Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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Title: Aqueous Shunts and Stents for Glaucoma

Description/Background

GLAUCOMA

Glaucoma is the leading cause of irreversible blindness worldwide and is characterized by elevated intraocular pressure (IOP). In 2020, glaucoma affected approximately 52.7 million individuals globally, with a projected increase to 79.8 million in 2040.[1,] Glaucoma has been reported to be 7 times more likely to cause blindness and 15 times more likely to cause visual impairment in Black individuals as compared to White individuals. In the U.S. in 2010, Black individuals had the highest prevalence rate of primary open angle glaucoma at 3.4% compared to 1.7% among White individuals.

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), drains into collector channels, and then 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

Ocular Medication

First-line treatment typically involves pharmacologic therapy. Topical medications either increase the aqueous outflow (prostaglandins, alpha-adrenergic agonists, cholinergic agonists, Rho kinase inhibitors) or decrease aqueous production (alpha-adrenergic agonists, betablockers, carbonic anhydrase inhibitors). Pharmacologic therapy may involve multiple medications, have potential side effects, and may be inconvenient for older adults or incapacitated patients.

Surgery

Surgical intervention may be indicated in patients with glaucoma when the target IOP cannot be reached pharmacologically. Surgical procedures for glaucoma aim to reduce IOP from impaired aqueous humor drainage in the trabecular meshwork and/or Schlemm canal. 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, bleb-related endophthalmitis) and long-term failure. Other surgical procedures (not addressed herein) include trabecular laser ablation, deep sclerectomy (which removes the outer wall of the Schlemm canal and excises deep sclera and peripheral cornea), and Viscocanalostomy (which unroofs and dilates the Schlemm canal without penetrating the trabecular meshwork or anterior chamber). Canaloplasty involves dilation and tension of the Schlemm 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 the Schlemm canal and to pass the suture loop through the canal. Insertion of shunts from outside the eye (ab externo) is another surgical option to lower IOP. Examples of ab externo devices cleared by the U.S. Food and Drug Administration (FDA) include the Ahmed, Baerveldt, Molteno, and EX-PRESS mini-shunt, which shunt aqueous humor between the anterior chamber and the suprachoroidal space. These devices differ by explant surface areas, shape, plate thickness, presence or absence of a valve, and details of surgical installation. Generally, the risk of hypotony (low pressure) is reduced with aqueous shunts compared with trabeculectomy, but IOP outcomes are worse 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 lower with shunts than with trabeculectomy, and failure rates are similar (»10% of devices fail annually). The primary indication for aqueous shunts is for failed medical or surgical therapy, although some ophthalmologists have advocated their use as a primary surgical intervention, particularly for selected conditions such as congenital glaucoma, trauma, chemical burn, or pemphigoid.

Minimally Invasive Glaucoma Surgeries

MIGS are alternative, less invasive techniques that are being developed and evaluated. MIGS, which use microscopic-sized equipment and smaller incisions, involves less surgical manipulation of the sclera and the conjunctiva compared with other surgical techniques. There are several categories of MIGS: miniaturized trabeculectomy, trabecular bypass, milder laser photocoagulation, and totally internal or suprachoroidal stents (ab interno). Shunts and stents can be administered through an external flap of the conjunctiva and sclera (ab externo) or in a small incision in the cornea with the devices inserted through the anterior chamber of the eye (ab interno). Some ab interno microstents may be inserted with injectors.

Examples of ab interno devices either approved or given marketing clearance by the 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; iStent Inject; iStent Infinite and XEN gelatin stent.

Because aqueous humor outflow is pressure-dependent, the pressure in the reservoir and venous system is 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, iStent Inject, and Hydrus Microstent may be useful in patients with early-stage glaucoma to reduce the burden of medications and problems with compliance. One area of investigation are 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. Also, most devices

do not preclude subsequent trabeculectomy if needed. It may also be possible to insert more than one stent to achieve desired IOP.

Regulatory Status:

The regulatory status of the various aqueous shunts and microstents is summarized in Table 1. The first generation Ahmed (New World Medical), Baerveldt (Advanced Medical Optics), Krupin (Eagle Vision), and Molteno (Molteno Ophthalmic) aqueous shunts received marketing clearance from the U.S. Food and Drug Administration (FDA) between 1989 and 1993; modified Ahmed and Molteno devices were 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 received premarket approval from the FDA in 2001 for the maintenance of subscleral space following non-penetrating deep sclerectomy. In 2003, the Ex-PRESS™ Mini Glaucoma Shunt was cleared for marketing by FDA through the 510(k) process. The Ex-PRESS shunt is placed under a partial thickness scleral flap and transports 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, ab externo	510 (k)	<1993
Baerveldt®	Advanced Medical Optics	Aqueous glaucoma shunt, ab externo	510 (k)	<1993
Krupin	Eagle Vision	Aqueous glaucoma shunt, ab externo	510 (k)	<1993
Molteno®	Molteno Ophthalmic	Aqueous glaucoma shunt, ab externo	510 (k)	<1993
EX-PRESS®	Alcon	Mini-glaucoma shunt, ab externo	510 (k)	2003
XEN® Gel Stent	AqueSys/Allergan	Aqueous glaucoma shunt, ab externo	510 (k)	2016
[a]iStent®; iStent inject®	Glaukos	Microstent, ab interno	515(d) in conjunction with cataract surgery	2018
[a]CyPass®	Alcon	Suprachoroidal stent, ab interno	Company voluntarily recalled	2018
[a]Hydrus™	Ivantis	Microstent, ab interno	PMA approval	2018
Beacon Aqueous Microshunt	MicroOptx	Micro-Shunt, ab externo	Not approved; in clinical trial	
PRESERFLO®	Santan	Micro-Shunt; ab externo	Not approved; in	

MicroShunt			clinical trial	
iStent Infinate	Glaukos	Microstent, ab interno	501K	2022

FDA: Food and Drug Administration; PMA: premarket approval.
[a]These stents are indicated for use in conjunction with cataract surgery for the reduction of IOP in adult patients with mild to moderate primary open-angle glaucoma.

In August 2018, Alcon announced an immediate voluntary recall of the CyPass microstent, which had been approved by the FDA in 2016 for use in conjunction with cataract surgery in adults with mild-to-moderate open-angle glaucoma. The recall was based on five-year post-surgery data from the COMPASS-XT long-term safety study. Results showed a statistically significant increase in endothelial cell loss among patients receiving the CyPass microstent compared with patients receiving cataract surgery alone.[2]

FDA product codes: OGO, KYF

Medical Policy Statement

The safety and effectiveness of the insertion of U.S. Food and Drug Administration (FDA) approved aqueous shunts and stents have been established. They are useful therapeutic options for reducing intraocular pressure in individuals with glaucoma in whom medical therapy has failed to adequately control intraocular pressure.

Insertion of ab externo aqueous shunts approved by the U.S. Food and Drug Administration is established as a method to reduce intraocular pressure in individuals with glaucoma in whom medical therapy has failed to adequately control intraocular pressure.

Use of an ab externo aqueous shunt for all other conditions, including in individuals with glaucoma when intraocular pressure is adequately controlled by medications, is considered experimental/ investigational.

Insertion of ab interno aqueous stents approved by the Food and Drug Administration as a method to reduce intraocular pressure in individuals with glaucoma in whom medical therapy has failed to adequately control intraocular pressure, is considered established.

Implantation of 1 or 2 FDA-approved microstent(s) in conjunction with cataract surgery may be considered established in individuals with mild to moderate open-angle glaucoma currently treated with ocular hypotensive medication.

The use of ab interno stents for all other conditions is considered experimental/investigational.

Inclusionary and Exclusionary Guidelines

Inclusions:
Insertion of FDA-approved aqueous shunts is considered established as a method to reduce intraocular pressure in patients with mild to moderate open-angle glaucoma when conventional pharmacologic treatments have failed to control intraocular pressure adequately.

Currently available FDA-approved shunts include:
- Ahmed™ glaucoma implant
- Baerveldt® seton
- Ex-PRESS® mini glaucoma shunt
- Glaucoma pressure regulator
- Krupin-Denver valve implant
- Molteno® implant
- Schocket shunt
- Xen Gel Stent
- [a]CyPass® Micro-Stent (recalled)
- [a]iStent®
- [ab]iStent inject®
- iStent Infinate®
- [a]Hydrus™

[a] These stents are indicated for use in conjunction with cataract surgery for the reduction of IOP in adult patients with mild to moderate primary open-angle glaucoma.
[ab] The iStent Inject® comes pre-loaded with two stents.

Exclusions:
- The use of an aqueous shunt for all other conditions, including patients with glaucoma when intraocular pressure is controlled by medications.
- Insertion of aqueous shunts that are not FDA approved.
- For the Trabecular Micro-Bypass iStent and the iStent Inject, patients with the following conditions are not appropriate candidates and the insertion of this stent would be considered experimental/investigational:
  - Quick or sudden increase in eye pressure
  - Inflammation of the eye tissue (uvea)
  - Neovascular glaucoma
  - Noticeable birth irregularities on the front of the eye
  - Orbital tumor
  - Thyroid eye disease
  - Sturge-Weber syndrome
  - Any other type of condition that may cause elevated pressure in the veins of the eye
- For the Hydrus Microstent, patients with the following conditions are not appropriate candidates and the insertion of this stent would be considered experimental/investigational:
  - When the colored part of the eye (iris) is pushed up against the drainage pathway or when other material blocks the drainage pathway
  - Traumatic glaucoma, malignant glaucoma, or inflammation of the eye tissue
  - Glaucoma associated with the growth of abnormal blood vessels in the eye
  - Noticeable birth irregularities of the anterior chamber angle

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

Established codes:

66179	66180	66183	66184	66185	66982
66983	66984	66987	66988	68989	66991
0449T	0450T	0474T	0671T		

Other codes (investigational, not medically necessary, etc.):

66999	0253T

Rationale

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.

AQUEOUS SHUNTS AND STENTS FOR GLAUCOMA

Clinical Context and Therapy Purpose

The purpose of aqueous shunts and stents in patients who have glaucoma is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of aqueous shunts and stents improve the net health outcomes of patients with glaucoma compared to standard of care (including medical therapy or trabeculectomy)?

The following **PICOs** were used to select literature to inform this review.

Populations
The relevant populations of interest are:

- Individuals with refractory open-angle glaucoma (OAG)
- Individuals with mild-to-moderate OAG who are undergoing cataract surgery
- Individuals with indications for glaucoma treatment other than cataract surgery or refractory OAG

Interventions
The therapies being considered are:

- For individuals with refractory OAG:
    - Ab externo aqueous shunts
    - Ab interno aqueous stents
- For individuals with mild-to-moderate OAG undergoing cataract surgery: ab interno aqueous stents
- For individuals with indications for glaucoma treatment other than cataract surgery or refractory OAG: ab externo aqueous shunts or ab interno aqueous stents

Comparators
Comparators include medical therapies and trabeculectomy.

Outcomes
The general outcomes of interest are change in intraocular pressure (IOP) and change in medication use.

Timing
Changes in IOP and medication use are measured for at least 12 months. Safety measures involve longer follow-up, for several years.

Setting
Insertion of aqueous shunts and stents are performed in tertiary care centers.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

a. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
b. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
c. To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
d. Studies with duplicative or overlapping populations were excluded.

AB EXTERNO AQUEOUS SHUNTS

Systematic Reviews
A 2006 Cochrane review by Minckler et al evaluated 15 randomized or pseudo-randomized controlled trials (RCTs), with a total of 1,153 participants, on the Ahmed, Baerveldt, Molteno, and Schocket shunts.[2] Trabeculectomy was found to result in a lower mean intraocular pressure (IOP) (by 3.8 mm Hg) than the Ahmed shunt at 1 year. A limitation of this report is that complications were not compared, as the authors considered them to be too variably reported to allow comparative tabulation. There was no evidence of superiority of one shunt

over another. An update by Tseng et al (2017) identified 27 studies, 4 of these studies compared Ahmed or Baerveldt shunts to trabeculectomy and 2 compared different types of shunts.[3,] There was some evidence that Baerveldt and Molteno implants may reduce eye pressure more than Ahmed, and Molteno may lower eye pressure better than the Shocket.

A technology assessment on commercially available aqueous shunts, including the Ahmed, Baerveldt, Krupin, and Molteno devices, for an American Academy of Ophthalmology (AAO) technology assessment, was published in 2008.[4] This review indicated that the IOP will generally settle at higher levels (≈18 mm Hg) with aqueous shunts than after standard trabeculectomy (14-16 mm Hg) or after trabeculectomy with anti-fibrotic agents 5-fluorouacil or mitomycin C (8-10 mm Hg). In one study, mean IOPs with the Baerveldt shunt and adjunct medications were found to be equivalent to trabeculectomy with mitomycin C (13 mm Hg). Five-year success rates for the two procedures were found to be similar (50%). The assessment concluded that based on level 1 evidence, aqueous shunts were comparable with trabeculectomy for IOP control and duration of benefit. The risk of postoperative infection was less with aqueous shunts than after 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 described as accelerated damage to the corneal endothelium over time.

Zhang et al (2022) compared the effectiveness of trabeculectomy and Ahmed and EX-PRESS implants in the treatment of primary and secondary glaucoma via a systematic review and network meta-analysis.[5] The review included 14 RCTs, involving 866 eyes of 808 patients. Overall, there were 339 eyes in the trabeculectomy group, 368 eyes in the EX-PRESS group, and 159 eyes in the Ahmed group. Results revealed that after 3 months, trabeculectomy was associated with similar improvement in IOP as compared to Ahmed (weighted mean difference [WMD], 0.014; 95% confidence interval [CI], -0.14 to 0.18) and EX-PRESS (WMD, 0.014; 95% CI, -0.072 to 0.097). However, at 1 year, EX-PRESS was associated with a significant improvement in IOP (WMD, 0.097; 95% CI, 0.008 to 0.18) as well as complete success (relative risk [RR], 0.73; 95% CI, 0.57 to 0.93) as compared to trabeculectomy. In a comparison of EX-PRESS and Ahmed implants, EX-PRESS was found to be superior to Ahmed with regard to reduction in the number of post-operative medications. Limitations of this meta-analysis included the presence of publication bias and heterogeneity of the included data.

Baerveldt Glaucoma Shunt

Randomized Controlled Trials

Results from the open-label multicenter randomized Tube Versus Trabeculectomy (TVT) study were reviewed in the 2008 AAO technology assessment, and in 2012, Gedde et al reported 5-year follow-up from this study.[4,6,7] The study included 212 eyes of 212 patients (age rage 18-85 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, randomized to tube (Baerveldt shunt) or trabeculectomy. 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 vs. 1.2 in the trabeculectomy group) were significantly different with intent-to-treat analysis. The cumulative probability of failure over the 5 years was lower in the tube group (29.8%) than the trabeculectomy group (46.9%), and the

rates of reoperation were lower (9% vs. 29% respectively). 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).

Subsequent publications have reported no significant differences between the groups for vision-related quality of life or visual field outcomes from the Tube vs Trabeculectomy study.[8,9]

EX-PRESS Mini Shunt

Systematic Reviews

A Cochrane review by Wang et al (2015) evaluated the efficacy of adjunctive procedures for trabeculectomy.[10] Three RCTs were included and compared trabeculectomy alone with trabeculectomy plus EX-PRESS Mini Shunt. These trials were rated as having 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 pooled analysis, IOP was slightly 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). An updated analysis by Park et al (2023) identified a total of 8 studies (7 with EX-PRESS and 1 with PreserFlo MicroShunt).[11,] Low-certainty evidence showed that adjunct EX-PRESS resulted in lower IOP at 1 year (MD, -1.76; 95% CI, -2.81 to -0.70).

Randomized Controlled Trials

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).[12] 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): mean IOP was 14.7 mm Hg on 0.9 medications in the EX-PRESS group and 14.6 mm Hg on 0.7 medications in the trabeculectomy group. 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%).

Additional single-center RCTs have corroborated the results of the multicenter trial.[13-17]

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	Pts w/primary OAG not controlled by IOP medication	Ex-PRESS (n=39)	Trabeculectomy (n=39)
Netland et al (2014)	U.S., Canada	7	NR	Pts w/OAG treated with IOP medications who	Ex-PRESS (n=59)	Trabeculectomy (n=61)

				were candidates for glaucoma surgery		
Wagschal et al (2015) Gonzalez-Rodriquez et al (2016)	Canada	1	2011-2012	Pts w/primary OAG not controlled by IOP medication	Ex-PRESS (n=33)	Trabeculectomy (n=31)
Konopinska et al (2021)	Poland	1	2016-2019	Patients with OAG not controlled by IOP medication who qualified for both cataract and OAG surgery	Phaco EX-PRESS (n=43)	Phaco - Trabeculectomy (n=38)

Pts: patients; 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
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)

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

Comparative Effectiveness Analyses

Five-year results of two 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 and Baerveldt Glaucoma Implant in 276 adults with previous incisional eye surgery or refractory glaucoma. [18,19] The ABC was funded by National Eye Institute, Research to Prevent Blindness, and New World Medical. The Ahmed Versus Baerveldt (AVB) study, reported by Christakis et al (2016), was an international, multicenter RCT enrolling 238 patients with uncontrolled glaucoma despite maximally tolerated medical therapy that was funded by the Glaucoma Research Society of Canada.[20]

Christakis et al (2017) analyzed 5-year pooled data from the ABC and AVB trials comparing the relative efficacy of the 2 implants.[21] 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 Ahmed 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 the FDA approval or marketing clearance.

Xen Glaucoma Treatment System

Systematic Reviews

Lim et al (2022) conducted a systematic review and meta-analysis of 14 studies (N=963 eyes) involving the stand alone XEN45 gel stent ab interno device implant.[22] The review included 7 prospective and 7 retrospective studies. The mean age of included patients was 66 years and the maximum follow-up duration ranged from 6 to 30 months. A variety of surgical techniques were employed across the studies; however, surgical steps were largely consistent. Results revealed that implantation of the XEN45 gel stent significantly decreased IOP ($p<.001$) across all timepoints (1 day, 1 week, 1, 3, 6, 12, 18, and 24 months) with a mean decrease of 7.44 mmHg at 24 months. The use of IOP-lowering medications was also reduced significantly ($p<.001$) post-implantation across all timepoints (1 week, 1, 3, 6, 12, 18, and 24 months) with a mean reduction of 1.67 medications at 24 months. Serious adverse events occurred rarely with transient numerical hypotony the most common postoperative complication. Postoperative needling procedures were required in 38% of eyes during the entire follow-up period. The overall quality of the evidence within the systematic review was low, with most included studies being case series with relatively short follow-up durations and a lack of standardized definitions of treatment success and failure. Additional RCTs with a clinically meaningful definition of success and failure are needed.

Another systematic review and meta-analysis that evaluated the efficacy of the XEN gel stent implant in 78 eligible studies reported similar conclusions.[23] Following XEN stent implantation, there was a significant reduction in IOP ($p<.001$) and the number of anti-glaucoma medications used ($p<.001$) through 48 months post-surgery. However, the quality of included studies was noted to be relatively low and the definition of outcomes was inconsistent across the included studies.

Randomized Controlled Trial

Sheybani et al (2023) conducted a randomized, noninferiority trial comparing XEN45 gel stent to trabeculectomy in patients (N=139) with an IOP of 15 to 44 mm Hg while receiving topical IOP medication.[24,] At 12 months XEN45 was noninferior to trabeculectomy in terms of surgical success which was defined as at least a 20% reduction in IOP without a medication increase, clinical hypotony, vision loss, or secondary surgical intervention (between group difference, -6.1%; 95% CI, -22.9% to 10.8%). XEN45 resulted in fewer postoperative interventions and faster visual recovery than trabeculecomy.

Non-Randomized Comparative Studies

Schlenker et al (2017) published a multicenter, retrospective comparative study that compared the risk, safety, and efficacy for standalone ab interno microstent implantation with mitomycin

C (MMC) and trabeculectomy plus MMC (Table 4).[25] Implantations of the abinterno XEN 45 gelatin microstent is a less invasive surgery than 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 two consecutive IOP readings of less than 6 mm Hg, including vision loss. Success was measured by the withdrawal of glaucoma-related medications at one month post-surgery. 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. Changes in IOP and medication use appear in Table 5.

Wagner et al (2020) also reported similar success rates for trabeculectomy (65.5%, 95% CI, 55.6 to 75.9%) and XEN Implant (58.5%, 95% CI, 47.6 to 69.4%, p =.16; adjusted odds ratio 0.66, 95% CI, 0.32 to 1.37) but a greater reduction in IOP with trabeculectomy (10.5 mm Hg) compared to the XEN implant (7.2 mm Hg; p =.003).[26] Baseline measurements showed older age (73.0 vs 67.2) and a lower number of medication classes (2.0 vs 3.0) for the XEN group. A regression mixed model that adjusted for gender, age, preoperative IOP, and medications did not indicate a difference in the proportion of success for the 2 groups.

Stoner et al (2021) conducted a retrospective comparative study of 100 eyes that had undergone either XEN or EX-PRESS standalone shunt implantation at a single center.[27] Surgical success was defined as IOP between 6 and 18 mm Hg without reoperation, loss of light perception, device removal, or use of glaucoma medications. The incidence of adverse effects during the first 3 months was lower with the XEN implant, but the failure rate at 1 year was higher (HR 3.94, 95% CI, 1.73 to 9.00, p =.001) compared to EX-PRESS. Sensitivity analysis to adjust for differences in baseline characteristics between the groups in this retrospective study achieved similar results.

Non-Comparative Observational Studies

The largest study with a follow-up of longer than 1 year was by Gabbay et al (2021), who reported a retrospective analysis of 205 patients/eyes that had received an XEN implant.[28] At 3 years, 25% of eyes met the criteria for success, with a failure rate of 25% and requirement for needling in 36.6%. For eyes that retained an XEN implant, IOP decreased from an average of 22.6 mmHg (standard deviation [SD], 7.0) before surgery to 14.0 (SD, 2.9) at 3 years; the number of medications decreased from an average of 2.6 (SD, 1.1) to 0.6 (SD, 1.0) at 3 years. The failure rate was higher in non-Caucasians (74% of 13) compared to Caucasians (21% of 188, p <.001), with Caucasians comprising 93.5% of the study population.

Table 4. Summary Characteristics for Non-Randomized Comparative Studies Using the XEN Implant for Refractory Open-Angle Glaucoma

Study	Country	Participants	Treatment Delivery	FU
Schlender et al (2017)	Austria, Belgium, Canada,	Pts with OAG, psuedoexfoliation, pigment dispersion, normal-tension,	• XEN alone (n=185 • Trabeculectomy (n=169)	Up to 30 mo

	Germany	angle recession, combined mechanism, history of angle closure, or juvenile glaucoma and no prior incisional surgery		
Wagner et al (2020)	Germany	Consecutive patients with refractory OAG, pseudoexfoliation, pigment dispersion, or normal-tension glaucoma who underwent surgery from January 2016 to February 2018	• XEN alone (n=82 eyes) • Trabeculectomy (n=89 eyes)	1 year
Stoner et al (2021)	U.S	Patients with uncontrolled glaucoma with either IOP uncontrolled by medications or progression of glaucoma.	• XEN (n=52) • EX-PRESS (n=48)	1 year

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

Table 5. Summary of Results for the XEN Implant for Refractory Open-Angle Glaucoma

Study	Population	Median IOP (SD), mm Hg		Medication, Median (SD)	
		Baseline	1 Year[a]	Baseline	1 Year[a]
Schlender et al (2017)	XEN alone	24.0 (IQR: 19-32)	13.0 (IQR: 10-15)	3.0 (IQR: 3-4)	0.0 (IQR: 0-1)
	Trabeculectomy	24.0 (IQR: 19-30)	13.0 (IQR: 10-16)	3.0 (IQR: 3-4)	0.0 (IQR: 0-0)
Wagner et al (2020)	XEN	19.0 (IQR 16.8–25.0)	7.2 (8.2) reduction	2.0 (1.0–3.0)	0.3 (0.5)
	Trabeculectomy	21.0 (IQR 17.0–27.0)	10.5 (9.2) reduction	3.0 (2.0–4.0)	0.2 (0.5)
Stoner et al (2021)	XEN	21.4 (1.2)	13.0 (0.6)	2.8 (0.2)	1.5 (0.2)
	Trabeculectomy	18.9 (1.1)	11.5 (0.8)	3.2 (0.2)	0.5 (0.2)

IOP: intraocular pressure; IQR: interquartile range; NR: not reported; SD: standard deviation
[a] Follow-up for Schlender (2017) was not 1 year, but last visit in retrospective chart review

Section Summary: Ab Interno Aqueous Stents

Clearance for the XEN gel stent as a stand-alone procedure was based on a review in which the FDA concluded that while there were technical differences between the stent and predicate devices (shunts), the differences did not affect safety and effectiveness in lowering IOP and medication use. Evidence for the use of the XEN implant consists of nonrandomized comparative studies which retrospectively reviewed charts of patients either receiving the XEN implant or undergoing a trabeculectomy or implantation of an EX-PRESS shunt. Additional evidence consists of single-arm studies. The RCT found XEN45 to be noninferior to trabeculectomy. The nonrandomized comparative studies included patients with different types of glaucoma and found that patients receiving the XEN implant experienced reductions in IOP and medication use similar to patients undergoing trabeculectomy. A retrospective study compared the XEN implant with the EX-PRESS implant and found fewer adverse events in the first 3 months, but lower efficacy and higher failure rates at 1 year. Although there was little information on how patients were chosen to receive the different treatments in these comparative trials, statistical methods were used to address baseline differences between the groups. The single-arm studies, with up to 3 years of follow-up, consistently show that patients

receiving the XEN implant experience reductions in IOP and medication use. RCTs with longer follow-up are needed to compare the outcomes of the different surgical treatments.

AQUEOUS MICROSTENTS WITH CATARACT SURGERY

The iStent and iStent *inject,* which is preloaded with two stents, have FDA approval for use in conjunction with cataract surgery. An additional stent, the CyPass, had FDA approval but was voluntarily recalled by the manufacturer in 2018, as follow-up data has shown significant endothelial cell loss among patients receiving the CyPass in conjunction with cataract surgery compared with patients receiving cataract surgery alone. Studies comparing implantation of stents during cataract surgery with cataract surgery alone are discussed below.

iStent

Systematic Reviews

A 2019 Cochrane review on the iStent in patients with open-angle glaucoma was published by Le et al (2019, see Table 6).[29] The authors identified seven RCTs, all of which were considered to be at high or unclear risk of bias. Four of the trials compared iStent in combination with cataract surgery to cataract surgery alone, two RCTs compared treatment with iStent or iStent *inject* to medical therapy, and one RCT compared one, two, or three iStents. Results of the meta-analyses on use of the iStent in combination with cataract surgery are shown in Table 7. Implantation of 1 or 2 iStents resulted in a higher proportion of patients who were drop free (relative risk: 1.38) and reduced the mean number of drops when compared to phacoemulsification alone (-0.42 drops). The review concluded that based on the four trials, there was very low-quality evidence that iStent may result in a higher proportion of patients who are drop free or achieve better IOP control.

An industry-sponsored meta-analysis of standalone iStents was reported by Healy et al (2021).[30] The investigators included 4 RCTs and 9 non-randomized or single-arm studies with at least 6 months of follow-up. The number of eyes in the studies ranged from 15 to 99 (total N=778). The pooled weighted reduction in IOP was reported as 31.1% at 6 to 12 months and 32.9% at 60 months with a reduction of approximately 1 medication in the pooled analysis. In the individual studies, the reduction in IOP ranged from -1.0 to -10.7; the largest reduction in IOP was in a prospective case series (n=44) with 25% loss to follow-up. The lowest reduction in IOP (-1.0) was in a larger RCT (n=77) with low loss to follow-up (2.5%). Notably, the systematic review did not report the number of device failures in these studies. Additional limitations are the inclusion of retrospective case series and the high heterogeneity between studies, which would typically preclude meta-analysis.

Table 6. Meta-analysis Characteristics

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Le et al (2019)	Aug 2018	7	Eyes with open-angle glaucoma	765 (33 to 239)	RCT	42 months

Table 7. Meta-analysis Results

Study	Drop Free Compared to Phacoemulsification Alone	Change in Drops Compared to Phacoemulsification Alone	Change in IOP Compared to Phacoemulsification Alone

Le et al (2019)			
N	239 (2 RCTs)	282 (2 RCTs)	284 (3 RCTs)
Pooled effect (95% CI)	RR: 1.38 (1.18 to 1.63)	-0.42 (-0.60 to -0.23)	-1.24 mmHg
I^2 (p)	67% (p)	0%	

CI: confidence interval; IOP: intraocular pressure; RCT: randomized controlled trial; RR: relative risk

iStent and iStent inject Pivotal Trials

Included in the Cochrane review were results from the iStent U.S. investigational device exemption, open-label, 29-site, multicenter RCT. Results were reported to the 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 8).[31,32] Trial objectives were to evaluate the incremental effect on IOP of iStent implantation compared to cataract surgery alone and to determine the potential benefit of combining two therapeutic treatments into a single surgical event. A total of 240 patients (mean age, 73 years) with cataracts and mild-to-moderate OAG (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. 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. 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 endpoint, p<0.001). The proportion of patients achieving the secondary efficacy endpoint 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 one year (see Table 9). At 2-year follow-up, 199 (83%) patients remained in the study. The primary endpoint (unmedicated IOP ≤21 mm Hg) was reached by 61% of patients in the treatment group and 50% of controls (p=0.036).[25] Secondary outcomes-IOP reduction of 20% or more without medication (53% vs. 44%) and the mean number of medications used (0.3 vs. 0.5) no longer differed significantly between groups at 2 years. As noted by the FDA, this study was conducted in a restricted population with an unmedicated IOP of 22 mm Hg or higher and a medicated IOP of 36 mm Hg or lower.

The pivotal trial on the iStent *inject* was reported by Samuelson et al (2019).[33] A total of 505 patients undergoing cataract surgery were randomized after lens implantation to insertion of 2 smaller iStents or control. Results were assessed by intention-to-treat analysis and per-protocol analysis, with patients requiring additional surgical procedures considered to be failures. The addition of medications was based on a standardized protocol. At the 2-year follow-up, a greater percentage of patients had achieved at least a 20% reduction in IOP (75.8% vs. 61.9%, p=0.005), had a greater reduction in IOP (7.0 vs. 5.4, p<0.001), and required fewer topical medications (0.4 vs. 0.8, p<0.001).

Limitations of these studies are described in Tables 10 and 11. The two main limitations are that there was no masking to treatment and durability of these microstents after two years was not reported. Continued patency of the stents and need for additional treatments has been evaluated through 4 years in studies from the Microinvasive Glaucoma Surgery (MIGS) study group and are described below.

Table 8. Summary of Pivotal RCT Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Samuelson et al (2011); Craven et al (2012)	U.S	29	2005-2007	Patients with mild-tomoderate POAG, unmedicated IOP ≥22 and ≤36 mm Hg	iStent plus cataract surgery(n=116)	Cataract surgery alone (n=123)
Samuelson et al (2019)	U.S		2011-	Patients with mild-to moderate POAG, unmedicated IOP ≥21 and ≤36 mm Hg	iStent *inject* (2 stents) plus cataract surgery (n=387)	Cataract surgery alone (n=118)

IOP: intraocular pressure; POAG: primary open-angle glaucoma; RCT: randomized controlled trial.

Table 9. Summary of Pivotal RCT Results

Study	> 20% Reduction in Unmedicated IOP at 24 mo n (%)	Mean Reduction in IOP at 24 mo mm Hg (SD)	Mean IOP (SD), mm Hg		p	Mean Medication Use (SD)		p
			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)	0.016
Year 2			17.1 (2.9)	17.8 (3.3)	NR	0.3 (0.6)	0.5 (0.7)	
Samuelson et al (2019) iStent inject	288/380 (75.8%)	7.0 (4.0)	17.1 (3.6)			0.4 (0.8)		
Cataract Alone	73/118 (61.9%)	5.4 (3.7)	17.8 (3.5)			0.8 (1.0)		
p-Value	0.005	<0.001				<0.001		

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

Table 10. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Samuelson et al (2011)					Patency after 2 years is unknown
Samuelson et al (2019)					Patency after 2 years is unknown

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 11. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective	Data	Power[e]	Statistical[f]

			Reporting[c]	Completeness[d]		
Samuelson et al (2011)		2, 3. No blinding of assessors				
Samuelson et al (2019)		2, 3. No blinding of assessors				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

One non-randomized comparative study was reported by Hooshmand et al (2019) on outcomes with the use of the iStent inject, which simultaneously injects 2 stents through a single ab interno opening, compared to the first generation single iStent.[34] The iStent inject was developed to provide easier ab interno insertion and comes preloaded with two stents that are smaller than the first generation iStent. There was no significant difference between the earlier model and the second generation device on outcomes at 12 months but Kaplan-Meier analysis found an earlier time to add topical medications in the iStent inject patients. Limitations of the study include the length of follow-up, which was limited by the time that the iStent inject had been available, and the nonrandomized design . In addition, the study compared two cohorts from different time periods, those who had been treated with the first generation device and those who had been treated with the second-generation device.

Al Yousef et al (2020) conducted a matched comparison of the iStent inject and ab interno trabeculectomy in 78 eyes.[35] IOP was reduced in both groups at 1-month follow-up but began to rise at 12 months in the iStent inject group. By 24 months, the IOP in the iStent inject group had returned to near preoperative levels. The IOP in the Trabectome group was lower than the iStent inject group throughout follow-up.

Efficacy of the iStent inject at 3-year follow-up was reported by Salimi et al (2021) in a consecutive case series of 124 eyes with different glaucoma subtypes and severities.[36] Mean IOP in patients who retained an implant was reduced from 16.9 mm Hg preoperatively to 13.17 mm Hg ($p < .001$) with a reduction in medications from 2.38 to 1.16 ($p < .001$). The 3-year survival rate of the implant was only 74%.

Hydrus Microstent

Systematic Reviews

A Cochrane review by Otarola et al (2020) included 3 studies with 808 participants.[37] Two studies (described below) were conducted in patients with cataracts and OAG (n=653), and compared the Hydrus microsent combined with cataract surgery to cataract surgery alone.[38,39] They found moderate-certainty evidence that adding the Hydrus microstent to cataract surgery in patients with mild or moderate OAG increased the proportion of participants who were medication-free at 12 month (risk ratio 1.59, 95% confidence interval 1.39 to 1.83) and 24 month follow-up (risk ratio 1.63, 95% confidence interval 1.40 to 1.888), and reduced unmedicated IOP by 2 mm Hg, the number of medications by -0.41, and the need for secondary glaucoma surgery. The third study compared the Hydrus microstent with the iStent

in patients without cataract surgery.[40] This study is described in the next section on microstents as a stand-alone procedure.

Randomized Controlled Trials

Pfeiffer et al (2015) reported on a single-masked, randomized trial with 100 patients (100 eyes) that compared the effectiveness of the Hydrus Microstent plus cataract surgery with cataract surgery alone.[38] At the 24-month follow-up, the proportion of patients with a 20% reduction in IOP was significantly higher with the Hydrus Microstent (80% vs. 46%, p<0.001) and the mean IOP after medication washout was lower (16.9 mm Hg vs. 19.2 mm Hg, p=0.009) compared with cataract surgery alone, respectively. The microstent group used significantly fewer medications (0.5 vs. 1.0, p=0.019) and had a higher proportion of patients taking no hypotensive medications at the time of cataract surgery (73% vs. 38%, p=0.001).

Samuelson et al (2019) reported on a multicenter RCT comparing implantation of a single Hydrus Microstent following cataract surgery vs. cataract surgery alone.[39] Patients were blinded to treatment assignment for the course of the study. The primary endpoint was percent demonstrating a 20% reduction in unmedicated IOP. Significantly more patients receiving the microstent following cataract surgery experienced a 20% reduction in unmedicated IOP compared with patients undergoing cataract surgery alone (77% vs. 58%; p<0.001).

Table 12. Summary of Key RCT Characteristics for the Hydrus Microstent

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Pfeiffer (2015)	Germany, Italy, Spain, Netherlands	7	2011-2012	Patients with concurrent open-angle glaucoma and cataract	Cataract surgery plus Hydrus Microstent implantation (n=50)	Cataract surgery alone (n=50)
Samuelson (2019)	Germany, Italy, Mexico, Philippines, Poland, Spain, United Kingdom, United States	26	2012-2015	Patients with age-related cataract and mild to moderate primary open angle glaucoma	Cataract surgery plus Hydrus Microstent implantation (n=369)	Cataract surgery alone (n=187)

RCT: randomized controlled trial

Table 13. Summary of Key RCT Results for the Hydrus Microstent

Study	Mean Washed Out IOP			Mean Medication Use		
	Hydrus Microstent	Cataract Alone	p	Hydrus Microstent	Cataract Alone	p
Pfeiffer (2015)						
Baseline	26.3 +/- 4.4	26.6 +/- 4.2	0.7	2.0 +/- 1.0	2.0 +/ - 1.1	0.8
Year 2 Change	16.9 +/- 3.3	19.2 +/- 4.7	0.009	0.5 +/- 1.0	1.0 +/- 1.0	0.02
Samuelson (2019)						
Baseline Mean	25.5 +/- 3.0	25.4 +/- 2.9	NS	1.7 +/- 0.9	1.7 +/- 0.9	NS
Year 2	17.4 +/- 3.7	19.2 +/- 3.8	NR	0.3 +/- 0.8	0.7 +/- 0.9	<0.001

IOP: intraocular pressure; NR: not reported; NS: not significant; RCT: randomized controlled trial.

Observational Study

Fea et al (2017) conducted a retrospective review of 92 patients undergoing cataract surgery plus Hydrus Microstent implantation.[41] Two-year follow-up showed improvements in IOP and medication use. Mean IOP at baseline was 19.4 mm Hg, decreasing significantly by 6 months to 15.6 mm Hg, which was maintained at 2 years of follow-up (15.7 mm Hg). Mean number of medications was 2.1 at baseline, decreasing significantly by six months to 0.5, which was maintained through two years of follow-up (0.7).

CyPass

The FDA evaluated the clinical performance of the CyPass Micro-Stent system based on the pivotal Clinical Study to Assess the Safety and Effectiveness of the Transcend CyPass Glaucoma Implant in Patients With OAGUndergoing Cataract Surgery (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 POAG in patients undergoing cataract surgery. Evidence from the RCT supported the use of the CyPass stent in conjunction with cataract surgery; however, in August 2018, the manufacturer voluntarily withdrew the device from the market because a long-term study showed that patients receiving CyPass in conjunction with cataract surgery experienced statistically significant endothelial cell loss compared with patients who underwent cataract surgery alone.

Section Summary: Ab Interno Aqueous Microstents

Implantation of 1 or 2 microstents has received FDA approval for use in conjunction with cataract surgery for reduction of IOP in adults with mild-to-moderate OAG currently treated with ocular hypotensive medication. RCTs and meta-analyses of RCTs have compared cataract surgery alone to microstent implantation in conjunction with cataract surgery when IOP is at least partially controlled with medication. When compared to cataract surgery alone, the studies showed modest but statistically significant decreases in IOP and medication use through the first 2 years when stents were implanted in conjunction with cataract surgery. A decrease in topical medication application is considered to be an important outcome for patients and reduces the problem of non-compliance that can affect visual outcomes.

Microstent Implantation as a Stand-Alone Procedure

iStent

The iStent was approved by the FDA to be used in conjunction with cataract surgery to reduce IOP in patients with mild-to-moderate open-angle glaucoma. However, the iStent infinite is approved as a stand-alone device. The studies described below evaluated the use of the iStent, iStent inject or iStent Infinite as a stand-alone procedure.

Systematic Reviews

The Cochrane review by Le et al (2019) on the iStent in patients with open-angle glaucoma identified 2 RCTs that compared treatment with iStent, or iStent inject to medical therapy and 1 RCT that compared 1, 2, or 3 iStents.[29] Meta-analysis was not performed due to heterogeneity. However, in both trials, iStent implantation resulted in a higher proportion of patients who were drop free and reduced the mean number of drops when compared to medical therapy. One RCT indicated that compared to implantation of 1 stent, implantation of 2 or 3 stents resulted in a similar proportion of patients who were drop free at 36 months or less, but a higher proportion of patients who were drop free after 36 months. The 2 studies included in the 2019 Cochrane review are described in greater detail below.

Table 14. Meta-analysis Results

Study	Drop Free Compared to Medical Therapy	Drop Free with 2 Stents Compared to 1 Stent at 42 months	Drop Free with 3 Stents Compared to 1 Stent at 42 months
Le et al (2019)			
N	2 RCTs	1 RCT	1 RCT
Pooled effect (95% CI)	90% of patients in the iStent groups were drop free	RR:0.51 (0.34 to 0.75)	RR:0.49 (0.34 to 0.73)

CI: confidence interval; RCT: randomized controlled trial; RR: relative risk.

A 2014 industry-sponsored, multicenter, unblinded, randomized trial compared implantation of 2 iStent inject devices to 2 ocular hypotensive agents.[42] The 192 patients enrolled in this unmasked trial had an IOP not controlled by 1 hypotensive medication. At 12-month follow-up, the 2 groups were comparable for IOP reduction of at least 20%, IOP of 18 mm Hg or less, and mean decrease in IOP. A greater proportion of patients in the iStent inject group achieved an IOP reduction of at least 50% (53.2% vs. 35.7%, respectively). One patient in the iStent inject group experienced elevated IOP (48 mm Hg) and 4 required ocular hypotensive medication. Longer-term studies are in progress.

Vold et al (2016) reported results of an RCT comparing 2 stand-alone iStent inject implants to topical travoprost (1:1 ratio) in 101 phakic eyes with an IOP between 21 and 40 mm Hg and newly diagnosed POAG, pseudoexfoliative glaucoma, or ocular hypertension that had not been treated previously.[43] The patients were not undergoing cataract surgery. The trial 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 with visiting surgeons from the U.S. 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 to 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 and 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 would suggest that two iStents might reduce the number of medications required to maintain target IOP compared with travoprost but also hasten time to cataract surgery. However, the study methods were poorly reported, and statistical analyses were not reported.

Four year follow-up of iStent inject is reported in 2 phase 4 publications from the MIGS study group.[44,45] Berdahl et al (2020) reported on 53 patients who were on 2 preoperative medications who received 2 iStent inject implants and started on travoprost on postoperative Day 1. At 48 month follow-up, 85% of eyes had reduced IOP (> 20%) with a single medication as compared to the baseline IOP on 2 medications. Mean IOP on 1 medication was 11.9 to 13.0 mm Hg, compared to 19.7 on 2 medications preoperatively. Lindstrom et al (2020) reported on 57 patients who were on 1 preoperative medication before implantation of 2 iStent inject devices. Month 48 IOP without medication was reduced (> 20%) in 95% of eyes with iStent inject. There were no adverse events that were considered to be related to the devices.

Hydrus versus iStent

Hydrus microstent was compared with the iStent in a double-blind multicenter RCT by Ahmed et al (COMPARE, 2020).[40] Eyes (n=152) with mild-to-moderate glaucoma and an IOP of 23 to 39 after washout of medication were randomized to either 1 Hydrus stent or 2 iStents as a stand-alone treatment. Both stents have FDA approval in the U.S. when used in conjunction with cataract surgery but not as a stand-alone procedure. Follow-up was performed through 12 months post-operatively with medications added at the investigator's discretion. The Hydrus outperformed 2 iStents in nearly every measure. Eyes implanted with the Hydrus microstent were able to maintain IOP < 18 mm Hg on fewer medications and a greater percentage of patients were medication-free compared to the iStent group (46.6% vs. 24.0%, p<0.001). The decision to increase medications was up to the investigator and not pre-specified, but posthoc analysis indicated that the IOP at which medications were increased was similar in the two groups.

Table 15. Summary of RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	**Comparator**
Fea et al (2014)	EU, Armenia	8		Patients with OAG not controlled on one medication, Post washout IOP >22 and <38 mmHg	iStent inject (n=94)	Two medications (n=98)
Vold et al (2016)	Armenia with U.S. surgeons	1		Patients with Patients with OAG (n=101) or PEX (n=1) who were naive to therapy with IOP > 21 and < 40 mmHg	Two iStents (n=54)	One medication (n=47)
Ahmed et al (2019)	U.S., E.U., Canada, Asia	12	2013-2015	152 patients with mild-to-moderate glaucoma (OAG, PEX, or PG and IOP 23 to 39 mmHg after washout	Hydrus (n=75)	Two iStents (n=77)

IOP: intraocular pressure; PEX: pseudoexfoliative glaucoma; PG: pigmentary glaucoma; OAG: open-angle glaucoma; RCT: randomized controlled trial.

Table 16. Summary of RCT Results

Study	>20% reduction in IOP n (%)	IOP < 18 mmHg	Mean IOP mmHg (SD)	Mean reduction in IOP from baseline mmHg (SD)	Mean number of medications at 12 months	Percent Medication Free at 12 months n (%)
Fea et al (2014)	At 12 months	at 12 months n (%)	at 12 months			
iStent inject	89/94 (94.7)	87/94 (92.6)	13.0 (2.3)	8.1 (2.6)		
Medical therapy	88/98 (91.8)	88/98 (89.8)	13.2 (2.0)	7.3 (2.2)		
p-Value	0.02	NR	NR	0.43		
Vold et al (2016)	IOP < 18 mmHg n (%) at 24 months	at 36 months	at 36 months			
iStent	90%	91%	14.6 mmHg			
Medical therapy	87%	79%	15.3 mmHg			
p-Value						

Ahmed et al (2020)		Without medication				
Hydrus	39.7%	30.1%	17.3 (3.7)	-8.2 (3.7)	1.0	34 (46.6)
2 iStents	13.3%	9.3%	19.2 (2.4)	-5.1 (2.9)	1.7	18 (24.0)
p-Value	<0.001	<0.001	0.037	0.003	<0.001	0.006

IOP: intraocular pressure; NR: not reported; RCT: randomized controlled trial; SD: standard deviation.

Table 17. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Fea et al (2014)					1. Follow-up was limited to 12 months. Monitoring for occlusion of the stents at longer follow-up is needed
Vold et al (2016)		4. Not the currently marketed device			
Ahmed et al (2019)			4. Not the currently marketed device		1. Follow-up was through 12 months, longer follow-up is continuing.

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 18. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Fea et al (2014)	3. Randomization procedure was not described	1, 2, 3. Study could not be blinded		1. Unequal loss to follow-up in the 2 groups, and the subjects lost to follow-up were treated as failures	1. Power calculations not reported	
Vold et al (2016)	3. Randomization procedure was not described	1, 2, 3. Study could not be blinded		1. There was 27% loss to follow-up at 36 months	1. Power calculations not reported	4. Statistical analysis not reported
Ahmed et al (2020)		2, 3. Investigators were not blinded and there was no independent adjudication or preset criteria for				2. Did not use repeated measures for multiple assessments

		increase in medication				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Greater Than Two Stents

An RCT comparing the efficacy of 1 iStent with multiple iStent devices was published by Katz et al (2015).[46] This trial, from a single-institution in Armenia, randomized 119 patients with mild-to-moderate OAG 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 primary endpoint was the percentage of patients with a reduction of 20% or more in IOP off medications at 12 months. This endpoint was reached by 89.2% of the 1-stent group, by 90.2% of the 2-stent group, and by 92.1% of the 3-stent group. The secondary endpoint (percentage of patients achieving an IOP £15 mm Hg off medication) was reached by 64.9% of the 1-stent group, by 85.4% of the 2-stent group, and by 92.1% of the 3-stent group. Forty-two-month follow-up results for 109 patients were published by Katz et al (2018).[47] Post-washout IOP was 17.4±0.9, 15.8±1.1 and 14.2±1.5 mmHg, for 1, 2, or 3 stents, respectively. The need for additional medication increased in single stent eyes from 4 eyes at 12 months to 18 eyes at 42 months, suggesting a reduction in patency of the microstents over time. The need for additional medication did not increase from months 12 and 42 in multi-stent eyes. No between-group statistical comparisons were reported.

Nonrandomized Studies

Sarkisian et al (2023) published the results of an open-label, single-arm, pivotal study evaluating iStent infinite in patients with OAG uncontrolled by prior surgical or medical therapy.[48,] The trial enrolled a total of 72 patients from 15 sites. The majority of patients had failed prior surgery (n=61) and the remainder were uncontrolled on medical therapy (n=11). At 12 months the proportion of patients achieving at least 20% reduction in IOP and receiving the same or fewer medications was 76.1% (95% CI, 66.2% to 86.1%). The mean reduction in IOP at 12 months was 5.9 mm Hg (standard error, 0.6; 95% CI, 4.8 to 7.1). No serious device-related adverse events were reported; however, blepharitis (4.2%), IOP increase requiring surgical intervention (4.2%), loss of best spectacle corrected visual acuity of 2 lines or more (8.3%), ocular surface disease (9.7%), and visual field loss of at least 2.5 dB were commonly reported adverse events. Stent migration and stent obstruction were each reported in 2 patients. Although this trial indicates positive outcomes with iStent infinite, the small sample size and lack of a control group are significant limitations.

Section Summary: Microstent Implantation as a Stand-Alone Procedure

The evidence on microstents as a stand-alone procedure in patients with mild-to-moderate glaucoma that is controlled on medical therapy includes a nonrandomized study, RCTs and a systematic review of three heterogeneous RCTs. Two RCTs indicate that implantation of a microstent can reduce IOP at a level similar to ocular medications at 12-month follow-up. Reduction in medications is an important outcome for patients with glaucoma, both for the patients themselves and because lack of compliance can lead to adverse health outcomes. Whether microstents remain patent after 12 months is uncertain, and whether additional stents

can subsequently be safely implanted is unknown. Some evidence on longer-term outcomes is provided by an RCT that compared implantation of a single iStent with multiple iStents. At longer term (42-month) follow-up, the need for additional medication increased in eyes implanted with a single iStent but not with multiple iStents. The durability of multiple iStents is unknown. A fourth RCT compared implantation of the Hydrus microstent to two iStents. Outcomes from the Hydrus microstent were significantly better than two iStents, both statistically and clinically, for all outcome measures. The primary limitation of this study is that the duration of follow-up in the present publication is limited to 12 months. Longer-term follow-up from this study is continuing and will answer important questions on the durability of the procedure. Corroboration in an independent study and comparison with a medical therapy control group would also increase confidence in the results.

SUMMARY OF EVIDENCE

For individuals who have refractory OAG who receive ab externo aqueous shunts, the evidence includes RCTs, retrospective studies, and systematic reviews. Relevant outcomes are a change in disease status, functional outcomes, medication use, and treatment-related morbidity. RCTs assessing the FDA-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. The FDA-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 five 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 OAG who receive ab interno aqueous stents, the evidence includes a nonrandomized retrospective comparative study and several single-arm studies. Relevant outcomes are a 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. The single-arm studies, with 12-month follow-up results, consistently showed that patients receiving the stents experienced reductions in IOP and medication use. Reductions in IOP ranged from 4 mm Hg to over 15 mm Hg. In addition, the FDA has given clearance to a gel stent based on equivalent IOP and medication use reductions as seen with ab externo shunts. Clearance for the stent was based on a review in which the FDA concluded that while there were technical differences between the stent and predicate devices (shunts), the differences did not affect safety and effectiveness in lowering IOP and medication use. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have mild-to-moderate OAG who are undergoing cataract surgery who receive aqueous microstents, the evidence includes RCTs and meta-analyses of RCTs. The relevant outcomes are a change in disease status, functional outcomes, medication use, and treatment-related morbidity. Implantation of one or two microstents has received the FDA 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. When compared to cataract surgery alone, the studies showed modest but statistically significant decreases in IOP and medication through the first two years when stents were implanted in conjunction with cataract surgery. A decrease in topical medication application is considered to

be an important outcome for patients and reduces the problem of noncompliance that can affect visual outcomes. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with mild-to-moderate OAG who are not undergoing cataract surgery who receive aqueous microstents as a stand-alone procedure, the evidence includes RCTs. Relevant outcomes are a change in disease status, functional outcomes, medication use, and treatment-related morbidity. Several RCTs have evaluated the use of multiple microstents but comparators differed. Two RCTs indicate that implantation of a microstent can reduce IOP at a level similar to ocular medications at 12-months follow-up. Reduction in medications is an important outcome for patients with glaucoma, both for the patients themselves and because lack of compliance can lead to adverse health outcomes. Whether microstents remain patient after 12 months is uncertain, and whether additional stents can subsequently be safely implanted is unknown. Some evidence on longer-term outcomes is provided by an RCT that compared implantation of a single iStent to implantation of multiple iStents. At longer-term (42-month) follow-up the need for additional medication increased in eyes implanted with a single microstent but not with multiple microstents. The durability of multiple iStents is unknown. A fourth RCT compared implantation of the Hydrus microstent and two iStents. Outcomes from the Hydrus microstent were significantly better than two iStents, both statistically and clinically for all outcome measures. The primary limitation of this study is that the duration of follow-up in the present publication is limited to 12 months. Longer-term follow-up from this study is continuing and will answer important questions on the durability of the procedure. Corroboration is an independent study and comparison with a medical therapy control group would also increase confidence in the results. The evidence is insufficient to determine the effects of the technology on health outcomes.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 19.

Table 19. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT01841450[a]	A prospective, randomized, controlled, parallel groups, multicenter post-approval study of the Glaukos® iStent® trabecular micro-bypass stent system in conjunction with cataract surgery	360	Jul 2021
NCT04658095[a]	A Prospective, Randomized, Multicenter Study To Compare The Safety And Effectiveness Of The OMNI® Surgical System And The iStent Inject In Pseudophakic Eyes With Open Angle Glaucoma. The TRIDENT European Trial	459	Jul 2023
NCT04629521[a]	An Observational Multicenter Clinical Study to Provide Additional Long-Term Follow-up Beyond 60 Months for Subjects Implanted With a CyPass Micro-Stent in the COMPASS Trial	374	Aug 2023
NCT02327312[a]	Multicenter Investigation of Trabecular Micro-Bypass Stents vs. Laser Trabeculoplasty	1200	May 2024
NCT04440527	Intraocular Pressure After Preserflo /Innfocus Microshunt vs Trabeculectomy: a Prospective, Randomised Control-trial (PAINT-Study)	70	Jul 2024
Unpublished			
NCT01444040[a]	A prospective, randomized evaluation of subjects with open-angle glaucoma, pseudoexfoliative glaucoma, or ocular	200	Jun 2018 (unknown)

	hypertension naïve to medical and surgical therapy, treated with two trabecular micro-bypass stents (iStent Inject) or Travosprost ophthalmic solution 0.004%.		
NCT01461278a	A prospective, randomized, single-masked, controlled, parallel groups, multicenter clinical investigation of the Glaukos® suprachoroidal stent model G3 in conjunction with cataract surgery	1200	Apr 2019

NCT: national clinical trial
[a] Denotes industry-sponsored or cosponsored trial.

SUPPLEMENTAL INFORMATION

Clinical Input Received from Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests from BCBSA, input was received from 1 physician specialty societies and 2 academic medical centers while this policy was under review in 2013. The input supported use of aqueous shunts in patients with glaucoma uncontrolled by medication. Input supported use of a single microstent in patients with mild to-moderate glaucoma undergoing cataract surgery to reduce adverse effects of medications and to avoid noncompliance.

PRACTICE GUIDELINES AND POSITION STATEMENTS

American Glaucoma Society

In 2020, the American Glaucoma Society published a position paper on microinvasive glaucoma surgery.[42] The Society supports efforts that facilitate patient access to these procedures, including more flexible regulatory pathways for new devices, expansion of the indications for already approved devices, and greater availability of information obtained by regulatory authorities.

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.[2] The assessment indicated that in general, the IOP will settle at higher levels (approximately 18 mm Hg) with shunts than after standard trabeculectomy (14–16 mm Hg). Five-year success rates of 50% have been found for the two 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.

AAO's 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.[41] 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 Care Excellence
The U.K.'s National Institute for Health and Care Excellence provided guidance on trabecular stent bypass microsurgery for open angle glaucoma in 2017.[43] The updated guidance stated that "Current evidence on trabecular stent bypass microsurgery for open-angle glaucoma raises no major safety concerns. Evidence on efficacy is adequate in quality and quantity."

The National Institute for Health and Care Excellence (2018) published a guidance entitled "Microinvasive subconjunctival insertion of a trans-scleral gelatin stent for primary open-angle glaucoma".[44] The guidance states that evidence is limited in quantity and quality and therefore, the procedure should only be used with special arrangements and that patients should be informed of the uncertainty of the procedure.

Government Regulations

National:

There is no NCD on this topic.

Local:

WPS LCD: Category III codes (L35490), For services effective on or after 03/28/2024. 0253T, 0474T An anterior segment aqueous drainage device, utilizing the internal approach, for use in combination with cataract surgery to reduce pressure inside the eye (intraocular pressure) in adult patients with mild or moderate open-angle glaucoma on medication. 0449T, 0450T Insertion of an aqueous drainage device is 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 above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Corneal Hysteresis Determination by Air Impulse Stimulation
- Optical Coherence Tomography Imaging, Anterior Eye
- Suprachoroidal Delivery of Pharmacologic Agent
- Viscocanalostomy and Canaloplasty

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through September 2024, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
1/1/09	12/1/08	12/14/08	Joint policy established, "I**nsertion of Anterior Segment Aqueous Drainage Device for Glaucoma**"
5/1/10	3/16/10	2/16/10	Policy title changed from "Insertion of Anterior Segment Aqueous Drainage Device for Glaucoma" to "**Glaucoma Surgery using Aqueous Shunts and Transluminal Dilation Devices**." Combined another policy, "Canaloplasty and Viscocanalostomy" into this policy.
9/1/11	6/21/11	6/21/11	Title changed from "Glaucoma Surgery using Aqueous Shunts & Transluminal Dilation Devices" to "**Glaucoma Surgery**." 0176T and 0177T were replaced by 66174 and 66175, respectively, 66175 is still considered experimental/ investigational. Canaloplasty (66174) status changed to "established." 0253T added as experimental and investigational. Updated references and rationale. Added code 66999 to be used for Trabectome.
9/1/11	8/16/11	8/16/11	Correction made to coding; 66175 changed to "established" as it is a form of canaloplasty. Code 66999 still considered experimental and investigational for 31 Viscocanalostomy as well as Trabectome. **Effective date remains 9/1/11.**

Next review date: The policy "**Glaucoma Surgery**" will no longer be reviewed. This topic is has been split out into separate policies: "Aqueous Shunts and Stents for Glaucoma" and "Viscocanalostomy and Canaloplasty."

11/1/13	8/20/13	9/10/13	Policy split out into a separate policy and named "Aqueous Shunts and Stents for Glaucoma" to mirror BCBSA policy.
1/1/15	10/21/14	11/3/14	Routine maintenance. Added additional inclusion: "Implantation of a single FDA-approved microstent in conjunction with cataract surgery may be considered established in patients with mild to

			moderate open-angle glaucoma currently treated with ocular hypotensive medication.´ Rationale and references updated. Revised 0191T verbiage and added 0376T as experimental/investigational.
11/1/15	8/24/15	9/14/15	Added additional CPT code 66179, 66184 and 66185; revised verbiage for 66180. No other changes to policy.
9/1/16	6/21/16	6/21/16	Routine policy maintenance. Updated references and rationale. No change in policy status.
5/1/17	2/21/17	2/21/17	Code update, added 0449T and 0450T as noncovered effective 1/1/17. 0474T added to policy as noncovered effective 7/1/17. Routine policy maintenance.
11/1/17	8/15/17	8/15/17	Updated policy to reflect FDA approval for various implants. No changes to policy status.
11/1/18	8/21/18	8/21/18	Routine policy maintenance, added references 1, 6, 13, 17-26, 31-32, 36, 40 and 46. Policy statements changed, ab externo and ab interno devices are addressed in 2 separate policy statements.
11/1/19	9/5/19		ab interno stents now established. 1 or 2 microstents allowed with FDA approved, additions to inclusions/exclusions. Updated rationale section, added references 15, 20 and 40. Added statement identifying which stents were used in conjunction with cataract surgery.
5/1/20	2/18/20		Added codes 66987 and 66988 as established effective 1/1/20. No change in policy status.
5/1/21	2/16/21		Rationale reformatted, references 20, 23-25, 28 and 32-33 added. Some references removed. No change in policy status.
5/1/22	2/15/22		Added codes 66989 and 66991 as established effective 1/1/22, removed codes 0191T and 0376T.
1/1/23	10/18/22		Exclusion section updated with input from Dr. Katz, rationale updated, references 4 and 20 added. No change in policy status.
1/1/24	10/17/23		Added code 0671T as established, updated rationale section. No change in

			policy status. Vendor managed: N/A (ds)
1/1/25	10/15/24		Routine policy maintenance, no change in status. Vendor managed: N/A (ds)

Next Review Date: 4TH Qtr. 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: AQUEOUS SHUNTS AND STENTS FOR GLAUCOMA

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply
BCNA (Medicare Advantage)	See government section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.