Glaucoma Update

Dr. James Thimons, Founding Partner, Medical Director

Ophthalmic Consultants of Connecticut

Disclosures

- Speaker
  - Alcon
  - Allergan
  - PRN
  - Tear Lab
  - Shire
  - Zeiss
  - B&L
  - Diopsys
  - Reichart
  - Glaukos
  - InFocus
  - Aerie


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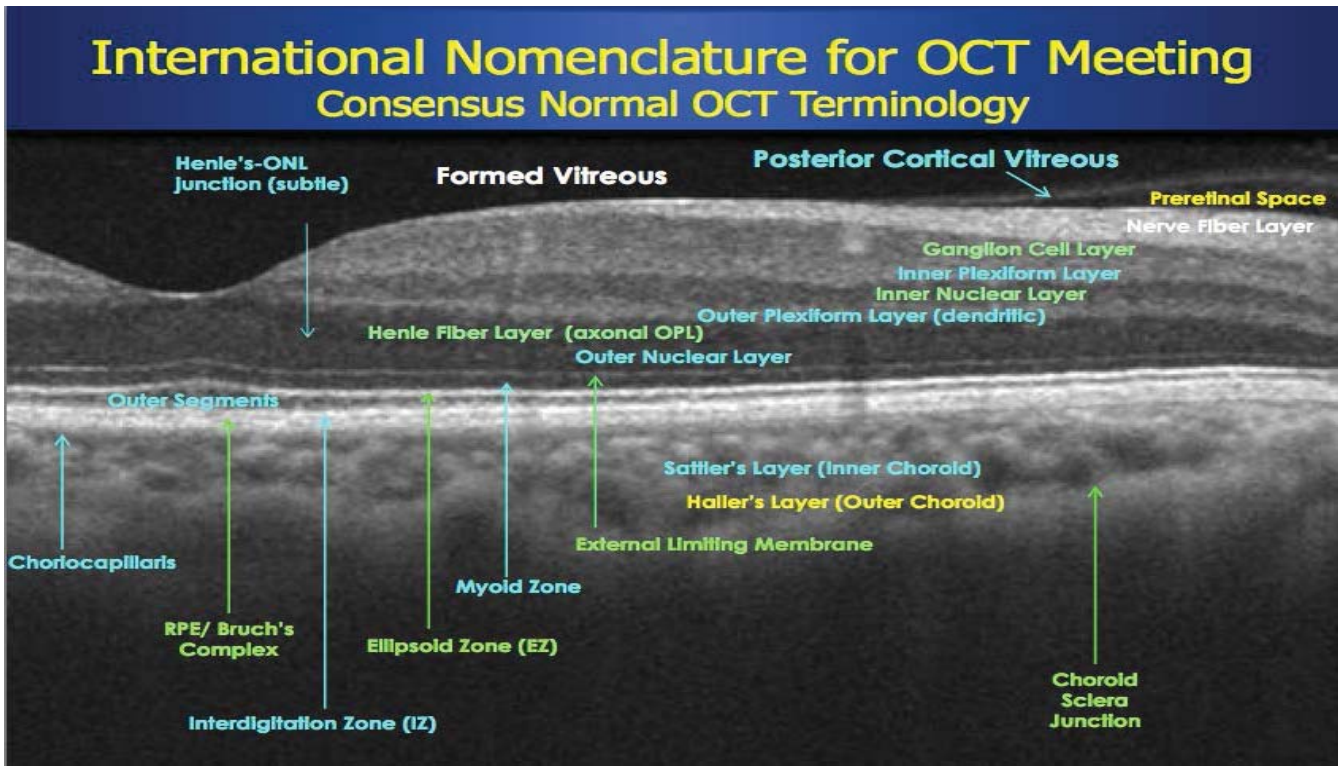
Welcome to Connecticut

The Glaucoma Explosion

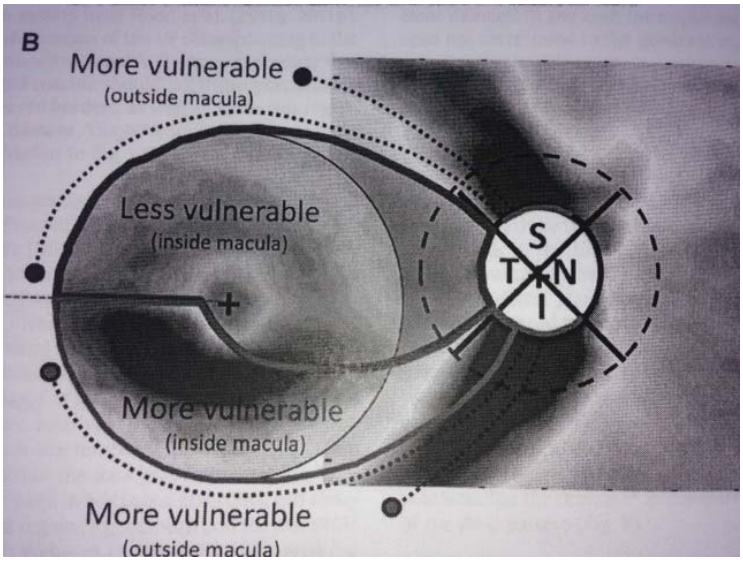
- New Technologies for the Primary Care Clinician
- Finally, New Weapons for Medical Management!
- The Next Generation of Therapeutics
- MIGS: The Evolving Science of Surgery In Glaucoma

Advances in OCT Technology: Automated Intelligence for the ECP

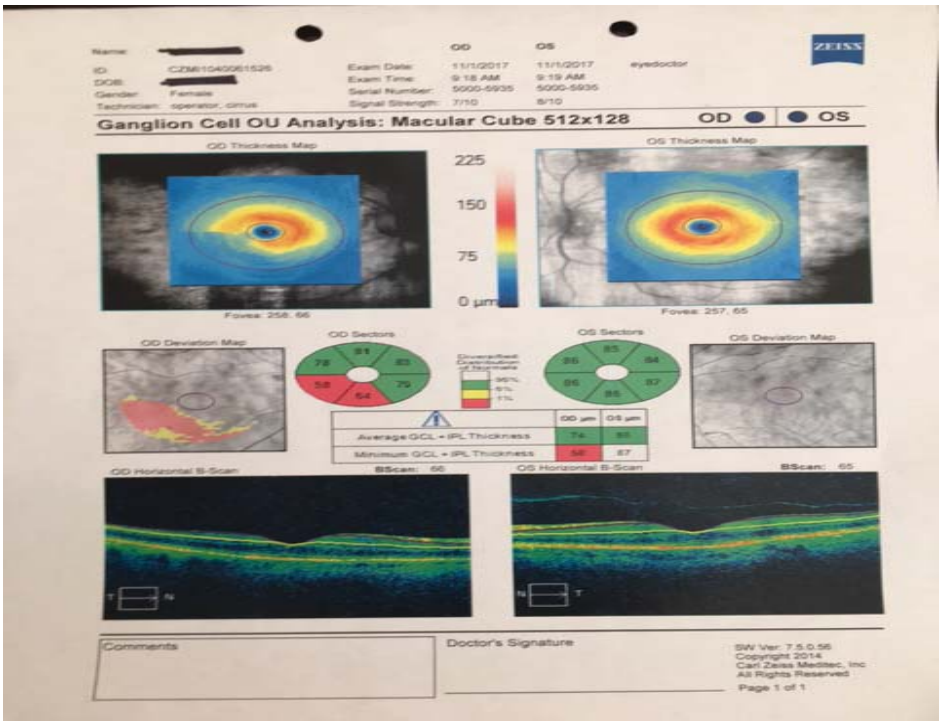
- Ganglion Cell Analysis: A New Horizon in Primary Care
- HD SD/OCT Anterior Segment
- OCT Angiography in Glaucoma



Ganglion Cell Anatomy



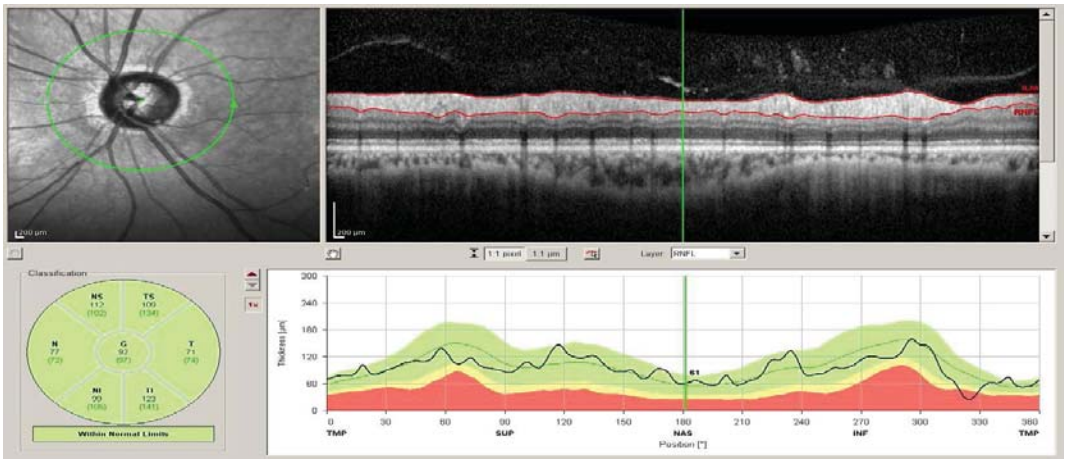
“Wiper” Defect

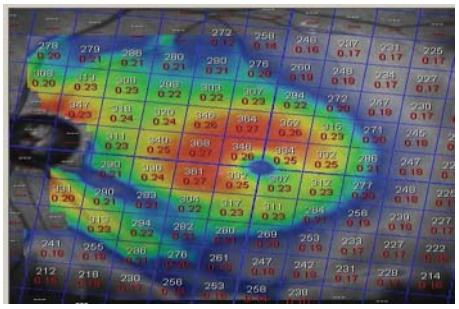


Ganglion Cell Anatomy

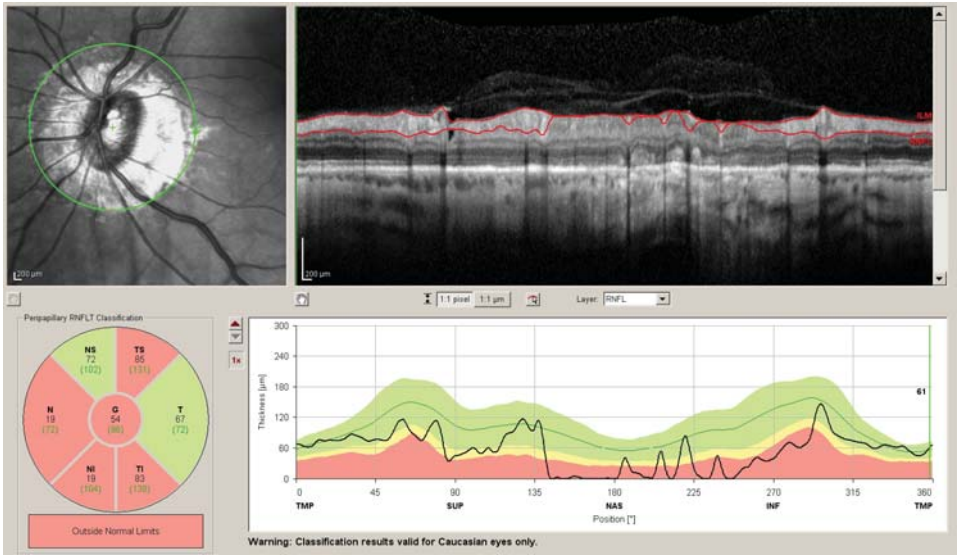
- Analysis of VF in RGC loss in Glaucoma
  - 24-2 protocol has 6 degrees separation allowing for thinning the RGC to be missed to due point placement
    - Drazdo t al: Vision Research 2007
  - 10-2 testing substantially improves correlation with RGC analysis
    - Hood and Raza; Vis Science 2011
  - Stamper(1984) identified the relationship between NTG and macular damage with typically near fixation visual field loss.
  - Heijl & Lundqvist 1984
    - 45 patients followed from normal to abnormal VF’s using test points at 5,10,15 & 20 degrees from fixation
    - Largest number at 15 degrees but a surprising number at 5 degrees confirming Hood’s work showing that early damage occurs in the macula as well as more traditional arcuate zones

“Green Disease”



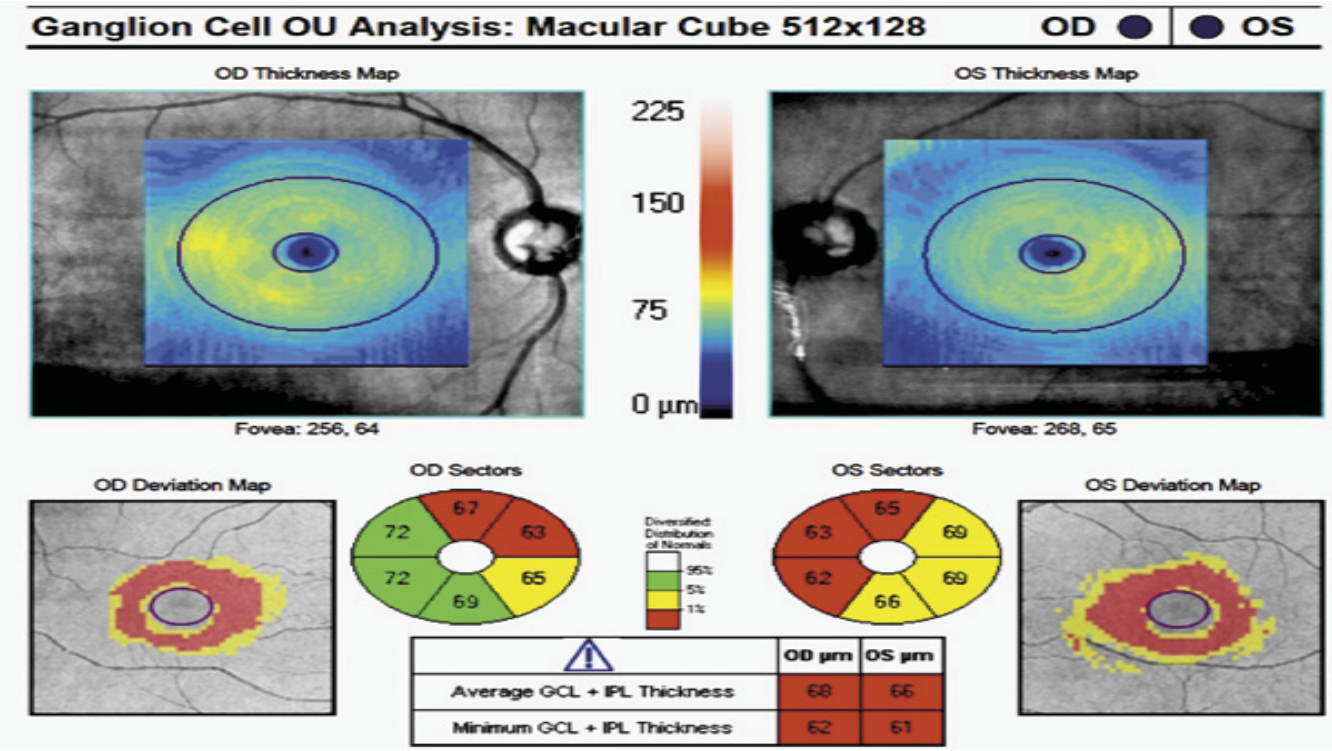


Myopia = “Red Disease”



Optical Coherence Tomography as a Biomarker for Diagnosis, Progression, and Prognosis of Neurodegenerative Diseases
Satue, etal AJO 2016

- Recent research using the latest SD OCT imaging technology has demonstrated that an early damage of the anterior visual pathway occurs in MS, PD, and AD and that the ganglion cell layer is the ultimate biomarker for disease diagnosis, severity, and progression.
- Thus, OCT technology should be used as a common and very useful clinical complement in the diagnosis and control of neurodegenerative disorders.
- 85 Citations



American Journal of Ophthalmology
December 2017

Baseline Fourier-Domain Optical Coherence Tomography Structural Risk Factors for Visual Field Progression in the Advanced Imaging for Glaucoma Study

David Huang, MD etal

AIG/ 2016

- A total of 277 eyes of 188 participants were followed up for 3.7 ± 2.1 years.
- VF progression was observed in 83 eyes (30%).
- Several baseline NFL and GCC parameters, but not disc parameters, were found to be significant predictors of progression on univariate Cox regression analysis.
- The most accurate single predictors were the GCC focal loss volume (FLV), followed closely by NFL-FLV. An abnormal GCC-FLV at baseline increased risk of progression by a hazard ratio of 3.1

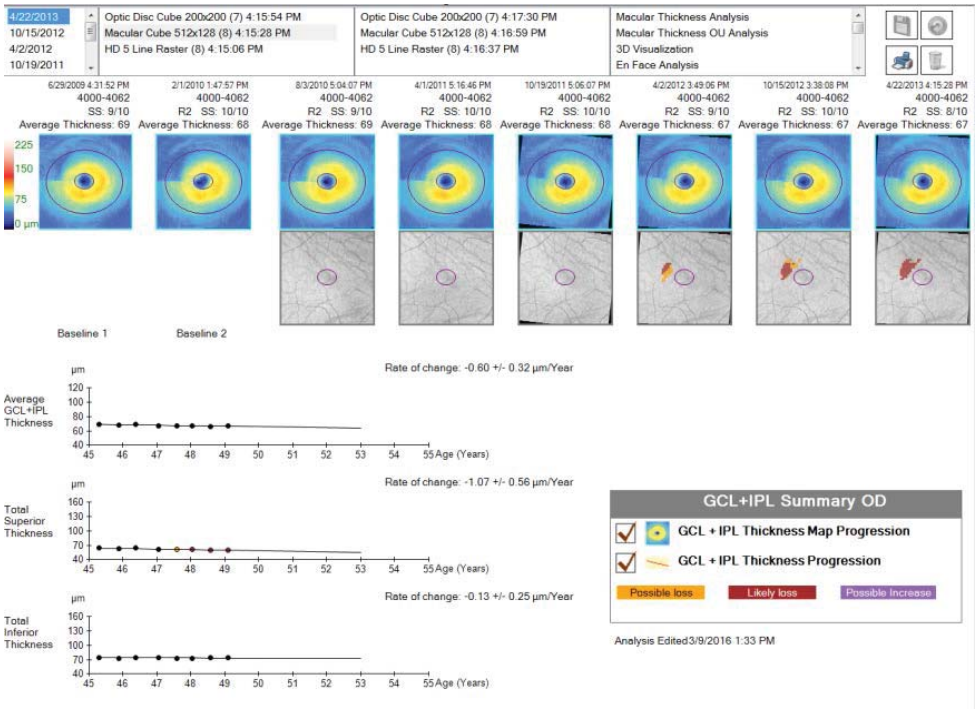
New Perspectives on Disease Management

- SD-OCT is superior in identifying progression in glaucoma suspects, pre-perimetric glaucoma, mild glaucoma and early moderate disease compared with SAP are superior in identifying progression, after an initial VF to set baseline.
- Average time to identification of statistically significant progression is 2-3 years with SD-OCT and up 6 years with SAP
- Intra-test variability is up to 10x less with OCT(3%) than VF(20%)

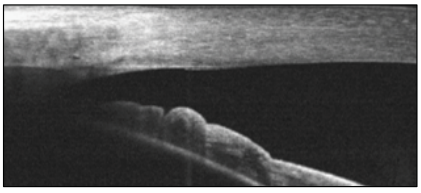
New Perspectives on Disease Management

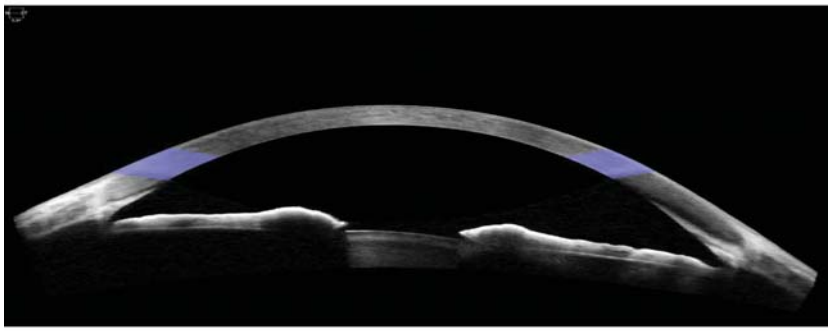
- RNFL “Floor” limits usefulness in late moderate to advanced glaucoma (50-60 microns)
- GCC progression analysis can continue to be useful in late moderate to advanced glaucoma due to density of fibers in the macula and the later involvement of central vision in the disease

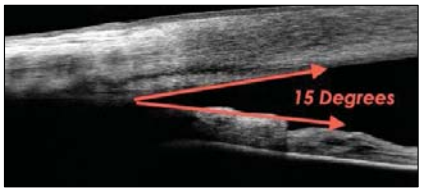
GCC Progression Analysis

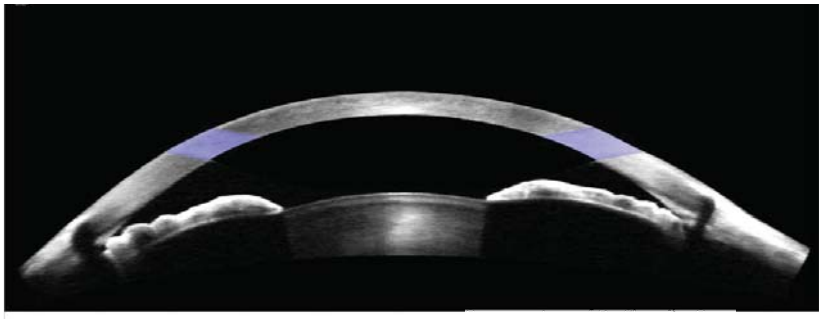


Normal/Shallow Chamber

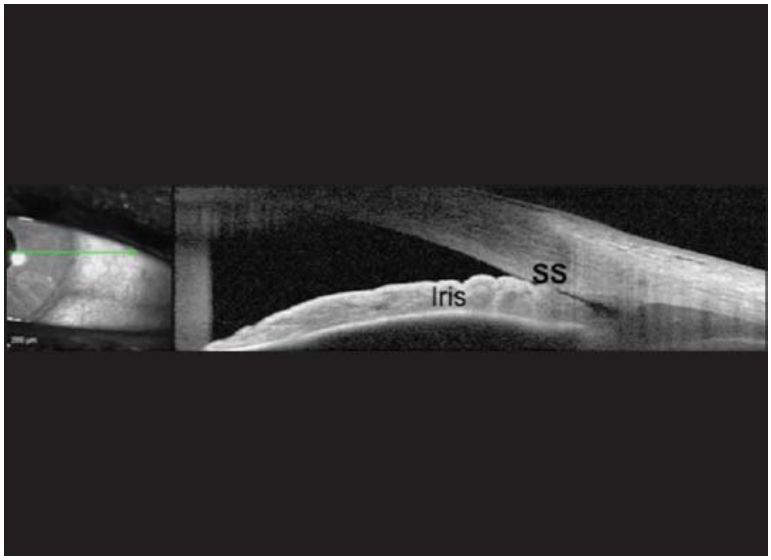




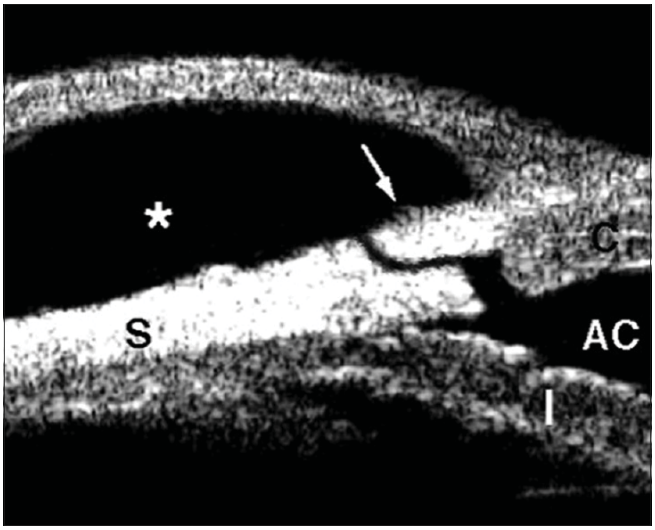


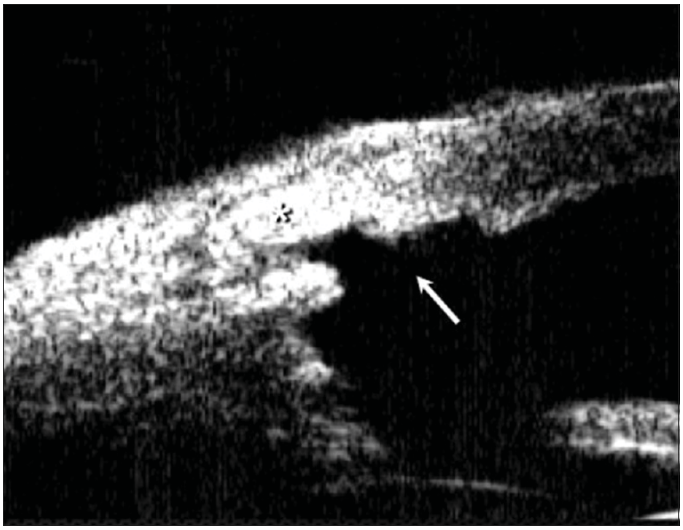


Primary Angle Closure

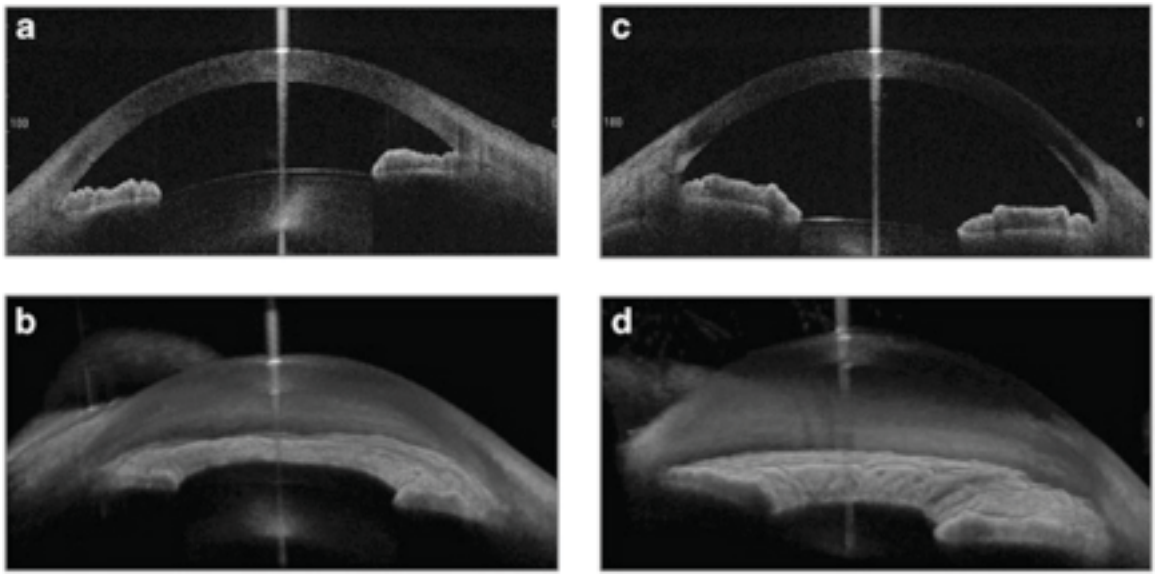


Bleb Morphology

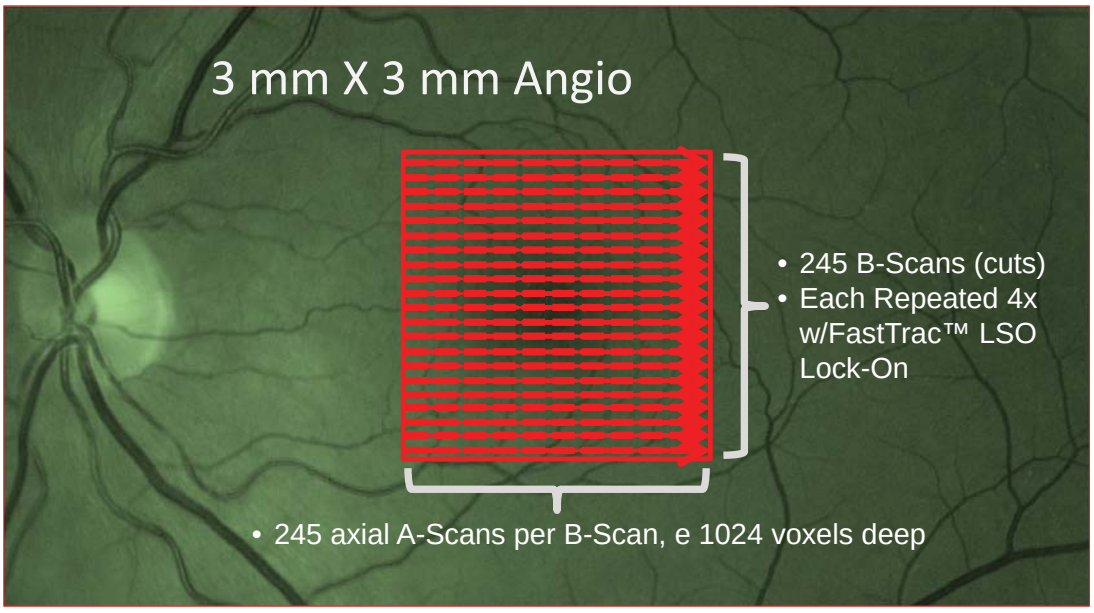




Casia Swept Source AS-OCT (Tomey)

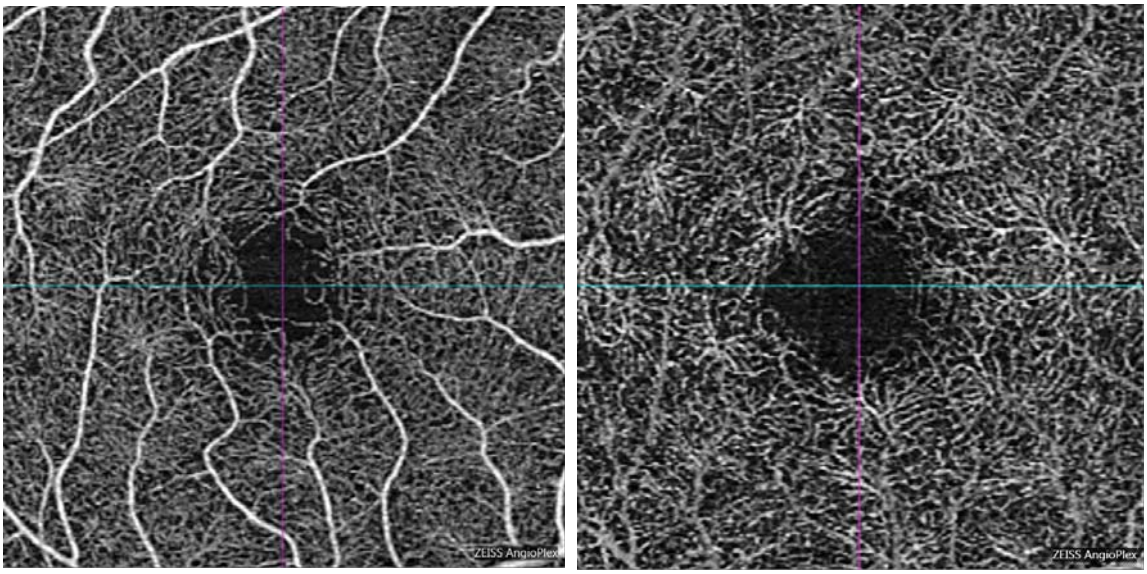


Zeiss AngioPlex™ = One Fast Cubic Scan x4

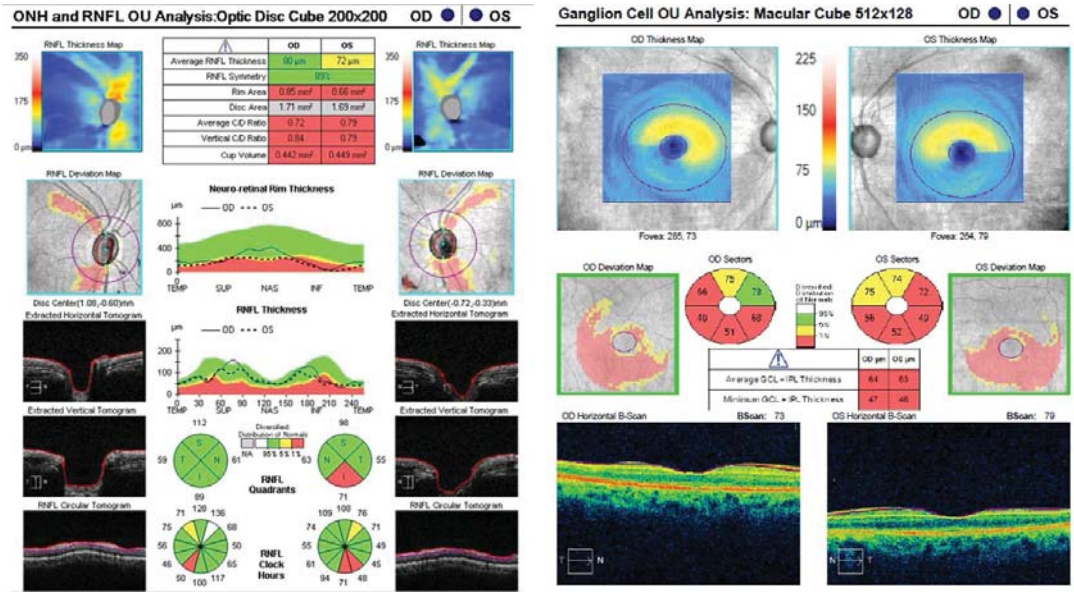


Total = **240,000 A-scans,** ~ 5.0 secs

Normal 3x3 Angio Cube OD - Full Retina (L) and Deep Plexus (R)

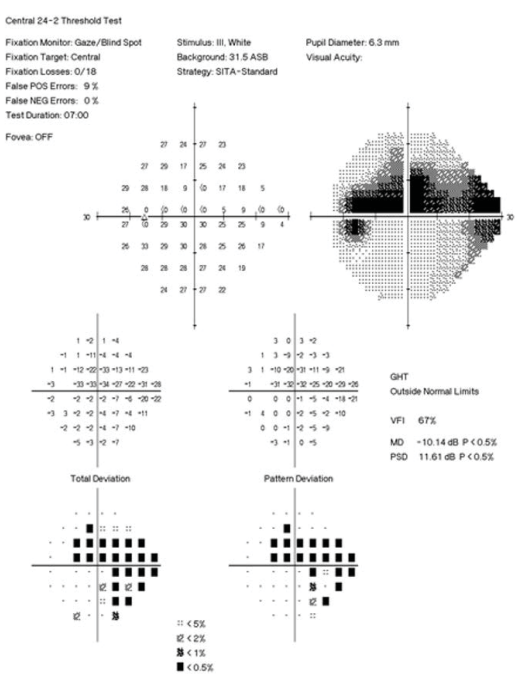


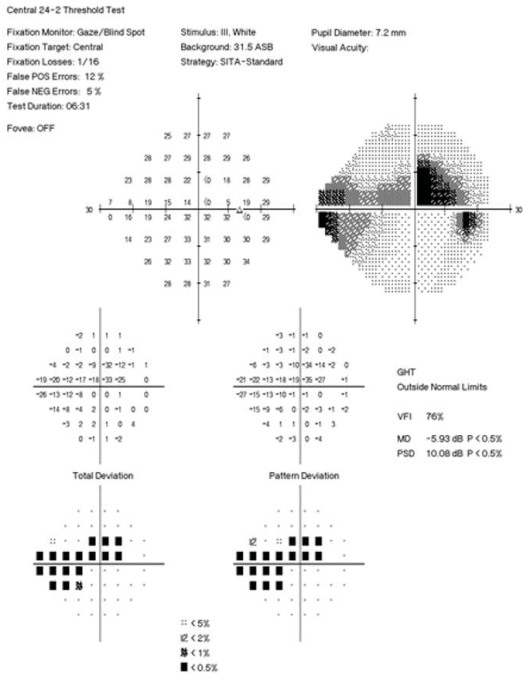
Glaucoma



This case courtesy of **Carolyn Majcher, OD**. Incarnate Word, San Antonio

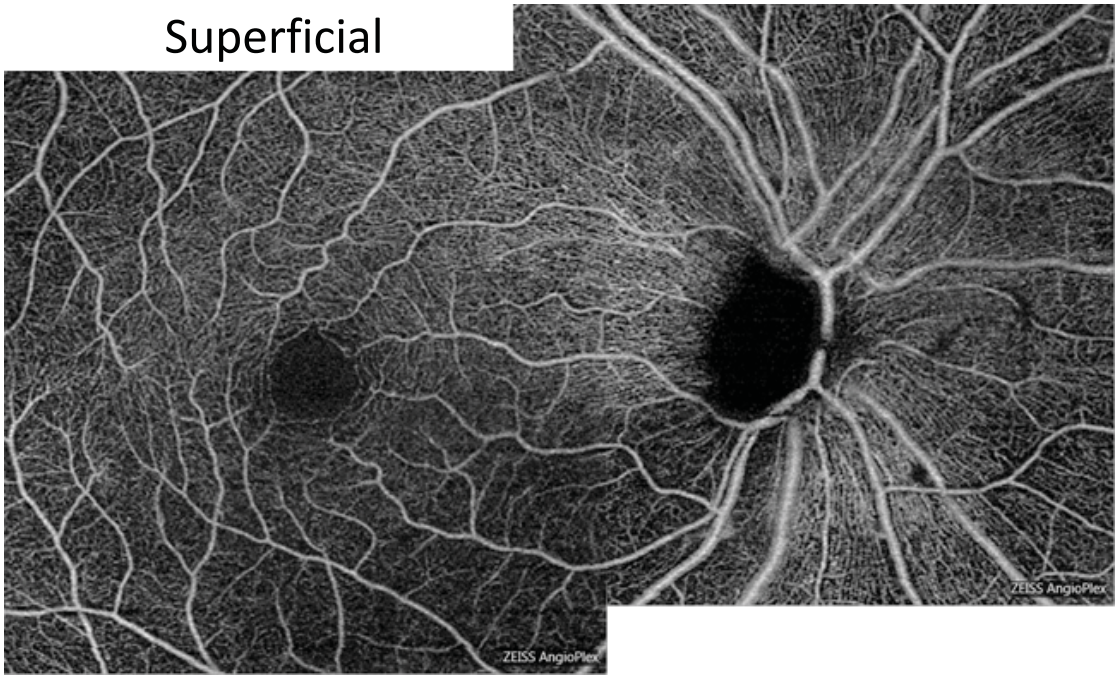
Glaucoma



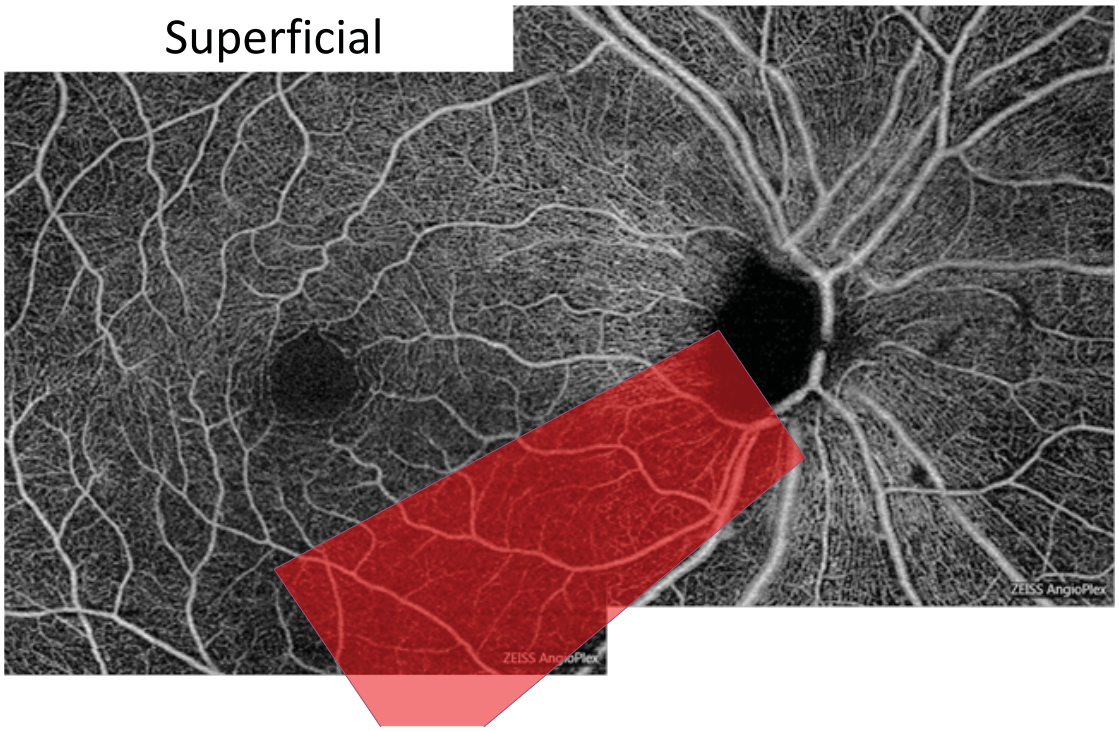


Glaucoma

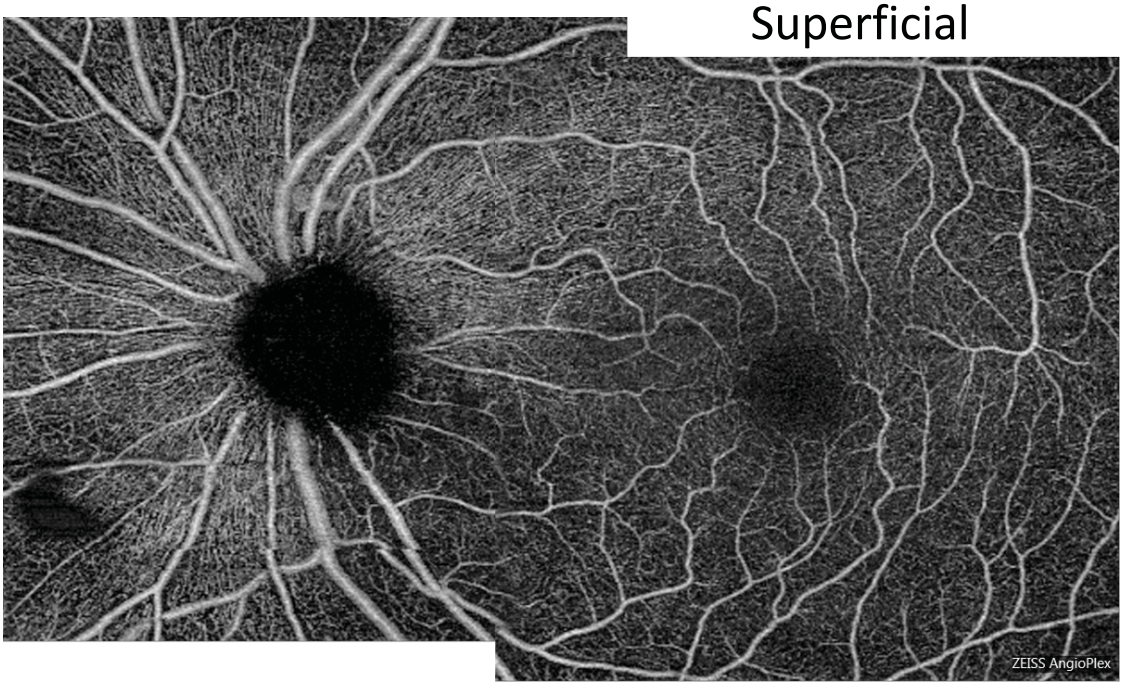
Superficial



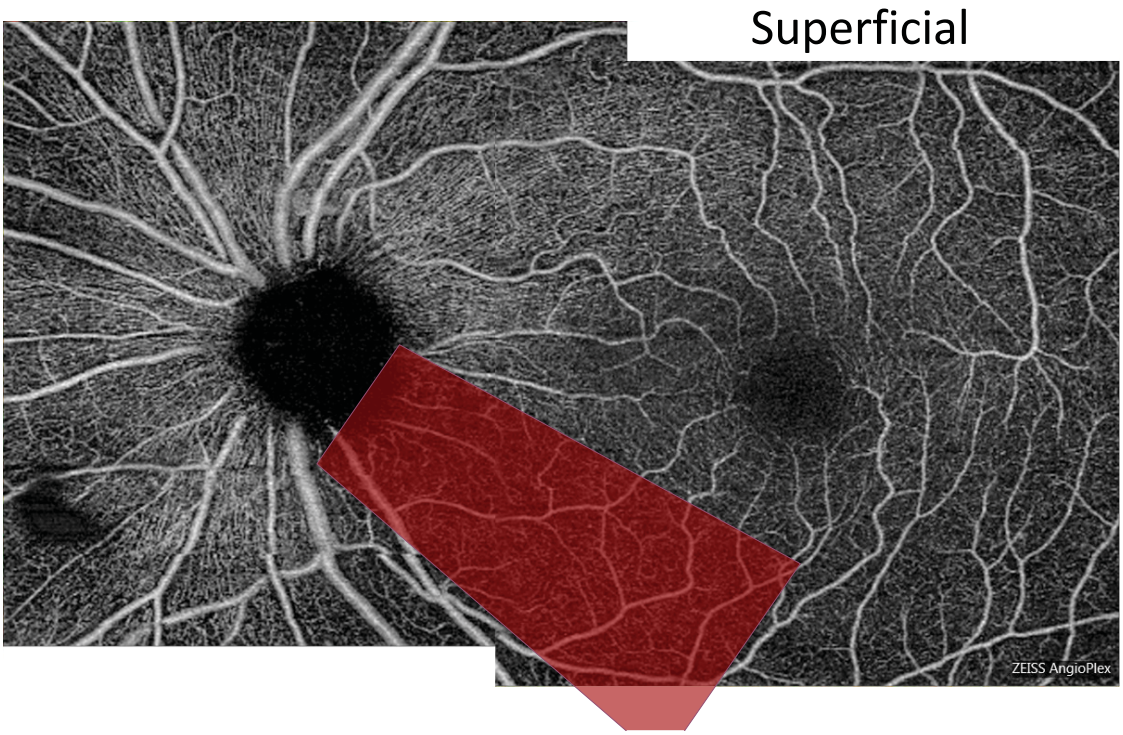
Glaucoma



Glaucoma



Glaucoma

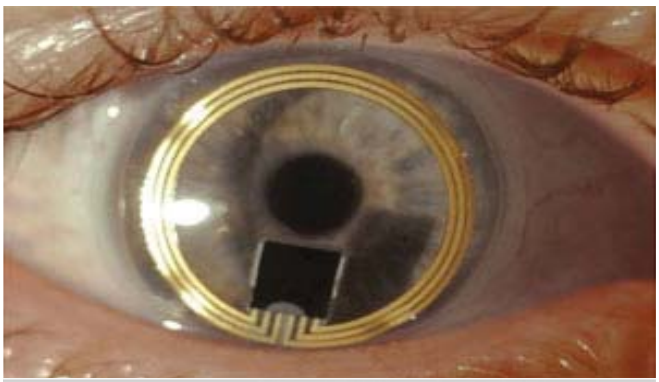


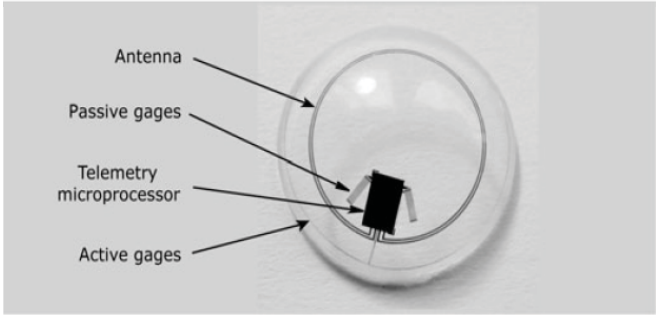
Telemetrics: The Future of Medicine

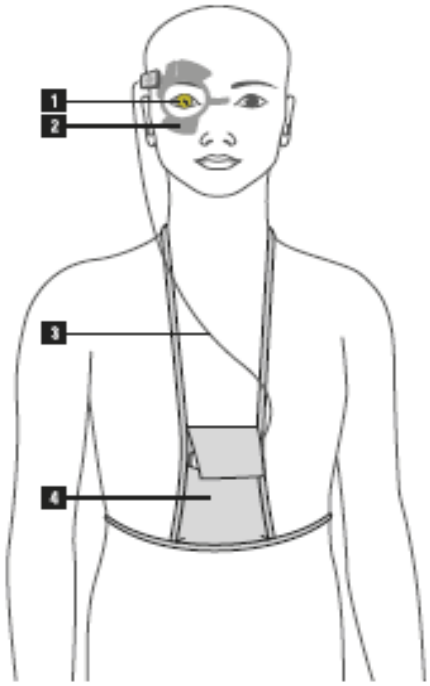
Triggerfish:Tracking the Elusive Diurnal!

- Sensimed: Swiss medical device company. Jean Marc Wismer CEO
- Tracks fluid pressure in the eye and beams data to palm size recorder.
- Uses a circular antenna taped around the eye and connected to a battery powered portable recorder.
- This transmits radio frequency energy to an utlra thin gold ring in the CL. This powers a chip embedded in the lens.
- Additionally on the lens in an ultra thin platinum ring that stretches in response in variation in eye shape secondary to pressure.
- Available in Europe. Primary trial at University Hospitals of Geneva

"Triggerfish"





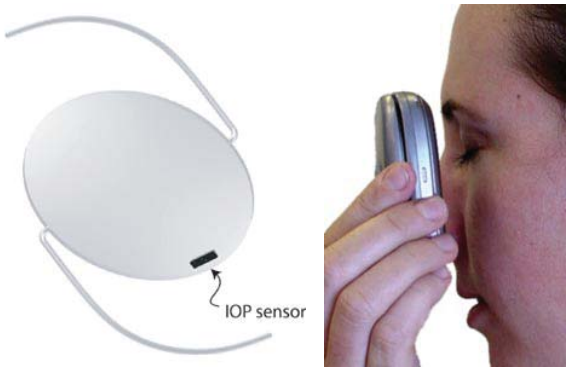


TriggerFish

- Based on assumption that IOP and corneal curvature radius are related
- Meausurements are taken every 5 minutes for 30 sec seconds
- Results are presented as an arbitrary unit not mmHg

Launch Point Technologies

IOL Tonometry

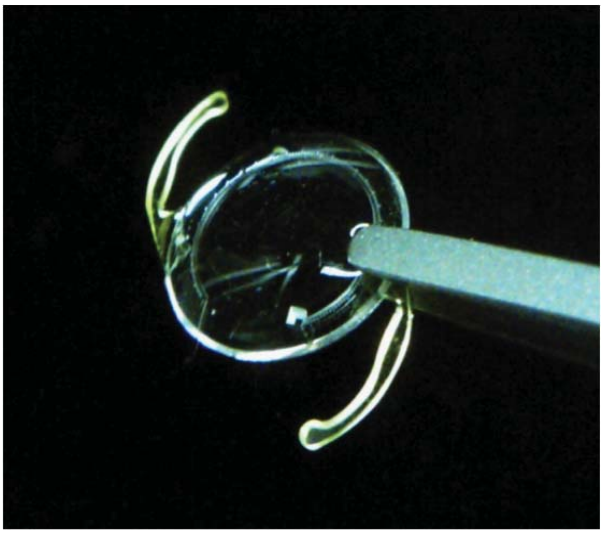


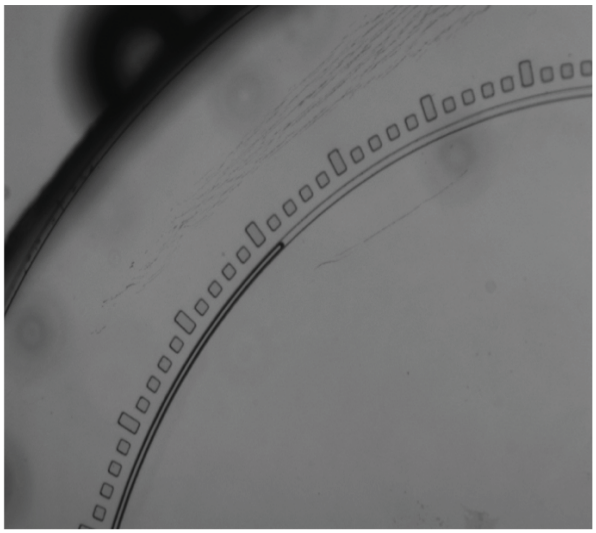
http://www.launchpnt.com/portfolio/biomedical/intraocular-pressure-sensor

There's an App for That

- Nature Medicine 2014
  - Yossi Mandel, Bar-Ilan/ Stephen Quake, Stanford
  - Utilizes a variable float tube in the IOL
  - Smart Phone app allows acquisition of data
  - In development

There's an App for That

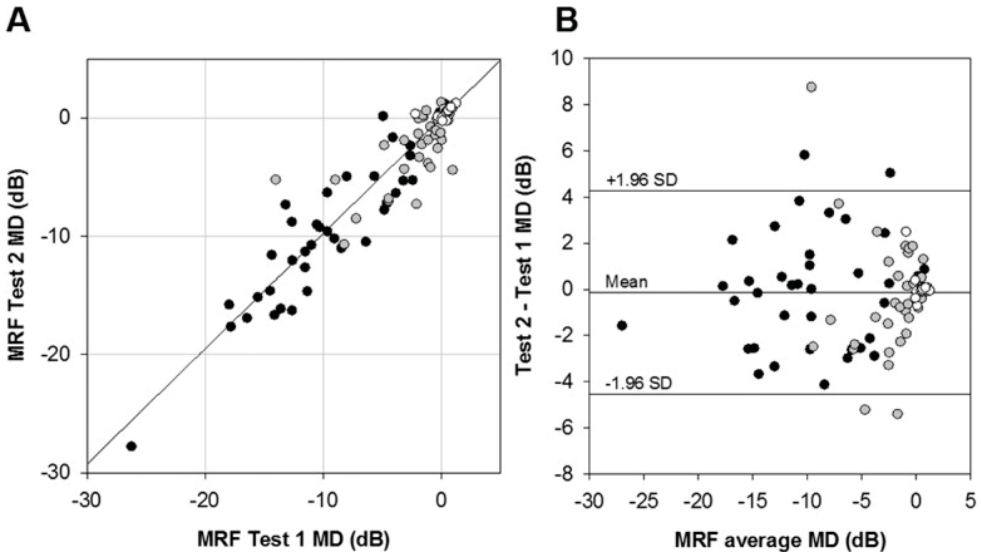




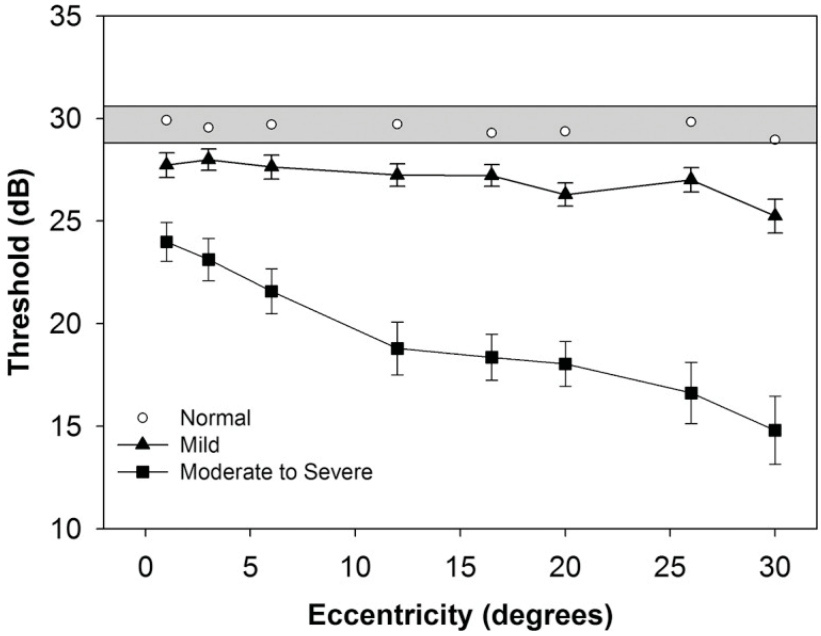
A Comparison of Perimetric Results from a Tablet Perimeter and Humphrey Field Analyzer in Glaucoma Patients

- Y. Kong, M. He, J Crowston, A Vingrys
- Transl Vis Sci Technol. 2016 Nov; 5(6):2
- University of Melbourne College of Optometry

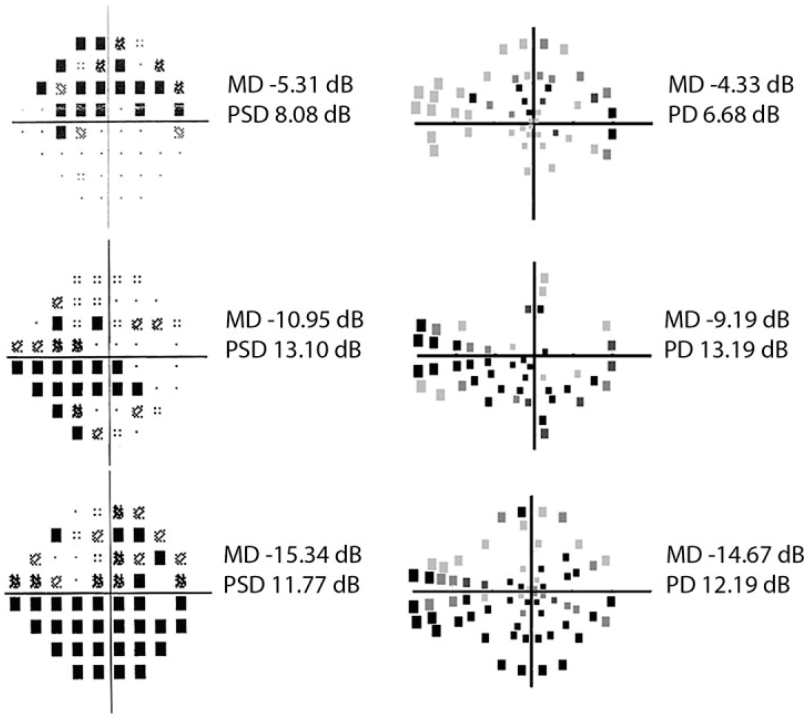
Melbourne Rapid Fields



MRF


35
30
25
20
15
10
Threshold (dB)
0
5
10
15
20
25
30
Eccentricity (degrees)
Normal
Mild
Moderate to Severe

MRF


MD -5.31 dB
PSD 8.08 dB
MD -4.33 dB
PD 6.68 dB
MD -10.95 dB
PSD 13.10 dB
MD -9.19 dB
PD 13.19 dB
MD -15.34 dB
PSD 11.77 dB
MD -14.67 dB
PD 12.19 dB

Dr. Goldmann Move Over !

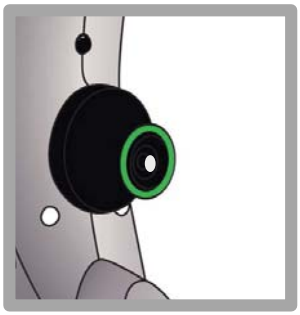
Icare HOME tonometer

- IOP, date, time, eye recognition (right/left) and measurement quality are all stored in the internal memory.
- Data is transferred to a PC for further analysis by the prescribing physician.
- New features: positioning light, automatic eye recognition system, series or single measurements, new user interface panel.

EasyPos: Positioning Light

Red and green light signals help patients correctly position the tonometer.

Correct alignment



Incorrect alignment

Incorrect alignment

EyeSmart: Automatic Eye Recognition

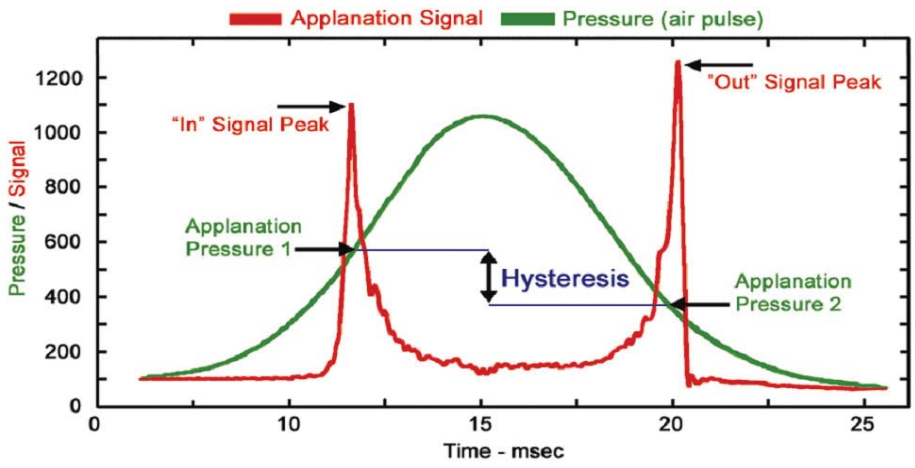
The tonometer includes an automatic eye recognition system that identifies which eye is being measured.

- Two infrared LED transmitters below probe (1)
- One infrared LED sensor above probe (2)
- The infrared light is reflected from nose back to the sensor
- The sensor knows from which transmitter the reflected infrared light came from and thus which eye, right or left, was measured
- The resulting eye indication is stored into the memory of the tonometer

CORNEAL HYSTERESIS: The Newest Disruptive Technology In Glaucoma

- **2002: Clinical research with ORA commences**
- **2005: The 1st generation ORA was made commercially available**
- **2012: Generation II ORA was launched**
- **3rd Generation "ORA G3" introduced September 2015**

  Measures:
  - Corneal Hysteresis (CH)
  - Goldmann-correlated IOP (IOP_g)
  - Corneal compensated IOP (IOP_{CC})



CH: Average Values in Normal Subjects

CH Values in Normals around the world	N	CH*
Brazil[1]	105	10.1 ± 1.8
UK[2]	272 pairs	10.2 ± 1.2
China[3]	125	10.9 ± 1.5
Japan[4]	204	10.2 ± 1.3
Spain[5]	88	10.8 ± 1.5
USA[6]	44	10.5 ± 1.2

*CH units are mmHg

1. Fontes BM J Refract Surg. 2008 Nov;24(9):941-5.
2. Carbonaro. The Heritability of Corneal Hysteresis and Ocular Pulse Amplitude A Twin Study doi:10.1016/j.ophtha.2008.02.011
3. Lam A. Et Al. Optom Vis Sci. 2007 Sep;84(9):909-14
4. Kamiya Et Al. J Refract Surg. 2009 Oct;25(10):888-93
5. Ortiz Et Al. J Cataract

Clinical Evidence – Study 1
Corneal Hysteresis found to be associated with progression

- The first observational study to investigate the relationship of Corneal Hysteresis to a variety of other parameters in a glaucoma population

- 230 POAG or suspected POAG patients were included in the study
  - POAG was defined by a reliable visual field that was abnormal according to OHTS criteria, with an optic nerve image, photo, or CDR thought to be consistent with the field damage by a fellowship-trained glaucoma specialist.
  - GAT, ORA, CCT and Axial Length measurements (IOL master) were recorded
  - Among persons with three or more reliable fields over three or more years, or with five reliable fields in less than three years, progression was defined as having achieved the OHTS standard of “conversion” (if previously normal), or (if previously damaged as evidenced by an abnormal GHT or PSD) having worsened by 1 dB or greater per year in either MD or PSD.
  - A stepwise model was not used nor were any hypotheses about interactions made.

POAG Primary Open Angle Glaucoma; GAT Goldmann Applanation Tonometry; IOP intraocular pressure; ence limit.
CCT Central Corneal Thickness; CH Corneal Hysteresis
Congdon NG et al. *Am J Ophthalmol.* 2006;141:868-875.

Clinical Evidence – Study 1

Corneal Hysteresis found to be associated with progression

	OR	LCL	UCL	*P*-value
Age per year <65	1.12	1.01	1.24	.03
Age per year >65	1.08	1.01	1.15	.02
GAT IOP per mmHg	1.22	0.95	1.58	.12
Treatment	1847.6	3.16	10^6	.02
IOP by treatment interaction	0.79	0.61	1.03	.08
CCT per 100 microns	1.65	0.66	0.98	.30
Years with glaucoma	1.00	0.96	1.04	.98
Baseline IOP	0.99	0.93	1.06	.79
CH per mmHg	0.81	0.66	0.98	**.03**

Conclusions: Corneal Hysteresis was the parameter most associated with progressive field worsening

GAT Goldmann Applanation Tonometry; IOP intraocular pressure; OR odds ratio; LCL lower confidence limit; UCL upper confidence limit.

CCT Central Corneal Thickness

Congdon NG et al. *Am J Ophthalmol*

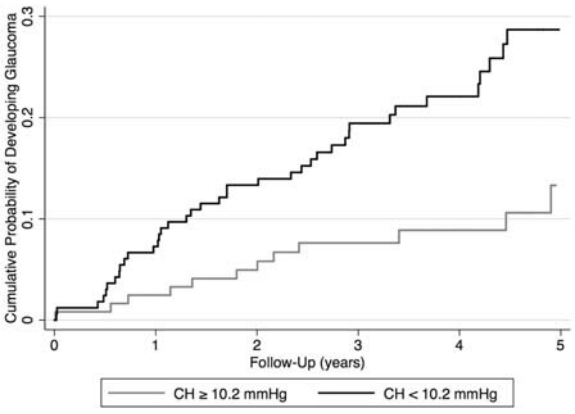
Corneal Hysteresis in Glaucoma

Predictive of conversion to Glaucoma in pre-perimetric Glaucoma Suspects

Purpose: To investigate the role of CH as a risk factor for **development** of glaucoma in a prospective longitudinal study.

Results: Fifty four (19%) of the 287 eyes developed repeatable visual field defects during a 4 year follow-up.

CH was *independently* predictive of conversion to glaucoma even when adjusted for age, IOP, and CCT.

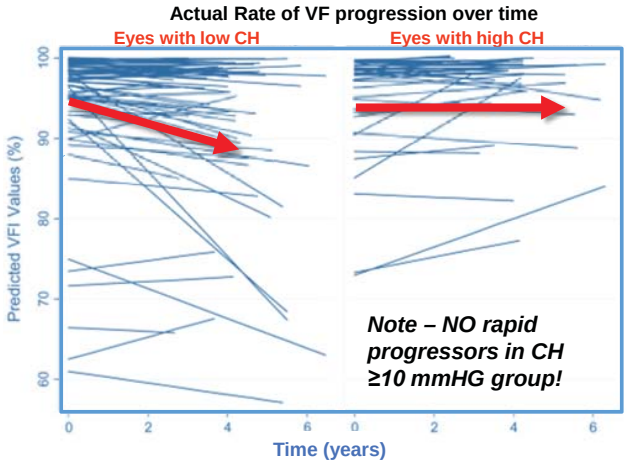


Each 1mmHg lower CH was associated with an increase of 21% in the risk of developing glaucoma during follow up

A Prospective Longitudinal Study to Investigate Corneal Hysteresis as a Risk Factor for Predicting Development of Glaucoma
AJOPHT 10365 – in press
Author Block: Feilin Zhu , Alberto DinizFilho, Linda M. Zangwill , Felipe A. Medeiros

Corneal Hysteresis in Glaucoma

Predictive of Progression in Prospective, Longitudinal Study (DIGS)



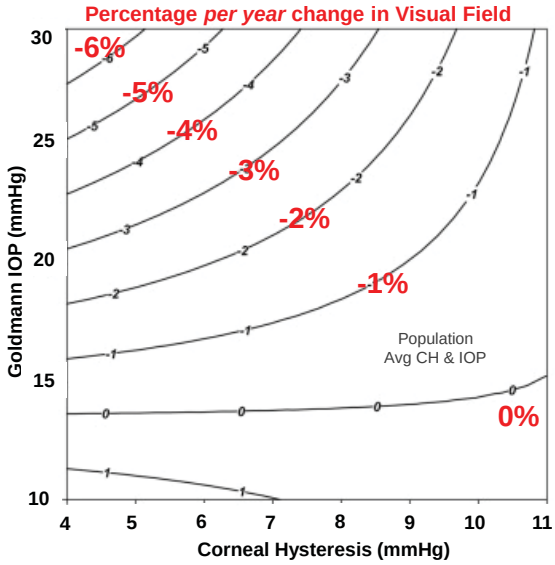
- Each 1 mmHg lower CH was associated with a 0.25% per year **increase** in rate of Visual Field loss
  - 2X more predictive of VF loss than GAT IOP (IOP associated w 0.11% per year loss)
- CH was more than **3X more associated** with rate of VF loss than CCT (explained 17.4% vs 5.2%)

"The prospective longitudinal design of this study supports the role of CH as an important factor to be considered in the assessment of risk for glaucoma progression"

Medeiros FA et al. *Ophthalmology.* 2013;120:1533-1540.

Corneal Hysteresis in Glaucoma

Predictive of Progression in Prospective, Longitudinal Study (DIGS)



"The Effect of IOP on rates of progression was dependent upon Corneal Hysteresis"

- For eyes with lower CH, the impact of IOP on VF loss was significantly greater
- **IOP of 30** is not so bad with a CH of 11.
- **IOP of 20** is very bad with a CH of 6

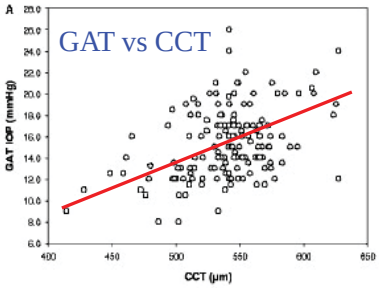
Medeiros FA et al. *Ophthalmology.* 2013;120:1533-1540.

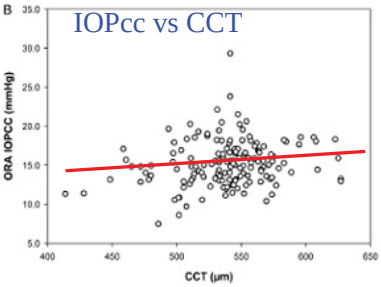
IOPcc – a superior indicator of IOP

Not correlated with CCT

TABLE 1. Clinical Characteristics of the 153 Eyes Included in the Study

Parameter	Mean ± Standard Deviation	Range
CCT (μm)	538 ± 35	414-627
Corneal curvature (mm)	7.74 ± 0.33	7.00-9.04
Axial length (mm)	23.82 ± 1.08	20.92-26.70
GAT IOP (mm Hg)	15.3 ± 3.3	8.0-26.0
ORA IOPCC (mm Hg)	15.2 ± 3.0	7.4-29.3
CRF (mm Hg)	9.47 ± 1.75	4.68-14.15





IOPcc provides an estimate of IOP that agrees with GAT on average but is less influenced by corneal properties

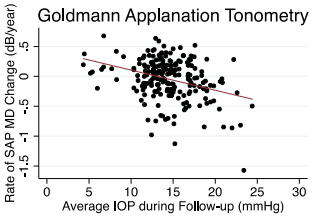
Evaluation of the Influence of Corneal Biomechanical Properties on Intraocular Pressure Measurements Using the Ocular Response Analyzer.
Felipe A. Medeiros, MD and Robert N. Weinreb, MD
J Glaucoma 2006;15:364–370.

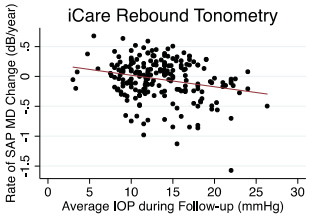
IOPcc – a superior indicator of IOP

More associated with actual glaucoma progression

Association between IOP by 3 different Tonometers and rates of Glaucoma Visual Field Progression over time

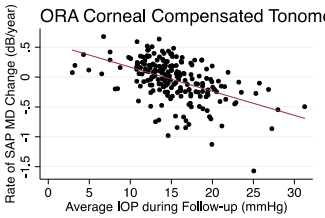
GAT R^2= 12.8%





iCare R^2= 6.5%

IOPcc had the strongest association with visual field loss vs GAT & iCare



IOPcc R^2= 27.4%

Case: What would you do?

The Non-compliant Patient

- 66 yo, African American Female w 15yr history various practices
- Pre Tx highest IOP**: 39 OD 35 OS**
- Poor compliance. Intermittently using meds.
- IOP 1-month after recent attempt at Tx: 20 OD / 19 OS
- 1 month later discontinued meds (burning): IOP **25 OD / 28 OS**
- CCT: 589 OD 612 OS microns
- V Cup to Disc Ratio: 0.67 OD / 0.57 OS
- Patient States IOP “always been high” doesn’t want meds

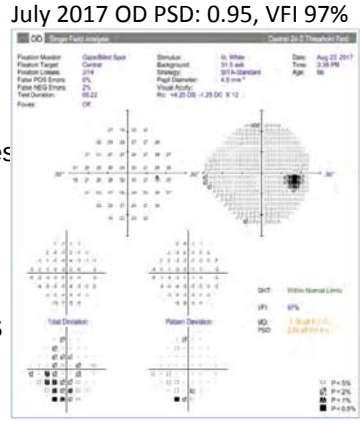
ORA Measurements

- CH = 12.7 mmHg
- IOP cc = 23.5 mmHg

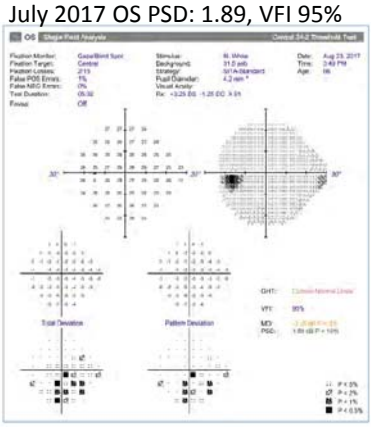
- HIGH CH indicates low risk of visual field loss
- In agreement with 15+ years of actual findings.
- Decision made to monitor patient without meds

Courtesy of: Michael Chaglasian, OD

July 2017 OD PSD: 0.95, VFI 97%



July 2017 OS PSD: 1.89, VFI 95%



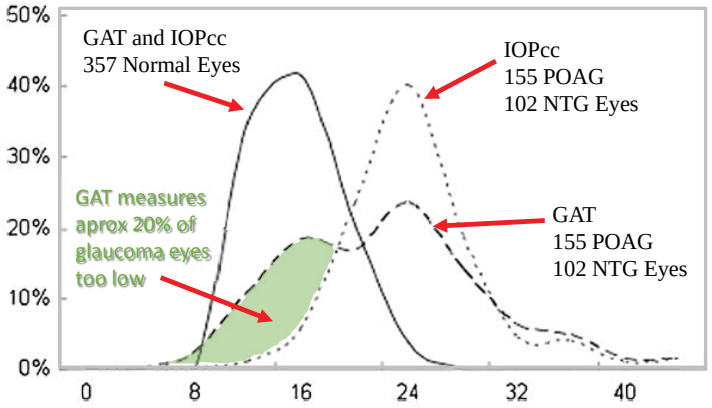
Corneal Compensated IOP

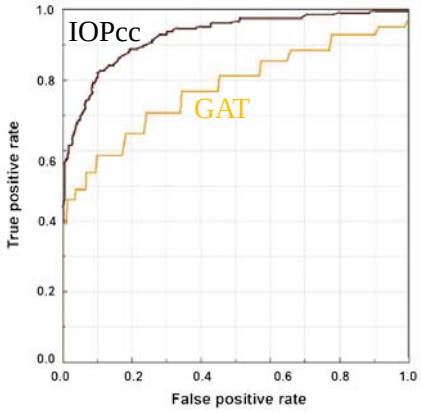
- Superior to Goldmann in all forms of post Refractive Surgery IOP measurements

IOPcc Key Benefit #2
IOPcc is superior for glaucoma risk assessment

IOPcc is clinically superior to GAT, other NCTs, and iCare because it is more associated with Glaucoma risk, status of glaucoma, and glaucoma progression

"the results of this study suggest that IOPcc may represent a superior test for the evaluation of glaucoma"





AUC .93 for IOPcc vs .78 for GAT

Goldmann applanation tonometry compared with corneal-compensated intraocular pressure in the evaluation of primary open-angle Glaucoma
Joshua R Ehrlich, Nathan M Radcliffe, and Mitsugu Shimmyo

Not shown here from this study:

- **39%** of NTG eyes would be re-classified as POAG with IOPcc
- Average IOPcc was **5 mmHg higher** than GAT in NTG eyes

- In conclusion, IOPcc measurements were more strongly associated with rates of visual field progression in glaucoma patients as compared to GAT and RBT. By correcting for corneal-induced artifacts, IOPcc measurements may present significant advantages for predicting clinically relevant outcomes in glaucoma patients

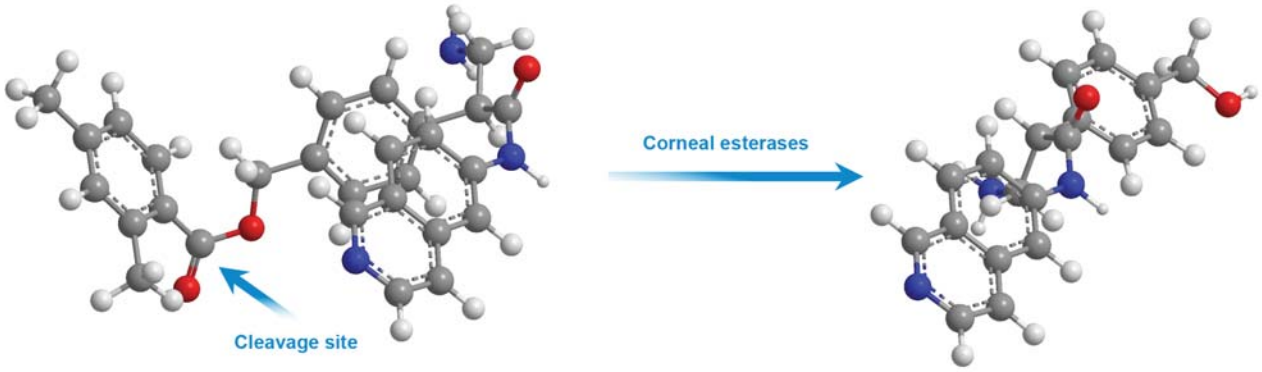
2017: A Great Year for Glaucoma Therapy

INTRODUCING RHOPRESSA® (NETARSUDIL OPHTHALMIC SOLUTION) 0.02%

- RHOPRESSA® is a new class of drug and has a white cap
- RHOPRESSA® is available in 1-month supply (2.5 mL)
- After opening, the product may be kept at room temperature for up to 6 weeks

RHOPRESSA® (NETARSUDIL OPHTHALMIC SOLUTION) 0.02% IS A ONCE-DAILY THERAPY DESIGNED TO INHIBIT ROCK

RHOPRESSA® PRODRUG[1] | **ACTIVE METABOLITE[1]**



- RHOPRESSA® was specifically designed to target the TM at the cellular level[1,2]
- RHOPRESSA® prodrug is converted by corneal esterases into an active metabolite that has 5× higher potency for ROCK inhibition[1]
- RHOPRESSA® inhibits the creation of stress fibers in the TM tissues to relax the meshwork and improve trabecular outflow[1,2]

1. Lin et al. *J Ocul Pharmacol Ther.* 2018; 34:40. 2. Rao PV, et al. *Invest Opthalmol Vis Sci.* 2001;42:1029.

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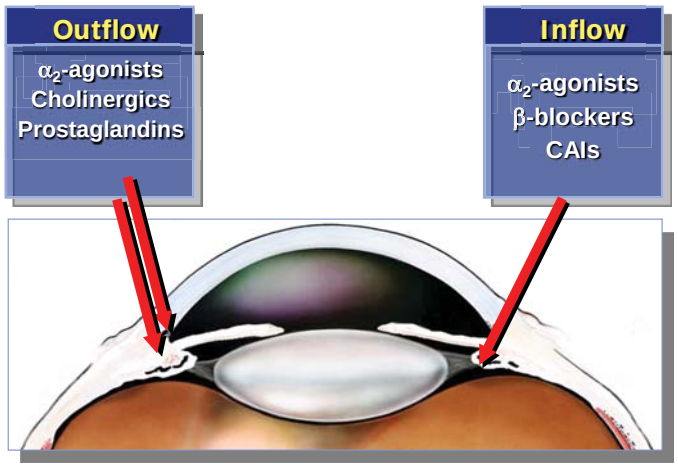
Pathways to Lower IOP



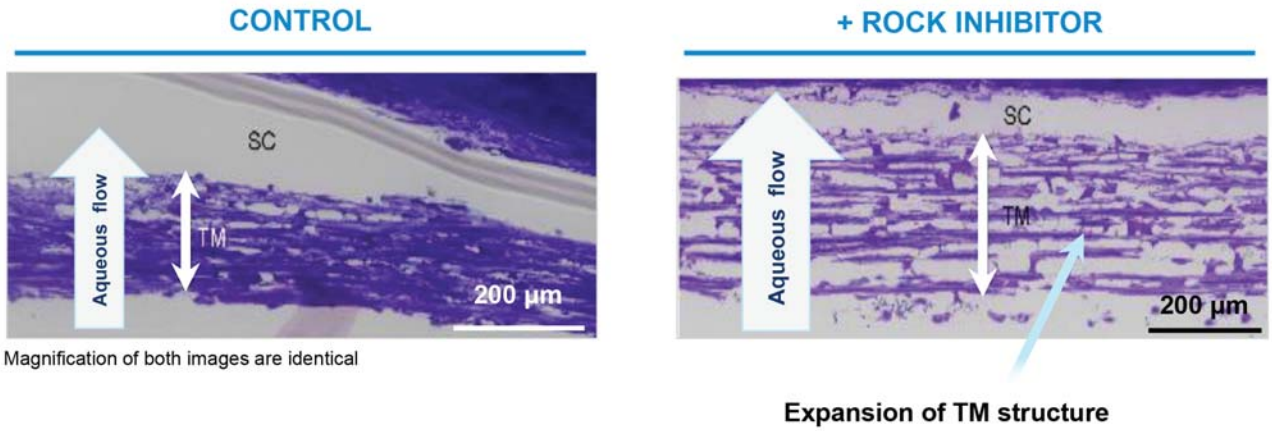
Rhopressa

Inhibitor of Rho Kinase (ROCK)
and Norepinephrine
Transporter (NET)

Potentially lower IOP by three mechanisms

1. Increasing TM outflow
2. Reducing episcleral venous pressure
3. Reducing aqueous production (via NET inhibition

ROCK INHIBITION RELAXES THE TM STRUCTURE



Magnification of both images are identical

Expansion of TM structure

Morphology of the TM in perfused human donor eyes was examined using light microscopy. Images were taken by using a 20× objective along the inner wall of the SC.

ROCK, Rho kinase; SC, Schlemm's canal; TM, trabecular meshwork.

1. Ren et al. *Invest Ophthalmol Vis Sci*. 2016;57:6197.

IN A ROBUST CLINICAL TRIAL PROGRAM, OVER 800 PATIENTS WERE TREATED WITH RHOPRESSA® (NETARSUDIL OPHTHALMIC SOLUTION) 0.02%

- RHOPRESSA® 0.02% QD (PM) was compared with timolol 0.5% BID in ROCKET 1, ROCKET 2, and ROCKET 4[1,2]
- Primary efficacy endpoint for all trials was mean IOP at week 2, week 6, and month 3[1,2]

	n	PRIMARY EFFICACY ANALYSIS	SAFETY ANALYSIS	PRIMARY EFFICACY POPULATION
ROCKET 1[1] (NCT02207491)	n=202 (RHOPRESSA®) n=209 (timolol)	3 months	3 months	<27 mmHg (*post hoc* analysis, <25 mmHg)
ROCKET 2[1] (NCT02207621)	n=251 (RHOPRESSA®) n=251 (timolol)	3 months	12 months	<25 mmHg
ROCKET 4[2] (NCT02558374)	n=351 (RHOPRESSA®) n=357 (timolol)	3 months	6 months	<25 mmHg

BID, twice daily; IOP, intraocular pressure; QD, once daily.
1. Serle et al. *Am J Ophthalmol.* 2018;186;116. 2. Khouri et al. Association for Research in Vision and Ophthalmology oral presentation 2017 [E-abstract 2461].

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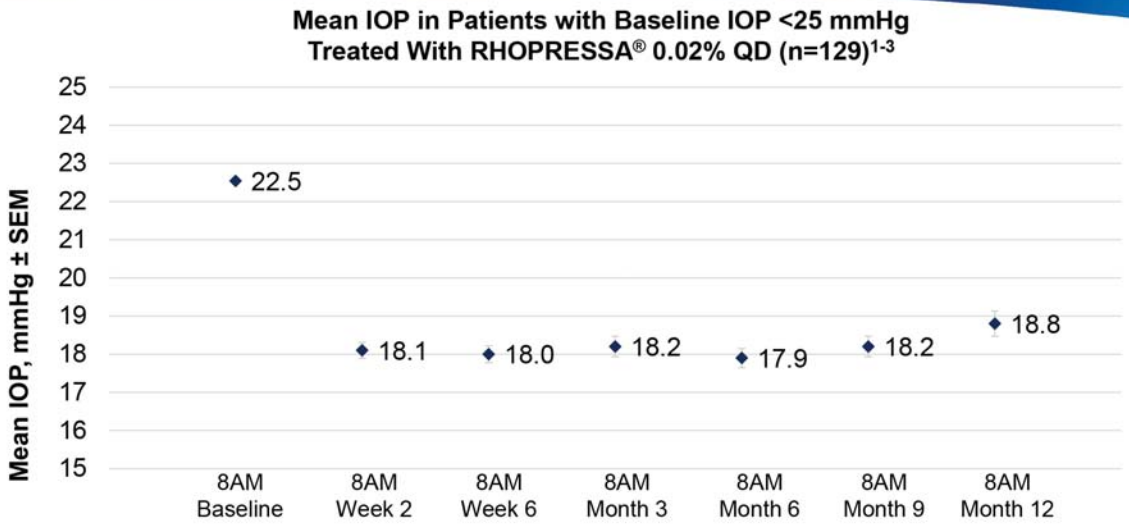
RHOPRESSA® (NETARSUDIL OPHTHALMIC SOLUTION) 0.02% MAINTAINED EFFICACY THROUGH 1 YEAR IN THE ROCKET 2 TRIAL



- IOP was collected at 8 AM only at months 6, 9, and 12 as a safety measure

For important safety information refer to the RHOPRESSA® Prescribing Information at the end of this presentation or at www.RHOPRESSA.com.
IOP, intraocular pressure; QD, once daily; SEM, standard error of the mean.
1. Serle et al. Abstract accepted at Association for Research in Vision and Ophthalmology 2018 annual meeting. 2. Serle et al. *Am J Ophthalmol.* 2018;186;116-127. 3. Data on file, Aerie Pharmaceuticals Inc.

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RHOPRESSA® (NETARSUDIL OPHTHALMIC SOLUTION) 0.02% OCULAR ADVERSE EVENT PROFILE

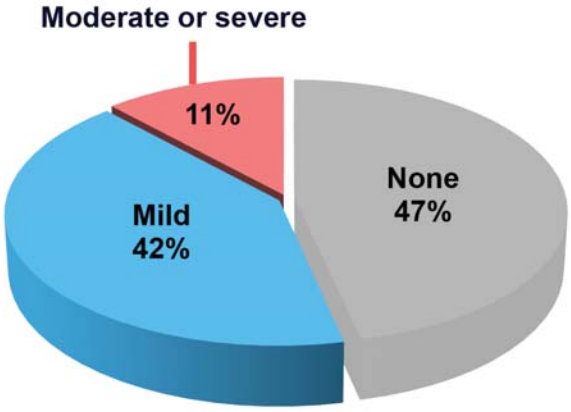
PREFERRED TERM (with Incidence ≥5% [pooled safety population[a]])	RHOPRESSA® 0.02% QD (N=805) n (%)	TIMOLOL 0.5% BID (N=816) n (%)
Eye Disorders		
Conjunctival hyperemia	428 (53.2)	85 (10.4)
Cornea verticillata (corneal deposits)	162 (20.1)	2 (0.2)
Conjunctival hemorrhage	137 (17.0)	15 (1.8)
Vision blurred	60 (7.5)	12 (1.5)
Lacrimation increased	53 (6.6)	5 (0.6)
Erythema of eyelid	52 (6.5)	4 (0.5)
Visual acuity reduced	44 (5.5)	13 (1.6)
General Disorders and Administration Site Conditions		
Instillation site pain	158 (19.6)	175 (21.4)
Instillation site erythema	74 (9.2)	13 (1.6)
Investigations		
Vital dye staining cornea present	65 (8.1)	57 (7.0)

[a]Includes ROCKET 1, ROCKET 2, and ROCKET 4.
1. Data on file, Aerie Pharmaceuticals, Inc.

CONJUNCTIVAL HYPEREMIA IN THE POOLED ROCKET STUDIES WAS REPORTED AS MILD BY THE PHYSICIANS UPON BIOMICROSCOPY

- Hyperemia may begin by the second week of treatment in patients treated with RHOPRESSA® (netarsudil ophthalmic solution) 0.02% QD[1]
- In approximately 9 out of 10 patients, either no hyperemia or mild hyperemia was reported[2]
- Severity did not increase with continued dosing[1]
- Hyperemia was observed by biomicroscopy at baseline in ~15%-20% of patients[1]

Grading of Conjunctival Hyperemia Adverse Events in Patients Treated With RHOPRESSA® 0.02% QD (N=805)[2]



1. Serle et al. *Am J Ophthalmol*. 2018;186;116-127. 2. Data on file, Aerie Pharmaceuticals, Inc.

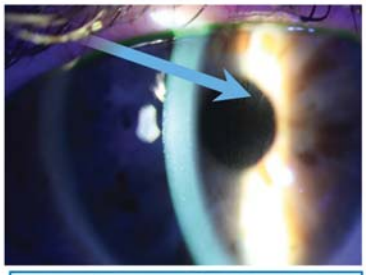
Corneal Verticillata

- Corneal Verticillata
  - Corneal verticillata occurred in approximately 20% of the patients in controlled clinical studies.
  - The corneal verticillata seen in RHOPRESSA-treated patients were first noted at 4 weeks of daily dosing.
  - This reaction did not result in any apparent visual functional changes in patients. Most corneal verticillata resolved upon discontinuation of treatment.

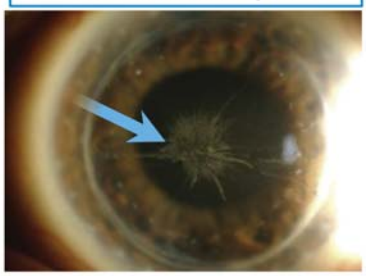
IN THE POOLED ROCKET STUDIES, CORNEA VERTICILLATA WAS MILD AND DID NOT AFFECT VISION

- Whorl-like pattern of phospholipid deposits caused by several cationic amphiphilic drugs[1]
- The corneal verticillata were first noted at 4 weeks of daily dosing in RHOPRESSA® (netarsudil ophthalmic solution) 0.02% -treated patients [2]
- Were asymptomatic and did not result in an apparent change in visual function[2]
- Resolved in majority upon discontinuation of RHOPRESSA®[2]

RHOPRESSA®-treated patient[3]



Amiodarone-treated patient[1]



QD, once daily.

1. Raizman et al. *Surv Ophthalmol.* 2017;62:286. 2. RHOPRESSA® (netarsudil ophthalmic solution) 0.02% Prescribing Information. 3. Courtesy of ROCKET investigator.

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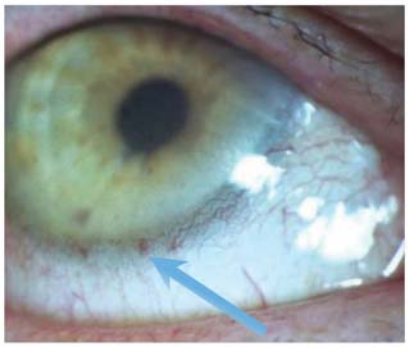
IN THE POOLED ROCKET STUDIES, MILD CONJUNCTIVAL HEMORRHAGE WAS SELF-RESOLVING AND RARELY RESULTED IN DISCONTINUATION

- Typically small microhemorrhages localized to the limbal area which may be related to vasodilatory effect of the molecule[1]
- Onset was variable, and duration was typically 1-3 weeks[1]
- Conjunctival hemorrhage was mild in 90% of cases and self-resolving with continued dosing[2]
- Resulted in discontinuation in 1% of patients treated with RHOPRESSA® (netarsudil ophthalmic solution) 0.02% QD[2]



Mild conjunctival hemorrhage[2]

QD, once daily.
1. Serle et al. *Am J Ophthalmol.* 2018;186;116. 2. Data on file, Aerie Pharmaceuticals, Inc.

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Rhopressa

RHOPRESSA 0.02% was evaluated in three randomized and controlled clinical trials in patients with open-angle glaucoma or ocular hypertension.

- Studies 301 and 302 enrolled subjects with baseline IOP lower than 27mmHg
- Study 304 enrolled subjects with baseline IOP lower than 30 mmHg.
- The treatment duration was 3 months in Study 301, 12 months in Study 302, and 6 months in Study 304.

Rhopressa 0.02%: Two Sides to Every Story

For patients with baseline IOP < 25 mmHg, the IOP reductions with RHOPRESSA 0.02% dosed once daily were similar to those with timolol 0.5% dosed twice daily (see Table 1).

Patients with baseline IOP equal to or above 25 mmHg RHOPRESSA 0.02% resulted in smaller mean IOP reductions at the morning time points than timolol 0.5% for study visits on Days 43 and 90 T

The difference in mean IOP reduction between the two treatment groups was as high as 3 mmHg, favoring timolol.

Netarsudil Mesylate in Development

- Phase III studies with mixed results
- Current development plan is in combination with latanoprost.

N=298 total	Latanoprost	Netarsudil mesylate	Fixed combination
Baseline IOP	26.0 mmHg	25.4 mmHg	25.1 mmHg
Final IOP	18.4 mmHg	19.1 mmHg	16.5 mmHg
IOP Reduction	7.6 mmHg	6.3 mmHg	8.6 mmHg

Katz J. ARVO 2016. E-abstract 4279.
Bacharach AGS 2015.

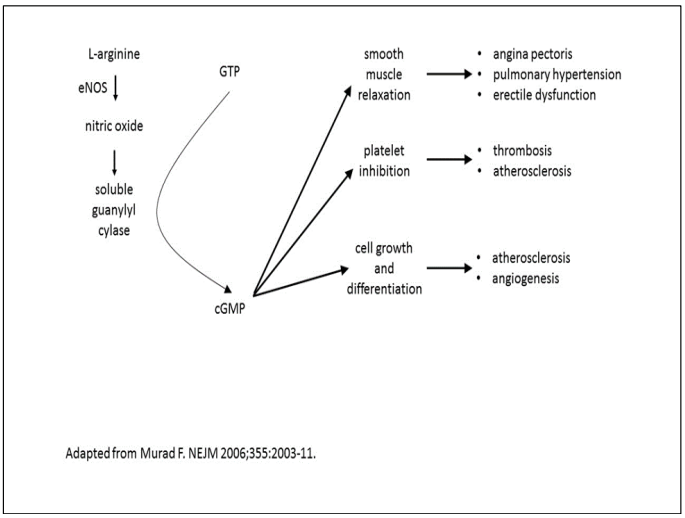
Vyzulta
(Latanoprostene Bunod)

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[1]**
- **NO donors lower IOP in normal and POAG eyes**
- **A major site of action for NO donors is the TM**
  - **NO relaxes the TM and ciliary muscle**
  - **NO donors increase outflow facility in anterior segments, mediated by a decrease in TM cell volume**
  - **Endothelial NO synthase (eNOS) overexpression increases conventional outflow and lowers IOP in a mouse eye model**

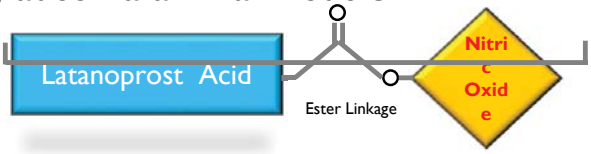
Latanoprostene Bunod: NO-Donating Latanoprost

- NO plays key roles in both health and disease throughout the body, including the eye



Vyzulta

- **Nitric Oxide (NO)-donating prostaglandin F2α agonist that is rapidly metabolized in situ to latanoprost acid and BDMN, a NO-donating moiety**
- **Exhibited potent and effective intraocular pressure (IOP)-lowering activity in 3 ocular hypertensive glaucoma animal models[1]**



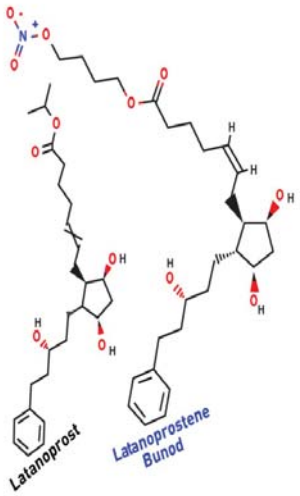
BOL-303259-X

BDMN: Butanediol mononitrate.

[1]Krauss AH, Impagnatiello F, Toris CB, et al. Ocular hypotensive activity of BOL-303259-X, a nitric oxide donating prostaglandin F2α agonist, in preclinical models. *Exp Eye Res.* 2011;93: 250-5.

Latanoprostene-bunod: Mechanism of Action

- Latanoprostene = latanoprost
  - Increases uveoscleral outflow
- Bunod modification donates nitric oxide
  - Exerts its effect in trabecular smooth muscle
  - Activating cGMP signaling pathway
  - Resulting in trabecular relaxation and increased conventional outflow
- Mechanisms would be expected to additive



Cavet ME, Vittitow JL, Impagnatiello F, et al. *Invest Ophthalmol Vis Sci.* 2014;55:5005-5015; Ellis DZ, Dismuke WM, Chokshi BM. *Invest Ophthalmol Vis Sci* 2009; 50: 1808–1813.

VOYAGER Clinical Trial Design

Phase 2, multicenter, single-masked, parallel-group dose finding study in subjects with OAG or OHT

- LBN 0.006% (n=82)
- LBN 0.012% (n=85)
- LBN 0.024% (n=83)
- LBN 0.040% (n=81)
- Latanoprost 0.005 % (n=82)

28-day study

Primary Objective

- To assess the efficacy and safety of various doses of LBN QD compared with latanoprost 0.005% QD
- Determine the optimum concentration of LBN in reducing IOP

Primary endpoint

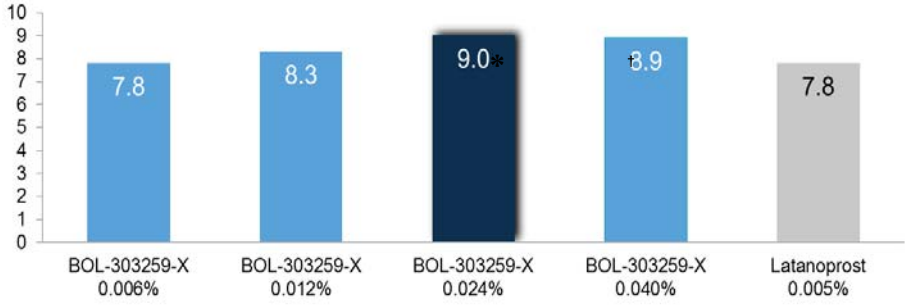
- Reduction in mean diurnal IOP on Day 28

1. Weinreb RN, et al. *Br J Ophthalmol* 2015;99:738–45.

Efficacy Results: Primary Endpoint Voyager Study

At highest doses, lowered IOP 1-1.5 mmHg more than latanoprost

Most common AE: pain upon instillation

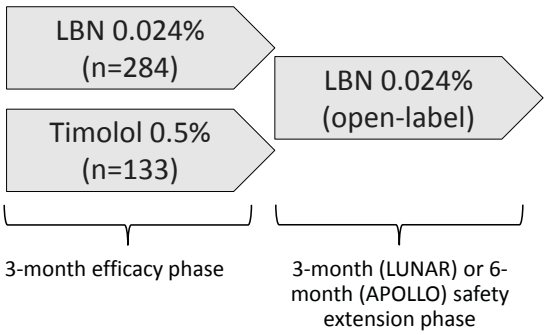


REDUCTION IN MEAN DIURNAL IOP ON VISIT 6 (DAY 28)

1. Weinreb RN et al. Br J Ophthalmol. 2015;99(6):738-45

APOLLO and LUNAR Clinical Trial Design

Phase 3, randomized, multicenter, double-masked, parallel-group studies in patients with OAG or OHT



Primary Objective

- Evaluate noninferiority of LBN 0.024% QD in the evening vs timolol maleate 0.5% BID

Primary endpoint

- IOP measured at 9 assessment time points in the study eye

Secondary endpoints

- Change from baseline (CFB) in IOP at 9 assessment time points
- CFB in diurnal IOP at Week 2, Week 6, and Month 3

1. Weinreb RN, et al. *Ophthalmology* 2016;123(5):965-73. **2.** Medeiros FA, et al. *Am J Ophthalmol.* 2016;168:250-9.

APOLLO and LUNAR: Change from Baseline by Visit (ITT, LOCF)

- LBN 0.024% was non-inferior to timolol in both studies and demonstrated significantly greater IOP lowering over timolol at all but one time point in the two studies.

	Week 2			Week 6			Month 3		
	8 AM	12 PM	4 PM	8 AM	12 PM	4 PM	8 AM	12 PM	4 PM
APOLLO									
LBN mean CFB (mm Hg)	-9.0	-8.5	-7.7	**-9.1**	-8.7	-7.9	-9.0	-8.7	-7.9
Timolol mean CFB (mm Hg)	-7.8	-7.2	-6.6	-8.0	-7.4	-6.7	-7.9	-7.4	-6.6
Treatment difference	-1.21	-1.37	-1.11	-1.03	-1.24	-1.26	-1.02	-1.27	-1.33
Primary objective	NI	NI	NI	NI	NI	NI	NI	NI	NI
Secondary objective	<.001	<.001	<.001	.002	<.001	<.001	.002	<.001	<.001
LUNAR									
LBN mean CFB (mm Hg)	-8.3	-8.1	**-7.5**	-8.8	-8.5	-7.8	-8.8	-8.6	-7.9
Timolol mean CFB (mm Hg)	-7.9	-7.3	-6.9	-7.9	-7.7	-6.8	-7.9	-7.4	-6.6
Treatment difference	-0.44	-0.76	-0.69	-0.92	-0.84	-0.98	-0.88	-1.29	-1.34
Primary objective	NI	NI	NI	NI	NI	NI	NI	NI	NI
Secondary objective	.216	.022	.025	.005	.007	.003	.006	<.001	<.001

NI: Claimed if upper CI ≤1.5 mm Hg at all time points and ≤1.0 mm Hg for at least 5 of 9 time points.
Superiority: Claimed if upper CI ≤0 mm Hg at all time points

1. Weinreb RN, et al. *Ophthalmology* 2016;123(5):965-73. **2.** Medeiros FA, et al. *Am J Ophthalmol.* 2016;168:250-9.

APOLLO and LUNAR: Adverse Events

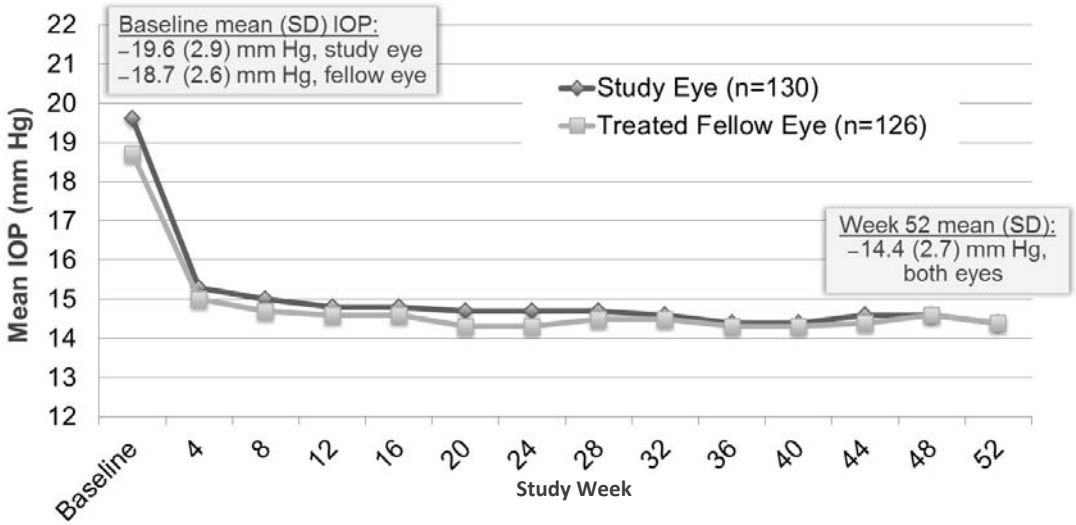
Clinical Studies

- The most common ocular adverse reactions observed in patients treated with Vyzulta™ (n=811, across both studies) were
  - conjunctival hyperemia (6%)
  - eye irritation (4%)
  - eye pain (3%)
  - instillation site pain (2%)
- Approximately 0.6% of patients discontinued therapy due to ocular adverse reactions including ocular hyperemia, conjunctival irritation, eye irritation, eye pain, conjunctival edema, vision blurred, punctate keratitis and foreign body sensation.

VYZULTA™ [prescribing information]. Bridgewater, NJ; Bausch + Lomb, 2017.

JUPITER: Sustained IOP-lowering Efficacy through One Year

- IOP was reduced by ≥22% with LBN at each post-treatment visit vs. baseline (*P*<0.001 for all).



1. Kawase K, et al. *Adv Ther* 2016;33:1612-27

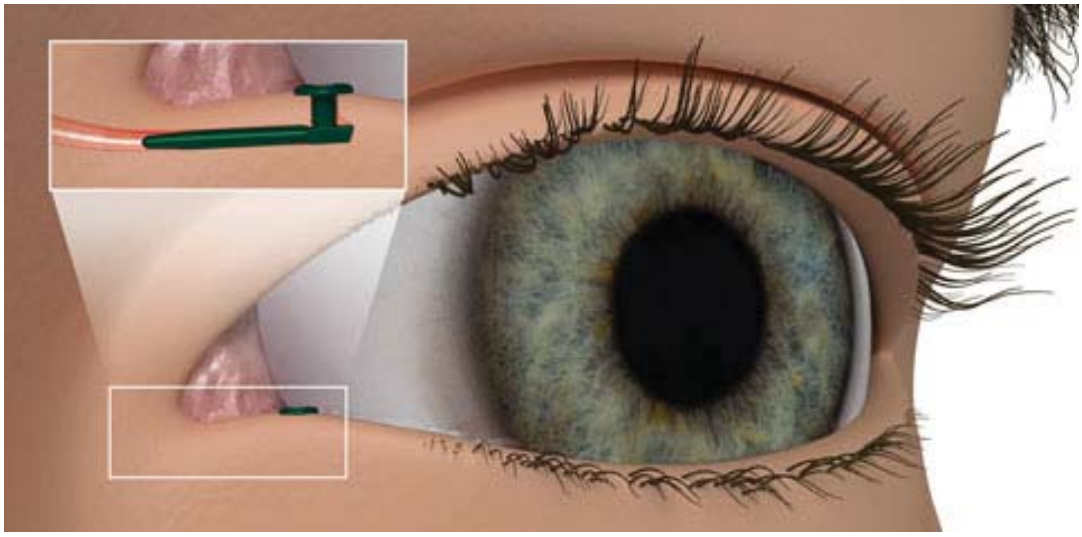
The Next Generation of Medical Management in Glaucoma

- **Sustained Release Systems**

Mati Therapeutics

- The Evolute has an L-shaped design and is inserted into the nasolacrimal duct. The device is cosmetically invisible, but can be easily seen with eversion of the lower lid.
- The glaucoma product has a core of latanoprost-polymer matrix that is surrounded by silicone, and it delivers the medication into the tear film at a constant rate.
- In a phase II clinical trial, the latanoprost punctal plug was found to be comfortable. It was associated with a 20% lowering from baseline IOP over a 3-month period, and in two separate clinical trials.
- Retention rate of 92% and 96%, respectively.

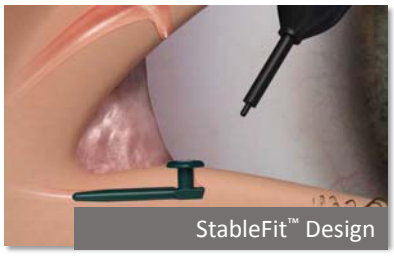
Mati Therapeutics

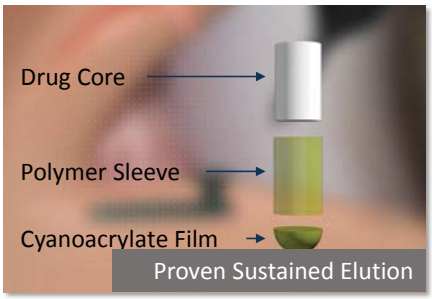


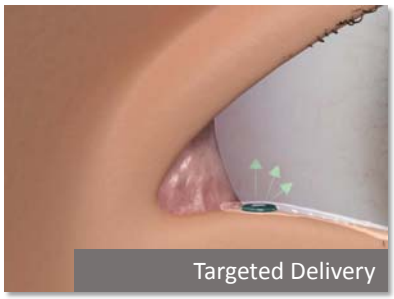
Evolute® Punctal Plug Delivery System

Successful By Design

1. Easy to place and remove
2. Cosmetically invisible – easy to identify
3. Tolerable
4. Consistent, sustained efficacy
5. Use in multiple disease states





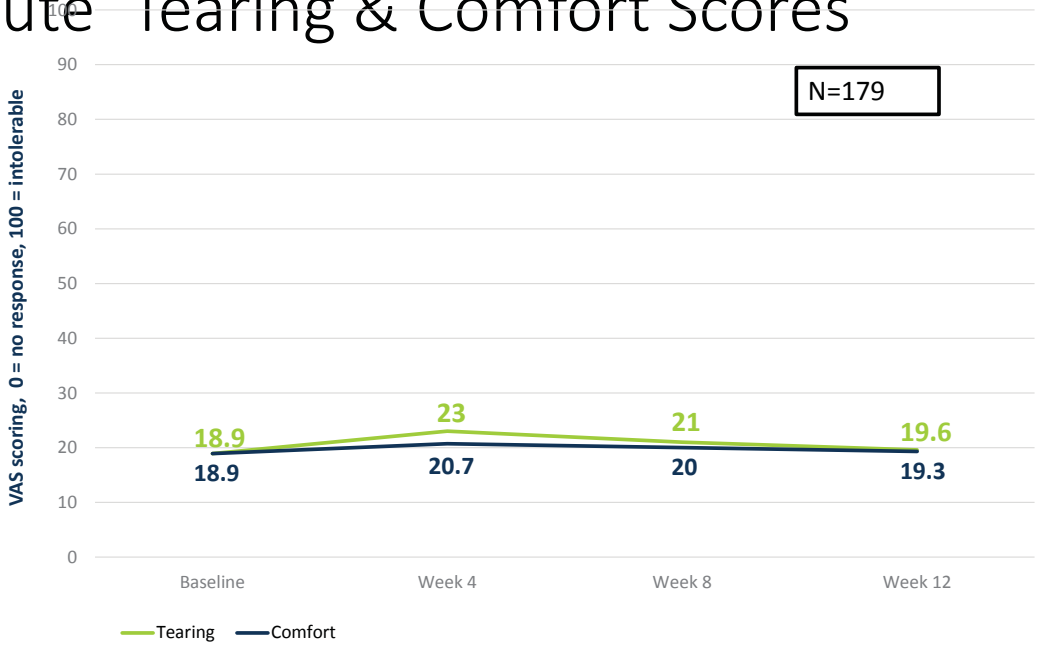


Excellent Plug Retention Rates Over 12 Weeks

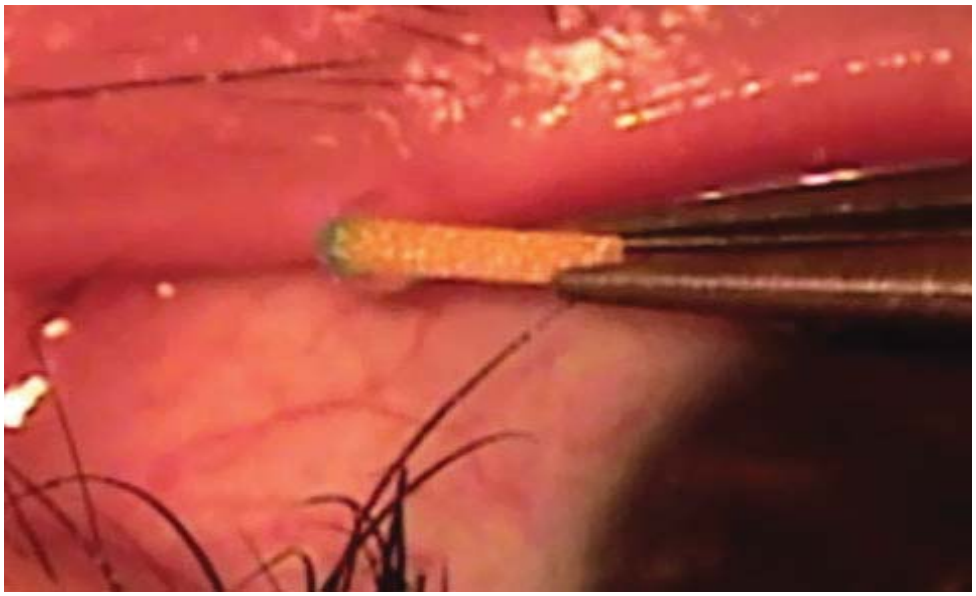
U.S. Phase II Multi-center Trials – Lower Puncta

Study	Week 4	Week 8	Week 12
Glau 12 (n = 92)	98%	97%	96%
Glau 13 (n = 87)	98%	96%	92%

Evolute® Tearing & Comfort Scores



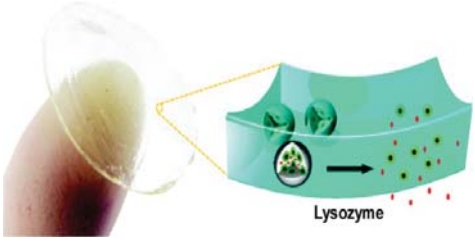
Ocular Therapeutix



Ocular Therapeutix

- Phase II study randomly assigned 73 patients into two groups to receive either the travoprost plug with twice daily artificial tears or timolol 0.5% twice daily with placement of a drug-free punctal plug.
- At 90 days, there was a 4.5 to 5.7 mm Hg reduction from baseline IOP in patients who had the travoprost punctal plug, which was clinically meaningful.
- However, the control group had an average IOP lowering of 6.4 to 7.6 mm Hg.
- The safety profile was good—no hyperemia was seen. The retention rate at 60, 75, and 90 days was 91%, 88%, and 48%, respectively.

Contact Lens Embedded IOP Lowering Drug



- Dean Ho, UCLA Dentistry School Research Team
- Nanogel that is embedded in CL's
- IOP lowering capacity
- Uses nanotechnolgy with small diamonds that timolol until tear enzymes (lysozyme) activate it
- The octohedron structure of the nanodiamonds has a unique charge that binds drugs to its surface
- Chitosan, A natural polymer is used to bind the drug
- Anticipated NDA is 2016

Latanoprost-Eluting Contact Lenses in Glaucomatous Monkeys.
Ciolino, J, Kohane,DS etal Ophthalmology 2016

- **RESULTS:**
- Latanoprost ophthalmic solution resulted in IOP reduction of 5.4±1.0 mmHg on day 3 and peak IOP reduction of 6.6±1.3 mmHg on day 5.
- The CLLO reduced IOP by 6.3±1.0, 6.7±0.3, and 6.7±0.3 mmHg on days 3, 5, and 8, respectively.
- The CLHI lowered IOP by 10.5±1.4, 11.1±4.0, and 10.0±2.5 mmHg on days 3, 5, and 8, respectively.
- For the CLLO and CLHI, the IOP was statistically significantly reduced compared with the untreated baseline at most time points measured.
- The CLHI demonstrated greater IOP reduction than latanoprost ophthalmic solution on day 3 ($P = 0.001$) and day 5 ($P = 0.015$), and at several time points on day 8 ($P < 0.05$).
- Coating Polylactic co-glycolic acid (PLGA) is coated with films containing Polyhydroxy-methacrylate by UV polymerization

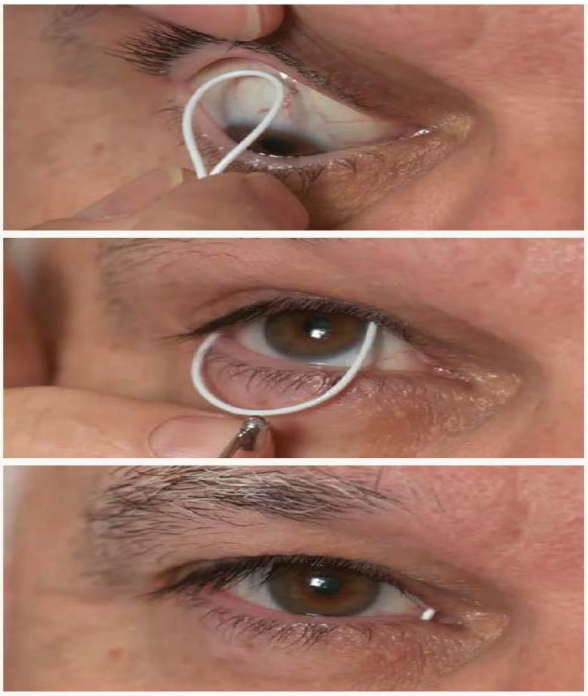
Bimatoprost SR

Bimatoprost SR

Bimatoprost SR is currently in phase 3 clinical trials.

- In phase 2 trials, the device produced a mean IOP reduction:
  - 7.2 to 9.5 mm Hg from baseline in 75 eyes 4 months after the injection.
- Patients' fellow eyes received qd topical bimatoprost 0.03%
  - IOP reduction of 8.4 mm Hg at 4 months.
- The implant lowered IOP;
  - 92% of patients at 4 months
  - 71% at 6 months.
  - No serious adverse ocular events, and the most common adverse events were related to the injection procedure

Bimatoprost Ring



Bimatoprost Ring

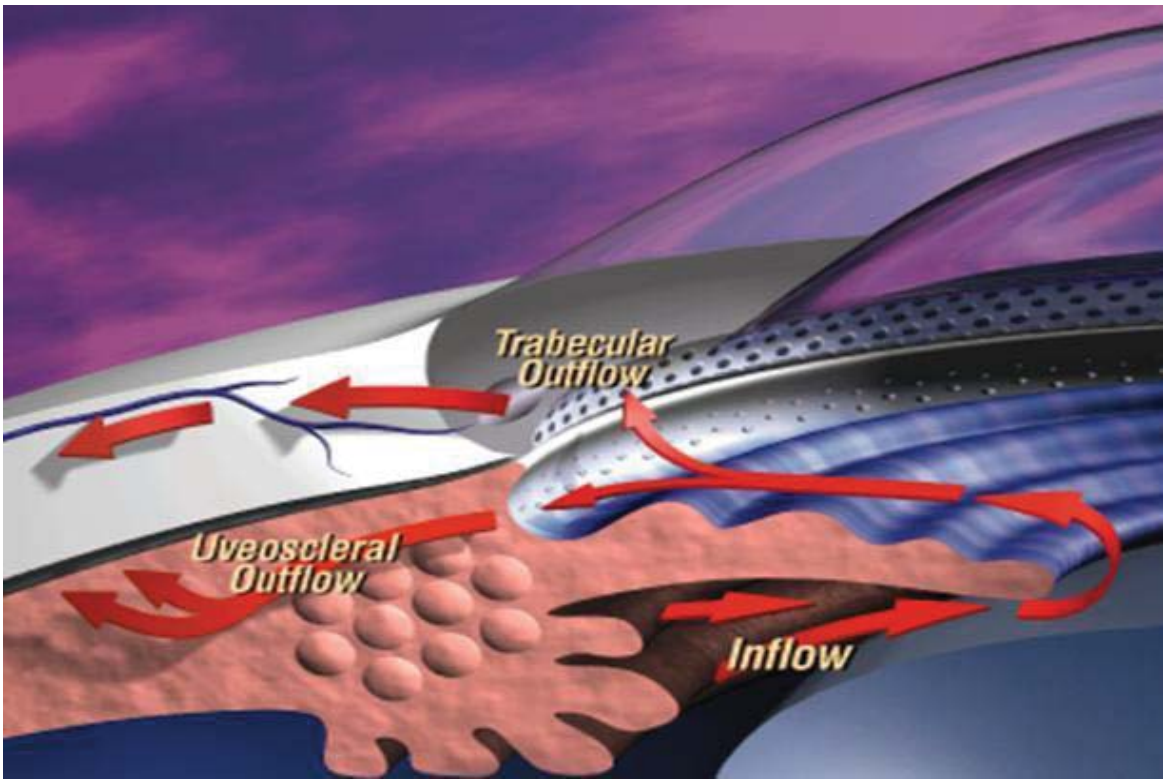
- The bimatoprost-impregnated insert produced:
  - More than 20% IOP lowering at all time points
  - It was slightly (0-1.5 mm Hg) less efficacious than twice-daily timolol at the nine time points.
- The pharmacokinetics of prostaglandin analogues; constant dosing tends to produce a lesser effect than pulsed dosing regimens.
- Maintenance of the insert in place without a physician's reintervention:
  - 93.1% at 12 weeks
  - 88.5% at 6 months.
- Adverse events were relatively low. Of the 161 patients who wore a nonmedicated insert for the first month, 151 reported no discomfort.

Glaukos iDose

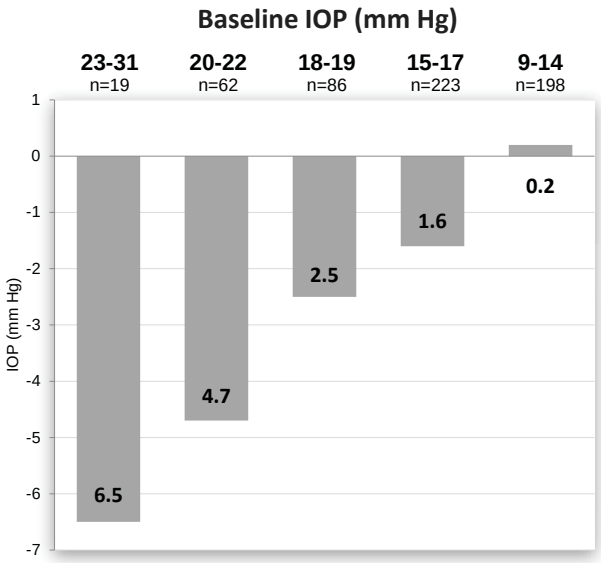
- The iDose is a titanium implant that is comparable in size to Glaukos' proprietary devices for microinvasive glaucoma surgery
- The 150-patient, multicenter, randomized, double-blind phase 2 trial evaluated two models of the iDose delivery system with different travoprost elution rates in comparison to a topical timolol maleate ophthalmic solution, 0.5%.
- The unit is filled with a formulation of travoprost specific to the device and capped with a membrane designed for continuous controlled drug elution into the anterior chamber.

Glaukos iDose

MIGS: Not Just a Soviet Fighter Jet Anymore



Effect of Cataract Surgery on IOP Reduction

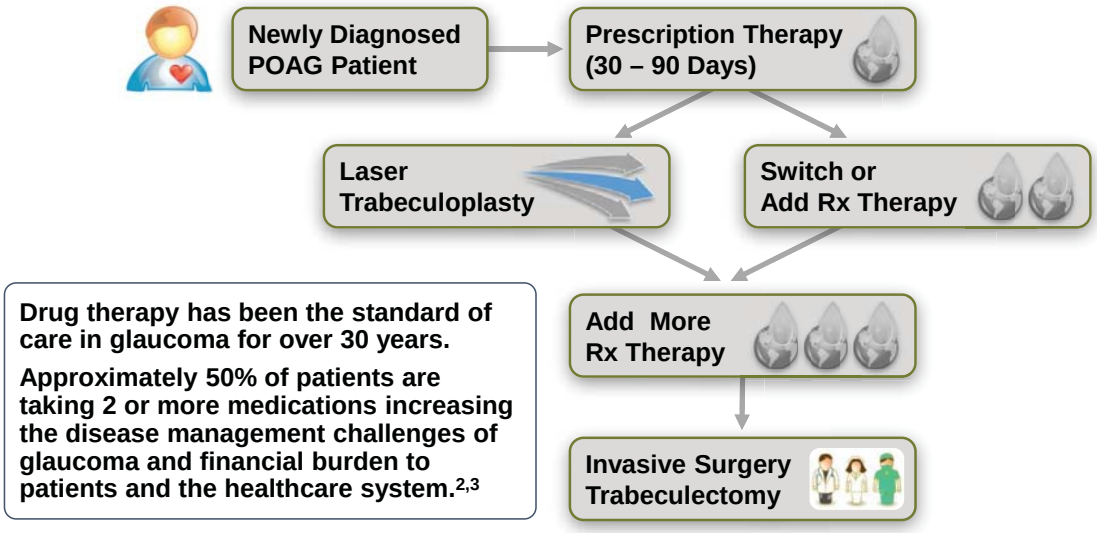


According to the AAO Preferred Practice Patterns, cataract surgery with IOL implantation alone results in a modest reduction in IOP of less than 2mm Hg on average.[1]

- Chart review of 588 normotensive and OHT subjects[2]
- 53% had a mean reduction of 1.6 to 2.5 mm Hg[2]

[1]American Academy of Ophthalmology, Preferred Practice Patterns, 2010.
[2]Poley BJ, Lindstrom RL, et al. Long-term effects of phacoemulsification with intraocular lens implantation in normotensive and ocular hypertensive eyes. J *Cataract Refract Surg* .2008;34(5):735-42.

Current OAG Treatment Algorithm[1]



Drug therapy has been the standard of care in glaucoma for over 30 years.

Approximately 50% of patients are taking 2 or more medications increasing the disease management challenges of glaucoma and financial burden to patients and the healthcare system.[2,3]

[1]AAO Preferred Practice Pattern; Primary Open Angle Glaucoma. AAO committee 2003.
[2]Stein J, Newman-Casey P, Niziol L, et. al. Association between the use of glaucoma medications and mortality. *Arch Ophthalmol. 2010;*128(2):235-245.
[3]Market Scope Quarterly Glaucoma Report, 4th quarter 2013.

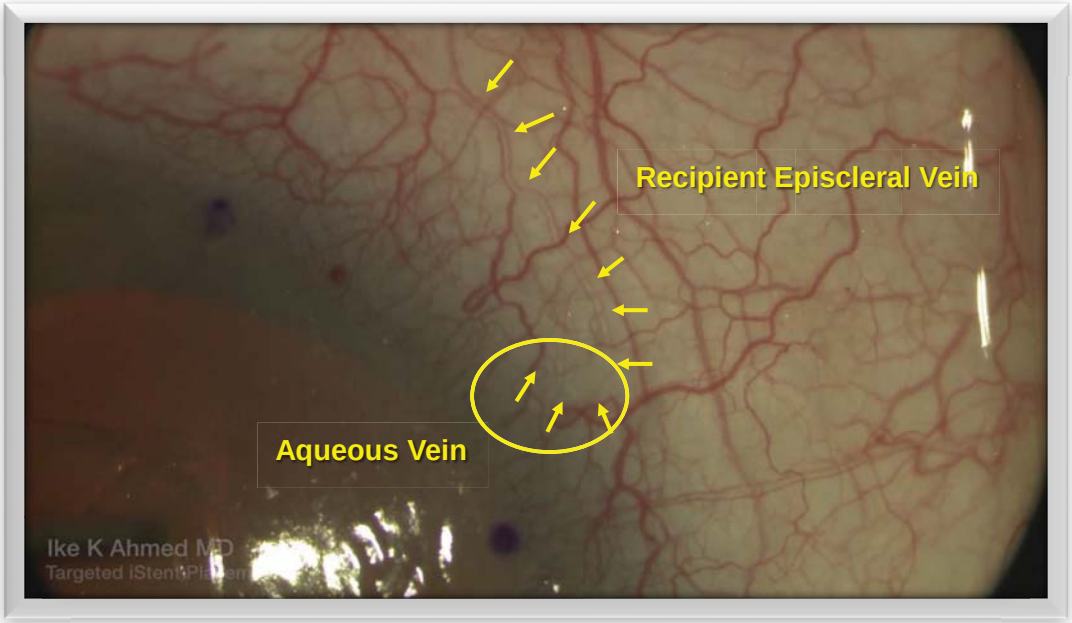
Top MIG"s in 2018

- Glaukos iStent
- Xen Glaucoma Implant
- CyPass
- Canaloplasty
- Trabectome

iStent® Indication for Use (US Label)

The iStent Trabecular Micro-Bypass Stent is indicated for use in conjunction with cataract surgery for the reduction of intraocular pressure (IOP) in adult patients with mild to moderate open-angle glaucoma currently treated with ocular hypotensive medication

Aqueous Veins



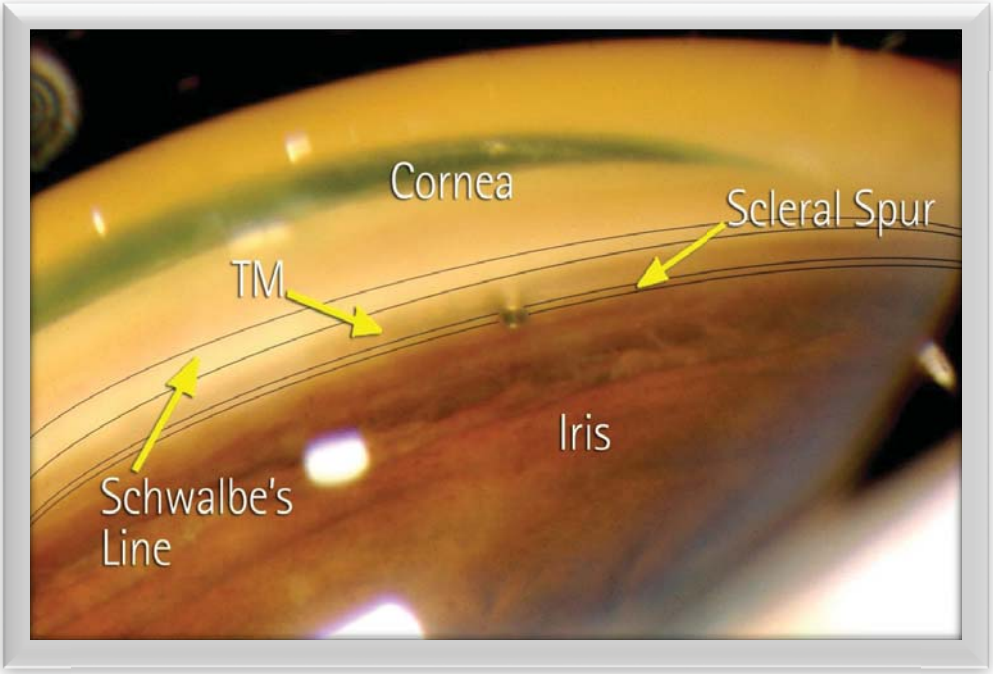
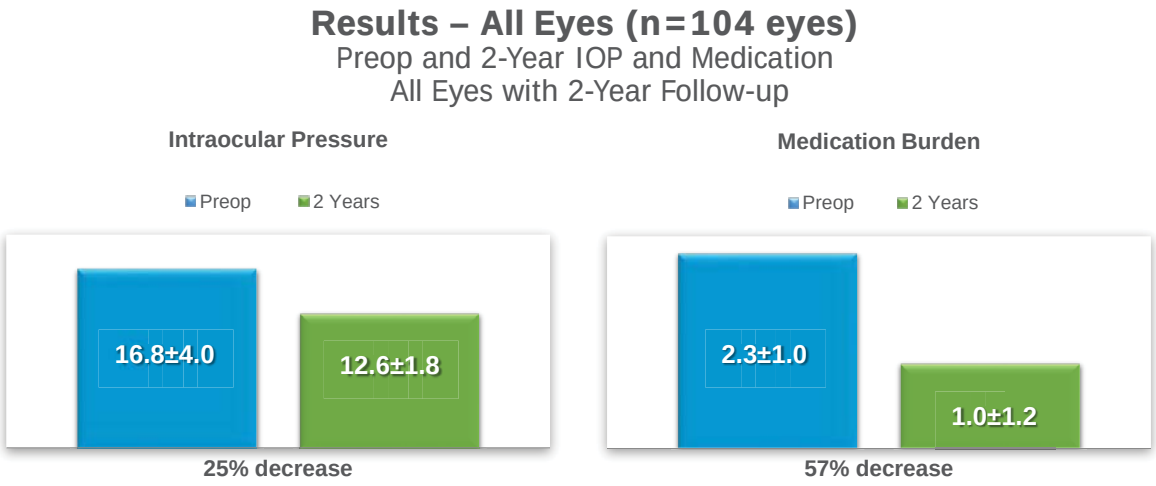


Photo courtesy of Tom Samuelson, MD

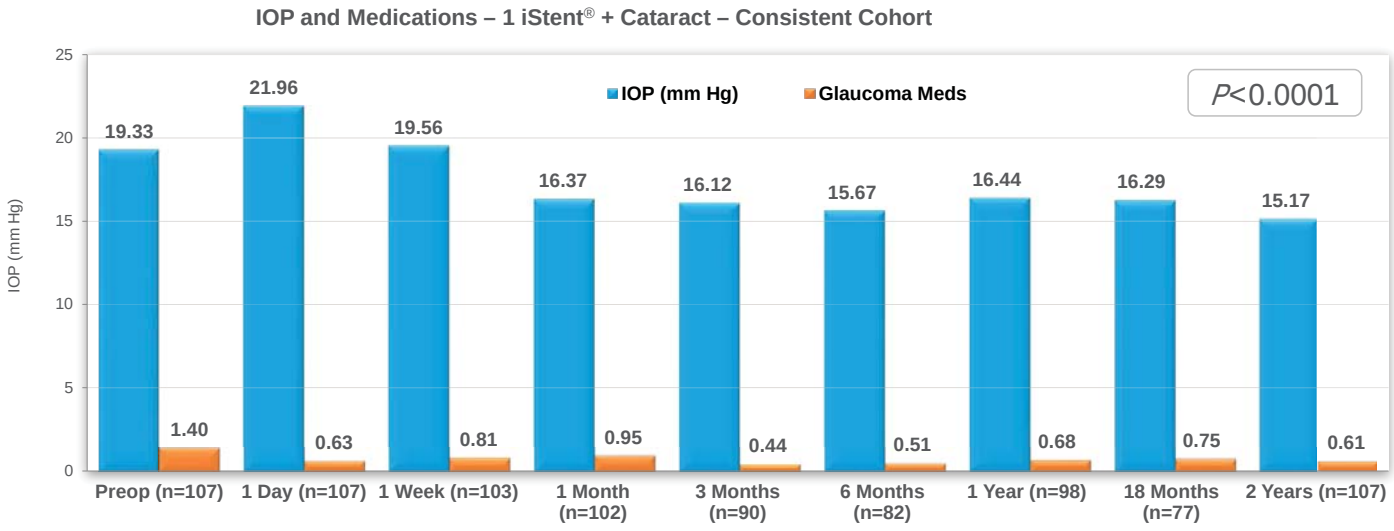
- At 2 years, 95% of eyes had an IOP ≤ 15 mmHg, 100% ≤ 18 mmHg
- 50% were on 0 medications, compared to 6% preop



Mark Gallardo, MD El Paso Eye Surgeons El Paso, TX. Presented at ASCRS 2017, Los Angeles, CA.

Retrospective Case Series (Ferguson, Berdahl)

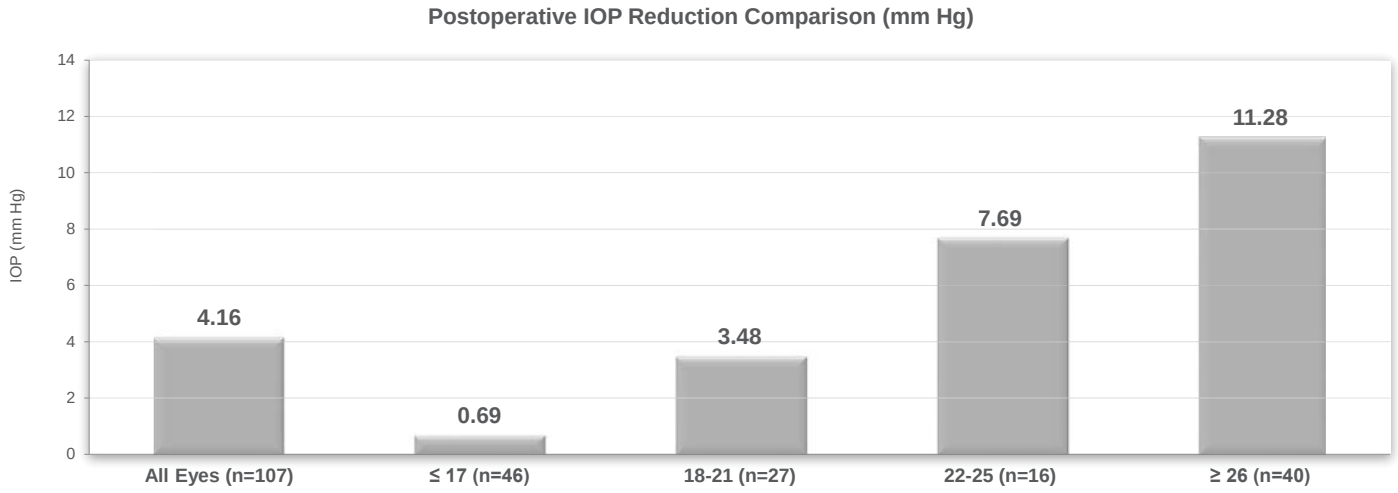
- Large series (n=107)
- At 2 years, mean IOP reduction was **22%** with a **56%** reduction in mean medications



Ferguson TJ, Berdahl JP, Schweitzer JA, Sudhagoni RG. Clinical evaluation of trabecular microbypass stents with phacoemulsification in patients with open-angle glaucoma and cataract. Clinical Ophthalmology 2016:10 1767-1773

Retrospective Case Series (Ferguson, Berdahl)

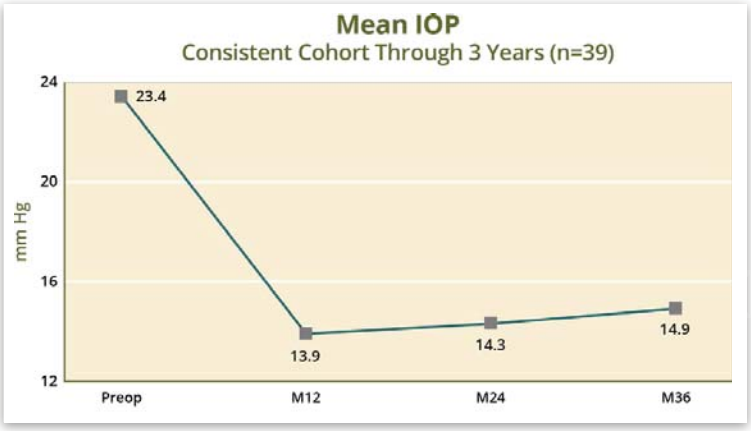
- IOP reduction higher with higher baseline IOP
- Patients with pre-op IOP ≥ 26 achieved mean IOP reduction of 11.28 mm Hg

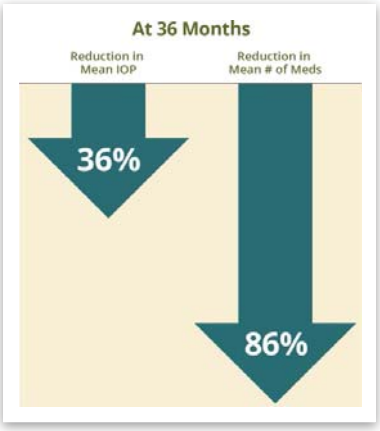


Ferguson TJ, Berdahl JP, Schweitzer JA, Sudhagoni RG. Clinical evaluation of trabecular microbypass stents with phacoemulsification in patients with open-angle glaucoma and cataract. Clinical Ophthalmology 2016:10 1767-1773

iStent® + Cataract Surgery Through 3 Years (T) . Neuhann

- At 3 years mean IOP was < 15 mm Hg with an 86% reduction in medications





- Consecutive series of 62 eyes: decision to implant based on patient desire to reduce topical meds and intent to offer surgical treatment with favorable safety profile

Neuhann TH. Trabecular micro-bypass stent implantation during small-incision cataract surgery for open-angle glaucoma or ocular hypertension: Long-term results. J Cataract Refract Surg 2015; 41:2664–2671.

Co-Management Coding

- iStent implantation is described by CPT code 0191T
  - 0191T is a Category III (new technology) code
  - 0191T has no assigned Relative Value Units or Global Period
  - There is no postop co-management fee for any T-code
  - Medicare carriers will not recognize modifiers -54 & -55 for 0191T
- Modifiers -54 & -55 can still be appended to CPT code 66984
  - Modifier -54: surgical care only
  - Modifier -55: all/part of outpatient postoperative care
  - Surgeon MUST initiate the notification to Medicare by using modifier -54 with the claim
  - In localities where Medicare has a higher physician payment for 0191T than for 66984 and where 66984 is reduced by 50%, payment for 66984-550 will be reduced by 50%

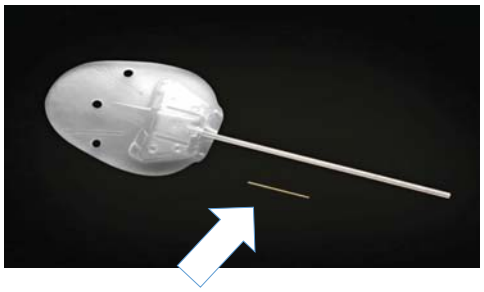
Allergan:XEN

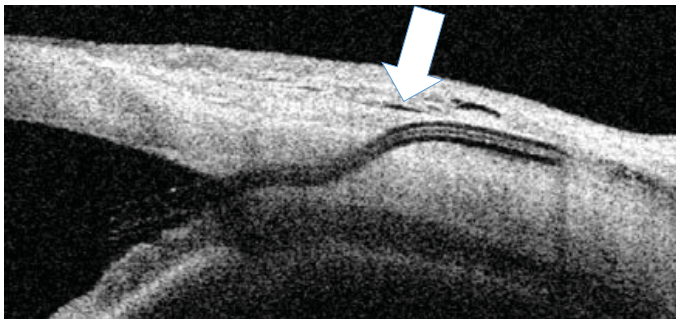
XEN Glaucoma Implant™ Mechanism of Action

Ab Interno Sub-Conjunctival Drainage

- Surgical "Gold Standard" IOP reduction in minimally invasively procedure
- Clinically proven outflow pathway
- Bypasses all potential outflow obstructions
- Conjunctiva sparing: alternative surgical options remain
- Single implant delivers desired effectiveness

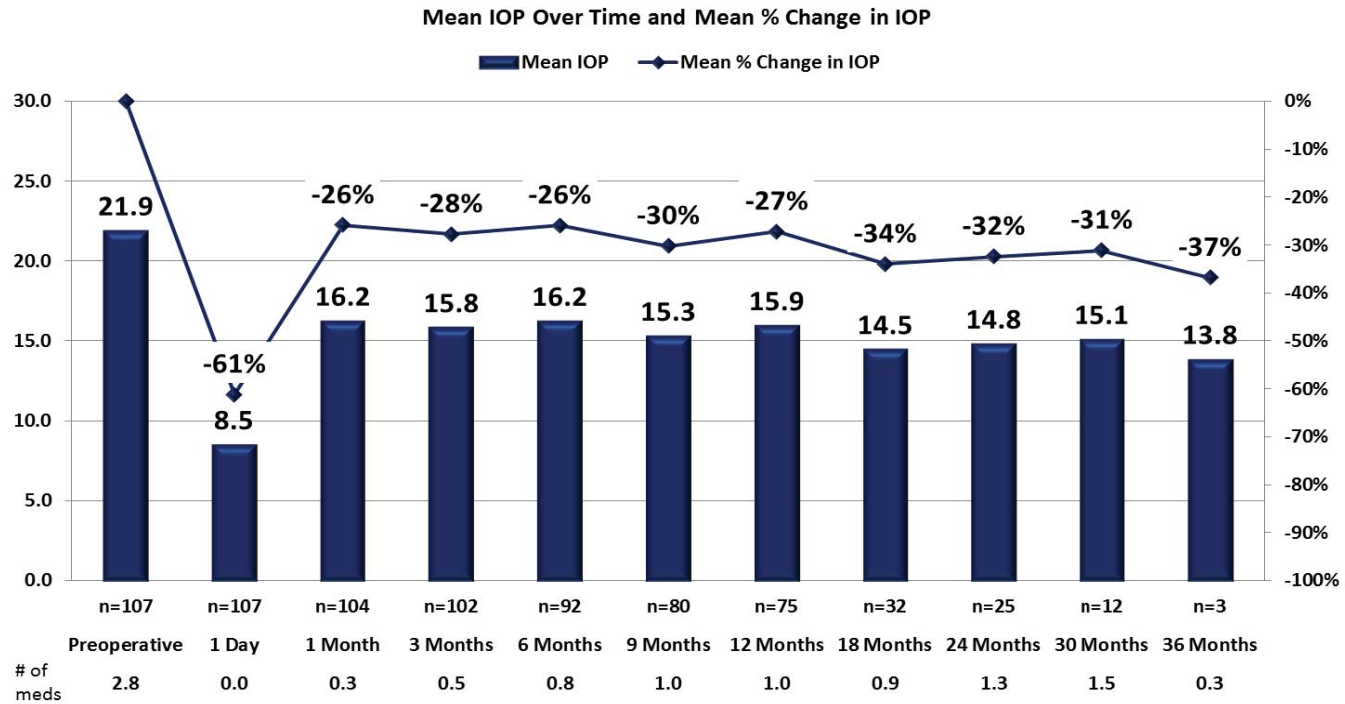
Gelatin Material is Tissue Conforming





POAG Only

Summed patients: primary, combined and refractory



**Mean preoperative IOP is best medicated. Patients were not washed out prior to surgery.*

Initial Clinical Results: From A Multi-Center Study on Early Moderate Stage Population

N = 62 Pre op IOP 21.8 ± 3.5 mmHg Meds 2.6	12M (N=37)	18M (N=14)	24M (N=8)
Mean IOP mmHg *Std. Dev.*	**15.7** *3.5*	**14.7** *2.9*	**14.9** *2.8*
Mean Post Op Meds *Mean Meds % Reduction*	**0.9** *-65%*	**1.0** *-61%*	**1.0** *-61%*
% IOP reduction from Best Rx *From Washout IOP**	**-28%** *-45%*	**-33%** *-48%*	**-32%** *-47%*
% ≤21 mmHg and/or -20%	**100%**	**100%**	**100%**
% ≤18 mmHg and/or -20%	**100%**	**86%**	**100%**
% ≤16 mmHg and/or -30%	**84%**	**86%**	**63%**

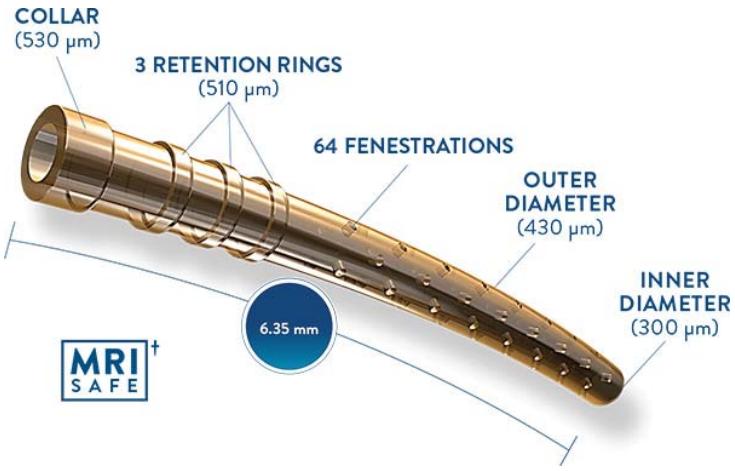
* Washout IOP calculated at +30% from medicated

Initial Clinical Results: From A Multi-Center Study on Severe/Refractory Population

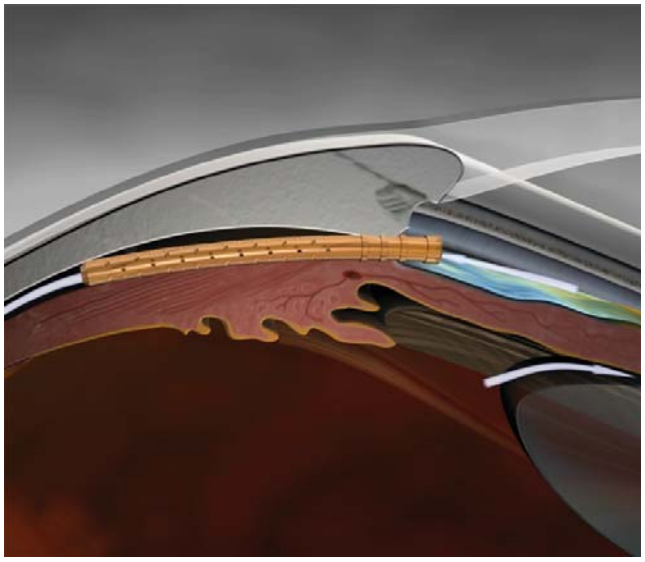
N = 39 Pre op IOP 22.6 ± 4.3 mmHg Meds 3.1	12M (N=29)	18M (N=12)	24M (N=12)
Mean IOP mmHg *Std. Dev.*	**13.9** *4.6*	**12.9** *3.4*	**13.7** *4.7*
Mean Post Op Meds *Mean Meds % Reduction*	**1.1** *-66%*	**1.1** *-66%*	**1.3** *-57%*
% IOP reduction from Best Rx *From Washout IOP**	**-38%** *-52%*	**-43%** *-55%*	**-39%** *-53%*
% ≤21 mmHg and/or -20%	**100%**	**100%**	**100%**
% ≤18 mmHg and/or -20%	**97%**	**100%**	**100%**
% ≤16 mmHg and/or -30%	**79%**	**92%**	**83%**

* Washout IOP calculated at +30% from medicated

Cypass: Suprachoroidal Stent



Cypass: Suprachoroidal Stent



CyPass

Initial Clinical Experience With the CyPass Micro-Stent: Safety and Surgical Outcomes of a Novel Supraciliary Microstent.

- Mean±SD follow-up was 294±121 days.
- Preoperative baseline mean IOP was 20.2±6.0 mm Hg and mean number of IOP-lowering medications was 2.0±1.1.
- Cohort 1 (>21 mmHg) showed a 35% decrease in mean IOP and a 49% reduction in mean glaucoma medication usage;
- Cohort 2 (< 21 mmHg) demonstrated a 75% reduction in mean medication usage while maintaining mean IOP<21 mm Hg. For all eyes, mean IOP at 12 months was 15.9±3.1 mm Hg (14% reduction from baseline).
- Early and late postoperative IOP elevation occurred in 1.2% and 1.8% of eyes.
- Two subjects demonstarted mild transient hyphema, and
- None exhibited prolonged inflammation, persistent hypotony, or hypotony maculopathy

Alcon Voluntarily Withdraws CyPass Micro-Stent For Surgical Glaucoma From Market

August 29, 2018, 01:21:00 AM EDT By RTT News

Shutterstock photo

(RTTNews.com) - Alcon, the eye care unit of Novartis (NVS), announced Wednesday an immediate, voluntary market withdrawal of the CyPass Micro-Stent from the global market. Alcon also advised surgeons to immediately cease further implantation with the CyPass Micro-Stent and to return any unused devices to Alcon.

The move is based on an analysis of five-year post-surgery data from the COMPASS-XT long-term safety study. The COMPASS-XT study was designed to collect safety data on the subjects who participated in the COMPASS study for an additional three years, with analysis of the completed data set at five years post-surgery. At five years, the CyPass Micro-Stent group experienced statistically significant endothelial cell loss compared to the group who underwent cataract surgery alone.

The US Food and Drug Administration or FDA approved the CyPass Micro-Stent in July 2016 for use in conjunction with cataract surgery in adult patients with mild-to-moderate primary open-angle glaucoma based on the results of the landmark two-year COMPASS study.

The COMPASS study demonstrated a statistically significant reduction in intraocular pressure at two years post-surgery in subjects implanted with the CyPass Micro-Stent at the time of cataract surgery, as compared to subjects undergoing cataract surgery alone.

At two years post- surgery, there was little difference in endothelial cell loss between the CyPass Micro-Stent and cataract surgery-only groups, and results were consistent with peer-review literature benchmarks of cataract-related endothelial cell loss.

Stephen Lane, Chief Medical Officer, Alcon, said, "Although we are removing the product from the market now out of an abundance of caution, we intend to partner with the FDA and other regulators to explore labeling changes that would support the reintroduction of the CyPass Micro-Stent in the future."

The voluntary market withdrawal applies to all versions of the CyPass Micro- Stent.

Preliminary ASCRS CyPass Withdrawal Consensus Statement

ASCRS CyPass Withdrawal Task Force
Leads: Douglas Rhee, MD; Nathan Radcliffe, MD; and Francis Mah, MD
Glaucoma: Leon Herndon, MD; Marlene Moster, MD; Thomas Samuelson, MD; Steven Vold, MD
Cornea: Ken Beckman, MD, FACS; John Berdahl, MD; Marjan Farid, MD; Preeya Gupta, MD

- The COMPASS XT study followed a smaller number of patients than the COMPASS trial. By 60 months, there were roughly 200 CyPass patients and 53 control patients.
- Of note, as the study was being assembled at 36 months, there are too few (n=36 patients) presenting at 36 months to make any meaningful comparisons.
- Aside from ECL, outlined below, there were no other significant safety concerns.
-

CyPass Recall

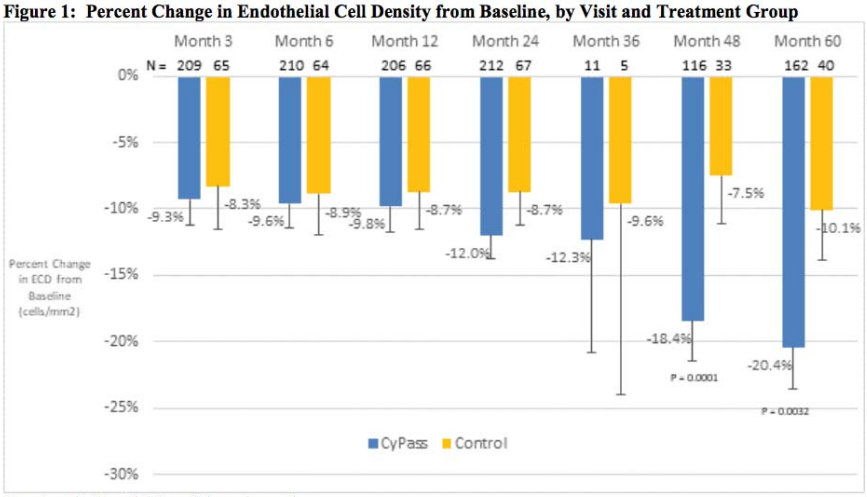
- At 5 years, there was more ECL in CE with CyPass compared to CE alone (control). Baseline endothelial cell counts (ECCs) were 2432 for CyPass and 2434 for control, falling at 48 months to 1992 in CE with CyPass (n=116) vs 2303 in control (n=33) and at 60 months to 1931 in CE with CyPass (n=163) vs 2189 in the control group (n=40).
- This represented an 18.4% reduction in ECL in CE with CyPass vs 7.5% ECL in the control group at month 48, and to a 60-month CE with CyPass ECL of 20.5% compared to 10.1% in the control group.
- The difference in ECL between CE with CyPass and control decreased slightly between 48 and 60 months. ANSI Z80:27 standards consider 30% ECL at 5 years to be meaningful. The percentage loss was 27.2% in CyPass vs 10% in controls.

CyPass Recall

- For eyes with no rings showing (n=69), the rate was 1.39%/year, for 1 ring showing (n=98) 2.74%/year, and for 2-3 rings showing (n=27) 6.96%/year.
- No patients in COMPASS XT required corneal surgery by 5 years. Four patients underwent a CyPass trimming procedure for a CyPass with 3 rings visible in the anterior chamber that was observed in the first postoperative week.
- In all cases, the corneas remained clear and the ECC remained stable at month 60. One patient in the COMPASS trial (two-year follow up) did undergo a Descemet's stripping endothelial keratoplasty (DSEK) at month 13 with the procedure being thought to be related to the CE and not to the CyPass, which was well positioned with 1 ring visible.
- Some eyes with >2 rings visible in the anterior chamber experienced minimal ECL. Thus, clinically relevant, judicious, and periodic monitoring of corneal health is advised.
-

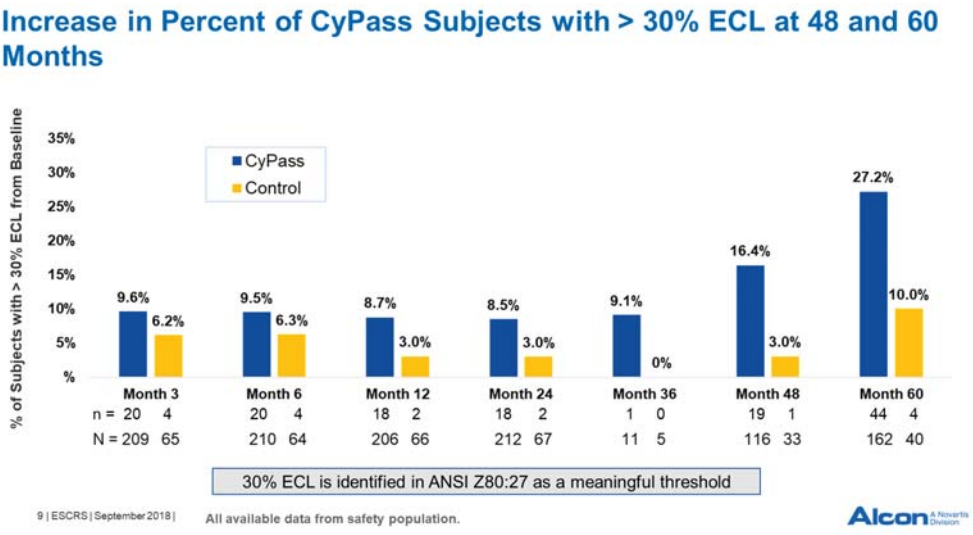
CyPass Recall

Figure 1: Percent Change in Endothelial Cell Density from Baseline, by Visit and Treatment Group

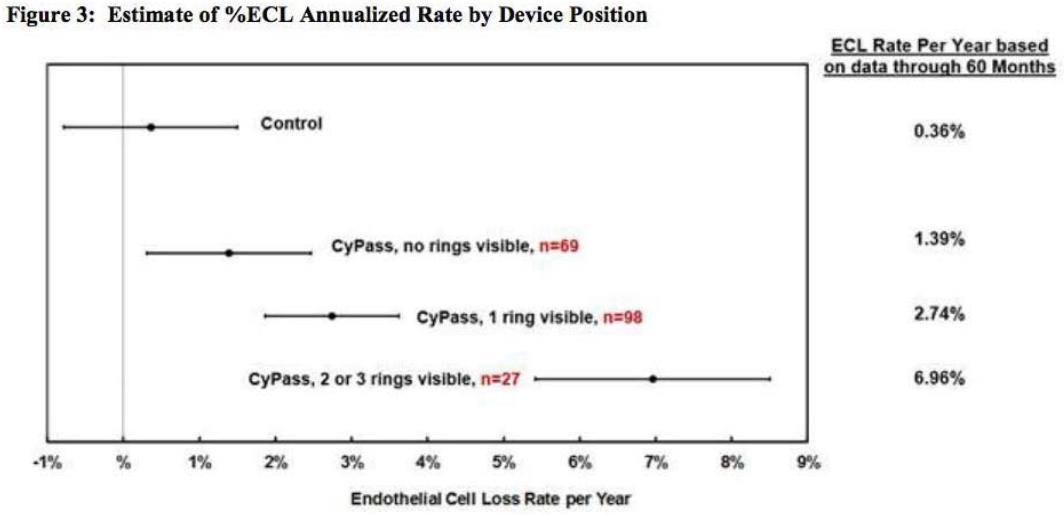


Error bars indicate 95% confidence intervals

CyPass Recall



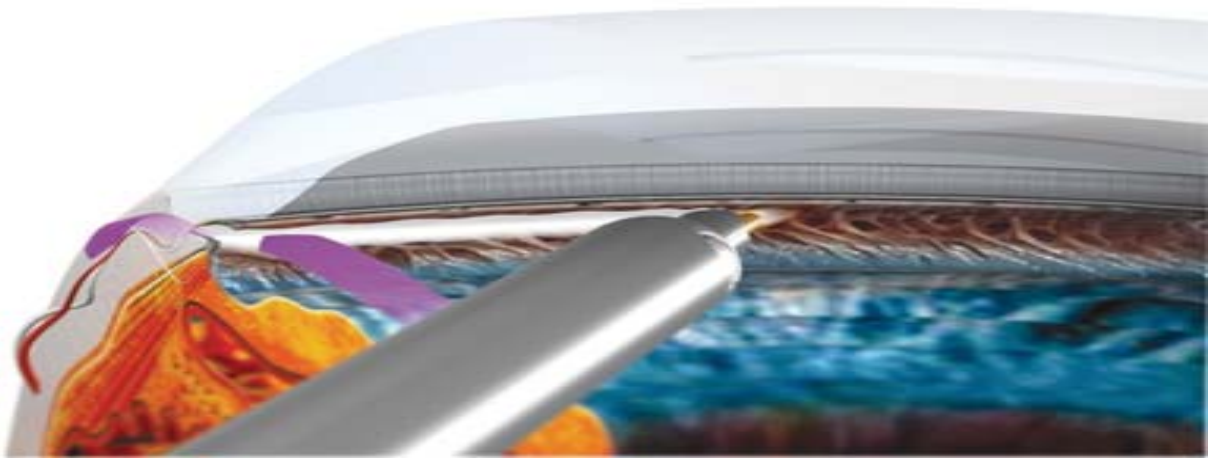
CyPass Recall



Considerations for Device Revision

- If corneal decompensation develops and >1 ring of the device is visible, the surgeon may consider CyPass repositioning, removal, or proximal end trimming.
- It was the consensus of the group that implant repositioning i.e. deeper implantation, would be most safe if performed within 7-10 days of implantation.
- Beyond this time period, there was concern expressed by the group that fibrosis around and/or through the filtration holes of the device may create a higher risk of complications with device repositioning.
- Due to the potential for fibrosis around and possibly investing the device, device removal was not favored by the group.
- Trimming of the proximal end is likely to be the preferred procedure if the patient and physician desire intervention. Technical descriptions of the procedures are described in the CyPass micro-stent Instructions for Use “IFU.”
-

Trabectome



Evaluation of the long-term results of Trabectome surgery
Yildrum,Y etal Int. Ophthalmology 2016

A total of 70 eyes followed up with a diagnosis of open-angle glaucoma (OAG) and undertaken trabectome surgery were included in the study.

The criteria of success were accepted as an IOP value ≤21 mmHg or ≥30 % reduction in IOP and no need for a second operation.

Mean IOP was decreased by 38 % from a preoperative value of 28.77 ± 5.34 to 17.62 ± 2.81 mmHg at the end of 18 months.

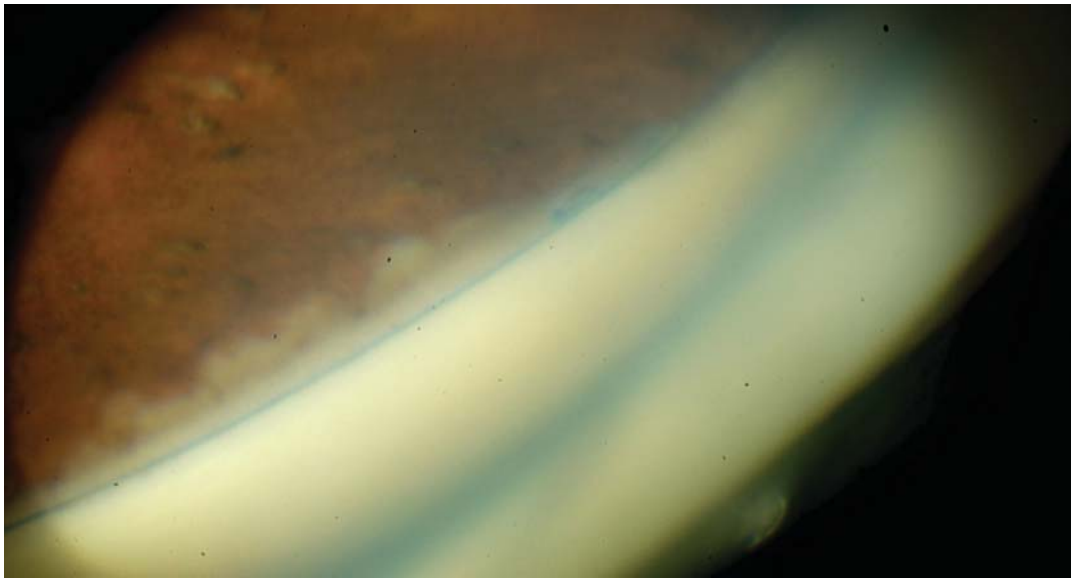
Likewise, mean drug usage was decreased by 48 % from a preoperative value of 3.3 ± 1.01 to 1.7 ± 1.16 at the end of 18 months. Both decreases were statistically significant ($p < 0.05$).

Postoperative success rates were:

1. 82.8 % in the 6th month
2. 81.4 % in the 9th month
3. 77.1 % in the 12th month
4. 470 % in the 18th month.

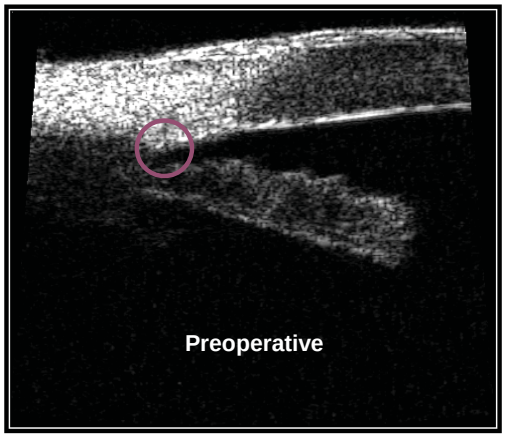
Most common complication observed was intraoperative reflux hemorrhage and no serious complication was observed.

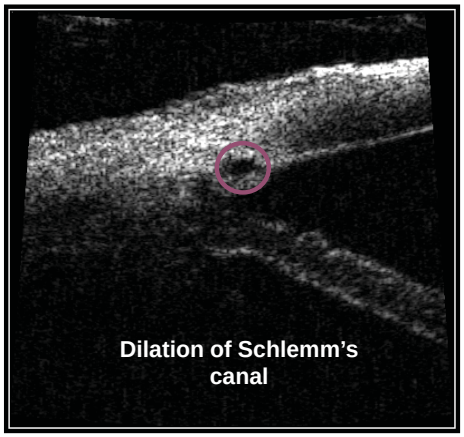
Canaloplasty

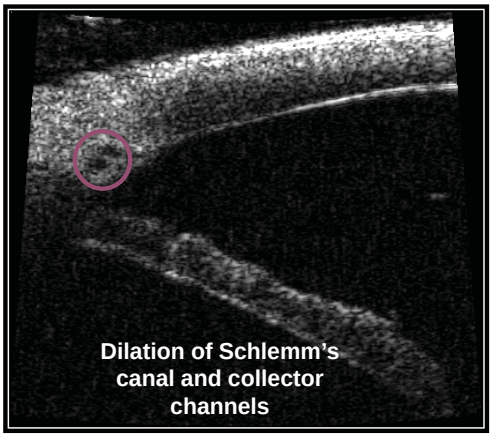


Viscodilation

Dilation of Schlemm's canal visualized with UltraSound







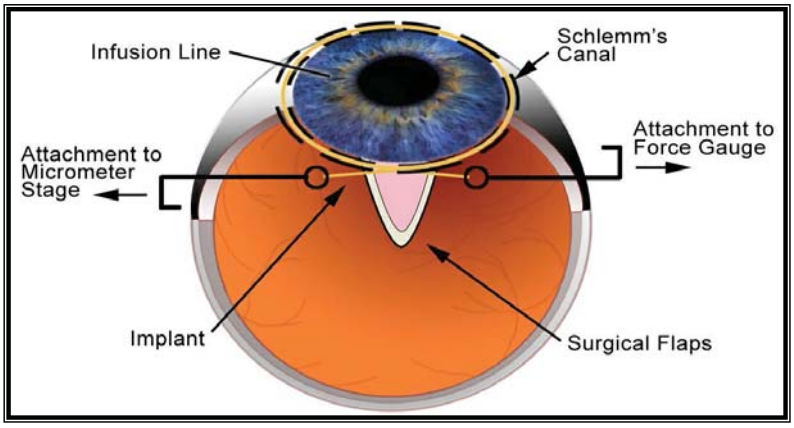
Effects of Suture Tension

Ex-Vivo Perfusion Study, Utilizing Morton Grant Flow Model

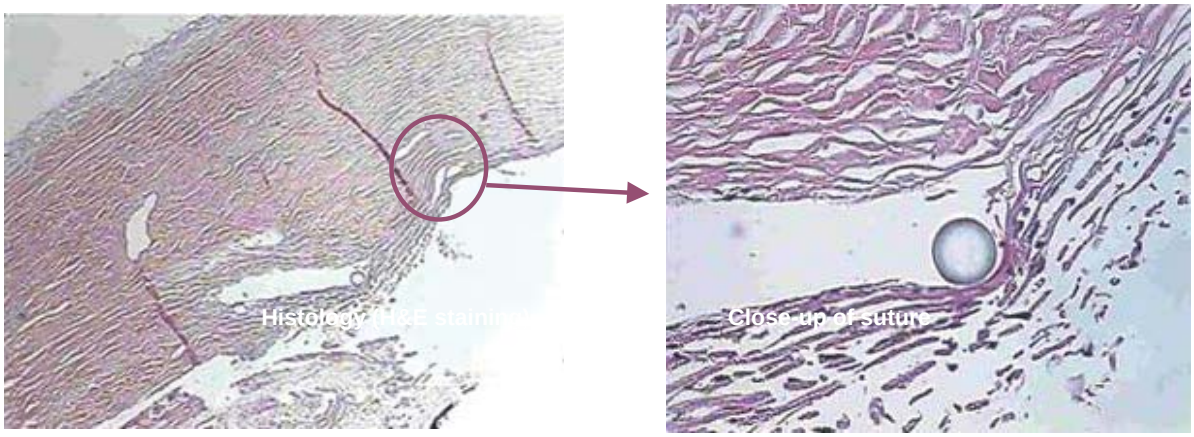
Pressurize globe to a range of physiologic pressures

Apply tension to a suture implanted through the canal

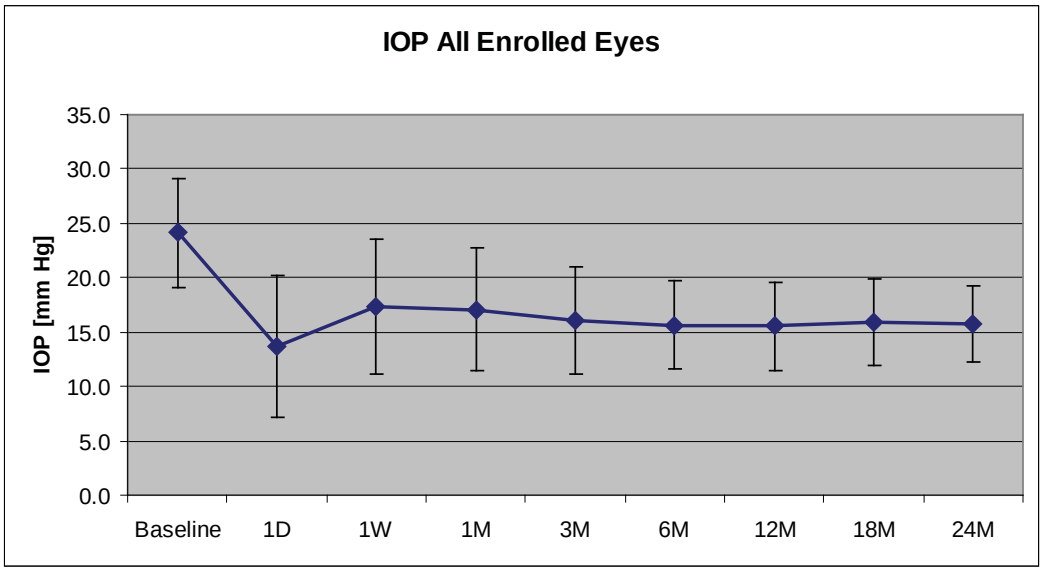
Measure outflow facility (*uL/Min* / *mmHg*)



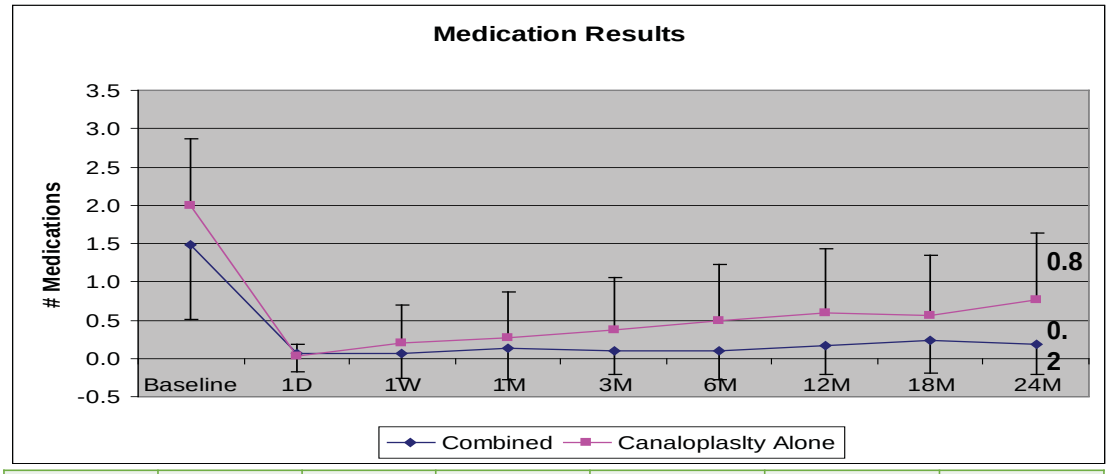
Canaloplasty, Suture Tension



Canaloplasty

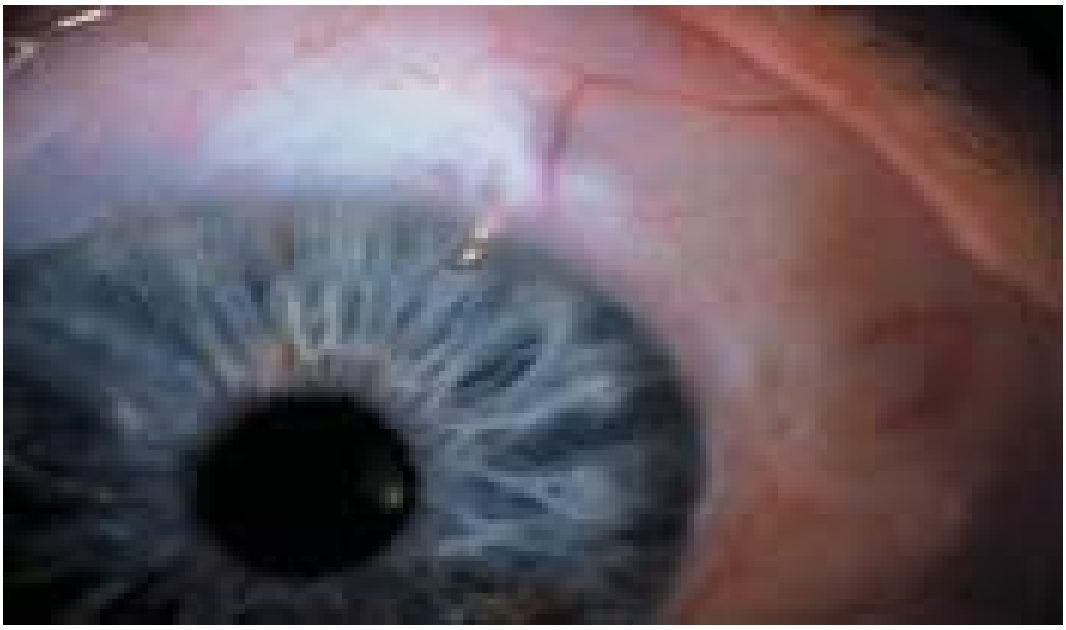


Combined Procedure Results



	Baseline	3 Months	6 Months	12 Months	18 Months	24 Months
Meds/Pt	1.5	0.1	0.1	0.2	0.2	0.2
Meds SD	1.0	0.3	0.4	0.4	0.4	0.4
N	50	41	43	36	26	26
Meds/Pt	2.0	0.4	0.5	0.6	0.6	0.8
Meds SD	0.9	0.7	0.7	0.8	0.8	0.9
N	146	126	118	108	88	66

Trabeculectomy with Express Minishunt



Retrospective Case Series

- Final percent IOP lowering was similar
- Moorefields Bleb Grading System
  - Less vascularity and height but more diffuse area associated with the Ex-PRESS blebs
- Fewer cases of early postoperative hypotony and hyphema
- Quicker visual recovery
  - The Ex-PRESS group required fewer postoperative visits compared with the trabeculectomy group ($P < .000$).

Good TJ. Assessment of bleb morphologic features and postoperative outcomes after Ex-PRESSdrainage device implantation versus trabeculectomy. Am J Ophthalmol. 2011 Mar;151(3):507-13.e1. Epub 2011 Jan 13.

Ex-PRESS in prior operated eyes

- Success complete in 60(60%) and qualified in 24 (24%) eyes
- Mean IOP
  - 27.7 ± 9.2 mm Hg with 2.73 ± 1.1
  - 14.02 ± 5.1 mm Hg with 0.72 ± 1.06 drugs ($p < 0.0001$)
- Failure
  - Uncontrolled IOP (11%)
  - bleb needling (4%)
  - persistent hypotony (1%)

Lankaranian D. Intermediate-term results of the Ex-PRESS(TM) miniature glaucoma implant under a scleral flap in previously operated eyes. Clin Experiment Ophthalmol. 2010 Dec 22.

5 year study Ex-press vs Trabeculoectomy

- EX-PRESS more effective without medication
  - At year 1 12.8% of patients required IOP meds after EX-PRESS implantation vs 35.9% after trabeculectomy
  - At year 5 (41% versus 53.9%)
- Responder rate was higher with EX-PRESS
- Time to failure was longer
- Surgical interventions for complications were fewer after EX-PRESS implantation

deJong et al. Five-year extension of a clinical trial comparing the EX-PRESS glaucomafiltration device and trabeculectomy in primary open-angle glaucoma. Clin Ophthalmol. 2011;5:527-33. Epub 2011 Apr 29.