Ask The Experts: Glaucoma

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Experience EXPO With Us!

- Vision Stage – *Tangerine Ballroom – Room WF1*
  Our Vision Stage sessions feature free, promotional content for all attendees.
- Vision Series - *Thursday 3/12 and Friday 3/13*
  Grab a bite to eat and continue learning over *Breakfast 8:30-9:30am* or *Lunch 12:00-1:00pm!**
  Listen to industry leaders as they address the latest clinical innovations in a relaxed and collaborative environment.

  **Open to Optometrists only. Not for Credit. Meals offered on first-come, first-serve basis. Education Badge required.*
- Exhibit Hall Hours

Thursday, March 12	9:30am – 6:00pm
Friday, March 13	9:30am – 6:00pm
Saturday, March 14	9:30am – 3:00pm

- Conferee Cafe – Exhibit Hall – Booth 2902
- Education Lounge - Level 2 - Conference Area Tangerine Ballroom – Room WF2

vision expo

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DISCLOSURES – DR. GADDIE

Tarsus – Consultant, Clinical Trials
Bausch & Lomb – Consultant
AbbVie – Consultant
Topcon – Consultant
Harrow – Consultant
MediPrint – Shareholder, Consultant

All relevant relationships have been mitigated.

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DISCLOSURES – DR. MARRELLI

Alcon
Balance Ophthalmics
Bausch & Lomb
Carl Zeiss Meditec
Glaukos
iCare
Topcon Healthcare

All relevant relationships have been mitigated

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What's New on the Diagnostic Side of Glaucoma?

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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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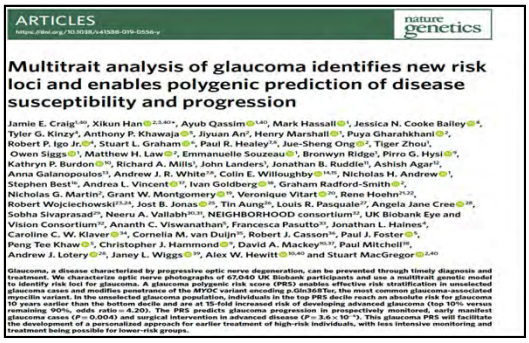

ARTICLES

nature genetics

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

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

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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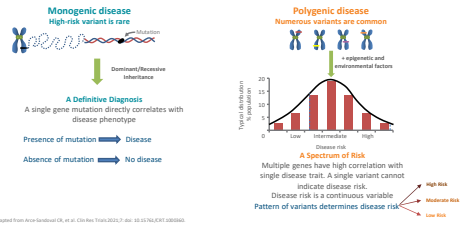
Inheritance of Glaucoma is both Monogenic and Polygenic

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



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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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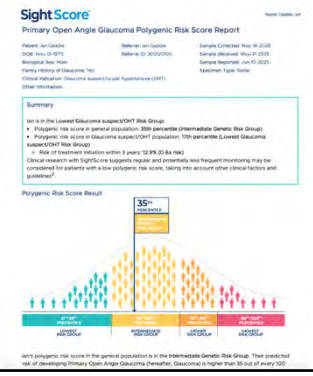
SightScore
Primary Open Angle Glaucoma Polygenic Risk Score Report
Summary
Polygenic Risk Score Result
35TH PERCENTILE

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How IOP is Usually Measured

- Typically a **single observation**
- During **office hours**
- A moment in time or representative of the entire day?
- Are we missing spikes, peak, or elevated IOPs at other times of day?

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The Problem of 24 Hour IOP

- Both measuring and Controlling it

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When Is The Peak IOP?

- 3,025 IOP readings on 1,072 eyes
- NTG, POAG, Pre-perimetric Glaucoma, OHT
- Results:

Peak IOP:

7AM – 20.4%
Noon – 17.8%
5PM - 13.9%
9PM – 26.7%

– Jonas, Budde, et al. AJO, June 2005;139:136-137

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Jonas study conclusion

- "Any single IOP measurement taken between 7AM and 9PM has a higher than 75% chance to miss the highest point of the diurnal curve."
- Stresses the need for serial tonometry.

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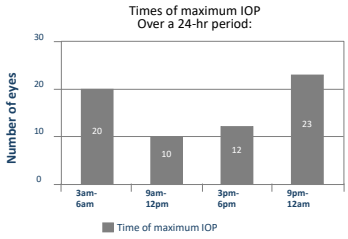
Peak IOP Outside Office Hours for 2/3 of Eyes



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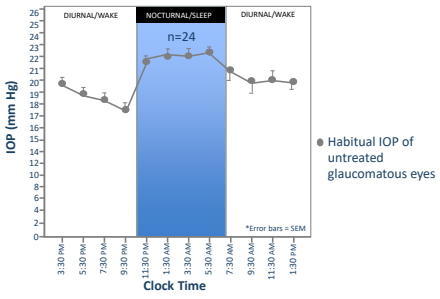
IOP is Higher at Night



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Observations

- Reducing IOP reduces risk of progression[1-5]
- Peak IOPs often occur outside normal office hours[6-9]
- IOP during office hours does not provide a complete picture of diurnal and nocturnal IOP[6-9]
- What does this mean about your choice of medical therapy?

1. Heijl A, et al. *Arch Ophthalmol.* 2002; 120(10): 1268-1279.
2. Kass MA, et al. *Arch Ophthalmol.* 2002; 120(10): 701-713.
3. AGIS Investigators. *Am J Ophthalmol.* 2000; 130(4): 429-440.
4. Lichter PR et al. *Ophthalmology* 2001; 108: 1943-1953.
5. CNTGS. *Am J Ophthalmol.* 1998; 126(4): 487-497.
6. Nakakura S, et al. *J Glaucoma* 2007; 16(2): 201-204.
7. Mosaed S, et al. *Am J Ophthalmol.* 2005; 139: 320-324.
8. Hughes E, et al. *J of Glaucoma* 2003; 12: 232-236.
9. Liu JH et al. *Invest Ophthalmol Vis Sci.* 2003; 44: 1586-1590.

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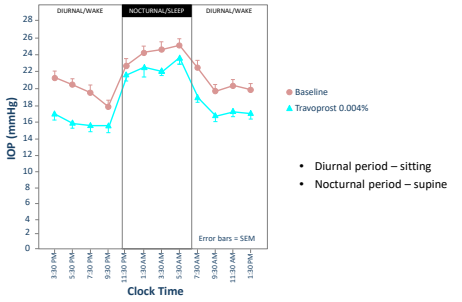
Effect of Travoprost on Diurnal and Nocturnal IOP (cont'd)



- Diurnal period – sitting
- Nocturnal period – supine

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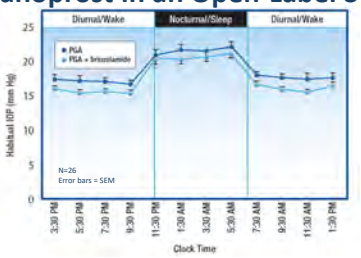
Brinzolamide: Adjunct to Latanoprost in an Open-Label Study



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In home tonometry

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iCare Home Tonometer

- Rebound tonometer
- No anesthesia
- Automatic R/L eye recognition
- Red and Green lights guide alignment
- Push button "switch"
- Can take 1 reading or 6 consecutive
- Data stored in instrument
- Download data in doctor's office

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iCare Home Tonometry

- Readings are not printed out or displayed to patient
- Readings are in mmHg
- No CPT code currently
- Not reimbursable – because it is administered by patient
- There is a rental model either by prescribing doctor or outsourced leasing model
  - Rental rate is set by doctor or third party
  - ABN (waiver of benefits) must be signed by the patient

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iCare Home Tonometer Is It Feasible?

- Pronin, Brown, et al – Jama Ophthalmol (online) 8/31/17
- Report on reproducibility and acceptability of IOP as measured by patients

- All patients had COAG or Ocular Hypertension
- GAT and iCare tonometry performed in office by doctor
- iCare home tonometry performed by patient in office

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So…

- More IOP readings give us more data points from which to make decisions
- It is reproducible
- It is feasible
- But…exactly what do we do with this information

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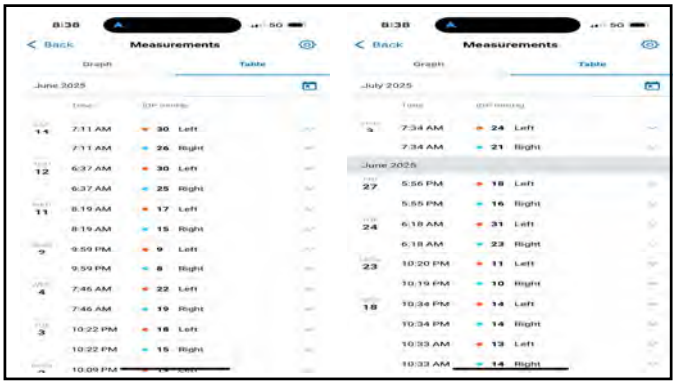

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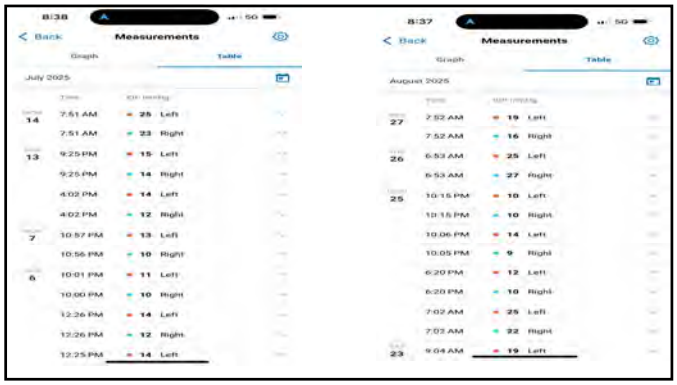

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Are We Using OCT Correctly?
Assumptions, Unknowns, Myths

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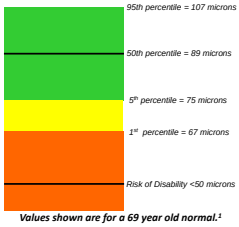
OCT and Progression Range

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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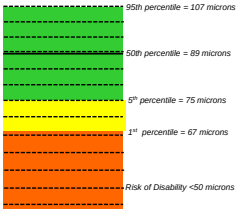
SDOCT measurements are highly reproducible.

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.



- 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 .

Values shown are for a 69 year old normal.

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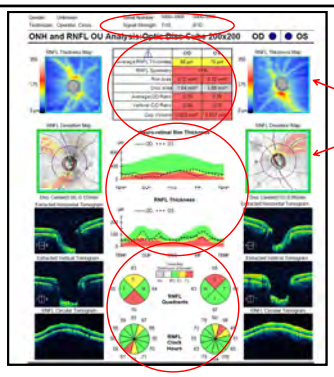

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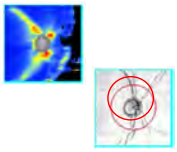
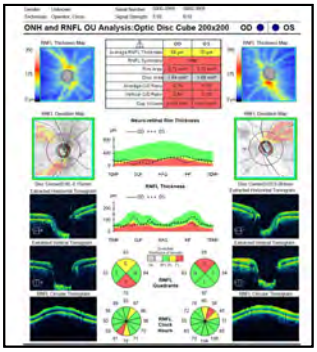
Systematic Strategy

1. Quality
   - Signal Strength
   - Circle Placement
   - Movement?





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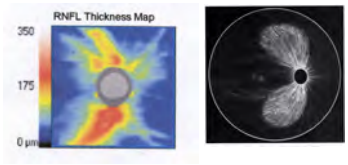
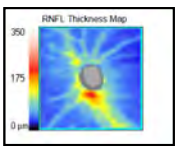
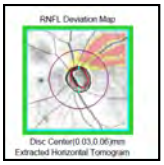
Systematic Strategy

- Thickness Map
- Deviation Map







IMPORTANCE OF BLOOD VESSELS!!!!

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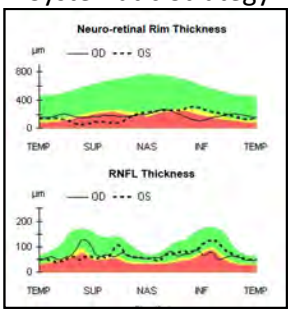
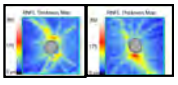
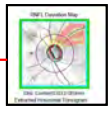
Systematic Strategy

Thickness Profiles
- Compared to normative data





Good at picking up notches in NRR



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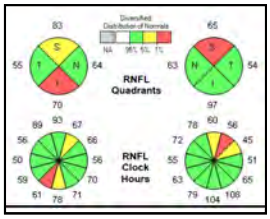
Systematic Strategy

- Quadrant and Clock Hour RNFL analysis



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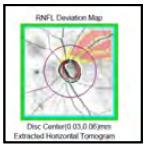
Systematic Strategy

- Quantitative Parameters
  - Average RNFL
    - Measures average thickness around calculation circle
    - Affected by blood vessels, astrocytes, glial cells
    - Global measure (will miss focal loss)
  - RNFL Symmetry



	OD	OS
Average RNFL Thickness	68 µm	70 µm
RNFL Symmetry	14%	
Rim Area	0.72 mm²	0.72 mm²
Disc Area	1.64 mm²	1.88 mm²
Average C/D Ratio	0.76	0.75
Vertical C/D Ratio	0.84	0.78
Cup Volume	0.823 mm³	0.637 mm³

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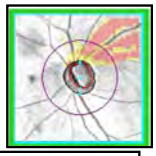
Systematic Strategy

- Quantitative Parameters
  - Rim Area
    - Uses Bruch's membrane as edge of disc
    - Range 0.75-2.38mm (avg 1.31)
  - Disc Area
    - Range 1.06-3.38 mm2 (avg 1.83)
    - Small: <1.63
    - Med 1.63-1.97
    - Large >1.97
  - C/D ratio
  - Cup Volume



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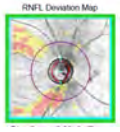
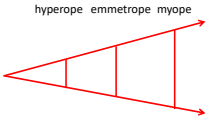
Importance of Disc Size & Axial Length/Refractive Error





12 degree scan projection
- Axial hyperope <3.4 mm
- Axial emmetrope = 3.4 mm
- Axial myope >3.4 mm

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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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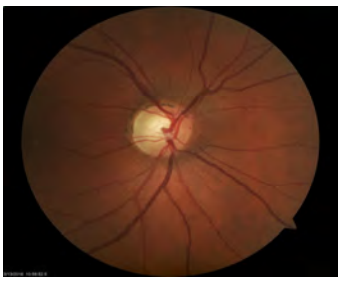

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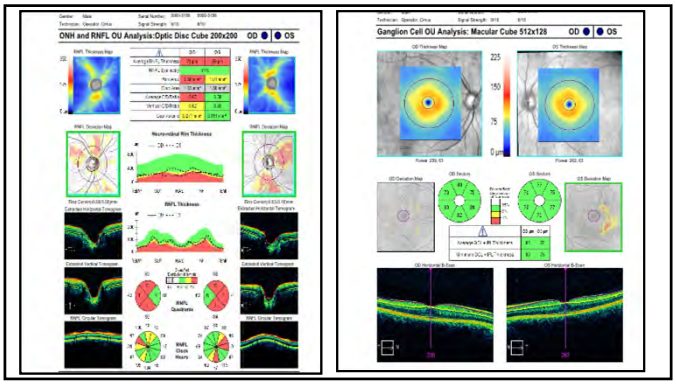

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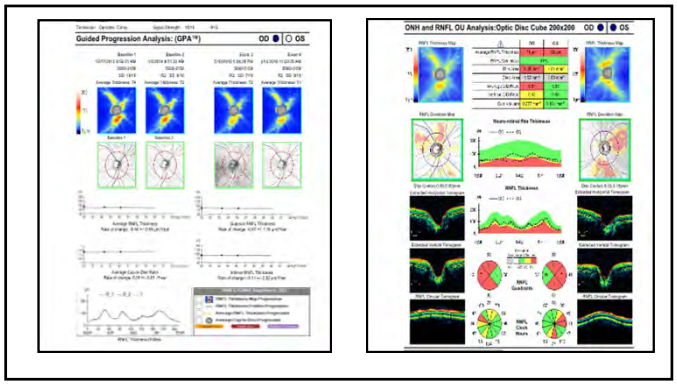

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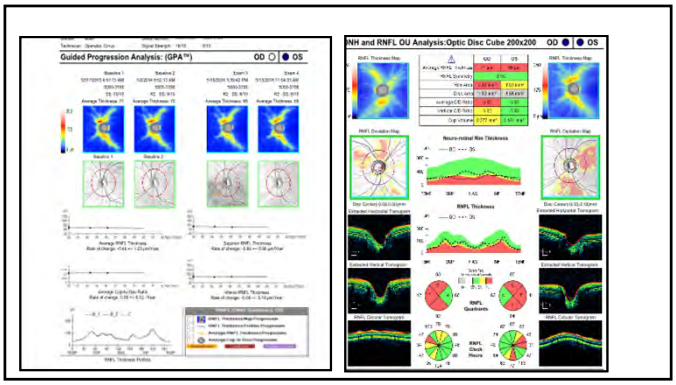

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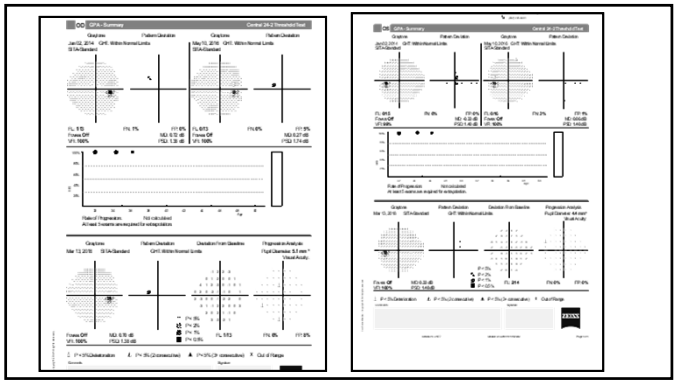


53

Pitfalls in OCT Interpretation

- Over-reliance on red/yellow/green colors of the reference or normative database for diagnostic purposes
- Artifacts
- Non-glaucoma Conditions (“Mimickers”)

54


REVIEW

Glaucoma versus red disease: imaging and glaucoma diagnosis

Gabriel T. Chong and Richard K. Lee

55

KEY POINTS

- Glaucoma imaging is an integral part of the glaucoma management armamentarium for glaucoma screening, diagnosis, and follow-up, that is real disease.
- Glaucoma imaging results can be easily misunderstood without a good understanding of the underlying technology limitations and result in false-positive results and diagnosis, that is red disease.
- The normative databases for the different imaging technologies have limitations in defining what is a normal versus a glaucomatous optic nerve head.

56


REVIEW

Green disease in optical coherence tomography diagnosis of glaucoma

Mohamed S. Sayed, Michael Margolis, and Richard K. Lee

57

KEY POINTS

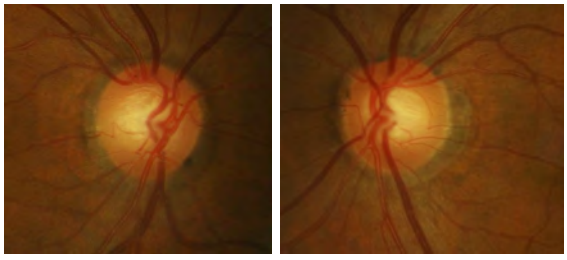
- OCT is an integral part of modern glaucoma practice that is now considered standard of care in the diagnosis and follow-up of glaucoma patients and suspects.
- Careful evaluation of serial OCT analyses over extended follow-up periods with careful clinical examination and structure–function correlation is paramount in glaucoma practice.
- A single normal (i.e., green labeled) OCT analysis may confer false sense of security, leading to unrecognition of early-onset glaucoma or glaucoma progression.
- A number of conditions as well as limitations inherent to the imaging technology may lead to artifactual green labeling of OCT analysis in glaucoma, giving rise to 'green disease.'

58

Case: Victor, 61 yo HM

- BCVA: 20/20 OD, OS
- Pupils, EOMs, CVF: normal OU
- Slit lamp: normal, (-) secondary signs
- Gonioscopy: open to CB, normal
- IOP: 18mmHg OD 15mmHg OS
- See ONH and VF

59



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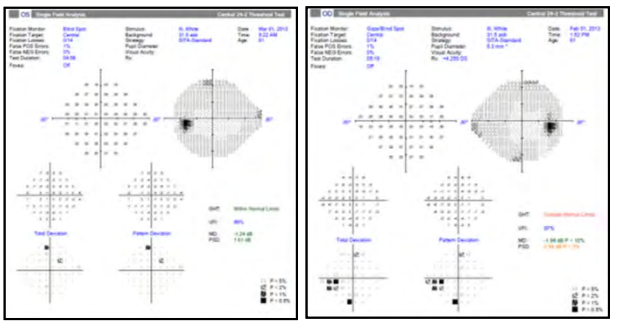

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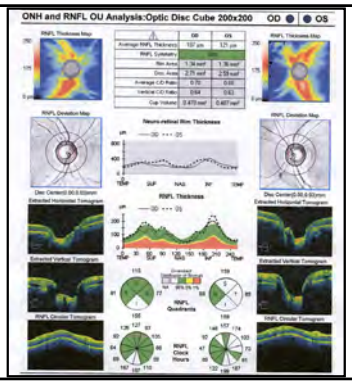

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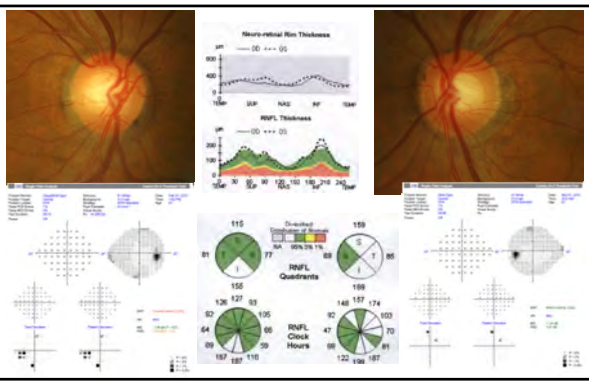

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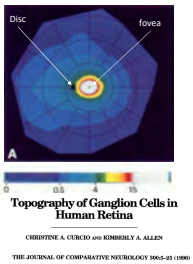
Macular Ganglion cell density



Topography of Ganglion Cells in Human Retina

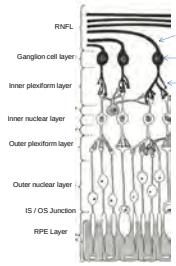
CHRISTINE A. CURCIO AND KIMBERLY A. ALLEN

THE JOURNAL OF COMPARATIVE NEUROLOGY 300:5–25 (1990)

- 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

64

Retinal Ganglion Cells extend through three retinal layers



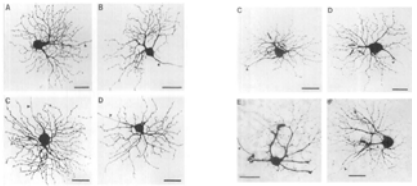
GCC is:

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

65

Dendritic Shrinkage

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

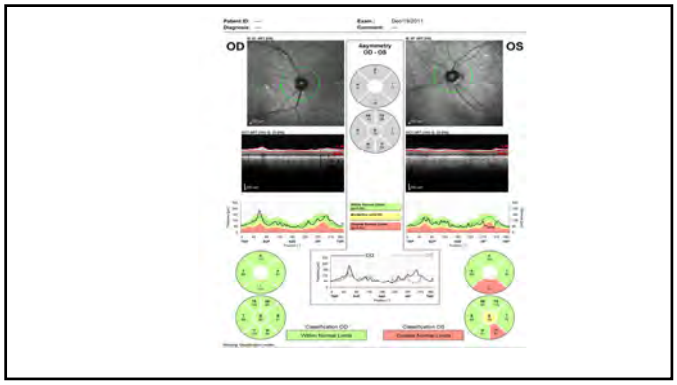


Normal Ganglion cells (Primate) Glaucoma model Ganglion cells (Primate)

Morphology of Single Ganglion Cells in the Glaucomatous Primate Retina

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

66



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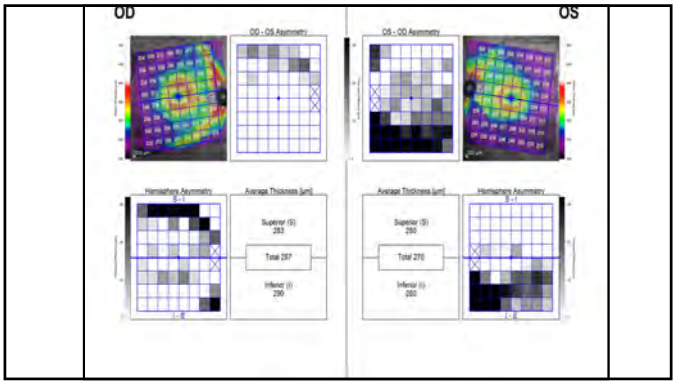

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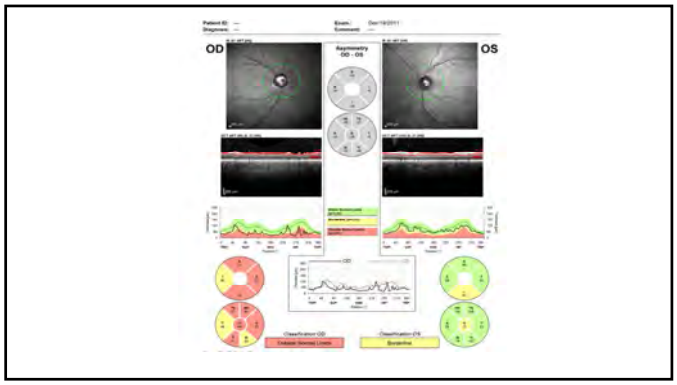

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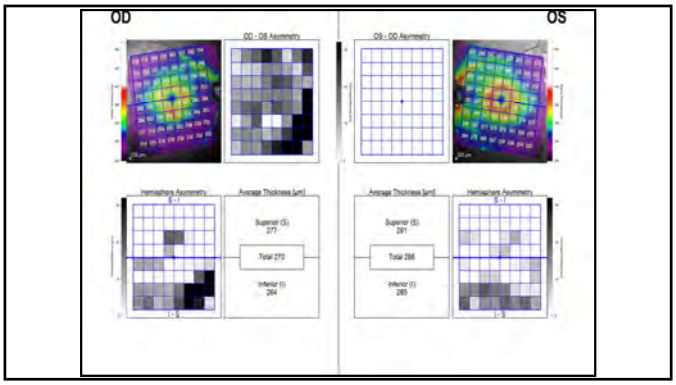

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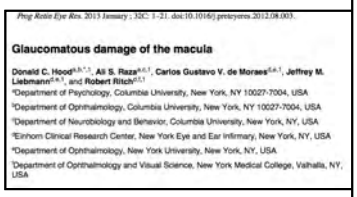
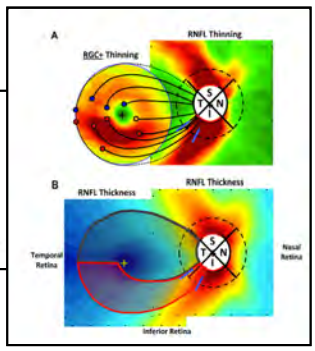
Macular Vulnerability Zone



Glaucomatous damage of the macula



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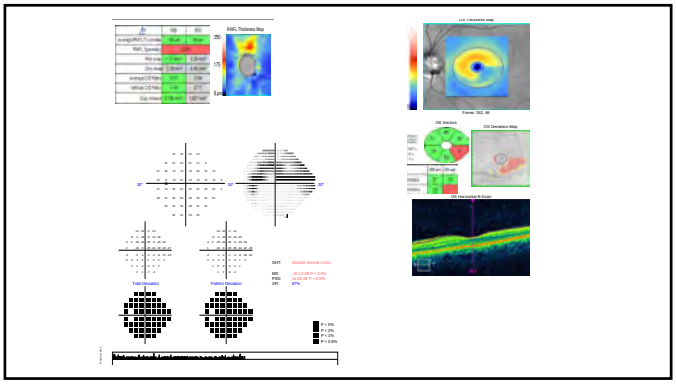

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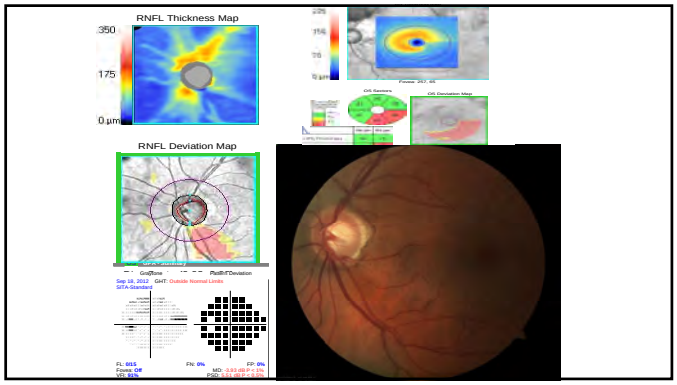
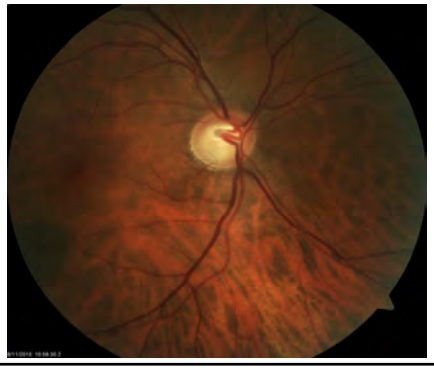


73

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

74



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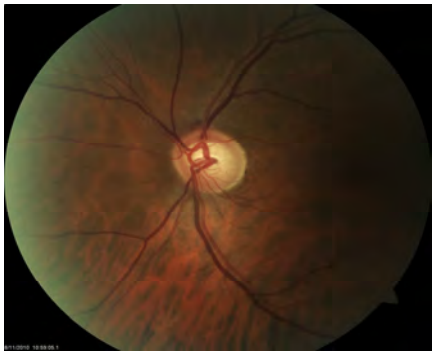

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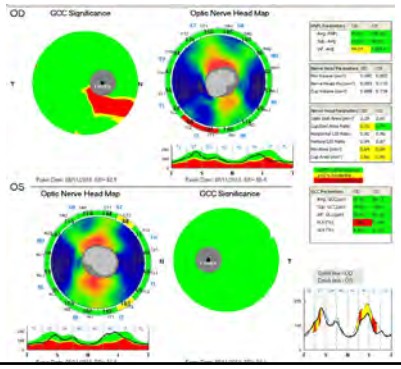

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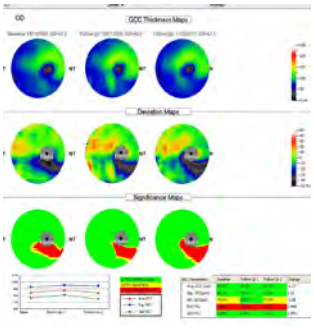

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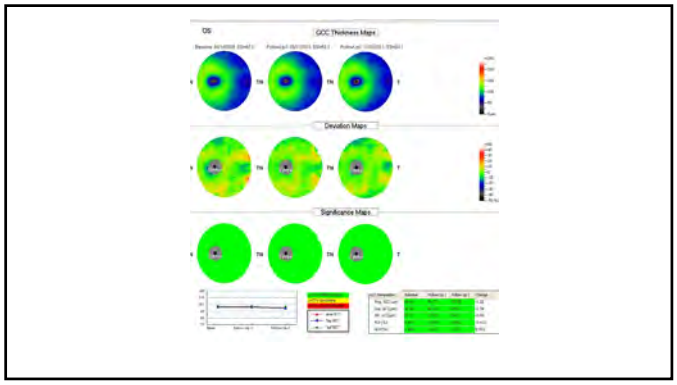

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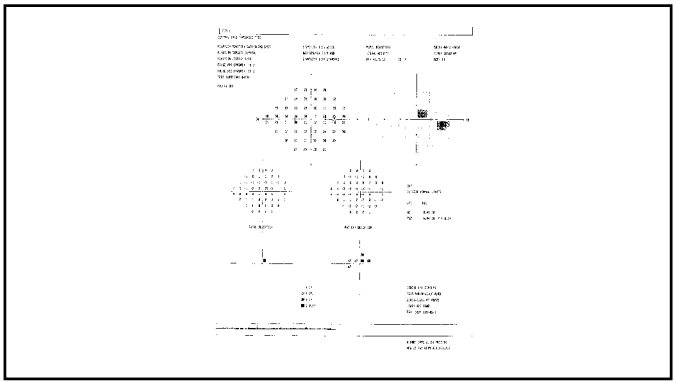

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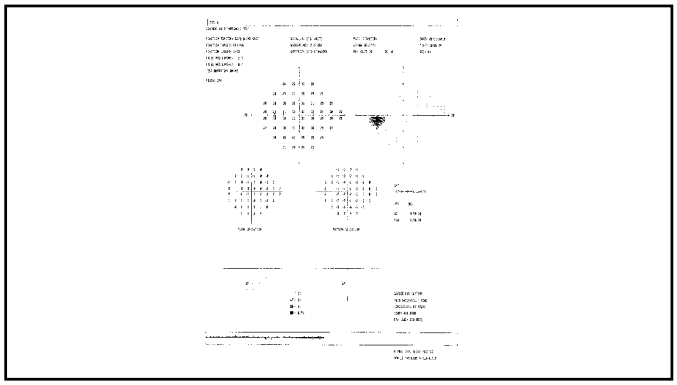
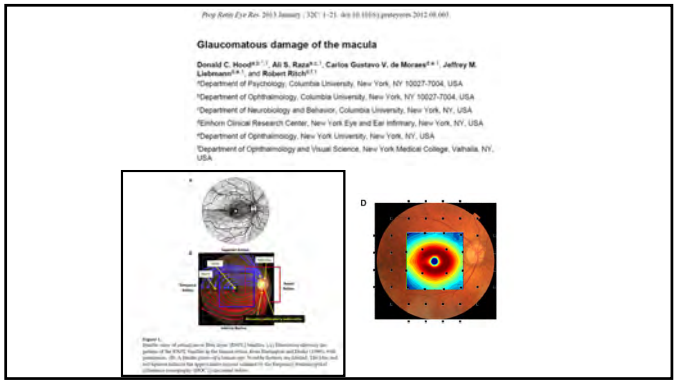


81

What about the 10-2 VF?

- Central 8 degrees from the center of the foveal contains more than 30% of retinal ganglion cells
- 24-2 and 30-2 test strategies use a 6 degree test grid pattern; these points fall outside of the densest region of ganglion cells
- 10-2 test strategy uses a 2 degree test grid
- Recent research has shown that in some patients with small regions of macular gangion cell loss, 10-2 testing may be better able to detect VF loss

82



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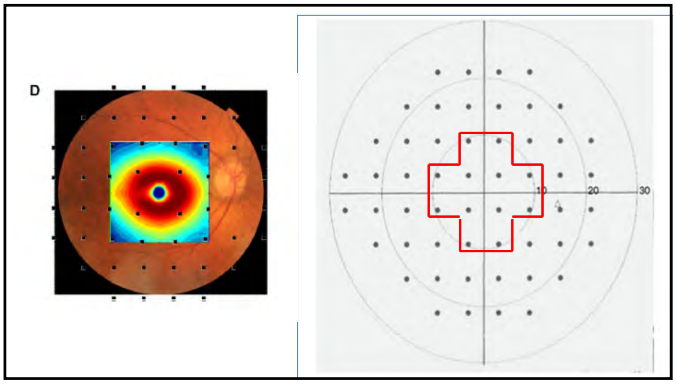

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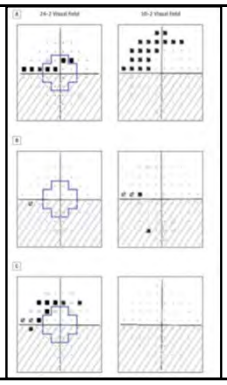
Original Investigation | CLINICAL SCIENCES

Prevalence and Nature of Early Glaucomatous Defects in the Central 10° of the Visual Field

Ilene Traynis, BS; Carlos G. De Moraes, MD; Ali S. Raza, BA; Jeffrey M. Liebmann, MD; Robert Ritch, MD; Donald C. Hood, PhD

JAMA Ophthalmology March 2014 Volume 132, Number 3



85

Qualitative Evaluation of the 10-2 and 24-2 Visual Field Tests for Detecting Central Visual Field Abnormalities in Glaucoma

ADI ORBACH, GHEE SOON ANG, ANDREW S. CAMP, DEREK S. WELSBIE, FELIPE A. MEDEIROS, CHRISTOPHER A. GIRKIN, MASSIMO A. FAZIO, WON HYUK OH, ROBERT N. WEINREB, LINDA M. ZANGWILL*, AND ZHICHAO WU*

Am J Ophthalmol 2021;229: 26–33

- Purpose:To determine whether glaucomatous central visual field abnormalities can be more effectively detected using a qualitative, expert evaluation of the 10-2 test compared with the topographically corresponding central 12 locations of the 24-2 test

86

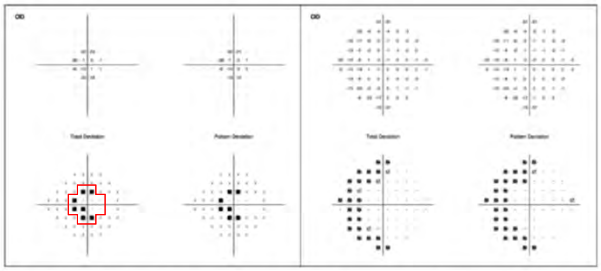


FIGURE 1. Example of the 24-2 (Left) and 10-2 visual field reports (Right) used in this study, with the results of only the central 12 locations shown for the 24-2 visual field test to ensure that only the topographically matched locations to the 10-2 test are shown. OD = right eye.

87

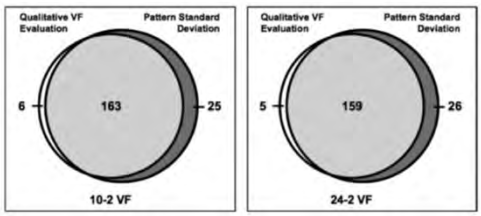


FIGURE 2. Proportional Venn diagram illustrating the level of agreement between the number of cases (eyes with, suspected of, or at risk of having glaucoma) that were detected at 95% specificity based on a qualitative evaluation by grader 1 of the 10-2 (Left) and central 12 locations of the 24-2 visual fields (VF; Right) or their pattern standard deviation values.

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What does this mean?

- "These findings should still not be taken to imply that 10-2 visual field testing is not useful in the early detection of glaucomatous central visual field abnormalities."
- Consider:
  - Potential impact on already limited healthcare resources if additional testing is routinely performed
  - Potential delay in time taken to recognize visual field progression in non-central regions if 10-2 are performed in lieu of 24-2 testing strategy.

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Value of 10-2 Visual Field Testing in Glaucoma Patients with Early 24-2 Visual Field Loss

Michael E. West, MASc, Glen P. Sharpe, MSc, Donna M. Hutchison, BSc, Paul E. Rafuse, MD, PhD, Lynne M. Shuba, MD, PhD, Marcelo T. Nicolela, MD, Jayme R. Vianna, MD, Balwantray C. Chauhan, PhD

Ophthalmology 2021;128:545-553

- 10-2 and central 12 test locations of 24-2 compared (total deviation and pattern deviation) for 97 glaucoma patients and 65 controls
- Results: No significant difference between 24-2 and 10-2 test
  - Sensitivity of 24-2 was significantly higher

90

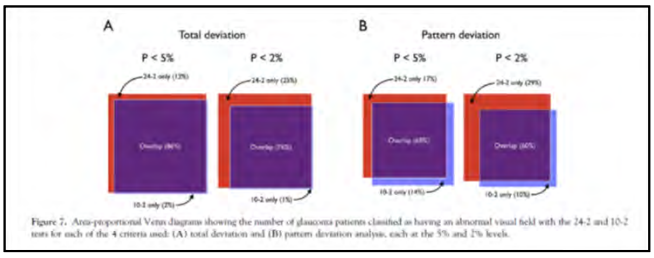
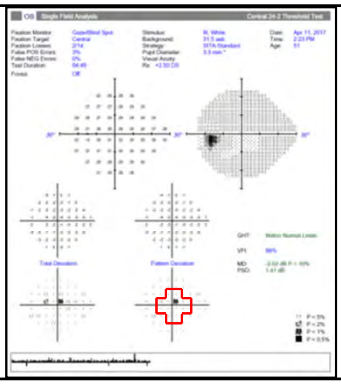


Figure 7. Area-proportional Venn diagrams showing the number of glaucoma patients classified as having an abnormal visual field with the 24-2 and 10-2 tests for each of the 4 criteria used: (A) total deviation and (B) pattern deviation analysis, each at the 5% and 2% levels.

Conclusion: Little evidence that adding the 10-2 test revealed additional undetected defects

91



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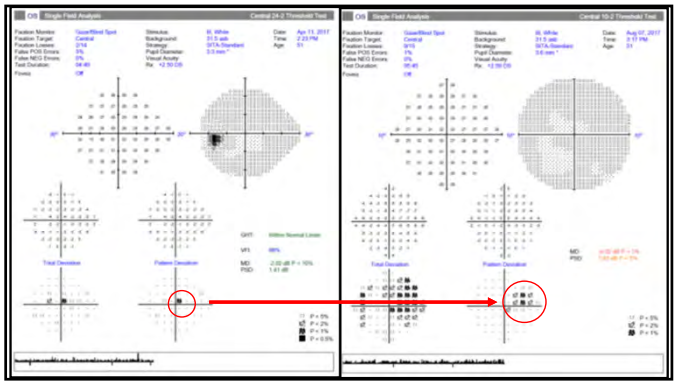

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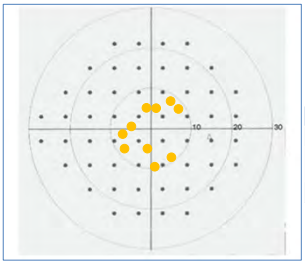
SITA Faster 24-2C Pattern on HFA3

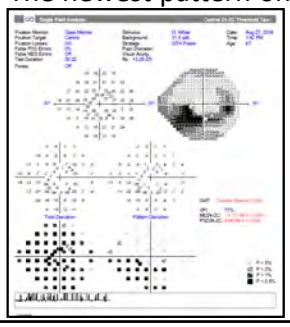


The 24-2C test pattern combines all 24-2 points + ten selected 10-2 points (shown in OD orientation)

Large Gray	24-2 pattern
Large Orange	Ten additional 24-2C points
Small Gray	10-2 pattern

94

24-2C: The newest pattern on the HFA



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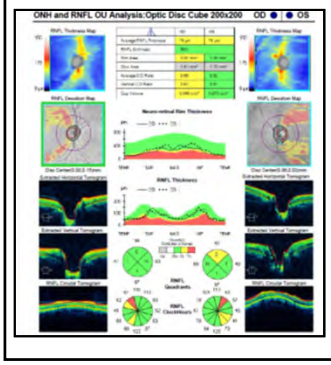

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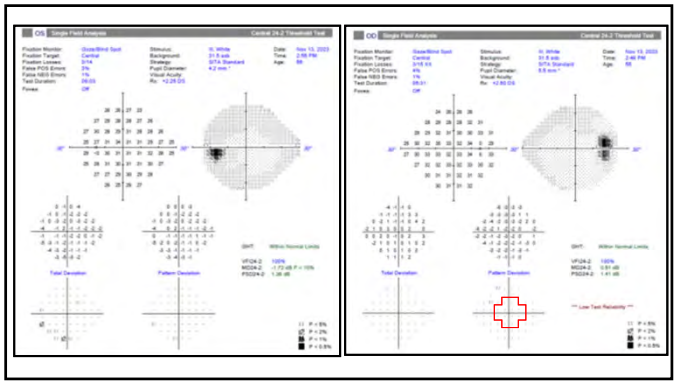

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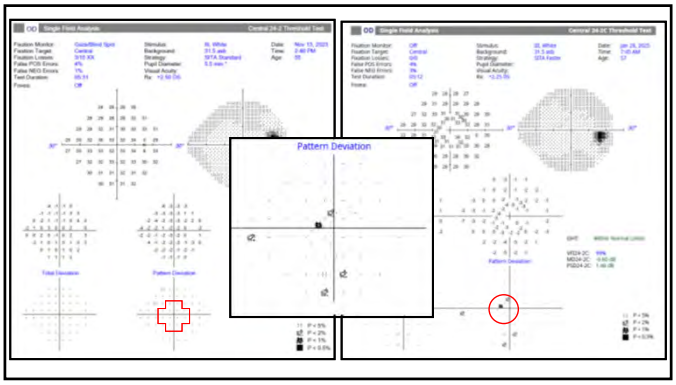
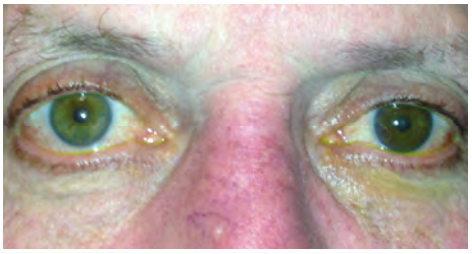


98

Identifying and managing allergies and sensitivities to glaucoma medications

99

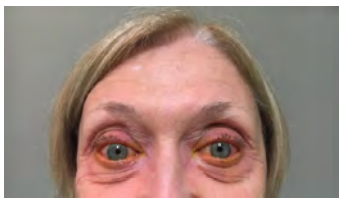


100

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

101



Brimonidine Allergy

102

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):719-730. Fingeret M, Sudder W, Bloomenstein M. Latanoprostene bunod ophthalmic solution 0.024%: a new treatment option for open-angle glaucoma and ocular hypertension. Clin Exp Optom. 2020;103(5):543-550.

103

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

Adverse Reactions	LBN (n=832)	TIMOLOL 0.68% (n=413)
Conjunctival Hyperemia	5.9%	1.5%
Eye Irritation	4.8%	2.8%
Eye Pain	3.8%	2.2%
Ocular Hyperemia	2.9%	0.7%
Instillation Site Pain	2.0%	1.9%

*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 0.4% 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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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 this 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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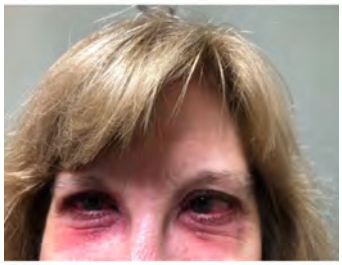

Rho Kinase
”Brimonidine effect”

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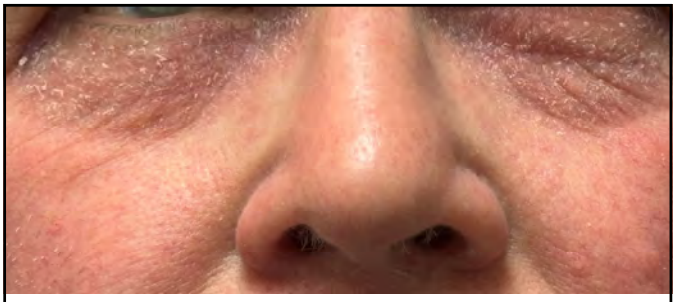

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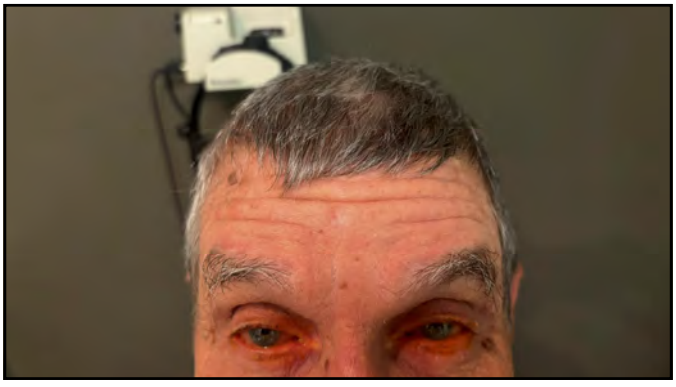

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54 YOWM

- History of HTN and Hypercholesterolemia
- History of Lymphoma; Treated and in remission
- Medications: Rosuvastatin, Losartan
- Ocular History: Unremarkable

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54 YOWM

- Presents to a screening where a retinal photograph was taken and blood discovered on review; Not a Drance Heme but active blood leakage
- Referred immediately for exam

- Baseline IOP Max=43mmHg OU
- Pachymetry 602 OD and 601 OS
- Gonio: open to CB 360 degrees OU with 3 + patchy pigment

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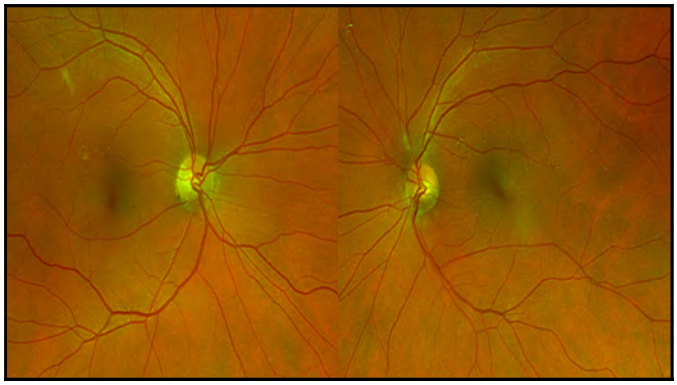

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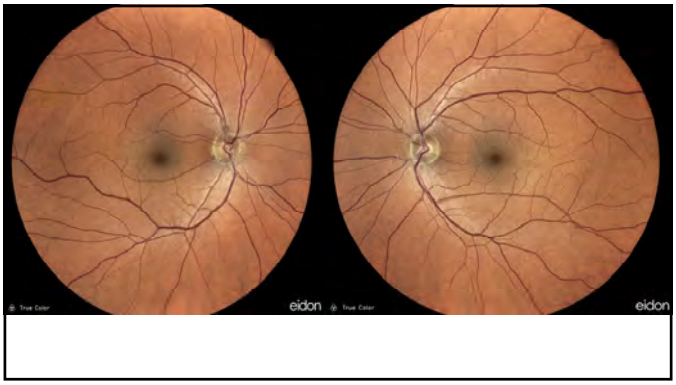

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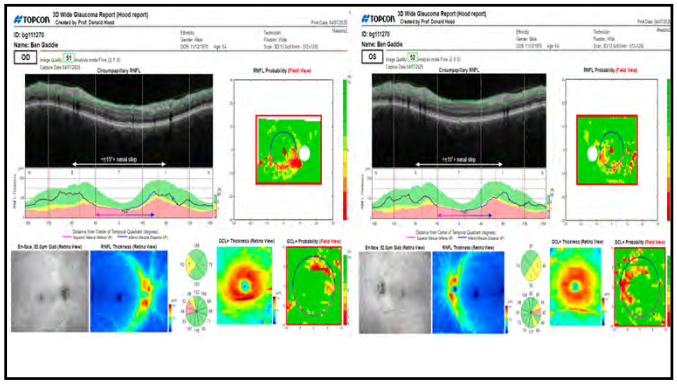

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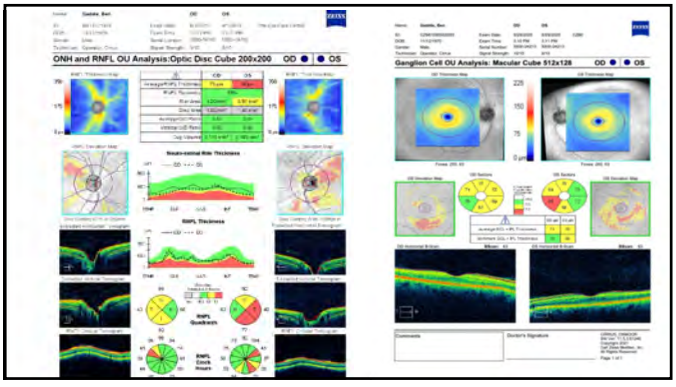

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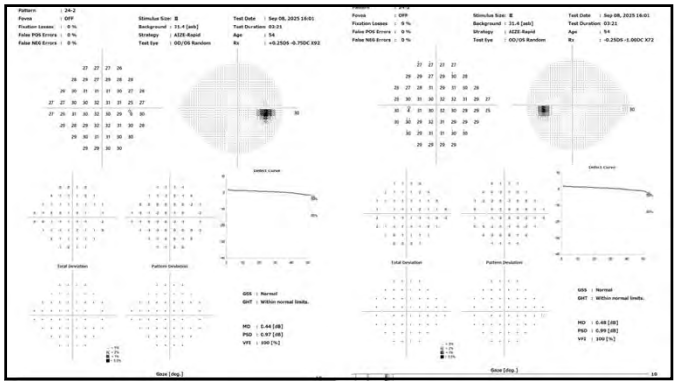

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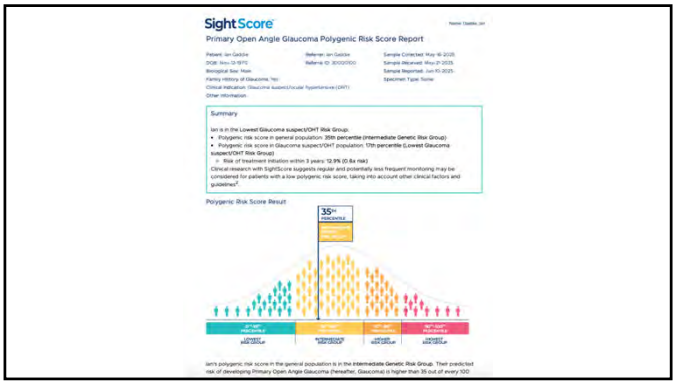

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Home IOP

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Started Treatment 4/20/25

- Latanoprostene (Vyzulta) QD HS OU
- Added OTC off label
  - Nitric Oxide orally
  - Pyruvate orally

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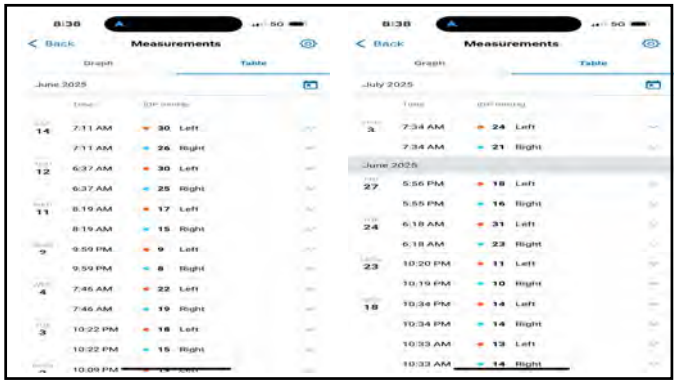

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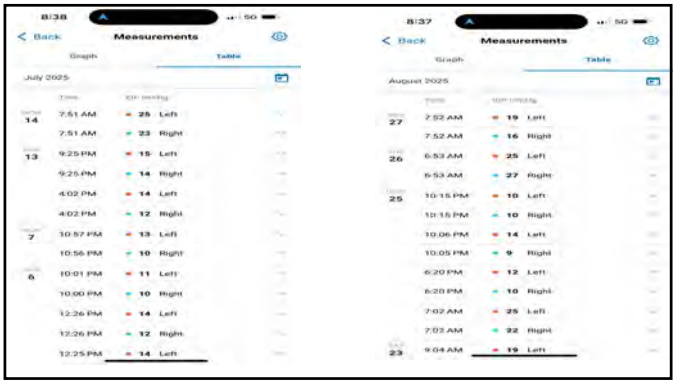

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Most Recent Treatments

- Still on Latanoprostene
- Direct SLT OS
- Standard SLT OD

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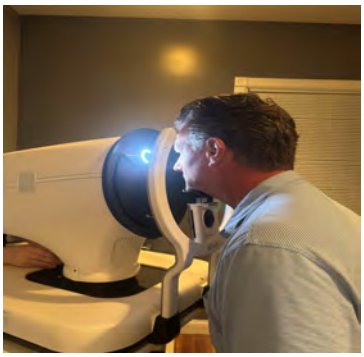

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AMERICAN ACADEMY OF OPHTHALMOLOGY

Randomized Noninferiority Trial of Direct Selective Laser Trabeculoplasty in Open-Angle Glaucoma and Ocular Hypertension

GLAUrious Study

Gus Gazzard, MA(Cantab), FRCOphth,[1,2] Nathan Congdon, MD, MPH,[3,4,5] Augusto Azuara-Blanco, PhD,[3] Eytan Z. Blumenthal, MD,[6,7] Ketevan Gomelauri, MD,[8] Monika Zaliniyan, MD,[9] Carlo E. Traverso, MD,[10] Zohar Bracha, MD,[11] Ana Dvalishvili, MD,[12] Yoram Solberg, PhD,[13] Michael Belkin, MA(Cantab), MD,[13,14] Thomas W. Samuelson, MD,[15] on behalf of the GLAUrious Study Group

Purpose: Effective glaucoma treatment is limited by nonadherence to medications and access to selective laser trabeculoplasty (SLT). The GLAUrious study compared automated, gonioscopy-free, noncontact, image-guided direct selective laser trabeculoplasty (DSLT) with conventional SLT in open-angle glaucoma (OAG) and ocular hypertension (OHT) to reduce intraocular pressure (IOP).

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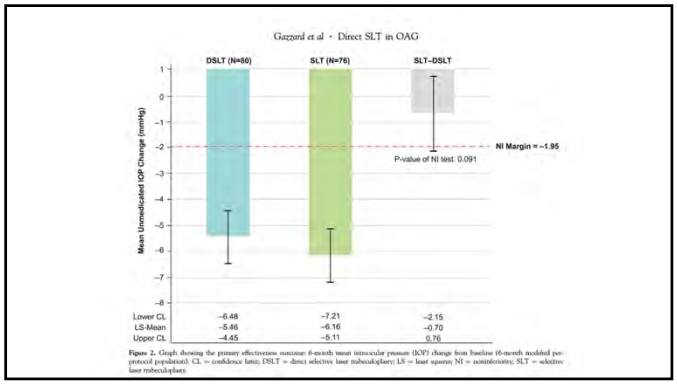

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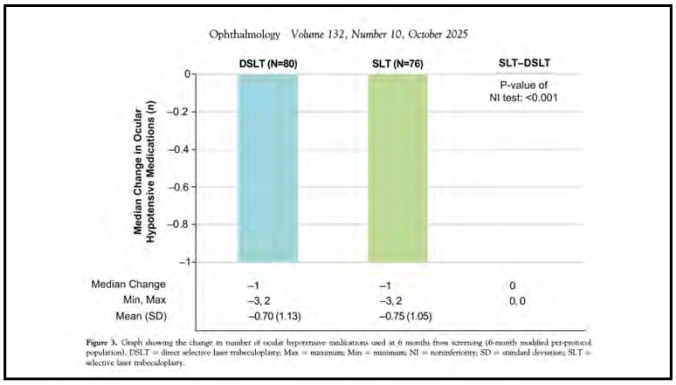

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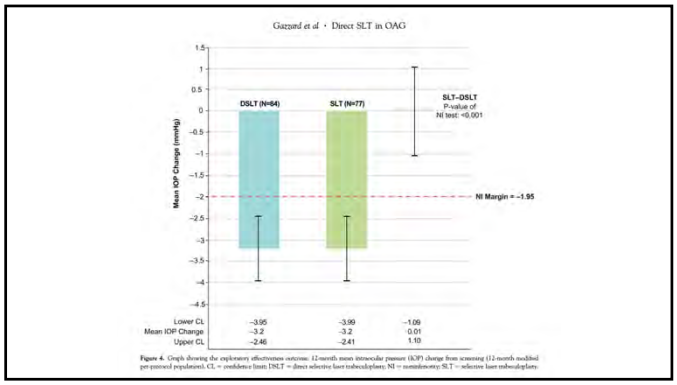

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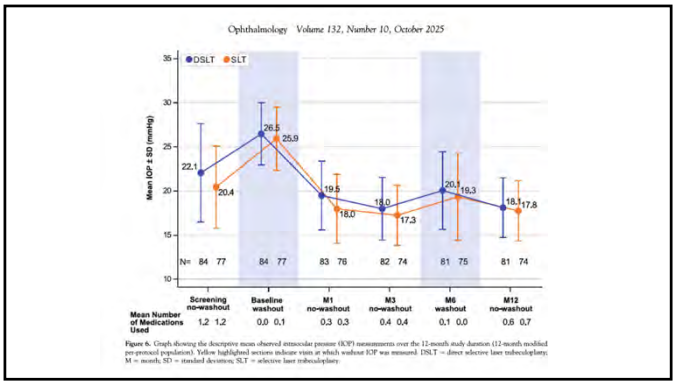

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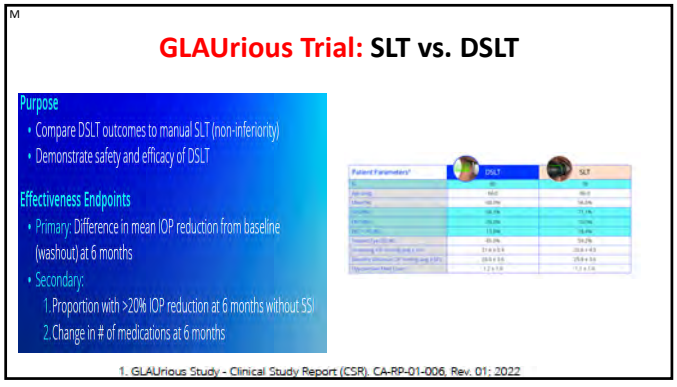

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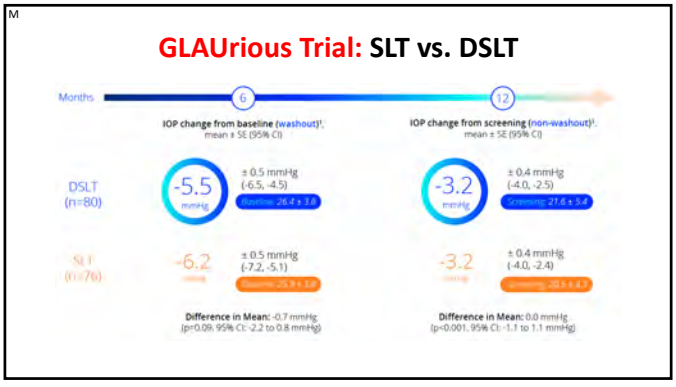

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Low-Energy Selective Laser Trabeculoplasty Repeated Annually: Rationale for the COAST Trial

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Abstract

At the 2018 annual meeting of the Association for Research in Vision and Ophthalmology (ARVO), Stephano Gandolfi presented a retrospective study of his patients at the University of Parma, Italy, in which a regimen of low-energy selective laser trabeculoplasty (SLT) repeated annually irrespective of intraocular pressure (IOP) produced significantly longer medication-free survival than standard SLT repeated as needed, in patients with primary open-angle glaucoma

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Abstract

At the 2018 annual meeting of the Association for Research in Vision and Ophthalmology (ARVO), Stephano Gandolfi presented a retrospective study of his patients at the University of Parma, Italy, in which a regimen of low-energy selective laser trabeculoplasty (SLT) repeated annually irrespective of intraocular pressure (IOP) produced significantly longer medication-free survival than standard SLT repeated as needed, in patients with primary open-angle glaucoma (POAG) or high-risk ocular hypertension (OHTN).[1] Specifically, newly-diagnosed POAG eyes were treated primarily either with ALT 360° performed once, standard SLT 360° repeated as needed at standard energy, and low-energy 360° SLT (0.4 mJ/spot x 50–60 spots) repeated annually at low energy regardless of IOP. After 10 years of follow-up, medication-free rates were 22.6% in the ALT group, 25.0% in the standard SLT group, and 58.3% in the low-energy SLT group ($p<0.001$). The median times to medication were 2.8 years, 3.2 years, and 6.2 years, respectively. In light of the recent Laser in Glaucoma and Ocular Hypertension Trial (LiGHT)

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~15 years after the diagnosis of POAG.[11,19] If we validate an SLT treatment strategy that extends the duration of medication-free disease control, we move one step closer to the possibility of a drop-free lifetime for our patients. Delaying the need for medications by 3, or 5, or 7 years not only confers all the benefits of medication-freedom during this period (which will be all that many patients would need in their lifetimes)—it also allows time for development of safer and more effective drugs dosed infrequently via sustained-release delivery systems, as well as better surgical options, for patients whose lifespans exceed SLT responsiveness. Thus, a new treatment paradigm consisting of SLT, then sustained-release medications, followed by minimally invasive glaucoma surgery and then—for the few who will progress this far—filtering procedures could offer the majority of glaucoma patients the very real possibility of a drop-free lifetime of therapy. As instruments to measure glaucoma *treatment-related* quality of life are developed and validated, the benefits of freedom from the responsibility and detractions of daily medication self-dosing on our patients' well-being are likely to become apparent as well.

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Baseline Considerations to Co-Manage with a Glaucoma Specialist

- First you need to figure out what you are comfortable with managing:
  - Do you need help making the diagnosis at times, but comfortable managing primary therapy?
  - Do you need help when primary therapy consists of SLT?
  - Do you need help when needing adjunctive therapy (meds or SLT)?
  - Are you uncomfortable after 2 bottles of medications?
  - Are you uncomfortable when you discover progression of glaucoma?
  - Do you need help when referring a patient for cataract surgery who has glaucoma?
- For these needs, find a glaucoma oriented OD or MD in your community!

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Baseline Considerations to Co-Manage with a Glaucoma Specialist

- Do you need help with a Xen stent, Trab/Tube or advanced MIGS?
- Complicated angle closure/plateau iris cases requiring
  - Lensectomy
  - Goniosynechiaelysis
  - Persistent narrow angles after LPI
  - Narrow angles after NAG attack despite LPI
- Patients experiencing larger fluctuations in glaucoma that are difficult to control
  - Example PXE/PG
  - Patients who have lost substantial or all vision in one eye from glaucoma

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Baseline Considerations to Co-Manage with a Glaucoma Specialist

- Absolute no-no's for sending patients to a glaucoma specialist
  - You don't want to treat or "mess with" glaucoma
  - You don't have the equipment to diagnose or manage glaucoma
  - You don't take medical insurance

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What Data Do I Need Before Even Considering Referral to a Glaucoma Specialist?

- At least 3 but preferably 5-10 years of Visual Field and OCT RNFL testing
  - Very few patients present with newly diagnosed glaucoma and need glaucoma surgery within 3-5 years
- Tmax in each eye and IOP trends for as long as they are available
  - Initial response to PGA/SLT
- Pachymetry readings
- Gonioscopic findings
- Medications tried and their effect on IOP
- Any medication allergies/side effects

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Common Complications of Glaucoma Surgery for the Referring Doctor

- Hypotony
- Bleb leak
- Hyphema
- Choroidals
- Inflammation of bleb
- Scarring
- Pupil issues

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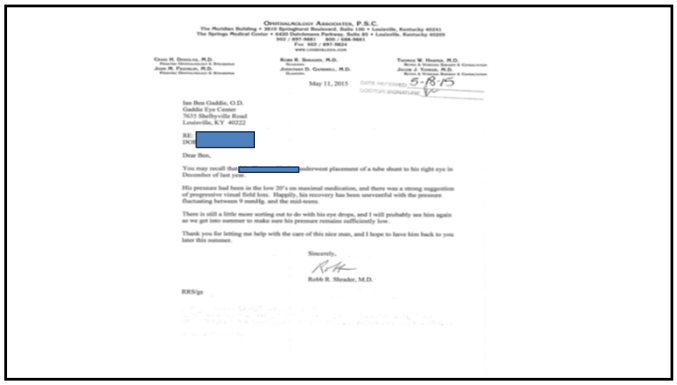

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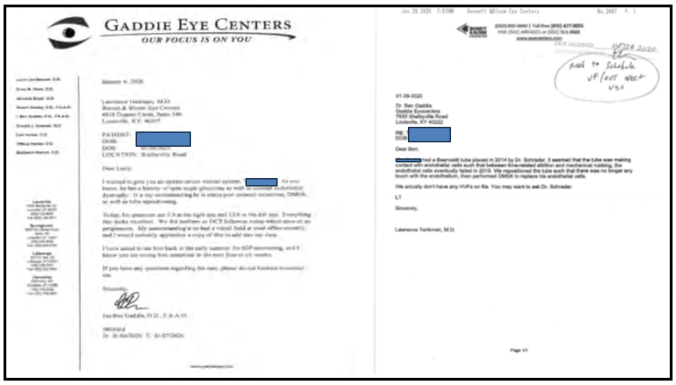

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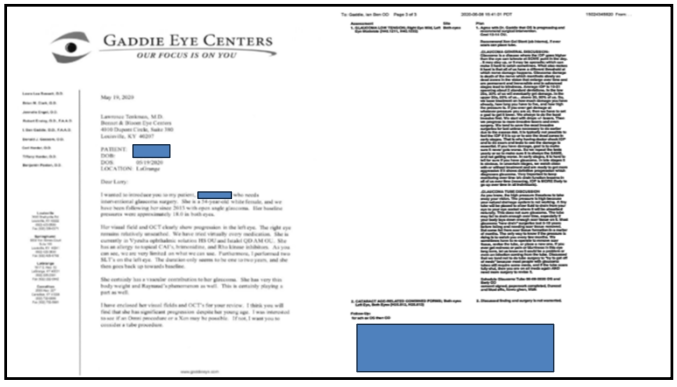

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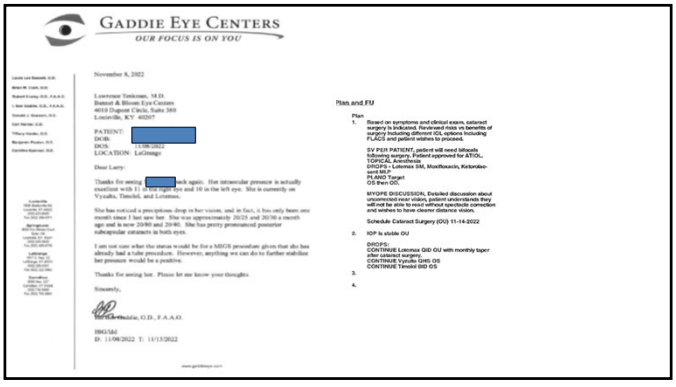

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Additional Considerations When Co-Managing Glaucoma with a Glaucoma Specialist

- When you are watching IOP after surgery or other intervention, let the specialist know what the IOPs have been running; possibly after each visit or every 6 months
- Forward copies of VF and OCT RNFL as appropriate if further surgery is being contemplated

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