Detecting Progression In Glaucoma

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Disclosures for Dr Schmidt

- Dr Schmidt is a consultant or advisor for the following:
  - Tarsus
  - Allergan
  - B&L
  - Visus
  - M&S Technologies
  - Avellino Labs
  - Peripherex
  - Topcon
  - Sight Science

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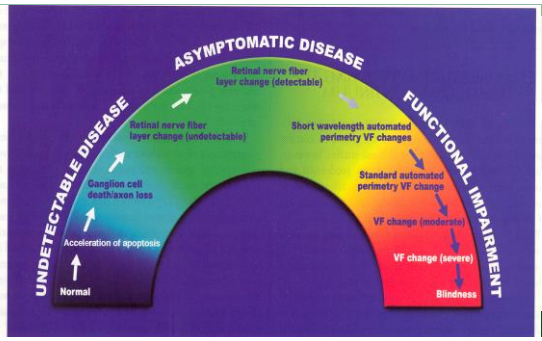

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How Often Does POAG REALLY Progress?

- POAG affects 2.7 million people over age 40 in the US (NEI website 2017)
- Glaucoma decreases visual function – at a rate far greater than previously thought
  - ~10% of all TREATED POAG pxs experience VF loss (GRF website 2017)
- It may stay stable for years!

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Rate Of Progression

- RGC loss in normals ~0.5% /yr
- RGC loss in Glaucoma – 3.5% / yr
- RGC loss in treated G – 1.5%/yr

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Rate of Progression for Various Glaucomas

- NTG- 56% progression at 6 yrs
- POAG -74% progression rate (6 yrs)
- PXG – 93 % - progression rate at 6 yrs
- Pxs older than 68 progressed much faster compared to younger pxs

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Glaucoma Damage

- Occurs in a curvilinear/logarithmic plot as opposed to a linear fashion
- The further the disease has progressed the more rapid the RGC loss is
- Early glaucoma rate of RGC loss is 1.5%dB change/yr
- Late stage rate translates to 10%dB change/yr)

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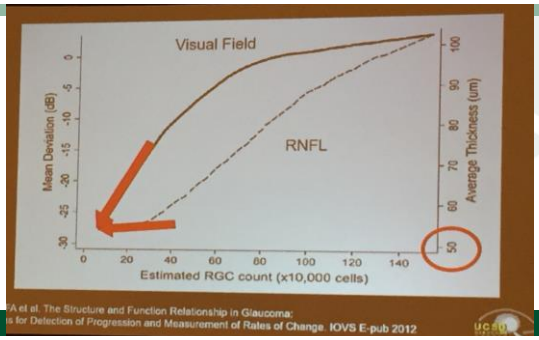

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Predictive Factors For Progressing POAG

- Older age
- Advanced VF damage
  - Worsening MD (-4)
- Smaller neuroretinal rim
- Larger zone Beta
  - Martus, Jonas, et.al. AJO, June 2005
- Baseline IOP, *but not Mean IOP*
  - Martinez-Bello, et al, AJO March 2000.
- Lower CH

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Lower Corneal Hysteresis is Associated With More Rapid Glaucomatous Visual Field Progression

Carlos Gustavo V. De Moraes, MD,† Victoria Hill, BS,*‡ Celso Tello, MD,*‡ Jeffrey M. Liebmann, MD,*†§ and Robert Ritch, MD*‡*

- 153 glaucomatous eyes, with >8 visual fields, followed for > 5 years
- Progressing eyes (n=25) had lower CCT (525µ vs 542µ, P=0.04) and lower CH (7.5 mmHg vs 9.0 mmHg), P<0.01) compared with nonprogressing eyes.
- By multivariate analysis, peak intraocular pressure (OR=1.13, P<0.01), age (OR=1.57, P=0.03), and CH (OR=1.55, P<0.01) were significant predictors of progression.

De Moraes, G. et al. J Glaucoma. 2011; ePub.

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Baseline CH predicts progression risk

- Prospective study of 114 eyes of 68 patients with glaucoma followed for an average of 4 years.
- Rates of progression calculated with the visual field index, baseline risk factors were studied
- CH was associated with a 0.25%/year faster rate of VFI loss for each mm Hg lower CH (**P<** 0.001).
- CH accounted for > 3X as much VFI change as CCT (17.4% vs. 5.2%, respectively).
- Combination of low CH, high IOP was highest risk

Medeiros FA, Meira-Freitas D, Lisboa R, et al. Corneal hysteresis as a risk factor for glaucoma progression: a prospective longitudinal study. Ophthalmology. 2013;120:1533-40.

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Clinical Evidence – Study 1

Corneal Hysteresis found to be associated with progression

	OR	LCL	UCL	*P* value
Age per year <65	1.12	1.01	1.24	.03
Age per year >65	1.08	1.01	1.15	.02
GAT IOP per mmHg	1.22	0.95	1.58	.12
Treatment	1847.6	3.16	10^9	.02
IOP by treatment interaction	0.79	0.61	1.03	.08
CCT per 100 microns	1.65	0.66	0.98	.30
Years with glaucoma	1.00	0.96	1.04	.98
Baseline IOP	0.99	0.93	1.06	.79
CH per mmHg	0.81	0.66	0.98	**.03**

Conclusions: Corneal Hysteresis was the parameter most associated with progressive field worsening

Gonglon NG et al. Am J Ophthalmol. 2006;141:868-875.

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Clinical Evidence – Study 4
CH Associated with Rate of VF Progression

Time-adjusted Logistic Regression with VF Progression as Binary Outcome

	Univariate Model		Multivariate Model	
Variable	OR (95% CI)	P	OR (95% CI)	P
Age (per decade older)	1.72 (1.15-2.59)	< 0.01	1.57 (1.03-2.36)	0.03
Sex (Female)	0.52 (0.21-1.25)	0.14	—	—
Ethnicity (non-Caucasians)	0.87 (0.35-3.77)	0.80	—	—
XFG presence	0.83 (0.26-2.80)	0.76	—	—
Baseline VF MD (dB)	1.02 (0.95-1.10)	0.53	—	—
Baseline VF PSD (dB)	0.96 (0.86-1.07)	0.47	—	—
Baseline IOP (per mm Hg higher)	1.04 (0.93-1.15)	0.46	—	—
Peak IOP (per mm Hg higher)	1.14 (1.05-1.23)	< 0.01	1.13 (1.04-1.23)	< 0.01
Mean follow-up IOP (mm Hg higher)	1.19 (1.03-1.36)	0.01	—	—
CCT (per 40 μ thinner)	1.68 (1.02-2.78)	0.03	—	0.41
CH (per mm Hg lower)	1.66 (1.22-2.24)	< 0.01	1.55 (1.14-2.10)	< 0.01 *

Our study adds information regarding rates of VF change and CH, showing that glaucomatous eyes with low CH not only reach event-based progression endpoints but also progress more rapidly (in dB/y)

** Note: CH is what caused CCT to fall out of the multivariate model*

ORF=corneal resistance factor; IOP_{cc}=corneal compensated intraocular pressure; IOP_g=Goldmann-correlated IOP; MD=mean deviation; PSD=pattern standard deviation; VF=visual field; XFG=exfoliative glaucoma.

De Moraes CG et al. J Glaucoma. 2013;22:209-213.

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IOP and VF Progression

- United Kingdom Glaucoma Treatment Study – 2013
- Rate of progression is poorly predicted by IOP

The IOP measurements that best predict progression rate are
- IOPcc
- GAT+CH

CCT is not related to the rate of progression

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Risk Factors For Progression with "Good IOP" Medeiros – OGS 2021

- Lower CH
- Thin Pachs
- Older Age
- Low BP (especially at "higher IOP)

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Early Stage Optic Disk Progression (J Glaucoma) 2013

- 27% progression rate
- Median of 6.1 yrs
- Of those disks that progressed
  - 89% excavation
  - 54% rim thinning
  - 16% notching
  - 56% showed 2 or more features
  - Inferotemporal most frequent location but 30% showed more than 1 locale

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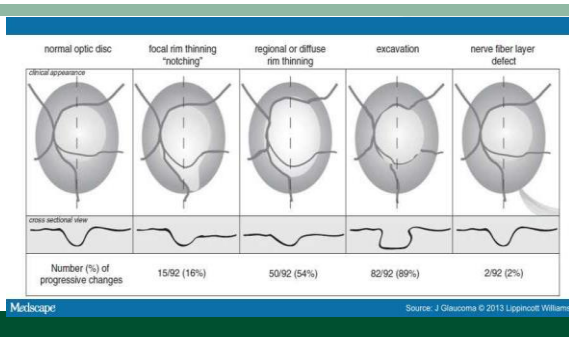

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So How Is the Best Means Of Determining Progression?

- OCT?
- IOP?
- VF?
- FP?
- Or All Of The Above???
- Or None Of the Above???

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The most accurate and efficient means to determine progression is…

- GETTING MULTIPLE TESTS
  - VF tests
  - OCT images
  - IOP readings
  - Fundus photos
- GET AS MUCH DATA AS POSSIBLE
  - Use progression software

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Variability of Intraocular Pressure Measurements in Observation Participants in the Ocular Hypertension Treatment Study

Anjali M. Bhorade, MD,[1] Mae O. Gordon, PhD,[1] Brad Wilson, MA,[1] Robert N. Weinreb, MD,[1] Michael A. Kass, MD,[1] for the Ocular Hypertension Treatment Study Group

- 13% of eyes had 20% change in IOP between consecutive visits. [1]
- 66% of eyes had a change in IOP within 3 mmHg
- 10% of eyes had a change in IOP 5 mmHg between visits.
- Left & right eyes differ differ by 3 and 2 mm Hg or more in at least 20% and 36% of cases, respectively.[2]

1. Bhorade AM, Gordon MO, Wilson B, et al. Ophthalmology. 2009;116:717-24.
2. Liu JH, Realini T, Weinreb RN. Asymmetry of 24-hour intraocular pressure reduction by topical ocular hypotensive medications in fellow eyes. Ophthalmology. 2011;118:1995-2000.

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How Low should We Go?

- AAO Preferred Practice Guidelines
  - "Lowering the pretreatment IOP by 25% or more has been shown to slow progression of POAG"
  - Based upon age of px, time of occurrence and other risk factors
    - Prum et al, Ophthalmology. 2016

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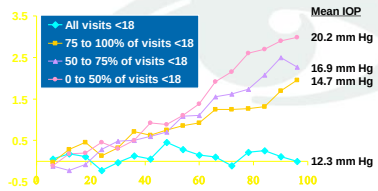
Consistently Low IOP Reduces Vision Loss



AGIS 7, AJO, 2000

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AGIS Results

- Diurnal Curve Is Real Important
  - Avg IOP of 15mm with a curve btwn 13mm – 17mm progresses less than if curve is btwn 11mm – 19mm
- The peak IOP is important
- Which tx best affect the diurnal curve?
- Also remember risk/benefit ratio

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Progression according to CIGTS

- Seen in 56.7% in 6 years
  - Biggest risk factors
    - Inadequate IOP control
    - Disk hemorrhage
- Proving once again that if you diagnose a px with POAG REALLY treat them!

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How Do You Know If IOP Is Spiking?

- Get multiple IOP Readings
- At different times of the day?
- What about serial tonometry?

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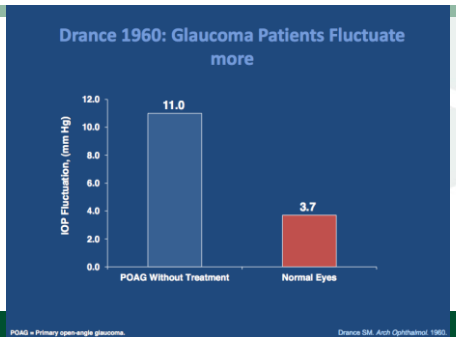

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- For pxs who showed progression of glaucoma despite IOP at acceptable range
  - 3% showed a peak IOP >21mm
  - 35% showed a range of IOP >5mm
    - Collaer, Caprioli, et.al, J Glaucoma 2005;14(3): 196-200
- Underscores the importance of serial tonometry *even in well controlled pxs*

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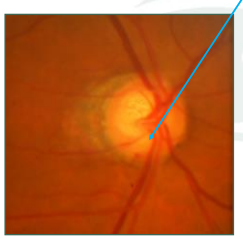
Did you see the disc hemorrhage?



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

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

Main Outcome Measures: Incidence of optic disc hemorrhages and POAG end points.
Results: Median follow-up was 96.3 months. Stereophotography-confirmed glaucomatous optic disc hemorrhages were detected in 128 eyes of 123 participants before the POAG end point. Twenty-one cases (16%) were detected by both clinical examination and review of photographs, and 107 cases (84%) were detected only by review of photographs ($P<0.0001$). Baseline factors associated with disc hemorrhages were older age, thinner corneas, larger vertical cup-to-disc ratio, larger pattern standard deviation index on perimetry, family history of glaucoma, and smoking status. The occurrence of a disc hemorrhage increased the risk of developing POAG 6-fold in a univariate analysis ($P<0.001$; 95% confidence interval, 3.6–10.1) and 3.7-fold in a multivariate analysis

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- Disc hemorrhages detected in 128 eyes of 123 participants
- 21 cases detected by both doctor and photos
- **107 cases (84%) were detected only by a review of photography**

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

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Of Note:

Incidence of Progressing to POAG

- No Disc Heme: 5.2%
- + Disc Heme: 13.6%
- Presence of a disc heme increase risk of developing POAG 6 fold

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Thirteen-Year Follow-up of Optic Disc Hemorrhages in the Ocular Hypertension Treatment Study

Donald L. Budenz, Julia Beiser Huecker, Steven J. Gedde, Mae Gordon, Michael Kass for the Ocular Hypertension Treatment Study Group

DOI: http://dx.doi.org/10.1016/j.ajo.2016.10.023

- ODH 179 eyes of 169 participants
- Incidence of POAG in eyes with ODH was **25.6% vs. 12.9%** in eyes without ODH
- ODH increased the risk of developing POAG
- Risk Factors for ODH:
  - Older age, thinner central corneal thickness, larger vertical cup to disc ratio, higher intraocular pressure, and self-reported black race

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Advanced Glaucoma Intervention Study (AGIS)

- Recruitment began 1988, closed in 1992
- 789 eyes (591 pts) with **"advanced"** glaucoma
- Minimum 5 yr follow up
- Primary outcome (APDVA, APDVF, APDV)
  - Average % with decrease visual acuity, visual field, vision
- Subsidiary outcome: Is there a racial difference b/w treatment regiments?

- **Results:** No statistical difference in treatment sequences after medical therapy

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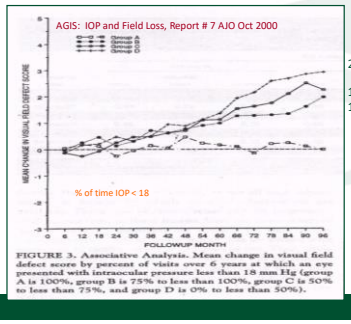

FIGURE 3. Associative Analysis. Mean change in visual field defect score by percent of visits over 6 years at which an eye presented with intraocular pressure less than 18 mm Hg (group A is 100%, group B is 75% to less than 100%, group C is 50% to less than 75%, and group D is 0% to less than 50%).

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AGIS: IOP and Field Loss Implications??

- Results specific for patients with POAG
  - Do not apply to OHT or NTG
- Patients in the study with moderate/severe VF Loss
- **Strive to achieve IOP in the "low teens" range**
  - Likely to require multiple meds
  - Laser and/or surgery may be required

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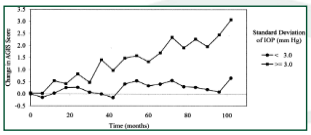
AGIS: Visit to Visit Fluctuation in IOP Correlated Best with Progression and **NOT Mean IOP**



- Eyes with variation < 3 mm Hg: no average progression
- Eyes with variation ≥ 3 mm Hg: on average, significant progression

Nouri-Mahdavi et al. Ophthalmology. 2004.

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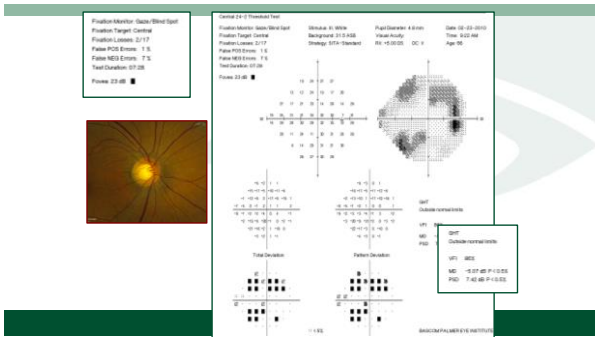

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SITA Faster vs SITA Fast

- SITA Faster produces similar results to SITA Fast
- No loss of reproducibility
- Improved reliability
- SITA Faster results integrate into the existing Guided Progression Analysis (GPA) of that individual patient

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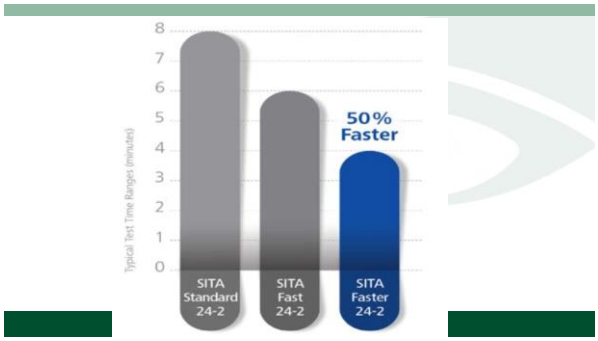

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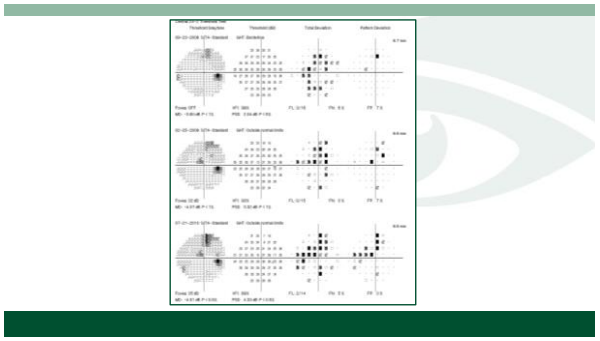

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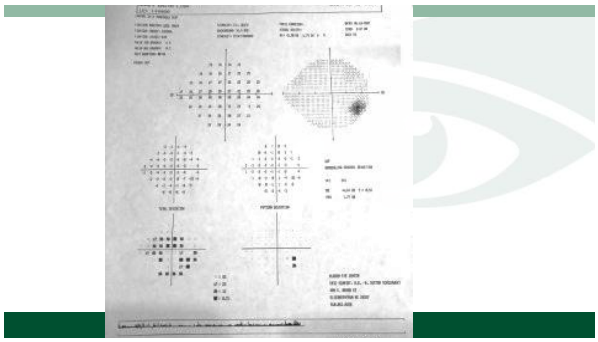

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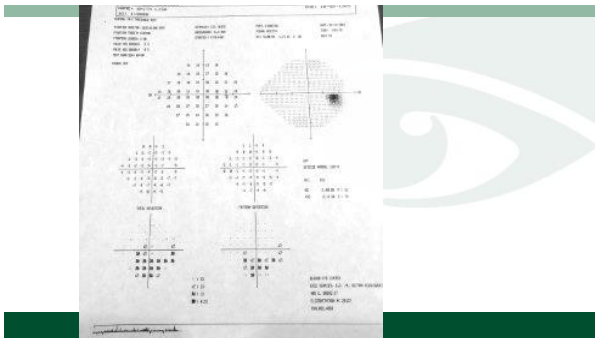

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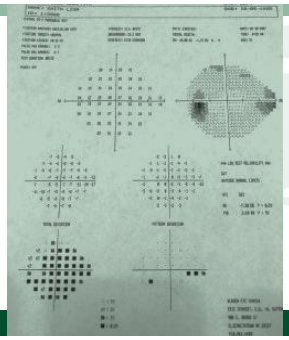

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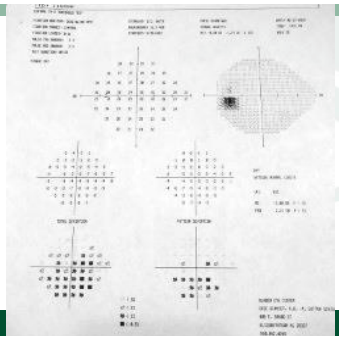

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So How Can We Use The VF To Detect Progression Earlier?

- Perform more tests
  - 3 tests/yr reduces false positives to 5% (2 tests/yr FP~35%)
  - Look at slope change as well as trend data
  - PSD index is very sensitive in central 10 degrees
    - Medeiros –OGS 2021
- Make use of GPA software

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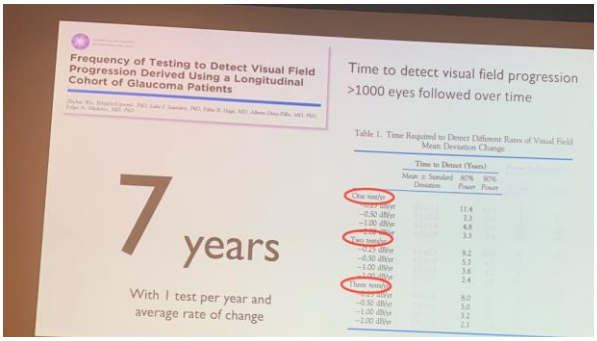

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What about the VFI??

- VFI plots linear regression
- "Predicts" future progression
- A Rate of Change Index
- Utilizes underlying Ganglion Cell loss to calculate the VFI

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VFI – AGS 2014

- VFI underestimates the amount of neural loss in Early Glaucoma
- Provides a false sense of security
- VFI more useful in moderate glaucoma
- OCT better for early disease

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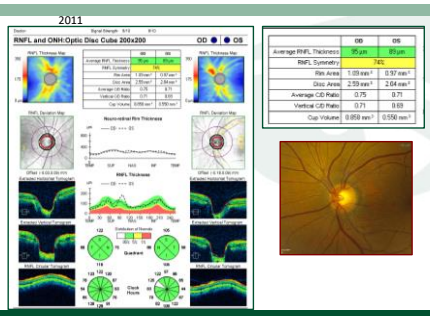
2011



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Estimating the Lead Time Gained by Optical Coherence Tomography in Detecting Glaucoma before Development of Visual Field Defects

Tammy M. Kuang, MD,[1,2,3] Chunwei Zhang, MD,[1,4] Linda M. Zangwill, PhD,[1] Robert N. Weinreb, MD,[1] Felipe A. Medeiros, MD, PhD[1]

- At 95% specificity, up to **35% of eyes had abnormal average RNFL thickness** 4 years before development of visual field loss and **19% of eyes had abnormal results 8 years before field loss.**
- **Conclusions:** Assessment of RNFL thickness with OCT was able to detect glaucomatous damage before the appearance of VF defects on SAP. In many subjects, significantly large lead times were seen when applying OCT as an ancillary diagnostic tool.

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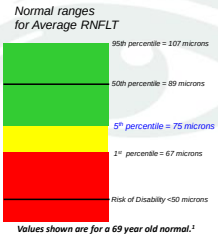
There is a Large "Range" of Normal

- *Just like perimetry, the average patient can lose a third of his/her RNFL or neuro-retinal rim and still be inside the normal range.*

Average RNFL Thickness
75 microns – tipping point

Floor Affect in Advanced Glaucoma
40-50 microns



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

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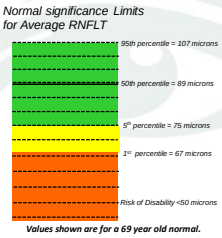
Fortunately, SDOCT measurements are highly reproducible.

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



Values shown are for a 69 year old normal.

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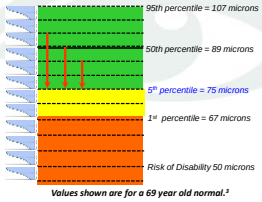
What This Means For Everyday Clinical Care

- ***Implication 1:***

SDOCT can now measure 2 to 4 statistically significant RNFL progression steps for the typical glaucoma suspect while the patient is still is in the green zone.

- ***Implication 2:*** *It may be possible to view SDOCT change from baseline as an early detection strategy in glaucoma suspects.*



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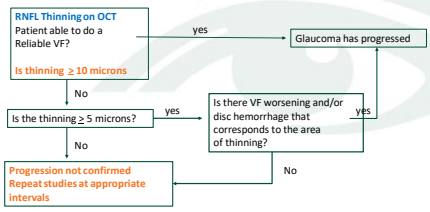
Detecting Glaucoma Progression Using OCT - RNFL



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Does this difference in the OCT represent progression?

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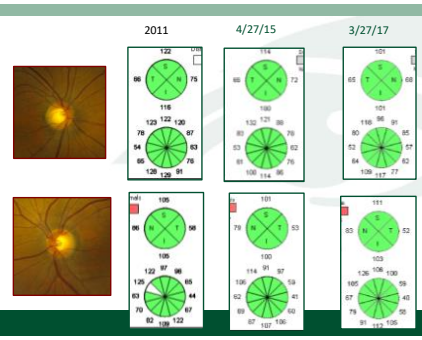

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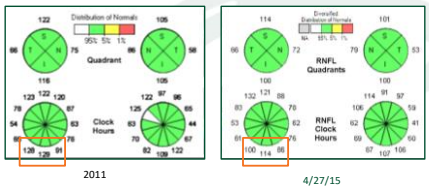

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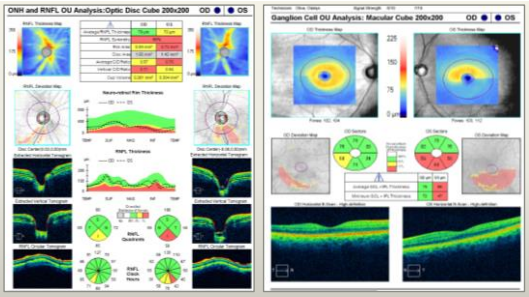

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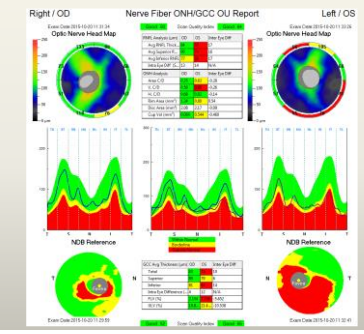

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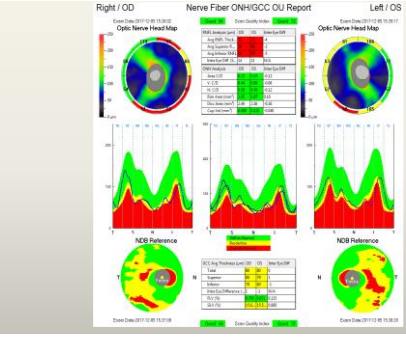

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So using an OCT; How do we tell if they are getting worse?

- Progression Analysis Software!!!!!!

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So How do we best measure progression?

- Visual Field analysis
  - PSD
  - MD
  - VFI
- Serial OCT
- Multiple IOP readings

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So What Do We Do When We Identify Progression?

- LOWER THE IOP!!!
- How Low Do I Go??
  - AS LOW AS YOU NEED TO!!
    - Risk Factors, Age, rim width
    - 40-50% reduction – FROM HIGHEST UNTREATED IOP

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Thank You All So Much!!!!!

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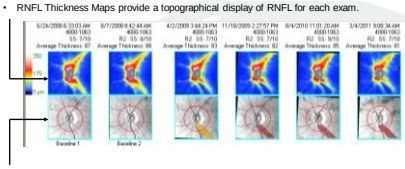
GPA™ Analysis

- RNFL Thickness Maps provide a topographical display of RNFL for each exam.



- RNFL Thickness Change Maps demonstrate change in RNFL between exams
- Up to 6 progression maps are compared to baseline.
- Areas of statistically significant change are color-coded yellow when first noted and then red when the change is sustained over consecutive visits.

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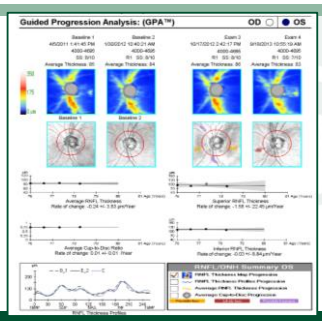

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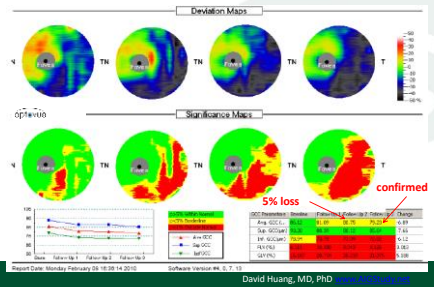
GCC Progression Analysis (visit every 6 months)



David Huang, MD, PhD

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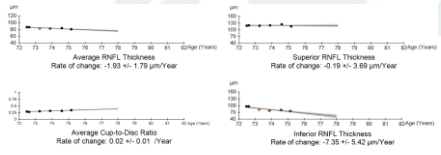
GPA™ Analysis

Summary Parameter Trend Analysis

- Rate and significance of change shown in text
- RNFL thickness values for overall Average Superior Average, and Inferior Average are plotted for each exam
- Yellow marker denotes change from both baseline exams
- Red marker denotes change from 3 of 4 comparisons



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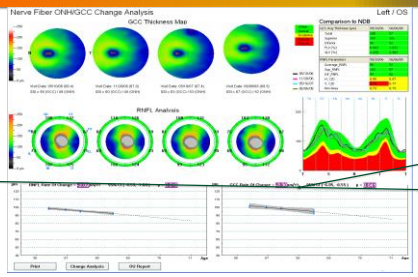
Trend Analysis Shows RNFL and GCC Loss Over Time



RNFL Rate of Change = -3.09µ/Year

GCC Rate of Change = -3.30µ/Year

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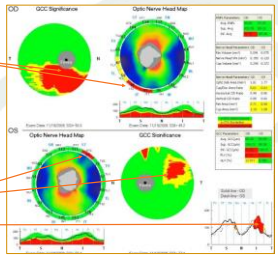
RNFL, Optic Disc & GCC Analysis



Inferior RNFL and GCC Loss OD

Superior RNFL and GCC Loss OS

Abnormal RNFL Asymmetry Graph

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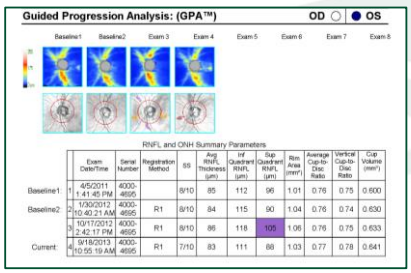

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Focal Loss Volume (FLV%) and Global Loss Volume (GLV%)

FLV% - Quantify Focal Loss Volume on GCC Map (Similar to PSD on a VF printout)

GLV% - Global Loss Volume (Similar to Mean Defect (MD) on a VF printout)

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FLV% and GLV%: Why are these numbers so powerful?

- Advanced Imaging Glaucoma Study
  - *3 clinical centers*
  - *Longitudinal followed up to 9 years*
  - *Normal follow-up every 1 year and glaucoma/glaucoma suspect follow-up every 6months*
- Ganglion cell complex focal loss volume (GCC-FLV) was the best predictor of VF conversion in 513 glaucoma suspect/pre-perimetric glaucoma eyes followed for an average of 52 months
  - *82% VF conversion preceded by abnormal OCT*

Zhang X et al. for the AIG Study Group. Predicting development of glaucomatous VF conversion using baseline FD-OCT *Am J Ophthalm* 2016; 163:29

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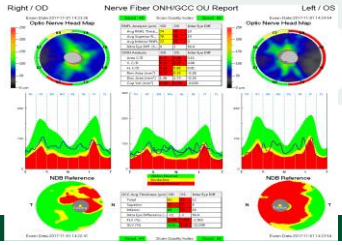
You have to take all the information in context with all the other information



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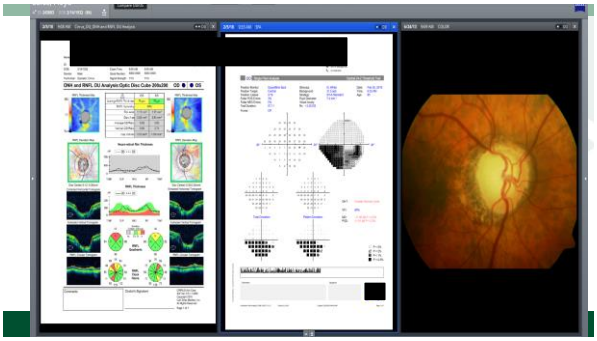

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