

the Ophthalmologist

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A Brief History of MIGS

The long and controversial journey to microinvasive glaucoma surgery (MIGS), and the quest to retire trabeculectomy

By Ike Ahmed



When I began my career in ophthalmology, glaucoma was not necessarily a popular field of study. I was attracted to it because I saw it as a field ripe for innovation. You see, I grew up in the medication era of glaucoma, but the more we developed medications, the more we realized their shortcomings as well as their benefits. My first choice was to pursue a fellowship in glaucoma, and I was fortunate to do that in a pretty innovative place. At the Moran Eye Center in Salt Lake City, we did a lot of non-penetrating surgery like deep sclerectomy and viscocanalostomy as alternatives to trabeculectomy.

After I came back to Canada, I started doing some of the newer glaucoma surgeries, like deep sclerectomy with mitomycin-C, which was a twist on what we had previously been doing. Very few surgeons had taken this surgery up due to questions on efficacy and technical difficulty. But I gravitated to the challenge and exhilaration of dissecting into

Schlemm's canal and peeling away juxtacanalicular meshwork. Although I knew non-penetrating surgery was not the final solution, I learned a lot about outflow anatomy and knew we could do better than what we were doing. I had also built up considerable experience in complex anterior segment surgery, taking on many extremely challenging cases that most surgeons didn't want to touch. For me, I was drawn to non-traditional ideas and challenges, especially when told, "That's not possible."

About three years into my career, I started to present and publish some of my work on glaucoma surgery, and it was one of the engineers at Glaukos who came to me at a meeting and said, "We want to talk to you about how we can better understand the iStent's potential." At that point, I had already worked on SOLX's Gold Shunt, as I was involved in their North American trial comparing it against New World Medical's Ahmed glaucoma valve. That was the first device

iStent

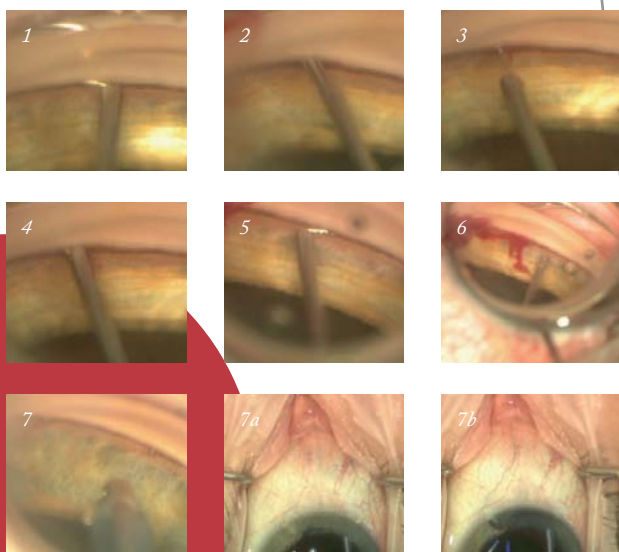
The *iStent* is implanted prior to phacoemulsification. The head has been turned, the microscope tilted, and a Swan-Jacob gonioscope positioned to visualize the nasal angle.

1. Enter the meshwork at a 30° angle in the supernasal angle. With this acute angle, the self-trephinating tip approaches with adequate entrance into the canal, avoiding entrapment within the inner wall.
2. Once one-third of the device is in the canal, lift toward the hand and straighten the hand out to allow smooth passage of the implant within the canal.
3. Release the snorkel end gently, observing its position within the inner wall.
4. Then tap the implant to push it against the canal while pushing the snorkel end against the outer wall to ensure adequate placement.

At this point, it's normal to see blood reflux from the insertion and from the snorkel end.

5. A second *iStent* can be placed in a backhanded fashion, again approaching at a 30° angle. After the self-trephinating tip incises the inner wall, the main body of the device is slid into the canal by straightening the hand and pulling slightly.
6. The snorkel is gently released from the implanter, and the tip is used to push it against the outer wall. Tapping ensures the device is well-seated, as its elbow must be placed fully within the canal. Viscoelastic helps with visualization and moving blood away from the area of interest.
7. A third *iStent* can be placed in a similar fashion. It's important that the eye moves very little, to ensure that the surgeon doesn't torque it and hit the outer wall during implantation. The three implants are placed approximately two clock hours away from each other.

7a/b. Toward the end of the case, irrigation and injection of trypan blue nicely shows the distal outflow passage. The visible pattern of filling and blanching of the episcleral vessels nasally, superior and infranasally, is only present in the area nasally where the implants have been placed.



company I worked with, and I learned a lot about what it takes to run a large glaucoma surgical trial. I also was the principal investigator for a five-year randomized prospective study (the AVB study) that compared the Ahmed valve and AMO's Baerveldt glaucoma implant.

Developing the *iStent*

So 10 years ago I began to consult for Glaukos and immediately started working with the *iStent*. I quickly realized that we weren't maximizing the ability of microstenting Schlemm's canal. I felt that there were issues with proper stent placement, and I wondered about the potential value of placing multiple devices. Looking back at seminal work done on distal aqueous outflow in the 1940s, I felt that we needed to do a better job at targeting stent placement and accessing larger areas of outflow. We started building up our studies from there and just kept on improving our surgical techniques. At the time, there wasn't really much training – it was very much, “Here's the device, Dr Ahmed, go and use it.”

When you're working toward innovation, you have to take the plunge. We didn't do anything without the right thought process; we planned carefully, chose the right patients, and did everything with institutional review board and regulatory approval. But when we went for it, we just dove right in. The beauty of this procedure is that it's so safe that the worst outcome is being unable to insert it – as opposed to a procedure that actually changes the structure of the eye. I think that's what made me much more willing to jump into it rather than wait on the sidelines; I felt that there was a certain degree of safety that allowed me to push the envelope a bit.

My role with most companies has been a strategic one – developing and moving existing technologies to the next level. Glaukos had already started their pivotal FDA *iStent* study (phaco compared with phaco with a single *iStent*), so my immediate thought was to go past that and implant multiple targeted devices. And not only that, but work to perfect the surgical technique. It was a great opportunity for me; this new glaucoma surgical space was in its infancy and I was learning so much every day. It's interesting when a clinician-scientist like me interacts with the business of medicine. Sometimes we're aligned, and sometimes we butt heads. But I have to give Glaukos credit for supporting me to do the scientific work we did. It also helped to be in Canada and work with a very supportive hospital and Health Canada to push studies forward.

For my initial population, I chose patients who needed better IOP control, but were high-risk candidates for traditional filtering surgery. I was able to discuss my ideas with Health Canada and get their support to try this entirely new

technology on a compassionate basis. That's how it started; we had the perfect mix of scientific curiosity, personal interest, patients that were not being best served by current technology, industry collaboration, and being in the right place at the right time. The first place that glaucoma stent technology was fully approved was actually in Europe, where it was CE marked. However, the uptake in Europe at the time was in fact poor. I suspect that this was because the IOP reductions were less than expected – but this was because our understanding of surgical technique and strategic placement was still in its infancy at that stage.

The rise of MIGS

At the time I started working with Glaukos and the iStent, I was also consulting for three other MIGS companies – AqueSys with their development of the Xen subconjunctival gel stent, Ivantis and the development of the Schlemm's canal scaffold Hydrus microstent, and Transcend Medical with their CyPass suprachoroidal microstent. I feel very fortunate to have worked with these companies at the earliest stage of device development and to help shape the products and how they are used. It may seem odd that I have worked with each MIGS company at such a deep level; each a competitor in some way. Confidentiality was therefore critical, but I always made it clear to everyone that I worked with that my interests lay in science and patient care. I've always felt that I don't serve individual companies; I serve my patients.

My journey in developing these new devices also took me all over the world as I worked with international collaborators. Hours and hours of tireless work in the lab were at times frustrating, but the prospect of the end result kept things in perspective. I think few people understand the painstaking work that comes with early-stage device development. One has to be prepared for failure early on, and believe in the concept of critical appraisal and leaving no stone unturned. I do have to admit that at times I had my doubts, but my optimism and desire to do better for my patients gave me the perseverance to continue.

Within a few years, I felt it was important to distinguish these devices from what was already being done in the glaucoma surgery field. Clinicians, patients and industry professionals needed to understand that these were different products. I toyed with the right words – I started with “minimally invasive,” but other medical specialties had used that term, and I thought, “No, we're talking about the eye. We're talking about microns here. This is not just minimally invasive, this is a microinvasive procedure.” So then it evolved to microinvasive, and that's how I coined the term “MIGS”: microinvasive glaucoma surgery. This was truly a revolutionary

The Essence of MIGS

1. *Ab interno microincision* Surgery through a clear corneal incision allows easy visualization of anatomic landmarks for better device placement, combines easily with cataract surgery, and prevents significant scarring of the conjunctiva. The smaller the incision, the safer the procedure, improving the surgeon's ability to maintain the anterior chamber, retain the natural ocular anatomy, and minimize changes in refractive outcome.

2. *Minimal trauma* The device should cause minimal disruption of normal eye anatomy and function. Surgeons should take a broad view of manufacturing materials and placement, with the ultimate goal of enhancing the natural outflow pathways of the eye.

3. *Efficacy* MIGS procedures should have at least modest efficacy. Initial assessments of device and placement efficacy are often made using case series; the final determination and quantification of a procedure's efficacy should be made by randomized clinical trial.

4. *Favorable safety profile* MIGS procedures should avoid the serious complications that can arise with other forms of glaucoma surgery.

5. *Rapid recovery* Speed and ease of use are both vital characteristics of MIGS. The procedure should have minimal impact on patients' quality of life.

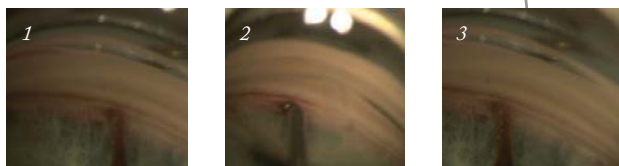
MIGS Timeline

- 1999: Glaukos Corporation produces its first micro-bypass glaucoma stent prototype
- 2001: First human implant of Glaukos' iStent
- 2004: The iStent receives a CE mark
- 2005: The FDA grants an IDE for US clinical trials of the iStent
- 2008: Transcend Medical's CyPass micro-stent receives a CE mark
- 2009: Ike Ahmed coins the term “MIGS”
- 2010: The iStent receives Health Canada approval
- 2011: The second generation of iStents (Inject and Supra) both receive CE certification
- 2011: AqueSys' XEN gel micro-stent receives a CE mark
- 2012: AqueSys' XEN stent begins FDA trials
- 2012: The iStent receives FDA approval and becomes the first MIGS device approved in the United States
- 2013: The Transcend CyPass begins FDA trials
- 2014: The iStent is available in 17 countries
- 2015: The AqueSys XEN receives a medical license in Canada
- 2015: Transcend Medical announces its plan to file a Premarket Approval Application with the FDA for CyPass
- 2015: Transcend Medical announces its plan to file a Premarket Approval Application with the FDA for CyPass

Cypass

The Cypass suprachoroidal microstent is implanted using gonioprism to visualize the angle.

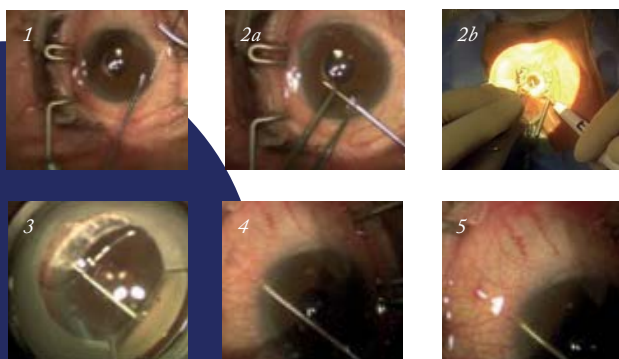
1. Identify the trabecular meshwork and the scleral spur. Aim the tip of the applicator for the scleral spur, allowing the guide wire to disinsert the iris at the point of the spur. 2. Pass the implant forward. The guide wire is curved to follow the undersurface of the sclera. Place the implant so that at least two rings of the collar can be seen in the anterior chamber, to avoid a deep implantation. If using viscoelastic, inject it around the device at this point. 3. Release the device from the cannula, ensuring that the proximal end can be seen sitting at the appropriate point in the meshwork to avoid corneal contact.



AqueSys Xen45 One-Handed

The AqueSys Xen45 suprachoroidal microstent is implanted using gonioprism to visualize the angle.

This is a new, lightweight one-handed injector for the AqueSys XEN45 implant (a 45 µm lumen implant preloaded into the injector). It places the implant in the subconjunctival, interscleral and anterior chamber space. 1. Remove the injector from its packaging and examine it under the microscope to locate the metal post within the lumen of the 27 G needle (intended to prevent the implant from moving during shipping). Remove this post. 2a. The clear corneal incision was made in the infratemporal quadrant to direct the needle toward the supranasal quadrant. 2b. Notice the overhand grip – two fingers straddling the proximal portion of the injector with the thumb on top. 3. Use the goniolens to localize the angle and structures of the eye, then place the needle into the area of the spur-meshwork junction. 4. Fill the anterior chamber with viscoelastic, then use a spatula to rotate the eye down to facilitate adequate visualization and passage of the needle. 5. Once the needle is visualized through the sclera, advance the sliders to inject the implant and then retract the needle into the cannula. The free hand can be used to fixate the globe and rotate the eye if necessary for visualization.



new way to look at glaucoma treatment, offering patients something we could never offer before.

At first, of course, it was a term nobody had heard and people were laughing at it, but now it seems everybody wants to call their device a “MIGS device.” It’s funny how things have exploded; right now, we have thousands of patients in trials around the world with MIGS devices. It’s incredible considering that, prior to the iStent, there had never been a formal, well-designed glaucoma device study of that scale – so that really spawned a whole era of glaucoma surgical clinical trials. The iStent wasn’t the first approach to draining aqueous in glaucoma patients, but it was years ahead of the other technology available at the time. So other companies started thinking, “Can we drain into this space better? Can we drain into other spaces using stents with a different technology?” And now there are three other stent companies focusing on these kinds of developments.

Improving implantation

Microstent implantation is getting better and easier, but I think it’s still a complex procedure that takes a lot of thought and dexterity to get it just right. It’s not something anyone, even an experienced surgeon, can just pick up and do. There’s definitely a learning curve, but it is well worth it. Mentorship and proctorship are key ingredients to success. I’ve been fortunate to learn from others and teach others – to me, that’s what medicine is all about. It’s thrilling to have surgeons from all around the world visit my OR to learn some of these new techniques and take their experience back to hopefully benefit their own patients. One by one, we’ve built this MIGS-surgeon international fraternity of sorts.

We’re continuing to work on technologies to identify the best patients for these procedures and help with stent implantation. Preoperative and intraoperative imaging will help us select our optimal stent approach and placement. We are working on better intraoperative visualization tools and instrumentation to enhance the surgical technique. In the meantime, we’ve developed some very good clinical and surgical techniques even without technological assistance.

The power of people

At first, I didn’t like social media; I thought it was a waste of time. But then we set up a medical professional page for me on Facebook, and I realized what a powerful medium it is for communication. Facebook and in particular YouTube have been very important for me in disseminating information. People no longer pick up a textbook or journal to read about clinical issues or surgical techniques– they go online.

My group of collaborators has multiplied hugely over time.

I love it, because I love people. The biggest draw to innovation for me is the opportunity to build relationships. Working together as a team, whether it's in the clinic, the operating room, or with engineers, scientists and businessmen, is a thrill. My personal approach is very collaborative; I don't really keep my ideas to myself. I believe in sharing and in just getting things done, even at the expense of losing some intellectual property rights. I realize that companies have to make money and continue producing new things, but I believe medicine works best in collaboration. I'm a clinician first and foremost, so my primary goal isn't to make money, it's to improve patient care – because it's all about people.

It's important to work hard at what you want to do, but it's also important to learn how to prioritize, delegate and understand where to invest your time and resources. Anticipation and timing are everything when it comes to success.

That translates to my life in general, too. I think I've gotten a little better – I've cut down my clinical load a lot – but my philosophy is to work hard and play hard. I'm very fortunate to have a great family and an awesome wife (who is also a physician) who have been supportive as I find myself often bringing work home! However, one thing my family knows is that I am a huge proponent of “family time!”

Changing the culture

Being at the forefront of innovation is a lonely journey in many ways, but it's a journey worth taking because I see what our patients can get out of it. In general, people don't like change – especially glaucoma specialists! And for good reason – our patients have a blinding chronic disease, with little room for error. We're not looking for a flash in the pan, but something that is proven to help our patients. There are a couple of things that seem very certain these days; firstly, that there is still an unacceptably high rate of glaucoma patients going blind under our watch, and secondly, that traditional filtering surgery is very much looked at as a late-stage treatment option. I also think we need to reframe glaucoma treatment to understand that it really goes beyond just IOP lowering, and that selecting treatment based on quality of life is becoming more and more important. Whether it is multiple daily drops, side effects or compliance issues, or high surgical risk – glaucoma treatment takes its toll on a patient's wellbeing. MIGS is very much at the center of changing the traditional glaucoma treatment paradigm.

My colleagues are starting to perform procedures I helped to develop. The culture of glaucoma treatment is slowly changing. Before it was very much “sit back, analyze, medicate, analyze, analyze, more medications, laser, wait, wait, and as a last resort, go to surgery.” Now it's becoming more active

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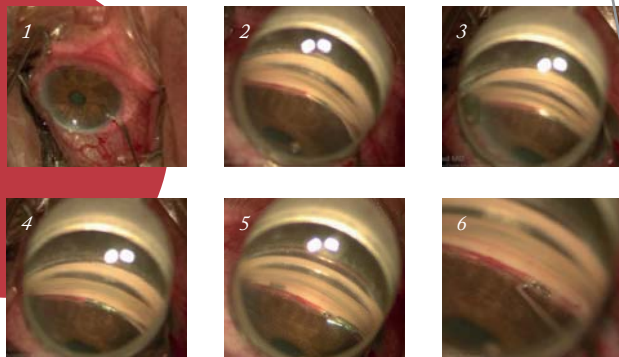
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to arrange
a demo

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Hydrus Implant

The Hydrus Microstent is implanted into the eye using an ab interno clear corneal approach.

1. Make the incision to the right of the cornea (as you view it) to allow for the unique curvature of the cannula.
2. Use the distal tip of the cannula to incise the inner wall. Only about 100 μm of this tip will actually enter the canal. There will be some torquing of the eye and positive pressure on the canal to allow penetration.
3. Relax the hand slightly and advance the roller wheel to place a device into the canal.
4. The device is placed in an upward fashion to ensure adequate passage.
5. Relax the hand again to release tension on the outer wall and direct the implant smoothly into the canal.
6. Use the slide interlock to release the inlet from the implantation device, then the cannula is then withdrawn.
7. Evaluate the position of the device using a Sinsky hook to manipulate the eye. At this point, there may be normal blood reflux behind the three windows in the canal, which are scaffolding the inner wall and keeping the canal open. The inlet is slightly inside the anterior chamber, with a transition zone visible where the incision has been made into the inner wall.



and interventional. New innovations in drug delivery are on the horizon and they are going to change things as well. I'm excited about that, and by the way, I see synergy between MIGS and new methods of drug delivery. I see that as the next step, because I think that combination can be very powerful.

Given other options, most patients would rather not choose a trabeculectomy – so we hope to offer an alternative that can be used earlier in the treatment paradigm through a combination of MIGS and drug formulations. Back when I started my fellowship, my goal was to retire the trabeculectomy before I retired. We've still got a lot of work to do, but I'm excited to see continued innovation in this space. We're at level one, MIGS 1.0," at the moment – and we're on the cusp of "MIGS 2.0." Thus far the storyline for MIGS has been about safety – the major Achilles heel of trabeculectomy. Now that we're gaining confidence in the safety of MIGS, we're seeing efforts made to enhance the efficacy of these devices. Examples of this include multiple targeted iStents, scaffolding Schlemm's canal with stents like the Hydrus, viscoexpansion with the suprachoroidal CyPass stents, and use of mitomycin-C with the subconjunctival Xen stent.

I've described "MIGS plus" now. I use that term for new devices and technologies that encompass the qualities of MIGS, but have a bit more power – and involve a bit more risk. We've been trying things like using the Xen gel stent with mitomycin-C (well-established in the trabeculectomy world) and seeing significant IOP lowering while maintaining the

Ike Ahmed Timeline

- 1995: Graduates from the University of Toronto, Faculty of Medicine, Canada
- 2000: Completes his ophthalmology residency at the University of Toronto.
- 2001: Completes his glaucoma and anterior segment fellowship at the John Moran Eye Center, University of Utah, in Salt Lake City
- 2001: Joins the academic faculty at the University of Toronto and University of Utah, and starts his practice at Credit Valley Hospital, Mississauga, ON
- 2002: Founds and directs the Toronto Cataract Course, an annual conference that has become one of the biggest in Canada and attracts over 300 participants
- 2002: Invents the Capsular Tension Segment with Morcher GmbH for use in complex cataract surgery
- 2003: Develops the first micro-instrumentation system for

- complex anterior segment repair with MST Surgical
- 2004: Participates in the North American trial comparing SOLX's Gold Shunt with the New World Medical's Ahmed glaucoma valve
- 2005: Glaukos approaches Ahmed to work together on iStent development
- 2005: Initial work with AqueSys on an ab-interno delivered subconjunctival microstent that will be called the Xen implant
- 2006: Starts working with Ivantis on a Schlemm's canal scaffold microstent that will later be named the Hydrus
- 2006: Collaborates with Transcend Medical to develop the CyPass suprachoroidal microstent
- 2009: Coins the term "MIGS" to describe a new genre of highly safe and minimally invasive glaucoma interventions
- 2010: Selected as one of Canada's "Top 40 Under 40," a prestigious national award recognizing significant achievements at a young age
- 2010: Best Glaucoma Paper award for "The Ahmed versus

minimally invasive nature of the procedure. So we're moving toward using devices with drugs to improve their efficacy. This is another aspect of MIGS 2.0, but we're only just getting started with it.

Despite the optimism I have toward MIGS, there is much need for further large-scale and longer-term studies to show efficacy, cost-effectiveness, and enhanced quality of life. I have colleagues who are skeptical of these new technologies, often questioning the IOP-lowering potential of these devices. I tell them, "You know what? This isn't the final frontier. This is just the beginning: the first frontier." It's important to keep the environment fertile to keep building on our early results. Don't close the door on innovation just as we're starting to have some bursts of enthusiasm and success. But let's do it right – it can be difficult to separate medicine from business, but it isn't impossible for those two interests to work together to improve patient care. Most innovations in medicine would not have come about without that kind of collaboration.

Ike Ahmed is chief of ophthalmology at Trillium Health Partners, medical director at Credit Valley and Osler EyeCare, research director at the Kensington Eye Institute and co-medical director of TLC Laser Eye Center in Mississauga, Ontario, Canada. He is also a professor at the University of Utah and an assistant professor and the director of the Glaucoma and Advanced Anterior Segment Surgery fellowship at the University of Toronto, Canada.

Ike's financial disclosures are available at: top.txp.to/0715/MIGS

Baerveldt Study: Two-Year Follow-Up Results" by the Canadian Ophthalmological Society

- 2012: Starts working with the InnFocus Microshunt, a subconjunctival device made from a novel material
- 2013: Selected as Head of Ophthalmology at Trillium Health Partners, Mississauga, ON, Canada
- 2013: Selected as Research Director, Kensington Eye Institute, University of Toronto
- 2014: Receives American-European Congress of Ophthalmic Surgery Visionary Award
- 2014: Receives the prestigious Binkhorst medal from the American Society of Cataract and Refractive Surgery for outstanding contributions to the understanding and practice of cataract surgery and IOL implantation
- 2014: Ranks #7 in The Ophthalmologist 2014 Power List
- 2015: Awarded and delivers the AGS Surgery Day Lecture at the American Glaucoma Society annual meeting



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