BlueCross BlueShield of Alabama

Name of Policy:

Aqueous Shunts and Stents for Glaucoma

Policy #: 324
Category: Surgery

Latest Review Date: July 2018
Policy Grade: B

Background/Definitions:

As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. *The technology must have final approval from the appropriate government regulatory bodies;*
2. *The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
3. *The technology must improve the net health outcome;*
4. *The technology must be as beneficial as any established alternatives;*
5. *The improvement must be attainable outside the investigational setting.*

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. *In accordance with generally accepted standards of medical practice; and*
2. *Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
3. *Not primarily for the convenience of the patient, physician or other health care provider; and*
4. *Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.*

Description of Procedure or Service:

Glaucoma surgery is intended to reduce intraocular pressure (IOP) when the target IOP cannot be reached with medication. Due to complications with established surgical approaches such as trabeculectomy, a variety of devices, including aqueous shunts and transluminal dilation procedures, are being evaluated as alternative surgical treatments for patients with inadequately controlled glaucoma. Microstents are also being evaluated in patients with mild to moderate open-angle glaucoma currently treated with ocular hypotensive medication.

Glaucoma

Surgical procedures for glaucoma aim to reduce intraocular pressure (IOP) resulting from impaired aqueous humor drainage in the trabecular meshwork and/or Schlemm's canal. In the primary (conventional) outflow pathway from the eye, aqueous humor passes through the trabecular meshwork, enters a space lined with endothelial cells (Schlemm's canal) and then drains into the aqueous veins. Increases in resistance in the trabecular meshwork and/or the inner wall of Schlemm's canal can disrupt the balance of aqueous humor inflow and outflow, resulting in an increase in IOP and glaucoma risk.

Treatment

Surgical intervention may be indicated in patients with glaucoma when the target IOP cannot be reached pharmacologically. Trabeculectomy (guarded filtration surgery) is the most established surgical procedure for glaucoma, which involves dissecting the conjunctiva, creating a scleral flap and scleral ostomy then suturing down the flap and closing the conjunctiva, allowing aqueous humor to directly enter the subconjunctival space. This procedure creates a subconjunctival reservoir, which can effectively reduce IOP, but commonly results in filtering "blebs" on the eye, and is associated with numerous complications (e.g., hemorrhage, scarring, hypotony, infection, leaks or bleb-related endophthalmitis) and long-term failure. Other surgical procedures (not addressed in this policy) include trabecular laser ablation, deep sclerectomy, (which removes the outer wall of Schlemm's canal and excises deep sclera and peripheral cornea), and viscocanalostomy, (which unroofs and dilates Schlemm's canal without penetrating the trabecular meshwork or anterior chamber).

Currently, minimally invasive glaucoma surgeries (MIGS) are alternative, less invasive techniques that are being developed and evaluated. Similar to trabeculectomy, the objective of MIGS is to lower IOP by improving outflow of eye fluid; however, MIGS involves less surgical manipulation of the sclera and the conjunctiva compared than a trabeculectomy. MIGS can either be performed outside the eye (ab externo) or inside the eye (ab interno).

The Trabectome™ is a recently developed electrocautery device with irrigation and aspiration designed to selectively ablate trabecular meshwork and Schlemm's canal inner wall without external access or creation of a subconjunctival bleb. IOP with this ab interno procedure is typically higher than the pressure achieved with standard filtering trabeculectomy. Canaloplasty involves dilation and tension of Schlemm's canal with a suture loop between the inner wall of the canal and the trabecular meshwork. This ab externo procedure uses the iTrack™ illuminated microcatheter (iScience Interventional) to access and dilate the entire length of Schlemm's canal and to pass the suture loop through the canal (*see Medical Policy #505, Viscocanalostomy and Canaloplasty*).

Examples of ab externo devices cleared by the U.S. Food and Drug Administration include the Ahmed™ (New World Medical), Baerveldt (Advanced medical optics), Molteno (IOP), and ExPress mini-shunt (Alco); and the SOLX DeepLight Gold Micro-shunt (SOLX), which shunts aqueous humor between the anterior chamber and the suprachoroidal space. These devices differ depending on explant surface areas, shape, plate thickness, the presence or absence of a valve, and details of surgical installation. Generally, the risk of hypotony (low pressure) is reduced with aqueous shunts in comparison with trabeculectomy, but IOP outcomes are higher than after standard guarded filtration surgery. Complications of anterior chamber shunts include corneal endothelial failure and erosion of the overlying conjunctiva. The risk of postoperative infection is less than after trabeculectomy, and failure rates are similar, with about 10% of devices failing each year. The primary indication for aqueous shunts is when prior medical or surgical therapy has failed, although some ophthalmologists have advocated their uses as a primary surgical intervention, particularly for selected conditions such as congenital glaucoma, trauma, chemical burn, or pemphigoid.

Examples of ab interno devices either approved or given marketing clearance by FDA include the iStent, which is a 1-mm long stent inserted into the end of the Schlemm canal through the cornea and anterior chamber; the CyPass suprachoroidal stent; and XEN gelatin stent.

Because aqueous humor outflow is pressure dependent, the pressure in the reservoir and venous system are critical for reaching the target IOP. Therefore, some devices may be unable to reduce IOP below the pressure of the distal outflow system used, (e.g., < 15 mm Hg) and are not indicated for patients for whom very low IOP is desired (e.g., those with advanced glaucoma). It has been proposed that stents such as the iStent, CyPass, and Hydrus Microstent may be useful to lower IOP in patients with early-stage glaucoma to reduce the burden of medications and problems with compliance. One area of investigation is patients with glaucoma who require cataract surgery. An advantage of ab interno stents is that they may be inserted into the same incision and at the same time as cataract surgery. In addition, most devices do not preclude subsequent trabeculectomy if needed. It may also be possible to insert more than 1 stent to achieve the desired IOP. Therefore, health outcomes of interest are the IOP achieved, reduction in medications, ability to convert to trabeculectomy, complications, and durability of the device.

Policy:

Insertion of ab externo aqueous shunts approved by the U.S. Food and Drug Administration (FDA), meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage as a method to **reduce intraocular pressure in patients with glaucoma where medical therapy has failed to adequately control intraocular pressure.**

Insertion of ab interno aqueous stents approved by the Food and Drug Administration as a method to **reduce intraocular pressure in patients with glaucoma where medical therapy has failed to adequately control intraocular pressure, does not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational**.

Use of an ab externo aqueous shunt or ab interno aqueous ~~shunt~~ stents for all other conditions, including in patients with glaucoma when intraocular pressure is adequately controlled by medications, does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational.**

Implantation of a single FDA-approved micro-stent in conjunction with cataract surgery meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage in patients with **mild to moderate open-angle glaucoma currently treated with ocular hypotensive medication.**

Use of a micro-stent for all other conditions does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational**.

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member's contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

The most recent literature review was updated through March 05, 2018.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be

relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Ab Externo Aqueous Shunts
This section will review the evidence for ab externo aqueous shunts that have received FDA-approval. Evidence on non-approved devices in included in a later section.

Systematic Reviews
A Cochrane review by Minckler et al (2006) included 15 randomized or pseudo-RCTs (total N=1153 participants) evaluating the Ahmed, Baerveldt, Molteno, and Schocket shunts. Trabeculectomy was found to lower mean intraocular pressure (IOP) by 3.8 mm Hg more than the Ahmed shunt at 1 year. This systematic review did not compare complications, because reviewers considered them to be too variably reported to permit comparative tabulation. There was no evidence of the superiority of 1 shunt over another.

A technology assessment on commercially available aqueous shunts, including the Ahmed, Baerveldt, Krupin, and Molteno devices, from the American Academy of Ophthalmology (AAO) was published in 2008. It indicated that the IOP will generally settle at higher levels (18 mm Hg) with aqueous shunts than with standard trabeculectomy (14-16 mm Hg) or trabeculectomy with antifibrotic agent's 5-fluorouacil or mitomycin C (8-10 mm Hg). In 1 study, mean IOPs with the Baerveldt shunt and adjunct medications were equivalent to trabeculectomy with mitomycin C (13 mm Hg). Five-year success rates for the 2 procedures were similar (50%). The assessment concluded that, based on Level 1 evidence, aqueous shunts were comparable to trabeculectomy for IOP control and duration of benefit. The risk of postoperative infection was less with aqueous shunts than with trabeculectomy. Complications of aqueous shunts included: immediate hypotony after surgery; excessive capsule fibrosis and clinical failure; erosion of the tube or plate edge; strabismus; and, very rarely, infection. The most problematic long-term consequence of anterior chamber tube placement was accelerated damage to the corneal endothelium over time.

A 2012 comparative effectiveness review (CER) on glaucoma treatments was prepared by the Johns Hopkins Evidence-based Practice Center for the Agency for Healthcare Research and Quality in 2012. The CER found that the data available on the role of aqueous drainage devices in open-angle glaucoma (primary studies, systematic review) were inadequate to draw conclusions on the comparative effectiveness of these treatments versus laser and other surgical treatments.

Baerveldt Glaucoma Shunt

Randomized Controlled Trials

Early results from the open-label multicenter randomized Tube Versus Trabeculectomy (TVT) study were reviewed in the 2008 AAO technology assessment, and in 2012, reported in the 5-year follow-up from this study by Gedde et al. The study included 212 eyes of 212 patients (18 to 85 years) who had previous trabeculectomy and/or cataract extraction with intraocular lens implantation and uncontrolled glaucoma with IOP of 18 mm Hg or greater and 40 mm Hg or lower on maximum tolerated medical therapy. Excluding patients who had died, the study had 82% follow-up at 5 years, with a similar proportion of patients in the tube and trabeculectomy groups. At 5 years, neither IOP (14.3 mm Hg in the tube group and 13.6 mm Hg in the trabeculectomy group) nor number of glaucoma medications (1.4 in the tube group, 1.2 in the trabeculectomy group) differed significantly from intention. The cumulative probability of failure over the five years was lower in the tube group than the trabeculectomy group (29.8% vs. 46.9%) and the rate of reoperation was lower (9% vs. 29%). The rate of loss of 2 or more lines of visual acuity was similar in the 2 groups (46% in the tube group and 43% in the trabeculectomy group).

Kotecha et al (2017) assessed vision-related quality of life outcomes in the TVT study. Quality of life was measured using the National Eye Institute Visual Functioning Questionnaire-25, administered at baseline and annual follow-ups over 5 years. A comparison of composite quality of life scores and change in scores over time among the 2 groups revealed no significant differences at any of the follow-up measurements.

Ex-PRESS Mini Shunt

Systematic Reviews

A Cochrane review by Wang et al (2015) evaluated the efficacy of adjunctive procedures for trabeculectomy. Three RCTs were included and compared trabeculectomy alone with trabeculectomy plus EX-PRESS Mini Shunt. These trials were rated as having a high or unclear risk of bias using the Cochrane criteria. None of the RCTs reported a significant improvement for the EX-PRESS group. However, in the pooled analysis, IOP was lower in the combination group than in the trabeculectomy alone group (weighted mean difference, -1.58; 95% confidence interval [CI], -2.74 to -0.42). Pooled analysis also showed that subsequent cataract surgery was less frequent in the combination group than in trabeculectomy alone (relative risk, 0.34; 95% CI, 0.14 to 0.74). The combination group had a lower rate of some complications (e.g., hyphema, needling).

Randomized Controlled Trials

In 2009, de Jong reported a randomized study of the EX-PRESS® mini shunt compared with standard trabeculectomy in 78 patients (80 eyes) with a diagnosis of open-angle glaucoma that could not be controlled with maximal-tolerated medical therapy (see Table 2). Five-year follow-up was reported in 2011. The 2 groups were similar after randomization, with the exception of difference in the mean age (62 years for the EX-PRESS® group, 69 years for the trabeculectomy group). At 12-month follow-up, mean IOP and antiglaucoma medications use decreased in both groups (see Table 2). Twelve-month Kaplan-Meier success rates (defined as an IOP of >4 mm Hg and ≤18 mm Hg without use of antiglaucoma medications) were 82% for the EX-PRESS® shunt and 48% for trabeculectomy. At 5 years, the success rates did not differ significantly

between groups. In the EX-PRESS® group, IOP remained stable from year one (12.0 mm Hg) to year five (11.5 mm Hg), while in the trabeculectomy group, IOP decreased from year 3 (13.5 mm Hg) to year five (11.3 mm Hg) (see Table 3). There were more complications after trabeculectomy than after EX-PRESS® implantation.

A U.S. multicenter randomized trial, reported by Netland et al (2014), compared trabeculectomy with EX-PRESS implantation in 120 patients (120 eyes) (see Table 2). Comparator groups were similar at baseline, with a preoperative IOP of 25.1 mm Hg on a mean of 3.1 medications for the EX-PRESS group and 26.4 mm Hg on a mean of 3.1 medications in the trabeculectomy group. Throughout 2-year postsurgical follow-up, average IOP and number of medications were similar between groups (see Table 3). Surgical success was 90% and 87% at 1 year and 83% and 79% at 3 years in the EX-PRESS and trabeculectomy groups, respectively. Visual acuity returned to near baseline levels at 1 month after EX-PRESS implantation (median, 0.7 months) and at 3 months after trabeculectomy (median, 2.2 months; p=0.041). Postoperative complications were higher after trabeculectomy (41%) than after EX-PRESS implantation (18.6%).

One additional small RCT was published by Wagschal et al (2015), presenting 1-year results, and by Gonzalez-Rodriguez et al (2016); presenting 3-year results (see Table 2). The trial corroborated the results of the earlier RCTs, reporting no differences between trabeculectomy and Ex-PRESS shunt groups on outcomes for mean IOP, success rates, number of medications used, or complication rates (see Table 3).

Table 2. Summary of Key RCT Characteristics for the Ex-PRESS Trial

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	**Comparator**
de Jong et al (2009); de Jong et al (2011)	Netherlands	1	2003-2004	Patients with primary OAG not controlled by IOP medication	Ex-PRESS (n=39)	Trabeculectomy (n=39)
Netland et al (2014)	U.S., Canada	7	NR	Patients with OAG treated with IOP medications who were candidates for glaucoma surgery	Ex-PRESS (n=59)	Trabeculectomy (n=61)
Wagschal et al (2015); Gonzalez-Rodriguez et al (2016)	Canada	1	2011-2012	Patients with primary OAG not controlled by IOP medication	Ex-PRESS (n=33)	Trabeculectomy (n=31)

IOP: intraocular pressure; NR: not reported; OAG: open-angle glaucoma; RCT: randomized controlled trial.

Table 3. Summary of Key RCT Results for Ex-PRESS

Study	Mean IOP (SD), mm Hg		p	Mean Medication Use (SD)	
	EX-PRESS	**Trabeculectomy**		**Ex-PRESS**	**Trabeculectomy**
de Jong et al (2009); de Jong et al (2011)					
Baseline	23.6 (7.0)	20.7 (7.0)	0.09	NR	NR
Year 1	12.2 (3.8)	13.9 (3.8)	0.05	0.31	0.74
Year 2	12.0 (3.3)	13.8 (3.2)	0.01	0.49	1.05
Year 3	12.1 (3.4)	13.5 (3.4)	0.08	0.62	1.28
Year 4	11.4 (2.5)	11.6 (2.5)	0.69	0.69	1.33
Year 5	11.4 (2.2)	11.2 (2.2)	0.71	0.85	1.10

Netland et al (2014)					
Baseline	25.1 (6.0)	26.4 (6.9)	0.27	3.1 (1.1)	3.1 (1.2)
Month 6	13.8 (4.7)	11.9 (4.6)	0.03	NR	NR
Year 2	14.7 (4.6)	14.6 (7.1)	0.93	0.9 (1.3)	0.7 (1.2)
Wagschal et al (2015); Gonzalez-Rodriguez e al (2016)					
Baseline	22.6 (10.2)	21.9 (6.8)	0.75	3.5 (0.9)	3.4 (1.3)
Year 1	11.2 (4.3)	10.7 (3.5)	0.85	0.4 (1.0)	0.6 (1.0)
Year 2	12.5 (5.1)	10.3 (3.7)	0.07	0.6 (1.3)	1.3 (1.5)
Year 3	13.3 (4.5)	11.1 (4.4)	0.10	1.4 (1.7)	1.2 (1.3)

IOP: intra-ocular pressure; NR: not reported; SD: standard deviation.

Observational Studies

Dib Bustros et al (2017) published a retrospective chart review that offered 1-year results from 56 African American patients who underwent Ex-PRESS (n=28) implantation or trabeculectomy (n=28). Outcomes included IOP and glaucoma medication used presurgery, postsurgery, and at 12-months of follow-up. In both groups, IOP and glaucoma-related medication use dropped significantly. Postoperative and follow-up interventions included 5-fluorouracil injections and laser suture lysis. Patients who underwent trabeculectomy needed a significantly greater number of laser suture lysis and 5-fluorouracil interventions in the 3 months after surgery (trabeculectomy: 3.89; EX-PRESS: 2.36, p=0.007). The results showed that Ex-PRESS was noninferior to trabeculectomy in reducing IOP and reducing the need for glaucoma-related medications.

Comparative Effectiveness of Shunts

Five-year results of 2 RCTs comparing the Ahmed and Baerveldt shunts have been published. The Ahmed Baerveldt Comparison (ABC) study was a multicenter international RCT evaluating the comparative safety and efficacy of the Ahmed Glaucoma Valve FP7 and Baerveldt Glaucoma Implant BG 101-350 (1:1 ratio) in 276 adults with previous incisional eye surgery or refractory glaucoma. ABC was funded by National Eye Institute, Research to Prevent Blindness and New World Medical. Mean IOP was 14.7 mm Hg in the Ahmed group and 12.7 mm Hg in the Baerveldt group at 5 years (p=0.01). The number of glaucoma medications in use at 5 years, cumulative probability of failure at 5 years, and visual acuity at 5 years did not differ statistically significantly between the 2 groups. The number of patients with inadequately controlled IOP or reoperation for glaucoma was 46 (80%) with the Ahmed shunt and 25 (53%) with the Baerveldt shunt (p=0.003). The 5-year cumulative reoperation rate for glaucoma was 21% in the Ahmed group versus 9% in the Baerveldt group (p=0.01). Late complications were defined as those developing after 3 months. Late complications occurred in 56 (47%) patients in the Ahmed group and 67 (56%) patients in the Baerveldt group during 5 years of follow-up (p=08). The cumulative incidences of serious complications at 5 years were 16% and 25% in the Ahmed and Baerveldt groups, respectively (p=0.03).

The Ahmed Versus Baerveldt (AVB) study was an international, multicenter RCT enrolling 238 patients with uncontrolled glaucoma despite maximum tolerated medical therapy. AVB is funded by the Glaucoma Research Society of Canada. Patients were randomized in a 1:1 ratio to the Ahmed FP7 implant and the Baerveldt 350 implant. Failure of the shunt implant was the primary outcome or was defined as any one of the following: IOP of less than 5 mm Hg or more than 18 mm Hg or less than a 20% reduction from baseline for 2 consecutive visits after 3 months; de

novo glaucoma surgery required; removal of the implant; severe vision loss related to the surgery; or progression to no light perception for any reason. The cumulative failure rate was 53% in the Ahmed group and 40% in the Baerveldt group at 5 years (p=0.04). In the Ahmed and Baerveldt shunts, mean percent reduction in IOP was 47% and 57% (p=0.001) and mean percent reduction in medication use was 44% and 61% (p=0.03), all respectively. Hypotony was reported in 5 (4%) patients in the Baerveldt group but not in the Ahmed group (p=0.02).

Christakis et al (2017) analyzed 5-year pooled data from the ABC and AVB trials comparing the relative efficacy of the 2 implants. Patients were randomized to an Ahmet implant (n=267) or a Baerveldt implant (n=247). IOP, glaucoma medication use, and visual acuity were compared. At year 5, mean IOP was 15.8 mm Hg in the Ahmed group and 13.2 mm Hg in the Baerveldt group (p=.007). The cumulative failure rate in the Ahmed group was 49%; in the Baerveldt group, it was 37%. Mean glaucoma medication use was significantly lower in patients receiving the Baerveldt implant than in patients receiving the Ahmed implant (p=0.007). Visual acuity was similar between both groups. While efficacy measures were significantly better in the Baerveldt group, these patients experienced more hypotony (4.5%) than patients in the Ahmet group (0.4%; p=.002).

Section Summary: Ab Externo Aqueous Shunts

Evidence for the use of ab externo aqueous shunts for the treatment of open-angle glaucoma uncontrolled by medications consists of RCTs comparing shunts with trabeculectomy. Outcomes of interest are IOP and antiglaucoma medication use. Follow-up among the trials ranged from 1 to 5 years. Results showed that ab externo aqueous shunts are noninferior to trabeculectomy. Adverse event rates were higher among patients undergoing trabeculectomy.

The comparative effectiveness of 2 ab externo devices (the Ahmed and Baerveldt stents) has been evaluated in 2 trials, the AVB and the ABC trials. These trials reported similar results, with both devices lowering IOP significantly. Compared with patients receiving the Ahmed shunt, patients receiving the Baerveldt shunt experienced lower IOP and needed fewer medications. However, patients receiving the Baerveldt shunt experienced higher rates of hypotony-related complications.

Ab Interno Aqueous Stents

This section reviews the evidence for ab interno stents with FDA approval or marketing clearance.

Xen Glaucoma Treatment System

Observational Studies

Comparative Studies

Schlenker et al (2017) published a multicenter, retrospective interventional cohort study that compared the risk, safety, and efficacy for stand-alone ab interno microstent implantation with mitomycin C (MMC) and trabeculectomy plus MMC. Implantations of the ab interno XEN 45 gelatin microstent is a new less invasive surgery than trabeculectomy. This study included 293 patients (354 eyes) across 4 ophthalmology centers in Canada, Germany, Austria, and Belgium. One hundred fifty-nine patients (185 eyes) underwent the microstent implantation, and 139 patients (169 eyes) underwent trabeculectomy. Outcomes included: IOP differences, medication

reductions, interventions, complications, and the need for additional surgery. The primary outcome was the hazard ratio of failure. Failure was defined as 2 consecutive IOP readings of less than 6 mm Hg, including vision loss. Success was measured by the withdrawal of glaucoma-related medications at 1 month postsurgery. The adjusted hazard ratio of failure of the microstent relative to trabeculectomy was 1.2 for complete success (95% CI, 0.7 to 2.0). Both surgeries had a 75% survival of approximately 10 months for complete success. During the last reported follow-up (varying times), antiglaucoma medications were being used by 25% of patients who received the microstent implantation and 33% of trabeculectomy patients. Patients in both groups reported similar numbers of postoperative interventions, such as laser suture lysis and needling. The need for reoperation was higher among those who had undergone microstent implantation—but this difference was not statistically significant. The authors concluded that the ab interno gelatin microstent with MMC was noninferior to trabeculectomy plus MMC.

Noncomparative Studies

Mansouri et al (2018) reported on results from a study of 149 eyes (113 patients); 109 eyes received the XEN implant plus cataract surgery and 40 eyes received the implant alone (see Table 4). There was a range of glaucoma severity represented in the study sample, with most patients in the mild-to-moderate stages. Of the 149 eyes, data for 87 (58%) eyes was available at 12 months. The high loss to follow-up was mainly due to high travel times for patients referred to the study treatment center from various provinces and countries, and to lack of interest among physicians to treat referred patients. At 12 months, mean IOP and mean medication use both decreased (see Table 5). The proportion achieving 20% or more reduction in IOP was higher among patients receiving XEN alone than those undergoing cataract surgery and XEN implantation. Adverse events included bleb revision (n=5), choroidal detachment (n=2), and second glaucoma surgery (n=9).

Grover et al (2017) published results from the single-arm, open-label clinical study evaluating the effectiveness and safety of the XEN Glaucoma Treatment System in 65 patients with refractory glaucoma (see Table 4).20 Effectiveness data were collected for 12 months and safety data for 18 months. The mean diurnal IOP was 25 mm Hg at baseline on a mean of 3.5 IOP-lowering medications. Forty-six (75%) patients of 61 with available data had a 12-month mean diurnal IOP reduction of 20% or more without increasing IOP-lowering medications. The mean IOP reduction at 12 months was -9.1 mm Hg (95% CI, -10.7 to -7.5 mm Hg) on a mean of 1.7 medications (see Table 5). Efficacy was consistent across age groups, baseline IOP, baseline medication use, sex, and ethnicity. The most common adverse events were glaucoma surgery, hypotony, IOP increase of 10 mm Hg or more and needling procedures. FDA cited results from this study to conclude that the XEN System was as safe and effective as predicate devices.

Hengerer et al (2017) retrospectively analyzed 146 patients (242 eyes) receiving the XEN implant for treatment refractory to antiglaucoma medication or glaucoma surgery (see Table 4). In the subset of eyes with 12-month data (n=148), IOP reduction of 20% or more was achieved by 73.0% of patients. Mean antiglaucoma medications decreased (see Table 5). The decreases in IOP and medication use were statistically significant, in patients receiving the XEN implant alone and in patients receiving the XEN implant while undergoing cataract surgery.

Five smaller case series have also assessed the use of the XEN implant (see Tables 4 and 5). These case series, by Perez-Torregrosa (2016), De Gregorio et al (2017), Galal et al (2017), Ozal et al (2017), and Tan et al (2018), reported significant reductions in IOP and medication use. Low rates of the following complications were reported: hypotony (which resolved), need for bleb intervention, iris tissue obstruction, implant extrusion, and choroidal detachment.

Table 4. Summary of Key Case Series Characteristics for the XEN Implant

Study	Country	Participants	Treatment Delivery	FU
Mansouri et al (2018)	Switzerland	Patients with OAG and uncontrolled IOP, progressive glaucoma, and/or refractory to IOP medications	• XEN alone (n=40) • XEN plus cataract surgery (n=109)	12 mo
Grover et al (2017)	U.S.	Patients with OAG and uncontrolled IOP, refractory to IOP medications	• XEN, not specified if cataract surgery also performed (N=65)	12 mo
Hengerer et al (2017)	Germany	Patients with OAG and uncontrolled IOP, optic disc damage, and refractory to IOP medications or prior surgery	• XEN alone (n=203) • XEN plus cataract surgery (n=39)	12 mo
Perez-Torregrosa et al (2016)	Spain	Patients with OAG and cataract and taking at least 2 IOP-lowering medications	• XEN plus cataract (N=30)	12 mo
De Gregorio et al (2017)	Italy	Patients with OAG under maximally tolerated medical therapy and with cataract	• XEN plus cataract (N=41)	12 mo
Galal et al (2017)	Germany	Patients with OAG	• XEN alone (n=3) • XEN plus cataract surgery (n=10) • Both groups also received subconjunctival mitomycin-C	12 mo
Ozal et al (2017)	Turkey	Patients with OAG and uncontrolled IOP, progressive glaucoma, and/or refractory to IOP medications or prior surgery	• XEN alone (n=9) • XEN plus cataract surgery (n=6)	12 mo
Tan et al (2018)	U.K.	Patients with OAG and taking at least 1 IOP-lowering medication	• XEN alone (N=39)	12 mo

FU: follow-up; IOP: intraocular pressure; OAG: open-angle glaucoma.

Table 5. Summary of Key Case Series Results for the XEN implant

Study	IOP (SD), mm Hg		Medication Use (SD)	
	Baseline	**12 Months**	**Baseline**	**12 Months**
Mansouri et al (2018)	20.0 (7.1)	13.9 (4.3)	1.9 (1.3)	0.5 (0.8)
Grover et al (2017)	25.1 (3.7)	15.9 (5.2)	3.5	1.7
Hengerer et al (2017)	32.2 (9.1)	14.2 (4.0)	3.1 (1.0)	0.3 (0.7)
Perez-Torregrosa et al (2016)	21.2 (3.4)	8.1 (3.0)	3.1	0.2 (0.7)
De Gregorio et al (2017)	22.5 (3.7)	13.1 (2.4)	2.6 (0.9)	0.4 (0.8)
Galal et al (2017)	16 (4)	12 (3)	1.9 (1)	0.3 (0.5)
Ozal et al (2017)	36.1	16.7	3.6 (0.5)	0.3 (0.9)
Tan et al (2018)	24.9 (7.8)	14.5 (3.4)	3	0.7

IOP: intraocular pressure.

Section Summary: Ab Interno Aqueous Stents

Evidence for the use of the XEN implant to treat open-angle glaucoma consists of a nonrandomized comparative study and several single-arm studies. The comparative study reported that patients receiving the XEN implant experienced reductions in IOP and medication

use similar to patients undergoing a trabeculectomy. However, there was no discussion on how patients were chosen to receive the different treatments. The single-arm studies, with 12 months of follow-up, showed that patients receiving the XEN implant experienced reductions in IOP and medication use. Comparative studies with longer follow-up periods are needed.

Aqueous Microstents with Cataract Surgery

Aqueous microstents have been used with cataract surgery. Most evidence addresses single stent use as an adjunct to cataract surgery. Both the iStent and CyPass have been assessed in RCTs comparing implantation of a single stent during cataract surgery with cataract surgery alone. There have also been studies of multiple implants, all been performed with iStent devices; these RCTs and observational studies are discussed in the following section.

<u>iStent</u>

Randomized Controlled Trials

Results from the iStent U.S. investigational device exemption, open-label, 29-site, multicenter RCT were reported to FDA in 2010, with 1-year results published by Samuelson et al (2011) and 2-year results published by Craven et al (2012) (see Table 6). Trial objectives were to compare the incremental effect on IOP of iStent implantation with that of cataract surgery alone and to determine the potential benefit of combining 2 therapeutic treatments into a single surgical event. A total of 240 patients (mean age, 73 years) with cataracts and mild-to-moderate open-angle glaucoma (IOP ≤24 mm Hg controlled on 1-3 medications) underwent a medication washout period. Patients were randomized to cataract surgery plus iStent implantation or cataract surgery only if unmedicated IOP was between 22 and 36 mm Hg. Follow-up visits were performed at 1, 3, 6, and 12 months. Results were assessed by intention-to-treat analysis with the last observation carried forward and per protocol analysis. Of the 117 subjects randomized to iStent implantation, 111 underwent cataract surgery with stent implantation, and 106 (91%) completed the 12-month postoperative visit. Of the 123 subjects randomized to cataract surgery only, 117 underwent cataract surgery, and 3 exited the trial because of surgical complications. Of the remaining 114 subjects, 112 (91%) completed the 12-month visit. The proportion of eyes meeting both the primary (unmedicated IOP ≤21 mm Hg) and secondary outcomes (IOP reduction ≥20% without medication) was higher in the treatment group than in the control group through 1-year follow-up (72% of treatment eyes vs 50% of control eyes achieved the primary efficacy end point, $p<0.001$). The proportion of patients achieving the secondary efficacy end point was 66% in the treatment group and 48% in the control group ($p=0.003$). Ocular hypotensive medications were initiated later in the postoperative period and used in a lower proportion of patients in the treatment group throughout 1-year follow-up (e.g., 15% vs 35% at 12 months). Mean reduction in IOP was similar in both groups; though the control group used slightly more medication (mean, 0.4 medications) than the treatment group (0.2 medications) at 1 year (see Table 7).

At 2 year follow-up, there were 199 patients (83%) remaining in the study. The primary endpoint, (IOP ≤21 mm Hg without use of medication) was reached by 61% of patients in the treatment group compared to 50% of controls ($p=0.036$). The secondary outcomes of IOP reduction of 20% or more without medication (53% vs. 44%) and mean number of medications used (0.3 vs. 0.5) were no longer significantly different between the groups at 2 years. As noted by FDA, this study was conducted in a restricted population of patients who had an

unmedicated IOP of 22 mm Hg or higher and 36 mm Hg or lower. Study results indicate that treatment of this specific population with a microstent is likely to improve outcomes at one year compared with cataract surgery alone, however, 2 year results make it difficult to conclude with certainty that health outcomes improved (see Table 7).

Fea et al (2010) reported on a randomized, double-blind, trial of 36 cataract surgery patients who did or did not receive an iStent implantation (2:1 ratio) (see Table 6). Inclusion criteria were a previous diagnosis of primary open-angle glaucoma with an IOP above 18 mm Hg at 3 separate visits and taking 1 or more hypotensive medications. Investigators were masked to the treatment condition and conducted follow-up at 24 hours, 1 week, and 1, 2, 3, 6, 9, 12, and 15 months. Prescription of hypotensive medications was performed according to preset guidelines. Primary outcomes were IOP and reduction in medication use over 15 months and IOP after a 1-month washout of ocular hypotensive agents (16 months postoperatively). Mean IOP at 15 months decreased in both treatment groups (see Table 7). Eight (67%) of 12 patients in the stent group and 5 (24%) of 21 in the control group did not require ocular hypotensive medication. Because treatment compliance is an ongoing concern for most ophthalmologists, trialists sought to keep patients as medication free as possible postoperatively. Patients in the stent group had significantly lower medication use than patients in the cataract alone group. After washout of medications, mean IOP was 16.6 mm Hg in the stent group and 19.2 mm Hg in the control group. No adverse events related to stent implantation were reported. Four-year follow-up from this study was published by Fea et al (2015). Twenty-four of 36 patients were available at 4 years. Differences between treatment groups remained statistically nonsignificant (mean IOP, 15.9 mm Hg in the stent group vs 17 mm Hg in the control group).

Table 6. Summary of Key RCT Characteristics for the iStent

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	**Comparator**
Samuelson et al (2011); Craven et al (2012)	U.S.	29	2005-2007	Patients with mild-to-moderate OAG, IOP ≥22 and ≤36 mm Hg	iStent plus cataract (n=116)	Cataract alone (n=123)
Fea et al (2010); Fea et al (2015)	Italy	1	NR	Patients with primary OAG	iStent plus cataract (n=24)	Cataract alone (n=12)

IOP: intraocular pressure; NR: not reported; OAG: open angle glaucoma; RCT: randomized controlled trial.

Table 7. Summary of Key RCT Results for the iStent

Study	Mean IOP (SD), mm Hg		p	Mean Medication Use (SD)	
	iStent	**Cataract Alone**		**iStent**	**Cataract Alone**
Samuelson et al (2011); Craven et al (2012)					
Baseline	18.6 (3.4)	17.9 (3.0)	NR	1.6 (0.8)	1.5 (0.6)
Year 1	17.0 (2.8)	17.0 (3.1)	NR	0.2 (0.6)	0.4 (0.7)
Year 2	17.1 (2.9)	17.8 (3.3)	NR	0.3 (0.6)	0.5 (0.7)
Fea et al (2010); Fea et al (2015)					
Baseline	17.9 (2.6)	17.3 (3.0)	0.51	1.9 (0.9)	1.8 (0.7)
Month 15	14.8 (1.2)	15.7 (1.1)	0.31	0.4 (0.7)	1.3 (1.0)
Year 4	17.5 (2.3)	20.4 (3.2)	0.02	0.5 (0.8)	0.9 (1.0)

IOP: intraocular pressure; NR: not reported; SD: standard deviation.

Observational Studies
Kurji et al (2017) reported on 2 surgical methods, phaco-trabectome and phaco-iStent, to control IOP in patients with open-angle glaucoma undergoing cataract surgery. Fifty-five patients (70 eyes) were analyzed in this retrospective comparative case series, 36 receiving PT and 34 receiving phaco-iStent. Outcomes included IOP reduction, glaucoma medication reduction, patients' safety profile, and best-corrected visual acuity. At baseline, the mean IOP of patients in the phaco-trabectome group (30 patients [36 eyes], 20.92 mm Hg]) was higher than those in the phaco-iStent group (25 patients [34 eyes], 17.47 mm Hg; p=0.026]). At 12-month follow-up, both groups experienced significant reductions in IOP; however, there was no statistically significant difference between groups (phaco-trabectome, -5.09 mm Hg 24% relative reduction vs phaco-iStent, -3.84 mm Hg, 22% relative reduction; p=0.331). Glaucoma medication usage did not decrease significantly from baseline to 12 months in either group; moreover, there was no significant difference in reduction between the groups. Phaco-iStent patients had fewer individual complications.

Ferguson et al (2018) reported on a series of 59 patients with severe primary open-angle glaucoma who were implanted with 1 trabecular micro-bypass stent (iStent) during cataract surgery. Patients were followed for 2 years. IOP at baseline was 19.3 mm Hg at baseline, decreasing significantly to 14.4 mm Hg at 12 months and 14.9 mm Hg at 24 months ($p<0.01$). Mean number of glaucoma medications also decreased, from 2.3 at baseline to 1.6 at 24 months.

<u>CyPass</u>
Randomized Controlled Trials
FDA evaluated the clinical performance of the CyPass Micro-Stent system based on the pivotal COMPASS trial (NCT01085357). COMPASS was a multicenter RCT comparing the safety and efficacy of CyPass Micro-Stent plus cataract surgery with cataract surgery alone for treating mild-to-moderate primary open-angle glaucoma in patients undergoing cataract surgery. Vold et al published 2-year results in 2016. A total of 505 patients (1 eye per patient) were assigned in a 1:3 ratio to phacoemulsification only (control) or to supraciliary microstenting with phacoemulsification (microstent). Baseline mean IOPs and number of IOP-lowering medications were similar in the 2 treatment groups (=24.4 mm Hg and 1.4 medications, respectively). In the intention-to-treat analysis, 58% of controls versus 73% of microstent patients achieved 20% or greater unmedicated IOP lowering at 24 months compared to baseline ($p=0.002$). The difference in mean IOP reduction at 24 months was 1.8 mm Hg (95% CI, 1.0 to 2.6 mm Hg; $p<0.001$), favoring the microstent group. In the control group, 59% were medication free at 24 months versus 85% in the microstent group. Mean medication use decreased to 0.6 drugs at 24 months in the control group and to 0.2 drugs in the microstent group ($p<0.001$). There were no vision-threatening microstent-related adverse events. Thirty-nine percent of microstent patients versus 36% of control patients experienced ocular adverse events in the 24-month period. The following ocular adverse events were reported: hypotony (3% microstent vs 0% control), maculopathy (1.3% microstent vs 0.8% control), corneal edema (4% microstent vs 2% control), cyclodialysis cleft greater than 2 mm in circumference (2% microstent vs 0% control), iritis (9% microstent vs 4% control), and subconjunctival hemorrhage (2% microstent vs 1% control). Best-corrected visual acuity was 20/40 or better in

more than 98% of all patients. Eleven patients in the microstent group versus 1 patient in the control group died during the 24-month period; however, the deaths were classified as unrelated to the intervention.

Section Summary: Aqueous Microstents with Cataract Surgery
Two identified RCTs compared cataract surgery plus a single iStent with cataract surgery alone. Results of these trials were mixed, with one showing a significant benefit in the stent group and the other reporting no statistically significant benefit but similar effect size. One RCT compared CyPass plus cataract surgery with cataract surgery alone. Reduction in IOP was greater, and fewer IOP-lowering medications were needed in the CyPass group at 2 years. A low rate of complications (e.g., stent malposition, hyphema) was reported in all trials.

Other Indications for Glaucoma Treatment
Glaucoma shunts and microstent have also been studied in patients for indications other than glaucoma. The following section compares implantation of single stents with multiple stents or multiple stents with medical management.

Multiple Stents
Randomized Controlled Trials
Fernández-Barrientos et al (2010) randomized 33 patients with open-angle glaucoma or ocular hypertension to 2 iStent devices plus cataract surgery or cataract surgery alone. The study was performed at a center in Spain. Eligible eyes had a medicated IOP between 17 and 31 mm Hg (exclusive) and between 21 and 35 mm Hg after medication washout. Mean IOP reduction was greater in the iStent plus surgery group (6.6 mm Hg) than in the surgery alone group (3.9 mm Hg; p=0.002). The mean number of IOP-lowering medications was also significantly lower in the iStent group (0.0 vs 0.7, respectively; p=0.007).

An RCT comparing the efficacy of 1 iStent to multiple iStent devices was published by Katz et al in 2015. This study, from a single institution in Armenia, randomized 119 patients with mild to moderate open-angle glaucoma and an IOP between 22 and 38 mm Hg (off medications) to 1 stent (n=38), 2 stents (n=41), or 3 stents (n=40). Randomization was performed using a pseudorandom number generator. The main outcome measure was IOP at 12 months. The primary end point was the percentage of patients with a 20% or more reduction in IOP off medications. This end point was reached by 89.2% (95% CI, 74.6% to 97.0%) of the 1-stent group, by 90.2% (95% CI, 76.9% to 97.3%) of the 2-stent group, and by 92.1% (95% CI, 78.6% to 98.3%) of the 3-stent group. The secondary end point (percentage of patients achieving an IOP ≤15 mm Hg off medication) was reached by 64.9% (95% CI, 47.5% to 79.8%) of the 1-stent group, by 85.4% (95% CI, 70.8% to 94.4%) of the 2-stent group, and by 92.1% (95% CI, 78.6% to 98.3) of the 3-stent group. Forty-two-month follow-up results for 109 patients were published by Katz et al (2018).36 Mean medicated IOPs for the 1-stent, 2-stent, and 3-stent groups were 15.0 - 2.8 mm Hg, 15.7 - 1.0 mm Hg, and 14.8 - 1.3 mm Hg, respectively. No between-group statistical comparisons were reported.

Vold et al (2016) reported results of an RCT comparing 2 standalone iStent implants to topical travoprost (1:1 ratio) in 101 phakic eyes with IOP between 21 and 40 mm Hg inclusive and newly diagnosed primary open-angle glaucoma, pseudo-exfoliative glaucoma, or ocular

hypertension that had not undergone any prior treatment. The patients were not undergoing cataract surgery. The study was unmasked and methods for allocation concealment and calculation of power were not described. One hundred patients (54 iStent; 47 travoprost) completed 24 months of follow-up and 73 completed 36 months of follow-up. The trial was performed at a single center in Armenia. Statistical analyses were not provided. Baseline mean IOP was 25 mm Hg in both groups. Mean IOP at 3 years was 15 mm Hg in both groups. Medication (or second medication) was added in 6 eyes in the iStent group and 11 eyes in the travoprost group. Progression of cataract was reported in 11 eyes in the iStent group versus 8 eyes in the travoprost group, with cataract surgery being performed in 5 eyes in the iStent group and 1 eye in the travoprost group. The results suggest that 2 iStents might reduce the number of medications required to maintain target IOP compared to travoprost but also hasten time to cataract surgery. However, the study methods were poorly reported and statistical analyses were not reported. The study was funded by the iStent manufacturer.

Observational Studies

Use of multiple iStent devices with cataract surgery was reported in an open-label, prospective series of 53 eyes (47 patients) by Belovay et al (2012). Twenty-eight of 53 eyes were implanted with 2 stents and 25 with 3 stents, based on the need for greater IOP control, as determined by the operating surgeon. Best-corrected visual acuity improved or remained stable in 89% of eyes. IOP decreased from a mean of 18.0 to 14.3 mm Hg, and the number of hypotensive medications decreased from a mean of 2.7 to 0.7 at 1 year postoperatively. Target IOP was reached in 77% of eyes, while 59% of patients discontinued all medications for the study eye. At 1 year, the mean number of hypotensive medications decreased to 1.0 in the 2-stent group and 0.4 in the 3-stent group. Medication use ceased in 46% of eyes in the 2-stent group and 72% in the 3-stent group. Stent blockage occurred in the early postoperative period in 15% of eyes and was successfully treated with laser.

Donnenfeld et al (2015) published a prospective case series enrolling 39 patients with open-angle glaucoma and IOP between 18 and 30 mm Hg. Each patient received 2 micro stents and medications as needed, and was followed for 3 years. At trial completion, mean reduction in IOP was 9.1 mm Hg (95% CI, 8.0 to 10.1 mm Hg). There was 1 postoperative complication (hyphema), which resolved without further intervention.

Vlasov et al (2017) conducted a retrospective chart review of patients with open-angle glaucoma receiving either 1 iStent (n=39) or 2 iStents (n=30) during cataract surgery. Both groups experienced statistically significant reductions in IOP, and there was no significant difference between them in IOP reduction. Only the group receiving 2 iStents experienced a statistically significant reduction in medication use.

Section Summary: Other Indications for Glaucoma Treatment

Several RCTs have evaluated the use of multiple stents, but comparators differed in each RCT. One RCT compared implantation of 2 stents plus cataract surgery with cataract surgery alone; it reported that patients receiving the stents experienced lower IOP and lower medication use. Another RCT compared implantation of a single iStent with 2 or 3 stents; it reported similar rates of patients with a 20% or more reduction in IOP. There were some group differences in secondary outcomes, but statistical testing was not reported. One RCT compared 2 iStents with

travoprost. Two iStents might reduce the number of medications required to maintain target IOP compared with travoprost but could also hasten time to cataract surgery; this RCT was not well reported.

Summary of Evidence

For individuals who have refractory open-angle glaucoma who receive ab externo aqueous shunts, the evidence includes RCTs, retrospective studies, and systematic reviews. Relevant outcomes are change in disease status, functional outcomes, medication use, and treatment-related morbidity. RCTs assessing U.S. Food and Drug Administration–approved shunts have shown that the use of large externally placed shunts reduces IOP to slightly less than standard filtering surgery (trabeculectomy). Reported shunt success rates show that these devices are noninferior to trabeculectomy in the long term. Food and Drug Administration–approved shunts have different adverse event profiles and avoid some of the most problematic complications of trabeculectomy. Two trials have compared the Ahmed and Baerveldt shunts. Both found that eyes treated with the Baerveldt shunt had slightly lower average IOP at 5 years than eyes treated with the Ahmed but the Baerveldt also had a higher rate of serious hypotony-related complications. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have refractory open-angle glaucoma who receive ab interno aqueous stents, the evidence includes a nonrandomized comparative study and several single-arm studies. Relevant outcomes are change in disease status, functional outcomes, medication use, and treatment-related morbidity. The comparative study reported that patients receiving the stent experienced similar reductions in IOP and medication use as patients undergoing trabeculectomy. However, there was no discussion on how the patients were chosen to receive the different treatments. The single-arm studies have reported 12-month follow-up results and found that patients receiving the stents experienced reductions in IOP and medication use. Comparative studies with longer follow-up periods are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have mild-to-moderate open-angle glaucoma who are undergoing cataract surgery who receive aqueous microstents, the evidence includes RCTs. Relevant outcomes are change in disease status, functional outcomes, medication use, and treatment-related morbidity. Two microstents have received the Food and Drug Administration approval for use in conjunction with cataract surgery for reduction of IOP in adults with mild-to-moderate open-angle glaucoma currently treated with ocular hypotensive medication. RCTs have been conducted in patients with cataracts and less advanced glaucoma, where IOP is at least partially controlled with medication. Trial results have shown that IOP may be lowered below baseline with a decreased need for medication through the first 2 years. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with indications for glaucoma treatment other than cataract surgery or refractory open-angle glaucoma who receive aqueous shunts or microstents, the evidence includes RCTs. Relevant outcomes are change in disease status, functional outcomes, medication use, and treatment-related morbidity. Several RCTs have evaluated the use of multiple microstents, but comparators differed. One RCT compared a single microstent with multiple microstents. This

trial reported no difference in the primary outcome (percentage of patients with ≥20% reduction in IOP); secondary outcomes favored the multiple microstent groups. One RCT compared 2 iStents with travoprost. This trial did not report statistical comparisons. The evidence is insufficient to determine the effects of the technology on health outcomes.

Practice Guidelines and Position Statements

American Glaucoma Society

A 2012 position statement by the American Glaucoma Society (AGS) states that new technology whose intraocular pressure-lowering effect allows for a reduction in medications, or a reduction in the need for more advanced surgical care, or improves patient adherence to care, would provide advantages to glaucoma patients. If effective and safe, the AGS believe that these benefits and the fact that these technologies will not have bleb-related complications would represent an "improvement in net health outcomes." In addition, the AGS states that some categories of new surgical devices and techniques used at the time of concomitant cataract surgery. Because cataract surgery alone has been shown to lower IOP, a control group of patients with similar entry criteria undergoing cataract surgery alone may be appropriate for these technologies.

American Academy of Ophthalmology

The American Academy of Ophthalmology (AAO) published a 2008 technology assessment on commercially available aqueous shunts, including the Ahmed, Baerveldt, Krupin, and Molteno devices. The assessment indicated that, in general, the IOP will settle at higher levels (approximately 18 mm Hg) with shunts than after standard trabeculectomy (14 to 16 mm Hg). Five-year success rates of 50% have been found for the 2 procedures, indicating that aqueous shunts are comparable with trabeculectomy for IOP control and duration of benefit (based on Level I evidence; well-designed randomized controlled trials). The assessment indicated that although aqueous shunts have been generally reserved for intractable glaucoma when prior medical or surgical therapy has failed, indications for shunts have broadened (based on Level III evidence; case series, case reports, and poor-quality case-control or cohort studies). The AAO concluded that based on Level I evidence; aqueous shunts offer a valuable alternative to standard filtering surgery or to cyclodestructive therapy for many patients with refractory glaucoma.

A 2011 technology assessment from the AAO (literature search up to October 2009) reviewed the evidence on novel, or emerging, glaucoma procedures. Included in the technology assessment were devices and procedures that either had U.S. Food and Drug Administration clearance or were in Phase III clinical trials in the United States at the time. These included the Ex-PRESS™ mini glaucoma shunt, the SOLX Gold Shunt, and the iStent, along with various surgical procedures. The technology assessment concluded that these techniques and devices are still in the initial state (<5 years) of clinical experience and lacking widespread use. The clinical studies generally provided only Level III evidence in support of the procedures. Based on the literature available at the time, it was not possible to conclude if the novel procedures were superior, equal to, or inferior to surgery such as trabeculectomy or to one another.

The 2015 preferred practice patterns on primary open-angle glaucoma indicated that AAO considered laser trabeculoplasty as initial therapy in select patients or an alternative for patients

who cannot or will not use medications reliably due to cost, memory problems, difficulty with instillation, or intolerance to the medication. AAO stated that aqueous shunts have traditionally been used to manage refractory glaucoma when trabeculectomy has failed to control IOP or is unlikely to succeed but these devices are being increasingly used in other indications for the surgical management of glaucoma. AAO also stated that micro-invasive glaucoma surgeries (MIGS) that are frequently combined with phacoemulsification have limited long-term data but seem to result in modest IOP reduction with postoperative pressures in the mid to upper teens. Although they are less effective in lowering IOP than trabeculectomy and aqueous shunt surgery, MIGS may have a more favorable safety profile in the short term.

National Institute for Health and Clinical Excellence
The National Institute for Health and Care Excellence updated guidance on trabecular stent bypass microsurgery for open-angle glaucoma in 2017. The guidance stated that "Current evidence on trabecular stent bypass microsurgery for open-angle glaucoma raises no major safety concerns. Evidence of efficacy is adequate in quality and quantity."

European Glaucoma Society
The European Glaucoma Society's Terminology and Guidelines for Glaucoma (2014) provided evidence-based guidelines on the treatment of primary open-angle glaucoma. The guidelines were updated in 2017. The guidelines stated that there are no well-controlled comparative trials to support the superiority in safety or efficacy of MIGS, including both ab interno and ab externo procedures, over trabeculectomy.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Key Words:
Eyepass, Hydrus Microstent, iStent, trabecular shunt, Trabectome, Solx gold shunt, SOLX Gold Shunt, Ex-PRESS®, AquaFlow™, Ahmed™, Baerveldt, Krupin, Molteno®, iStent *supra*, Cy Pass, aqueous shunt, trabecular stent, micro-stent, iStent® Trabecular Micro-Bypass Stent, XEN Ab interno, ab externo, Hydrus

Approved by Governing Bodies:
The regulatory status of the various aqueous shunts and micro-stents is summarized in Table 1. The first generation Ahmed™ (New World Medical), Baerveldt® (Advanced Medial Optics), Krupin (Eagle Vision), and Molteno® (Molteno Ophthalmic) aqueous shunts were cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process between 1989 and 1993; modified Ahmed and Molteno devices were most recently cleared in 2006. Their indication for use is "in patients with intractable glaucoma to reduce intraocular pressure where medical and conventional surgical treatments have failed." The AquaFlow™ Collagen Glaucoma Drainage Device was approved by FDA through the premarket approval process for the maintenance of the subscleral space following non-penetrating deep sclerectomy.

In 2013, the EX-PRESS® Mini Glaucoma Shunt was cleared for marketing by FDA through the 510(k). The Ex-PRESS shunt is placed under a partial thickness scleral flap and transport aqueous fluid from the anterior chamber of the eye into a conjunctival filtering bleb.

In 2016, the Xen® Glaucoma Treatment System (Allergan), which consists of the XEN45 Gel Stent preloaded into the XEN Injector, was cleared for marketing by FDA through the 510(k) process as an aqueous shunt for management of refractory glaucoma. The approval was for patients with refractory glaucoma who failed previous surgical treatment or for patients with primary open-angle glaucoma unresponsive to maximum tolerated medical therapy. FDA determined that this device was substantially equivalent to existing devices, specifically the Ahmed™ Glaucoma Valve and the EX-PRESS® Glaucoma Filtration Device.

Table 1: Regulatory Status of Aqueous Shunts and Stents

Device	Manufacturer	Type	FDA Status	Date
AquaFlow™	Staar Surgical	Drainage device	PMA	2001
Ahmed ™	New World Medical	Aqueous glaucoma shunt	510(k)	<1993
Baerveldt®	Advanced Medical Optics	Aqueous glaucoma shunt	510(k)	<1993
Krupin	Eagle Vision	Aqueous glaucoma shunt	510(K)	<1993
Molteno®	Molento Ophthalmic	Aqueous glaucoma shunt	510(k)	<1993
Ex-PRESS™	Alco	Mini-glaucoma shunt	510(k)	2003
iStent®	Glaukos	Microsent	PMA	2012
Hydrus™	Ivantis	Microstent	Not Approved; PMA submission	2017
SOLX® Gold	SOLX	Micro-shunt, ab externo	Not approved; in clinical trial	
iStent *inject*®	Glaukos	Suprachoroidal stent	Not Approved; PMA submission	2017
iStent *supra*®	Glaukos	Suprachoroidal stent	Not Approved; in clinical trial	
CyPass®	Transcend Medical	Suprachoroidal stent	PMA	2016
XEN Gel Stent	AqueSys	Subconjunctival	510(k)	2016

FDA: Food and Drug Administration; PMA: premarket approval

In 2012, the iStent® Trabecular Micro-Bypass Stent (Glaukos Corp) was approved by FDA through the premarket approval process for use in conjunction with cataract surgery for the

reduction of IOP in adult patients with mild to moderate open-angle glaucoma currently treated with ocular hypotensive medication.

The labeling describes the following precautions:

1. The safety and effectiveness of the iStent Trabecular Micro-Bypass Stent has not been established as an alternative to the primary treatment of glaucoma with medications. The effectiveness of this device has been demonstrated only in patients with mild to moderate open-angle glaucoma who are currently treated with ocular hypotensive medication and who are undergoing concurrent cataract surgery for visually significant cataract.
2. The safety and effectiveness of the iStent® Trabecular Micro-Bypass Stent has not been established inpatients with the following circumstances or conditions which were not studied in the pivotal trial:
    - In children
    - In eyes with significant prior trauma
    - In eyes with abnormal anterior segment
    - In eyes with chronic inflammations
    - In glaucoma associated with vascular disorders
    - In pseudophakic patients with glaucoma
    - In uveitic glaucoma
    - In patients with prior glaucoma surgery of any type including argon laser trabeculoplasty
    - In patients with medicated intraocular pressure greater than 24 mmHg
    - In patients with unmedicated IOP less than 22 mmHg or greater than 36 mmHg after "washout" of medications
    - For implantation of more than a single stent
    - After complications during cataract surgery, including but not limited to, severe corneal burn, vitreous removal/vitrectomy required, corneal injuries, or complications requiring the placement of an anterior chamber IOL
    - When implantation has been without concomitant cataract surgery with IOL implantation for visually significant cataract

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.
ITS: Home Policy provisions apply
FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

Current Coding:

CPT Codes:

66183	Insertion of anterior segment aqueous drainage device, without extraocular reservoir, external approach
0191T	Insertion of anterior segment aqueous drainage device, without extraocular reservoir; internal approach, into the trabecular meshwork; initial insertion
0253T	Insertion of anterior segment aqueous drainage device, without extraocular reservoir; internal approach, into the suprachoroidal space
0376T	Insertion of anterior segment aqueous drainage device, without extraocular reservoir, internal approach, into the trabecular meshwork; each additional device insertion (List separately in addition to code for primary procedure)
0449T	Insertion of aqueous drainage device, without extraocular reservoir, internal approach, into the subconjunctival space; initial device **(Effective 01/01/17)**
0450T	; each additional device **(Effective 01/01/17)**
0474T	Insertion of anterior segment aqueous drainage device, with creation of intraocular reservoir, internal approach, into the supraciliary space **(new code effective 07/01/17)**

HCPCS:

L8612	Aqueous Shunt

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Policy History:

Medical Policy Group, July 2008 **(2)**
Medical Policy Administration Committee, August 2008
Available for comment August 13-September 26, 2008
Medical Policy Group, July 2010 **(1):** Policy statement updated, Description, Key Points
Medical Policy Administration Committee, June 2010
Available for comment June 18-August 2, 2010
Medical Policy Group, December 2010, Code update
Medical Policy Panel, May 2011
Medical Policy Group, May 2011 **(2):** Policy change, Key Points and References updated
Medical Policy Administration Committee, June 2011
Available for comment June 8 – July 25, 2011
Medial Policy Panel, September 2011
Medical Policy Group, September 2011 **(2):** Policy change, Key Points, References updated
Medical Policy Administration Committee, October 2011
Available for comment October 19 through December 5, 2011
Medical Policy Panel, May 2012
Medical Policy Group, June 2012 **(2):** Name changed from Viscocanaloplasty and Canaloplasty to Aqueous Shunts for Glaucoma, Updated policy, Key words, Key Points, Approved by Governing Bodies, References to reflect name of policy
Medical Policy Group, September **(2):** Removed all references to iTrack
Medical Policy Panel, October 2012
Medical Policy Group, October 2012 **(2)**: Policy updated with literature search through August 2012. Policy statement for use of micro-stent is investigational. Title, Key Words, FDA approval, Key Points and References updated to support non-coverage statement for use of micro-stent.
Medical Policy Administration Committee, November 2012
Available of comment November 14 through December 28, 2012
Medical Policy Panel, September 2013
Medical Policy Group, October 2013 **(2):** Policy updated with literature search through August 2013. Added policy statement that iStent is considered covered in patients intolerant of medications when implanted in conjunction with cataract surgery. Description, Key Points, Approved by Governing Bodies, and References updated to reflect findings in literature search and new policy statement.
Medical Policy Administration Committee, October 2013
Available for comment October 16 through November 30, 2013
Medical Policy Group, December 2013 **(1):** 2014 Coding Update: added new code 66183, effective 01/01/2014; moved deleted code 0192T to Previous Coding section, effective 01/01/2014.
Medical Policy Panel September, 2014
Medical Policy Group, September 2014 **(1):** Update to Description, Key Points and References. No Policy Statement change

Medical Policy Group, November 2014: 2015 Annual Coding update. Added code 0376T to current coding; Changed verbiage on 0191T to read 'initial insertion', no change to 0253T
Medical Policy Panel, September 2015
Medical Policy Group, September 2015 **(6):** Updates to Key Points, Key Words, Approved by Governing Bodies and References; no change in policy statement.
Medical Policy Panel, March 2016
Medical Policy Group, March 2016 **(6)**: Updates to Description, Key Points, Approved by Governing Bodies and References: no change to policy statement.
Medical Policy Group, December 2016 **(6)**: Removed Cypass from investigational status in Description of Procedure. FDA approved July 29, 2016, Updated Key Points.
Medical Policy Group, December 2016: 2017 Annual Coding Update. Added new cpt codes 0449T and 0450T to Current Coding.
Medical Policy Group, January 2016 **(6)**: Updates to Key Words and Approved by Governing Bodies to include the XEN glaucoma treatment system.
Medical Policy Panel, March 2017
Medical Policy Group, March 2017 **(6)**: Updates to Description, Key Points, Coding, Practice Guidelines, Governing Bodies and References.
Medical Policy Panel, May 2018
Medical Policy Group, June 2018 **(6)**: Updates to Description, Policy statement updated to distinguish ab interno vs ab externo, Key Points, Governing Bodies, Key words added (Ab interno, ab externo, Hydrus), L8612 added to Coding and References.
