New Developments in Glaucoma

Disclo$ure Wooldridge

- Speakers Bureau for Aerie, Alcon, Allergan, Bausch, Biotissue, Centervue, Oculus, Optovue, Reichert, Synemed

Relevant Disclosures Bacharach

Aerie	Ono
Alcon	*Optovue*
Allergan	Ora
Eyegate	Rigel
Glaukos	Santen
Heidelberg	Senju
Icon Bioscience	Sun
Injectsense	*Topcon*
Kala	Sylantis
Ocular Therapeutix	Valeant

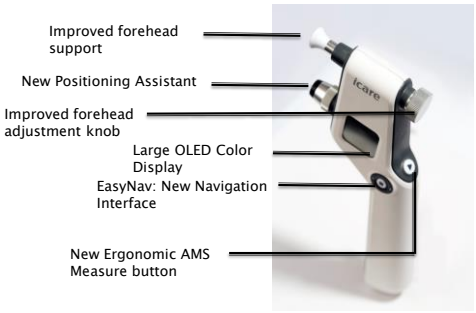
Flume Trail, Tahoe, Ca

What's New With Tonometry?

iCare Tonometer

- New design
- Enhanced Ergonomics
- Easy to use
- Accurate
- Precise

iCare Features

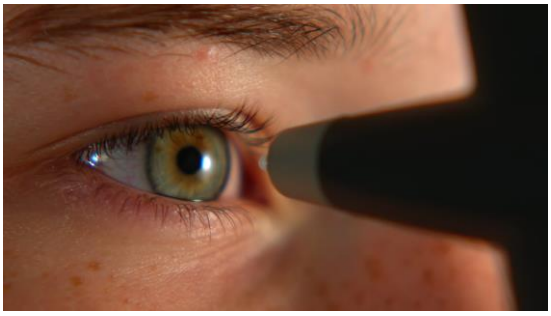


Rebound Technology

- Easy-to-use
- Quick, effective routine barely noticeable by the patient
- **No topical anaesthetics or disinfection needed**
- Disposable probe touches the cornea very lightly
- Suitable also for non-compliant patients and children
- Proven **accurate** by several independent studies
- Truly **portable**

Measurement Basics

- The probe touches the cornea very gently
- Measurement takes place in 0.1 seconds
- Corneal reflex after 0.2 seconds
- Measurement of motion parameters
- To be repeated 6 times in order to minimize deviation and to produce a calculated measurement value
- Whole procedure (6x both eyes) takes about one minute



Rebound Tonometry is Accurate

- Bench testing
- Repeatability (coefficient of variation): <8%

Range of IOP	Accuracy
≤ 20 mmHg	± 1.2 mmHg
> 20 mmHg	± 2.2 mmHg

Clinical Studies

REPRODUCIBILITY AND TOLERABILITY OF THE ICARE REBOUND TONOMETER IN SCHOOL CHILDREN

"Measurement of intraocular pressure (IOP) with the rebound tonometer (RBT) is a highly reproducible method in schoolchildren showing high intraobserver and interobserver correlation and it seems to be very comfortable when performing IOP measurements in schoolchildren without an anesthetic."

Sahin A, Basmak H, Niyaz L, Yildirim N.
J Glaucoma. 2007 Mar;16(2):185-8

AGREEMENT OF REBOUND TONOMETER IN MEASURING INTRAOCULAR PRESSURE WITH THREE TYPES OF APPLANATION TONOMETERS

"iCare agrees well with applanation tonometers"

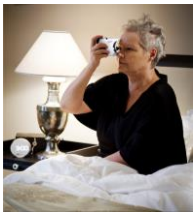
Nakamura M, Darhad U, Tatsumi Y, Fujioka M, Kusuhara A, Maeda H, Negi A
Am J Ophthalmol, 2006 Aug;142(2):332-4

iCare HOME tonometer

- Intended as an adjunct for monitoring IOP of adult patients (self-use). The HOME tonometer is designed for use at home or on the go.

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.



Positioning Light

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

Correct alignment | Incorrect alignment | Incorrect alignment

Automatic Eye Recognition

Automatic eye recognition system that identifies which eye is being measured.

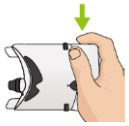
- Two infrared LED transmitters below probe (1)
- One infrared LED sensor above probe (2)
- The infrared light is reflected from nose back to the sensor
- The sensor knows from which transmitter the reflected infrared light came from and thus which eye, right or left, was measured
- The resulting eye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

Automatic Measurement Sequence

The tonometer can operate in two modes:

Series mode

Pressing the measurement button for a sustained period of time (more than 2 seconds) initiates the measurement function and the tonometer takes six measurements in rapid succession

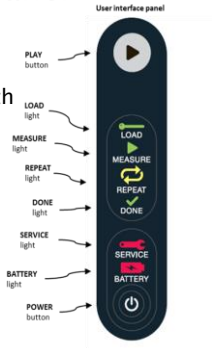


Single mode

The measurement button must be pressed each time to initiate the measurement, i.e. six samples for the whole measurement cycle

New User Interface Panel

- Simple Indicator Lights and Audible Alerts
- Interpretation only by a health care professional
- Does not display the IOP measurement
  - Mitigating concerns that the patient or caregiver might improperly use the information provided by the device



Should we adjust our GAT value based on the CCT?

Adjusting IOP for CCT Does Not Improve Prediction Models for POAG

- Reanalysis of the baseline prediction model for the development of POAG from OHTS substituting IOP adjusted for CCT for unadjusted IOP
- CONCLUSION:
- The calculation of individual risk for developing POAG in ocular hypertensive individuals is simpler and equally accurate using IOP and CCT as measured, rather than applying an adjustment formula to correct IOP for CCT.

Brandt JD Gordon MO et al Ophthalmology 2012 Mar;119(3):437-42

CCT in OHTS

"Assuming that CCT can be used as a correction factor for GAT is a misinterpretation of the results of OHTS… that couldn't be further from the truth. Adjusting IOP based on CCT is attempting to instill a degree of precision into a *flawed measurement*. You may actually correct in the wrong direction. The issues related to the most accurate tonometry need to include the material properties of the cornea"

James Brandt, MD
Director Glaucoma Services
UC Davis

The Cornea and IOP Measurement

"Correction nomograms that adjust GAT IOP based solely on CCT are neither valid nor useful in individual patients"

– Pg 18. Robert N. Weinreb, James D. Brandt, David Garway-Heath and Felipe Medeiros
World Glaucoma Association on Intraocular Pressure; Consensus Series 4; May 5, 2007

"We should not assume that corneal thickness is the parameter of greatest interest in monitoring glaucoma or in determining what features of the eye are important in optic nerve damage. Physiology is more important than anatomy"

– Harry Quigley, Director of Glaucoma Service, Wilmer Eye Institute

The problem with CCT-based IOP adjustment

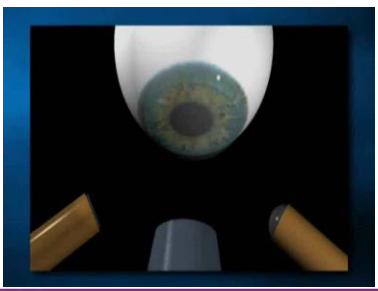
Thickness is NOT resistance

Ocular Response Analyzer Technology
The instrument

- 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})

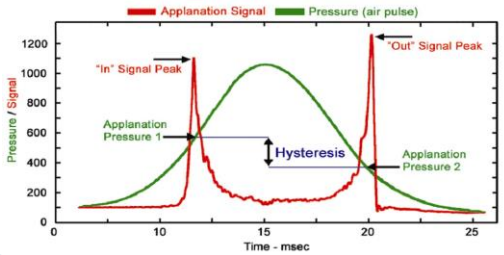
Ocular Response Analyzer Technology
How does it work?



Ocular Response Analyzer Technology

Corneal Deformation – 15 mmhg equivalent puff

Applanation Signal Plot



Define & Describe IOPcc

Corneal-Compensated Intraocular Pressure

- An Intraocular Pressure measurement that is less affected by corneal properties than other methods of tonometery, such as Goldmann (GAT). IOPCC has essentially zero correlation with CCT in normal eyes and stays relatively constant post-LASIK.
- – **IOPcc = P2 – (0.43*P1)**

ORA vs GAT: Biomechanical Properties of the cornea

- 153 eyes of 78 subjects (Normals, no OAG)
- Measured
  - Goldmann tonometry
  - IOPcc using Ocular Response Analyer
  - CCT
    Corneal curvature
  - Axial Length

Medeiros FA Weinreb RN J Glaucoma 2006;15:364-370

Results

- GAT IOP measurements were significantly associated with CCT (P=0.001)
  - Each100 um increase in CCT resulted in 2.7mm Hg increase in GAT IOP (P=0.001)
- and corneal curvature (P<0.001)
  - Each 1.0-um increase in the radius of corneal curvature resulted in3.3mm Hg decrease in GAT IOP (P<0.001)
- Axial length was not associated with GAT
- ORA IOPCC measurements were not associated with any of the ocular variables

Results/Conclusion

- The difference between GAT and IOPCC measurements was significantly influenced by CCT
  - Thicker corneas have higher GAT IOP measurements compared with IOPCC
  - In thin corneas, GAT IOP measurements tended to be lower than IOPCC.
- ORA IOPCC measurements seem to provide an estimate of IOP that is less influenced by corneal properties than those provided by GAT

Corneal Hysteresis as a Risk Factor for Development of Glaucoma

- Prospective observational study
  - 287 eyes of 199 patients suspected of having glaucoma followed for an average of 3.9 ± 1.8 yrs
  - VF normal at baseline
  - ***Progression =3 consecutive abnormal VF's***
- 54/287 (19%) showed progression
- CH lower in those showing progression
  - 9.5 +/- 1.5 mmHg in progressing
  - 10.2 +/-2.0 mmHg in non progressing P=0.012
  - Each 1mm lower CH means 22% greater risk progr.
  - Still predictive in multivariate analysis
    - After adjusting for age, IOP, CCT, PSD

Medeiros FA, Meira-Freitas D et al, *Ophthalmology* 2013;120(8):1533-1540.

Corneal Hysteresis and Progressive RNFL Loss in Glaucoma

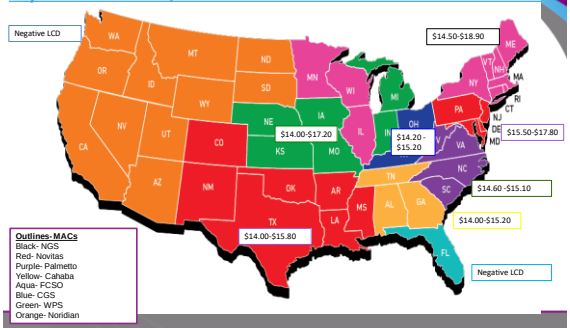
- 186 eyes of 133 patients with OAG followed for an average of 3.8 ± 0.8 years
- Investigate the relationship between baseline CH, CCT, average IOP and rates of RNFL loss during follow up
- Each 1mmHg lower CH was associated with a 0.13 um per year faster rate of RNFL loss. (P=0.015)
- GAT IOP was also associated with a faster rate of RNFL loss (P=0.010)
- CCT, older age and AA ancestry were ***not*** associated with faster rate of RNFL loss

Zhang C, Tatham AJ, Abe RY, Diniz-Filho A, Zangwill LM, Weinreb RN, Medeiros FA, AJO (2016), doi: 10.1016/j.ajo.2016.02.034

Implementing ORA in Your Practice
Reimbursement

- CPT code 92145 - code published January 1, 2015
  - 92145:Corneal hysteresis determination, by air impulse stimulation, unilateral or bilateral with interpretation and report
  - According to *An Insider's View* published by the AMA: "this test achieved Category I status because the clinical utility has been established and usage has grown since 2007 when the Category III code was implemented"
- Reichert is working with consultants, regional champion MDs, and MAC directors in strategic fashion to ensure positive payment policies (LCDS)
- Bilateral reimbursement approximately $16.00

Payments for 92145, Medicare Administrative Contracts: Jan 2016



Source: https://www.cms.gov/apps/physician-fee-schedule/search/search-results.aspx?Y=0&T=4&HT=1&CT=1&H1=92145&C=42&M=5

Wooldridge Conclusions

- Do use Goldmann
  - But recognize its limitations!
  - 60 year-old technology
- ORA Probably better, truer IOP measurements
- Currently using both instruments
- Frequently vary in IOP measurements

What's New in Perimetry

Should we do 10-2 Visual fields?

Prevalence and Nature of Early Glaucomatous VF Defects on 10-2

- 100 glaucomatous eyes with 24-2 MD < 6dB
  - Tested with 10-2
- As many abnormal 10-2 hemifields (53%) as abnormal 24-2 hemifields (59%).
- Of the eyes with normal 24-2 hemifields, 16% were classified as abnormal with the 10-2 test
- Of the abnormal 10-2 hemifields, 68%, 8%, and 25% were arcuatelike, widespread, and other, respectively
- Superior VF defects were deeper and closer to fixation than those in the inferior VF

Traynis I, JAMA Oph 2014;132(3):291-297.

Conclusion

- The 10-2 VF was abnormal in nearly as many hemifields as was the 24-2 VF, including some with normal 24-2 VF, suggesting that the 24-2 test is not optimal for detecting early damage of the macula.
- The pattern of the defects was in agreement with a recent model of macular damage.

10-2 vs. 24-2 VF Progression Analysis in Glaucoma

- Compare the efficacy of 10-2 vs. 24-2 VFs in detecting progression of initial parafoveal scotoma (IPFS) in glaucomatous eye
- 50 eyes followed for 5.7 years
- Ave. of 7.7 VF's obtained

Yungtai Kung; Sung Chul Park; Joseph Simonson; Daniel Su; Carlos Gustavo V. De Moraes; Xian Zhang; Donald C. Hood; Jeffrey M. Liebmann; Robert Ritch Invest Oph Visual Science March 2012, Vol.53, 202

Results

- Mean global progression rate was significantly greater in 10-2 analysis (-0.40±0.51 dB/yr) than in 24-2 analysis (-0.23 ± 0.28 dB/yr) (P=0.01).
- Within the central 10 degrees of VF, 10-2 analysis detected significantly more progressing eyes than 24-2 analysis (24 vs. 7 eyes; P<0.001).
- Within the central 10 degrees, mean localized progression rate (-1.3 vs. -0.4 dB/yr) and mean number of progressing points (2.5 vs. 0.5) were significantly greater in 10-2 than in 24-2 analyses (10-2 vs. 24-2; all P<0.001).

Conclusion

- In glaucoma patients with an IPFS, the 10-2 VF detects more progressing eyes than the 24-2 VF, suggesting that closer surveillance of the central VF using 10-2 VF is warranted in these eyes.

Comparing Glaucoma Progression on 24-2 and 10-2 Visual Field's

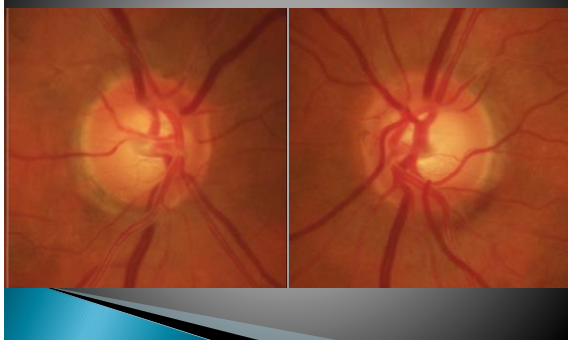
- Compared mean deviation change on 10-2 and 24-2 VF's
- 167 eyes with glaucoma
- Mean of 9 VF's obtained over 9 years FU
- Compared the rates of MD change in eyes with different severities of VF loss (early [MD better than −6 dB], moderate [−6 dB to −12 dB], advanced [−12 to −20 dB] and severe [MD worse than −20 dB]) at baseline (based on the MD on 24-2 VF)
- Median rate of MD change was comparable in mild (−0.45 dB/year vs. −0.40 dB/year, $P = 0.42$) and moderate (−0.32 dB/year vs. −0.40 dB/year, $P = 0.26$) VF loss categories
- Significantly greater on 10-2 VFs in advanced (−0.28 dB/year vs. −0.21 dB/year, $P = 0.04$) and severe (−0.18 dB/year vs. −0.06 dB/year, $P<0.001$) VF loss categories

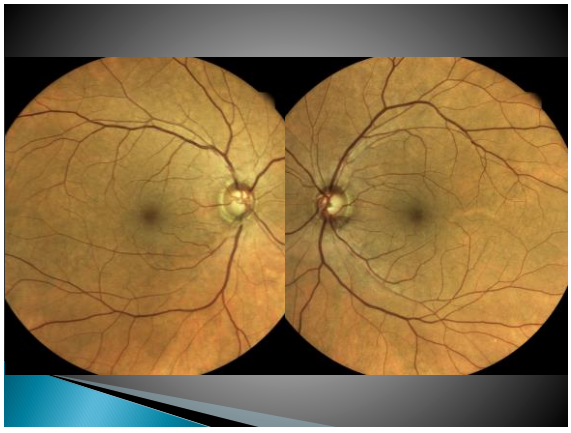
Rao HL, Begum VU et al PLOS ONE | DOI:10.1371/journal.pone.0127233 May 15, 2015

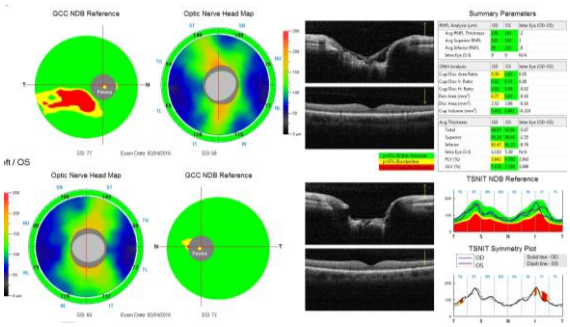
Annette

- 69yoWF referred with large cups
- IOP
  - R 16, 11, 14 mmHg
  - L 18, 13 , 16 mmHg
  - (three separate exams)
- ORA IOP R 15.3 L 17.5 CH R 9.8 L 9.9
- CCT R 599 L 603

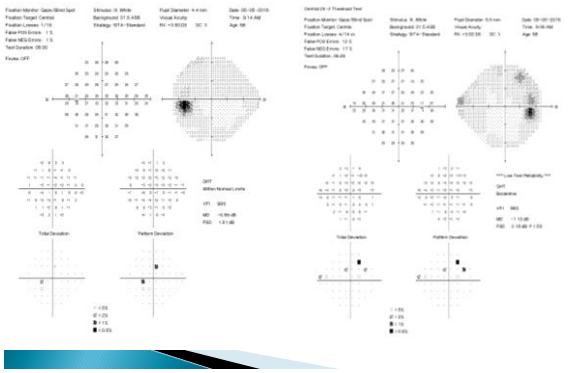
Annette 1 11 17



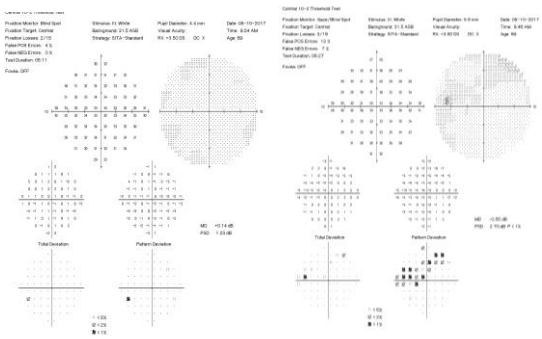


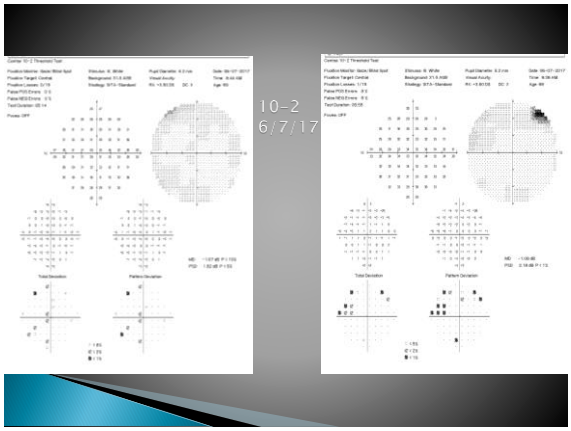


24-2 5/5/16



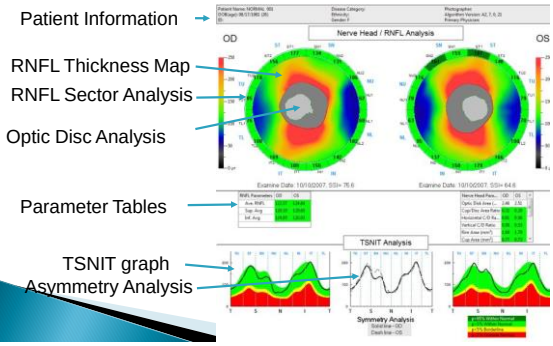
10-2 5/10/17





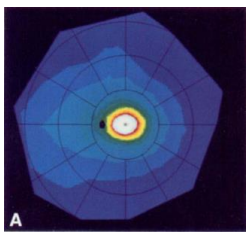
What's New in Imaging

Nerve Head Map (NHM4)
with Database comparisons



Macular Ganglion cell density

- 50% of ganglion cells located in central 4.5mm
- Peak ganglion cell density is 15,000 cells/mm^2 in macula(white region)
- GCC map covers central 6mm area

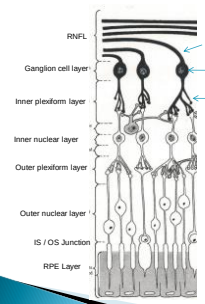


Topography of Ganglion Cells in Human Retina

CHRISTINE A. CURCIO AND KIMBERLY A. ALLEN

THE JOURNAL OF COMPARATIVE NEUROLOGY 300:5-25 (1990)

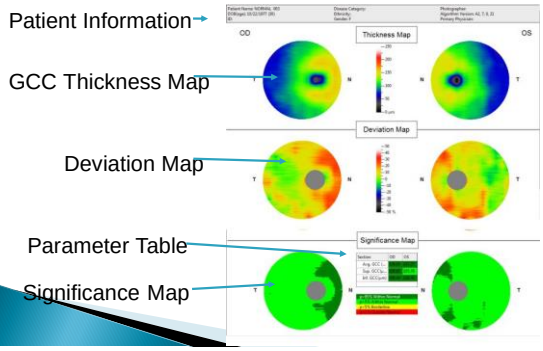
Retinal Ganglion Cells extend through three retinal layers



GCC is:

- Nerve Fiber Layer – Ganglion cell axons
- Ganglion cell layer – Cell bodies
- Inner-Plexiform Layer - Dendrites

Ganglion Cell Complex (GCC)
with Database comparisons



Diagnostic Accuracy: GCC vs FD OCT RNFL with RTVue

- Rao et al. found GCC had similar accuracy levels as FD RNFL (AROC = 0.81 for GCC vs 0.88 for RNFL)
- Seong et al. found similar results (AROC = 0.95 for GCC and 0.97 for RNFL)
- Kim et al. found AROC **values were higher for RNFL vs GCC in a group of advanced glaucoma** patients (AROC = 0.92 for GC vs 0.96 for RNFL), but **GCC values were higher than RNFL in a group of early glaucoma** patients (AROC = 0.83 for GCC vs 0.78 for RNFL)

Rao HL, Zangwill LM, Weinreb RN et al. Ophthalmology 2010; in press.
Seong M, Sung KR, Choi EH, et al. Invest Ophthalmol Vis Sci 2010; 51:1446-1452.
Kim NR, Lee ES, Sung GJ, et al. Invest Ophthalmol Vis Sci 2010; in press

RTVue FD OCT: GCC vs Disc vs RNFL

- Huang et al. compared the diagnostic accuracy for GCC, optic disc, and RNFL from the RTVue
- AROC for RNFL was highest (AROC = 0.92), with GCC second (AROC = 0.86), and vertical C/D ratio a close third (AROC = 0.854)
- They found the accuracy improved when they combined all three structures in an LDF (AROC = 0.97)

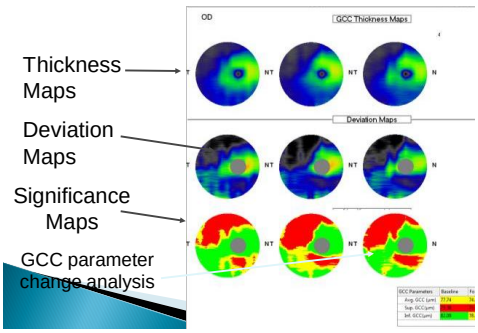
Huang JY, Pekmezci M, Mesiwala N, Kao A, Lin S. J of Glaucoma 2010

Ability of Fourier-domain OCT to Detect GCC Atrophy in Glaucoma Patients

- 113 patients with different stages of glaucoma; 30 normals
- Imaged NFL and GCC with Optovue RTVue-100
- Conclusions:GCC and NFL thickness measurements performed by FD-OCT showed high diagnostic ability in detecting glaucoma. Mean thickness values can be determined for each glaucoma stage.

Sevim MS; Buttanri B Journal of Glaucoma. 22(7):542-549, September 2013.

Glaucoma Progression Analysis
(GCC of stable glaucomatous eye)

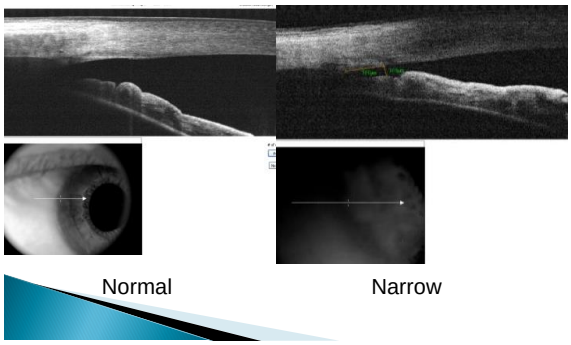


Age Effects on NFL and GCC

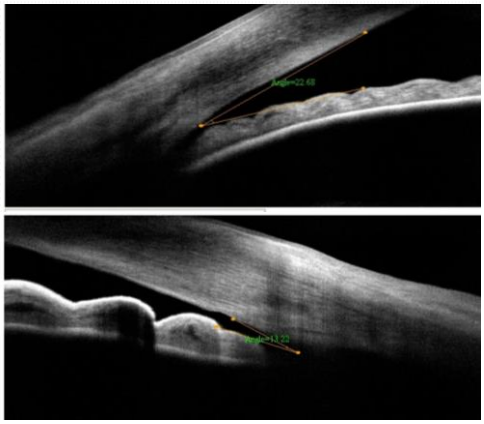
- Studied longitudinal (4 years) and cross sectional age and IOP effects on 192 normals (40-75yo)
- NFL thickness decreased 0.14 +/- 0.07 um per year (P = 0.04)
- NFL was 0.21 +/- 0.06 um thinner (P < 0.001).
- GCC thickness decreased 0.25 +/- 0.05 um per year (P < 0.001)
- GCC thickness was 0.17 +/- 0.05 um thinner per year of baseline age (P < 0.001)
- ***Equivalent to 0.2% per year***
- IOP had no effect on rate of thinning

Zhang X, Francis BA, et al. Trans Vis Sci Tech. 2016;5(2):1, doi:10.1167/5.2.1

Angle Measurements



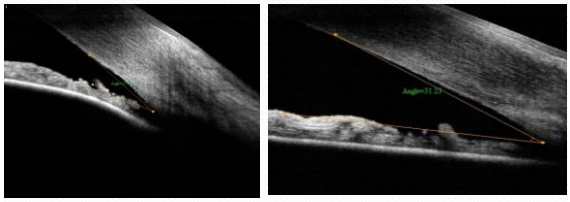
Normal Narrow



OD

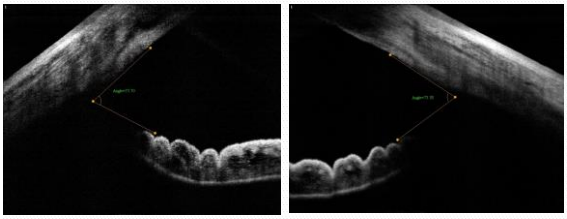
OS

OCT Angle



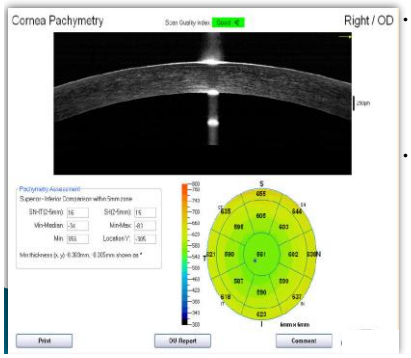
Pre-LPI Post-LPI

PDS with Iris Concavity



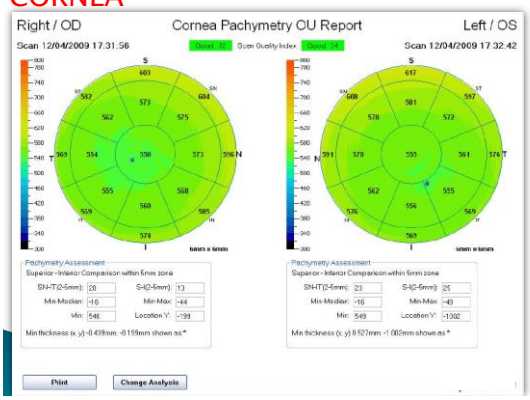
OD OS

CORNEA



- Full 6x6mm Pachymetry Mapping
  - Minimum Thickness Marker
- Change & Symmetry Analysis

CORNEA



What's New in Medical Treatment

VYZULTA (latanoprostene bunod ophthalmic solution), 0.024%

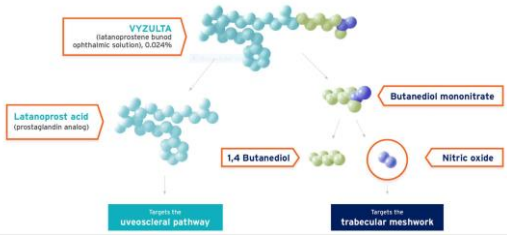
- **VYZULTA is metabolized into 2 moieties[1,6,7]**
- Latanoprost acid, a prostaglandin analog, works primarily within the uveoscleral pathway[2,8]
- Butanediol mononitrate releases nitric oxide, which is thought to relax the trabecular meshwork[9–12]

VYZULTA (latanoprostene bunod ophthalmic solution), 0.024%

- Indicated for the reduction of intraocular pressure (IOP) in patients with OAG or OHTN
- Increased pigmentation of the iris and periorbital tissue (eyelid) can occur. Iris pigmentation is likely to be permanent
- Gradual changes to eyelashes, including increased length, increased thickness, and number of eyelashes, may occur. These changes are usually reversible upon treatment discontinuation
- Use with caution in patients with a history of intraocular inflammation (iritis/uveitis). VYZULTA should generally not be used in patients with active intraocular inflammation
- Macular edema, including cystoid macular edema, has been reported during treatment with prostaglandin analogs. Use with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema
- There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products that were inadvertently contaminated by patients
- Contact lenses should be removed prior to the administration of VYZULTA and may be reinserted 15 minutes after administration
- Most common ocular adverse reactions with incidence ≥2% are conjunctival hyperemia (6%), eye irritation (4%), eye pain (3%), and instillation site pain (2%)

VYZULTA Prescribing Information. Bausch & Lomb Incorporated. 2017.

Metabolized into two molecules



Vyzulta qd vs. Timolol 0.5% bid

In APOLLO, baseline mean diurnal IOP was 26.7 mmHg and 26.5 mmHg in patients randomized to VYZULTA and timolol 0.5%, respectively[1]

APOLLO STUDY DESIGN

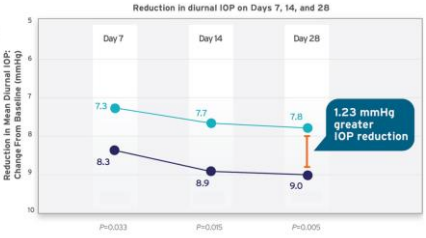
Weinreb RN, Sforzolini BS, et al *Ophthalmology.* 2016;123(5):965-973.

Vyzulta qd vs. Latanoprost qd

In the VOYAGER dose-ranging study, VYZULTA 0.024% lowered mean diurnal IOP by 1.23 mmHg more than latanoprost 0.005% at Day 28[5]

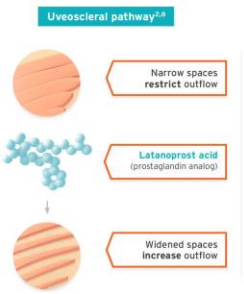
- LATANOPROST 0.005% (N=82)
- VYZULTA (LBN 0.024%) (N=83)

VOYAGER STUDY DESIGN

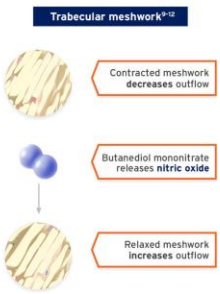


Weinreb RN, Ong T, Scassellati SB, et al. *Br J Ophthalmol.* 2015;99(6):738-745.

Latanoprost



Nitric Oxide



Vyzulta (latanoprostene bunod)

- There was a significant IOP reduction with the latanoprostene bunod treatment during the diurnal/wake period and during the nocturnal/sleep period compared to baseline. The nocturnal IOP-lowering effect of latanoprostene bunod appeared less than the effect during the diurnal period. Posture was not a factor for the relatively smaller nocturnal IOP-lowering effect, since both the 24-hour supine IOP profile and the 24-hour habitual IOP profile showed comparable diurnal vs nocturnal IOP reductions from the baselines.

Discussion

- Low OPP has been proposed as a risk factor for glaucomatous damages. Alteration of OPP pressure can occur by changes in BP and/or IOP. Although the mean arterial blood pressure did not change significantly under either test agent of latanoprostene bunod or timolol over the 24-hour period, the latanoprostene treatment increased the diurnal OPP over the baseline owing to a significant IOP reduction during the diurnal period. Treatment with timolol showed no significant effect on diurnal OPP, probably because of a relatively smaller IOP reduction. Results also showed a greater nocturnal OPP under the latanoprostene treatment compared to the timolol treatment, reflecting the smaller effect of timolol on IOP lowering combined with some reduction in MABP. The latanoprostene treatment is expected to be more beneficial than the timolol treatment if one considers the difference in ocular perfusion pressure during the day and at night.

Summary

- Treatment with latanoprostene bunod 0.024% once daily resulted in IOP lowering during the diurnal/wake period as well as during the nocturnal/sleep period. Treatment with latanoprostene bunod showed a greater nocturnal IOP-lowering efficacy compared to treatment with timolol 0.5% solution twice daily. Latanoprostene bunod treatment significantly increased diurnal ocular perfusion pressure from the baseline. Ocular perfusion pressure during the nocturnal period was higher under latanoprostene bunod treatment than under timolol treatment.

Vyzulta References

- 1. VYZULTA Prescribing Information. Bausch & Lomb Incorporated. 2017.
- 2. Braunger BM, Fuchshofer R, Tamm ER. The aqueous humor outflow pathways in glaucoma: a unifying concept of disease mechanisms and causative treatment. *Eur J Pharm Biopharm.* 2015;95(Pt B):173-181.
- 3. Tamm ER, Braunger BM, Fuchshofer R. Intraocular pressure and the mechanisms involved in resistance of the aqueous humor flow in the trabecular meshwork outflow pathways. *Prog Mol Biol Transl Sci.* 2015;134:301-314.
- 4. Winkler NS, Fautsch MP. Effects of prostaglandin analogues on aqueous humor outflow pathways. *J Ocul Pharmacol Ther.* 2014;30(2-3):102-109.
- 5. Cavet ME, DeCory HH. The role of nitric oxide in the intraocular pressure lowering efficacy of latanoprostene bunod: review of nonclinical studies. *J Ocul Pharmacol Ther.* 2017 Aug 7. doi: 10.1089/jop.2016.0188. [Epub ahead of print]
- 6. Krauss AH, Impagnatiello F, Toris CB, et al. Ocular hypotensive activity of BOL-303259-X, a nitric oxide donating prostaglandin F2alpha agonist, in preclinical models. *Exp Eye Res.* 2011;93:250-255.
- 7. Cavet ME, Vollmer TR, Harrington KL, VanDerMeid K, Richardson ME. Regulation of endothelin-1-induced trabecular meshwork cell contractility by latanoprostene bunod. *Invest Ophthalmol Vis Sci.* 2015;56(6):4108-4116.
- 8. Weinreb RN, Khaw PT. Primary open-angle glaucoma. *Lancet.* 2004;363:1711-1720.
- 9. Cavet ME, Vittitow JL, Impagnatiello F, et al. Nitric oxide (NO): an emerging target for the treatment of glaucoma. *Invest Ophthalmol Vis Sci.* 2014;55:5005-5015.
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- 11. Schneemann A, Dijkstra BG, van den Berg TJ, et al. Nitric oxide/guanylate cyclase pathways and flow in anterior segment perfusion. *Graefes Arch Clin Exp Ophthalmol.* 2002;240:936-941.
- 12. Wiederholt M, Sturm A, Lepple-Wienhues A. Relaxation of trabecular meshwork and ciliary muscle by release of nitric oxide. *Invest Ophthalmol Vis Sci.* 1994;35:2515-2520.
- 13. Doganay S, Evereklioglu C, Turkoz Y, et al. Decreased nitric oxide production in primary open-angle glaucoma. *Eur J Ophthalmol.* 2002;12:44-48.
- 14. Galassi F, Renieri G, Sodi A, et al. Nitric oxide proxies and ocular perfusion pressure in primary open angle glaucoma. *Br J Ophthalmol.* 2004;88:757-760.
- 15. Nathanson JA, McKee M. Alterations of ocular nitric oxide synthase in human glaucoma. *Invest Ophthalmol Vis Sci.* 1995;36:1774-1784.

Rhopressa (netarsudil ophthalmic solution) 0.02%

- Rho kinase inhibitor indicated for the reduction of elevated IOP in patients with OAG or OHTN
- Believed to lower IOP by increasing outflow through TM

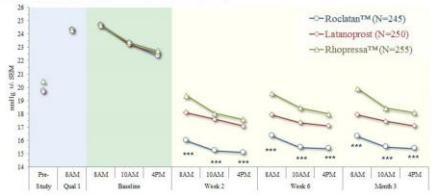
Roclatan (netarsudil ophthalmic solution) 0.02% and latanoprost

- May be first glaucoma product to lower IOP through all 4 mechanisms:
- increasing aqueous outflow through both the trabecular meshwork and the uveoscleral pathway,
- reducing aqueous production in the eye
- reducing episcleral venous pressure.
- Superior to its two components netarsudil and latanoprost used separately.

Roclatan

Roclatan Achieved Statistical Superiority Over Individual Components at All 9 Time Points

Mean IOP at Each Time Point (ITT)



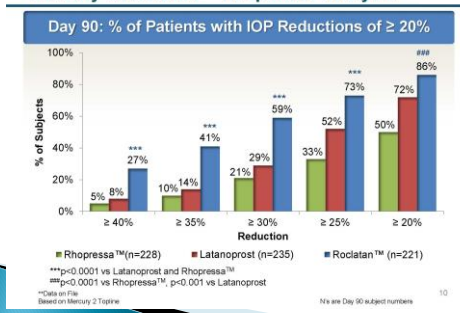
***p<0.0001 vs Latanoprost and Rhopressa™

Same p values obtained in Per Protocol, LOCF analyses

**Data on File
Based on Mercury 2 Topline

Rhopressa Latanoprost Roclatan

Mercury 2 Roclatan Responder Analysis



***p<0.0001 vs Latanoprost and Rhopressa™

###p<0.0001 vs Rhopressa™, p<0.001 vs Latanoprost

**Data on File
Based on Mercury 2 Topline

N's are Day 90 subject numbers

Roclatan Achieves Primary Efficacy Endpoint in Mercury 2

- Roclatan™ met the criteria for demonstrating superiority (p<0.0001) over both latanoprost and Rhopressa™ for the primary efficacy analysis
- IOP-lowering effect of Roclatan™ was greater (1-3 mmHg) than monotherapy with either latanoprost or Rhopressa™ throughout the duration of the study (i.e., Week 2, Week 6, Month 3)
- Roclatan™ reduced mean diurnal IOPs to 16 mmHg or lower in 56% of patients, a significantly higher percentage than observed in the comparator arms (25% Rhopressa™, 36% latanoprost)
- The most common adverse event for Roclatan™ was conjunctival hyperemia, which was reported in nearly 55% of patients and was scored as mild for ~70% of these patients
- There were no drug-related serious or systemic adverse events

Mercury 2 Results Consistent with Mercury 1 90-day Efficacy Results

**Data on File
Based on Mercury 1 Topline Interim 3-Month and Mercury 2 Topline

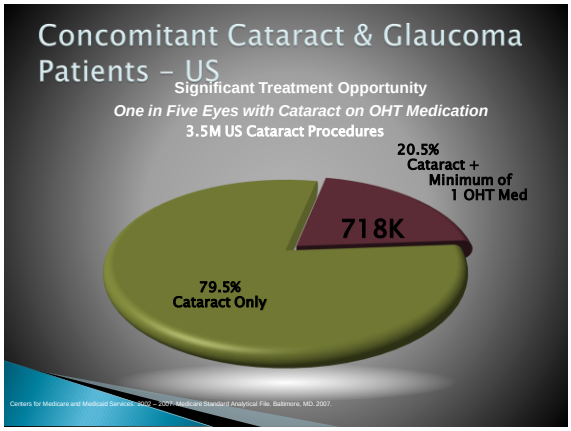
Recent Trends in Glaucoma Surgery

Minimally Invasive Glaucoma Surgery (MIGS)

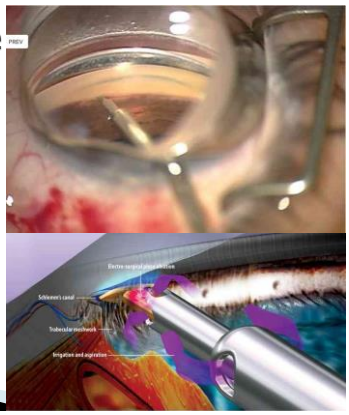
- Bypass trabecular meshwork or use suprachoroidal approach
- Usually performed in conjunction with cataract surgery
- More effective in lowering IOP than Phaco alone
- Easier for surgeon and patient than trabeculectomy though less effective
- May reduce or eliminate dependence on meds

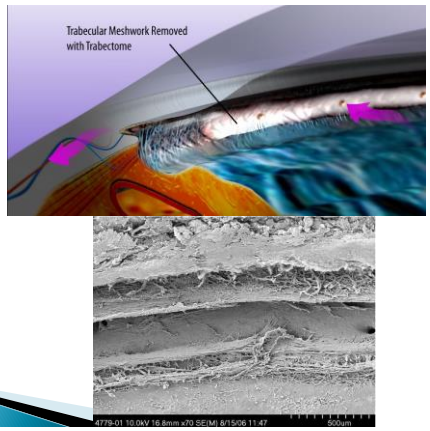
MIGS: Micro-Invasive Glaucoma Surgery

- Ab-interno approach
  - Clear corneal micro-incision (<2.0mm)
  - Conjunctival sparing
- Minimally traumatic
  - Negligible disruption of normal anatomy/physiology
- Reduce the need for more aggressive surgical options while preserving that option
- Reduce medication burden



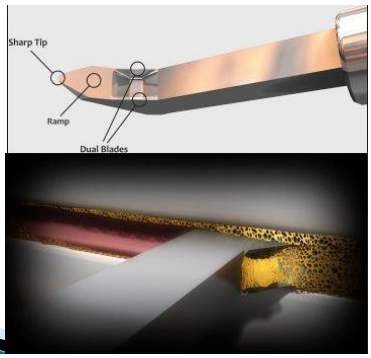
Trabectome





Kahook Dual Blade

- Unroof trabecular meshwork and inner wall of Sclemm's canal

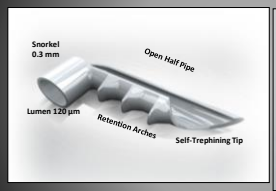


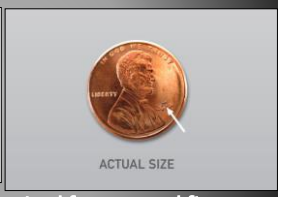
iStent Indication For Use

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

Specifications

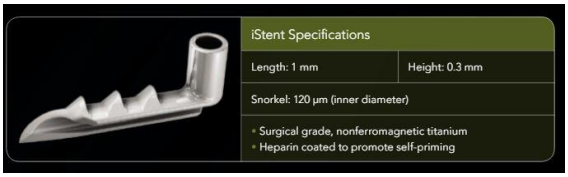
iStent is the smallest medical device known to be implanted in the human body and weighs just 60 µg





- **Dimensions are customized for a natural fit within the 270 µm canal space**

Specifications



Therapeutic Objectives

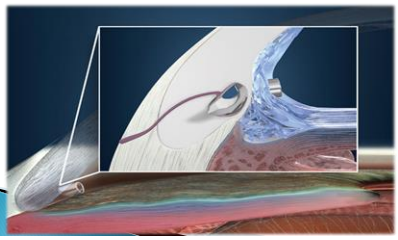
Designed to be used in conjunction with cataract surgery to safely and effectively reduce IOP while facilitating the eye's natural outflow in mild to moderate OAG patients.

- **Lowers IOP while helping to reduce medication burden**
- **Decrease risk of IOP fluctuations associated with non-adherence to prescription medication regimens**
- **Avoid serious complications associated with end-stage filtration and shunt procedures**
- **Spare the conjunctiva and safely preserve future treatment options**
- **Minimizes risks of hypotony and bleb related complications**

95

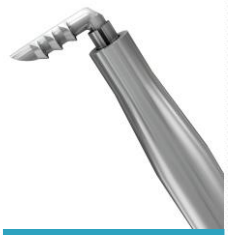
ab interno trabecular micro-bypass stent for the treatment of glaucoma:

- Placed in inferonasal locations with high presence of collector channel congregations
- Designed to improve continuous, physiological outflow in the lower nasal quadrants

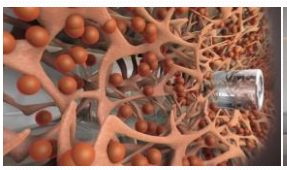


Injector System

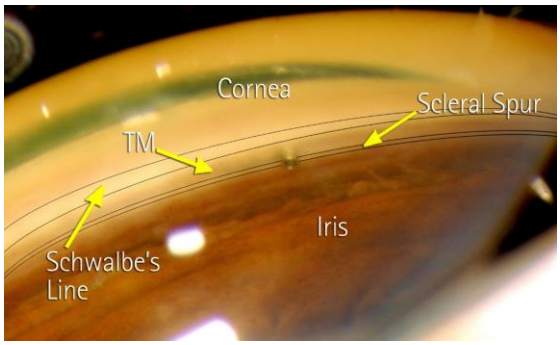
Single Use Disposable



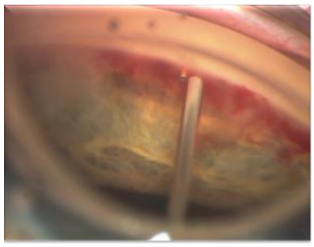
Pre-loaded

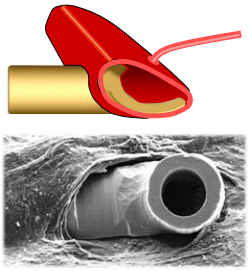


Snorkel in TM



Surgical Procedure

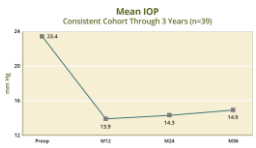


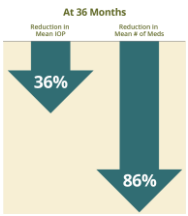


- **Rails are seated against scleral wall of Schlemm's canal**
- **Snorkel sits parallel to the iris plane**

Lasting Outcomes Through 3 Years (T. Neuhann)

Single iStent + Cataract Surgery Achieves IOP < 15 mm Hg Through 3 Years





- 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
- In consistent cohort of 39 eyes followed through 36 months, mean IOP was 14.9 mm Hg, a 36% reduction
- Over same period, mean number of topical meds declined from 1.9 to 0.3 or 86%

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.

Long-Term Data Through 5 Years

(International Study)

- Prospective, non-comparative, uncontrolled, non-randomized, interventional case series
  - 19 patients with uncontrolled mild to moderate OAG using 1 or more topical glaucoma medications
- Results after mean follow-up of 54 months
  - 42% of patients were medication free, with mean IOP reduction to 16.1 mm Hg
  - Mean IOP declined to 16.1 mm Hg versus preoperative medicated IOP of 19.4 mm Hg
  - Number of topical medications used declined from 1.3 to 0.8

Arriola-Villalobos P et al *Br J Ophthalmol* January 2012

iStent Post-operative Care

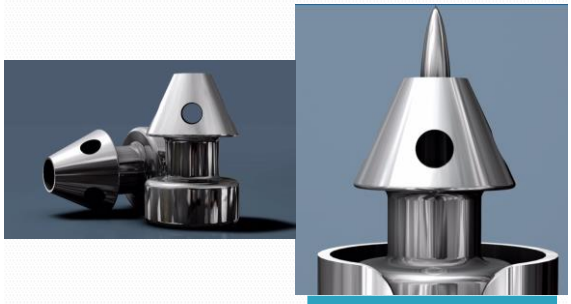
- Use normal postoperative medications
  - Antibiotic, steroid, NSAID of choice
- Continue current glaucoma medications
- Watch for IOP rise related to steroid response
- Evaluate IOP in context of target IOP
  - Degree of damage, patient age, likelihood of progression
- If indicated, decrease medical treatment in stepwise fashion
- Perform gonioscopy to confirm iStent position

Which is better? 1 or 2? Or 3?

- 1, 2 or 3 iStents in OAG subjects on drops
  - I stent: 38; 2 stents 41; 3 stents 40
- 12 month IOP reduction unmedicated IOP </= 15 mmHg
  - 1 stent: 64.9%
  - 2 stents: 85.4%
  - 3 stents: 92.1%
- 18 months, mean unmedicated IOP
  - 1 stent:15.9±0.9 mmHg
  - 2 stents: 14.1±1.0 mmHg
  - 3 stents: 12.2±1.1 mmHg
- Month 18 IOP reduction was significantly greater (P<0.001) with implantation of each additional stent, with mean of 1.84 mmHg for three-stent vs two-stent groups and 1.73 mmHg for two-stent vs one-stent groups.

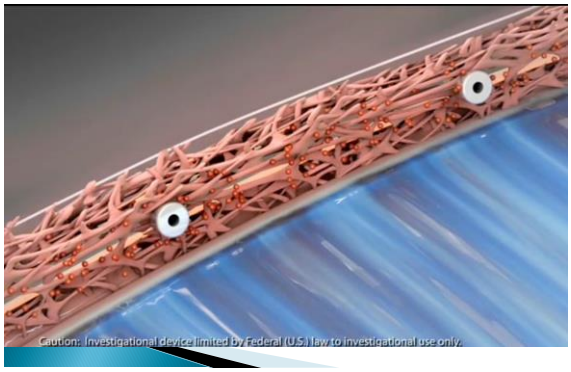
Katz LJ Clinical Oph 11 December 2015

iStent 2

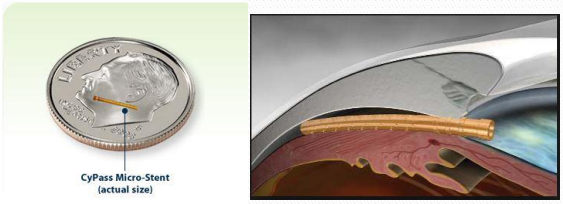


iStent in injector

2 iStents in position



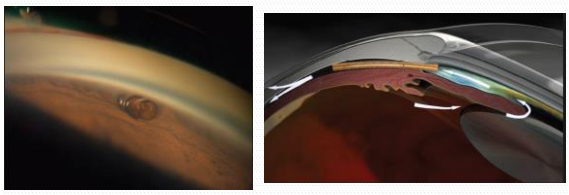
Cypass Shunt



Approved for use in conjunction with cataract surgery

Supra-ciliary Space

Cypass Aqueous Flow



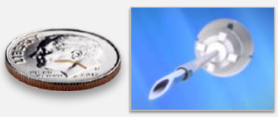
Cypass in position

Aqueous Flow

XEN Gel Stent

Innovative approach

- Requires a small corneal incision[1]
- The first ab-interno approach to create a new pathway for aqueous flow from the anterior chamber to the subconjunctival space in refractory glaucoma patients[1]
- XEN® is the first procedure that creates a low-lying, ab-interno bleb in refractory glaucoma[2]

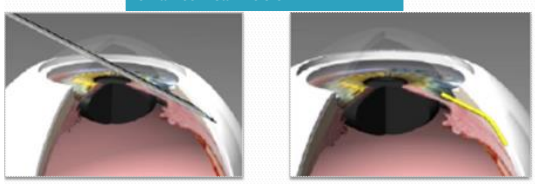


Gel stent design

- 6-mm length, 45-micron lumen diameter[1] —about the length of an eyelash[3]
- Gelatin, cross-linked with glutaraldehyde[1]
- Hydrates and minimally swells, softens, and becomes flexible after implantation[1]
- Preloaded, disposable injector[1] with a 27-gauge, double-beveled needle[2,4,5]

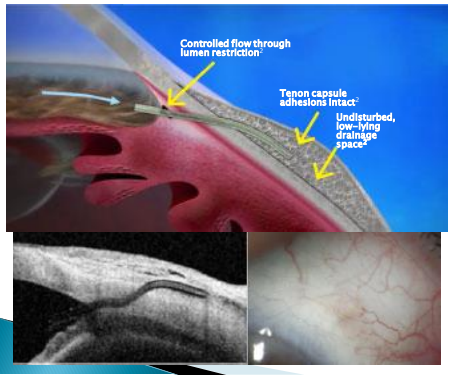
Xen Gel Stent

Minimally Invasive
Inserted using the XEN Injector via an ab-interno approach, through a small corneal incision.[1]



In the clinical investigation, standard ophthalmic surgery techniques, viscoelastic, and mitomycin C (0.2 mg/mL) were used before injection.[1]

Ab-Interno Bleb Low-lying diffuse



CLINICAL TRIAL CRITERIA

Established in a phase 3, prospective, multicenter, single-arm, open-label, 12-month, US clinical trial[1]

Study population[1]

- 65 patients with refractory glaucoma[1]
- Mean age: 70.0 years[1]
- Prior cataract surgery: 45 (69.2%)[1]
- Prior incisional glaucoma procedure: 41 (63.1%) (eg, trabeculectomy, tube shunt, canaloplasy, trabeculotomy, AquaFlow)[1,6]
- No prior glaucoma procedure and unresponsive to maximally tolerated medical therapy: 10 (15.4%)[1,6]
- Mean cup-to-disc ratio: 0.8[1]
- Mean visual field mean deviation (MD) score: −15 dB[1]
- Mean medicated IOP at baseline: 25.1 (± 3.7) mm Hg[1]
- Mean IOP-lowering medications at baseline: 3.5 (± 1.0)[1]

Primary effectiveness measures[6]

- Proportion of subjects at 12 months achieving ≥ 20% IOP reduction from baseline on the same or fewer number of medications than at baseline
- Mean decrease in IOP from baseline to 12 months

Primary safety measures[6]

- Procedure-related complications
- Biomicroscopic slit lamp and ophthalmoscopy findings
- Ocular adverse events

ESTABLISHED EFFECTIVENESS

Reduced IOP and medication use at month 12[1]

Mean IOP reduced to 15.9 mm Hg (N = 52) from 25.1 mm Hg at medicated baseline[1,*]

Mean IOP- lowering medications reduced to 1.7 (N = 52) from 3.5 at at medicated baseline[1,†]

*Baseline 25.1 (± 3.7) mm Hg; 12-month 15.9 (± 5.2) mm Hg.[1]
†Baseline 3.5 (± 1.0); 12-month average 1.7 (± 1.5) medications.[1]

Results of a prospective, multicenter, single arm, open-label, US clinical trial to evaluate the safety and effectiveness of the XEN® Gel Stent in refractory glaucoma subjects (N = 65) where previous filtering or cilioablative procedures failed, or IOP was unresponsive to maximally tolerated medication. Medication washout was not performed; all IOP lowering medications were discontinued on the day of surgery.[1]

Reduced mean IOP by ≥ 25% in 80.8% of eyes.[6]

15.4% (n = 10/65) of patients had no prior glaucoma procedures.[1]

- **Refractory patients unresponsive to maximally tolerated medical therapy[1]**

ESTABLISHED EFFECTIVENESS

Primary Effectiveness Analyses[1,a]	n/N (%) (95% CI)*	Mean ± SE (95% CI)†
Proportion of Subjects with 12-Month Mean Diurnal IOP Reduction of ≥ 20% from Baseline on Same or Fewer Medications (N=65)[b]	76.3% (65.8%, 86.8%)	
Mean Diurnal IOP Reduction from Baseline at the 12-Month Visit (N=65)[c]		−6.4 ± 1.1 mmHg (−8.7, −4.2)

[a] Study eyes undergoing glaucoma-related secondary surgical intervention and/or removal of XEN® 45 Gel Stent prior to the 12-month evaluation were considered to be nonresponders.[1]
Seven subjects in the study underwent needling procedures with mitomycin C; 4 of these subjects were considered responders.[1]
[b] Primary effectiveness analysis using observed data and failure for subjects with glaucoma-related secondary surgical intervention and multiple imputations for missing data.[1]
[c] Primary effectiveness analysis using observed data & worst within-eye IOP for subjects with glaucoma-related secondary surgical intervention and multiple imputations for missing data.[1]
* Exact confidence limits per Clopper-Pearson method.[1]
† Student's t distribution.[1]

DEMONSTRATED SAFETY

In the Pivotal Clinical Trial

- **0 of 65 subjects experienced intraoperative complications[1]**
  - **0% surgical complications**
  - **0% hyphema**
  - **0% conjunctival perforation**
  - **0% iris/lens damage**
- **0 of 65 subjects experienced persistent hypotony (IOP < 6 mm Hg at 2 visits > 30 days apart)[1,*]**
  - **Hypotony (IOP < 6 mm Hg at any time): 24.6% (16/65)[1]**

*No clinically significant consequences were associated with hypotony, such as choroidal effusions, suprachoroidal hemorrhage, or hypotony maculopathy. IOP < 6 mm Hg was defined as an adverse event, regardless of whether there were any associated complications or sequelae related to the low pressure. Thirteen cases occurred at the 1-day visit; there were no cases of persistent hypotony, and no surgical intervention was required for any case of hypotony.[1]

Pre-operative Considerations

- iStent Candidate
  - Mild to moderate open angle glaucoma (no more severe than a mean deviation of -12dB)
  - Visually significant cataract is present on examination
  - Patient desires to reduce dependence on glaucoma medications

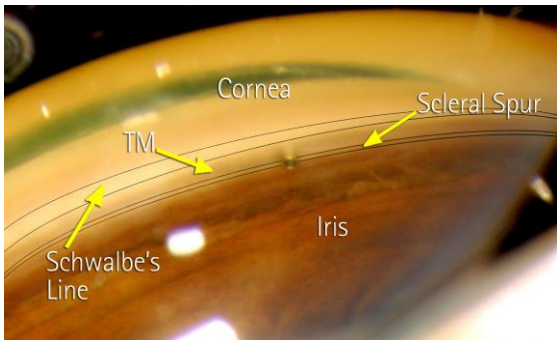
Any patient with cataracts being treated for mild to moderate open angle glaucoma with medications may be a potential candidate for an iStent[1]

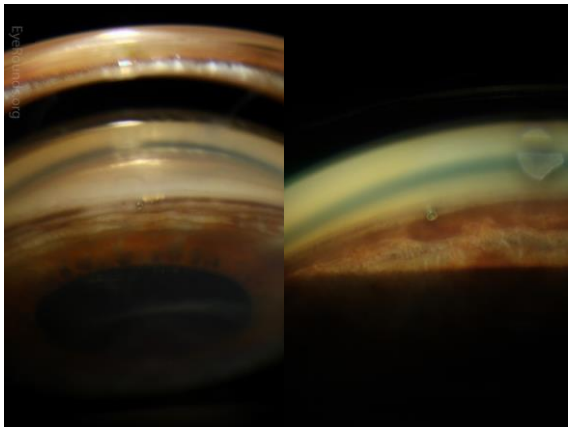
[1] See Directions for Use for a complete list of Contraindications and Precautions

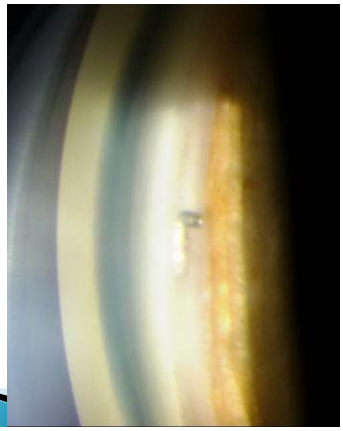
iStent Pre-op Care

- Review risks and benefits of possible medical and surgical treatment options
- Do NOT promise that the patient will be able to stop some or all of their glaucoma medications
- Continue current glaucoma medications through day of surgery
- Confirm patient's VF, ONP and OCT are up to date
- Gonioscopy – evaluating for synechia, iris processes, narrow anatomical angles, angle recession or any other abnormalities of the angle structure that may interfere with placement of the iStent

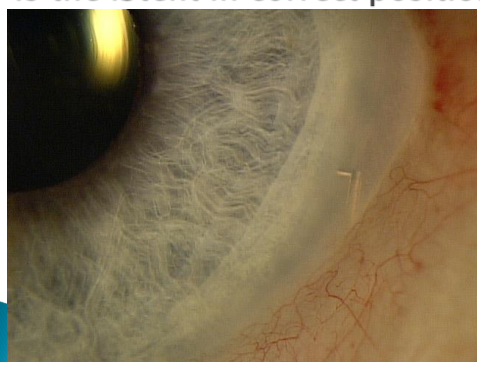
Post-op Complications

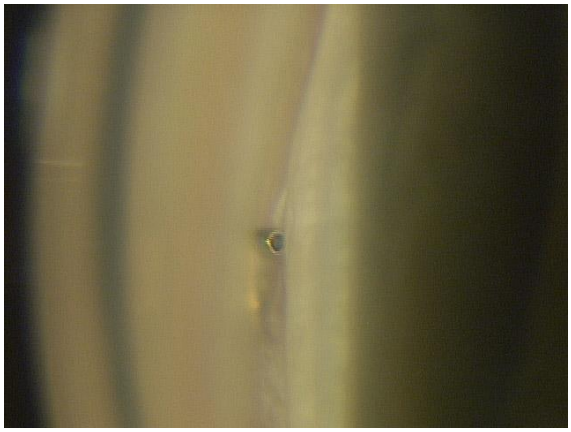






Is the iStent in correct position?





Hyphema due to iStent