Roadmap to Medical Management of Glaucoma

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Ben Gaddie Financial Disclosures 7/16/2025

****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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Are Optic Nerve Hemorrhages Pathognomic For Glaucoma?

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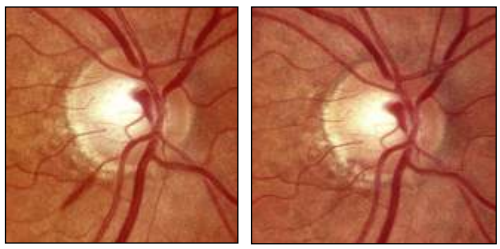
Optic Disc Hemorrhage

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, M.D., 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 ratios [OR], 1.8; 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;105:216–229*

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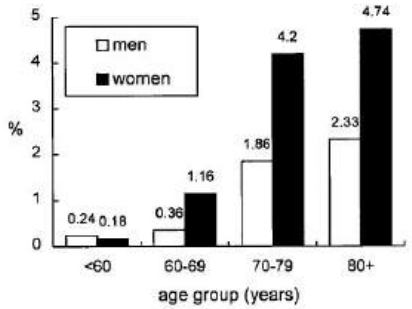

Figure 1. Prevalence of optic disc hemorrhages in 3582 participants by age and gender. Bar numbers indicate percent of subjects.

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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,[2] Richard K. Parrish II, MD,[1] Jody 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 1916 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 cornea, 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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Location of Disc Heme Related to VF Progression and Central VF Loss

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Associations between Clustered Visual Field Progression and Locations of Disc Hemorrhages in Glaucoma

A 3-Year Prospective Study

Tadamichi Akagi, MD, PhD,[1] Tahei Fukuchi, MD, PhD,[1] Tomomi Higashide, MD, PhD,[1] Sachiko Udagawa, PhD,[1] Shinji Ohkubo, MD, PhD,[1] Kazuhisa Sugiyama, MD, PhD,[1] Hidetoshi Tanihara, MD, PhD,[1] Makoto Araie, MD, PhD,[2] Goji Tomita, MD, PhD,[3] Chota Matsumoto, MD, PhD,[4] Akira Tomidokoro, MD, PhD,[5] Masayuki Hangai, MD, PhD,[6] Hitoshi Kanzaki, MS,[7] Mayu Inai, MS,[8] Yuki Tanaka, MS,[8] for the SVF Prospective Study Group

Purpose: To evaluate the impact of disc hemorrhages (DH) at different locations on clustered visual field (VF) progression in patients with primary open-angle glaucoma (POAG) over a 3-year prospective study.
Design: A prospective multicenter cohort study.
Participants: Patients diagnosed with POAG and intraocular pressure (IOP) ≤18 mmHg undergoing prostaglandin analog monotherapy.

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Methods: Visual field testing, IOP measurements, fundus photography, and OCT scans were conducted quarterly over a 3-year period. Disc hemorrhage locations were categorized into superior, inferior, temporal, and nasal quadrants. The VF was subdivided into superior, inferior, and central regions, with the central VF further divided into superior central and inferior central zones. A multivariable linear mixed-effects model with random intercepts and slopes was employed to analyze the relationship between DH history at specific locations and progressive changes in clustered total deviation (TD).
Main Outcome Measures: Association between DH location and the rate of clustered VF progression.
Results: Among 186 eyes from 109 patients, DH occurred in 61 eyes (32.8%). Superior, inferior, temporal, and nasal DH were observed in 19, 31, 21, and 2 eyes, respectively. A faster superior TD slope was significantly associated with inferior DH ($P = 0.032$), but not with superior or temporal DH. A faster inferior TD slope was significantly associated with a worse inferior baseline TD value ($P = 0.009$) and marginally associated with superior DH ($P = 0.053$) but not with inferior or temporal DH. A faster central TD slope was significantly associated with temporal DH ($P < 0.001$) and inferior DH ($P = 0.034$) but not with superior DH. Detailed analysis revealed that inferior DH was significantly associated with the superior central TD slope ($P = 0.010$) but not with the inferior central TD slope. Although DH recurrence was observed in 37 eyes, the number of DH events did not show an additive effect on corresponding clustered VF progression.
Conclusions: The location of DH was strongly associated with corresponding clustered VF progression in patients with POAG. Both temporal and inferior DH represent risk factors for central VF progression.
Financial Disclosure(s): Proprietary or commercial disclosure may be found in the Footnotes and Disclosures at the end of this article. *Ophthalmology Glaucoma* 2025;■:1–10 © 2025 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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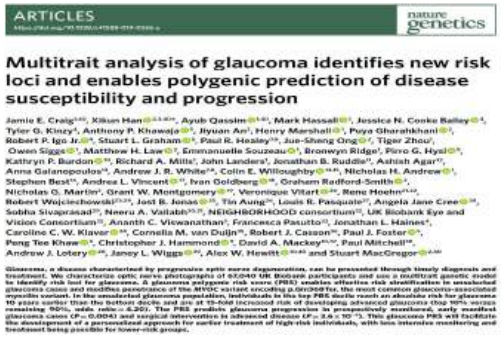
ARTICLES

nature genetics

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

Jamie E. Craig[1,2*], Xikun Han[3,4,5*], Ayub Qassim[6,7,8], Mark Hassall[9], Jessica N. Cooke Bailey[10], Tyler G. Kinzy[11], Anthony P. Khawaja[12], Jiyuan An[3], Henry Marshall[13], Puya Gharahkhani[13], Robert P. Igo Jr.[14], Stuart L. Graham[15], Paul R. Healey[16], Jue-Sheng Ong[17], Tiger Zhou[1], Owen Siggs[18], Matthew H. Law[19], Emmanuelle Souzeau[1], Bronwyn Ridge[1], Piero G. Hysi[20], Kathryn P. Burdon[19], Richard A. Mills[1], John Landers[1], Jonathan B. Ruddle[21], Ashish Agar[21], Anna Galanopoulos[16], Andrew J. R. White[7,8], Colin E. Willoughby[16,22], Nicholas H. Andrew[1], Stephen Best[16], Andrea L. Vincent[23], Ivan Goldberg[24,25], Graham Radford-Smith[26], Nicholas G. Martin[27], Grant W. Montgomery[28,29], Veronique Vitart[30,31], Rene Hoehn[32,33], Robert Wojciechowski[34,35], Jost B. Jonas[36,37], Tin Aung[38], Louis R. Pasquale[39], Angela Jane Cree[40], Sobha Sivaprasad[41], Neeru A. Vallabh[42,43], NEIGHBORHOOD consortium[44], UK Biobank Eye and Vision Consortium[45], Ananth C. Viswanathan[2], Francesca Pasutto[46], Jonathan L. Haines[47], Caroline C. W. Klaver[48,49], Cornelia M. van Duijn[48], Robert J. Casson[50], Paul J. Foster[51], Peng Tee Khaw[52], Christopher J. Hammond[53], David A. Mackey[54,55], Paul Mitchell[56], Andrew J. Lotery[57], Janey L. Wiggs[58], Alex W. Hewitt[16,22] and Stuart MacGregor[3,59]

Glaucoma, a disease characterized by progressive optic nerve degeneration, can be prevented through timely diagnosis and treatment. We characterize optic nerve phenotypes 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_{trend} = 0.004) and surgical intervention in advanced disease (P_{trend} = 3.4 × 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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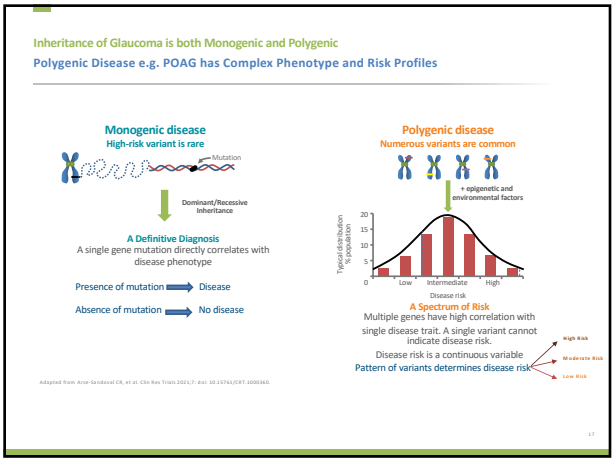

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Genome Wide Association Studies GWAS

- 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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Are We Using OCT Correctly? Assumptions, Unknowns, Myths

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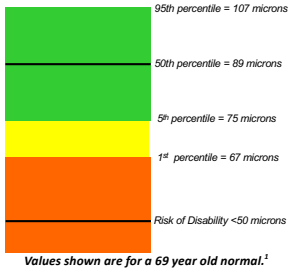
OCT and Progression Range

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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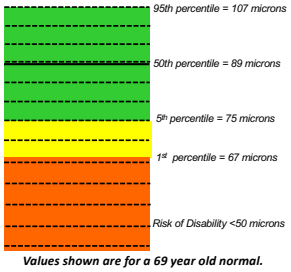
SDOCT measurements are highly reproducible.

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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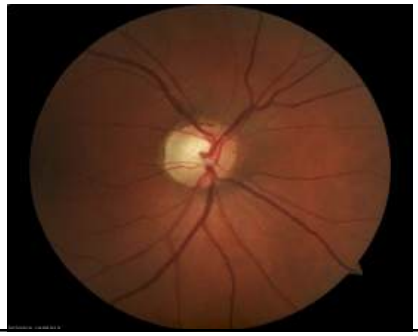

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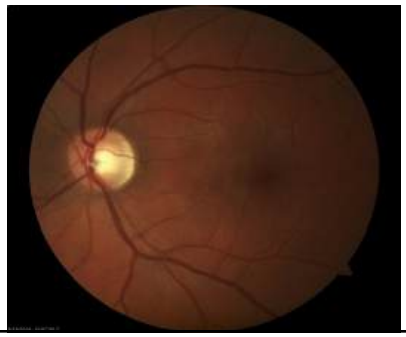

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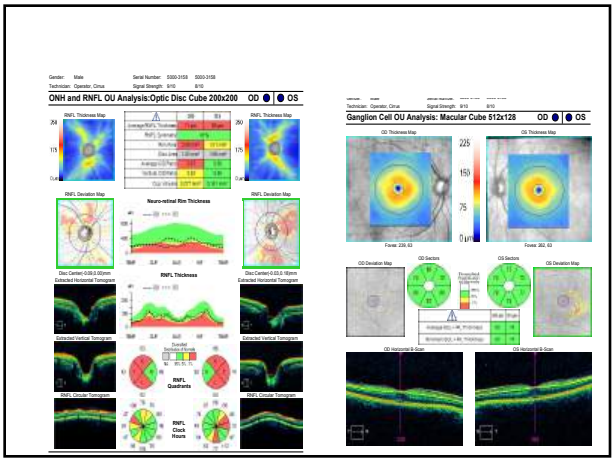

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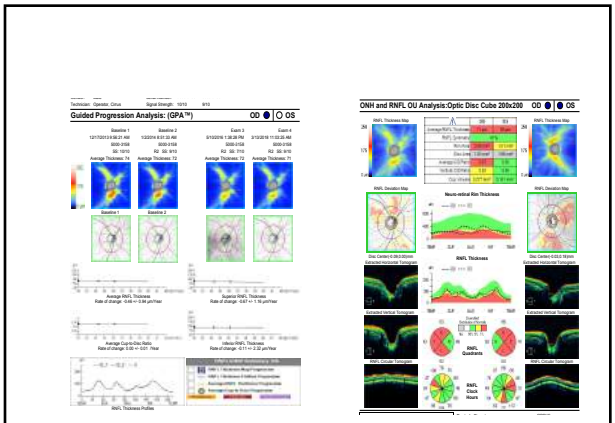

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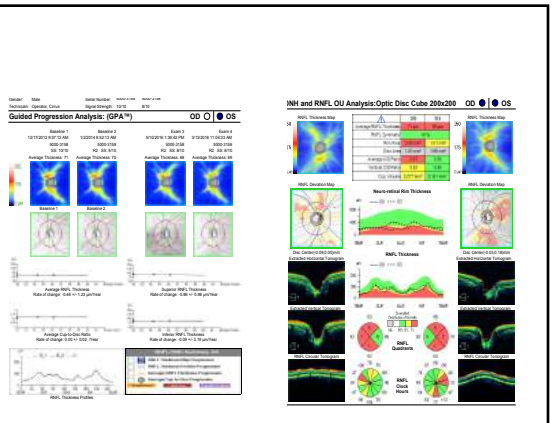

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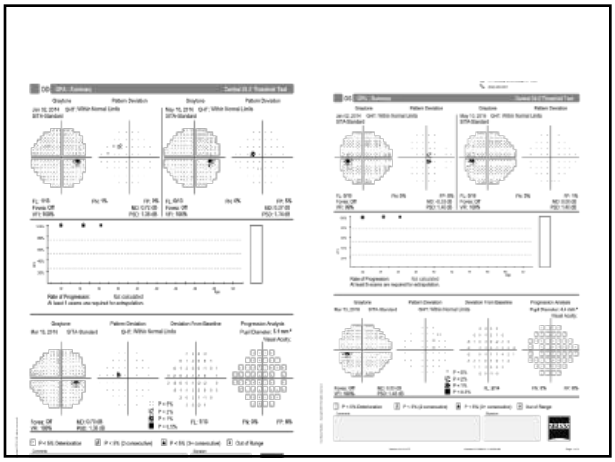

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Is this Glaucoma?

- 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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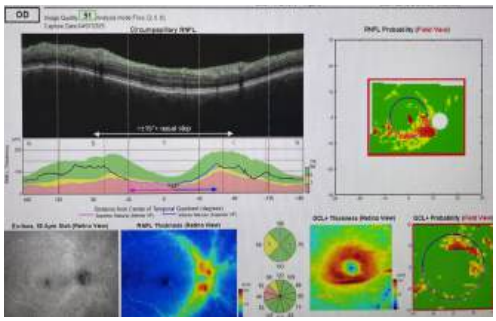

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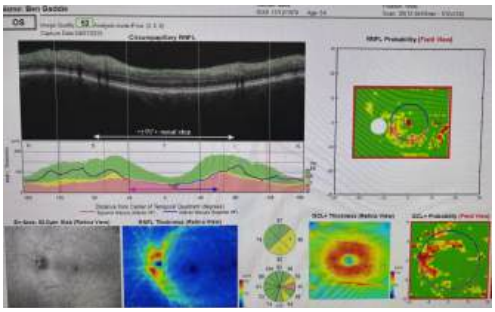

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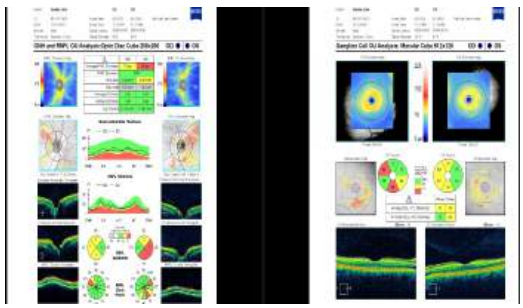

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Case Example

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

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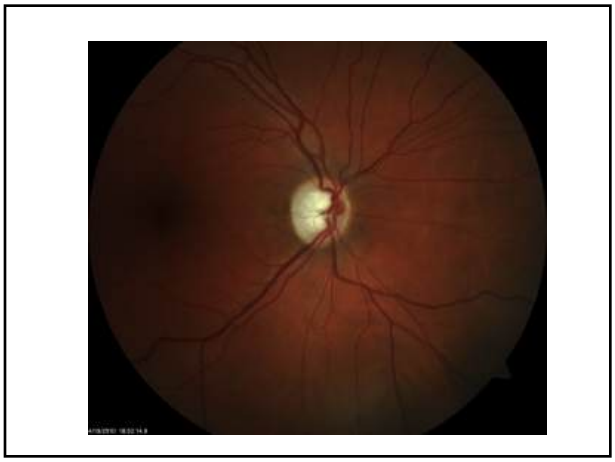

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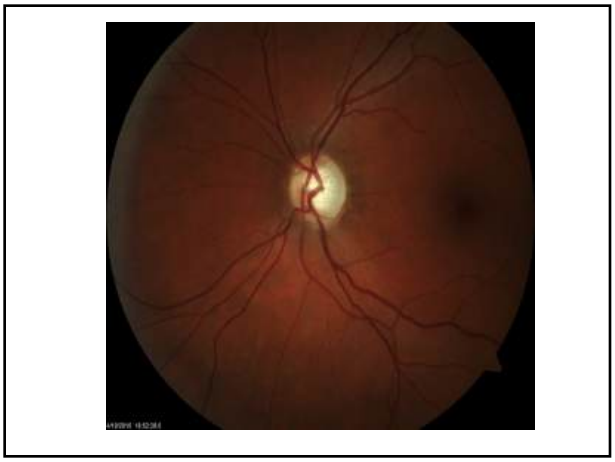

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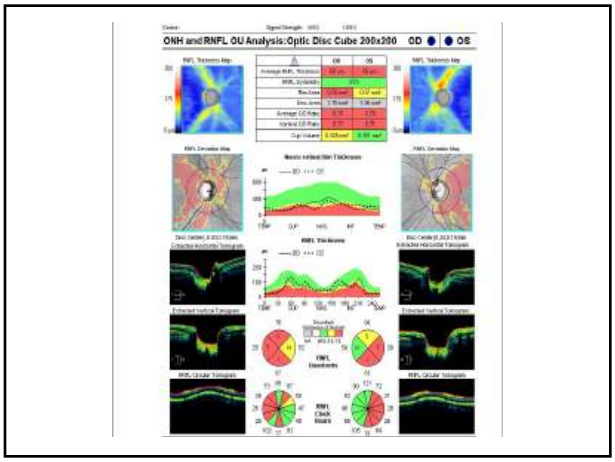

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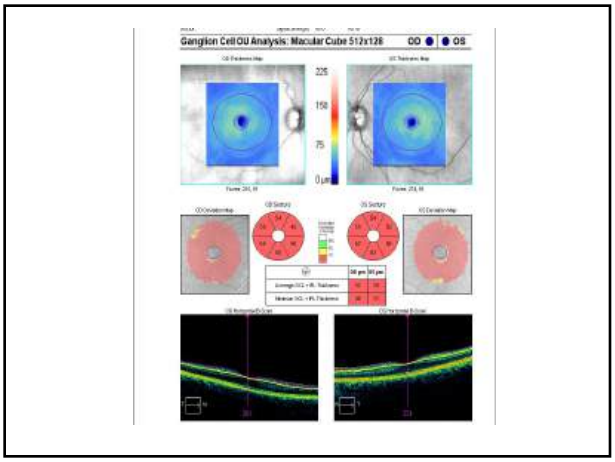

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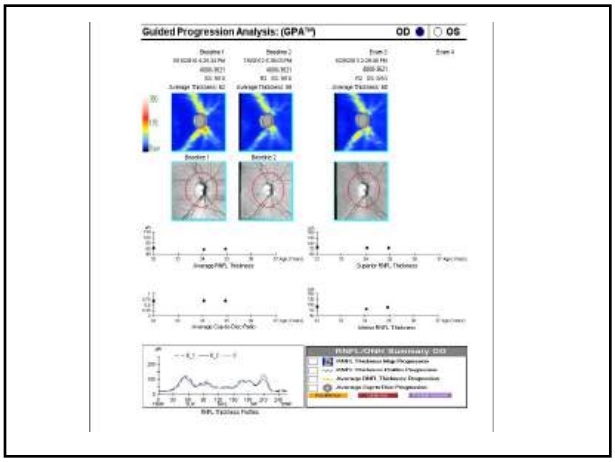

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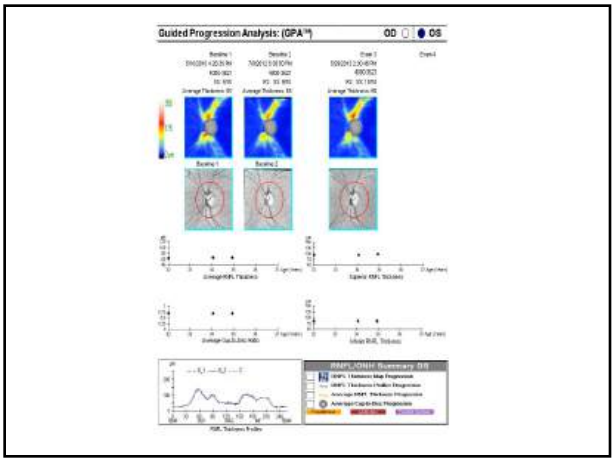

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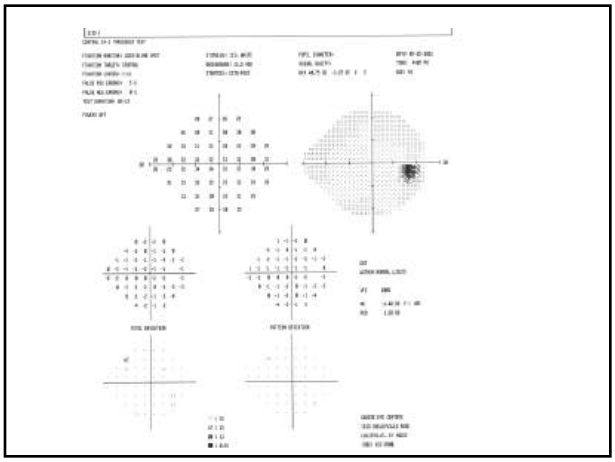

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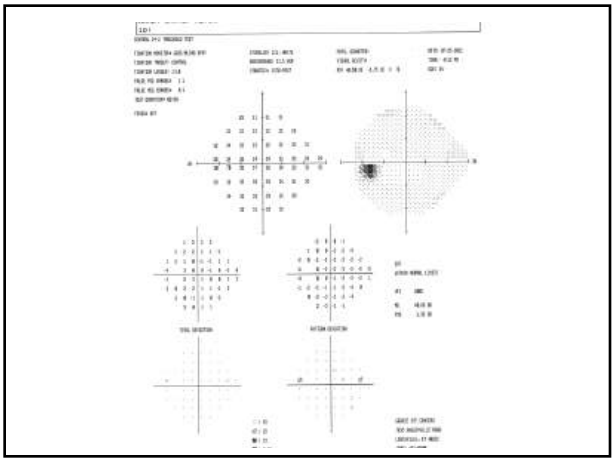

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Asymmetric Disease

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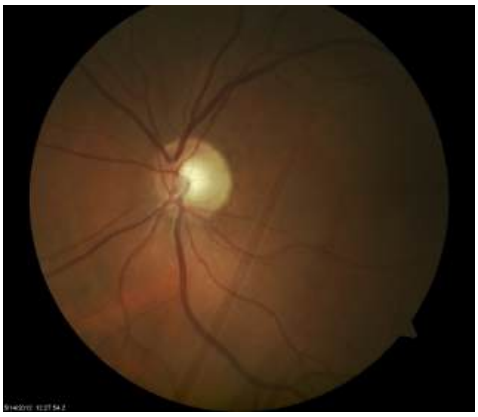

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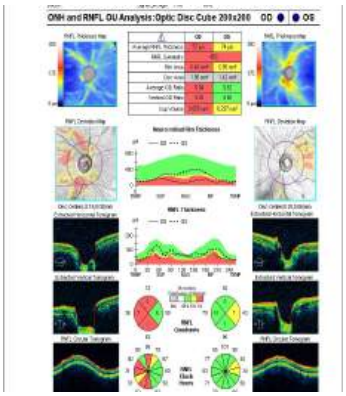

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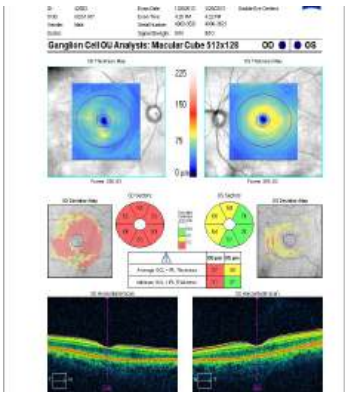

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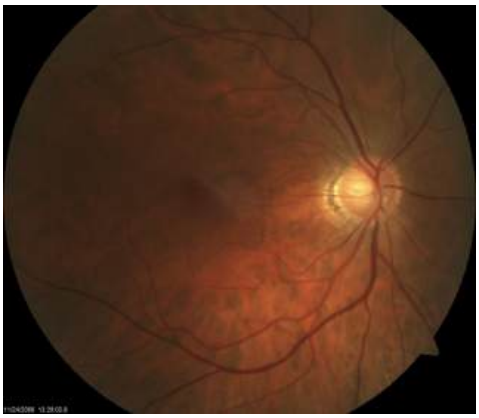

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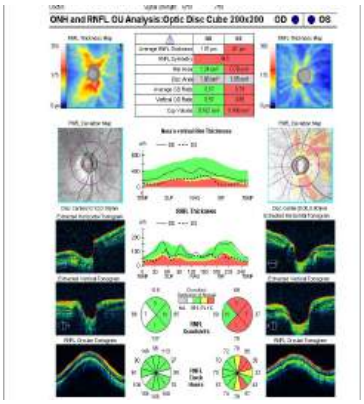

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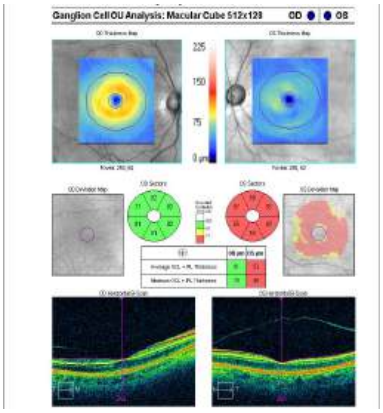

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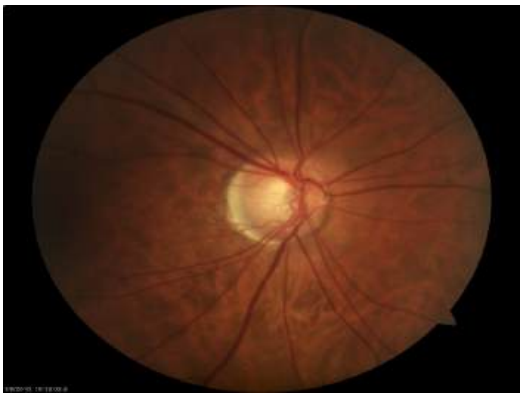

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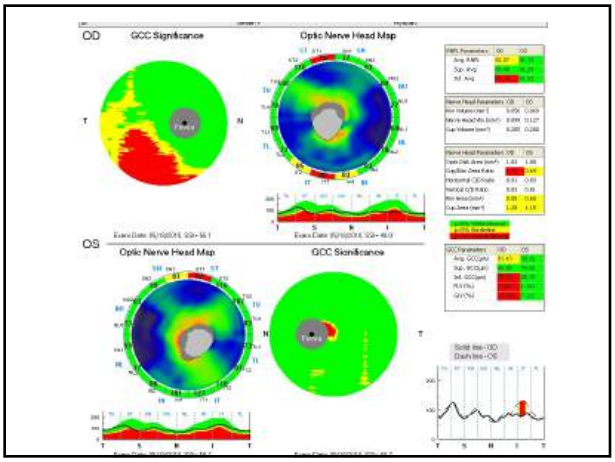

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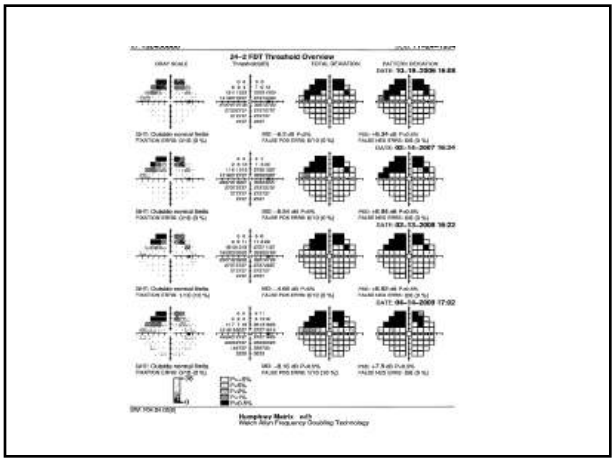

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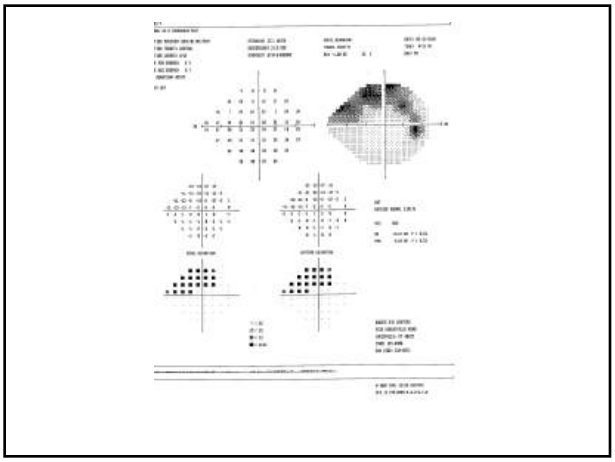

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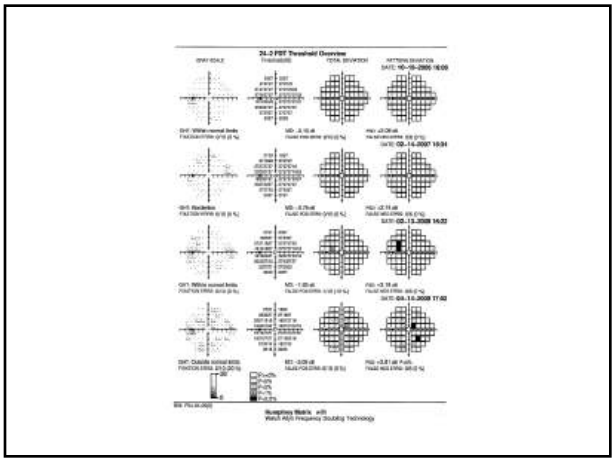

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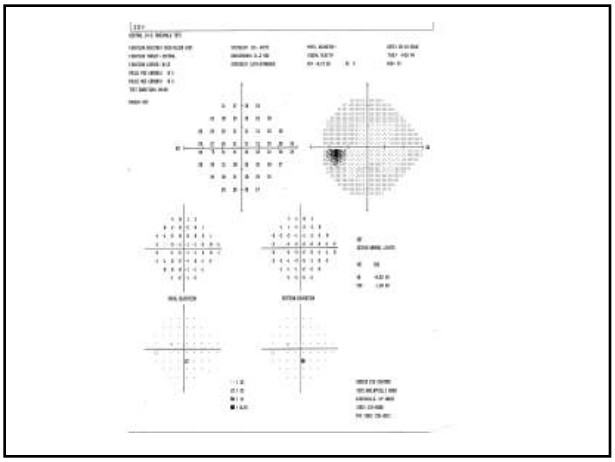


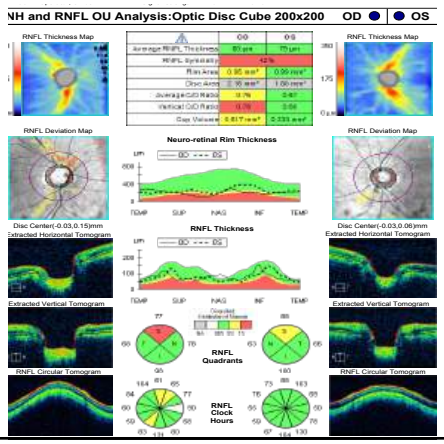
70

Case Example

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

- Is this glaucoma?

71



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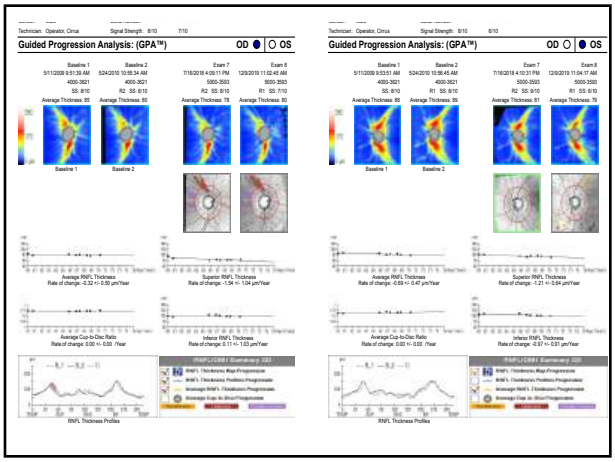
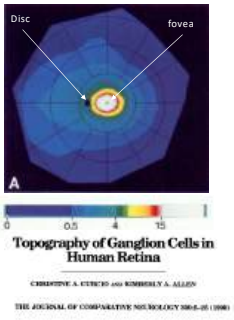


73

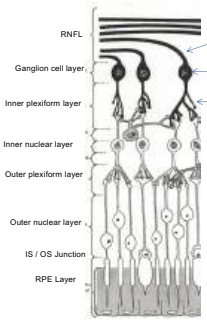
Macular Ganglion cell density



- 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

74

Retinal Ganglion Cells extend through three retinal layers



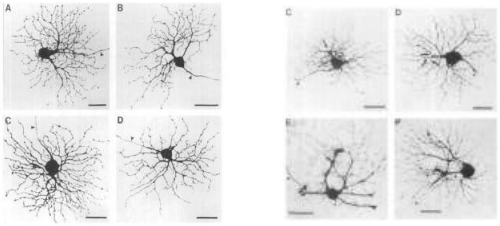
GCC is:

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

75

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

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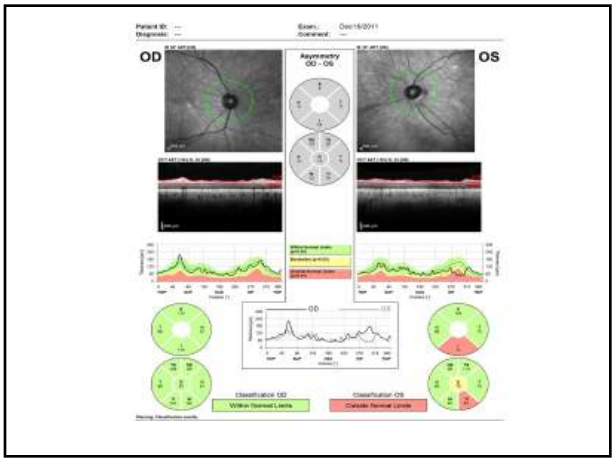

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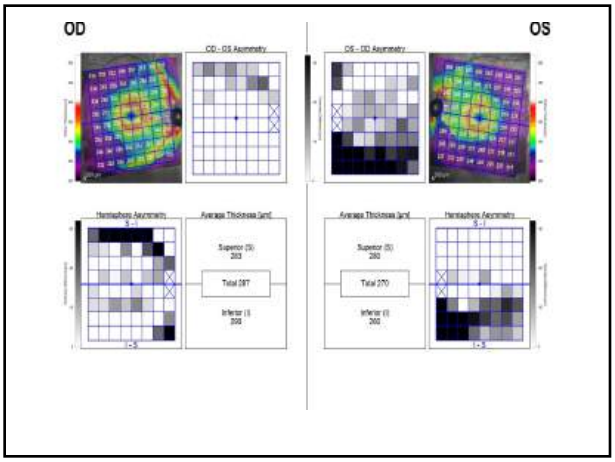

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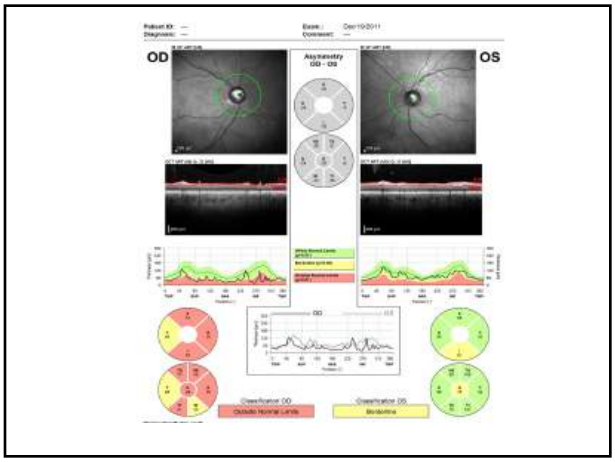

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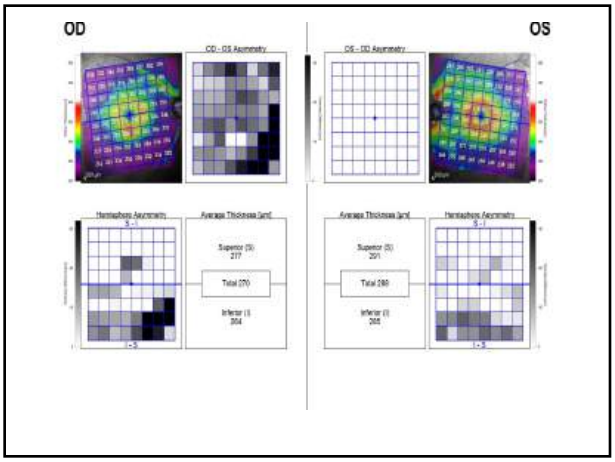

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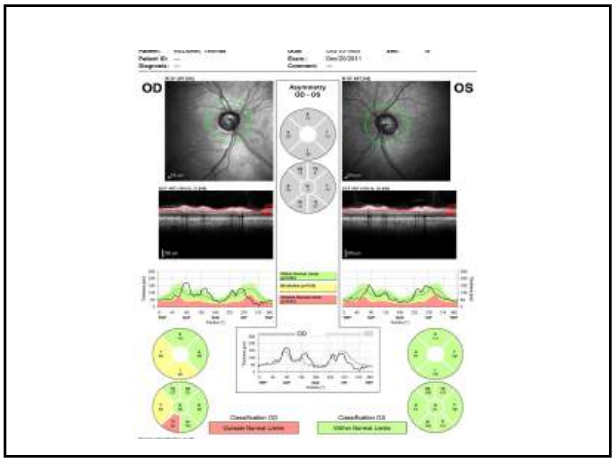

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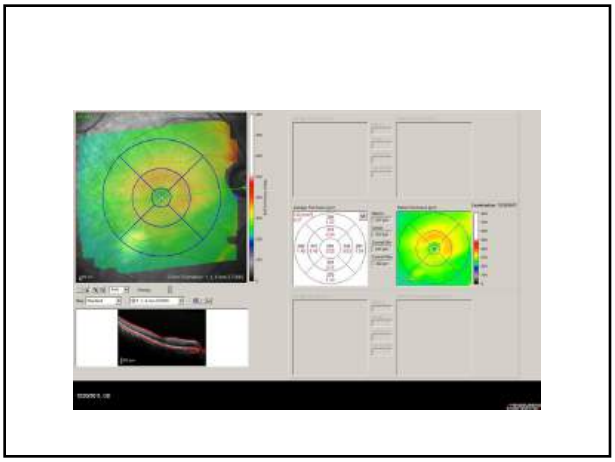

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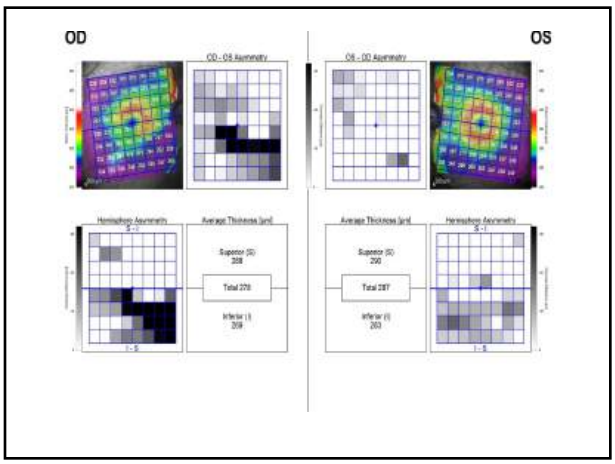
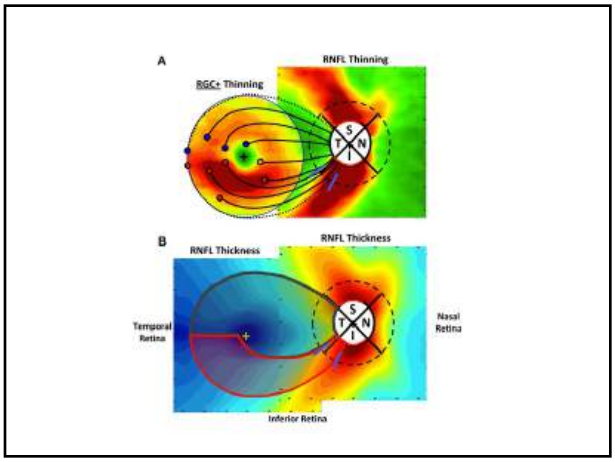


83

Macular Vulnerability Zone

Glucomatous damage of the macula

84



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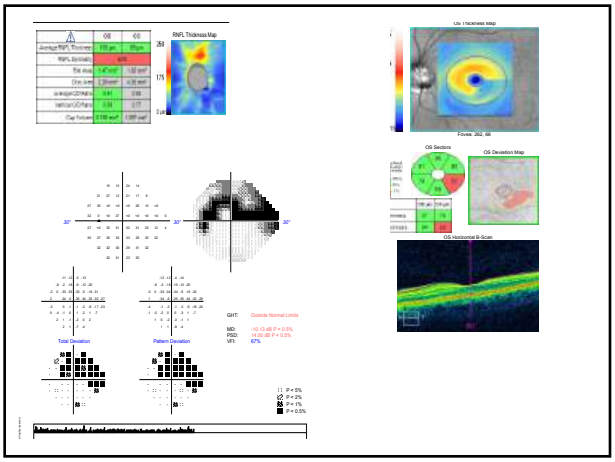

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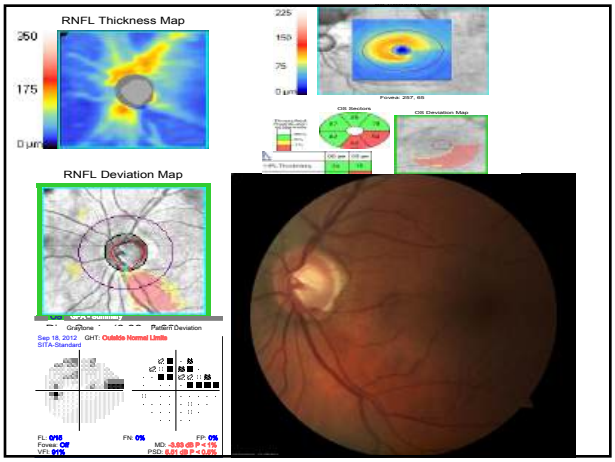
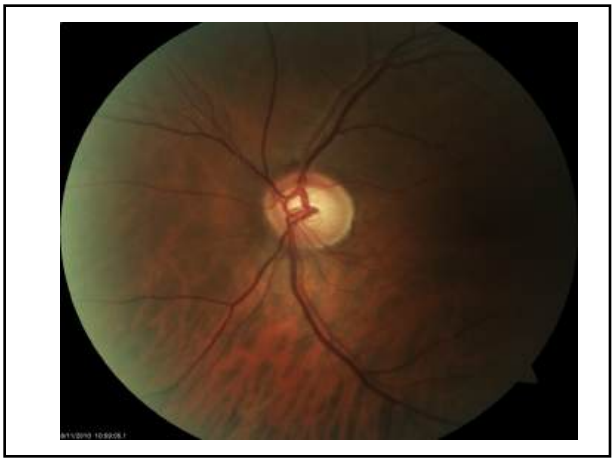


87

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

88

89



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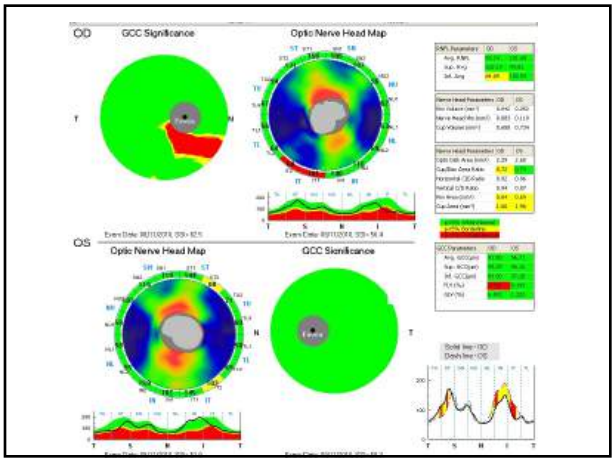

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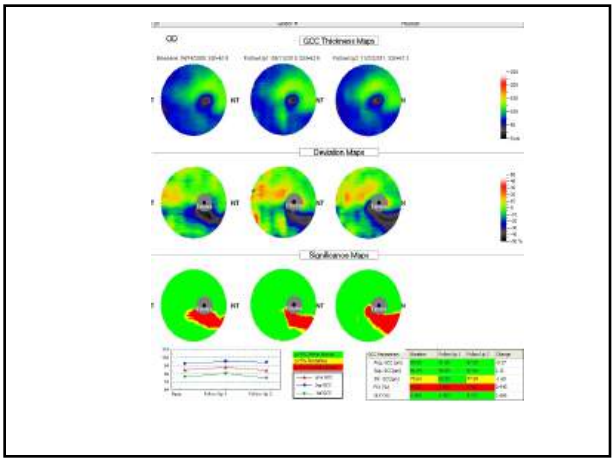

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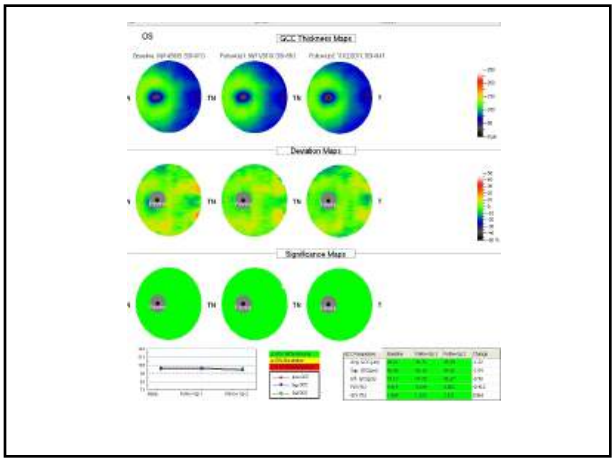

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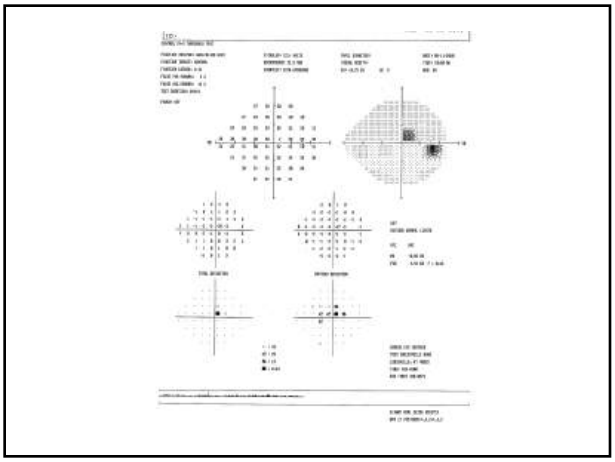

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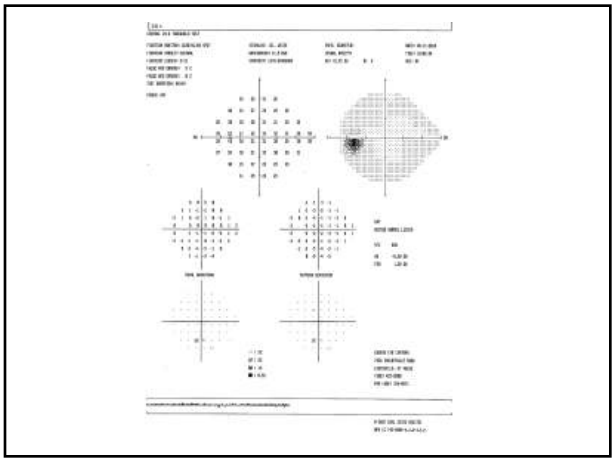

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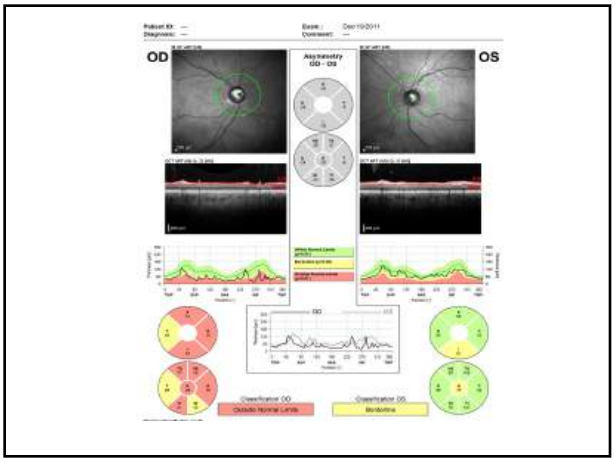

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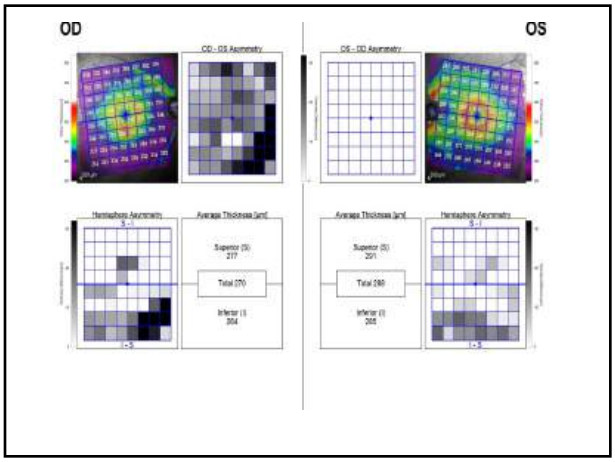

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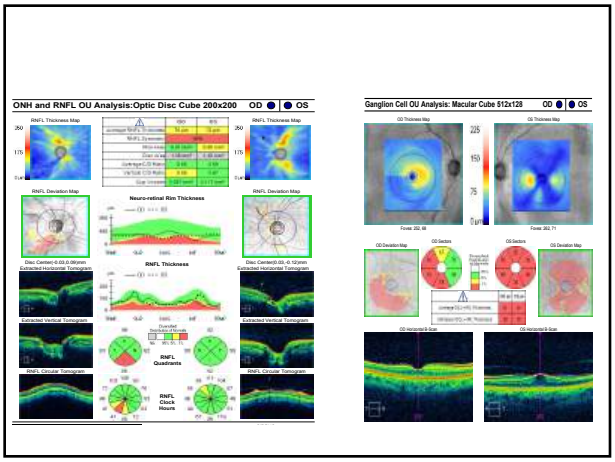

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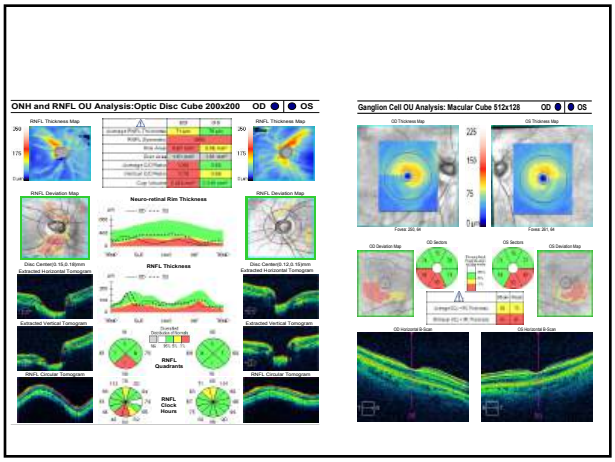

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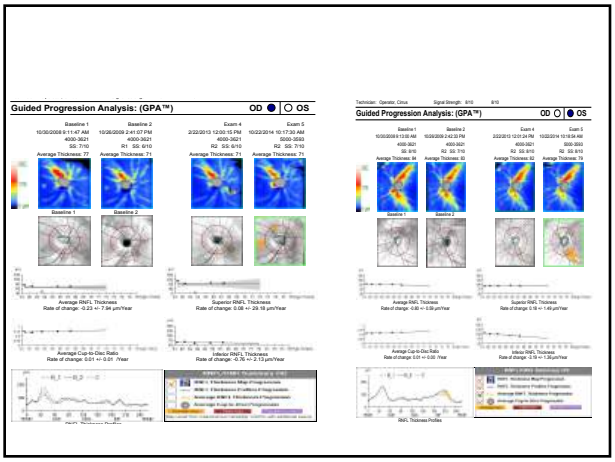

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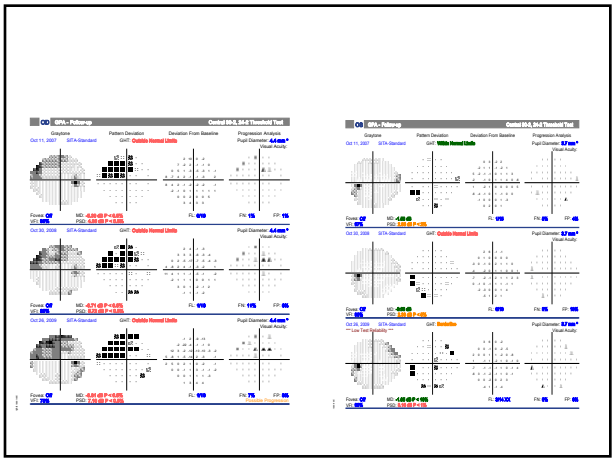

101

Update on Visual Field Testing

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

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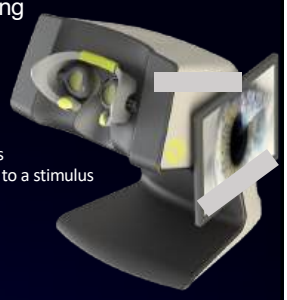
The Future of Visual Field Testing?

103

Objective Visual Field Testing

FDA 510(K) Cleared
Tests OU simultaneously in 7 minutes
Measures the response of the pupils to a stimulus



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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.

105

Starting and Advancing Therapy

106

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

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But does the monocular trial work?

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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

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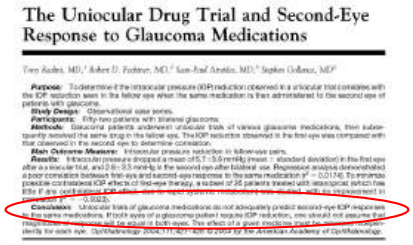
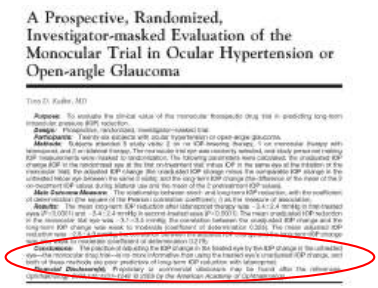


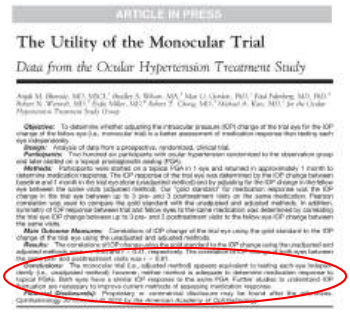
The Uniocular Drug Trial and Second-Eye Response to Glaucoma Medications

110



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

111



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The Utility of the Monocular Trial

Data from the Ocular Hypertension Treatment Study

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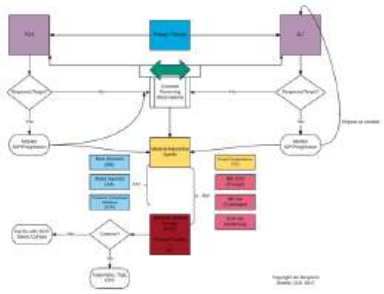
AAO PPP for POAG

- 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.

113



114

Are Topical Beta Blockers Safe to Use?

115

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

117

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, 6]

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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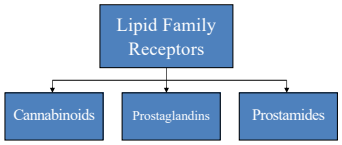
Lipid Family Receptors



120

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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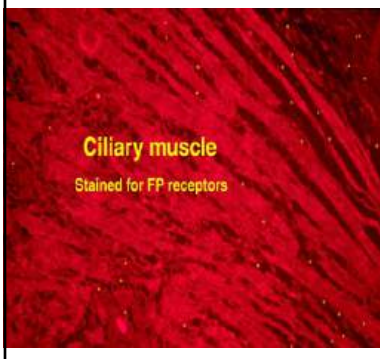

Pharmacology of Latanoprost

- 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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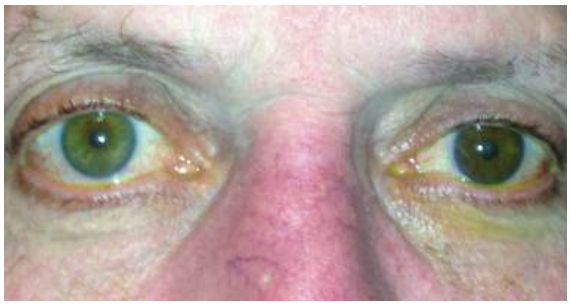

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What's new in glaucoma pharma?

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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Preservative-Free Formulations

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

	Visit 1 (preserved)		Visit 2 (preservative free)		
	No*	(%)	No*	(%)	p Value
Patient symptoms					
Discomfort upon instillation	196/340	57.6%	45/343	11.7%	<0.001
Patient presenting with at least one symptom between instillations	283/342	82.7%	133/344	35.9%	<0.001
Ocular signs found at the clinical examination (patients presenting with at least one)					
Palpebral sign (Blepharitis)	122/343	35.7%	30/346	14.5%	<0.001
Conjunctival sign	233/338	68.9%	74/338	21.9%	<0.001
Superficial punctate keratitis	85/334	25.4%	18/337	5.3%	<0.001

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

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

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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)

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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, 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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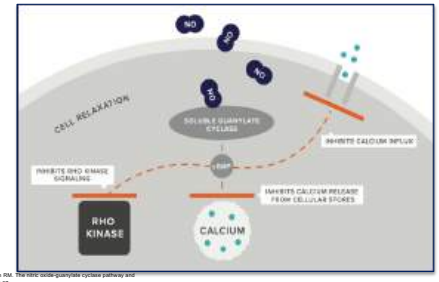
-Gas that can freely diffuse across plasma membranes

-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

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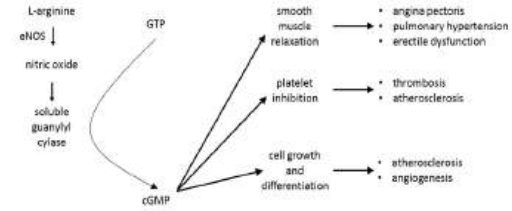

Adapted from Murad F. NEJM 2006;355:2003-11.

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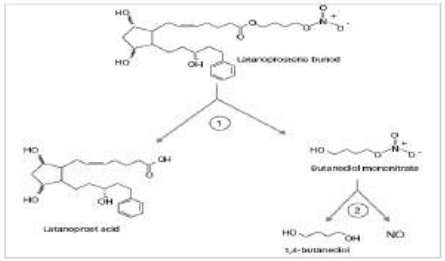
LBN is hydrolyzed by endogenous corneal esterases to

Latanoprost acid: the active compound of latanoprost

Butanediol mononitrate: a NO donating moiety



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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, Parker L, Birdsong OC, et al. Use of Rho kinase inhibitors in Ophthalmology: A Review of the Literature. Med Hypothesis Discov Innov Ophthalmol. 2018;7(2):50-111.

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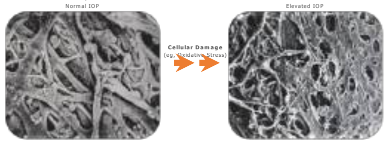
Disease at the TM is Responsible for Elevated IOP in Glaucoma[1,2]

Healthy TM
Normal IOP

POAG TM Stiffness
Elevated IOP



Cellular Damage
(eg, Oxidative Stress)

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. He et al. *Invest Ophthalmol Vis Sci.* 2008;49:1447.
2. Saccà et al. *J Cell Physiol.* 2015;230:510.

8

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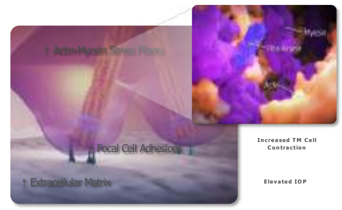
Rho-kinase Increases TM Contraction and Elevated IOP



Increased TM Cell Contraction

Elevated IOP

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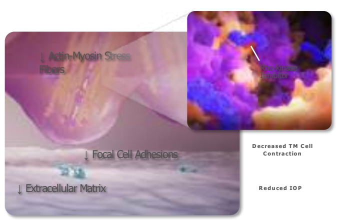
Rho-kinase Inhibitors Relax TM Cells and Reduce Fibrosis[1,2]



Decreased TM Cell Contraction

Reduced IOP

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

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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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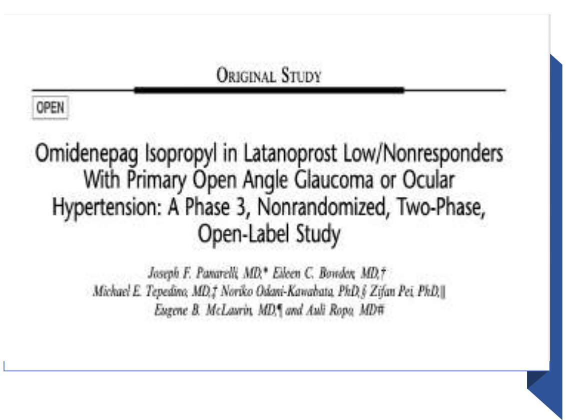

ORIGINAL STUDY

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#*

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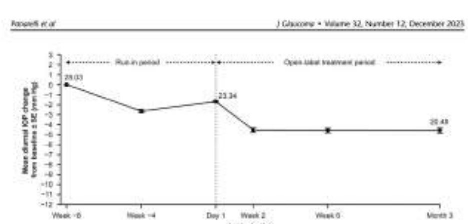

FIGURE 2. Mean diurnal IOP change from the start of run-in period (week −8) to month 3 by analysis visit. Efficacy analyses were performed on study eyes of the full analysis set. IOP indicates intraocular pressure.

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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

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

Adverse Reactions	LBN (n=811)	TIMOLOL 0.05% (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%
Instillation Site Pain	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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- **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)
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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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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)

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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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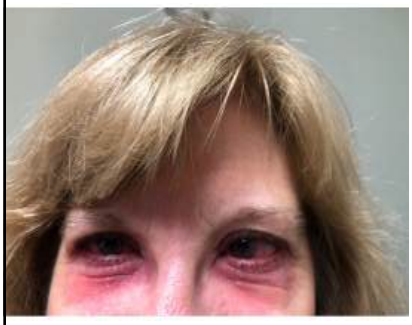

Rho Kinase
”Brimonidine effect”

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