
بسم الله الرحمن الرحيم

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Heidelberg Retina Tomograph (HRT)

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Incidence of Primary Open-Angle Glaucoma

- Affects >2 million over the age of 40 in the US (1.9%); expected to exceed 3 million by 2020 [1]
- Average age of onset 54 years of age [2]
- Most patients (63%) have had glaucoma >10 years [2]
- 2nd leading cause of blindness [3]

1. Friedman DS et al. Arch Ophthalmol. 2004;122:532-538.
2. Gallup Eye Health Survey. 2002.
3. Glaucoma Facts. Available at: www.glaucoma.org/learn/facts.html.

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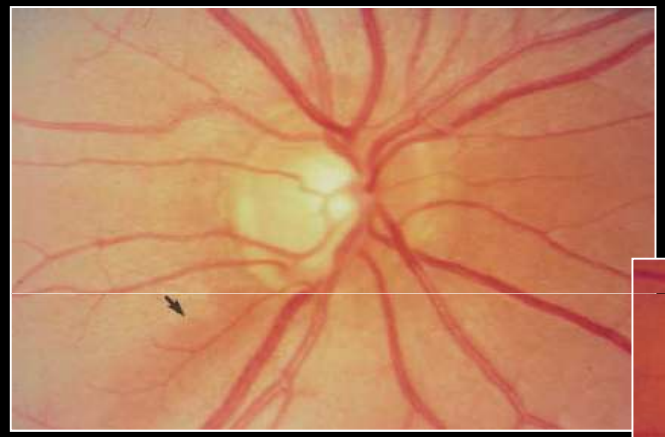
Under Diagnosis of Glaucoma

- Population studies suggest over half of all glaucoma cases in the US have not been diagnosed.
- Percentage of patients with undiagnosed glaucoma
  - Baltimore Eye Survey: 56% [1]
  - Proyecto VER: 62% [2]
- Many suffer severe Visual Field loss before diagnosis.[3]

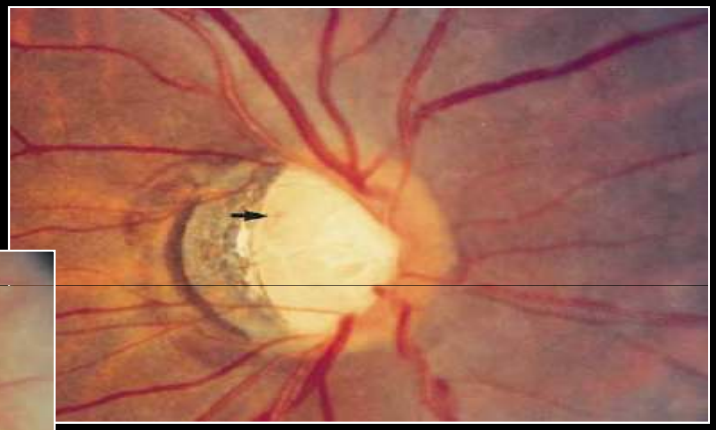
1. Sommer A et al. Arch Ophthalmol. 1991;109:1090-1095.
2. Quigley HA et al. Arch Ophthalmol. 2001;119:1819-1826.
3. Gillespie BW et al. Invest Ophthalmol Vis Sci. 2003;44:2613-2620.

5 Disc Classifications

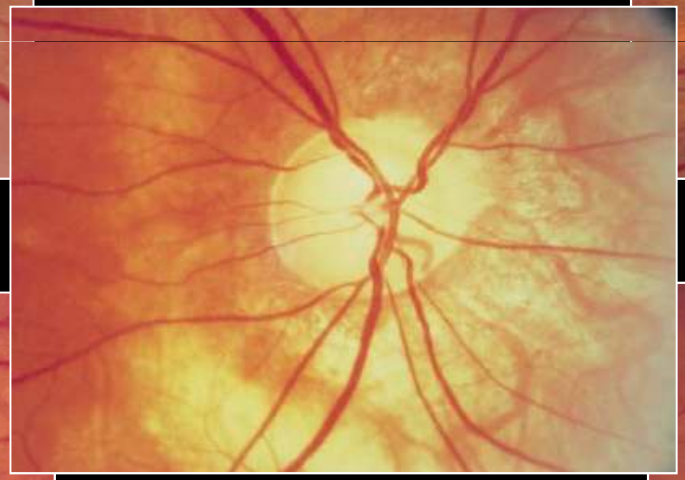
1 Focal



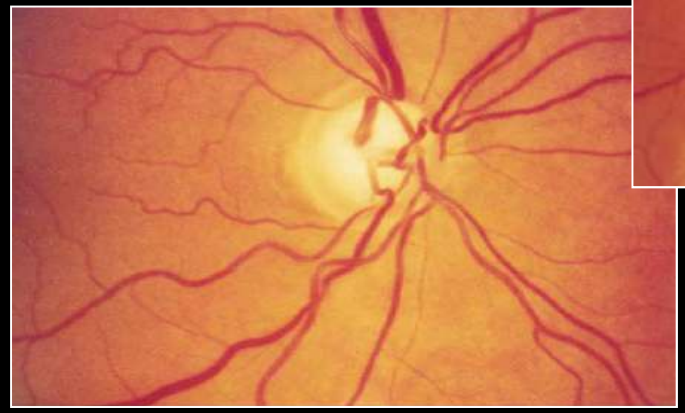
2 Myopic



3 Senile sclerotic



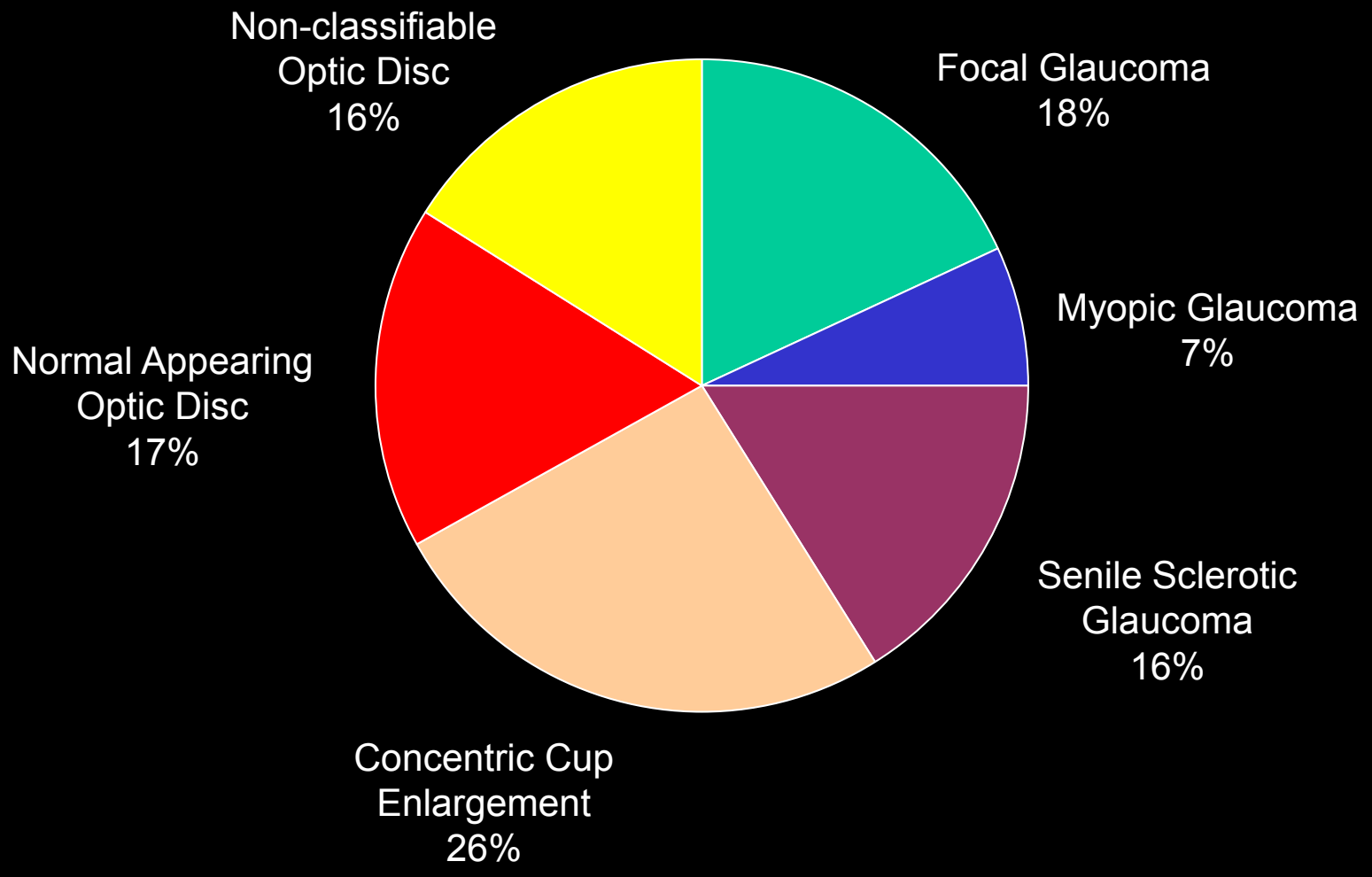
4 Concentric



5 Advanced

Broadway D.C, Nicolela M. T, Drance S.M., Survey of Ophthalmology 1999

Frequency of Glaucoma Disc Types



Nicolela et al., Am J Ophthalmol 2000;132:836-844

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Mixed Glaucoma

Only 7% of patients have pure optic disc types

64% of patients have optic discs with mixed appearance and two morphologic components

Nicolela et al, Am J Ophthalmol 2000;132:836-844.

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Multifactorial Glaucoma

- POAG develops in a multifactorial manner.
- There is huge diversity in the appearance of both the normal and the diseased disc.
- Early changes in the optic disc are subtle.
- May occur within the range of normal diversity.
- May be missed without careful serial examinations of the individual's disc.

Broadway D.C, Nicolela M. T, Drance S.M., Survey of Ophthalmology 1999

AIGS Consensus Redefines Glaucoma

- The committee on evidence-based glaucoma of the AIGS Consensus Meeting has proposed:

  "Progressive Structural Optic Nerve Damage"

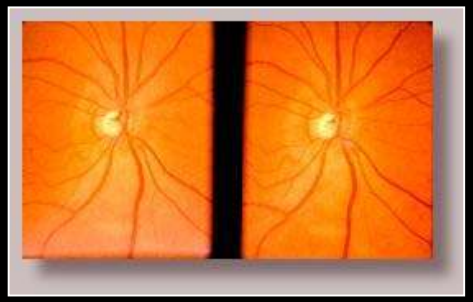
  as the NEW "Gold Standard".

Glaucoma Diagnosis – Structure and Function, Consensus Series - 1, AIGS 2004

AIGS* Consensus

- HRT discriminates glaucomatous from normal optic discs in a clinical setting at least as well as experts evaluating optic disc photographs.
- Should be considered when such expert advice is not available.

+



*Association of International Glaucoma Societies
Glaucoma Diagnosis – Structure and Function, Consensus Series - 1, AIGS 2004

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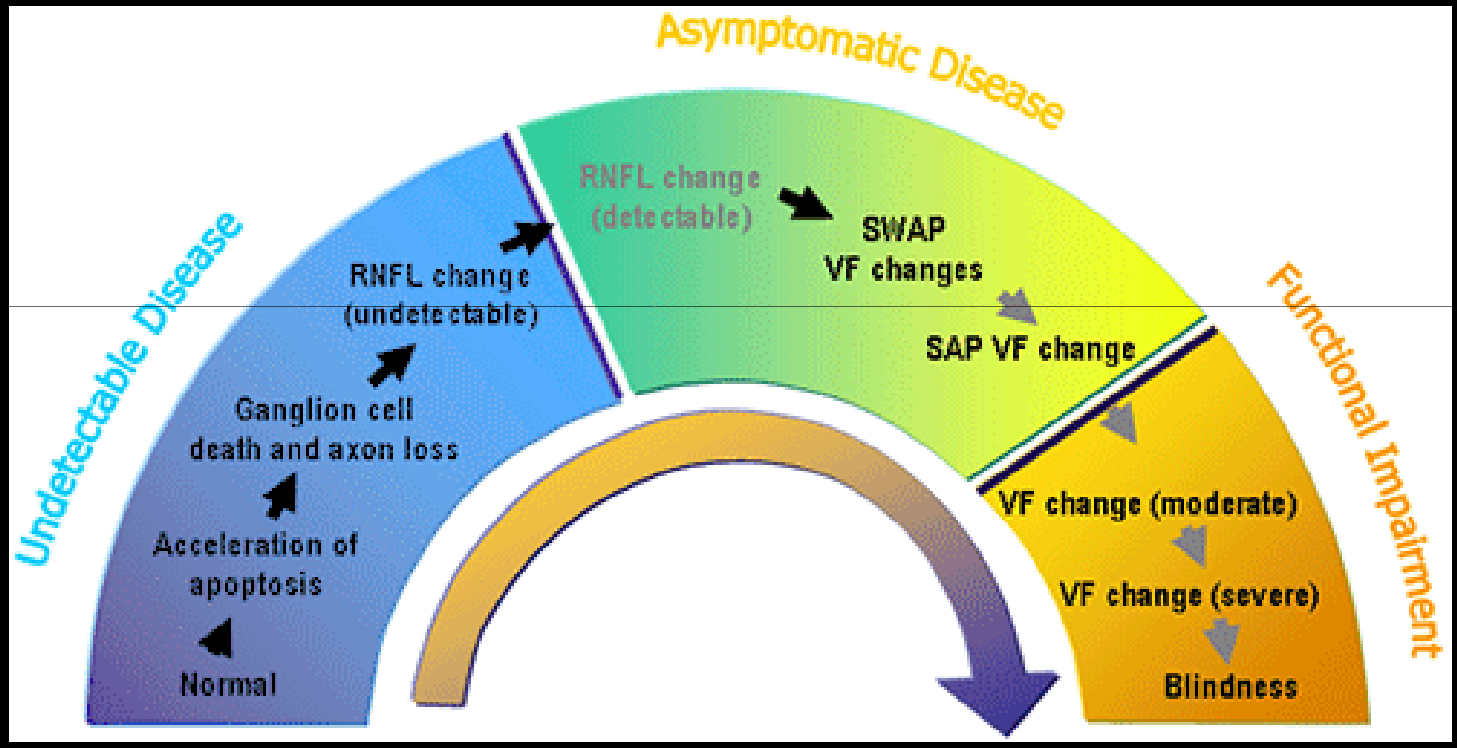
History of Glaucoma Diagnosis

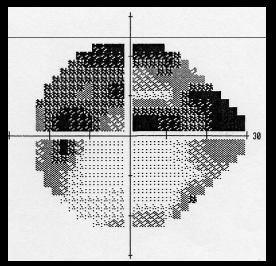
- Pre - 1980
  - Elevated IOP
- 1980 - 2000
  - Elevated IOP + visual field (VF) defect
- 2000 - present
  - Elevated IOP + visual field (VF) + Optic disc (ONH) + retinal nerve fiber layer (RNFL)


Asymptomatic Disease
Undetectable Disease
Functional Impairment
RNFL change
(detectable)
SWAP
VF changes
SAP VF change
RNFL change
(undetectable)
Ganglion cell
death and axon loss
Acceleration of
apoptosis
Normal
VF change (moderate)
VF change (severe)
Blindness

Glaucoma Diagnosis in Clinical Practice

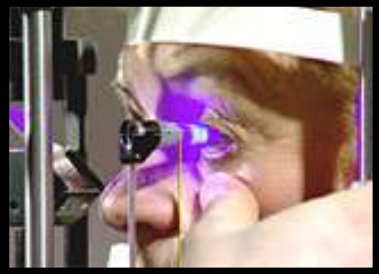
- Traditionally based on:
  - Intraocular Pressure (IOP)
  - Visual Fields (VF)
  - Subjective Assessment of the Optic Disc (ON)





IOP

- Benefits:
  - Rapid and convenient
- Limitations:
  - Large overlap between healthy and glaucoma eyes[1]
  - Corneal thickness affects accuracy[2]
  - IOP fluctuates[3]
  - IOP damage threshold varies
    - Ocular hypertensives (OHT)
    - Normal tension glaucoma (NTG)



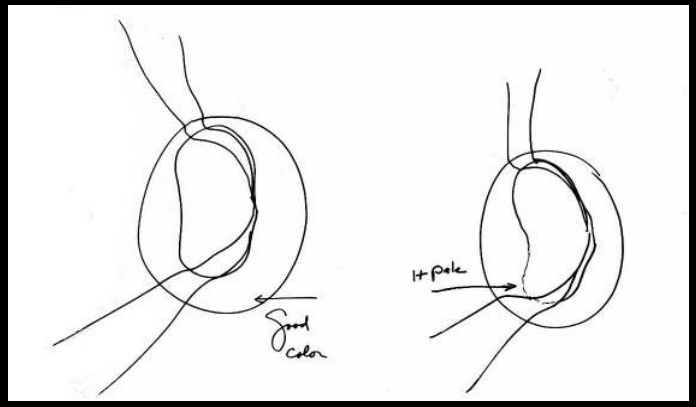
1. Leske et al., Ophthalmology 1997
2. Review by Doughty M.J., and Zaman M.L. Surv of Ophthalmol 2000; 44: 367
3. Liu, J.H.K., Zhang, X., Kripke, D.F., and Weinreb, R.N. IOVS 2003; 44:1586

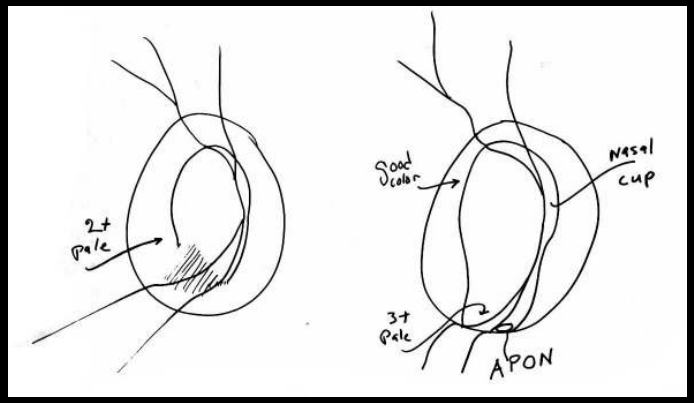
Visual Fields

- Benefits:
  - Provides functional assessment of damage.
  - Progression can be monitored.
- Limitations:
  - Subjective.
  - High variability.
  - Poor sensitivity for early detection.

Subjective Optic Disc Assessment

- Benefits:
  - Convenient.
  - 3-D evaluation
    (Slit Lamp Biomicroscopy).
- Limitations:
  - Subjective.
  - Requires pupil dilation.
  - Baseline drawing may be inaccurate.
  - Difficult to detect change.



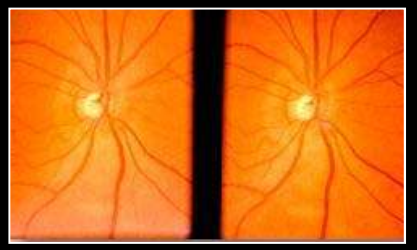


Drawings from Spaeth, G. L., and Varma, R. The Optic Nerve in Glaucoma. J.B. Lippincott Co. Philadelphia. 1993

Optic Disc Photographs

- The current "*Gold Standard*" for optic disc assessment is stereo fundus photography.

- But in US only 40% of general ophthalmologists make follow-up optic nerve assessment and optic nerve head documentation.[1]



1. Glaucoma Diagnosis – Structure and Function, Consensus Series -1, AIGS

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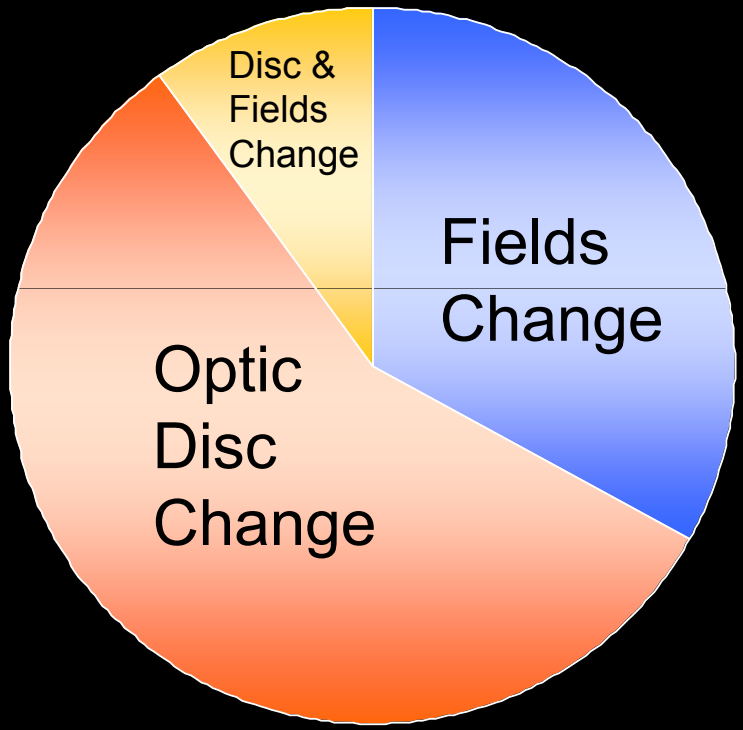
Subjective Disc Assessment with Photography

- Benefits:
  - Documents the appearance of the optic nerve head.
  - Allows detailed study of the optic disc.
- Limitations:
  - Requires clear media, dilated pupil, and skilled photographer.
  - Poor agreement in interpretation, even among experts.[1,2]
  - Progression missed up to 50% of the time by experts.[3]
  - Time consuming.
  - Not cost-effective in today‘s busy clinic?

1. Abrams et al., Ophthalmology 1994; 101:1662-1667
2. Zangwill et al., Am J Ophthalmol. 1995; 199:415-421
3. Coleman et al., J Glaucoma 1996; 5:384-389

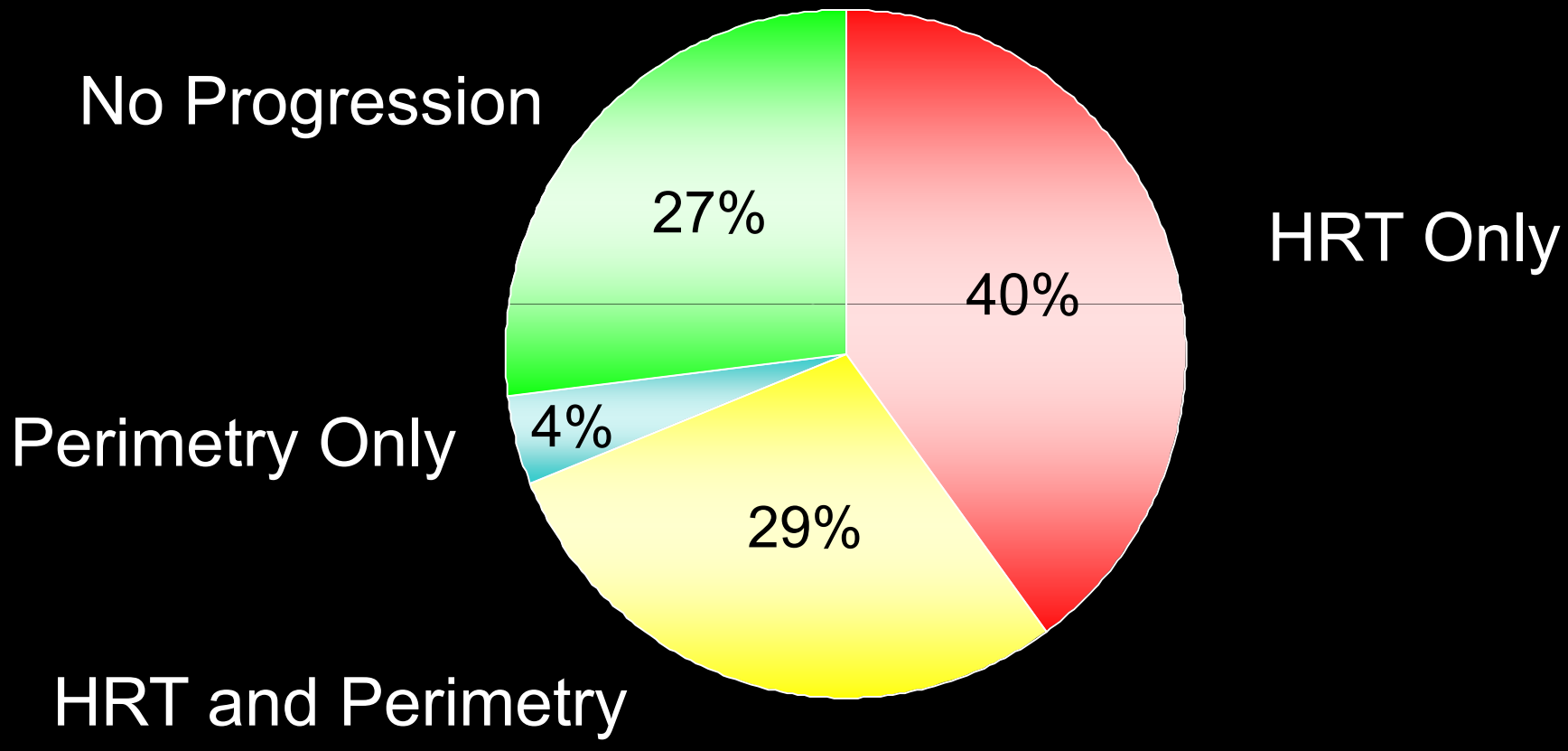
OHTS: Optic Disc Change is the Primary Indicator

- OHTS reports 55% of subjects reached endpoint (POAG) based on changes in the optic disc only.
- A further 10% of subjects had concurrent optic disc and visual fields changes.
- Only 35% of glaucoma was found by visual field changes.



Kass et al., Arch Ophthalmol. 2002;120:701-703

Confirms HRT Longitudinal Studies



Chauhan et al., Arch Ophthalmol 2001;119:1492-1499

OHTS ancillary study: Hazard Ratios

Table 3. Univariate and Multivariate Hazard Ratios and 95% Confidence Intervals (CIs) for the Development of POAG (Average of the Eyes)

	Hazard Ratio (95% CI)	
	Univariate	Multivariate*
CSLO measures		
Disc area (per 0.4 mm² greater)	0.84 (0.58-1.20)	0.86 (0.57-1.30)
Cup area (per 0.3 mm² greater)	1.22 (0.96-1.55)	1.21 (0.96-1.53)
Cup area-to-disc area (per 0.1 greater)	1.23 (1.00-1.50)	1.25 (1.02-1.53)
Mean cup depth (per 0.1 mm greater)	1.58 (1.14-2.20)	1.60 (1.15-2.22)
RNFL thickness (per 0.1 mm greater)	0.60 (0.34-1.06)	0.66 (0.35-1.23)
Standard deviation of mean image (per 6 µm greater)	1.15 (0.92-1.43)	1.04 (0.80-1.37)
Cup shape (per 0.1 greater)	1.24 (0.78-1.97)	1.02 (0.62-1.67)
Cup volume below surface (per 0.1 mm³ greater)	1.11 (0.96-1.28)	1.10 (0.97-1.25)
Rim area (per 0.2 greater)	0.58 (0.43-0.79)	0.57 (0.42-0.78)
Rim area/disc area (per 0.1 greater)	0.75 (0.60-0.94)	0.76 (0.62-0.93)
Reference height (per 0.1 mm greater)	1.42 (1.04-1.93)	1.49 (1.03-2.17)
Corneal curvature (per 0.2 mm greater)	1.16 (0.90-1.49)	1.03 (0.79-1.36)
RNFL cross-section (per 0.3 mm² greater)	0.68 (0.49-0.95)	0.72 (0.48-1.06)
Mean height contour (per 0.1 mm greater)	2.59 (1.69-3.98)	2.69 (1.62-4.49)
Rim volume above reference (per 0.1 mm³ greater)	0.63 (0.45-0.87)	0.65 (0.47-0.91)
Cup volume below reference (per 0.1 mm³ greater)	1.24 (1.02-1.52)	1.20 (1.01-1.43)
HRT classification 1 (per 1 unit greater)	0.72 (0.59-0.89)	0.75 (0.62-0.92)

Table 3. Univariate and Multivariate Hazard Ratios and 95% Confidence Intervals (CIs) for the Development of POAG (Average of the Eyes) (cont)

	Hazard Ratio (95% CI)	
	Univariate	Multivariate*
CSLO indexes		
HRT classification, outside normal limits vs within normal limits	2.47 (1.31-4.65)	2.54 (1.31-4.90)
MRA (outside normal limits vs within normal limits)		
Overall	2.72 (1.19-6.21)	2.39 (1.02-5.62)
Global	5.64 (1.94-16.44)	3.37 (1.13-9.99)
Nasal	1.99 (0.74-5.37)	1.59 (0.48-5.24)
Nasal inferior	4.44 (1.77-11.12)	4.19 (1.61-10.91)
Nasal superior	1.97 (0.43-8.96)	0.72 (0.11-4.63)
Temporal	3.28 (0.82-13.18)	2.48 (0.66-9.22)
Temporal inferior	5.02 (1.53-16.51)	5.80 (1.60-21.00)
Temporal superior	8.88 (2.58-30.56)	3.28 (0.98-10.98)
OHTS predictive factors		
Age (per decade)	1.27 (0.92-1.76)	NA
History of heart disease	4.25 (1.63-11.08)	NA
IOP (per mm Hg)	1.11 (0.99-1.23)	NA
CCT (per 40 µm thinner)	2.14 (1.44-3.18)	NA
PSD (per 0.2 dB greater)	1.15 (0.93-1.43)	NA
Horizontal cup-disc ratio (per 0.1 larger)	1.27 (1.09-1.49)	NA
Vertical cup-disc ratio (per 0.1 larger)	1.40 (1.16-1.68)	NA

Abbreviations: CCT, central corneal thickness; CSLO, confocal scanning laser ophthalmoscopy; HRT, Heidelberg Retina Tomograph; IOP, intraocular pressure; MRA, Moorfields Regression Analysis; NA, not applicable; OHTS, Ocular Hypertension Treatment Study; POAG, primary open-angle glaucoma; PSD, pattern standard deviation; RNFL, retinal nerve fiber layer.

*Multivariate model contains baseline age, IOP, PSD, CCT, and history of heart disease, with medication status as a time-dependent covariate. One hundred twelve eyes were excluded from the multivariate analyses because of missing CCT values.

Temporal MRA classifications have highest predictive value!

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OHTS ancillary study: HRT Predicts Glaucoma

- The latest OHTS Ancillary Study shows:
  - HRT (MRA; Moorfields Regression Analysis) is a top predictive factor for glaucoma.
  - HRT can identify those patients at high risk for developing the disease.

Zangwill et al., Arch Ophthalmol. 2005;123:1188-1197

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Evidence-Based Glaucoma diagnosis

- The HRT has been clinically proven for:

1. Progression.[1,2,3,4,5]
2. Diagnostic Accuracy approx. 90%.[6,7,8]
3. Reproducibility.[9,10,11]
4. Correlation with Visual Fields.[12,13]
5. Correlation with RNFL histology.[14]
6. RNFL thickness measurements (AROC > .90).[15]
7. Equal or better than Stereo Disc Photography.[16, 17]
8. Predicts Visual Fields.[18,19,20]

Tomographic Identification of Neuroretinal Rim Loss in High-Pressure, Normal-Pressure, and Suspected Glaucoma

James C. H. Tan, Darmalingum Poinoosawmy, and Roger A. Hitchings

1) Chauhan et al., Arch Ophthalmol. 2001; 119: 1492. 2) Kamal et al., Br J Ophthalmol. 1999; 83: 290. 3) Tan, Poinoosawmy and Hitchings IOVS 2004; 45: 2279. 4) Bowd et al., IOVS 2004; 45:2255. 5) Tan and Hitchings IOVS 2003; 44:2621. 6) Swindale et al., IOVS 2000; 41: 1730. 7) Bowd et al., IOVS 2002; 43: 3444. 8) Zangwill et al., IOVS 2004; 45: 3144. 9) Chauhan et al., AM J Ophthalmol. 1994; 118: 9. 10) Weinreb et al., Arch Ophthalmol 1993; 111: 636. 11) Rohrschneider et al., Ophthalmology 1994; 101: 1044. 12) Iester et al., J Glaucoma 1997; 6: 78. 13) Tsai et al., J Glaucoma 1995; 4:110. 14) Yucel et al., Arch Ophthalmol. 1998; 116: 493. 15) Zangwill et al., IOVS 2004; 45: 3144. 16) Zangwill et al. Am J Ophthalmol. 2004; 137:219-227. 17) Wollstein et al. Ophthalmology 2000; 107:2272-2277. 18) Bowd et al., IOVS 2004; 45:2255. 19) Kamal et al., Br J Ophthalmol. 1999; 83: 290. 20) Tan and Hitchings IOVS 2003; 44:2621.

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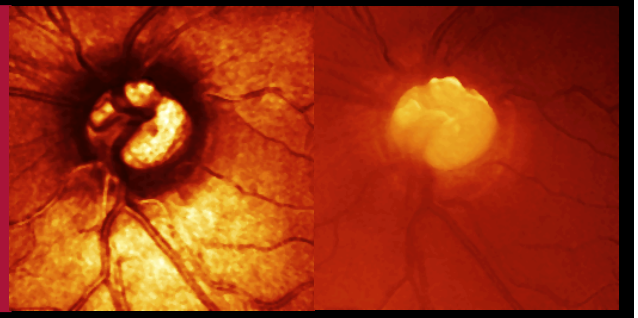
HRT *Image Acquisition and Image Quality*



HRT3

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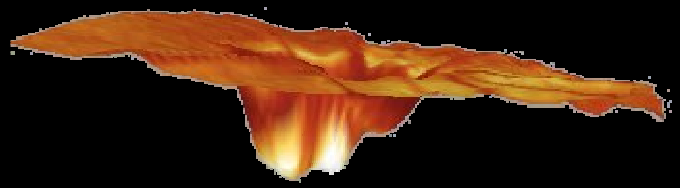
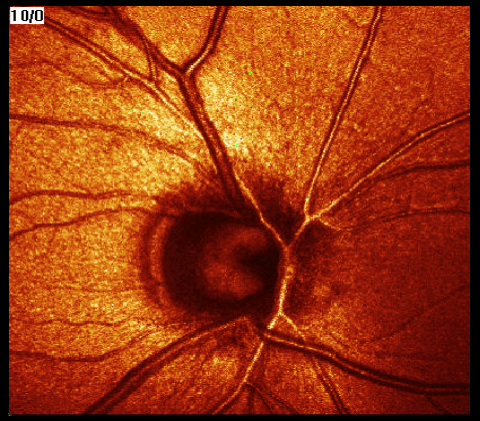
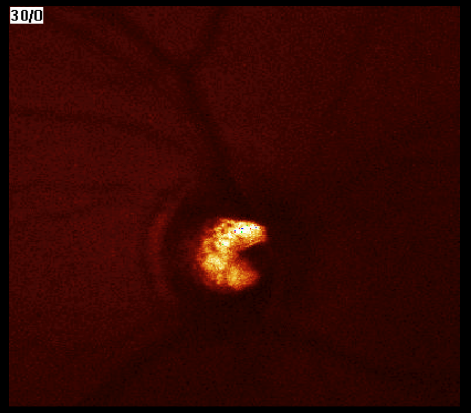
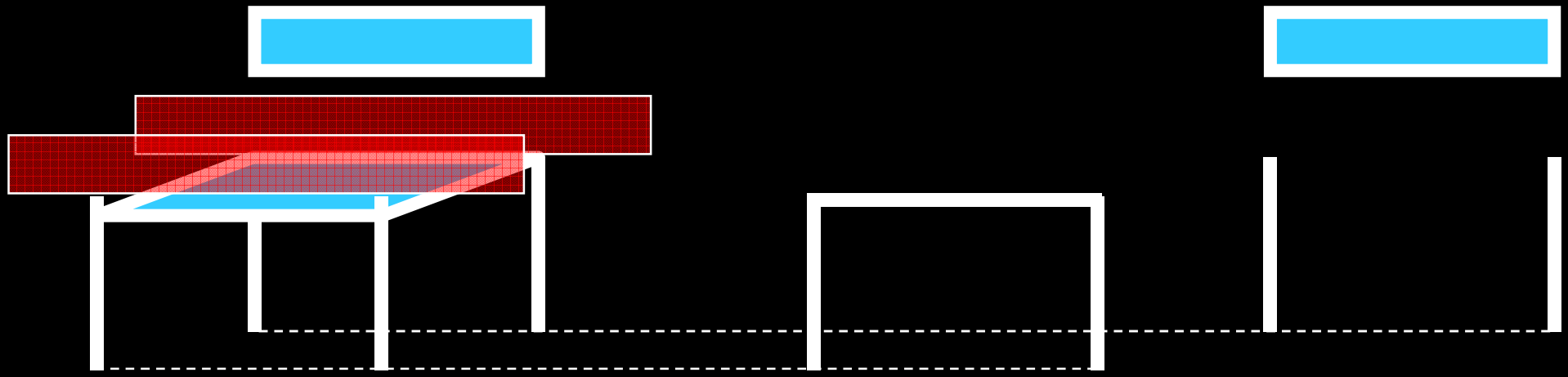
Confocal Principle

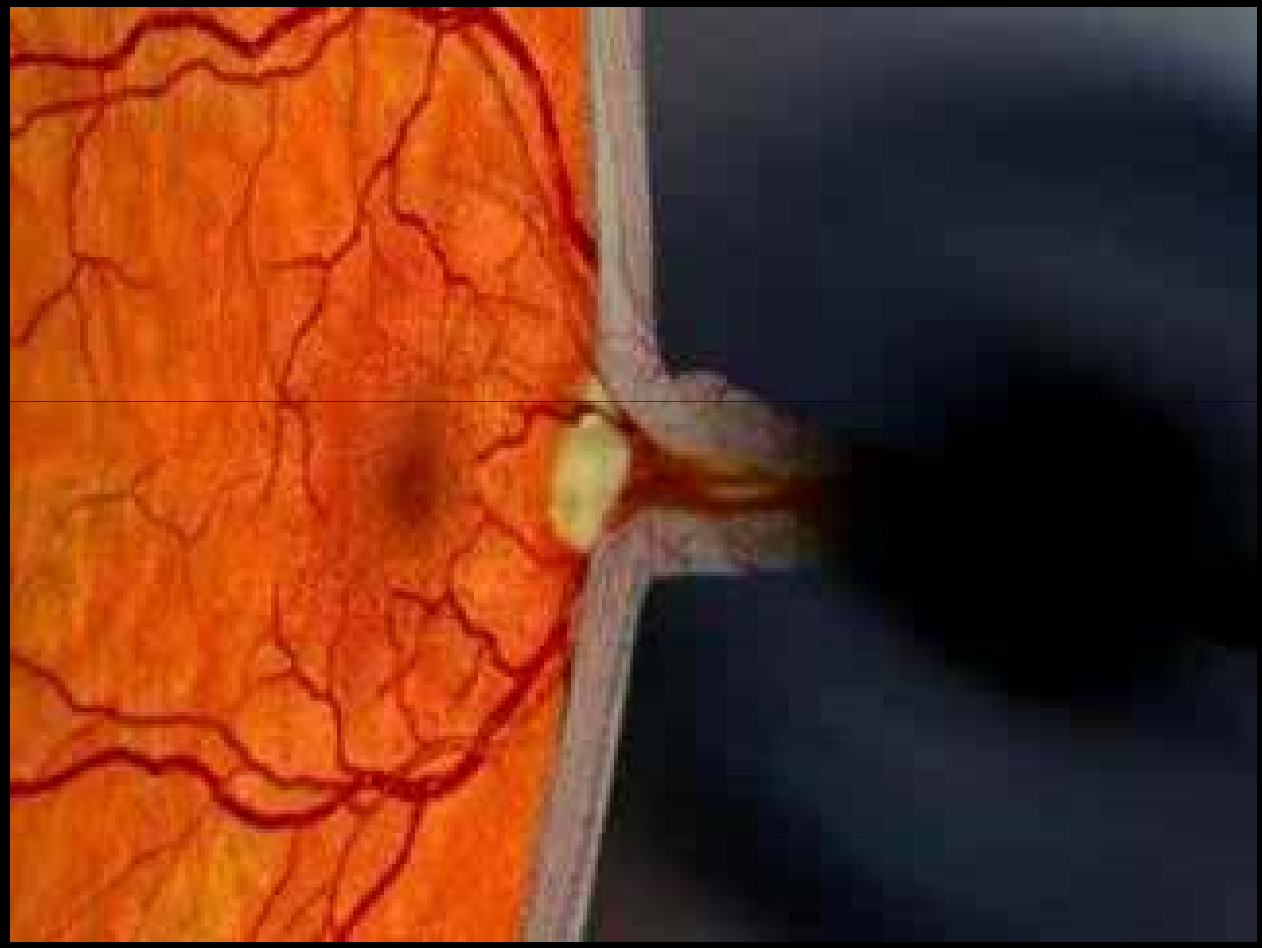




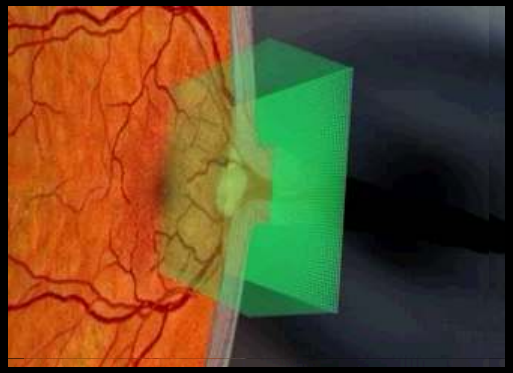




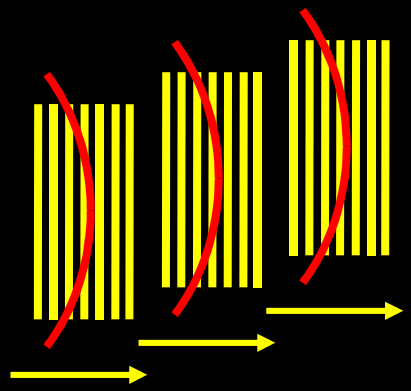
Confocal Principle



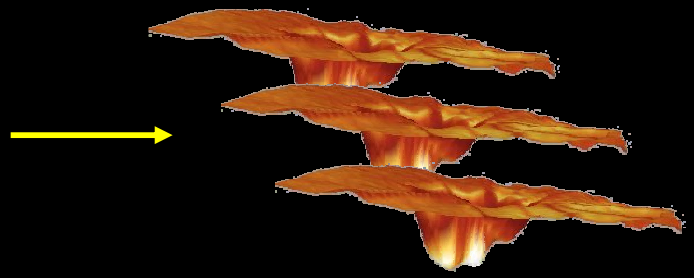
HRT II Acquisition and Signal Processing



147.456 individual local surface **height** measurements
147.456 local **variability** measures
147.456 individual local surface **reflectance** measurements



three **automatic** image series

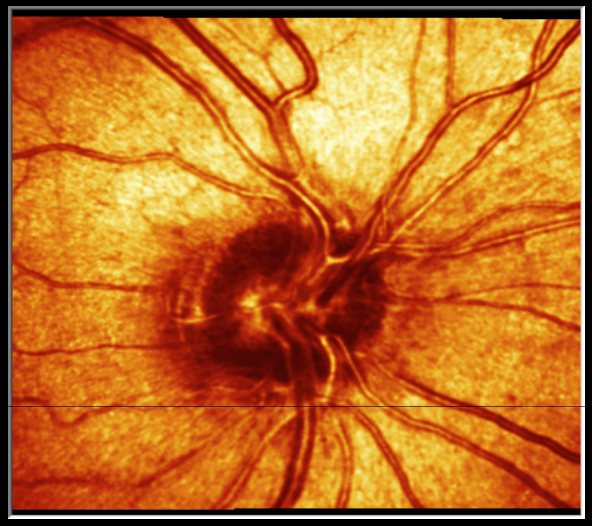


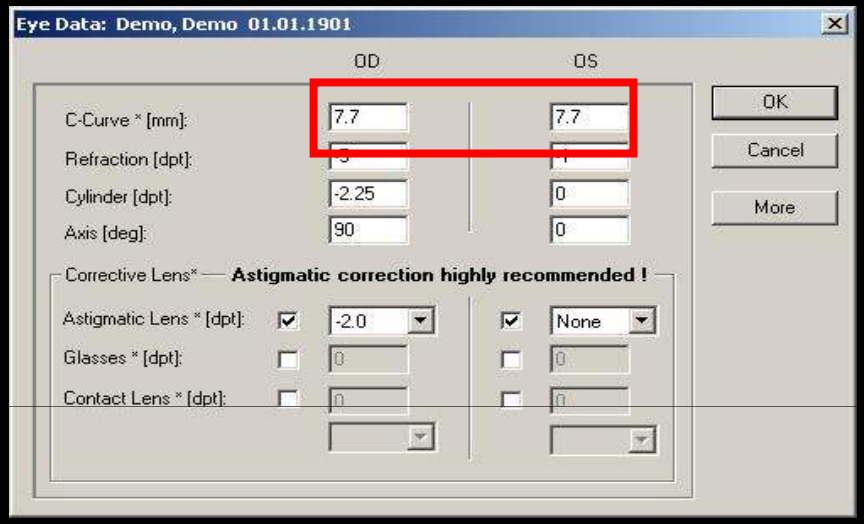
three topography images

mean topography image

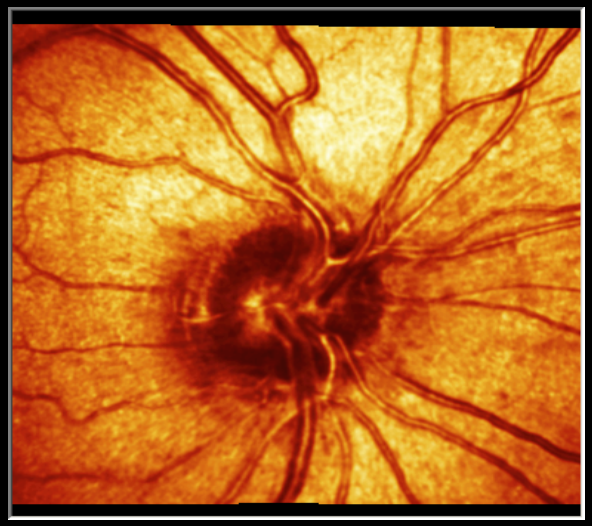
Inconsistent Eye Data

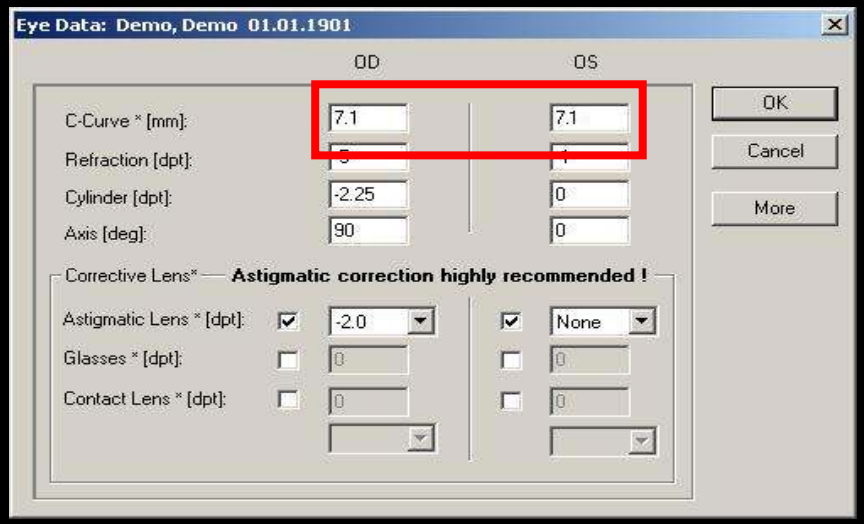
C-Curve = 7.7





C-Curve = 7.1 (same eye)





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Confocal Laser Scanning System

- Focused laser beam
- Sequential scanning on two dimensions
- Confocal pinhole
- Suppression of out-of-focus light
- Depth resolution
- Optical section images

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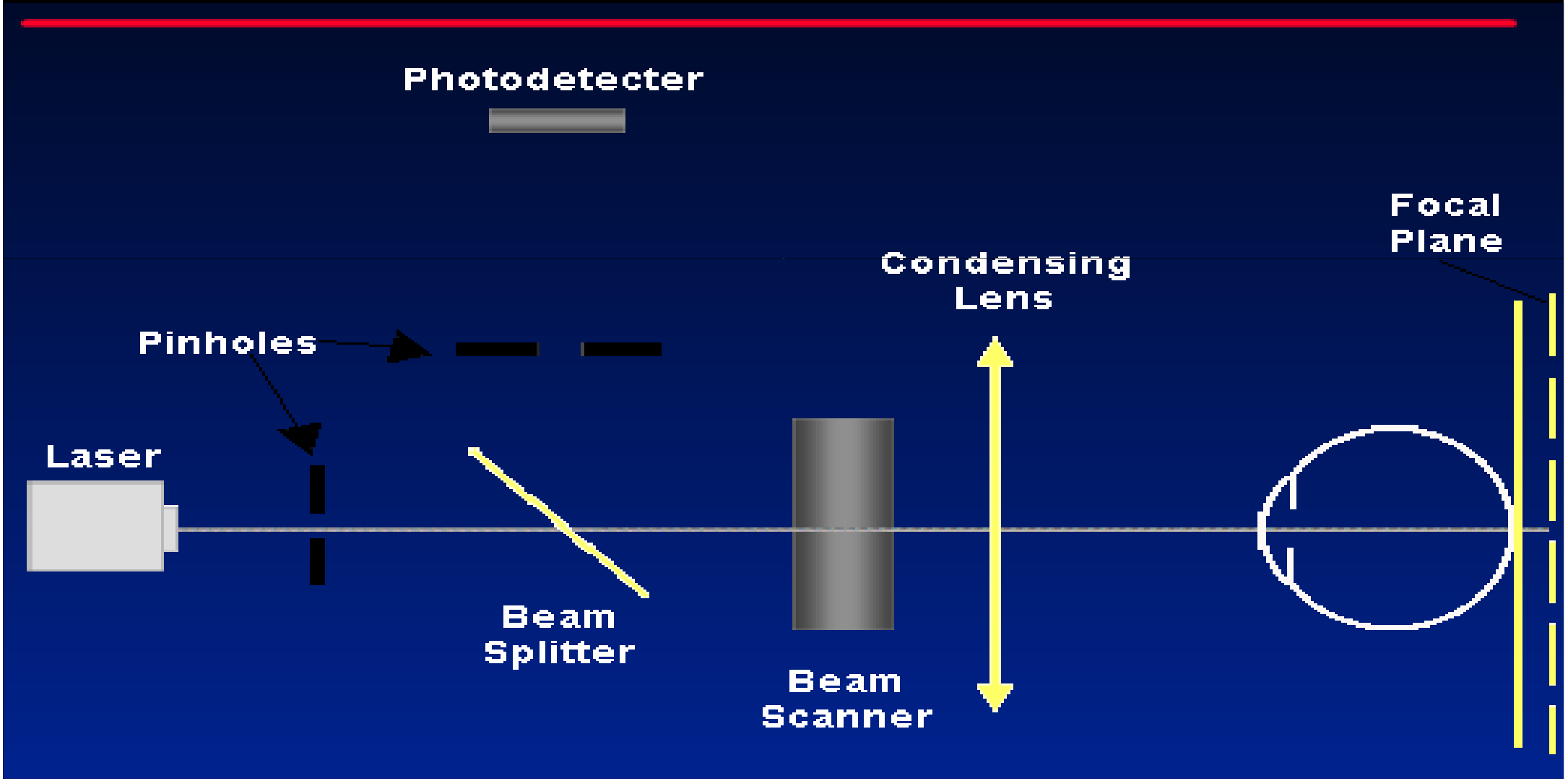
Confocal Laser Scanning System



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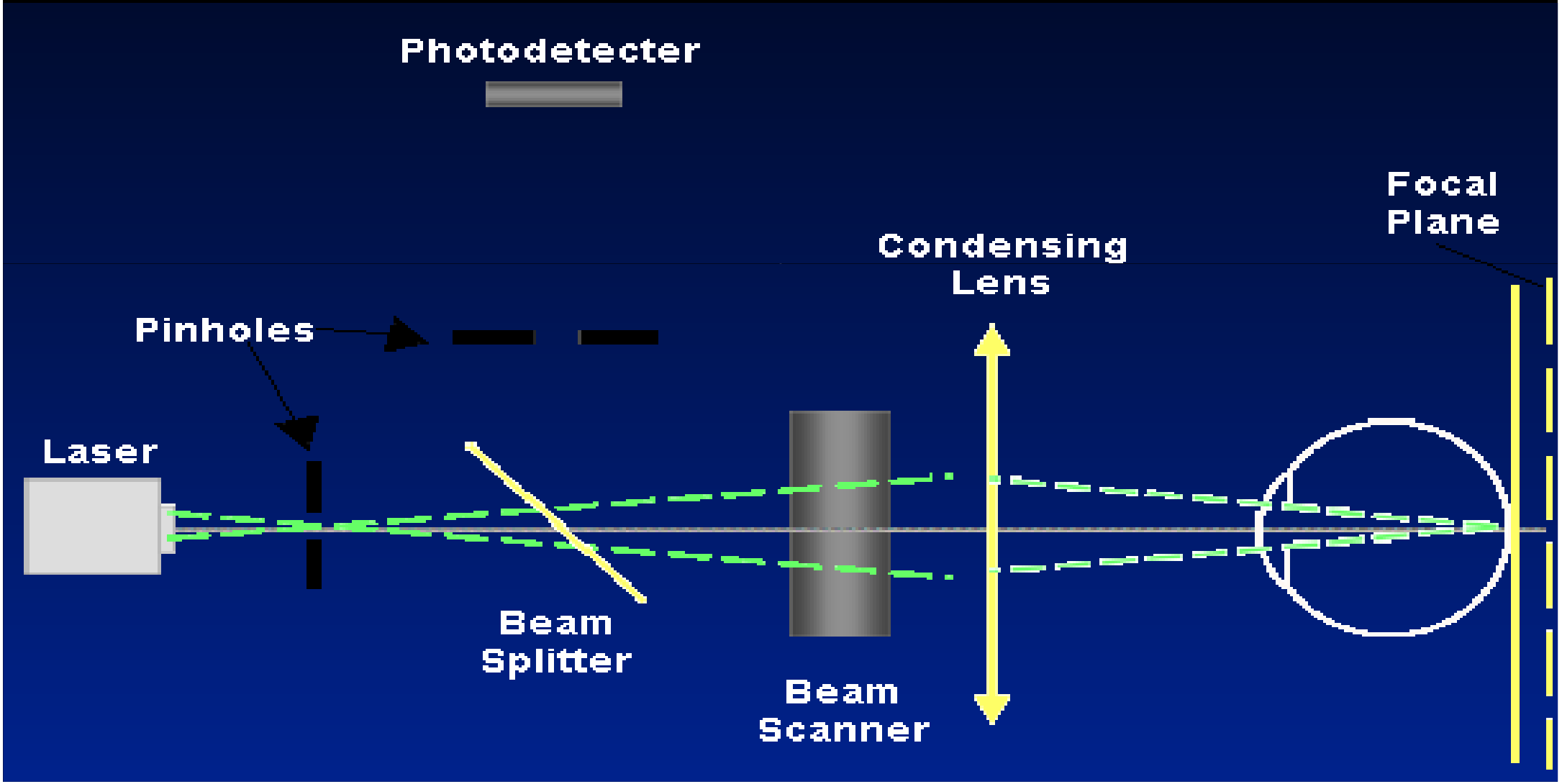

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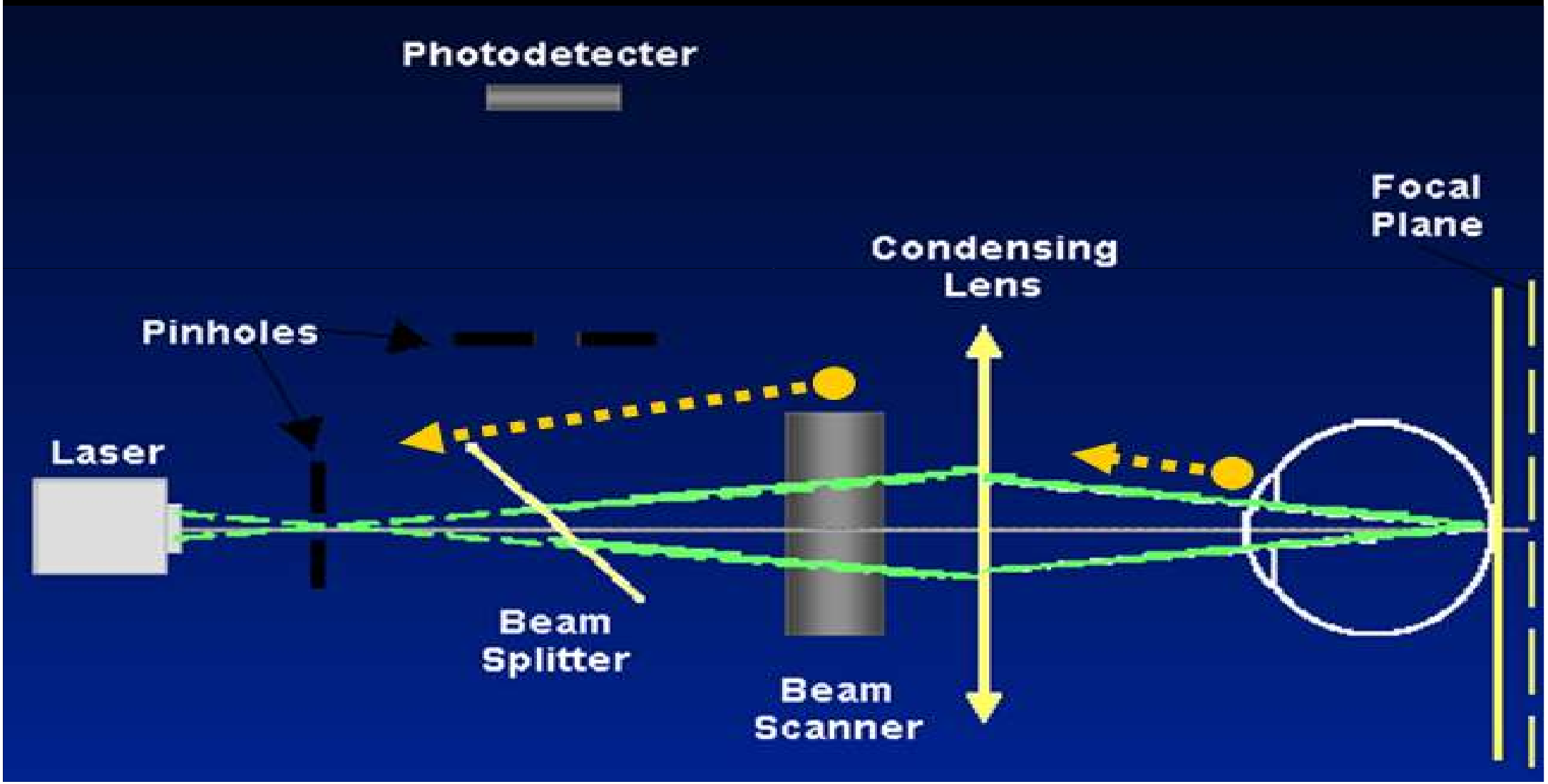

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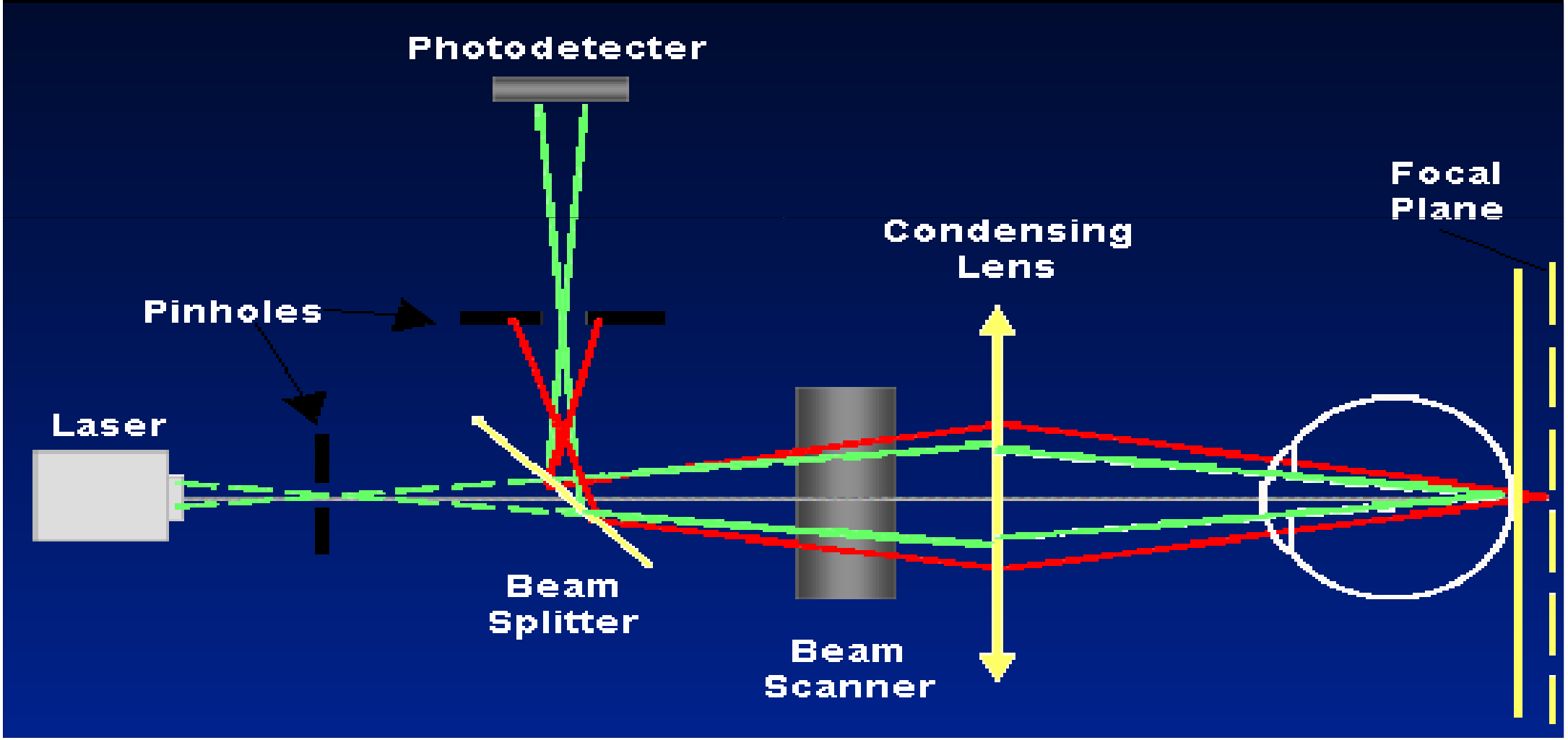
Confocal Laser Scanning System



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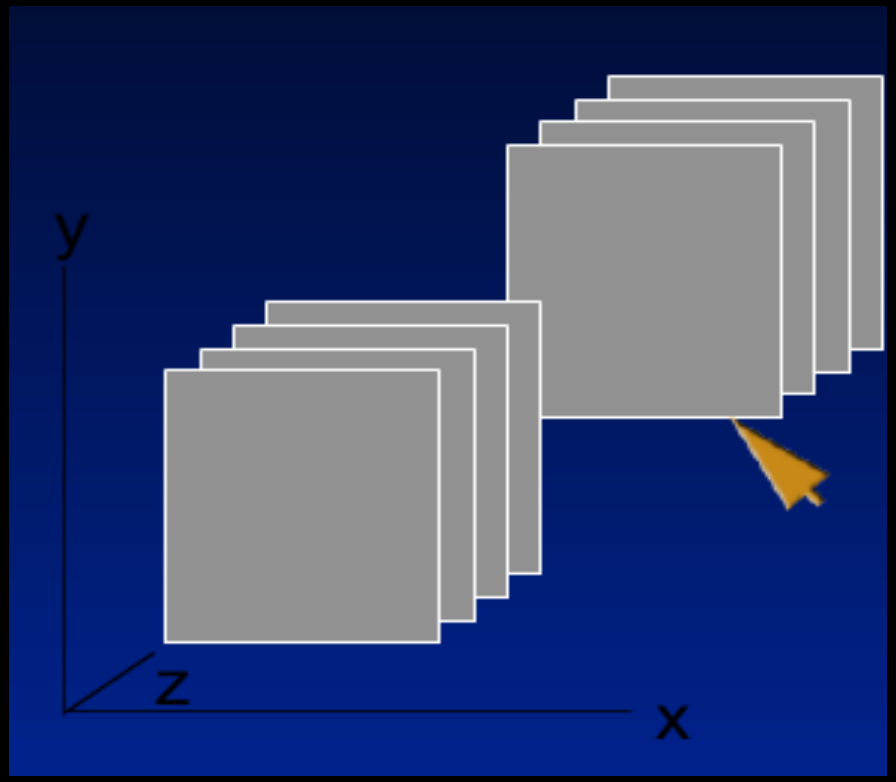
Three Dimensional Imaging

- Series of optical section images at different locations
- Layer-by Layer three dimensional image
- Laser scanning tomography
- Similar to CT Scan technology



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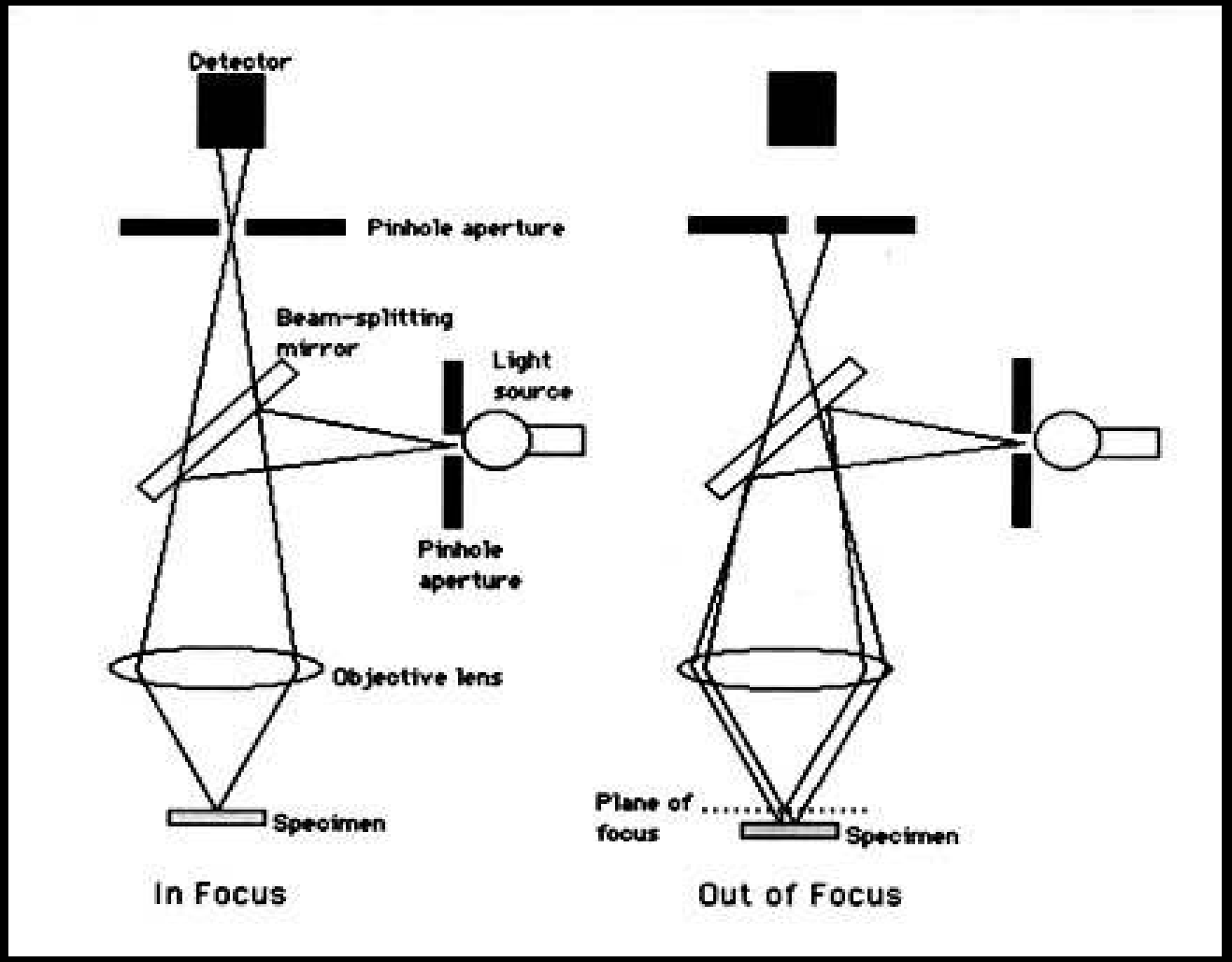
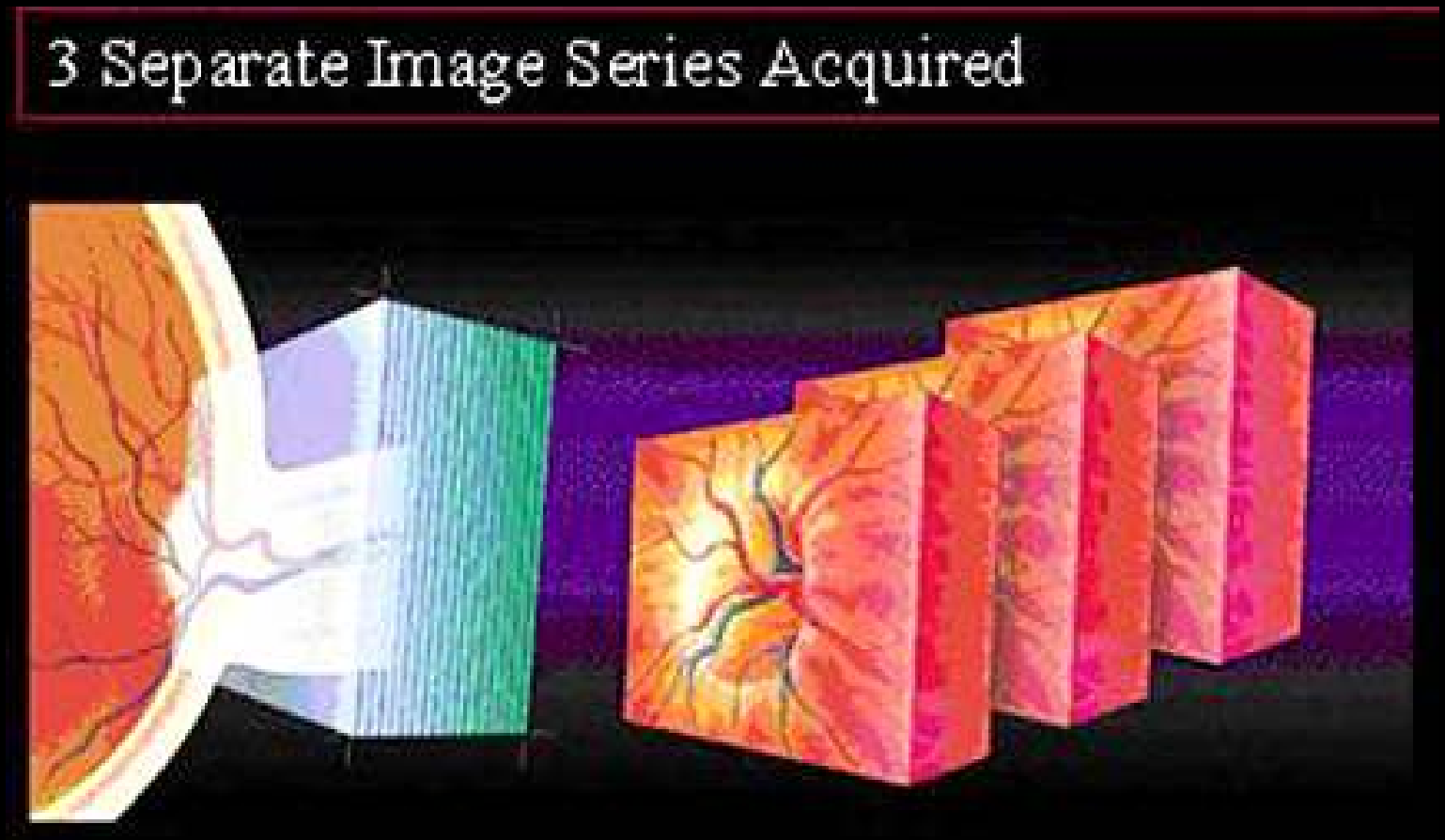
Confocal Laser Scanning System



Confocal Laser Scanning System



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Inconsistent Eye Data

Parameters	global
disc area [mm²]	2.44
cup area [mm²]	0.94
rim area [mm²]	1.50
cup/disc area ratio [ ]	0.39
rim/disc area ratio [ ]	0.61
cup volume [mm³]	0.34
rim volume [mm³]	0.23
mean cup depth [mm]	0.31
maximum cup depth [mm]	0.67
height variation contour [mm]	0.19
cup shape measure [ ]	-0.07
mean RNFL thickness [mm]	0.16
RNFL cross sectional area [mm²]	0.87
linear cup/disc ratio [ ]	0.62
maximum contour elevation [mm]	-0.06
maximum contour depression [mm]	0.13
CLM temporal-superior [mm]	0.15
CLM temporal-inferior [mm]	0.06
average variability (SD) [µm]	17
reference height [µm]	178
FSM discriminant function value [ ]	-0.19
RB discriminant function value [ ]	-0.03
modified ISNT rule fulfilled	no

C-Curve = 8.2

Parameters	global
disc area [mm²]	2.25
cup area [mm²]	0.86
rim area [mm²]	1.39
cup/disc area ratio [ ]	0.38
rim/disc area ratio [ ]	0.62
cup volume [mm³]	0.28
rim volume [mm³]	0.20
mean cup depth [mm]	0.28
maximum cup depth [mm]	0.61
height variation contour [mm]	0.17
cup shape measure [ ]	-0.06
mean RNFL thickness [mm]	0.15
RNFL cross sectional area [mm²]	0.79
linear cup/disc ratio [ ]	0.62
maximum contour elevation [mm]	-0.05
maximum contour depression [mm]	0.12
CLM temporal-superior [mm]	0.14
CLM temporal-inferior [mm]	0.05
average variability (SD) [µm]	16
reference height [µm]	168
FSM discriminant function value [ ]	-0.42
RB discriminant function value [ ]	-0.10
modified ISNT rule fulfilled	no

C-Curve = 7.7 (same eye)

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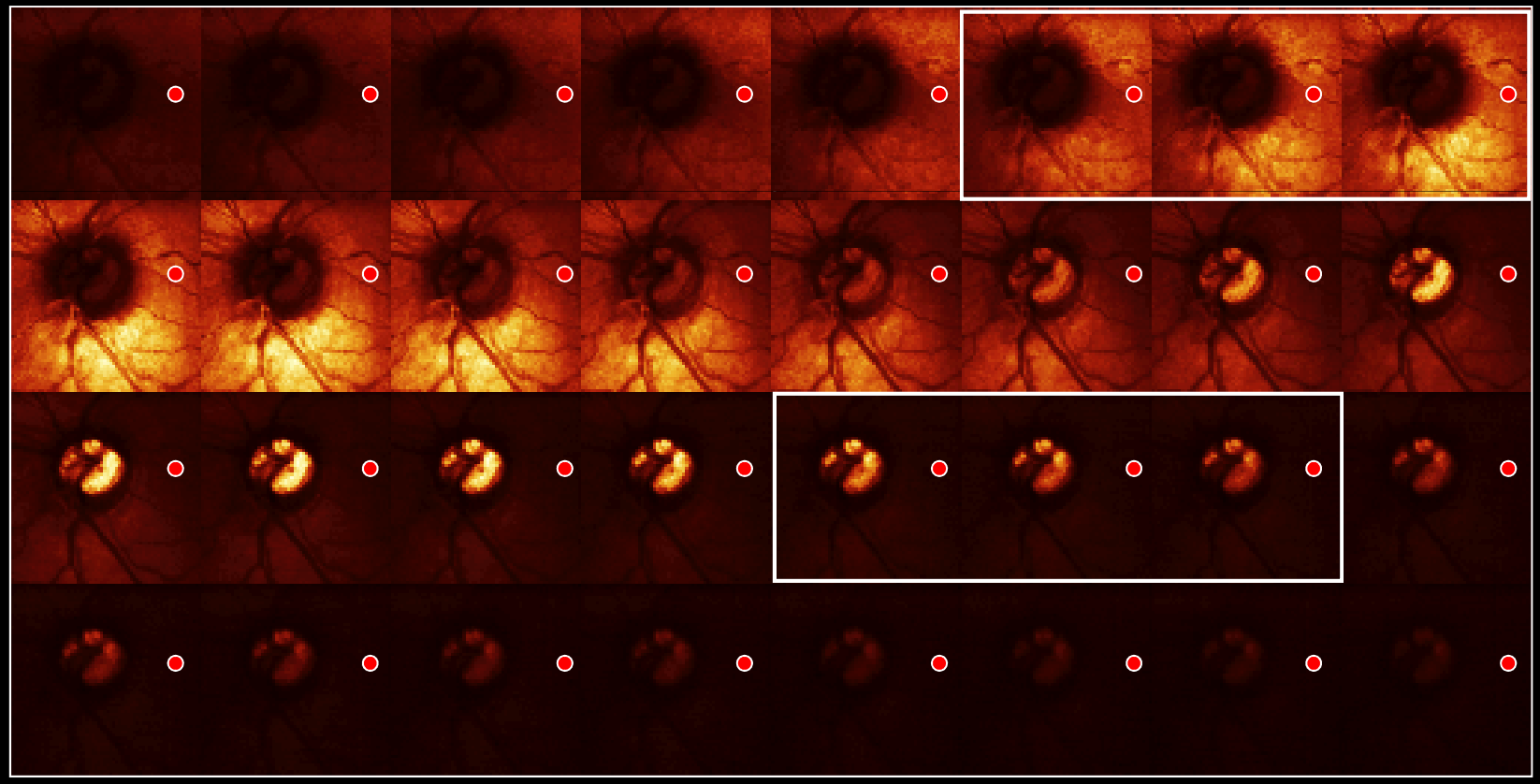
Image Acquisition Details

- Resolution
  - 16 optical sections per 1 mm scan depth
  - 384x384 pixels over 15 x 15 degrees (~ 4.4mm at 0 dpt)
- Acquisition time
  - 2 mm scan ~1 second
  - 4 mm scan ~2 seconds
- Automatic quality control
  - discards unusable series (blinking, lost fixation,…)
  - acquires additional series automatically

Three-Dimensional Imaging

- Series of optical section images at different locations of the ONH



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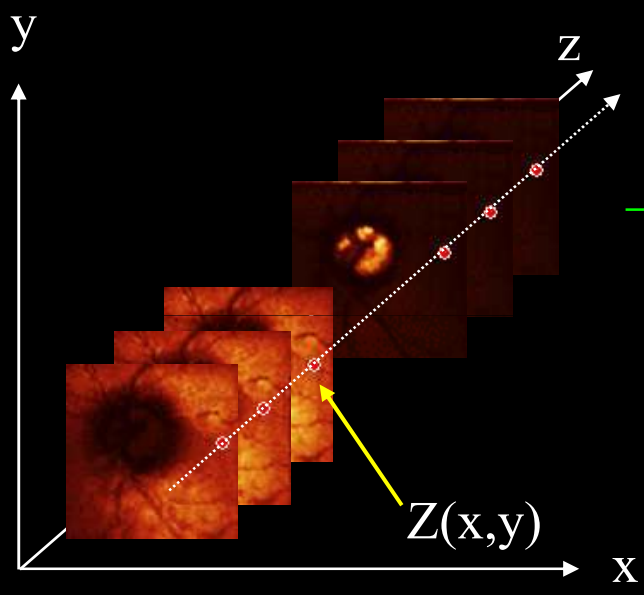
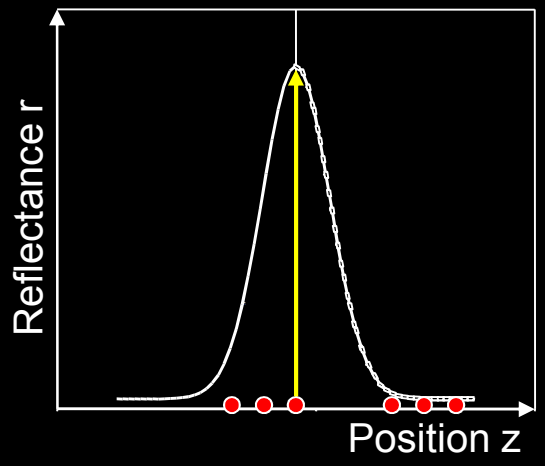
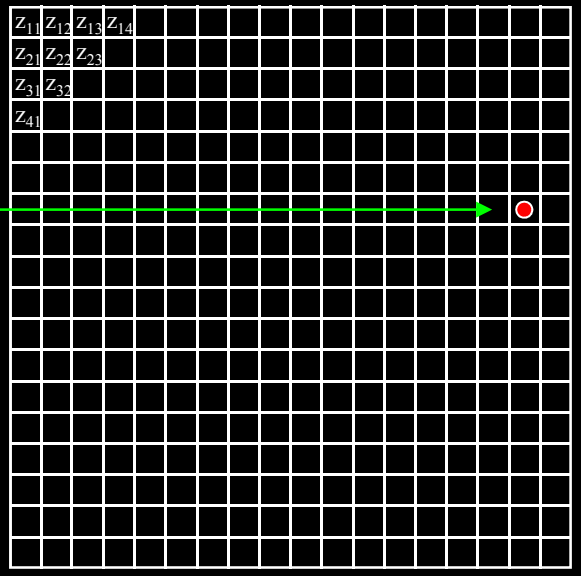
Retinal Surface Height Measurement





$Z(x,y) = z(r_{max})$



Z(x,y) = matrix of 384x384 = 147,456 local surface height measurements

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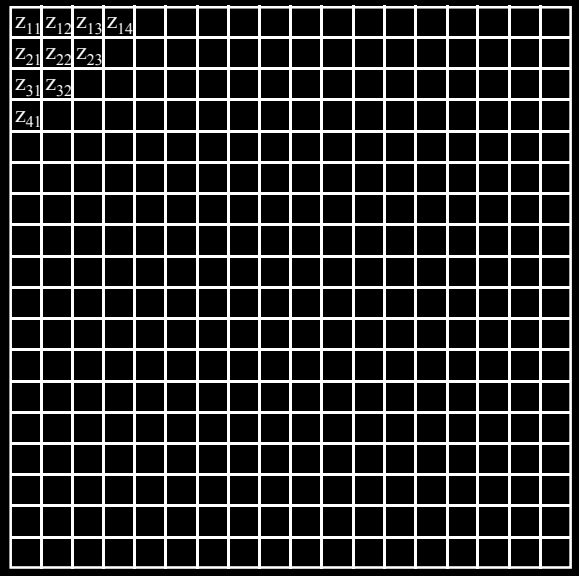
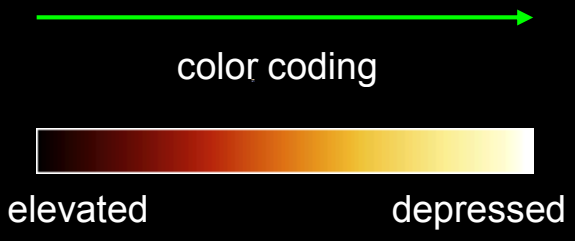
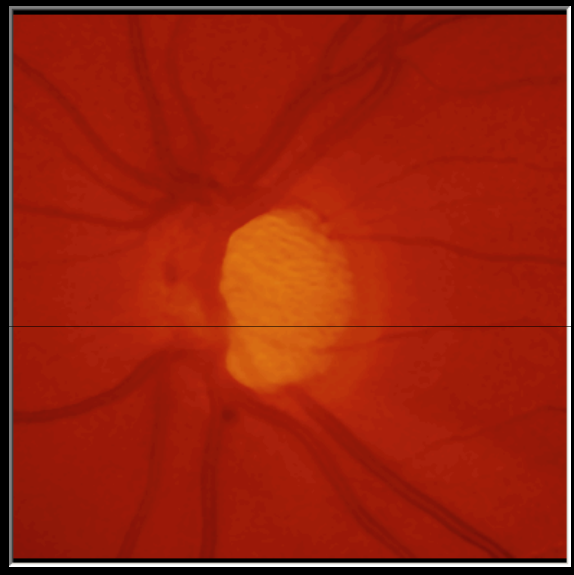
Topography Image



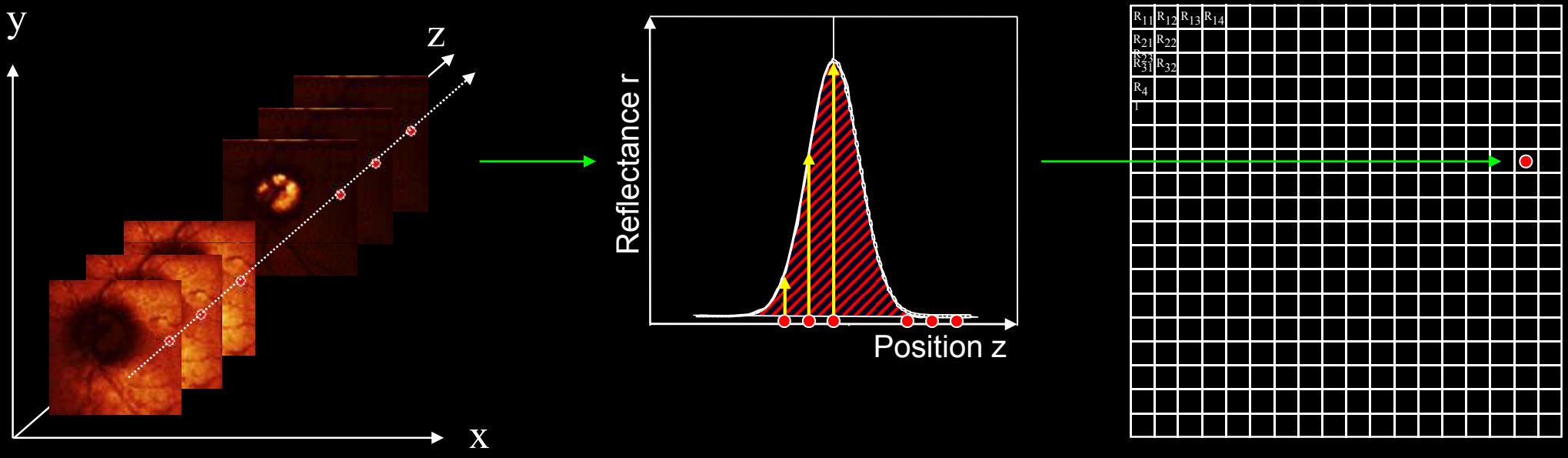




matrix of
384 x 384 = 147,456
local surface height
measurements

- topography image
- color coded
- color = height

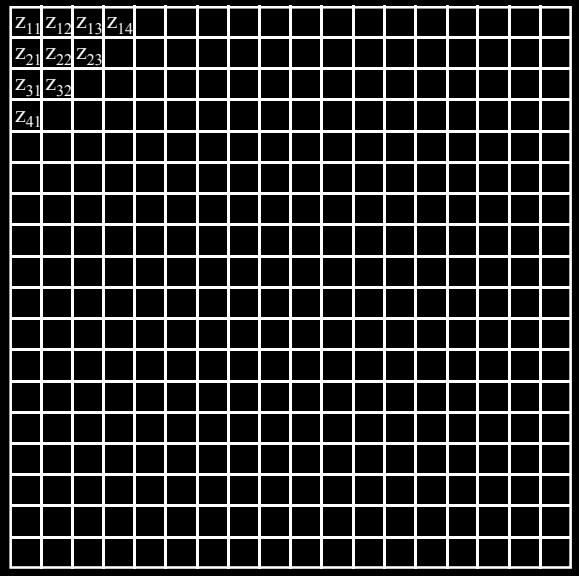
Reflectance Image

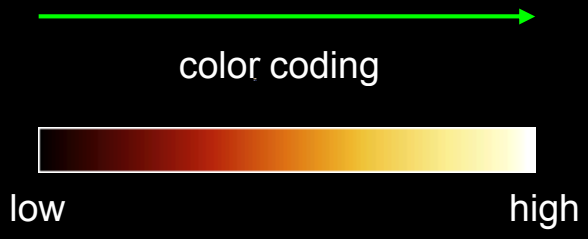


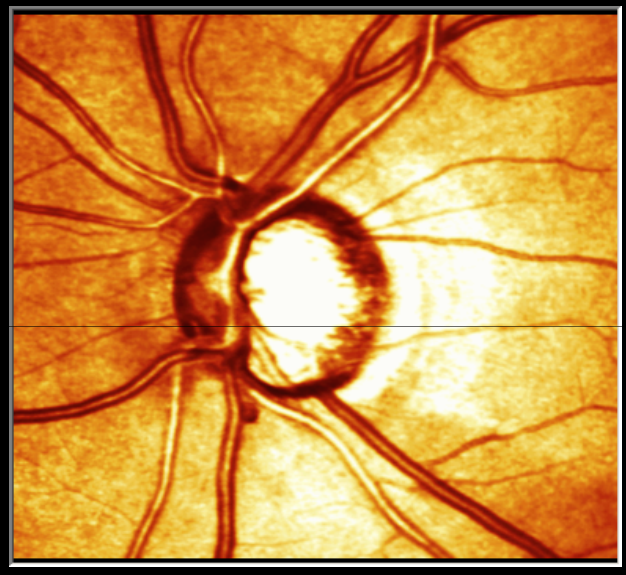
R(x,y) = matrix of
384x384 = 147,456
local surface reflectance
measurements

HEIDELBERG ENGINEERING

Reflectance Image



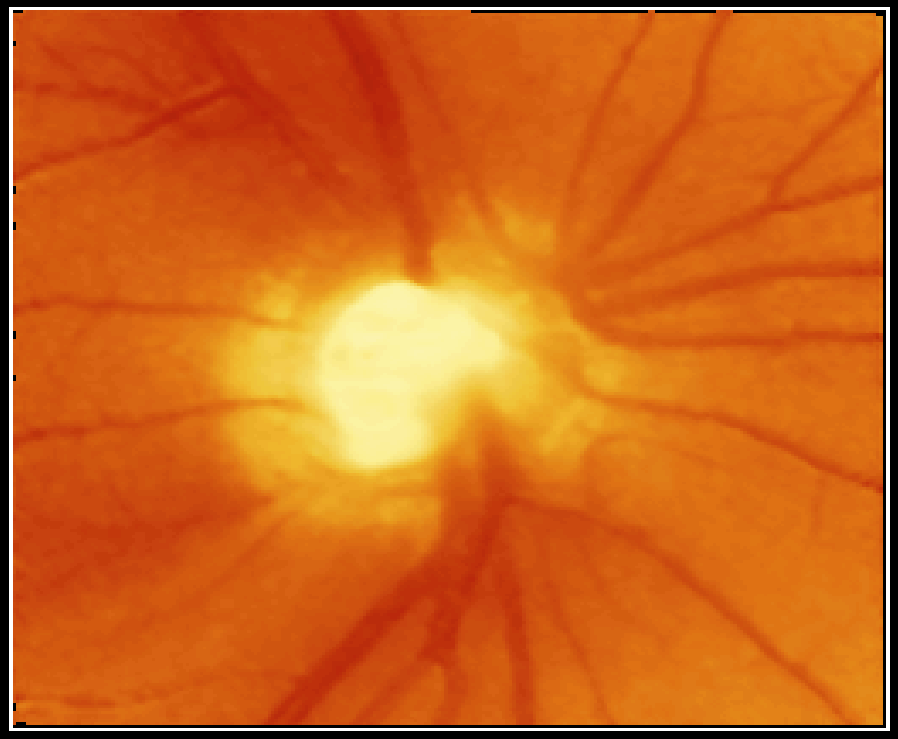


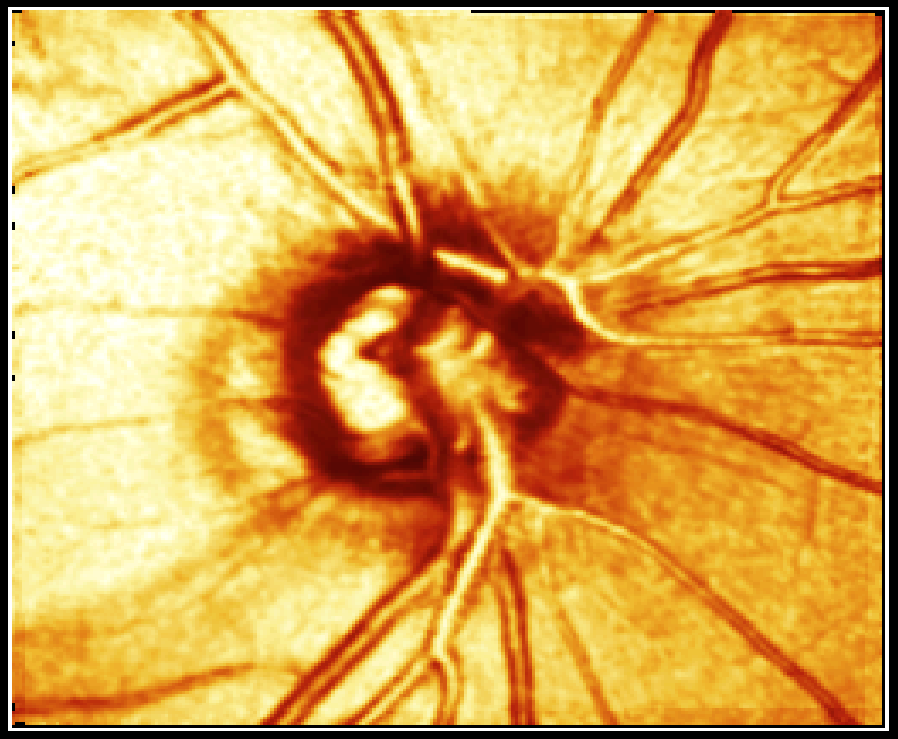


matrix of
384 x 384 = 147,456
local surface reflectance
measurements

- reflectance image
- color coded
- color = reflectance

Wrong Focus – Over Exposure





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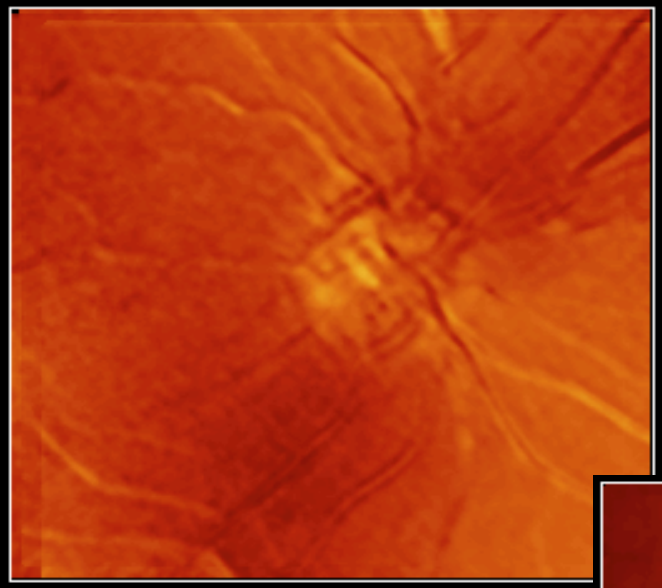
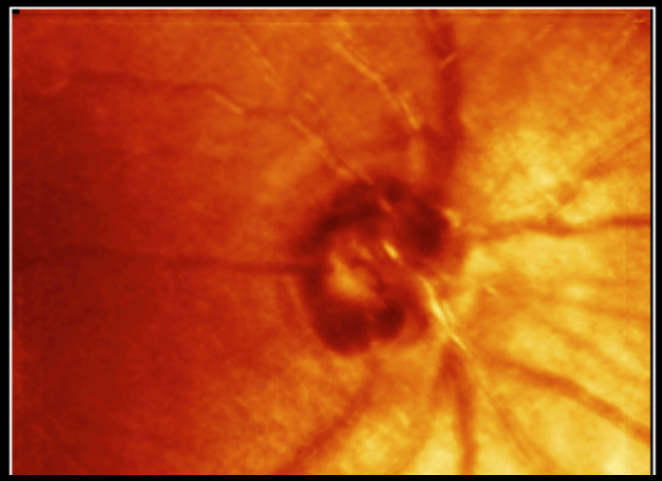
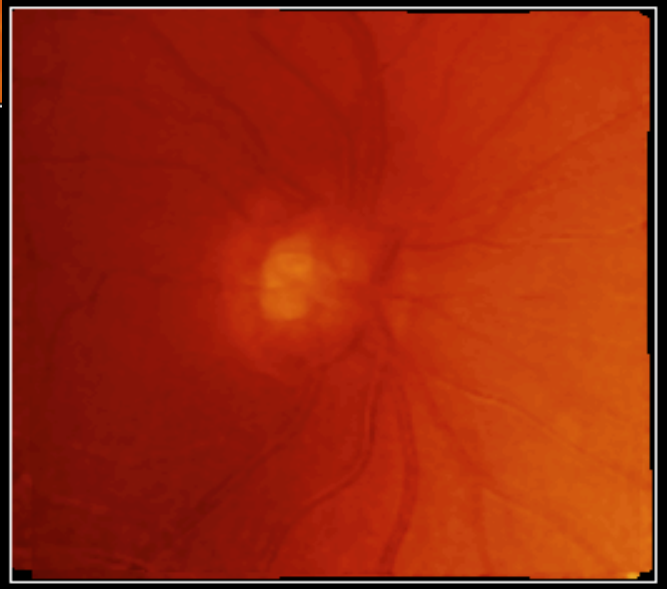
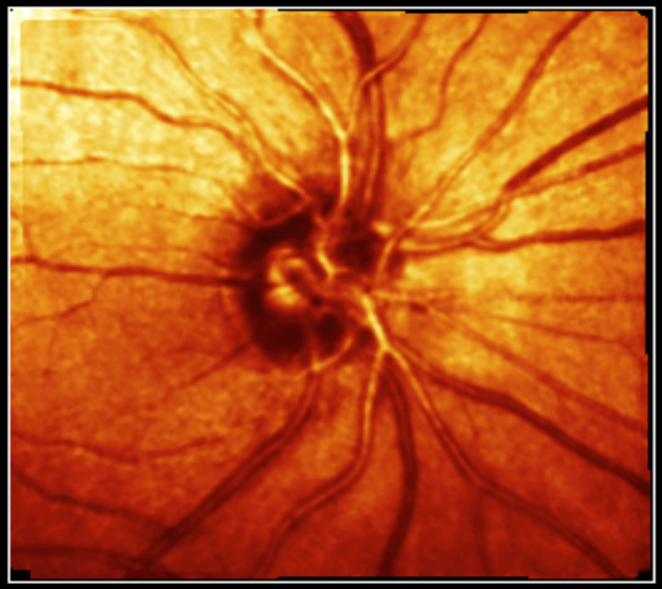
Focus

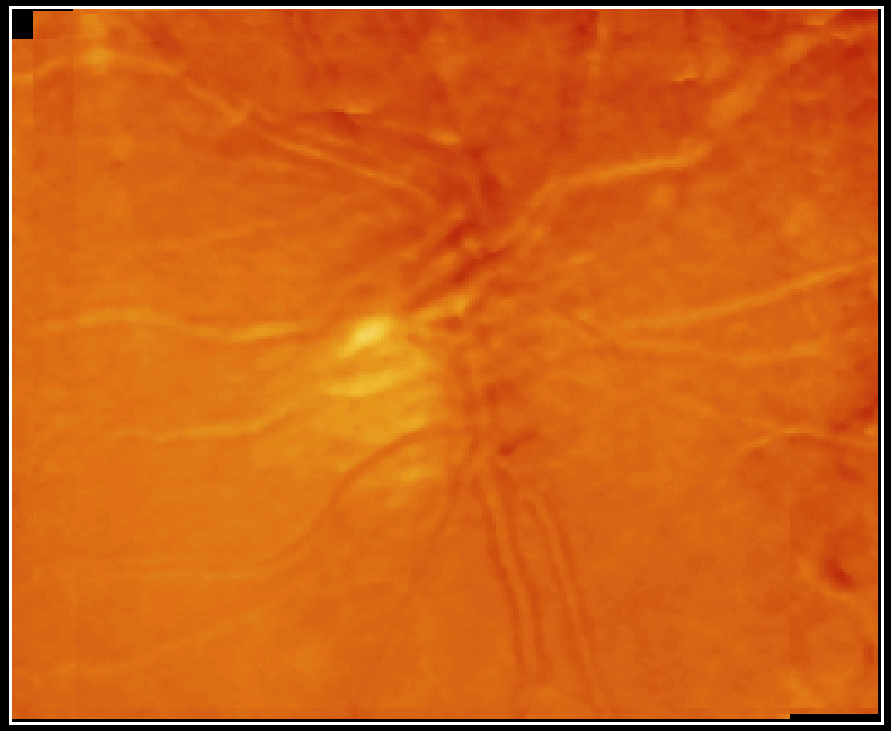


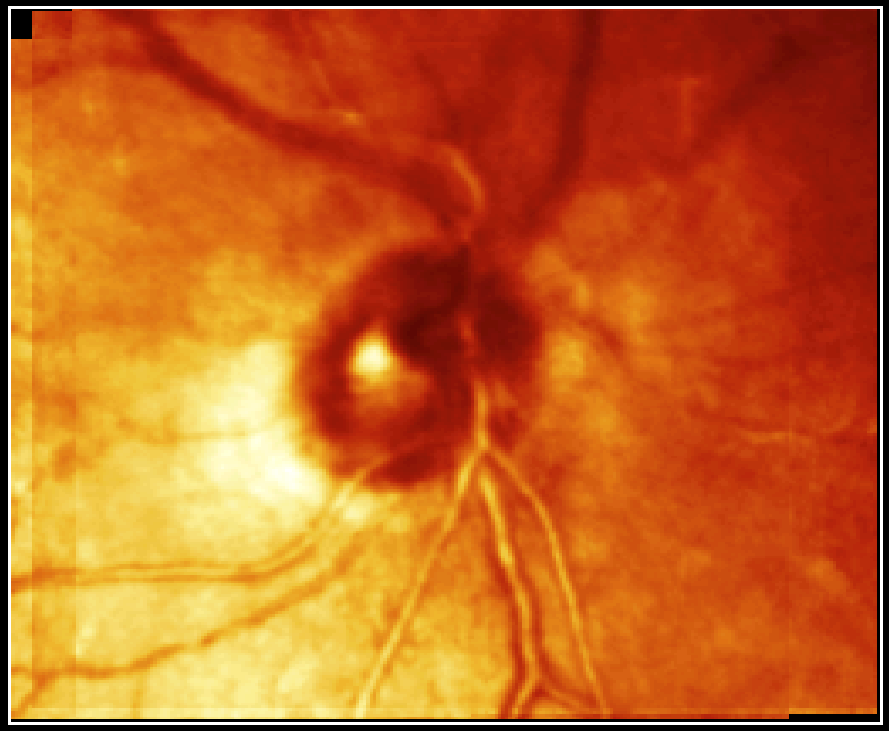




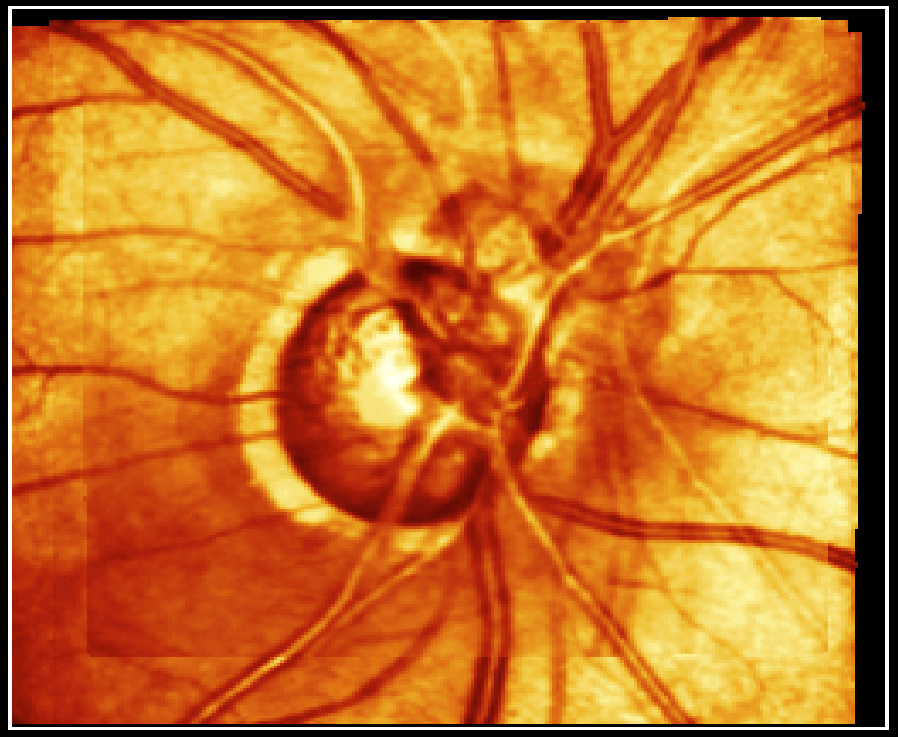


Uncorrected astigmatism





Double vessels - fixation loss



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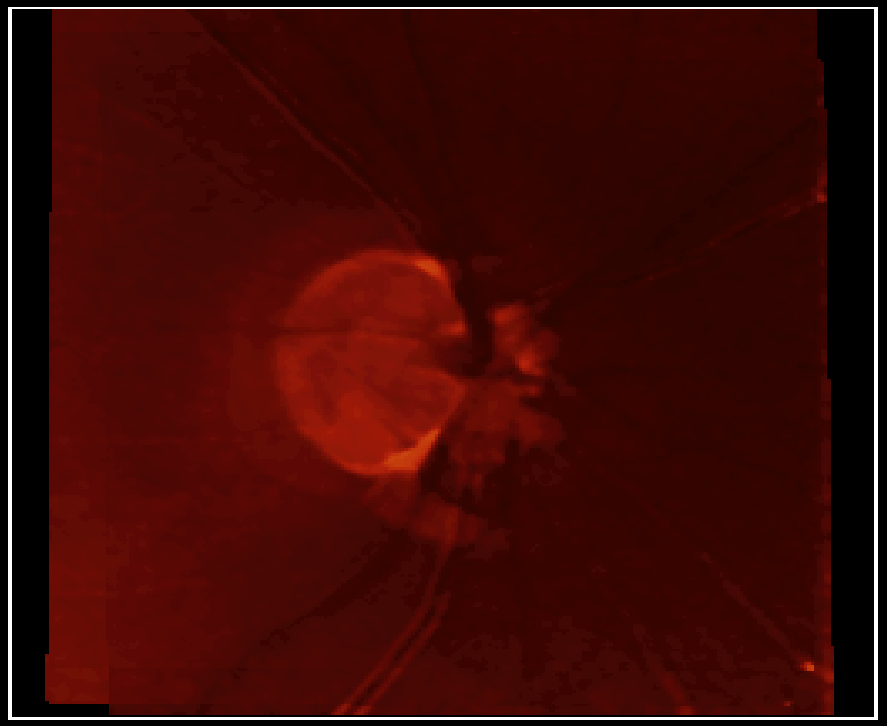
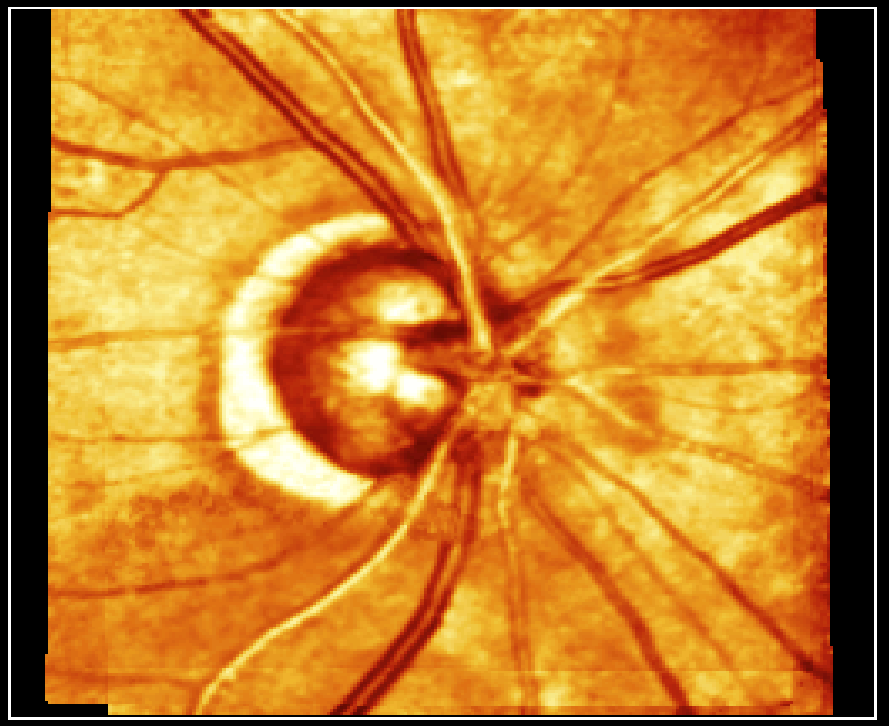
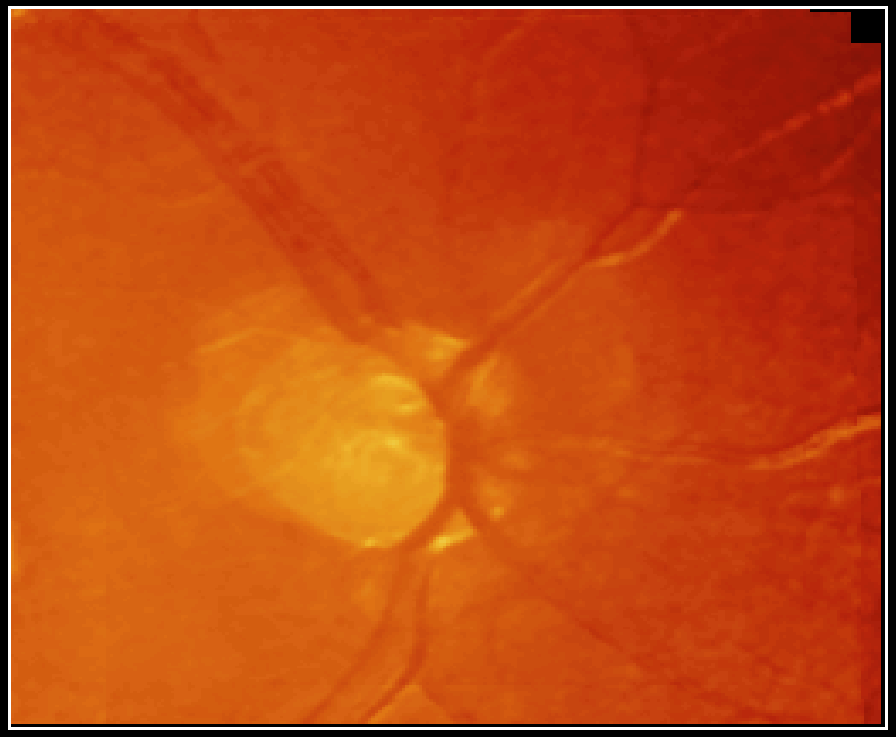
Movement

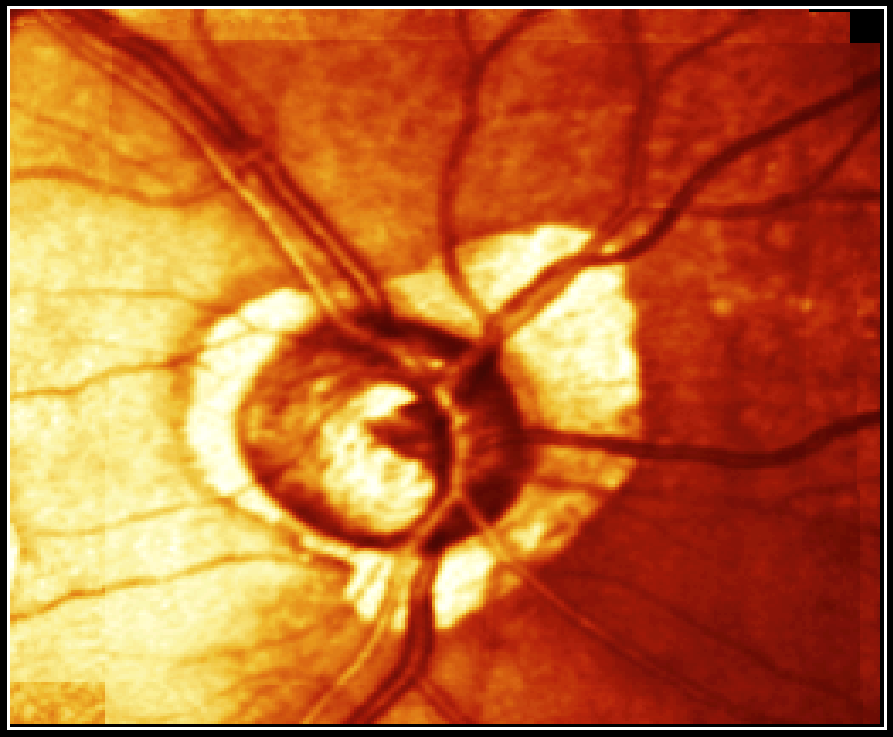




Scleral ring

Peripapillary Atrophy (PPA)





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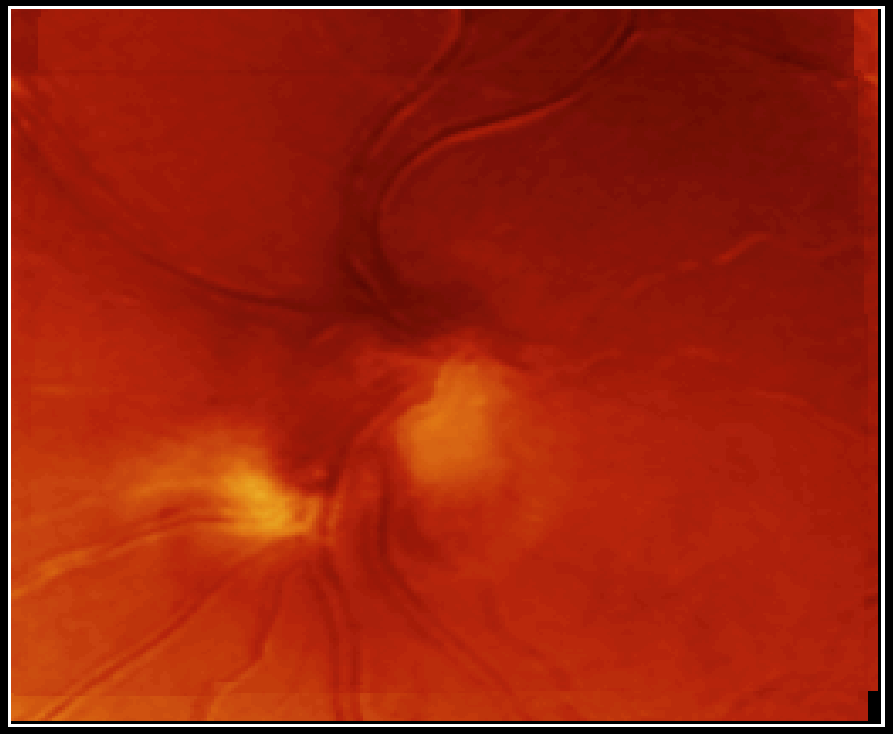
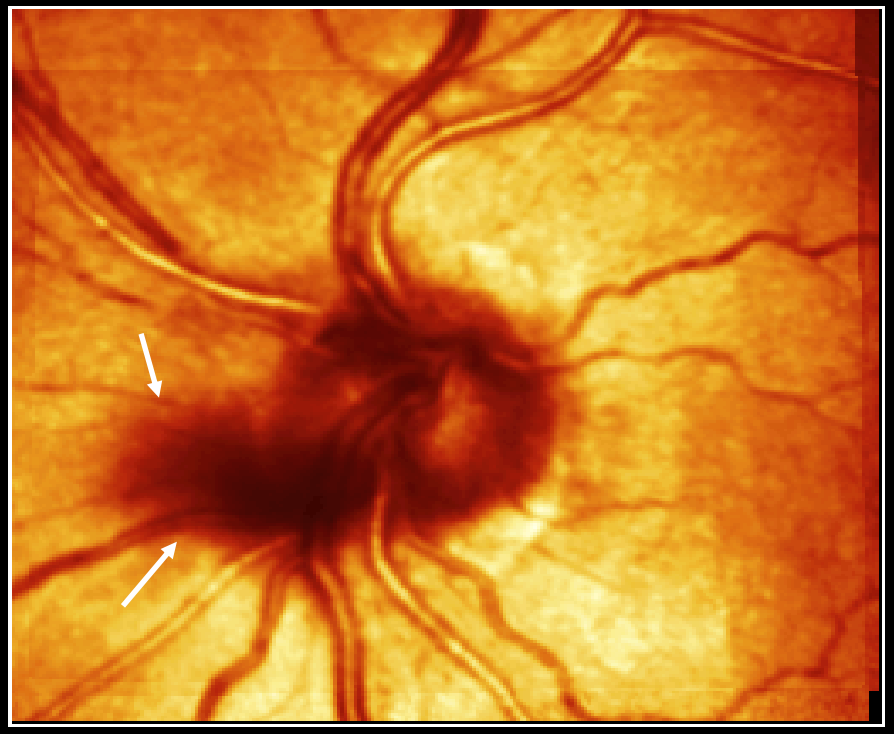
Floaters





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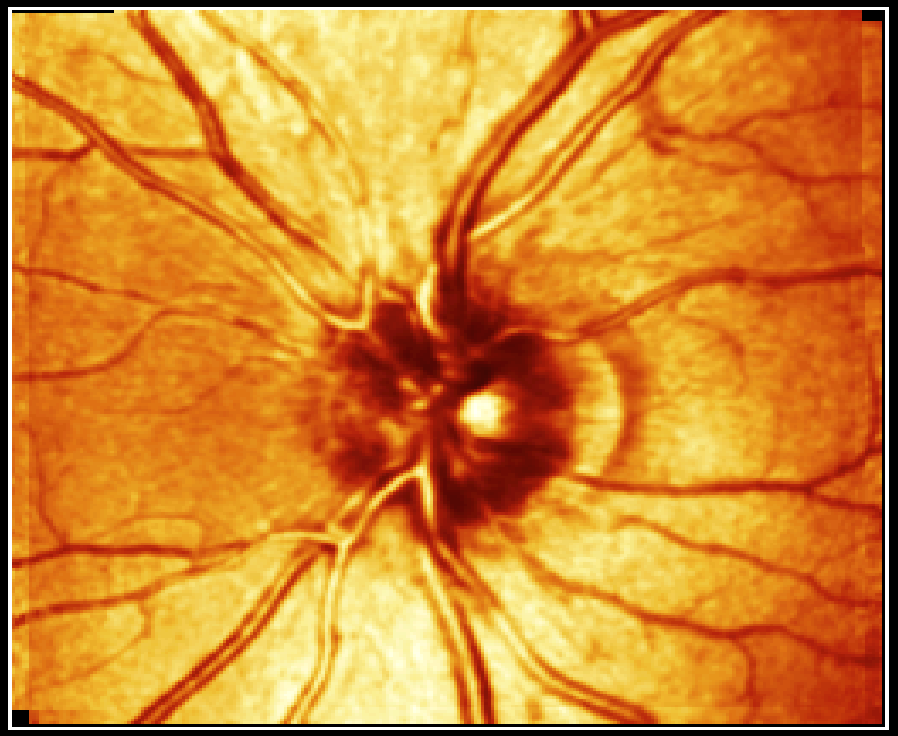
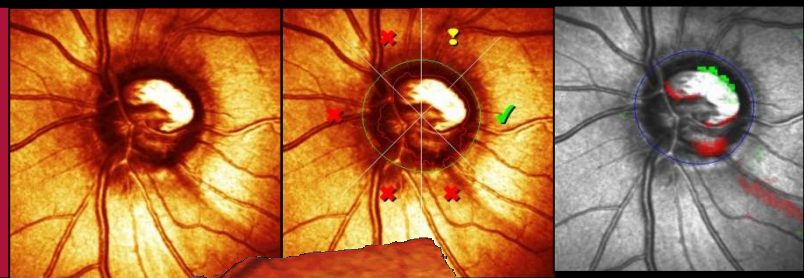
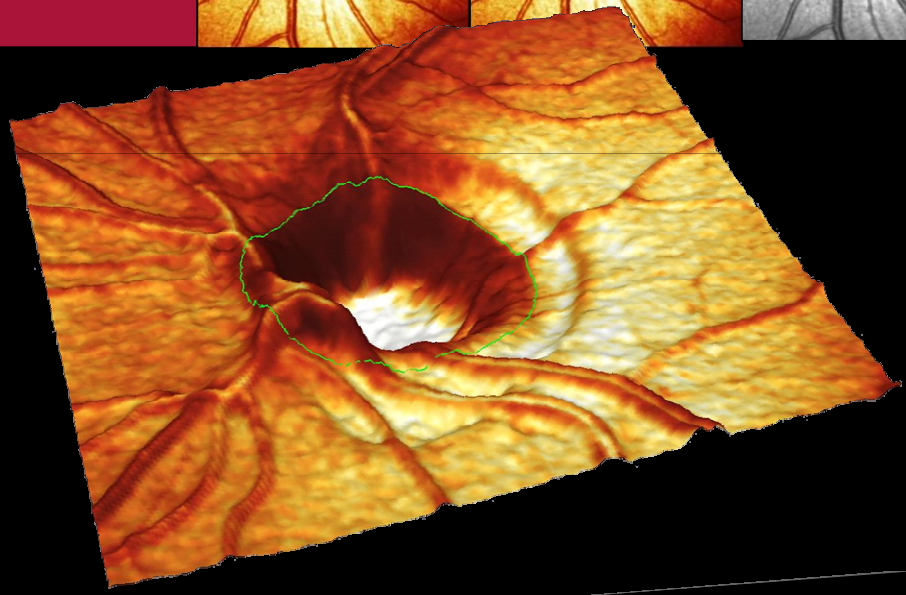
Good image = good data



How to draw the Contour Line



HRT3



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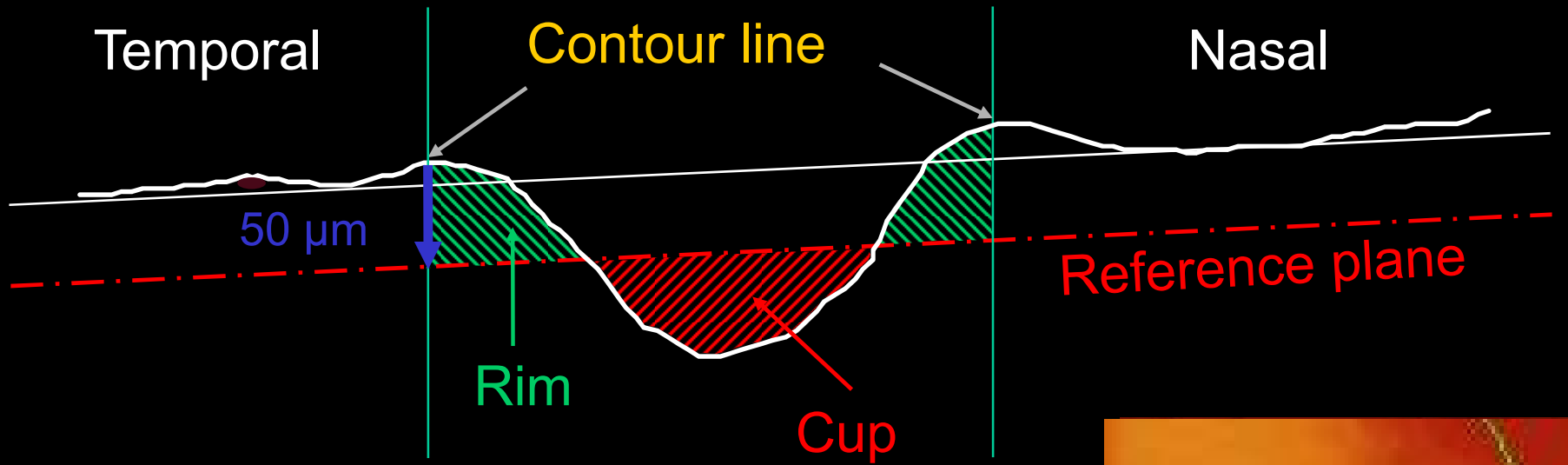
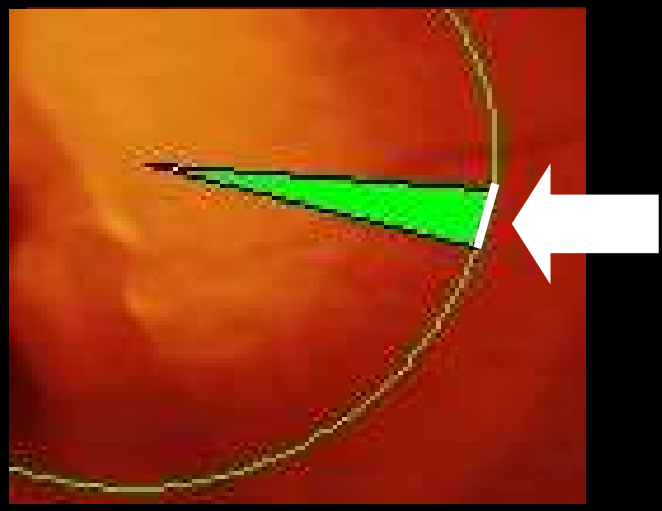
The Reference Plane



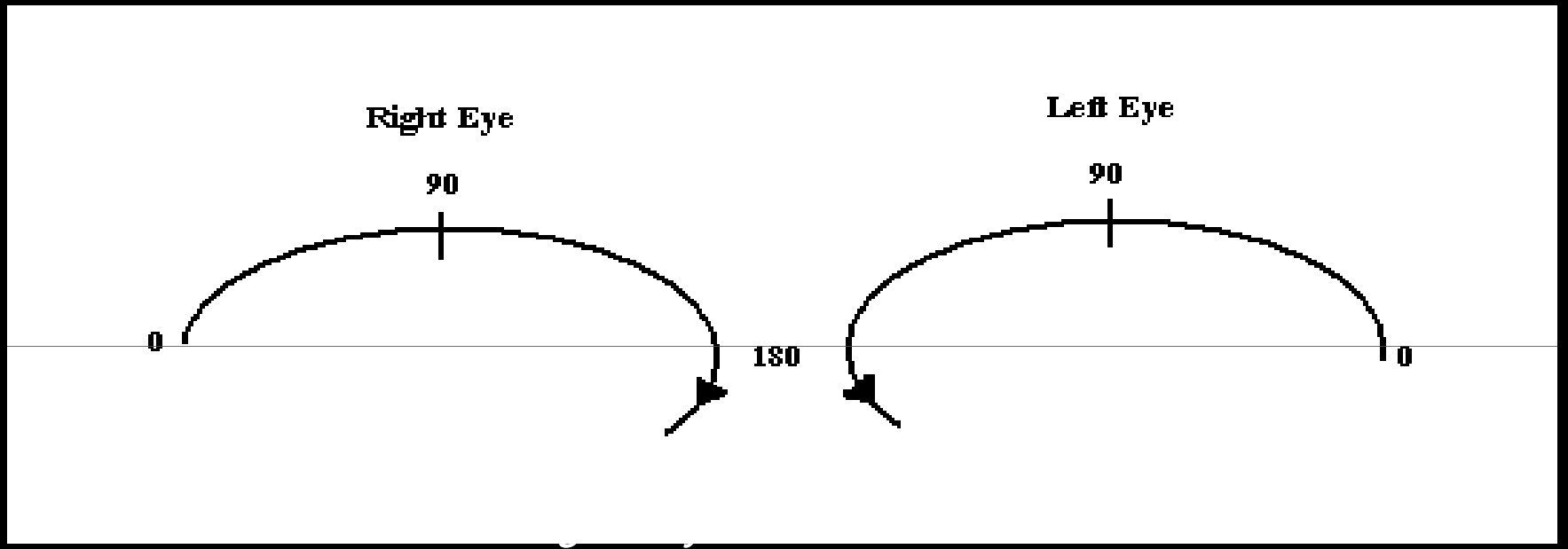
Reference plane…

…is located 50 µm below the mean height of the retinal surface along the contour line, between 350º-356º (papillo-macular bundle).

(Burk, Graefe's Arch. Clin. Exp. Ophthalmol. 2000, 238:375–384)



HEIDELBERG ENGINEERING



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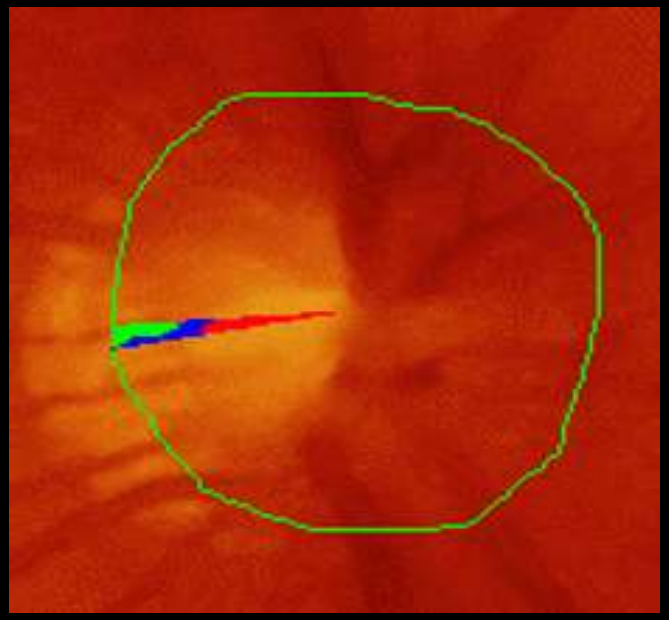
Standard Reference Plane

- Location of the reference plane specifies which Areas within the contour line are assigned to the optic nerve head cup and which areas are assigned to the neuro-retinal rim
- Reference plane:
  - *50 micron below retinal surface at papillomacular bundle located 350 – 356*
- Structure below reference plane: Cup
- Structure above reference plane: Rim

Standard Reference Plane

- Selected location based on research
- Bundle which remains intact through disease progression
- Average thickness of papillo-macular bundle located 350 – 356 found to be 50 micron



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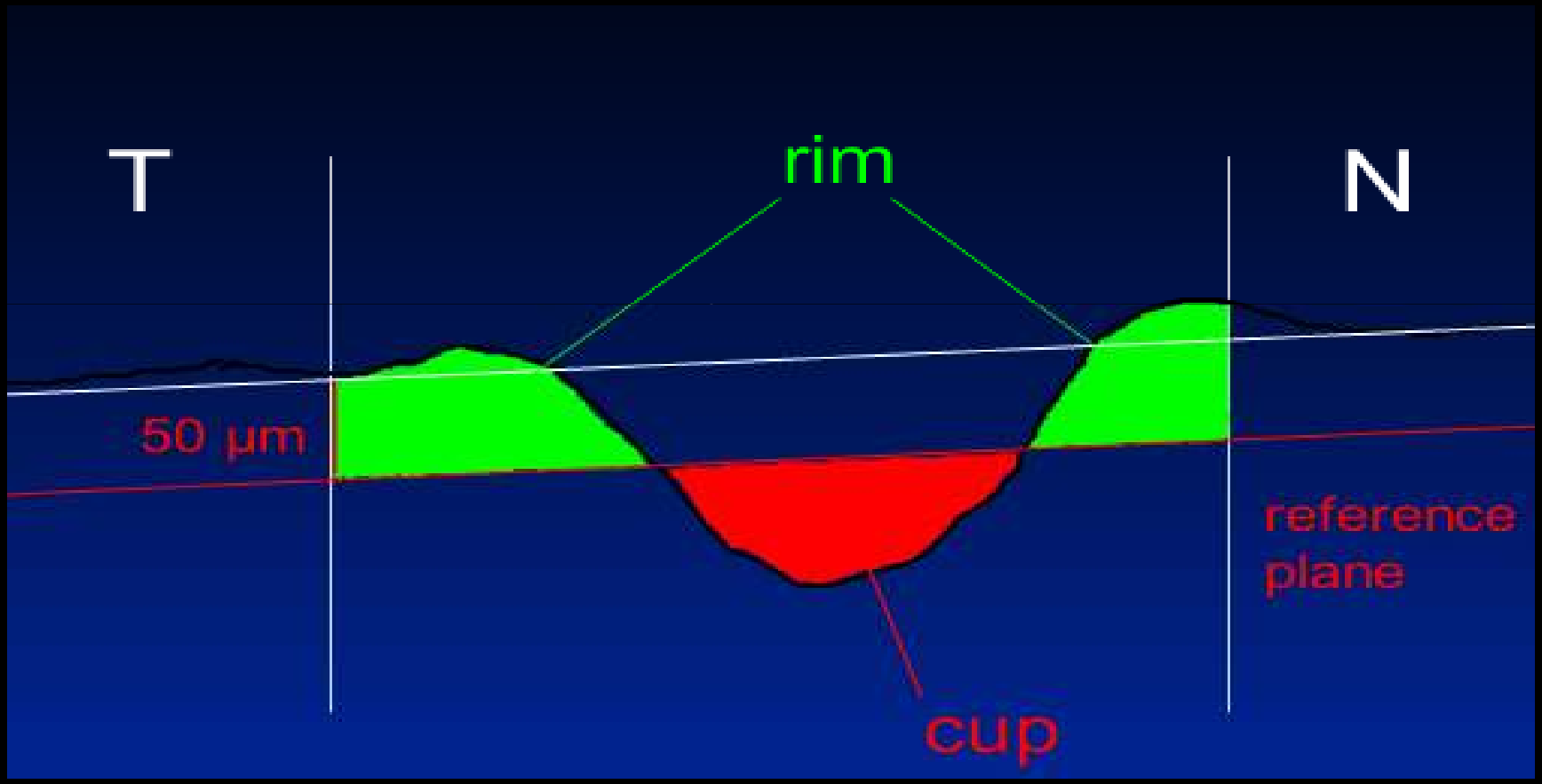
ONH Stereometric Analysis



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Contour line for follow-up exams

- The contour line is only drawn once for each eye.
- Automatically transferred to all follow-up exams.
- Changes of the contour line in one exam are automatically transferred to all other images of the eye.

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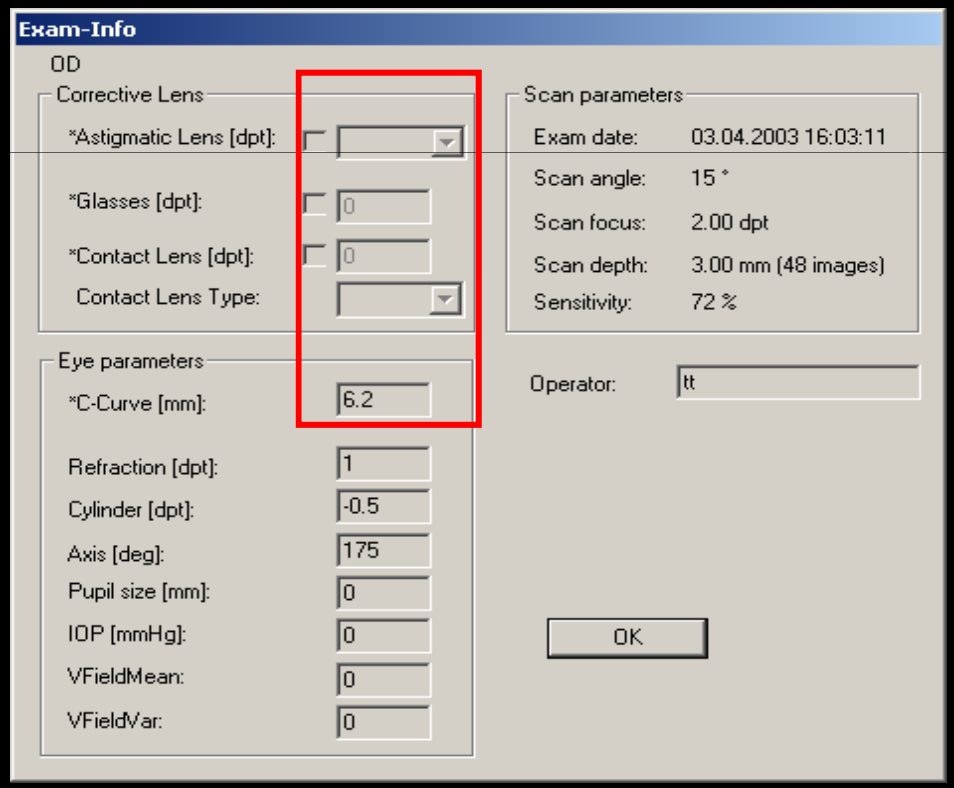
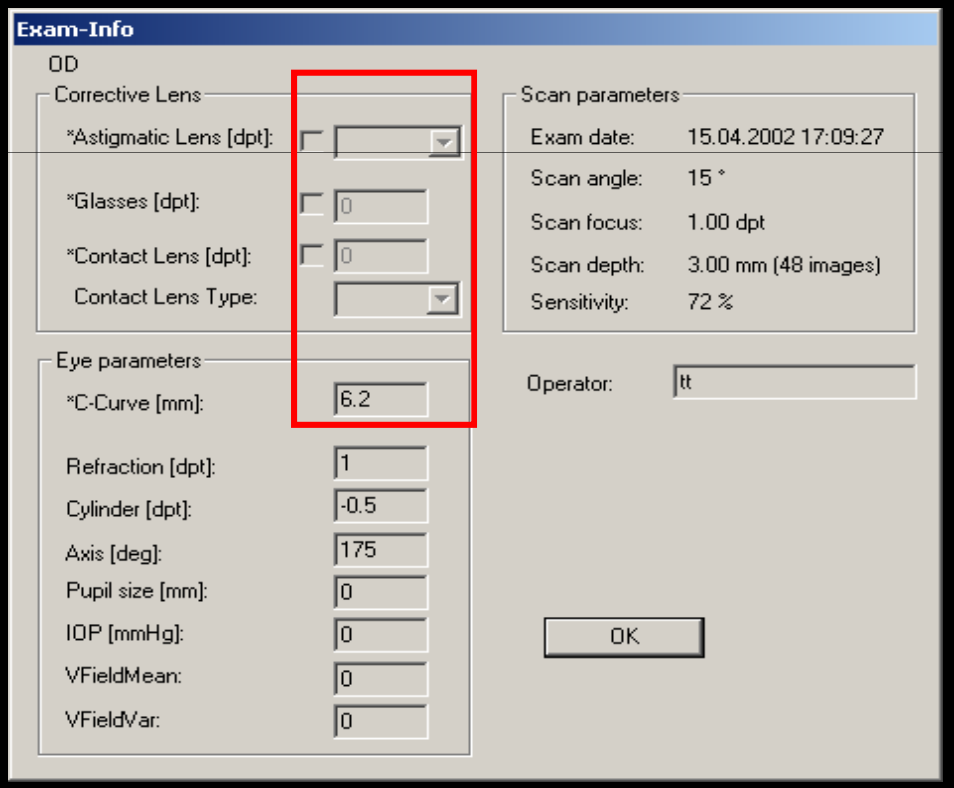
Detecting SMALL changes

- 1. High quality baseline image.
- 2. Low test-retest variability.

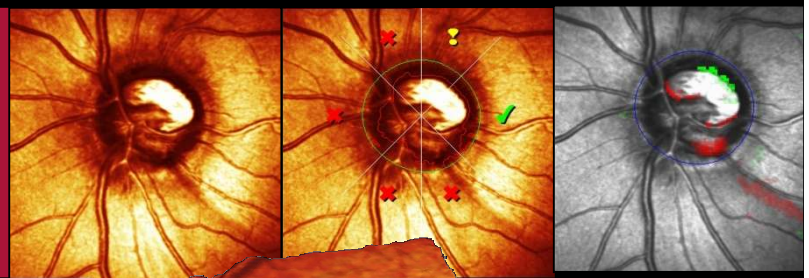
Final Check List

Important: Consistent eye data values for C-Curve, Astigmatism Lens, Glasses or Contact Lens !!!

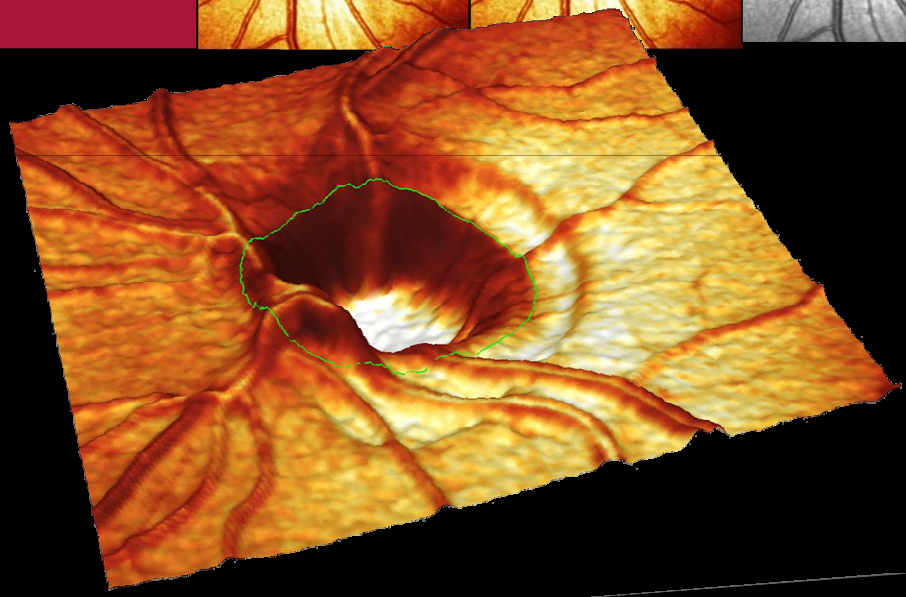




How to Interpret the Baseline Exam



HRT3



HEIDELBERG ENGINEERING

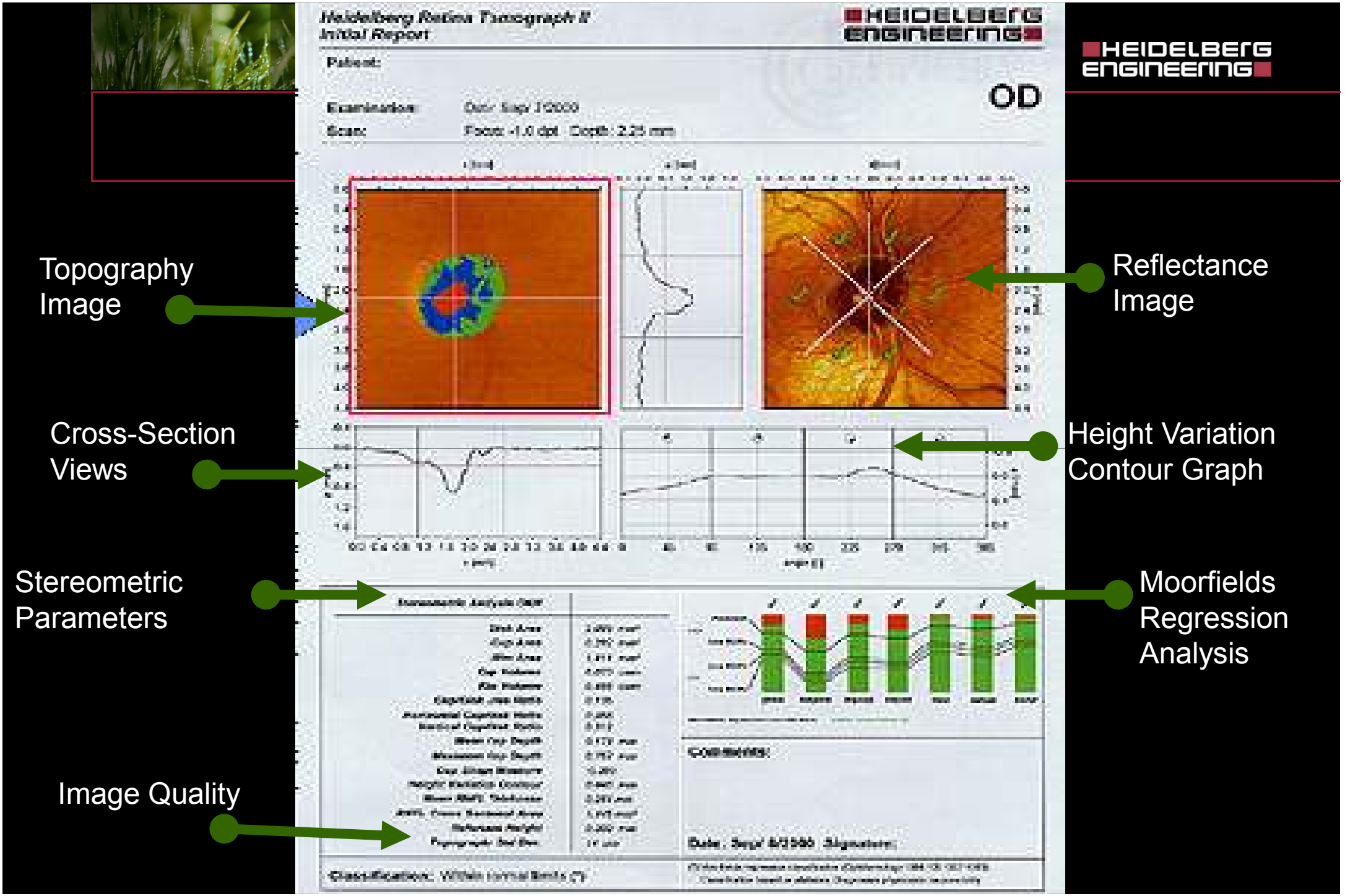
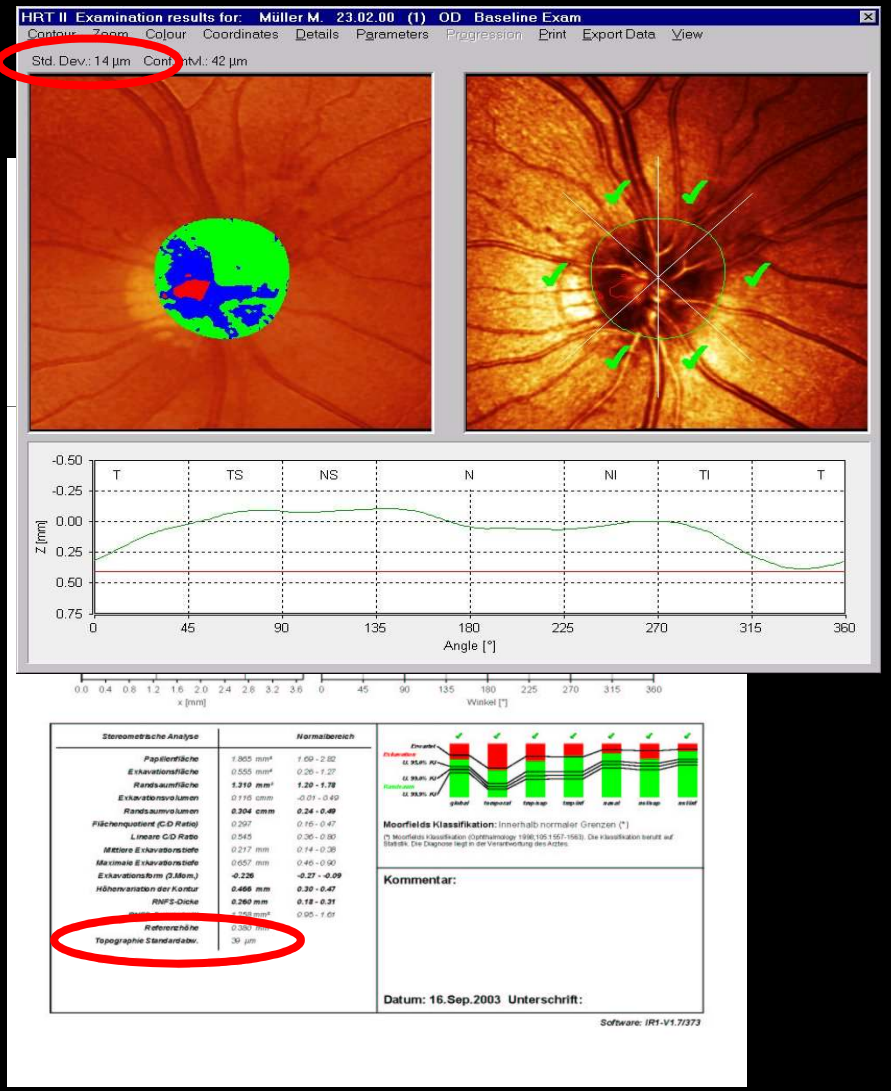
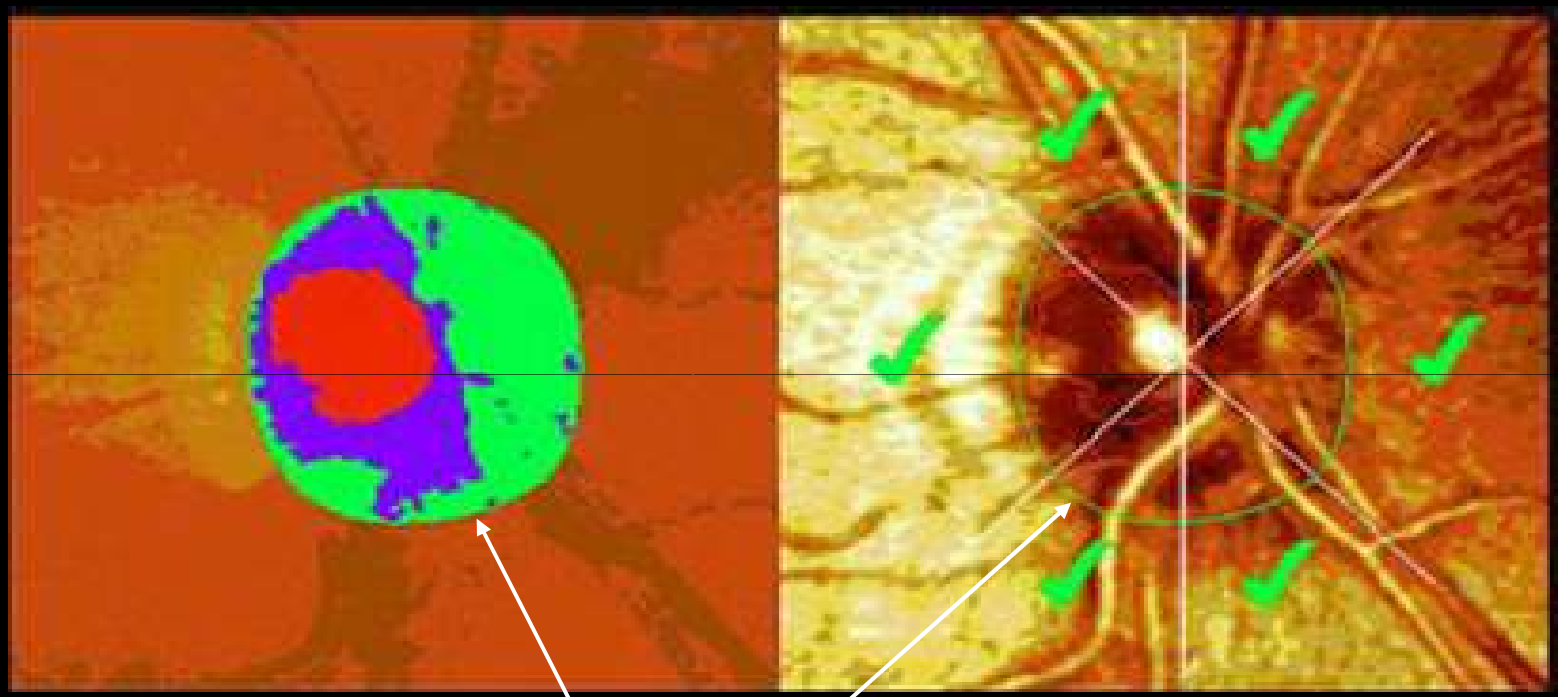

Heidelberg Retina Tomograph II
Initial Report
HEIDELBERG ENGINEERING
Patient:
OD
Examination
Scan:
Topography Image
Reflectance Image
Cross-Section Views
Height Variation Contour Graph
Stereometric Parameters
Moorfields Regression Analysis
Image Quality
Classification:

Image Quality: Standard Deviation

< 10	µm	excellent
10-20	µm	very good
20-30	µm	good
30-40	µm	acceptable
40-50	µm	try to improve
> 50	µm	poor quality, documentation only

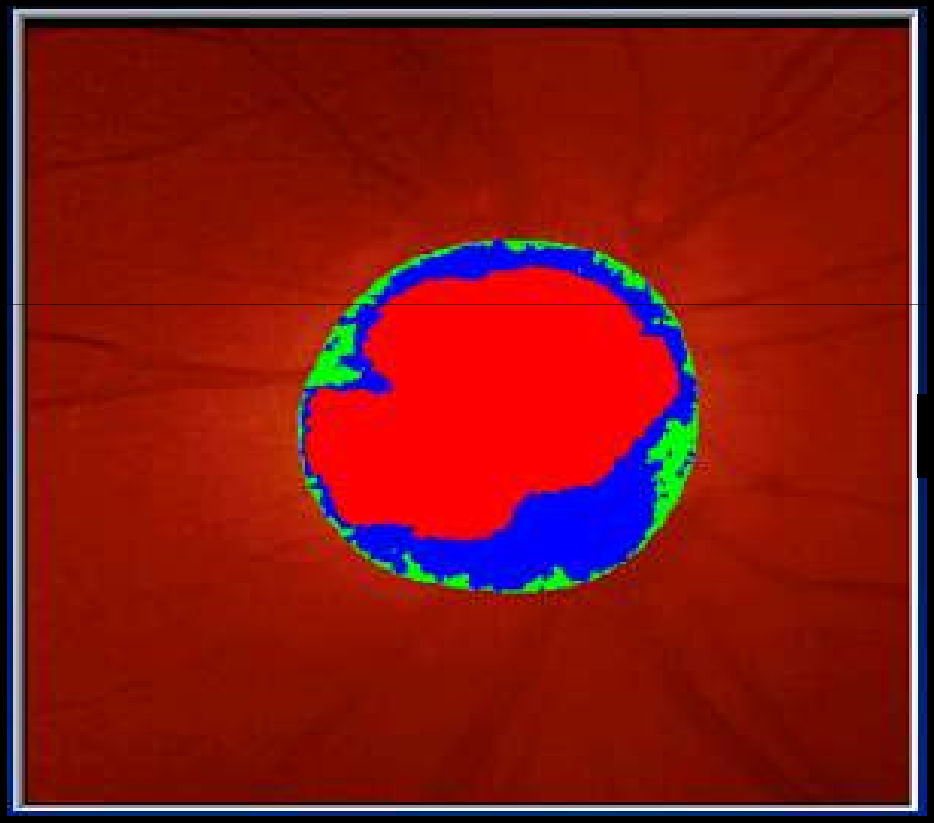


Contour Line



Contour Lines, drawn by OPERATOR

Color Coded Overly TOPOGRAPHY IMAGE



RED = CUP
GREEN = STABLE
BLUE = SLOPING
WHITE: INCORRECT CONTOUR LINE

Reflection Image

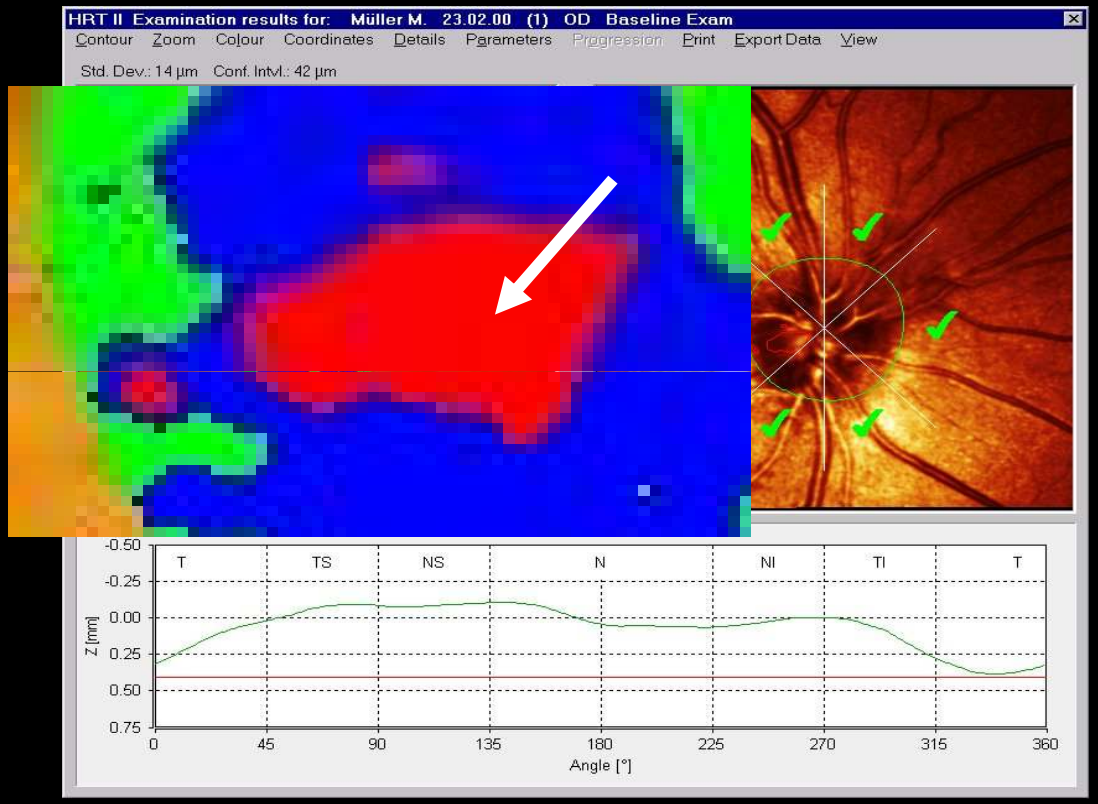
- The optic nerve divided into 6 sectors
- These sectors are compared to a normal database and then classified
- Depending on this patient's age and overall disc size the eye is then statistically classified as " *Within Normal Limits*", "*Borderline*", "*Outside Normal Limits*"

Within Normal Limits

Borderline

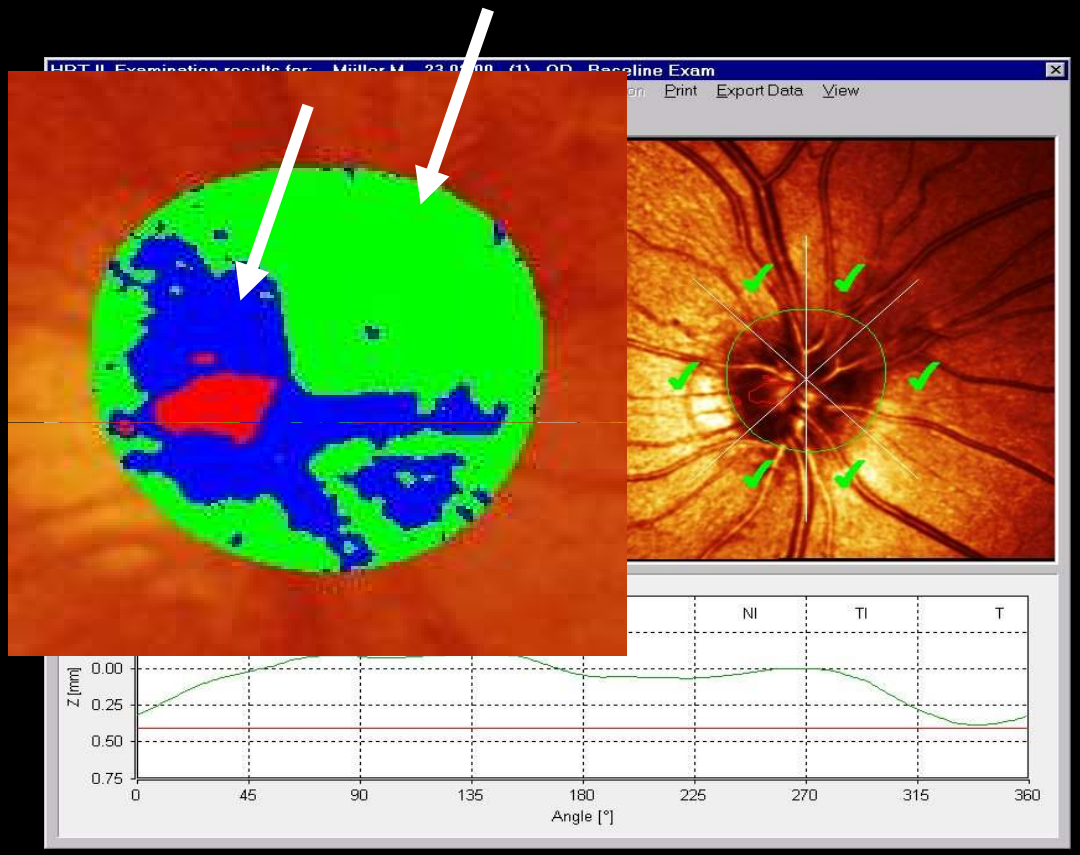
Outside Normal Limits

Stereometric Parameters - Cup Area



Area enclosed by the contour line and located beneath the reference plane.
The cup is displayed in red.

Stereometric Parameters - Rim Area



Area enclosed by the contour line and located above the reference plane. The rim is displayed in green (stable) and blue (sloping).

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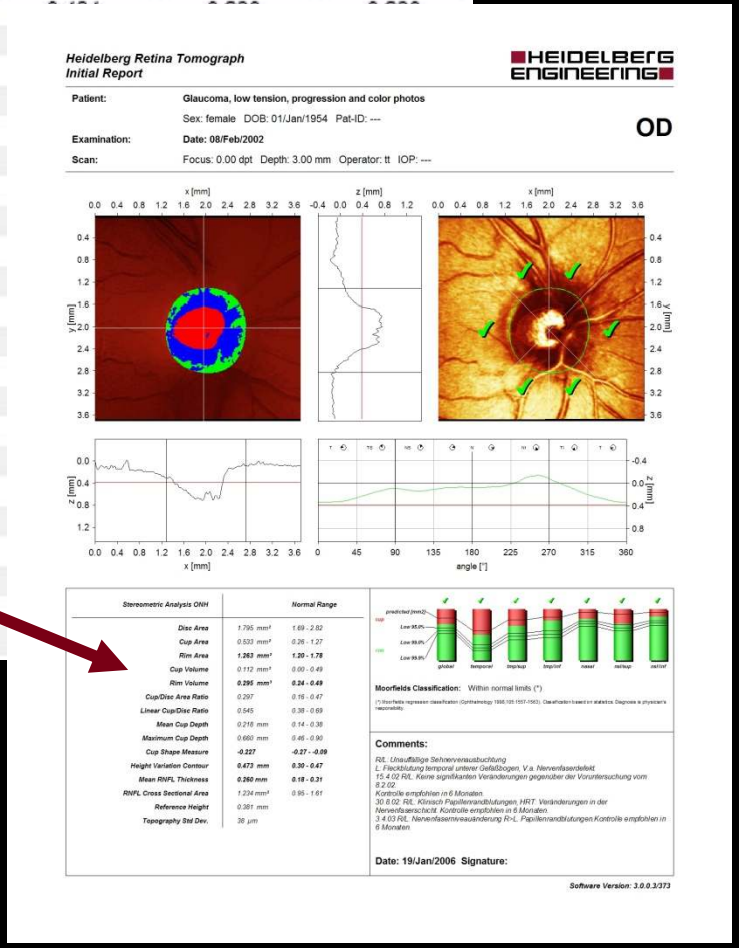
Stereometric Parameters

Parameters	global	temporal	tmp/sup	tmp/inf	nasal	nsl/sup	nsl/inf
disc area [mm²]	1.795	0.438	0.233	0.230			
cup area [mm²]	0.533	0.222	0.076	0.052			
rim area [mm²]	1.263	0.217	0.157	0.177			
cup/disc area ratio [ ]	0.297	0.506	0.328	0.227			
rim/disc area ratio [ ]	0.703	0.494	0.672	0.773			
cup volume [mm³]	0.112	0.035	0.019	0.010			
rim volume [mm³]	0.295	0.017	0.028	0.045			
mean cup depth [mm]	0.218	0.214	0.256	0.200			
maximum cup depth [mm]	0.660	0.550	0.624	0.585			
height variation contour [mm]	0.473	0.134	0.166	0.278			
cup shape measure [ ]	-0.227	-0.148	-0.103	-0.210			
mean RNFL thickness [mm]	0.260	0.080	0.227	0.328			
RNFL cross sectional area [mm²]	1.234	0.093	0.137	0.197			
linear cup/disc ratio [ ]	0.545	-	-	-			
maximum contour elevation [mm]	-0.137	-	-	-			
maximum contour depression [mm]	0.336	-	-	-			
CLM temporal-superior [mm]	0.147	-	-	-			
CLM temporal-inferior [mm]	0.248	-	-	-			
average variability (SD) [mm]	0.036	-	-	-			
reference height [mm]	0.381	-	-	-			
FSM discriminant function value [ ]	0.070	-	-	-			
RB discriminant function value [ ]	1.443	-	-	-			



Global and sectorial parameters automatically calculated.

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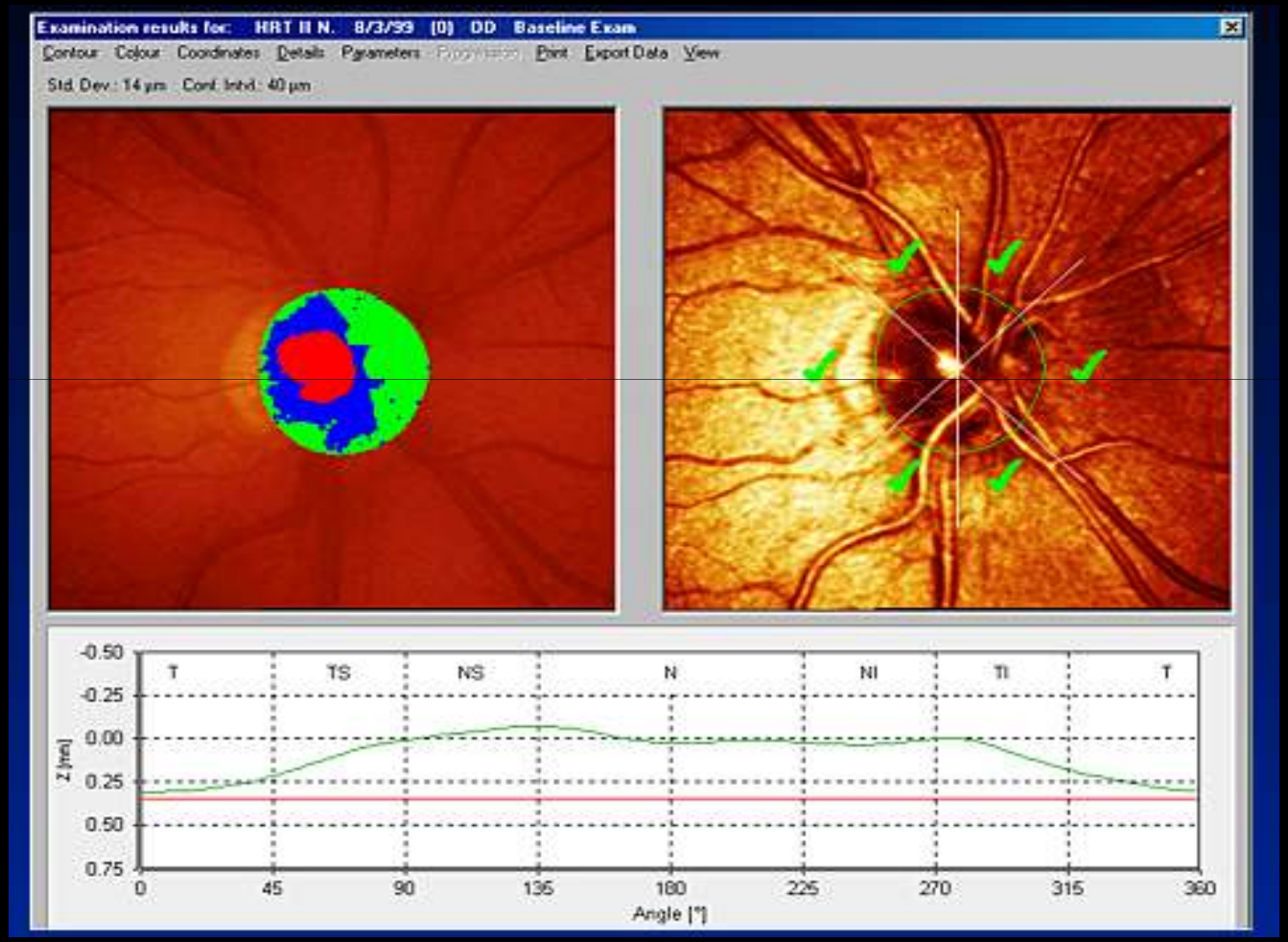
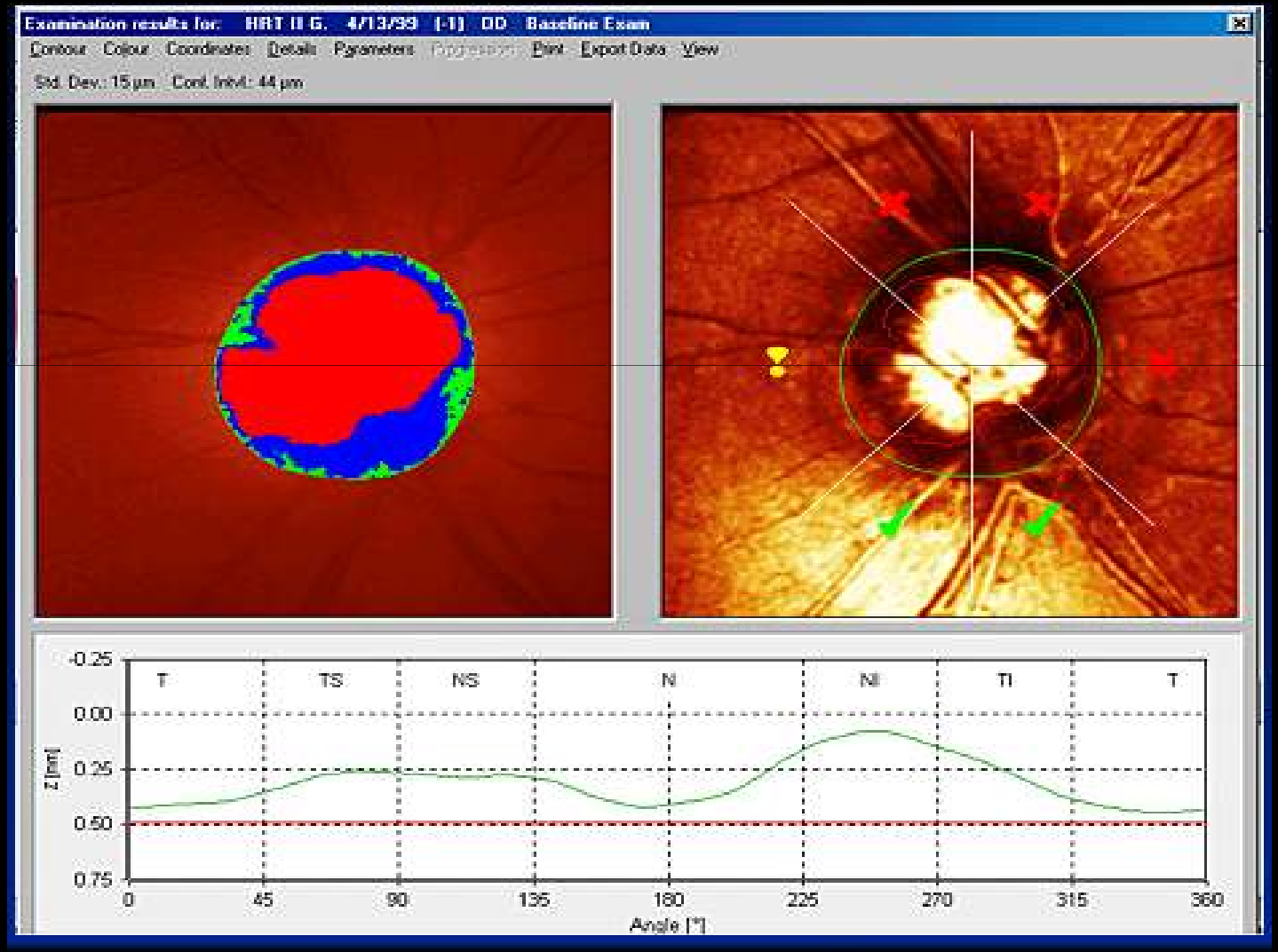


HEIDELBERG ENGINEERING



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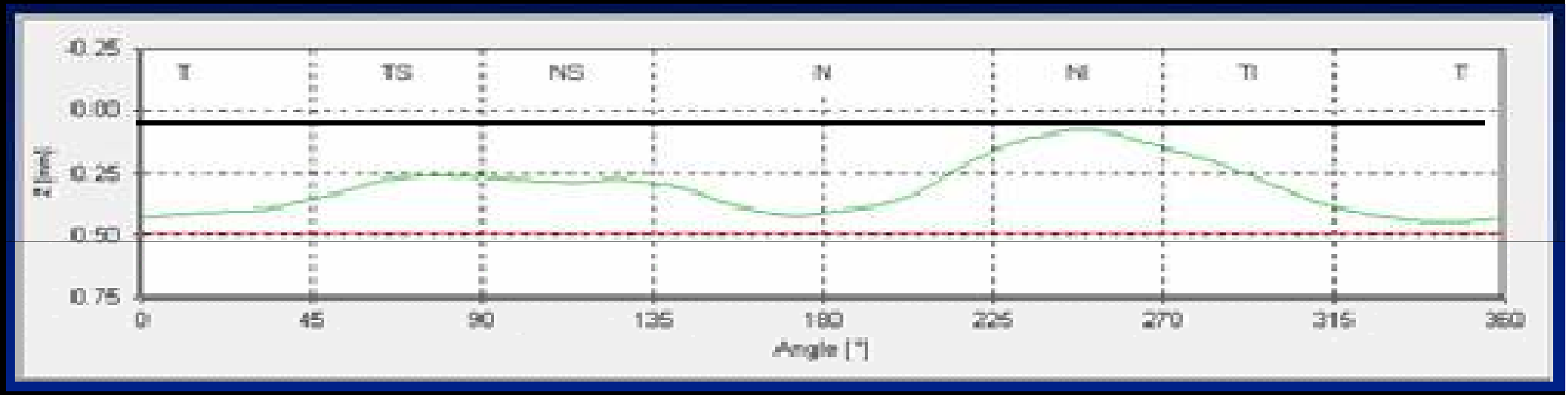
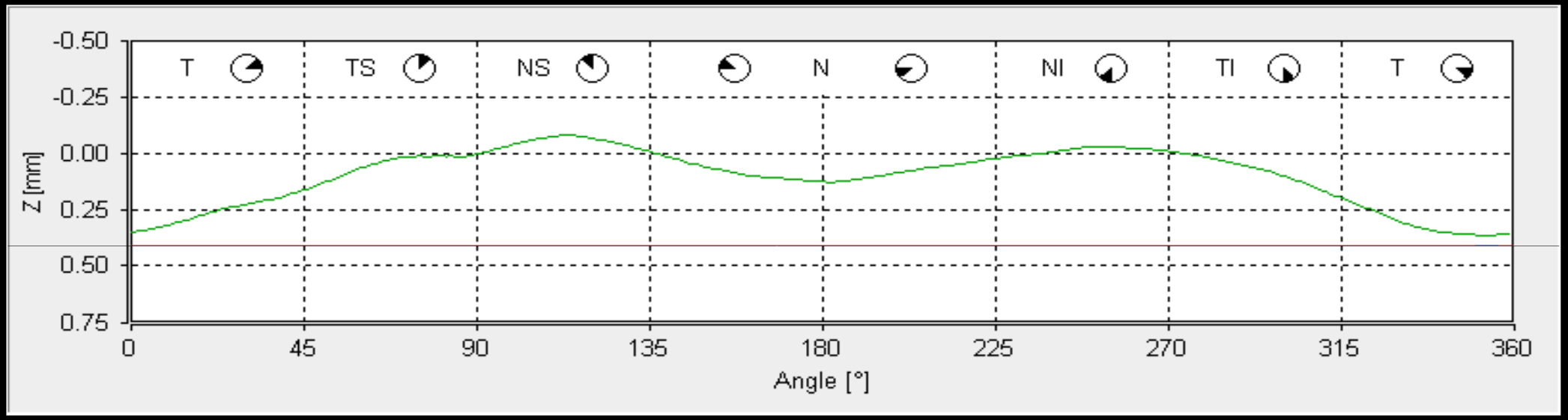


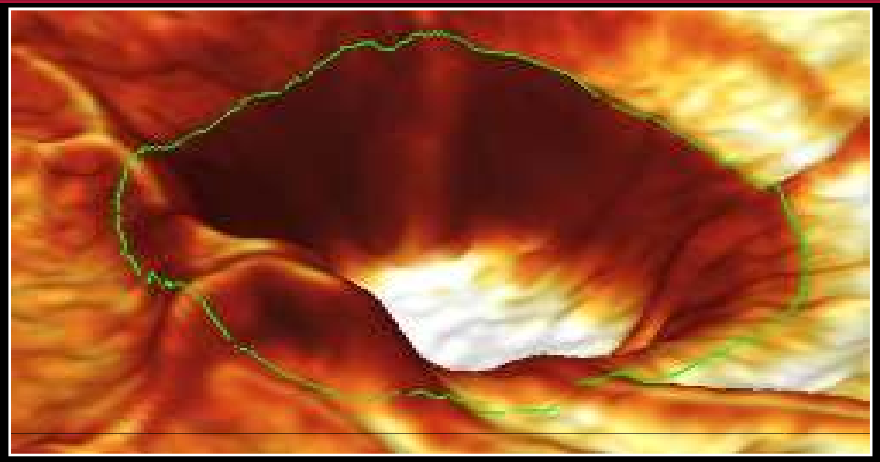
Mean Height Contour Graph

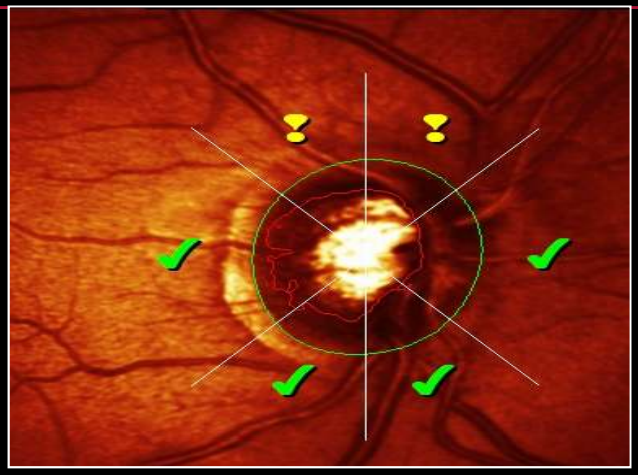
HEIDELBERG ENGINEERING

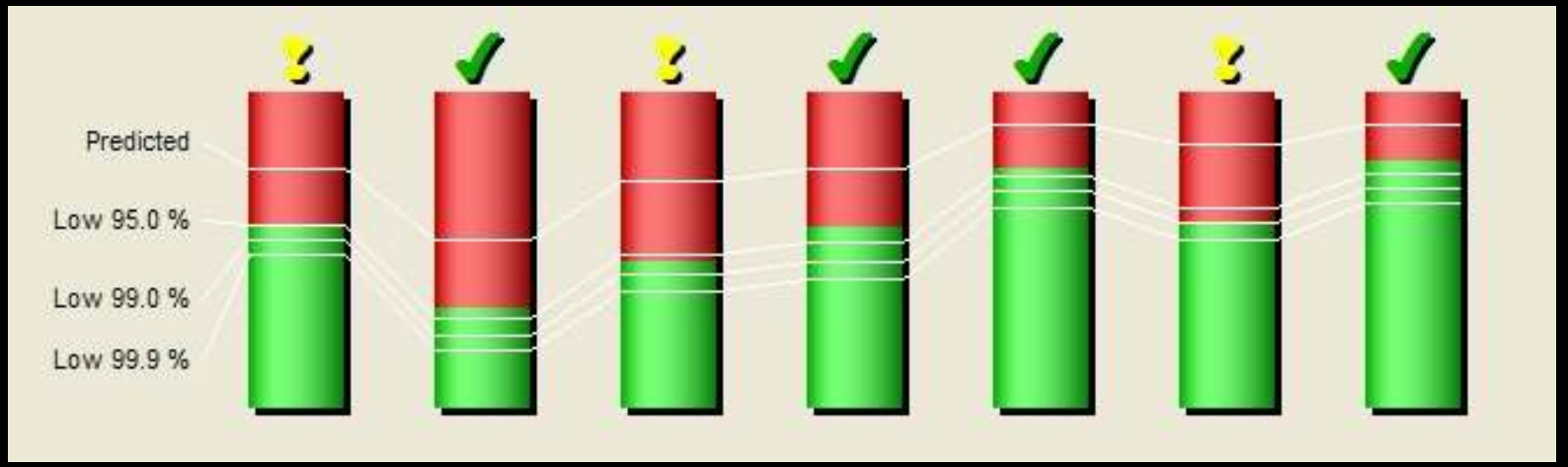


Mean Height Contour Graph

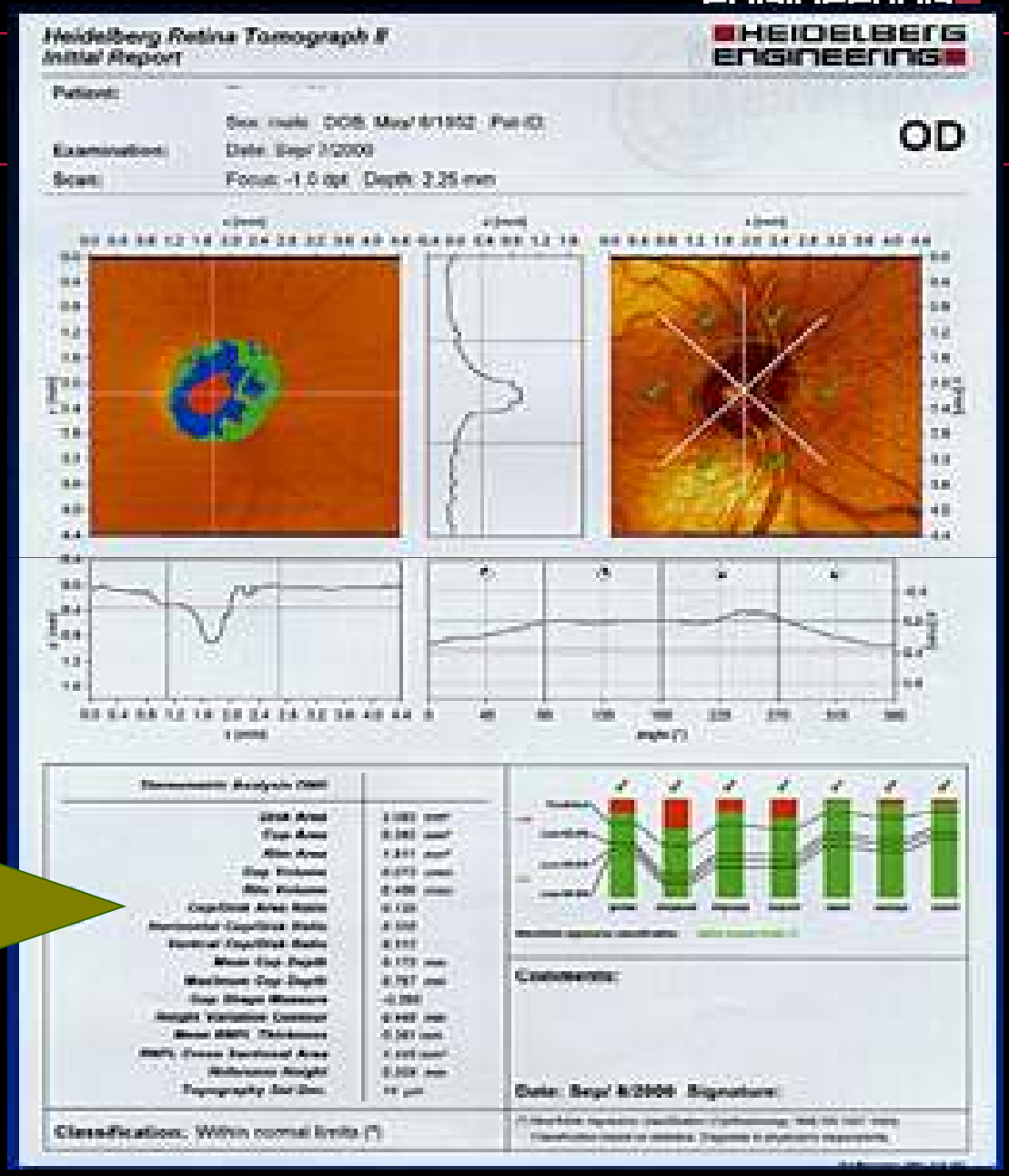
Moorfields Regression Analysis







HEIDELBERG ENGINEERING



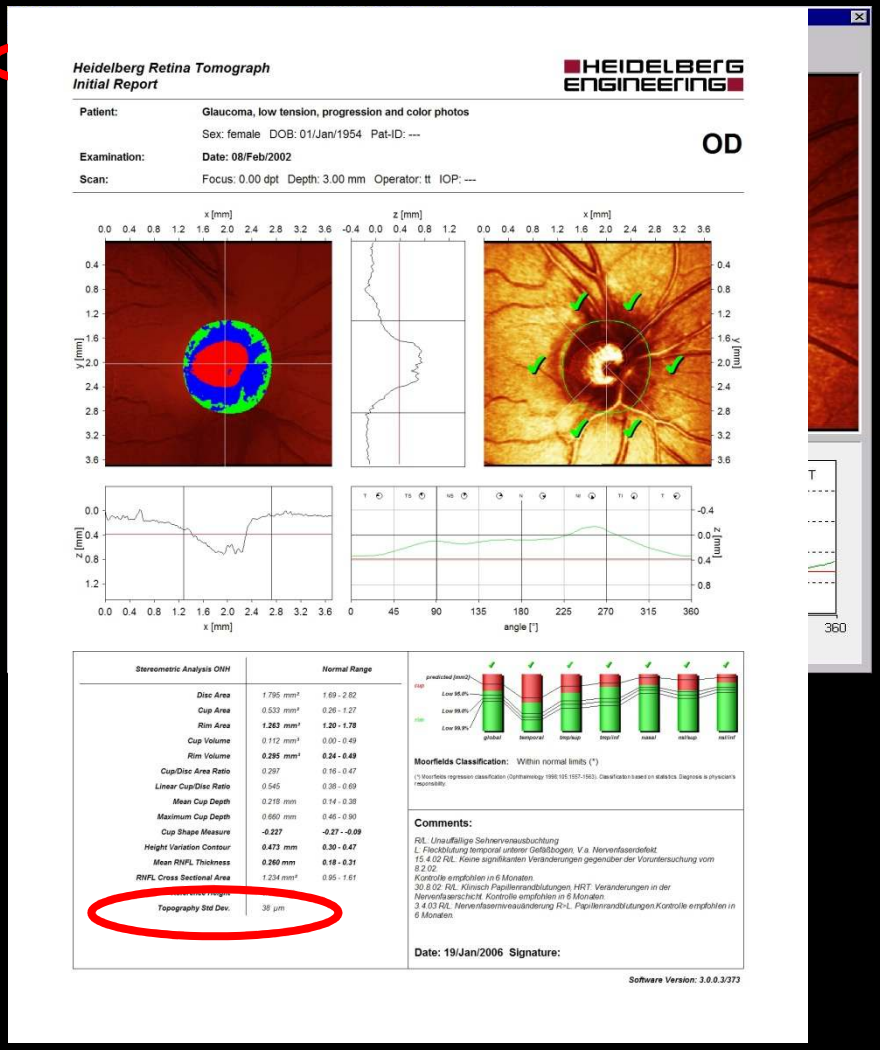
Stereometric Parameters

Stereometric parameters

Stereometric Analysis ONH	
Disk Area	1.518 mm²
Cup Area	0.287 mm²
Rim Area	1.232 mm²
Cup Volume	0.054 cmm
Rim Volume	0.333 cmm
Cup/Disk Area Ratio	0.189
Linear Cup/Disk Ratio	0.435
Mean Cup Depth	0.185 mm
Maximum Cup Depth	0.698 mm
Cup Shape Measure	-0.327
Height Variation Contour	0.378 mm
Mean RNFL Thickness	0.259 mm
RNFL Cross Sectional Area	1.134 mm²
Reference Height	0.347 mm
Topography Std Dev.	14 µm

Image Quality: Standard Deviation

< 10 µm	Excellent
10-20 µm	Very Good
20-30 µm	Good
30-40 µm	Acceptable
40-50 µm	Try to improve
> 50 µm	Poor Quality, documentation only



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Early Glaucoma Detection

Define the risk of a patient to develop glaucoma.

Qualitative

- Reflectivity of the NFL tissue
- Presence of NFL bundle defects
- Embedding of the vessels in the NFL tissue

Quantitative

- Disc size
- Rim configuration
- RNFL thickness
- Stereometric Parameters
- Multivariate Discriminant Analysis
- Moorfields Regression Analysis

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Stereometric Parameters

Heidelberg Retina Tomograph II
Initial Report

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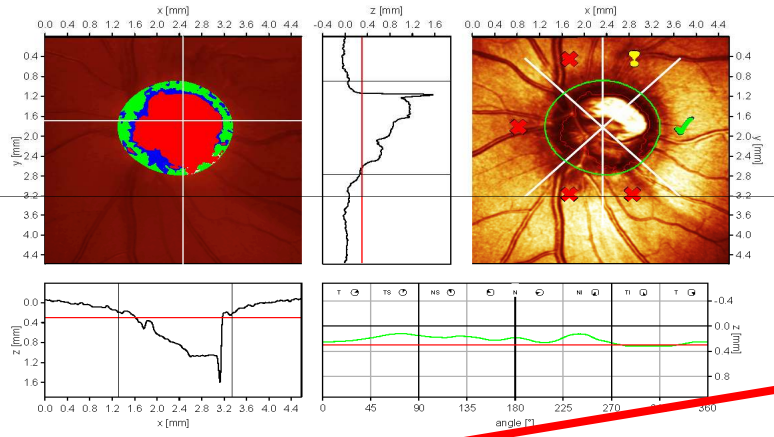
Patient: Glaucoma, Progression 1
Sex: female DOB: 20.Mai.1964 Pat-ID: ---

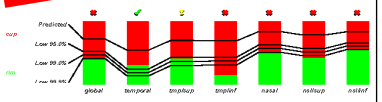
OS

Examination: Date: 17.Jul.2000

Scan: Focus: -3.00 dpt Depth: 2.75 mm Operator: --- IOP: ---



Stereometric Analysis ONH		Normal Range
Disk Area	3.027 mm²	1.69 - 2.82
Cup Area	1.813 mm²	0.26 - 1.27
Rim Area	**1.214 mm²**	**1.20 - 1.78**
Cup Volume	0.786 cmm	0.00 - 0.49
Rim Volume	**0.136 cmm**	**0.24 - 0.49**
Cup/Disk Area Ratio	0.599	0.16 - 0.47
Linear Cup/Disk Ratio	0.774	0.38 - 0.69
Mean Cup Depth	0.417 mm	0.14 - 0.38
Maximum Cup Depth	1.066 mm	0.46 - 0.90
Cup Shape Measure	**-0.158**	**-0.27 - -0.09**
Height Variation Contour	**0.204 mm**	**0.30 - 0.47**
Mean RNFL Thickness	**0.083 mm**	**0.18 - 0.31**
RNFL Cross Sectional Area	0.514 mm²	0.95 - 1.61
Reference Height	0.300 mm	
Topography Std Dev.	11 µm	



Moorfields Classification: Outside normal limits (*)

(*) Attention: Moorfields regression classification (Ophthalmology 1998;105:1557-1563). Results are based on normal eyes with refractive error of less than 6 diopters and optic disc sizes between 1.2 mm² and 2.8 mm². Classification based on statistics. Diagnosis is physician's responsibility.

Comments:

Date: 6 Jun 2005 **Signature:**

Software: IR1-V1.7.2.28/140

Parameters	global	temporal	tmp/sup	tmp/inf	nasal	nsl/sup	nsl/inf
disc area [mm²]	3.027	0.807	0.360	0.372	0.803	0.350	0.335
cup area [mm²]	1.813	0.552	0.209	0.314	0.391	0.200	0.147
rim area [mm²]	1.214	0.255	0.152	0.058	0.412	0.150	0.187
cup/disc area ratio [ ]	0.599	0.684	0.579	0.845	0.487	0.571	0.440
rim/disc area ratio [ ]	0.401	0.316	0.421	0.155	0.513	0.429	0.560
cup volume [mm³]	0.786	0.311	0.167	0.072	0.079	0.125	0.031
rim volume [mm³]	0.136	0.021	0.026	0.002	0.049	0.018	0.020
mean cup depth [mm]	0.417	0.559	0.771	0.256	0.222	0.553	0.193
maximum cup depth [mm]	1.066	1.081	1.335	0.531	0.773	0.966	0.475
height variation contour [mm]	0.204	0.135	0.068	0.057	0.096	0.031	0.137
cup shape measure [ ]	-0.158	-0.073	-0.040	-0.089	-0.228	0.074	-0.109
mean RNFL thickness [mm]	0.083	0.045	0.161	-0.007	0.087	0.131	0.123
RNFL cross sectional area [mm²]	0.514	0.071	0.121	-0.005	0.137	0.099	0.091
linear cup/disc ratio [ ]	0.774	-	-	-	-	-	-
maximum contour elevation [mm]	0.116	-	-	-	-	-	-
maximum contour depression [mm]	0.320	-	-	-	-	-	-
CLM temporal-superior [mm]	0.117	-	-	-	-	-	-
CLM temporal-inferior [mm]	-0.052	-	-	-	-	-	-
average variability (SD) [mm]	0.018	-	-	-	-	-	-
reference height [mm]	0.300	-	-	-	-	-	-
FSM discriminant function value [ ]	-0.946	-	-	-	-	-	-
RB discriminant function value [ ]	-0.620	-	-	-	-	-	-

Stereometric Analysis ONH		Normal Range
Disk Area	3.027 mm²	1.69 - 2.82
Cup Area	1.813 mm²	0.26 - 1.27
Rim Area	**1.214 mm²**	**1.20 - 1.78**
Cup Volume	0.786 cmm	0.00 - 0.49
Rim Volume	**0.136 cmm**	**0.24 - 0.49**
Cup/Disk Area Ratio	0.599	0.16 - 0.47
Linear Cup/Disk Ratio	0.774	0.38 - 0.69
Mean Cup Depth	0.417 mm	0.14 - 0.38
Maximum Cup Depth	1.066 mm	0.46 - 0.90
Cup Shape Measure	**-0.158**	**-0.27 - -0.09**
Height Variation Contour	**0.204 mm**	**0.30 - 0.47**
Mean RNFL Thickness	**0.083 mm**	**0.18 - 0.31**
RNFL Cross Sectional Area	0.514 mm²	0.95 - 1.61
Reference Height	0.300 mm	
Topography Std Dev.	11 µm	

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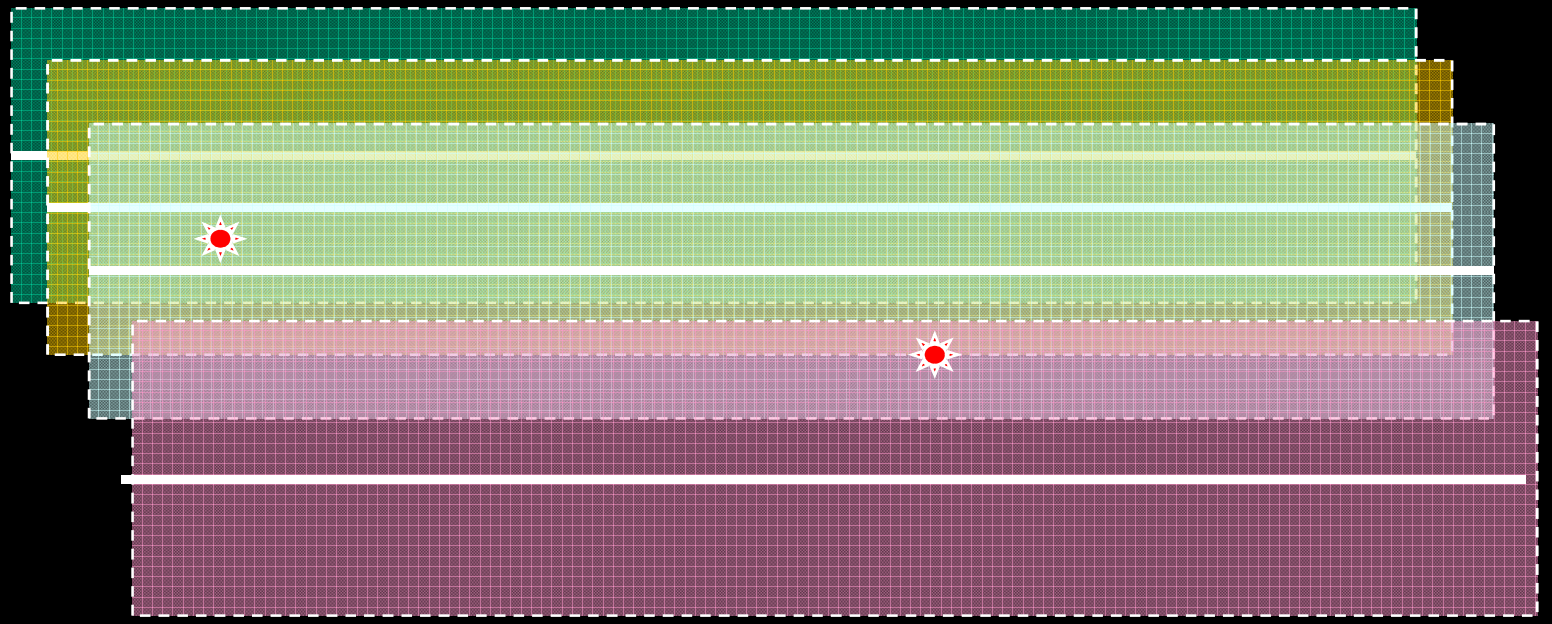
Detection of Glaucomatous Damage

Compare stereometric parameters with **normal values** (Top 5) Reinhard O.W. Burk, Heidelberg, 2000

Parameter	normal	early	moderate	advanced
Disc Area [mm²]	2.257 ± 0.563	2.346 ± 0.569	2.310 ± 0.554	2.261 ± 0.416
Cup Area [mm²]	0.768 ± 0.505	0.953 ± 0.594	1.051 ± 0.647	1.445 ± 0.562
Rim Area [mm²]	1.489 ± 0.291	1.393 ± 0.340	1.260 ± 0.415	0.817 ± 0.334
Cup Volume [mm³]	0.240 ± 0.245	0.294 ± 0.270	0.334 ± 0.318	0.543 ± 0.425
Rim Volume [mm³]	0.362 ± 0.124	0.323 ± 0.156	0.262 ± 0.139	0.128 ± 0.096
Cup/Disk Area Ratio	0.314 ± 0.152	0.380 ± 0.179	0.430 ± 0.203	0.621 ± 0.189
Horizontal Cup/Disk Ratio	0.567 ± 0.200	0.623 ± 0.221	0.658 ± 0.226	0.808 ± 0.185
Vertical Cup/Disk Ratio	0.460 ± 0.206	0.538 ± 0.214	0.573 ± 0.226	0.756 ± 0.194
Mean Cup Depth [mm]	0.262 ± 0.118	0.279 ± 0.115	0.289 ± 0.130	0.366 ± 0.182
Maximum Cup Depth [mm]	0.679 ± 0.223	0.680 ± 0.210	0.674 ± 0.249	0.720 ± 0.276
Cup Shape Measure	-0.181 ± 0.092	-0.147 ± 0.098	-0.122 ± 0.095	-0.036 ± 0.096
Height Variation Contour [mm]	0.384 ± 0.087	0.364 ± 0.100	0.330 ± 0.108	0.256 ± 0.090
Mean RNFL Thickness [mm]	0.244 ± 0.063	0.217 ± 0.076	0.182 ± 0.086	0.130 ± 0.061
RNFL Cross Sectional Area [mm²]	1.282 ± 0.328	1.155 ± 0.396	0.957 ± 0.440	0.679 ± 0.302

Physiologic Variability

- Rim area

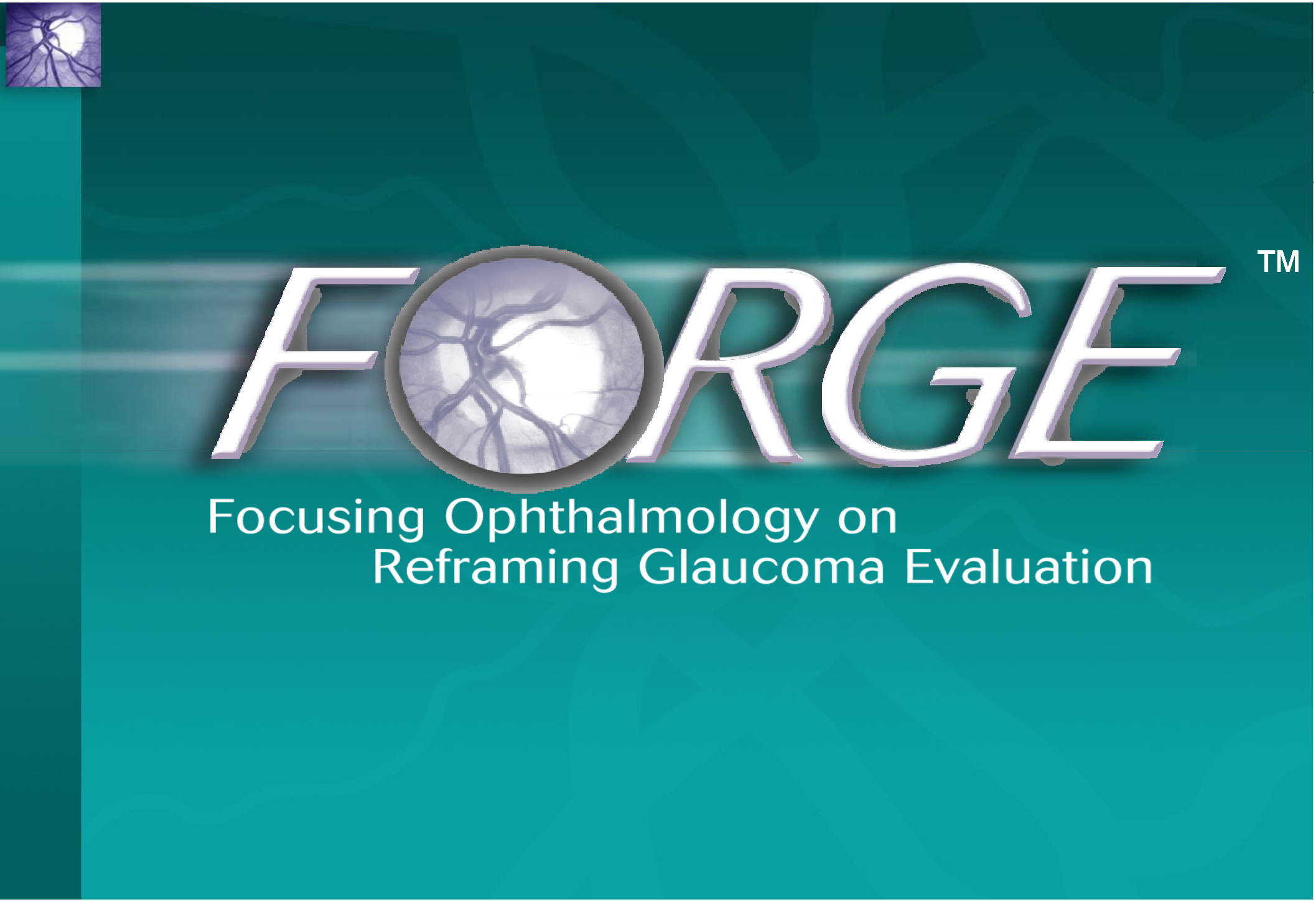


normal

early

moderate

advanced


FORGE
TM
Focusing Ophthalmology on
Reframing Glaucoma Evaluation

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FORGE

Optic Disc/RNFL Examination "The 5Rs"

1 Observe the scleral Ring to identify the limits of the optic disc and its size

2 Identify the size of the Rim

3 Examine the Retinal nerve fiber layer

4 Examine the Region of parapapillary atrophy

5 Look for Retinal and optic disc hemorrhages

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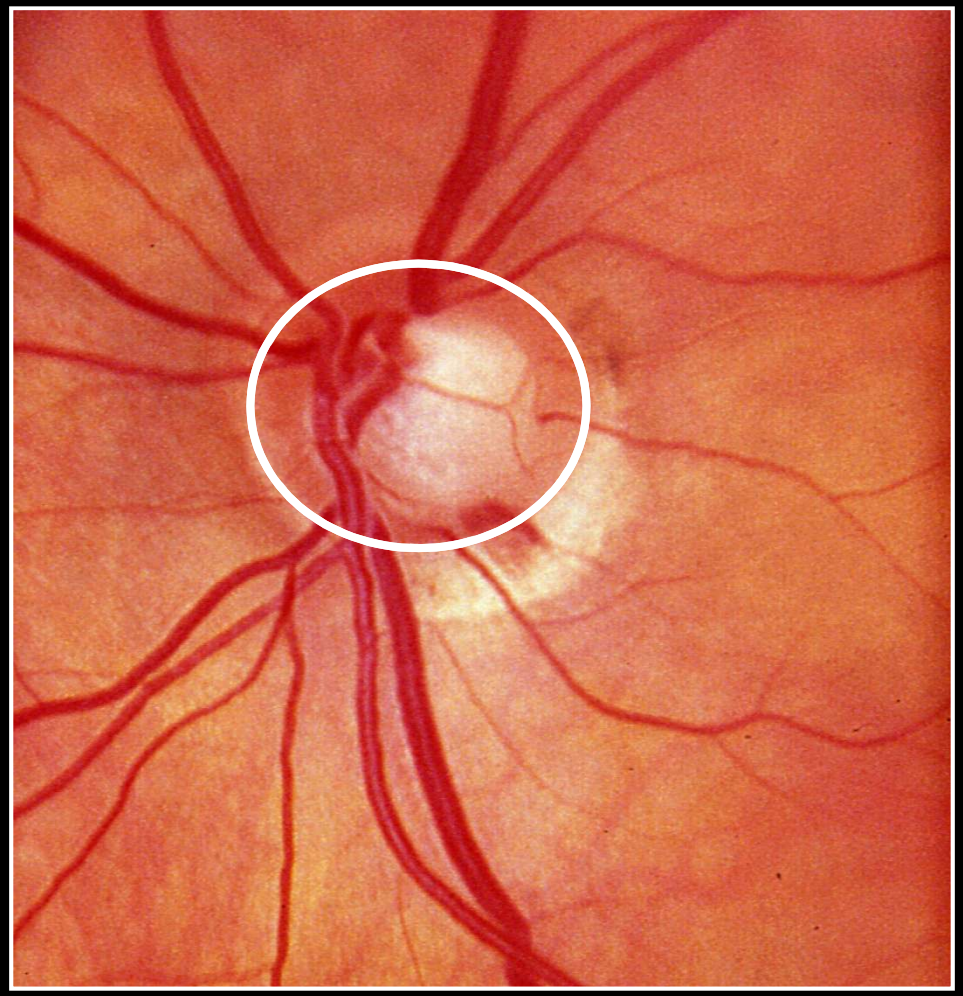
Applying FORGE & Jonas to HRT

HRT Analysis in 60 seconds

FORGE & Jonas

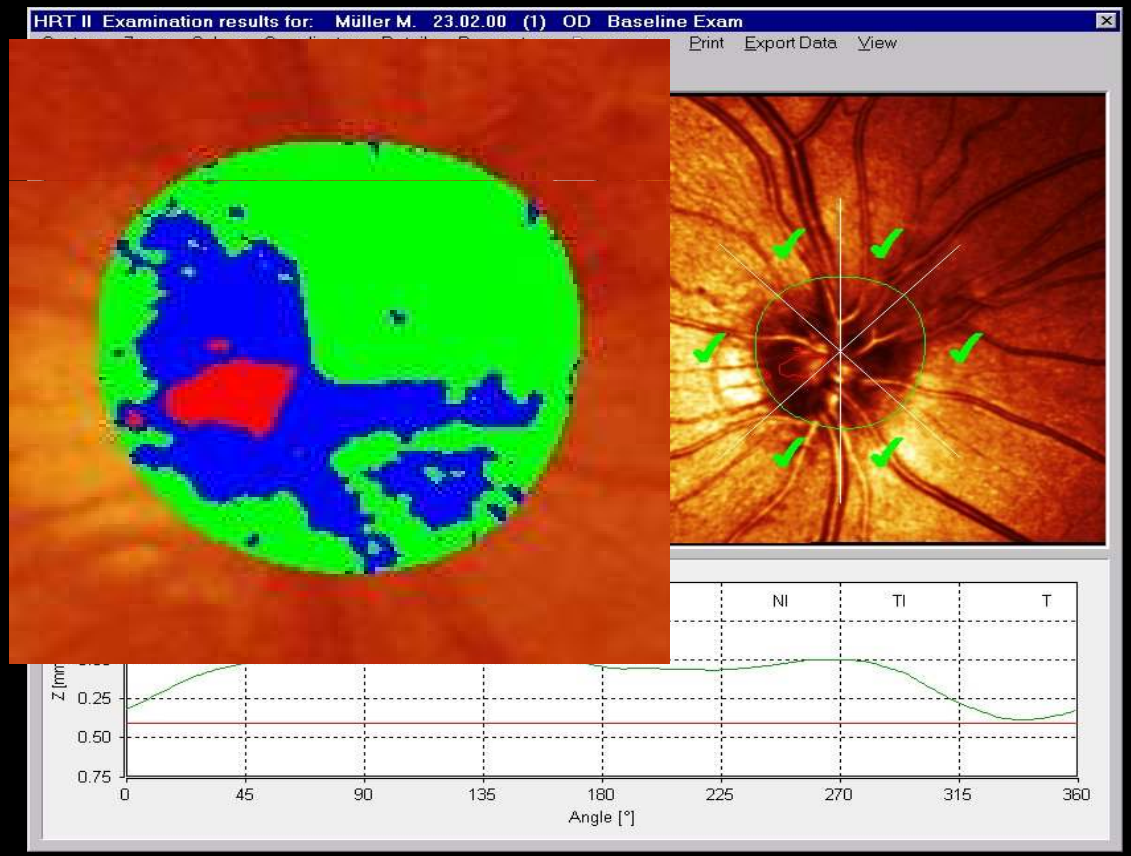
FORGE: Observe the scleral Ring to identify the limits of the optic disc and its size

Jonas: Observe size and shape of the optic disk



Disc Area

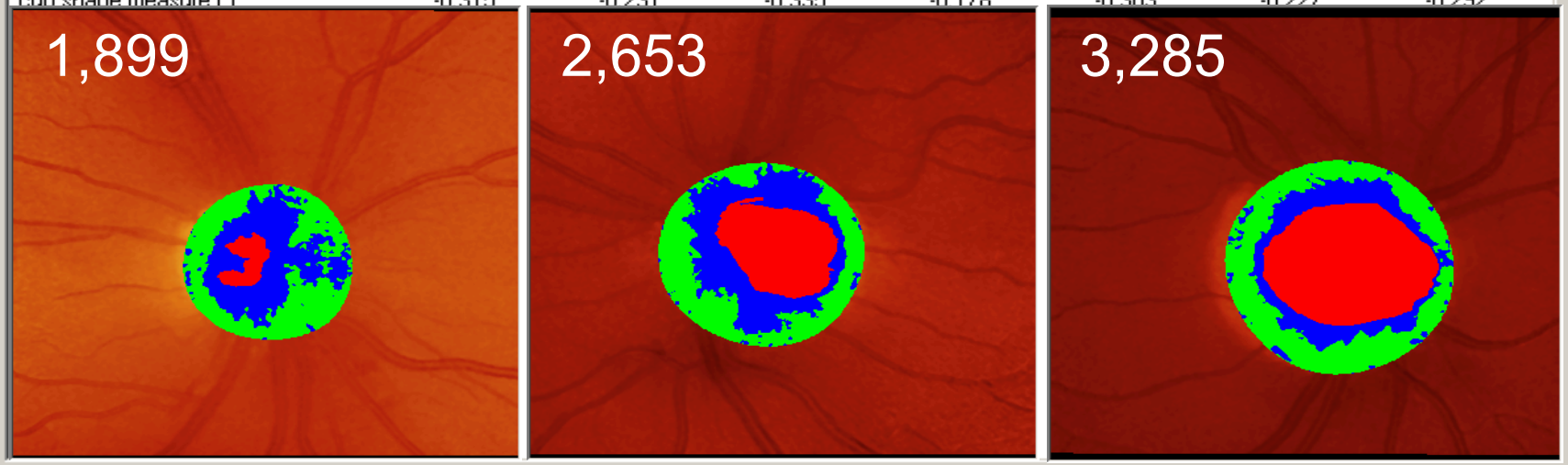
- Total area enclosed by the contour line



Disc Size & Shape

Predefined Segments: Demo E. 13.08.2002 (0) OD Baseline Exam ...

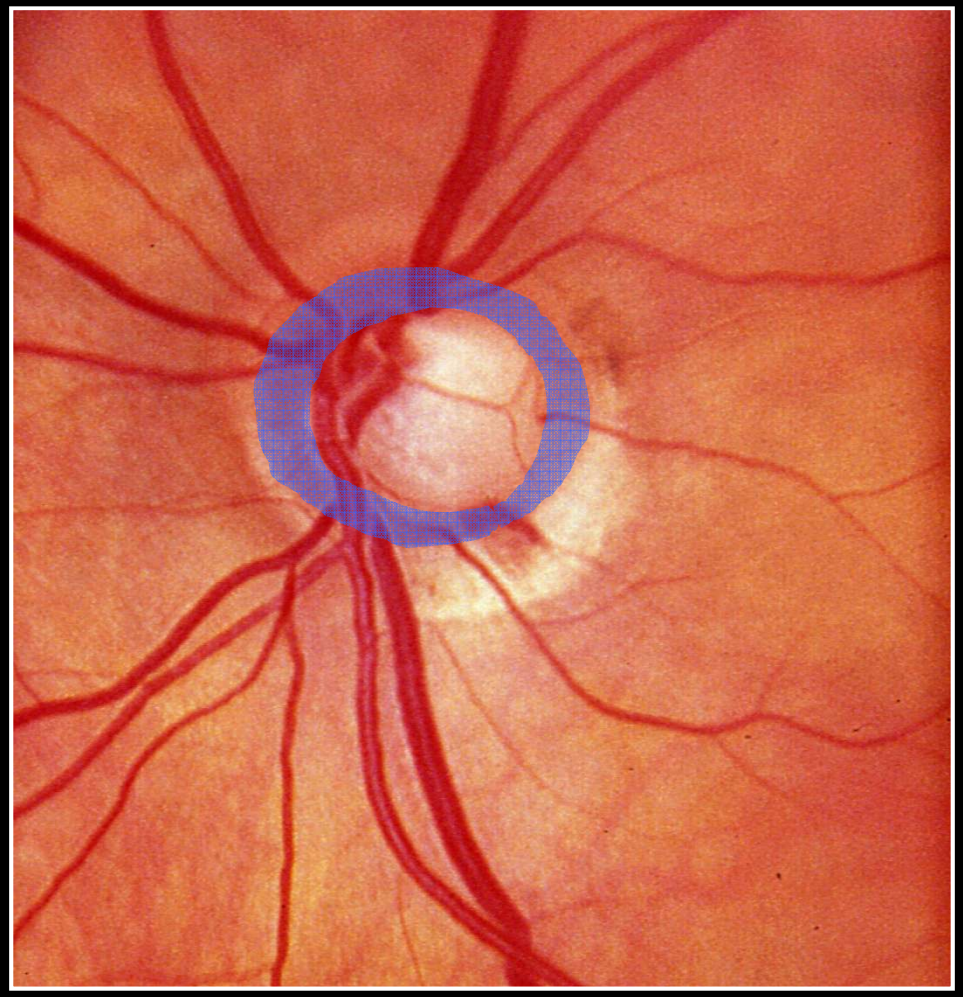
Parameters	global	temporal	tmp/sup	tmp/inf	nasal	nsl/sup	nsl/inf
disc area [mm²]	2.602	0.691	0.297	0.327	0.678	0.315	0.295
cup area [mm²]	0.977	0.366	0.114	0.120	0.195	0.101	0.082
rim area [mm²]	1.625	0.325	0.182	0.208	0.483	0.214	0.213
cup/disc area ratio [ ]	0.376	0.529	0.386	0.365	0.288	0.321	0.277
rim/disc area ratio [ ]	0.624	0.471	0.614	0.635	0.712	0.679	0.723
cup volume [mm³]	0.404	0.146	0.074	0.048	0.064	0.044	0.027
rim volume [mm³]	0.178	0.018	0.023	0.022	0.055	0.028	0.032
mean cup depth [mm]	0.279	0.308	0.375	0.274	0.207	0.290	0.225
maximum cup depth [mm]	0.867	0.832	1.063	0.706	0.657	0.822	0.722
height variation contour [mm]	0.157	0.085	0.039	0.048	0.061	0.034	0.064
cup shape measure [ ]	-0.315	-0.231	-0.335	-0.178	-0.303	-0.227	-0.292



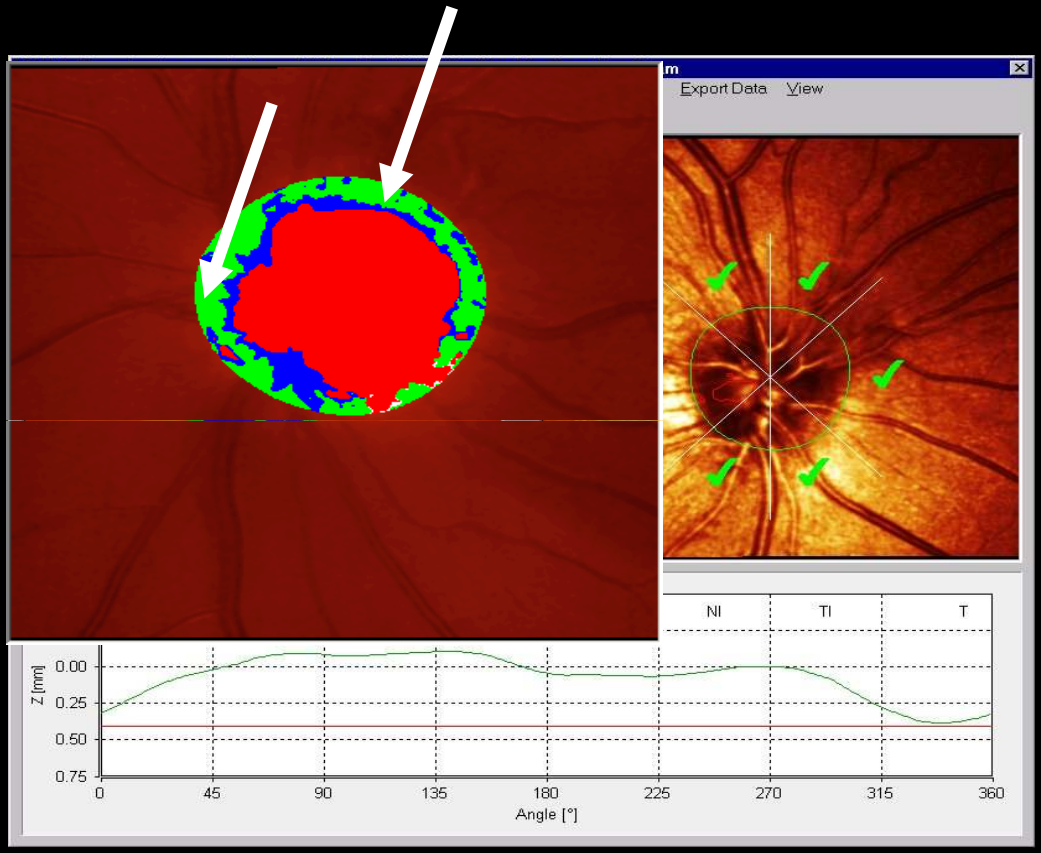
FORGE & Jonas

FORGE: Identify the size of the Rim (ISNT Rule)

Jonas: Identify size, shape, and pallor of the neuroretinal rim



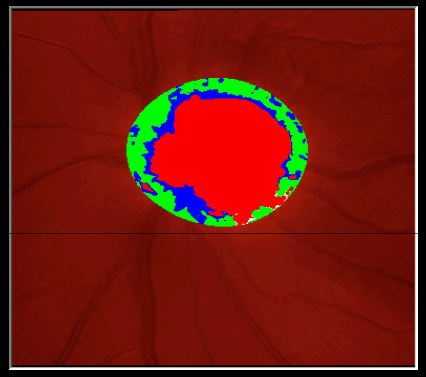
Stereometric Parameters - Rim Area



Area enclosed by the contour line and located above the reference plane. The rim is displayed in green (stable) and blue (sloping).

Rim Configuration

Parameters	global	temporal	tmp/sup	tmp/inf	nasal	nsl/sup	nsl/inf
disc area [mm²]	3.027	0.807	0.360	0.372	0.803	0.350	0.335
cup area [mm²]	1.813	0.552	0.208	0.314	0.391	0.200	0.147
rim area [mm²]	1.214	0.255	0.152	0.058	0.412	0.150	0.187
cup/disc area ratio [ ]	0.599	0.684	0.579	0.845	0.487	0.571	0.440

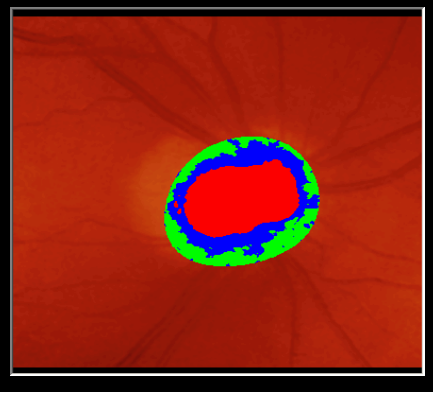


ISNT Rule

I = 0.250 S = 0.300 N = 0.412 T = 0.255

Irregular rim configuration

Parameters	global	temporal	tmp/sup	tmp/inf	nasal	nsl/sup	nsl/inf
disc area [mm²]	2.011	0.518	0.224	0.272	0.533	0.257	0.208
cup area [mm²]	0.840	0.271	0.085	0.082	0.276	0.103	0.043
rim area [mm²]	1.171	0.247	0.140	0.190	0.277	0.154	0.165
cup/disc area ratio [ ]	0.418	0.524	0.378	0.301	0.481	0.400	0.208



I = 0.355 S = 0.294 N = 0.277 T = 0.247

Regular rim configuration

Nasal rim includes vessels!

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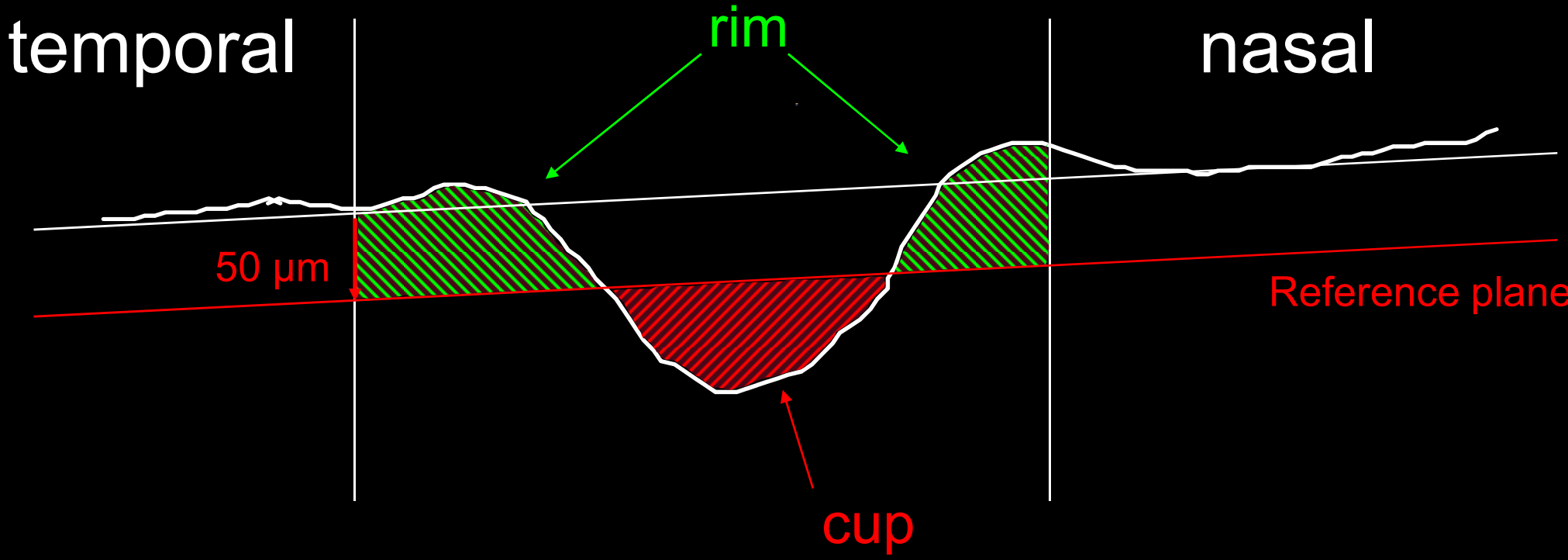
Rim Volume

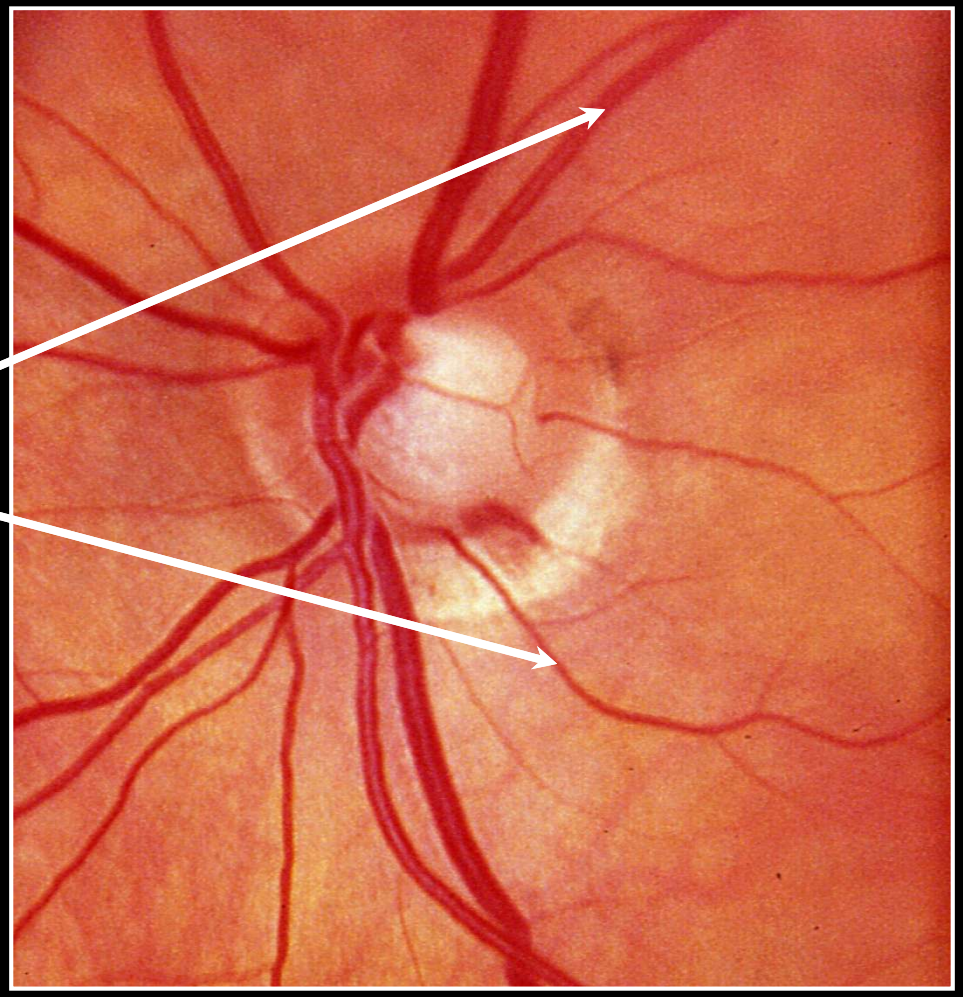
- Volume enclosed by the contour line and located above the reference plane



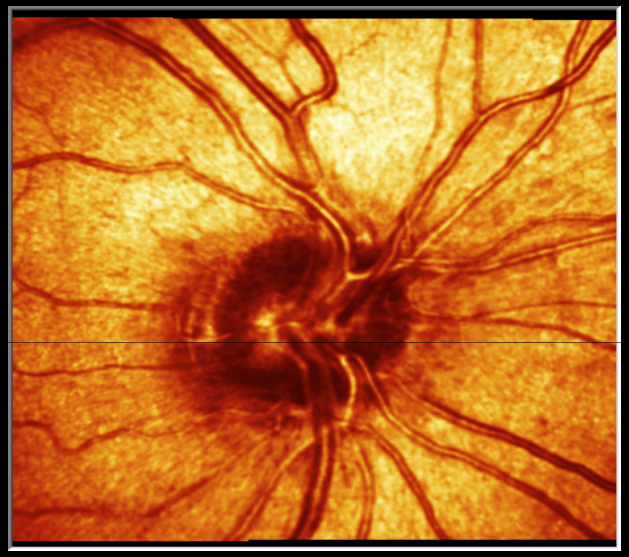
FORGE & Jonas

FORGE: Examine the Retinal nerve fiber layer

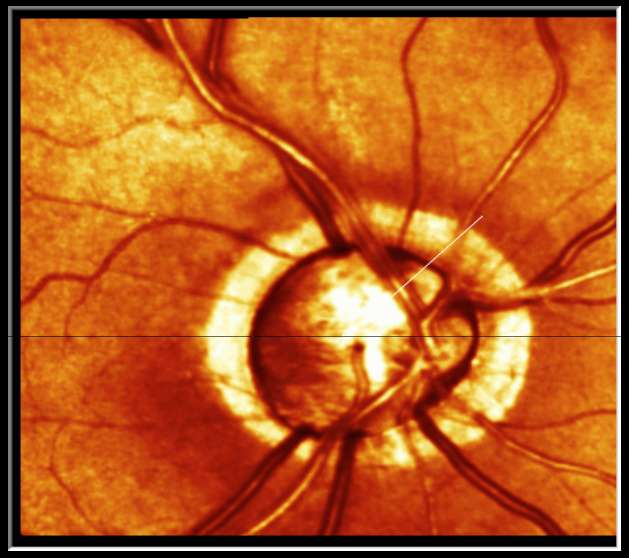
Jonas: Examine visibility of the retinal nerve fiber layer (RNFL)



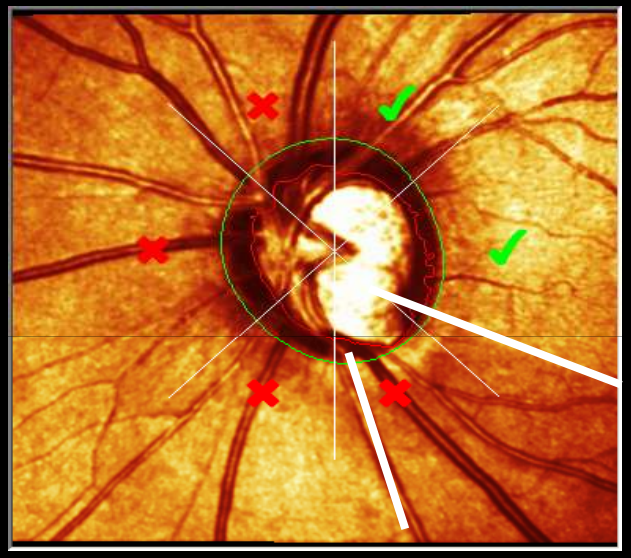
Qualitative Analysis: RNFL reflectivity



Healthy nerve fibers show good reflectivity



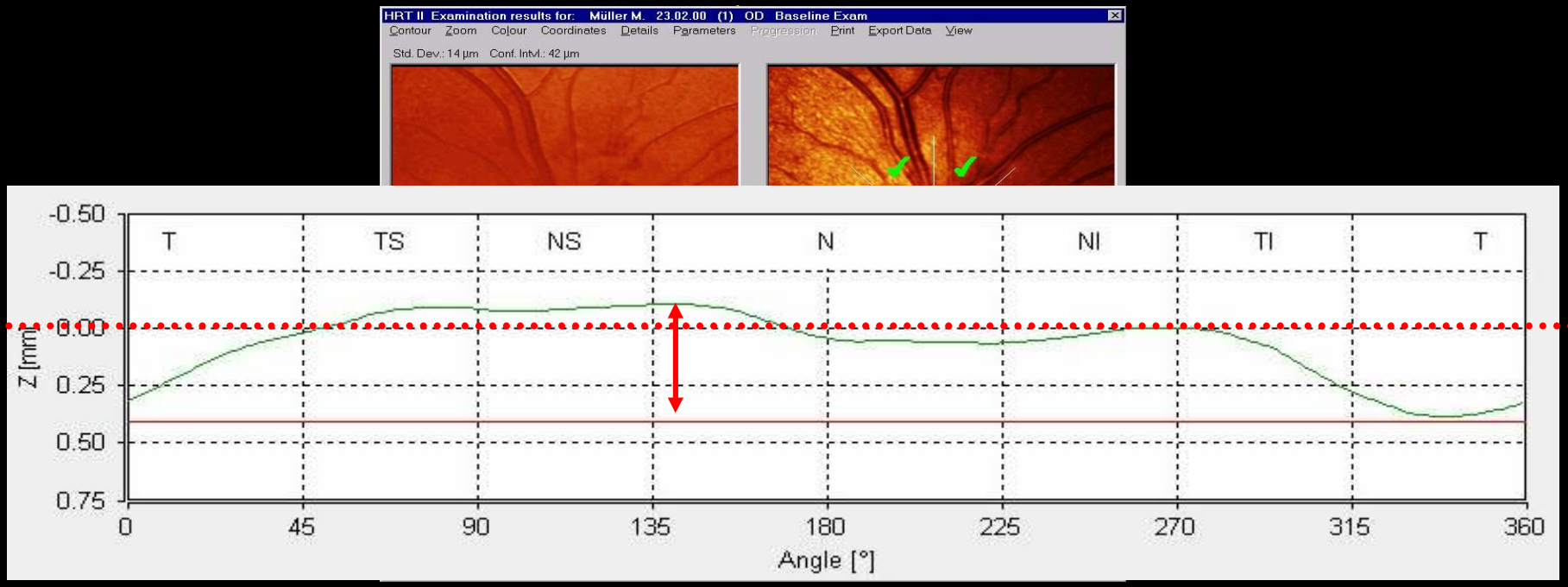
Reduced reflectivity in diffuse nerve fiber loss



NFL bundle defect confirmed by Moorfields classification

Height Variation Contour

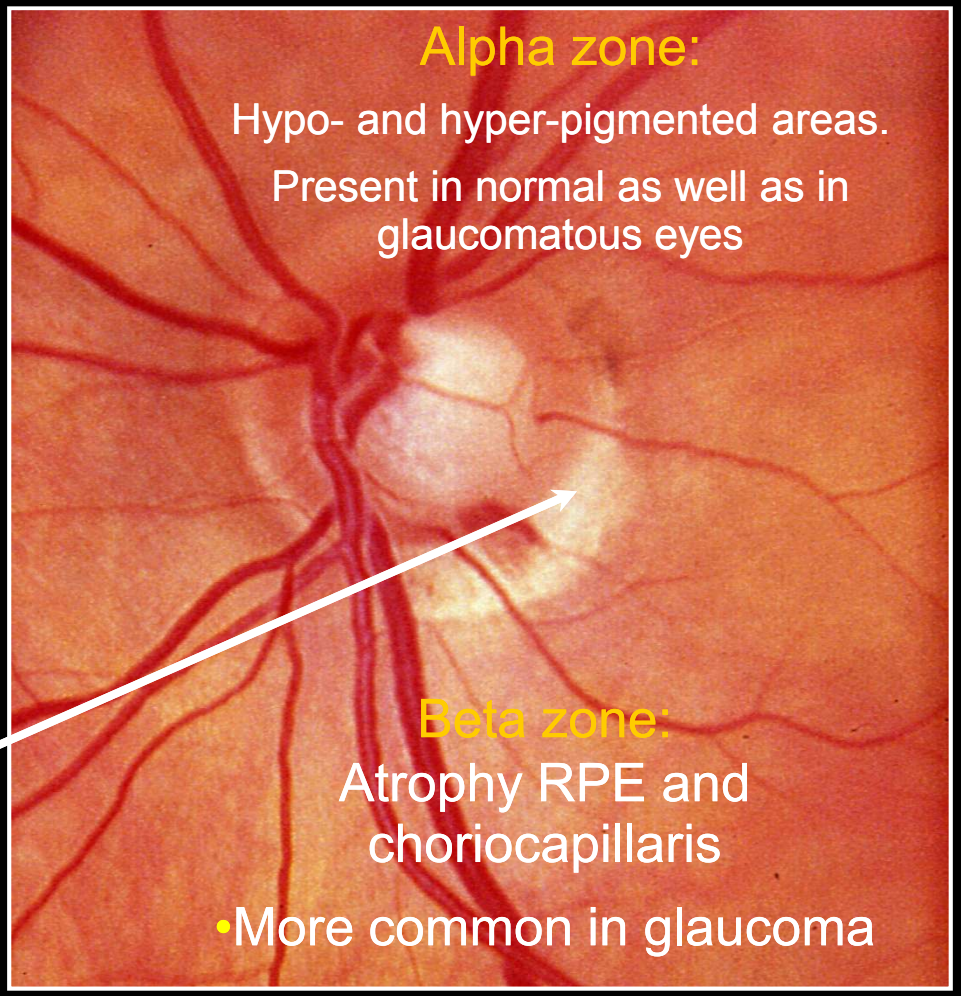
- Height difference between the most elevated and most depressed point of the contour line



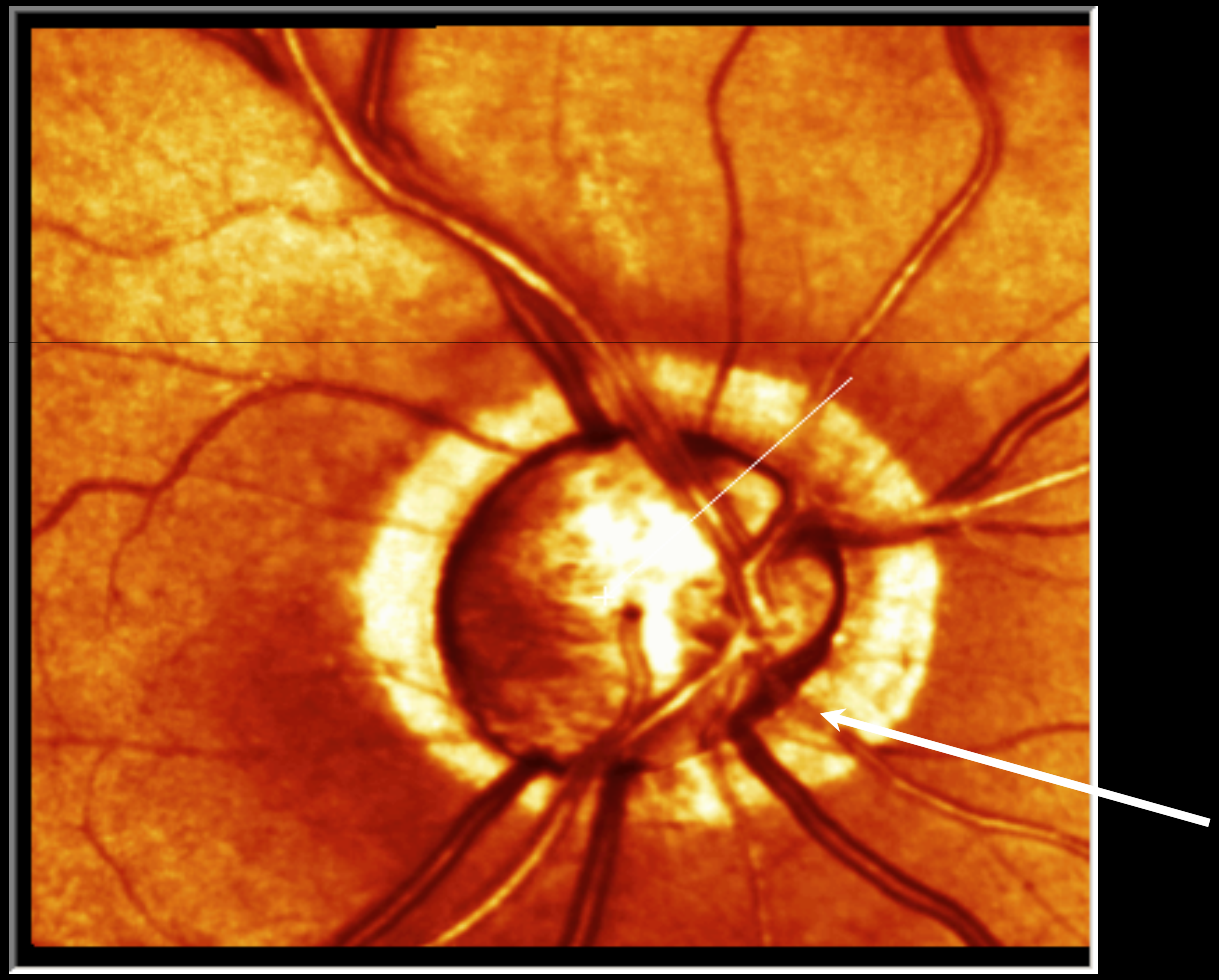
FORGE & Jonas

FORGE: Examine the Region of parapapillary atrophy

Jonas: Examine occurrence, size, configuration, and location of parapapillary chorioretinal atrophy



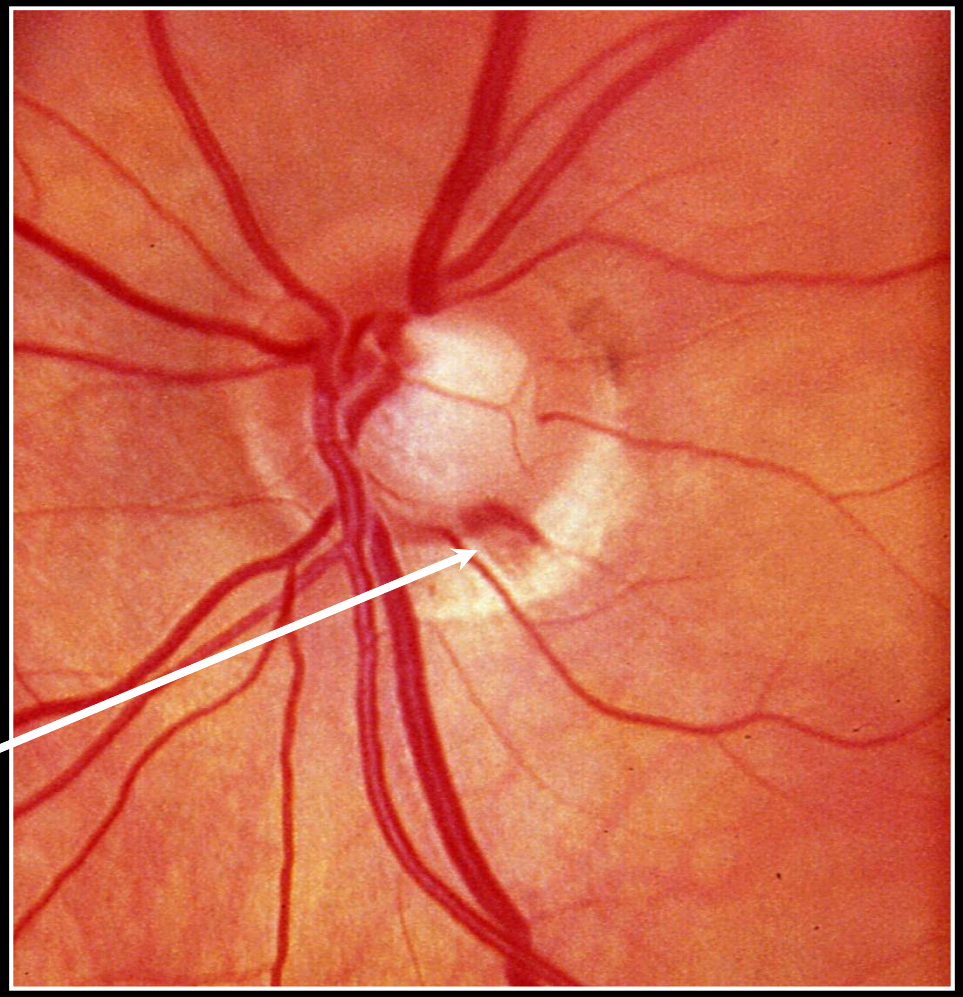
Examine the Region of parapapillary atrophy



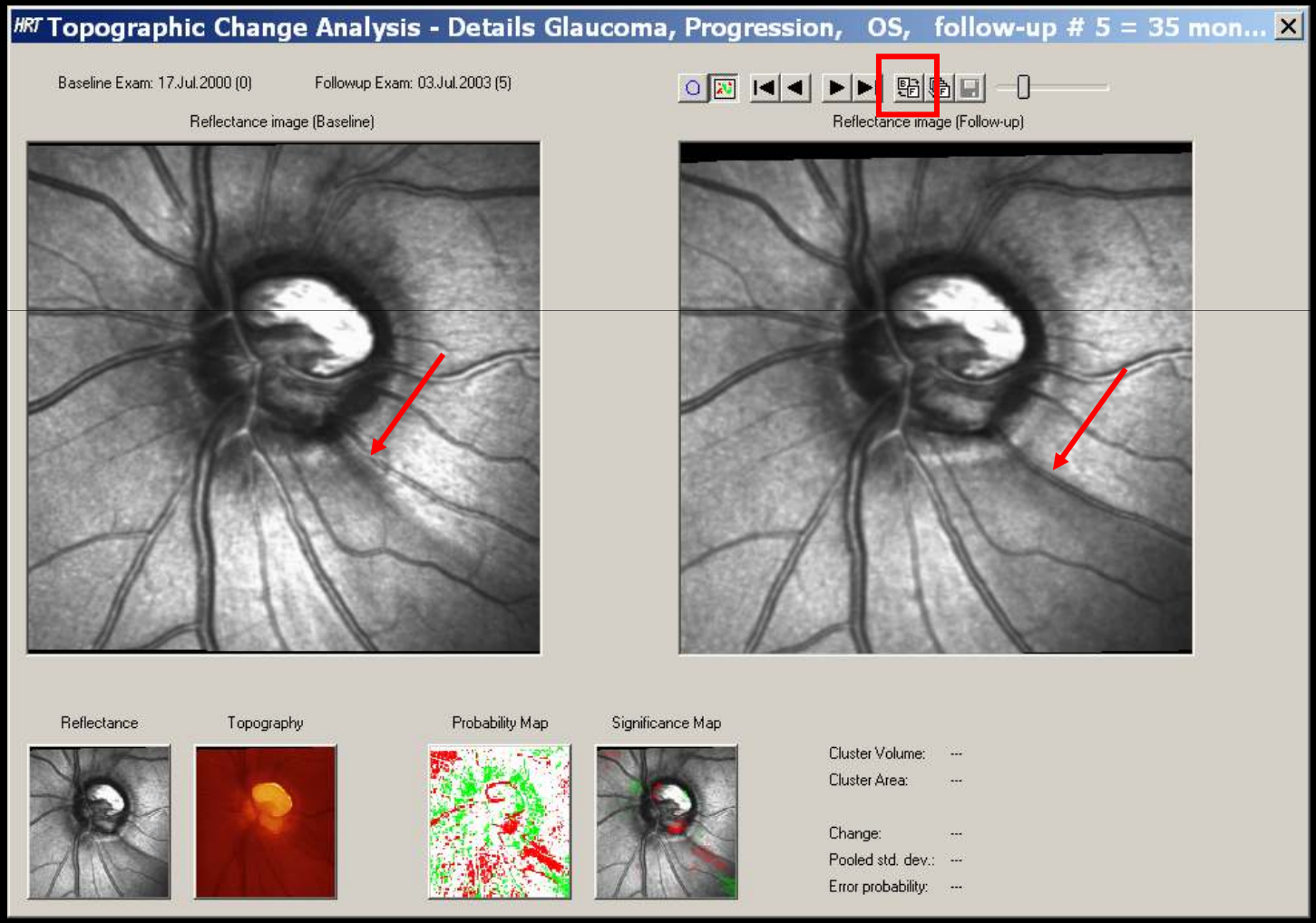
FORGE & Jonas

FORGE: Look for
Retinal and optic disc hemorrhages

Jonas: Look for
presence and location of splinter-shaped hemorrhages

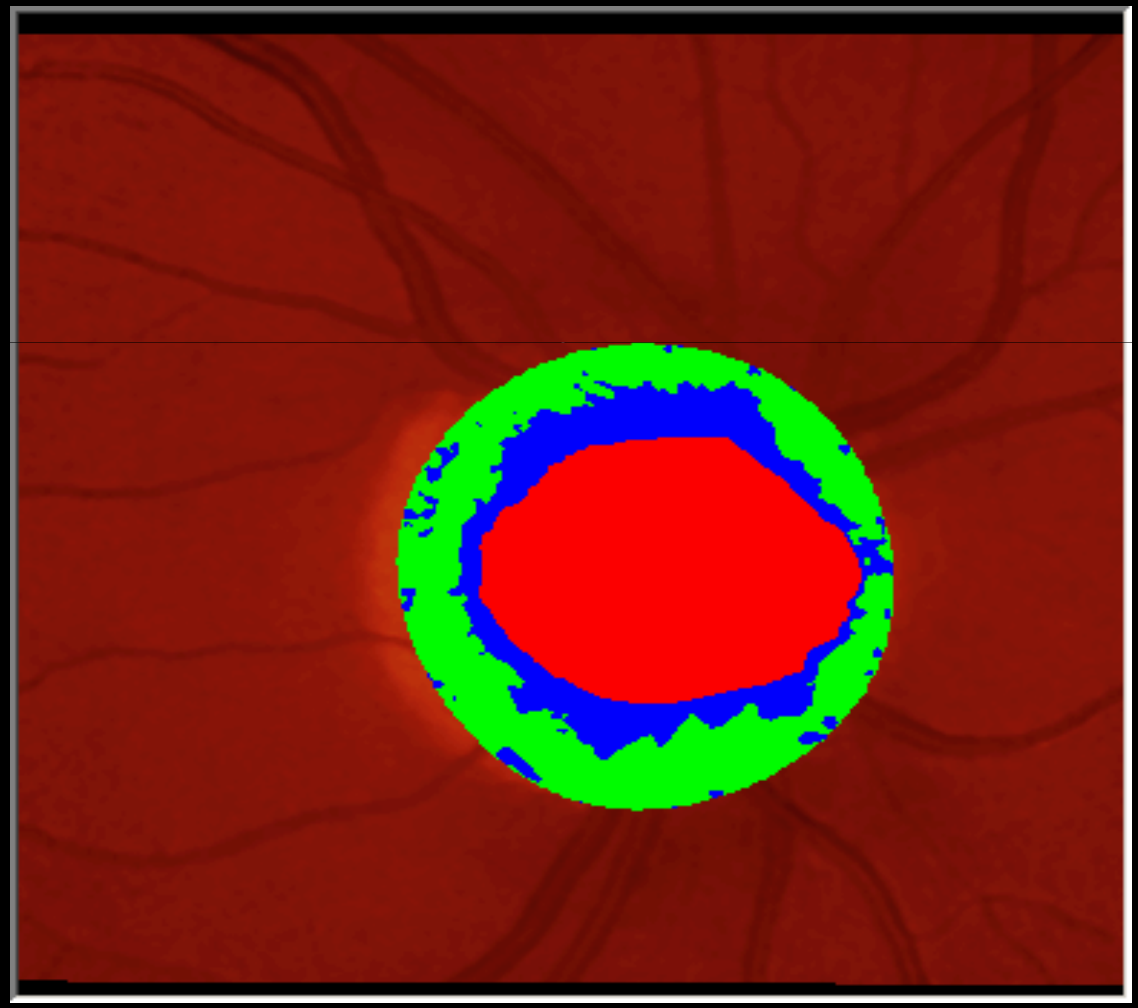


Flicker-Test can show hemorraghes



Configuration of the optic cup

Vertical pronunciation is a risk factor



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Cup Shape Measure

- The Cup Shape Measure (CSM) is a unique and powerful indicator that the walls of the cup are changing as a result of early glaucomatous damage.
- Discriminates normal from early glaucoma with high diagnostic precision.

Uchida et al., IOVS 1996;37:2393

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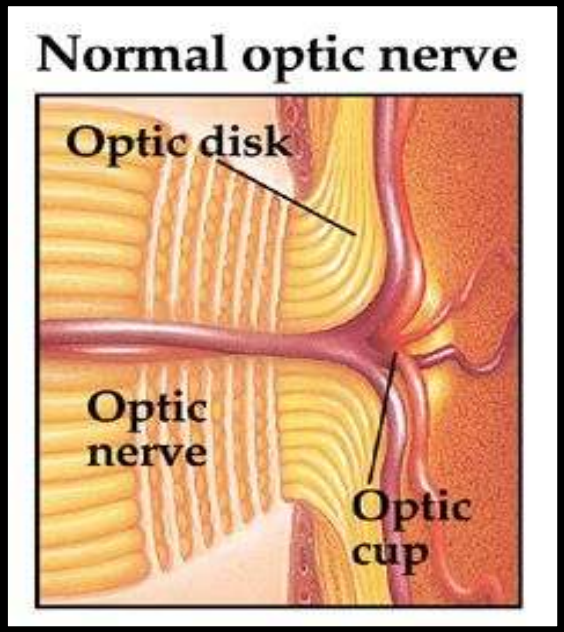
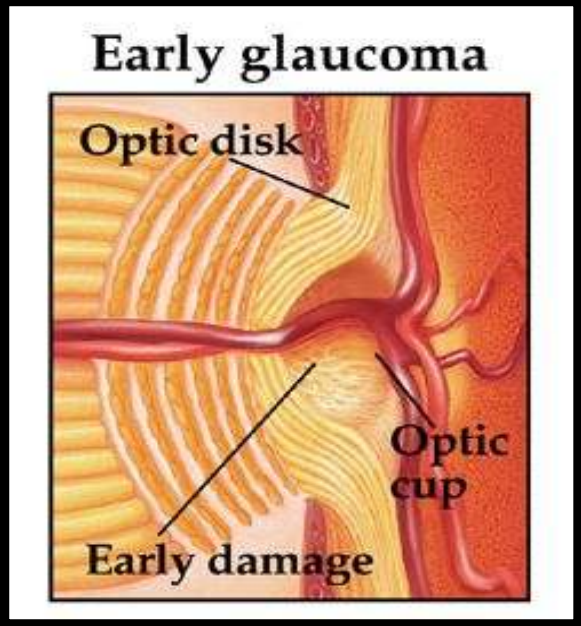
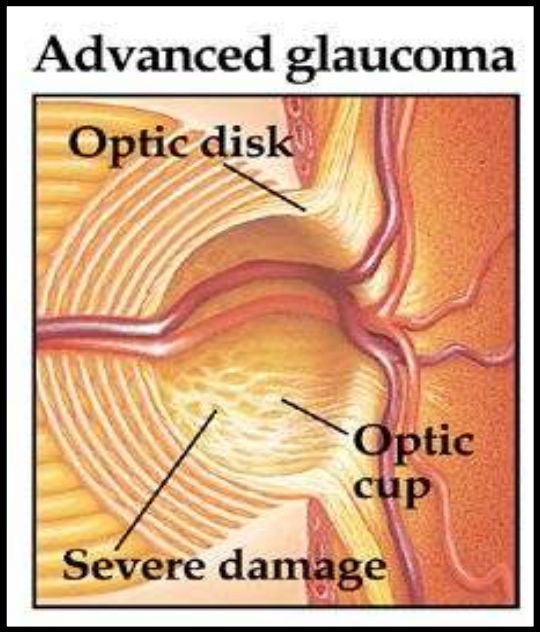
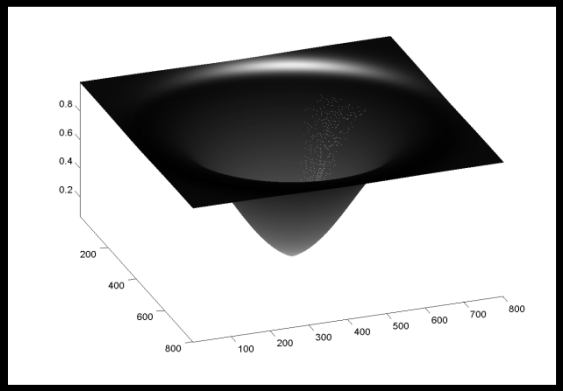
Cup Shape Measure

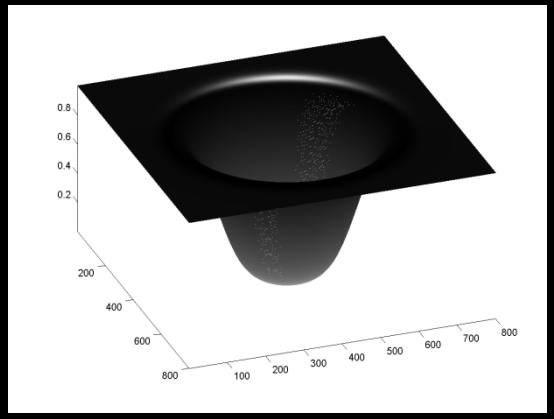




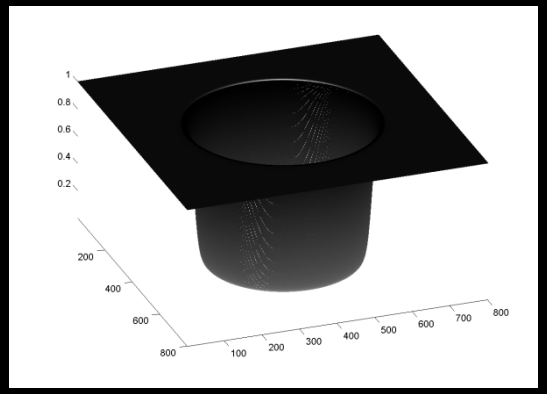




-0.180



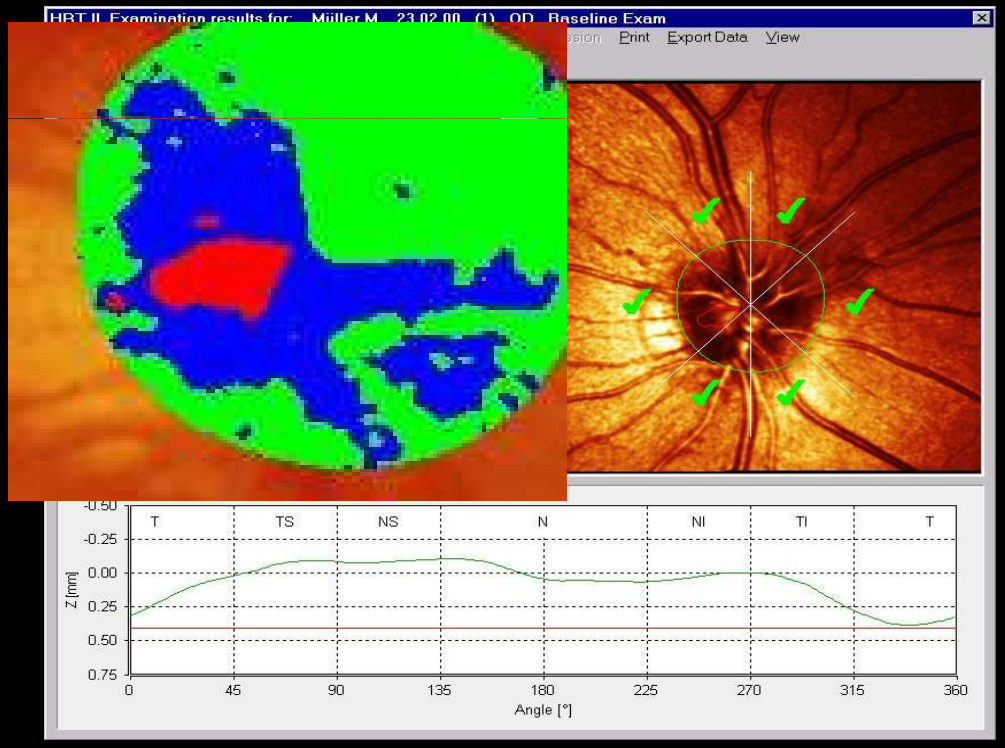
-0.120



-0.060

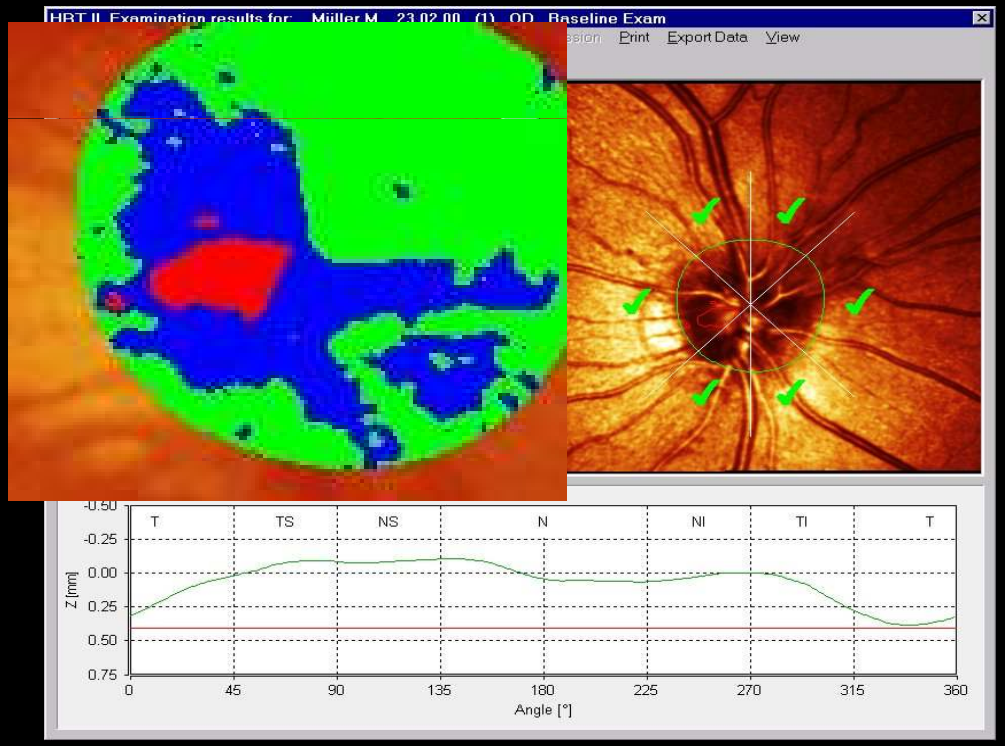
Depth of the optic cup

- Maximum depth of optic disc cupping (red area)



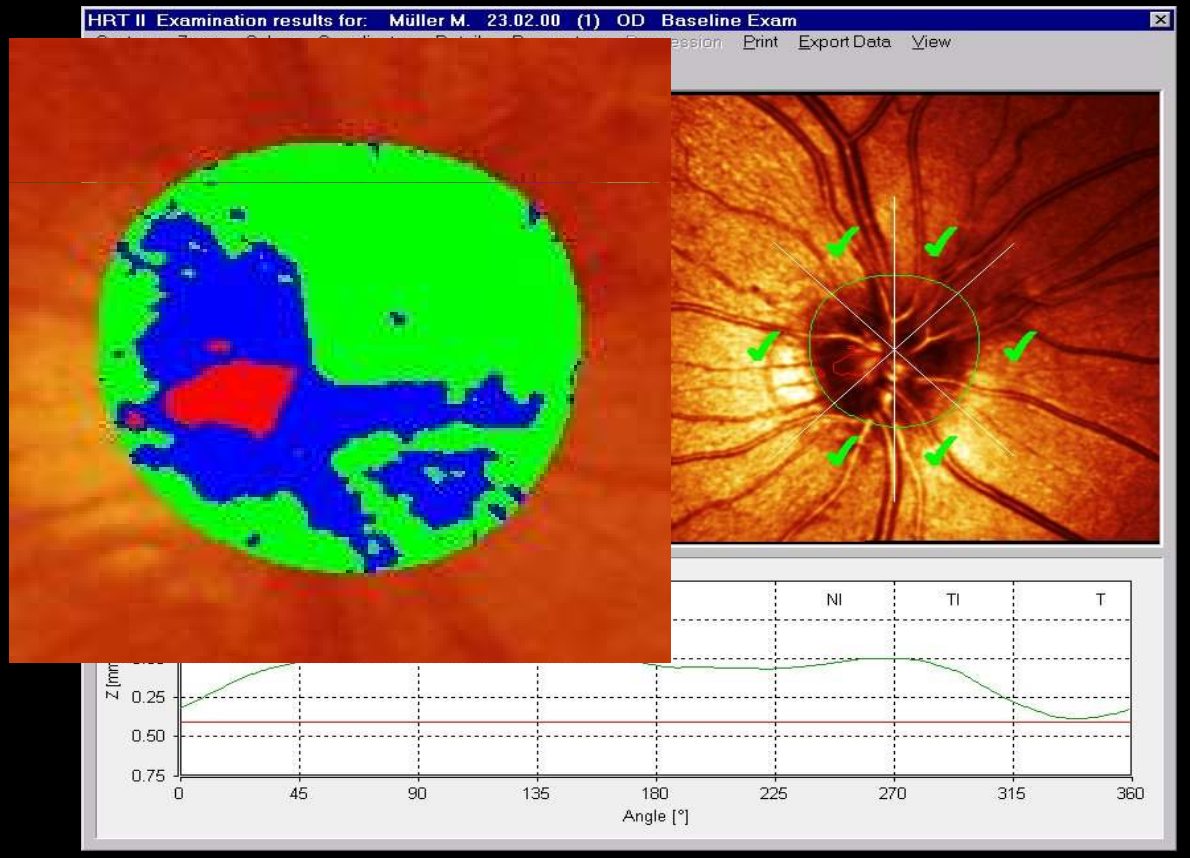
Depth of the optic cup

- Mean depth of optic disc cupping (red and blue area)

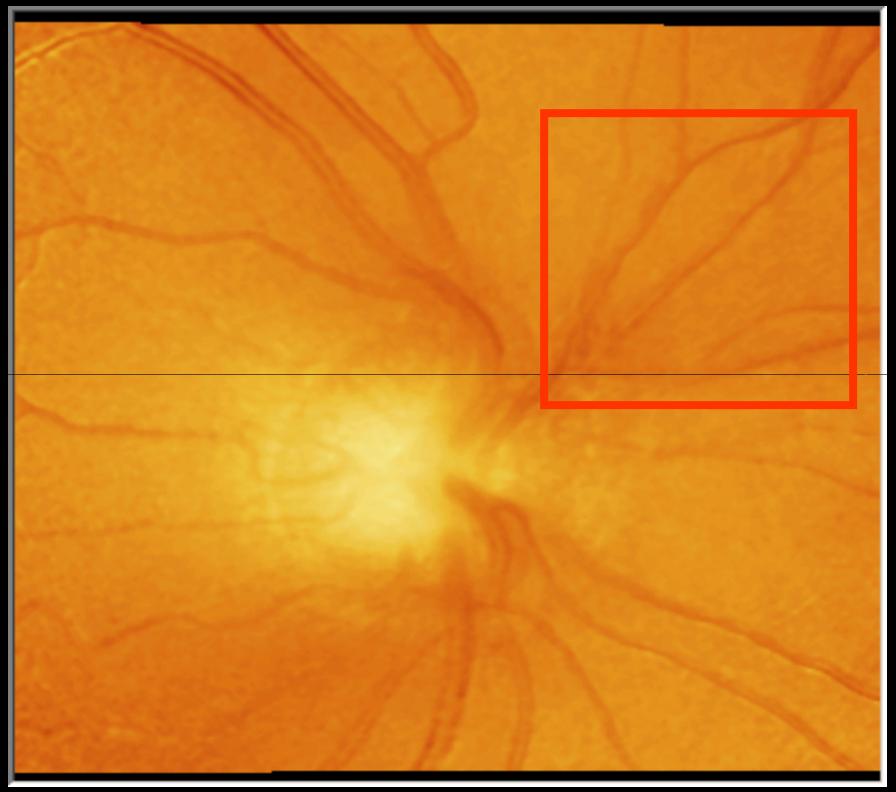


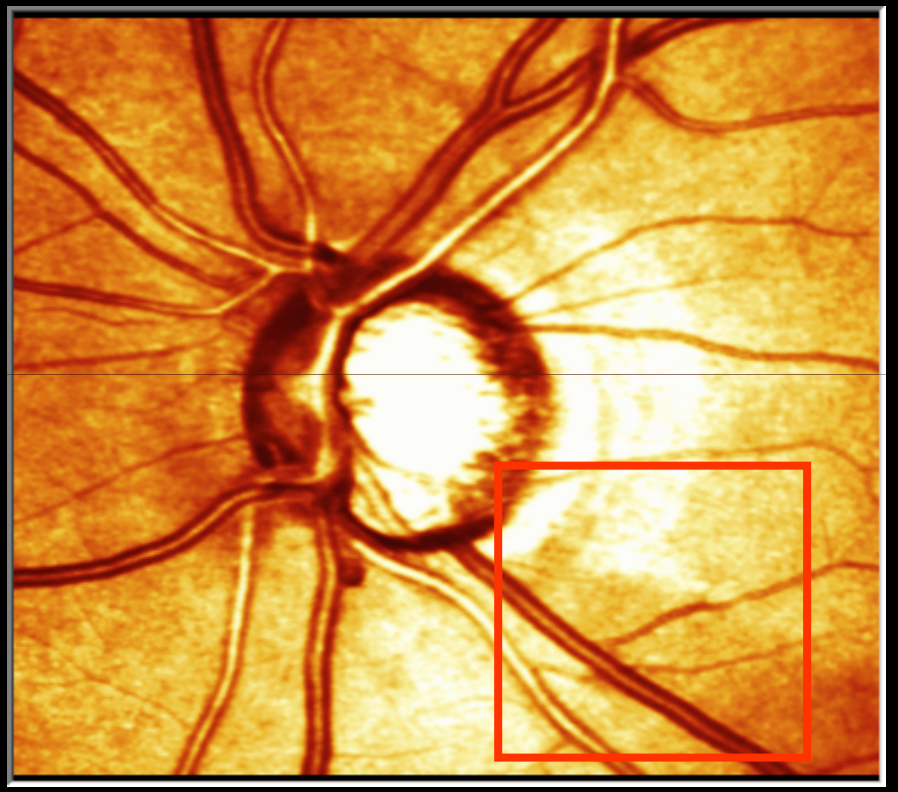
Cup/Disc Area Ratio

- Ratio between area of disc cupping and area of optic disc



Vessels: Embedding, Trunk, Diameter





Reflectance image reveals
focal NFL defect

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Detection of Glaucomatous Damage

Multivariate Discriminant Analysis (selection)

source	N norm/ glaucoma	VF mean deviation	HRT parameters	sensitivity	specificity
FSM → Iester et al., Ophthalmology 1997;104:545-548 (FSM)	60/93	-8.3 dB average	HVC, CSM, RV	64.7% - 83.3%	83.3% - 88.9%
Uchida et al., Nippon Ganka Gakkai Zasshi 1998;102:333-339	-/30	-3.7 dB average	HVC, CSM, RV	80%	83%
Bathija et al., J Glaucoma 1998;7:121-127	49/50	> -10 dB	HVC, RNFLT, CSM, RA	71.4% - 94.4%	81.8% - 92.6%
RB → Reinhard O. W. Burk, Perimetry Update 1998/1999; 463-474	78/58	<-5dB	CSM, CLM Independent from reference plane!	74.1%	85.9%
Gundersen et al., Acta Ophthalmol Scand 2000;78:137-141	153/75	-8.2 dB average	RDAR, RV, RNFLCA	70.7%	95.4%
Iester et al., Br J Ophthalmol 2000;84:464-468	194/161	-7.5 dB average	HVC, RNFLT, CSM, RA	84.2% - 90.9%	60.0% - 97.0%
Zangwill et al., Arch Ophthalmol 2001;119:985-993	50/41	-5.1 dB average	MHC - ni	81%	86%
Mardin et al., Br J Ophthalmol 1999;83:299-304	50/102	pre-perimetric	RA, RV, CV, CA, RNFLT, CSM	42.2%	95.0%
Bowd et al., IOVS 2002; 43:3444-3454	189/108	-6.1dB	(multiple)	88%	90%

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Multivariate Discriminant Analysis

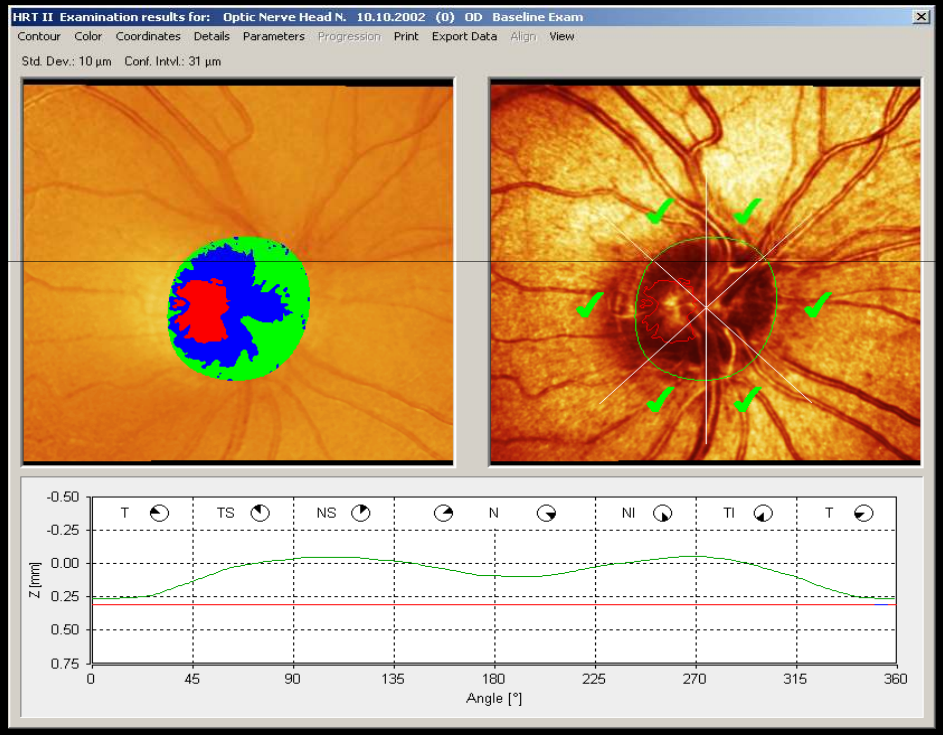
Predefined Segments: HRT II G. 4/13/99 (-1) OD Baseline Exam tilted/relative

Parameters	global	temporal	tmp/sup	tmp/inf	nasal	nsl/sup	nsl/inf
disc area [mm²]	3.381	0.849	0.413	0.432	0.844	0.432	0.412
cup area [mm²]	2.100	0.653	0.293	0.235	0.508	0.310	0.101
rim area [mm²]	1.282	0.195	0.120	0.197	0.337	0.122	0.311
cup/disc area ratio [ ]	0.621	0.770	0.710	0.544	0.601	0.717	0.246
rim/disc area ratio [ ]	0.379	0.230	0.290	0.456	0.399	0.283	0.754
cup volume [mm³]	0.778	0.202	0.123	0.080	0.196	0.145	0.032
rim volume [mm³]	0.194	0.016	0.017	0.031	0.043	0.019	0.069
mean cup depth [mm]	0.394	0.368	0.484	0.352	0.394	0.536	0.248
maximum cup depth [mm]	0.796	0.740	0.761	0.791	0.806	0.847	0.750
height variation contour [mm]	0.371	0.092	0.092	0.232	0.263	0.021	0.077
cup shape measure [ ]	-0.018	-0.001	0.170	-0.093	-0.031	0.103	-0.146
mean RNFL thickness [mm]	0.182	0.072	0.207	0.232	0.142	0.210	0.384
RNFL cross sectional area [mm²]	1.188	0.118	0.167	0.188	0.230	0.175	0.313
linear cup/disc ratio [ ]	0.788	-	-	-	-	-	-
maximum contour elevation [mm]	0.078	-	-	-	-	-	-
maximum contour depression [mm]	0.449	-	-	-	-	-	-
CLM temporal-superior [mm]	0.135	-	-	-	-	-	-
CLM temporal-inferior [mm]	0.159	-	-	-	-	-	-
average variability (SD) [mm]	0.025	-	-	-	-	-	-
				-	-	-	-
RB discriminant function value [ ]		-2.048		-	-	-	-
				-	-	-	-

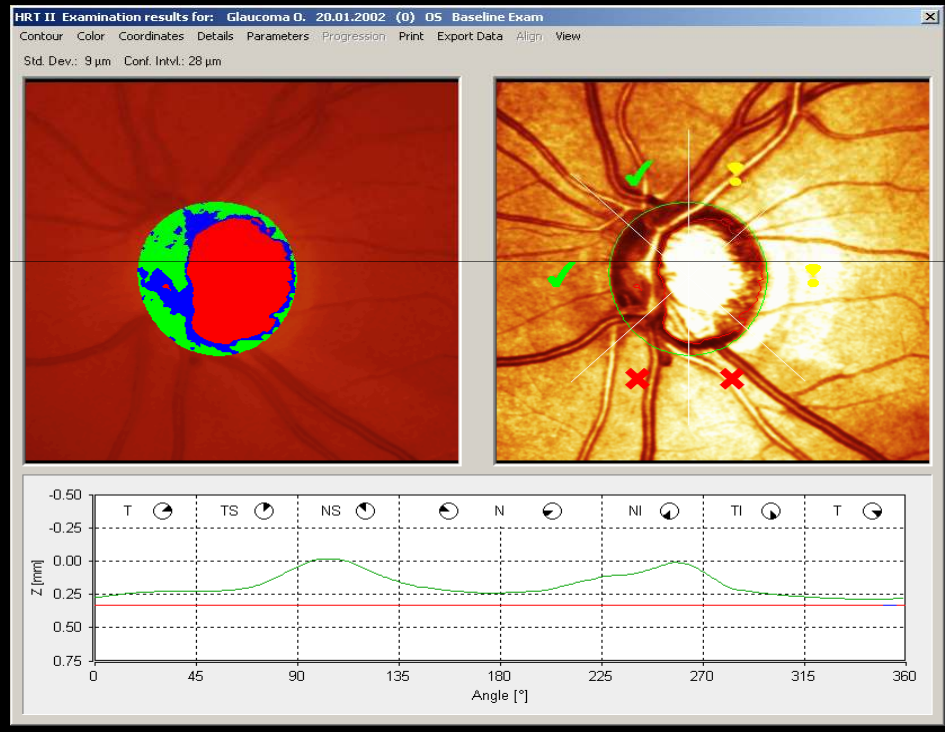
Detection of Glaucomatous Damage

Moorfields Regression Analysis

Wollstein et al., Ophthalmology 1998;105:1557-1563

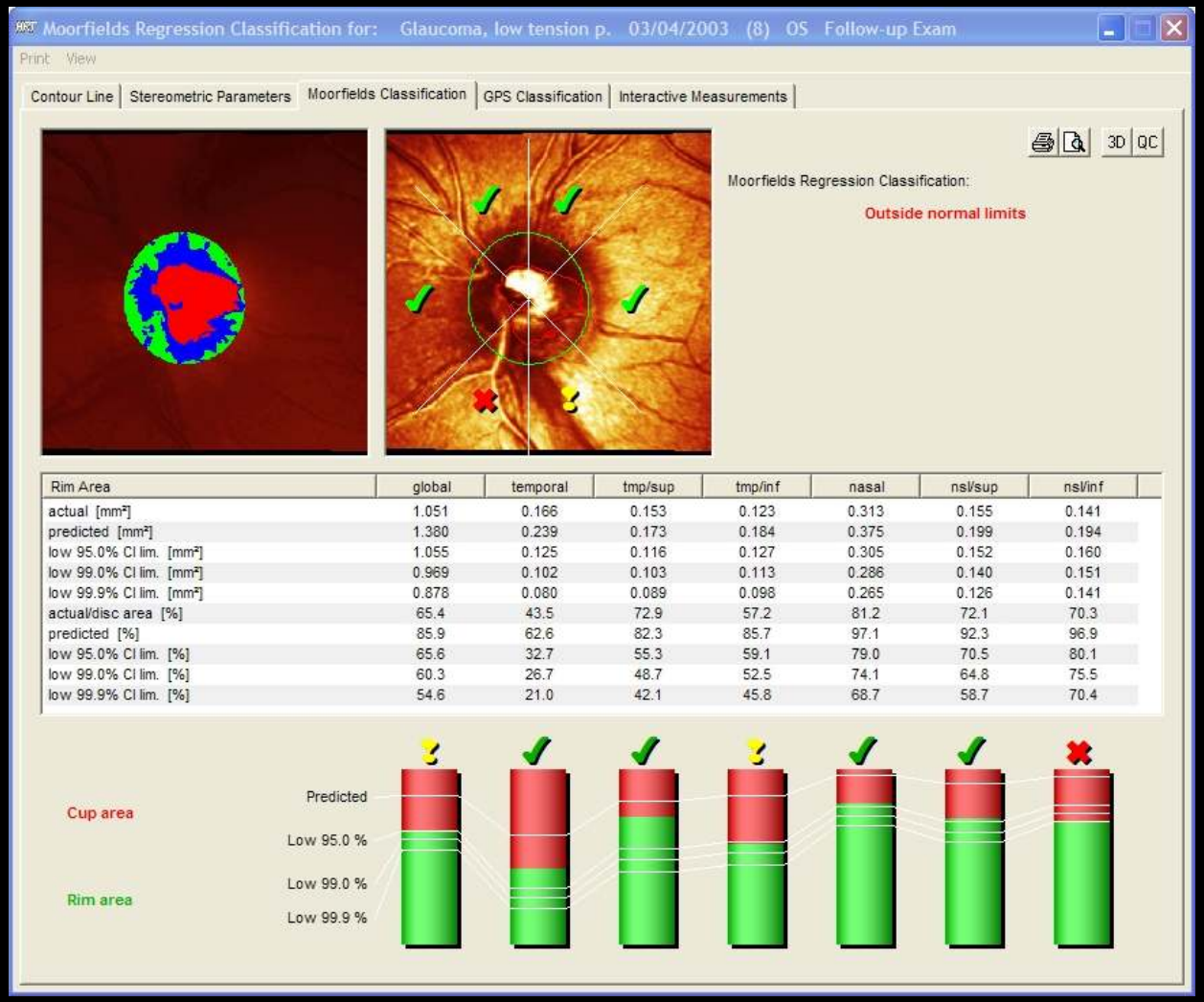


normal

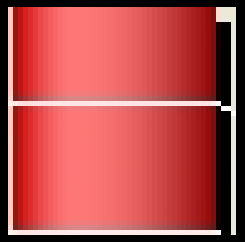


outside normal limits

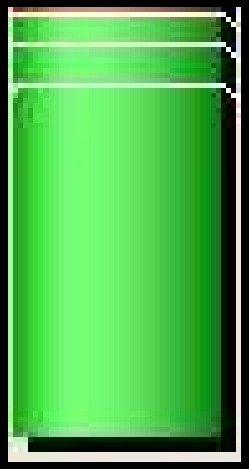
Moorfields Regression Analysis



Rim Area	global	temporal	tmp/sup	tmp/inf	nasal	nsl/sup	nsl/inf
actual [mm²]	1.051	0.166	0.153	0.123	0.313	0.155	0.141
predicted [mm²]	1.380	0.239	0.173	0.184	0.375	0.199	0.194
low 95.0% CI lim. [mm²]	1.055	0.125	0.116	0.127	0.305	0.152	0.160
low 99.0% CI lim. [mm²]	0.969	0.102	0.103	0.113	0.286	0.140	0.151
low 99.9% CI lim. [mm²]	0.878	0.080	0.089	0.098	0.265	0.126	0.141
actual/disc area [%]	65.4	43.5	72.9	57.2	81.2	72.1	70.3
predicted [%]	85.9	62.6	82.3	85.7	97.1	92.3	96.9
low 95.0% CI lim. [%]	65.6	32.7	55.3	59.1	79.0	70.5	80.1
low 99.0% CI lim. [%]	60.3	26.7	48.7	52.5	74.1	64.8	75.5
low 99.9% CI lim. [%]	54.6	21.0	42.1	45.8	68.7	58.7	70.4



CUP



RIM

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OHTS ancillary study: Hazard Ratios

Table 3. Univariate and Multivariate Hazard Ratios and 95% Confidence Intervals (CIs) for the Development of POAG (Average of the Eyes)

	Hazard Ratio (95% CI)	
	Univariate	Multivariate*
CSLO measures		
Disc area (per 0.4 mm² greater)	0.84 (0.58-1.20)	0.86 (0.57-1.30)
Cup area (per 0.3 mm² greater)	1.22 (0.96-1.55)	1.21 (0.96-1.53)
Cup area-to-disc area (per 0.1 greater)	1.23 (1.00-1.50)	1.25 (1.02-1.53)
Mean cup depth (per 0.1 mm greater)	1.58 (1.14-2.20)	1.60 (1.15-2.22)
RNFL thickness (per 0.1 mm greater)	0.60 (0.34-1.06)	0.66 (0.35-1.23)
Standard deviation of mean image (per 6 µm greater)	1.15 (0.92-1.43)	1.04 (0.80-1.37)
Cup shape (per 0.1 greater)	1.24 (0.78-1.97)	1.02 (0.62-1.67)
Cup volume below surface (per 0.1 mm³ greater)	1.11 (0.96-1.28)	1.10 (0.97-1.25)
Rim area (per 0.2 greater)	0.58 (0.43-0.79)	0.57 (0.42-0.78)
Rim area/disc area (per 0.1 greater)	0.75 (0.60-0.94)	0.76 (0.62-0.93)
Reference height (per 0.1 mm greater)	1.42 (1.04-1.93)	1.49 (1.03-2.17)
Corneal curvature (per 0.2 mm greater)	1.16 (0.90-1.49)	1.03 (0.79-1.36)
RNFL cross-section (per 0.3 mm² greater)	0.68 (0.49-0.95)	0.72 (0.48-1.06)
Mean height contour (per 0.1 mm greater)	2.59 (1.69-3.98)	2.69 (1.62-4.49)
Rim volume above reference (per 0.1 mm³ greater)	0.63 (0.45-0.87)	0.65 (0.47-0.91)
Cup volume below reference (per 0.1 mm³ greater)	1.24 (1.02-1.52)	1.20 (1.01-1.43)
HRT classification 1 (per 1 unit greater)	0.72 (0.59-0.89)	0.75 (0.62-0.92)

Table 3. Univariate and Multivariate Hazard Ratios and 95% Confidence Intervals (CIs) for the Development of POAG (Average of the Eyes) (cont)

	Hazard Ratio (95% CI)	
	Univariate	Multivariate*
CSLO indexes		
HRT classification, outside normal limits vs within normal limits	2.47 (1.31-4.65)	2.54 (1.31-4.90)
MRA (outside normal limits vs within normal limits)		
Overall	2.72 (1.19-6.21)	2.39 (1.02-5.62)
Global	5.64 (1.94-16.44)	3.37 (1.13-9.99)
Nasal	1.99 (0.74-5.37)	1.59 (0.48-5.24)
Nasal inferior	4.44 (1.77-11.12)	4.19 (1.61-10.91)
Nasal superior	1.97 (0.43-8.96)	0.72 (0.11-4.63)
Temporal	3.28 (0.82-13.18)	2.48 (0.66-9.22)
Temporal inferior	5.02 (1.53-16.51)	5.80 (1.60-21.00)
Temporal superior	8.88 (2.58-30.56)	3.28 (0.98-10.98)
OHTS predictive factors		
Age (per decade)	1.27 (0.92-1.76)	NA
History of heart disease	4.25 (1.63-11.08)	NA
IOP (per mm Hg)	1.11 (0.99-1.23)	NA
CCT (per 40 µm thinner)	2.14 (1.44-3.18)	NA
PSD (per 0.2 dB greater)	1.15 (0.93-1.43)	NA
Horizontal cup-disc ratio (per 0.1 larger)	1.27 (1.09-1.49)	NA
Vertical cup-disc ratio (per 0.1 larger)	1.40 (1.16-1.68)	NA

Abbreviations: CCT, central corneal thickness; CSLO, confocal scanning laser ophthalmoscopy; HRT, Heidelberg Retina Tomograph; IOP, intraocular pressure; MRA, Moorfields Regression Analysis; NA, not applicable; OHTS, Ocular Hypertension Treatment Study; POAG, primary open-angle glaucoma; PSD, pattern standard deviation; RNFL, retinal nerve fiber layer.

*Multivariate model contains baseline age, IOP, PSD, CCT, and history of heart disease, with medication status as a time-dependent covariate. One hundred twelve eyes were excluded from the multivariate analyses because of missing CCT values.

Temporal MRA classifications have highest predictive value!

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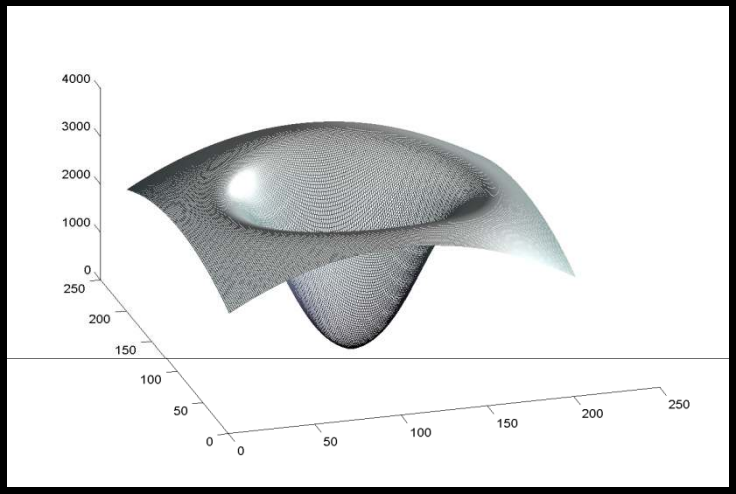
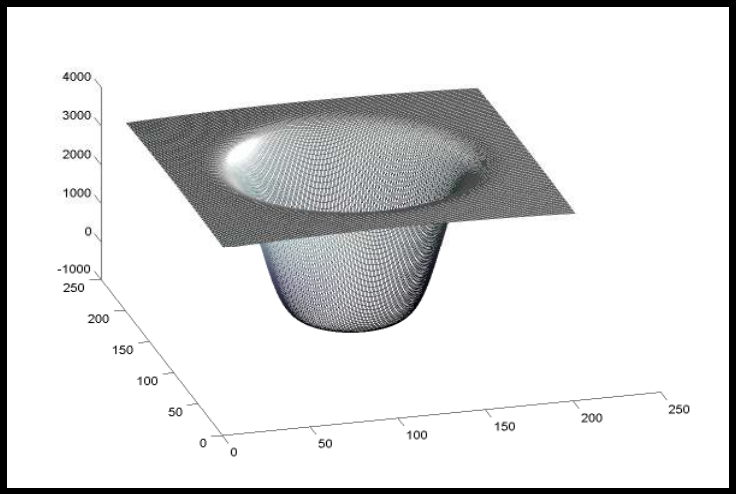
Mathematical Model

- Normal ONH



- Glaucomatous ONH



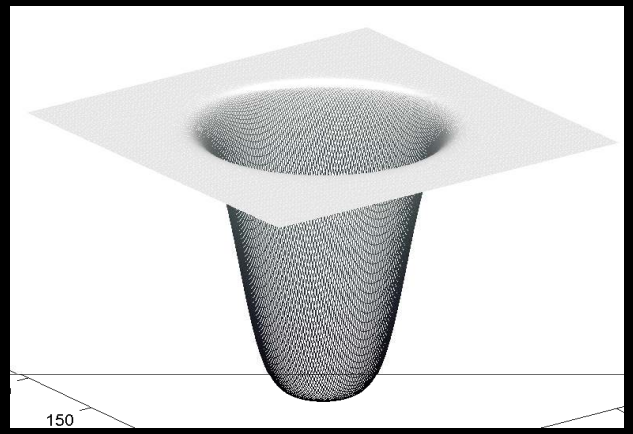
Classifications Parameter

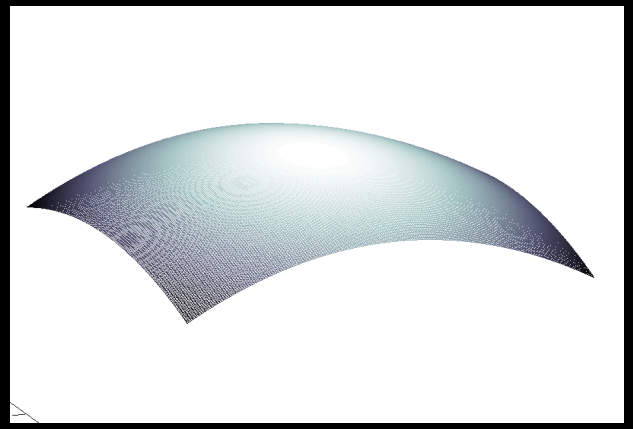
ONH:

- Slope
- Depth
- Width

Peripapillary surface:

- Horizontal and vertical curvature





topographisches Modell

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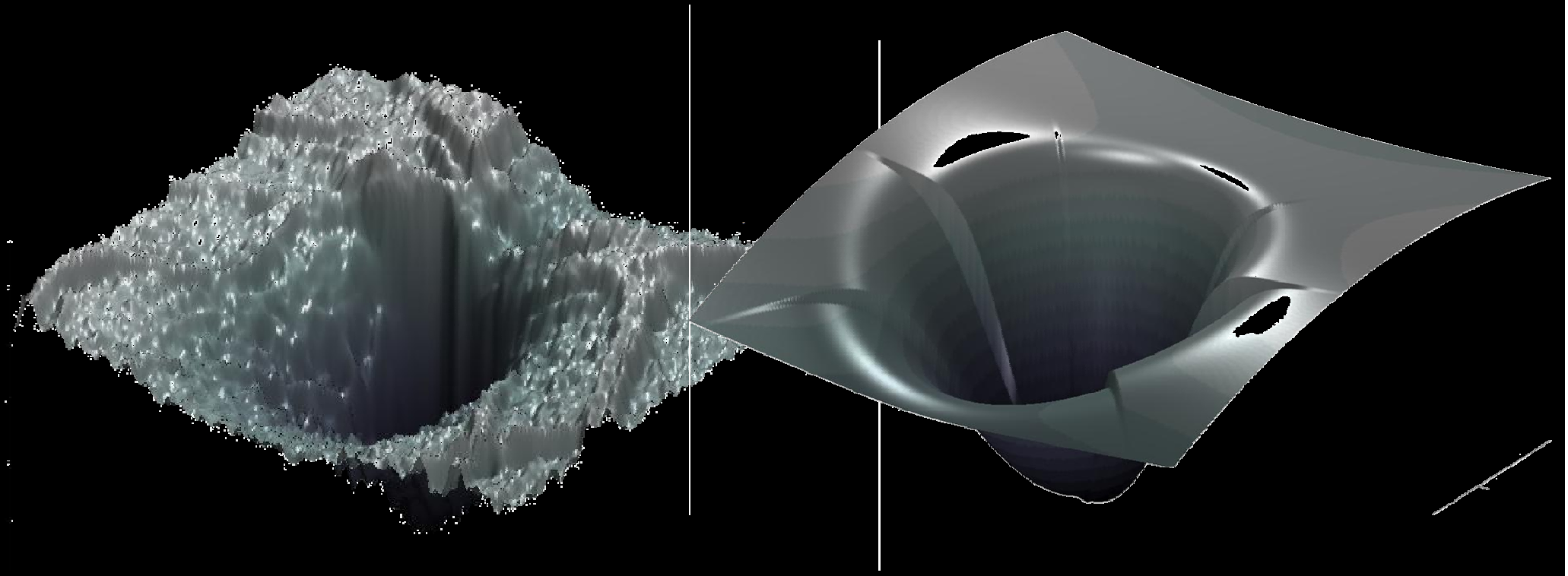
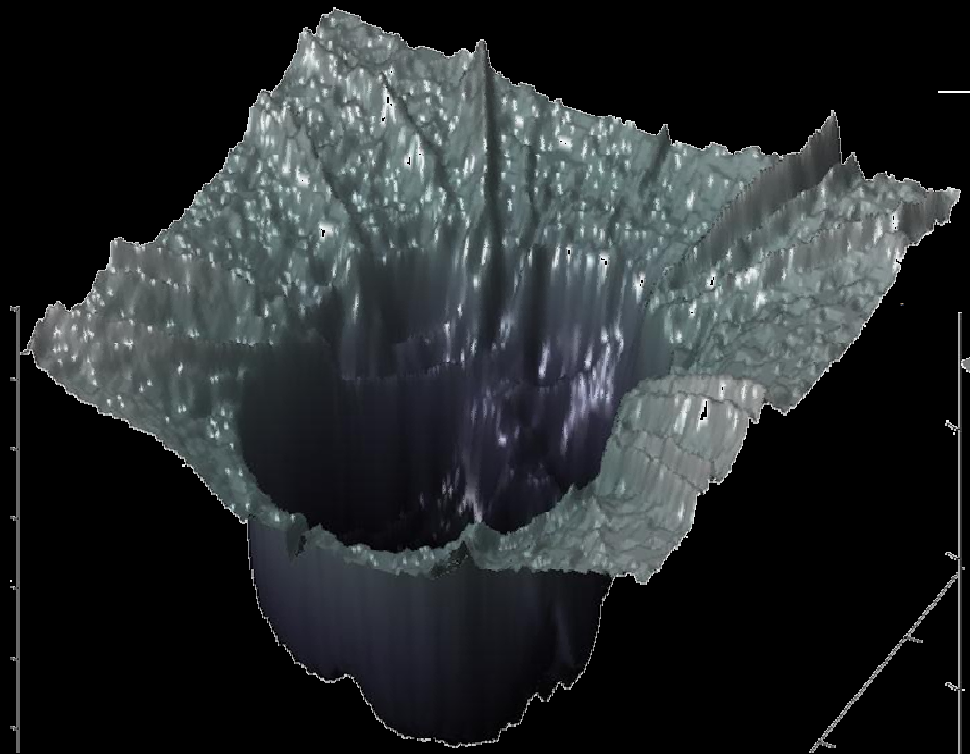
Model – normal



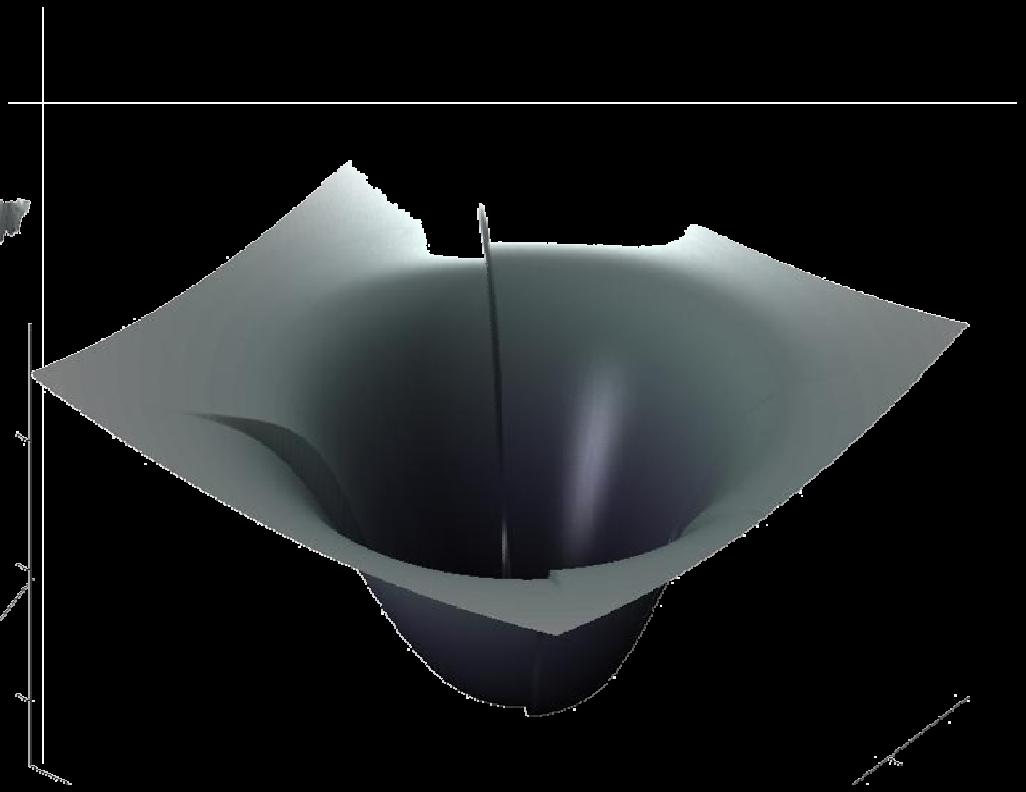
HRT

Model

Model - glaucomatous



HRT



Model

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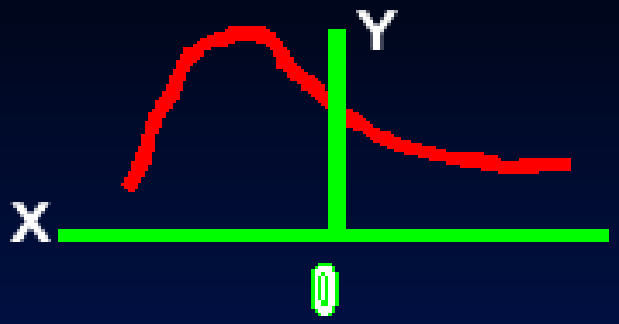
Cup shape measure

- **Frequency distribution**



- **Normal ONH**

- **Abnormal ONH**

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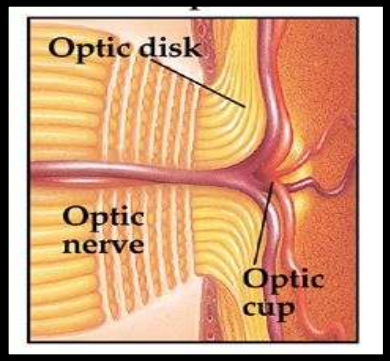
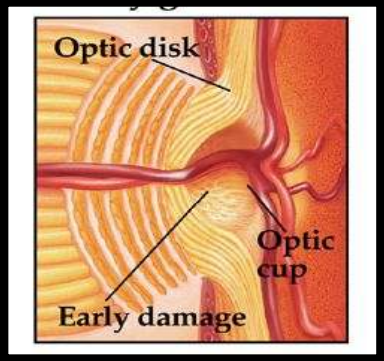
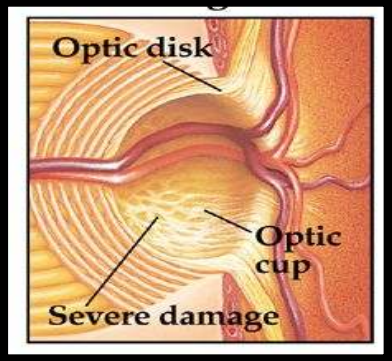
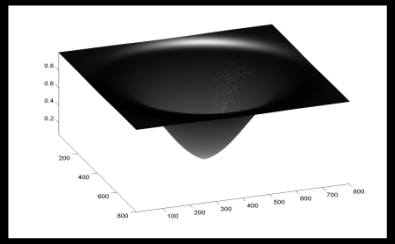
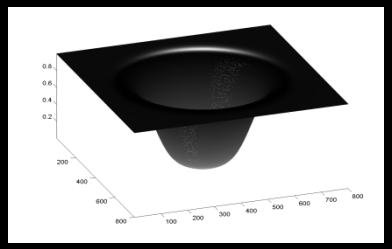
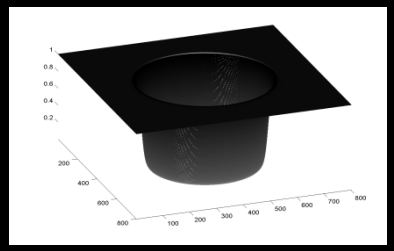
The Cup Shape changes from a negative slope towards a more positive slope with increasing glaucoma.

NORMAL	Early	Advanced
		
		
-0.180	-0.120	-0.060

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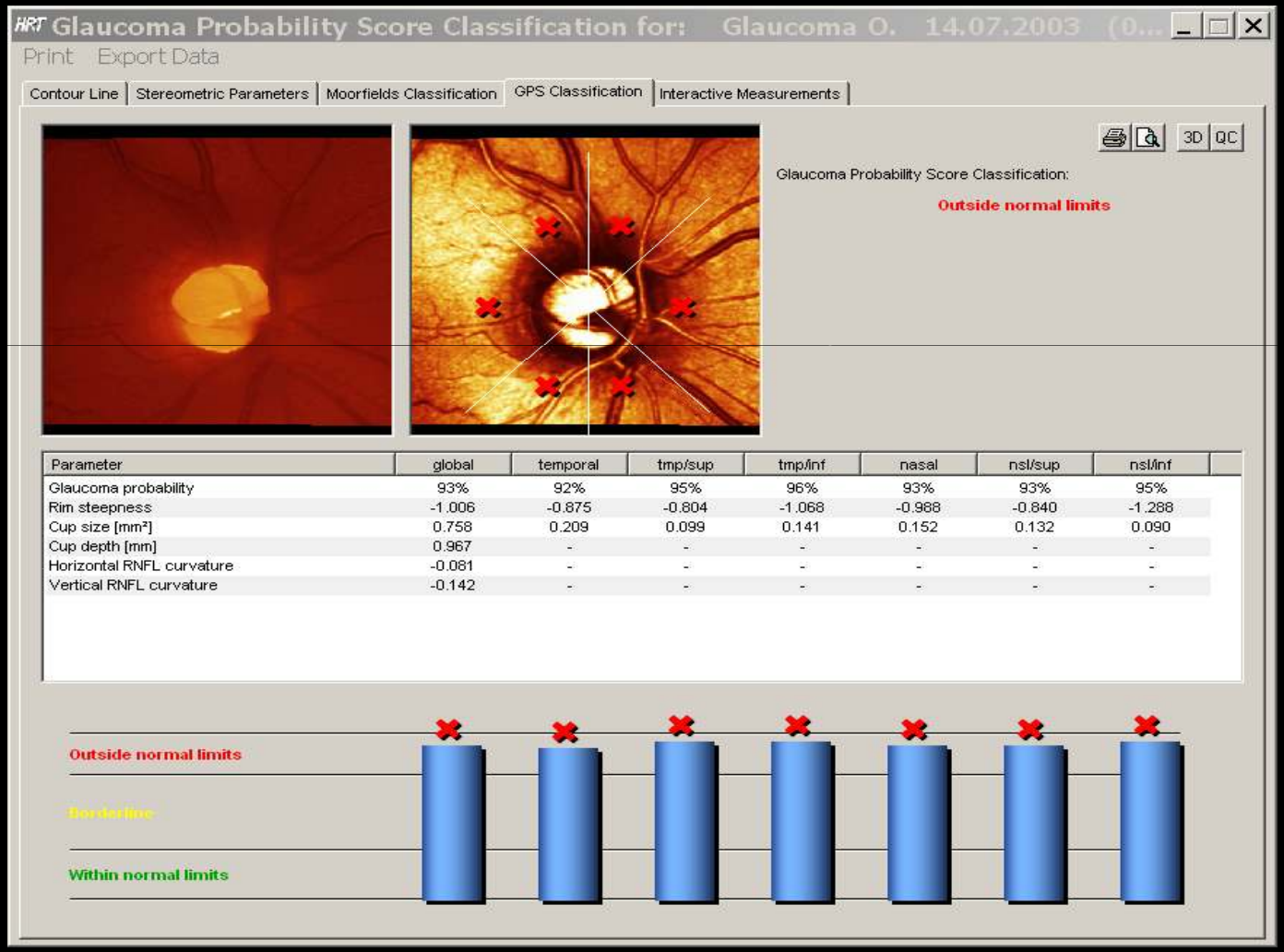
GPS



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Normative Databases

	now	disc size	*new*	disc size	*CUP*	*RIM*	*RFNL*
▪ 12 Stereometric Parameters [1]	743 eyes	1.1 - 4.2	743 eyes	1.1 - 4.2	✓	✓	✓
▪ FSM Discriminant Function [3]	153 eyes	2.2 - 2.5	153 eyes	2.2 - 2.5	✓	✓	✓
▪ RB Discriminant Function [4]	136 eyes	1.2 - 2.9	136 eyes	1.2 - 2.9	✓		✓
▪ Moorfields Regression Analysis [2]						✓	
Glaucoma Probability Score (GPS) [5]					✓+	✓+	✓+
Stereometric Parameters					✓	✓	✓
▪ Caucasian Controls*	112 eyes	1.2 - 2.8	733 eyes	1.0 – 3.6			
▪ African Origin Controls**	-	-	215 eyes	1.4 – 3.4			
▪ Indian Controls (not GPS)*	-	-	104 eyes	0.9 – 4.1			
▪ Glaucoma Probability Score (GPS) [5]					✓+	✓+	✓+
▪ Caucasian Early Glaucoma*	-		146 eyes	1.2 – 3.5			
▪ African Origin Early Glaucoma**	-		49 eyes	1.2 – 3.7			
	1144		**2279**				

*Refractive Error –6 to +6

**Refractive Error –5 to +5

1 - Burk ROW, Zeitschrift für praktische Augenheilkunde, ZPA, Mai 2001

2 - Wollstein et al., Ophthalmology 1998;105:1557-1563 (Moorfields)

3 - lester et al., Ophthalmology 1997;104:545-548 (FSM)

4 - Reinhard O. W. Burk, Perimetry Update 1998/1999; 463-474 (RB)

5 - Nicholas V. Swindale et. al, Investigative Ophthalmology & Visual Science, 6/2000;41-7:1730-1742

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Applying FORGE & Jonas to HRT

HRT Early Diagnosis in 60 seconds:

1. Good reflectivity?
2. Disc size (micro, normal, macro)
3. Configuration of cup (horizontal or vertical)
4. Configuration of rim (ISNT rule fulfilled?)
5. Symmetric double hump configuration of contour line height profile
6. Contour line height profile crosses mean height of retina?
7. Rim Volume: ~ 0,3 mm^3
8. CSM: -0,2 for normal ONHs - -0,1 for macropapillas
9. FMS & RB should be positive – FMS negative/RB positive is a sign for macropapillas
10. Check MRA temporal (less important in macro- or micropapillas)
11. Check GPS global (less important in macro- or micropapillas)

Heidelberg Retina Tomograph
GPS Report

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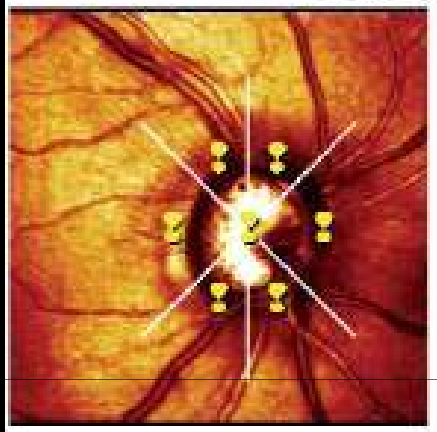
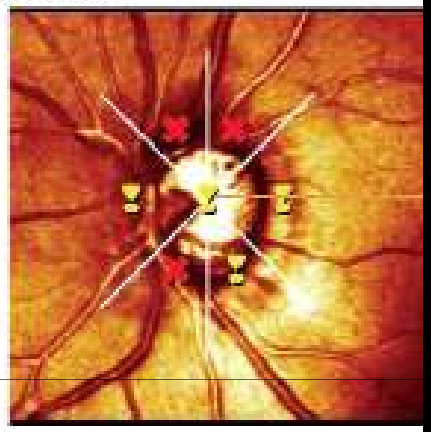
Patient: **DOB:** 1950 **Examination:** Mar/22/2001
Pat-ID: **Gender:** female **Ethnicity:** African origin

Initial Report

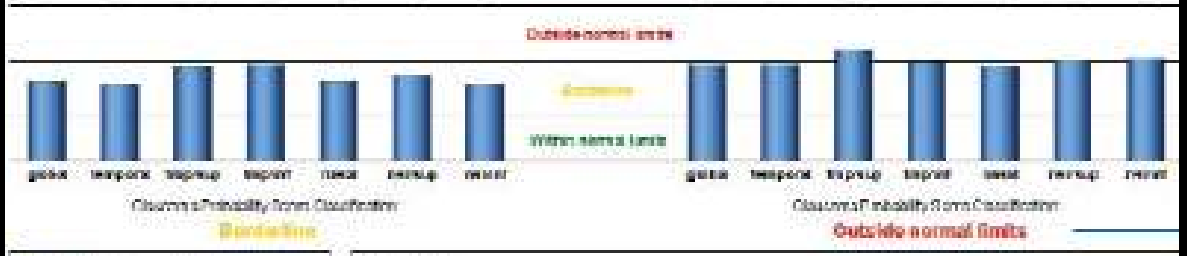
OD	OS
Quality: Very good (SD 14 µm)	**Quality:** Very good (SD 13 µm)
Focus: 2.00 dpt	**Focus:** 2.00 dpt
Operator: —	**Operator:** —

Glaucoma Probability Score (GPS)





global	temporal	temp/sup	nasal/sup	nasal	nas/inf	inf/temp	Parameter	global	temporal	temp/sup	nasal/sup	nasal	nas/sup	nas/inf
0.53	0.41	0.81	0.82	0.65	0.54	0.53	Glaucoma prob.	0.62	0.62	0.17	0.81	0.53	0.65	0.55
0.28	0.28	0.55	0.42	0.20	0.32	0.42	Rim/disc area	0.42	0.40	0.09	0.22	0.42	0.27	0.25
0.77	0.24	0.82	0.43	0.17	0.43	0.85	Cup/disc [mm²]	0.07	0.42	0.08	0.43	0.13	0.43	0.84
0.91	—	—	—	—	—	—	Cup depth [mm]	0.72	—	—	—	—	—	—
0.84	—	—	—	—	—	—	0.9981 corr.	0.91	—	—	—	—	—	—
0.14	—	—	—	—	—	—	0.9981 corr.	0.11	—	—	—	—	—	—



Within normal limits
Borderline
Outside normal limits

Comments:

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Progression in Glaucoma

- Physiologic variability of individual eyes is high.
- Difficult to classify eyes as normal or glaucoma based on a single test.
- Glaucoma is a progressive disease.

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Normative Databases

- RNFL varies in the normal population 600,000 to 1.4 million fibers.
- Great variability between normal optic disc sizes, shapes and appearance makes classification of individual eyes based on one parameter difficult or impossible when looking at one point in time.

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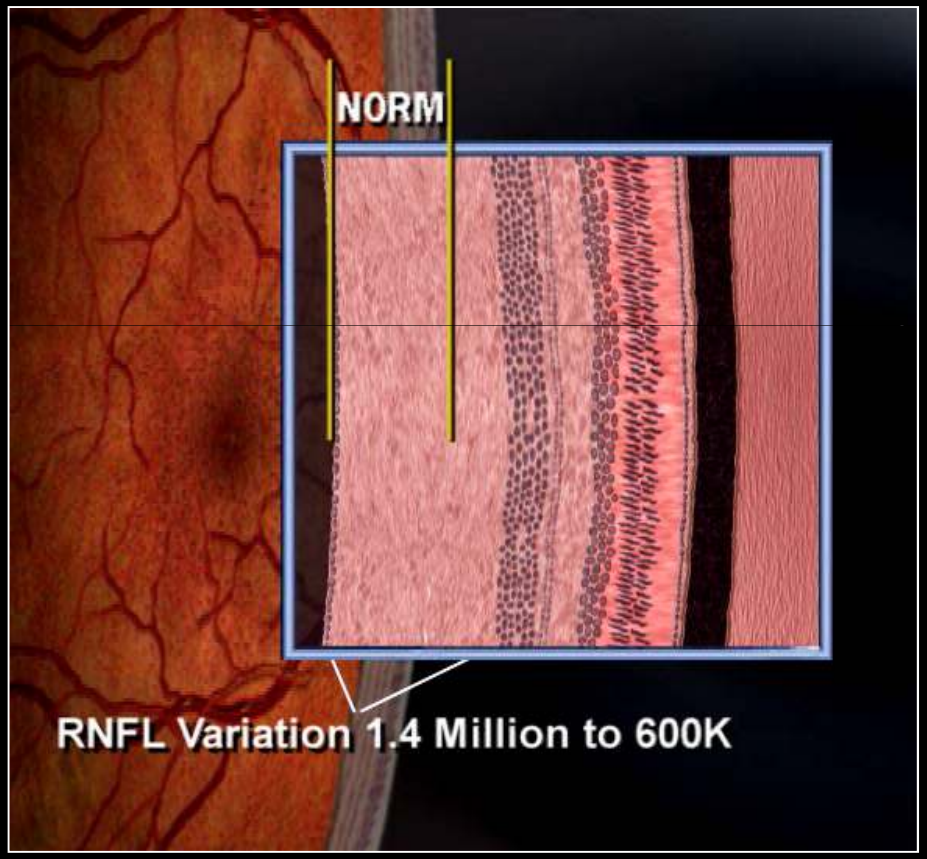
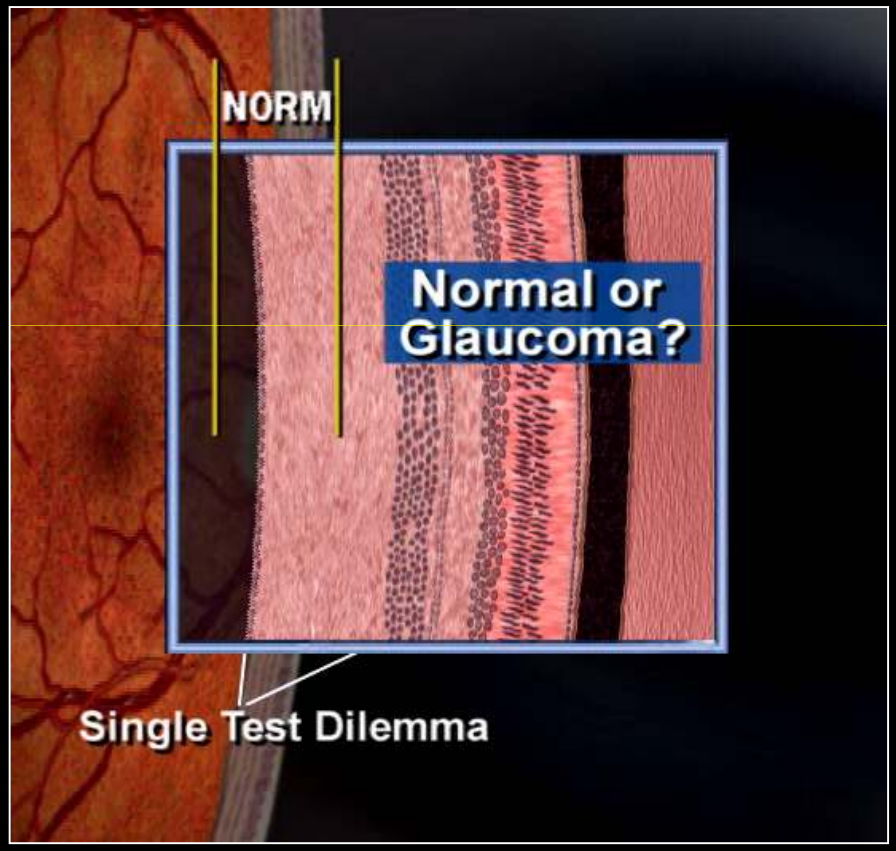
Normative Databases

- Single scans are unreliable.
- Overlap of normal precludes the ability to diagnose.
- Normative Databases are indicators and not specific enough for definitive diagnosis.
- The patient is his own best “normal”.
- Monitoring change over time is therefore the issue in glaucoma.

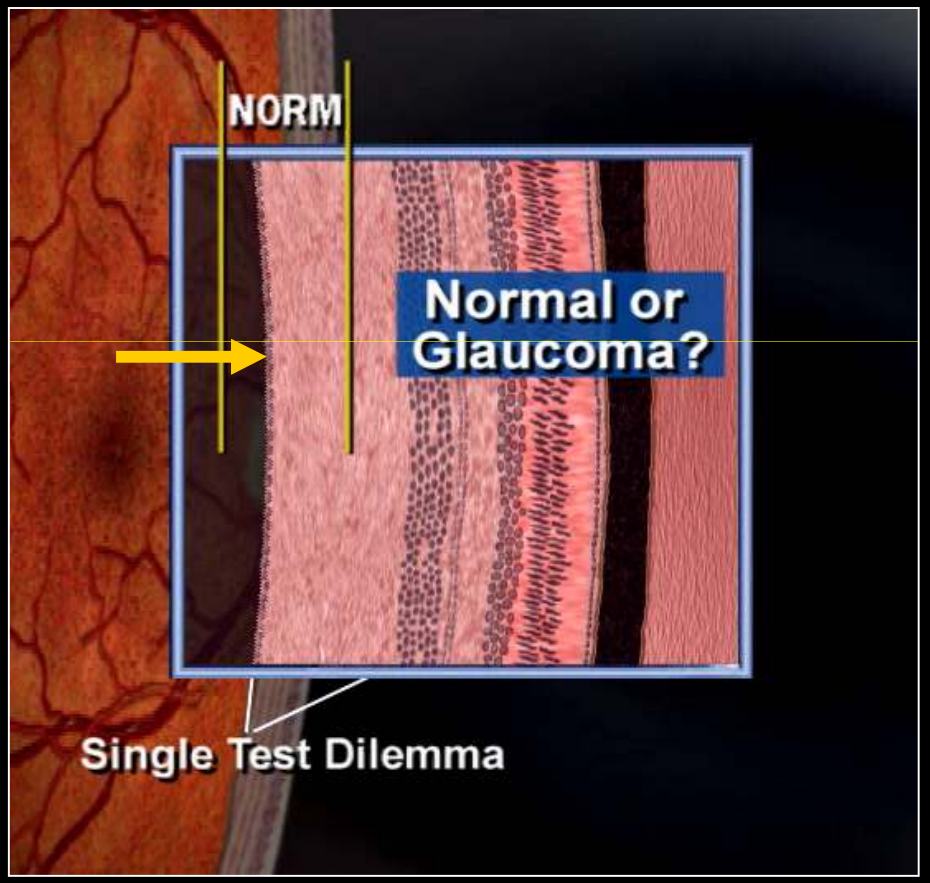
The Single Test Dilema





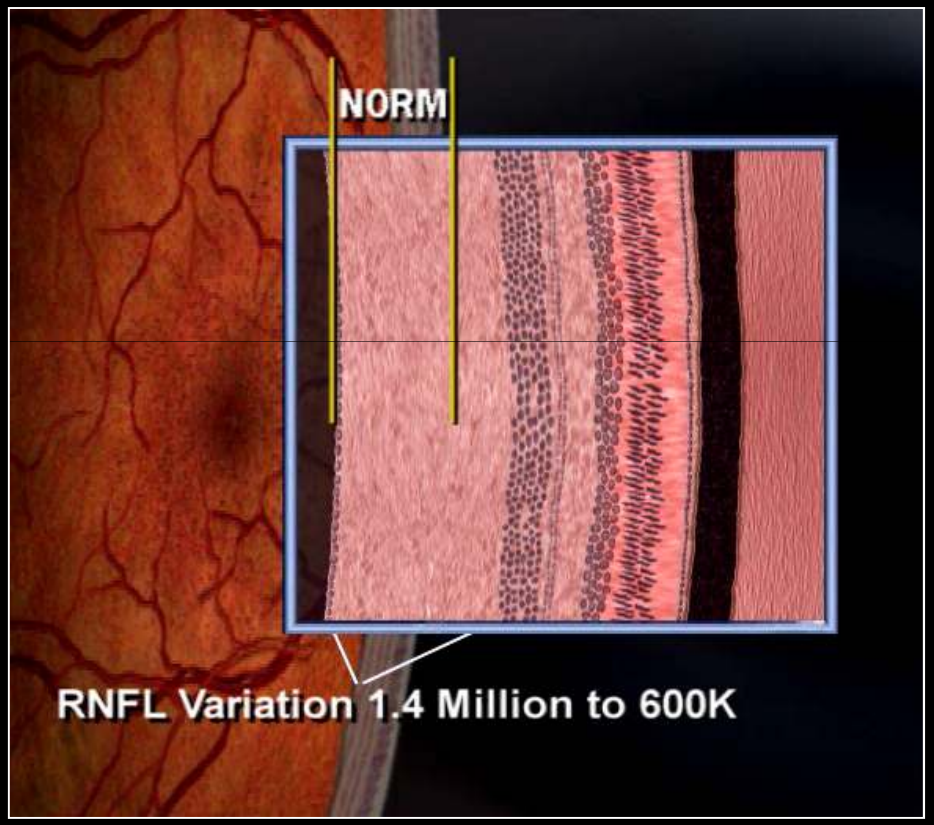
The Single Test Dilema

People in the statistically “normal range”may undergo optic disc changes over time and yet still remain within the normal range on the basis of any single exam alone.



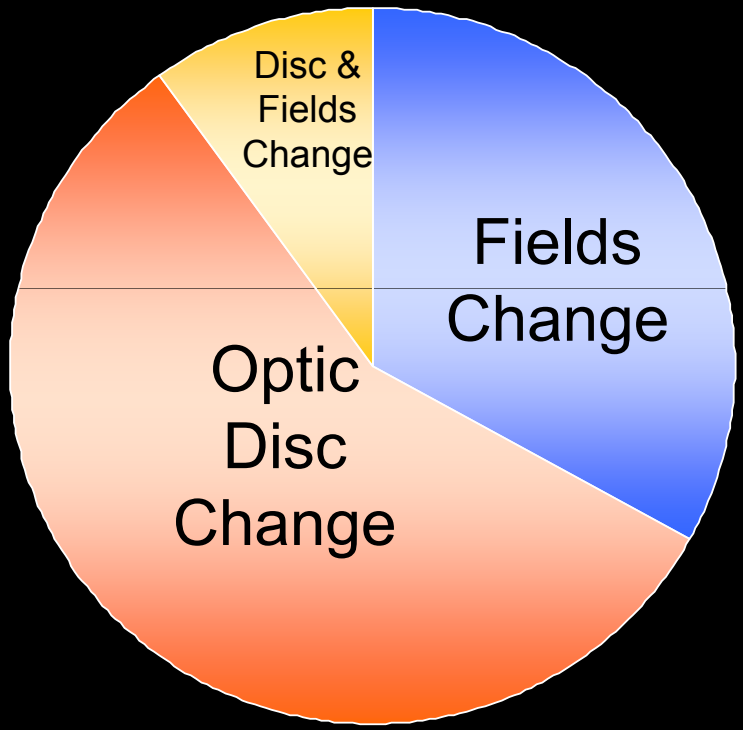
The Single Test Dilema

This patient could have started with a full set of nerve fibers.



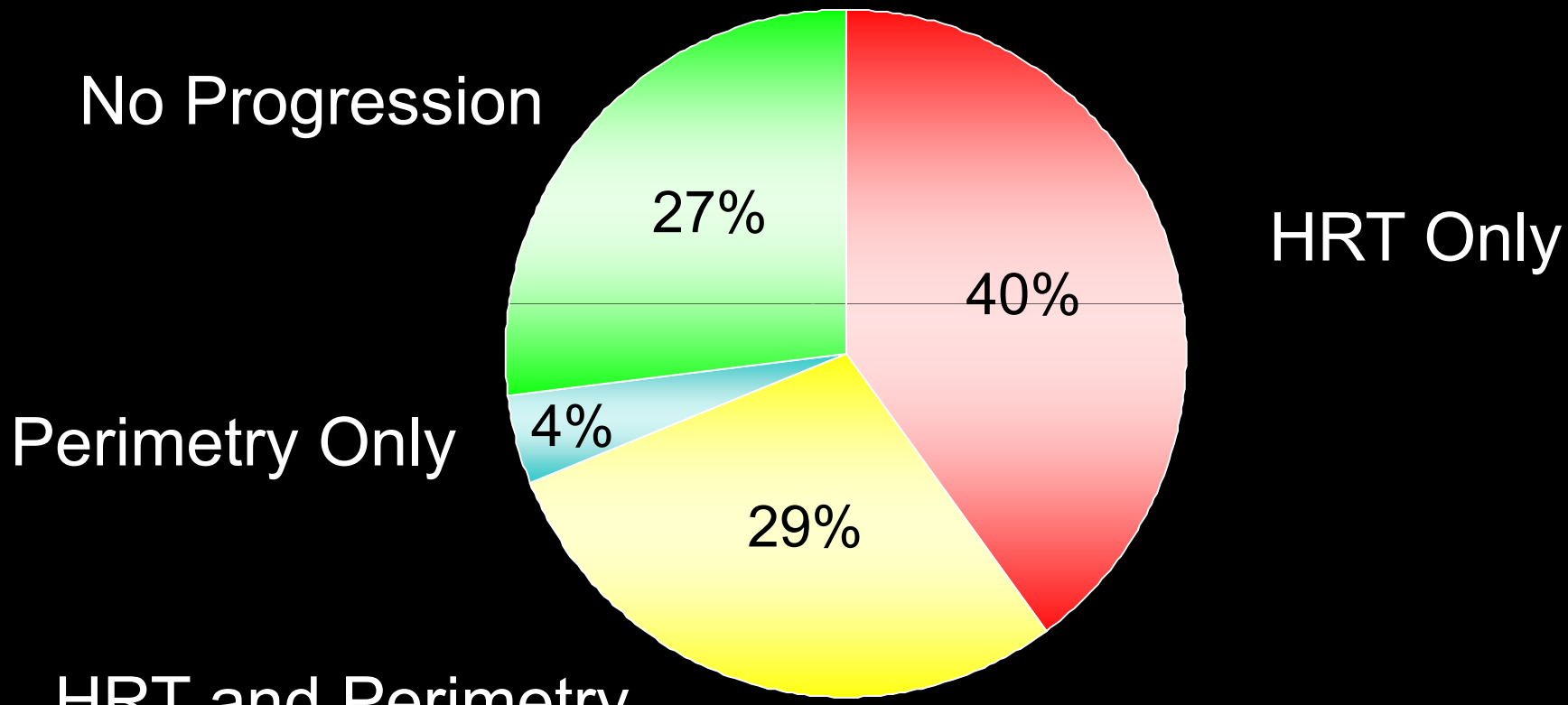
Optic Disc Change is the Primary Indicator

- OHTS reports 55% of subjects reached endpoint (POAG) based on changes in the optic disc only.
- A further 10% of subjects had concurrent optic disc and visual fields changes.
- Only 35% of glaucoma was found by visual field changes.



Kass et al., Arch Ophthalmol. 2002;120:701-703

HRT Longitudinal Studies



Chauhan et al., Arch Ophthalmol 2001;119:1492-1499

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Glaucomatous Progression

- Stereometric Parameters.
- Topographic Change Analysis (TCA).

Progression requires:

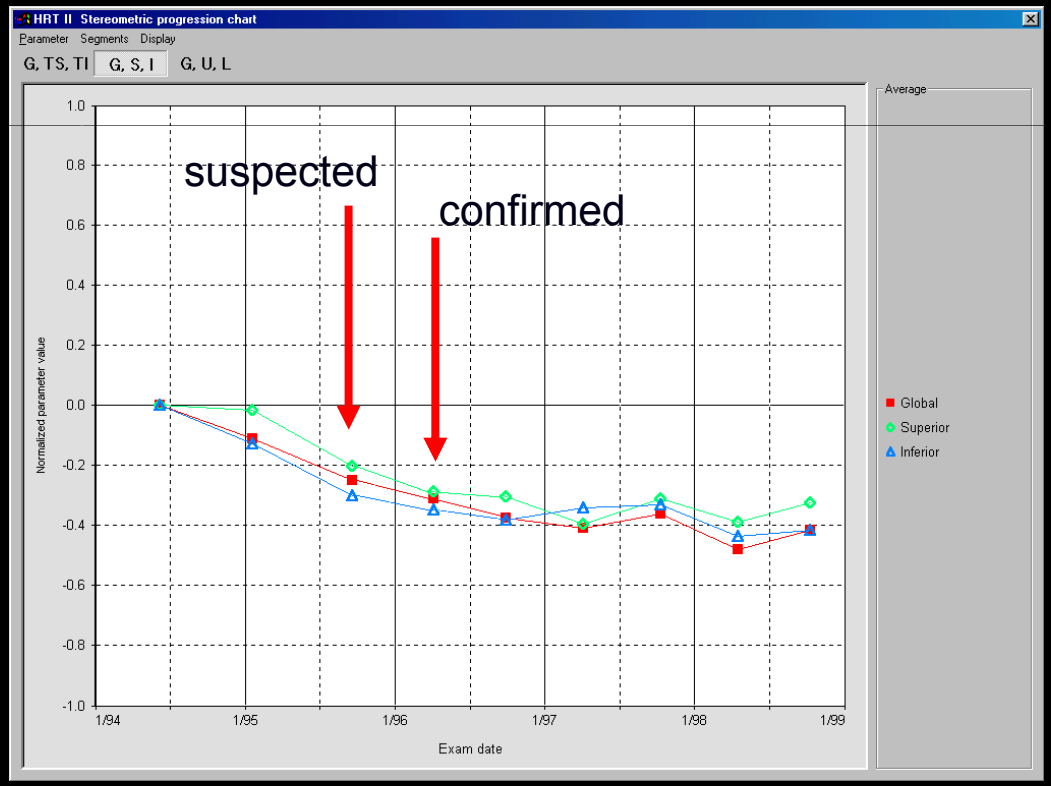
- Baseline + 2 Follow-up exams.
- Images automatically aligned to each other.

When is a Parameter Change Significant?

- Rule:
  If average normalized parameter value decreases by more than ~ **-0.05**

  in 2 consecutive exams:
  suspected progression

  in 3 consecutive exams:
  confirmed progression



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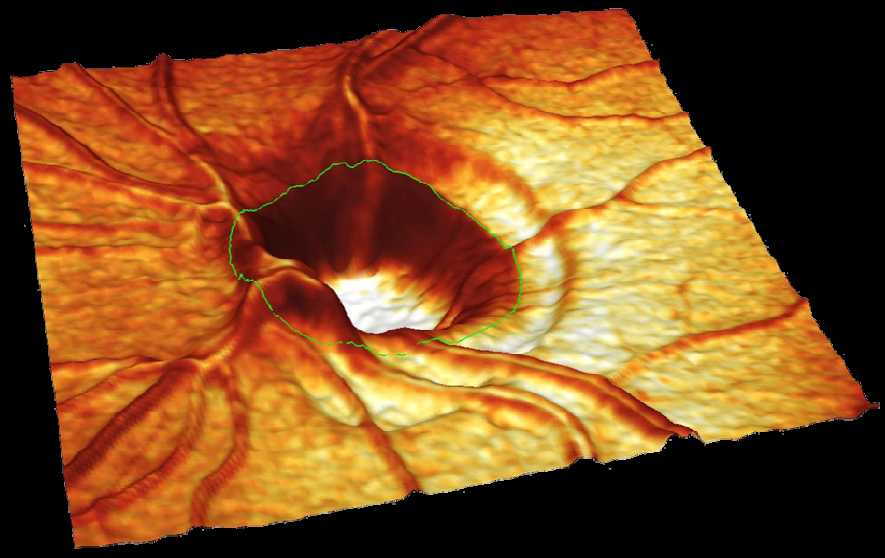
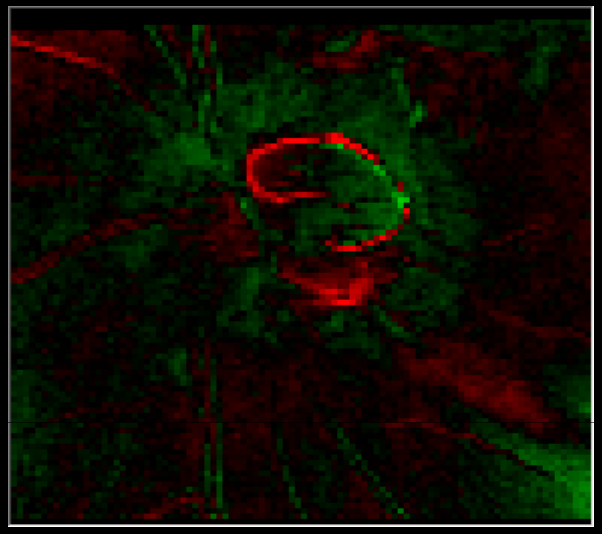
Topographic Change Analysis (TCA)

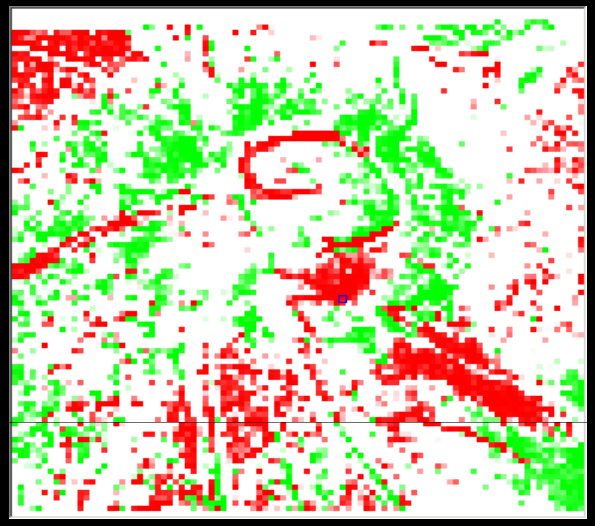
- Independent of Reference Plane.
- Independent of Contour Line.
- Compares Mean Topography images.
- Calculated automatically.



Presentation of follow-up exams



Absolute Change

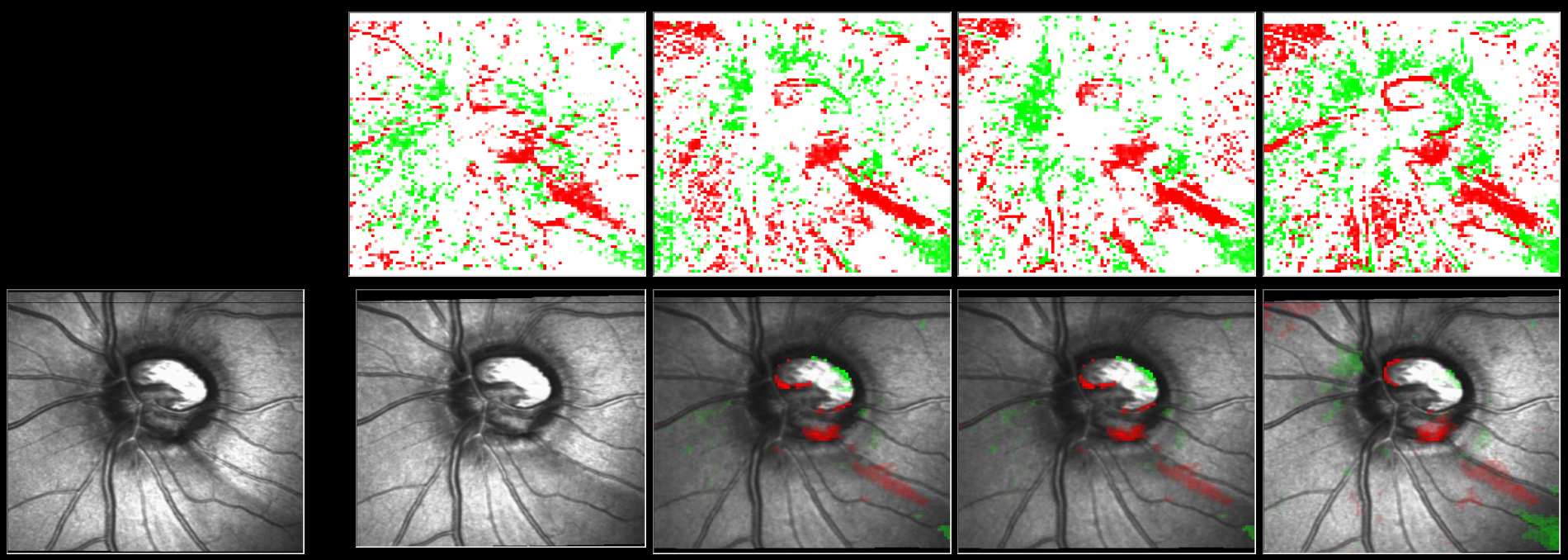


Statistically Significant Change

Statistically Significant and Reproducible* Change.

*reproduced in 2 or 3 or 4 follow-up exams

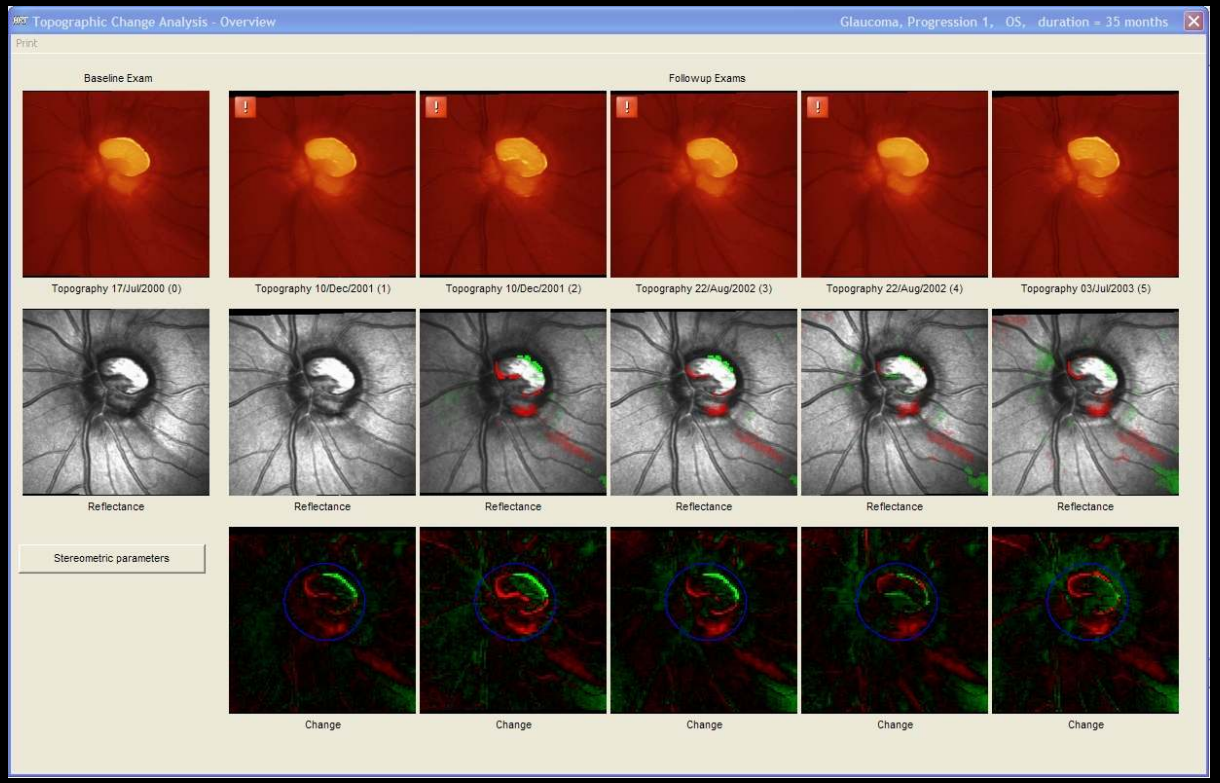
Presentation of follow-up exams



Baseline | 1. Follow-up | 2. Follow-up 2 out of 2 | 3. Follow-up 3 out of 3 | 4. Follow-up 3 out of 4

Presentation of follow-up exams

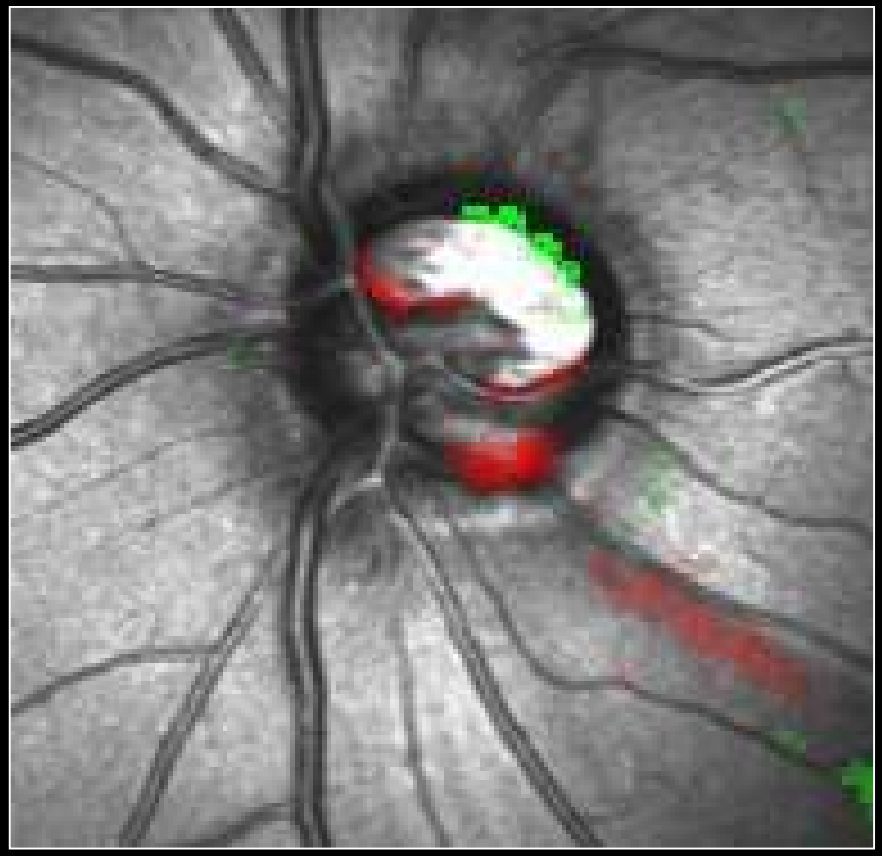
- Topography
- Reflectance
- Difference Maps



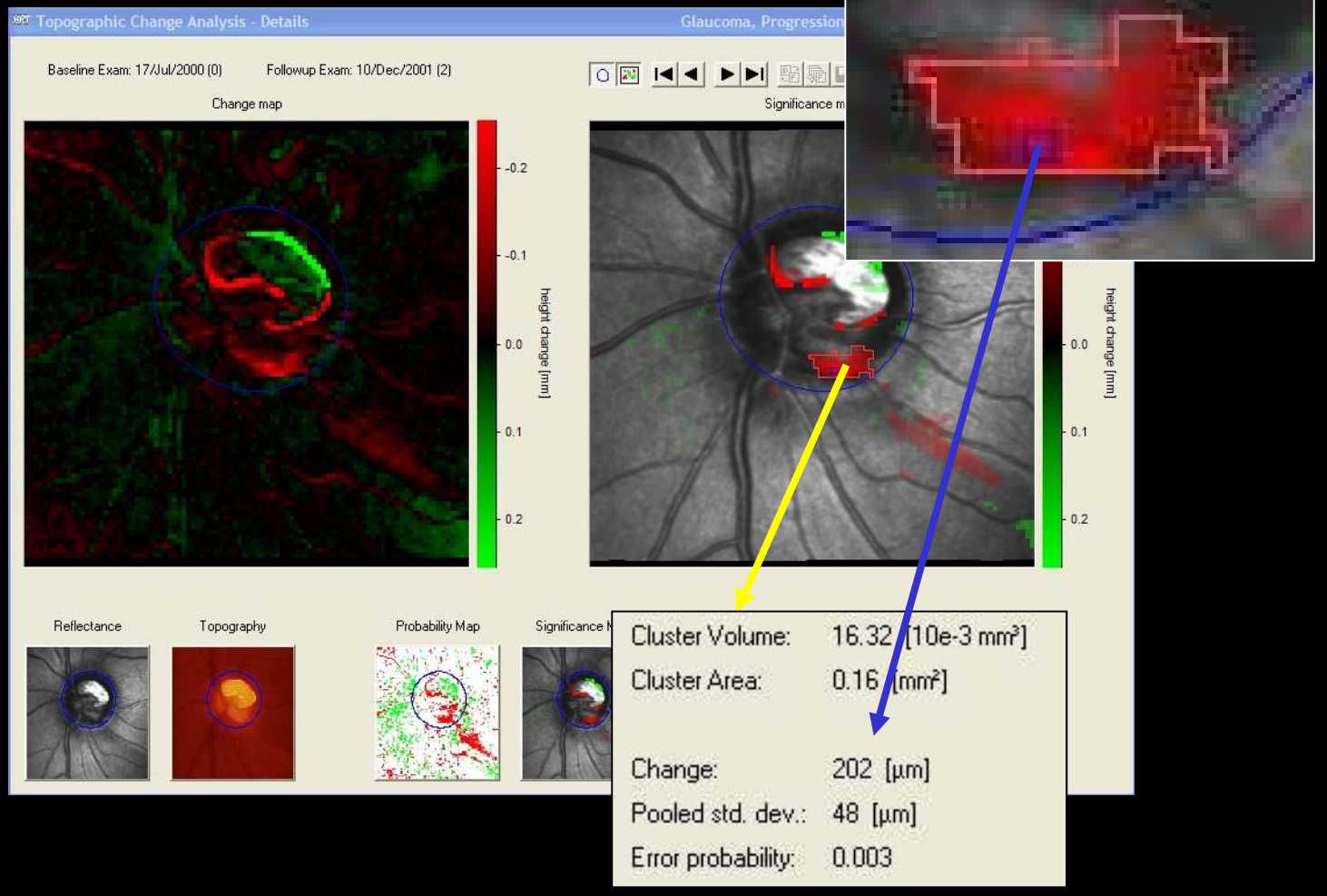
Indicate height changes of the ONH and retinal surface measured in each follow-up compared to baseline exam. Show ***overall*** change irrespective of significance of change.

Change Probability Map

- Super Pixels (4 x 4 pixels).
- Analysis of Variance (F-test).
- Error Probability (p): Probability that height change occurs by chance alone.
- Super Pixel in red or green indicates a significant change ($p < 0.05$).
- Red = Significant Depression
- Green = Significant Elevation



Cluster & Pixel Analysis



Cluster & Pixel Analysis

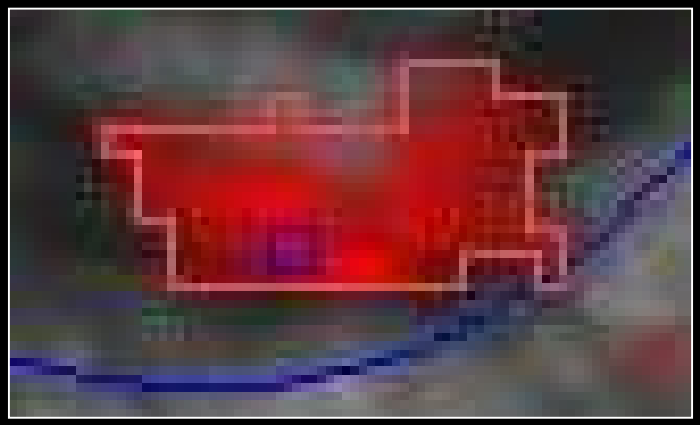
- Cluster Volume = Depth of Change.
- Cluster Area = Area of Change.

- Change = Local change in surface height measured in microns at the location selected.

  NOTE.
  A negative value (-) denotes an elevation in the follow-up compared to baseline.

- Pooled Standard Deviation
  - The combined local variability of baseline and follow-up exam in microns.
  - Lower numbers = consistent quality.

- Error Probability
  - Low number = true change more likely.



Cluster Volume:	16.32 [10e-3 mm³]
Cluster Area:	0.16 [mm²]
Change:	202 [µm]
Pooled std. dev.:	48 [µm]
Error probability:	0.003

New Printout – TCA Cluster Analysis

Heidelberg Retina Tomograph
TCA Overview

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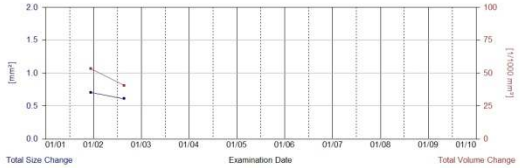
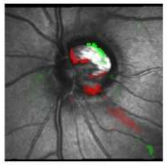
Patient: Glaucoma, Progression 1
Sex: female DOB: 20/May/1964 Pat-ID: ---

Examination: Baseline: 17/Jul/2000 Last Follow-Up: 22/Aug/2002 Elapsed: 25 months

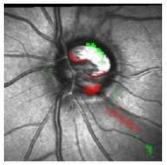
OS

Baseline: 17/Jul/2000





Follow-Up: #2, 10/Dec/2001



Follow-Up: #3, 22/Aug/2002

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Frequency of Examinations

- Time determines progression of disease.
- Disease cannot be shown simply by doing more exams.
- Try to get more follow-up exams early to establish rate of progression.
- Follow current Visual Fields practice.
  - High risk patients – every 3-4 months.
  - High risk = Race, age, family history, IOP increases, thin cornea.
  - Low risk patients – annually.

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TCA – Early Start

- Increase the number of exams in order to start monitoring for change earlier.
- 1 high quality baseline and 2 follow-up exams of the same quality at 2nd visit.