GLAUCOMA WORKSHOP
APPROCCIO DIGNOSTICO ALLA PATOLOGIA DEL GLAUCOMA

Ruolo dell'OCT nell'algoritmo diagnostico del glaucoma

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Ospedale Britannico

IRCCS Fondazione G.B.Bietti

Roma

Roma, 7 ottobre 2022

L’evoluzione dell’OCT

1991: time domain

2016: Spectral domain
Swept source…

Spectral Domain OCT vs TD-OCT

- Velocità di acquisizione dell' immagine 40-110 volte maggiore del TD
- 24000-70000 (100000) A-scan/sec, con una risoluzione assiale di 3-5 µm (Time domain:400 A-scan/sec, risoluzione assiale di ca 10µm)
- Minori artefatti di movimento
- Maggiore quantità di dati acquisiti per ogni punto, algoritmi avanzati di post-processing
- Ricostruzioni 3D

OCT nel Glaucoma

1. Quando prescrivere l'esame OCT (diagnosi, progressione, screening)?
2. Come interpretare le informazioni che ne derivano?
3. Come integrare tali informazioni nel quadro clinico del paziente?

OCT e Glaucoma

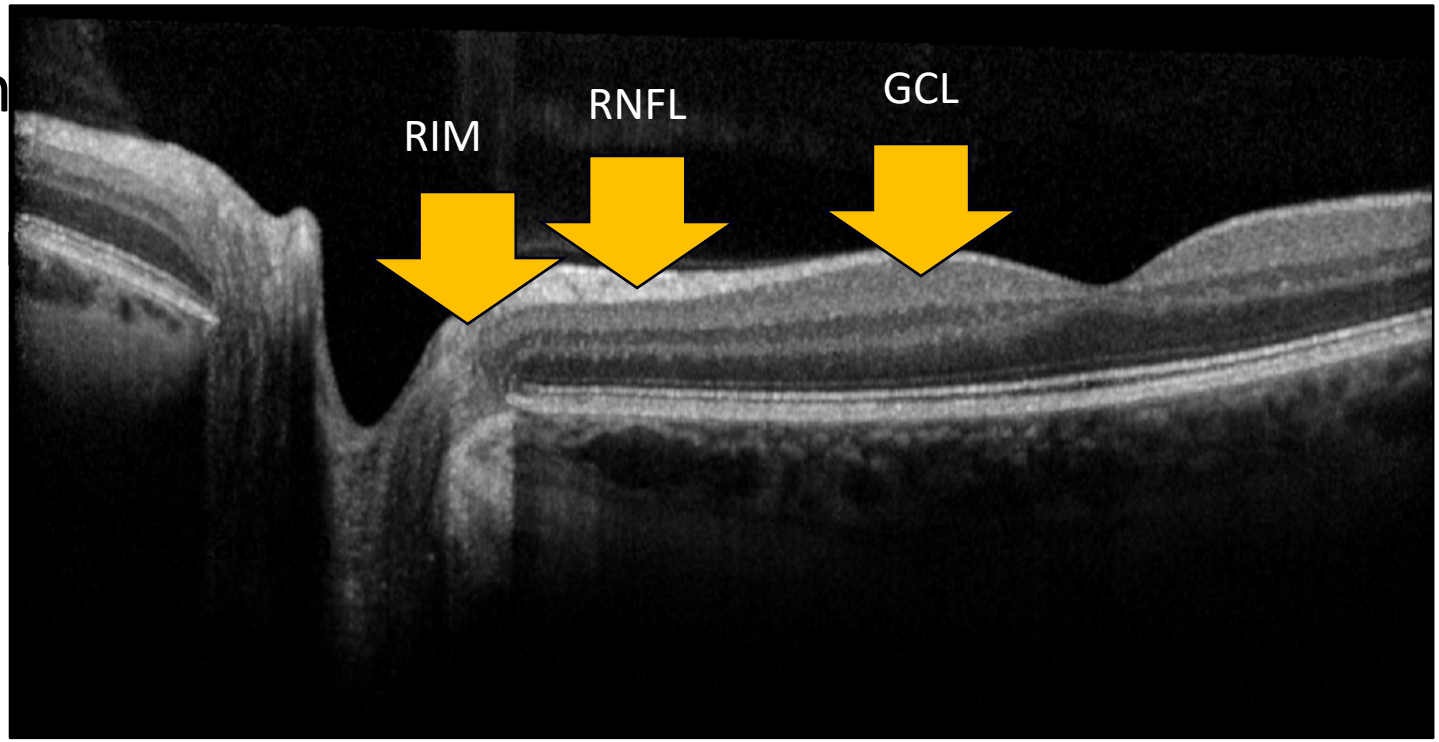
Necessario per il clinico…

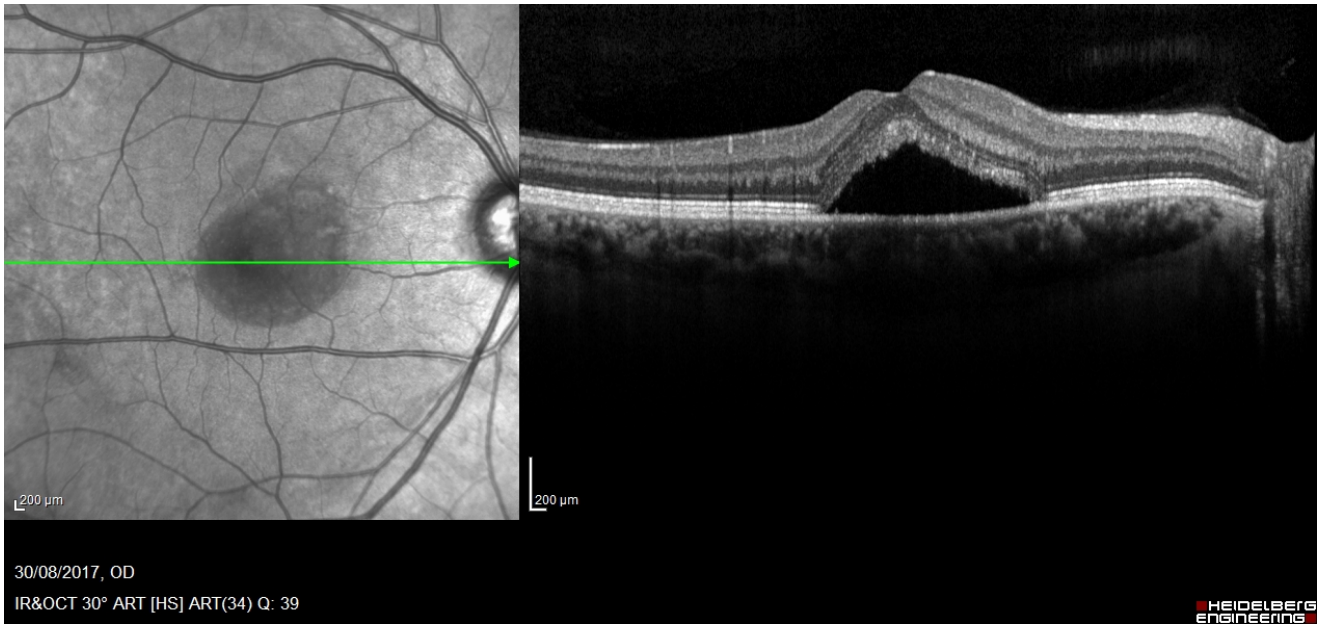
- Conoscere i protocolli di scansione
- Saper interpretare correttamente l'output
- Conoscere i limiti e le capacità diagnostiche (parametro più valido, meno significativo)
- Identificare possibili fattori confondenti (qualità delle immagini, artefatti, patologie concomitanti)
- Saper come e se confrontare i diversi OCT oggi disponibili

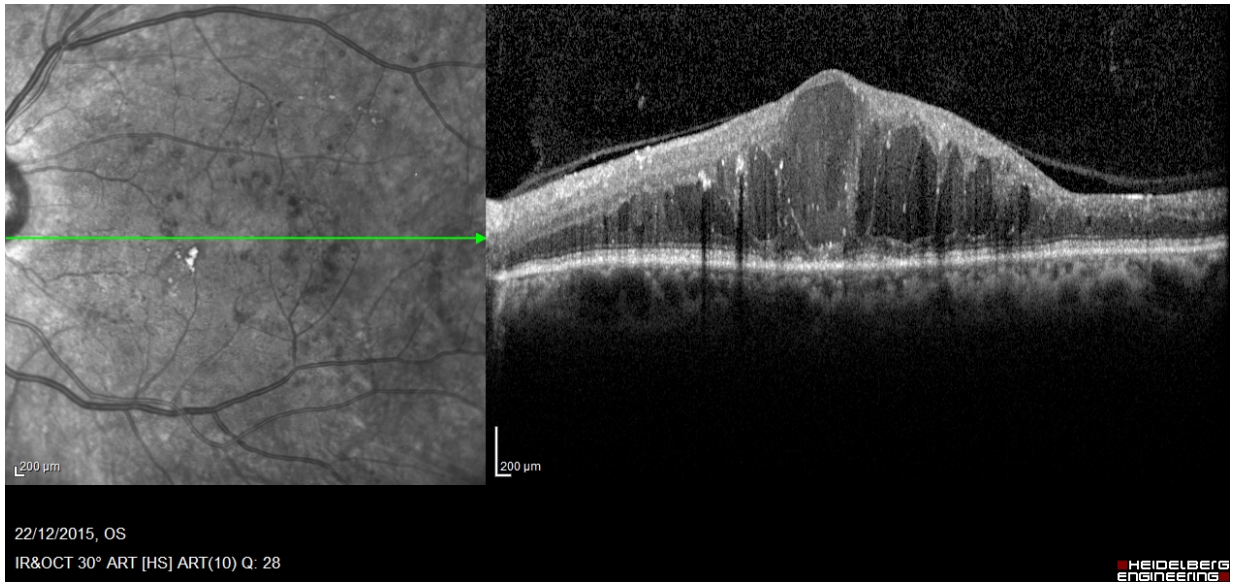
Spectral Domain-OCT

Elementi in comune

- Studio dell' RNFL, dell'ONH, della regione maculare
- An
- Pa




200 µm
200 µm
30/08/2017, OD
IR&OCT 30° ART [HS] ART(34) Q: 39
HEIDELBERG ENGINEERING


200 µm
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22/12/2015, OS
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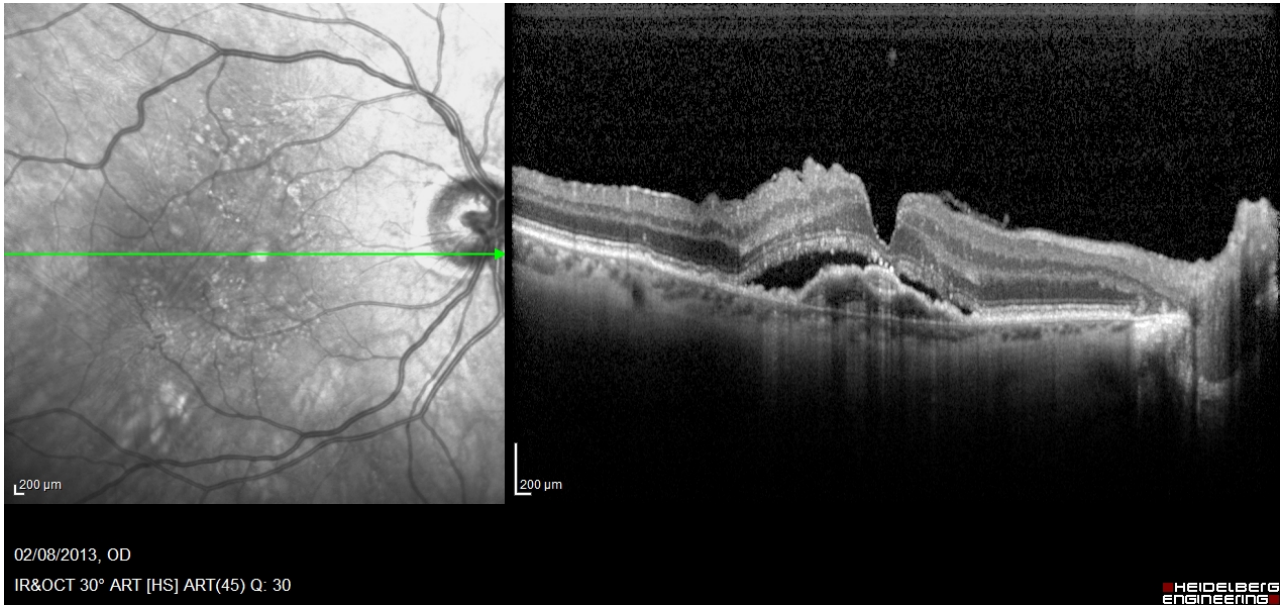
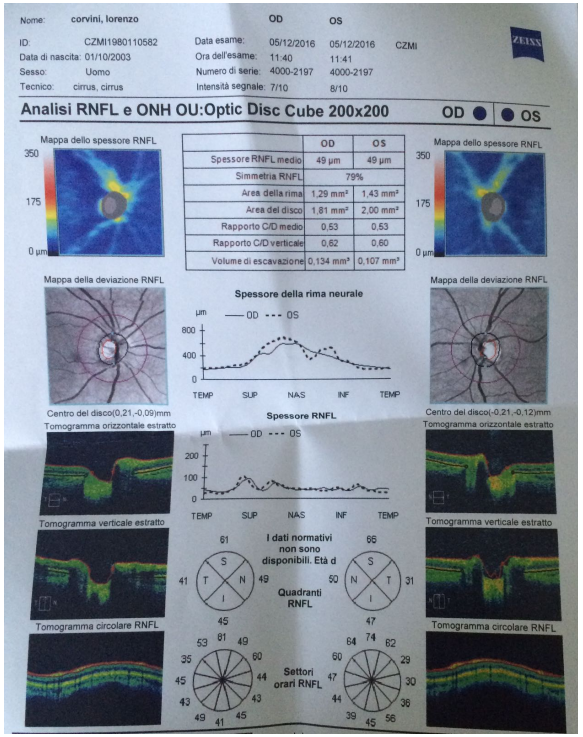
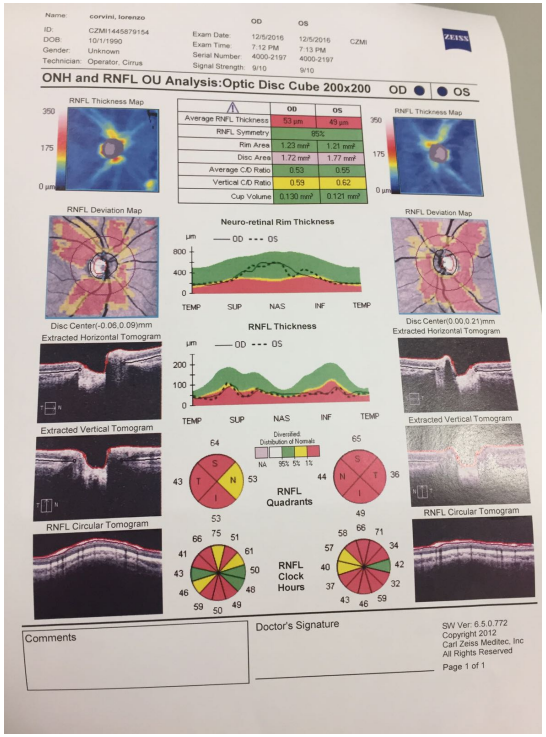

200 µm
200 µm
02/08/2013, OD
IR&OCT 30° ART [HS] ART(45) Q: 30
HEIDELBERG ENGINEERING


Nome: corvini, lorenzo
ID: CZMI1980110582
Data di nascita: 01/10/2003
Sesso: Uomo
Tecnico: cirrus, cirrus
OD OS
Data esame: 05/12/2016 05/12/2016 CZMI
Ora dell'esame: 11:40 11:41
Numero di serie: 4000-2197 4000-2197
Intensità segnale: 7/10 8/10
Analisi RNFL e ONH OU:Optic Disc Cube 200x200 OD OS
Mappa dello spessore RNFL
Spessore RNFL medio 49 µm 49 µm
Simmetria RNFL 79%
Area della rima 1,29 mm² 1,43 mm²
Area del disco 1,81 mm² 2,00 mm²
Rapporto C/D medio 0,53 0,53
Rapporto C/D verticale 0,62 0,60
Volume di escavazione 0,134 mm³ 0,107 mm³
Mappa della deviazione RNFL
Spessore della rima neurale
TEMP SUP NAS INF TEMP
Centro del disco(0,21,-0,09)mm
Centro del disco(-0,21,-0,12)mm
Tomogramma orizzontale estratto
Spessore RNFL
Tomogramma verticale estratto
I dati normativi non sono disponibili. Età d
Quadranti RNFL
Tomogramma circolare RNFL
Settori orari RNFL


Name: corvini, lorenzo
ID: CZMI1445879154
DOB: 10/1/1990
Gender: Unknown
Technician: Operator, Cirrus
OD OS
Exam Date: 12/5/2016 12/5/2016 CZMI
Exam Time: 7:12 PM 7:13 PM
Serial Number: 4000-2197 4000-2197
Signal Strength: 9/10 9/10
ONH and RNFL OU Analysis:Optic Disc Cube 200x200 OD OS
RNFL Thickness Map
Average RNFL Thickness 53 µm 49 µm
RNFL Symmetry 85%
Rim Area 1.23 mm² 1.21 mm²
Disc Area 1.72 mm² 1.77 mm²
Average C/D Ratio 0.53 0.55
Vertical C/D Ratio 0.59 0.62
Cup Volume 0.130 mm³ 0.121 mm³
RNFL Deviation Map
Neuro-retinal Rim Thickness
TEMP SUP NAS INF TEMP
Disc Center(-0.06,0.09)mm
Disc Center(0.00,0.21)mm
Extracted Horizontal Tomogram
RNFL Thickness
Extracted Vertical Tomogram
RNFL Quadrants
RNFL Circular Tomogram
RNFL Clock Hours
Comments
Doctor's Signature
SW Ver: 6.5.0.772
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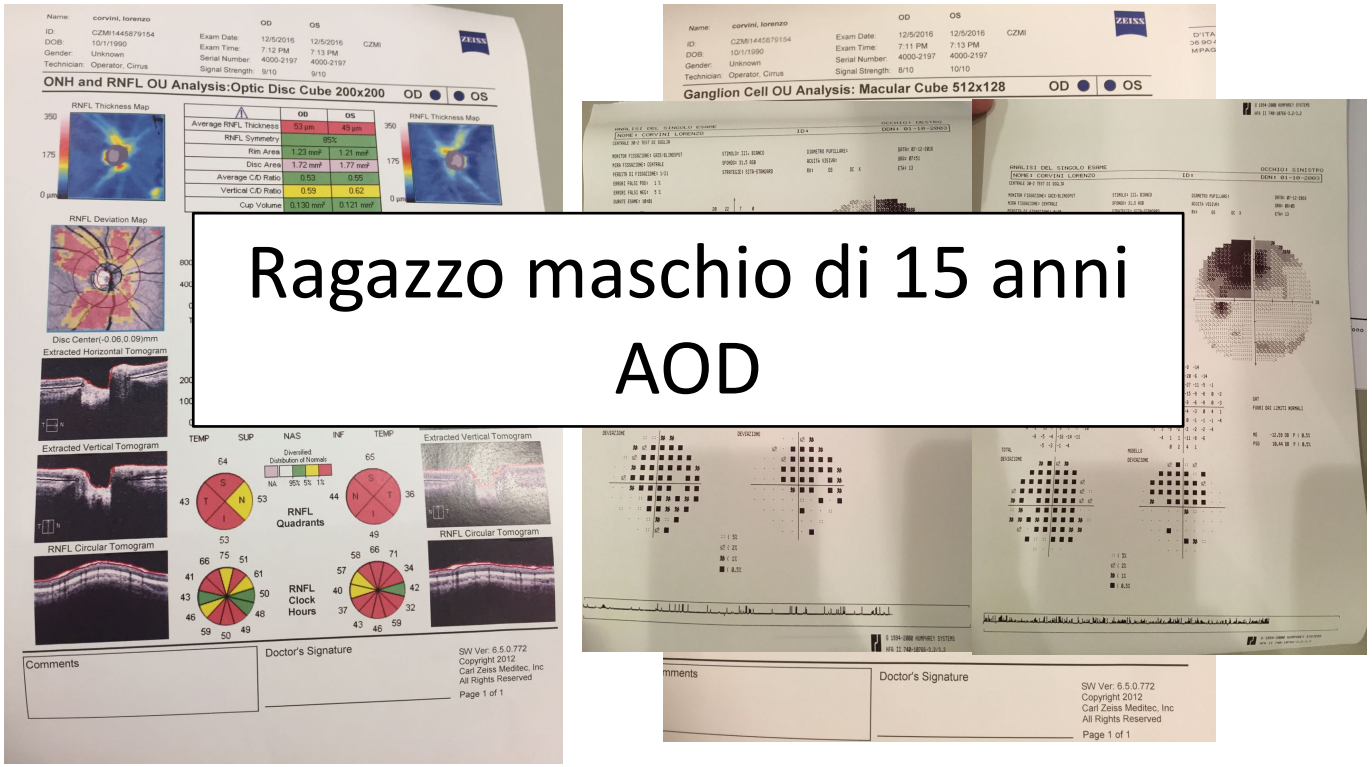
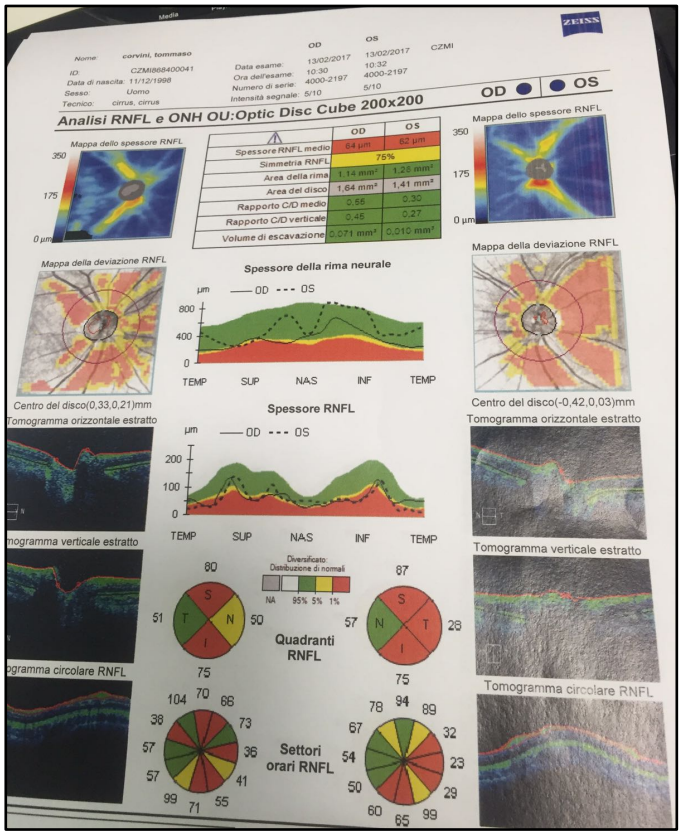
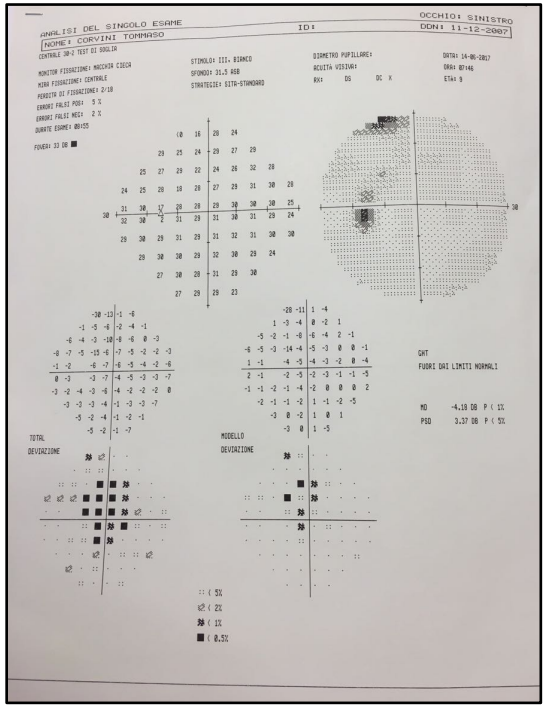
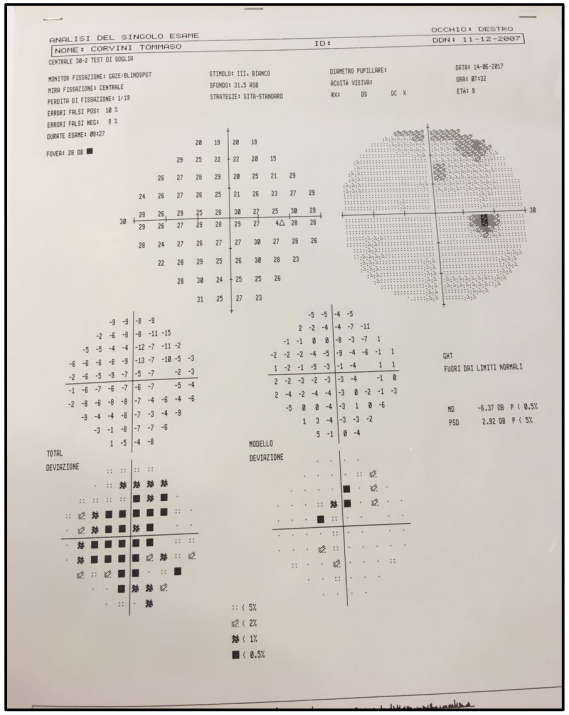
Page 1 of 1



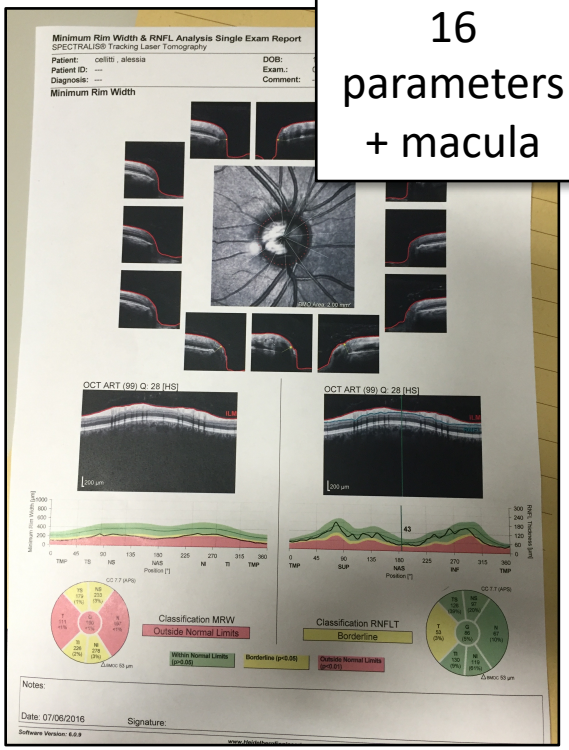
Ragazzo maschio di 15 anni
AOD


ZEISS
Nome: corvini, tommaso
ID: CZMI868400041
Data di nascita: 11/12/1998
Sesso: Uomo
Tecnico: cirrus, cirrus
Data esame: 13/02/2017 10:30
Ora dell'esame: 4000-2197
Numero di serie: 5/10
Intensità segnale: 5/10
OD 13/02/2017 10:32 4000-2197 5/10
OS
CZMI
Analisi RNFL e ONH OU:Optic Disc Cube 200x200
OD
OS
Mappa dello spessore RNFL
Spessore RNFL medio 64 µm 62 µm
Simmetria RNFL 75%
Area della rima 1.14 mm² 1.25 mm²
Area del disco 1.64 mm² 1.41 mm²
Rapporto C/D medio 0.56 0.30
Rapporto C/D verticale 0.45 0.27
Volume di escavazione 0.071 mm³ 0.010 mm³
Mappa della deviazione RNFL
Spessore della rima neurale
TEMP SUP NAS INF TEMP
Centro del disco(0,33,0,21)mm
Centro del disco(-0,42,0,03)mm
Tomogramma orizzontale estratto
Spessore RNFL
Tomogramma verticale estratto
Tomogramma circolare RNFL
Quadranti RNFL
Settori orari RNFL

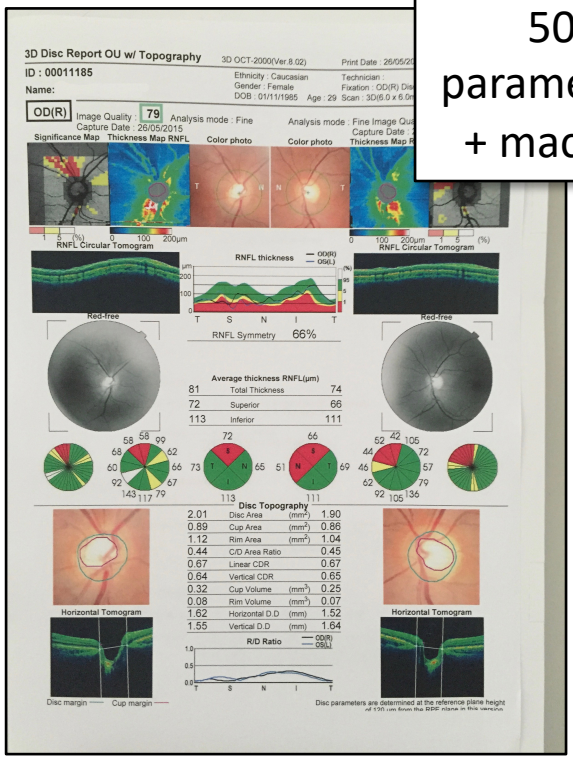

ANALISI DEL SINGOLO ESAME
OCCHIO: SINISTRO
NOME: CORVINI TOMMASO
ID:
DDN: 11-12-2007
CENTRALE 30-2 TEST DI SOGLIA
GHT
FUORI DAI LIMITI NORMALI
MD -4.18 DB P (1%
PSD 3.37 DB P (5%
TOTAL DEVIAZIONE
MODELLO DEVIAZIONE


ANALISI DEL SINGOLO ESAME
OCCHIO: DESTRO
NOME: CORVINI TOMMASO
ID:
DDN: 11-12-2007
CENTRALE 30-2 TEST DI SOGLIA
GHT
FUORI DAI LIMITI NORMALI
MD -6.37 DB P (0.5%
PSD 2.92 DB P (5%
TOTAL DEVIAZIONE
MODELLO DEVIAZIONE

Managing the output



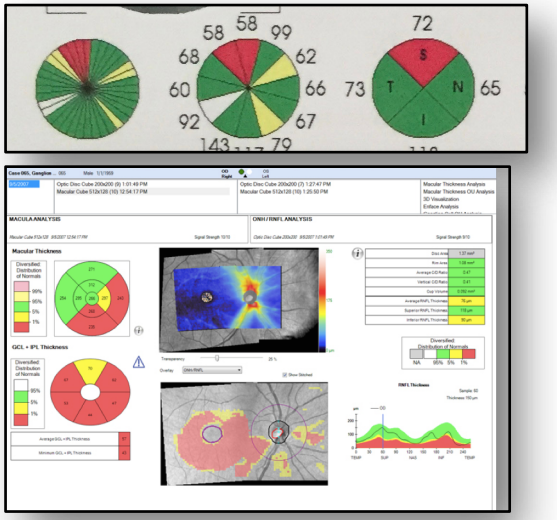
16 parameters + macula



50 parameters + macula

Diagnostic tests vs Diagnosis

- There is a temptation for a busy clinician to read the output from the OCT (e.g. RNFL Av) and take it to be the "diagnosis" [1]

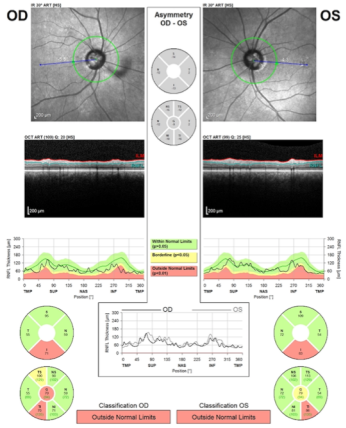


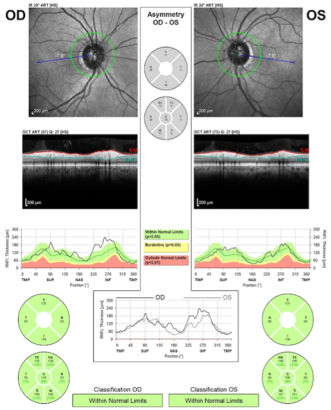
1. DF. Garway-Heath. Progr Brain Res 2008

"Red disease" and "green disease"

Glaucoma versus red disease: imaging and glaucoma diagnosis

Gabriel T. Chong and Richard K. Lee





Green disease in optical coherence tomography diagnosis of glaucoma

Mohamed S. Sayed[a], *Michael Margolis*[a,b], *and Richard K. Lee*[a]

«Results from these tests must be interpreted in the context of the clinical examination and other supplementary tests in order to avoid falsely concluding that a **statistically abnormal result** on any quantitative imaging study represents true disease»

PPP-AAO

Limits of normative classifications

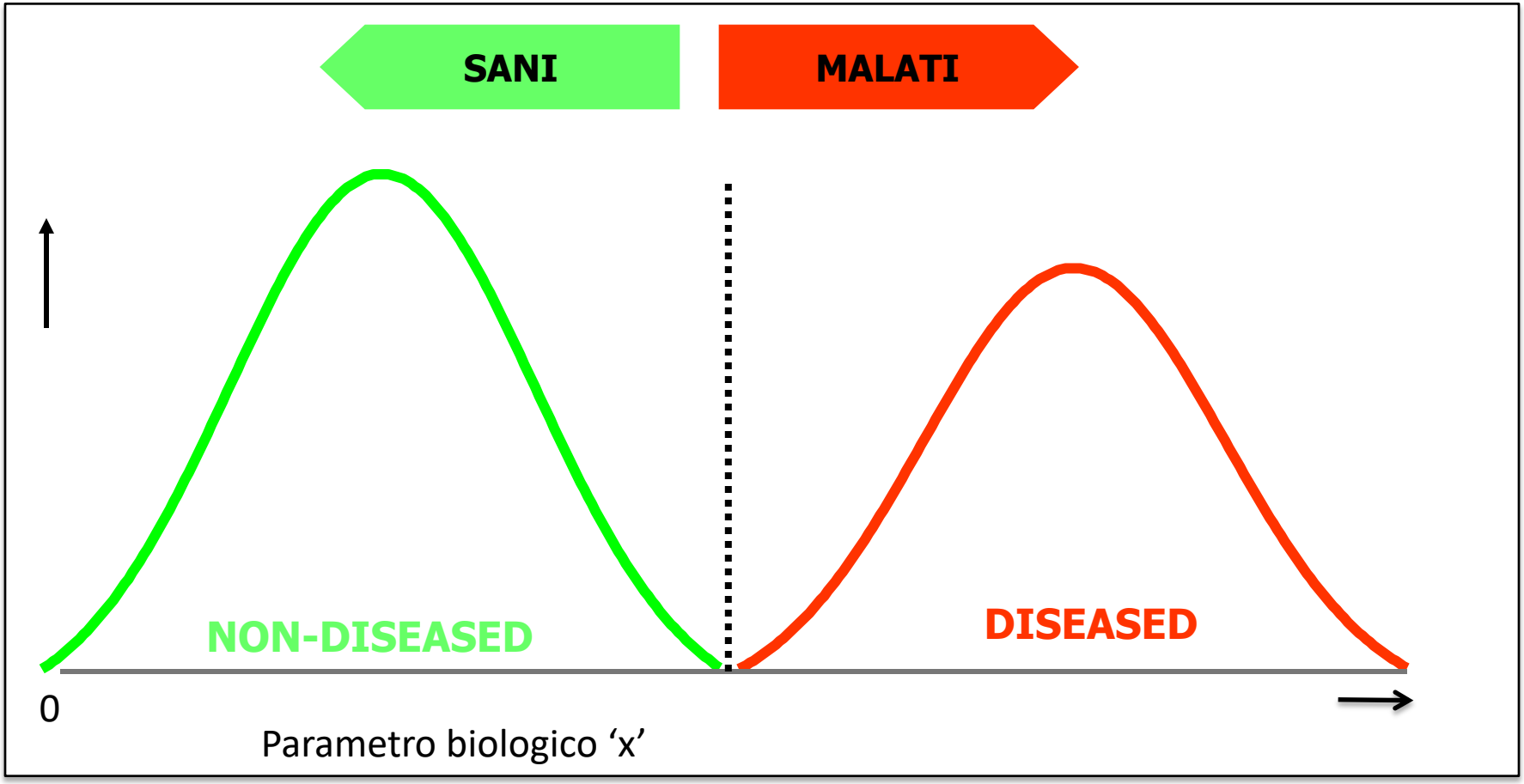
- Normative databases have strict inclusion criteria
- Consist largely of patients of European ancestry
- Exclude those with high refractive error or ocular comorbidities
- Normal structural measurements vary widely between individuals, increasing the chances of misclassification
- In some cases, because of the wide range of normal, significant neural losses may occur before a patient is deemed to be outside normal limits

Errors in diagnostic information

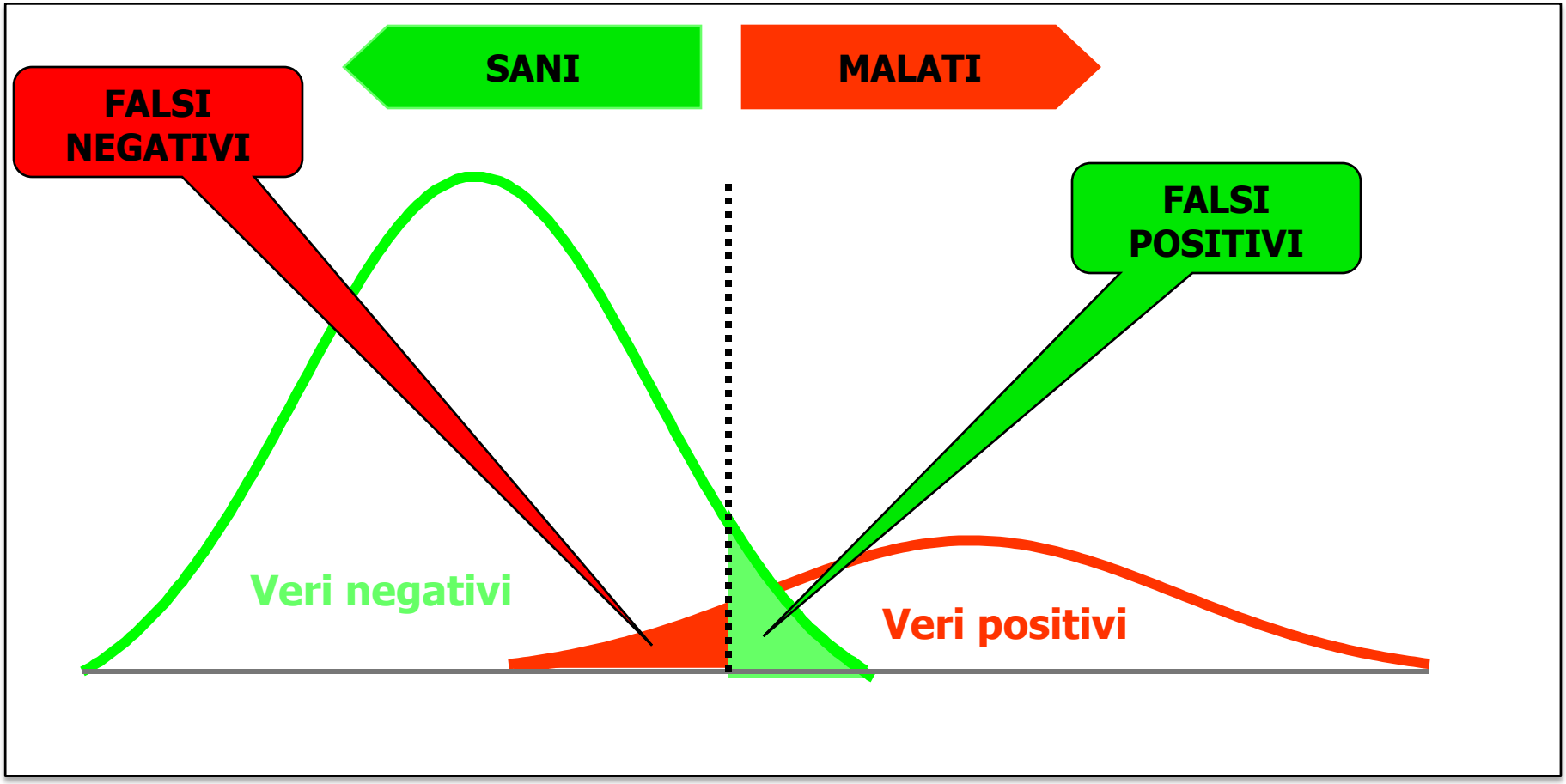
- Both false positives and false negatives are possible
- The rates of FP and FN will differ between different pieces of information

We should know how to select and interpret information to minimize the impact of such errors

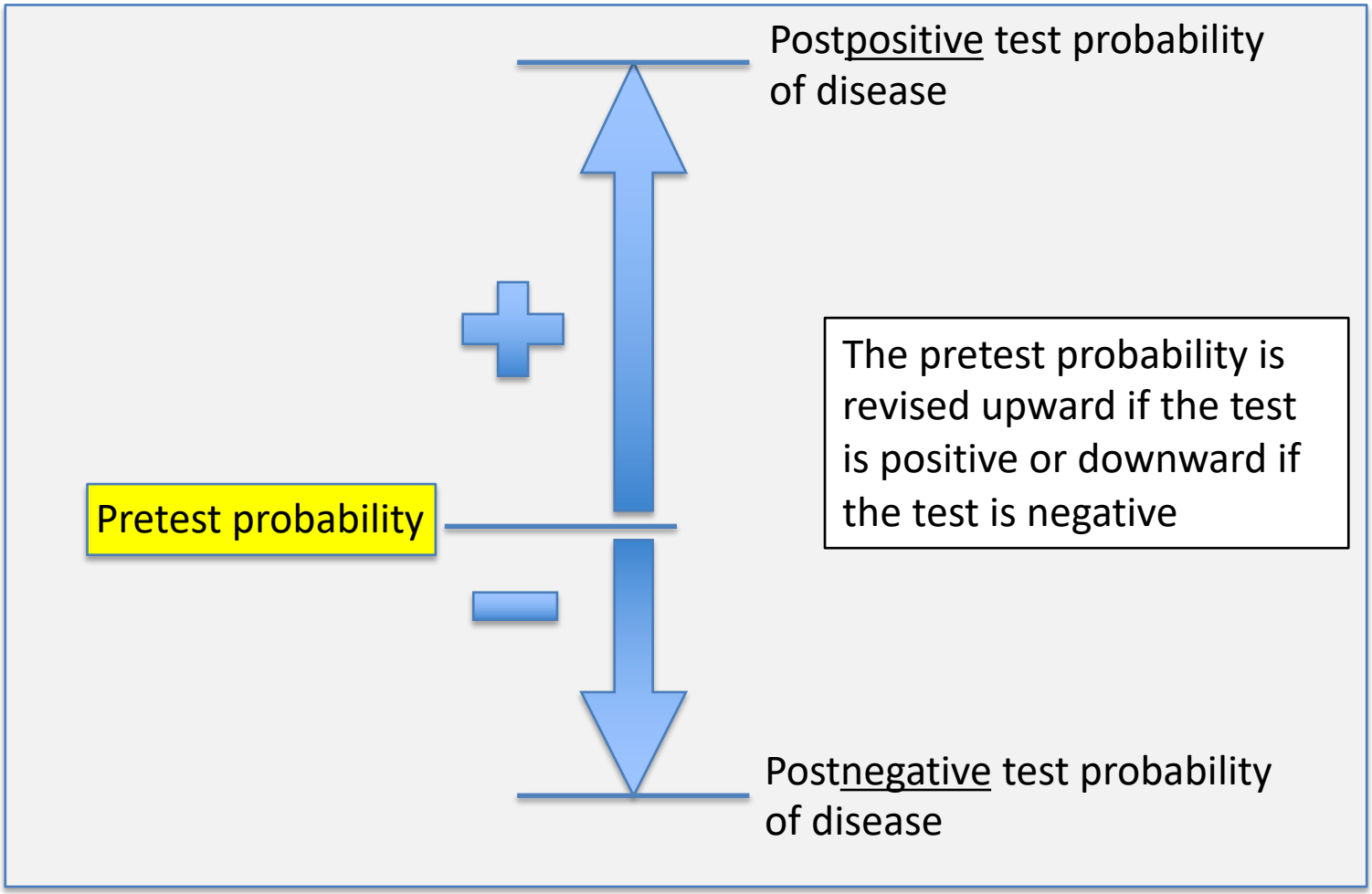
Distribuzione ideale



Distribuzione reale

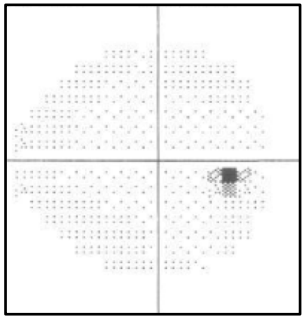


Probability revision

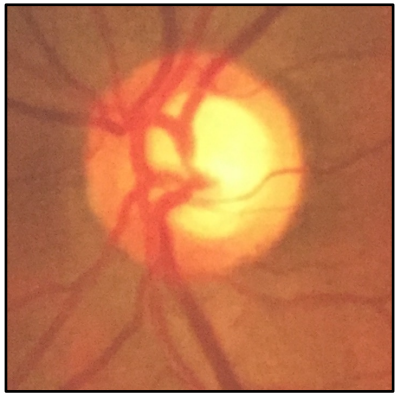


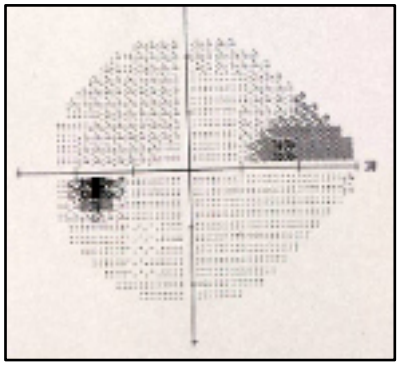
Post-test probability

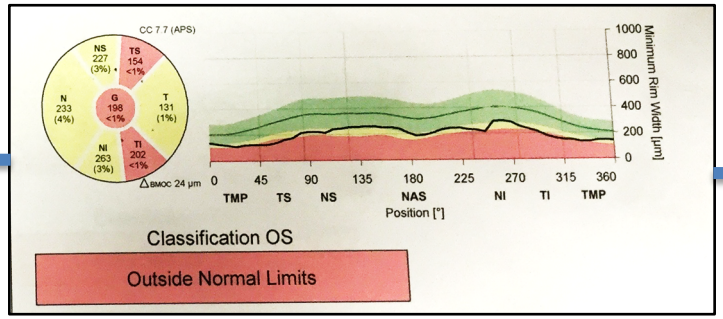
25 yrs old subject selected at random from the general population



47 yrs old, + family Hy, referred for high IOP



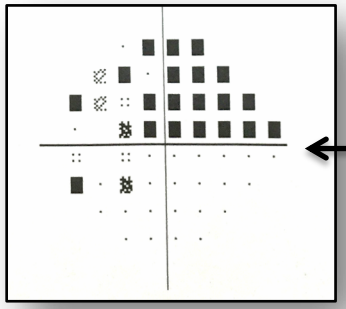


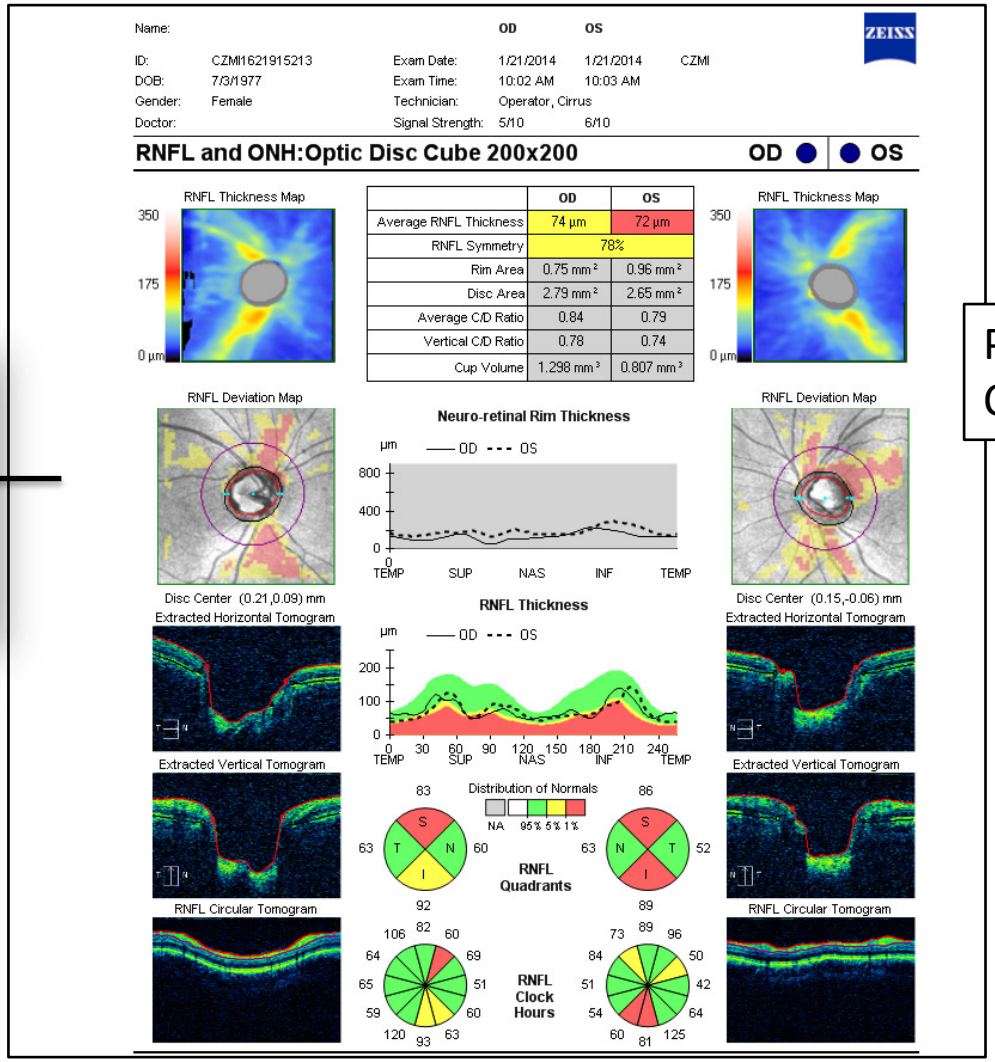


Sensitivity and Specificity

- Describe how often a test is correct in diseased and non diseased groups
  - **Sensitivity:** measures the proportion of people with the disease that test positives
  - **Specificity:** measures the proportion of people without the disease that test negatives

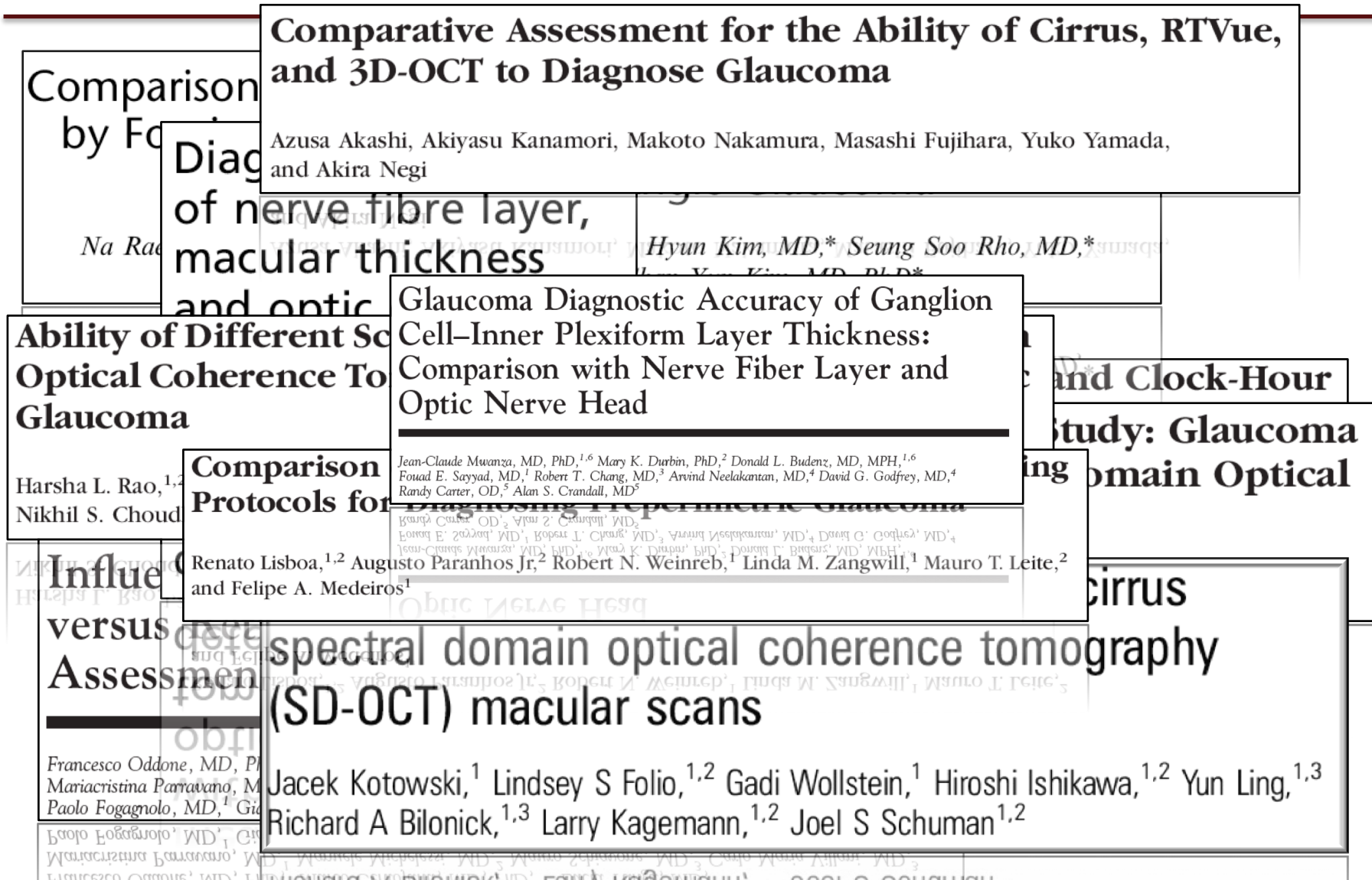
Cirrus HD





Protocollo Optic disc Cube 200 X 200

Studi Accuratezza diagnostica



Optic nerve head and fibre layer imaging for diagnosing glaucoma (Review)

Michelessi M, Lucenteforte E, Oddone F, Brazzelli M, Parravano M, Franchi S, Ng SM, Virgili G

THE COCHRANE COLLABORATION®

106 studi inclusi: 16260 occhi, 8353 casi, 7907 controlli

Cohrane Database Syst Rev. Nov 2015

Alte specificità

2 Relative accuracy of all parameters for each test

Test (parameter)	**Sensitivity**	**Specificity**	**Relative DOR**	**p-value**
OCT ONH				
Cup/disc area ratio	0.66 (0.56-0.74)	0.93 (0.90-0.95)	0.82 (0.57-1.19)	0.2963
Horizontal cup/disc ratio	0.56 (0.45-0.66)	0.93 (0.88-0.95)	0.49 (0.29-0.82)	0.0062
Vertical cup/disc ratio	**0.68 (0.58-0.76)**	**0.94 (0.91-0.96)**	**Reference 31.63 (18.90-52.93)**	**Reference**
Cup area	0.57 (0.46-0.67)	0.93 (0.90-0.95)	0.57 (0.37-0.88)	0.0116
Cup volume	0.44 (0.34-0.55)	0.93 (0.90-0.96)	0.35 (0.22-0.56)	<.0001
Disc area	0.31 (0.22-0.41)	0.92 (0.87-0.95)	0.15 (0.09-0.25)	<.0001
Nerve head volume	0.59 (0.48-0.69)	0.92 (0.88-0.96)	0.55 (0.31-0.98)	0.0415
Rim area	0.65 (0.55-0.73)	0.94 (0.91-0.96)	0.90 (0.62-1.30)	0.5759
Rim volume	0.57 (0.46-0.68)	0.94 (0.91-0.97)	0.73 (0.41-1.27)	0.2647
OCT RNFL				
Average	**0.69 (0.64-0.73)**	**0.95 (0.93-0.95)**	**Reference 37.84 (29.66-48.29)**	**Reference**
Inferior sector	0.70 (0.66-0.75)	0.93 (0.92-0.95)	0.90 (0.73-1.13)	0.3734
Nasal sector	0.30 (0.25-0.35)	0.93 (0.91-0.94)	0.15 (0.12-0.19)	<.0001
Superior sector	0.59 (0.54-0.64)	0.94 (0.92-0.95)	0.58 (0.46-0.72)	<.0001
Temporal sector	0.31 (0.26-0.36)	0.93 (0.92-0.95)	0.17 (0.13-0.21)	<.0001

Summary of findings tables

Test parameter	N. studies (participants)	Sensitivity (95% CI)	Specificity (95% CI)	Implications in 1000 patients referred from primary care for clinician's assessment, assuming 200 have glaucoma		
				Glaucoma cases detected	Missed	Referred, but no glaucoma
OCT C/D vertical ratio	15 (2389)	0.72 (0.60-0.81)	0.94 (0.92-0.95)	144	56	48
OCT RNFL mean thickness	57 (8223)	0.72 (0.65-0.77)	0.93 (0.92-0.95)	140	56	56

Rilevanza per la pratica clinica

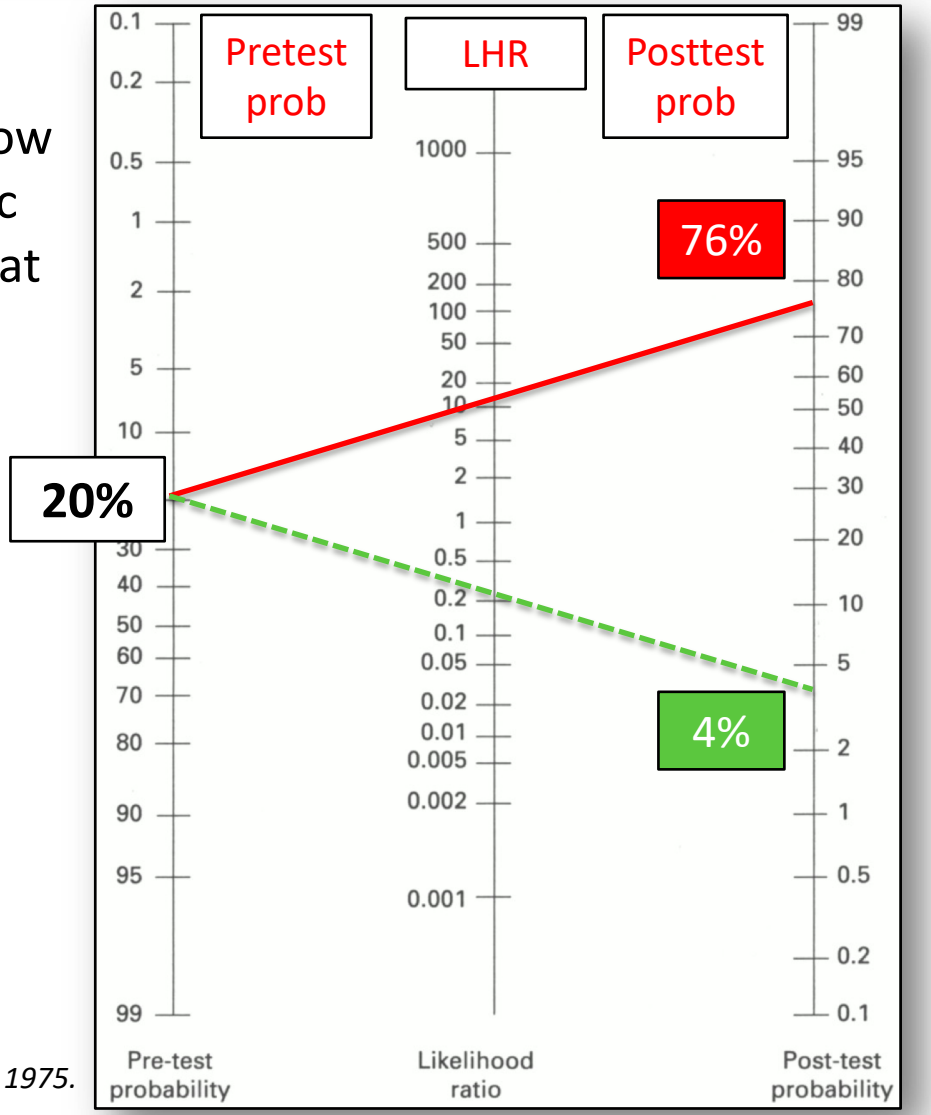
- Prendendiamo 1000 soggetti e ipotizziamo una prevalenza di glaucoma del 20% (800 sani, 200 malati).
- Avere una Sn/Sp di 72 e 94%, significa che:
  - **Dei 200 malati**, 144 vengono diagnosticati correttamenti come malati
  - Però ne vengono **diagnosticati come sani (sbagliando) 56**.
  - **Degli 800 normali 752 vengono correttamente classificati come sani e 48 vengono sbagliati** e diagnosticati come malati (falsi positivi)

Likelyhood ratios

- They tell us how many times more likely a positive or negative test result is in a patient compared with a healthy individual
  - **LHR+ sensitivity/(1-specificity)**
  - **LHR- (1-sensitivity)/specificity**

Post OCT probabilities of Glaucoma

The **Fagan nomogram** is a graphical tool for estimating how much the result on a diagnostic test changes the probability that a patient has a disease



OCT V C/D ratio

Sn 72%

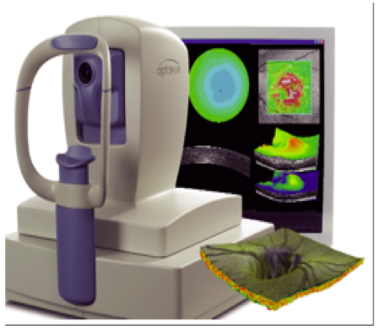
Sp 94%

+LHR 12

-LHR 0.30

Michelessi et al 2015; Fagan. NEJM 1975.

Uno vale l'altro? Sono Intercambiabili?



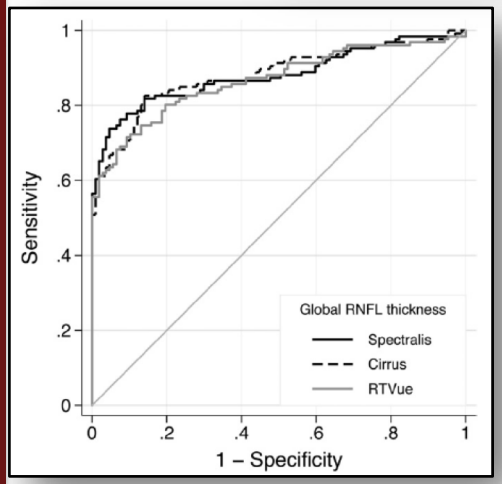
Comparison of the Diagnostic Accuracies of the Spectralis, Cirrus, and RTVue Optical Coherence Tomography Devices in Glaucoma

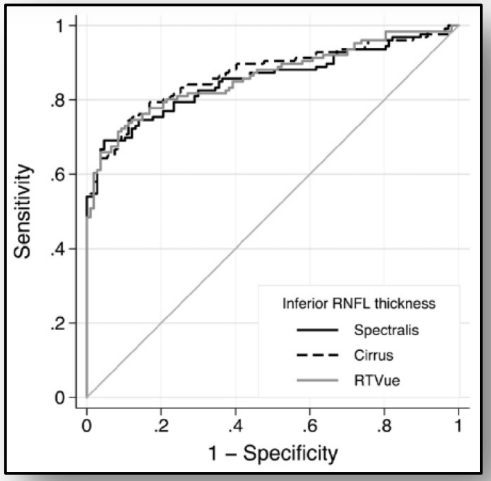
Mauro T. Leite, MD,[1,2] Harsha L. Rao, MD,[1,3] Linda M. Zangwill, PhD,[1] Robert N. Weinreb, MD,[1] Felipe A. Medeiros, MD, PhD[1,2]

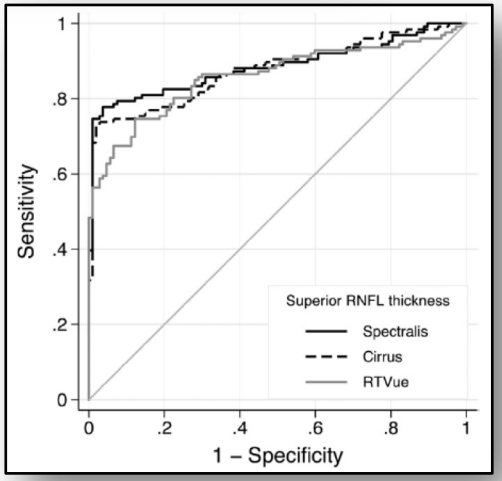
Ophthalmology 2011

Table 2. Race and Age-Adjusted Areas Under Receiver Operating Characteristic Curves (95% Confidence Interval) for the Different Parameters of Each Instrument

Sector	Spectralis (Heidelberg Engineering, Dossenheim, Germany)	Cirrus (Carl Zeiss Meditec, Dublin, CA)	RTVue (Optovue Inc., Fremont, CA)	P Value*
Global thickness	0.88 (0.82–0.94)	**0.88 (0.82–0.94)**	**0.87 (0.81–0.93)**	0.34
Inferior thickness	0.85 (0.79–0.92)	0.87 (0.81–0.93)	0.86 (0.80–0.92)	0.28
Superior thickness	**0.88 (0.83–0.94)**	0.88 (0.82–0.93)	0.86 (0.79–0.92)	0.18
Nasal thickness	0.73 (0.64–0.81)	0.60 (0.51–0.71)	0.71 (0.62–0.81)	0.01†
Temporal thickness	0.70 (0.61–0.80)	0.69 (0.58–0.79)	0.72 (0.63–0.81)	0.26







Agreement Among Spectral-Domain Optical Coherence Tomography Instruments for Assessing Retinal Nerve Fiber Layer Thickness

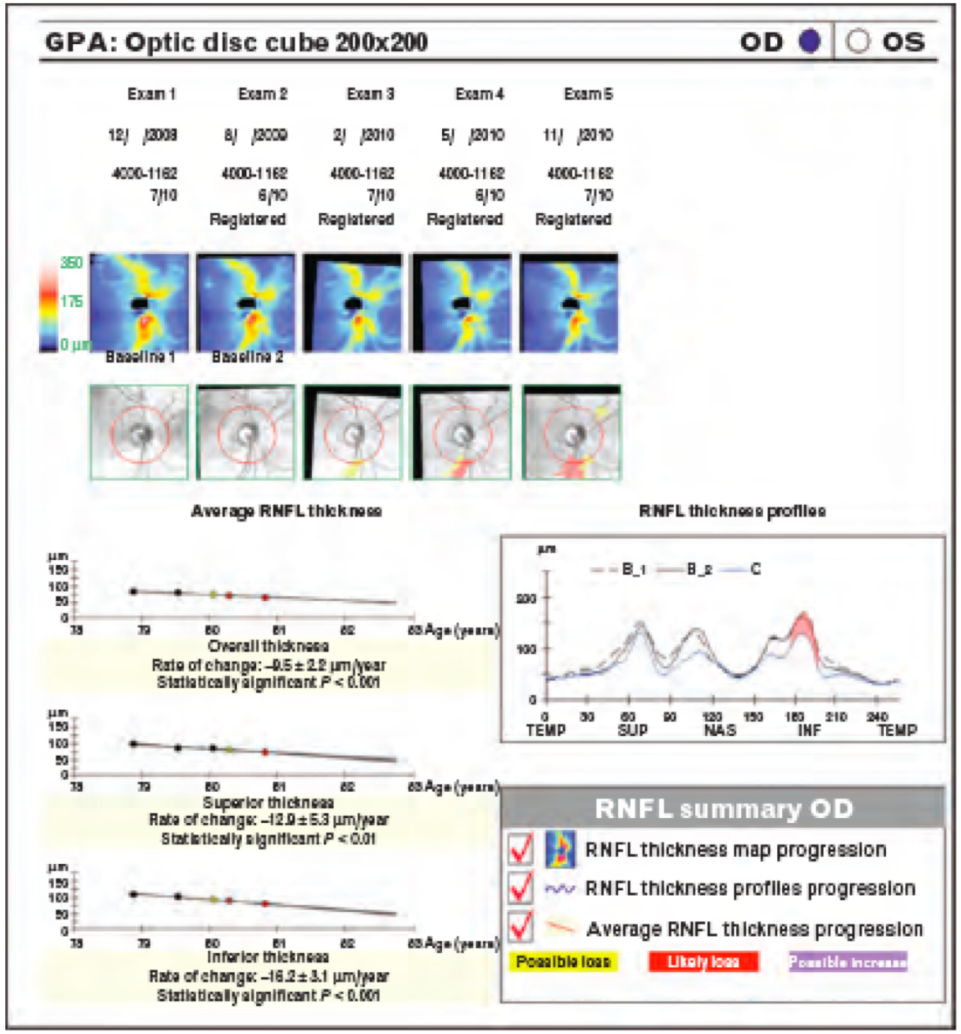
MAURO T. LEITE, HARSHA L. RAO, ROBERT N. WEINREB, LINDA M. ZANGWILL, CHRISTOPHER BOWD, PAMELA A. SAMPLE, ALI TAFRESHI, AND FELIPE A. MEDEIROS

	RTVue	Cirrus	Spectralis
Average thickness (μm)	92 (91.2–94.2)	83 (81.5–85.3)	85 (83.4–86.7)
Superior thickness (μm)	110 (108.4–112.3)	101 (98.7–102.9)	99 (97–101.7)
Temporal thickness (μm)	69 (67.8–70.6)	58 (56.4–59)	66 (64.2–67.2)
Inferior thickness (μm)	119 (116.5–121.2)	104 (102–106.9)	111 (107.8–113.2)
Nasal thickness (μm)	72 (70.9–73.8)	68 (67.2–69.6)	65 (62.9–66.3)

Spessori maggiori con l'Rtvue rispetto al Cirrus /Spectralis

Am J Ophthalmol 2011

Analisi di progressione: Cirrus



Analisi della Progressione

Sia l'RNFL che i parametri maculari mostrano promettenti risultati (maculari migliori nelle forme avanzate?)

Problemi

- Follow up brevi, relativamente pochi studi disponibili
- Cambiamenti dovuti all'età come fattore confondente
- Effetto pavimento (cambiamenti funzione della baseline)
- Sviluppo di opacità dei mezzi (cataratta)

Fattori confondenti la qualità dell'immagine

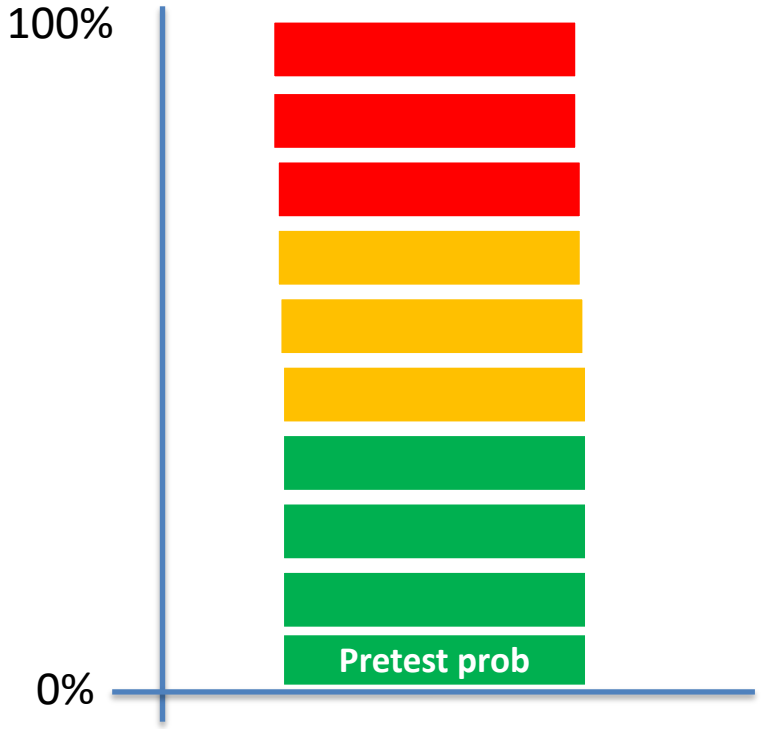
- Occhio secco
- Cataratta
- Corpi mobili vitreali
- Ammiccamento durante la scansione
- Distacco posteriore di vitreo/trazioni VM
- Artefatti di movimento
- Opacità della lente
- Immagine troncata per incorretto allineamento
- Errata identificazione dei margini
- Segmentazione inaccurata

Glaucoma diagnosis: a bayesian approach

RISK FACTORS/DIAGNOSTIC TESTS

- Family history
- Older age
- Suspicious disc/field
- Increased IOP
- Reduced CCT
- PEX
- Afro-caribbean origin
- Imaging test ONL

PROBABILITY OF HAVING THE DISEASE
(physician confidence in the diagnosis)



Risk stratification to guide decision making

- This method of risk stratification can allow to **allocate treatment** for those glaucoma **suspects at highest risk** of having the disease and just monitoring those at lower risk

Managing Uncertainty

RISK FACTORS/DIAGNOSTIC TESTS

- Family history → **uncertain**
- Age → **middle**
- IOP → **lower twenties**
- CCT → **normal range**
- PEX → **absent**
- VF test → **unreliable**
- Imaging test → **borderline**

Physician confidence in the diagnosis starts to waver

Diagnosing by monitoring changes

- In many eyes with early glaucoma, the **diagnosis is uncertain** when the patient is first seen
- Given the progressive nature of glaucoma, **careful follow-up** to identify structural or functional changes **might enable a diagnosis to be made**

DF. Garway-Heath. Progr Brain Res 2008

Are Structural Changes Relevant to the Patient?

- **Each 1-micron/year** faster rate of cpRNFL loss was associated with a **2-times higher risk** of a visual field defect developing[1]
- **Similar results were found in eyes with established glaucoma**, with progressive RNFL thinning on trend-based progression analysis strongly predictive of visual field loss[2]

1. Miki A et al . Ophthalmology 2014
2. Yu M et al. Ophthalmology 2016

How Are Measurements Affected by Aging?

- Lack of longitudinal reference databases to determine whether an observed rate of change is pathologic or expected for age
- **Trend-based analysis** of RNFL thickness change **should involve testing the statistical significance of its change relative to the mean estimate of age-related changes** (similarly to evaluating visual field progression using mean deviation instead of mean sensitivity)

Wu Z et al. AJO 2017

Monitoring with OCT or VF?

- **Simultaneous** detection of change in structural and functional measurements **is rare**
- **Eyes with less severe disease** at baseline have a higher chance of being detected as progressing **by OCT**
- **Eyes with more advanced disease** have a higher chance of being detected as progressing **by SAP**
- Both **structural and functional** tests should be **monitored** for optimal assessment of glaucoma progression

Tatham et al. Ophthalmology 2017

J Glaucoma. 2022 Aug 11. doi: 10.1097/IJG.0000000000002101. Online ahead of print.

Frequency of Optical Coherence Tomography Testing to Detect Progression in Glaucoma

Bruna Melchior [1 2], Carlos Gustavo De Moraes [1], Jayter S Paula [2], George A Cioffi [1], Christopher A Girkin [3], Massimo A Fazio [3], Robert N Weinreb [4], Linda M Zangwill [4], Jeffrey M Liebmann [1]

Affiliations + expand

PMID: 35980865 DOI: 10.1097/IJG.0000000000002101

Conclusion: With high specificity and less variability than perimetry, a 6-month testing interval provides a reasonable trade-off for following glaucoma patients using OCT.

Take home messages

- The OCT is an **evolving technology**
- The test output should be interpreted as a **statistical support** to alter the pre-test probability that a subject has the disease and not as a diagnostic verdict itself
- **Evidence of progression** sometimes is the only way to support an accurate diagnosis
- The diagnosis still remains the result of the integration of clinical, functional and structural information that only the **Human Brain** can accomplish

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GLAUCOMA WORKSHOP
APPROCCIO DIGNOSTICO ALLA PATOLOGIA DEL GLAUCOMA

Ruolo dell'OCT nell'algoritmo diagnostico del glaucoma

Francesco Oddone

Responsabile Unità Operativa Glaucoma

Ospedale Britannico

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Roma

Roma, 7 ottobre 2022