Controversies in the Basic Glaucoma Evaluation
COPE #41717-GL

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Disclosures

- *Financial disclosures:*
  - Speakers Bureaus/Consultant:
    - ✓Alcon
    - ✓Allergan
    - ✓Optovue
    - ✓Zeiss-Meditec
    - ✓VSP
    - ✓B&L
    - ✓Ivantis
- *I have no personal financial interests in any of these companies*

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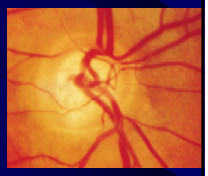
Glaucoma is an Optometric Problem

- > 2 million Americans are diagnosed with Glaucoma
  - 1% – 2 % of those > 40 years
  - 1.6% > 40 (Framingham Eye Study)
- As many as 95,000 Americans lose some degree of sight to Glaucoma each year
  - 12,000 become blind



It is estimated that 1 million Americans with glaucoma are undiagnosed!

Glaucoma

- The most common types:
  - Angle Closure Glaucoma
    - Acute or Chronic
  - Primary Open Angle Glaucoma
  - Secondary Glaucomas
    - Pseudoexfoliation
    - Pigment Dispersion
    - Uveitic
    - Angle Recession

Prevalence of POAG and CACG

Group	Angle-Closure (million)	Open-Angle (million)
China	22.3	7.4
India	5.6	5.6
South Asia	4.2	4.2
Europe	0.6	6.9
Africa	0.05	7.0
Latin America	0.5	1.3
Near East	0.3	0.7
Total	33.5	33.1

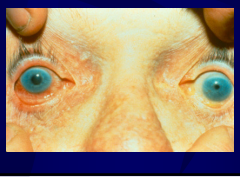
POAG = primary open-angle glaucoma.
CACG = chronic angle-closure glaucoma.

Adapted from Quigley HA. *Br J Ophthalmol.* 1996;80:391.

4

Angle Closure Glaucoma

- < 10% of diagnosed cases of glaucoma
- Estimated that 2%-8% of the population have angles that are narrow enough to close
  - 5% will progress to ACG



Angle Closure Glaucoma Risk Factors

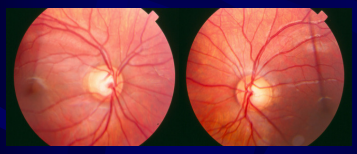
- **Race**:
  - Acute ACG is thought to be very rare in Blacks
  - ACG prevalence in Whites = 8%-16% of POAG rates
- **FHx**:
  - 3-6X greater risk with 1st degree relative
- **Age**:
  - Incidence increases with age (peak 60's-70's)

Angle Closure Glaucoma Risk Factors

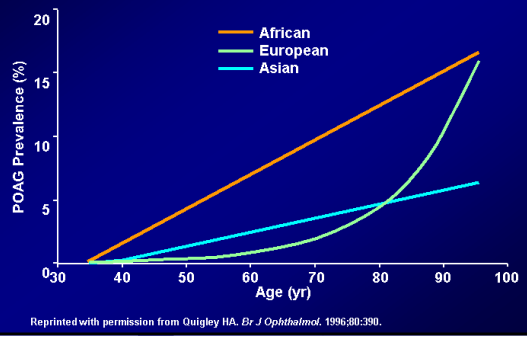
- **Gender**:
  - Females > Males
- **Refractive error**:
  - Narrow angles and ACG occur more frequently in Hyperopes versus Myopes or Emmetropes.

Primary Open Angle Glaucoma

- ~2.5 million Americans have POAG
  - About 1/3 of the POAG is undiagnosed
- ~ 25% of all cases of POAG are African Americans



Prevalence of POAG in European, African, and Asian People by Age



Reprinted with permission from Quigley HA. *Br J Ophthalmol.* 1996;80:390.

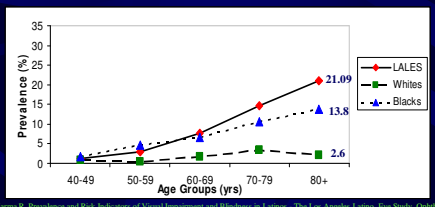
Clinical Workup Controversies

- Are there other high incidence ethnicities?

Risk Factors

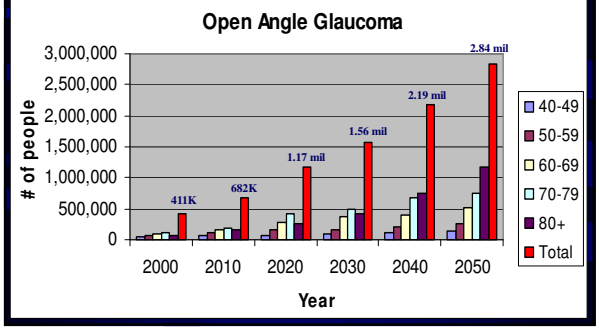
- Race: African Americans ~5X > whites

Comparison of prevalence of Glaucoma in LALES Latinos and African-Americans and Whites in the Baltimore Eye Study



Varma R, Prevalence and Risk Indicators of Visual Impairment and Blindness in Latinos - The Los Angeles Latino Eye Study, Ophth. 2004;111:1132–1140

Projected # of Latinos with Open angle Glaucoma



General Risk Factors of Glaucoma

- Elevated IOP
- Larger diurnal IOP flux
- Compromised ocular hemodynamics
  - Vascular dysregulation
    - *The more complex the regulative system, the more susceptible it is for dysregulation and the more dramatic the potential damage*

- Grieshaber M, Mozaffarich M, Flammer J, What is the Link Between Vascular Dysregulation and Glaucoma, Survey Ophth #52, Supp #2, Nov 2007

General Risk Factors of Glaucoma

- Patient characteristics:
  - Large C/Ds
  - Increased age
  - Race
  - FHx
  - Systemic conditions: HTN – Diabetes
  - Myopia
  - Corneal thickness
  - Sleep Apnea

Clinical Workup Controversies

- Is sleep apnea a true risk factor?

General Risk Factors of Glaucoma

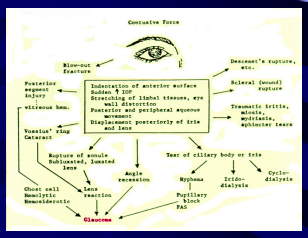
- ***NTG in Patients With Obstructive Sleep Apnea/Hypopnea Syndrome***
- 209 patients were OSAHS and 38 normals underwent polysomnographic exams to diagnose obstructive sleep apnea/hypopnea syndrome (OSAHS) to determine the prevalence of normal tension glaucoma (NTG) and further investigate whether the severity of OSAHS would increase the risk of glaucoma.
- NTG was found in 12 patients with a prevalence of 5.7%, which was higher than that in the normal group.
- The prevalence of NTG in moderate/severe OSAHS patients was 7.1%, significantly higher than that in normal/mild OSAHS patients.
- Clinicians need to consider the possibility of glaucoma in patients with moderate and severe OSAHS.
- SOURCE: Lin PW, Friedman M, Lin HC, et al. Normal tension glaucoma in patients with obstructive sleep apnea/hypopnea syndrome. J Glaucoma 2010; Sep 16

General Risk Factors of Glaucoma

- ***Sleep Apnea Syndrome Represents A Risk for Glaucoma in a Veterans' Affairs Population***
- A total of 70,960 unique records were included for analysis. Of the 2,725 patients with a diagnosis of sleep apnea, 228 (8.37%) also had a diagnosis of glaucoma.
- *Conclusions*. Results of this investigation suggest that SAS may represent a significant risk factor for glaucoma and this should be considered when managing patients who report that diagnosis.
- SOURCE: Waaker MB, Semes L, et al. Sleep Apnea Syndrome Represents a Risk for Glaucoma in a Veterans' Affairs Population. ISRN Opthalmology Vol 2011, Article ID 920767

Glaucoma Clinical Workup

- History:
  - PMHx
    - HTN – Diabetes
    - Head injuries
  - POHx
    - Ocular injuries
  - FHx
    - POAG vs ACG vs secondary glaucomas



Glaucoma Clinical Workup

- VAs
- IOP:
  - Screening:
    - Good sensitivity & specificity
    - Tonopen: NCT reCare
      - Sensitivity 79%
      - Specificity 64%
  - Diagnostic:
    - Goldmann Tonopen
    - Pascal dynamic contour tonometer?
  - Serial tonometry??
    - Every 2 hrs during a day

1 Review by Cvenkel B, Kaluzny JJ, Fuchsmann M, Perovšek D. Ophthalmologica 2000; 44: 367
2 Liu, J.H.K. Cheng, A. Hoguet, H.K. , and Weitzman, M. 2003; 44:1586

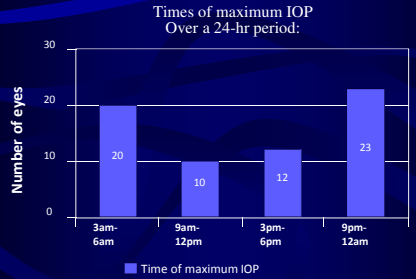
Clinical Workup Controversies

- If IOP is poorly sensitive & specific for glaucoma, does it need to be done?
- Are there differences between the tonometers?
- Is NCT dependable enough to follow glaucoma?
- Do I need to upgrade to a Pascal?

Physiological Factors influencing measured IOP

- Diurnal variation
- Position, etc.

Peak IOP Outside Office Hours for 2/3 of Eyes



Nakakura S, et al. *J Glaucoma* 2007; 16(2): 201-204

Peak IOP Outside Office Hours

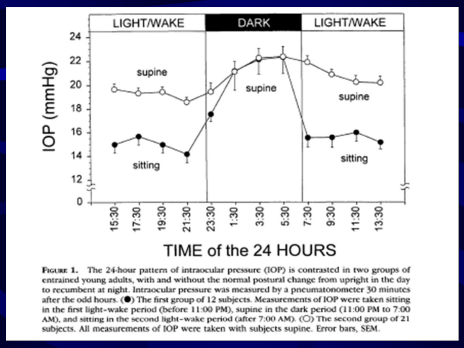
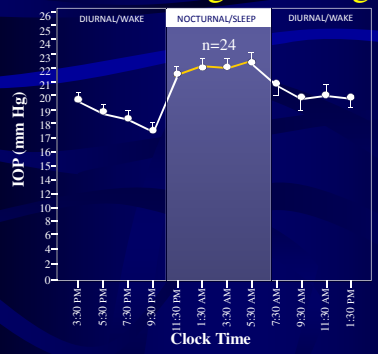


FIGURE 1. The 24-hour pattern of intraocular pressure (IOP) is contrasted in two groups of entrained young adults, with and without the normal postural change from upright in the day to recumbent at night. Intraocular pressure was measured by a pneumatonometer 30 minutes after the odd hours. (●) The first group of 12 subjects. Measurements of IOP were taken sitting in the first light–wake period (before 11:00 PM), supine in the dark period (11:00 PM to 7:00 AM), and sitting in the second light–wake period (after 7:00 AM). (○) The second group of 21 subjects. All measurements of IOP were taken with subjects supine. Error bars, SEM.

Liu JH et al. *Invest Ophthalmol Vis Sci*. Dec 1998; Vol 39 #13

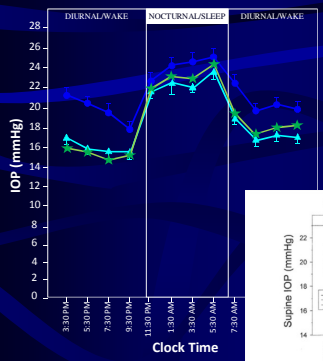
IOP is Higher at Night



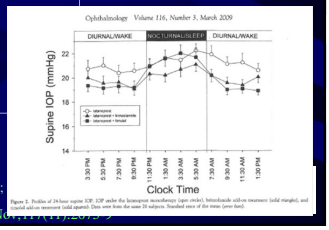
- Habitual IOP of untreated glaucomatous eyes

Liu JH et al. *Invest Ophthalmol Vis Sci*. 2003; 44: 1586-1590

Medication Effects on Diurnal and Nocturnal IOP



- Baseline
- Travoprost 0.004%[1]
- Brimonidine 0.2%[2]



1) Sit AJ, et al. *Am J Ophthalmol*. 2006;

2) Liu JH et al. *Ophthalmology*, 2010 No

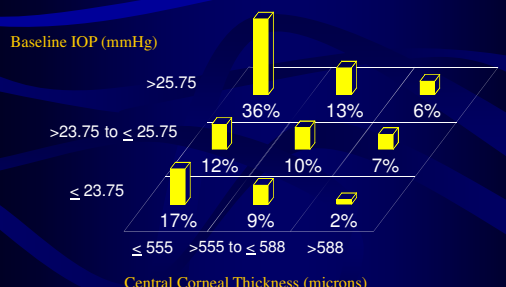
Physiological Factors influencing measured IOP

- Diurnal variation
- Position, etc.
- Arterial (pulse) pressure
- Blood Flow
- Exercise
- Accommodation
- CCT
- Etc. . .

Clinical Workup Controversies

- Is this the standard of care?
  - Must Pachymetry be done for all glaucoma patients?

POAG Endpoints by Central Corneal Thickness and Baseline IOP (mmHg) in Observation Group



Central Corneal Thickness and IOP

- Medeiros, et al, *AJO* 2003:
  - Thinner CCT was predictive in developing VF loss
    - Mean CCT was 558 microns +/- 37 microns
    - <545 microns had > 2X risk of converting to abnormal VF
    - <555 microns gave 3X risk of developing glaucoma
    - 40 micron thinner corneas than 558 microns gave 60% increase risk in developing VF changes
  - "It has been consistently demonstrated that patients with normal tension glaucoma have thinner corneas than patients with high tension glaucoma or normal subjects."

Clinical Workup Controversies

- Should IOP always be adjusted based on nomograms for a corrected value?
- Doesn't CCT predict risk?
  - Yes, of conversion from OHT to glaucoma in the OHTS
  - In fact, thin CCT was a "powerful risk factor"

Clinical Workup Controversies

- Adjusting IOP for CCT does <u>not</u> improve prediction models for POAG.
- **<u>Conclusions</u>**: The calculation of individual risk for developing POAG in ocular hypertensive individuals is simpler and equally accurate using IOP and CCT as measured, rather than applying an adjustment formula to correct IOP for CCT.
  - Brandt JD; Gordon MO, et al. Ophth. 2012; 119(3):437-42

Clinical Workup Controversies

- Is Gonioscopy required on all glaucoma patients?
- Does it need to be done more than once?
  - I only get paid once in their lifetime!

Glaucoma Clinical Workup

- AAO Preferred Practice Pattern Guidelines:
  - *Perform gonioscopy periodically (e.g., 1-5 years).*
- AOA Clinical Practice Guidelines:
  - *To rule out the development of an angle closure component in the glaucoma, gonioscopy should be repeated periodically.*

Gonioscopy.org

~ A Video Atlas ~

http://gonioscopy.org/

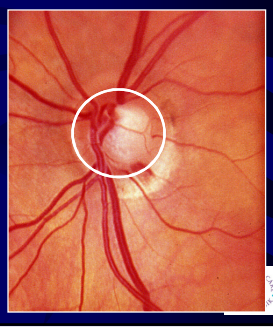
Wallace L.M. Alward
Frederick C. Blodi Chair in Ophthalmology
Director, Glaucoma Service
University of Iowa Carver College of Medicine

Glaucoma Clinical Workup

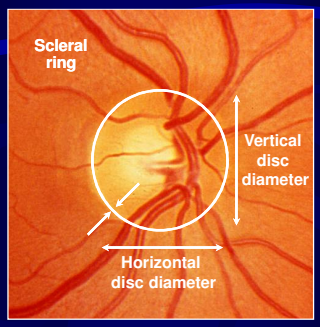
- Optic Nerve Evaluation:
  - Slit lamp lenses:
    - 90D/78D/60D Volks
  - BIO

Assessment of the Optic Disc in Glaucoma

1 Observe the scleral Ring to identify the limits of the optic disc and its size



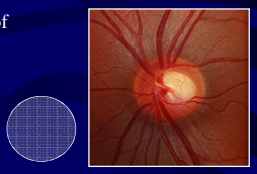
Optic Disc Size



Optic Disc Size

Measurement of optic disc size with direct ophthalmoscope

Small aperture (5 degree) of Welch-Allen direct ophthalmoscope



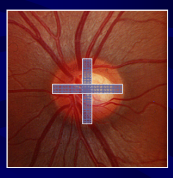
Size of light spot ~ size of average optic disc

Optic Disc Size

Measurement of optic disc size with biomicroscopy

Volk lens
Measure length of slit beam

Correction factors
Volk 60D – x 1.0
Volk 78D – x 1.1
Volk 90D – x 1.3



Avg vertical diameter: 1.8 mm
Avg horizontal diameter: 1.7 mm

Optic Disc Size

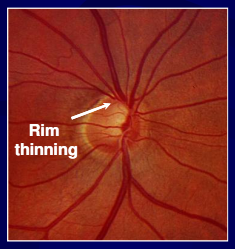
Size of cup varies with size of disc
Large discs have large cups in healthy eyes

Small | Average | Large

Identify small and large optic discs
Small discs: avg vertical diameter <1.5 mm (1.1 X 1.3 = 1.43)
Large discs: avg vertical diameter >2.2 mm (1.7 X 1.3 = 2.21)

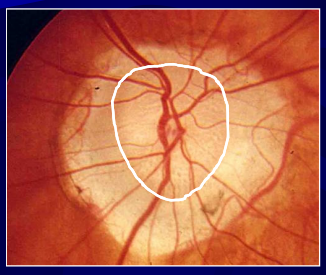
Optic Disc Size

Small discs with glaucoma may have small cups



Optic Disc Size

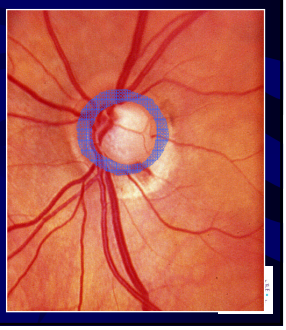
Be cautious with myopic discs



Assessment of the Optic Disc in Glaucoma

1 Observe the scleral Ring

2 Identify the size of the Rim



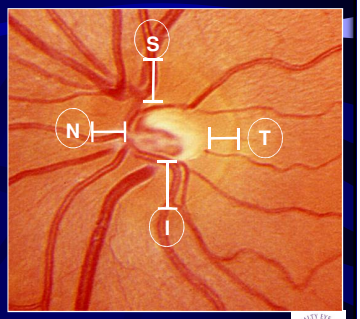
"ISNT" Rule

Rim width

Distance between border of disc and position of blood vessel bending

ISNT rule

Inferior >
Superior >
Nasal >
Temporal



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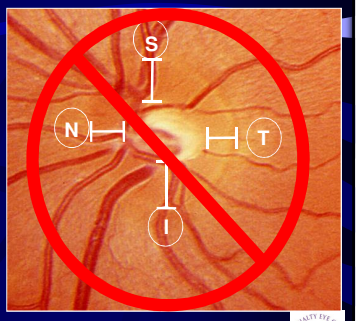


"ISNT" Rule

- Original "ISNT" research:
  - Jonas J, Gusek G, et al, *IOVS*, July 1988, Vol. 29: 1151-1158
    - "It was broadest in the inferior optic disc region ($P < 0.001$), followed by the superior, nasal and temporal ($P < 0.001$) regions."
  - Harizman N, Olivera C, et al, *Arch Oph.* Nov 2006; Vol 124:1579-1583
    - "The ISNT rule is useful in differentiating normal from glaucomatous optic nerves and is unaffected by race."

"ISNT" Rule

- Original "ISNT" research:
  - Sihota R, Srinivasan G, et al, Is the ISNT rule violated in early primary open-angle glaucoma?. *Eye* (2008) Vol 22: 819–824
    - "The ISNT rule was applicable in 71% of normal eyes and 68% of early glaucoma eyes."

"ISNT" Rule

- More recent "ISNT" research:
  - Pogrebniak A, Wehrung B, et al, "Violation of the ISNT Rule in Nonglaucomatous Pediatric Optic Disc Cupping", *IOVS*, Feb 2010, Vol 51:890-895
    - "Violation of the ISNT rule occurs with greater frequency in the pediatric population with large optic disc cups of nonglaucomatous origin, compared with the pediatric population with normal optic discs"

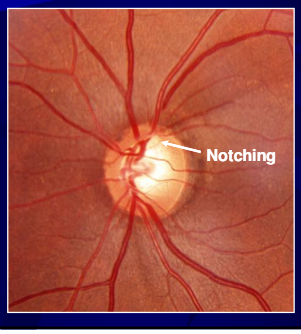
"ISNT" Rule

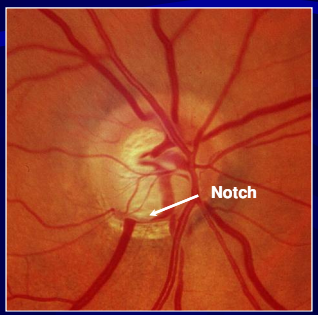
- More recent "ISNT" research:
  - Morgan J, Bourtsoukli I, et al, "The Accuracy of the Inferior>Superior>Nasal>Temporal Neuroretinal Rim Area Rule for Diagnosing Glaucomatous Optic Disc Damage", *Ophthalmology*, April 2012, Vol 119:723-730
    - "The ISNT rule has limited utility in the diagnosis of open-angle glaucoma."

"ISNT" Rule

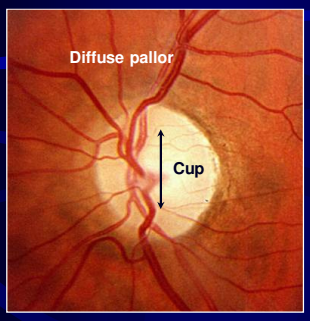
- More recent "ISNT" research:
  - Law SK, Kornmann HL, et al, Evaluation of the "IS" Rule to Differentiate Glaucomatous Eyes From Normal, J Glaucoma. May '14
    - "…we agree with the conclusion of Morgan ,et al, that the ISNT rule has only limited utility in the diagnosis of glaucomatous optic neuropathy…"
    - "We demonstrated that a diagnostic test that combines the different features of the optic disc (increase of CDR and ISNT or IS rule) may improve the diagnostic accuracy of glaucoma based on optic disc evaluation."

Localized Rim Thinning/Notching





Pallor



Pallor > cup

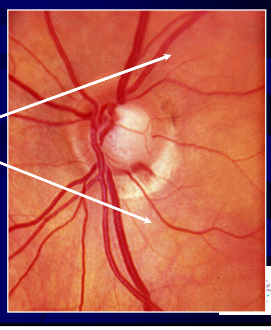
Non-glaucomatous neuropathy

Assessment of the Optic Disc in Glaucoma

1 Observe the scleral Ring

2 Identify the size of the Rim

3 Examine the Retinal nerve fiber layer



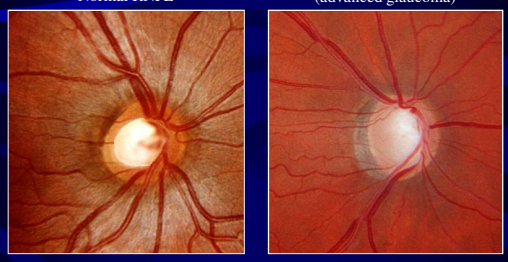
RNFL Examination

- Best performed using red-free light (red-free photographs or green light)
- Look at
  - Striations
  - Brightness
  - Visibility of parapapillary retinal vessels
- Look for **diffuse** and **localized** RNFL loss

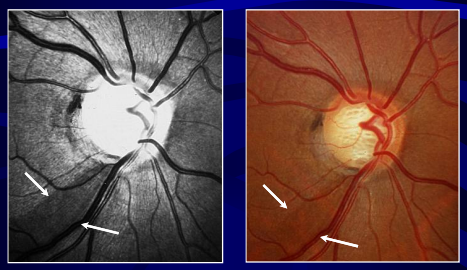
Diffuse RNFL Loss

Normal RNFL

Diffuse RNFL loss (advanced glaucoma)



Localized RNFL Loss



Localized RNFL defect
Wedge-shaped dark area

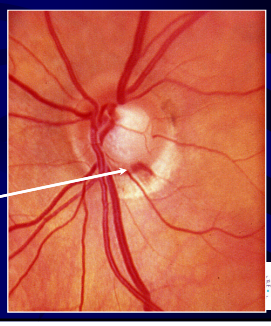
Assessment of the Optic Disc in Glaucoma

1 Observe the scleral Ring

2 Identify the size of the Rim

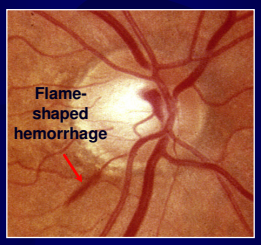
3 Examine the Retinal nerve fiber layer

4 Look for Retinal and optic disc hemorrhages



Optic Disc Hemorrhage

Indicative of glaucoma progression

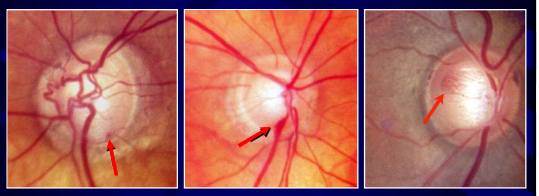


Optic Disc Hemorrhage

Normally disappears after 2-6 months

Optic Disc Hemorrhage

Detection of disc hemorrhages requires careful optic disc examination



Glaucoma Clinical Workup

- Optic Nerve Evaluation:
  - Slit lamp lenses:
    - 90D/78D/60D Volks
  - BIO
  - Stereo Fundus photos

Clinical Workup Controversies

- Is fundus photography still the standard of care?

Glaucoma Clinical Workup

- RNFL defects are the earliest sign of glaucoma[1]
- RNFL defects precede visual field loss[2]
  - 60% OHT converts had RNFL defects 6 years prior to VF defect
- RNFL defects precede ONH changes[3]
  - 50% OHT converts had RNFL defects that progressed
  - 20% OHT converts had ONH defects that progressed

[1] Hoyt and Newman, *Lancet*. 1972; 1:692
[2] Sommer A, et al. *Arch Ophthalmol*. 1991; 109:77
[3] Quigley HA, et al *Ophthalmology*. 1992; 99:19-28

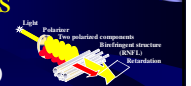
RNFL defects precede ONH changes[1]

[1]Quigley HA, et al *Ophthalmology*. 1992; 99:19-28

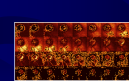
Glaucoma Clinical Workup

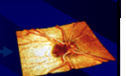
- Optic Nerve Evaluation:
  - Slit lamp lenses:
    - 90D/78D/60D Volks
  - BIO
  - Stereo Fundus photos
  - Scanning instruments:

3 Imaging technologies have been shown to be effective in detecting and managing ocular pathologies

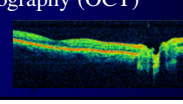


- Scanning Laser Polarimetry (SLP)
- Confocal Scanning Laser Ophthalmoscopy (CSLO)





- Optical Coherence Tomography (OCT)



Glaucoma Clinical Controversies

- Do I need to have a NFL analyzer?
- What is the current standard of care for retina/ONH monitoring?

Glau… …ersies

REVIEW

Glaucoma versus red disease: imaging and glaucoma diagnosis

Gabriel T. Chona and Richard K. Lee

Purpose of review

Recent findings

Summary

Keywords

INTRODUCTION

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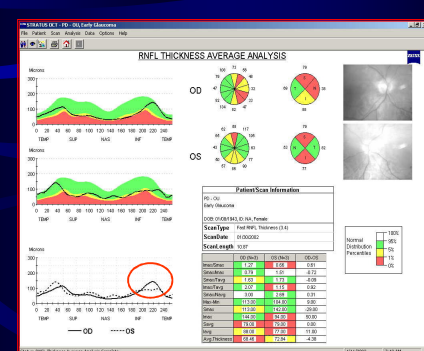
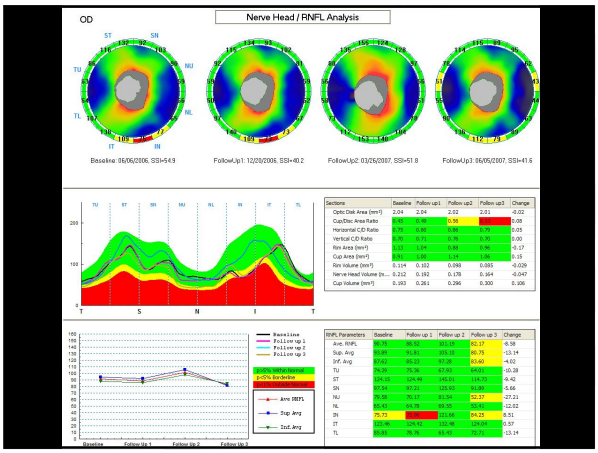
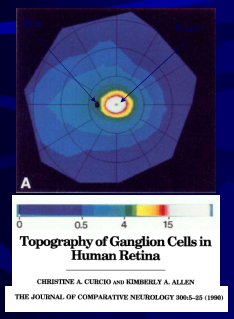
RNFL Thickness Average Analysis





Macular Ganglion cell density



- 50% of ganglion cells located in central 4.5mm (16°)
- 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

Macula thinning in Glaucoma

- Greenfield et al, showed thinning of the macula in glaucoma patients using Time Domain (TD) OCT (Stratus)
- Guedes et al, also found significant macula thinning in glaucoma patients compared to normals with TD OCT

- Greenfield DS, Bagga H, Knighton RW. Arch Ophthalmol. 2003; 121:41-46.
- Guedes V, Schuman JS et al. Ophthalmology 2003; 110: 177-189.

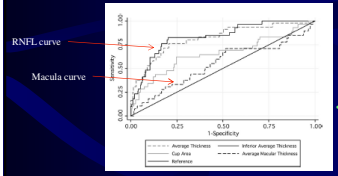
Diagnostic Accuracy with TD OCT: Macula vs RNFL

- Medeiros et al, found the diagnostic accuracy of peripapillary RNFL thickness was significantly more accurate than macula thickness
- Wollstein et al, found similar results where RNFL thickness was significantly more accurate for detecting glaucoma than macula thickness

- Medeiros FA, Zangwill M, Bowd C et al. Am J Ophthalmol. 2005; 139:44-55
- Wollstein G, Ishikawa H, et al. Am J Ophthalmol 2005; 139: 39-43.

Progression: Macula vs RNFL

- Using TD OCT, Medeiros et al, compared the accuracy for detecting progression using RNFL versus macula thickness and found the RNFL was significantly more sensitive and specific than macula thickness



- Medeiros FA, et al. Invest. Ophthalmol Vis Sci 2009; 50:5741-5748

TD OCT Study Limitations

- Major disadvantage in these studies is that TD OCT typically measures full retinal thickness only (does not isolate ganglion cells)
- TD OCT does not have enough depth resolution to image and segment the ganglion cells accurately and reliably

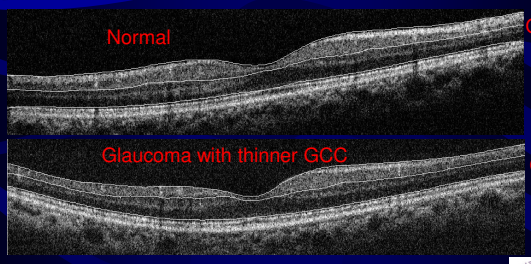
Glaucoma Clinical Controversies

- Do I have to upgrade to the new generation OCTs?

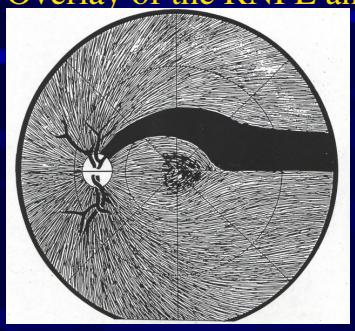
Fourier Domain OCT Advantage

- Faster speed also allows for greater density of sampling points and reduces artifacts from eye-movements
  - RTVue FD OCT has 26,000 A scans/sec vs Stratus TD OCT with 400 A scans/sec

GCC Thinning in Glaucoma



Overlay of the RNFL and GCC



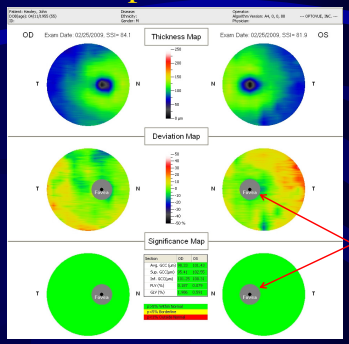
GCC Report: Normal

Patient Information
Exam Date and Quality

GCC Thickness Map

Deviation Map

Significance Map

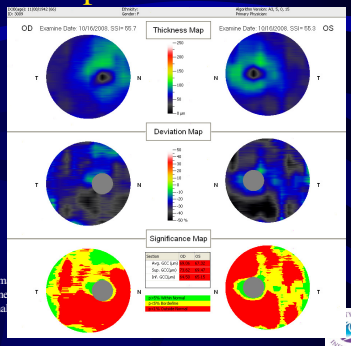


GCC Report: Glaucoma

Thickness Map
• Dark colors represent GCC thinning (blue and green)

Deviation Map
• Black areas indicate 50% GCC loss or worse compared to Norm Data Base

Significance Map
• Green areas-within norm
• Yellow areas – borderline
• Red areas-outside norma



GCC Change Analysis

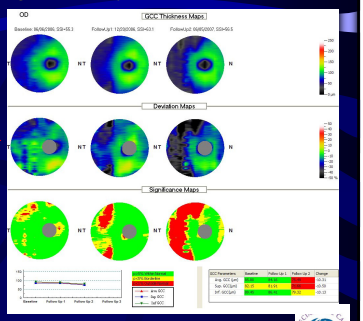
Thickness Maps

Deviation Maps

Significance Maps

Trend Analysis

GCC parameter change analysis



Revisiting the Macula

- Can imaging the ganglion cells in the macula with FD OCT improve glaucoma detection?

Diagnostic Accuracy: GCC vs FD OCT RNFL

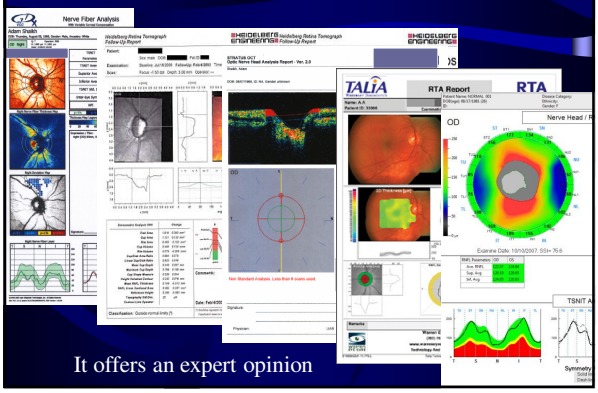
- Rao et al, found GCC had similar accuracy levels as FD RNFL
- Seong et al, found similar results
- Kim et al, found values were higher for RNFL vs GCC in a group of **advanced** glaucoma patients, but GCC values were higher than RNFL in a group of **early** glaucoma patients

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

GCC Summary

- GCC thickness correlates well with VF
- More reproducible and more accurate for detecting glaucoma than macula thickness with TD OCT
- Similar accuracy for detecting glaucoma as FD OCT RNFL thickness
- Best in early glaucoma

What does digital technology do for us?



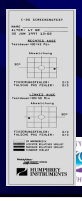
It offers an expert opinion

Visual field & OCT results show poor correlation in advanced RNFL loss

- A retrospective study of patients with early to advanced glaucoma showed a wide variation in mean deviation in patients with advanced retinal nerve fiber layer loss when comparing visual field sensitivity with retinal nerve fiber layer thickness.
- Jessica Neuville, OD, presented at AAOpt 2010, a study that suggests the OCT is moderately correlated to visual function in early loss, but is a poor predictor of visual function at advanced levels of RNFL loss

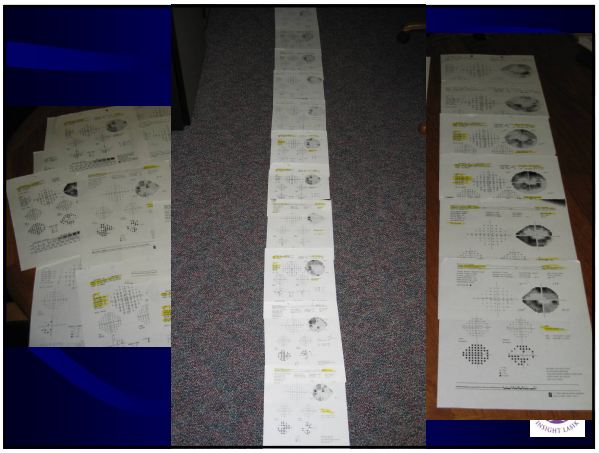
Glaucoma Clinical Workup

- Visual Fields:
  - Highly variable!
  - OHTS showed that VFs were repeatable only 14% of the time!

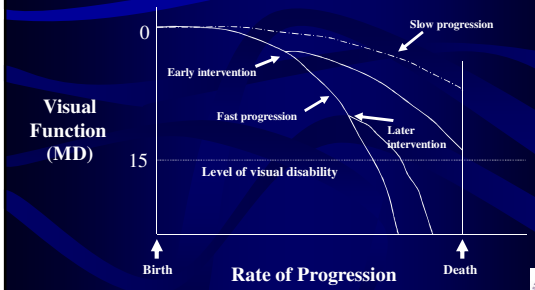


Glaucoma Clinical Controversies

- Is the FDT/Matrix = to SAP?
- Must SWAP be done on all patients?
- Is SAP the standard of care?



Visual Field Progression

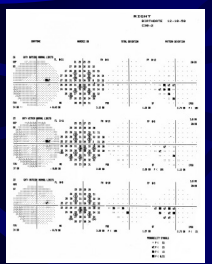


SOURCE: Adapted from Caprioli J, The Importance of Rates in Glaucoma, AJO 2008 Vol 145, No. 2 , Pg 192

Visual Fields: Highly Variable

OHTS

- 86% of visual field abnormalities not replicated on retesting[1]



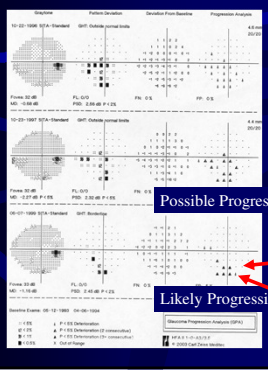
1st VF abnormal
(GHT Outside Normal Limits)

2nd VF normal
(GHT Within Normal Limits)

3rd VF abnormal
(GHT Outside Normal Limits)

*VF defect defined as GHT outside normal limits, CPSD < .05%, or both
[1] Keltner JL, Johnson CA et al. *Arch Ophthalmol.* 2000; 118:1187-1194

Identifying Progression - VF

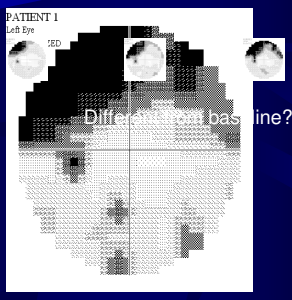


Changing points

Repeatable change

GPA™ confirms repeatable, consistent change at five points in the field

Event Analysis



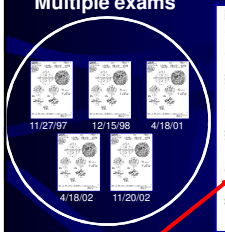
Baseline

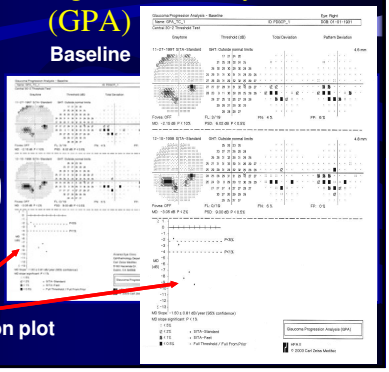
Different from baseline?

Glaucoma Progression Analysis (GPA)

Multiple exams

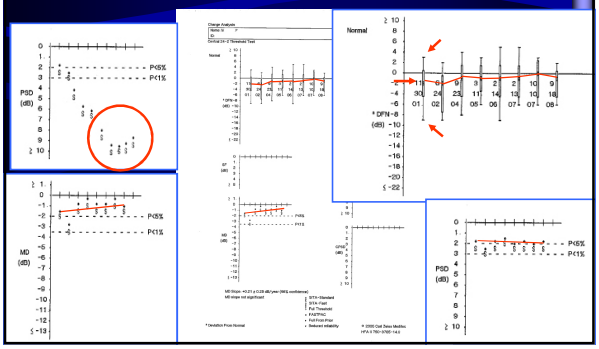
Baseline





Rate-of-progression plot

Change Analysis



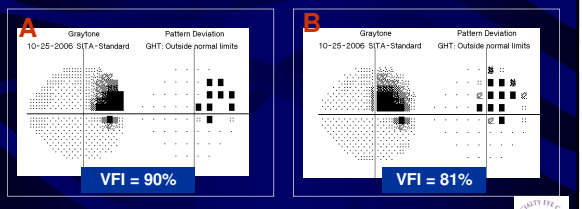
Visual Field Index

- The VFI is less sensitive to worsening cataract or removal of cataract than is mean deviation index (MDI).
- The predictive value of VFI depends on the validity of the assumption that "past performance predicts future performance".

SOURCE: Bengtsson B, Heijl A: A Visual Filed Index for Calculation of Glaucoma Rate of Progression, AJO 2008 Vol 145, No. 2 , Pg 343-353

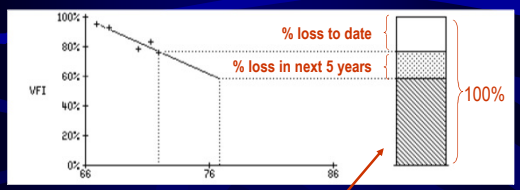
Visual Field Index

- Central points weighted more heavily than on periphery
- Reduces cataract effect to the measurement of VF loss



"B"has more damaged central points and lower VFI than "A"

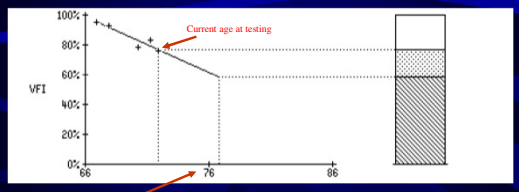
Visual Field Index



Visual Field Index Bar

- Shows vision loss in terms of %
- Enhanced visual presentation

Visual Field Index



VF Index plotted against age:

- Characterizes trend significance over next 5 years
- Aids in interpretation & patient education
- Helps formulate individualized treatment decisions

Summary of Functional Tests

	SITA SAP	SITA SWAP	FDT Matrix
Advantages	"Gold Standard"	As fast as SITA SAP Possibly more sensitive	More portable Tolerates blur Possibly more sensitive Variability does not increase with severity
Disadvantages	Not sensitive enough to detect early glaucoma	Limited clinical evaluation Variability Cataract effects	Limited clinical evaluation
Best use	Baseline VF and following progression in advanced disease	Early diagnosis Younger patients	Early diagnosis

Visual Fields: Poor Sensitivity

- A large number of RGCs often are lost prior to detectable visual field abnormalities
- As many as 50% optic nerve fibers can be lost prior to a standard perimetric defect [1,2]
- By the time there is a 5 dB loss, there is a corresponding 25% loss of RGCs[2]

[1]Quigley HA, Addicks EM, Green WR. *Arch Ophthalmol*. 1982; 100:135
[2]Quigley HA, Dunkelberger GR, Green WR. *Am J Ophthalmol*. 1989; 107:453

Controversies in Treatment

- Is ALT/SLT a better option as primary treatment than medication?

Glaucoma Laser Trial (GLT)

- Prospective, randomized, multi-center clinical trial
- Funded by National Eye Institute
- 271 Patients with newly-diagnosed POAG
  - 203 patients in follow-up trial
- Eyes randomly assigned to:
  - "Laser first" (LF)
    - ALT first, then medications if necessary
  - "Medications first" (MF)
    - Stepped regimen only, no laser

Glaucoma Laser Trial Research Group (1995) The Glaucoma Laser Trial (GLT) and Glaucoma Laser Trial Follow-up Study (GLTFS): VII. Results *Am. J. Ophthalmol* **120**:718-731

Interpreting the GLT Results

- Initial treatment with ALT is at least as effective as initial treatment topical medication in patients with POAG in terms of control of IOP, optic disc and visual field
- Ultimately, ALT will need to be supplemented with other modes of intervention
- What about SLT????

SLT as an alternative to PGAs

- SLT vs. latanoprost for IOP control in OHT and POAG
- 12-month study
- 90°, 180°, 360° SLT
- Success criterion
  - 20% - 30% IOP reduction from baseline

Nagar M, et al. Br J Ophthalmol 2005;89:1413–1417

SLT as an alternative to PGAs

- Results
  - More 360° SLTs (60%) achieved success criterion (> 30% IOP reduction) than did 90° or 180°
  - Latanoprost-treated eyes achieved success criterion in more cases than 90° or 180° and did as well as 360° in maintaining diurnal IOP reduction

Nagar M, et al. Br J Ophthalmol 2005;89:1413–1417

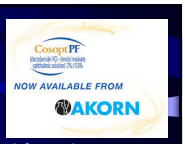
Medicinal Management

- Prostaglandin Derivatives
- Topical CAI's
- Adrenergics
- Beta-Blockers
- Combos
- Cholinergics/Anticholinesterases
- Oral CAI's

Combinations

- ***Simbrinza***™ (Alcon)
  - Brinzolamide 1% & Brimonidine 0.2%
  - As effective as separate dosing
  - Better convenience & compliance
    - Less sting!!
  - 21%-35% IOP decr
  - tid use
    - Used bid in Europe

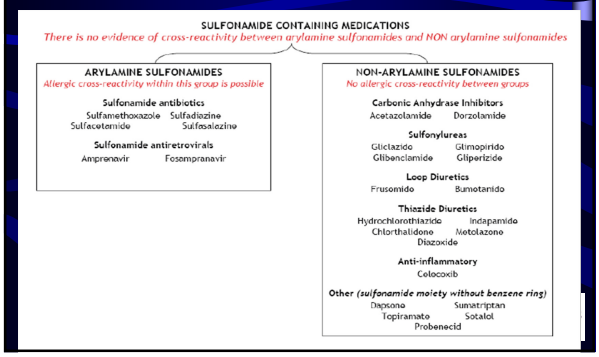
Combinations



- ***Cosopt***® (was Merck but now is Akorn)
  - Timolol 1/2% & Dorzolamide 2%
    - As effective as separate dosing (?)
  - Better convenience & compliance
    - Still stings!!
  - 32%-38% IOP decr
  - bid use

- ***Cosopt PF***® (was Merck but now is Akorn)
  - Preservative Free!!

Oral CAI's



Back to the Future!

- Nutritional Treatments:
  - Blood flow enhancers
    - Mirtrogenol® (120 mg b.i.d.)
      - commercial composition of Bilberry extract (Mirtoselect®) and French maritime pine bark (Pycnogenol®)
    - Gingko biloba (80 mg b.i.d.)
      - also works as an antioxidant

Back to the Future!

- Nutritional Treatments:
  - Blood flow enhancers
    - Mirtrogenol® (120 mg b.i.d.)
    - Gingko biloba (80 mg b.i.d.)
  - Calcium channel blockage (i.e. Nifedipine)
    - Increase blood flow therefore poss neuroprotection
      - Significant SE's noted in studies (1/3 dropout from SE's)
        - » HA's, flushing, dizziness, swelling, low BP, nausea
    - Lomerizine HCl (Santen's DE-090)
      - Only CA++ antagonist being developed as oral glaucoma treatment
        - » Excellent safety and minimal SEs to date

Back to the Future!

- Vitamin Treatments:
  - Magnesium: (<350 mg qday is well tolerated)
    - Considered "Nature's calcium channel blocker"
      - Usually 125 mg bid (d/c with oral antibiotic use)
  - Vitamin B-complex (water soluble)
    - In combination with E and Omega 3 (DHA), shown to stabilize VF
  - Vitamin D
    - Early '14 study supported association of Vit. D deficiency with presence of glaucoma
    - No supplementation needed but may want to test for deficiency in NTG

Back to the Future!

- Vitamin Treatments:
  - Magnesium: (<350 mg qday is well tolerated)
  - Vitamin B-complex (water soluble)
  - Vitamin D
  - Vitamin E (fat-soluble):
    - Diet alone is sufficient
    - Not > 400 IU daily

Prostaglandins

- Current commercial PGAs all bind to the $PGFP_{2\alpha}$ receptor
  - Bimatoprost may also bind to $PGEP_1$
- Newest research is in $PGEP_{2\text{-}4}$
  - Early studies suggest a decrease in IOP that was long-lasting and greater than $PGFP_{2\alpha}$
    - $PGEP_2$ was less stable in aqueous solution
  - Allergan's Butaprost binds to $PGEP_2$
  - ONO Pharmaceuticals' ONO-0476
    - Prodrug of prostanoid EP_2

Nitric Oxide Donation

- In the past, nitric oxide (NO) was considered "toxic" as one of several environmental pollutants (i.e. cigarette smoke & smog)
  - ≠ nitrous oxide (N_20) "Laughing Gas"
- By late '90s, it was determined that NO is a fundamental player in general body physiology as a messenger molecule
  - Essential to daily functions ranging from BP regulation & digestion to antimicrobial defense

NO-Prostaglandins

- Nitric Oxide-Donating Prostaglandin F2-Alpha PGAs:
  - Latanoprostene bunod (Allergan NCX 116)
- Dual Mechanism:
  - $PGF_{2\alpha}$: enhanced uveoscleral outflow
  - NO: affects outflow through TM
    - ?? Analogous to RKIs

NO-Prostaglandins

- Nitric Oxide-Donating Prostaglandin F2-Alpha PGA s:
  - Pfizer/Nicox Research are investigating NO-Donating Bimatoprost 0.004% (NCX 470)

Rho Kinase Inhibitors

- Several companies with phase I to III trials
- Likely not to be packaged with BAK
- Amenable to alternative delivery modes:
  - Punctal plugs, gel vehicle etc.

Rho Kinase Inhibitors

- Mechanism:
  - Rhokinase is a serine/threonine kinase that serves as an important downstream effector of Rho GTPase
  - It plays a critical role in regulating the contractile tone of smooth muscle tissues in a calcium-independent manner
  - ROCK inhibitors reduce IOP by enhancing aqueous humor drainage through the trabecular meshwork

Rho Kinase Inhibitors

- Current status:
  - April 2014: Rhopressa Phase 3 Trial (Rocket 1) Misses Primary Endpoint
    - All end points of subjects <26 were met but not about above
    - FDA allowed modification of study endpoints
    - Phase 2 as met and Phase 3 is underway
  - AMA0076 (Amakem) goes forward

Rho Kinase Inhibitors

- Current status:
  - Roclatan:
    - Essentially, Rhopressa + Latanoprost

Rho Kinase Inhibitors

- Current status:
  - Roclatan:
    - Essentially, Rhopressa + Latanoprost
    - June 2014, Phase 2b results:
      - All clinical endpoints met
      - Efficacy >Latanoprost by 1.6-3.2 mm Hg. at all time points
        - » Hyperemia remains the #1 adverse reaction reported

Adenosine Receptor Agonists

- Like ROCK inhibitors, these molecules can work on the TM but much less is known of them
- A_3 adenosine receptor (A_3AR) agonists:
  - A_3 agonists have been found to protect normal cells from undergoing apoptosis via the down regulation of death signals
    - Therefore, potentially neuroprotective

Adenosine Receptor Agonists

- A_1 receptors:
  - Stimulation of A_1 adenosine receptor in the TM causes a improvement in metabolic activity which helps to clear the pathway for the aqueous to flow out of the eye (lowering IOP)
    - This metabolic activity takes the form of an increase or upregulation of proteases - such as Protease A or MMP-2 - that digest and remove accumulated proteins which can block the flow of aqueous humor out of an eye with glaucoma

Adenosine Receptor Agonists

- A_1 Adenosine receptor agonists:
  - Trabodenoson (Inotek INO-8875)
    - Appears to work primarily by increasing the outflow of aqueous via the TM pathway

RNAi (RNA Interference)

- Interference RNA (RNAi) is a promising technology with therapeutic applications
  - Sylentis is developing a treatment based on silencing the action of genes involved in aqueous humor production and/or genes which regulate its drainage, so as to reduce IOP
- Discovered in plants in the 1990s, RNAi consists of highly efficient selective & specific inhibition of gene expression

RNAi (RNA Interference)

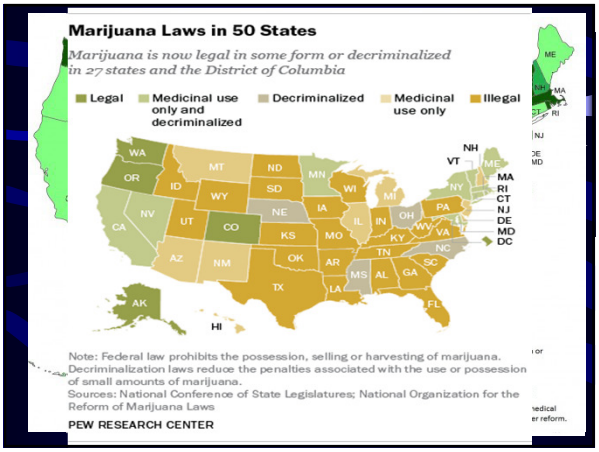
- RNAi is mediated by small fragments of double-stranded RNA, consisting of 19-23 nucleotides, which promote degradation of mRNA, thus inhibiting synthesis of the proteins for which they code
- As this mechanism is used naturally by cells to regulate gene expression in a way that is both non-toxic and highly effective, RNAi has great therapeutic potential

Controversies in Treatment

- Do all patients need to be treated?
- If the eye is NLP, what are the treatment goals?

Controversies in Treatment

- Dude….Can you prescribe medical marijuana for my glaucoma?



MJ & Glaucoma

- Glaucoma ranks among the most frequently cited reasons for using medical marijuana and is one of the indications for which the federal government once granted permission for compassionate marijuana use
- Research findings from as early as the 1970s show that both marijuana and THC reduce IOP

MJ & Glaucoma

- The first such reports generated considerable interest because at the time conventional medications for glaucoma caused a variety of adverse side effects
  - Pilocarpine and Diamox were among the few drugs available to treat glaucoma in the late 1970s
- Currently other treatments for the disorder have since eclipsed marijuana-based medicines

MJ & Glaucoma

- Several clinical studies have found that synthetic cannabinoids or marijuana reduce IOP as well as do most conventional glaucoma medications
  - This is true whether administered orally (eaten), intravenously or by inhalation
  - NOT when they are applied directly to the eye
  - In most trials a single dose of marijuana or cannabinoid maintained this effect for three to four hours

MJ & Glaucoma

- Researchers have yet to explain how marijuana and cannabinoids reduce IOP
- Marijuana reduces blood pressure and reduced blood pressure could decrease blood flow to the optic nerve, counteracting the benefits of reducing IOP

MJ & Glaucoma

- The short duration of effect means that marijuana-based medicines must be taken up to 8 X per day, which most patients are unlikely to do!
  - Other medicines reduce IOP equally well and need only be taken once or twice a day
- This is an important difference because patients need to control IOP continuously due to the progressive nature of glaucoma

Controversies in Treatment

- There are far better management regimens now available
  - 3-4 hr efficacy ≠ good control
  - Constant intoxication ≠ good citizens
  - Health concerns ≠ future safety profile
- Colorado ODs can be certified for DEA Schedules 3 narcotic – 5
  - Marijuana is still Schedule 1