New Developments in Glaucoma
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New Developments in Glaucoma

What’s New in Photography

Discllosure

- Speakers Bureau for Alcon, Allergan, EyeiC/MatchedFlicker, Merck, Oculus, Optovue, Synemed, VSP

Glaucoma Progression Analysis

Knowledge of chronology of optic disc stereophotographs influences the determination of glaucomatous change

- Two sets of stereo disc photos presented to three glaucoma specialists
- Photographs of patients enrolled in the Advanced Glaucoma Intervention Study and Collaborative Initial Glaucoma Treatment Study studies from Wills Eye Hospital
- Five year interval between photos
- Evaluated for glaucomatous progression each time
- First presented in chronologic order with dates shown
- Presented again three months later with order shuffled so observers did not know sequence

Agreement Among Glaucoma Specialists in Assessing Progressive Disc Changes From Photographs in OAG Patients

- 3 glaucoma specialists looked at stereophotos of 164 eyes
- Interobserver agreement was slight to fair
- After masked adjudication, in 40% of the cases in which the optic disc appeared to have progressed in glaucoma severity, the photograph of the “worse” optic disc was in fact taken at the start of the study.
- “Caution must be exercised when using disc change on photographs as the "gold standard" for diagnosing open-angle glaucoma or determining its progression.”


Altangerel U, Bayer, A et al Oph 2005 Jan; 112(1): 40-3
Results

- Intraobserver agreement between chronologically masked and unmasked readings was 61%, 64%, and 71% for the 3 observers, respectively.
- The number of cases identified as having deteriorated was significantly higher (101 vs. 54) when the observer knew the chronological order with which the photographs were taken (P=0.007).
- CONCLUSIONS:
  - When disc photographs are read with knowledge of the chronology with which they were obtained, the observations differ considerably from when the readings are made without this knowledge.

Can We Do Better?

Detecting Glaucoma Progression with MatchedFlicker

- Automated alternation flicker for the detection of optic disc hemorrhages
  - Purpose
    - To determine whether automated alternation flicker (AFF) enhances the detection of disc hemorrhages in serial images when compared to side-by-side photographic evaluation and single-image display
    - 394 eyes, 234 patients
  - Eyes with ONH's and no ONH's randomized into AAF, side-by-side or single image
  - Seven expert graders viewed all images and assessed for the presence or absence of ONH's

Scheie Eye institute

Results

- Sensitivity
  - AAF: 0.878
  - Side-by-side 0.705; p = 0.002
  - Single photographs 0.757; p = 0.01
  - No specificity difference between pairs of presentation groups (all p ≥ 0.7).
- Automated alternation flicker was a more sensitive method for disc hemorrhage detection than the current clinical standards and may have an important role in the management of glaucoma.

Computerized stereochronoscopy and alternation flicker to detect ONH contour change

- Scheie Eye institute
- Two sets of optic disc photographs, separated in time by 1 to 18 years, of 25 eyes with and without glaucomatous optic disc progression were digitized
- Compared standard stereo photos to flicker
- High concordance found between standard stereoscopic comparison and alternation flicker. In several cases, reinspection of stereo comparison led to a revised judgment on the basis of disc changes rendered more obvious with alternation flicker.
Comparing inter- and intra-observer agreement using flicker technology and side-by-side photo inspection for the evaluation of PPA progression

Serial photographs from 131 eyes of 68 patients were evaluated

Two graders masked to chronology

Both graders identified significantly more cases of PPA progression using flicker compared to photography (27–34% vs 8–13%; both p< or =0.003)

Inter–observer agreement using flicker was better than using photographs (kappa=0.52 vs 0.18, p=0.02).

Conclusion
- Flicker identified more cases of progressive PPA than photographic review. Agreement between observers was significantly higher when using the automated flicker technology.

Peer-Reviewed Publications


I Can Only Imagine
Retinal Disease Progression Analysis

- Monitor natural progression
- Response to treatment
- Age-related macular degeneration
- Diabetic retinopathy
- Central serous retinopathy
- Choroidal nevi
- Choroidal melanoma

What’s New With Tonometry?
Can We Calculate a Corrected IOP based Upon CCT?

CCT in OHTS

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

- James Brandt, MD
  Director Glaucoma Services
  UC Davis

The Cornea and IOP Measurement

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

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

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

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

The problem with CCT-based IOP adjustment

FORCE
Pine 2x4

FORCE
Oak 2x4

Thickness is NOT resistance

Ocular Response Analyzer (ORA)

- IOPG – Goldmann Correlated IOP
- IOPCC – Corneal Compensated IOP
- CH – Corneal Hysteresis
- CRF – Corneal Resistance Factor
Define & Describe IOPcc
Corneal-Compensated Intraocular Pressure

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

- \[ \text{IOPcc} = P2 - (0.43 \times P1) \]

Repeatability

Our results showed overall good intraexaminer and interexaminer repeatability for ORA measurements in non-operated eyes, with the current biomechanical model showing a trend toward the performance of digits better than the IOP estimates.

- Moreno-Montañés et al.

Conclusions: ORA measurements show good short-term repeatability in normal volunteers. Thus, this device appears to be applicable in clinical practice.

- Kyriopoulos M. et al.

CH, “DIOP” differentiate Glaucomatous Eyes

Higher mean DIOP, and lower mean CH were found in the GLC group compared with OH, GS, and NML groups. When DIOP was left out of the models, CH replaced DIOP in the GLC vs. NML analysis with nearly equal statistical power.

- “GAT-IOP was unable to differentiate between diagnostic groups in this study.”

Wooldridge Conclusions

- Do use Goldmann
  - But recognize its limitations!
  - 60 year-old technology
- ORA and DCT
  - Probably better, truer IOP measurements
- Currently using all three
  - Frequently vary

What’s New in Perimetry
Oculus Easy Field Perimeter

- Screening AND Threshold fields
- Color LCD-Display
- Fixation monitoring
  - CCD camera
- Stores up to 40,000 exams
- Built-in printer

Oculus Easyfield C Perimeter

- C stands for Comfort
- Designed as screener and Full Threshold Perimeter
- USB connectivity
  - Easier to run with laptop
- Networkable
  - Glaucoma, macula and neurological tests

Easyfield C

- Fixation control
  - CMOS camera
  - Central threshold
- Color LCD with touch screen
- Adjustable testing speed
  - Adaptive, Fast, Normal
  - Slow
- Compact
  - 12 x 16 x 21"a

Physical Improvements

- Moving Cone
- Built-in Double chinrest
  - Adjusts with cone
- Eye Shields
  - No patch necessary
- Lens holder

Software Improvements

- SPARK: Uses correlations between areas in VF to speed up threshold examinations
- SPARK Precision
  - New threshold strategy
  - 3 minutes for FT
  - 10-2, 24-2, 30-2
- SPARK Light
  - For FU or screening
  - ½ time of Precision
- SPARK Training
  - 40 secs.
  - Reduces learning effects in main test

Progression Analysis

- Threshold Noiseless Trend (TNT)
  - Improves sensitivity of progression detection in early glaucoma
Glaucoma Staging Program (GSP) - New Progression Analysis

A Comparison of Humphrey SITA–Standard Perimetry With Both Screening Oculus Easyfield Perimetry And With Screening FDT
  - Dept. of Oph., Johns Hopkins University

Objective
- To determine the sensitivity and specificity of the screening modes of the Oculus Easyfield Perimeter and Frequency Doubling Testing when compared with SITA standard threshold perimetry.

Methods
- One hundred one subjects had the following perimetric testing: Frequency Doubling Technology (screening mode), Oculus Easyfield Perimetry (suprathreshold mode), and Zeiss Humphrey SITA Standard C–24–2 threshold perimetry.

Results
- The sensitivity and specificity of detecting any glaucomatous visual field defect using an abnormal Glaucoma Hemifield Testing criterion was 76% and 89% for the FDT and 86% and 98% of the Oculus Perimeter, respectively.

Results, cont.
- When screening for moderate to severe visual field loss using the Hodapp criteria, the Oculus Easyfield had a higher sensitivity (93%) and specificity (91%) than the FDT sensitivity (83%) and specificity (85%).
Results, cont.

- The mean times need to complete various tests were: Humphrey Visual Field SITA 24–2: 422(±170) seconds, Oculus Easyfield Suprathreshold: 96(+/-36) seconds and Frequency Doubling Technology: 65 (±29) seconds.

Conclusions

- Both smaller screening perimeters were relatively quick. Although the Oculus was just 30 seconds slower than the FDT, its increased sensitivity and specificity could be much more cost effective in the treatment of glaucoma.

Conclusions, cont.

- The Oculus Easyfield technology utilizes the relatively familiar 24–2 data display pattern found in the Humphrey C-24 SITA standard. This may provide better characterization of the pattern of visual field loss, allowing for easier correlation during the screening examination with perceived optic nerve structure abnormalities.

What’s New in Imaging

Fourier Domain OCT: The RTVue

Nerve Head Map (NHM4) with Database comparisons

- Patient Information
- RNFL Thickness Map
- RNFL Sector Analysis
- Optic Disc Analysis
- Parameter Tables
- TSNIT graph
- Asymmetry Analysis
Patient Information

GCC Thickness Map
Deviation Map
Parameter Table
Significance Map

Ganglion Cell Complex (GCC) with Database comparisons

Glaucoma Progression Analysis (GCC of stable glaucomatous eye)

Thickness Maps
Deviation Maps
Significance Maps
GCC parameter change analysis

Angle Measurements

Normal
Narrow

iVue OCT
- Spectral-Domain OCT
- 26,000 Scans per second
- 5 micron resolution
- Five standard scans
  - Retina map with 5 Raster high-res lines
  - High Resolution Cross Line
  - Glaucoma - pPrNFL, NFL map
  - Cornea Pachymetry Map
  - ANGLE / Line scan for irido-corneal angle and central cornea imaging
- Live En face “SLO” for targeting
- Large OCT Normative Database – Age/Optic Disc Size/Signal Strength adjusted

Compact System
User Friendly
And Portable when needed

Normal Narrow
Maria 2001
- 47yo WF referred as glaucoma suspect
- Seen by ophthalmologist
- VA 20/20 OU
- IOP 20 OU
- C/D 0.4x0.3 OU
- VF Normal OU
- RTC prn

Maria 2006–07
- 52yo WF Referred as glaucoma suspect
- FH neg.
- VA 20/20 OU
- IOP 18 OU
- CCT R 577 L 591
- C/D 0.8x 0.7 OU with sloping rim
**Does blood flow to the optic nerve matter in glaucoma?**

**The Evidence Against Blood Supply as a Risk Factor for Development of Glaucoma**

**OHTS: Factors NOT Predictive**
- Migraine
- Cerebral vascular accident
- High OR low blood pressure
- Use of oral
  - Beta blockers
  - Calcium channel blockers

**Diabetes**
- Initially found to be protective in both univariate and multivariate analyses
- Later reassessed and found to be neither protective nor a risk factor
  - European Glaucoma Prevention Study
    - Diabetes did NOT decrease or increase risk
Early Manifest Glaucoma Trial
Baseline Factors—No Added Risk

- High blood pressure
- Cardiovascular disease
- Migraine or Raynaud’s Disease
- Smoker (current or prior)
- Glaucoma family history
- Sex
- Central Corneal Thickness! (CCT)
- Refractive error

Ocular Perfusion Pressure and Glaucoma

Ocular Perfusion Pressure and Glaucoma: Terminology

- OPP – Ocular Perfusion Pressure
- SPP – Systolic Perfusion Pressure
- DPP – Diastolic Perfusion Pressure
- MPP – Mean Perfusion Pressure

Ocular Perfusion Pressure and Glaucoma

- OPP = Ocular Perfusion Pressure
- SPP = SBP – IOP
- DPP = DBP – IOP
- MPP = 2/3 mean arterial pressure – IOP
- Arterial Pressure = DBP + 1/3(SBP – DBP)

Ocular Perfusion Pressure and Glaucoma: Population Studies

Baltimore Eye Survey
- AA and Caucasian

Egna-Numarkt Study
- Caucasian

Barbados Eye Study
- African–Caribbean

Proyecto Ver
- Hispanic

Hayreh SS. Trans Am Acad Ophthalmol 1974;78:240-54

Hayreh SS. Trans Am Acad Ophthalmol 1974;78:240-54


36yo WF referred as glaucoma suspect
MH: no illnesses; no migraines
VA 20/15 OU
Ta: R 26 L 25
CCT: R 595 L 608
DCT: R 28 L 23

Plan:
◦ Advised of ORB of Rx v. no Rx, asymptomatic nature of early glaucoma and need for careful FU
◦ Will follow without Rx for now

Lower IOP improves OPP
Higher systemic BP improves OPP but don’t necessarily want to raise BP
◦ Stroke #3 cause of death in US behind CVD and CA!
Avoid drugs that lower systemic BP beyond patient’s desired systemic control
Avoid nocturnal hypotension
**Nocturnal Hypotension and OPP**
- Low BP at night, coupled with high IOP in supine position, compromise OPP
- Using systemic BP meds in the AM to minimize nocturnal hypotension makes sense
- Using IOP lowering drugs that lower IOP while sleeping makes sense
- Avoiding IOP meds that LOWER systemic BP at night (beta blockers, alpha agonists) makes sense

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**IOP is Higher at Night**

**PURPOSE:** To characterize the 24 hr pattern of IOP in untreated patients

**METHODS:**
- 24 untreated patients with newly diagnosed glaucomatous optic discs and/or abnormal visual fields
- 24 hr IOP values obtained with a pneumotonometer at 2 hr intervals, in the sitting and supine position during the diurnal/wake period and in the supine position during the nocturnal/sleep period

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**Travoprost Diurnal/Nocturnal**

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**Diurnal v. Nocturnal Effect of Medications**

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**IOP is Higher at Night**

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**Nocturnal and Diurnal Habitual IOP**

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References:

*Error bars = SEM*
Comparing Diurnal and Nocturnal Effects of Brinzolamide and Timolol on IOP in Patients Receiving Latanoprost Monotherapy

Results:
- Diurnal period, the mean IOP under brinzolamide or timolol add-on treatment was significantly lower than the baseline IOP in both the sitting and supine positions. There was no statistical difference between the 2 add-on treatments.
- Nocturnal period, the supine IOP under brinzolamide add-on treatment was significantly lower than both the baseline and the timolol add-on treatment.
- There was no difference in nocturnal IOP between the timolol add-on treatment and the baseline.


Diurnal and Nocturnal Effects of Brimonidine Monotherapy on Intraocular Pressure

- 0.1% brimonidine TID for 4 weeks
- Results: The diurnal IOP mean was significantly lower than the baseline IOP in both the sitting and supine positions.
- No statistically significant change in IOP under the brimonidine treatment from the baseline during the nocturnal period.

Liu JH et al AJO 2010

OPP and Glaucoma Medications

- Cross over study of effect of different classes of IOP lowering meds on DPP
  - PGA and CAI significantly increased DPP at all time points
  - Beta-blocker significantly increased DPP from 4AM to 4PM but had no effect at other times
  - Alpha agonist significantly reduced DPP at multiple time points, primarily due to significant decrease in systemic BP

Zioptan (tafluprost) Packaging

1 Carton
3 Pouches
30 Single-use containers

Zioptan (tafluprost)

› Single use vials
› Once daily use

Tafluprost v latanoprost

Primary efficacy measurement: Mean change from baseline of IOP on worse eye at all 9 time points during the study (8 AM, 10 AM, and 4 PM at weeks 2, 6, and 12).

Results at 6 Months

Mean IOP (mmHg)

Primary endpoint:

Results at 24 Months

Simbrinza Suspension

› Combination drug
  - Brinzolamide 1%
  - Brimonidine 0.2%
› Indicated in the reduction of elevated IOP in patients with OAG/OHTN
› Primary or Adjunct use
› TID dosage
› LOW BAK conc.
Contraindications/Precautions

- Contraindications
  - patients who are hypersensitive to any component of this product and neonates and infants under the age of 2 years

- Warnings/precautions
  - Sulfonamide Hypersensitivity Reactions
  - Corneal Endothelium
  - Severe Hepatic or Renal Impairment

Clinical Studies

- Double-masked, randomized, multi-center, active-controlled, parallel group
- Study 1: 660 patients enrolled
- Study 2: 690 patients enrolled

Objective:
- Compare IOP-lowering efficacy of SIMBRINZA™ Suspension to each of its individual components
- Both studies were identical in design, except Study 2 included a three-month safety extension

Clinical Study Design

- Primary Efficacy:
  - Mean IOP at Month 3 for all time points
  - Time points for IOP: 8 AM, 10 AM, 3 PM and 5 PM

- Supportive Efficacy Endpoints:
  - Mean IOP at Week 2 and Week 6 for all time points
  - Time points for IOP: 8 AM, 10 AM, 3 PM and 5 PM

<table>
<thead>
<tr>
<th>IOP Times</th>
<th>8 AM*</th>
<th>10 AM</th>
<th>3 PM*</th>
<th>5 PM</th>
<th>10 PM</th>
</tr>
</thead>
</table>

*Dose measured 15 min before dosing. Ex., 8am IOP, 8:15am dose medication

Study Design

- Supportive Efficacy Endpoints:
  - Mean IOP at Week 2 and Week 6 for all time points
  - Time points for IOP: 8 AM, 10 AM, 3 PM and 5 PM

IOP Control at All Time Points at Month 3 (Studies 1,2)
Two clinical trials of 3 months duration
- most frequent reactions occurring in 3–5% of patients
  - blurred vision
  - eye irritation
  - dysgeusia (bad taste)
  - dry mouth
  - eye allergy
- Adverse reaction rates with Simbrinza were comparable to those of the individual components.
- Treatment discontinuation, mainly due to adverse reactions: 11%

Only fixed–combination without a beta–blocker
- Delivers 21–35% IOP–lowering efficacy when used alone
- Additional 1–3 mm Hg IOP–lowering compared to the individual components
- Adverse events profile consistent with those of its individual components

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

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

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

- Dimensions are customized for a natural fit within the 270 µm canal space
- Made of surgical-grade nonferromagnetic titanium
- Heparin-coated to promote self-priming

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**Therapeutic Objectives**

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

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

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

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

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**Injector System**

Sterile, single-use system, pre-loaded with one iStent designed to deliver into Schlemm’s canal through the trabecular meshwork

- Disposable
- Re-acquisition capability
- Sterile, Pre-loaded w/ iStent®

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**Surgical Procedure**

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

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**Clinical Experience**

Cumulative human experience

- Over 4000 subjects have been implanted to date
- Clinical experience in US and OUS studies demonstrate IOP and medication reduction with an overall favorable safety profile
Pivotal US IDE Trial

Prospective, randomized, multi-centered study of POAG patients who underwent iStent + cataract surgery vs. cataract surgery (CE) alone.

- 290 subjects at 29 sites
  - 240 randomized subjects with cataract and mild-to-moderate OAG (1:1 randomization)
  - 50 additional non-randomized subjects for safety

Patient population

- Mild-to-moderate POAG (also PXE and PDS)
- IOP ≤ 24 mm Hg on 1-3 medications
- Post-medication washout

Efficacy endpoints

- Primary: IOP ≤ 21 mm Hg without medications at month 12
- Secondary: IOP reduction ≥ 20% without medications at month 12

Follow-up through 2 years postoperatively

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Primary Endpoint

≤ 21 mm Hg IOP with no medications

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<thead>
<tr>
<th></th>
<th>Stent + Cataract</th>
<th>Cataract</th>
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<tbody>
<tr>
<td>68%</td>
<td>56%</td>
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18% more patients with CE plus iStent achieved target pressures of ≤ 21 mm Hg with no medications

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Secondary Endpoint

≥ 20% IOP reduction with no medications

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<thead>
<tr>
<th></th>
<th>Stent + Cataract</th>
<th>Cataract</th>
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<tbody>
<tr>
<td>64%</td>
<td>47%</td>
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17% more patients with CE plus iStent achieved ≥ 20% reduction in IOP with no medications

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Reduction in IOP after CE:OHTS

- IOP compared in 63 eyes undergoing CE to those that did not have CE (743)
- Mean of three pre and postop IOP measurements
- CE Group:
  - Preop IOP 23.9 +/- 3.2
  - Postop IOP 19.8 +/- 3.2 P<0.001
  - Ave. decrease IOP = 16.5%
  - Decrease of 20%+ in 39.7%
  - IOP remained lower for at least 36 mos.
- No change in control group

Mansberger SL Gordon MO et al Oph 2012: 119: 1826-1831

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Carl 10-3-12

- 72yo WM treated for COAG Travatan-Z OU
- Ran out of Travatan while on vacation in June
- Never refilled Rx
- IOP R 23 L 18
- S/P ½ SLT OS
- VA R 20/20 L 20/50
- Contrast Sensitivity/Glare 20/100 OU
Conclusions (Wooldridge)

- Which MIGS is the best?
  - Time will tell
- What role will MIGS play in the management of OAG?
  - Near Future: Expect increasing use
  - Distant Future: Will depend on early success/failure rate

What Have We Learned?

- IOP is not a definite measurement
  - Cannot be calculated based upon CCT
  - Newer devices may be better than Goldmann
    - But GAT is still the standard of care
- Perimeters and OCT’s continue to improve
  - Ganglion Cell Complex measurements are of value
- Some meds work 24hrs. Some do not!
  - Prostaglandins, CAI’s DO
  - Timolol, alphaagonists DO NOT