Advancing our Understanding of Glaucoma Progression

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OVERVIEW

- Glaucoma is a chronic disease
- Multiple treatments developed
  - Topical
  - Nutritional
  - Laser
  - Interventional
  - Surgical
- Great treatments, but still no cure

OVERVIEW

- Many glaucoma clinical trials, data collected over multiple years or decades
- A proportion of treated and untreated glaucoma remains stable
- Majority of glaucoma progressively worsens
- Many progress at a slow rate
- A few show rapid or even catastrophic progression
- Detecting significant change over time is critical
- Progression occurs in
  - clinical testing
  - structural analysis
  - visual function

COMING UP
POLL #2

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Poll 1. Graham Lakkis: Progression analysis is most useful in:

OVERVIEW

- Progression analysis is essential for:
- Glaucoma patients
  - are they stable or are they progressing?
  - if progressing, what is their progression rate?
- What about glaucoma suspects?
- At any age group, there are as many suspects as those diagnosed with glaucoma
- Are suspects stable, or progressing into definitive glaucoma?
- Suspects require *exactly* the same progression strategies as those with glaucoma

OVERVIEW

- One of the basics of glaucoma therapy is to set a target pressure
- However, the purpose of glaucoma treatment is not to ‘reach target IOP’
- The purpose is to (ideally) stop disease progression
- Target IOP is only an estimate of the safe pressure
- No one truly know the safe IOP for that particular patient’s optic nerve
- Regular re-testing is necessary to detect any deterioration of structure and function
- If stable, target IOP selected is safe and appropriate
- If worsening, target IOP has to be reduced further

OVERVIEW

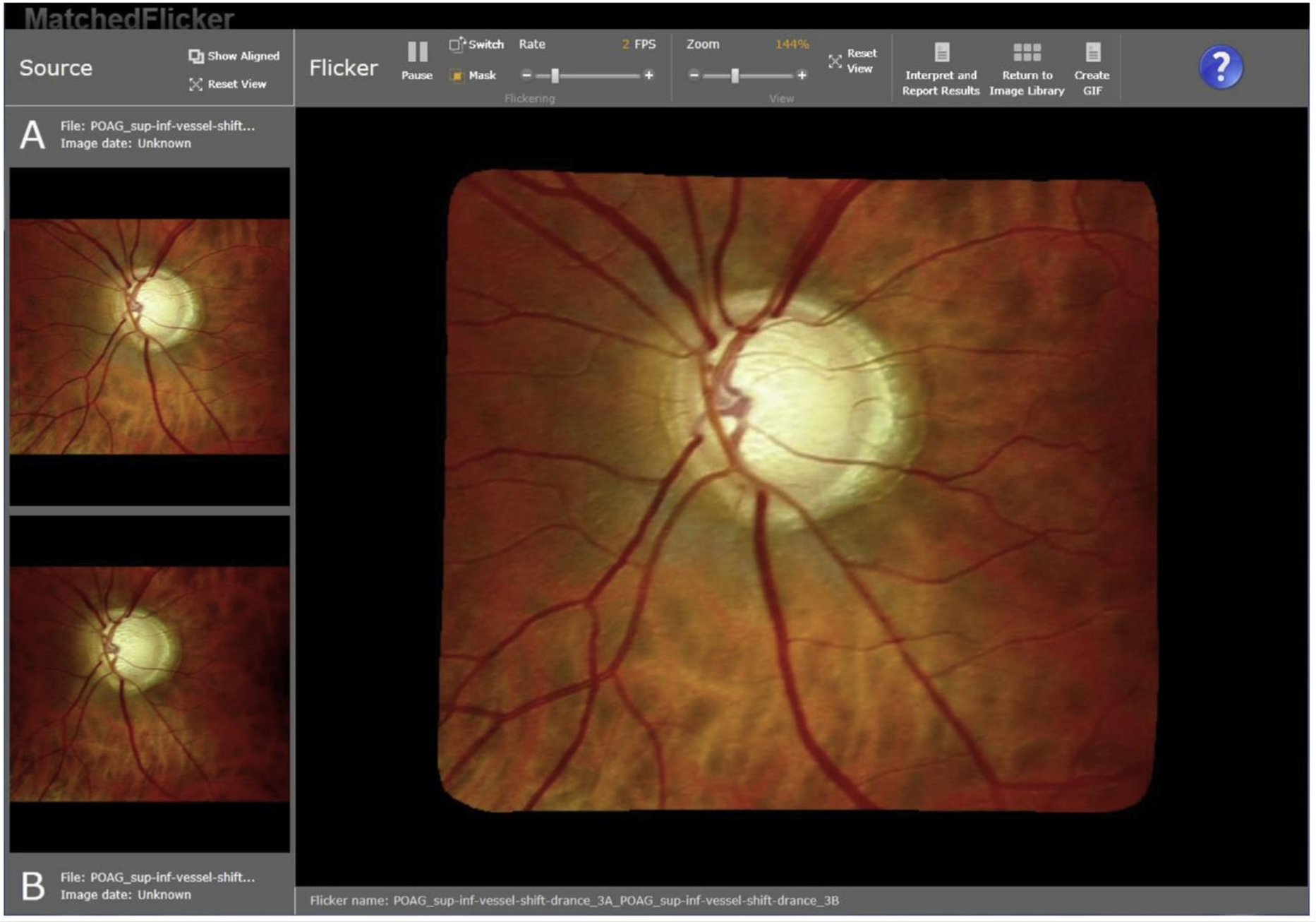
- Identifying significant progression allows
  - treatment to be initiated in suspects
  - treatment to be escalated in glaucoma
- Retinal ganglion cells are irreplaceable
- Treatment changes made at earliest opportunity reduce the amount of future ganglion cell loss
- But..
  - how much change is statistically significant?
  - how much change is clinically significant?
  - what strategies can detect progression at the earliest possible time?

1. CLINICAL PROGRESSION

- Deterioration in clinical parameters
  - Increased C/D ratio
  - Changes in NRR morphology
  - Increased zone-beta PPA
  - Lamina cribrosa remodelling
  - Vascular bayonetting and baring
  - Development of disc haemorrhages

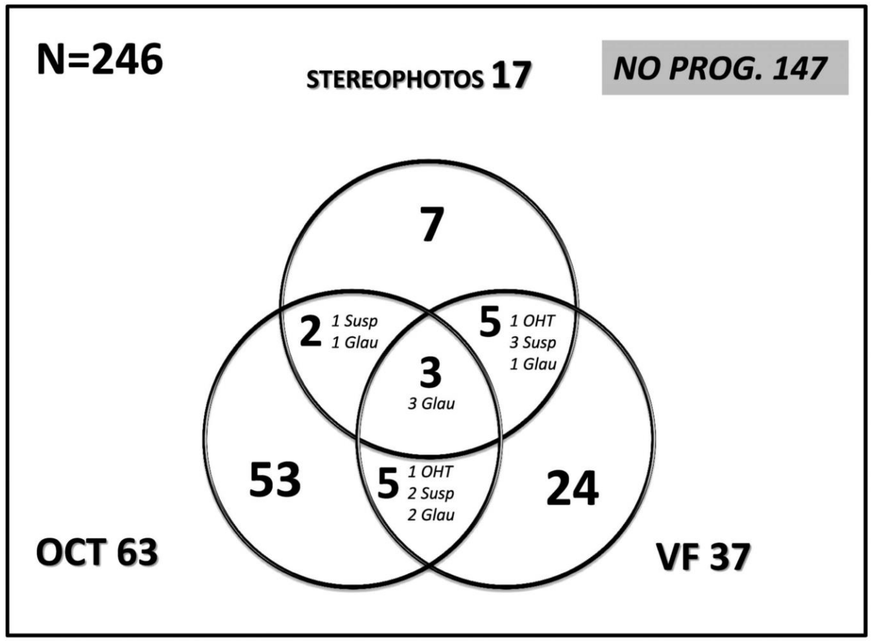
CLINICAL PROGRESSION - DISC CHANGES

- Disc parameter changes used in studies prior to OCT
  - disc photography at each visit
- Most changes impossible to detect with clinical disc assessment at slit lamp
  - visits spaced out over time
  - written notes not descriptive enough
- Disc photography *and* image comparison software required
  - Matched Flicker
  - Oxford Image Compare Tool
  - Metadata2Go Comparison Tool
  - Adobe Photoshop
  - NVIDIA Image Comparison & Analysis Tool (ICAT)



CLINICAL PROGRESSION - DISC CHANGES

- In clinical practice, disc photography mostly replaced by OCT
  - Micron-level sensitivity to change
- However, comparison studies still show progression sometimes detectable via photography alone, not OCT or VF.



147 no progression
117 with progression
64% OCT RNFL
32% VF loss
15% Disc Photos

Banegas et al. Investigative Ophthalmology & Visual Science February 2015, Vol.56, 1253-1260.

CLINICAL PROGRESSION - DISC HAEMORRHAGES

- Disc haemorrhages can have multiple aetiologies
  - PVD
  - Valsalva
  - Systemic hypertension
  - Papilloedema, AION, neuroretinitis
  - Glaucoma
- In a glaucoma suspect or glaucoma patient, they could be a sign of unstable or progressive disease
- In NTG they are the *worst* of all the clinical signs for progression
  - not always so for those with POAG or OHT

Prognostic Factors	Diagnostic Group	Association	Direction	Number of Studies		
		1=no, 2=possible, 3=probable, 4=definite	Increased progression with:	Univariate analysis	Multivariable analysis	Total
Age	*OAG*	4	Older age	39	26	47
Disc hemorrhages	*NTG*	4	Presence	5	6	7
Baseline visual field loss	*OAG*	3	More loss	47	36	61
Baseline IOP	*OAG*	3	Higher IOP	22	17	28
Exfoliation syndrome	*OAG*	3	Presence	11	6	13
Central corneal thickness	*OAG*	3	Thinner	5	3	5
OBF resistivity index	*OAG*	3	Higher index	3	3	3
Anticardiolipin antibody in blood	*OAG*	3	Higher level	2	1	2
Peripapillary atrophy	*NTG*	3	Presence	0	2	2
Previous visual field progression	*OAG*	3	More progression	2	1	2
Stroke	*NTG*	3	Presence	2	2	2
Gender	*OAG*	2	Female sex	23	17	31
Cup disc ratio	*OAG*	2	Higher ratio	14	7	17
Age	*NTG*	2	Older age	10	11	16
Myopic refractive error (spherical equivalent)	*OAG*	2	Higher error	12	10	16
Diabetes	*OAG*	2	Presence	9	5	12
African descent	*OAG*	2	Presence	7	5	9
Baseline untreated IOP	*OAG*	2	Higher IOP	6	6	9
Disc hemorrhages	*OAG*	2	Presence	7	3	8
Diastolic blood pressure	*OAG*	2	Lower pressure	5	4	6
Systemic hypertension	*NTG*	2	Presence	4	4	6
Recovery rate from cold exposure test	*NTG*	2	Lower rate	0	5	5
Baseline IOP fluctuation	*OAG*	2	Higher fluctuation	3	2	4
Migraine	*NTG*	2	Presence	4	1	4
Ocular perfusion pressure (overall)	*OAG*	2	Lower pressure	3	3	4
Pulse rate	*OAG*	2	Higher rate	1	2	3
Central corneal thickness	*NTG*	2	Thinner	3	2	3

CLINICAL PROGRESSION - DISC HAEMORRHAGES

"After a median follow-up of 13 years, the incidence of ODH was 0.5% per year during an average of 13 years before the development of POAG and 1.2% per year during an average of 6 years after the development of POAG. **The cumulative incidence of POAG in eyes with ODH was 25.6% compared to 12.9% in eyes without ODH.**"

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, and Michael Kass, for the Ocular Hypertension Treatment Study Group

CLINICAL PROGRESSION - DISC HAEMORRHAGES

- If DH occurs in NTG, almost certain sign of progression
  - adjust treatment to lower IOP further 10%
- If DH occurs in glaucoma suspect, OHT or POAG
  - 50% increased risk of progression, but not guaranteed progression
  - same treatment, watch more closely, increase review to every 3 months
  - if repeated DH, then commence or escalate treatment
- OCT and VF changes don’t occur immediately after DH
  - OCT: 2-3 years
  - VF: 5-6 years
  - In NTG, do not wait for OCT/VF changes before adjusting treatment plan

COMING UP
POLL #2

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Poll 2. No longer being able to reach target IOP is a sign of clinical progression:

CLINICAL PROGRESSION - IOP

- At commencement of glaucoma treatment, target pressure is set
  - e.g. 25% reduction from baseline
- Medications added and adjusted until target IOP reached
- Regular review to ensure IOP remains at target
- After a period, IOP can rise above target
  - loss of drug efficacy (tachyphylaxis) e.g. beta blockers
  - loss of compliance
  - worsening glaucoma
- After addressing compliance and tachyphylaxis, what if IOP still off target?

CLINICAL PROGRESSION - IOP

- Target pressure is an *estimate* of IOP that will slow or stop glaucoma progression
- No one knows the true target IOP for each individual or each eye
- If IOP is off-target and there is NO structural or functional progression
  - keep treatment plan as is
  - maybe initial target was overly aggressive?
- Keep monitoring regularly

COMING UP
POLL #3

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Poll 3. What proportion of glaucoma patients continue to progress even after reaching target IOP?

POLL #3

- What proportion of glaucoma patients continue to progress even after reaching target IOP?

  - A. 5%
  - B. 15%
  - C. 25%
  - D. 50%

CLINICAL PROGRESSION - IOP

- 20-30% of treated glaucoma continues to progress even at target IOP
- Possible reasons:
  - initial target selected was not low enough?
  - aggressive disease
    - systemic factors
    - secondary factors e.g. PXF
- If IOP is off-target *and* progression is occurring
  - adjust treatment plan to lower target IOP further 10%
  - keep lowering IOP in 10% increments until progression stops/slows

•Susanna R Jr, et al, Why Do People (Still) Go Blind from Glaucoma? Transl Vis Sci Technol. 2015 Mar 9;4(2):1.

COMING UP
POLL #4

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Poll 4. How much does OCT-RNFL thickness change with normal ageing?

2. OCT PROGRESSION

- RNFL and GCC thin gradually from birth with normal aging
  - 1.3 to 1.5 million retinal ganglion cells at birth
  - average 6,500 retinal ganglion cells lost per year
- We can’t count ganglion cells in clinic
  - OCT is the correlate
- What is normal rate of OCT loss with age?
  - variable between individuals
  - depends on instrument
  - varies with study population/race
  - varies with age group
- Normal age-related **RNFL** progression
  - -0.3 microns/year (cross-sectional data)
  - -0.5 microns/year (longitudinal data)

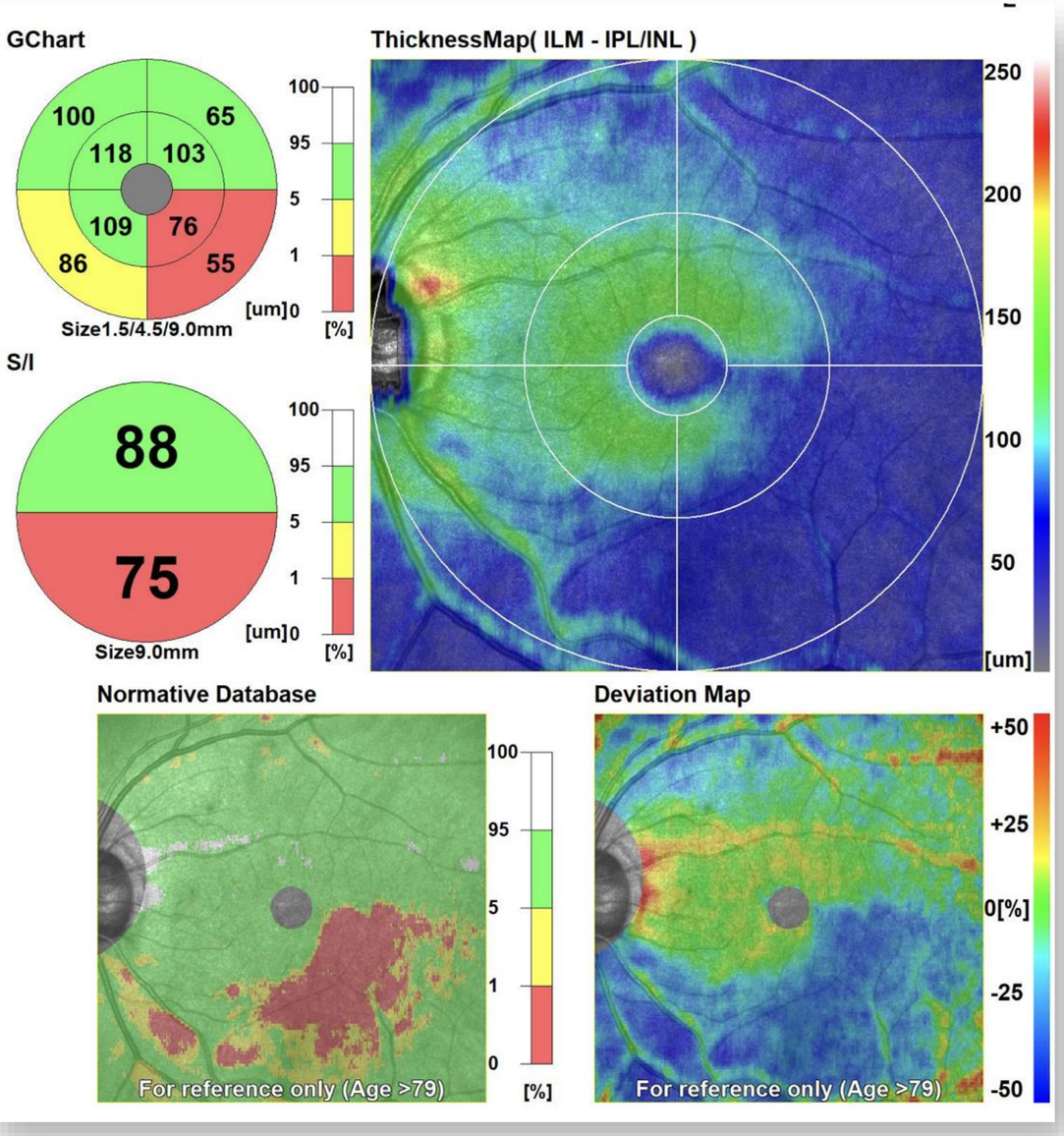
OCT PROGRESSION

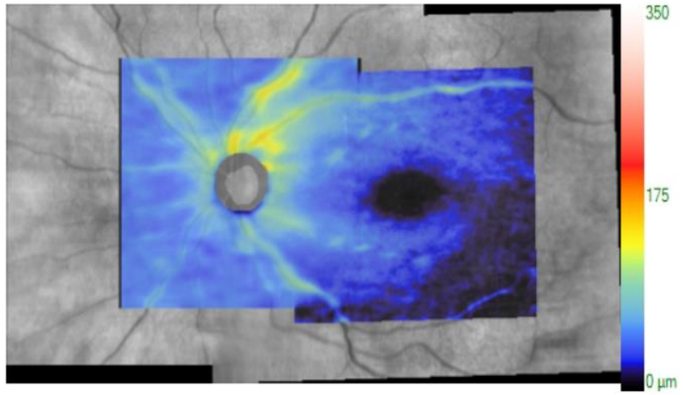
- To detect OCT glaucoma progression at earliest opportunity, need to measure a rate of change greater than normal aging
  - i.e. over -0.5 microns/yr
- What happens to patients already under glaucoma treatment?
- Few are totally stable, majority gradually lose RNFL and GCC
- RNFL progression rate varies between -0.75 to -1.5 microns/year
  - average -1.12 microns/year (I like to round off to -1.0 um/yr)
  - i.e. *treated* glaucoma patients lose RNFL at twice the normal aging rate
- OCT RNFL glaucoma progression rate paradigm
  - Stable -0.5 to -1.0 microns/year
  - Slow progression -1.0 to -2.0 microns/year
  - Rapid progression -2.0 to -3.0 microns/year
  - Catastrophic progression over -3.0 microns/year

OCT PROGRESSION

- What about GCC?
- GCC macular scans much less standardised than RNFL
  - Nidek, RTVue — RNFL/GCL/IPL
  - Cirrus — GCL/IPL
  - Spectralis — Full retina, RNFL, GCL
  - Topcon — RNFL or GCL/IPL or RNFL/GCL/IPL
- Creates difficulty in comparing data

GCC: Ganglion Cell Complex

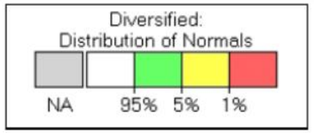




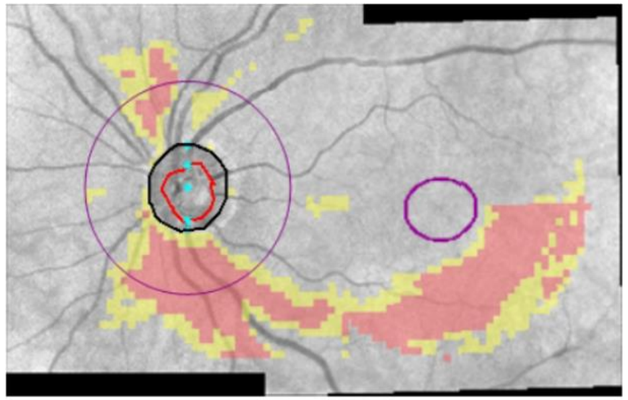
Combined GCA and RNFL Deviation Map

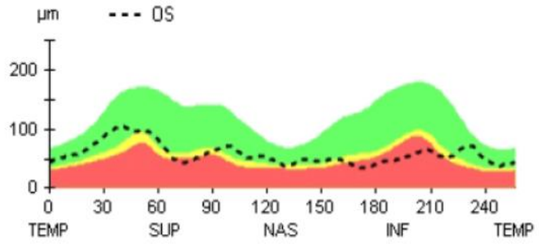
4

Disc Area	1.47 mm²
Rim Area	0.85 mm²
Average C/D Ratio	0.64
Vertical C/D Ratio	0.66
Cup Volume	0.097 mm³
Average RNFL Thickness	59 µm
Superior RNFL Thickness	76 µm
Inferior RNFL Thickness	50 µm

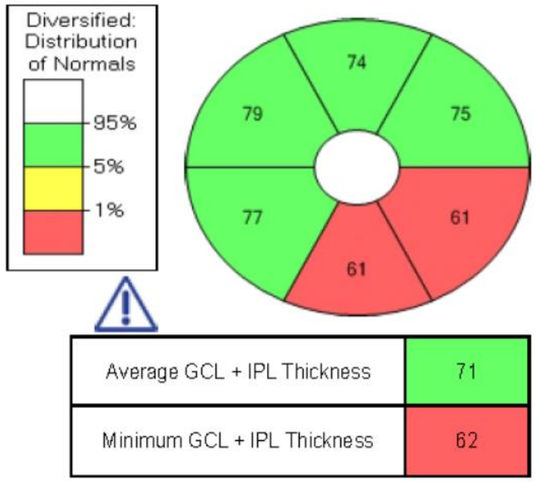


RNFL Thickness



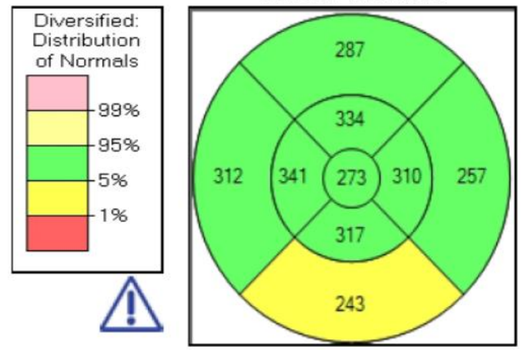


GCL + IPL



Average GCL + IPL Thickness	71
Minimum GCL + IPL Thickness	62

Macular Thickness



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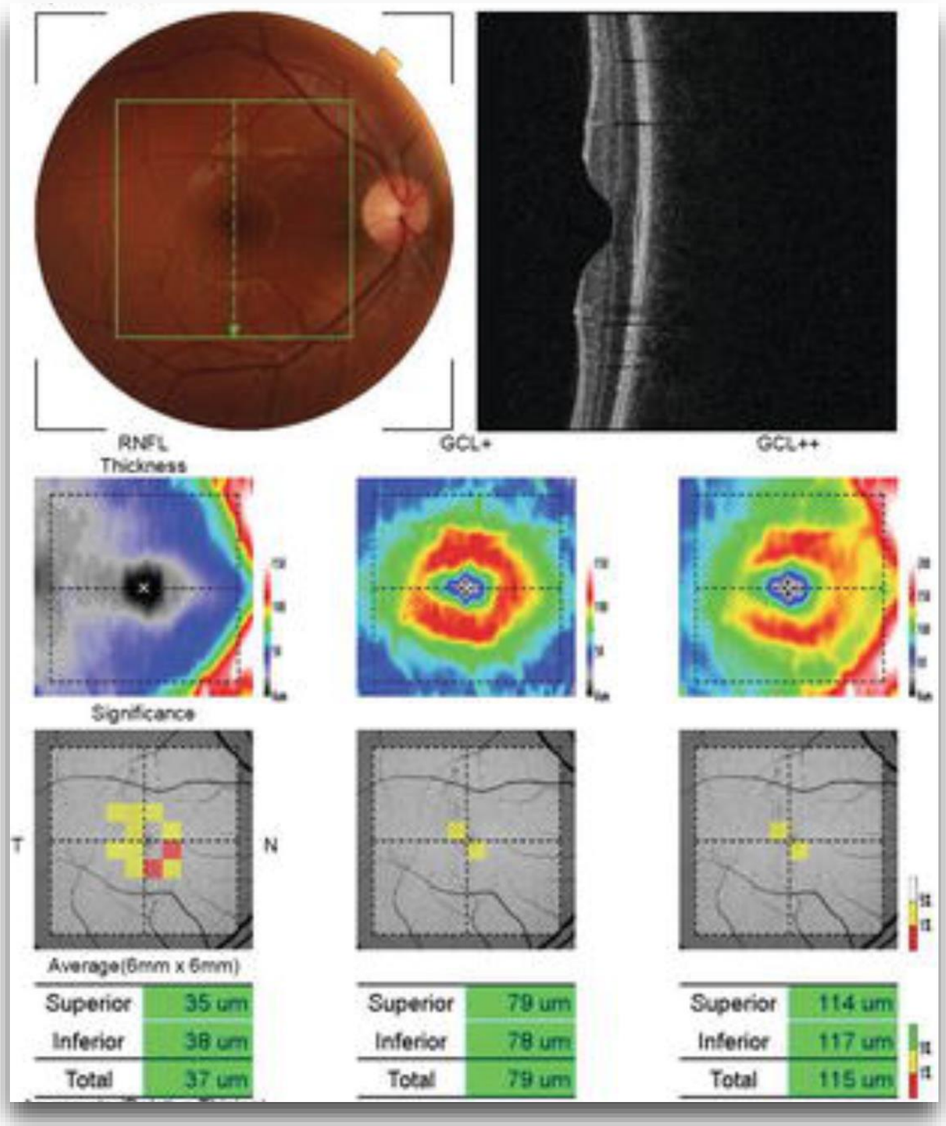
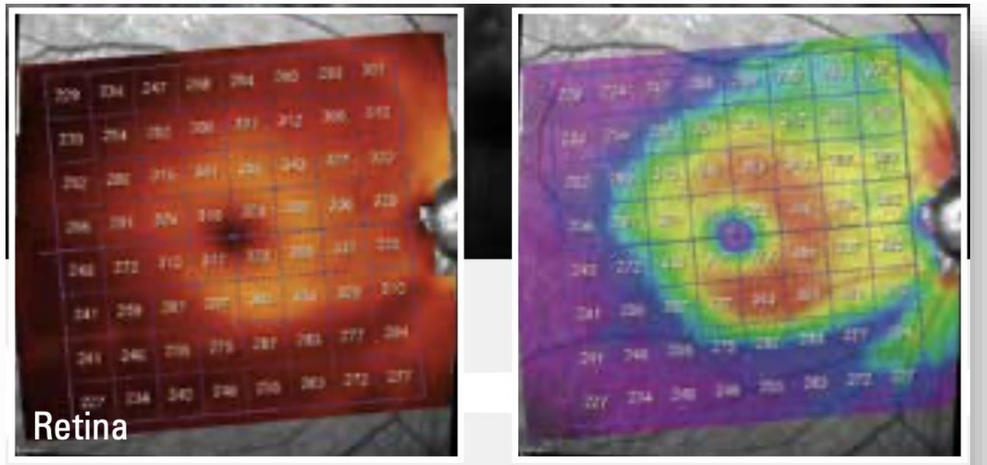
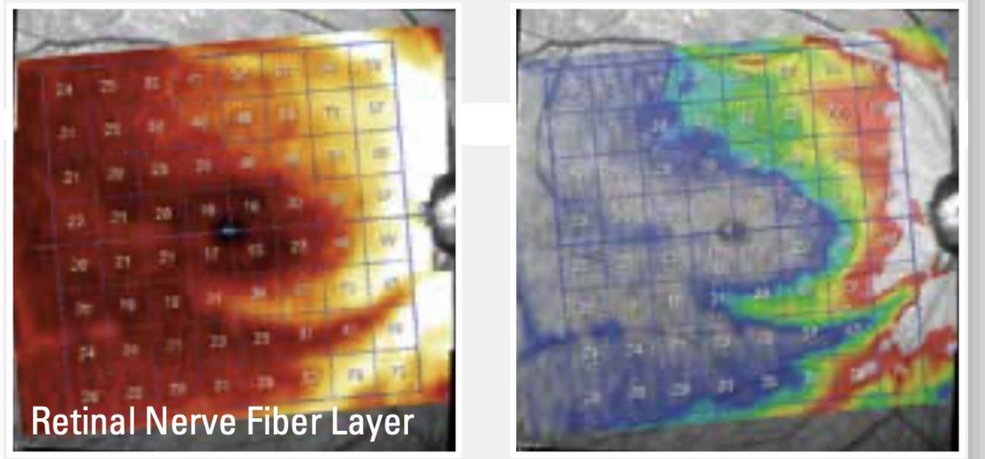
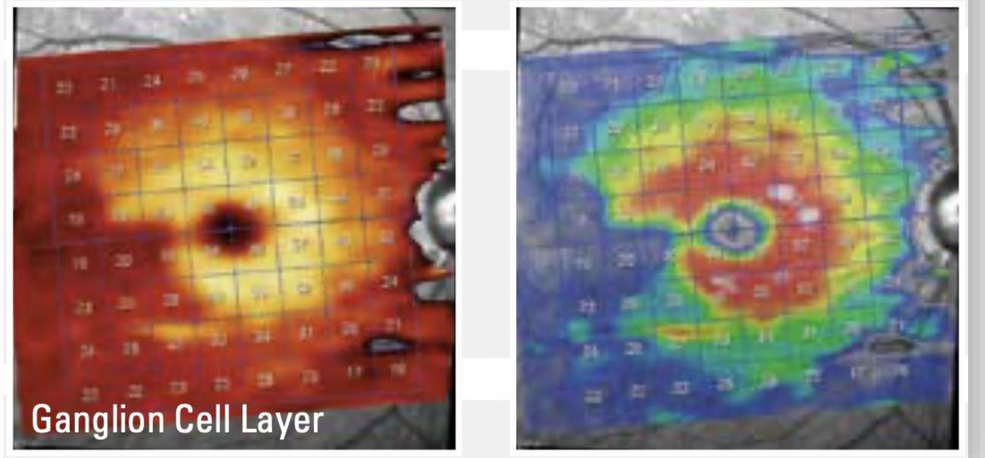
GCC: Ganglion Cell Complex









Optometry AUSTRALIA

OCT PROGRESSION

- GCC progression rate in normals -0.3 microns/year
- GCC progression rates in glaucoma patients under treatment varies
  - -0.15 to -0.56 microns/year
- A progression rate faster than -1.3 micron/year is strongly suggestive of uncontrolled glaucoma
- Similar paradigm to RNFL progression
  - Stable -0.5 microns/year
  - Slow progression -0.5 to -1.0 microns/year
  - Rapid progression -1.0 to -2.0 microns/year
  - Catastrophic progression over -2.0 microns/year

OCT PROGRESSION

- Linear regression analysis
- Detects progression that is
  - greater than the rate of age-normal loss in normative database
  - greater than test-retest variability of the instrument and patient
- Statistical analysis of multiple tests (>4)
- Required for both GCC and RNFL scans
- Don’t rely on value changes only, need regression analysis

OCT GLAUCOMA PROGRESSION ANALYSIS

- Looking at the “numbers”
  - e.g. “Rule of 5”
- How much OCT change is significant?
- Average RNFL and GCC ~ 100 micron
- OCT hits ‘floor’ ~50 microns
- Loss is 100-50 = 50 microns
- 10% of this has been suggested as significant change i.e. 5 microns
- Unfortunately “5 micron rule” doesn’t work

Results: At 5 years, the hit rate for trend-based analysis (62.9%) was significantly greater than that of the Rule of 5 (37.5%).

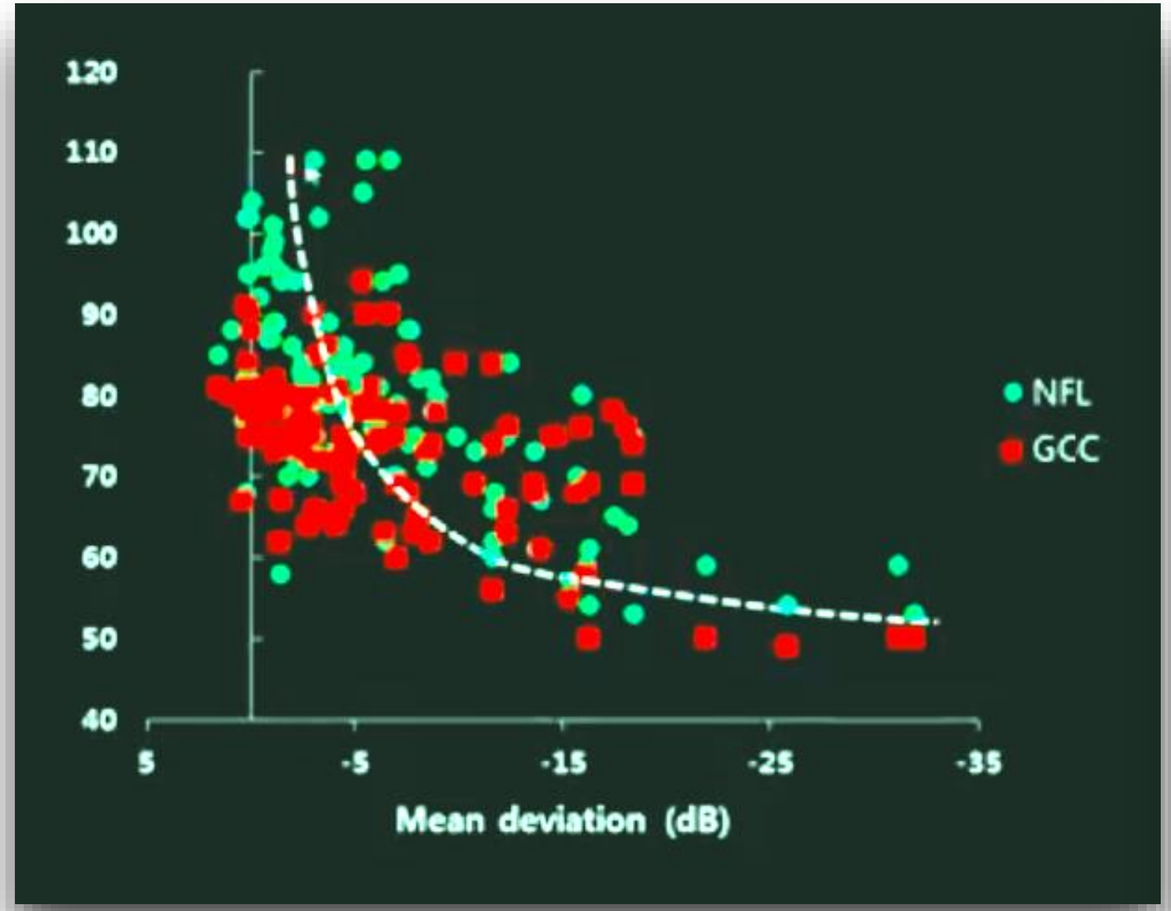
Conclusion: Trend-based analysis was superior to the simple rule of 5 for identifying progression in glaucoma eyes, and should be preferred as a method for longitudinal assessment of global SD-OCT RNFL change over time.

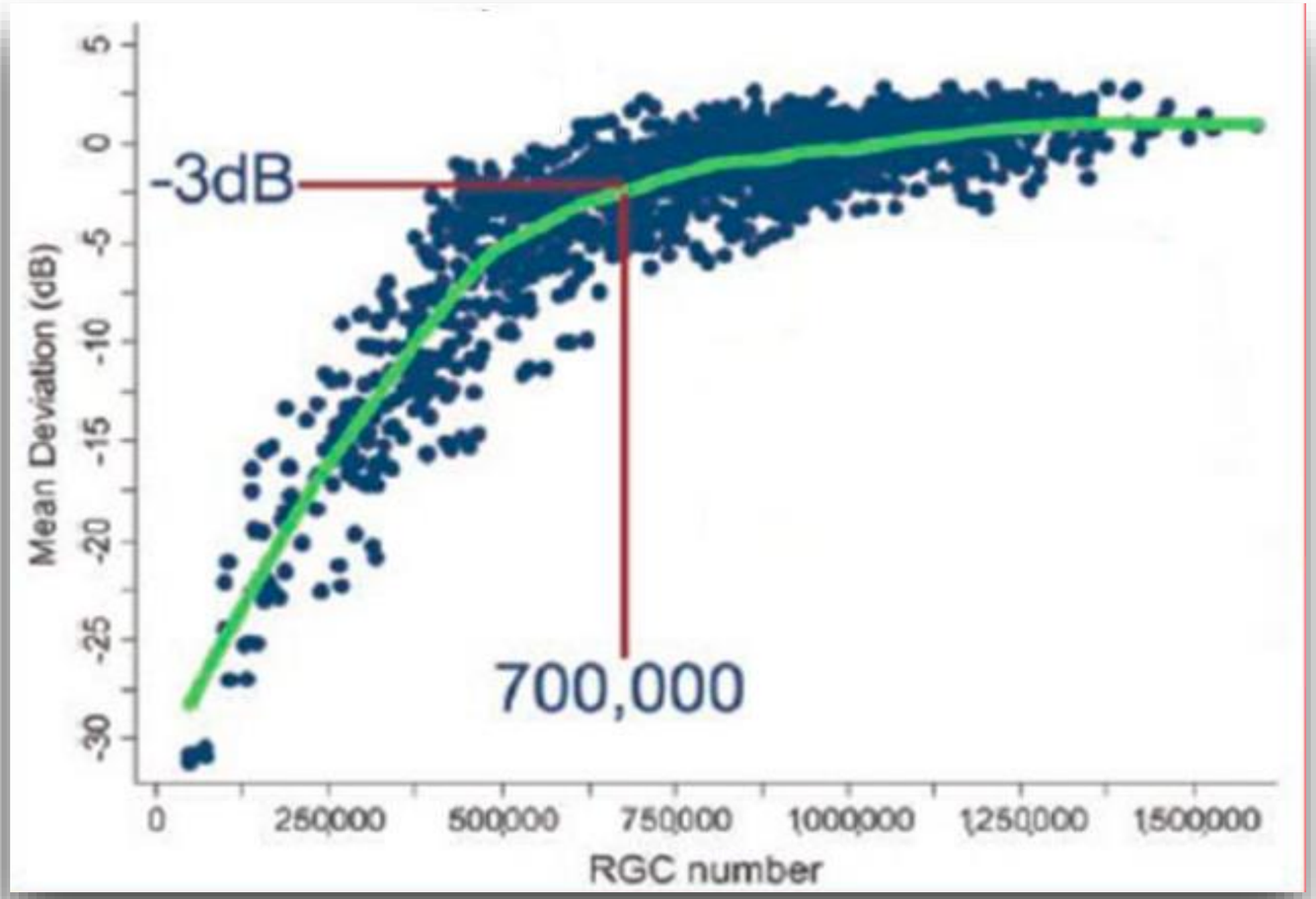
Thompson, A. Ophthalmol Glaucoma . 2020 ; 3(6): 414–420

OCT PROGRESSION

- OCT hits a floor around 40-50 microns
- GCC and RNFL values will not go lower even as disease progresses
- Non-ganglion cells structures that support the retina do not disappear
  - blood vessels
  - glial cells
  - Muller cells
- Once OCT gets close to the floor, no longer useful for progression analysis
- Visual field analysis then become more beneficial

OCT v Visual Fields





2011/02/18_L:MACULA MAP X-Y(6.0mm x 6.0mm[512 x 128])

Eye:L

RS-3000 OCT RetinaScan

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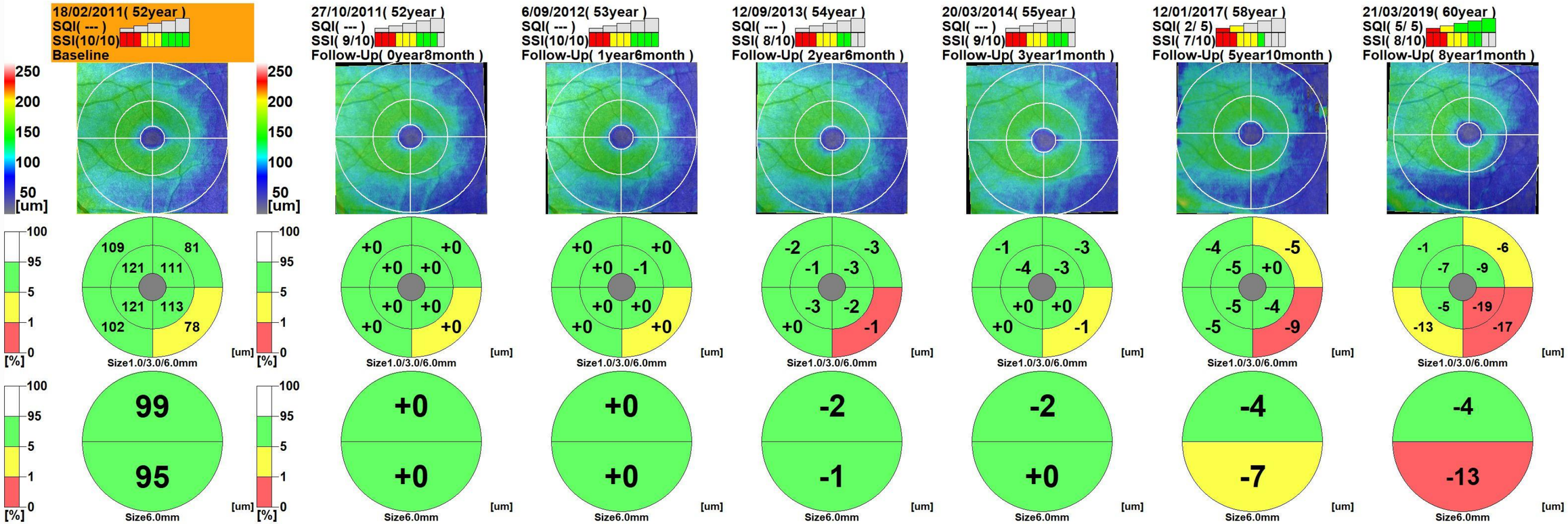

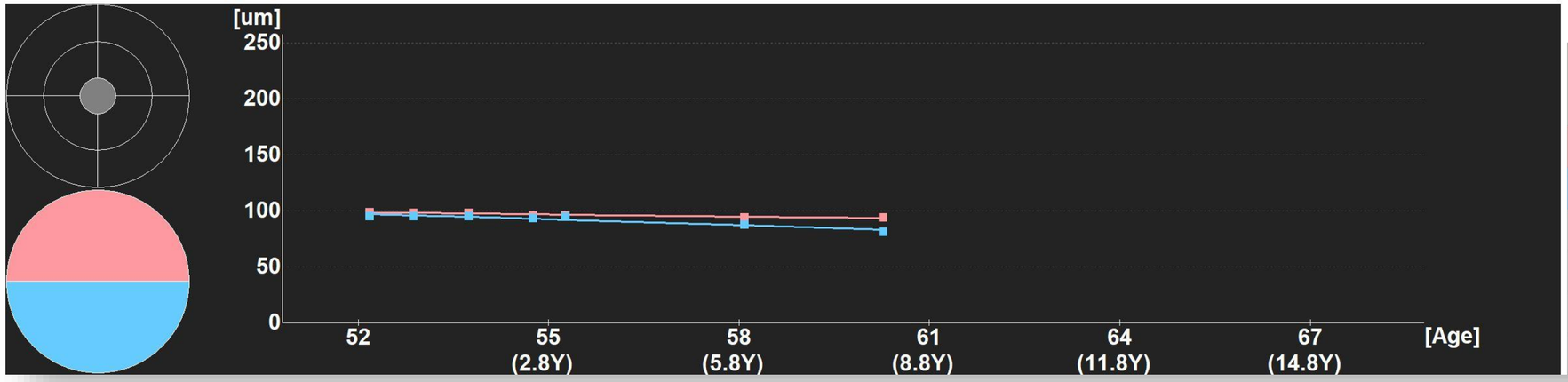

	ALL	
	Slope[/Y]	pValue
1	-0.64 um	< 0.01
2	-1.73 um	< 0.01

18/02/2011_R:MACULA MAP X-Y(6.0mm x 6.0mm[512 x 128])

Eye:R RS-3000 OCT RetinaScan

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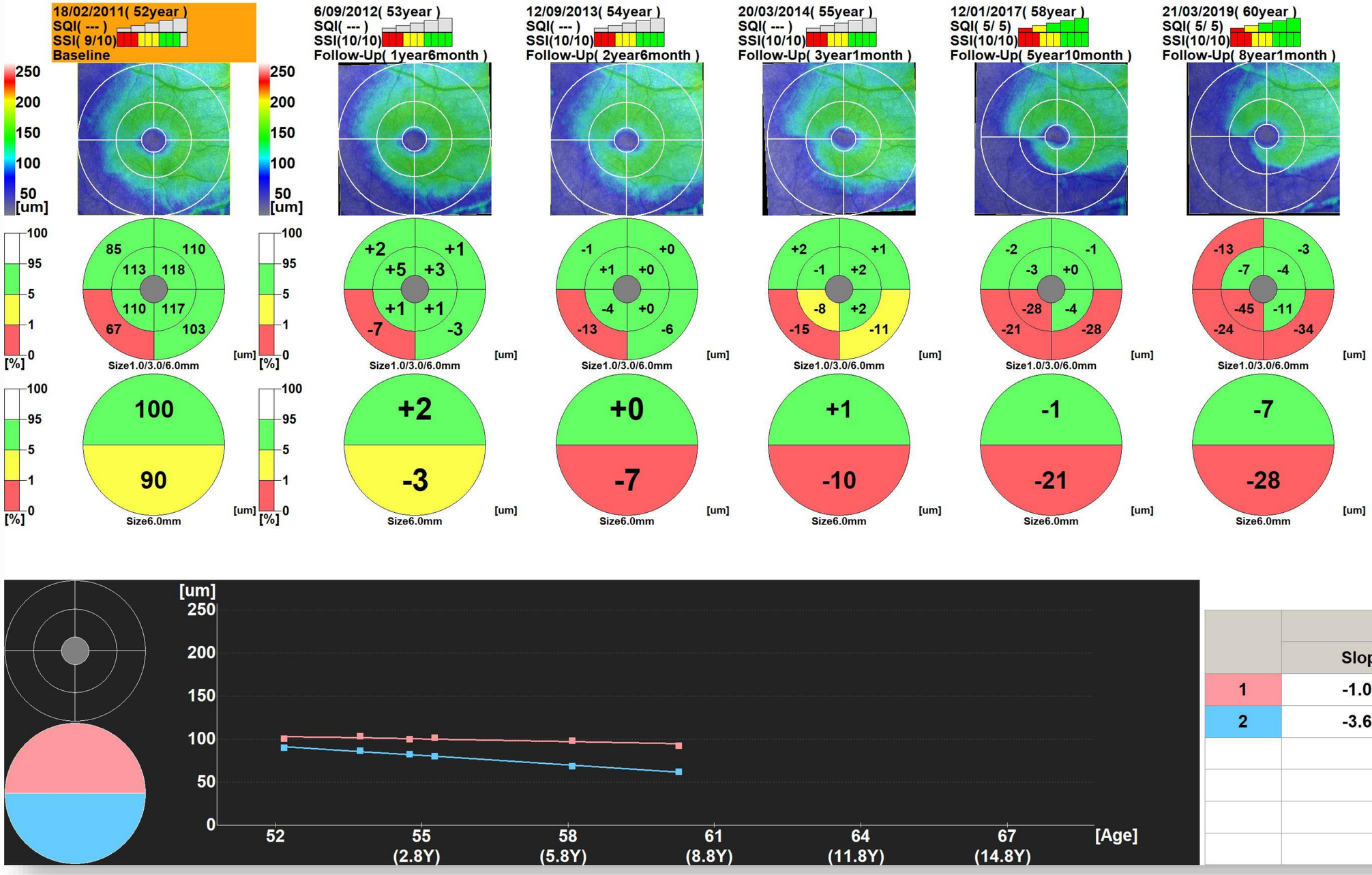


	ALL	
	Slope[/Y]	pValue
1	-1.07 um	< 0.05
2	-3.65 um	< 0.01

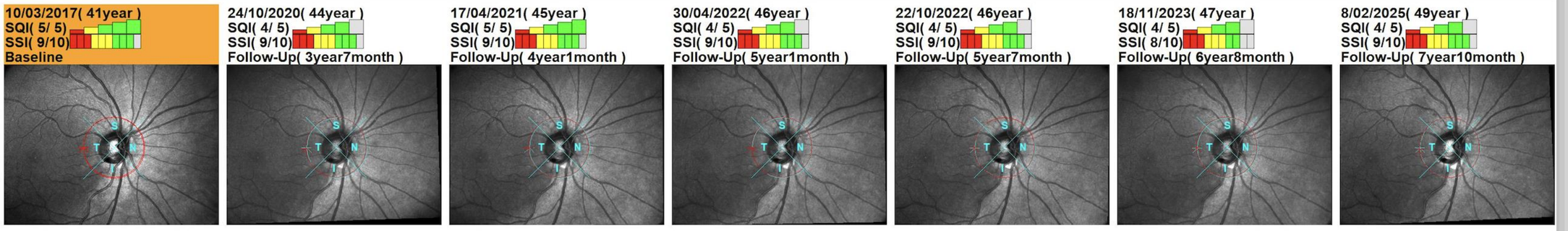
10/03/2017_R:DISC CIRCLE(3.45mm[1024])

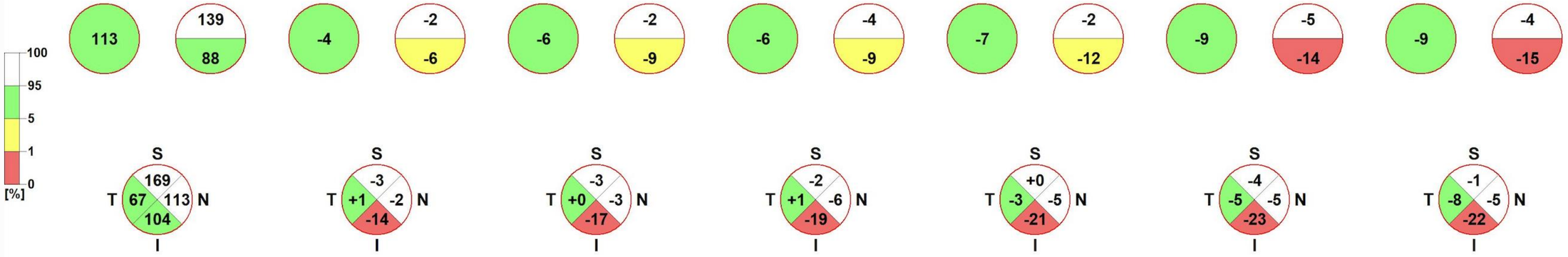
Eye:R

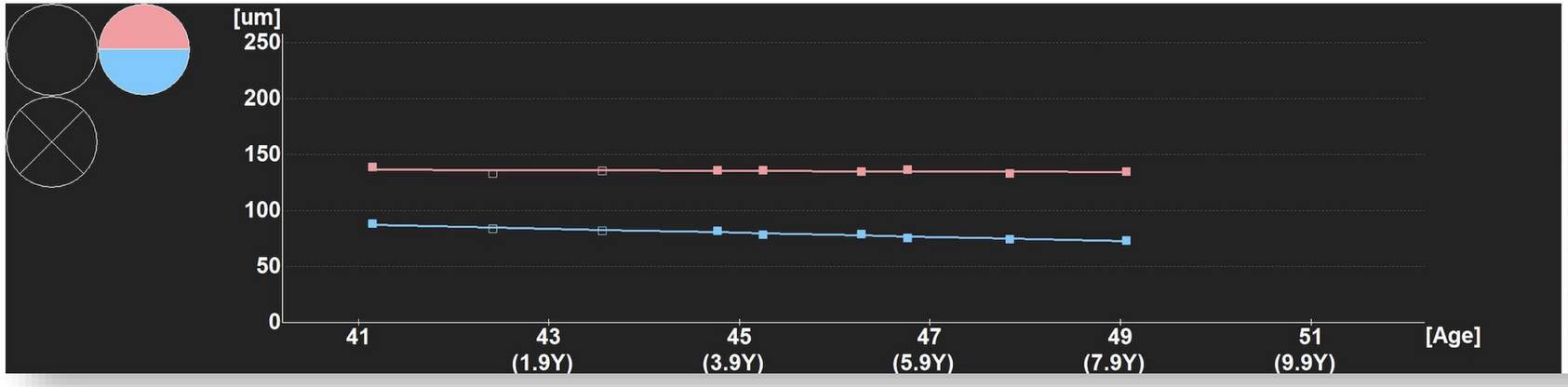
RS-3000 OCT RetinaScan Advance

Optometry AUSTRALIA

10/03/2017(41year) Baseline	24/10/2020(44year) Follow-Up(3year7month)	17/04/2021(45year) Follow-Up(4year1month)	30/04/2022(46year) Follow-Up(5year1month)	22/10/2022(46year) Follow-Up(5year7month)	18/11/2023(47year) Follow-Up(6year8month)	8/02/2025(49year) Follow-Up(7year10month)
SQI(5/ 5) SSI(9/10)	SQI(4/ 5) SSI(9/10)	SQI(5/ 5) SSI(9/10)	SQI(4/ 5) SSI(9/10)	SQI(4/ 5) SSI(9/10)	SQI(4/ 5) SSI(8/10)	SQI(4/ 5) SSI(9/10)







	ALL	
	Slope[/Y]	pValue
1	-0.30 um	-
2	-1.84 um	< 0.01

3. VISUAL FIELD PROGRESSION

- VF testing is inherently subjective and inherently variable
  - makes it more difficult to detect statistically significant progression
- Patients who are poor test takers with highly variable test thresholds will take m
- Strategies to aid detection of progression:
- 2 or 3 reliable baseline VF's
  - establishes baseline values for global indices of MD, PSD, VFI
  - measures sensitivity of each point in visual field with +/- error bars
  - determines the patient's test-retest variability

VISUAL FIELD PROGRESSION

- Baseline VF's need to be taken close together in time so that any changes are due to patient performance *not* progression of the disease process
- Statistical analysis software is essential, can't be 'eyeballed'
- Most researched and established software is HFA
  - Guided Progression Analysis (GPA)
- GPA uses 2 methods to detect progression:
  - Event Analysis
  - Trend Analysis

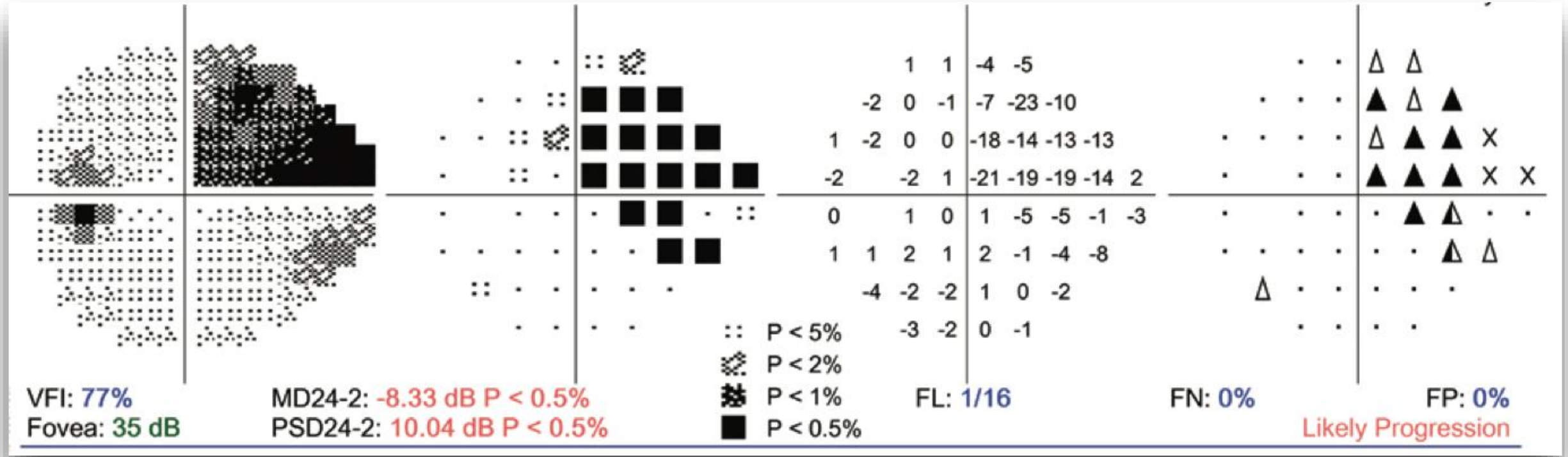
VISUAL FIELD PROGRESSION

- EVENT ANALYSIS
- Looks for significant change in each point on the VF
  - Deepening of an existing scotoma
  - Widening of an existing scotoma
  - New scotoma developing in a different part of the field
- Based on Pattern Deviation plot, not on Mean Deviation (MD)
- Flags each point that has changed more than the patient's inherent variability

VISUAL FIELD PROGRESSION

- Requires minimum of 3 VF exams
  - 2 baselines and 1 follow-up
  - will show points that are worse then baseline on 1 test
- Best progression sensitivity is after 6 VF's
  - will show if a point has worsened 3 times in a row from baseline
  - highly statistically significant, much fewer false positives
- Event analysis tells us:
  - *if* progression has occurred
  - *where* it has occurred
  - but does not tell us the *rate* of progression

VISUAL FIELD PROGRESSION



Δ P < 5% Deterioration ◭ P < 5% (2 consecutive) ▲ P < 5% (3+ consecutive) X Out of Range

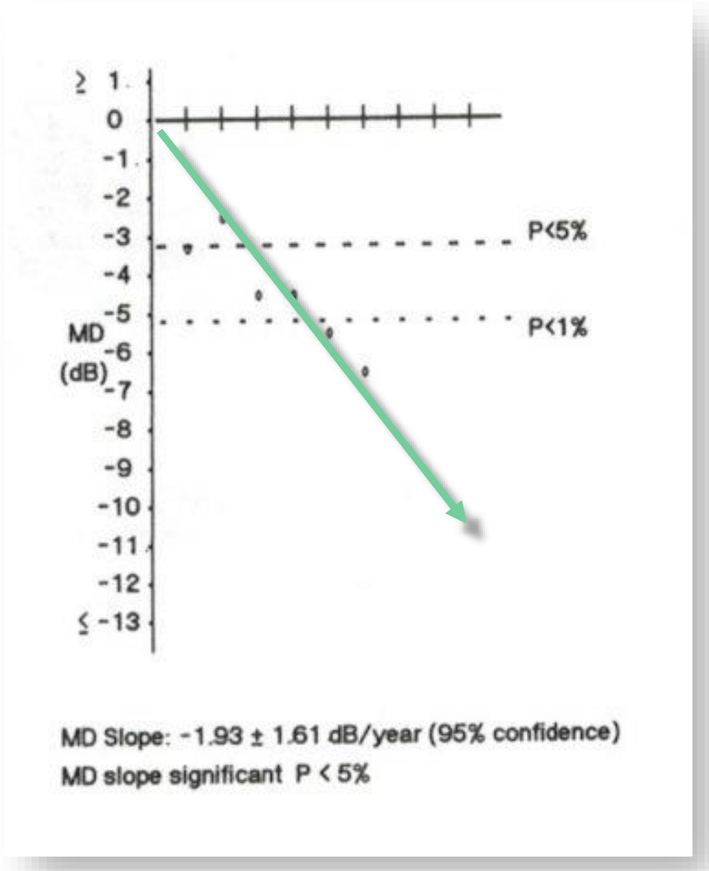
GPA “Possible Progression” 18.5% False Positives

GPA “Likely Progression” 2.6% False Positives

VISUAL FIELD PROGRESSION

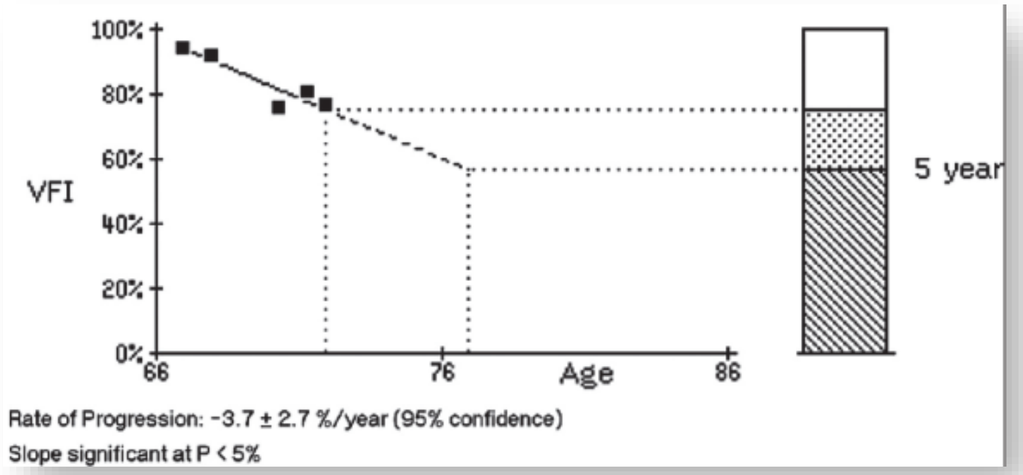
- TREND ANALYSIS
- Looks for progression over the entirety of the VF, not each point
  - Using global data from Mean Deviation (MD) or Visual Field Index (VFI)
- Requires a minimum 5 to 6 reliable VF exams to plot the linear regression
- Trend Analysis calculates the *rate* of progression
- Does not tell us which part of the VF is worsening
  - Event analysis is for that
- Rate of progression can predict future VF loss and time to blindness

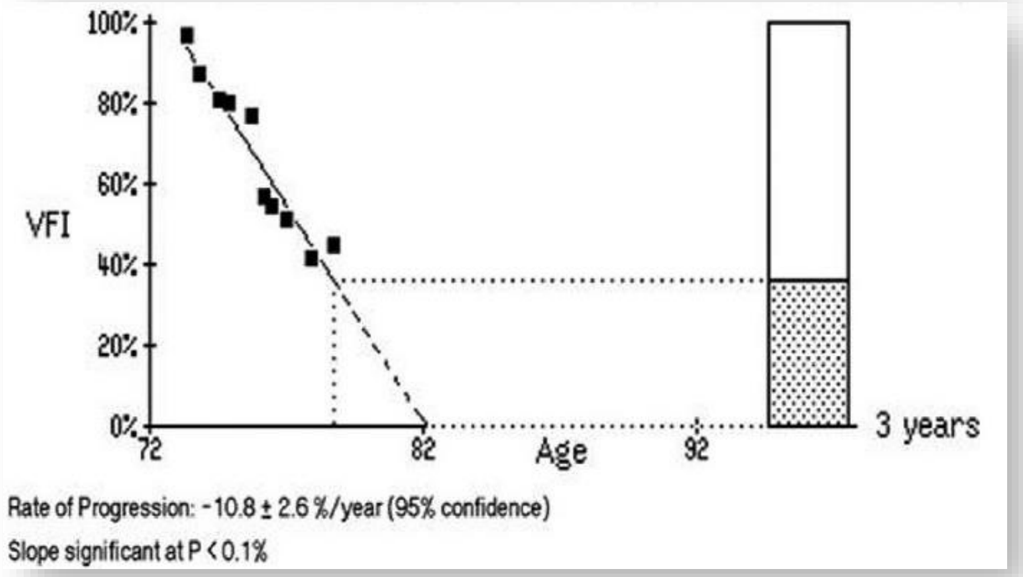
VISUAL FIELD PROGRESSION



Mean Deviation

VFI





VISUAL FIELD PROGRESSION

- GPA report is produced after 3 reliable VF tests (2 baseline, 1 follow-up)
- However takes 6 fields to show highly statistically significant information
  - Event “Likely Progression”
  - Trend “Rate of Progression”
- Therefore, at a *minimum* we require 6 reliable VF’s to detect true progression
  - excessive FP’s or FL’s will be excluded from analysis
- Need to detect VF progression at the earliest opportunity before too much VF is lost
  - Therefore we need the 6 VF tests in the shortest time possible
- However, we need to allow time for a progressive disease like glaucoma to actually worsen
  - No point doing a VF test every week for 6 weeks in a row!

VISUAL FIELD PROGRESSION

- European Glaucoma Society Guidelines ^
  - Newly diagnosed glaucoma
  - 6 visual fields in first 2 years
- Allows true progression rate to be determined
  - 2 years in a reliable test taker
  - 3-4 years in a more variable patient
- Aim is to find patients progressing > -1.0 dB MD/year
  - these persons are most likely to progress to blindness

^ European Glaucoma Society. *Terminology and Guidelines for Glaucoma* 2008 Available at: http://www.eugs.org/eng/EGS_guidelines.asp.

VISUAL FIELD PROGRESSION

*

Progression rate (dB/year)	Variability of MD		
	Low	Moderate	High
One exam per year	*Years to progress*		
-0.25	13.0*	19.0	30.0
-0.50	9.0	13.0	19.0
-1.00	6.0	9.0	13.0
-2.00	5.0	6.0	9.0
Two exams per year	*Years to progress*		
-0.25	6.5	8.5	15.0
-0.50	4.5	6.5	8.5
-1.00	3.0	4.5	6.5
-2.00	2.5	3.0	4.5
Three exams per year	*Years to progress*		
-0.25	4.3	6.3	10.0
-0.50	3.0	4.3	6.3
-1.00	2.0	3.0	4.3
-2.00	1.7	2.0	3.0

*Practical recommendations for measuring rates of visual field change in glaucoma. Chauhan BC et al. Br J Ophthalmol 2008; 92:569-573.

COMING UP
POLL #5

Scan QR or www.slido.com & 3450 959

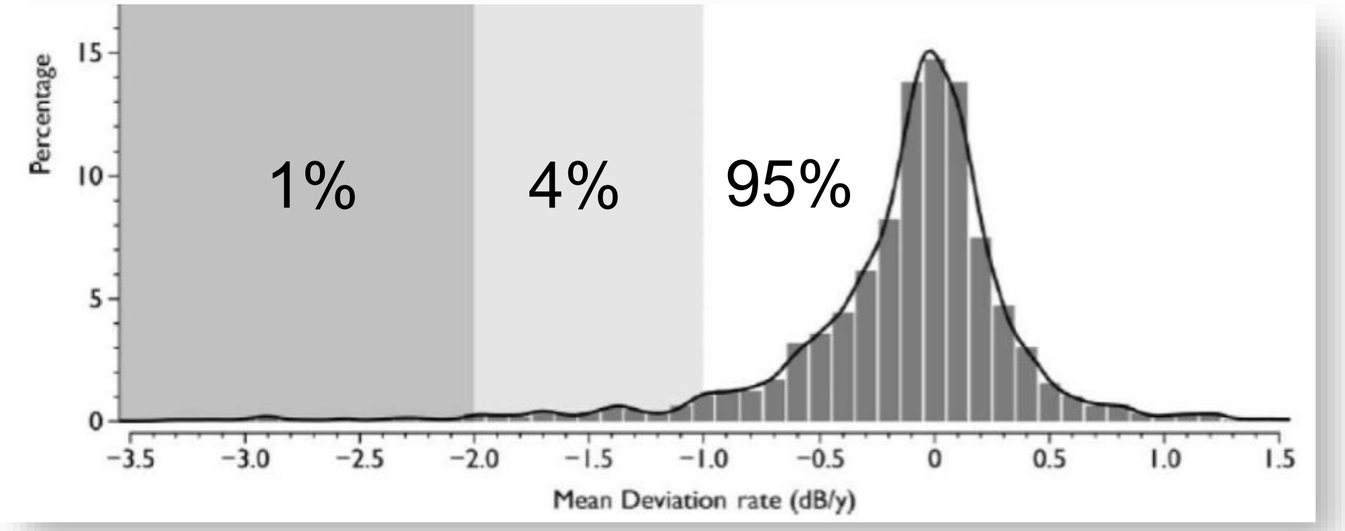
Poll 5. What is the average rate of visual field trend progression in glaucoma patients?

VISUAL FIELD PROGRESSION

- Visual Field progression rate measured in
  - dB/year of MD loss (earlier software)
  - %/year of VFI loss
- Average rate of loss in treated glaucoma is -0.06 dB/yr.
  - i.e. Zero
- Why? OCT data shows progression throughout life, and more rapid progression in all glaucomas
- 1. reactivation of sick/dysfunctional ganglion cells that have not died yet
- 2. loss of spare/overlapping ganglion cells

VISUAL FIELD PROGRESSION

Rates of Vision Loss…a decade of data
Boodhna T et al. Eye. 2015 Dec; 29(12):1613-9



- VF progression grading:
- “Slow” less than -1.0 dB/year (95%)
- “Rapid” -1.0 to -2.0 dB/yr (4%)
- “Catastrophic” more than -2.0 dB/yr (1%)
- Therefore, most treated glaucoma has stable or slow VF progression
  - treatment slows the progression rate
  - prevents significant lifetime vision loss

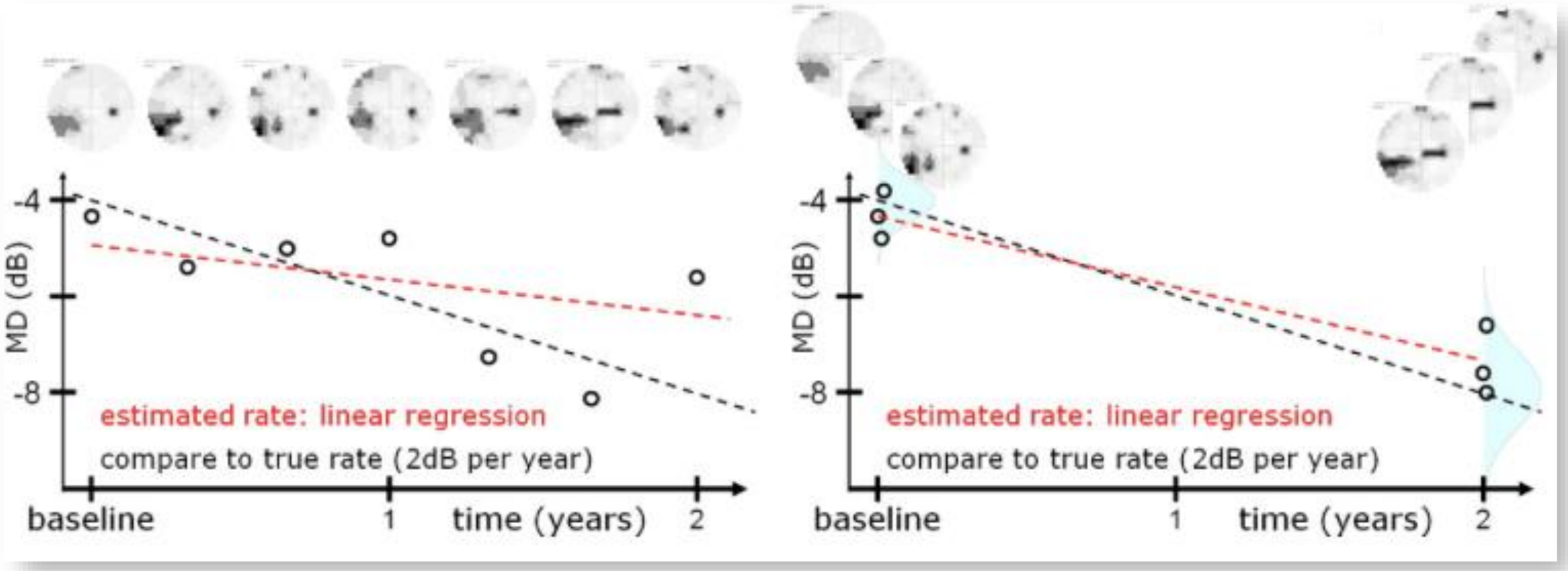
VISUAL FIELD PROGRESSION

- 6 reliable VF exams required in the first 2 years
- Does it matter how they are achieved?
- Some options:
  - 2 baseline exam then 1 VF exam every 4 months = 8 in 24 months
  - 2 baseline exams then 1 VF exam every 6 months = 7 in 24 months
  - 3 baseline exams then another 3 VF 2 years later = 6 in 24 months
    - “Front-loading” VF’s
- Which alternative is better at detecting progression?

VISUAL FIELD PROGRESSION

	6 monthly VF (evenly spaced)	4 monthly VF (evenly spaced)	Clustered VF (3 baseline then 3 @ 2 years)
Detection of Catastrophic Progression (> -2.0 dB/yr)	58%	82%	95%
False Positive Rate	2.9%	5.9%	0.4%

VISUAL FIELD PROGRESSION



Intervals between visual field tests when monitoring the glaucomatous patient.
Crabb DP, Garway-Heath DF. Invest Ophthalmol Vis Sci. 2012 May 17;53(6):2770-6.

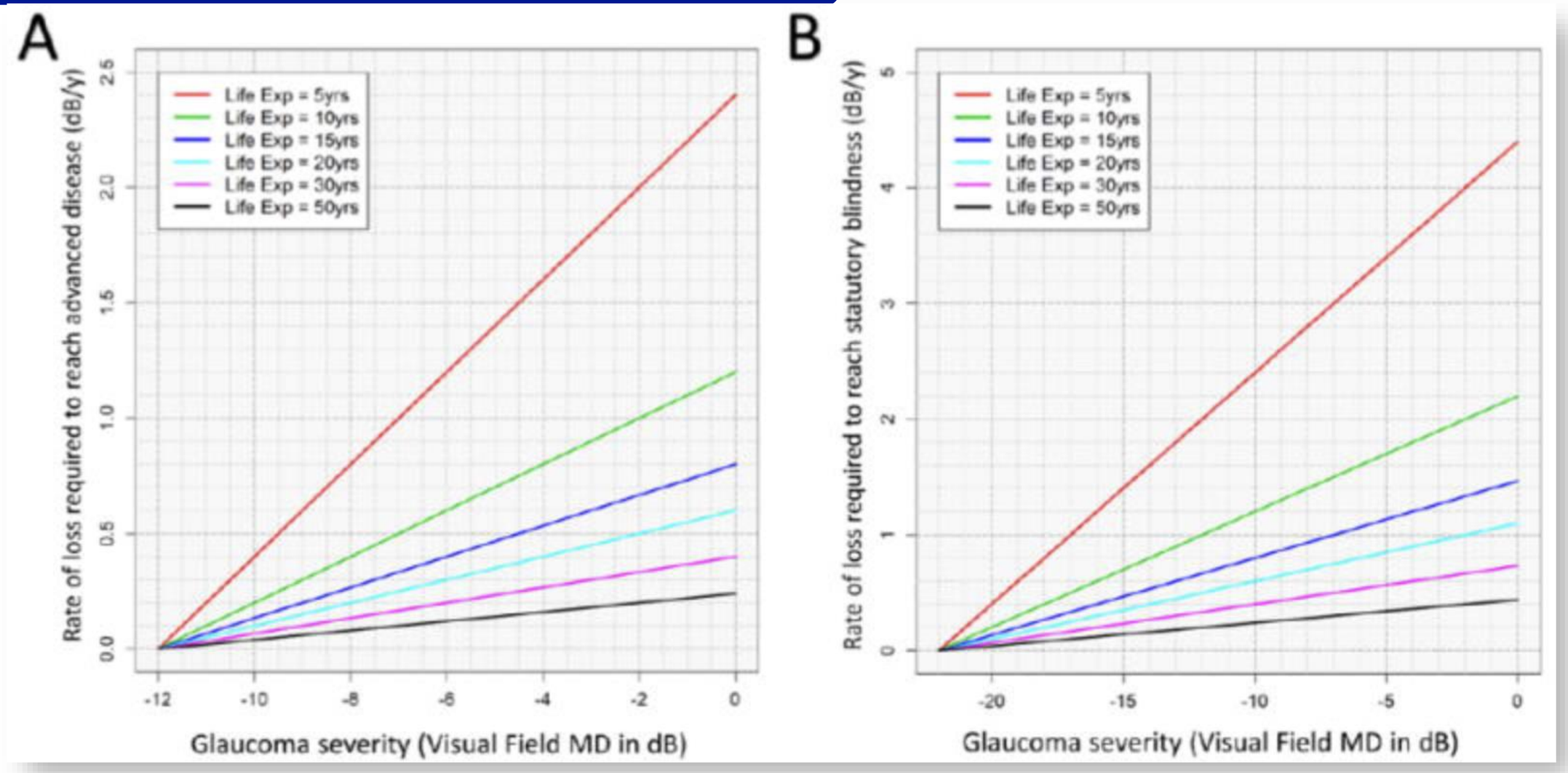
4. WHAT IS SIGNIFICANT PROGRESSION?

- Statistically Significant Progression v Clinically Significant Progression
- Instrument software generates statistical data
- p Value determines statistical significance
- Not all values equal
  - not so concerned at p=0.05
  - much more concerned at p=0.01 or 0.001
- Clinician decides whether it is clinically significant or not
- Depends on
  - progression rate
  - age of patient
  - severity grading of glaucoma at that time

SIGNIFICANT PROGRESSION

- The younger the patient, the faster the progression rate, a worse disease severity
  - more *clinically* significant
  - must escalate therapy
- Older patients can tolerate faster progression rates as may not live long enough to lose significant vision
- Mild progression rates can be highly clinically significant in younger patients
- e.g.
  - 55 YO Female, baseline MD -5.0 dB, progression rate -0.5 db/yr
  - will lose another 15 db by age 85 = -20 dB
  - early perimetric glaucoma will become end stage glaucoma

SIGNIFICANT PROGRESSION



Saunders LJ et al. What rates of glaucoma progression are clinically significant? Expert Rev Ophthalmol. 2016;11(3):227-234.

CONCLUSION

- Progression analysis is most important aspect of glaucoma management
- Determine an accurate progression rate as soon as you can
- Find the small proportion that are rapid or catastrophic progressors
  - aggressive treatment
  - frequent review
  - early referral for surgery
- Take care of all the rest yourself!

THANK YOU !

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