Ask The Experts: When You are Treating Glaucoma Patients

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****All relevant relationships have been mitigated******

- Tarsus-Consultant, Clinical Trials
- Bausch and Lomb-Consultant
- AbbieVie-Consultant
- Topcon-Consultant
- Harrow-Consultant
- MediPrint-Shareholder/Consultant

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Agenda

- Making the diagnosis:
  - Optic nerve hemorrhages: What do they mean?
  - Genetic testing in glaucoma
  - Are we utilizing OCT correctly for glaucoma?
    - Variability/Rate of progression
    - Macular findings/staging
  - Update on visual field testing
    - Wearables
    - 10-2 vs 24-2
    - Tempo
  - AI?
- Starting therapy
  - Monocular drug trials: Are they useful?
  - Are Topical beta blockers safe to use?
  - PGA's-What to consider

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Agenda-Continued

- Surveilling for and detecting progression in glaucoma
  - VF/OCT progression
  - Pressure fluctuations and failure to meet target IOP
- Advancing Therapy
  - Replacement of primary agent
  - Single agent adjunct
  - Combination agents
  - Rho Kinase inhibitors
  - SLT
- Side Effects of secondary agents
- When to refer for surgical intervention

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Are Optic Nerve Hemorrhages Pathognomic For Glaucoma?

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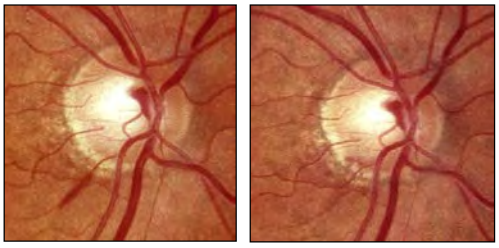
Optic Disc Hemorrhage

Normally disappears after 2-6 months



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Optic Disc Hemorrhages

- Optic Disc Hemorrhages in a Population with and without Signs of Glaucoma
  - Healey PR, Mitchell IP, et al Ophthalmology 1998 (Blue Mountains Eye Study)
- Overall prevalence in either or both eyes 1.4% of general population
  - More common in women
  - Prevalence increased with age
- Prevalence in individuals with OAG 13.8%
  - 8% High Tension
  - 25% Low Tension
  - 1.5% OHTN

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Optic Disc Hemorrhages in a Population with and without Signs of Glaucoma

Paul R. Healey, BMedSc, MBBS,[1] Paul Mitchell, MD, FRCOphth,[1] Wayne Smith, BMed, MPH,[2] Jie Jin Wang, MMed (Clin Epi)[1]

Objective: This study aimed to determine the prevalence and associations of optic disc hemorrhage in a well-defined older Australian population.

Design: The study design was a population-based, cross-sectional study.

Participants: A total of 3654 persons 49 years of age or older, representing 88% of permanent residents from an area west of Sydney, participated in the study.

Main Outcome Measures: Participants underwent a detailed eye examination. The diagnosis of optic disc hemorrhage was made from masked photographic grading; disc hemorrhages were subclassified as flame or blot in shape. Open-angle glaucoma was diagnosed from matching visual field loss and optic disc rim thinning.

Results: The overall prevalence of disc hemorrhage in either or both eyes was 1.4%. Disc hemorrhage prevalence was higher in women (odds radios [OR], 1.9; confidence interval [CI], 1.0–3.5) and increased with age (OR, 2.2 per decade; CI, 1.7–2.8 per decade). The overall prevalence in subjects with open-angle glaucoma was 13.8% (8% in high-pressure glaucoma and 25% in low-pressure glaucoma) and 1.5% in subjects with ocular hypertension. Disc hemorrhages were associated with increasing intraocular pressure (OR, 1.7 per 5 mmHg; CI, 1.3–2.3 per 5 mmHg), pseudoexfoliation (OR, 3.5; CI, 1.1–11.8), diabetes (OR, 2.9; CI, 1.4–6.3), and increasing systolic blood pressure (OR, 1.1 per 10 mmHg; CI, 1.0–1.3) after adjusting for age and gender. Among subjects without open-angle glaucoma, disc hemorrhages were more frequent in eyes with larger vertical cup–disc ratios and in subjects with a history of typical migraine headache (OR, 2.2; CI, 1.1–4.6). No associations were found among subjects with a history of vascular events, smoking, regular aspirin use, or myopia.

Conclusions: Disc hemorrhage prevalence in this population is higher than that in the two previous population-based reports. Although the strong association of disc hemorrhage with open-angle glaucoma was confirmed (particularly low-pressure glaucoma), most disc hemorrhages (70%) were found in participants without definite signs of glaucoma. *Ophthalmology 1998;105:216–223*

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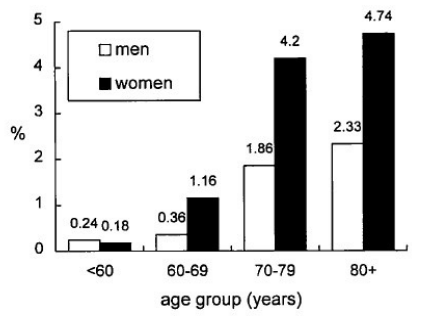

Figure 1. Prevalence of optic disc hemorrhages in 3582 participants by age and gender. Bar numbers indicate percent of subjects.

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Best Method to Detect ONH Hemorrhages is Inspection of Disc Photographs

Budenz Ophthalmology 2006

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Detection and Prognostic Significance of Optic Disc Hemorrhages during the Ocular Hypertension Treatment Study

Donald L. Budenz, MD, MPH,[1] Douglas R. Anderson, MD,[1] William J. Feuer, MS,[1] Julia A. Beiser, MS,[2] Joyce Schiffman, MS,[1] Richard K. Parrish II, MD,[1] Judy R. Piltz-Seymour, MD,[3] Mae O. Gordon, PhD,[2] Michael A. Kass, MD,[2] Ocular Hypertension Treatment Study Group

Purpose: To compare the rates of detection of optic disc hemorrhages by clinical examination and by review of optic disc photographs at the Optic Disc Reading Center (ODRC), to assess the incidence of and the predictive factors for disc hemorrhages in the annual disc photographs of the Ocular Hypertension Treatment Study (OHTS), and to determine whether optic disc hemorrhages predict the development of primary open-angle glaucoma (POAG) in the OHTS.

Design: Cohort study.

Participants: Three thousand two hundred thirty-six eyes of 1618 participants.

Methods: Both eyes of participants were examined for optic disc hemorrhages every 6 months by clinical examination, with dilated fundus examinations every 12 months, and by annual review of stereoscopic disc photographs at the ODRC.

Main Outcome Measures: Incidence of optic disc hemorrhages and POAG end points.

Results: Median follow-up was 96.3 months. Stereophotography-confirmed glaucomatous optic disc hemorrhages were detected in 128 eyes of 123 participants before the POAG end point. Twenty-one cases (16%) were detected by both clinical examination and review of photographs, and 107 cases (84%) were detected only by review of photographs ($P<0.0001$). Baseline factors associated with disc hemorrhages were older age, thinner corneas, larger vertical cup-to-disc ratio, larger pattern standard deviation index on perimetry, family history of glaucoma, and smoking status. The occurrence of a disc hemorrhage increased the risk of developing POAG 6-fold in a univariate analysis ($P<0.001$; 95% confidence interval, 3.6–10.1) and 3.7-fold in a multivariate analysis that included baseline factors predictive of POAG ($P<0.001$; 95% confidence interval, 2.1–6.6). The 96-month cumulative incidence of POAG in the eyes without optic disc hemorrhage was 5.2%, compared with 13.6% in the eyes with optic disc hemorrhage. In eyes with a disc hemorrhage in which a POAG end point developed, the median time between the 2 events was 13 months.

Conclusions: Review of stereophotographs was more sensitive at detecting optic disc hemorrhage than clinical examination. The occurrence of an optic disc hemorrhage was associated with an increased risk of developing a POAG end point in participants in the OHTS. However, most eyes (86.7%) in which a disc hemorrhage developed have not experienced a POAG end point to date. *Ophthalmology 2006;xx:xxx © 2006 by the American Academy of Ophthalmology.*

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Glaucoma: Which Genes Do We Already Know

- Genes associated with Adult Onset Glaucoma (Autosomal Dominant/Monogenic)
  - MYOC
    - Autosomal Dominant inherited POAG as well as JOAG
  - LOXYL1
    - Exfoliation syndrome/glaucoma
      - Encodes enzyme that crosslinks elastin and collagen
  - PMEL
    - Premelanosome protein in pigmentary dispersion syndrome/glaucoma
  - OPTN
    - Optineurin, involved in neuroprotection
  - WDR36
  - TBK1
    - Tank binding kinase 1
    - NTG primarily
- **All one of these genes account for less than 5% of all cases of adult onset glaucoma**
  - ***Note-No genetic associations for steroid-induced glaucoma***

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ARTICLES
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nature genetics

Multitrait analysis of glaucoma identifies new risk loci and enables polygenic prediction of disease susceptibility and progression

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Glaucoma, a disease characterized by progressive optic nerve degeneration, can be prevented through timely diagnosis and treatment. We characterize optic nerve photographs of 67,040 UK Biobank participants and use a multitrait genetic model to identify risk loci for glaucoma. A glaucoma polygenic risk score (PRS) enables effective risk stratification in unselected glaucoma cases and modifies penetrance of the MYOC variant encoding p.Gln368Ter, the most common glaucoma-associated myocilin variant. In the unselected glaucoma population, individuals in the top PRS decile reach an absolute risk for glaucoma 10 years earlier than the bottom decile and are at 15-fold increased risk of developing advanced glaucoma (top 10% versus remaining 90%, odds ratio = 4.20). The PRS predicts glaucoma progression in prospectively monitored, early manifest glaucoma cases ($P = 0.004$) and surgical intervention in advanced disease ($P = 3.6 \times 10^{-5}$). This glaucoma PRS will facilitate the development of a personalized approach for earlier treatment of high-risk individuals, with less intensive monitoring and treatment being possible for lower-risk groups.

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Most Glaucoma is not voiced by monogenic programming

- More commonly, POAG is a complex inherited trait with:
  - Multiple genes with small effect combining to form "risk"
  - Environmental triggers or "turning on" the gene
  - Proximity to a given Loci
- All necessary for "Disease" development
- These genes are not the common ones described on the previous slides
- Over 127 loci have been identified by Genome Wide Association Studies (GWAS)
  - -16 of which are targeted by current existing glaucoma drugs

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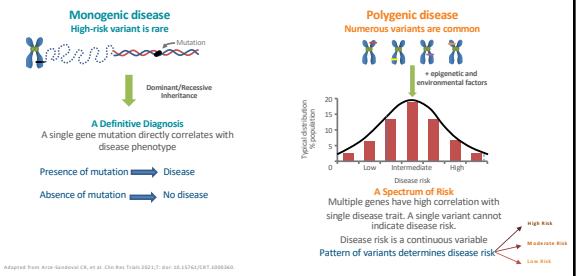
Inheritance of Glaucoma is both Monogenic and Polygenic

Polygenic Disease e.g. POAG has Complex Phenotype and Risk Profiles



Adapted from Arce-Sandoval CR, et al. Clin Res Trials 2021;7: doi: 10.15761/CRT.1000360.

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Genome Wide Association Studies GWAS

- Several large population based GWAS are in existence and used in this study
  - UKB
    - Population based study in UK of 500,000 participants
    - 7800 POAG vs. 119,000 controls
  - ANZRAG
    - 3100 cases of European ancestry POAG along with 6750 controls
  - Neighborhood GWAS
    - Meta analysis from 8 independent datasets of European Ancestry in US
    - 3900 POAG vs. 35,000 controls
  - BMES
    - Population based cohort study of common ocular diseases in people over 50 in Australia
  - Progressa-prospective longitudinal study of genetic risk factors in 388 patients with early glaucoma

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GWAS

- Allows pathway analysis for POAG associated risk loci
  Some of these genes have been associated with mechanisms for POAG development

  Examples:
  -Endoplasmic reticulum stress response
  -Extracellular matrix
  -Cell adhesion
  -TGF alpha and beta signaling
  -Vascular development
  -Lipid metabolism
  -Endogenous Nitric Oxide Synthetase)
  -Mitochondrial Function

  - However none of them on their own would lead to development of disease

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Methods

- Develop a glaucoma Polygenic Risk Score (PRS)
- Characterize 67,000 Optic Nerve Photographs of UK Biobank participants
  - Used vertical C/D ratio (VCDR) as an endophenotype for glaucoma
  - Also used genetic data from large genetic study using IOP as endophenotype
  - Combined with multitrait analysis of GWAS to identify new genetic loci
    - MTAG

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Results

- In addition to the already established 127 gene loci, this study identified another 176 loci from VCDR/IOP/GWAS MTAG
- Optimized the prediction of glaucoma risk by combining correlated or associated traits
- Outcome of a Polygenic Risk Score (PRS)
- This PRS had a better prediction ability than any of the input traits alone (IOP, VCDR, GWAS)

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Main Outcomes

- PRS Prediction
  - Individuals in the top PRS decile reach an absolute risk of glaucoma ***10 years earlier*** than those in the bottom decile **(6.34 x higher likelihood of having POAG)**
  - These same individuals in the top PRS decile are at a ***15-fold increased risk of developing advanced glaucoma***
  - PRS ***predicts glaucoma progression*** in prospectively monitored, early manifest glaucoma cases
  - PRS ***predicts need for surgical intervention*** in advanced glaucoma cases
  - ***PRS will facilitate a personalized approach for earlier treatment of high-risk individuals with less intensive monitoring and treatment for lower-risk patients***

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Implications For Clinical Care

- Currently, gene based diagnostic tests are available for congenital and juvenile POAG
  - Monogenic or single gene mutation is sufficient to produce the disease phenotype
    - Commercially available monogenic test
- What about for everyone else?

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Implications For Clinical Care

- For adult-onset, complex-inherited forms of glaucoma, polygenic risk scores are being investigated as a potential tool for personalized risk stratifications
- **Genetic Eye Disease Panel For Optic Nerve Disease and Early Manifest Glaucoma (GEDi-O)**
  - Available via Ocular Genomic Institute @ Massachusetts Eye and Ear
    - 22 genes including inherited retinal diseases
    - Glaucoma: 97% sensitivity and 100% specificity

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Anticipated New Commercial Glaucoma Genetic Polygenic Risk Score

- Seonix Bio
- Expected Q1 2025
- Cheek Swab
- 2-3 week turn around
- Cost unknown
- Insurance unknown

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SeonixBio

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What genes are tested by SightScore?

SightScore is a polygenic risk score. It tests over 2,500 genetic variants spread across the genome. SightScore does not test for rare genetic variants, like Myocilin.

Does the SightScore test work on all types of glaucoma?

No. The SightScore test is only looks at a patient's genetic risk of developing adult-onset primary open angle glaucoma (POAG). It does not test for angle closure glaucoma. It does not test for juvenile glaucoma.

How does SightScore relate to family history?

How do I refer SightScore?

You refer online. Please contact Seonix Bio at info@seonixbio.com and we will set you up with an account on our secure Seonix Clinician Portal. It's easy to setup and referral is simple and fast.

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Are We Using OCT Correctly? Assumptions, Unknowns, Myths

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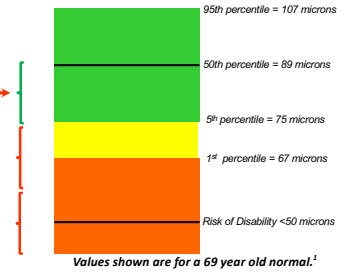
OCT and Progression Range

Normal ranges for Average RNFL

- *Just like perimetry, the average patient can lose a third of his/her RNFL or neuro-retinal rim and still be inside the OCT normal range.*
- *Normal person losses 2um/decade due to aging*



Values shown are for a 69 year old normal.[1]

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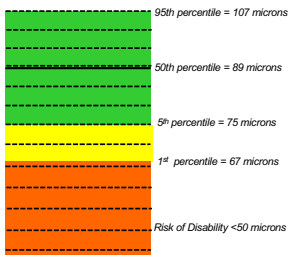
SDOCT measurements are highly reproducible.

2-4 Steps in Range

Normal significance Limits for Average RNFL

- *We can measure multiple steps of statistically significant change while a glaucoma suspect still is in the green normal range.*



Values shown are for a 69 year old normal.

- *Leung et al. Ophthalmology 2009;116:1257*
- *Roh et al. Ophthalmology 2013;120:969*
- *Wong et al.* Optom Vis Sci 2014;92
- Matlatch et al, IOVS Sep 2014 .

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- 36 YOWM
- Suspicious ONH cupping led to glaucoma eval
- IOP's 18-22 over 5 years
- Pachs 538 OD and 547 OS

- Did you say 36 year old white male? What??!?

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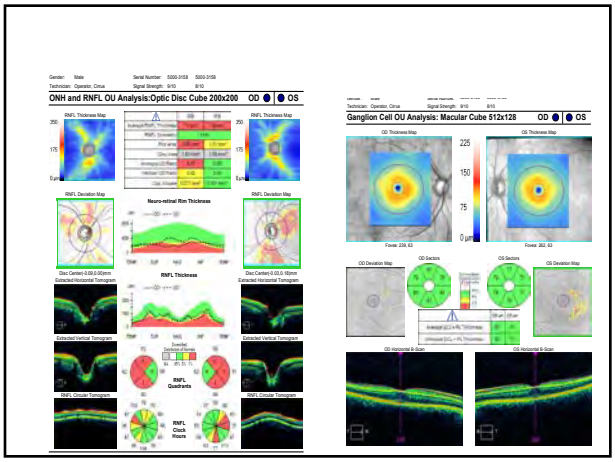

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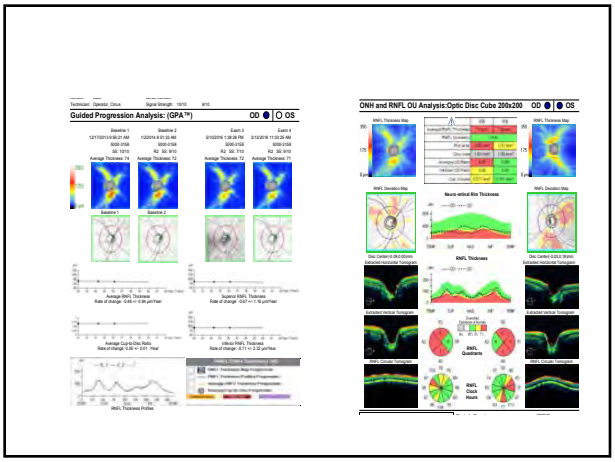

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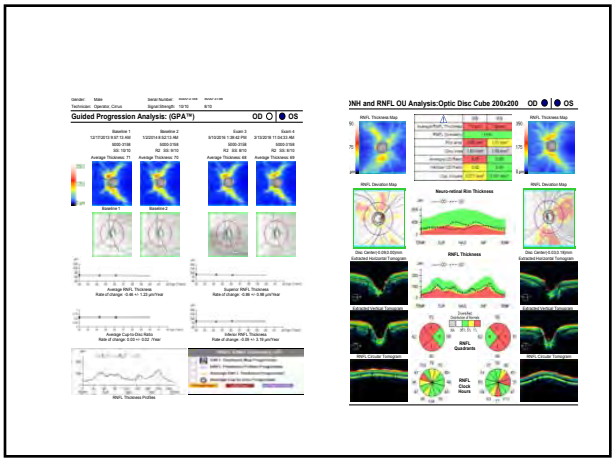

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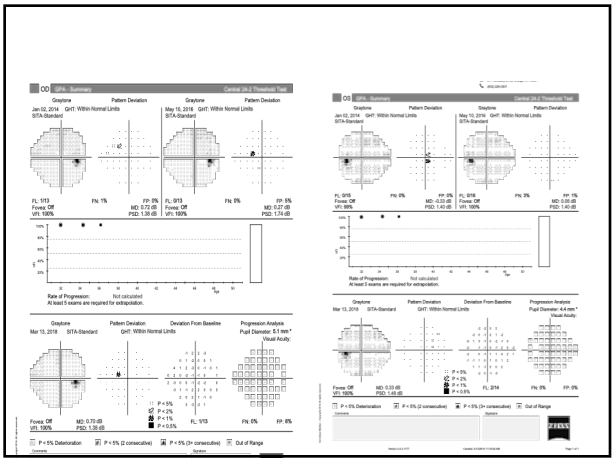

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Is this Glaucoma?

- Red Disease?
- Maybe he really does have it?
- But no change in any parameters over 5 years?
- What is follow up?
- Refer?

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Case Example

- Is this glaucoma or just a masquerader?
- 34 YO WF
- Fam Hx Glaucoma

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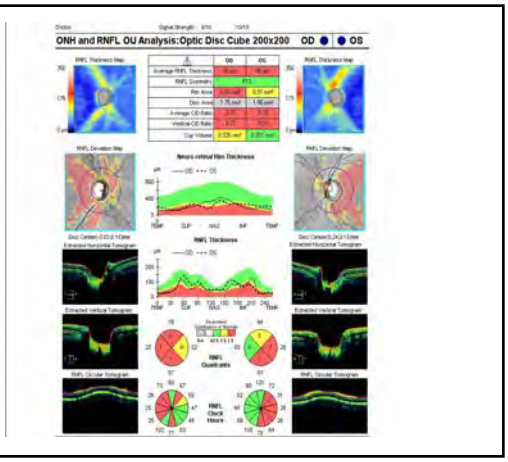

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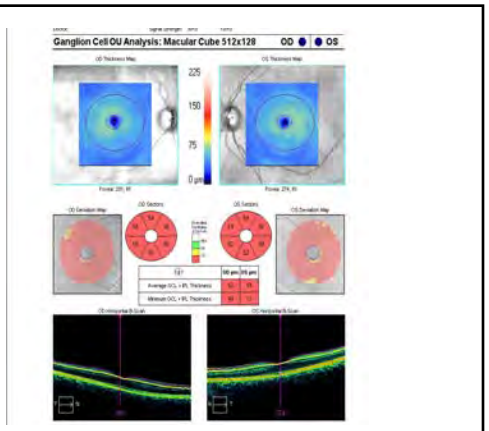

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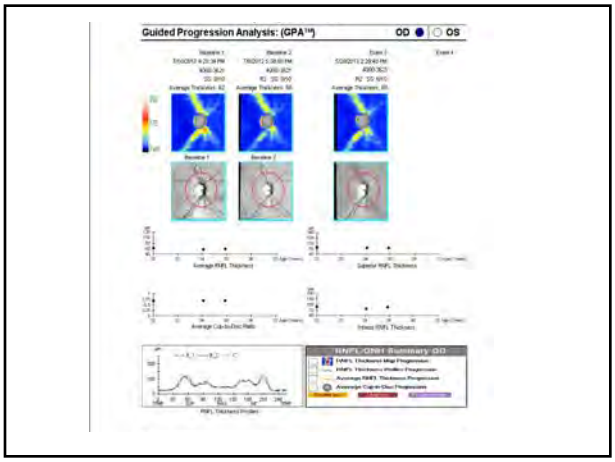

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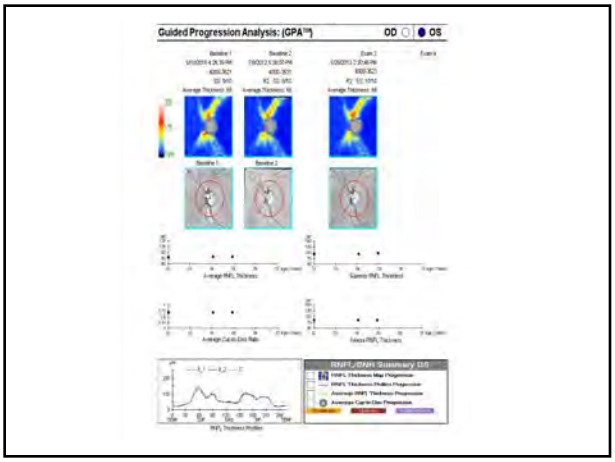

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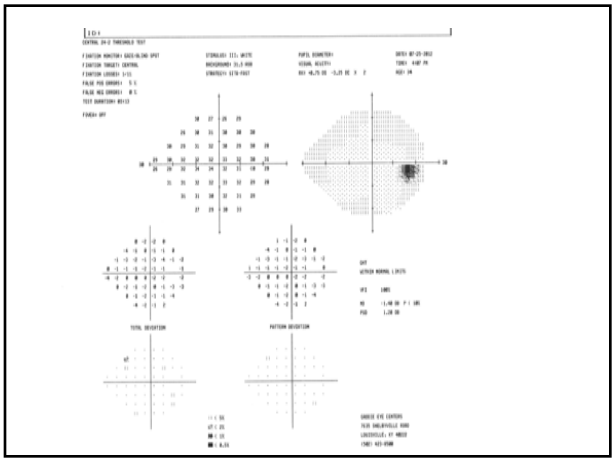

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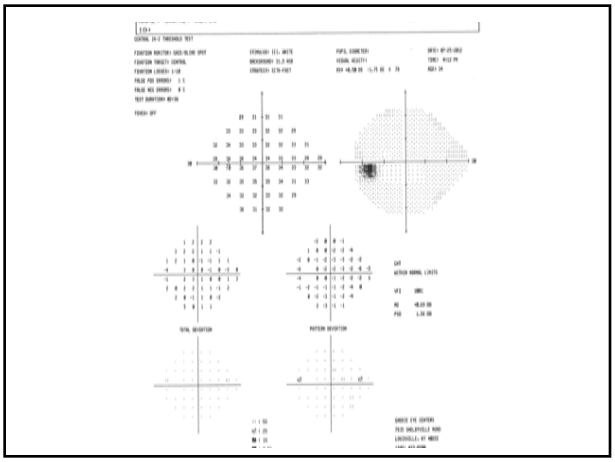

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Asymmetric Disease

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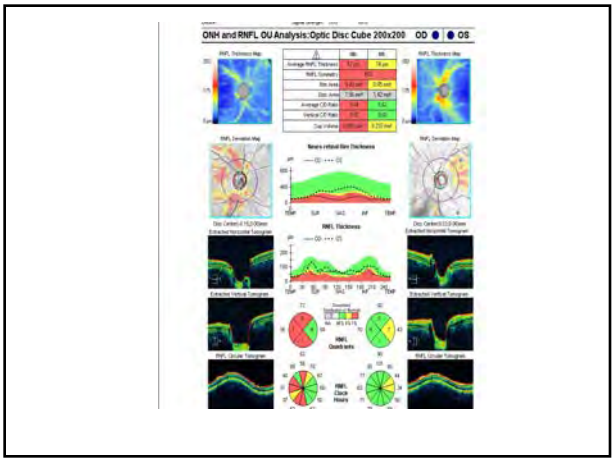

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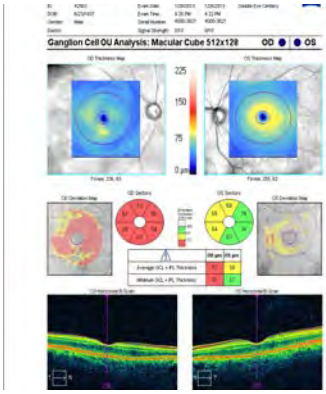

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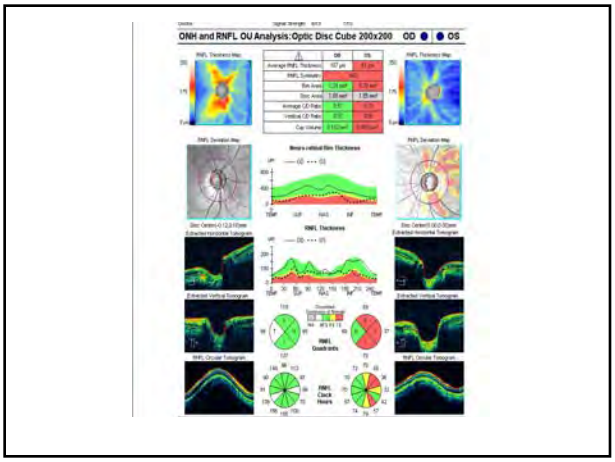

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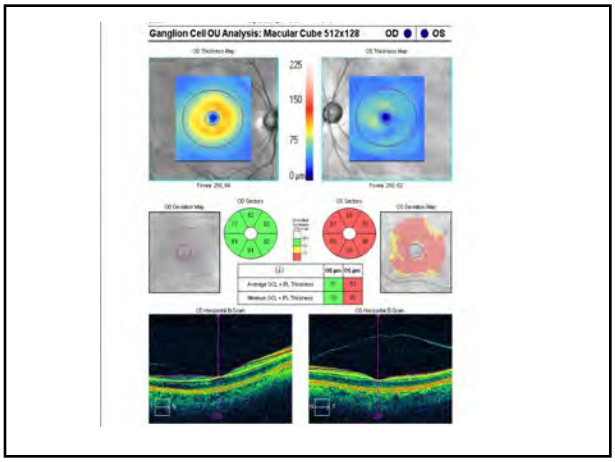

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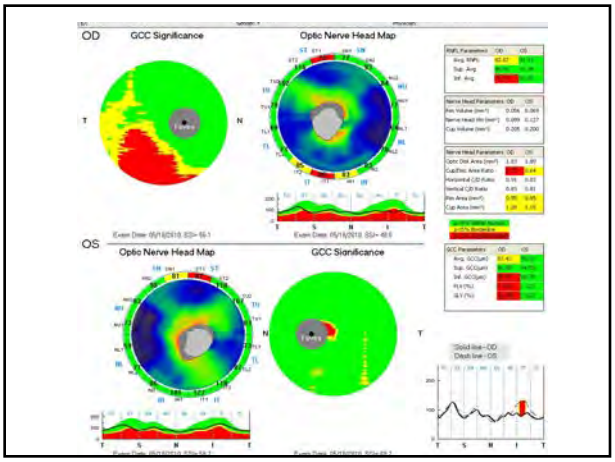

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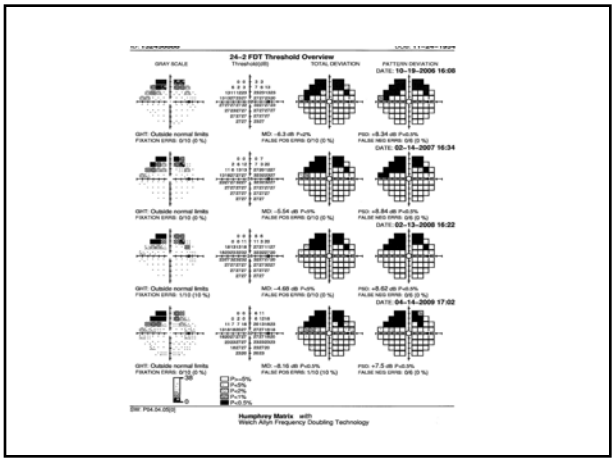

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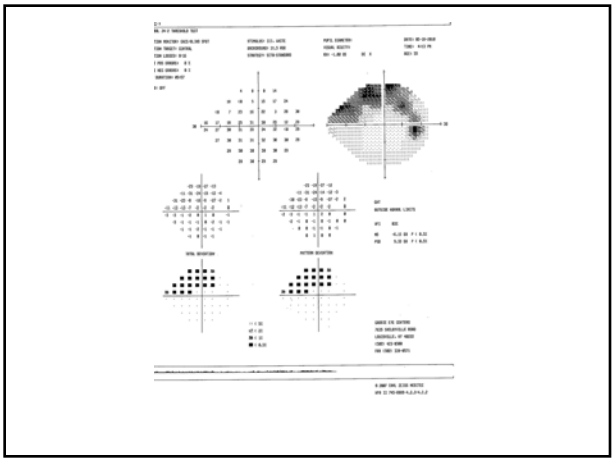

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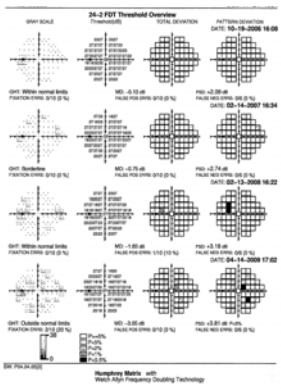

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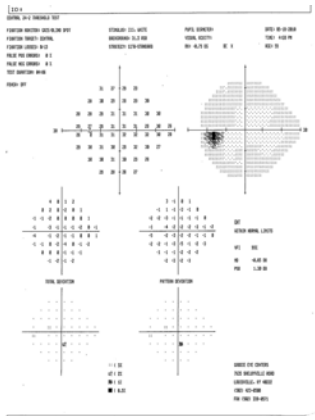

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Case Example

- 67 YO WM
- Glaucoma suspect x 7 years
- No Visual Field Loss
- IOP 15 OU
- Pach 551/543

- Is this glaucoma?

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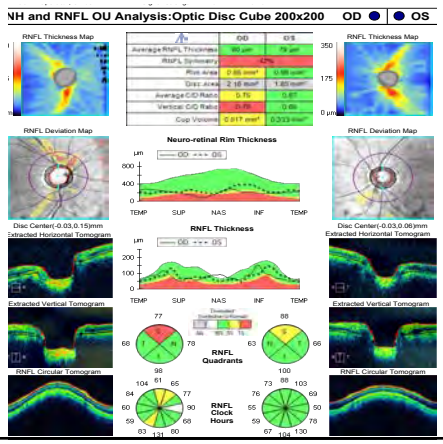

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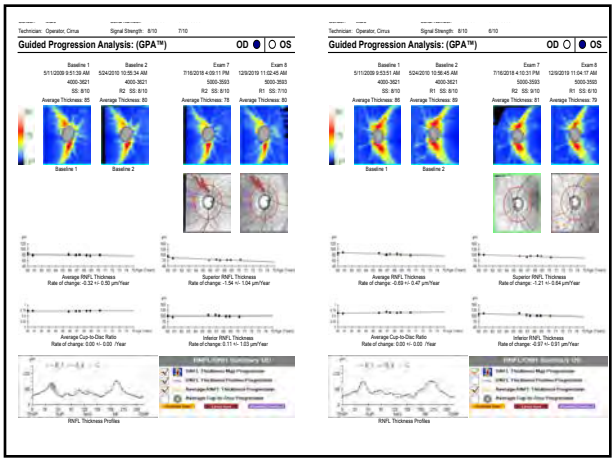

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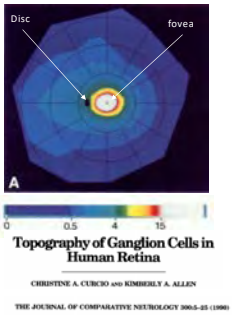
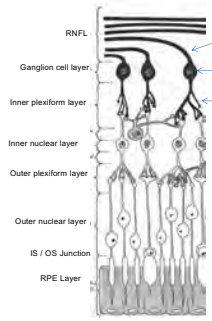
Macular Ganglion cell density



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

66

Retinal Ganglion Cells extend through three retinal layers



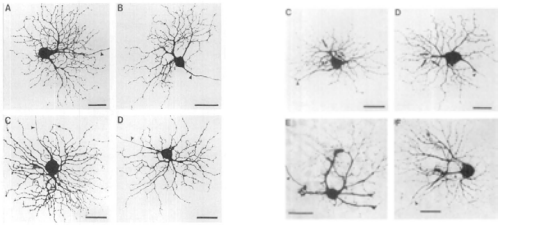
GCC is:

- Nerve Fiber Layer – Ganglion cell axons
- Ganglion cell layer – Cell bodies
- Inner-Plexiform Layer - Dendrites

67

Dendritic Shrinkage

- The first structural change from glaucoma was a shrinkage of the ganglion cell dendritic fields



Normal Ganglion cells (Primate) Glaucoma model Ganglion cells (Primate)

Morphology of Single Ganglion Cells in the Glaucomatous Primate Retina

IOVS, November 1998, Vol. 39, No. 12

Arthur J. Weber,[1] Paul L. Kaufman,[2] and William C. Hubbard[3]

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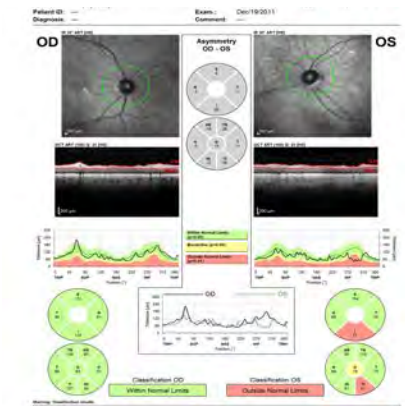

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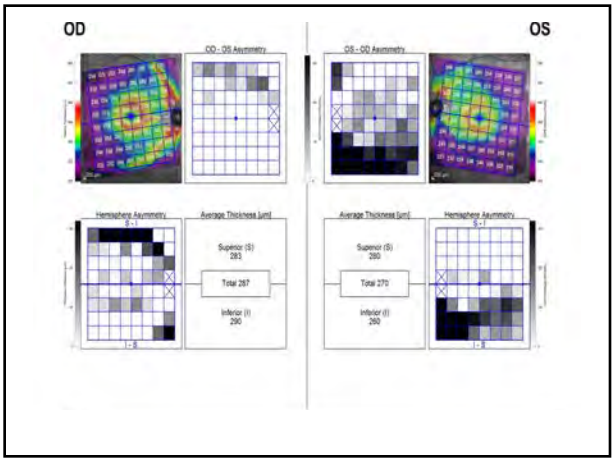

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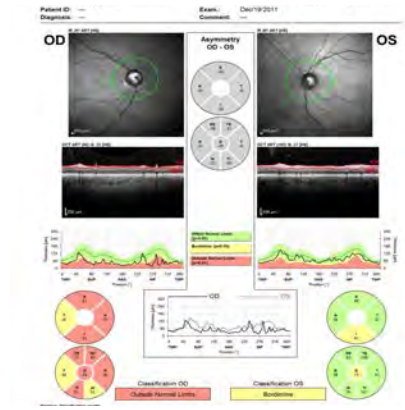

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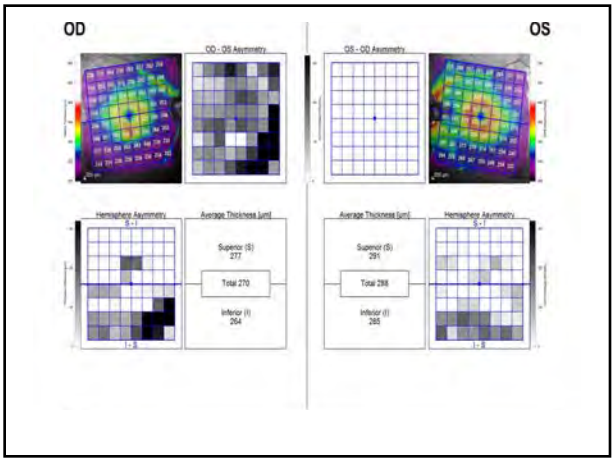

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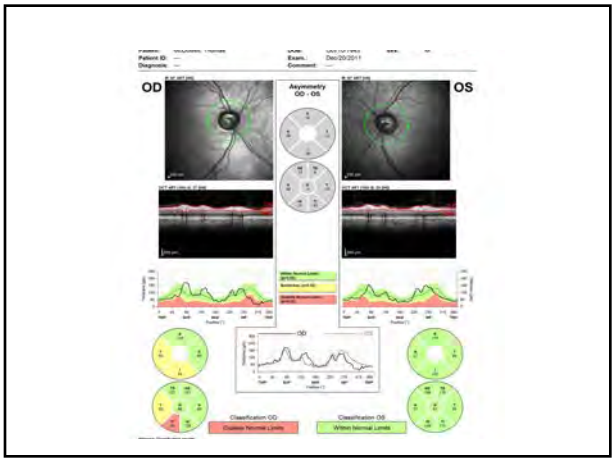

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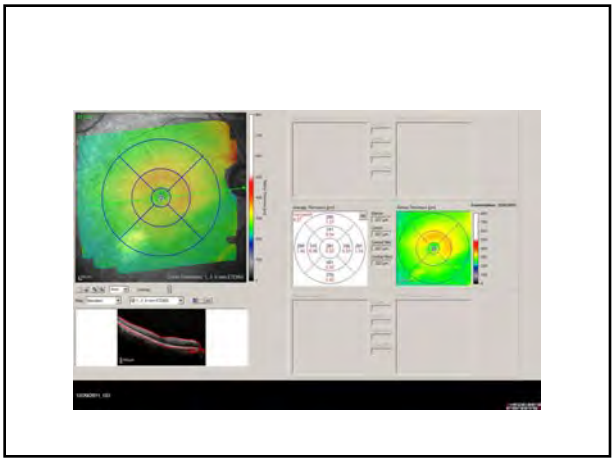

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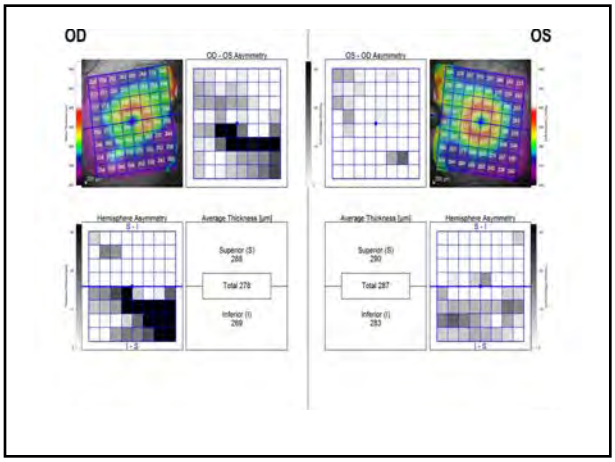

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Macular Vulnerability Zone

Glaucomatous damage of the macula

Donald C. Hood[1,2,*], Ali S. Raza[1,2], Carlos Gustavo V. de Moraes[3,4], Jeffrey M. Liebmann[3,4], and Robert Ritch[3,5]

[1]Department of Psychology, Columbia University, New York, NY 10027-7004, USA
[2]Department of Ophthalmology, Columbia University, New York, NY 10027-7059, USA
[3]Department of Neurobiology and Behavior, Columbia University, New York, NY, USA
[4]Einhorn Clinical Research Center, New York Eye and Ear Infirmary, New York, NY, USA
[5]Department of Ophthalmology, New York University, New York, NY, USA
[6]Department of Ophthalmology and Visual Science, New York Medical College, Valhalla, NY, USA

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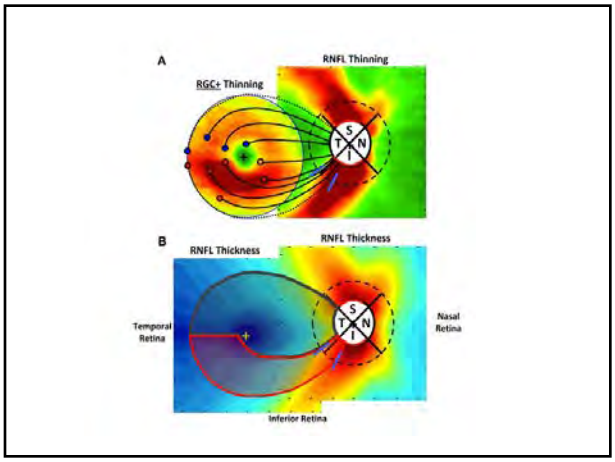

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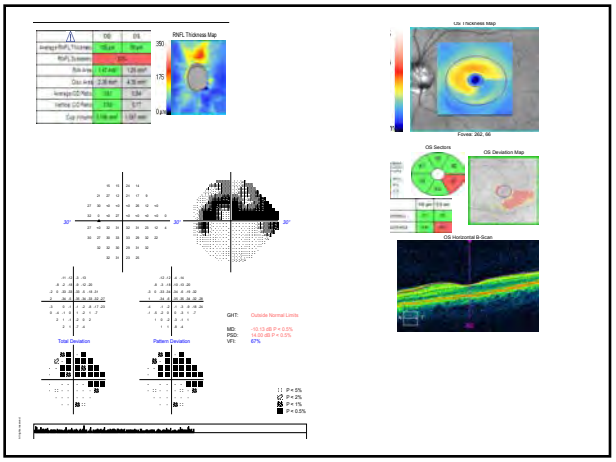

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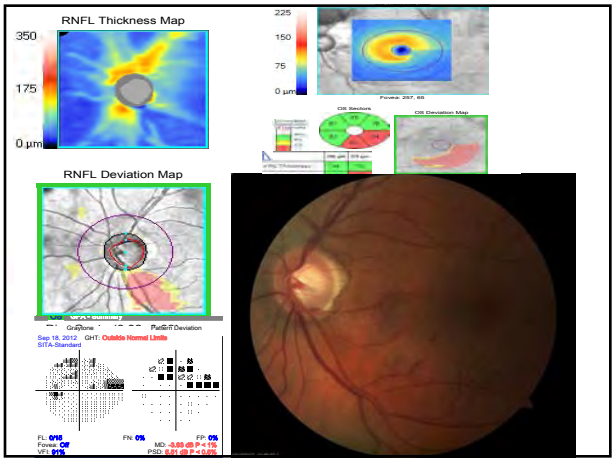

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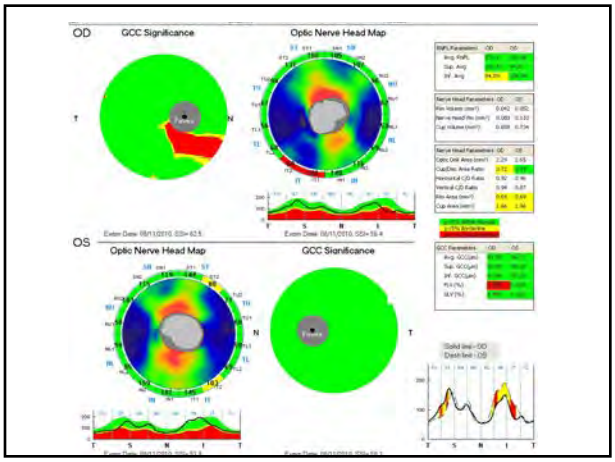
- 53 YO WM
- Father with glaucoma
- Pach 531/601 (OD lasik)
- CH 6.8 OD and 9.1 OS
- IOP 21/23 highest

80

81

82



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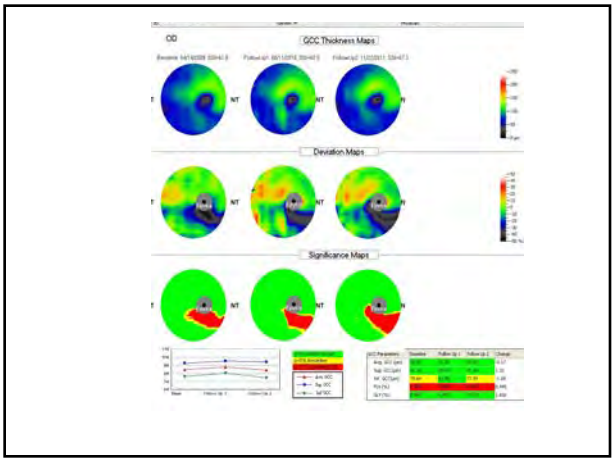

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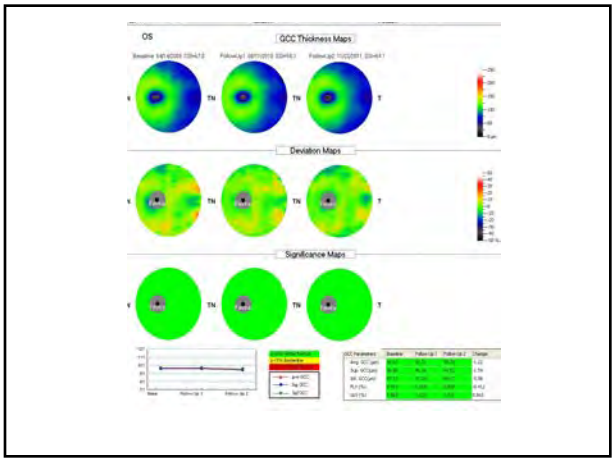

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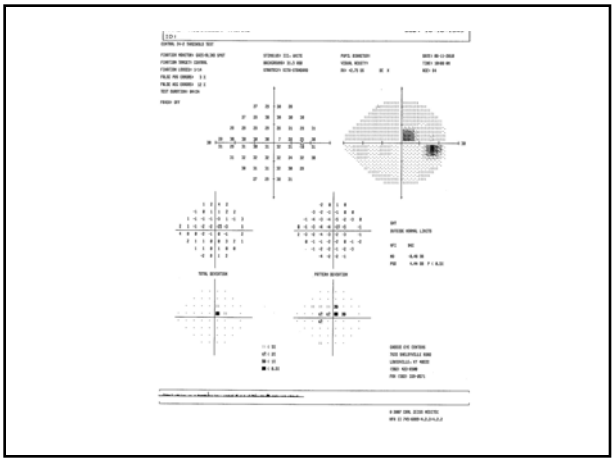

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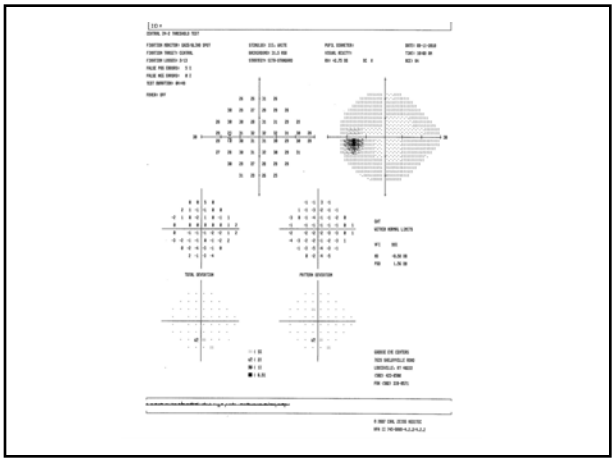

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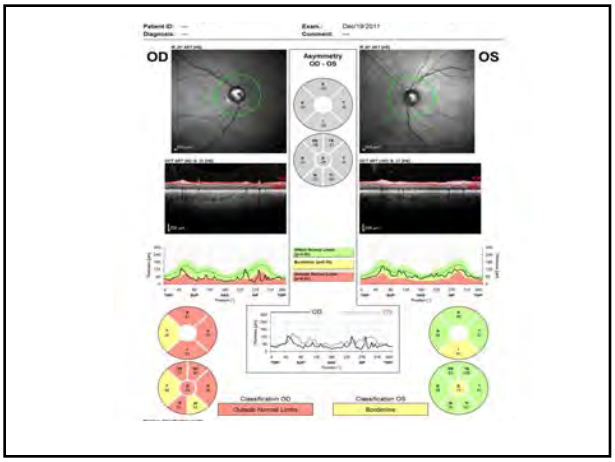

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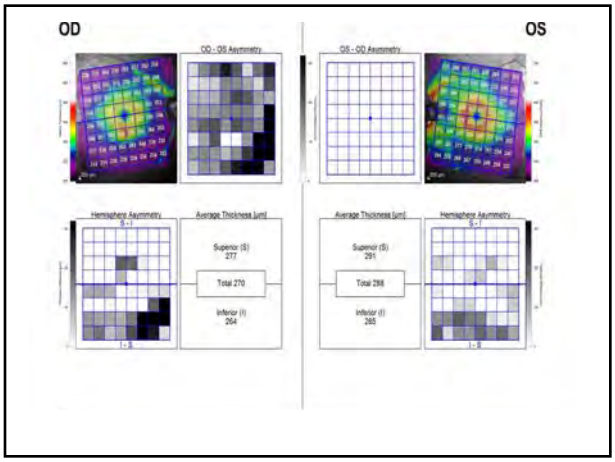

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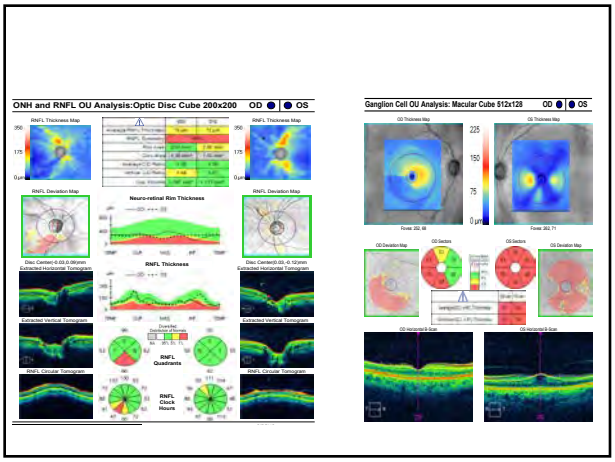

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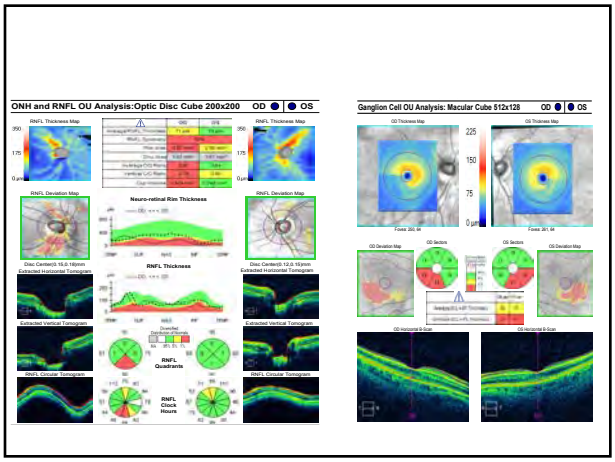

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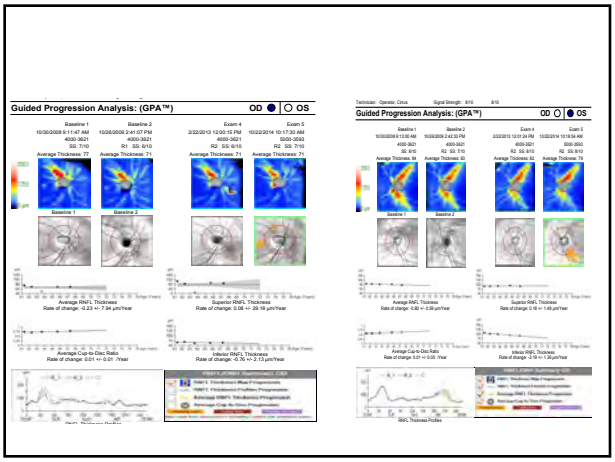

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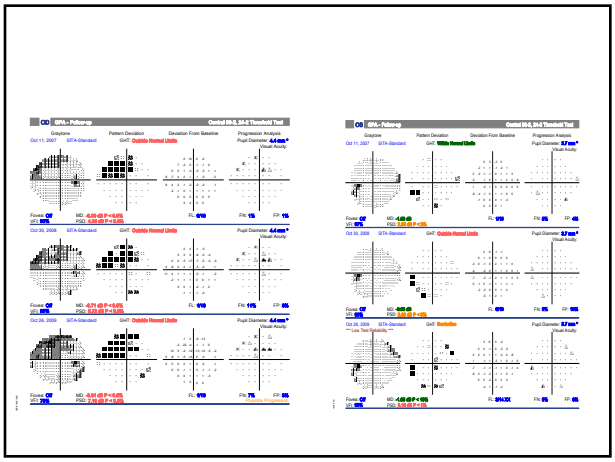

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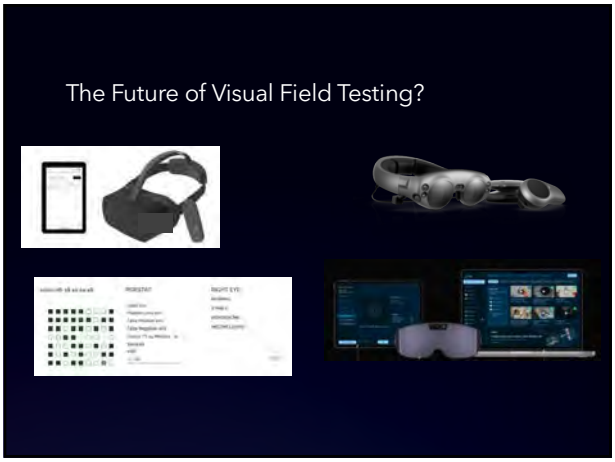
Update on Visual Field Testing

- Head Mounted Devices
- Subjective visual fields
- Binocular visual fields

94



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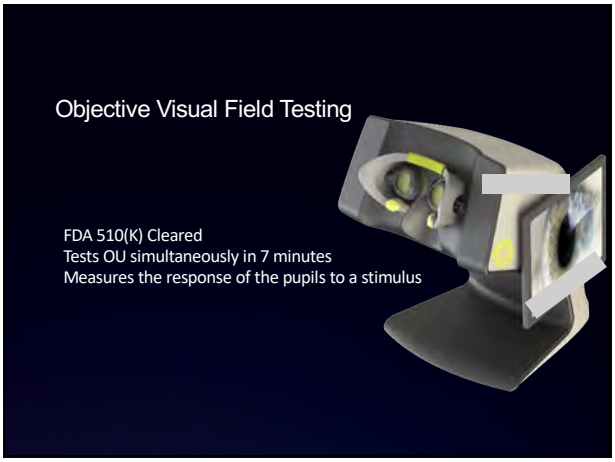

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Subjective/Binocular Visual Field Testing

39% faster than SAP in clinical testing and functions in ambient light.[1]

Equivalent to SAP with repeatability.[1]

Random binocular testing

1. Comparison between New Perimetry Device (IMOvifa®) and Humphrey Field Analyzer" M Eslani, T Nishida, S Moghimi, JM Arias, C Vasile, V Mohammadzadeh, RN Weinreb; Invest. Ophthalmol. Vis. Sci. 2022;63(7):1272 – A0412.

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Starting and Advancing Therapy

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The Monocular Drug Trial

- Measure IOP in both eyes
- Treat one eye for ~ 4 weeks or so
- Measure IOP in both eyes again (same time of day)
  - IOP change in untreated eye = spontaneous variation
  - IOP change in treated eye = spontaneous variation + therapeutic IOP effect
- Calculate the therapeutic IOP effect:

IOP change in treated eye
– IOP change in untreated eye
Therapeutic IOP effect in treated eye

99

But does the monocular trial work?

100

Monocular Trial Assumptions

- Spontaneous IOP variation is symmetric
- Diurnal curve is reproducible over time
- Medication has no crossover effect
- Both eyes respond similarly to the same medication
- Patients use their drops as prescribed

101

The Uniocular Drug Trial and Second-Eye Response to Glaucoma Medications

Tony Realini, MD,[1] Robert D. Fechtner, MD,[2] Sam-Paul Arvelos, MD,[1] Stephen Gollance, MD[2]

Purpose: To determine if the intraocular pressure (IOP)-reduction observed in a uniocular trial correlates with the IOP reduction seen in the fellow eye when the same medication is then administered to the second eye of patients with glaucoma.
Study Design: Observational case series.
Participants: Fifty-two patients with bilateral glaucoma.
Methods: Glaucoma patients underwent uniocular trials of various glaucoma medications, then subsequently received the same drug in the fellow eye. The IOP reduction observed in the first eye was compared with that observed in the second eye to determine correlation.
Main Outcome Measure: Intraocular pressure reduction in fellow-eye pairs.
Results: Intraocular pressure dropped a mean of 5.7 ± 3.8 mmHg (mean ± standard deviation) in the first eye after a uniocular trial, and 2.8 ± 3.3 mmHg in the second eye after bilateral use. Regression analysis demonstrated a poor correlation between first-eye and second-eye response to the same medication ($r^2 = 0.0174$). To minimize possible contralateral IOP effects of first-eye therapy, a subset of 26 patients treated with latanoprost (which has little if any contralateral IOP effect due to local ocular, not systemic, mechanisms) was studied, with no improvement in correlation ($r^2 = 0.0023$).
Conclusion: Uniocular trials of glaucoma medications do not adequately predict second-eye IOP responses to the same medications. If both eyes of a glaucoma patient require IOP reduction, one should not assume that [illegible] glaucoma will be equal in both eyes. The effect of a given medicine must be assessed [illegible] identify for each eye. *Ophthalmology* 2006;113:601–604 © 2006 by the American Academy of Ophthalmology.

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A Prospective, Randomized, Investigator-masked Evaluation of the Monocular Trial in Ocular Hypertension or Open-angle Glaucoma

Tony D. Realini, MD

Purpose: To evaluate the clinical value of the monocular therapeutic drug trial in predicting long-term intraocular pressure (IOP) reduction.

Design: Prospective, randomized, investigator-masked trial.

Participants: Twenty-six subjects with ocular hypertension or open-angle glaucoma.

Methods: Subjects attended 3 study visits; 2 on no IOP-lowering therapy, 1 on monocular therapy with latanoprost, and 2 on bilateral therapy. The monocular trial eye was randomly selected, and study personnel making IOP measurements were masked to randomization. The following parameters were calculated: the unadjusted IOP change (IOP in the randomized eye at the first on-treatment visit minus IOP in the same eye at the initiation of the monocular trial), the adjusted IOP change (the unadjusted IOP change minus the comparable IOP change in the untreated fellow eye between the same 2 visits), and the long-term IOP change (the difference of the mean of the 2 on-treatment IOP values during bilateral use and the mean of the 2 pretreatment IOP values).

Main Outcome Measure: The relationship between short- and long-term IOP reduction, with the coefficient of determination (the square of the Pearson correlation coefficient, r) as the measure of association.

Results: The mean long-term IOP reduction after latanoprost therapy was −3.4±2.4 mmHg in first-treated eyes ($P<0.0001$) and −3.4±2.4 mmHg in second-treated eyes ($P<0.0001$). The mean unadjusted IOP reduction in the monocular trial eye was −3.1±3.4 mmHg; the correlation between the unadjusted IOP change and the long-term IOP change was weak to moderate (coefficient of determination 0.325). The mean adjusted IOP reduction was −2.8±4.0 mmHg; the correlation between the adjusted IOP change and the long-term IOP change was moderate to strong (coefficient of determination 0.276).

Conclusions: The practice of adjusting the IOP change in the treated eye by the IOP change in the untreated eye—the monocular drug trial—is no more informative than using the treated eye's unadjusted IOP change, and both of these methods are poor predictors of long-term IOP reduction with latanoprost.

Financial Disclosure(s): Proprietary or commercial disclosure may be found after the references.

Ophthalmology 2009;116:1242–1247 © 2009 by the American Academy of Ophthalmology

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ARTICLE IN PRESS

The Utility of the Monocular Trial

Data from the Ocular Hypertension Treatment Study

Anne M. Bhorade, MD,[1] Keith J. Wilson, MA,[1] Paul Palmberg, MD, PhD,[1] Robert N. Weinreb, MD,[1] Dale Miller, MD,[1] Robert T. Chang, MD,[1] Michael A. Kass, MD,[1] for the Ocular Hypertension Treatment Study Group

Objective: To determine whether adjusting the intraocular pressure (IOP) change of the trial eye for the IOP change of the fellow eye (i.e., monocular trial) is a better assessment of medication response than testing each eye independently.

Design: Analysis of data from a prospective, randomized, clinical trial.

Participants: Two hundred six participants with ocular hypertension randomized to the observation group and then started on a topical prostaglandin analog (PGA).

Methods: Participants were started on a topical PGA in 1 eye and retested in approximately 1 month to determine medication response. The IOP response of the trial eye was determined by the IOP change between baseline and 1 month in the trial eye alone (unadjusted method) and by adjusting for the IOP change in the fellow eye between the same visits (adjusted method). Our "gold standard" for medication response was the IOP change in the trial eye between up to 3 pre- and 3 posttreatment visits on the same medication. Pearson correlation was used to compare the gold standard with the unadjusted and adjusted methods. In addition, symmetry of IOP responses between trial and fellow eyes for the same medication was determined by correlating the trial eye IOP changes between up to 3 pre- and 3 posttreatment visits to the fellow eye IOP change between the same visits.

Main Outcome Measures: Correlations of IOP change of the trial eye using the gold standard to the IOP change of the trial eye using the unadjusted and adjusted methods.

Results: The correlations of IOP change using the gold standard to the IOP change using the unadjusted and adjusted methods were 0.63 and 0.47, respectively. The correlation of IOP change between the pre- and posttreatment visits was $r = 0.81$.

Conclusions: The monocular trial (i.e., adjusted method) appears equivalent to testing each eye (bilaterally) (i.e., unadjusted method); however, neither method is adequate to determine medication response to topical PGAs. Both eyes have a similar IOP response to the same PGA. Further studies to understand IOP response are necessary to improve current methods of assessing medication response.

Financial Disclosure(s): Proprietary or commercial disclosure may be found after the [illegible]

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AAO PPP for POAG

- 2003: When starting a new topical agent, it is often useful to begin by treating only one eye and comparing the relative change of the IOP in the two eyes at follow-up visits.
- 2010: It may be useful to begin by treating only one eye and comparing the relative change of the IOP in the two eyes at follow-up visits. However, because the two eyes of an individual may not respond equally to the same medication, and because of the possibility of asymmetric spontaneous fluctuations and the potential for contralateral effect of monocular topical medications, it is acceptable to compare the effect in one eye relative to multiple baseline measurements.
- 2015: Though monocular trials have been recommended in the past to determine whether a topical ocular hypotensive agent is effective, recent studies have shown that such trials are not good predictors of long-term efficacy. A better way to assess IOP-lowering response is to compare the effect in one eye with multiple baseline measurements in the same eye, but the number of necessary baseline measurements will vary among patients.

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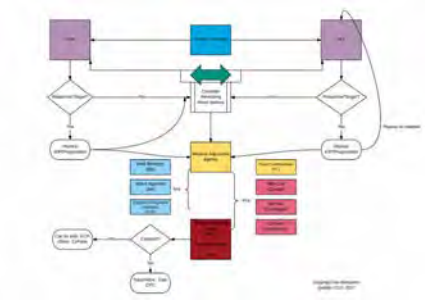

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Are Topical Beta Blockers Safe to Use?

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Beta Blockers

- More prevalent than it's use as a single agent
  - Combigan
  - Cosopt
- Other practical considerations:
  - Are they on an oral beta blocker?
  - What is the patient's pulse
    - Avoid BP lowering effect in susceptible populations
  - What is happening at night?
  - Could we just be reducing blood flow with B Blockers?

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OHTS and Safety Issues

- No differences in SF-36 or participant self-reported ocular or systemic symptoms except for those associated with prostaglandin analogues
- Slight excess in cataract surgery in medication group (5.1%) compared to observation group (2.5%), p=.17

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Acta Ophthalmol. 2018 Nov;96(7):705-711. doi: 10.1111/aos.13663. Epub 2018 Feb 1.

Pulmonary safety of ophthalmic beta-blockers: a nationwide registry-based cohort study

Mathias L Kristensen [1], Jan H Simonsen [2], Christian Torp-Pedersen [3 4], Henrik Vorum [2 5], Kristian Aasbjerg [2 4]

Affiliations + expand

PMID: 29389089 DOI: 10.1111/aos.13663

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Results: The cohort consisted of 97 463 individuals. Odds ratios for drug switch in individuals without concomitant obstructive pulmonary disease (n = 86 568) were as follows: 1.47 for beta-blockers (95% confidence interval (CI): 1.35-1.61; p < 0.001), 2.68 for parasympathomimetics (95% CI: 2.32-3.10; p < 0.001) and 4.80 for alfa-2-agonists (95% CI: 4.17-5.53; p < 0.001). Odds ratios in individuals with concomitant obstructive pulmonary disease (n = 10 895) were as follows: 2.61 for parasympathomimetics (95% CI: 1.83-3.72; p < 0.001), 2.96 for beta-blockers (95% CI: 2.31-3.78; p < 0.001) and 3.54 for alfa-2-agonists (95% CI: 2.56-4.88; p < 0.001). There was no significant association between treatment class and new onset of obstructive pulmonary disease (p = 0.30).

Conclusion: Ophthalmic beta-blockers were associated with an increased risk of drug switch. However, the absolute risk was very small. No increased risk of new onset of obstructive pulmonary disease was found. Our data suggest that more patients might be eligible for ophthalmic beta-blockers.

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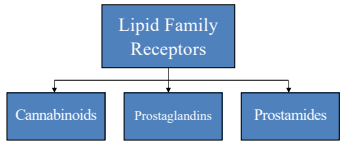
Lipid Family Receptors



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Prostaglandin analogues- Branded

- Xalatan (latanoprost 0.005%) – Prostaglandin Analogue
- Travatan-Z (travaprost 0.004%) – Prostaglandin Analogue
- Lumigan (bimatoprost 0.03%) – Prostamide (ocular hypotensive lipid)
- Zioptan PF (tafluprost 0.015%)- Prostaglandin
- IYUZEH Non preserved, Thea Latanoprost 0.0055

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Latanoprost

- Acts as a selective F2α agonist (FP receptor agonist)
- FP receptors have been identified in ciliary muscle, ciliary epithelium and sclera
- Enhances outflow through the uveoscleral pathway by
  - upregulating matrix metalloproteinase expression
  - remodeling of the ciliary muscle's extracellular matrix resulting in Increased extracellular remodeling, increased permeability, decreased outflow resistance

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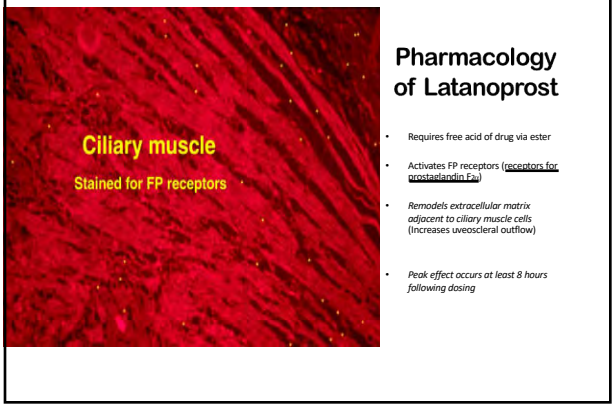

Pharmacology of Latanoprost

- Requires free acid of drug via ester
- Activates FP receptors (receptors for prostaglandin $F_{2\alpha}$)
- *Remodels extracellular matrix adjacent to ciliary muscle cells* (Increases uveoscleral outflow)
- *Peak effect occurs at least 8 hours following dosing*

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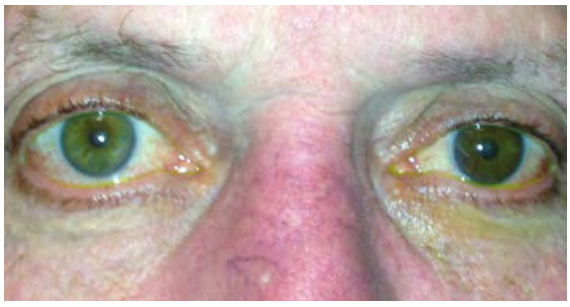

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What's new in glaucoma pharma?

latanoprost 0.005% PF

1 **Clinical Trials**
Discussion on clinical data from two Phase 3 clinical trials: Phase 3 US trial and Phase 3 European trial.

2 **Efficacy Comparison**
Is efficacy as good with preservative free vs BAK preserved?

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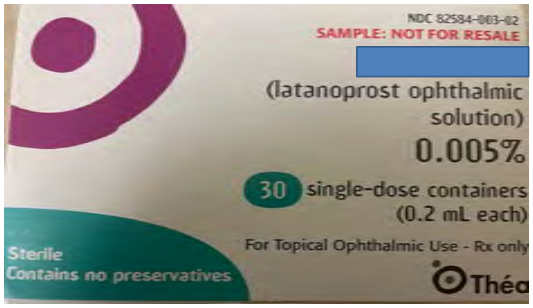

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Preservative-Free Formulations

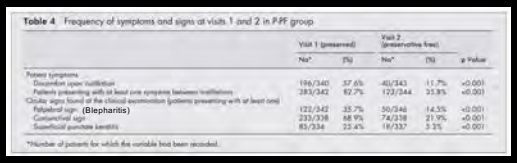

Table 4 Frequency of symptoms and signs at visits 1 and 2 in PF group

	Visit 1 (preserved)		Visit 2 (preservative free)		
	No*	(%)	No*	(%)	p Value
Patient symptoms					
Discomfort upon instillation	196/340	57.6%	40/343	11.7%	<0.001
Patients presenting with at least one symptom between instillations	283/342	82.7%	123/344	35.8%	<0.001
Clinic signs found at the clinical examination (patients presenting with at least one)					
Palpebral sign (Blepharitis)	122/342	35.7%	50/346	14.5%	<0.001
Conjunctival sign	233/338	68.9%	74/338	21.9%	<0.001
Superficial punctate keratitis	85/334	25.4%	19/337	5.3%	<0.001

*Number of patients for which the variable has been recorded.

Pisella, P. J., P. Pouliquen, and C. Baudouin. Prevalence of ocular symptoms and signs with preserved and preservative free glaucoma medication

122

PF-Latanoprost

	Phase 3 (US) Trial (n=325)		Phase 3 (Europe) Trial (n=353)	
	PF-Latanoprost	Xalatan	PF-Latanoprost	Xalatan
Mean baseline IOP ± SD(mmHg)	18.8 ± 2.9	19.2 ± 3.1	24.1 ± 1.8	24.0 ± 1.7
Mean IOP reduction from baseline (mmHg) (range)	2.7 (2.2 - 3.0)	3.4 (2.9 - 3.8)	8.6 (8.3 - 8.8)	8.9 (8.8 - 9.0)

123

Latanoprostene Bunod 0.024%(LBN)

- First nitric oxide donating compound investigated for topical ophthalmic use
- Novel nitric oxide donating prostaglandin F2α receptor agonist
- Received FDA approval in 2017
- The data has demonstrated significant IOP lowering and a favorable safety profile
- Dual mechanism of action

Hoy SM. Latanoprostene Bunod Ophthalmic Solution 0.024%: A Review in Open-Angle Glaucoma and Ocular Hypertension [published correction appears in Drugs. 2018;78(8):857]. *Drugs*. 2018;78(7):773-780. Fingeret M, Goddé IR, Bloomenstein M. Latanoprostene bunod ophthalmic solution 0.024%: a new treatment option for open-angle glaucoma and ocular hypertension. *Clin Exp Optom*. 2019;102(6):543-550.

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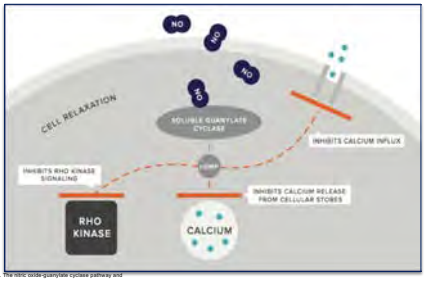
125

-Gas that can freely diffuse across plasma membranes

-Signals via second messenger cGMP with inhibition of 3 key contractile signals (calcium influx, intracellular calcium stores and Rhokinase activity)

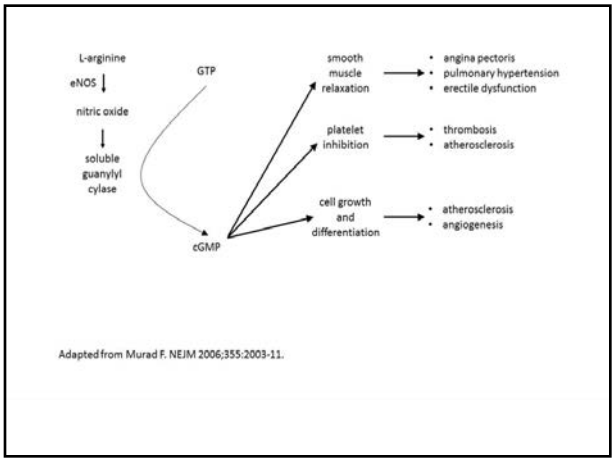
-Relaxes vascular smooth muscle cells → Vasodilation

Exerts relaxing effect on highly contractile TM cells causing cytoskeleton relaxation and enhanced outflow via TM/Schlemm canal



Wareham LK, Buys ES, Sappington RM. The nitric oxide-guanylate cyclase pathway and glaucoma. *Nitric Oxide*. 2018;77:75-87

126



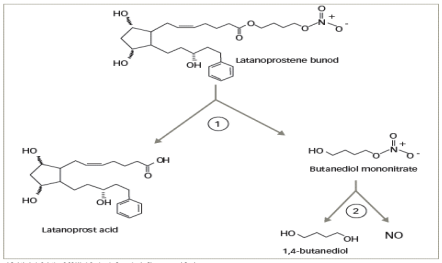
Adapted from Murad F. NEJM 2006;355:2003-11.

127

LBN is hydrolyzed by endogenous corneal esterases to

Latanoprost acid: the active compound of latanoprost

Butanediol mononitrate: a NO donating moiety



Hoy SM. Latanoprostene Bunod Ophthalmic Solution 0.024%: A Review in Open-Angle Glaucoma and Ocular Hypertension [published correction appears in Drugs. 2018;78(8):857]. Drugs. 2018;78(7):773-780. Fingeret M, Gaddie IB, Bloomenstein M. Latanoprostene bunod ophthalmic solution 0.024%: a new treatment option for open-angle glaucoma and ocular hypertension. Clin Exp Optom. 2019;102(6):541-550.

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Voyager Phase 2b dose ranging study vs. Branded Xalatan

VOYAGER study design: Phase 2, randomized, investigator-masked, parallel-group, dose-ranging study vs Xalatan in patients with open-angle glaucoma or ocular hypertension (N=413) to determine the optimal drug concentration of latanoprostene bunod in reducing IOP.[3]

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Rho Kinase Inhibitors

Netarsudil ophthalmic solution 0.02%

- Rho kinase drug discovery program initiated in 2006
- Goal to identify an effective and well-tolerated ROCK inhibitor with a durable IOP lowering effect.
- Most effective compounds were ROCK/NET inhibitors (norepinephrine transporter)
- In addition to trabecular outflow, animal and donor eye studies showed a decrease in aqueous humor production and episcleral venous pressure
- The decrease in EVP is felt to be related to NET inhibition.

Moshirfar M, Hsiehl L, Ibrahim OC, et al. Use of rho kinase inhibitors in ophthalmology: A review of the literature. Med Hypothesis Discov Innov Ophthalmol. 2018;7(3):107-111.

130

Disease at the TM is Responsible for Elevated IOP in Glaucoma[1,2]

Scanning electron microscopy (2000x) was used to examine human TM under physiological conditions and in patients with POAG.2
POAG, primary open-angle glaucoma; TM, trabecular meshwork.
1. Tian et al. *Invest Ophthalmol Vis Sci*. 2009;50:1442.
2. Sacca et al. *J Cell Physiol*. 2015;230:516.

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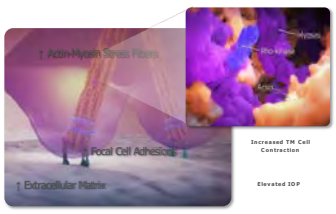
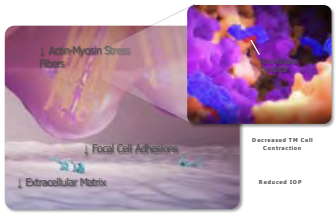
131

Rho-kinase Increases TM Contraction and Elevates IOP



132

Rho-kinase Inhibitors Relax TM Cells and Reduce Fibrosis[1,2]



1. Rao et al. *Exp Eye Res.* 2017;158:23.

133

Omidenepag Isopropyl Ophthalmic

- Various selective E-prostanoid subtype 2 (EP2) agonists such as taprenepag isopropyl, aganepag isopropyl, and omidenepag isopropyl (OMDI) are currently under investigation as topical intraocular pressure (IOP) lowering medications in the management of glaucoma and ocular hypertension.
- The OMDI ophthalmic solution 0.002% (Eybelis, Santen Pharmaceutical Co., Ltd., Osaka, Japan) works by increasing aqueous humor drainage through the trabecular and uveoscleral outflow pathways. [1] OMDI was first introduced in Japan in November 2018, with approval and release following in five countries and regions by February 2021.
- Unlike prostaglandin analogs working on F-prostanoid (FP) receptor, OMDI has not been associated with periorbitopathy with comparable IOP-lowering effects to prostaglandin analogs. [2]

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ORIGINAL STUDY

OPEN

Omidenepag Isopropyl in Latanoprost Low/Nonresponders With Primary Open Angle Glaucoma or Ocular Hypertension: A Phase 3, Nonrandomized, Two-Phase, Open-Label Study

Joseph F. Panarelli, MD, Eileen C. Bowden, MD,† Michael E. Tepedino, MD,† Noriko Odani-Kawabata, PhD,§ Zifan Pei, PhD,‖ Eugene B. McLaurin, MD,¶ and Auli Ropo, MD#*

135

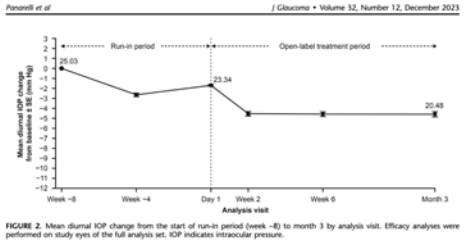

FIGURE 2. Mean diurnal IOP change from the start of run-in period (week −8) to month 3 by analysis visit. Efficacy analyses were performed on study eyes of the full analysis set. IOP indicates intraocular pressure.

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Identifying and managing allergies and sensitivities to glaucoma medicaitons

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Alpha Agonists (Alpha-2 selective)

- This sensitivity has been called many things
  - Allergy
  - Follicular Conjunctivitis
  - Atopic reaction
- ~20 % rate of reaction with .2%
  - When on branded .1% it is suspected to be less than 5% rate
  - When combined in branded combigan drops to about 10% but still 1 in 10 will get the allergy, usually 6-12 mos after starting

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Brimonidine Allergy

139

Latanoprostene Bunod 0.024%(LBN)

- First nitric oxide donating compound investigated for topical ophthalmic use
- Novel nitric oxide donating prostaglandin F2α receptor agonist
- Received FDA approval in 2017
- The data has demonstrated significant IOP lowering and a favorable safety profile
- Dual mechanism of action

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Most Common Ocular Adverse Reactions in APOLLO and LUNAR*[1,2]

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

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

Less than 1% discontinuation due to ocular adverse reactions[1]

- Approximately 0.6% of patients discontinued therapy due to ocular adverse reactions
- These included ocular hyperemia, conjunctival irritation, eye irritation, eye pain, conjunctival edema, vision blurred, punctate keratitis, and foreign body sensation

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Preferred Term (with Incidence ≥5% (Pooled Safety Population)	Netarsudil 0.02% QD (N=839) n (%)	Timolol 0.5% BID (N=839) n (%)
Eye Disorders		
Conjunctival Hyperemia	456 (54.4)	87 (10.4)
Cornea Verticillata (corneal deposits/corneal opacity)	175 (20.9)	2 (0.2)
Conjunctival Hemorrhage	144 (17.2)	15 (1.8)
Vision Blurred	62 (7.4)	12 (1.4)
Lacrimation Increased	60 (7.2)	5 (0.6)
Erythema of Eyelid	57 (6.8)	6 (0.7)
Visual Acuity Reduced	44 (5.2)	13 (1.5)

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- Cornea verticillata (lipid micro-deposits in the corneal epithelial layer)
- Rocklatan (netarsudil .02% + latanoprost .005% FDC)™: ~5%
- Rhopressa (netarsudil .02%)™: ~4%
  - ~5-9% reported in Rocket 1 and Rocket 2
- Asymptomatic
- Only visible via biomicroscopy evaluation
- Benign corneal deposits (phospholipidosis) are a familiar outcome with other drugs such as amiodarone

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- Cornea verticillata observed (20.9%)
  - Resolved in 95.6% of patients after treatment ended (OBS01); 2 patients still being followed
  - Not associated with changes in visual function
- Cornea verticillata well-studied in patients on amiodarone therapy[1,2]
  - Approved 1984 USA, observed for decades
  - Present in >98% of patients taking standard oral dosages of amiodarone
  - Rarely interferes with vision

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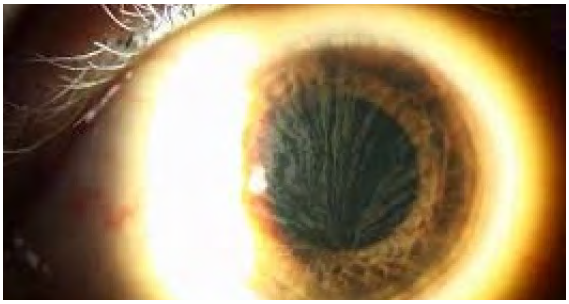

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Table 2. Safety summary

	Netarsudil/ Latanoprost FDC (n=238)	Netarsudil 0.02% (n=243)	Latanoprost 0.005% (n=237)
Eye disorders, n (%)			
Conjunctival hyperemia	150 (63.0)	125 (51.4)	52 (21.9)
Conjunctival hemorrhage	31 (13.0)	44 (18.1)	3 (1.3)
Cornea verticillata	42 (17.6)	33 (13.6)	0 (0)
Eye pruritus	27 (11.3)	22 (9.1)	3 (1.3)
Punctate keratitis	12 (5.0)	18 (7.4)	10 (4.2)
Lacrimation increased	17 (7.1)	20 (8.2)	1 (0.4)
Visual acuity reduced	13 (5.5)	13 (5.3)	6 (2.5)
Vision blurred	11 (4.6)	15 (6.2)	3 (1.3)
Blepharitis	14 (5.9)	8 (3.3)	5 (2.1)
Administration site conditions, n (%)			
Instillation site pain	55 (23.1)	60 (24.7)	18 (7.6)

Adverse events occurring in ≥5% of patients in any treatment arm are presented.
Patients with known contraindications or hypersensitivity to latanoprost were ineligible for participation in the study.
FDC, fixed-dose combination.

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Netarsudil Side Effects: Conjunctival Hemorrhage

- Conjunctival hemorrhage (17.2%)
  - Small
  - Transient
  - Visualized by examiner with slit lamp magnification
- Do not appear to be associated with or cause ocular pathology

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Rho Kinase
"Brimonidine effect"

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SLT and the LIGHT Study

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Introduction

- SLT reduces IOP by increasing trabecular outflow with a single, painless outpatient procedure with good safety profile and limited recovery time
- Approved by the FDA in 2001
- IOP lowering effect comparable to medication without medication associated side effects
- While not permanent, it is repeatable
- Still not routinely offered as first line treatment

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Selective Laser Trabeculoplasty versus eye drops for first-line treatment of ocular hypertension and glaucoma

- United Kingdom study set in 6 hospitals
  - Recruited patients from 2012-2014
  - Observer masked
  - Randomized
  - Treatment naïve patients/newly diagnosed OAG
    - No previous IOP lowering drops, laser or surgery

153

LIGHT Study Design

- 718 patients entered the study (1235 eyes)
- Patients randomized on a 1:1 basis to either:
  - SLT (356 patients, 613 eyes)
  - Drops (362 patients, 622 eyes)

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Topical Medication Algorithm

- Drug classes for 1st, 2nd, and 3d line treatment were determined by the NICE guidelines[5]
- First line-PGA's
- Second line- Beta Blockers
- Third line- TCAI or Alpha Agonist
- Fixed combinations were allowed
- MMT=Clinician judged max most intensive combination of medicines that could be tolerated

155

Results

- Overall 509 (95%) of 536 SLT treated eyes were at target IOP @ 3 years
- Target IOP achieved without medication in 419 (78.2%) of 536 eyes treated in SLT arm
  - 321 eyes (76.6%) required only one SLT session

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Results

- 499 (93.1%) of the 526 eyes treated medically were at target IOP @ 3 years
  - 346 (64.6%) were using a single medication
- At 3 years:
  - 93.0% of visits were at target IOP for SLT group
  - 91.3% of visits were at target IOP for med group

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Treatment Escalations and Progression of Disease During Study

- More treatment escalations occurred in the SLT group (348 eyes) than the Medication group (299 eyes)
- Progression
  - 36 eyes in the Medication group showed algorithm-confirmed progression
    - 3 eyes converted from OHT to OAG
    - 33 eyes with OAG progressed
  - 23 eyes in the SLT group
    - 2 eyes converted from OHT to OAG
    - 21 eyes with OAG progressed
- 11 eyes (1.8%) in the Medication group required incisional glaucoma surgery
  - NO EYES IN SLT GROUP REQUIRED INCISIONAL SURGERY

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Adverse Events

- SLT Group
  - 6 eyes had an IOP rise of 5mm Hg or more on day of treatment
    - Only 1 eye required treatment
  - 122 eyes (34.4%) had transient discomfort, blurred vision or photophobia not requiring treatment
- Medication Group
  - 150 eyes had aesthetic side effects or allergic reactions

159

Cost of Therapy

- Eye drops were approximately double the cost effect of SLT
- Difficult to extrapolate to US market but general financial math should apply
- Eventual ophthalmic surgery (trab, tube, cataract etc) over the 3 years was significantly less in the SLT group compared to the Medication group

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Cost and Cost Effectiveness

- SLT as first line resulted in a significant cost savings relative to surgery and medication
  - Approximately 451 dollars/pounds savings in provider related visit costs per patient
  - For every patient given SLT in lieu of drops, the cost savings are greater than the cost of SLT for **2 additional patients!**
  - This is also equal to the cost of five additional office visits

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Clinical effectiveness of SLT vs. Drops

- IOP Control
  - SLT first approach provided better IOP control over 3 years with more visits at target IOP compared to drops
    - Less intense drop treatment than Medication group
    - NO glaucoma surgeries required compared to Medication group
  - Could be due to adherence with SLT vs. Drops

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Clinical effectiveness of SLT vs. Drops

- IOP Control
  - SLT provides better diurnal IOP stability[6]
    - Could be due to continuous effect on TM versus episodic administration of medication
  - Primary SLT afforded drop free control of IOP for 3 years in 74.2% of patients
    - This is much higher than in previous studies with less stringent success criteria
    - Prior treatment and more severe disease likely reduce the effect of SLT in those patients[7]
    - Likely the reason for such a robust response in treatment naïve patients in this study

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Safety of SLT vs. Drops

- This study showed a greater safety profile of SLT than previously reported
  - No systemic side effects reported
  - Only 1 eye had an IOP spike
    - Compared to previously reported rates of 28.8%[8]
    - 2-week IOP checks did not change management for any patient and appears to be unnecessary
      - Avoidance of this could save more $ to the system
  - Lower rate of cataract surgery in SLT arm which supports the existing evidence of drops increasing incidence of cataract and surgery[9]

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Conclusions

- Selective laser trabeculoplasty provides superior IOP stability to drops, at a lower cost AND
  - 74% or ¾ of patients are successfully controlled without drops for at least 3 years after a single treatment

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Conclusions

- Selective laser trabeculoplasty as an initial treatment for glaucoma is associated with the following:
  - Lower cost
  - Good clinical outcomes
    - 2-week follow up not necessary
  - Lower symptom scores
  - Drop-freedom for most patients
- SLT should be offered as an alternative to IOP lowering drops as initial therapy on a more widespread basis

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Automated Direct SLT (VOYAGER)

Advantages of SLT vs medications

LiGHT Trial 3 year and 6-year results

Automated Direct SLT vs traditional SLT

Speed and accuracy

167

LiGHT trial: 6-year results of primary selective laser trabeculoplasty versus eye drops for the treatment of glaucoma and ocular hypertension

Gus Gazzard, Evgenia Konstantakopoulou, David Garway-Heath, Mariam Adeleke, Victoria Vickerstaff, Gareth Ambler, Rachael Hunter, Catey Bunce, Neil Nathwani, Keith Barton, on behalf of the LiGHT Trial Study Group

Primary Outcome - Quality of Life at 6 years
Secondary Outcome – clinical effectiveness and safety

Conclusions:
No significant difference in QOL
26.8% VS 19.6% progressed drops vs SLT
Trab required in 32 eyes in drops arm compared to 13 eyes in the SLT arm
69.8% of SLT Drop Free @ 6 Years

168

Low-Energy SLT Repeated Annually: Rationale for the COAST Trial

Tony Realini, MD, MPH, Gus Gazzard, MD, Mark Latina, MD, Michael Kass, MD

Newly diagnosed POAG treated with:
1. ALT 360 x 1
2. Standard SLT 360 as needed
3. Low-energy SLT 360 repeated annually

10-year Results
Medication Free Rates
1. ALT – 22.6%
2. Standard SLT -25.0%
3. Low-energy SLT – 58.3%

10-year Results
Median Times to Treatment
1. ALT – 2.8 years
2. Standard SLT -3.2 years
3. Low-energy SLT – 6.2 years

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Automated Direct SLT (VOYAGER)

Automated Direct Selective Laser Trabeculoplasty: First Prospective Clinical Trial

Mordechai Goldenfeld[1], Michael Belkin[2], Masha Dobkin-Bekman[3], Zachary Sacks[3], Sharon Blum Meirovitch[1], Noa Geffen[4,5], Ari Leshno[1,4], and Alon Skaat[1,4]

Purpose: Direct selective laser trabeculoplasty (DSLT) is a rapid, noncontact automated procedure performed directly through the limbus without gonioscopy. In this first nonrandomized clinical trial we assessed its safety and ability to reduce intraocular pressure (IOP).

Methods: Fifteen patients (15 eyes: 10 with open-angle glaucoma [OAG], 4 with ocular hypertension, and 1 with pseudoexfoliation glaucoma), naive or after medication washout, with an IOP ≥22 mm Hg, underwent DSLT by irradiation with 100 or 120 sequential noncontact 532-nm, Q-switched laser shots (0.8–1.4 mJ) automatically applied during 1.5 or 2.3 seconds on the limbus, guided by image analysis and eye tracking. Results were assessed at 1 and 3 hours, 1 day, 1 week, and 1, 3, and 6 months.

Results: The mean ± standard deviation baseline IOP (mm Hg) in all eyes was 26.7 ± 2.3. At 1, 3, and 6 months, this value was significantly reduced to 21.7 ± 4.2 (by 18.1%), to 20.8 ± 2.5 (by 21.4%), and to 21.5 ± 4.1 (by 18.8%), respectively. In six patients treated with 1.4 mJ/shot, the mean IOP at 6 months decreased from 26.7 ± 3.2 to 19.3 ± 2.0 (27.1%, $P = 0.03$). There was a significant reduction in hypotensive medications from 1.6 ± 1.0 to 0.4 ± 0.7, $P = 0.03$). No serious adverse events occurred.

Conclusions: Automated DSLT appears to be an effective and safe noncontact, rapid modality for reducing IOP in patients with OAG. Higher energy usage led to better results.

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iStent Infinite: Efficacy and Safety

Treated Subjects: Mean Baseline Characteristics
- Mean of 3.1 hypotensive medications at baseline
- History of 2 failed prior glaucoma surgeries

Significant IOP Lowering w/ Standalone Treatment
- **76%** of subjects achieved **20% or greater reduction in mean diurnal IOP** from baseline on same or lower ocular hypotensive medication burden
- **≥50%** subjects achieved **30% or greater reduction in mean diurnal IOP** from baseline
- In addition: **13%** mean **reduction in medication burden** from baseline

Favorable Safety Outcomes
- No explants, infections, device-related interventions or hypotony

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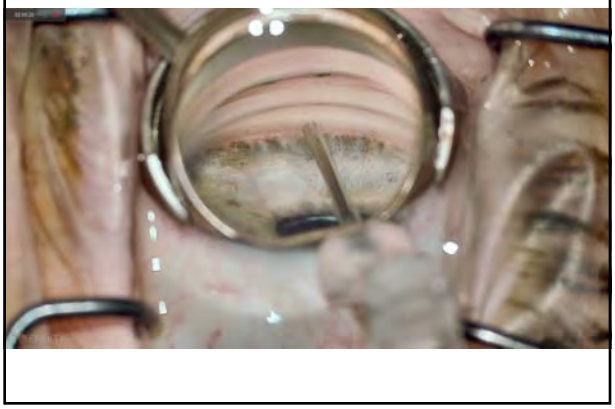

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Travoprost intraocular implant (iDose)

Indication	Comparison	Clinical Trials
The reduction of intraocular pressure in patients with POAG or OHT	Compare and contrast versus other glaucoma drug delivery device on the market – bimatoprost SR (Durysta).	Review the data from the two Phase 3 pivotal trials (GC-010 and GC-012)

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Travoprost intraocular implant

36 Month Update
1. 70% and 68% of subjects in fast and slow-release were well-controlled on fewer or same medications as baseline.
2. Average IOP reductions were 8.3 mmHg and 8.5mmHg in the fast and slow-release arms.

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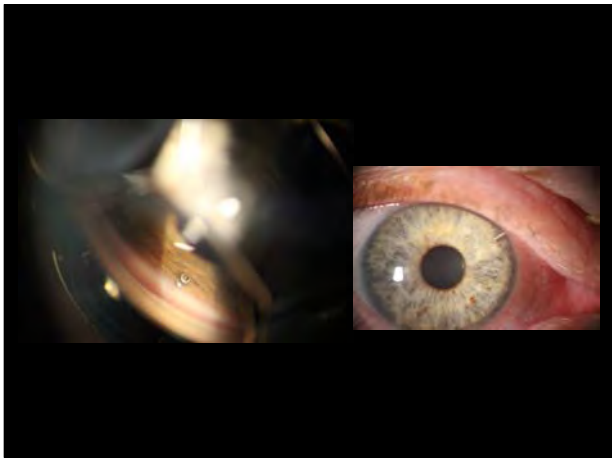

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Bimatoprost SR

(10-microgram bimatoprost sustained-release implant)

- Biodegradable bimatoprost sustained-release implant
- FDA-approved and indicated to reduce IOP in patients with open angle glaucoma or OHT
- Single intracameral administration
- Phase I/II/III Studies

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Innovations for NTG

- Nonsurgical, non-pharma way to lower IOP
- Lowers IOP in every eye, every time
- Lowers IOP safely
- Can be used in combination with existing therapies
- Titrates IOP to target pressure level
- Lowers IOP during the vulnerable period at Night
- Ability to monitor usage, encourage compliance, and obtain data

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THE SOLUTION IS BASED ON PHYSICS

The atmosphere pressurizes the entire body	By lowering the pressure only over the eye, it lowers the IOP relative to the rest of the body	It's just physics, and physics works every time	IOP can be dialed into the specific target

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2 Multi-Center Randomized Controlled Trials

- **Apollo – POAG**
  - N = 128 eyes of 64 Subjects
  - Contralateral Eye Served as Control
  - IOP Inclusion - 13-32 mmHg
  - **POAG, NTG, OHT, and Glaucoma Suspects**
  - 89.7% had IOP Reduction of >20%
  - 100% of eyes had IOP Reduction
  - **IOP decreased from 19.4 to 12.9 mmHG (34%)**
  - IOP Decreased in addition to existing therapy
  - IOP Decrease regardless of Baseline IOP
  - No SAEs
  - ~20% of eyes had temporary lid edema
- **Artemis – NTG**
  - N = 182 eyes of 91 Subjects
  - Contralateral Eye Served as Control
  - IOP Inclusion - ≤ 21 mmHg
  - **NTG Only – IOP Measure Overnight in Sleep Lab**
  - 98.2% had IOP Reduction of >20% at night
  - 100% of eyes had IOP Reduction
  - **IOP decreased from 20.2 to 12.2 mmHG (39%)**
  - IOP Decreased in addition to existing therapy
  - IOP Decrease regardless of Baseline IOP
  - No SAEs
  - ~17% of eyes had temporary lid edema

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The Future of Visual Field Testing?




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Progression in Glaucoma

- Very complicated to look at progression of glaucoma as a topic itself
- Must confirm if glaucoma is truly progressing
- Many factors have contributed to higher rates of progression
  - CH at baseline
  - CCT at basline
  - Family History
  - Magnitude of IOP lowering
  - Treatment vs. no treatment
  - Macular ganglion cell layer thickness at baseline
  - IOP at baseline
  - Extent of presenting disease burden

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Detecting Progression in Glaucoma

- Important to correlate and look at both functional and structural changes to call out progression in glaucoma
- Visual Field testing is both subjective and yields poor reliability requiring multiple repeats to establish progression[1]
- OCT is objective and precise but is thought to be less helpful in advanced glaucoma due to the floor effect[2]

1. Chauhan BC, Garway-Heath DF, Goni FJ, et al. Practical recommendations for measuring rates of visual field change in glaucoma. Br J Ophthalmol. 2008;92(4):569–573.
2. Bussel, Wollstein G, Schuman JS. OCT for glaucoma diagnosis, screening and detection of glaucoma progression. Br J Ophthalmol. 2014;98(Suppl 2):ii15–19.

183

- Most investigators feel OCT is more useful in pre-perimetric or early glaucoma while VF is more useful in moderate to advanced disease progression[3-5]

3. Sommer A, Katz J, Quigley HA, et al. Clinically detectable nerve fiber atrophy precedes the onset of glaucomatous field loss. Arch Ophthalmol. 1991;109(1):77–83.
4. Zhang X, Loewen N, Tan O, et al. Predicting Development of Glaucomatous Visual Field Conversion Using Baseline Fourier-Domain Optical Coherence Tomography. Am J Ophthalmol. 2016;163:29–37.
5. Estimating Lead Time Gained by Optical Coherence Tomography in Detecting Glaucoma before Development of Visual Field Defects. Ophthalmology. 2015;122(10):2002–2009.

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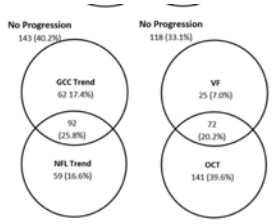
Comparison of Glaucoma Progression Detection by Optical Coherence Tomography and Visual Field

X Zhang et al. Am J Ophthalmol. 2017; 184:63-74

- "OCT is a more sensitive than VF for the detection of progression in early glaucoma. While the value of NFL declines in advanced glaucoma, GCC appears to be a useful progression detector from early to advanced stages."

185

Pre-perimetric progression via various measures



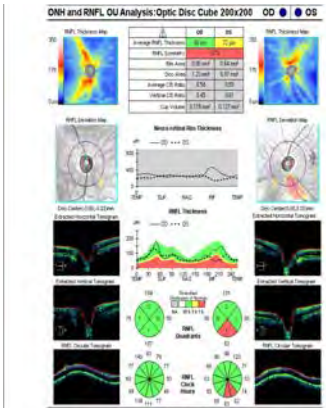
186

Importance of Detecting Early Structural Change

- Evidence that progressive structural changes on OCT often precede functional loss and patients with faster change on OCT are at risk for worsening VF[6]

6. Tatham AJ et al. Detecting Structural Progression in Glaucoma with Optical Coherence Tomography. Ophthalmology 2017 Dec;124(12S):S57-S65.

187



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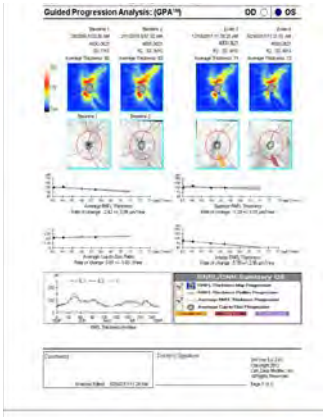

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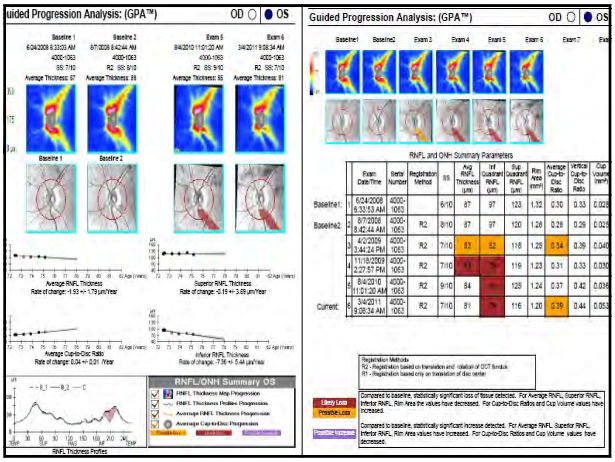

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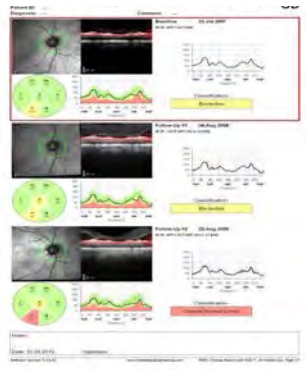

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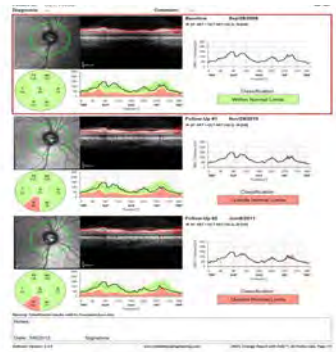

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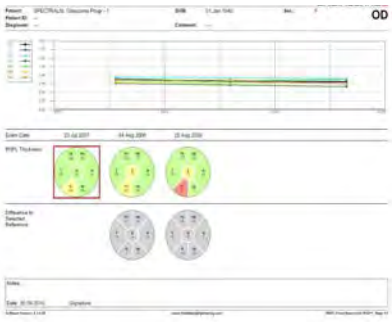

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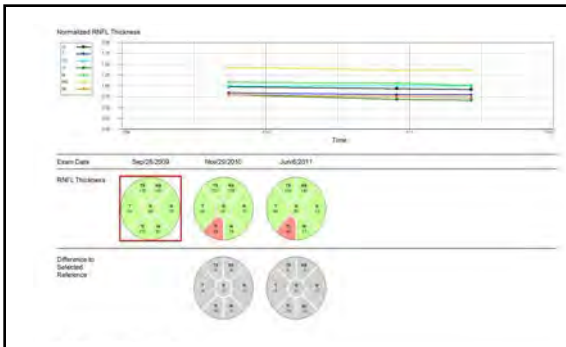

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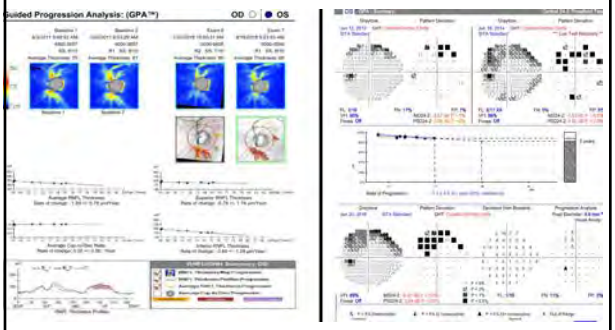
Has Progression Occurred Here? OCT vs. Visual Field



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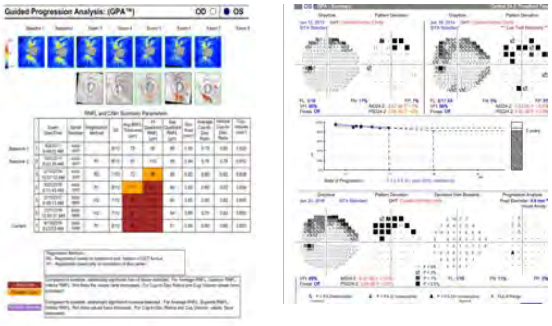
Has This Glaucoma Progressed?



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Case Example

- 58 YOWM
- Diagnosed with glaucoma 3 yrs ago
- Suspect prior to that for 4 years
  - IOP always <24
- Then IOP shot up to 30 and treatment began
  - Pretreatment IOP 24 OD and 30 OS
  - Pachymetry 503 OD and 512 OS
  - CH 7.5 OD and 9.6 OS

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- Then IOP shot up to 30 and treatment began
  - Pretreatment IOP 24 OD and 30 OS
  - Pachymetry 503 OD and 512 OS
  - CH 7.5 OD and 9.6 OS
- Treated with latanoprost and IOP 14-15 OU x 3 years
- Why is he progressing? What should we do?

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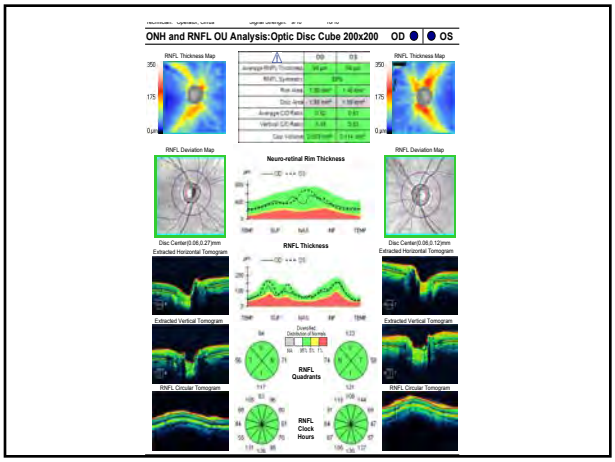

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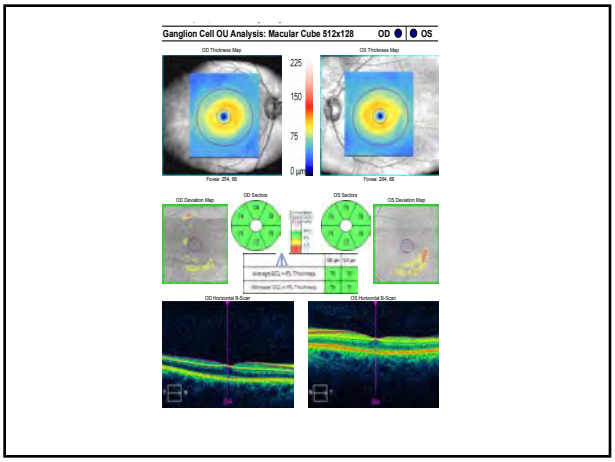

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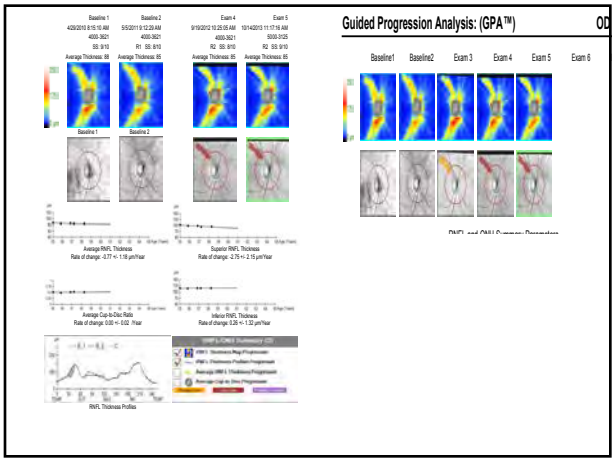

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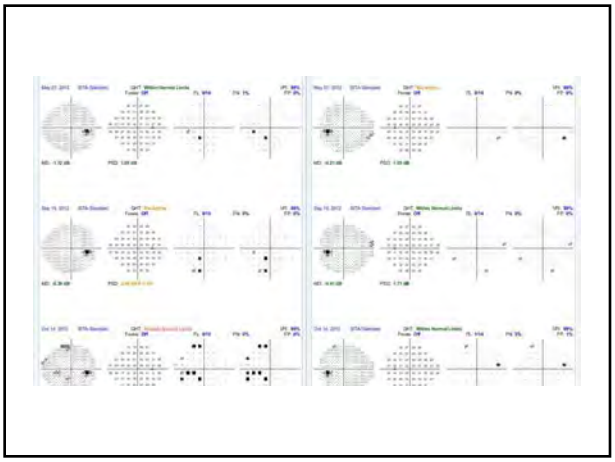

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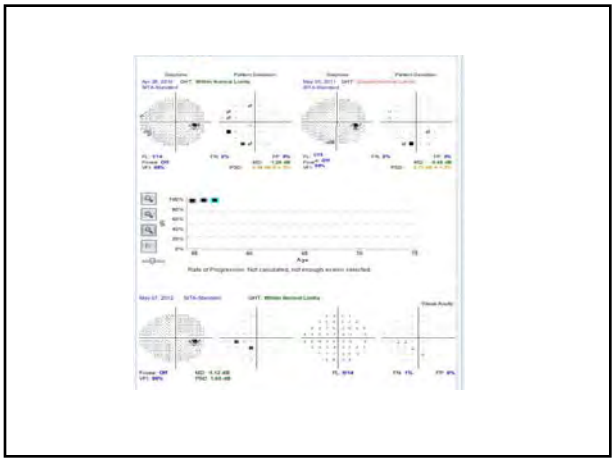

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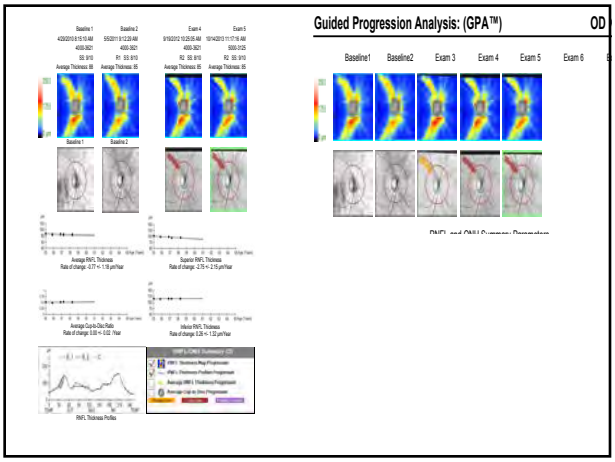

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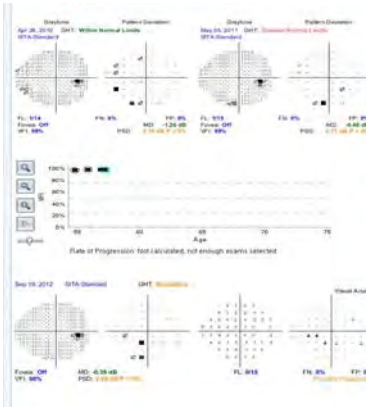

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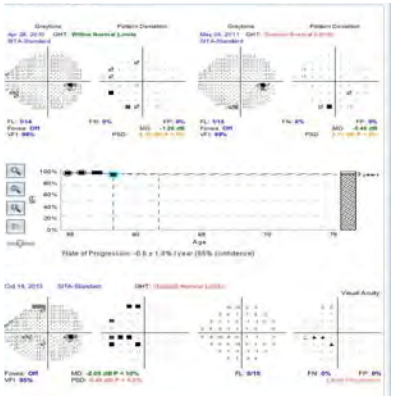

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- Even though IOP has been lowered by 38 and 50 % respectively, we are still seeing progression
- Is this progression seen from original damage (latency) or new?
- Note CH and CCT as negative prognostic indicators for progression

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Plan?

- Plan: Given relative youth and quick early progression, SLT performed OU

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6 week Post OP SLT OU

- IOP 9mm Hg OD and 11 mmHg OS
- Is this low enough?
- How do you know?
  - Re baseline, monitor VF and OCT
- What are future treatment options:
  - Repeat SLT
  - Combo medicine
  - Combined cataract with ECP or Glaukos
  - Incisional glaucoma surgery/MIGS

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Case Example

- 60 YO African American Female
- Presented 2014 as a glaucoma suspect
- IOP in 2014 OD 21 and OS 18
- CH OD 9.2 and OS 6.7
- PACHS 525 OU

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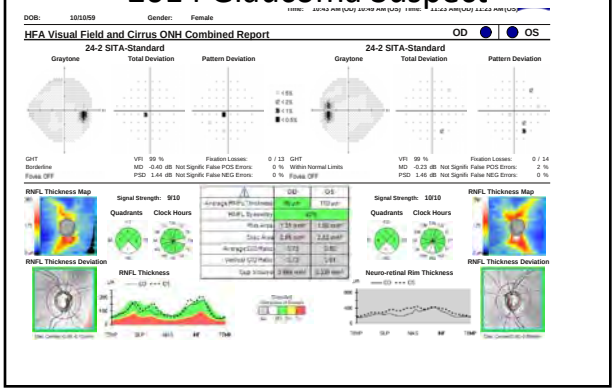
2014 Glaucoma Suspect



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2015-2018

- Patient did not return for follow up
- July 2018 returns for an exam
- IOP 28 OD and 23 OS

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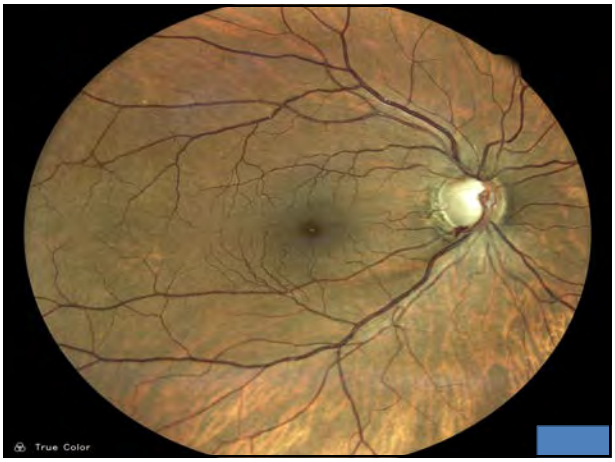

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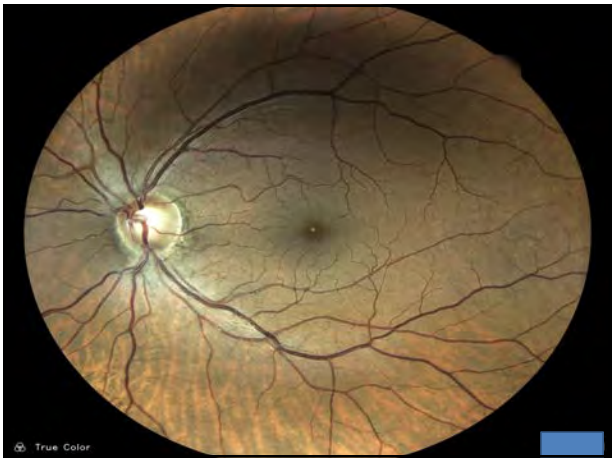

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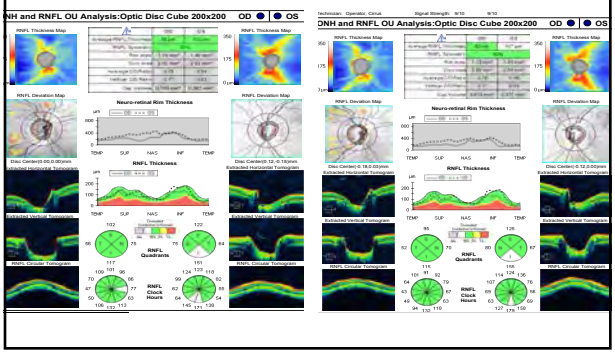
2018 2019



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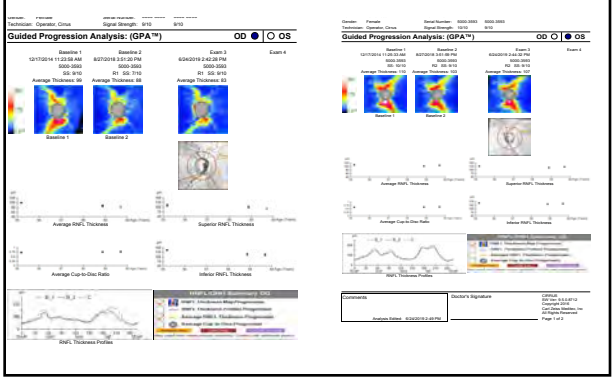
RNFL GPA OU



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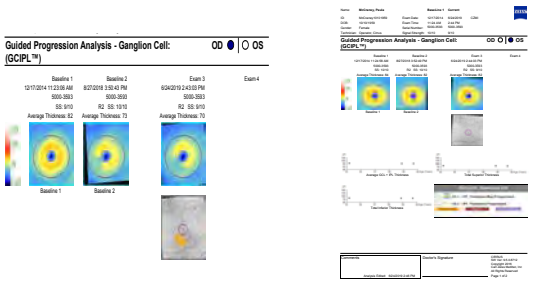
GCC GPA OU
Temporal Macular Involvement



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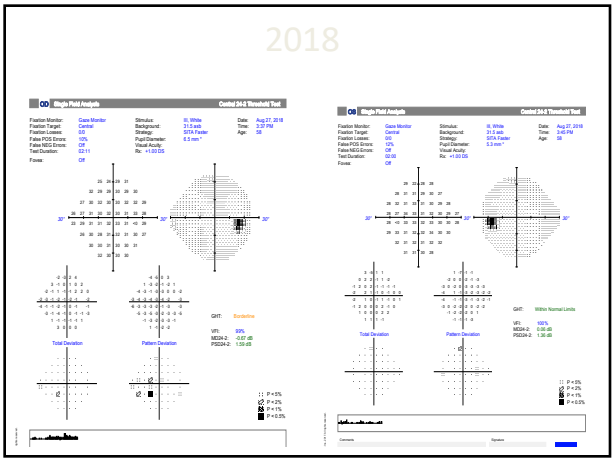

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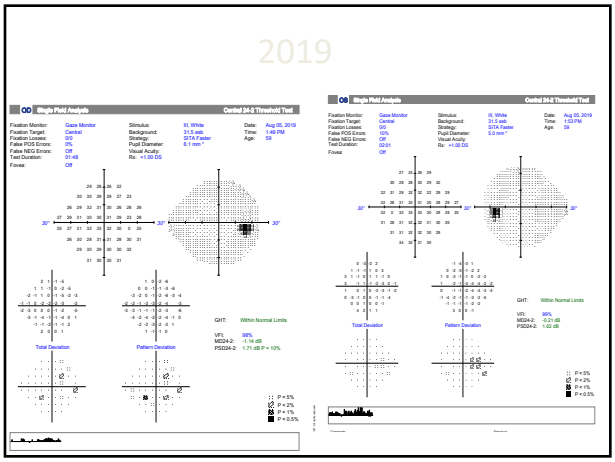

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When to Refer For Glaucoma Surgery

- Progressive VF loss especially central
- Progression despite further IOP lowering and reaching MMT
- Quick Progressors
- Patients with cataracts and glaucoma
- Narrow angles (add even s/p LPI)
- IOP that can't be controlled by meds or SLT

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When to Refer For Glaucoma Surgery

- Notes
  - Try all the medications first; don't just stop at a PGA
    - Why? The glaucoma specialists will do this first every time before they contemplate glaucoma surgery
    - Gives you experience working with all the agents and how to recognize side effects
  - Consider SLT earlier in your sequencing
  - Make sure to repeat VF and OCT to determine stability or rate of progression
    - Just don't send on one VF or OCT

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