

# POAG: The greater part of glaucomas

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Professor



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## Disclosure

- ▶ Principal investigator for FDA iVue OCT trial
- ▶ Principal investigator Topcon FDA trials
  - ▶ FDA Topcon NDB Maestro and OCT 2000
  - ▶ FDA Topcon OD and Retina study
  - ▶ FDA NDB II study
  - ▶ FDA Maestro AP II study
- ▶ Principal investigator FDA Zeiss GDx PRO NDB study
- ▶ Consultant for Optovue and Topcon
- ▶ Speakers bureau Sanofi- Genzyme and Allergan



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## Objectives

- 1) Define and understand limitation of definition of primary open angle glaucoma
- 2) Understand intraocular pressure and its importance in POAG management
- 3) Examining nerve for glaucoma and setting target pressure.
- 3) Review land mark studies and understand the clinical implications
- 3) Cases



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58 BF

- ▶ BCVA 20/20 OU
- ▶ H/O + FH mother glaucoma, became blind
- ▶ Cataract NS I+ OU
- ▶ IOP GAT at 11.40 AM
  - ▶ OD 18 mmHg
  - ▶ OS 20 mmHg
  
- ▶ Anterior chamber grade 4 OU Van Herick's angle grading

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Disc evaluation

- ▶ OD 0.50 H 0.60V- Nasal notch, deep cupping
- ▶ OS 0.50 H 0.60V – Temporal rim thin

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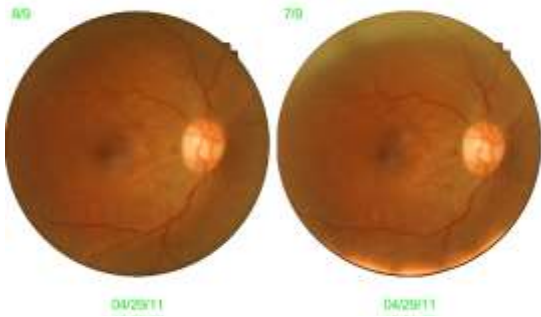
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Posterior pole



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Optic disc



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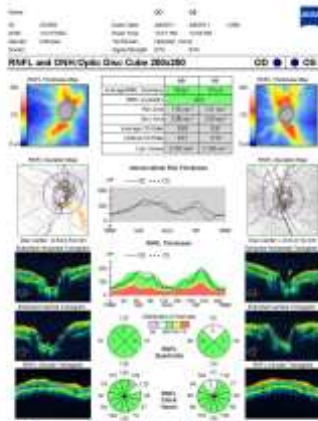
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OCT 200x200



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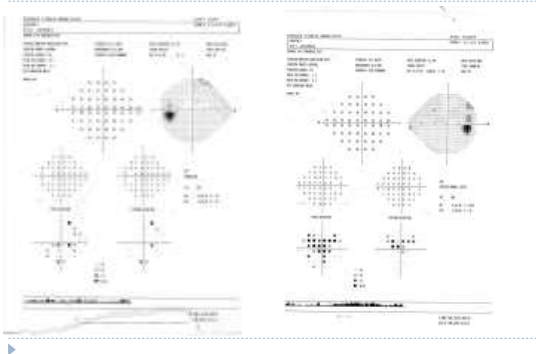
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VF 24-2 SITA standard




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Pachymetry




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- ▶ OAG suspect
- ▶ Plan
- ▶ No treatment
- ▶ Follow-up 3 months IOP check
- ▶ 6 months
- ▶ Repeat OCT,VF
- ▶ Perform gonioscopy

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### What is glaucoma?

▶ **Definition:**

- ▶ “Ocular tissue damage at least partially related to intraocular pressure”
- ▶ Where glaucoma is concerned agreement is limited among clinicians and scientists.

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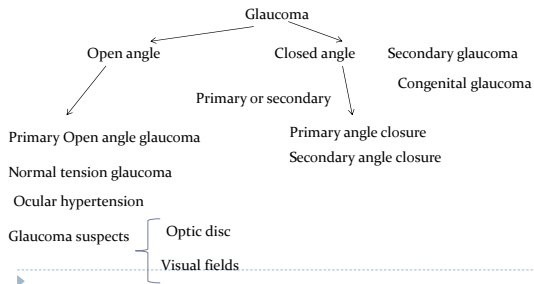
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### Types of glaucoma




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### Definition

- ▶ A chronic, bilateral, often asymmetrical disease in adults, featuring acquired loss of optic nerve fibers and abnormality of visual field with an open anterior chamber angle.

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Definition A.A.Ophthalmology

- ▶ POAG is a multifactorial optic neuropathy in which there is a characteristic acquired loss of retinal ganglion cells and atrophy of the optic nerve.

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Issue related to primary or secondary

- ▶ Classification important for clinical management.
- ▶ The division into primary and secondary is arbitrary because...
  
- ▶ A term idiopathic open angle glaucoma is possibly better suited instead of POAG

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POAG

- ▶ Chronic
- ▶ Bilateral
- ▶ Often asymmetric
- ▶ Adults
- ▶ Acquired optic nerve fiber loss.
- ▶ Acquired visual field loss.

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POAG -2

- ▶ Open chamber angle with normal appearance
- ▶ IOP often over 21 mmHg

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Pathophysiology

- ▶ Needs to be established.
- ▶ A process causes death of retinal ganglion cells by apoptosis

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Goals

- ▶ Document status of optic nerve structure and function
- ▶ Target pressure- so damage is unlikely to happen
- ▶ Maintain IOP below target pressure

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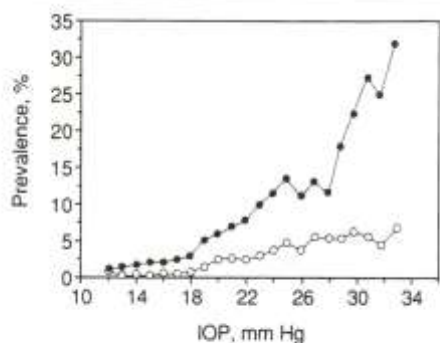
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**Figure 1.** Prevalence of primary open-angle glaucoma in relation to screening IOP  
 Note: The curve is smoothed using a running mean with window width of 7 mm Hg.  
 Caucasian American subjects, n = 5,700 eyes (open circles); African American subjects, n = 4,074 eyes (closed circles).

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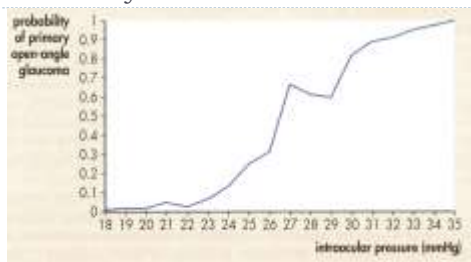
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Probability of POAG relative to IOP



**At IOP of 30 there is about 80% probability of primary open angle glaucoma**




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IOP related statistics

- ▶ Inter-individual variation in susceptibility of optic nerve to IOP-related glaucoma damage
- ▶ Only 1/10<sup>th</sup> of patients with elevated IOP have VF loss (Sommer 1991)
- ▶ Approx 10% of OHT develop glaucoma in 5 years (OHTS 2002)




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Race- Risk factor

- ▶ Prevalence of POAG is 4-5 times in African Americans when compared to Caucasians
- ▶ IOP in Caucasians is similar to African Americans
- ▶ Blindness due to glaucoma 8 –times more common in African Americans than in Caucasians

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Other risk factors

- ▶ Age
- ▶ Family history
- ▶ Low diastolic perfusion pressure
- ▶ DM no detectable association

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Systematic evaluation of nerve

- ▶ Five rules or R's
- ▶ Compilation of clinically useful information and suggestions on how to examine the optic nerve
- ▶ Developed by Bob Weinreb, Medeiros and Susanna Jr for Allergan.

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Rule 1

- ▶ I. Observe the scleral ring to identify the limits of the optic disc and evaluate its size.

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Disc size & nerve

- ▶ Cup size is associated with disc size
- ▶ Effects any casual observer for cup to disc ratio measurement
- ▶ Rim thickness varies with disc size

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Methods to measure

- ▶ Direct ophthalmoscope
- ▶ Slitlamp lenses
- ▶ Contact lenses like the Goldmann lens
- ▶ HRT, OCT, to some extent even the GDx



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### Rule 2, Neuroretinal rim

- ▶ Color of rim- pale rims not good
- ▶ Width of rim in all sectors
- ▶ ISNT rule – Jonas from University of Heidelberg, Heidelberg, Germany
- ▶ ISNT rule is accurate about 70% of times



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### Rule 3 RNFL

- ▶ Healthy eye has striations
- ▶ A certain amount of NFL is required for visibility
- ▶ RNFL loss can be diffuse, localized or mixed



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### RNFL cont...

- ▶ Diffuse – reduction in RNFL brightness
- ▶ Localized – wedge shaped defect
- ▶ Localized RNFL defects should traced back the disc



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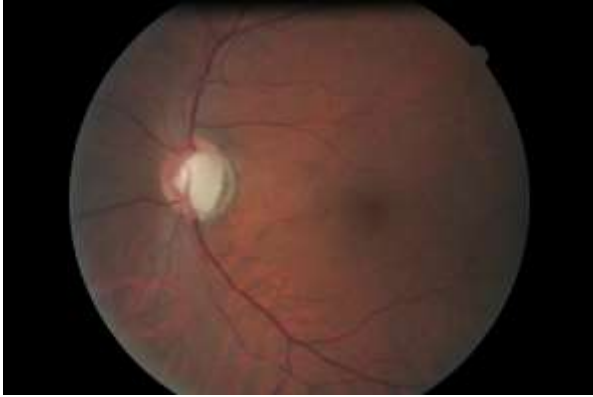
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Peripapillary atrophy

- ▶ Where
- ▶ How large

▶ 1/8, 1/4, 1/2, 3/4, 1, > 1 DD



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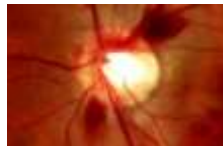
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Rule 5- retinal and optic disc hemorrhages

- ▶ Transient
- ▶ Inferior temporal or superior temporal regions mainly



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Disc hemorrhage or Drance hemorrhages

- ▶ At least 1/3 rd of glaucoma patients show hemorrhage at one time or another (Gloster 1981)
- ▶ Disc hemorrhages are considered to be an important risk factor in development and progression of glaucomatous damage\*\*

\*\* (Airaksinen 1984, Diehl et al., 1990, Drance et al., 1977, Siegner et al., 1996, Sonnsjo et al., 2002)

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Disc hemorrhage - 2

- ▶ First signs of glaucoma development (Bengtsson et al., 1981)
- ▶ Show greater progression both in terms of visual field damage and optic disc changes (Siegner and Netland 1996)

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Disc hemorrhage - 3

- ▶ Disc hemorrhage are mainly found in inferior and superior regions (Jonas and Schiro 1994, Siegner and Netland 1996)
- ▶ It is associated with localized nerve fiber layer loss in same region (Jonas and Schiro 1994, Siegner and Netland 1996 and Sugiyama et al., 1997 & 1999).

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Disc hemorrhages and RNFL

Patients with disc hemorrhage and glaucoma progression had on average – progressive loss in 2 years or so\*

▶ Additionally it was noticed that damage is not limited to the region of disc hemorrhage.\*

▶ \*Gunvant, et al., Predicting subsequent visual field loss in glaucoma subjects with disc hemorrhage using RNFL polarimetry. *Journal of Glaucoma*, 2005 Feb;14(1):20-25



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Current consensus related to disc hemorrhage

- ▶ Watch these patients carefully
- ▶ Disc hemorrhage by in itself does not mean progression in glaucoma



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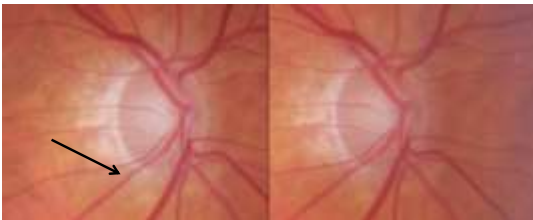
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Retinal vessels – “6<sup>th</sup> R” new rule?



▶ **Look for this in patients that you suspect NTG**



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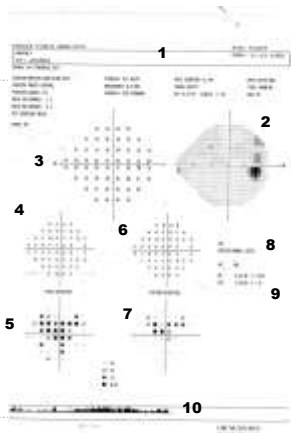
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1  
 Watch out for  
 Pupil size  
 Reliability index  
 Type of test  
 24-2 SITA STD  
 age  
 refractive error




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2 Grey Scale  
 Look for patterns  
 Global view  
 Not for diagnosis  
 Types of visual field defects

3 Raw data  
 Normals centrally low 30's  
 Peripherally high 20's

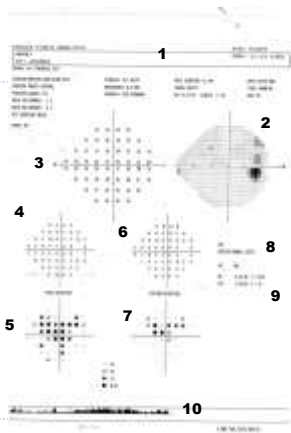


4 Total  
 deviation  
 Deviation from average

5 Total  
 deviation probability plot

6 Pattern  
 deviation  
 Removes any generalized  
 defects  
 Cataract  
 Pupil miosis

7 Pattern  
 deviation probability plot




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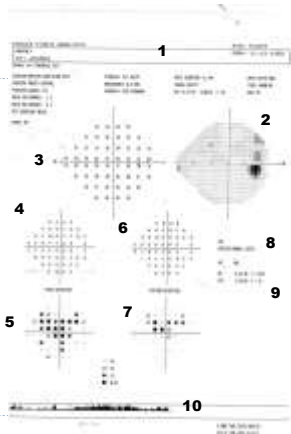
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sensitivity

9 global indices

MD mean deviation  
 PSD pattern  
 Standard Deviation

10 gaze tracking




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Early detection

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Screening methods - IOP

- ▶ IOP poor screening tool
  - ▶ Sensitivity 47.1% specificity 92.4%
  - ▶ Numerous individuals with POAG will have pressures below 22 on a random screening test
  - ▶ Most people with high pressures do not have or never develops POAG (OHTS and EPGS results give additional evidence)

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Screening methods

- ▶ Screening can be made more effective by including ONH and RNFL assessment.
- ▶ Standard visual field is time consuming.
- ▶ Frequency doubling technology shows promise as a screening tool

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Screening cont...

- ▶ Screening can be more efficient if
  - ▶ Targeted to specific groups
    - ▶ Older population
    - ▶ African Americans
    - ▶ Relatives of glaucoma patients

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Target pressure

- ▶ A theoretical value below which visual field and ONH appear stable (not deteriorating).
- ▶ Calculated from highest recorded IOP.
- ▶ Conventionally 20-30% decrease in IOP.
- ▶ 40% or more if severe glaucoma

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Recommended time to follow-up

Target IOP Achieved	Progression of Damage	Duration of Control (months)	Follow-up Interval
yes	no	<6	1-6 months
yes	no	>6	3-12 months
yes	yes	(n/a)	1 week - 3 months
no	no	(n/a)	1 day - 3 months
no	yes	(n/a)	1 day - 1 month

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Recommended time to visual fields

Target IOP Achieved	Progression of Damage	Duration of Control (months)	Follow-up Interval (months)
yes	no	<6	6-18
yes	no	>6	6-24
yes	yes	(n/a)	2-6
no	no	(n/a)	2-6
no	yes	(n/a)	1-6

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Recommended time to ONH evaluation

Target IOP Achieved	Progression of Damage	Duration of Control (months)	Follow-up Interval (months)
yes	no	<6	6-12
yes	no	>6	6-18
yes	yes	(n/a)	3-12
no	no	(n/a)	3-12
no	yes	(n/a)	3-12

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Prognosis

- ▶ Most POAG patients will retain useful vision for their entire life
- ▶ Incidence of blindness 27% vs 9% (unilateral versus bilateral) at 20 years following diagnosis.
- ▶ Prevalence of bilateral blindness 8% vs 4% (black versus white population)

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Prognosis -2

- ▶ Lowering IOP has shown a significantly reduce progression and possibly halt it.

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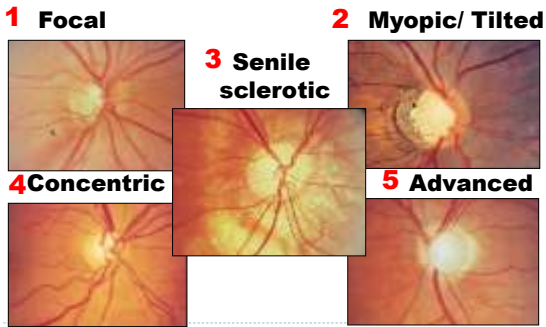
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Types of nerve heads



Broadway D.C, Nicoletta M. T, Drance S.M., Survey of Ophthalmology 1999

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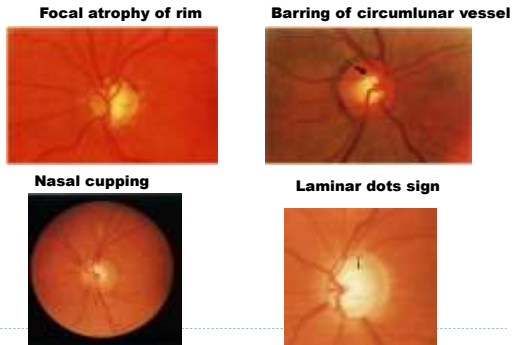
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Signs to look for



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Signs to look for

Bayonetting sign



Disc hemorrhage



Nerve fiber layer defects



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CD ratio

- ▶ Vertical
- ▶ Horizontal
- ▶ Largest
- ▶ CD ratio of imaging devices will not match your findings!



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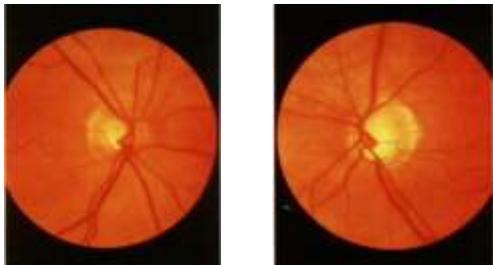
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Focal atrophy of neural rim



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Focal atrophy of neural rim-2



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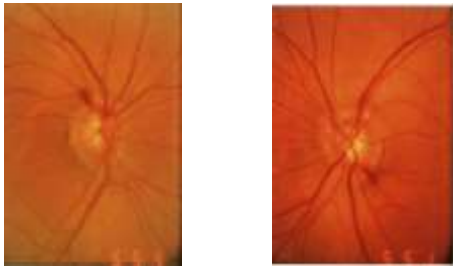
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Optic disc hemorrhages



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Optic disc hemorrhages-3



3 years later



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Barring of circumlinear vessels



- ▶ Vessels that runs along margin between cup and neural rim.
- ▶ Found supero and infero temporally

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Barring of circumlinear vessels



- ▶ As rim becomes thinner it leaves an area of pallor between the rim and the circumlinear blood vessel.

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Barring of circumlinear vessels



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Nasal cupping



- ▶ Usually seen in advanced glaucoma.
- ▶ Space between Nasal rim and blood vessels.

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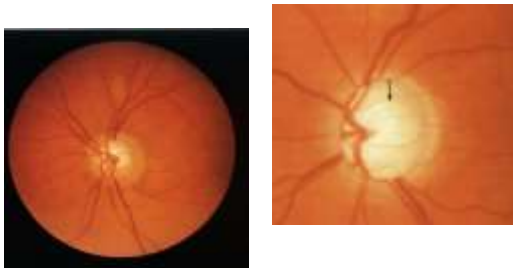
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Laminar dot sign



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Bayonetting

- ▶ Double angulation of blood vessel.



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Nerve fiber bundle defect

- ▶ Rim changes also produces RNFL defects.
- ▶ Dark stripes or wedge shapes defect paralleling the normal striations.
- ▶ Common after disc hemorrhages



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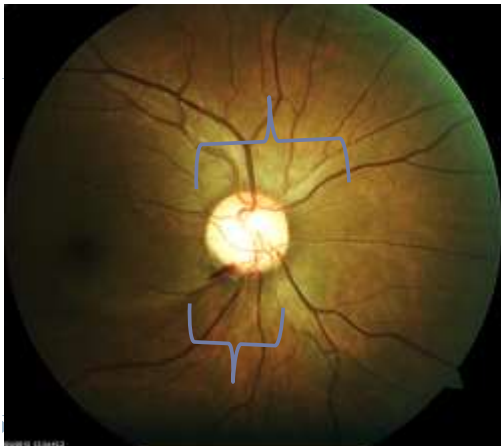
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Clinical trials in glaucoma

Treatment versus no treatment

Early Manifest Glaucoma Trial

- ▶ Newly diagnosed POAG
- ▶ Aims:
  - ▶ Compare treatment versus no treatment to evaluate effectiveness of IOP reduction in early previously untreated OAG
  - ▶ Secondary aims
    - ▶ Factors related to glaucoma progression
    - ▶ Natural history of disease

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EMGT cont...2

- ▶ Population based screening in Sweden
- ▶ 44,243 screened
- ▶ 316 eyes of 255 patients recruited.
- ▶ Betaxolol and ALT vs observation
- ▶ Follow-up 6 years

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Study details

- ▶ Every 3 months, IOP and perimetry (30-2)
- ▶ Every 6 months fundus photos
- ▶ Primary outcome measure
- ▶ VF loss in 3 consecutive fields
- ▶ Or disc damage change interpreted by masked observers.

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Summary of results

- ▶ Mean untreated IOP 20.6 mmHg
- ▶ Progression rates were highly variable
- ▶ Progression 62% vs 45% untreated vs treated
- ▶ Risk of progression increased with higher baseline IOP compared to lower IOP
- ▶ More nuclear cataract in treated group vs controls
- ▶ VF identified progressors more readily than optic disc

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EMGT - Outcomes

- ▶ Treated group experience less and later progression than observation group (45% vs 62 %)
- ▶ Some patients showed no signs of progression despite no treatment.
- ▶ Results not applicable to high IOP or advanced glaucoma

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EMGT Results cont...

- ▶ Pseudoexfoliation independent risk factor
- ▶ Post-hoc analysis
  - ▶ Thin CCT a risk factor in POAG
  - ▶ Low blood pressure risk factor in NTG
- ▶ IOP fluctuations was not a risk factor
- ▶ Quality of life not different in treated vs untreated.

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OHT VS POAG

- ▶ Differentiating OHT from early POAG may be very difficult.
- ▶ Look for signs of early damage
- ▶ Short wavelength automated perimetry and Frequency doubling technology perimetry may aid in early diagnosis of POAG when compared to white on white perimetry
  - ▶ Although there is evidence now that this may not be the case

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▶

- ▶ In eyes with signs of early damage of optic disc the diagnosis of POAG should be considered and treatment initiated.
- ▶ Change if recorded can be diagnostic of early POAG

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Ocular Hypertension Treatment Study

- ▶ Efficacy of topical hypotensive medications in delaying or preventing onset of glaucoma in ocular hypertensive patients.
  
- ▶ Medication versus observation
- ▶ N = 1636
- ▶ Follow-up 5 years
- ▶ Patients with IOP 24 to 32 mmHg one eye
- ▶ Other eye between 21 and 32 mmHg
- ▶ Randomly assigned to either treatment or observation group

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Treatment goal

- ▶ IOP < 24 mmHg and at least 20% less than baseline
  
- ▶ Primary outcome
  - ▶ Development of POAG
    - ▶ As seen by VF abnormality
    - ▶ Or by disc abnormality

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OHTs summary of results

- ▶ Mean IOP reduction was 22.5%
- ▶ Control group IOP decrease was 4% (why did control group decrease?)
- ▶ 4.4% of treated group progressed
- ▶ 9.5% of observation group progressed
- ▶ Treatment definitely shows a reduction of risk of glaucoma in OHT.
- ▶ Cataract formation was greater in treated group

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OHTS outcomes

- ▶ Baseline factors that predict onset of POAG
- ▶ Older age
- ▶ Larger vertical or horizontal CD ratio
- ▶ Greater PSD
- ▶ Higher IOP
  
- ▶ Strongest association was CCT
- ▶ Disc hemorrhage – increased risk of POAG development

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OHTS outcomes cont...

- ▶ However most untreated group did not deteriorate after 5 year of follow-up
- ▶ But the difference in treated versus untreated convertors increased with time.
  
- ▶ Both VF and disc evaluation is important; why?

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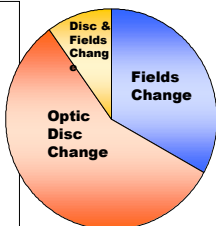
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▶

- ▶ OHTS reports 55% of subjects reached endpoint (POAG) based on changes in the optic disc only.
- ▶ A further 10% of subjects had concurrent optic disc and visual field changes.
- ▶ Only 35% of glaucoma was found by visual field changes.



Kass et al., Arch Ophthalmol. 2002;120:701-703

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### European glaucoma prevention study

- ▶ Similar to OHTS
- ▶ Efficacy of Dorzolamide in preventing or delaying POAG in ocular hypertensive patients.
- ▶ IOP between 22 and 29 mmHg
  
- ▶ Main outcome VF and optic disc changes

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### Summary

- ▶ 1081 patients 120 developed POAG
  - ▶ Duration of follow-up 55.3 months
  - ▶ Mean IOP reduction
  - ▶ 15% after 6 months
  - ▶ 22% after 5 years
- } treatment group
- 
- ▶ 9% after 6 months
  - ▶ 19% after 5 years
- } control group (because of regression to mean)

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Results summary

- ▶ Same factors as OHTS predicted conversion to POAG
- ▶ Study failed to detect statistical significance between chosen treatment and placebo in either IOP lowering effect or in rate of conversion.




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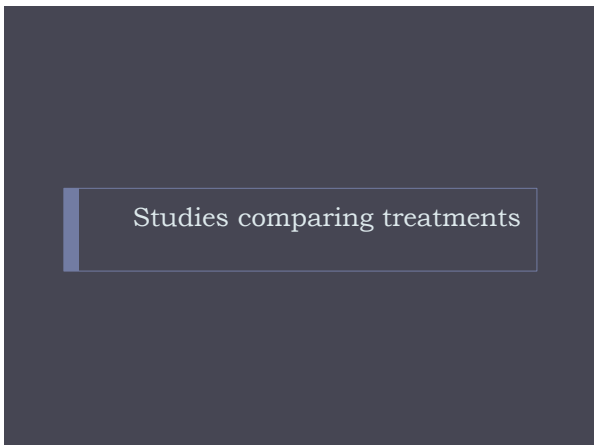
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Advanced Glaucoma Intervention Study - AGIS

- ▶ POAG after medical treatment failure
- ▶ No previous surgery
- ▶ Laser trabeculoplasty vs trabeculectomy
- ▶ N = 591 (789 eyes)
- ▶ Follow-up 4-7 years




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AGIS outcomes

- ▶ Initially acuity loss was greater with trabeculectomy
- ▶ At 5 years VF loss was lesser with trabeculectomy in Caucasians
- ▶ Black patients had less progression with laser trabeculoplasty
- ▶ Dose-response relationship between IOP and VF progression likely

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Collaborative Initial Glaucoma Treatment Study- CIGTS

- ▶ New POAG
- ▶ Medicine vs trabeculectomy
- ▶ N= 607
- ▶ Follow-up 5 years

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CIGTS- Outcomes

- ▶ Outcomes very similar
- ▶ Surgical group had slightly more ocular symptoms early in the study

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## Normal tension glaucoma


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### Background NTG or LTG or POAG?

- ▶ Controversial
- ▶ IOP continuous variable
- ▶ No distinct dividing line
- ▶ Arbitrary dividing line 21 or as in some studies 24 mm Hg
  
- ▶ What about NTG with – thin cornea
  - ▶ IOP corrected is >21 Is this POAG now?

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### Clinical Features -2

- ▶ Damage present despite lower than statistically normal pressures
- ▶ Factors other than IOP play a role

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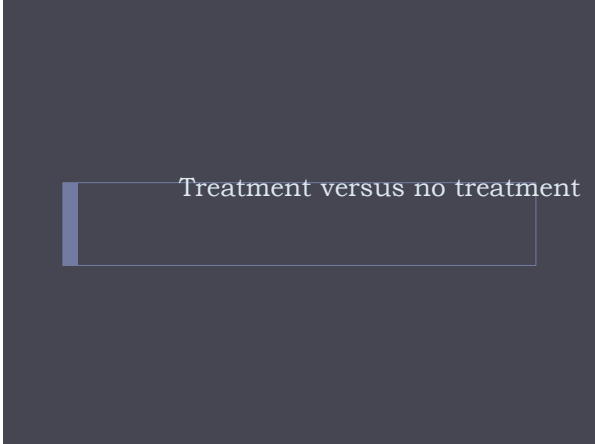
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Outcome

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- ▶ **Progression**
  - ▶ 12% treated group vs 35% control group
- ▶ **Cataract**
  - ▶ 38% treated group vs 14% controls
  - ▶ Cataracts greater for surgical group vs meds or laser

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Collaborative normal tension glaucoma study -outcomes

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- ▶ Lowering IOP retards the progression rate of visual field loss compared with untreated eyes.
- ▶ Treatment effect was only obvious after removal of effect of cataract.

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### Collaborative Normal Tension Glaucoma Study (CNTGS)

- ▶ Reduction of IOP by 30% reduced the rate from 35 to 12% confirming a clear role of IOP
- ▶ Other factors are indeed present because some progressed despite reduction of IOP

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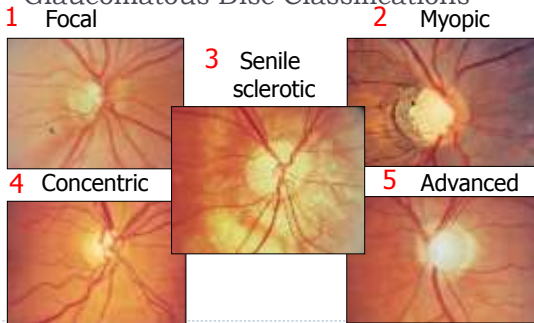
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### Glaucomatous Disc Classifications



Broadway D.C, Nicoletta M. T, Drance S.M., Survey of Ophthalmology 1999

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### Differential diagnosis

- ▶ Diurnal IOP is a useful in determining the peak IOP
- ▶ Also useful in establishing target IOP
- ▶ CCT and IOP issue

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Overall picture based on all studies

- ▶ IOP reduction benefit is seen in POAG and OHT of various stages.
- ▶ Lower IOP means better protection but greater IOP reduction may not benefit all patients.
- ▶ IOP lowering treatment may not benefit all
- ▶ 20% IOP reduction in OHT patients may not prevent progression.
- ▶ Measurement of CCT in OHT and POAG patients must be done.
  - ▶ May benefit OHT but not POAG management

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57 BF Nov 2009

- ▶ wanted to transfer care
- ▶ H/O glaucoma on Lumigan qhs (Bimatoprost) OU X 4 years
- ▶ H/O cataract extraction with PCIOL
- ▶ H/O dry eye- restasis use
  
- ▶ Ocular examination –
- ▶ IOP OU 15 mmHg at 11.50 AM
- ▶ CD ratio
- ▶ OD 0.35 H 0.35V
- ▶ OS 0.40H 0.5V




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- ▶ Plan:
- ▶ Continue meds
- ▶ Request record
- ▶ See again soon--- not recorded well, lost in some paper work

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Repeat visit February 2011

- ▶ H/o Same as before
- ▶ Patient using meds as a advised.
- ▶ Records still not available
- ▶ BCVA
- ▶ OU 20/20
  
- ▶ IOP OU 12 mmHg 11.28 AM
- ▶ Van Herick's angle grading
  - ▶ OD grade 4
  - ▶ OS grade 3

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- ▶ Disc evaluation
- ▶ OD NRR intact
- ▶ 0.40 H 0.40 V
  
- ▶ OS 0.40 H 0.5V
- ▶ Plan
- ▶ Continue medications
- ▶ IOP, Fundus photos, VF , OCT, Pachy and Gonioscopy

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Return March 2011

**IOP**  
**OD 14**  
**OS 16 at 11.10 AM**

**Gonio wide open grade 4**  
**Iris processes OU**



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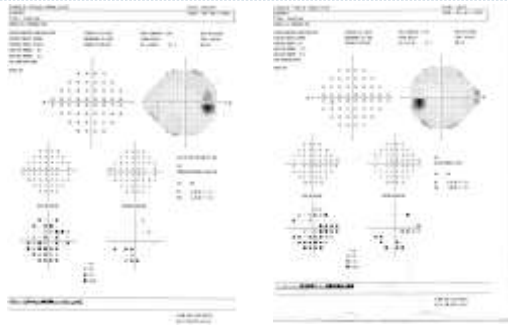
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Visual fields



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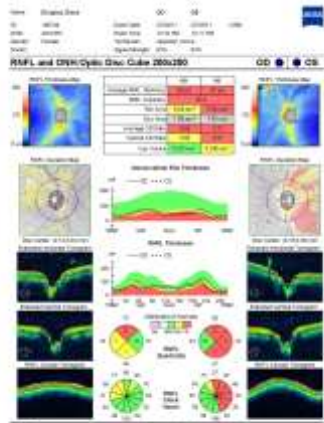
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Accutome Rech V  
Date: Fri 03/18/2011  
Time: 01:01 PM

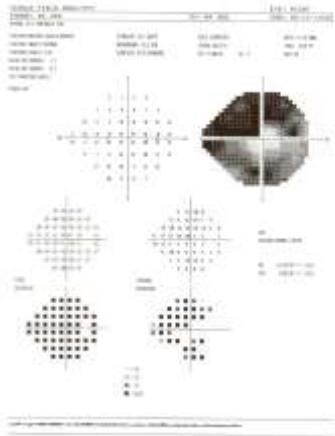
Patient's Name: \_\_\_\_\_

CCT Reading	DD	OS
1	483	486
2	497	484
3	503	485
4	494	481
5	508	484
6	512	478
7	528	482
8	509	489
9	506	481
Average CCT	505	484
NIOP	14	15
TIOP	15	19

- ▶ Plan
- ▶ Continue meds
- ▶ IOP recheck 3 months
  
- ▶ Any thoughts?

PATIENT 202 age 70 at evaluation






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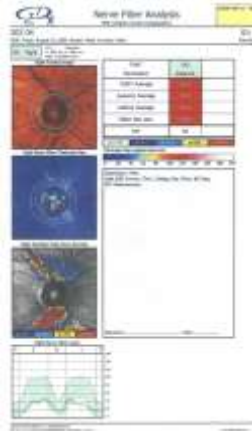
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**Your thoughts?**

**Management?**

**Where would you like to see IOP?**

- 10-13
- 15-18
- 20?

**Cataract surgery?**

**Combined procedure?**

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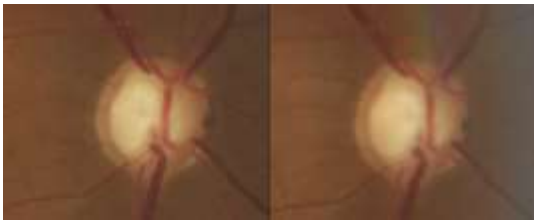
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Patient 206 OD Age 50 at evaluation




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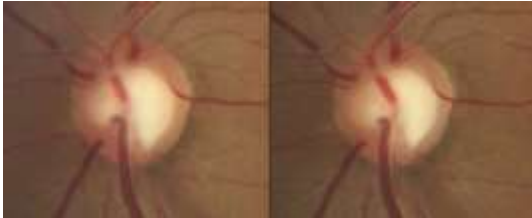
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OS



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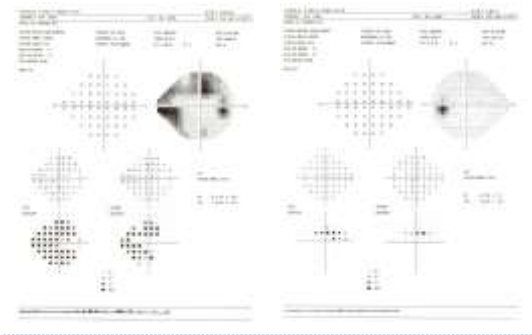
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Visual fields



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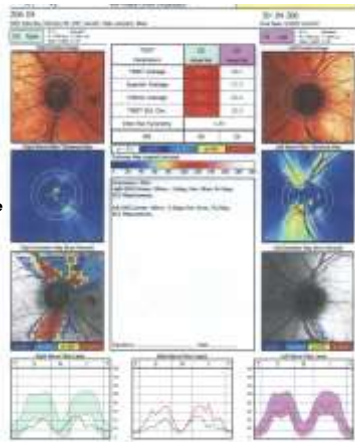
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Patient 206

Your thoughts?  
Management?  
Where would you like to see IOP?  
10-13  
15-18  
20?  
Cataract surgery?  
Combined procedure?



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