



the
Ophthalmologist

**INTERVENTIONAL
GLAUCOMA**

New Attitudes
and Approaches to Treatment

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Challenges in the Visual Field

In an ever-changing field, what's the current state of glaucoma treatment?

As medical and surgical interventions for glaucoma become increasingly sophisticated, ophthalmologists have more options than ever to address disease management and progression. However, it can often be difficult to keep up with new ideas, and in the midst of increasingly busy practice, it's all too easy for ophthalmologists to stick to what they know. This is increasingly important when disease treatment shifts from a medicine first approach towards more interventional techniques and this has absolutely been the case with glaucoma. So, aiming to spread the word about the changes in the field and the shift towards interventional treatment, recent roundtables brought together some of the leaders in ophthalmology to discuss the current state of glaucoma treatment. The panels, moderated by Ike Ahmed, consisted of Nate Radcliffe, Paul Singh, Mark Gallardo, Deborah Ristvedt, John Berdahl, Tom Samuelson, Davinder Grover and Sahar Bedrood – all of whom agreed that treatment options

have markedly increased and that ophthalmologists are slowly moving toward a much more interventional approach.

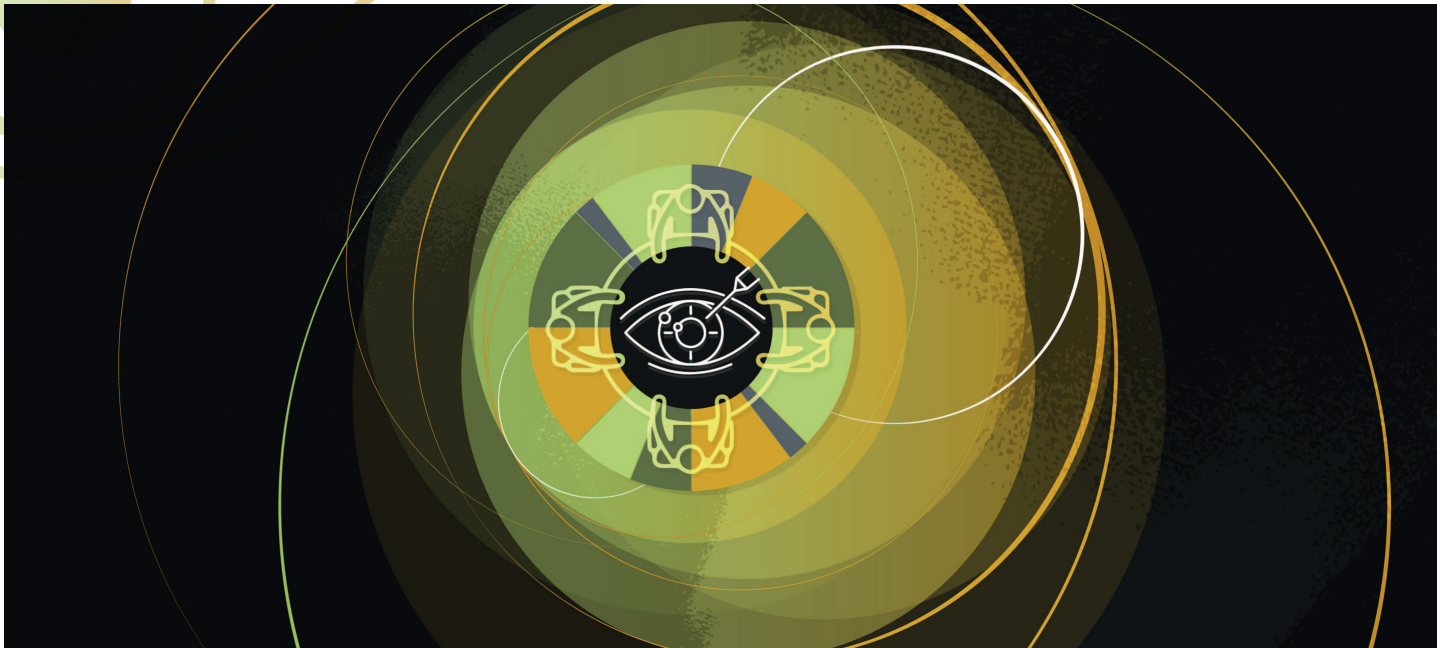
But they also agreed that, despite these advances, one of the principal challenges in glaucoma treatment is patient compliance. Medication adherence – or lack thereof – is a major factor in disease progression so, as Paul Singh pointed out, when patients are struggling to effectively use a particular therapy, doctors should be decisive in recommending the newer alternatives that have emerged over the past decade.

Deborah Ristvedt concurred, making the point that it's important for the wider ophthalmic community to be not just reactive to patients – who may progress even to the point of vision loss as documented in numerous studies (1) – but proactive in preserving both visual acuity and quality of life. This involves a challenge to the wider optometric and ophthalmic communities to shift their mindset away from simply relying on drops that can too often be detrimental to quality of life and visual acuity. Coming straight from his own clinic, Nate Radcliffe described a day of listening to patients share the various hurdles from forgetfulness to cost to the challenges of navigating an increasingly complex pharmaceutical system.

Clearly, the traditional regimen of front-loading medication isn't working for far too many patients, irritating the ocular surface (and even, as Ike Ahmed pointed out) leading to progressive dry eye disease and failing to halt disease progression. So, the move to make interventional treatment the standard in glaucoma is vital because the longer ophthalmologists take to treat, the more advanced the disease can become and the lower the IOP needed to manage it successfully. At the level of pathology, a longer wait time for interventional treatment leads to physiological changes in the trabecular meshwork, such as fibrosis and scarring, that can make treatment less effective and cause secondary health problems in the long term.

Cataract treatment has moved relatively easily to a more





interventional mindset in the past two decades, so the question has to be asked: why is an interventional approach to glaucoma treatment not as common? Tom Samuelson pointed out that recent data showed that even the most simplified drop treatment – one drop a day – got results that were not as good as even a minimally invasive procedure like selective laser trabeculoplasty (2). With experts calling for change – and Ike Ahmed pointing out that the current treatment model is in crisis – we must confront the challenges in precipitating this shift. As Davinder Grover explained, there are more resources available than ever before to help precipitate a mindset shift to a more interventional approach with everything from wet labs, to peer support and more online resources to give surgeons the best, most up to date information.

On the patient side, the main obstacle is nervousness around surgery – even a minimally invasive procedure. Patients might also be more comfortable with the non-invasive option of using drops (even though, as the panel pointed out, stacking drops to manage IOP can also increase toxicity and ocular surface irritation over time and patients often fail to administer them properly).

From the doctor's perspective, hesitance comes from questions around whether early surgery is both safe and necessary. MIGS, and other approaches to Interventional glaucoma management can prevent disease progression but, as several doctors pointed out, it requires physician confidence to intervene earlier – as Deborah Ristvedt pointed out

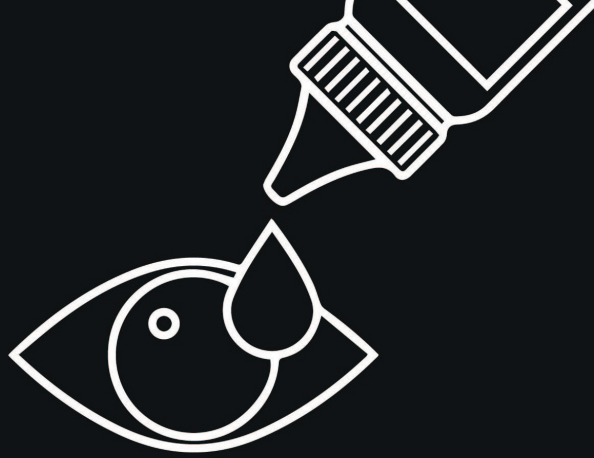
physicians also need to think about the patient perspective – if the doctor needed treatment what would they want? John Berdhal concurred, highlighting that in their own experience eye-care professionals would personally much rather go straight to something like selective laser trabeculoplasty rather than drops if they needed treatment. For doctors, confidence in that early intervention comes not just from thinking about the increased availability of surgical tools but also from reliable data showing consistent IOP reduction and visual acuity – emphasizing the importance of continued research into the efficacy of new and emerging treatments. Keep a lookout for our next piece, exploring the current surgical options available in the interventional glaucoma armamentarium as we dive deeper into the world of interventional glaucoma.

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References

1. M. Mehrdad et al., "Long-Term Trends in Glaucoma-Related Blindness in Olmsted County, Minnesota," *Ophthalmology*, 121, 134, (2014). PMID: 24823760
2. G. Gazzard et al., "Selective laser trabeculoplasty versus eye drops for first-line treatment of ocular hypertension and glaucoma (LiGHT): a multicentre randomised controlled trial," *The Lancet*, 393, 1505, (2019), PMID: 30862377





The Mindset Shift

If the “drops first” method is no longer working well – what are the new options for glaucoma treatment?

Talk to a glaucoma specialist and before too long you'll hear a familiar story – the three big problems of compliance, tolerability and adherence come up again and again. Patients find drops difficult, the pharmacy system by which they get their drops hard to navigate and the often complex regimen of drops hard to follow. All of this adds up to one thing – inevitable disease progression and vision loss. Happily, as some recent roundtable discussions show, there are more options than ever for doctors to treat patients without loading up the ocular surface with drops.

The roundtables, moderated by Ike Ahmed, brought together Nate Radcliffe, Davinder Grover, Paul Singh, Mark Gallardo, Deborah Ristvedt, Tom Samuelson, John Berdahl and Sahar Bedrood. To understand the changes that the last decade has seen in glaucoma treatment, Mark Gallardo pointed out that a decade or more ago, the treatment pathway generally moved from maxing out a patient on drops before laser treatment and then a filtration procedure. This depended on a patient already having progressed into moderate or severe glaucoma. Bedrood agreed, highlighting the ways in which this previous paradigm had been relatively inflexible and didn't take into account the differences between patients. One of the upsides of the new plethora of treatment options is greater flexibility and tailoring in treatment design for each patient – something which has only increased as MIGS devices have built an ever-better safety profile.

As Davinder Grover highlighted, when the first MIGS devices were being introduced, regulators didn't allow implants in patients who didn't need surgery. As the last decade or so has proven, the devices generally have a solid safety record, and as Grover put it, this has freed surgeons to move towards an interventional mindset. Nate Radcliffe explained an important aspect of this shift was in terms of patient wellbeing. Combining MIGS with cataract surgery has a huge positive impact on wellbeing and quality of life measures – even if patients are not permanently drop free post interventional glaucoma

surgery. Here then, the flexibility of interventional glaucoma preserves the potential for further treatment in the future and leaves patients more likely to engage with that, as they've already experienced successful treatment.

The challenge of the new interventional mindset is to get surgeons to think about not only proactive screening and monitoring of patients recently diagnosed with glaucoma, but also to appreciate the extent of the options which are now available. Multiple participants – Ike Ahmed and John Berdahl – brought up the development of using Selective Laser Trabeculoplasty (SLT) as a front-line treatment rather than drops. Ahmed brought up the LIGHT trial (1) a major study led by Moorfields Eye Hospital which compared the effectiveness of treatment between SLT and a standard drop regimen. The study results showed that over 36 months SLT was shown to be both more cost-effective and efficacious with 74% of patients in the SLT group requiring no medication to maintain their target IOP. As a result the National Institute for Health and Care Excellence has recommended SLT be adopted as the first line treatment for glaucoma in the UK.

However, this doesn't seem to be adopted as widely in the US. For some, it may be that patients don't respond well to hearing the term “laser” – Paul Singh described his approach as avoiding the term with patients, instead describing SLT as a beam of light which rejuvenates the trabecular meshwork. This shift in language certainly helps but as Nate Radcliffe pointed out, it's important for physicians to be proactive and forthright in encouraging patients towards these more interventional approaches. With the interventional mindset shift in full swing, the next article in this series will go into more detail about one of the key MIGS devices pushing interventional glaucoma forward.

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1. G. Gazzard et al., “Selective laser trabeculoplasty versus eye drops for first-line treatment of ocular hypertension and glaucoma (LiGHT): a multicentre randomised controlled trial,” *Lancet* 393: 1505, (2019). PMID: 30862377.



New Paradigm, New Product

The concept of early procedural intervention is gaining support among thought-leading ophthalmologists – does iStent meet the needs of this new approach?

Continuing our series on interventional glaucoma, the panel of experts turn their attention to the new possibilities offered by the interventional approach. Standard glaucoma management relies on topical medication to control IOP – until visual field losses demand riskier approaches. But eye-drops have some depressingly familiar disadvantages – including ocular surface damage and reduced quality of life – resulting in irregular compliance and therefore suboptimal efficacy. Even with efficacious drops, as Davinder Grover points out, long term usage of drops could also damage the eye and its outflow pathway. Indeed, even perfectly compliant patients may not benefit from eye-drops as much as first thought. As Ike Ahmed says, “Measuring IOP over 24 hours reveals significant fluctuation – a risk factor for progression.” He asserts that relying on medication in early disease carries risk in itself: “The longer we delay intervention, the more the damage to the outflow system – irreversible pathology which itself interferes with therapy.”

Paul Singh agrees, saying, “Delayed intervention just gives you more aggressive disease and more challenging IOP targets.” The answer, surely, as Deborah Ristvedt suggests, is early procedural intervention to optimize natural outflow pathways before they become irreparable.

But an earlier procedural approach demands interventions that are both safe and effective without the unwanted side effects of traditional, invasive surgery. Does the iStent infinite meet these criteria? Data from the infinite pivotal clinical trial (1) are very promising. In brief, the trial reported over 20 percent IOP reduction

in over 70 percent of patients; a remarkable efficacy rate in this complex population, says Tom Samuelson. Mark Gallardo notes that even subjects with refractive glaucoma (maximum tolerated medical therapy and/or tube or trabeculectomy history) achieved reduced medication and lower IOP. Nate Radcliffe points out that many iStent infinite recipients dispensed with eye-drops altogether, and suggests this may be because device implantation does not give rise to the IOP fluctuations associated with intermittent medication.

John Berdahl sums up the infinite trial like this: “I was surprised – not that the results were good, but by just how good they were!” He also notes that the study refutes the idea that the natural outflow pathway cannot be resurrected after traditional, invasive surgeries were performed in the past. “The trial challenges old dogma,” he says, “and gives patients a better option.”

Singh emphasizes the flexibility of the iStent approach, in that responder rates and IOP reduction can be improved by implanting additional iStents – up to three per eye.

Regarding safety, Ahmed points out that the iStent has been in use for a decade. “With over one million implantations, I think we’d know if there were any concerns – it’s probably the safest glaucoma procedure that surgeons undertake,” he says. “Even in the difficult cohort recruited for the infinite trial, there were no implant failures or serious adverse events.”

Gallardo concurs: “I’m very comfortable implanting iStent infinite in phakic or pseudophakic patients, even when they are on just one medication. I also recommend it to patients who have had or are undergoing filtration surgery.” Radcliffe points out that the large, statistically robust trial gives doctors and patients a high level of confidence in the product. Samuelson agrees, and points out that canal-based surgery is never associated with hypotony and is therefore safer than many other glaucoma procedures. Similarly, Berdahl notes that early intervention with iStent should reduce the need for secondary surgical interventions, and thus avoid their associated risks. Radcliffe reminds us that discussions of iStent safety should take account of the fact that glaucoma itself is not safe, in that it jeopardizes patient vision, and that medication also has risks. “Poor compliance – which occurs weekly with most patients – can trigger extraordinarily high IOP within hours,” he says.

Bedrood notes that the iStent infinite safety profile makes it a good option for a very broad range of patients, not limited to mild-to-moderate cases.

In conclusion, says Ahmed, early glaucoma presents a one-time opportunity for changing the course of disease. “If you miss that chance, the patient’s needs and risk-benefit profile change adversely,” he says. “Ideal early intervention methods would be better than eye-drops in terms of preventing progression and reducing the need for major surgery, such as trabeculectomy.”

Fortunately, as Gallardo points out, intervention options have improved: “New products now allow us to safely intervene very

“The longer we delay intervention, the more the damage to the outflow system – irreversible pathology which itself interferes with therapy.”

early – we're seeing a paradigm shift in patient care." Radcliffe expects iStent infinite to significantly contribute to this step-change: "It will drive things forward, not least because of all the effort behind it." The infinite also brings helpful practical benefits; Singh notes that reducing a patient's medication burden by one drop may save the practice four minutes per patient visit: "This would significantly improve practice efficiency."

That said, not all practices are aware of the potential benefits of MIGS – or that iStent is safe and effective enough to be potentially used as a first-line, standalone intervention. As

Ahmed says, "This new era raises a new challenge, which is to make new interventional approaches available to all glaucoma patients, not just those undergoing cataract surgery. And this will require us to reconsider optimal patient profiles and management. In short, it will need a different way of thinking!"



References

1. *infinite pivotal clinical trial*

Changed Minds, Changed Algorithm

Now that procedural intervention in early glaucoma is becoming more broadly accepted, how should the treatment algorithm change?

Historically, glaucoma management has relied on controlling IOP with topical medications until surgery can no longer be deferred. This situation is changing – early intervention with devices such as iStent technologies is increasingly seen as safe and effective in mild-to-moderate patients. John Berdahl provides an example: "At a symposium of 150 optometrists, we asked how they would want their own eyes treated after a diagnosis of early glaucoma; 95 percent chose procedural intervention, not drops!" Clearly, a paradigm shift is underway, implying the need to reconsider patient management and treatment algorithms – but how?

Such a change might also encourage surgeons to schedule standalone MIGS procedures rather than just prescribing another eye-drop.

Nate Radcliffe asserts that managing patient psychology will be important. "Rather than simply providing patients with options, we should be confidently recommending early intervention," he says. Berdahl agrees, and suggests ophthalmologists should do what is best for the patient, not necessarily what is easiest – and that may require changing old habits.

Which patients should qualify for early intervention? Ike Ahmed proposes that suitable patients include those on maximum tolerated medical therapy (MTMT) who need to reduce IOP but who are not bleb surgery candidates. "Other qualifying patients include individuals who are non-compliant, fluctuating, or progressing," he says.

Similarly, Mark Gallardo suggests that most MTMT patients with high IOP qualify for angle-based MIGS. Berdahl concurs and adds, "Patients deserve stand-alone procedures if they can't

afford, tolerate or administer eye-drops – or if their glaucoma is progressing despite medication." He adds that many cases meet those criteria, and notes that the safety of MIGS makes it suitable for first or second-line use. Similarly, Deborah Ristvedt believes iStent technologies are an attractive option for a range of patients.

Paul Singh outlines three categories of patients he deems suitable for early intervention. "First: patients whose IOP can be controlled with medication, but who find compliance difficult; here, the goal is to reduce medication burden. Second: mild-to-moderate patients with high IOP despite heavy medication. In these cases, MIGS procedures can reduce IOP while potentially avoiding the need for riskier, more invasive surgery such as trabeculectomy in the future," he says. "And third: medicated patients with IOP in the 20s and a target IOP in the low teens, who would not comply with additional eye-drops."

Gallardo concisely sums up: "In general, I'd offer iStent technologies to any mild-to-moderate patient and any high-IOP patient on MTMT."

"Medication is a failure not just when it fails to reduce IOP, but also when it fails to meet patient needs in terms of quality of life and budget." – Davinder Grover



“Procedural Pharmaceuticals like iDose[®]TR have great potential and will change the way we treat glaucoma.” – Davinder Grover

In this context, Ahmed wonders if it is time to redefine important terms, such as MTMT and refractory glaucoma. “Are three or four eye-drops really that much better than one or two? Should we be more open to trying surgical routes before loading the eye with yet more medication?”

Gallardo agrees. “If topically-medicated patients have hyperemia, ocular discomfort, or foreign body sensation, we can call them refractory,” he says. “Basically, if they won’t use their medication, they have refractory glaucoma.” Sahar Bedrood also concurs, and suggests that the ophthalmology

community should change its mindset and start recommending surgery after even only one or two drops, noting that it makes sense to intervene “while the TM tissue is actively pumping” to facilitate flow early in disease. Singh adds that the excellent MIGS safety record supports the rationale for relaxing the refractory glaucoma definition.

In conclusion, Ahmed shares a bold ambition: “We should upend the algorithm – apply interventional therapy in early disease, and prescribe medications later.” In any case, Ahmed says it is clear that the continued demonstration that early intervention gives better outcomes and quality of life will demand radical changes in the treatment algorithm. At this point in the ongoing paradigm shift, however, Ahmed believes we must start by offering stand-alone MIGS procedures to specific glaucoma patients – in particular, those whose IOP is not controlled by medication, but who do not need trabeculectomy or bleb surgery. If early intervention with MIGS can give these patients effective 24-hour IOP control with tolerable levels of medication, says Ahmed, it would be a success; “In brief, we must grasp the opportunity provided in early glaucoma to fundamentally alter the course of the disease – and the patient experience.”





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