Glaucoma Update

Dr. James Thimons, Founding Partner, Medical Director
Ophthalmic Consultants of Connecticut
Chairman, National Glaucoma Society

1

Financial Disclosures

- Alcon
- Allergan
- PRN
- Tear Lab
- Shire
- Zeiss
- B+L
- Diopsys
- Reichart
- Glaukos
- InFocus
- Aerie
- Kala
- IVantis

2

3

4

Welcome to Connecticut

5

6

New Concepts in Glaucoma Diagnosis and Treatment

- OCT vs VF
- The Rise of The Ganglion Cell
- CH in Glaucoma Suspects
- SLT as Primary Therapy
- Repeat SLT
- OCTA in Glaucoma

7

Macular Vulnerability Zone

Prog Retin Eye Res. 2013 January ; 32C: 1–21. doi:10.1016/j.preteyeres.2012.08.003.

Glaucomatous damage of the macula

Donald C. Hood[a,b,*,1], **Ali S. Raza**[a,c,1], **Carlos Gustavo V. de Moraes**[d,e,1], **Jeffrey M. Liebmann**[d,e,1], and **Robert Ritch**[d,f,1]

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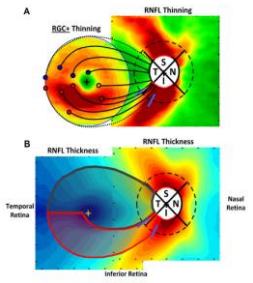
8



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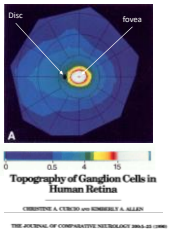
Macular Ganglion cell density



- 50% of ganglion cells located in central 4.5mm (16º)
- Peak ganglion cell density is 15,000 cells/mm^2 in macula(white region left)
- Area represents only 7.3% of total retinal area
- RTVue Ganglion cell complex map covers central 6mm area

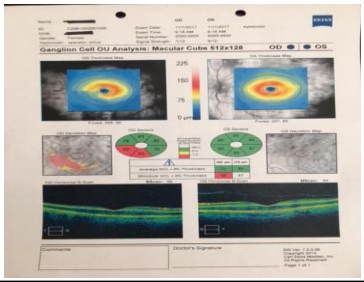
10

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

11

"Wiper" Defect



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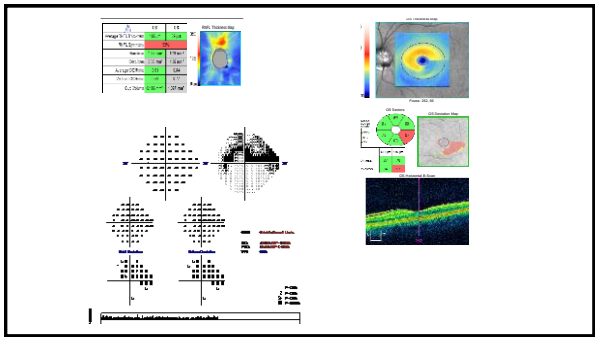

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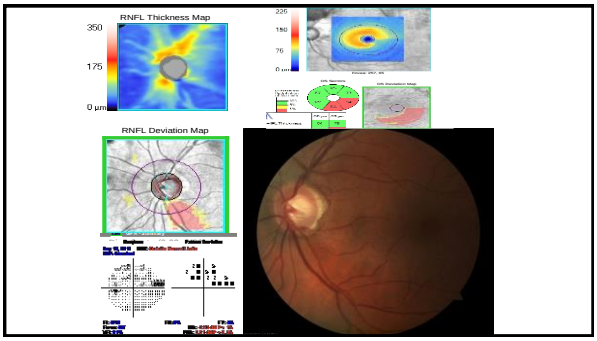

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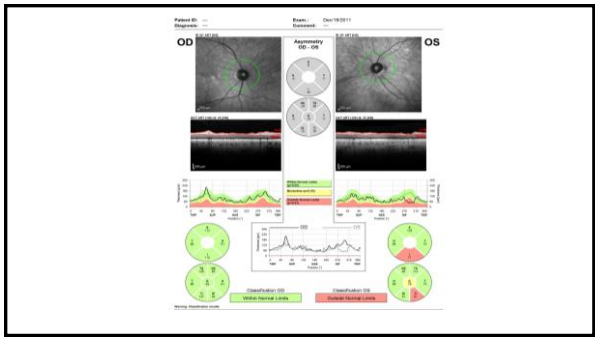

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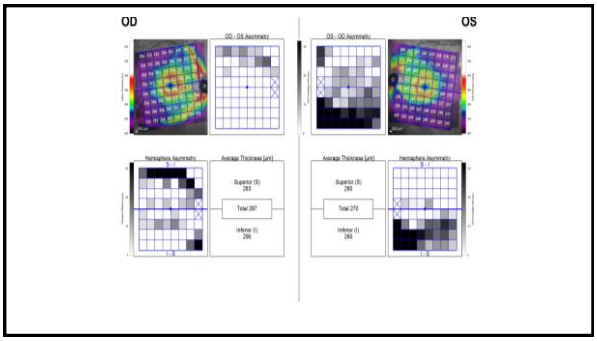


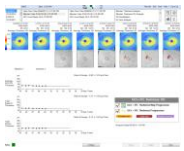
16

Product Description

Ganglion Cell Guided Progression Analysis

•For Glaucoma Patients

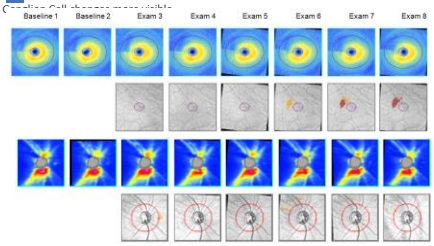
- Potentially detect **structural change sooner than ONH/RNFL** changes (Reference)
- Determine **if statistically significant change** in **Ganglion Cell + Inner Plexiform Layer** has occurred
- Complements ONH/RNFL Guided Progression Analysis to provide a **Comprehensive Glaucoma Analysis**



17

Product Description

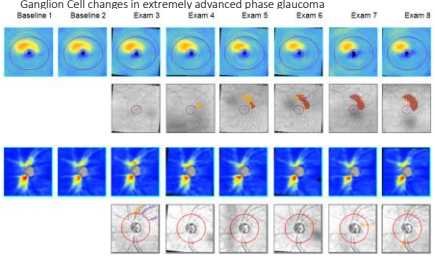
Ganglion Cell vs ONH/RNFL Progression



18

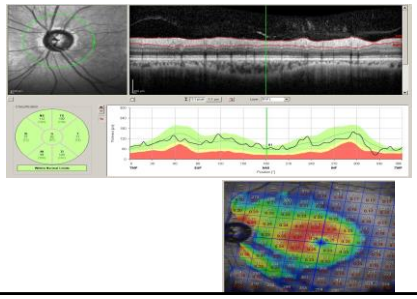
Ganglion Cell and ONH/RNFL Progression

Ganglion Cell changes in extremely advanced phase glaucoma



19

"Green Disease"



20

Green Disease – What is it?

- OCT artifact/misinterpretation
- Caused by falsely labelled normative values relative to the normative database in the presence of progressing glaucoma
- BAD because a quick overlook of the values can result in misinterpretation of the nerves and therefore mistreatment of the patient.

21

Normative Values

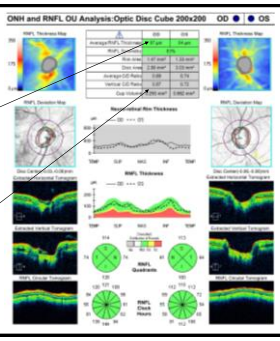
- Normative data base not available for patients under 18 years of age
- When there are no normative values to be compared to, they are therefore shaded grey
- When disc area is less than $1.8mm^2$ or greater than $2.5mm^2$, values are shaded grey
- Asymmetry of RNFL thickness greater than 7-8um is statistically significant
  - May be indicative of early glaucomatous changes

	OD	OS
Average RNFL Thickness	97 µm	84 µm
RNFL Symmetry	83%	
Rim Area	1.47 mm²	1.33 mm²
Disc Area	2.88 mm²	3.03 mm²
Average C/D Ratio	0.69	0.74
Vertical C/D Ratio	0.67	0.72
Cup Volume	0.293 mm³	0.552 mm³

22

ONH and RNFL OU Analysis

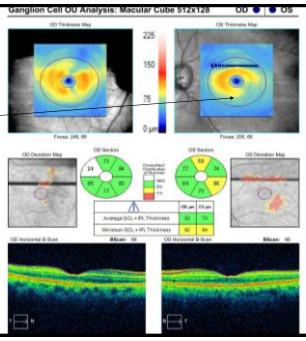
- Asymmetric RNFL thickness
- RFNL thickness appears green- indicating that the numeric values are normal in comparison to the normative database
- Other values such as Rim, disc area, vertical and average CD ratio and cup volume are shaded grey
- The values say that it is normal because it is green



23

Ganglion Cell OU

- Shows wiper defect in OS
- Indicates signs of Glaucoma



24

Explaining Green Disease

- Megalopapilla where disc area is >2.5mm^2
  - Px Disc area OD 2.88mm^2 OS 3.03mm^2
- RNFL thickness is measured from a specific location defined by a circle of 3.46mm in diameter
- RNFL thickness is more bunched up closer to the ONH
- Distance between the scan and the ONH decreases in Megapapilla
- Sampling of the RNFL area is larger in a normal disc than in Megalopapilla.
- In megalopapilla, it is sampling where the RNFL is most dense
- This leads to overestimation of the RNFL thickness with large ONH
  - Hence "Green Disease"

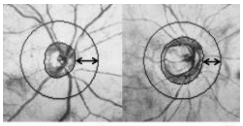
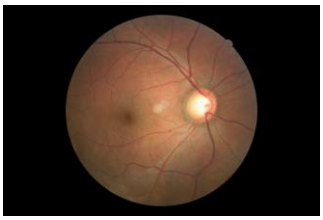


Image from Gama et. al. A: Normal Disc. B: Megalopapilla

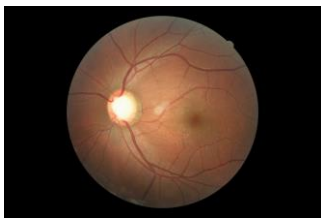
25

Green Disease



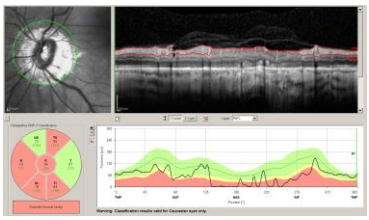
26

Green Disease?



27

Myopia = "Red Disease"

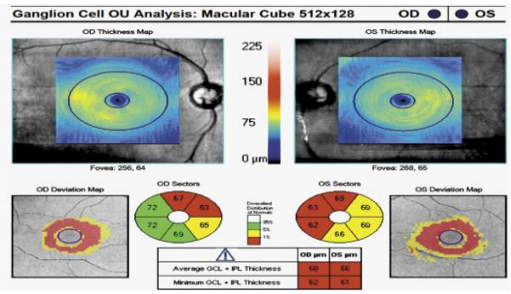


28

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

29



30

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

31

AIG/ 2017

- 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

32

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%)

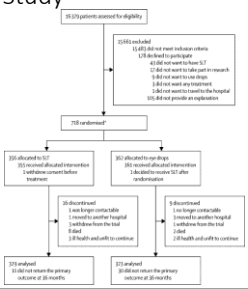
33

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

34

The LIGHT Study



35

THE LANCET
THE "LIGHT" STUDY

VOLUME 393, ISSUE 10180, P1505-1516, APRIL 13, 2019

- **Selective laser trabeculoplasty versus eye drops for first-line treatment of ocular hypertension and glaucoma (LiGHT): a multicentre randomised controlled trial**
- Gus Gazzard, FRCOphth
- Evgenia Konstantakopoulou, PhD
- Prof David Garway-Heath, MD
- Anurag Garg, FRCOphth
- Victoria Vickerstaff, MSc
- Rachael Hunter, MSc
- et al.

36

LIGHT Study

- Standardization of laser delivery was achieved by protocol-defined settings and clinical endpoints.[14]
- Selective laser trabeculoplasty was delivered to 360° of the trabecular meshwork. 100 non-overlapping shots (25 per quadrant) were used, with the laser energy varied from 0·3 to 1·4 mJ by the clinician, using an appropriate laser gonioscopy lens.
- One re-treatment with selective laser trabeculoplasty was allowed, provided there had been a reduction in intraocular pressure after the initial treatment; the next escalation was medical therapy.
- Significant complications of selective laser trabeculoplasty (eg, a spike in intraocular pressure) precluded repetition of selective laser trabeculoplasty.

37

LIGHT Study

- Drug classes for first, second, or third line treatment were defined by NICE[15]and European Glaucoma Society[19]guidance
- First line was prostaglandin analogues, second line was β blockers, third or fourth line was topical carbonic anhydrase inhibitors or α agonists. Fixed combination drops were allowed.
- Systemic carbonic anhydrase inhibitors were only permitted while awaiting surgery. Maximum tolerated medical therapy was defined by the treating clinician as the most intensive combination of drops an individual could reasonably, reliably, and safely use and thus varied between patients.
- A need for treatment escalation beyond maximum tolerated medical therapy triggered an offer of surgery.

38

The Light study

- **Methods**
- **In this observer-masked, randomized controlled trial treatment-naive patients with open angle glaucoma or ocular hypertension and no ocular comorbidities were recruited between 2012 and 2014 at six UK hospitals.**
- **They were randomly allocated (web-based randomization) to initial selective laser trabeculoplasty or to eye drops.**
- **An objective target intraocular pressure was set according to glaucoma severity.**
- **The primary outcome was health-related quality of life (HRQoL) at 3 years (assessed by EQ-5D). Secondary outcomes were cost and cost-effectiveness, disease-specific HRQoL, clinical effectiveness, and safety.**
- **Analysis was by intention to treat. This study is registered at controlled-trials.com (ISRCTN32038223).**

39

The Light study

- **Findings**
- **Of 718 patients enrolled, 356 were randomised to the selective laser trabeculoplasty and 362 to the eye drops group. 652 (91%) returned the primary outcome questionnaire at 36 months.**
- **Average EQ-5D score was 0·89 (SD 0·18) in the selective laser trabeculoplasty group versus 0·90 (SD 0·16) in the eye drops group, with no significant difference (difference 0·01, 95% CI −0·01 to 0·03; p=0·23).**
- **At 36 months, 74·2% (95% CI 69·3–78·6) of patients in the selective laser trabeculoplasty group required no drops to maintain intraocular pressure at target.**
- **Eyes of patients in the selective laser trabeculoplasty group were within target intracoluar pressure at more visits (93·0%) than in the eye drops group (91·3%), with glaucoma surgery to lower intraocular pressure required in none versus 11 patients.**
- **Over 36 months, from an ophthalmology cost perspective, there was a 97% probability of selective laser trabeculoplasty as first treatment being more cost-effective than eye drops first at a willingness to pay of £20 000 per quality-adjusted life-year gained.**

40

Efficacy of Repeat Selective Laser Trabeculoplasty in Medication-Naive Open-Angle Glaucoma and Ocular Hypertension during the LiGHT Trial

AnuragGargFRCOphth; VictoriaVickerstaffMSc; NeilNathwaniBSc; DavidGarway-HeathMD; EvgeniaKonstantakopoulouPhD; GarethAmblerPhD; CateyBunceDSc; RichardWormaldFRCOphth; KeithBartonFRCS; GusGazzardMD; Laser

41

Repeat SLT

- Participants
- Treatment-naive OAG or OHT requiring repeat 360-degree SLT within 18 months. Retreatment was triggered by predefined IOP and disease-progression criteria (using objective individualized target IOPs).
- Methods
- After SLT at baseline, patients were followed for a minimum of 18 months after second (repeat) SLT. A mixed-model analysis was performed with the eye as the unit of analysis, with crossed random effects to adjust for correlation between fellow eyes and repeated measures within eyes. Kaplan–Meier curves plot the duration of effect.
- Main Outcome Measures
- Initial (early) IOP lowering at 2 months and duration of effect after initial and repeat SLT.
- Results
- A total of 115 eyes of 80 patients received repeat SLT during the first 18 months of the trial. Pretreatment IOP before initial SLT was significantly higher than before retreatment IOP of repeat SLT (mean difference, 3.4 mmHg; 95% confidence interval (CI), 2.6–4.3 mmHg; $P < 0.001$). Absolute IOP reduction at 2 months was greater after initial SLT compared with repeat SLT (mean difference, 1.0 mmHg; 95% CI, 0.2–1.8 mmHg; $P = 0.02$). Adjusted absolute IOP reduction at 2 months (adjusting for IOP before initial or repeat laser) was greater after repeat SLT (adjusted mean difference, −1.1 mmHg, 95% CI, −1.7 to −0.5 mmHg; $P < 0.001$). A total of 34 eyes were early failures (retreatment 2 months after initial SLT) versus 81 later failures (retreatment >2 months after initial SLT). No significant difference in early absolute IOP reduction at 2 months after repeat SLT was noted between early and later failures (mean difference, 0.3 mmHg; 95% CI, −1.1 to 1.8 mmHg; $P = 0.655$). Repeat SLT maintained drop-free IOP control in 67% of 115 eyes at 18 months, with no clinically relevant adverse events.
- Conclusions
- These exploratory analyses demonstrate that repeat SLT can maintain IOP at or below target IOP in medication-naive OAG and OHT eyes requiring retreatment with at least an equivalent duration of effect to initial laser.

42

Repeat SLT

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43

Repeat SLT

- Conclusions
- These exploratory analyses demonstrate that repeat SLT can maintain IOP at or below target IOP in medication-naive OAG and OHT eyes requiring retreatment with at least an equivalent duration of effect to initial laser.

44

OCTA: The Next Horizon in Imaging

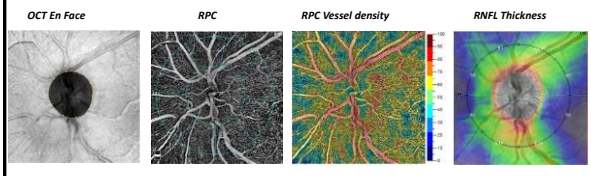
45

Lee JY, Shin JW, Lee A, et al. Association of baseline optical coherence tomography angiography with the development of glaucomatous visual field defects in preperimetric glaucoma eyes. *Br J Ophthalmol*. Published online August 5, 2022. doi:10.1136/bjo-2021-321025

- With an average follow-up of 3.1 years, the researchers observed that 9.0% of eyes developed glaucomatous VF defects. The study shows lower inferior temporal cpVD (hazard ratio [HR], 0.934; 95% CI, 0.883-0.988; $P = .017$) and thinner inferior RNFL (HR, 0.895; 95% CI, 0.839-0.956; $P = .001$) are predictive of glaucomatous VF loss.
- The researchers also report that a lower inferior temporal cpVD and thinner RNFL at baseline were associated with a faster rate of global VF sensitivity loss (β=0.015; $P = .001$).

46

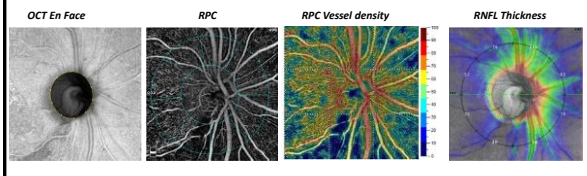
OCTA the New View (Normal Eye)



Images and data courtesy of Robert Weinreb, MD and Linda Zangwill, PhD, UC San Diego

47

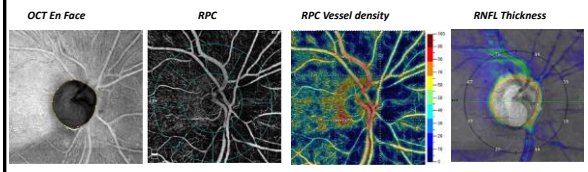
OCTA Moderate Glaucoma



Images and data courtesy of Robert Weinreb, MD and Linda Zangwill, PhD, UC San Diego

48

Advanced Glaucoma



Images and data courtesy of Robert Weinreb, MD and Linda Zangwill, PhD, UC San Diego

49

AI and Glaucoma

- **nGoggle allows assessment of brain function using virtual reality**
- At the Glaucoma 360: New Horizons Forum, **Felipe Medeiros, MD, PhD,** professor of ophthalmology at Duke University, discusses the development of the nGoggle, a device that merges virtual reality goggle technology with electroencephalogram technology to help assess visual function.
- *JAMA Ophthalmology,* Medeiros described the use of the nGoggle, a wearable brain-computer interface, to objectively assess visual function and distinguish glaucomatous eyes from healthy ones. The nGoggle integrates dry electroencephalogram and electro-oculogram systems to wirelessly detect multifocal steady-state visual evoked potentials in response to visual field stimulation.
- "The idea is that we perform this test and we can then transmit the results through the cloud or via Bluetooth," Medeiros said. The raw data that is collected can be complex and needs to go through several stages of processing.
- "Recently we implemented some machine learning methods to be able to extract the information that has diagnostic value," he said.

50

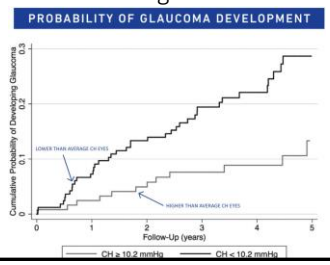
New Technologies in Glaucoma Diagnosis and Management

51

CORNEAL HYSTERESIS: The Newest Disruptive Technology In Glaucoma

68

Corneal Hysteresis as a Biomarker of Glaucoma: Current Insights



69

Falck Medical Multi-Function DEVICE

70

71

Intraocular Pressure

- ✓Optical Applanation Measurement
- ✓Compensates for Corneal Biomechanics
- ✓Multiple Serial IOP Measurements – N Value
- ✓Systolic and Diastolic IOP
- ✓Average IOP Displayed
- ✓IOP Variation with Cardiac Cycle - OPA
- ✓Precision Displayed

72

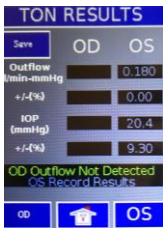
OPHTHALMODYNAMOMETRY

- ✓ Mean Central Artery Pressure (MCRAP) measurement.
- ✓ Data Captured During Multiple Cardiac Cycles.
- ✓ Mean Arterial BP Displayed.
- ✓ MCRAP – IOP = True Ocular Perfusion Pressure (OPP).
- ✓ Reduced OPP is a risk factor for glaucoma progression.
- ✓ Abnormal OPH - Increased Risk of Stroke

73

TONOGRAPHY

- ✓ Optical Aqueous Humor Outflow Measurement.
- ✓ Aqueous Outflow Decreased in Glaucoma.
- ✓ Decreased Outflow = Increased TM Resistance.
- ✓ Decreased Outflow = Increased IOP Fluctuation.
- ✓ Document Therapeutic Efficacy of Outflow Interventions.
- ✓ Document Need for Additional Intervention.
- ✓ Glaucoma risk assessment.



74

The Case of the Missing Diagnosis

- PT a 72 y/o Caucasian female presented for IOP evaluation.
- Prior Hx of PI OU x 5 years
- Tx: for COAG OU x 5 years
- C/O blur OU x 6 months
- Pain OS x 4 -5 weeks
- VA: 20/50 OD / 20/70 OS

75

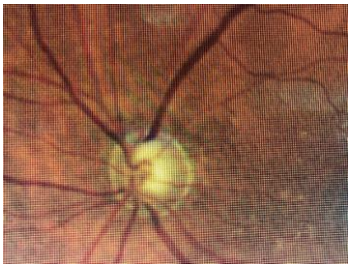
The Case of the Missing Diagnosis

- SLE: 3+4 NS OD / 4+ NS OS
- Falck IOP: 23 OD/ 38 OS
- Gonio:
  - OD AT 360 with occasional open to pressure
  - OS 360 AT with synechiae 360
- Tonography: OD 0.016 / OS 0.011

76

The Case of the Missing Diagnosis

77



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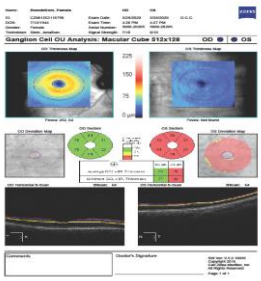

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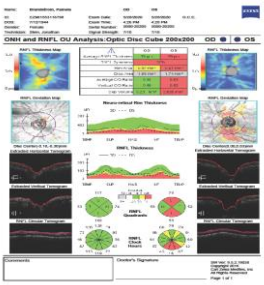

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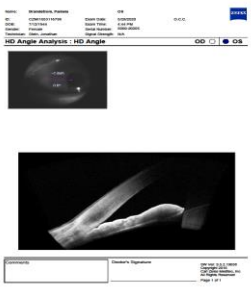


81

82

The Case of the Missing Diagnosis

- Office Tx:
  - Diamox 250g po x 2
  - Combigan 1 gtt x2
  - Pilo 1% 1 gtt x 2
  - IOP at 1 hour 17/26
- Surgical Tx: CEX, OMNI, Hydrus OS
- IOP post Tx: 16/12
- Tongraphy: 0.017/ 0.028

83

Wide Field Imaging

- **Clarus**

84

85

86

Equinox: The New Horizon in Glaucoma Therapy

- Dr. John Berdahl
- Non Pharmacologic/ Non Surgical Glaucoma Therapy

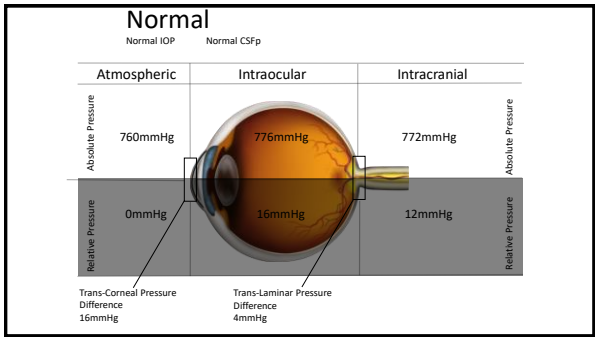
87

Visual Impairment and Intracranial Pressure - VIIP

Optic Disc Edema, Globe Flattening, Choroidal Folds, and Hyperopic Shifts Observed in Astronauts after Long-duration Space Flight

Thomas H. Mader, MD,[1] C. Robert Gibson, OD,[2] Anastas F. Pass, OD, JD,[3] Larry A. Kramer, MD,[4] Andrew G. Lee, MD,[5] Jennifer Fogarty, PhD,[6] William F. Tarver, MD,[6] Joseph P. Dervay, MD,[6] Douglas R. Hamilton, MD, PhD,[7] Ashot Sargsyan, MD,[7] John L. Phillips, PhD,[8] Duc Tran, DO,[2] William Lipsky, MD,[2] Jung Choi, OD,[2] Claudia Stern, MD, PhD,[9] Raffi Kuyumjian, MD,[10] James D. Polk, DO[9]

88



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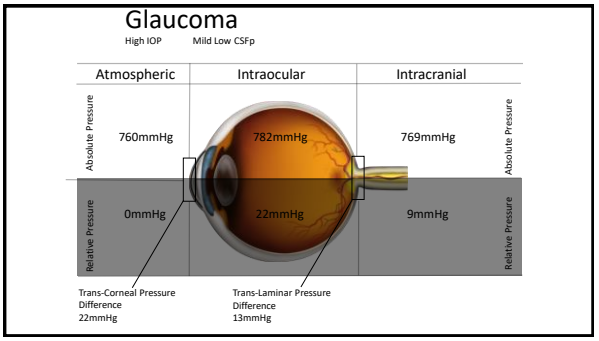

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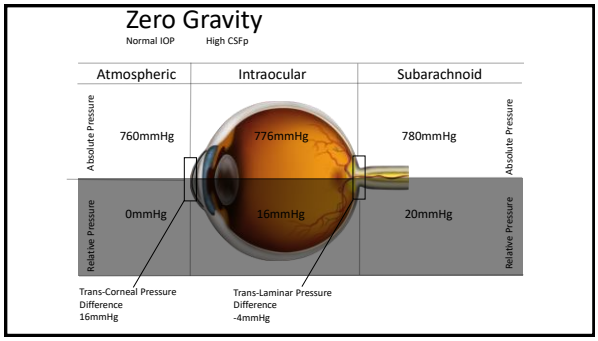

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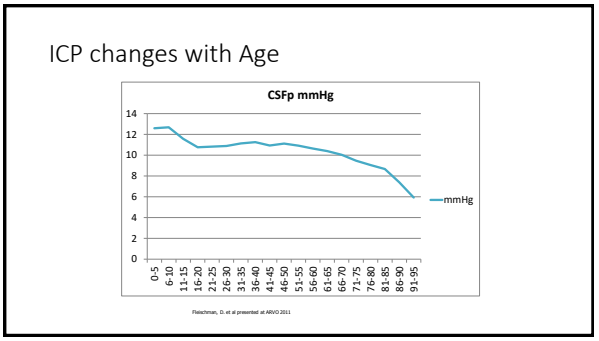

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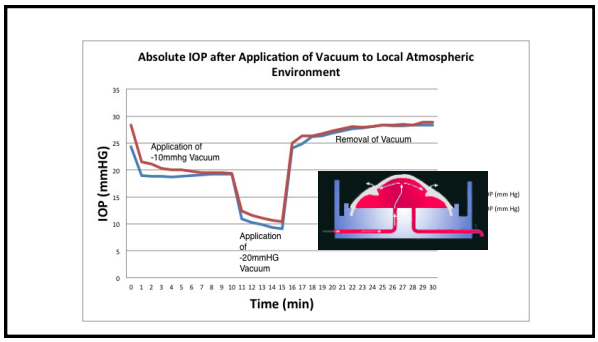

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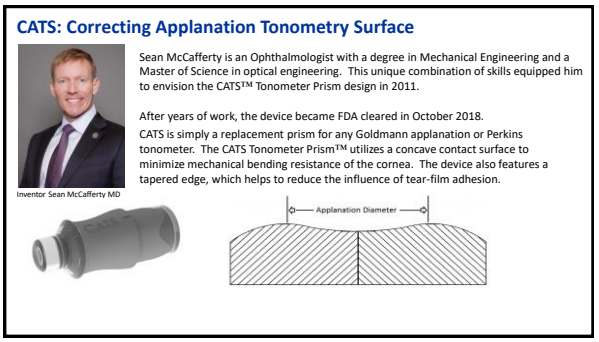
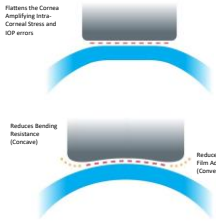


94

CATS: Correcting Applanation Tonometry Surface

Traditional GAT Prism – No change in 65 Years

CATS™ Tonometer Prism – the New Shape of IOP

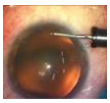


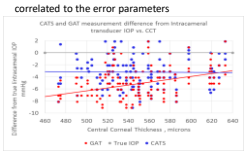
95

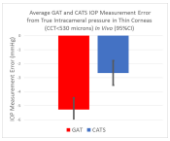
CATS Intercameral Pressure Validation

Methods:

- Intracameral IOP measured on 58 eyes undergoing cataract surgery
- IOP manometrically modulated to 10, 20, and 40 mmHg
- Difference between the CATS and GAT IOP measurements from true intracameral pressure correlated to the error parameters







The CATS prism is significantly more accurate compared to the GAT prism compared to true intracameral pressure, and is unaffected by CCT.

96

Glaucoma Therapy for the 21st Century

97

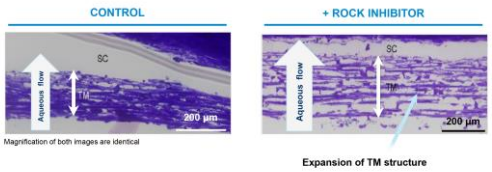
Rocklatan® and Rhopressa® Usage

- Rocklatan® (netarsudil and latanoprost ophthalmic solution) 0.02%/0.005% is a new combination drug product and has a white cap
- Rocklatan® is available in a 1-month supply (2.5 mL)
- Protect from light. Must remain refrigerated

- Rhopressa® (netarsudil ophthalmic solution) 0.02% is a new class of drug and has a white cap
- Rhopressa® is available in a 1-month supply (2.5 mL)
- Refrigerate until opened. After opening, the product may be kept at room temperature for up to 6 weeks

98

ROCK INHIBITION RELAXES THE 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.

99

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

PREFERRED TERM (with incidence ≥5% [pooled safety population*])	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)

*Includes ROCKET 1, ROCKET 2, and ROCKET 4.
1. Data on file, Aerie Pharmaceuticals, Inc.

100

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]

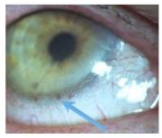
Amiodarone-treated patient[1]

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

101

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]

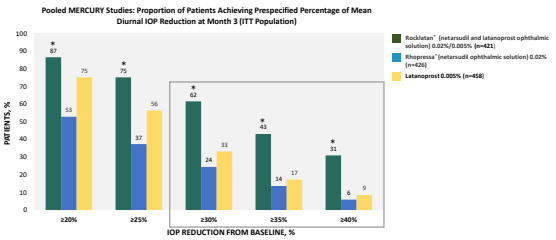


Mild conjunctival hemorrhage[2]

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

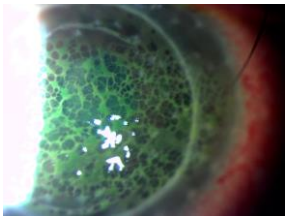
102

Over 60% of Rocklatan® Patients Achieved ≥30% Mean IOP Reduction at 3 Months[1]



*P<0.0001 vs Rhopressa® and latanoprost. ITT, intent-to-treat
1. Data on file, Aerie Pharmaceuticals, Inc.

103



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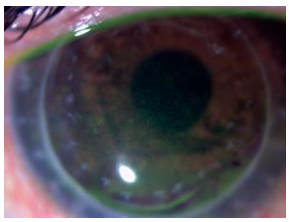

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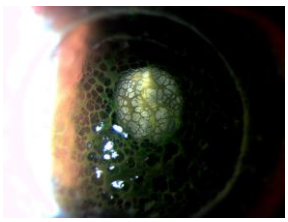
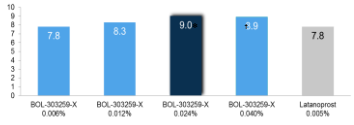


106

Efficacy Results: Primary Endpoint Voyager Study

At highest doses, lowered IOP 1-1.5 mmHg more than latanoprost
Most common AE: pain upon instillation



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

107

Vyzulta (Latanoprostene Bunod)

108

Statistically Superior Efficacy vs Xalatan 0.005%[1,2]

VYZULTA delivered significantly greater mean IOP reduction vs Xalatan 0.005%

42% of VYZULTA patients **achieved ≥2 mmHg IOP reduction** vs Xalatan 0.005% mean diurnal IOP reduction[2†]

†Post-hoc analysis; Xalatan 0.005% mean diurnal IOP reduction of 7.8 mmHg.

Percentage of VYZULTA patients that achieved even greater IOP reductions than the Xalatan 0.005% mean diurnal IOP reduction[2]:

- 30% achieved ≥3 mmHg
- 19% achieved ≥ 4 mmHg
- 12% achieved ≥ 5 mmHg

1. Weinreb RN, Ong T, Scassellati SB, Vittitow JL, Singh K, Kaufman PL. *Br J Ophthalmol*. June 2015;99(6):738-745. 2. Data on File. Bausch & Lomb Incorporated.

109

Only 6 out of 811 Patients Discontinued VYZULTA Due to Ocular Adverse Events in APOLLO and LUNAR[1]

Less than 1% of patients treated with VYZULTA discontinued due to ocular adverse reactions in the APOLLO and LUNAR clinical studies[1]

- These included ocular hyperemia, conjunctival irritation, eye irritation, eye pain, conjunctival edema, vision blurred, punctate keratitis, and foreign body sensation

Most Common Ocular Adverse Reactions in ≥2% of Study Eyes*[1,2]

Adverse Reactions	VYZULTA (n=811)	TIMOLOL 0.5% (n=271)
Conjunctival Hyperemia	5.9%	1.1%
Eye Irritation	4.6%	2.6%
Eye Pain	3.6%	2.2%
Ocular Hyperemia	2.0%	0.7%
Instillation Site Pain	2.0%	1.8%

*Pooled data from all tested time points in the APOLLO and LUNAR studies: ocular adverse reactions occuring in ≥2% of study eyes.

1. VYZULTA Prescribing Information. Bausch & Lomb Incorporated. 2. Weinreb RN, Liebmann JM, Martin KR, et al. *Glaucoma*. January 2019;27(1):7-15.

110

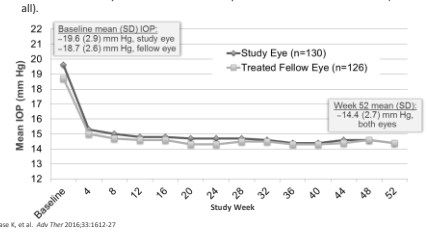
The Next Generation of Medical Management in Glaucoma

- **Sustained Release Systems**

111

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

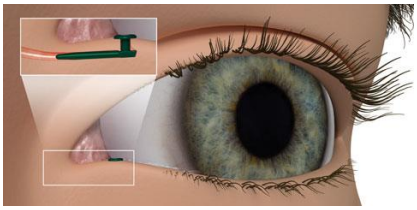
112

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.

113

Mati Therapeutics

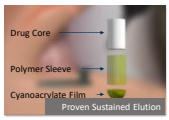


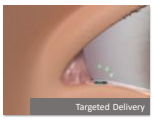
114

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





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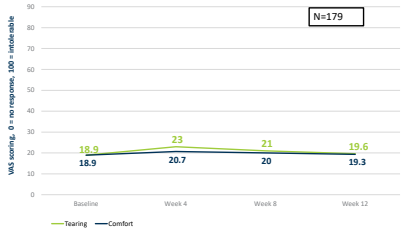
115

Evolute® Tearing & Comfort Scores



116

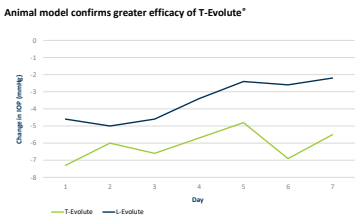
116

L-PPDS – Target Dosing

- Commercial latanoprost – Xalatan :
  - Concentration : 0.005% latanoprost
  - Dosing : Once a day
- Assumptions :
  - Drop volume = 25µL to 35µL
  - Delivery efficiency = 10%
- Estimated concentration the surface of the eye receives from a drop:
  - 15µg to 25µg per day of active therapeutic
- Amount of latanoprost delivered per day by Evolute® Punctal Plug
  - 0.5µg to 0.7µg per day of active therapeutic without any preservatives

117

Animal IOP Model (Mean Time Points) -Travoprost

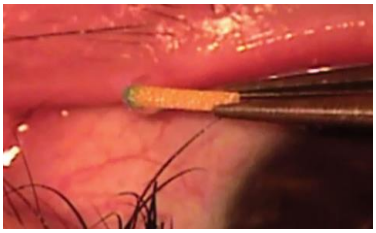


118

Durysta™ (Bimatoprost Implant) for Intracameral Administration

119

Ocular Therapeutix



120

Bimatoprost Implant

- Bimatoprost is a prostamide that has been shown to reduce IOP when administered topically
- A biodegradable implant has been developed
- The implant is designed to be placed intracamerally in the eye and provide slow release of bimatoprost over time

Gonioscopic photographs of bimatoprost sustained-release implant 10 µg in the anterior chamber of an eye of a representative patient diagnosed with open-angle glaucoma

IOP = intraocular pressure

Lewis R, et al. *Am J Ophthalmol* 2017;175:137-147.

121

Drug Delivery Technology Modifications for Glaucoma

- The drug delivery system can be modified to provide different release profiles[1]
- For glaucoma treatment, the drug delivery system used with the bimatoprost implant has been modified to provide a steady state release of medication[1*]

Bimatoprost implant applicator system

*While the rate at which the body eliminates most drugs is proportional to the concentration administered, known as **first order kinetics**, drugs that work by zero order kinetics work at a predictable, constant rate.[2]

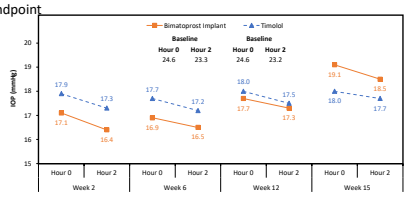
1. Lewis R, et al. *Am J Ophthalmol* 2017;175:137-147.2. Study.com Zero Order Kinetics. Website: https://study.com/academy/lesson/zero-order-kinetics-definition-plot-equation-examples.html Accessed 9/18/2018.

122

Mean IOP by Treatment Group and Treatment Difference in Mean IOP

ARTEMIS Study 1

Primary Endpoint



Bimatoprost Implant vs. Timolol (95% CI)				
Hour 0	-0.8 (-1.47, -0.14)	-0.8 (-1.47, -0.21)	-0.3 (-1.09, 0.43)	1.1 (0.22, 1.89)
Hour 2	-0.9 (-1.50, -0.31)	-0.7 (-1.27, -0.04)	-0.2 (-0.90, 0.46)	0.9 (0.10, 1.64)

1. DURYSTA™ [package insert]. Irvine, CA: Allergan USA, Inc., March 2020.

123

Contraindications

- **Contraindications:**
  - Active or suspected ocular or periocular infections
  - Corneal endothelial cell dystrophy (e.g. Fuch's Dystrophy)
  - Prior corneal transplantation or endothelial cell transplants (e.g., Descemet's Stripping Automated Endothelial Keratoplasy [DSAEK])
  - Absent or ruptured posterior lens capsule, due to the risk of implant migration into the posterior segment
  - Hypersensitivity to bimatoprost or any other components of the product

Please also see the Durysta full prescribing information.

1. DURYSTA™ [package insert]. Irvine, CA: Allergan USA, Inc., March 2020.

124

Laser's In Eyecare

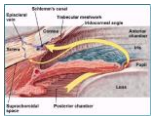
J. James Thimons,O.D.,FAAO
Chairman, National Glaucoma Society
www.nationalglaucomasociety.org

125

Major Types of Glaucoma

Then-Von Graefe (1850)
- Acute
- Chronic
- Secondary

Now (1954)
- Open-angle glaucoma
- Angle-closure glaucoma
- Normal (low) tension glaucoma
- Juvenile glaucoma
- Congenital glaucoma
- Secondary glaucomas



Normal Drainage of Aqueous Humor

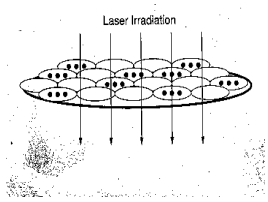
126

Trabecular Meshwork

- Cellular and Structural Components
- TM cells are phagocytic and contain variable amounts of melanin
- ALT induces focal scarring and coagulative damage with reduced flow through the laser-treated site

127

Mixture of Pigmented and Non-pigmented TM cells



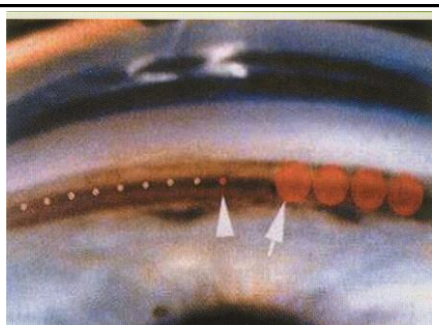
M. Latina, M.D.

128

Selective Laser Trabeculoplasty Latina et al.

- Selective Photothermolysis
  - Requirements
    - Intracellular target chromophore (melanin) and no competing chromophores
    - Targets must absorb laser energy better than surrounding tissues
    - Short Laser Pulse to generate and confine heat
  - Only pigmented cells within the irradiation zone will be targeted

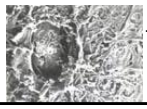
129

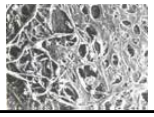


130

Selective Laser Trabeculoplasty

- Results comparable to ALT (argon laser trab.)
- 50 spots to nasal trabecular meshwork
- Less "traumatic" than ALT
- 70% of pts respond IOP reduced by > 3 mmHg, mean 23.5%


ALT


SLT

131

SLT Contraindications

- Inflammatory or uveitic glaucoma
- Congenital glaucoma/ICE syndromes/NVG and angle recession – membrane grows over angle; laser contraindicated in these patients
- Narrow angle glaucoma or patients in whom it is difficult to visualize TM
  - 400 um spot size – this is large spot size; so need good/deep angle to fit this spot size
  - Might try pilo prior to tx to see if can visualize more of angle

132

SLT

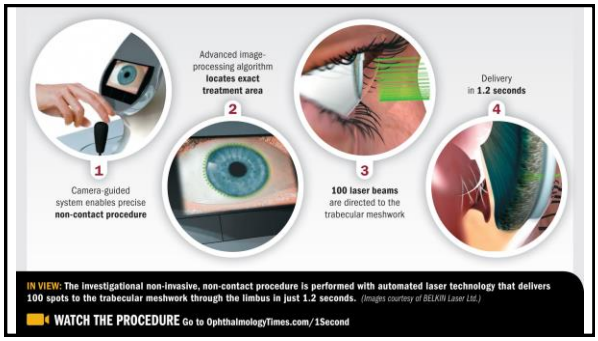
- Pre-op meds: alphagan P or combigan topical anesthesia
- Goldmann three-mirror lens or Latina lens
- Focus on TM and aim for light bubble formation
- 50 ± 5 contiguous spots along 180 degrees
- Post-op meds – PF QID for 4 days ?
- AT's as needed

133

•BELKIN DSLT

ARVO Annual Meeting Abstract | April 2014**Direct Trans-Scleral Selective Laser Trabeculoplasty (SLT) Without a Gonioscopy Lens**
Michael Belkin; Noa Geffen; Shay Ofir; Audrey Kaplan Messas; Yaniv Barkana; Avner Belkin; Ehud Assia; Direct Trans-Scleral Selective Laser Trabeculoplasty

134



135

Belkin DSLT

- An investigational IOP-lowering modality, direct selective laser trabeculoplasty (DSLT) (BELKIN Laser), is being developed for its potential as a first-line treatment for ocular hypertension (OHT) open-angle glaucoma (OAG) and possibly for angle-closure glaucoma (ACG) that overcomes the limitations of current initial therapeutic options.
- The non-invasive, non-contact procedure is performed with automated laser technology that delivers 100 spots to the trabecular meshwork through the limbus in just 1.2 seconds.
- A proof-of-concept study provided evidence for the efficacy and safety of the transscleral approach to laser beam delivery using a conventional SLT instrument, and studies are under way outside of the United States using the external automatic glaucoma laser device itself

136

Belkin DSLT

- **Results**: In the trial group (N=16), IOP decrease from an average of 20.21 mmHg before treatment to 15.50 at 6 months.
- The corresponding numbers for the control group (n=16), were 21.14 mmHg and 15.00. There was no statistical difference between the two groups in IOP reduction.
- Complications rate was significantly higher in the control group (p<0.0001, OR 6.881, 95% CI 1.676/28.248).
- Anterior chamber inflammation and superficial punctate keratitis rates were significantly higher in the control group and compared to the study group (p=0.006).

137

NARROW ANGLE GLAUCOMA

- DEFINING THE DISEASE
  - INTERMITTENT ANGLE CLOSURE
  - SUBACUTE ANGLE CLOSURE
  - ACUTE ANGLE CLOSURE
  - CHRONIC ANGLE CLOSURE
  - COMBINED ANGLE CLOSURE
  - PLATEAU IRIS SYNDROME

138

NARROW ANGLE GLAUCOMA

- EPIDEMIOLOGY
  - 5% OF GENERAL POPULATION@ RISK
  - 0.65% OCCLUDABLE
  - GENETICALLY DETERMINED(TORNQUIST)
  - AGE RELATED
  - REFRACTIVE ERROR
  - RACE

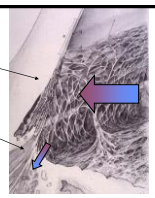
139

NARROW ANGLE GLAUCOMA

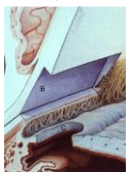
- DIAGNOSING THE DISEASE
  - CLINICAL EXAMINATION
    - GONIOSCOPY
    - HD ASOCT
    - IOP
    - OPTIC NERVE ASSESSMENT
    - VISUAL FIELDS

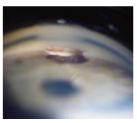
140

Aqueous outflow



Trabeculectomy





141

GONIOSCOPY

Then- Goldmann mirrored contact lens in 1938

- Differentiates:
  - Open Angle
  - Closed Angle
  - Recessed Angle

Now

CB
SS
TM

40º
PAS
Pigm

142

NARROW ANGLE GLAUCOMA

- GRADING THE ANGLE
  - SCHAFER
  - SPAETH
  - ANATOMIC NOTATION
  - INDENTATION TECHNIQUE

143

NARROW ANGLE GLAUCOMA

- SYMPTOMS
  - PAIN/DISCOMFORT
  - BLURRED VISION
  - HALOS
  - NAUSEA

144

NARROW ANGLE GLAUCOMA

- CLINICAL SIGNS(ACUTE)
  - MID-DILATED PUPIL
  - VENOUS CONGESTION
  - CORNEAL EDEMA
  - INCREASED IOP
  - SHALLOW A/C

145

NARROW ANGLE GLAUCOMA

- CLINICAL SIGNS(CHRONIC)
  - PERIPHERAL ANTERIOR SYNECHIA
  - SECTOR ATROPHY
  - DISC/FIELD DAMAGE
  - GLAUKOMFLECKEN

146

NARROW ANGLE GLAUCOMA

- TREATMENT
  - CAREFUL HISTORY
  - EXAMINATION OF AFFECTED AND NON-AFFECTED EYE
  - ORAL CAI'S
  - TOPICAL BETA-BLOCKER
  - PATIENT IN SUPINE POSITION

147

NARROW ANGLE GLAUCOMA

- TREATMENT (CON'T)
  - REASSESS ANGLE/IOP AT 1 HOUR
  - IOP DECREASED =PILO 1%
  - IOP SAME=ORAL ISOSORBIDE
  - REASSESS @ 30MINUTES
  - IOP SAME= CONSIDER MANNITOL
  - IOP DECREASED CONTINUE TOPICAL TX

148

NARROW ANGLE GLAUCOMA

- SURGICAL THERAPY
  - IRIDOPLASTY
  - PERIPHERAL IRIDOTOMY
  - SURGICAL IRIDECTOMY
  - TX FELLOW EYE

149

NARROW ANGLE GLAUCOMA

- POST OPERATIVE CARE
  - ASSESSING ANGLE
  - CHECKING PERIPHERAL IRIDOTOMY
  - IOP
  - TX MIXED MECHANISM

150

151

MIGS Glaucoma Video Grand Rounds

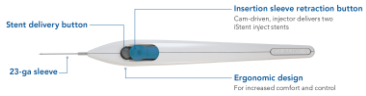
152

MIGS or LIGS?

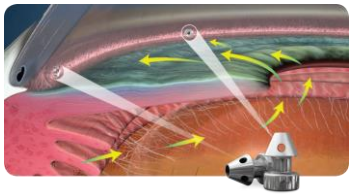
- Trabecular Bypass/Canal Enhancement
  - Istent G1
  - Istent Inject
  - Hydrus
- Goniotomy
  - Trabectome
  - Kahook Dual Blade
  - Omni
  - GATT
- Canal Expansion
  - ABIC
  - Omni
- Suprachoroidal Space
  - None (Cypass)
- Entire Outflow System Bypass
  - Xen
  - Innfocus
- Cyclophotocoagulation
  - ECP
  - TCP

153

154



155



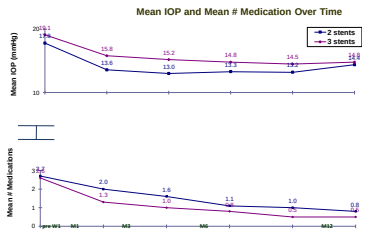
156

Microbypass Stent

10/16/16

157

Multiple Trabecular Bypass in Combined Phaco[5]



R. Noecker, MD – 2011 OSN NY

158

Case Report

- 75 year old female with modérate POAG but with some angle narrowing
- Treated with latanoprost and timolol/brimonidine
- IOP 20/21 Peak IOPs 26/27
- Inferior thinning of RNFL on OCT, with VF nasal steps
- Visual acuity 20/50 OU due to modérate NS cataracts
- Treated with combined OMNI/cataract OU
- Several days of post-op microhyphema
- IOP 18/19 on no meds post-op

159

Ab interno Viscocanalostomy

160

Ivantis /Hydrus Microstent

- The FDA's approval was based on the 24-month results from the HORIZON trial, the largest MIGS study to date.
- The study included 556 mild to moderate glaucoma patients randomly assigned to undergo cataract surgery with or without the microstent.
- More than 77% of patients with the implant exhibited a significant decline in unmedicated IOP, compared with 58% of the control group.
- On average, the device reduced IOP by 7.5 mmHg, approximately 2.3 mmHg more than the cataract surgery-only group.

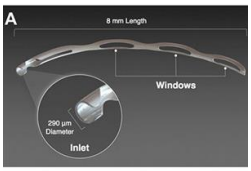
161

Hydrus™ Aqueous Implant

- **Flexible canal "scaffold"**
- Composed of biocompatible alloy (Nitinol)
- Scalloped and open design allows aqueous flow
- 3 clock-hour length targets multiple collector channels

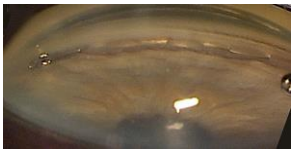
162

Hydrus Microstent



163

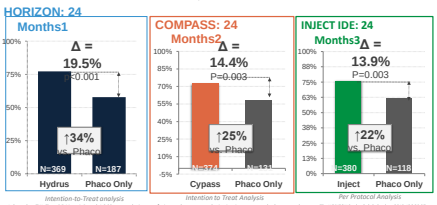
Hydrus Microstent



164

Primary Endpoint Comparison

IOP REDUCTION ≥ 20% AFTER MEDICATION WASH OUT



165

Hydrus

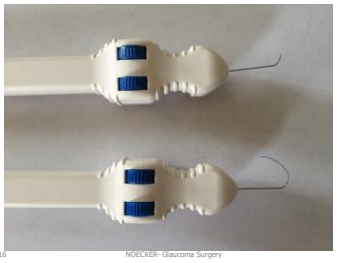
166

Case Report

- 65 year old female with modérate POAG sp cataract surgery with dry eyes
- Treated with latanoprost and timolol/dorzolamide
- IOP 18 OU Peak IOPs 25 OU
- Inferior thinning of RNFL on OCT, with VF mild nasal steps
- Visual acuity 20/25 OU
- Treated with Trab360 goniotomy OU
- Two days of post-op microhyphema
- IOP 18 OU post op off meds
- Ocular surface improved

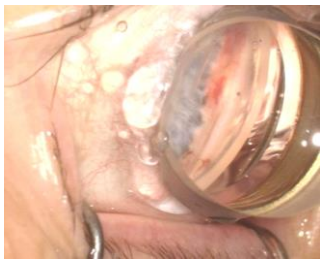
167

Ab Interno Trabeculotomy (Trab 360)



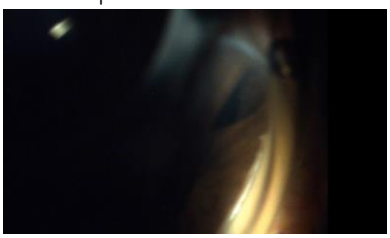
168

Trab 360



169

Post – Op Gonio



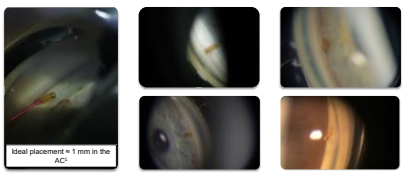
Courtesy of Leonard K. Seibold, MD

170

XEN

171

Anterior Chamber Images



1. XEN® Directions for Use.

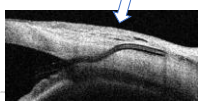
172

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

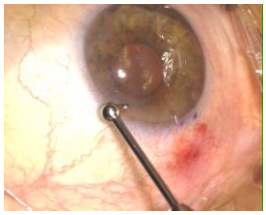


173

Case Report

- 66 year old female with modérate POAG sp cataract surgery with dry eyes sp SLT
- Treated with bimatoprost and timolol/dorzolamide
- IOP 21 OU Peak IOPs 25 OU
- Inferior and Superior thinning of RNFL on OCT, with VF defects above and below
- Target IOP 15
- Treated with Xen OU
- IOP 8 OU post op Day 1 off meds
- IOP 12/13 after 3 months

174

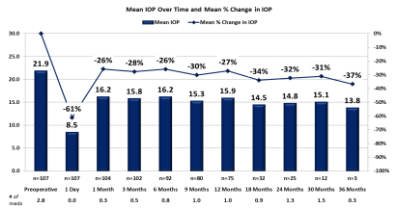


175

175

POAG Only

Summed patients: primary, combined and refractory



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

176

Case Report

- 85 year old asían female sp angle closure right eye/ narrow angle plateau iris OS
- Sp LPI OU
- Va 20/80 right eye, 20/50 left Eye
- IOP 30 OD 20 OS on maximal meds including diamox
- Treated w/cataract/ECP surgery to shrink ciliary processes
- IOP 15 - tapered off meds over two months

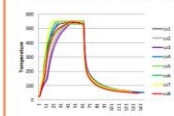
177

Micropulse Transscleral Cyclophotocoagulation

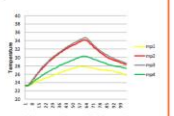
NUHS

TEMPERATURE GENERATED

- **Conventional** CPC – T max **> 550 ° C**
- **Micropulse** CPC – T max **35 ° C**



G probe



Micropulse CPC probe

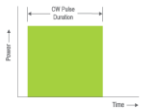
NUH

178

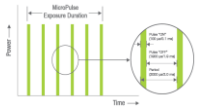
How MicoPulse® Works

MicroPulse technology finely controls thermal elevation by "chopping" a continuous-wave (CW) beam into an envelope of repetitive short pulses.

Continous-Wave (CW) Mode



MicroPulse Mode



179