CURRENT TOPICS IN GLAUCOMA

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DISCLOSURE:

Joseph Sowka, OD **is/ has been a Consultant/ Speaker Bureau/ Advisory Board member for Alcon Laboratories, Allergan, Sucampo, Merck, Glaukos, B&L, and Carl Zeiss Meditec. Aerie Pharmaceuticals bought him dinner. Dr. Sowka has no direct financial interest in any of the diseases, products or instrumentation mentioned in this presentation.**

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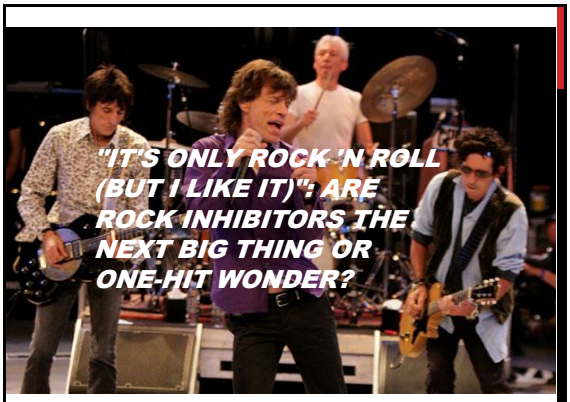
GLAUCOMA EPIDEMIOLOGY AND TREATMENT

Current Medical Treatments for OAG

↓Aqueous Production	↑ Aqueous Outflow	
	Conventional	Unconventional
β-blocker CAI α_2-agonist	Cholinergic agonist NO donating PGA RhoKinase inhibitor	Prostaglandin analog α_2-agonist

2016-2017 MEDICAL MANAGEMENT OF GLAUCOMA…

…HAS GOTTEN BORING



ROCK/Norepinephrine Transporter (NET) Inhibitors

Netarsudil 0.02% (Rhopressa ™)- approved 12/18/17

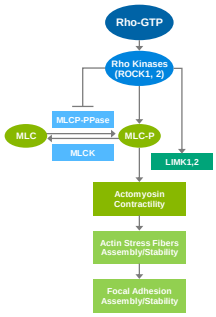
Netarsudil/latanoprost 0.02%/0.005% (Roclatan ™)

aerie pharmaceuticals, inc.

Rho Kinase (ROCK) Inhibition

New Development in IOP Reduction

- Rho activation increases contractility of TM cells
  - Reduces outflow of aqueous humor
- Rho kinase inhibition relaxes TM cells
  - Reduces actin stress fibers/focal adhesions
  - Increases outflow of aqueous humor
- Rho kinase inhibition may also:
  - Increase ocular blood flow
  - Increase retinal ganglion cell survival

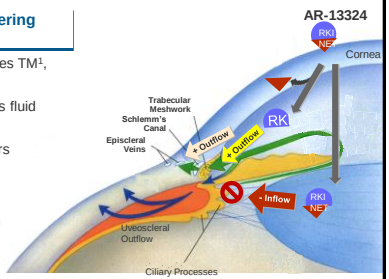


Uehata M, et al. *Nature* 1997;389:990-994
Hirata A, et al. *Graefes Arch Clin Exp Ophthalmol.* 2008;246(1):51-59
Wang SK, Chang RT. *Clin Ophthalmol* 2014;8:883-890

Netarsudil ophthalmic solution 0.02% (ROCK-NET Inhibitor) Triple-Action

3 Identified IOP-Lowering Mechanisms

- ROCK inhibition relaxes TM[1], increases outflow[1,2]
- NET inhibition reduces fluid production[2]
- ROCK inhibition lowers Episcleral Venous Pressure (EVP)[3]



1. Wang SK, Chang RT. An emerging treatment option for glaucoma: Rho kinase inhibitors. *Clin Ophthal* 2014;8:883-890.
2. Wang RF, Williamson JE, Kopczynski C, Serle JB. Effect of 0.04% AR-13324, a ROCK, and norepinephrine transporter inhibitor, on aqueous humor dynamics in normotensive monkey eyes. *J Glaucoma* 2015. 24(1):51-4.
3. Kiel JW, Kopczynski C. Effect of AR-13324 on episcleral venous pressure (EVP) in Dutch Belted rabbits. *ARVO* 2014. Abstract 2900

Netarsudil ophthalmic solution 0.02%: Rhopressa™ (Rocket 1) Efficacy Results At Different Baseline IOPs

Baseline IOP (mmHg)	Non-inferiority	Numerical Superiority
<27*	Did not meet	Met 2 time points
<26***	Met	Met 4 time points
<25***	Met	Met 7 time points
<24**	Met	Met All 9 time points
<23***	Met	Met All 9 time points

- Per Protocol population (baseline IOP < 27 mmHg)
- Netarsudil did not meet criteria for non-inferiority to Timolol
- Inferiority was driven by a small subset of Netarsudil patients with the highest baseline IOPs

* Primary endpoint
** Pre-specified secondary endpoint
*** Post-Hoc Analysis

Netarsudil ophthalmic solution 0.02: Rocket 2 study

- Rocket 2 is a 12-month Phase 3 study of Netarsidil vs. Timolol
- The patient group to be used for Rocket 2 primary endpoint analysis was changed with FDA agreement
  - ➢ Primary endpoint analysis will include only patients with a baseline IOP above 20 mmHg and below 25 mmHg
- ➢ Rhopressa QD and BID met criterial for non-inferiority to timolol (baseline < 25 mm)
- Seems to work best at lower/ modest IOP baseline

Netarsudil ophthalmic solution 0.02% Rhopressa ™

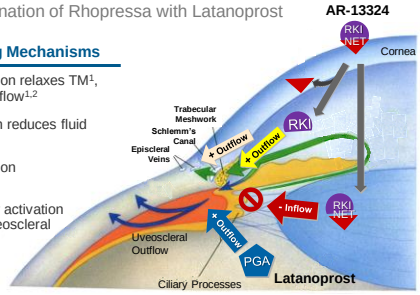
- In two phase III studies, more than half of patients experienced conjunctival hyperemia compared to 8% to 10% of timolol patients.
  - More complaints of eye redness with Rhopressa.
- 9% and 5% of Rhopressa once-daily patients reported corneal deposits (vortex keratopathy) across the two phase III studies compared to 0.4% and 0% of the timolol patients.
- Blurry vision was reported by 7% and 5% of Rhopressa patients compared to 3% and 0.5% of timolol patients in the studies.

Roclatan™ (netarsudil/latanoprost ophthalmic solution) 0.02%/0.005%

Fixed Combination of Rhopressa with Latanoprost

4 Identified IOP-Lowering Mechanisms

- ROCK inhibition relaxes TM[1], increases outflow[1,2]
- NET inhibition reduces fluid production[2]
- ROCK inhibition lowers EVP[3]
- PGA receptor activation increases uveoscleral outflow[4]



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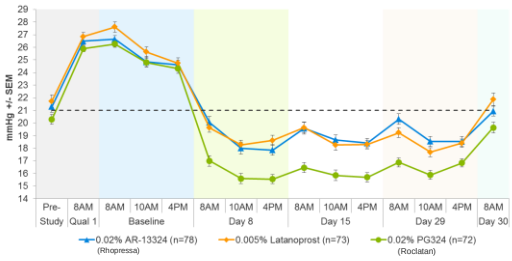
3. Kiel JW, Kopczynski C. Effect of AR-13324 on episcleral venous pressure (EVP) in Dutch Belted rabbits. ARVO 2014. Abstract 2900
4. Latanoprost prescribing information

Roclatan Achieved Statistical Superiority Over Individual Components at All Time Points (p<0.001)

Mean IOP at Each Time Point (Primary Efficacy Measure)

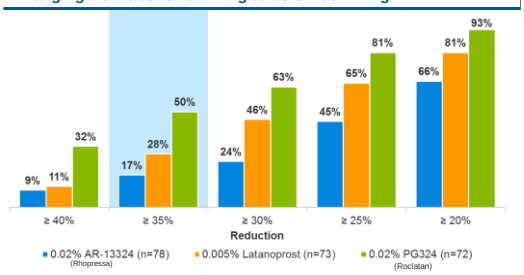


PG324 Phase 2b, Intent to Treat

Source: Bacharach J, Levy B, Ramirez N, Kopczynski CC, Novack GD for the PG324-CS201 Study Group. Evaluation of PG-324, a fixed dose combination of AR-13324 and latanoprost, in patients with elevated intraocular pressure in a double-masked, randomized, controlled study. American Glaucoma Society 2015 (in press).

Roclatan (netarsudil/latanoprost) 0.02%/0.005% Phase 2b Responder Analysis

Day 29 – % of Patients with IOP Reductions of ≥ 20%: baseline IOPs ranging from above 20 mmHg to below 36 mmHg



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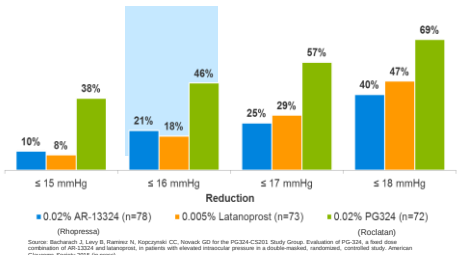
Roclatan Phase 2b Responder Analysis

Day 29 – % of Subjects with IOP Reduced to ≤ 18 mmHg: baseline IOPs ranging from above 20 mmHg to below 36 mmHg



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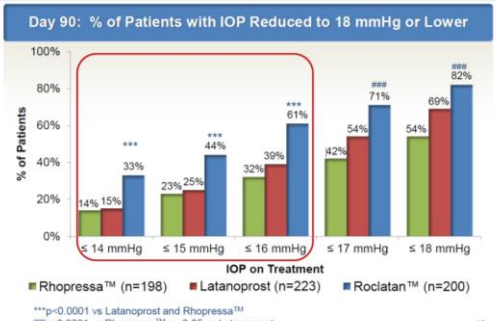
Roclatan (netarsudil/latanoprost) 0.02%/0.005% Phase 3 Clinical Trial (Mercury 1)

- Roclatan achieved its primary efficacy endpoint demonstrating statistical superiority over each of its components, including Aerie product candidate Rhopressa (netarsudil ophthalmic solution) 0.02%, and latanoprost, all of which were dosed once daily in the evening, according to a company news release.
- The study evaluated patients with maximum baseline IOPs ranging from above 20 mmHg to below 36 mmHg. The IOP-lowering effect of Roclatan was 1 mmHg to 3 mmHg greater than monotherapy with either latanoprost or Rhopressa throughout the duration of the study.

Roclatan™ Phase 3 Responder Analysis

Day 90: % of Patients with IOP Reduced to 18 mmHg or Lower



***p<0.0001 vs Latanoprost and Rhopressa™
###p<0.0001 vs Rhopressa™, p<0.05 vs Latanoprost

Roclatan (netarsudil/latanoprost) 0.02%/0.005% Phase 3 Clinical Trial (Mercury 1)

- Roclatan reduced mean diurnal IOPs to 16 mmHg or lower in 61 percent of patients, a significantly higher percentage than observed in the comparator arms.
- The most common Roclatan adverse event was hyperemia, which was reported in approximately 50 percent of patients, or 30 percent above baseline, and was scored as mild for the large majority of these patients. Conjunctival hemorrhage was also noted. There were no drug-related serious adverse events for any of the comparators in the trial.

Roclatan 12-Month Safety and Efficacy Highlights for Mercury 1

- Safety results for Roclatan for the 12-month period were consistent with those observed for the 90-day efficacy period in the trial.
- Roclatan IOP lowering exceeded that of both latanoprost and Rhopressa in a range from 1 to 3 mmHg.
  - Levels of IOP lowering were consistent with those observed in the Mercury 1 and Mercury 2 90-day efficacy results for all arms of the study.
  - Roclatan also demonstrated consistent levels of IOP lowering across the 12-month study period.
- Most common adverse event for Roclatan was conjunctival hyperemia, (60 percent of patients- considered mild), petechiael conjunctival hemorrhages (often not noticed by patients), and vortex keratopathy (reversible).

latanoprost bunod (LBN)-Vysulta™

- Vysulta™
  - FDA approved 11/2/17
  - Currently called Nitric oxide-donating prostaglandin F2-alpha analog licensed by Nicox to Bausch + Lomb In Phase 3 studies, LBN reached its desired primary endpoint of non-inferiority to timolol maleate 0.5%, actually showing superiority to the beta blocker.
- LBN showed a reduction in mean IOP of 7.5 to 9.1 mmHg from baseline between 2 and 12 weeks through Phase 3 studies

latanoprost bunod (LBN) Vysulta™

- Upon instillation in the eye, latanoprostene bunod is rapidly metabolized to two actives; latanoprost acid, a prostaglandin analog, and nitric oxide.
- Nitric oxide is an important physiological signaling molecule, which plays a key role in IOP regulation in healthy eyes.
- LBN/Vysulta is thought to increase aqueous humor outflow by acting on both the uveoscleral (non-conventional) pathway via latanoprost acid, and trabecular meshwork and Schlemm's canal (conventional pathway) via nitric oxide signaling.

latanoprost bunod (LBN) Vysulta™

- VOYAGER/ LUNAR Studies, it was seen that latanoprost bunod 0.024% dosed once daily gave significantly greater IOP lowering and comparable side effects relative to latanoprost 0.005%. The most common side effect was hyperemia, which was well tolerated.

Trabodenoson™

- Inotek Pharmaceutical's compound is considered to be a first-in-class selective adenosine mimetic whose action appears to be increased trabecular aqueous outflow.
- Trabodenoson™ -long duration of action, making QD dosing possible
- Approximates the IOP lowering efficacy of prostaglandin analogs.
- It also appears to have an additive effect to other second-line glaucoma medications such as beta blockers and carbonic anhydrase inhibitors
- Adverse effects don't seem to increase with dose doubling/ tripling
- 2019 or 2020?

…ONLY TIME WILL TELL

A ROCKET MAN?

TERMINOLOGY

- **Compliance: The act of conforming, acquiescing, or yielding; cooperation or obedience**
  - Pejorative term

TERMINOLOGY

- **Adherence: A measure of the degree to which a patient follows prescribed instructions during a defined time period.**
  - E.g. Timolol BID over 30 days; patient uses 20 drops; adherence is 33%
  - Allows the patient to have lapses in drug use and summarizes the percent of days that the patient uses the drug
- **41%- 76% adherence in glaucoma**

TERMINOLOGY

- **Persistence: A metric that evaluates the time until a patient first discontinues the use of a medication.**
  - BID drug used QD and patient refills each month and stockpiles medication has excellent persistence (100%) and poor adherence (50%)
- **White Coat Adherence: Patient adherence rises sharply 1 week before examination and then declines 30 days following**

ADHERENCE BY DRUG CLASS AND THERAPY

- **PGAs have higher degree of persistence and adherence**
- **Nearly half of monotherapy patients had stopped using medications at 6 months**
- **Less adherence and persistence with polytherapy**
- **A second drug leads to reduced filling of first-prescribed medication**

BARRIERS TO ADHERENCE AND PERSISTENCE

- **Cost**
- **Tolerability**
- **Dosing schedule**
- **Denial**
- **Lack of education about disease**
- **Forgetfulness**
- **Travel**
- **Schedule**

INDICATIONS FOR NON-ADHERENCE

- **High IOP at follow up**
  - Meds don't fail overnight
- **Lack of complaints about adverse effects**
- **Visit default**
  - Rates of admitted non-adherence higher among visit defaulters
  - Worse adherence correlates with worse follow up
- **Progression despite seemingly good IOP**

Friedman et al. Arch Ophthalmol 2005 ; 123:1134; Quigley et al. Ophthalmology 2007; 114:1599.

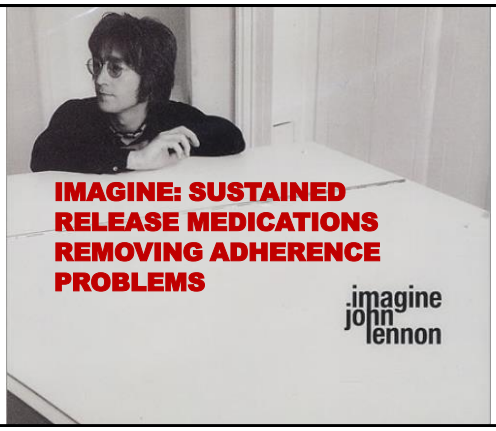
DETECTING NON-ADHERENCE

- **Videotaped encounters followed by doctor and patient questionnaires and interviews**
- **Doctor-patient dialog generally physician centered**
  - Doctor speaks 70% of words
  - Closed-ended questions designed to elicit "yes/no" response
- **Failed to identify non-adherence**

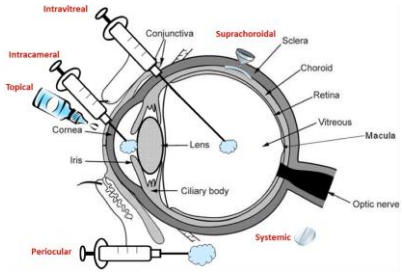
Friedman et al. Ophthalmology 2008; 115:1320

IMPROVING PATIENT ADHERENCE AND PERSISTENCE

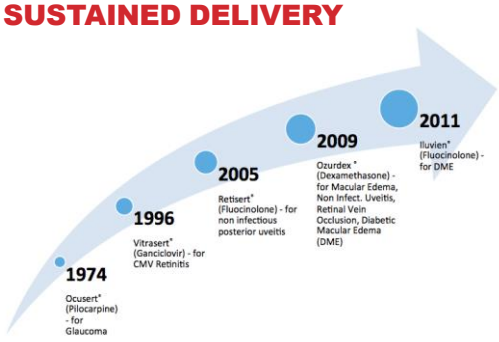
- **Use easy dosing**
  - Monotherapy
  - Once daily dosing with PGA
- **Ask open ended questions**
- **Acknowledge that dosages are going to be missed. Encourage patient to report more accurately in non-confrontational manner**
- **Positive support of patient attempts to adhere**



OPTIONS FOR DRUG DELIVERY



EVOLUTION OF SUSTAINED DELIVERY



PLATFORMS DELIVERED INSIDE THE EYE

News Release

- **Allergan is currently performing phase 3 clinical trials on its bimatoprost sustained-release implant (bimatoprost SR), which is an intracameral depot implant injected into the anterior chamber.**

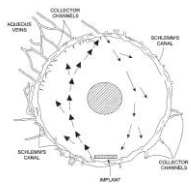


FIG. 2

News Release

- **Implant comprising a prostamide associated with a biodegradable polymer matrix that releases an amount of a prostamide**

BIMATOPROST SR

- **Phase 2 trials of the implant showed mean overall IOP reductions from baseline through week 16 after the first implantation of the bimatoprost sustained-release device**
  - 7.2, 7.4, 8.1, and 9.5 mm Hg with the 6-, 10-, 15-, and 20-microgram doses compared with an 8.4 mm Hg decrease in the pooled fellow eyes treated with topical bimatoprost (0.03%).

BIMATOPROST SR

- **The implant lowered IOP in 92% of patients at 4 months and 71% at 6 months.**
  - Did not need additional rescue therapy
- **There were no serious adverse ocular events**
  - The most common adverse event was transient conjunctival hyperemia (median duration of 5 days), which developed within 2 days after the implant was injected.
- **In 24 eyes that did require another treatment to control IOP, the overall mean IOP reduction from the baseline IOP was 8.0 mm Hg through 16 weeks after the repeat bimatoprost sustained-release treatment.**

TRAVOPROST SR

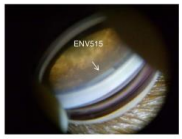
ENV515 Intracameral Extended-Release

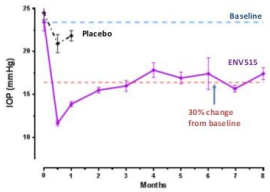
Target Product Profile
- 24/7 control of IOP (25-30% decrease)
- 6 month duration of action
- Less hyperemia than drops
- Easy administration
- Fully biodegradable
- Excellent safety

Extended-release biodegradable travoprost formulation puts the treatment of the disease in the hands of the doctor, not the patient

TRAVOPROST SR

8 Months of IOP Reduction in Hypertensive Beagle Dogs





32% reduction in baseline IOP over 8 months from single dose of ENV515

TRAVOPROST SR

- ENV515- phase 2a open-label, 28-day dose-ranging study of 21 patients yielded 28% IOP lowering at day 25 in one group, which was comparable to once-daily Travatan Z
- Envisia is planning to advance to a 12-month study to evaluate the long-term IOP lowering of ENV515.

Envisia Therapeutics Pipeline

IDOSE™ TRAVOPROST INTRAOCULAR IMPLANT

iDose Travoprost: First-of-a-Kind Intraocular Drug Delivery Device

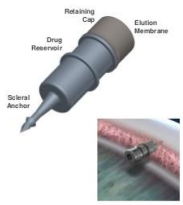
iDose TRAVOPROST

Titanium implant (1.8 mm x 0.5 mm) designed for continuous drug delivery directly into anterior chamber

Filled with proprietary, novel and uber-potent formulation of travoprost; membrane-controlled Fickian elution; zero-order rates demonstrated *in vitro* and *in vivo*

Elegant and facile injectable procedure; bypassing cornea allows for micro-elution rates to achieve therapeutic index

Anchor keeps device in place and facilitates straightforward exchange upon drug depletion



GLAUKOS

IDOSE™ TRAVOPROST INTRAOCULAR IMPLANT

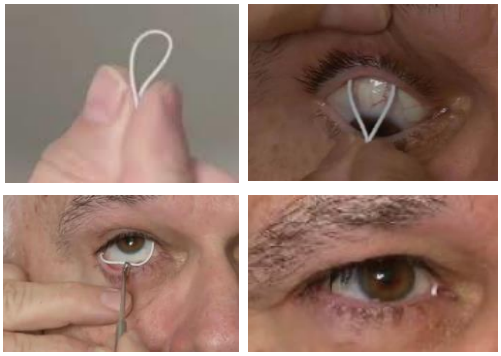
- Injected through a clear corneal incision and secured in the anterior chamber
- Continuously elutes therapeutic levels of medication from within the eye
- Achieved an approximate 30% reduction in mean IOP vs. baseline IOP through 12 months

PLATFORMS DELIVERED OUTSIDE THE EYE

HELIOS (FORSIGHT VISION5)

- Bimatoprost-laden polymer-matrix insert embedded in a compliant ring.
- The ring is positioned under the upper and lower eyelids and rests on the conjunctiva.
- It is visible only at the caruncle once it is in place.
- The ring is designed to be replaced by an optometrist or ophthalmologist every 6 months.

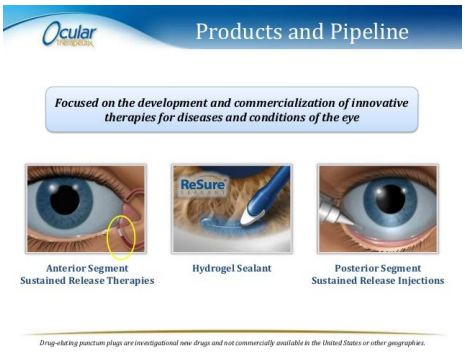
HELIOS (FORSIGHT VISION5)



HELIOS (FORSIGHT VISION5)

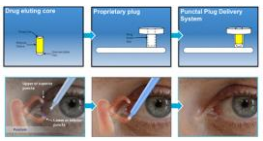
- In a phase 2 randomized, double-masked controlled study, the Helios with bimatoprost and artificial tears was compared to a placebo insert and timolol 0.5% BID.
- The bimatoprost insert lowered IOP, but less than did topical timolol 0.5% dosed twice daily in eyes with placebo insert
- Retention was 90% at 6 mos
- ForSight Vision5 recently acquired by Allergan
- Bimatoprost/timolol FC ring in development

PUNCTAL DELIVERY SYSTEM



OTX-TP

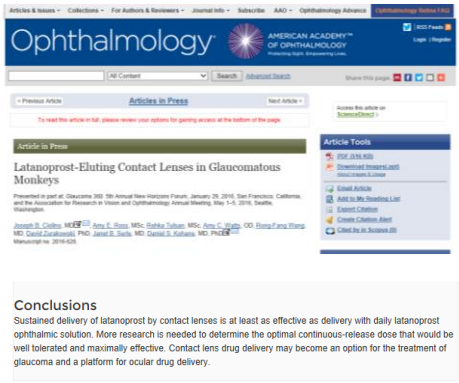
- Releases travoprost and is visible via fluorescence.
- May require flushing the canaliculus with saline or other maneuvers if removal is needed.
- Retention of the OTX-TP device was 91% at 60 days and 48% at 90 days.



PUNCTAL DELIVERY SYSTEM

PUNCTAL DELIVERY SYSTEM

- **Mati Therapeutics device, L-PPDS (latanoprost-punctal plug delivery system), is a drug-eluting punctal plug.**
- **L-PPDS releases latanoprost and is grossly visible.**
- **As a superficial punctal plug, it can be pulled out relatively easily.**



GREAT THINGS ABOUT SUSTAINED DELIVERY

- **Compliance is greatly enhanced**
- **Potentially fewer issues for patients**

NOT SO GREAT THINGS ABOUT SUSTAINED DELIVERY

- **Injectable meds and implants- if med doesn't work topically or has adverse effects, drop is stopped; can't easily stop implantable devices.**
- **Implants can theoretically block parts of the angle**
- **Complications with invasive options**
  - Endophthalmitis
- **Decreased access to care?**

NOT SO GREAT THINGS ABOUT SUSTAINED DELIVERY

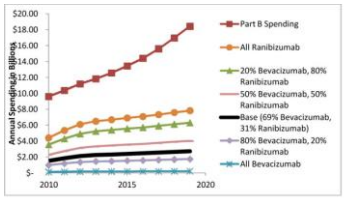
- **Patients still have to verify if plug or ring is still in place**
  - May be challenging for some
    - If patients have to check daily- why not just use a drop?
- **Contact lens-delivery system:**
  - Older patients handling lenses?
  - Issues with infectious keratitis

NOT SO GREAT THINGS ABOUT SUSTAINED DELIVERY

- Limitations- how many drugs can you load into a ring or put in the anterior chamber? Patients only have 2 puncta per eye- may still need topical therapy as well
- Drugs may work better in pulsatile form and not so well in constant delivery
- PGAs less effective at BID dosing- receptor supersaturation and desensitization
  - Downtime between drops prevents desensitization

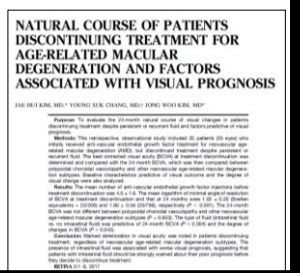
NOT SO GREAT THINGS ABOUT SUSTAINED DELIVERY

- SR products seem less effective than drops
- Will insurance pay for it just to increase compliance?



ANTI-VEGF MODEL FOR AMD

- Compared to clinical trials, VA outcomes are worse and there are fewer injections done in the real world. Patients lost to follow-up are doing poorly.
- Drop out rate 20%-30%



NATURAL COURSE OF PATIENTS DISCONTINUING TREATMENT FOR AGE-RELATED MACULAR DEGENERATION AND FACTORS ASSOCIATED WITH VISUAL PROGNOSIS

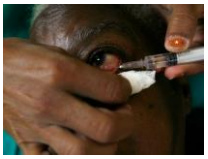
JAE HUI KIM, MD,* YOUNG SUK CHANG, MD,† JONG WOO KIM, MD*

WILL PATIENTS GO FOR IT?

- Electronic surveys were administered to 150 individuals at two glaucoma clinics
- The majority of participants would accept contacts (59%), rings (51%), plugs (57%) and subconjunctival injections (52%) if they obviated glaucoma surgery
- Fewer would accept these devices if they reduced (23% to 35%) or eliminated (27% to 42%) drops. Most participants would also accept contacts (56%), plugs (55%) and subconjunctival injections (53%) if they were more effective than eye drops, while only 47% would accept a ring; fewer would accept any device if it were equally or less effective than drops. Participants were also 36% less likely to accept rings and 32% less likely to accept subconjunctival injections as compared to contacts.
- Researchers determined that most glaucoma patients considered sustained drug-delivery modalities acceptable alternatives to IOP-lowering eye drops, but only when they were said to obviate surgery or demonstrate greater efficacy than eye drops.

Varadaraj V, Kahook MY, Ramulu PY, et al. Patient acceptance of sustained glaucoma treatment strategies. J Glaucoma. 2018; Feb 16.

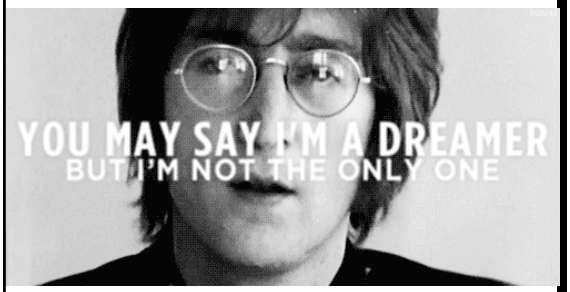
WILL PATIENTS GO FOR IT?



CONCLUSIONS

- Strong push for sustained drug delivery
- Several years away
- Some options will be invasive
  - Limit access to care
- Most options will be non-invasive
- All offer some benefits combined with limitations
- Drops, SLT, and surgery will not become obsolete
- Will these options revolutionize glaucoma management?

NEW MEDICATIONS AND SUSTAINED DRUG DELIVERY REVOLUTIONIZING GLAUCOMA



ISSUES IN IMAGING

- OCT technology is readily available and present in contemporary practice
- No one single parameter is more important than the others.
- Never base a clinical decision based upon only one piece of data.
- OCT is not a Silicon Valley Rumplestilskin. You cannot put in straw and get out gold

ISSUES IN IMAGING

Interpretation is a three-step process

1. Understand what the printout says
2. Apply experience and value judgement
3. Correlate to the clinical findings

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ISSUES IN IMAGING

- You cannot make a diagnosis of glaucoma based solely upon imaging results.
- The use and overemphasis of imaging technology to the exclusion of additional clinical findings and assessment of risk will put patients in peril.
- Exactly how much confidence should an OCT give you as to whether or not a patient has glaucoma?
  - Depends how much confidence you had before you imaged the patient.

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OCT TO VERIFY GLAUCOMA – THE OPTIC NERVE HEAD?

Using OCT to Verify Early Glaucoma

A healthy, 39-year-old Caucasian man was referred for evaluation for pigment dispersion. The patient had a moderately elevated cup-to-disc ratio of 0.5 to 0.6, as per his optometrist. His IOP was 13 mm Hg OD and 14 mm Hg OS.

This patient was a glaucoma suspect, so I wanted to get good baseline data. His visual field and central corneal thickness tests were normal, but his OCT scan was abnormal.

To verify the OCT, I carefully examined his optic nerves and found that his cup-to-disc ratio was 0.85 x 0.85 OD and 0.85 x 0.80 OS.

ISSUES IN IMAGING

- Normative Database
- Signal Quality
- Blink/Saccades
- Segmentation Errors
- Media Opacities
- Axial Length

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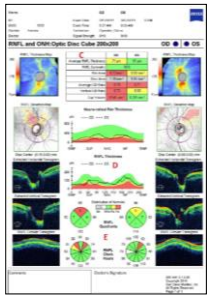
OCT DATABASE INFORMATION

- **Spectralis: 201 patients**
  - All Caucasian
  - Age 18-78
  - New database more representative of US population
- **Cirrus: 284 eyes**
  - Age 19-84
  - Ethnic Groups: Causasian, Asian, African-American, Hispanic
- **RTVue: 600 eyes**
  - Disc Size
  - African-American, Chinese, Japanese, Caucasian, Hispanic, Indian

WHAT TO LOOK FOR WHEN INTERPRETING OCT SCANS

- **Quality score**
- **Illumination**
- **Focus clarity**
- **Image centered**
- **Any signs of eye movement**
- **Segmentation accuracy**
- **B Scan Centration**
- **Missing data**
- **Media issues**
- **Maculopathy for GCC scans**



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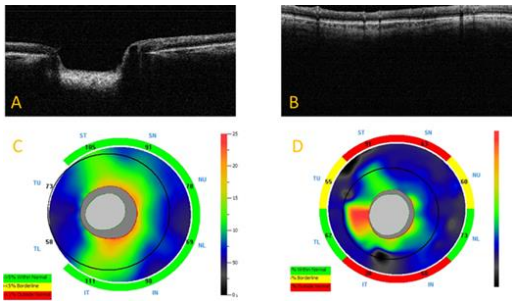
RTVue-100



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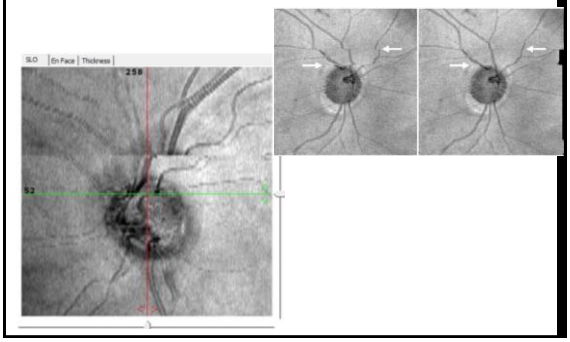
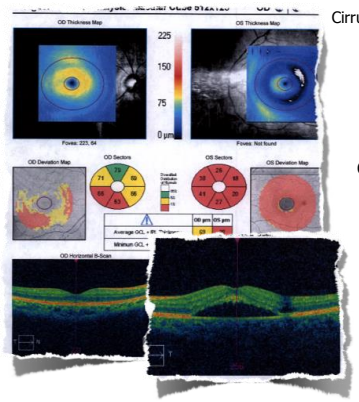
EYE MOVEMENT

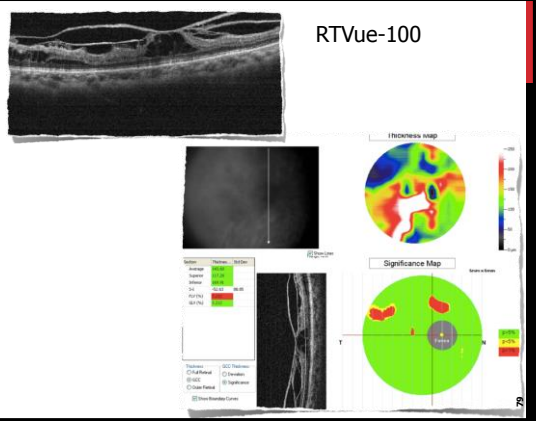


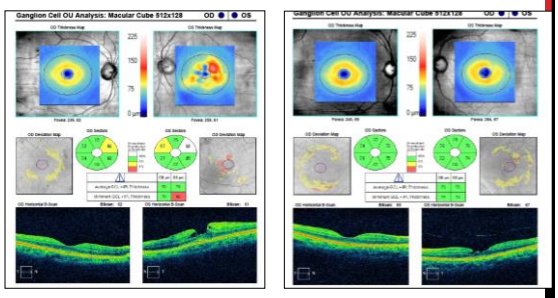
Cirrus



Accidentally find CSC when looking for glaucoma

RTVue-100





Cirrus

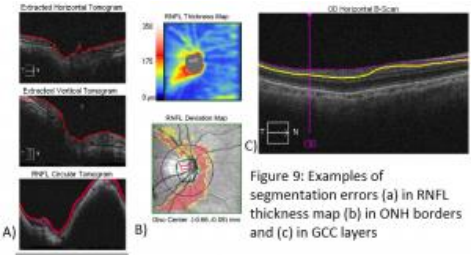
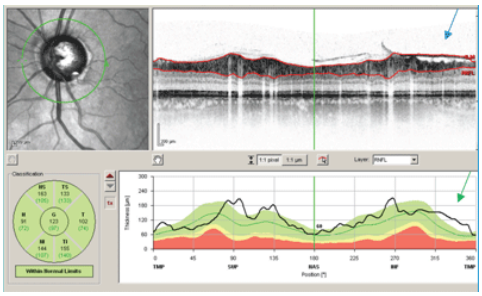
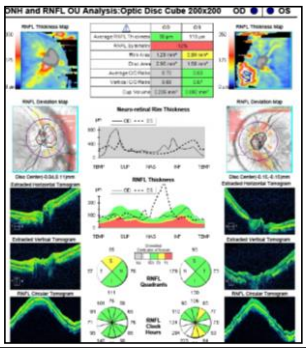


Figure 9: Examples of segmentation errors (a) in RNFL thickness map (b) in ONH borders and (c) in GCC layers

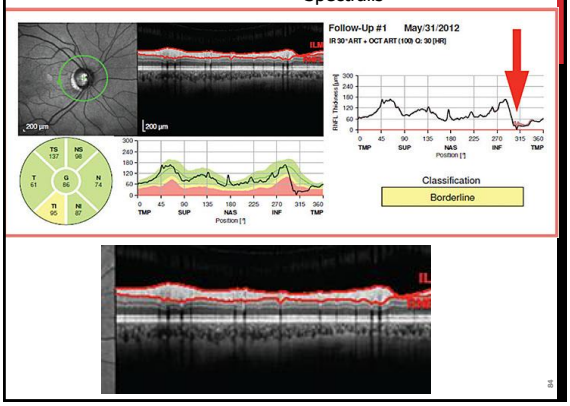
Spectralis



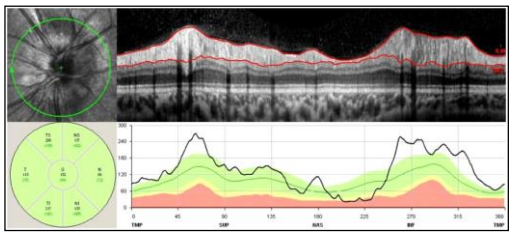
IF YOU THINK DEVICES MEASURE TISSUE ACCURATELY EVERY TIME…

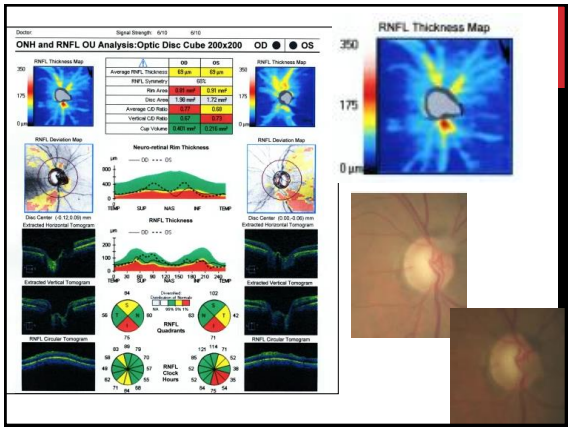


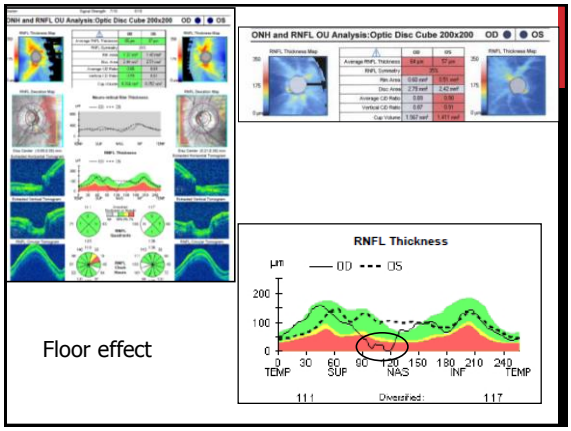
Spectralis



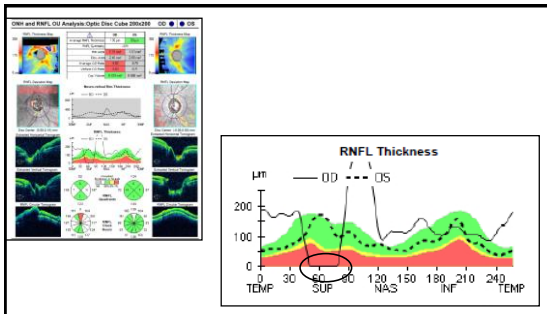
Spectralis







Floor effect



Don't make clinical decisions based upon bad data

The diagnostic imaging doesn't agree with my diagnosis? Now what?

ANSWER:

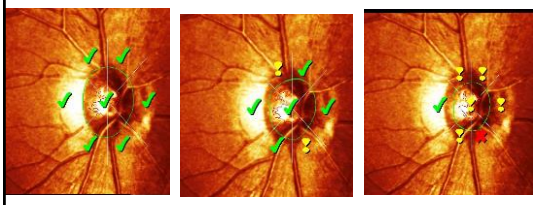
- **Things have to make sense. If the imaging findings to not fit with the anatomic and functional correlates of pathophysiologic change, trust your own knowledge and judgment.**
- **When in doubt, repeat the imaging study and the visual field or both.**

RED DISEASE – A NEW CLINICAL NON-ENTITY

- **A supratentorial, non-glaucomatous masquerade disease**
- **Afflicts the educated patient (especially with Internet access) with good health care plans and/or wealth**
- **Debilitating to the patient and painful for the visual care provider to treat**

2005. *Journal of Irreproducible Results and Senseless Studies*

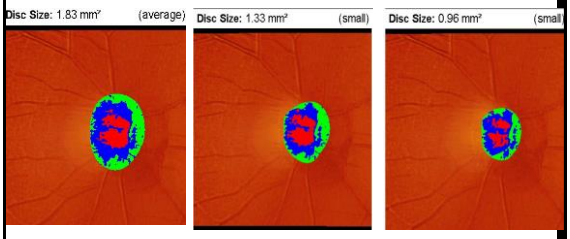
SCANNING LASER OPHTHALMOSCOPY EXAMPLE OF RED DISEASE



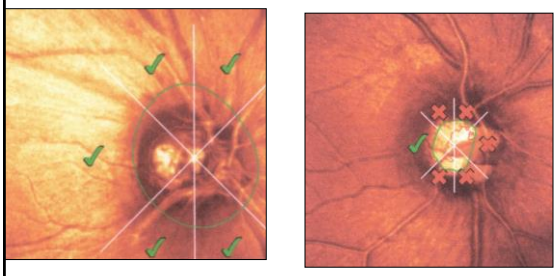
First Visit | Follow up visit #1 | Follow up visit #2

HRT3 Optic Nerve Head Changes
How long did this change take?

WITHIN 15 MINUTES! HRT DISC SIZING ARTIFACT



WHAT DO YOU MAKE OF THESE…?

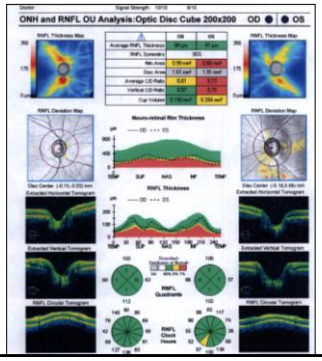


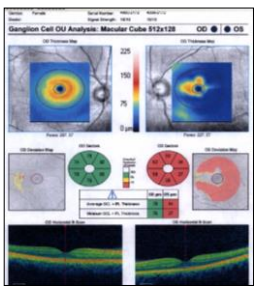
Garbage in, Garbage out.

HELP! THE DIAGNOSTIC IMAGING DOESN'T AGREE WITH MY DIAGNOSIS!

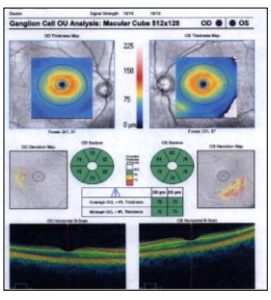
- **Low risk OHTN**
- **Local OD wants imaging for baseline**

OCT RNFL NORMAL…



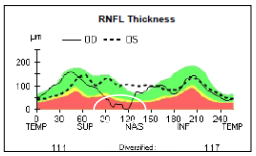


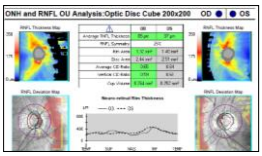
…but markedly abnormal GCC OS

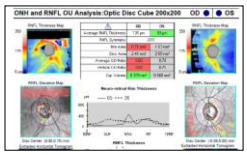


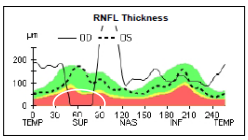
Same patient, same day, same quality, GCC now normal

Signal strength: 10/10 OD, OS on both images





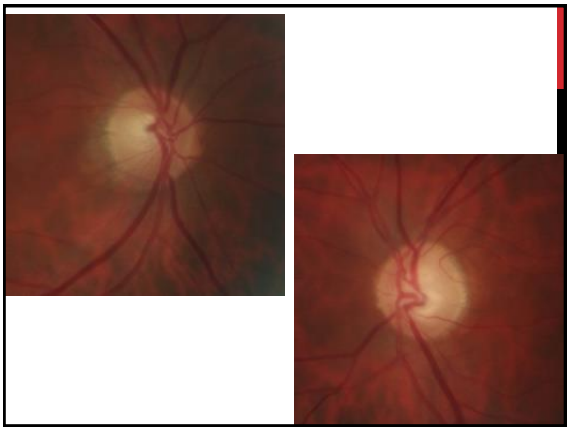


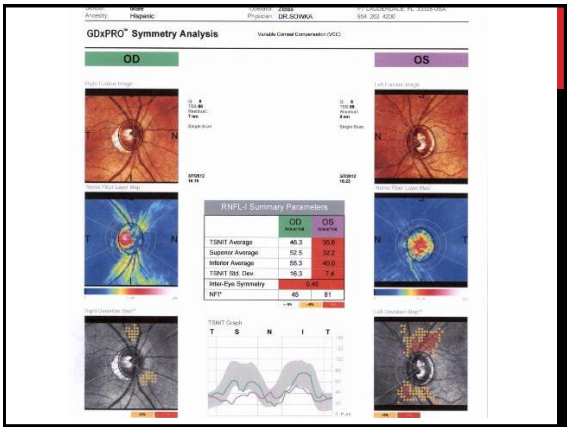


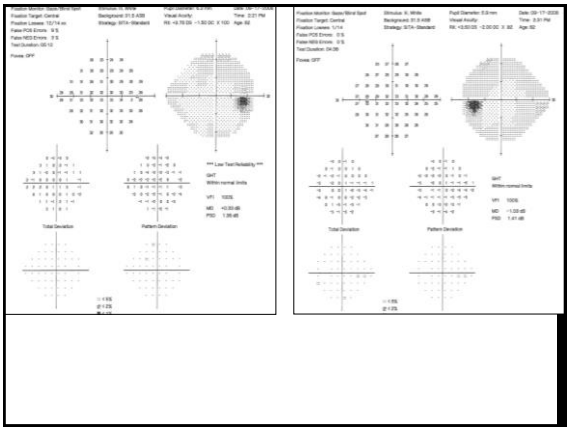
Don't make clinical decisions based upon bad data

CASE: 62 YOHM

- **Asymptomatic; 20/20 OD; OS**
- **TA 30 mm OD, 28 mm OS**
  - Isolated measurement
  - 12-17 mm OD, 13-17 mm OS
    - 11 visits
- **Gonio: open OU w/o abnormalities**
- **CCT: 597 OU**







So, What are your thoughts?

Debate: Treat or Observe?
Debate: Why the disparate findings?
Debate: Why the isolated IOP elevation?

GREEN DISEASE– AN INSIDIOUS CLINICAL *ENTITY*

A glaucomatous process masquerading as non-disease

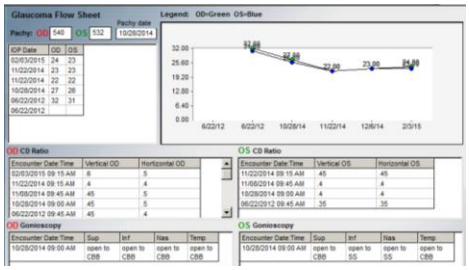
Afflicts inexperienced, poorly-educated, and lazy doctors who simply want a machine to make all clinical decisions for them

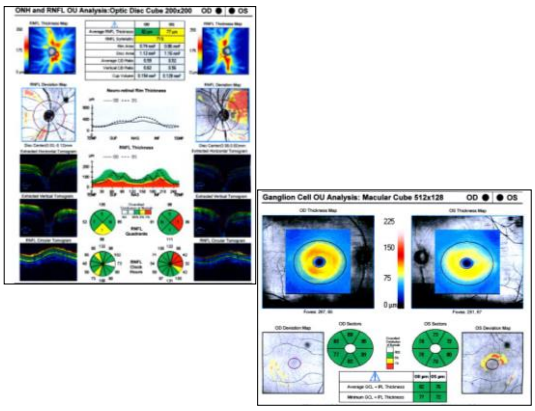
Debilitating to the patient and painful for the visual care provider, but a boon for malpractice attorneys

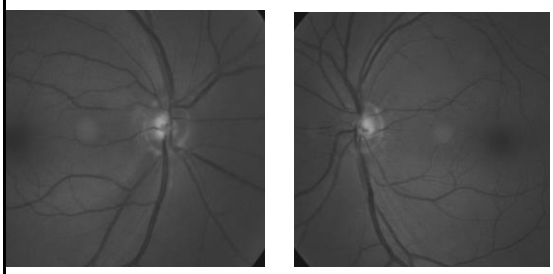
2015. *Journal of Irreproducible Results and Senseless Studies*

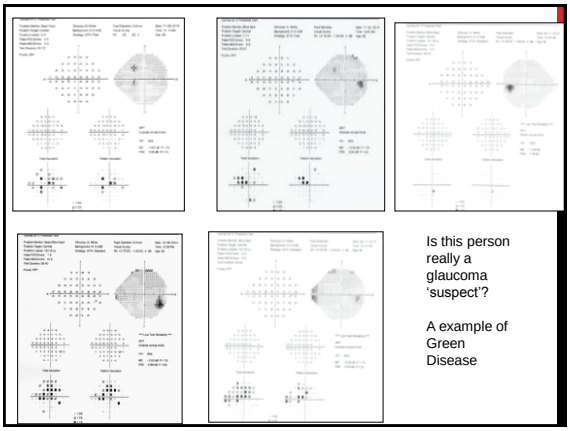
HELP! THE DIAGNOSTIC IMAGING DOESN'T AGREE WITH MY DIAGNOSIS!

- **56 YOM- Glaucoma suspect since 2012**





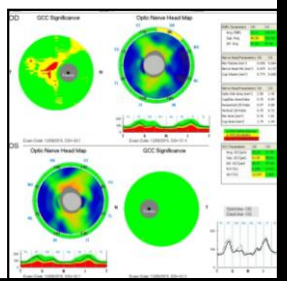




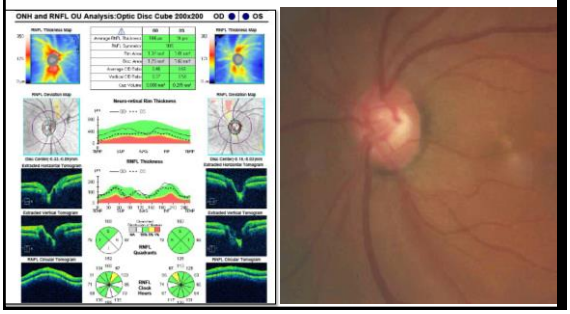
Is this person really a glaucoma 'suspect'?

A example of Green Disease

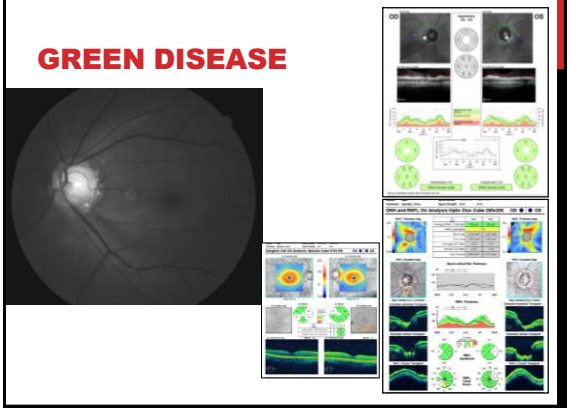
Green Disease



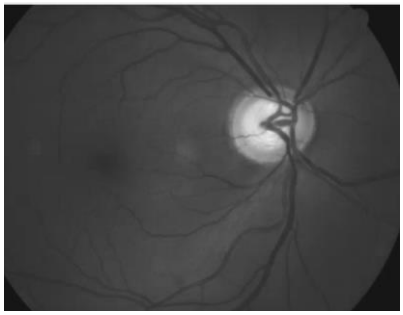
GREEN DISEASE

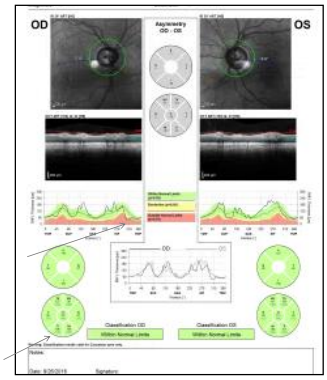


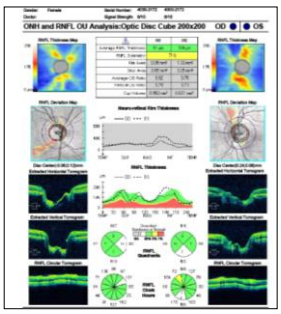
GREEN DISEASE

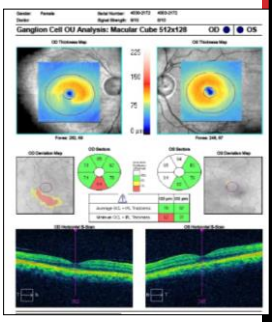


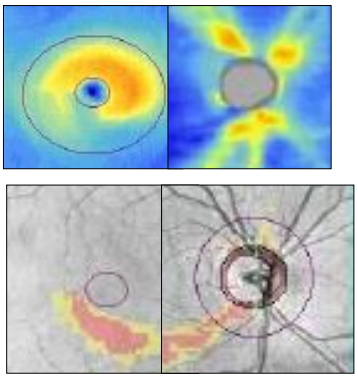
RED + GREEN = YELLOW DISEASE?



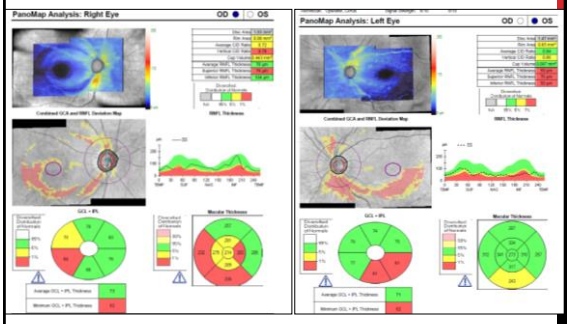




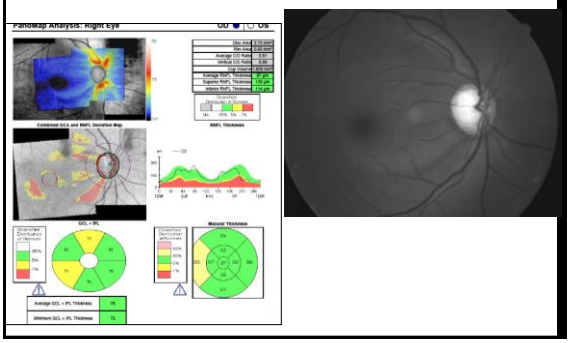




PANOMAP VERSION 8.0



PANOMAP VERSION 8.0



OCT IMAGING TAKE HOME POINTS

- Serial overlays/imaging to determine baseline (intra-session) noise
- Good signal strength
- Good segmentation without errors
- Optic nerve head exam for disc hemorrhage, pallor, myopic, and tilted nerve heads
- Determine structure-function correlation
- Follow all ancillary tests visual fields and optic nerve head photos for progression

CAUTIONS ABOUT IMAGING

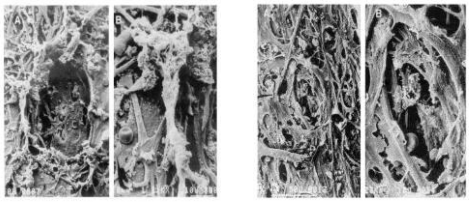
- No current technology is better than the human eye and common sense
- Beware of "Red Disease"
- Treat Real Disease and not Red Disease
- Don't miss Green Disease
- Know the limitations of the technology: normative database, reproducibility, resolution, quality of imaging
- Technologies come and go

Surgical updates

SURGICAL OPTIONS

- Laser trabeculoplasty
  - Argon laser trabeculoplasty (ALT)
  - Selective laser trabeculoplasty (SLT)
- Trabeculectomy with an antifibrotic agent
- Tube shunt
- Newer glaucoma surgical procedure (MIGS)
  - MEGS?

- **ALT** **SLT**



Kramer TR, Noecker RJ. *Ophthalmology* 2001;108:773-9.

ALT VS SLT

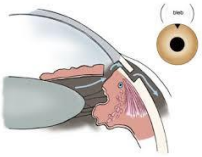
Author/Year	Eyes	IOP Decrease
Damji, 1999	18 ALT	22%
	18 SLT	21%
Popiela, 2000	27 ALT	13.0%
	27 SLT	13.4%
Martinez-de-la-Casa, 2004	20 ALT	19.5%
	20 SLT	22.2%

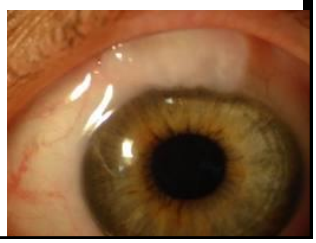
TRABECULECTOMY

Trabeculectomy (1968)

+/- anti-metabolite

- Bleb forming procedure
- Long established procedure with vast experience





OUTCOMES: TRABECULECTOMY

Success After 20 Years:

- 57% = complete success
- 88% = qualified success (w/ meds)

Complications:

- Cataract: 55%
- Loss of ≥3 lines of acuity: 21%
- Bleb-related problems: 10%
- Infection: 4%

Jampel HD. Ophthalmol 2012
Gedde SJ. Arch Ophthal 2012

TRABECULECTOMY – HAS IT BECOME A RELIC?

- **What filter (trabeculectomy) surgery is**
  - Fistulization between AC and subconjunctival space
- **Indications**
  - Moderate/ advanced disease, very high initial IOP, progressing disease, need for low and stable IOP
    - (CIGTS primary procedure?)
- **Risks and complications**
  - Several
- **Is it being done less with MIGS now available?**
  - Yes, but not for the reasons that you think

TRABECULECTOMY

- **Historically performed by general ophthalmologists**
- **As ophthalmology has evolved, most general ophthalmologists have abandoned trabs to glaucoma specialists**
- **Established glaucoma specialists have now learned tubes and seatons (drainage implants)**
- **Newer glaucoma specialists are increasingly learning drainage implants**
- **So, yes traditional trabeculectomy is becoming a relic compared to drainage devices (not MIGS)**

DRAINAGE DEVICES

- **Ahmed valve; Baerveldt implant**
- **Good when previous trab failed or is expected to fail**
- **Now becoming popular as a primary procedure**
- **TVT Study**
  - Trab with MMC and tube shunt can give sustained low teen IOP
  - Tube shunt has greater success than trab with MMC in eyes with ***prior*** cataract and/or glaucoma surgery
  - Similar safety profiles- tubes becoming popular

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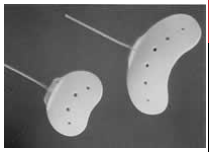
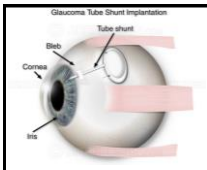
TUBE SHUNTS

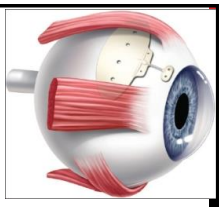
- **Indications**
  - Neovascular glaucoma
  - Uveitic glaucoma
  - Previous ocular surgery (e.g. CE, failed filter)
  - Perilimbal conjunctival scarring
  - ICE syndrome
  - Congenital glaucoma refractory to angle surgery
  - Primary surgical procedure?

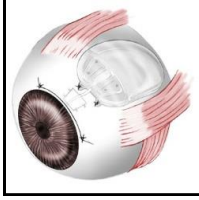
DRAINAGE DEVICES/ TUBE SHUNTS

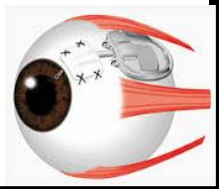


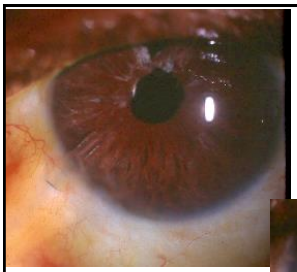
- **AC tube**
  - Shunts aqueous from AC to plate
  - Maintains patency of fistula
- **Episcleral plate (explant)**
  - Located in equatorial region of globe
  - Forms a nonadherent capsule

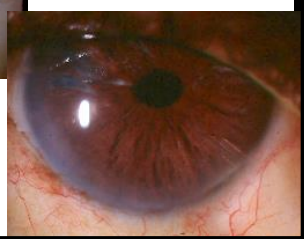




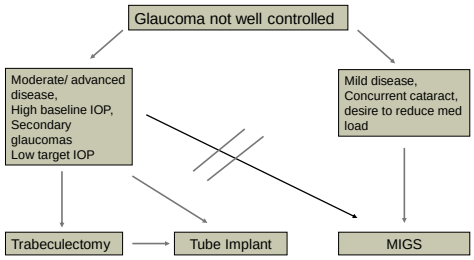








GLAUCOMA SURGICAL PROCEDURES



TRABECULECTOMY COMES ROARING BACK?

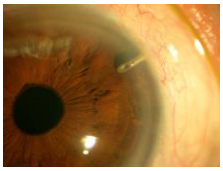
- **PTVT Study**
  - Tube vs Trab with MMC as ***primary*** procedure
- **1 year tube failure 17.3% vs 7.9% for Trab**
- **IOP better and improved for trab at 3 mos, 6 mos, 12 mos**

Gedde S. Treatment outcomes in the Primary Tube Versus Trabeculectomy (PTVT) study after 1 year of follow-up. Presented at: American Academy of Ophthalmology annual meeting; Oct. 14-18, 2016; Chicago.

EX-PRESS™ MINI GLAUCOMA SHUNT

E-Shunt (Alcon)

- FDA 2002
- NOT a MIGS procedure
  - **still is a bleb forming procedure**
- Stainless steel implant into angle
- Generally good outcomes, about on par with standard trabeculectomy
- Reported fewer complications



MIGS

- **MIGS**
  - Micro Invasive Glaucoma Surgery
- **Emerging category of devices and procedures**
  - Fills a gap between medications and trabeculectomy
  - Overall fewer complications than trabeculectomy
  - Typically combined with cataract extraction and generally "easy" to perform
    - *"MEGS?"*

MIGS

- **Appear to have improved safety profile over trabeculectomy, but reduced efficacy**
- **Procedures:**
  - Canaloplasty
  - Trabectome*
  - Glaukos iStent
  - ECP
  - Cypass
  - XEN Gel stent
    - Bleb forming
  - Kahook Dual Blade*

* Modified goniotomy

TRABECTOME (NEOMEDIX)

FDA Approved 2004

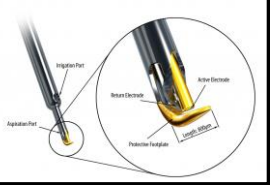
A thermal cautery device with irrigation and aspiration

Used to remove a 2-4 clock hour segment of TM/SC

Less traumatic and safer than trabeculectomy surgery

Is combined with CE

<u>Modest</u> IOP lowering



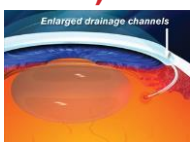
CANALOPLASTY (ISCIENCE)

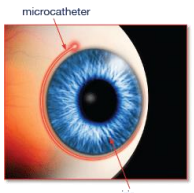
FDA Approved 2008

The goal of this procedure is to enlarge Schlemm's canal and enhance outflow.

A prolene suture is passed 360 degrees through Schlemm's canal with the aid of a microcatheter and viscoelastic to dilate the canal.

One drawback of this procedure is that it is technically challenging.





ISTENT (GLAUKOS CORP.)

iStent: Trabecular Micro-Bypass Stent

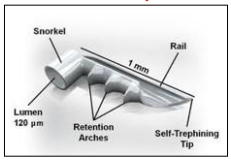
- FDA Approved 2012 for:

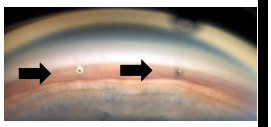
Mild to Moderate glaucoma in patients who need cataract surgery

No Bleb is formed

- Few complications

Relatively Easy to perform

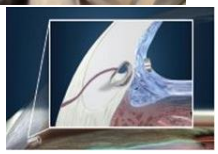




ISTENT

iStent safely improves outflow by creating a patent bypass between the anterior chamber and Schlemm's canal.

iStent is surgical-grade nonferromagnetic titanium micro-bypass stent preloaded in a single-use, sterile inserter.



ISTENT: TWO YEAR DATA

OAG patients to have CE alone or with <u>single</u> iStent

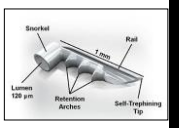
Results:

- 61% in iStent had IOP ≤ 21 mmHg vs. 50% CE alone
- IOP similar at first (~17), but then 1mmHG higher in CE alone
- iStent group had fewer medications
- Results will likely improve once approval granted for multiple devices

Craven. J Cataract Refract Surg 2012

ISTENT ADVANCEMENTS

- **iStent inject**
  - Preloaded needle that injects two stents, for which Glaukos has completed a phase 1 clinical trial.
    - Involving patients unresponsive to two glaucoma medications, patients were randomized to receive one, two or three stents
    - Each additional stent gives an incremental decrease in intraocular pressure.



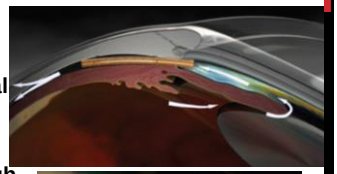
ISTENT ADVANCEMENTS

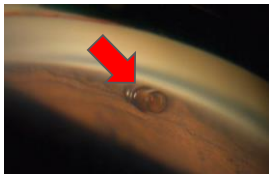
- iStent Supra
  - Meant to treat patients with ***severe glaucoma***
  - Suprachoroidal space
  - More collateral damage, bleeding and hypotony.

CYPASS

Supraciliary microstent that increases uveoscleral outflow.

It is implanted through a clear corneal incision and can be combined with cataract surgery



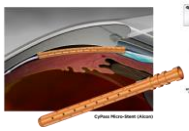


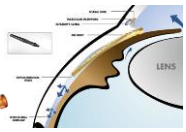
CYPASS

•Placed in angle between ciliary body and sclera and drains to suprachoroidal space.

• 2 year outcome: Phaco plus CyPass- 7.4 mm IOP reduction

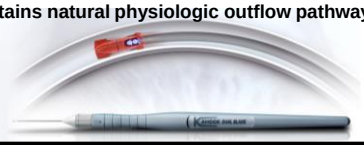
• Phaco alone- 5.4 mm IOP reduction





KAHOOK DUAL BLADE

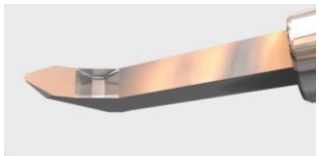
- Single use, ophthalmic blade
- Utilizes ab interno approach through a clear cornea micro incision
- Precision engineered to fit in the canal of Schlemm
- Dual blades positioned for precise parallel incisions of the trabecular meshwork with minimal residual leaflets
- Maintains natural physiologic outflow pathways

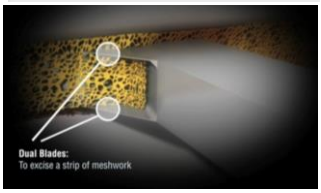


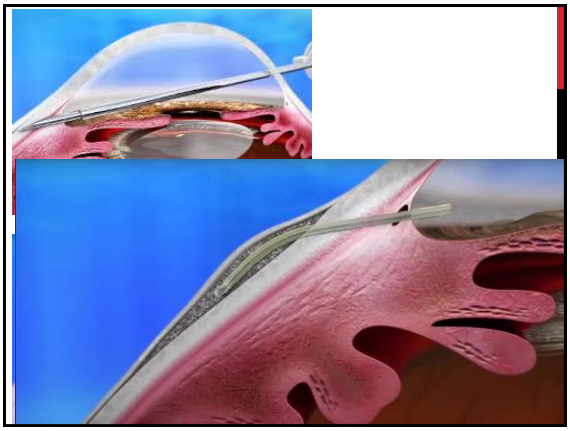
KAHOOK DUAL BLADE

- Tip of the blade is pierced across the trabecular meshwork, then the dual blades create two incisions as the blade is advanced.
- Beveling allows for apposition with outer wall of Schlemm's canal and advancement of the dual blade neatly excises a strip of trabecular meshwork for 90 to 150 degrees of the angle.
- An analysis of post-op outcomes at three months found a 33% reduction in IOP, from 17.5 mm Hg pre-op to 11.8 mm Hg post-op. Sixty-nine percent of patients were able to stop using at least one of their glaucoma medications after surgery.
- Must have good visualization of the angle
- Vision can be decreased due to hyphema
- Can be used stand alone or with cataract surgery

KAHOOK DUAL BLADE







XEN GEL STENT

- FDA approved the XEN45 Gel Stent and the XEN Injector for patients with refractory glaucoma who failed previous surgical treatment or in patients with primary open angle glaucoma, pseudoexfoliative or pigmentary glaucoma with open angles that are unresponsive to maximum tolerated medical therapy
- "Lower maintenance" bleb-forming procedure
- Potential for low (<15 mm) IOP

XEN GEL STENT

- The stent is a soft, permanent, subconjunctival implant that shunts fluid from the anterior chamber to the subconjunctival space.
- 6-mm long and the width of a human hair
- Preloaded in a disposable Xen injector and is implanted through a small, self-sealing corneal incision.
- The stent's collagen-derived non-inflammatory gelatin material allows it to conform to the ocular tissue, possibly minimizing many of the issues seen with synthetic materials such as migration, erosion and corneal endothelial damage.

XEN GEL STENT

- In the pivotal trial conducted in refractory glaucoma patients, XEN reduced IOP from a mean medicated baseline of 25.1 (+ 3.7) mmHg to 15.9 (+ 5.2) mmHg at 12 months postop.
- The mean baseline number of IOP-lowering medications was 3.5 versus an average use of 1.7 medications at 12 months.
- XEN also allows for other IOP-reduction techniques should they be required after surgery.

XEN GEL STENT

- Allergan plans to launch the device in the US in 2017. Xen is already approved for use in the EU, Canada, Switzerland and Turkey, with more than 10,500 stents distributed worldwide.
- Complications may include choroidal effusion, hyphema, hypotony, implant migration, implant exposure, wound leak, need for secondary surgical intervention, and intraocular surgery complications.

XEN GEL STENT

- The most common postoperative adverse events included BCVA loss of $\geq$ 2 lines ($\leq$ 30 days 15.4%; > 30 days 10.8%; 12 months 6.2%), hypotony IOP < 6 mm Hg at any time (24.6%; no clinically significant consequences were associated, no cases of persistent hypotony, and no surgical intervention was required), IOP increase $\geq$ 10 mm Hg from baseline (21.5%), and needling procedure (32.3%).

WHERE ARE WE TODAY?

- MIGS
  - Several new options/procedures that will be offered by a growing number of general ophthalmologists to manage patients with mild glaucoma requiring IOP in the high teens
- Trabeculectomy
  - Will continue as the mainstay procedure by glaucoma specialists for patients with moderate stage glaucoma requiring IOP in the low teens
- Primary tube implants are increasing in use as glaucoma surgeons become more comfortable

ENDOCYTOPHOTOCOAGULATION (ECP)

- Intraocular procedure performed as a stand alone or combined with cataract surgery
- Ablation of the ciliary body under direct visualization
- Inflow procedure - Decreases aqueous production to reduce IOP
- Partially destroys the ciliary body
- Cyclophotocoagulation is an external procedure

ECP - RISKS

- Endophthalmitis
- Suprachoroidal hemorrhage
- CME (10%)
- Not indicated for:
  - Patients with real high IOP
  - End stage glaucoma
  - Compromised outflow (NVG)

THANK YOU FOR YOUR ATTENTION.
ALWAYS REMEMBER TO RECYCLE AND PROTECT THE PLANET THAT WE WILL ULTIMATELY LEAVE TO KEITH RICHARDS