MINIMALLY INVASIVE GLAUCOMA SURGERY

Effectiveness and cost-effectiveness of minimally invasive glaucoma surgery in patients with glaucoma in British Columbia.

HEALTH TECHNOLOGY ASSESSMENT REPORT

A report for the BC Health Technology Assessment Committee [November, 2020]. Version 1.0

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List of Abbreviations

CADTH	Canadian Agency for Drug and Technologies in Health
INESSS	Institut national d'excellence en santé et en services sociaux
IOP	Intraocular pressure
MIGS	Minimally invasive glaucoma surgery
MMC	Mitomycin C
MSP	Medical Service Plan
OHQ	Ontario Health, Clinical Institutes & Quality Programs
SLT	Selective laser trabeculotomy

Executive summary

Three published reports and one unpublished report were obtained in scoping. The Canadian Agency for Drugs and Technologies in Health (CADTH) published a comprehensive report in 2019 on all the MIGS available in Canada that contained clinical effectiveness, cost-effectiveness, and patient experience. The Clinical Institutes & Quality Program at Ontario Health (OHQ) published a complementary report to the CADTH report that provided additional information on patient experience and budge impact in the Ontario context. Quebec's Institut National d'excellence en Santé et en Services Sociaux (INESSS) published an update of the CADTH report in 2020 that focused on iStent and iStent inject. The INESSS report included clinical effectiveness, cost-effectiveness analyses, and patient experience. An unpublished OHQ summary of the CADTH and INESSS report was also obtained. The unpublished OHQ report shared the similar objective as this review, therefore was not included in our summary.

There were 24 paired comparisons included in the CADTH report and four paired comparisons in the INESSS report. The clinical evidence found was generally of low quality. In general, clinical review found high quality evidence favouring only MIGS plus cataract surgery when compared with cataract surgery alone. The evidence found in other comparisons were low quality that contained a large amount of uncertainty.

Economic evaluation using a Markov model found a potential cost-effectiveness signal in two comparisons (MIGS vs pharmacotherapy and MIGS plus cataract surgery vs cataract surgery alone). Sensitivity analyses found that the incremental cost-utility ratio was sensitive to the maintenance of treatment effect and cost of treatment.

Clinical experts from British Columbia interviewed noted that for patients with open-angle

glaucoma whose intraocular pressure does not remain in the target range after first-line pharmacotherapy, either MIGS or selective laser trabeculotomy (SLT) are an option rather than proceeding to more complex medication regimens. SLT is publicly funded in BC, although due to the high initial cost of the equipment required it is not widely available. Despite the lack of an MSP billing code, MIGS is publicly provided in at least three locations (Vancouver General Hospital, Surrey Memorial Hospital, and Royal Jubilee Hospital). Patients referred to facilities not offering MIGS must pay out of pocket. MIGS procedures are performed in operating rooms; however, iStent is the only type of MIGS device approved for and in use in ambulatory surgical centres in BC. In the patient-pay model approved by the College, the patient pays for costs associated with the iStent device but not for the MSP-insured services required for the ophthalmologist to perform the procedure.

Patient experience from CADTH, INESSS and OHQ reports found the most common concern from patients were fear of blindness and adherence to eyedrops. Only a small portion of patients had to deal with surgery. The experience from receiving MIGS was generally positive.

The three published reports utilized robust methodology and were thorough in reporting. The evidence found in these reports were the best available evidence to-date. Further search at this time would be unlikely to yield evidence that would fundamentally change the conclusions drawn.

Chapter 1 Background and Problem

1.1 Purpose of this health technology assessment (HTA)

The Canadian Agency for Drugs and Technologies in Health (CADTH) published a comprehensive HTA report in 2019 that examined all the MIGS devices available in Canada. They included clinical effectiveness, cost-effectiveness, patient engagement, ethics issue analysis, and implementation issue analysis.[1] At the same time, Ontario Health Quality (OHQ) published a report to complement the CADTH report which provided a budget impact analysis for Ontario and a patient preference and value report.[2] In 2020, Institut national d'excellence en santé et en services sociaux in Quebec (INESSS) published an update of the CADTH report focusing on iStent and iStent inject that provided clinical effectiveness, cost-effectiveness, and budget impact analysis.[3] Lastly, an HTA report from the Clinical Institutes & Quality Program of Ontario Health (currently under review) was shared with BC's HTAO that summarizes the clinical and cost-effectiveness of iStent and iStent inject using the data from CADTH and INESSS reports.[4]

Given that several recent Canadian HTAs on various MIGS were available, the objective of this project was to critically appraise the health technology assessments already produced in Canada evaluating the clinical effectiveness, cost-effectiveness, and budget impact of the technologies used for minimally invasive glaucoma surgery (MIGS). These assessments are based on work by CADTH, INESSS, and OHQ and assess to what extent their findings can be extrapolated to support decision-making regarding treatment options for glaucoma in the BC context.

1.1.1 Primary policy questions

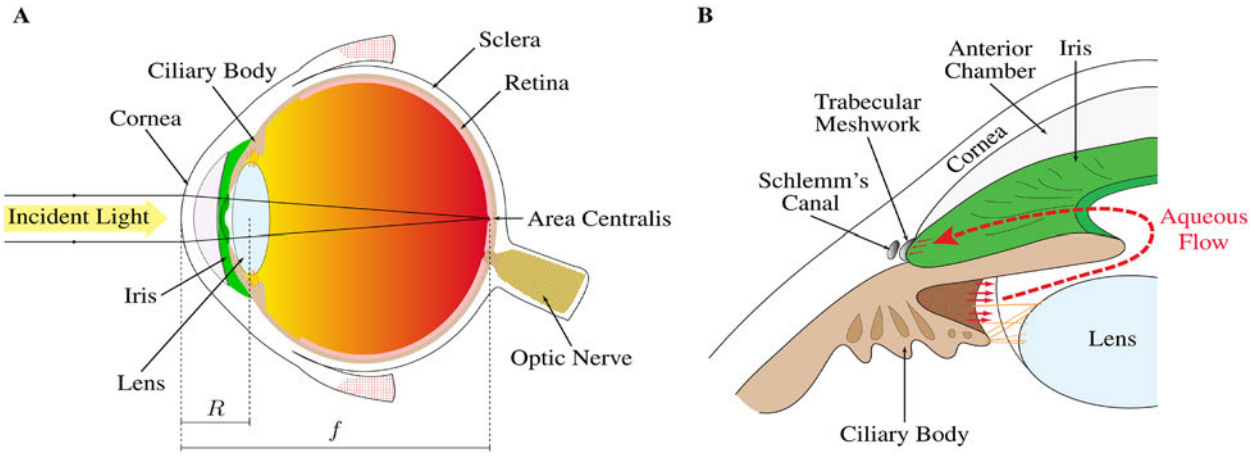
1. Are MIGS cost-effective for patients with glaucoma in BC?
2. What is the budget impact for expanding the use of MIGS in BC?

1.2 Nature of glaucoma

Glaucoma is an optic nerve disorder that is characterized by progressive degeneration of retinal ganglion cells. The retinal ganglion cells are cells that capture the visual signal and transmit the signal to the brain through the optic nerve at the back of the eye. Degeneration of retinal ganglion cells will cause progressive visual impairment and eventually blindness. The etiology of glaucoma is not well understood. The only treatable risk factor for developing and progression of glaucoma is ocular hypertension. Ocular hypertension is characterized by elevated intraocular pressure (IOP).[5-7] Glaucoma can occur with or without elevated IOP. However, when present, elevated intraocular pressure (IOP) is directly associated with the development and progression of glaucoma.[8] Therefore, lowering IOP is a benchmark for the treatment of glaucoma.

IOP is regulated in the eye by the production of aqueous humor, a fluid that nourishes the anterior structures within the eye, and the drainage of it. Aqueous humor is produced by the ciliary body in the posterior chamber, and drain through the trabecular meshwork and Schlemm canal in the anterior chamber (Figure 1.1).[9] In glaucoma, the IOP increases when the balance of this system is disrupted.

Figure 1.1. Anatomy of the eye and drainage of aqueous humor.[9]



Glaucoma can be subdivided into primarily open-angle glaucoma and angle-closure glaucoma. Open-angle glaucoma is characterized by the various degenerative processes of trabecular meshwork that reduces the drainage ability of aqueous humor, while aqueous flow within the anterior chamber is not affected.[5] As a result the IOP increases, which precedes visual deterioration over months or years. Open-angle glaucoma is often asymptomatic for a long time and typically occur when the disease is severe; symptoms include visual field loss starting from peripheral vision.[7]

Angle-closure glaucoma occurs when the path of aqueous flow in the anterior chamber is anatomically obstructed by the iris.[5] As the outflow of aqueous humor cannot reach the trabecular meshwork, the IOP increases and causes damage to the optic nerve. Angle-closure glaucoma can be acute or chronic. Acute angle-closure glaucoma can be an ophthalmic emergency that requires immediate surgical intervention.[5] Symptoms of acute angle-closure glaucoma includes headache, severe eye pain, blurred vision, seeing halo, nausea, and vomiting. Chronic angle-closure glaucoma can be asymptomatic until gradual vision loss has occurred.

1.3 Diagnosis of glaucoma

Glaucoma is often discovered through a routine eye exam. As vision loss usually occurs in severe disease, an examination of the visual field does not usually identify early glaucoma. Examination of the optic disc can provide valuable information in terms of early detection of glaucoma.[7] Structural abnormality of the optic disc, known as cupping, can be identified through the assessment of the optic disc through stereoscopic imaging.[7] Abnormal cup-to-disc ratio or optic disc hemorrhage can be early signs of glaucoma. Although IOP is the benchmark for the treatment of glaucoma, an elevated IOP does not necessarily warrant the diagnosis of glaucoma.

Recognizing risk factors is also a useful screening tool for glaucoma. Risk factors include ethnicity, age, family history of glaucoma, elevated IOP, and myopia.[7] People who have multiple risk factors should have an eye exam every one or two years.

1.4 Burden of illness

Glaucoma is the leading cause of visual impairment and irreversible blindness in the world.[6] There are more than 400,000 Canadians living with glaucoma, a 1.8% prevalence in Canada.[10] The prevalence of glaucoma increases with age; there are 2.7% of Canadians over age 40 and 11% over the age of 80 suffering from glaucoma.[10] Based on this prevalence, it is estimated that more than 9000 patients are living with glaucoma in BC. Open-angle glaucoma is the most common type of glaucoma that contributes to 85% to 90% of the cases.[11]

The burden of disease to an individual with glaucoma is primarily related to vision loss.[12] Even the diagnosis of irreversible eye disease can have an impact on the mental health of patients. A literature review focusing on quality of life found that patients diagnosed with glaucoma had a lower quality of life when compared with healthy subjects or patients with other eye disorders, such as cataracts.[13] The most frequent problem associated with vision loss are impairments in daily activities such as reading, walking, and recognizing people.[13] As vision loss in glaucoma is often permanent, the negative impact on the quality of life is also likely permanent.

1.5 Current treatment options

Since IOP is the only treatable risk factor of glaucoma, the treatment goal of glaucoma focuses on lowering IOP.[7] There are several treatment options available in Canada to lower IOP that include medications, laser trabeculoplasty, and surgery.

1.5.1 Medications

There are several classes of medications that can be used to treat glaucoma. Prostaglandin is one of the main classes of medications that can reduce IOP by increasing the outflow of aqueous humor.[7] It is administrated as an eye drop once daily. Common side effects include darkening iris color, redness of the eye, and longer eyelashes.

Beta-blockers are another main class of medication used to treat glaucoma. It can be administrated as eye drops and lowers IOP by reducing the production of aqueous humor.[7] However, beta-blockers can have significant cardiovascular side effects such as bradycardia, and are therefore contraindicated for patients with heart block, heart failure, and lung disease that requires treatment with beta-agonists.

Other less common classes of medications such as alpha agonists, carbonic anhydrase inhibitors, and cholinergic agonists can also be used. However, less tolerable side effects and compliance issues restrict their use.

Medications are publicly-funded, for eligible patients, through the BC Pharmacare program.

1.5.2 Laser treatments

There are several types of laser treatments available for glaucoma. Laser trabeculoplasty is the most widely used to treat open-angle glaucoma.[7] A laser is directed at the trabecular meshwork that facilitates aqueous outflow. The effect of laser trabeculoplasty can wear off over time and the procedure can be reapplied several times over the lifetime of the patients.[14] Common side effects of laser trabeculoplasty include inflammation, pain, and blurred vision. Laser treatment is covered under the Medical Services Plan (MSP).

Peripheral iridotomy is a procedure to treat angle-closure glaucoma. It can be performed as

an emergency procedure or preventive procedure. The procedure uses a laser to create a small opening on the iris that provides an alternative path for aqueous humor to drain.[14] Common side effects include inflammation and pain.

Cyclophotocoagulation is another laser treatment for more advanced open-angle or angle-closure glaucoma. Cyclophotocoagulation utilizes a laser to modify the ciliary body that reduces the secretion of aqueous humor.[7] Cyclophotocoagulation can be reapplied when the effect starts to wear off.[14] Common side effects include inflammation, abnormally low eye pressure, clouding of the cornea.[14]

1.5.3 Surgical treatments

Similar to laser treatment, surgical treatments aim at facilitating drainage or reducing the production of aqueous humor. Surgical treatment is more invasive and needs more intensive post-treatment care when compared with laser treatment. But it could be more permanent and have a longer-lasting effect. Surgical treatments are used when medical therapy and laser treatment do not achieve target IOP; it is rarely used as first-line treatment.[7] Common side effects of surgical treatment infection, pain, dry eye, blurred vision, and inflammation.[14] Surgical treatment is covered under MSP.

1.6 Minimally invasive glaucoma surgery

Minimally invasive glaucoma surgery (MIGS) is a type of surgical treatment that differs from surgical treatment because it is less invasive and only requires a small incision. The FDA defined MIGS as devices and procedures that intend to lower IOP by improving the outflow of eye fluid using either inside-the-eye or outside-the-eye-approaches, with limited or no dissection of the sclera and minimal or no manipulation of the conjunctiva.[15] There are many different types of

MIGS available in Canada with different approaches (Table 1.1).

MIGS potentially have an advantage over conventional surgery because MIGS is anticipated to have fewer side effects and a faster recovery.[15] MIGS can be considered together with laser treatment or surgical treatment to provide additional options for patients with open-angle glaucoma. MIGS can also be performed along with cataract surgery when indicated.

Table 1.1. MIGS available in Canada.[1]

MIGS	Approach
ECP	Reducing aqueous production
Trabectome	Increasing trabecular outflow by bypassing the TM using tissue ablation/removal
Kahook Dual Blade	Increasing trabecular outflow by bypassing the TM using tissue ablation/removal
iStent (first generation)	Increasing trabecular outflow by bypassing the TM using a device
iStent inject (second generation)	Increasing trabecular outflow by bypassing the TM using a device
iSTENT W	Increasing trabecular outflow by bypassing the TM using a device
Hydrus microstent	Increasing trabecular outflow by bypassing the TM using a device
GATT	Increasing trabecular outflow by bypassing the TM via 360º suture
XEN45 Gel Stent	Creating a subconjunctival pathway for filtration

Note: ECP = endoscopic cyclophotocoagulation; GATT = gonioscopy-assisted transluminal trabeculotomy; TM = trabecular mash work.

1.7 Research questions

1. In BC, what treatments are currently publicly funded for glaucoma, and what is their market share across the health authorities?
2. What are stakeholder perspectives and experiences with MIGS in BC?
3. How do MIGS affect the direct and indirect costs for BC patients, particularly for those from rural and remote areas?
4. What are the important aspects of the BC context that influence the choice of treatment?
5. What are patient perspectives and experiences with MIGS (as reported in the

Canadian HTAs)?

6. What is the comparative clinical effectiveness and cost-effectiveness of MIGS compared to the other treatment options (as reported in the Canadian HTAs)?
7. How does iStent compare with other MIGS technologies (considering existing assessments selected iStent for additional analysis – this will be within the context of the CADTH HTA on MIGS more generally)?
8. Are the INNESS and OHQ HTA reports on iStent comprehensive for the BC context (e.g., are there aspects relevant to the BC context that were overlooked)?
9. Can the findings from CADTH, OHQ, and INNESS be extrapolated at a high-level to support the decision making within BC with regards to resource allocation between the available treatments (e.g., investment, disinvestment, reallocation)
10. Are there options for additional analysis, and if, so how would these analyses support HTAC with their recommendations?

Chapter 2 Care pathway and stakeholder interviews

2.1 The care pathway

The BC care pathway was informed by the 2009 guideline for the treatment for adult glaucoma.[16] Since this guideline is more than 10 years old, additional input from two ophthalmologists with glaucoma subspecialties was incorporated to reflect the most current practice (Figure 2.1).

Since there are no MIGS specifically targeting angle-closure glaucoma, the BC care pathway starts with patients diagnosed with open-angle glaucoma. The next step in the care pathway is determining the severity of glaucoma. The severity of glaucoma helps to determine the target IOP and monitoring schedule of patients but does not alter the treatment sequence.

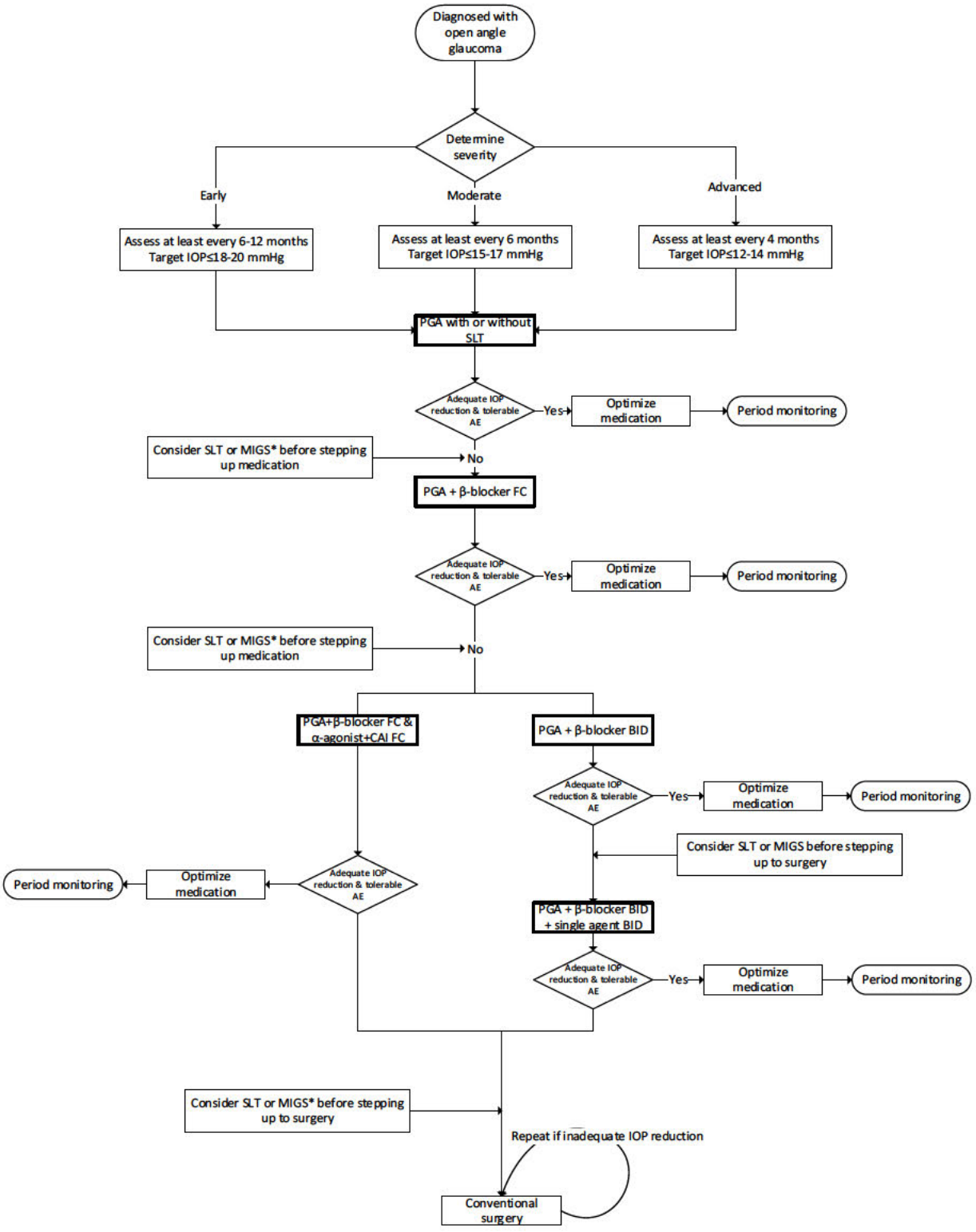
Pharmacotherapy is the backbone of glaucoma treatment; therefore, other treatment options revolve around pharmacotherapy. The first-line treatment is usually a medication such as a prostaglandin type medication. At this point, selective laser trabeculoplasty (SLT) can also be considered when indicated. After the initiation of first-line treatment, patients should be monitored periodically according to their severity. When the target IOP is not achieved by the first-line treatment, additional treatment should be considered. The next step up in medication is a prostaglandin plus beta-blocker fixed combination. But before stepping up, SLT or MIGS should be considered if appropriate.

If a prostaglandin and beta-blocker fixed combination is not able to achieve target IOP, there are two combinations of medications that can be considered as the next step. Patients can take two fixed combinations (prostaglandin and beta-blockers fixed combination, alpha agonist and carbonic anhydrase inhibitors fixed combination) or increase the frequency of beta-blockers

from once daily to twice daily in the prostaglandin and beta-blocker fixed combination. As the number of drops and the time of administration is becoming more complex, patient compliance should be a part of the treatment decision. SLT or MIGS might help decrease IOP so that patients do not have to take complex medication regimens.

At the end of the care pathway, when all other options are exhausted, conventional surgery can be considered to reduce the IOP. Conventional surgery can be repeated as needed; however, patients are exposed to a high risk of complications such as infection, inflammation, or elevated IOP. Only a small proportion of patients are likely to need repeat surgery to control the IOP.

Figure 2.1. BC care pathway for adult glaucoma.



Note: AE = adverse effects; BID = twice daily; CAI = Carbonic anhydrase inhibitors; FC = fixed combinations; IOP = intraocular pressure; MIGS = minimally invasive glaucoma surgery; PGA = prostaglandin analogue; SLT = selective laser trabeculoplasty
*MIGS can be given concurrently with cataract surgery when it's appropriate.

2.2 Stakeholder interviews

Two ophthalmologists, with subspecialties in glaucoma, were interviewed. Both stakeholders were identified by PHSA's Value Analysis Team on ophthalmology. One stakeholder practices at Vancouver General Hospital (Vancouver Coastal Health) and the other practices at Surrey Memorial Hospital (Fraser Health). Both stakeholders have significant experience with MIGS. The stakeholder interviews were not recorded. Both stakeholders reviewed the summary (presented below).

1. In BC, what treatment are currently publicly funded for glaucoma (and what is their market share)?

Both stakeholders indicated that eye drops are the first line treatment for glaucoma. These are covered through PharmaCare for those eligible to receive PharmaCare benefits. Many agents are covered by PharmaCare, however some of the agents require special authority to receive coverage. Patients may have extended benefits to help cover the costs for their medications. Manufacturers of some of the newer agents have applied to be listed on PharmaCare's formulary.

The cost of these medications range from $10-$25 per month for generic prostaglandins (when filled at Costco/Walmart) to $80-100 per month for other glaucoma therapies. Most of the name brand medications are typically in the range of $50 per month.

Selective laser trabeculoplasty (SLT) is publicly provided in BC. The laser device is quite expensive and is typically only available within in a group ophthalmological practice and is estimated to cost $80,000. The laser can also be combined with a YAG laser (estimated cost $125,000). SLT procedures are performed in the office, with the patient requiring 1-2 post-procedure follow-up visits. The procedure and the follow-up visits are covered by MSP. The

stakeholders noted that laser treatment typically reduces pressure by approximately 30% and can be very cost-effective.

Filtering / incisional surgery (trabeculectomy) is covered by MSP. This procedure is performed in the OR.

Both stakeholders estimated that, within their subspecialty glaucoma practices, >95% of glaucoma patients are treated with medications. Approximately 15%-40% receive SLT and 2%-15% receive surgery (both of these treatment groups typically continue with medications). Note that these treatment groups may overlap.

Both stakeholders indicated that a patient's ability to comply with their medications is linearly associated with the complexity of the medication regimen. When a patient is prescribed a prostaglandin drop (once per day) they are able to adhere. However, when polytherapy is necessary, requiring the patient to take several medications at various times throughout the day, they report that patients find it confusing and difficult to adhere. The stakeholders note that their patients "have lives they are trying to get on with". Among patients who have been prescribed polytherapy, MIGS may be discussed to help reduce the burden associated with multiple medications.

The stakeholders indicated that MIGS is currently performed and funded at Vancouver General Hospital, Surrey Memorial Hospital, and Royal Jubilee Hospital. MIGS is also performed by other ophthalmologists in the province, however patients may need to pay out-of-pocket.

The stakeholder from Vancouver General Hospital (Vancouver Coastal Health) estimates that they perform approximately 150 MIGS procedures per year. The stakeholder from Surrey Memorial Hospital (Fraser Health) estimates that they perform 100-200 MIGS procedures per year.

Both stakeholders confirmed that there is currently no MSP billing code for MIGS. MIGS procedures are performed in the OR, and patient suitability is determined by clinical judgement.

iStent (a type of MIGS) can also be performed in ambulatory day surgery centres. iStent is the only MIGS device approved for and is in use in ambulatory surgical centres in BC. This is a patient-pay model that was approved by the College. The patient pays for costs associated with the iStent device but not for the MSP insured services required for the ophthalmologist to perform the procedure (i.e., the surgeon bills MSP). If a patient prefers to cease pharmacotherapy and they aren't referred to a centre that offers MIGS, their only option is to pay out of pocket.

2. What are stakeholder perspectives and experiences with MIGS in BC?

Both stakeholders expressed that they have a duty to provide their patients with all available options. Consistent with the guidelines, medical therapy is the first option as well as SLT. However, for patients whose glaucoma is not responding to these treatments, all other options should be presented, including MIGS and options for surgical procedures that are not available in BC (including investigational surgery). One stakeholder indicated that they have had many patients choose to receive care out of province (Toronto) in order to access treatment options that are not available in BC.

Both stakeholders also indicated that among stable glaucoma patients who also have cataracts, when it is time to remove the cataracts the conversation regarding MIGS occurs as these procedures can be performed together.

3. How does MIGS affect the direct and indirect costs for BC patients, particularly for those from rural and remote areas?

Both stakeholders expressed that there is inequity with respect to access to MIGS. Whether MIGS is funded depends on where a patient lives and who they are referred to (i.e., an ophthalmologist who practices at a hospital that funds MIGS). There is a divide between rural and urban/suburban patients and access to MIGS. For example, MIGS is not offered in Northern Health. Both stakeholders indicated that MIGS may be offered at hospitals, other than Royal Jubilee, in Vancouver Island Health Authority.

Table 3.1. Fee codes.

Code	Disease	Description
2177	Glaucoma	Peripheral iridectomy (isolated procedure)
2178	Glaucoma	Filtering procedure, non-microscopic
2180	Glaucoma	Goniotomy
2184	Glaucoma	Cyclodialysis
2187	Glaucoma	Filtering procedure, microscopic
22070	Glaucoma	Molteno implant (includes phase 1 and phase 2)
22185	Glaucoma	Cycloablative procedures
22187	Glaucoma	Complicated trabeculectomy
S02072		Laster trabeculoplasty (per eye)

Note: Diagnosis code used were ICD9 = 365.9; ICD10 = H40.9.

Table 3.2. MIGS device available in BC.

Approach	MIGS	Utilized at VGH?	Utilized at Surrey Memorial?	Other notes
Reducing aqueous production	ECP	Y	Y	
Increasing trabecular outflow by bypassing the TM using tissue ablation/removal	Trabectome			Utilized in VIHA
Increasing trabecular outflow by bypassing the TM using tissue ablation/removal	Kahook Dual Blade	Y	Y	
Increasing trabecular outflow by bypassing the TM using a device	iStent (first generation)	Y	Y	

Approach	MIGS	Utilized at VGH?	Utilized at Surrey Memorial?	Other notes
Increasing trabecular outflow by bypassing the TM using a device	iStent inject (second generation)	Y	Y	
Increasing trabecular outflow by bypassing the TM using a device	iStent W	Y		
Increasing trabecular outflow by bypassing the TM using a device	Hydrus microstent	Y		
Increasing trabecular outflow by bypassing the TM via 360º suture	GATT	Y	Y	
Increasing uveoscleral outflow via suprachoroidal shunts	CyPass micro-stent		Y (before withdrawal)	NOTE- voluntarily withdrawn from the market
Creating a subconjunctival pathway for filtration	XEN 45 Gel Stent	Y	Y	
Creating a subconjunctival pathway for filtration	XEN 63 Gel Stent			
Creating a subconjunctival pathway for filtration	XEN 140 Gel Stent			
	Presserflow			Not yet available in BC
	Micropulse diode (laser)		Y	Not technically MIGS; more powerful laser

Note: ECP = endoscopic cyclophotocoagulation; GATT = Gonioscopy-Assisted Transluminal Trabeculotomy; TM = trademark; VIHA = Vancouver Island Health Authority.

Chapter 3 Summary of patient experience

This section summarizes the patient engagement processes and results from the recently conducted Canadian HTAs noted in section 1.1.

3.1 CADTH (Jan 2019)

The CADTH literature review on patient experiences and perspectives included qualitative-only studies or the qualitative component of mixed-method studies where these were separately reported. Four standard databases were searched for peer-reviewed and grey literature. Searches were completed as of November 2017. There were 7133 hits after duplicates were removed; 67 studies were retained for full-text review, and 15 met inclusion criteria. Fourteen of the included studies involved patients, and one involved family members and friends only. Of those retained, none were conducted in Canada. There were 329 patients involved in total and 31 family members.

Limited information about patient characteristics was provided by the included studies. Patients in six studies were reported to have an advanced or severe disease; in one study, patients were suspected to have glaucoma but had not been diagnosed, and none of the remaining eight gave information about severity. No studies included experience with MIGS itself.

CADTH assessed the overall quality of the studies as low, although study quality is not necessarily a bar to the ability of a research project to provide meaningful qualitative insights. Three common qualitative appraisal criteria were used: is the study credible (1 yes, 7 partly, 7 no); is the study trustworthy, or confirmable (2 yes, 7 partly, 6 no); is the study transferable, that is, is it relevant to the MIGS review (3=yes, 11=partly, 1=no). Note that these data come from the Appendix of CADTH's report; figures differ from those reported in the main text.

Some of the main themes described in the synthesis were the following:

- Glaucoma came as an unexpected diagnosis for many. Participants were often unaware of any family history of the disease, and experienced few or no symptoms. Changes in eyesight were often attributed to the course of presumed normal aging.
- Glaucoma is experienced more as a mental/emotional burden than a physical illness, characterized by profound fears of blindness.
- Eye drops, the main form of first-line treatment, can be a great disruption in terms of its demands for adherence to a regular regimen. This is particularly so when drops must be administered multiple times per day, or with multiple prescriptions. Some portion of the patient population reports physical difficulty in self-treatment, and some side-effects such as irritation or dryness can be bothersome.
- Few of the participants had received surgery. It was seen as a 'last resort' due to concerns about potential loss of vision, but it also offered the prospects of reduced use of eyedrops, which as noted could be burdensome.
- CADTH also conducted three interviews with patient partners, all female and diagnosed with glaucoma; two had received MIGS procedures at some point. CADTH concluded that the experience of these interviewees "mapped on" to the published qualitative literature. Some themes are explicitly noted as confirmed by these interviews, such as the struggle and burden of lifelong treatment after diagnosis at a relatively younger age); however, overall there is very limited direct reference in the report to any findings from these interviews.
- Data provided by a patient group, in the form of a patient survey -- Foundation

Fighting Blindness, along with the Canadian Council for the Blind and the CNIB – is reported in the patient experience section of this report as well. The survey was posted online on July 20, 2018. A total of 244 responses were received, mainly from Ontario (73%). The summary indicates that respondents found glaucoma to have a serious effect on their lives, both in mental preoccupation and in limits to activities of daily life. These themes are consistent with the literature reviewed.

3.2 OHQ (December 2019)

The patient experience component of this HTA consisted of a report on qualitative interviews conducted with ten people. This included seven patients, two caregivers, and one person who combined both the patient and caregiver perspectives and was interviewed about each. Purposive sampling was used for recruitment, with the aid of patient and partner organizations. Those who received surgical interventions, MIGS or otherwise, were asked about their perceptions of the benefits and limitations of such treatments.

The published report provides no additional demographic information about participants, such as age, gender, ethnicity, or area of residence. Participants can be grouped roughly according to intensity of intervention (though there is no evidence that this was a deliberate aspect of the sampling strategy): three participants had been treated with eye drops and/or laser therapy; four participants had received a MIGS procedure; and three participants had received filtration surgery, a more invasive form of treatment that typically is used when the other approaches have proven ineffective. Thus, “participation bias among those who agreed to be interviewed likely skewed the perceived effectiveness of certain types of treatments for glaucoma”.

Results of the interviews are provided for the sample as a whole, without separating

patient and caregiver perspectives. The authors note that their findings are broadly consistent with those of the CADTH literature review, described above. Relevant additional findings include the following:

- Several participants noted concerns about possible barriers to glaucoma care, including the costs associated with ongoing treatment using prescribed eyedrops. Others pointed out that wait times for surgical treatment could impact their quality of life.
- The issues raised by patients were quality-of-life issues, such as reduced ability to drive, read, cook etc.; participants did not comment on any improvement of visual acuity or in their visual field, common clinical outcomes, regardless of the type of treatment received.
- "Among people who had a MIGS procedure, they generally felt the treatment was successful, with few side effects and a short recovery time." Not having to use eyedrops subsequently was a welcome benefit. No respondents were in a position to make a direct personal comparison of the costs and benefits for the different types of treatment. Moreover, "no one we spoke with knew whether they had received an iStent so they could not comment on this specific MIGS procedure".

3.3 INESSS (2019)

The INESSS report in 2019 stated that consultation involved contact, by email, with representatives of patient associations, to invite them to contribute comments or otherwise participate in the HTA. Organizations were identified by a web search, and through INESSS knowledge of potentially interested groups based on previous HTA work. The number of

organizations contacted is not reported; one response was received. This group – The Foundation Fighting Blindness – re-shared the results of their previously conducted survey of glaucoma patients from the CADTH HTA. INESSS states that it performed independent secondary analysis of this data. However, specific results from the survey are rarely separately identified anywhere within the published documentation. While it is stated that they form part of the overall synthesis and assessment, the precise way in which this patient data contributed is not clearly presented.

3.4 Key Points

The following main points from the patient perspective appear across the HTA reports summarized here. Note this in some ways reflects consistency across data sources (triangulation) while in other ways the consistency is due to reporting of the same findings from the same data sources across all reports.

- The published patient literature comes from non-Canadian sources, and furthermore appears to be of relatively low methodological quality. These reports make some effort to incorporate additional survey or interview data from glaucoma patients in this country, albeit the large majority of this comes from Ontario. These HTA reports provide relatively little methodological information for this original data, so it is hard to determine its quality.
- The main issue for patients is fear of blindness, and the psychological burden of preoccupation with the disease—in most cases these are greater than physical impacts
- Many patients are asymptomatic; those who have observed deterioration in their vision report reduced ability to carry out such activities of daily living as driving,

reading, cooking, housework, sports/recreation and travel. Most participants in the studies are older adults, so few work-related impacts are noted.

- There can be difficulty for some patients in adhering to a drug treatment regime, especially when multiple eyedrops are prescribed in combination; this is often due to inconvenience, though some patients have physical limitations which make it difficult to self-administer eye drops. Some also report allergic reactions, or other unpleasant side effects (dryness, irritation etc.). Costs may be a factor for some patients, if not adequately covered by some pharmaceutical health insurance over the long-term. The ability to reduce or discontinue this form of treatment is one benefit perceived to accrue from surgery, including MIGS.
- Much of the published patient literature refers to experiences living with glaucoma, and a relatively small proportion deals with surgical treatment. The original qualitative research conducted for these HTAs provides some Canadian comment on this. Those who have had MIGS were largely satisfied with the outcomes and recovery time, which appear less than for more invasive surgical interventions; however due to limited patient knowledge of the type of treatment received, the reports cannot definitively link benefits with particular forms of MIGS technology, such as iStent.

Chapter 4 Assessment of Evidence

4.1 Objectives

To critically appraise the HTA reports from Canadian jurisdictions and summarize the findings of the effectiveness and cost-effectiveness of MIGS.

4.2 Methods

The clinical and economic findings from the reports were summarized. The first report was published by CADTH in 2019 that examined the clinical and cost-effectiveness of MIGS.[1] The second report was published by INESSS in 2020 which was an update of the CADTH report and specifically examined one MIGS (iStent).[3] OHQ published a report which contained patient experience and budget impact in 2019 in complement with the CADTH report.[2] The patient experience was summarized in Chapter 3. OHQ shared an unpublished report with BC's HTAO summarizing the iStent findings of CADTH and INESSS reports which were not summarized in this report.[4]

Critical appraisal of the clinical review in the HTA was done using the AMSTAR-2 checklist.[17] AMSTAR-2 is a tool to assess systematic reviews that include randomized control trials (RCT) and non-RCT. Critical appraisal was undertaken for the CADTH report only as the INESSS report was an update of one of the MIGS (iStent) reviewed in the CADTH report with a similar methodology.

4.3 CADTH report

4.3.1 Policy question and objective of the report

4.3.1.1 Policy question

1. What is the optimal use, including appropriate patient selection, of MIGS devices and procedures for adults with glaucoma?
2. Should MIGS devices and procedures be funded by the public health care system?

4.3.1.2 Objective

The purpose of the CADTH report was "to address the policy questions through an assessment of the clinical effectiveness and safety, cost-effectiveness, patient perspectives and experiences, ethical issues, and implementation issues of MIGS devices and procedures for adults with glaucoma."

4.3.2 Clinical review

4.3.2.1 Methods of CADTH review

CADTH conducted a systematic review of primary studies. Comparative studies in English and French were identified in multiple databases, including MEDLINE, Embase, CENTRAL, and CINAHL. The search date ranged from January 2000 to November 2017. A regular alert was set up to update the search until the publication of the final report in 2019. Studies were eligible for inclusion if they compared clinical effectiveness and safety of:

1. MIGS versus:
    a. A different MIGS OR
    b. Pharmacotherapy OR
    c. Laser therapy OR
    d. Filtration surgery
2. MIGS in combination with cataract surgery versus
    a. cataract surgery alone
    b. a different MIGS plus cataract surgery
    c. filtration surgery plus cataract surgery

Two reviewers independently screened the abstracts and full-text articles. The quality of evidence was assessed using Cochrane's Risk of Bias tool and Cochrane's Risk of Bias in Non-Randomized Studies of Interventions (ROBBINS-I). Meta-analysis was performed when appropriate using R. Heterogeneity was assessed using I-square and chi-square statistics. No subgroup analysis or sensitivity analysis was possible due to the sparsity of evidence.

The primary outcome of interest was health-related quality of life. Secondary outcomes included IOP, number of glaucoma medications used, vision-related quality of life, visual field loss, visual impairment, visual acuity, adverse events, and complications.

4.3.2.2 Critical appraisal of clinical review methodology

Using the AMSTAR-2 checklist, the CADTH review followed a high standard for a systematic review. The search strategy was developed by an information specialist. Two independent reviews screened and selected eligible studies. Meta-analysis was conducted when appropriate with a proper assessment of heterogeneity. All the outcomes were reported clearly. In terms of methodology, this is a high-quality review. The AMSTAR-2 checklist can be found Table 4.1.

Table 4.1. AMSTAR-2 checklist.[17]

AMSTAR-2 checklist
1. Did the research questions and inclusion criteria for the review include the components of PICO?
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?
3. Did the review authors explain their selection of the study designs for inclusion in the review?
4. Did the review authors use a comprehensive literature search strategy?
5. Did the review authors perform study selection in duplicate?
6. Did the review authors perform data extraction in duplicate?
7. Did the review authors provide a list of excluded studies and justify the exclusions?
8. Did the review authors describe the included studies in adequate detail?
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?
10. Did the review authors report on the sources of funding for the studies included in the review?
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?

13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

4.3.2.3 Findings

Thirty-two comparative studies, including RCTs and observational studies, examined the clinical effectiveness and safety of MIGS in 24 unique comparisons. The included interventions and the corresponding studies can be found in Table 4.2. In summary, three RCTs and six non-RCTs examined MIGS in a single intervention head to head comparison, and seven RCTs and 16 non-RCTs compared MIGS in combination with cataract surgery with another combination or single intervention. The mean age of patients was approximately 54 to 79 years with an equal proportion of men and women. All studies included patients with primary open-angle glaucoma; some studies also included patients with other types of glaucoma. The majority of study participants reported mild to moderate glaucoma.

Table 4.2. MIGS and comparison that were included in the CADTH report.[1]

Intervention	Comparator	RCT	Non-RCT
MIGS Vs. Pharmacotherapy			
2x iStent	Travoprost (prostaglandin F analog)	Vold 2016[18]	
2x iStent Inject	Combination Latanoprost/timolol (prostaglandin F analog and beta-blocker)	Fea 2014[19]	
MIGS Vs. Laser Therapy			
Hydrus Microstent	SLT		Fea 2017[20]
MIGS Vs. Another MIGS			
iStent vs. 2x iStent vs. 3x iStent	See column 1 for comparators	Katz 2018[21]; Katz 2015[22]	
MIGS Vs. Filtration Surgery			
ECP	Second GDD (BGI)		Murakami 2017[23]

Intervention	Comparator	RCT	Non-RCT
ECP	AGI		Lima 2004[24]
Trabectome	Trabeculectomy with MMC		Pahlitzsch 2017[25]; Jea 2012[26]
2x iStent Inject	Trabeculectomy with MMC		Pahlitzsch 2017[25]
Trabectome or 2x iStent Inject (grouped together)	Trabeculectomy with MMC		Pahlitzsch 2017[25]
XEN 45 microstent with MMC	Trabeculectomy with MMC		Schlenker 2017[27]
MIGS + Cataract Surgery Vs. Cataract Surgery Alone			
ECP + Phaco	Phaco alone		Kang 2017[28]; Perez Bartolome 2017[29]; Sheybani 2015[30]; Siegel 2015[31]; Francis 2014[32]
iStent + Phaco	Phaco alone	Fea 2015[33]; Fea 2010[34]; Craven 2012[35]; Samuelson 2011[36]	El Wardani 2015[37]
2x iStent + Phaco	Phaco alone	Fernandez-Barrientos 2010[38]	El Wardani 2015[37]
CyPass Micro-Stent + Phaco*	Phaco alone	Vold 2016[39]	
Hydrus Microstent + Phaco	Phaco alone	Samuelson 2018[40]; Pfeiffer 2015[41]	
MIGS + Cataract Surgery Vs. A Different MIGS + Cataract Surgery			
KDB + Phaco vs. iStent + Phaco	See column 1 for comparators		Dorairaj 2018[42]
Trabectome + Phaco vs. 2x iStent + Phaco			Kurji 2017[43]; Khan 2015[44]
Trabectome + MICS vs. 2x iStent Inject + MICS			Gonnermann 2017[45]
iStent + Phaco vs. 2x iStent+Phaco vs. 3x iStent + Phaco			Vlasov and Kim 2017[46]; Belovay 2012[47]
ECP + iStent + Phaco vs. iStent + Phaco			Ferguson 2017[48]
ECP + Phaco vs. Trabectome + Phaco			Moghimi 2018[49]
MIGS + Cataract Surgery Vs. Filtration Surgery + Cataract Surgery			
Trabectome + Phaco	Trabeculectomy with MMC + Phaco	Ting 2018[50]	
Trabectome + Phaco	Trabeculectomy + Phaco		Kinoshita-Nakano 2018[51]
ECP + Phaco	Trabeculectomy with MMC + Phaco		Marco 2017[52]

Note: 2x = two devices; 3x = three devices; AGI = Ahmed glaucoma implant; BGI = Baerveldt glaucoma implant 250 or 350; ECP = endoscopic cyclophotocoagulation; GDD = glaucoma drainage device; KDB = Kahook Dual Blade; MICS =

micro-incision cataract surgery; MIGS = minimally invasive glaucoma surgery; MMC = mitomycin C; Phaco = phacoemulsification; SLT = selective laser trabeculoplasty; vs. = versus.
* The CyPass Micro-Stent was voluntarily withdrawn from the global market by the manufacturer in August 2018 due to five-year data from a long-term safety study; however, at the time of report publication, this device was still active in the Medical Devices Active License Listing and is therefore included in this report.

4.3.2.3.1 CADTH appraisal of included studies

CADTH used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework to assess the overall quality of evidence in each outcome.[53] Most of the outcomes were judged to have very low to low quality of evidence with exception of the IOP and number of medication outcomes in MIGS plus cataract surgery versus cataract surgery comparison, which were graded as moderate to high quality. The most common reasons for downgrading the quality of evidence were serious risk of bias in the included studies and high level of imprecision (e.g. no measure of variability or wide variability).

4.3.2.3.2 Intraocular pressure and number of medications

The two key outcomes, IOP at the end of the follow-up period and the number of medications, are summarized in Table 4.3. The estimates presented in the table came from meta-analysis or the best quality study in the respective comparison. **Statistically significant estimates are displayed in bold**. Please note that in some cases, the estimate favors the comparator. Different MIGS showed very different results in different comparisons; therefore, each MIGS should be considered separately. It was not appropriate to consider all MIGS as a single homogeneous intervention.

Table 4.3. Key outcomes from the CADTH report.[1]

Intervention Vs. Comparator [follow up period]		Intervention estimate vs comparator in IOP mmHg (p value)	Intervention estimate vs comparator in # meds (p value)
MIGS vs. pharmacotherapy	2x iStent vs. Travoprost [36 months]	14.6 v 15.3 (NR)	-
	2x iStent Inject vs. Latanoprost + Timolol [12 months]	13 v 13.2 (NR)	-
MIGS vs. laser therapy	Hydrus Microstent vs. SLT [12 months]	-6 v -7 (NS)	***-1.4 v -0.5 (<0.001)***
MIGS vs. another MIGS	1 vs. 2 vs. 3 iStent(s) [18 months]	15.93 v 14.07 v 12.24 (NR)	-
MIGS vs. filtration surgery	ECP vs. GDD (BGI or AGI) [24 months]	18.1 v 14.6 (NS)	2 v 3 (p=0.61)
	Trabectome vs. Trabeculectomy with MMC [6 months]	14.7 v 12.9 (NR)	***2.34 v 0.5 (p<0.001)***
	2x iStent Inject vs. Trabeculectomy with MMC [6 months]	16 v 12.9 (NR)	***2.5 v 0.5 (p<0.001)***
	Trabectome or 2x iStent Inject (grouped together) vs. Trabeculectomy with MMC	14.8 v 12.9 (NR)	***1.81 v 0.5 (p<0.001)***
	Xen45 with MMC vs. Trabeculectomy with MMC [time period not reported]	13 v 13 (NR)	0 v 0 (NR)
MIGS + cataract surgery vs. cataract surgery alone	ECP + Phaco vs. Phaco alone [36 months]	***15 v 17 (p=0.003)***	***0.4 v 2.3 (p<0.001)***
	iStent + Phaco vs. Phaco alone [12 months]	MA WMD = -0.42 (p=0.34)	MA WMD = -0.25 (p=0.06)
	2x iStent + Phaco vs. Phaco alone [12 months]	***17.6 v 19.8 (p=0.04)***	0 v 1 (NR)
	Hydrus Microstent + Phaco vs. Phaco alone [24 months]	***MA WMD = -1.87 (p<0.0001)***	***MA WMD = -0.41 (p<0.0001)***
MIGS + cataract surgery vs. a different MIGS + cataract surgery	Goniotomy with KDB + Phaco vs. iStent + Phaco [6 months]	***-4.2 v -2.7 (p<0.001)***	0.6 v 1 (NR)
	Trabectome + Phaco vs. 2x iStent + Phaco*	-	-
	Trabectome + MICS vs. 2x iStent Inject + MICS [6 months]	-30% v -34% (NS)	1.4 v 1.3 (NS)
	Different numbers of iStent + Phaco [6 months]	13.8 v 14.8 (p=0.78)	1.2 v 0.4 (NR)
	ECP + iStent + Phaco vs. iStent + Phaco [12 months]	***14.35 v 16.18 (P<0.01)***	1.1 v 0.62 (NR)
	ECP + Phaco vs. Trabectome + Phaco [12 months]	16.7 v 15.4 (p=0.45)	1.2 v 0.7 (p = 0.12)
MIGS + cataract surgery vs. filtration surgery + cataract surgery	Trabectome + Phaco vs. Trabeculectomy with MMC + Phaco [12 months]	16.8 v 17.1 (p=0.57)	0.44 v 0.75 (p=0.41)
	Trabectome + Phaco vs. Trabeculotomy + Phaco [36 months]	14.6 v 14.6 (p=0.48)	2.7 v 2.5 (p=0.67)
	ECP + Phaco vs. Trabeculectomy with MMC + Phaco [6 months]	14.2 v 13 (P=0.24)	***1.39 v 0.48 (p=.0064)***

Note: AGI = Ahmed glaucoma implant; BGI = Baerveldt glaucoma implant; ECP = endoscopic cyclophotocoagulation; GDD = glaucoma drainage device; IOP = intraocular pressure; KDB = Kahook Dual Blade; MA = meta-analysis; MICS = micro-incision cataract; MMC = mitomycin C; NR = not reported; NS = not significant; Phaco = phacoemulsification; WMD = weighted mean difference. *The analysis pooled two heterogeneous retrospective cohort studies together to obtain the estimate which can be misleading.

4.3.2.3.3 Quality of life

Quality of life was evaluated in only one prospective cohort study that compared the effect of MIGS (either Trabectome or two iStent Injects, examined separately or grouped) with trabeculectomy with mitomycin C (MMC) using the National Eye Institute Visual Functioning Questionnaire-25.[54] Patients who received Trabectome compared with patients who received trabeculectomy with MMC were found to have better quality of life in the color vision category only. None of the other 12 categories demonstrated any difference between the comparisons.

4.3.2.3.4 Visual field

The visual field was assessed in four comparisons. The effect on the visual field was not clear when comparing MIGS with pharmacotherapy because the outcome was not statistically tested between interventions. No difference in the visual field was found between the three comparison groups. The other three comparisons that assessed visual field were examining:

1. Number of iStent
2. MIGS with cataract surgery vs. cataract surgery alone
3. Endoscopic Cyclophotocoagulation in combination with cataract vs. Trabectome with cataract surgery

4.3.2.3.5 Visual acuity

Visual acuity was assessed in seven comparisons:

1. MIGS vs. pharmacotherapy
2. MIGS vs. laser therapy
3. Number of iStent
4. MIGS vs. filtration surgery
5. MIGS with cataract surgery vs. cataract surgery alone
6. MIGS with cataract surgery vs. filtration surgery with cataract surgery
7. Different MIGS combined with cataract surgery

None of the comparisons found differences in visual acuity between the interventions. It is worth noting that visual acuity was measured using a decimal chart, Snellen VA, eye chart, or Snellen converted to logMAR. In addition to heterogeneity of outcome measurement instruments with respect to visual acuity, the instruments are known to have poor reliability.

4.3.2.3.6 Safety

The included studies reported mixed result for safety in MIGS. None of the studies reported how adverse events were counted. In many cases, the information regarding safety was reported without statistical testing. Most reported adverse events were minor. The evidence on safety was graded at very low quality, with large uncertainty between groups. Please refer to page 74 to 75 in the CADTH report for further discussion about safety data.

4.3.3 Economic evaluation

4.3.3.1 Methods of CADTH economic model

The current evidence did not allow comparison between MIGS devices. Therefore, the economic evaluation focused on comparing MIGS with other alternative therapies. A five-state Markov model was developed to estimate the cost-effectiveness of MIGS when compared against five comparators (e.g. pharmacotherapy, laser therapy, filtration surgery, cataract surgery, or filtration surgery + cataract surgery) from the Canadian health care payer perspective. The Markov model used clinical effectiveness in the reduction of IOP and mapped to change in the visual field. Then, the change in the visual field translated into the severity of glaucoma using the Hadapp-Parrish-Anderson staging system. The primary outcome of the model was the incremental cost per quality-adjusted life-years (QALYs) gained in 2018 Canadian dollars.

4.3.3.2 Findings

The findings from the five comparisons from the model can be found in Table 4.4.

Table 4.4. Lifetime probabilistic analysis: Reference case

Category	Costs ($)	QALYs	Incremental Cost ($) MIGS Vs. Comparator	Incremental QALYs MIGS Vs. Comparator	ICUR ($/QALY)	Device involved
Model 1: Pharmacotherapy MIGS	11,900 12,641	12.85 12.89	741	0.039	MIGS (vs. medication): 18,808	2x iStent inject vs. Lantanoprost + timolol
Model 2: Laser therapy MIGS	9,013 10,739	10.36 10.34	1,726	-0.023	MIGS dominated	Hydrus Microstent vs. SLT
Model 3a (moderate stage): MIGS Filtration surgery	12,672 13,375	12.42 12.49	-703	-0.07	MIGS was less costly but produced less QALY	Trabectome vs. Trabeculectomy with MMC
Model 3b (advanced stage): MIGS Filtration surgery	11,354 14,621	10.83 10.85	-3,267	-0.027	MIGS was less costly but produced less QALY	ECP vs. Glaucoma drainage device (BGI or AGI)
Model 4: Cataract surgery alone MIGS + cataract surgery	8,431 10,072	9.04 9.06	1,641	0.026	MIGS + Phaco (vs. Phaco alone): 63,626	Hydrus Microstent + Phaco vs. Phaco alone
Model 5: MIGS + cataract surgery Filtration surgery + cataract surgery	10,836 11,309	7.89 7.92	-473	-0.032	MIGS was less costly but produced less QALY	Trabectome + Phaco vs. trabeculotomy + Phaco

Note: ICUR = incremental cost-utility ratio; MIGS = minimally invasive glaucoma surgery; Phaco = phacoemulsification; QALYS = quality-adjusted life-years; vs. = versus.

The authors found that the lifetime cost-effectiveness of MIGS differed by comparison and baseline disease severity. MIGS seems to offer some clinical benefit at a high cost when compared with pharmacotherapy or when performed in combination with cataract surgery compared with cataract surgery alone. It is noteworthy that the only evidence incorporated in the MIGS plus cataract surgery was considered by CADTH to be high quality. The remaining studies were considered to be of low to very low-quality evidence.

Sensitivity analyses suggested that the ICUR is sensitive to medication cost. Please refer to Table 18, 19, 21, 22 and 24 in the CADTH report for the sensitivity analyses of the five comparisons.

4.4 INESSS report

4.4.1 Objective

To assess the clinical effectiveness and cost-effectiveness of iStent alone or in combination with cataract surgery when compared with appropriate comparators.

4.4.2 Clinical review

4.4.2.1 Methods

INESSS performed an update of the CADTH search to identify citations published after the CADTH report. The authors qualitatively summarized the results of the included studies and did not undertake a meta-analysis. INESSS also incorporated studies suggested by the manufacturer as well as grey literature search in their search strategy. Only RCT s were included in the INESSS report. New studies were critically appraised using the Cochrane Risk of Bias tools. Similar to CADTH, the quality of evidence was assessed using the GRADE approach.[53]

4.4.2.2 Findings

The INESSS report included nine publications from six RCTs. Seven of the included studies were identified in the CADTH report (Vold 2016, Fea 2015, Fea 2014, Craven 2012, Samuelson 2011, Fea 2010, Fernandex-Barrientos 2010).[18, 19, 34-36, 38] Two additional publications were identified and included in the INESSS report (Fechtner 2019, Samuelson 2019).[55, 56]

The included RCTs examined two comparisons that involved either two iStent or an iStent inject device administrated alone compared with pharmacotherapy or when performed concurrently with cataract surgery when compared with cataract surgery alone. Two RCTs examined the effect of two iStent against pharmacotherapy.[18, 55] One RCT examined the effect of two iStent inject device against pharmacotherapy.[19] The quality of evidence was graded as very low.

Table 4.5. Clinical result of IOP and number of medications from INESSS report.

Comparison	Follow up duration	Intervention vs comparator IOP (mmHg)	Intervention vs comparator # of med
2x iStent vs medications	60 months	16.5 vs 16.3 (NS)	-
2x iStent inject vs medications	12 months	13.0 vs 13.2 (NS)	-
2x iStent + Phaco vs Phaco alone	12 months	17.6 vs 19.8 (p=0.04)	0 v 0.7 (p=0.007)
2x iStent inject + Phaco vs Phaco alone	24 months	-	0.4 vs 0.8 (NS)

Note: IOP = intraocular pressure; NS = not significant; Phaco = Phacoemulsification.

No difference in terms of visual field or visual acuity was found in any of the comparisons. Quality of life was not reported in any of the included RCT. Most adverse events reported in the RCT were mild to moderate. Some commonly reported adverse events were progression of cataract, ocular surface disease, intraocular inflammation, and hyperemia of conjunctiva. The quality of safety was low and inconclusive.

4.4.3 Economic evaluation

4.4.3.1 Methods

The INESSS report used a Markov model to assess the cost-effectiveness of two iStents over a 15-year time horizon. The analysis used the perspective of the Quebec public health and social services payer.

4.4.3.2 Findings

Base case result from the INESSS economic evaluation can be found in Table 4.6.

Table 4.6. Result of base case economic analysis.

Comparison	Cost per patient (CA$)	QALY	ICUR (CA$)
2x iStent	$12,736	9536	$25,596 / QALY
Pharmacotherapy	$12,743	9497	
2x iStent + Phaco	$13,734	9467	$112,380 / QALY
Phaco only	$12,142	9452	-

Note: CA$ = Canadian dollar; ICUR = incremental cost utility ratio; Phaco = phacoemulsification; QALY = quality adjusted life year.

The INESSS report suggested that the ICER of two iStents, when compared with pharmacotherapy, was $25,596/QALY. The ICER was significantly influenced by the assumptions regarding the maintenance of the clinical benefit over time (ICER of 0% maintenance: $111,200/QALY; ICER with 100% maintenance: $6,100/QALY). This result should be interpreted with caution as the quality of evidence incorporated into the model was graded low to very low. Therefore, if better quality evidence becomes available; the estimates are very likely to change.

The ICER of two iStent in combination with cataract surgery when compared with cataract surgery alone was $112,380/QALY. The ICER was also influenced by the assumptions regarding the maintenance of clinical benefit over time (ICER with 0% maintenance: $503,000/QALY; ICER with 100% maintenance: $63,700/QALY). Similar to the previous analysis, the clinical evidence incorporated into the model was graded low to very low.

4.5 Overall conclusion

1. The CADTH reviewers indicated that although MIGS was categorized as a single class of intervention, each MIGS approach had a unique mechanism of action and different effectiveness profile. Therefore, the clinical effectiveness of each MIGS should be considered individually, not as a single class.
2. Both CADTH and INESSS found evidence that favor MIGS in combination with cataract surgery when compared with cataract surgery alone. The highest-quality

evidence came from RCTs of Hydrus Microstent. Other studies that used other MIGS were of low or very low quality.

3. In general, the findings did not demonstrate a significant benefit of MIGS when compared with pharmacotherapy, laser therapy, between different MIGS, or filtration surgery. This means there was not sufficient evidence to support the use of MIGS as stand-alone therapy compared with other alternative single interventions.
4. There was not sufficient evidence to compare different MIGS devices plus cataract surgery with each other or with filtration surgery plus cataract surgery.
5. The evidence for clinical effectiveness was based on indirect outcomes such as IOP and the number of medications. There was no evidence of direct measurements such as improvements in quality of life, visual field, or visual acuity. The CADTH authors concluded that there was insufficient evidence to offer specific conclusions regarding individual MIGS devices and procedures; and there was no definitive evidence regarding which MIGS might be preferable for all glaucoma patients or a specific subgroup.
6. The economic model offered some scenarios when MIGS could be cost-effective. In the comparison between MIGS versus pharmacotherapy and between MIGS plus cataract surgery versus cataract surgery alone, the ICUR offered signals that MIGS could be cost-effective. However, the result should be interpreted with caution as the clinical evidence incorporated in the model was mostly low-quality evidence, which means that the estimates were very likely to change should better quality evidence become available.
7. INESSS included only iStent or iStent inject as the intervention of interest. They found two additional articles since the publication of the CADTH report. The INESSS report found a similar result to the CADTH report in terms of both clinical

effectiveness and cost-effectiveness.

Chapter 5 Discussion

The CADTH report was published in January 2019 and included evidence identified up until the publication date. It was the most comprehensive review of MIGS devices to date and examined eight MIGS devices in 24 paired comparisons. The INESSS report performed an update of the CADTH report and focused on only one type of MIGS-- iStent or iStent inject. Both the CADTH and INESSS reports used robust methodology to search and critically appraise the available evidence. It is unlikely that a new systematic review would identify new evidence that could drastically change the conclusion in 2020.

MIGS is a very heterogeneous class of devices that utilize different mechanisms to lower the IOP in open-angle glaucoma. The evidence showed great variability in study design, choice of comparator, and clinical effectiveness outcomes between the different MIGS devices. Therefore, MIGS should not be considered as a single class, nor should the clinical outcomes from different MIGS be pooled for the purposes of a meta-analysis. In a policy decision, each MIGS approach should be evaluated individually.

The economic evaluation in the CADTH and INESSS reports used robust methodology and Canadian costs. CADTH found that only in two comparison, MIGS versus pharmacotherapy and MIGS plus cataract surgery versus cataract surgery alone, that the ICUR could potentially be cost-effective. The INESSS report found similar results using the data from iStent and Quebec costs. Reevaluating the cost-effectiveness of MIGS using BC costs is not likely to yield a fundamentally different result.

Using the clinical and cost-effective findings from the CADTH and INESSS reports is a reasonable way to move forward to inform a decision in BC. Once a MIGS device and scenario is

chosen, informed by the results from the CADTH and INESSS reports, a high-level budget impact assessment can be conducted utilizing BC costs.

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