SETTING THE STAGE FOR LOWERING IOP IN GLAUCOMA

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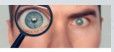
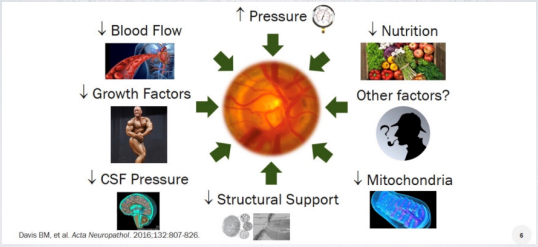
Polling Question



Which statement is true regarding the new treatment options available for glaucoma?

1. Vision loss is rare
2. Every patient can be controlled medically
3. MIGS controls everyone who is not controlled by meds
4. It's never been simpler to choose the right treatment for a patient
5. All of the above
6. None of the above

GLAUCOMA =MULTIFACTORIAL PATHOLOGY



Davis BM, et al. *Acta Neuropathol*. 2016;132:807-826.

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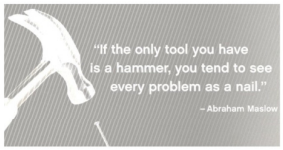
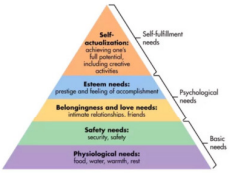
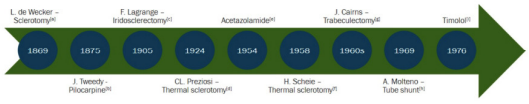
TREATMENT = IOP





Dohlman L, et al. *Int J Environ Res Public Health*. 2019;16.

Glaucoma Treatment: History



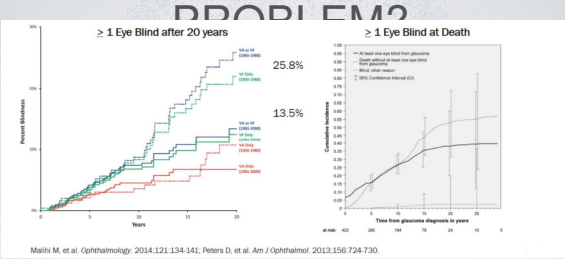
a. Laios K, et al. *Surgl Innov*. 2016;23:640-641; b. Packer M, et al. *Surv Ophthalmol*.1992;36:357-365; c. Lagrange H. *Br J Ophthalmol*. 1937;21:477-496; d. Preziosi CL. *Br J Ophthalmol*. 1924;8:414-417; e. Drance SM. *Br J Ophthalmol*. 1955;39:659-663; f. Scheie HG. *Am J Ophthalmol*. 1958;45:220-223; g. Cairns JE. *Am J Ophthalmol*. 1968;66:673-679; h. Molteno AC. *Br J Ophthalmol*. 1969;53:161-168; i. Katz IM, et al. *Invest Ophthalmol*. 1976;15:489-492.

1990 AND THE MEDS EXPLOSION

- 5-Fluorouracil
- Mitomycin C
- Apraclonidine
- Brimonidine
- Dorzolamide
- Brinzolamide
- Combination agents...
- Latanoprost
- 2001: Travoprost, bimatoprost

Crawley L, et al. *Ophthalmol Eye Dis*. 2012;4:43-64.

DID WE SOLVE THE PROBLEM?



Malihi M, et al. *Ophthalmology*. 2014;121:134-141; Peters D, et al. *Am J Ophthalmol*. 2013;156:724-730.

- 13.5 % for cases diagnosed 1981–2000 (blind by VA or VF)
- 25.8% for cases diagnosed 1965-1980

Necessity Is the Mother of Invention!

MEDS
- Latanoprostene bunod: new MOA!
- Netarsudil: new MOA!
- Netarsudil/latanoprost
- Tafluprost (preservative free)
- BAK-free latanoprost

MIGS
- Bypass trabecular meshwork
  - iStent®, Hydrus®, trabectome, GATT, KDB®
    - ABiC®, Omni® 360: viscocanalostomy +
  - Site of increased resistance to outflow
  - Intact system distal to TM prevents hypotony
- Divert fluid elsewhere
  - Suprachoroidal shunts: CyPass®, Supra®, STARflo®
  - Transscleral filtration: Xen®, PreserFlo®

Reduce fluid production
  - ECP
  - Micropulse CPC

HOW DO WE SOLVE THE PROBLEM?

- Medication options
- MIGS options
- Diverse patient concerns
  - Stage of disease
  - Ability to take meds
  - Expected longevity
  - Risk factors for bad outcomes
    - From glaucoma
    - From treatment
  - And so many others…

Polling Question

A patient you placed on latanoprost needs further IOP reduction. What is your usual next step?

1. Switch to a different prostaglandin analogue
2. Add single-agent aqueous suppression
3. Add fixed-combination aqueous suppression
4. Perform selective laser trabeculoplasty

TREATMENT

- Multiple pathways in treating glaucoma
- Helping patients go thru the most straightforward one
- Factors to consider:
  - Local and systemic side effects
  - Medication adherence
    - Complexity of drop regimen
  - SLT

LIGHT TRIAL

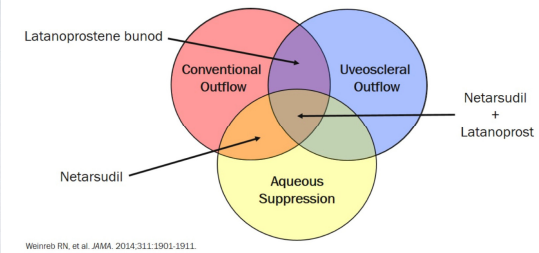
- SLT is a good first-line choice
- LiGHT trial
  - Newly diagnosed OHT or POAG randomly assigned to SLT (n = 356) or drops (n = 362)
  - 78.2% in the SLT group were drop free at 36 months
  - 95% were at target IOP at 36 months
  - No patients required trabeculectomy in SLT group

Control of disease		
Visits at target (cumulative)	91·3%	93·0%
Eyes at target IOP at 36 months	499 (93·1%)	509 (95·0%)
Mild OAG	261 (94·6%)	259 (96·3%)
Moderate OAG	69 (94·5%)	55 (96·5%)
Severe OAG	42 (85·7%)	44 (84·6%)
Treatment escalations§	348	399
Disease progression during the trial	36 (5·8%)	23 (3·8%)
From OHT to OAG¶	3	2
OAG progression	33	21
Algorithm defined VF progression	27	18
Algorithm defined optic disc progression	3	2
Algorithm defined VF and disc progression	3	1
Ocular surgeries during the trial		
Trabeculectomy	11	0
Trabeculectomy revision	7 (5 eyes)	0

PHARMACEUTICAL APPROACHES

- PGAs are first line class of choice
- 1/3 of Patients will require additional drops with in the first year
- Significant reduction in compliance with each additional medication
  - Increased complexity
  - More topical side effects
- Fixed combinations are increasingly utilized
  - More effective than a single agent
  - Simpler, less exposure to preservative

THE NEW KIDS ON THE BLOCK



Weinreb RN, et al. *JAMA*. 2014;311:1901-1911.

Treatment: Emerging Pharmaceutical Approaches

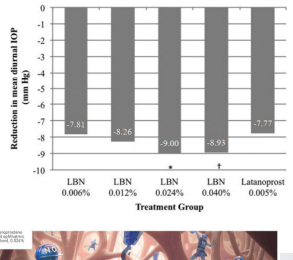
Latanoprostene bunod (LBN)

- Once-daily use
- Latanoprost acid and NO donating moiety
- Dual mechanism
  - Uveoscleral outflow and TM

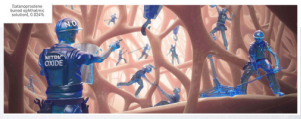
VOYAGER – phase 2

- LBN 0.006% (n = 82); LBN 0.012% (n = 85); LBN 0.024% (n = 83); LBN 0.040% (n = 81); latanoprost (n = 82)

LBN showed significantly greater reduction compared with latanoprost



*P = .005 versus latanoprost; † P = .009 versus latanoprost.
Weinreb RN, et al. *Br J Ophthalmol*. 2015;99:738-745.



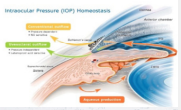
MECHANISM OF ACTION

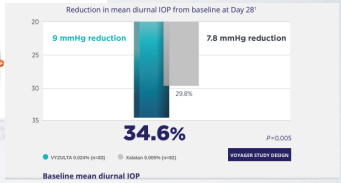
Nitric Oxide and Glaucoma

Patients with primary open-angle glaucoma (POAG) have lower levels of NO synthase activity in the trabecular meshwork (TM), Schlemm's canal, and ciliary muscle and reduced NO metabolites in the aqueous humor.[1,2]

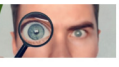
NO donors lower IOP in normal and POAG eyes.[3-5]

A major site of action for NO donors is the TM/Schlemm's canal.[4-6]





Treatment: Emerging Pharmaceutical Approaches (cont)



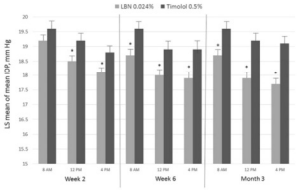
LUNAR – phase 3[a]

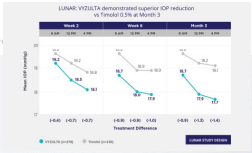
- LBN 0.024% (n = 259); timolol (n = 128)

APOLLO – phase 3[b]

- LBN 0.024% (n = 264); timolol (n = 123)

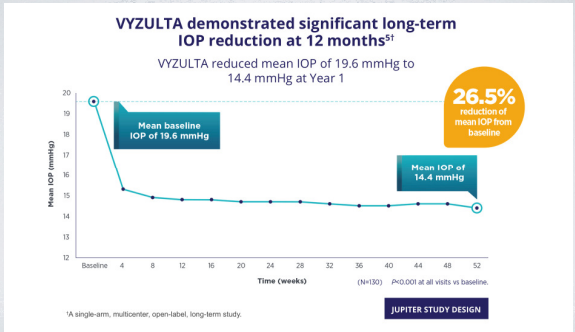
LBN noninferior to timolol at all time points





*P ≤ .002 versus timolol at the same assessment point.
a. Medeiros FA, et al. *Am J Ophthalmol*. 2016;168:250-259.
b. Weinreb RN, et al. *Ophthalmology*. 2016;123:965-973.

LBN: LONG TERM EFFECTS

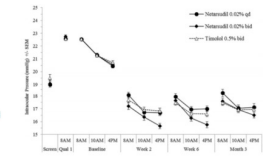


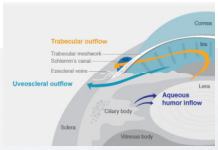
TRIPLE ACTION

Netarsudil 0.02%
- Once-daily use
- Triple mechanism
  - TM
  - Episcleral venous pressure
  - Aqueous production

ROCKET-1 and 2 – phase 3
- **ROCKET-1**: netarsudil (N = 202); timolol (N = 209)
- **ROCKET-2**: netarsudil once daily (N = 251); netarsudil twice daily (N = 254); timolol twice daily (N = 251)

Netarsudil noninferior to timolol



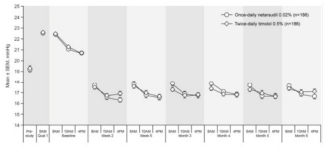


Serle JB, et al. *Am J Ophthalmol*. 2018;186:116-127.

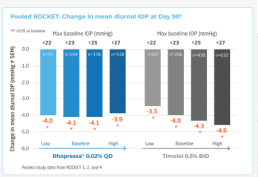
NETARSUDIL

ROCKET-4 – phase 3
- Netarsudil once daily (n = 351)
- Timolol twice daily (n = 357)

Netarsudil noninferior to timolol



Common side effects:
Hyperemia
Pinpoint SCH
Corneal verticillata

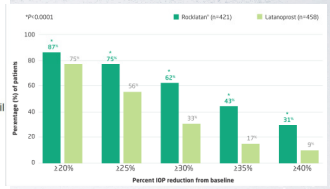


FIXED COMBO: NETARSUDIL + LATANOPROST

Netarsudil/latanoprost
- Once-daily use
- Quadruple mechanism
  - TM
  - Episcleral venous pressure
  - Aqueous production
  - Uveoscleral outflow

MERCURY - phase 3
- Netarsudil/latanoprost (n = 238); netarsudil (n = 244); latanoprost (n = 236)

Netarsudil/latanoprost superior to netarsudil and latanoprost across all time points



Asrani S, et al. *Am J Ophthalmol*. 2019;pii:S0002-9394(19)30284-3

Treatment: Emerging Pharmaceutical Approaches (cont)

- Common ocular side effects of these novel medications were mild and transient
- No systemic side effects
- Eye AEs occurring at 3 months of treatment:

	Netarsudil/ latanoprost[a]	Netarsudil[b]	LBN[b]
Conjunctival hyperemia	53.4%	41.0%	45.5%
Conjunctival hemorrhage	10.5%	13.9%	–
Eye pruritis/ irritation	7.6%	7.0%	4.6%
Corneal verticillata	5.0%	4.1%	–

a. Asrani S, et al. *Am J Ophthalmol*. 2019;pii:S0002-9394(19)30284-3.
b. Weinreb RN, et al. *J Glaucoma*. 2018;27:7-15.

Conclusion

- Presurgical treatment strategy for glaucoma is constantly evolving
- There is a shift toward eye drop minimalism
  - SLT as first-line therapy (LiGHT trial)
  - Increasing use of fixed-combination medications
- Novel medications
  - Focus on the conventional outflow pathway
  - Focus on multiple mechanisms
- It is still unclear how the novel medicines fit into the treatment scheme

Age-Related Changes in Trabecular Meshwork Imaging

Mark E. Gold,[1] Seema Kansara,[1] Kundandeep S. Nagi,[1,2] Nicholas P. Bell,[1,3] Lauren S. Blieden,[1,3] Alice Z. Chuang,[1] Laura A. Baker,[3] Kimberly A. Mankiewicz,[1] and **Robert M. Feldman**[1,3]

- Thickening of elastic fibers
- Decrease in aqueous drainage thru the pores
- Increase in intra cellular matrix, causing increase resistance to outflow
- Are we picking the wrong patients for these meds?

CHANGING PRACTICE PATTERNS

- Being a drop minimalist by choosing wisely
- Dual or multiple mech of action
- Moving away from palliative treatment—Timolol=decreasing aqueous production
- Moving toward improving aqueous outflow
- Treating where the disease is, but may need to use the meds earlier

USING MIGS: ANOTHER PIECE OF THE PUZZLE

MIGS and Beyond

Canal surgeries

- Indwelling devices
  - iStent®
  - iStent Inject®
  - Hydrus®
- Incisional/ablative/canal dilation
  - Canaloplasty (iTrack®, Omni®)
  - Segmental goniotomy
    - Trabectome
    - KDB®
    - Omni®
  - GATT

Beyond the canal

Supraciliary – On hold

- Transscleral
  - Xen®/PreserFlo®
  - Trabeculectomy
  - ExPress®
  - Baerveldt®
  - Ahmed ClearPath®
- CPC

WHO GETS WHAT?

Obvious

- Lens status: phakic vs pseudophakic? cataract? refractive status?
- Age, general health, disease severity, disease velocity, risk of progression
- Meds: compliance, tolerability, ability to administer, surface disease

Nuanced

- Coagulation status
- Axial length
- Conjunctiva – thin, scarred
- Steroid – perioperative, chronic

WHY DO I APPROACH GLAUCOMA SURGERY THE WAY I DO?

- Guiding principles:
  - Risk of glaucoma surgery should not exceed the disease risk
  - Individualize for each patient
  - The canal is dynamic and pulsation, not hollow and static
  - Retain normal physiology and anatomy when feasible
  - Respect HYPOTONY as much as HIGH IOPS
  - Iatrogenic vision loss keeps me awake at night

Two Broad Classes of Incisional Glaucoma Surgery

Phakic and/or lower risk	Pseudophakic and/or higher risk
Surgery to augment physiological outflow	Surgery to bypass physiological outflow
Canal surgery	~~Supraciliary~~ Transscleral

SAFETY ——— EFFICACY

Glaucoma Surgery
Before, During, and After Cataract Surgery

Emerging paradigm:

Medicines and laser until surgical cataract, then surgery for both phaco + canal / transscleral when disease warrants

Why Canal Surgery for Management of Cataract and Glaucoma?

Must first understand what happens to IOP following phaco

Cataract surgery lowers IOP at least modestly for most patients with mild to moderate glaucoma and elevated IOP

What is the level 1 evidence?

Clinical Trials

Randomized Evaluation of the Trabecular Micro-Bypass Stent with Phacoemulsification in Patients with Glaucoma and Cataract

1 US PMA Trial – iStent® *OPHTHALMOLOGY 2011*

A Randomized Trial of a Schlemm's Canal Microstent with Phacoemulsification for Reducing Intraocular Pressure in Open-Angle Glaucoma

2 European Hydrus® Trial *OPHTHALMOLOGY 2015*

Two-Year COMPASS Trial Results: Supraciliary Microstenting with Phacoemulsification in Patients with Open-Angle Glaucoma and Cataracts

3 US PMA Trial – CyPass® *OPHTHALMOLOGY 2016*

A Schlemm Canal Microstent for Intraocular Pressure Reduction in Primary Open-Angle Glaucoma and Cataract
The HORIZON Study

4 US PMA Trial – Hydrus® *OPHTHALMOLOGY 2019*

Prospective, Randomized, Controlled Pivotal Trial of an *Ab Interno* Implanted Trabecular Micro-Bypass in Primary Open-Angle Glaucoma and Cataract
Two-Year Results

5 US PMA Trial – iStent Inject® *OPHTHALMOLOGY 2019*

5 Prospective Randomized MIGS Trials

Phaco alone vs Phaco + MIGS
- iStent® – Gen 1: iStent® trial
- Hydrus® trial (Europe)
- CyPass ® -- "COMPASS" trial
- Hydrus® -- "Horizon" trial
- iStent Inject®

- In all 5 trials, the control arm (phaco alone) significantly lowered IOP
  - Foundation for phaco + canal MIGS strategy
- *Proposed axioms…*
  - Perform safe adjunct procedure
  - Retain the elegance of phaco visual outcomes
  - Retain normal anatomy and physiology and don't compete with the favorable phaco effect on IOP
  - For example, if phaco improves canalicular outflow don't divert fluid elsewhere (exceptions exist!)

The Growing Portfolio of Canal Surgeries

Indwelling Devices – approved only for use at the time of cataract surgery
- iStent®
- iStent Inject®
- Hydrus®

Less tissue disruptive, more stealth

Incisional/Ablative/Canal Dilation – covered as standalone procedures
- GATT
- Canaloplasty (iTrack®, Omni®)
- Segmental goniotomy
  - Trabectome
  - KDB ®
  - OMNI®

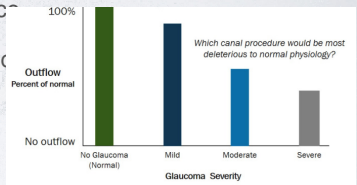
More tissue disruptive, no device retained

We must consider the possibility that over time some of our canal procedures could reduce outflow…

Due to scarring, tissue reaction, or disruption of normal physiological dynamic function

EVOLVING STRATEGY

- Try to pick a procedure synergistic with phaco
- Something to enhanc physiologic outflow
- Try the canal first— especially in mild to moderate disease



Schlemm Canal Microstent for IOP Reduction

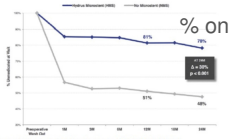
Ophthalmology 2019

A Schlemm Canal Microstent for Intraocular Pressure Reduction in Primary Open-Angle Glaucoma and Cataract

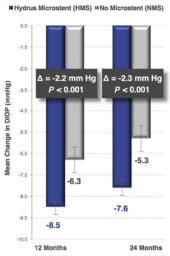
The HORIZON Study

Thomas W. Samuelson, MD,[1] Daniel F. Chang, MD,[2] Robert Marquis, MD, PhD,[3] Brian Flowers, MD,[3] K. Shawn Lim, MRCSE, MD,[4] Iqbal Ike K. Ahmed, MD,[5] Henry D. Jampel, MD, MPH,[6] Tin Aung, MD, PhD,[7] Alan S. Crandall, MD,[8] Kuldev Singh, MD, MPH,[9] *for the* HORIZON Investigators*

Objective: To compare cataract surgery with implantation of a Schlemm canal microstent with cataract surgery alone for the reduction of intraocular pressure (IOP) and medication use after 24 months.

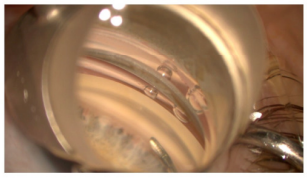


% on NO meds



Samuelson TW, et al. *Ophthalmology*. 2019;126:29-37.

Microstent



Trimodal Mechanism of Action

Camras LJ, et al. *Invest Ophthalmol Vis Sci*. 2012;53:6115-6121.

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HYDRUS IMPLANTATION

ucoma AHMED

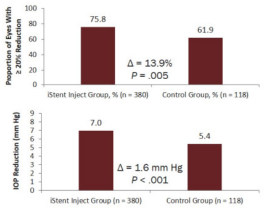
Trabecular Micro-Bypass

Ophthalmology 2019

Prospective, Randomized, Controlled Pivotal Trial of an *Ab Interno* Implanted Trabecular Micro-Bypass in Primary Open-Angle Glaucoma and Cataract

Two-Year Results

Thomas W. Samuelson, MD,[1] Steven R. Sarkisian, Jr., MD,[2] David M. Lubeck, MD,[3] Michael C. Stiles, MD,[4] Ti-Eng Duh, PhD,[5] Erke A. Boss, DSc,[6] Jane Ellen Giamporcaro, MD,[7] Dana M. Forenbak, MD, MPH,[8] L. Jay Katz, MD,[9] *for the* iStent inject Study Group*



Samuelson TW, et al. *Ophthalmology*. 2019;126:811-821.

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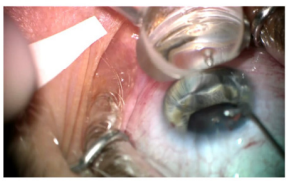
Incisional Canal Surgery

- KDB®, iTrack®, Omni®, trabectome, GATT
- When more aggressive approach is desired
- Considerably more tissue disruptive
- While outflow may improve, normal anatomy and physiology is disrupted
- More dramatic effect
  - In terms of IOP
  - In terms of potential side effects
  - Role of viscodilation unclear



Grover DS, et al. *J Glaucoma*. 2018;27:393-401.

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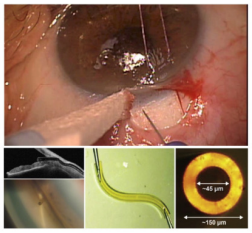
VERY CAUTIOUS WITH SEVERE DISEASE

- Sometimes, we need to be more aggressive
- Generally we start with canal surgery,
- But use all the tools when necessary:
  - Canal—>supracilliary—>transscleral(XEN, TRAB, TUBE)—>Cilioablative

Transscleral Filtration

- Greater risk, greater reward
  - Lower IOP
  - Less medication
  - Steroid tolerant
  - May be beneficial in patients with DES



Grover DS, et al. *Am J Ophthalmol*. 2017;183:25-36.

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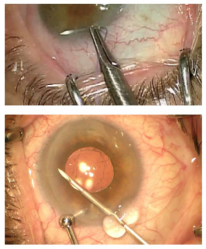
Transscleral Gel Stent

- Transscleral gel stent vs traditional filtration surgery
  - Standardized
  - Greater intraoperative efficiency
  - Less postoperative care/ manipulation (exception needling)
  - Less risk of profound hypotony
  - Trabeculectomy is titratable, gel stent is not



Grover DS, et al. *Am J Ophthalmol*. 2017;183:25-36.

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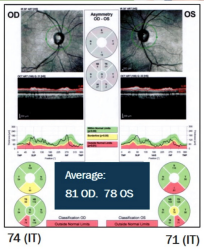
CASE STUDIES

Case 1

- 68-year-old woman presents for glaucoma evaluation
- She was told by her primary ophthalmologist that her glaucoma has worsened over the past several years
- Current glaucoma medications
  - Latanoprost once daily OU
  - Fixed combination timolol/brimonidine twice daily OU
- Mother with glaucoma
  - Patient states that she watched her mother's glaucoma get worse once they started with surgery
- SLT OU 2011

Case 1: Examination

- VA: 20/30 OU
- Rx: -4.00 OD, -4.50 OS
- CCT: 520 µm OU
- IOP: 18 mm Hg OD, 21 mm Hg OS
- Gonioscopy: Grade 4 OU
- 2+ NS with XFM on anterior lens capsule



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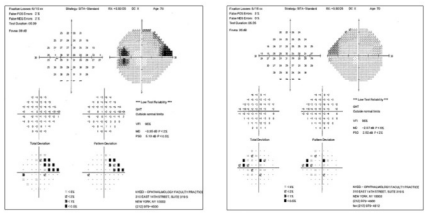
Case 1: VF From 3 Years Prior: Normal



Polling Question

What would you do?

1. Add another topical medication
2. Repeat SLT
3. Standalone MIGS
4. Phaco/trabecular bypass/ablation
5. Phaco/GATT
6. Phaco/subconjunctival MIGS

Case 1: Treatment

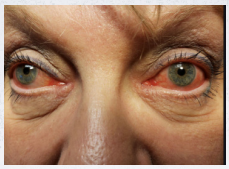
Medications
- Effects of adding a fourth drop
  - CAI, Rho-kinase inhibitor
- Switch to different combination agent
- Compliance
- Cost

SLT
- Does it work as well later in the game?
- When do you repeat?
- What do you tell your patient about chances of success?

MIGS
- Standalone vs combination with phaco
- Canal-based vs subconjunctival MIGS
- Better results for patients with XFG?

CASE 1: FIRST CHANGE

- Tried Rhopressa with moderate success, IOPS down to 13/15
- But...



NOW WHAT?

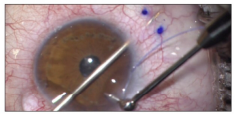
- She's not ready for CE IOL, despite having 2 + NSC
- Still uncomfortable about having surgery given mom's experience

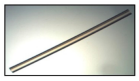
Case 1: MIGS

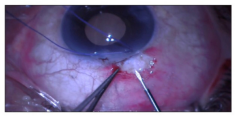
Procedure	Device	Approved in the United States	Standalone
Schlemm canal	iStent®/iStent Inject®	Yes	No
	Hydrus®	Yes	No
	Trabectome	Yes	Yes
	KDB®	Yes	Yes
	iTrack® (for GATT and ABiC®)	Yes	Yes
	Omni®/VISCO360®	Yes	Yes
Suprachoroidal	iStent SUPRA®	No	N/A
Subconjunctival	Xen® Gel Stent	Yes	Yes
	PreserFlo®/MicroShunt®	No	N/A

Case 1: XEN Gel Stent

- Made of porcine gelatin
- 6mm in length with a 45 µm luminal diameter
- Material and design mitigate traditional implant issues



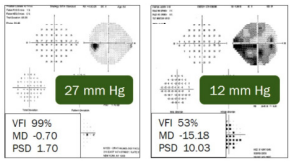




Results to date:
XEN in ou
Better IOP in OD but still requires drops in OD, OS mid teens no drops

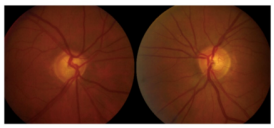
Case 2

- 76-year-old man presents with POAG referred for elevated IOP OS
- On 2 medications OS (latanoprost and dorzolamide)
- ALT OU "many" years prior
- S/p trabeculectomy OD 2014
- S/p GDI OD 2016
- Paternal grandmother (blindness)
- Lawyer who travels **A LOT**



Case 2 (cont)

• VA:	20/25	20/30
• IOP:	12 mm Hg	27 mm Hg
• CCT:	507 µm	502 µm
• Lens:	PCIOL	2+ NS



Polling Question

What should I do?

1. Add another topical medication
2. SLT (Does it matter that he had prior ALT?)
3. Standalone MIGS
4. Phaco/trabecular bypass/ablation/GATT
5. Phaco/subconjunctival MIGS
6. Phaco/traditional glaucoma surgery

*History of COPD
What about intracameral medications when they become available?

PROMISE IN SIGHT

- Shameless plug asking for your future