aqueous drainage device into the trabecular meshwork, without external reservoir, and without concomitant cataract removal, one or more

HCPCS Codes	Description
C1783	Ocular implant, aqueous drainage assist device
L8612	Aqueous shunt

Considered Experimental/Investigational/Unproven:

CPT®* Codes	Description
68841	Insertion of drug-eluting implant, including punctal dilation when performed, into lacrimal canaliculus, each
0253T	Insertion of anterior segment aqueous drainage device, without extraocular reservoir, internal approach, into the suprachoroidal space
0444T	Initial placement of a drug-eluting ocular insert under one or more eyelids, including fitting, training, and insertion, unilateral or bilateral
0445T	Subsequent placement of a drug-eluting ocular insert under one or more eyelids, including re-training, and removal of existing insert, unilateral or bilateral
0474T	Insertion of anterior segment aqueous drainage device, with creation of intraocular reservoir, internal approach, into the supraciliary space
0660T	Implantation of anterior segment intraocular nonbiodegradable drug-eluting system, internal approach
0661T	Removal and reimplantation of anterior segment intraocular nonbiodegradable drug-eluting implant

Procedures

Considered Medically Necessary when used to report canaloplasty performed either ab externo or ab interno when criteria in the applicable policy statement listed above are met:

CPT®* Codes	Description

66174	Transluminal dilation of aqueous outflow canal (eg, canaloplasty); without retention of device or stent
66175	Transluminal dilation of aqueous outflow canal (eg, canaloplasty); with retention of device or stent

Considered Experimental/Investigational/Unproven:

CPT®* Codes	Description
66999 [†]	Unlisted procedure, anterior segment of eye
0621T	Trabeculostomy ab interno by laser
0622T	Trabeculostomy ab interno by laser; with use of ophthalmic endoscope
0730T	Trabeculotomy by laser, including optical coherence tomography (OCT) guidance

†Note: Considered Experimental/Investigational/Unproven when used to report transiliary fistulization or viscocanalostomy (including phacoviscocanalostomy)

***Current Procedural Terminology (CPT®) ©2023 American Medical Association: Chicago, IL.**

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Revision Details

Type of Revision	Summary of Changes	Date
Annual review	No policy statement changes.	4/15/2024

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