


A Roadmap for Making the Diagnosis in Glaucoma

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Disclosures

Michael Chaglasian, O.D.

- In the past 12 months Dr Schmidt has received honoraria or compensation from the following Companies:
  - Aerie- Advisory Board, Speaker Bureau
  - Allergan- Advisory Board, Speaker Bureau
  - Avellino - Research
  - B+L- Advisory Board, Speaker Bureau
  - Carl Zeiss - Consultant, Advisory Board
  - Equinox- Research
  - Topcon- Consultant
  - Optos- Research

Eric E. Schmidt, O.D.

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  - Carl Zeiss – Consultant, Advisory Board
  - Sun- Advisory Board
  - Eyenovia – Consultant
  - Kala – Speakers Bureau

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Topics/Sections

1. **Who is the Glaucoma Suspect?**
   - **Know the Key Risk Factors**
2. **How to evaluate the glaucomatous optic disc?**
   - **Yes, you still have to do this**
3. **Perimetry: The Essentials**
   - **No, they haven't gone away.**
4. **OCT Imaging: The Essentials**
   - **Really get know your device and what it's telling (or not!)**

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Who is the Glaucoma Suspect?

This starts with a Risk Factor Assessment.

Risk Assessment in Clinical Practice: (quick look at 3)

- **Family History**
- **Diabetes**
- **Systemic Hypertension**

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Risk Factors: Family History

- POAG is a multi-factorial polygenetic disease
- Rotterdam Study:
  - the lifetime absolute risk of glaucoma at age 80 years was found to be almost 10 times higher for individuals having relatives with glaucoma, (22.0 versus 2.4%).
  - "family history alone cannot account for the observed proportion of the disease, suggesting that non-genetic factors play a significant role in the overall occurrence of glaucoma."

Ophthalmol 112(9) 2005

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Genetics in Glaucoma


Genetics and genetic testing for glaucoma

Matthew A. Miller, John H. Fingert, and Daniel I. Bettis


ARTICLE

The UK Biobank resource with deep phenotyping and genomic data

The African Descent and Glaucoma Evaluation Study (ADAGES) III

Contribution of Genotype to Glaucoma Phenotype in African Americans: Study Design and Baseline Data

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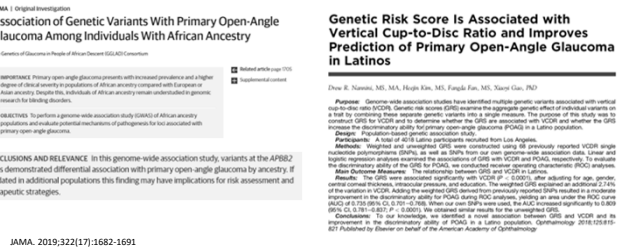
Genetics in Glaucoma



JAMA | Original Investigation

Association of Genetic Variants With Primary Open-Angle Glaucoma Among Individuals With African Ancestry

The Genetics of Glaucoma in People of African Descent (GGLAD) Consortium

IMPORTANCE Primary open-angle glaucoma presents with increased prevalence and a higher degree of clinical severity in populations of African ancestry compared with European or Asian ancestry. Despite this, individuals of African ancestry remain understudied in genomic research for blinding disorders.

OBJECTIVES To perform a genome-wide association study (GWAS) of African ancestry populations and evaluate potential mechanisms of pathogenesis for loci associated with primary open-angle glaucoma.

CONCLUSIONS AND RELEVANCE In this genome-wide association study, variants at the *APBB2* locus demonstrated differential association with primary open-angle glaucoma by ancestry. If validated in additional populations this finding may have implications for risk assessment and therapeutic strategies.

JAMA. 2019;322(17):1682-1691

Genetic Risk Score Is Associated with Vertical Cup-to-Disc Ratio and Improves Prediction of Primary Open-Angle Glaucoma in Latinos

Drew R. Nannini, MS, MA, Hojin Kim, MS, Fangda Fan, MS, Xiaoyi Gao, PhD

Purpose: Genome-wide association studies have identified multiple genetic variants associated with vertical cup-to-disc ratio (VCDR). Genetic risk scores (GRS) examine the aggregate genetic effect of individual variants on a trait by combining these separate genetic variants into a single measure. The purpose of this study was to construct GRS for VCDR and to determine whether the GRS are associated with VCDR and whether the GRS increase the discriminatory ability for primary open-angle glaucoma (POAG) in a Latino population.

Design: Population-based genetic association study.

Participants: Total of 6489 participants enrolled from Los Angeles.

Methods: Weighted and unweighted GRS were constructed using 68 previously reported VCDR single nucleotide polymorphisms (SNPs), as well as SNPs from our own genome-wide association data. Linear and logistic regression analyses examined the associations of GRS with VCDR and POAG, respectively. To evaluate the discriminatory ability of the GRS for POAG, we conducted receiver operating characteristic (ROC) analyses.

Main Outcome Measures: The relationship between GRS and VCDR in Latinos.

Results: The GRS were associated significantly with VCDR ($P < 0.0001$), after adjusting for age, gender, central corneal thickness, intraocular pressure, and education. The weighted GRS explained an additional 2.74% of the variation in VCDR. Adding the weighted GRS derived from previously reported SNPs resulted in a moderate improvement in the discriminatory ability for POAG during ROC analyses, yielding an area under the ROC curve (AUC) of 0.770 (95% CI, 0.753-0.787). When our own SNPs were used, the AUC increased significantly to 0.809 (95% CI, 0.791-0.827; $P = 0.0015$). We obtained similar results for the unweighted GRS.

Conclusions: To our knowledge, this is the first study to examine the association between GRS and VCDR and its improvement in the discriminatory ability of POAG in a Latino population. *Ophthalmology 2018;125:815-821* Published by Elsevier on behalf of the American Academy of Ophthalmology

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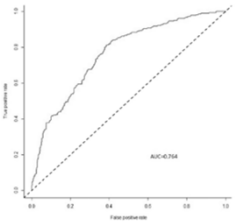
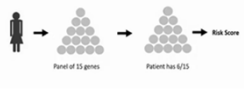
Genetic Factors and Screening



- To assess POAG genetic risk need to test multiple genes at once- 'genetic risk score'
- Polygenic risk scores based on sufficiently large and well-powered genome-wide association studies provide the best estimate of disease risk



Nat Genet. 2018 June ; 50(6): 778–782.

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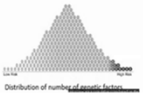
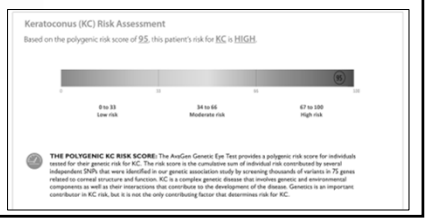
Polygenic Risk Score

Polygenic risk scores (PRS)

- PRS is the cumulative impact of genome-wide risk factors.
- Individuals are scored based on how many risk factors they carry.





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Risk Factors: Diabetes

- **Yes, a Risk Factor: ~1.35x greater risk**
  - **Just NOT very strong**
    - Beaver Dam Eye Study
    - Blue Mountains Eye Study
    - Nurses' Health Study
    - Los Angeles Latino Eye Study
- Progression Risk Yes:
  - EMGT and AGIS
- Progression NOT a Risk:
  - Barbados Eye Study

PLOS ONE

Diabetes Mellitus as a Risk Factor for Open-Angle Glaucoma: A Systematic Review and Meta-Analysis

Minwen Zhou[1-3], Wei Wang[1], Wenbin Huang[1], Xiulan Zhang[1-3]*

Abstract

Objective: To determine the association between diabetes mellitus (DM) and primary open-angle glaucoma (POAG).

Methods: This is a systematic review and meta-analysis of case-control and cohort studies. The literature search included two databases (PubMed and Embase) and the reference lists of the retrieved studies. Separate meta-analyses for case-control studies and cohort studies were conducted using random-effects models, with results reported as adjusted odds ratios (ORs) and relative risks (RRs), respectively.

Results: Thirteen studies—seven case-control studies and six population-based cohort studies—were included in this meta-analysis. The pooled RR of the association between DM and POAG based on the risk estimates of the six cohort studies was 1.40 (95% CI, 1.25–1.57). The pooled OR of the association between DM and POAG based on the risk estimates of the seven case-control studies was 1.35 (95% CI, 1.06–1.74). There was significant heterogeneity among the case-control studies that reported an association between DM mellitus and POAG ($I^2 = 0.001$) and no significant heterogeneity among the cohort studies ($I^2 = 0.377$). After omitting the case-control study that contributed significantly to the heterogeneity, the pooled OR for the association between DM and POAG was 1.35 (95% CI, 1.06–1.74).

Conclusions: Individuals with DM have an increased risk of developing POAG.

- Older Data:
- DM is NOT a risk factor:
  - Baltimore Eye Survey
  - Barbados Eye Study
  - European Glaucoma Prevention Study
  - Rotterdam Study
  - Visual Impairment Project

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Diabetes Summary

- The current literature does not provide a definitive link between DM and POAG.
- Vascular dysregulation in diabetes likely has a component in glaucoma disease but is likely *NOT a sole, initiating cause* of glaucoma,
- Should only be considered as a *modest* RF compared to other RFs (eg family history and CCT)

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Risk Factors: Systemic Hypertension

- No definitive link to elevated BP
  - NO association in several studies
  - High Blood Pressure may be "Protective"
  - **Low BP is a factor in Ocular Perfusion Pressure**
    - OPP=DBP-IOP
    - Increased at OPP of <50-55 mmHg
  - OVER treatment of HTN can be an issue (BP too low)
- Cardiovascular Disease
  - no solid evidence of RF link

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Some Basic Guidelines:

Short Overview and Highlights

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OHTS and Corneal Thickness

- For all IOP's, a *thinner cornea increased the risk* of developing glaucoma at 5 yrs

	CCT Microns		
IOP	<555	>555-<588	>588
>25.75	36%	13%	6%
>23.75-<25.75	12%	10%	7%
<23.75	17%	9%	2%

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OHTS & CCT: 3 Outcomes

- Thin: <555 µm — High Risk (thus treat!)
- Average: 555-588 µm — No change in Risk (treat or monitor, use other RFs)
- Thick: >588 µm — Low Risk

Applies to only to patients with ocular hypertension

Know this!

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Diagnosis In The Glaucoma Suspect —When To Treat?

- Glaucoma suspects can be (broadly) categorized into two groups:
  1. Ocular hypertensive subjects with risk factors for the future development of glaucoma
     - **These patients are addressed by OHTS data and who to treat**
  2. Subjects with questionable glaucomatous findings that cannot definitely be distinguished from normal
     - e.g., suspicious appearance of optic disk, RNFL/GCA or VF and
       - IOP that is 21 mmHg or lower

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Open Angle Glaucoma Suspect

- **The Decision Tree:**
  - The patient **without** OCT, VF or ONH damage
  - This may be someone with IOP >21 or <21 mmHg

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Who do you treat? Options, Bias, Preferences

- Rather than a simplistic approach of treating everyone with an IOP of over 21 mmHg, treatment is held off until there is sufficient evidence of glaucoma damage at some level (OCT, VF,)
  - This is a practice philosophy that can be followed for ***low risk*** patients
- **Or, we elect to treat those with the most significant risk factors.**

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Early Glaucoma or Not? Example findings

Pro

- Family history
- Elevated IOP

One Way to Organize and Sort Risk Factors

Mixed

- **Suspicious optic nerve**
- **CCT = 570**
- **Unreliable VF**

Con

- Normal OCT
- Younger age

What do you do?

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Glaucoma Suspect: The Ocular Hypertensive

- ***IOP 21-30+ mmHg with***
  - Normal appearing or suspicious optic nerve, But NO definitive changes!
    - no visual field defects
  - some risk factors
  - **Follow OHTS Treatment Guidelines:**

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Glaucoma Suspect: IOP under 21

- Management Options:
  - no single treatment plan nor guidelines, varies with every patient, must be individualized

1. Follow these patients every 3-6 months with observation and repeated: ONH, VF, OCT, IOP
   - Wait until confirmation of true OCT/VF defect, ONH *change*
2. Or, may initiate therapy for those with **3** or more risk factors:
   positive family history,
   - C/D ratio 0.8 or greater, asymmetry of the nerve heads
   - African American; diabetes, etc.
   - Questionable visual field defects, fluctuating IOP

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Patients Who Require Therapy:

- At any IOP
  1. *Glaucomatous* ONH Changes
     - As identified by you or via photograph, OR
  2. Strongly abnormal, characterstic and *reliable* OCT
     - This must have some "clinical correlation"
     - Rarely do you treat based upon this *alone* (patient has other findings)
     - Watch out for "Red Disease"
  3. Characteristic/Confirmed Visual Field Loss
     - (***not required for diagnosis***)
- OHTN with IOP over 30 mmHg
  - Some exceptions; eg very, thick cornea

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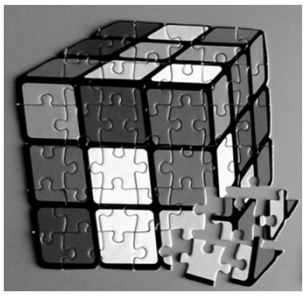
Glaucoma diagnosis can be a very complex puzzle:



- Requirements
  - Organized, step-by-step approach
  - Sort and organize the data
  - Identify good data
  - Ignore bad/unreliable data
  - Confirm data when necessary
  - Sort and organize again
  - No need to rush your decision
  - Individualize to your patient
- Begin therapy (later) or monitor

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CASE EXAMPLE

56 yo
+ Fam Hx of Glaucoma
Systemic HTN (lisinopril/HCTZ)

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Visit Date	OD	OS
04/11/2017	22	34
01/17/2017	22	32
11/15/2016	23	25
09/20/2016	19	20
03/14/2016	23	26
03/06/2014	18	20
10/15/2012	17	20

Discussion

OHTN?
Early Glaucoma?
Treat? Don't Treat?
Monitor? How Frequently?
Other Information?
Next Steps?

What is the future risk?

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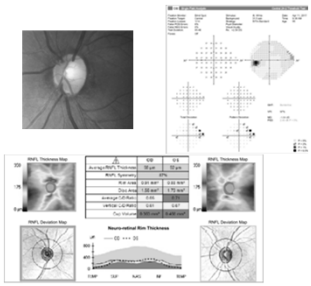
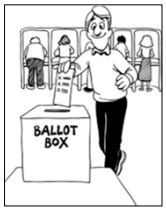
Back to our Patient: Treat or Observe?





Can we get additional information?

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How to Manage OHTN?

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OHTS Risk Calculator (online)

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OHTS Risk Calculator (online)

FACTORS							
Age 55	RIGHT EYE MEASUREMENTS			LEFT EYE MEASUREMENTS			
	1st	2nd	3rd	1st	2nd	3rd
Untreated Intraocular Pressure (mm Hg)	23	22	22	25	32	34
Central Corneal Thickness (microns)	556	556	556	561	561	561
Vertical Cup to Disc Ratio by Contour	0.40			0.60		
Pattern Standard Deviation (Humphrey (dB) / Octopus loss variance (dB))	1.7			2.4		

Print Reset 16.3% The patient's estimated 5-year risk (%) of developing glaucoma in at least one eye.

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What does OHTS Risk Mean?

Expert Panel Recommendations	
< 5%	No treatment
5-15%	Treatment optional
>15%	Treatment recommended

- These are suggested guidelines only, treat every case individually
  - Must consider all and other factors (family Hx, Drance Heme, age.)

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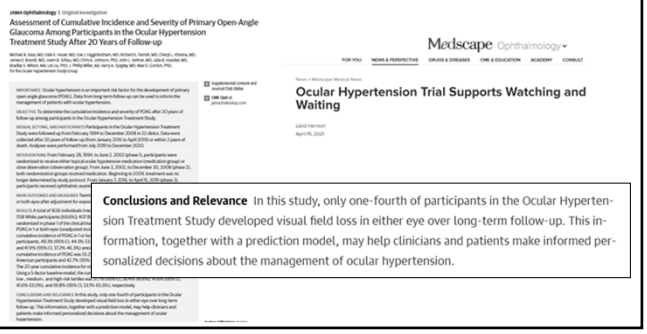
OHTS 20 Years: The difference is Risk Factors:



Assessment of Cumulative Incidence and Severity of Primary Open-Angle Glaucoma Among Participants in the Ocular Hypertension Treatment Study After 20 Years of Follow-up

Medscape Ophthalmology

Ocular Hypertension Trial Supports Watching and Waiting

Conclusions and Relevance In this study, only one-fourth of participants in the Ocular Hypertension Treatment Study developed visual field loss in either eye over long-term follow-up. This information, together with a prediction model, may help clinicians and patients make informed personalized decisions about the management of ocular hypertension.

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Ocular Hypertension: When is Therapy Indicated?

- When there are other (multiple) significant Risk Factors:
  - CCT under 555 microns
  - Family History
  - Disc Hemorrhage
  - Vertical CD ratio
  - Low Ocular Perfusion Pressure
- When Risk Calculation is over ~ 15%

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CASE EXAMPLE

with IOP in normal range

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CASE 2

44 yo, Black, Male
Last exam at Vision Center 1 month earlier
“large cupping”

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History and Clinical Data

- VA = 20/20 OD, OS
- Entrance Tests = normal
- Slit Lamp Exam = unremarkable
- IOP
  - 16 OD mmHg @ 9:00 AM
  - 15 OS
- Family History
  - Mother with POAG
    - On topical meds
- Gonioscopy
  - Open to Ciliary Body 360 OU
  - Moderate Pigment

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Discussion

Glaucoma with IOP in the Normal Range (Normal Tension Glaucoma)

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Nocturnal IOP and Glaucoma

- Most individuals spend 1/3rd of day asleep in recumbent position
- Habitual IOPs of most untreated glaucomas higher during nocturnal/sleep period than office hours
  - IOP measured sitting during day and supine position at night
- Important to understand and recognize this
  - May explain why glaucomatous damage occurring in certain individuals

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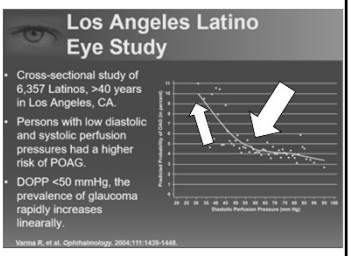
Ocular Perfusion Pressure (OPP) = <50mmHg

- The differential between arterial (diastolic) BP and IOP
  - OPP = DBP-IOP
    - eg 65 mmHg - 20 mmHg = 45
- Ocular perfusion is regulated to maintain constant blood flow to the optic nerve despite fluctuating blood pressure and IOP
- The major cause of reduced blood flow is thought to be secondary to vascular dysregulation in susceptible patients, resulting from abnormal/insufficient autoregulation.



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Clinical Control of OPP

- **Lower IOP improves OPP**
  - **Remains number 1 goal !!**
- **Measure blood pressure on your patients**
- **Higher systemic BP improves OPP, but you do not necessarily want to raise BP:**
  - **Stroke #3 cause of death in US behind CVD & CA!**
  - **Avoid drugs that lower systemic BP beyond patient's desired systemic control.**
  - **Avoid nocturnal hypotension.**
  - **Communicate with PCP**

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To treat or not to treat? IOP Guidelines: Randomized Clinical Trials

- IOP Is the Most Prominent and Consistent Glaucoma Risk Factor
  - Important Considerations and Facts
    - **Ocular Hypertension Treatment Study (OHTS)**
      - CCT of less than 555 µ has higher risk
      - IOP: every 1mmHg higher (>22) increased risk by 10%
    - **Early Manifest Glaucoma Trial (EMGT)**
      - Every 1mmHg of IOP reduction lowers risk of progression by 10%

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To treat or not to treat? IOP Guidelines: Randomized Clinical Trials

- **Advanced Glaucoma Intervention Study (AGIS)**
  - Another IOP related factoid:
    - IOP always under 18mmHg, or keeps a mean of 12mmHg, has a lower risk of progression
- **Collaborative Normal-Tension Glaucoma Study**
  - 30% reduction of IOP reduces risk of progression
  - Note that many patients with NTG do not progress, while other with 30% IOP reduction continue to progress

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Yes, you still need to look at the optic disc.

Optional Review Section

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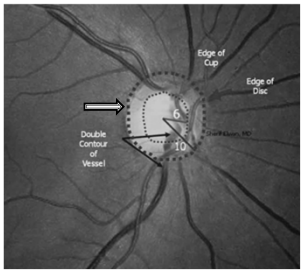
Optic Disc Defined

Neural Retinal Rim (NRR)



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Glaucomatous Disc Features

Descriptive terms to know : examples coming up

- *increased* (meaning it changed) cup-to-disc ratio or significant cup asymmetry;
- decreased or documented change in neuroretinal rim area;
- *notch* of the neuroretinal rim;
- *saucerization* of neuroretinal rim;
- flame-shaped *disc hemorrhage*;
- nerve fiber layer loss;
- peripapillary atrophy
- Laminar dot sign (non-specific)

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TIPS and PITFALLS

- Do not emphasize the C/D ratio
- Concentrate on the neural retinal rim
- Look for focal defects (notching) and and/or generalized thinning
- Evaluate symmetry between eyes
- Disc Hemes
- Peripapillary atrophy
- Baring of circumlinear vessels
  - Loss of NRR tissue

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Examples of ONHs

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CASE JM

54 YO, AA
IOP
IOP Range = 16- 20 OD; 16-19 OS
CCT= 462 OD 468 OS
CH = 8.8

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CASE LP

43 year old male
Referred for Possible Open Angle Glaucoma

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Visual fields: are still essential!

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GLAUCOMA SEVERITY SCALE DEFINITIONS:

- **Mild Stage:**
  - optic nerve changes consistent with glaucoma but *NO visual field abnormalities on any visual field test*
- **Moderate Stage:**
  - optic nerve changes AND glaucomatous visual field abnormalities in hemifield and not within 5 degrees of fixation.
- **Severe Stage:**
  - optic nerve changes consistent with glaucoma AND glaucomatous visual field abnormalities in both hemifields and/or loss within 5 degrees of fixation in at least one hemifield.
- ***If both of the patient's eyes are glaucomatous, code for the more severe stage of the two eyes.***

American Glaucoma Society

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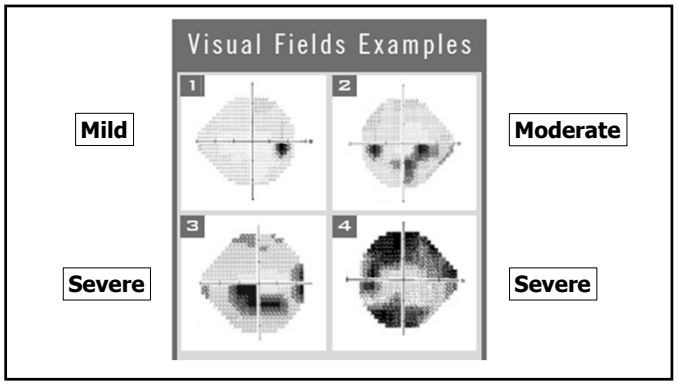

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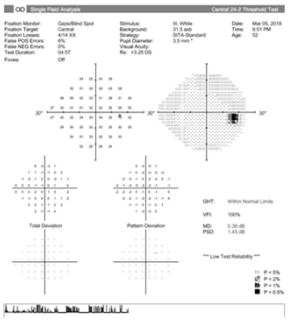
AGS def: Mild Stage Glaucoma



- Patient would have other definite signs of glaucoma:
  - ONH notching
  - OCT/RNFL loss
- **"Pre-Perimetric"** is another term that is sometimes used

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Perimetry: The Essentials

- Central VF Testing (cont.)
  - Rationale (Don Hood papers)
    - Macular Zone Vulnerability
- How and when use 10-2 VFs or the new 24-2C (adds 10 Central test points):
  - Good Test Takers, Younger patients
  - Minimal to no defects on 24-2
  - OCT Macula/Ganglion Cell scan is abnormal
  - High Risk Patients

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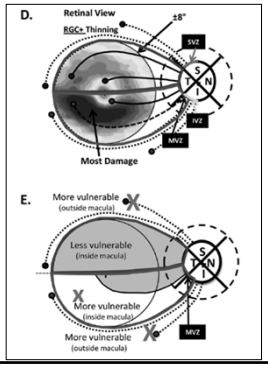
Review of Why?

Don Hood, PhD.


Progress in Retinal and Eye Research

Improving our understanding, and detection, of glaucomatous damage: An approach based upon optical coherence tomography (OCT)

Donald C. Hood



Progress in Retinal and Eye Research 57 (2017) 46e75

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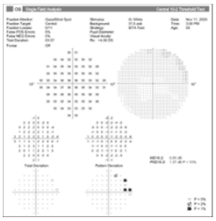
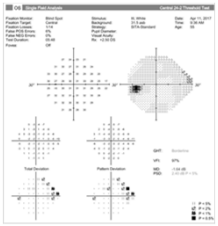
Central Field Testing: 10-2 vs 24-2

64 test Locations 2 deg sep

12 test Locations 6 deg sep





Limitations with Both

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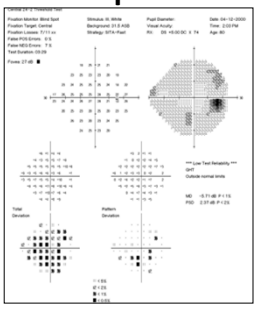
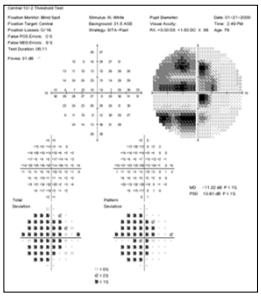
One Example: 24-2 10-2





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Now, no more choosing between 10-2 and 24-2, or having to do both:

"24-2C"

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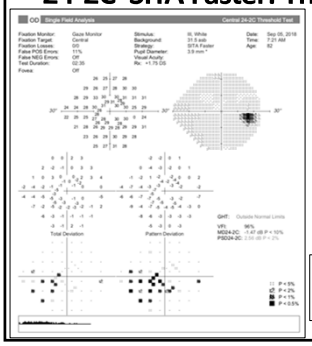
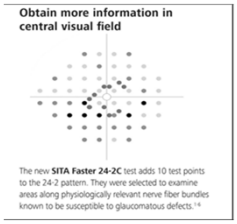
24-2C SITA Faster: The Latest Standard:





The 24-2C is able to detect visual field loss in the central 10° that corroborates with loss detected in the 10-2 pattern. The 24-2C exhibits potential to be used as a hybrid between the 24-2 and 10-2 to better evaluate visual field defects.

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24-2C and 10-2: Several Recent Publications

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

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

CONCLUSIONS:

- The similarity in performance of the 10-2 and C24-2 test suggests that the increased sampling density of the former does not significantly improve the detection of central visual field abnormalities, even when based on expert assessment.
- These findings should not be taken to mean that the 10-2 test is not useful, but it underscores the need for its utility to be clearly established before incorporating it as routine glaucoma standard of

Am J Ophthalmol. 2021 Sep;229:26-33. doi:

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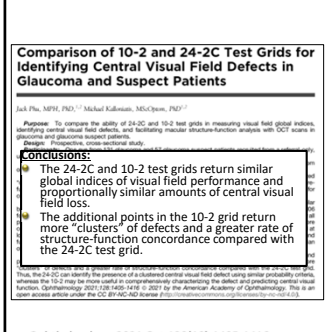


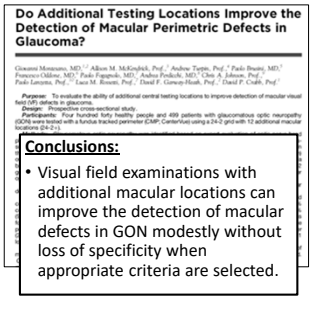
Comparison of 10-2 and 24-2C Test Grids for Identifying Central Visual Field Defects in Glaucoma and Suspect Patients

Jack Phu, MPH, PhD,[1,2] Michael Kalloniatis, MSc(Optom, PhD[1,2]

Conclusions:

- The 24-2C and 10-2 test grids return similar global indices of visual field performance and proportionally similar amounts of central visual field loss.
- The additional points in the 10-2 grid return more "clusters" of defects and a greater rate of structure-function concordance compared with the 24-2C test grid.

Ophthalmology. 2021 Oct;128(10):1405-1416



Do Additional Testing Locations Improve the Detection of Macular Perimetric Defects in Glaucoma?

Conclusions:

- Visual field examinations with additional macular locations can improve the detection of macular defects in GON modestly without loss of specificity when appropriate criteria are selected.

Ophthalmology 2021;128:1722-1735

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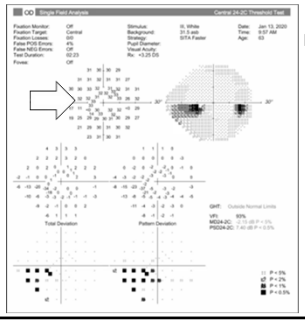
New 24-2C pattern: 10 additional central points



Note:
- Runs new SITA-Faster algorithm
- Test time ~2.5 minutes
- **Perhaps can avoid 10-2 VF**
  - **No published evidence for this yet**
- Can be integrated with other tests for Progression Analysis
- Can have high False Positives (>15%)
  - Best for reliable/good VF test takers
- May not compare exactly to other tests
- May not be best for baseline tests
  - Note both baseline tests must be the same in order to start GPA

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OCT, also Essential, Three Tips

Review of Key Points and Demonstrated on Case Examples

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Tip #1:
Know your OCT and its Report

(too) Many Options!!

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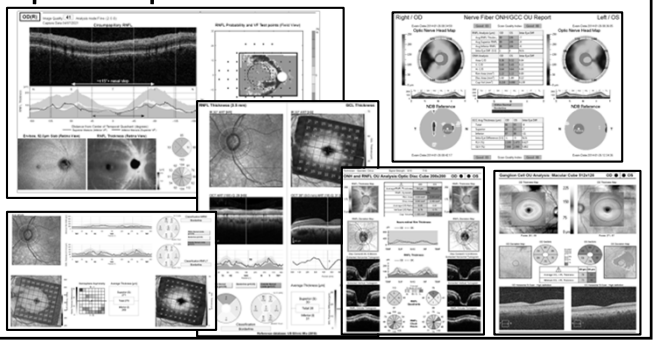
Report Examples: More similarities than differences



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Tip #2:
Assure a Quality Image without an Artifact

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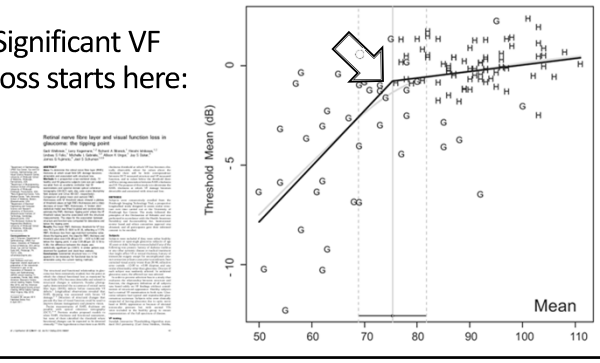
Significant VF loss starts here:



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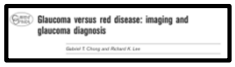
Common Forms of OCT B-Scan Segmentation Failure and Image Artifact

1. De-centration (28% of scans)
2. Error associated with posterior vitreous detachment (14%)
3. Posterior RNFL misidentification (8%)
4. Poor signal (5%)
5. High Myopia (2%)
6. Peripapillary atrophy associated error (1%)
7. Incomplete segmentation (1%)
8. Motion artifact (<1%)

- All have the potential of being misread by you as true disease, the so called "red disease"
- As any artifact is categorized as being outside the normative database, thus automatically depicted in red on the report
- Then leading to an erroneous diagnosis and possibly unnecessary treatment



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Tip #3:
Understand Structure-Function
Classic Confirmation vs. Normal Variability

Use this to confirm the presence of glaucoma vs other disease or artifact.

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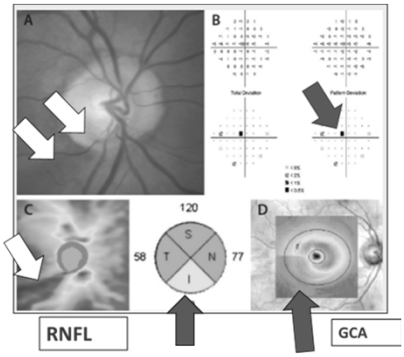
Classic S-F

All the pieces fit together.



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Questions?

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