GLAUCOMA WORKSHOP
APPROCCIO DIGNOSTICO ALLA PATOLOGIA DEL GLAUCOMA

L'importanza della macula nella diagnosi del glaucoma

Francesco Oddone
Responsabile Unità Operativa Glaucoma
Ospedale Britannico
IRCCS Fondazione G.B.Bietti
Roma

Roma, 7 ottobre 2022

L’analisi maculare

Perché tanto interesse per la macula?

Progress in Retinal and Eye Research 32 (2013) 1–21

Contents lists available at SciVerse ScienceDirect

Progress in Retinal and Eye Research

journal homepage: www.elsevier.com/locate/prer

Glaucomatous damage of the macula

Donald C. Hood [a,b,*,1], Ali S. Raza [a,c,1], Carlos Gustavo V. de Moraes [d,e,1], Jeffrey M. Liebmann [d,e,1], Robert Ritch [d,f,1]

There is a growing body of evidence that early morphological and functional damage involves the macula

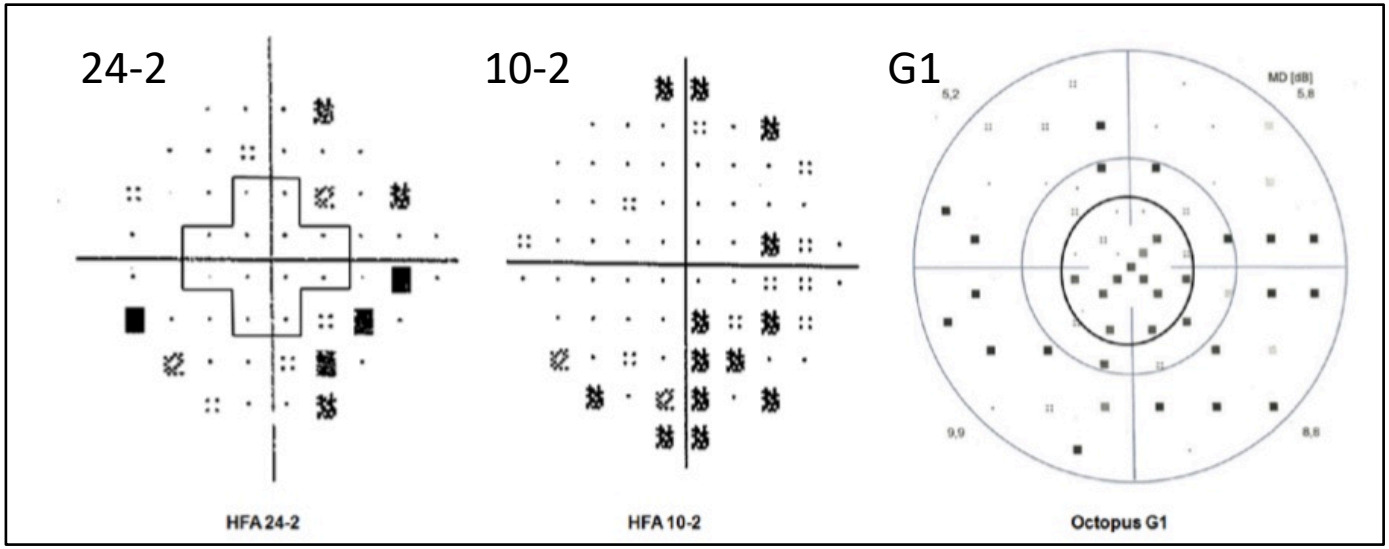
Hood DC, et al. 2012

Early Functional Macular Damage

RESEARCH ARTICLE

Detection of central visual field defects in early glaucomatous eyes: Comparison of Humphrey and Octopus perimetry

Gloria Roberti[1]*, Gianluca Manni[1,2], Ivano Riva[1], Gabor Holló[3], Luciano Quaranta[4], Luca Agnifili[5], Michele Figus[6], Sara Giammaria[7], Davide Rastelli[2], Francesco Oddone[1]



Plos One 2017

RGC in the macula

- RGC density is highest within the macula which hosts the the cell bodies of 50% of all RGC
- Additionally, the macula is the only place in the retina where more than a single RGC body exists in the ganglion cell layer (up to 7 layers)

Curcio CA, et al. J Comp Neurol. 1990
Zeimer R et al. Ophthalmology 1998

La Macula e il Glaucoma

La Macula…

- Il corpo cellulare è sostanzialmente più grande dell'assone della cellula, questo potrebbe migliorare la capacità di rilevare il danno anatomico
- Oggi possiamo segmentare e misurare il singolo strato
- Nella macula puoi valutare anche il RNFL (mRNFL)
- Possibile comparsa del danno con tempistiche diverse rispetto a ONH e RNFL
- Minore variabilità anatomica rispetto al nervo ottico

Curcio CA, et al. J Comp Neurol. 1990
Zeimer R et al. Ophthalmology 1998

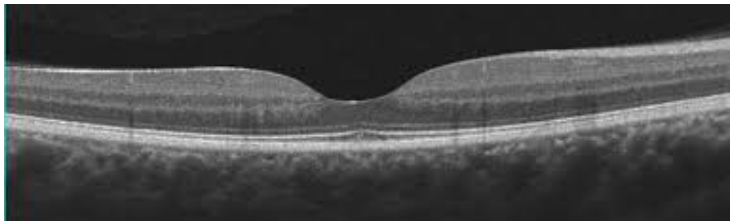
Less Anatomical variability and DA

- Compared to the ONH, the macula is a relatively simple structure that is devoid of large vessels
- The macula shape, more specifically the RGC layer, is generally less variable among healthy individuals
  - > Anatomical changes would more likely be the result of a pathologic process rather than the result of normal variation
    (higher specificity- > reduced FPR)

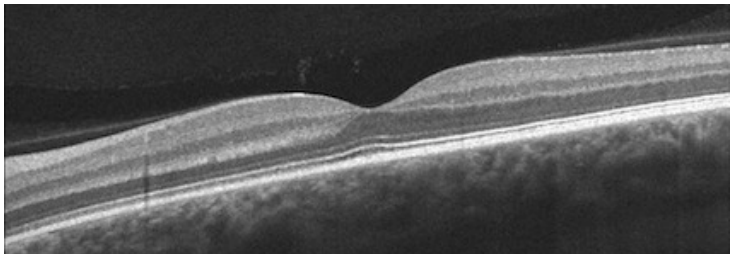
Less inter-eye anatomical variability of the macula

Macula is affected by less anatomical variability than ONH and pRNFL

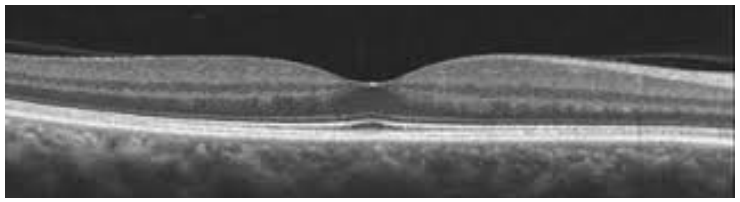
1



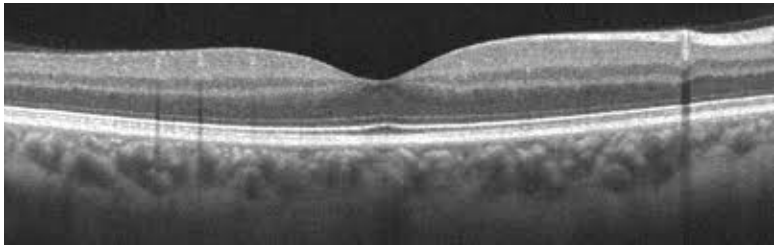
2



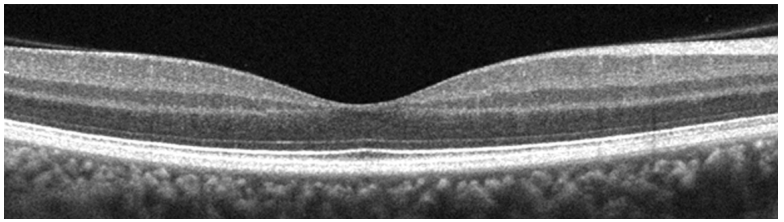
3



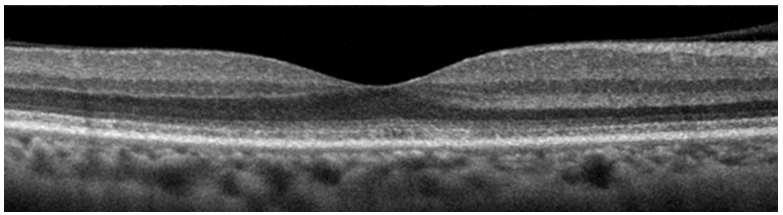
4



5

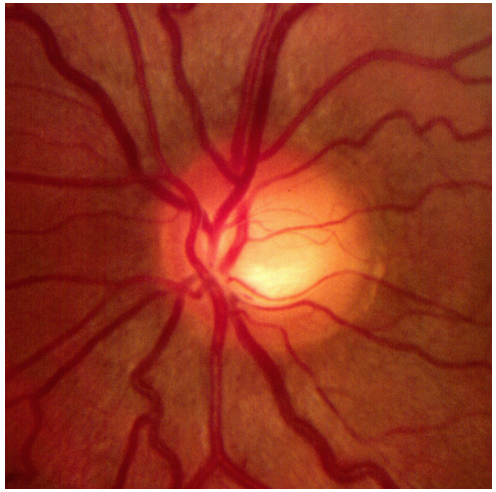


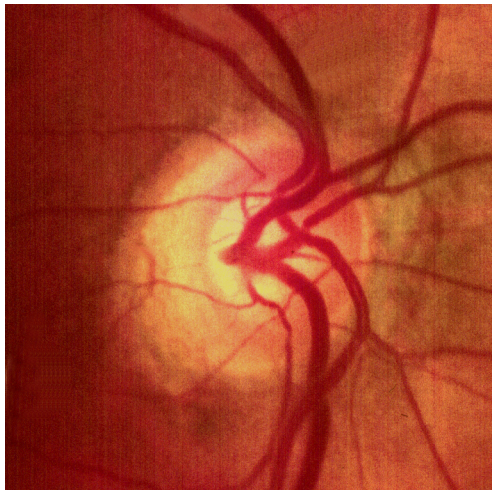
6



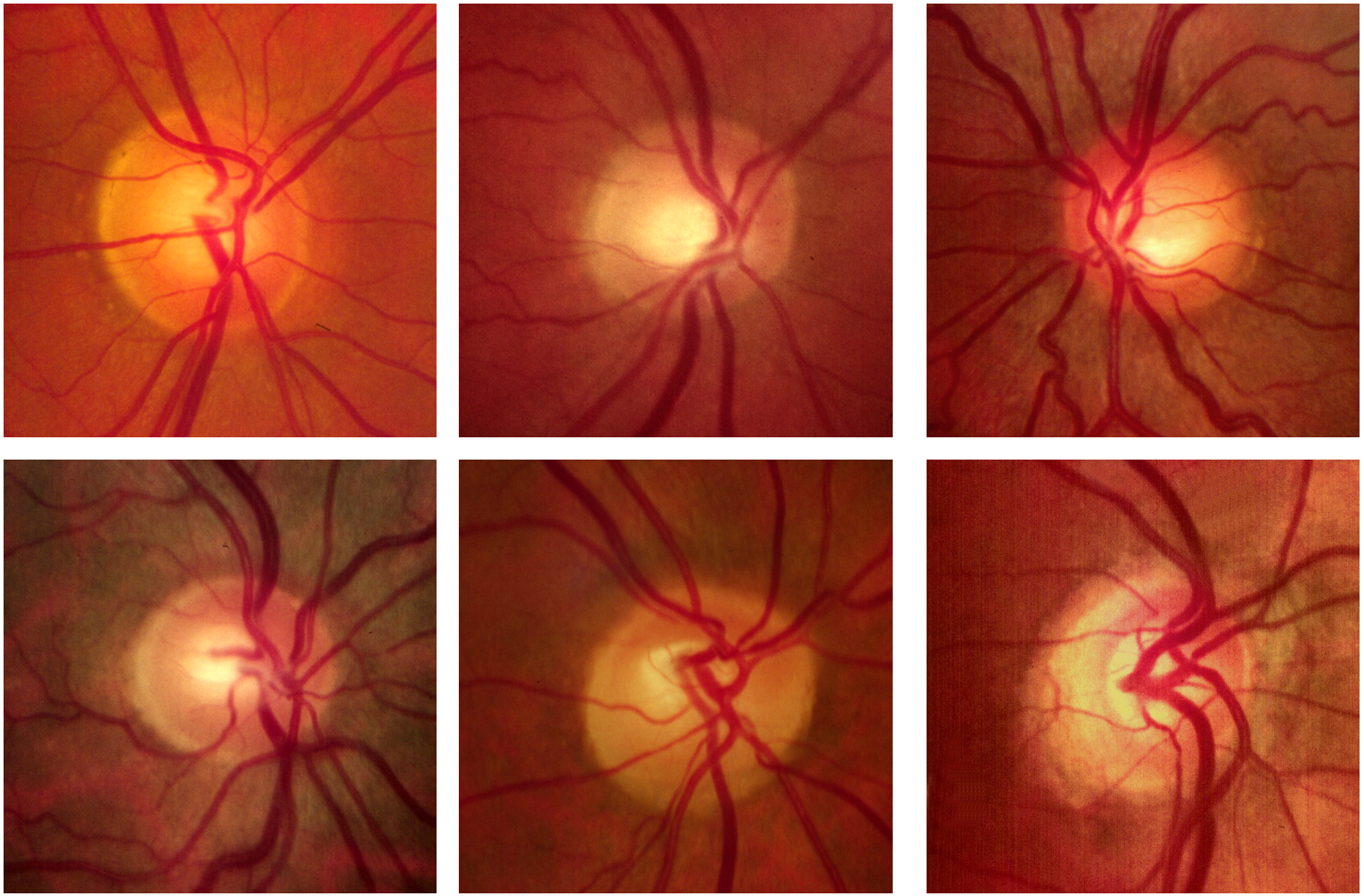
Anatomical variability of ONH

- ONH evaluation may be complicated by:
  - The high variability of ONH size and shape
  - The depth of the LC insertion
  - The configuration of the blood vessels
  - The angle of insertion of the ON (tilting)
- RNFL evaluation may be complicated by:
  - Displacement of RNFL boundle caused by ONH tilting
  - Peripapillary atrophy



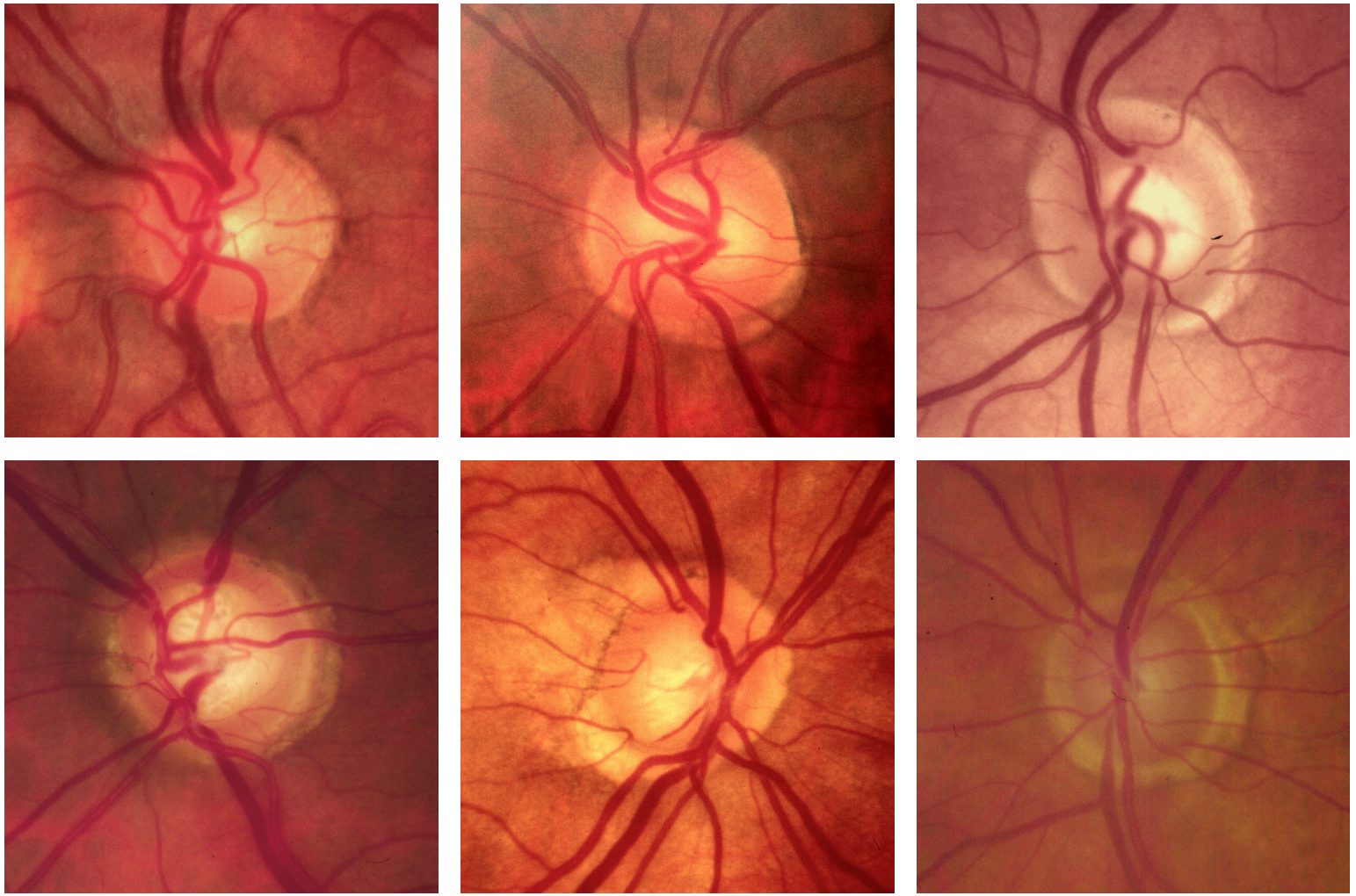


Inter-eye anatomical variability of ONH



Courtesy of DF Garway-Heath

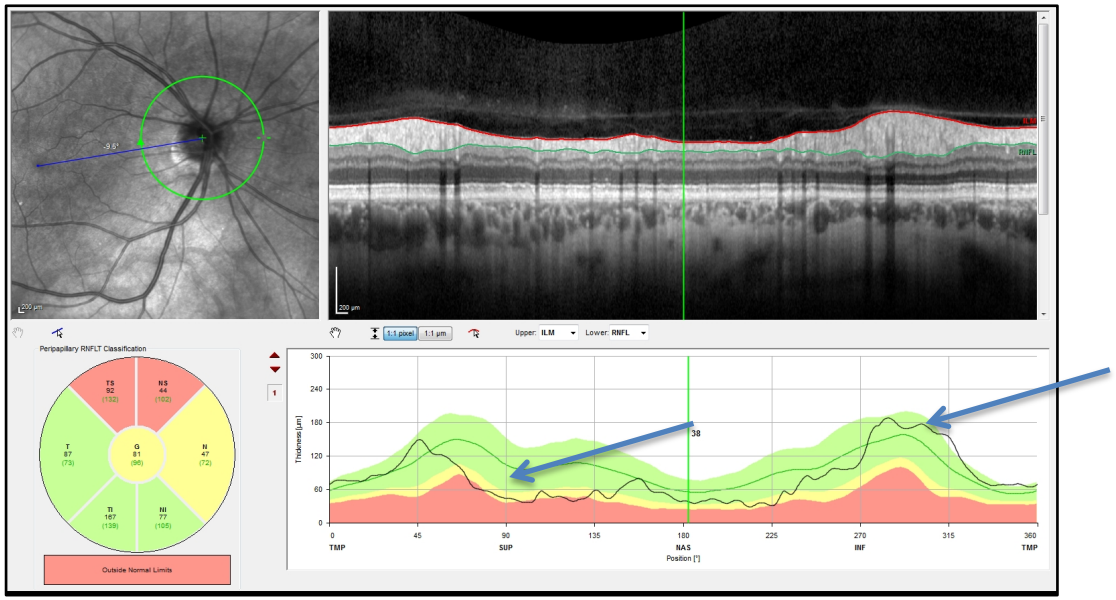
Inter-eye anatomical variability of ONH



Courtesy of DF Garway-Heath

Anatomical variability of pRNFL

- RNFL anatomy is less variable inter-individually but can be influenced by:
  - Displacement of RNFL boundle caused by ONH tilting
  - Peripapillary atrophy



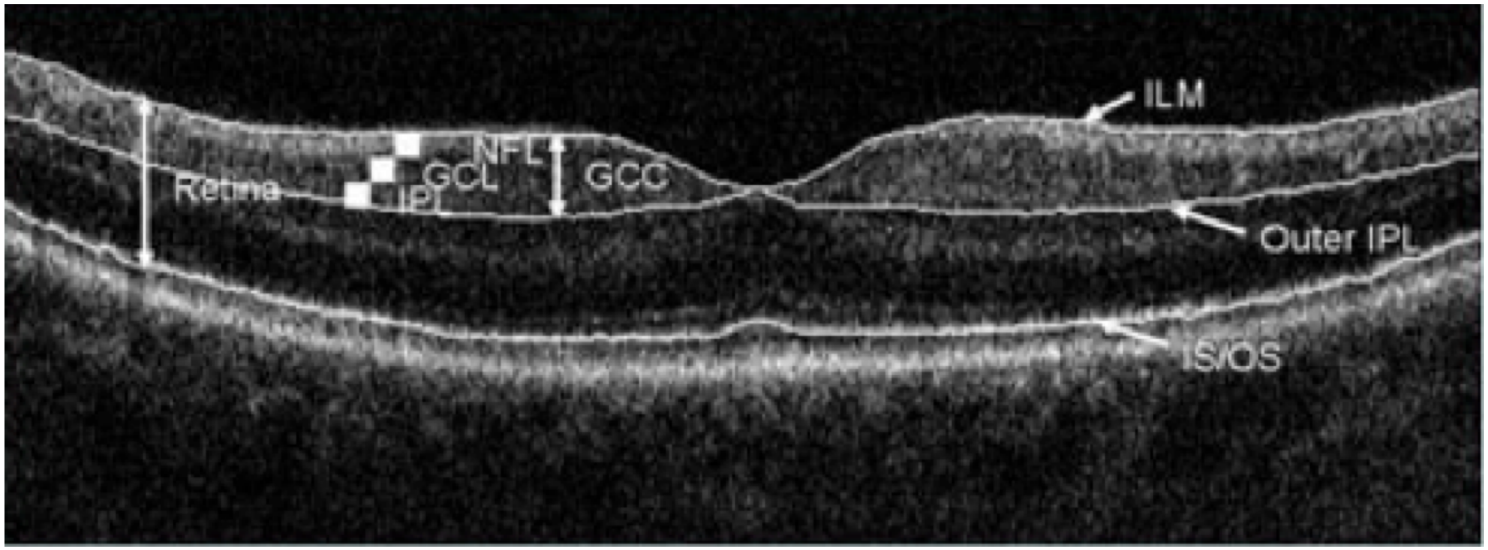
Total Macular Thickness & Glaucoma

- With TD-OCT the diagnostic accuracy of total macular thickness was found to be significantly worse than that of pRNFL thickness
- This could be related to the fact that the retinal layers affected by glaucoma constitute only **1/3** of the total macular thickness.
- The remaining **2/3** that are not affected by glaucoma might contribute to measurement variability

Lederer DE et al 2003; Giovannini A et al 2002; Greenfield DS et al 2003; Tanito M et al. 2004; Wollstein G et al 2004; Guedes V et al 2003

Segmentation now possible with SD-OCT

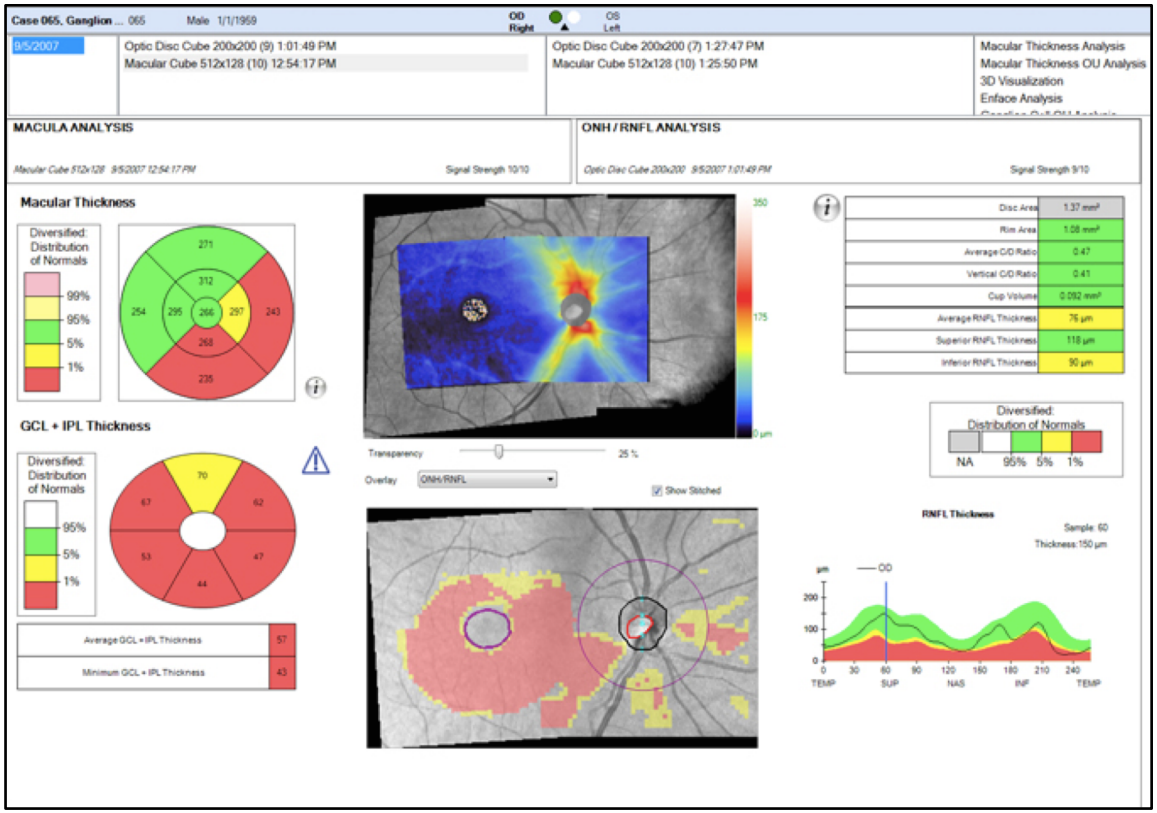
- Retinal nerve fiber layer (RNFL; assoni)
- Ganglion cell layer (GCL; corpo cellulare)
- Inner plexiform layer (IPL; dendriti)



Segmentation possible with SD-OCT

Cirrus HD: GCIPL

Ganglion cell layer (GCL) + Inner plexiform layer (IPL)



AMERICAN ACADEMY™ OF OPHTHALMOLOGY

Macular versus Retinal Nerve Fiber Layer Parameters for Diagnosing Manifest Glaucoma

A Systematic Review of Diagnostic Accuracy Studies

Francesco Oddone, MD,[1] Ersilia Lucenteforte, ScD, PhD,[2] Manuele Michelessi, MD,[1] Stanislao Rizzo, MD,[3] Simone Donati, MD,[4] Mariacristina Parravano, MD,[1] Gianni Virgili, MD[3]

34 clinical studies
5226 eyes

Table 3. Relative Diagnostic Odds Ratio with Reference to the Average Thickness Parameter (Upper Half of the Table) and the Parameter with the Highest Diagnostic Odds Ratio for Each Test (Lower Half of the Table)

OCT Device	Parameter	No. of Direct Studies (No. of Patients)	Sensitivity (95% CI)	Specificity (95% CI)	Relative DOR (95% CI)	*P* Value
Cirrus	RNFL inferior	7 (1178)	0.79 (0.67–0.87)	0.94 (0.92–0.96)	Reference 60.62 (29.04–126.56)	Reference
	GCIPL minimum		0.79 (0.68–0.88)	0.90 (0.87–0.93)	0.59 (0.35–0.98)	0.0420

GCC = ganglion cell complex; GCIPL = ganglion cell inner plexiform layer; RNFL = retinal nerve fiber layer.
Relative diagnostic odds ratios (DORs) are based only on studies that measure both parameters (i.e., on direct comparisons). Relative DORs are obtained from hierarchical summary receiver operating characteristic curves assuming parallelism of summary receiver operating characteristic curves by covariate levels (i.e., assuming curves with the same shape).

RNFL parameters are still preferable to macular parameters for diagnosing manifest glaucoma, but the differences are small.

Oddone F et al. Ophthalmology 2016

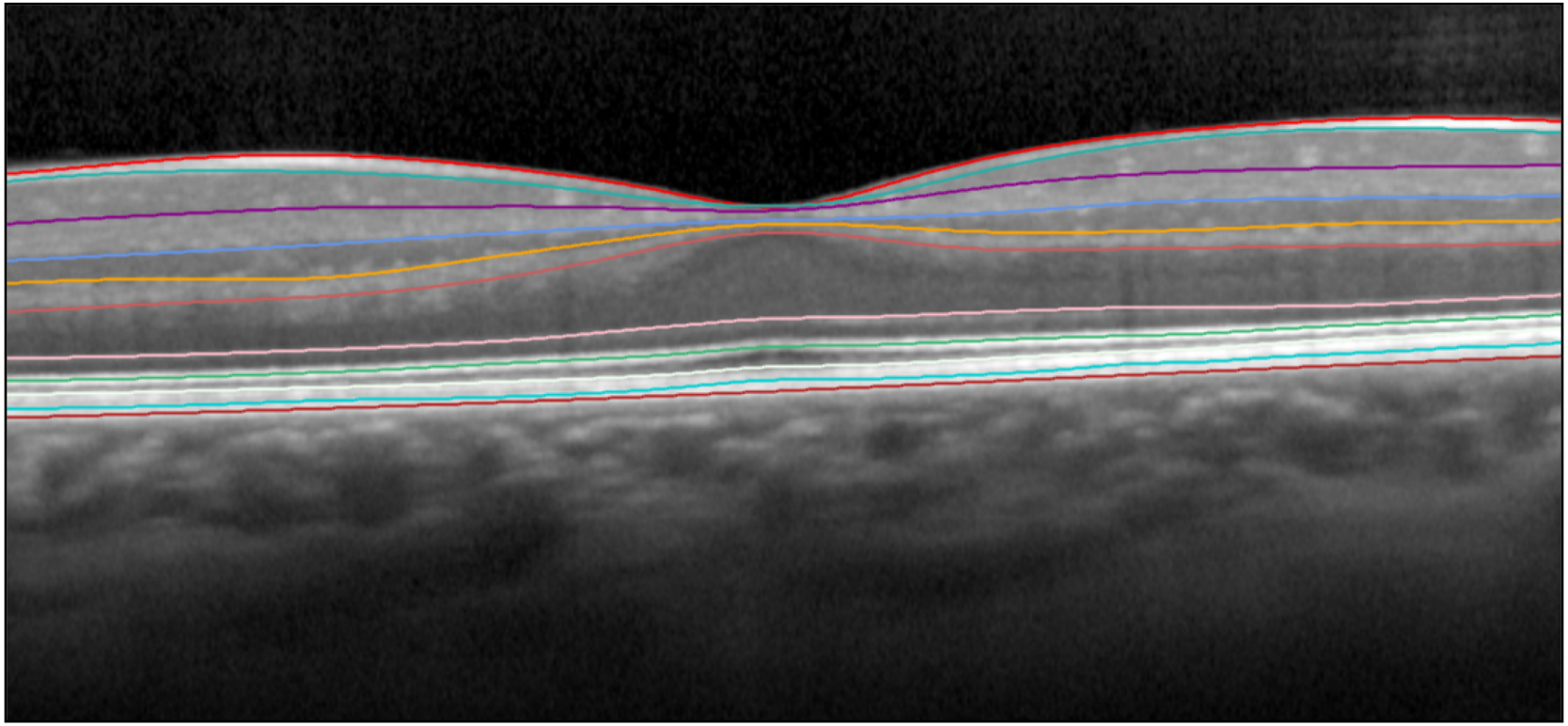
Key message

- With the use of OCT, RNFL parameters are still preferable to macular parameters for diagnosing manifest glaucoma, but the differences are small.
- Because of high heterogeneity, direct comparative or randomized studies of OCT devices or OCT parameters and diagnostic strategies are essential

SD-OCT: Layer by Layer Segmentation

- Today SD-OCTs can segment up to 9 individual layers of the retina at the macular level

Enhanced segmentations



Acta Ophthalmologica

Acta Ophthalmologica 2018

Macular versus nerve fibre layer versus optic nerve head imaging for diagnosing glaucoma at different stages of the disease: Multicenter Italian Glaucoma Imaging Study

Manuele Michelessi,[1] Ivano Riva,[1] Enrico Martini,[2] Michele Figus,[3] Paolo Frezzotti,[4] Luca Agnifili,[5] Gianluca Manni,[1,6] Luciano Quaranta,[7] Stefano Miglior,[8] Chiara Posarelli,[3] Stefano Fazio[4] and Francesco Oddone[1]

Multicentre Italian Glaucoma Imaging Study (MIGIS)

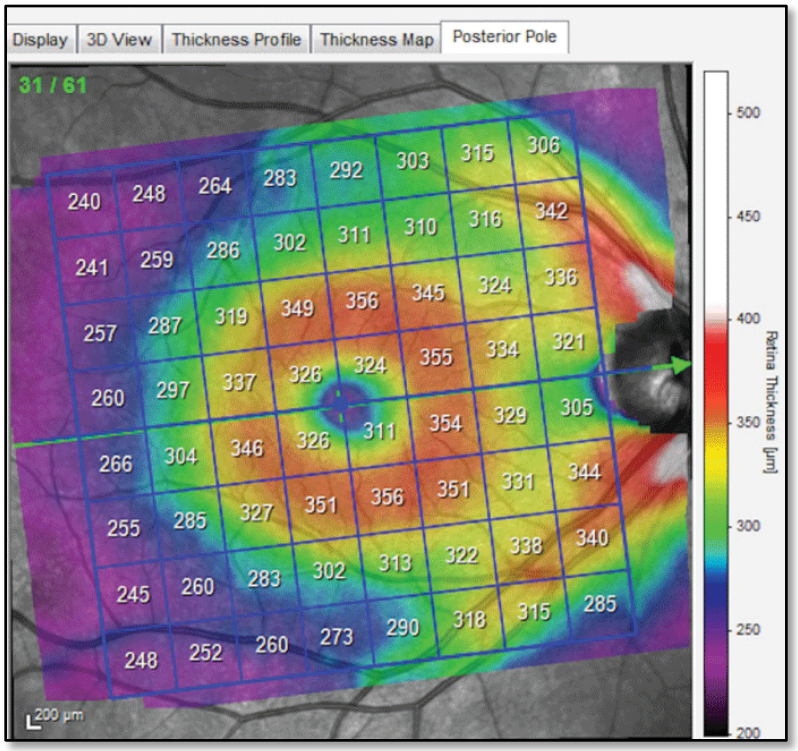
N= 300

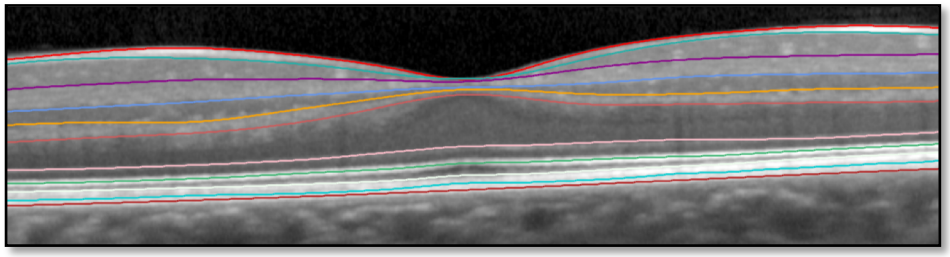
192 Glaucoma
90 Controls

Early
N= 72

Moderate
N= 60

Advanced
N= 60





1. Agnifili - Chieti
2. Figus - Pisa
3. Frezzotti - Siena
4. Iester - Genova
5. Maritini - Sassuolo
6. Mastropasqua - Chiet
7. Michelessi - Roma
8. Miglior - Monza
9. Oddone - Roma
10. Quaranta - Brescia
11. Riva – Brescia/Monza

Acta Ophthalmologica – 2018

Multicentre Italian Glaucoma Imaging Study (MIGIS)

Parameter	AUC (95% CI) Early	Moderate	Advanced
pRNFL			
Average	**0.929 (0.88–0.96)**	**0.933 (0.88–0.97)**	**0.96 (0.91–0.98)**
Supero-temporal	0.86 (0.79–0.91)*	0.868 (0.80–0.92)*	0.914 (0.85–0.95)
Temporal	0.76 (0.69–0.82)*	0.823 (0.75–0.88)*	0.903 (0.84–0.95)
Infero-temporal	0.89 (0.83–0.93)	0.927 (0.87–0.96)	0.96 (0.91–0.99)
Infero-nasal	0.846 (0.78–0.9)*	0.92 (0.86–0.96)	0.939 (0.88–0.97)
Nasal	0.856 (0.79–0.91)*	0.867 (0.80–0.92)*	0.883 (0.82–0.93)*
Supero-nasal	0.788 (0.72–0.85)*	0.865 (0.80–0.91)*	0.916 (0.85–0.96)
MRW			
Average	**0.956 (0.91–0.98)**	**0.961 (0.92–0.98)**	**0.994 (0.96–0.99)**
Supero-temporal	0.936 (0.85–0.97)	0.937 (0.89–0.97)	0.976 (0.93–0.99)
Temporal	0.88 (0.82–0.93)*	0.908 (0.85–0.95)*	0.96 (0.91–0.99)
Infero-temporal	0.952 (0.91–0.98)	0.960 (0.92–0.98)	0.982 (0.94–0.99)
Infero-nasal	0.945 (0.9–0.97)	0.956 (0.91–0.98)	0.993 (0.96–0.99)
Nasal	0.925 (0.87–0.96)	0.945 (0.90–0.98)	0.984 (0.94–0.99)
Supero-nasal	0.934 (0.88–0.97)	0.946 (0.90–0.98)	0.988 (0.95–0.99)
Macular			
mRNFL CMA	0.82 (0.75–0.88)	0.884 (0.82–0.93)	0.923 (0.86–0.96)
GCL CMA	0.869 (0.81–0.92)	0.928 (0.87–0.96)	0.976 (0.93–0.99)
IPL CMA	0.858 (0.79–0.91)	0.932 (0.88–0.97)	0.981 (0.94–0.99)
GCIPL CMA	0.866 (0.80–0.91)	0.934 (0.88–0.97)	0.981 (0.94–0.99)
GCC CMA	0.874 (0.81–0.92)	0.928 (0.87–0.96)	0.981 (0.94–0.99)

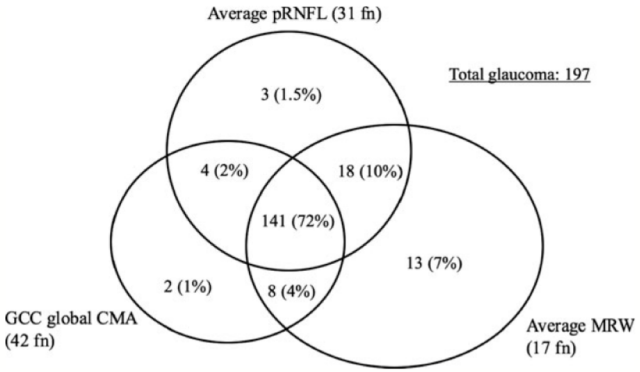
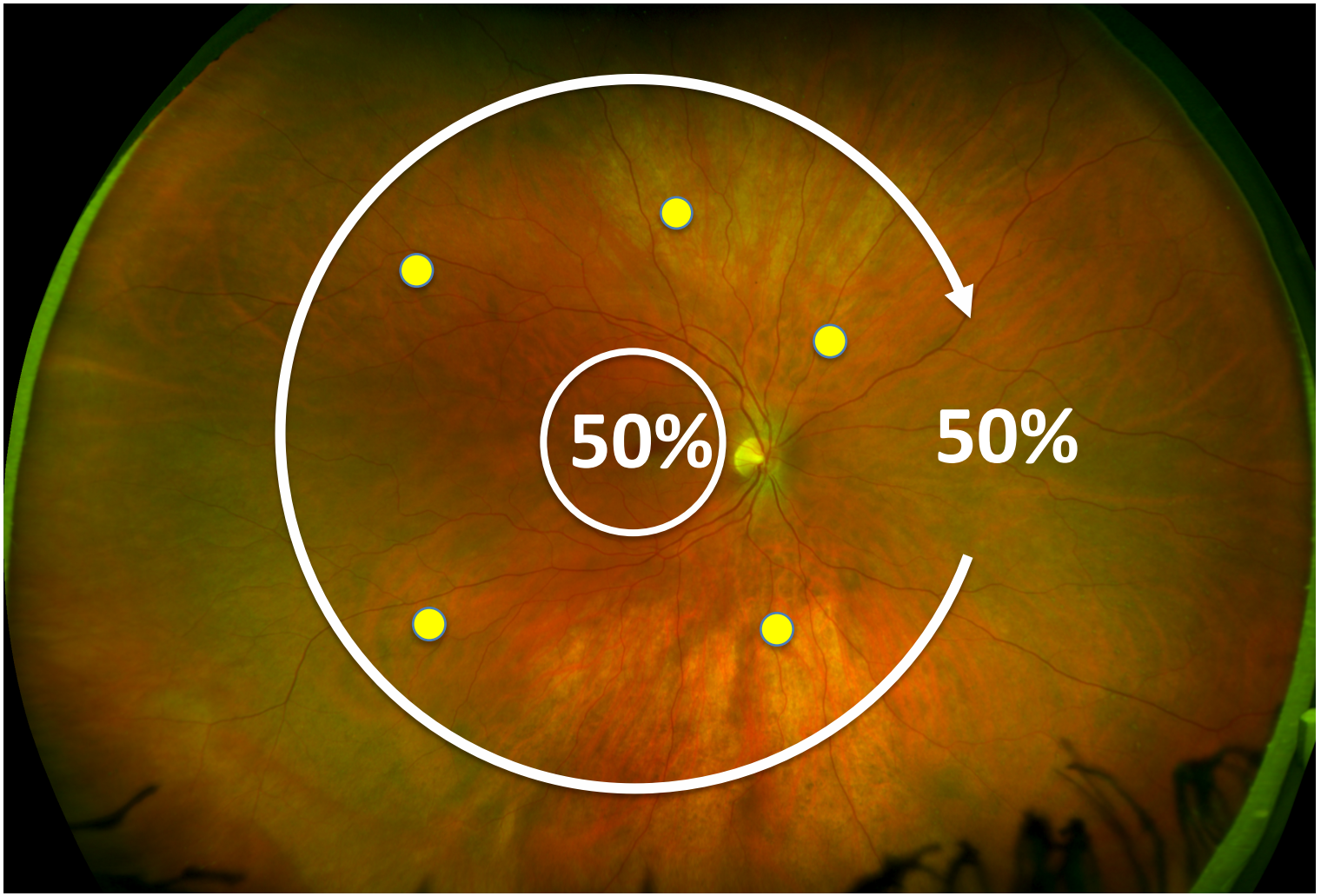


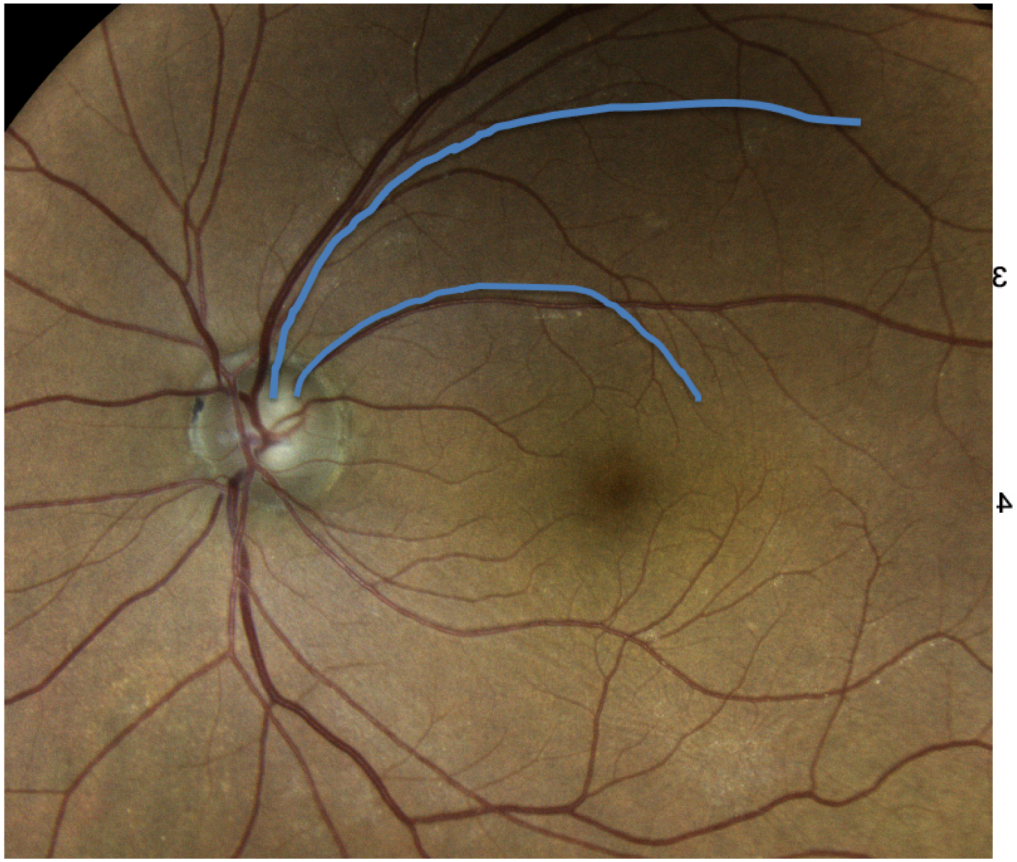
Fig. 2. Venn diagram illustrating the agreement between average MRW, average pRNFL and GCC CMA parameters in detecting glaucoma (true positives). fn = false negative.

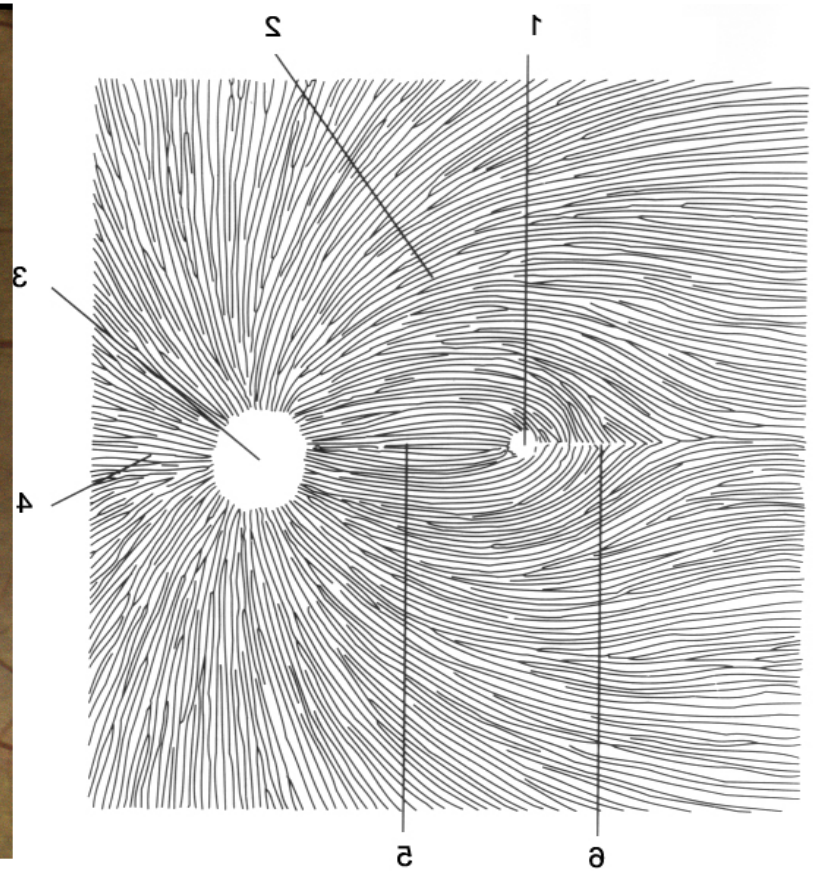
Acta Ophthalmologica – 2018

mRGCs vs Total RGCs



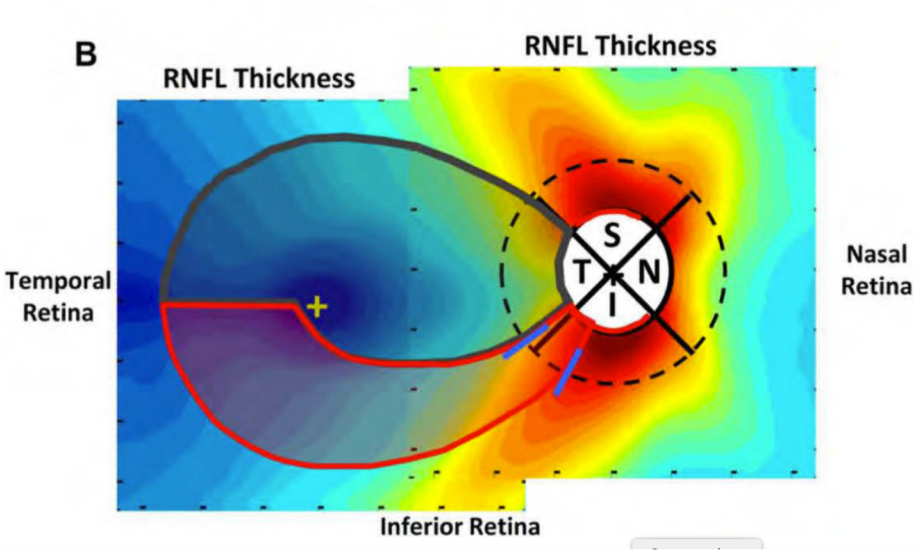
Importanza della sede del danno





Macular Vulnerability Zone (MVZ)

- Region extending from the inferior portion of the temporal quadrant of the macula to the temporal portion of the inferior quadrant of the disc
- That is particularly susceptible to glaucomatous damage
- All glaucoma patients with cp-RNFL defect in the MZV also showed inferior macular GCIPL loss, but the reverse was not true
- A longitudinal investigation confirmed this 20% of eyes with initially inferior macular GCIPL loss without cp-RNFL defect in the MZV subsequently showed an RNFL defect during a 3-year follow-up interval



Hood et al. 2013

Macular & Advanced Glaucoma

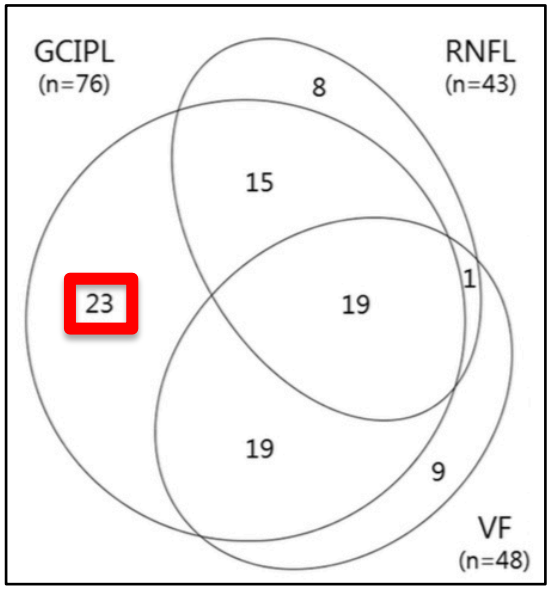
- Nel glaucoma avanzato la **progressione risulta più rapida** e **meglio concordante con il campo visivo** se analizzata attraverso l'analisi maculare **rispetto al pRNFL**[1]
- Una perdita progressiva del **pRNFL** è + difficile da rilevare nel glaucoma avanzato (la maggior parte dell'RNFL è già perso – **effetto pavimento**)
- **L'effetto pavimento** dell'analisi **maculare sarebbe più tardiva** rispetto all'analisi del pRNFL rendendola **più idonea** all'analisi di **progressione** nel glaucoma avanzato[2]

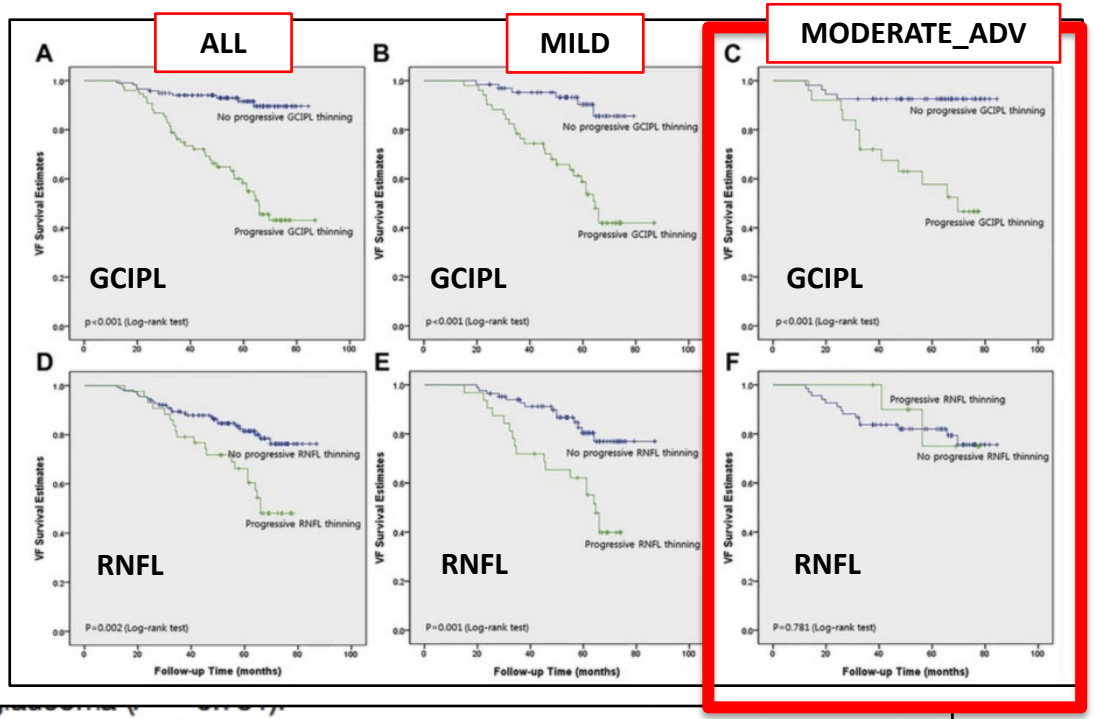
1. Sung KR et al. Ophthalmology 2011
2. Bowd C et al. AJO 2017

AMERICAN ACADEMY™ OF OPHTHALMOLOGY

Ganglion Cell–Inner Plexiform Layer Change Detected by Optical Coherence Tomography Indicates Progression in Advanced Glaucoma

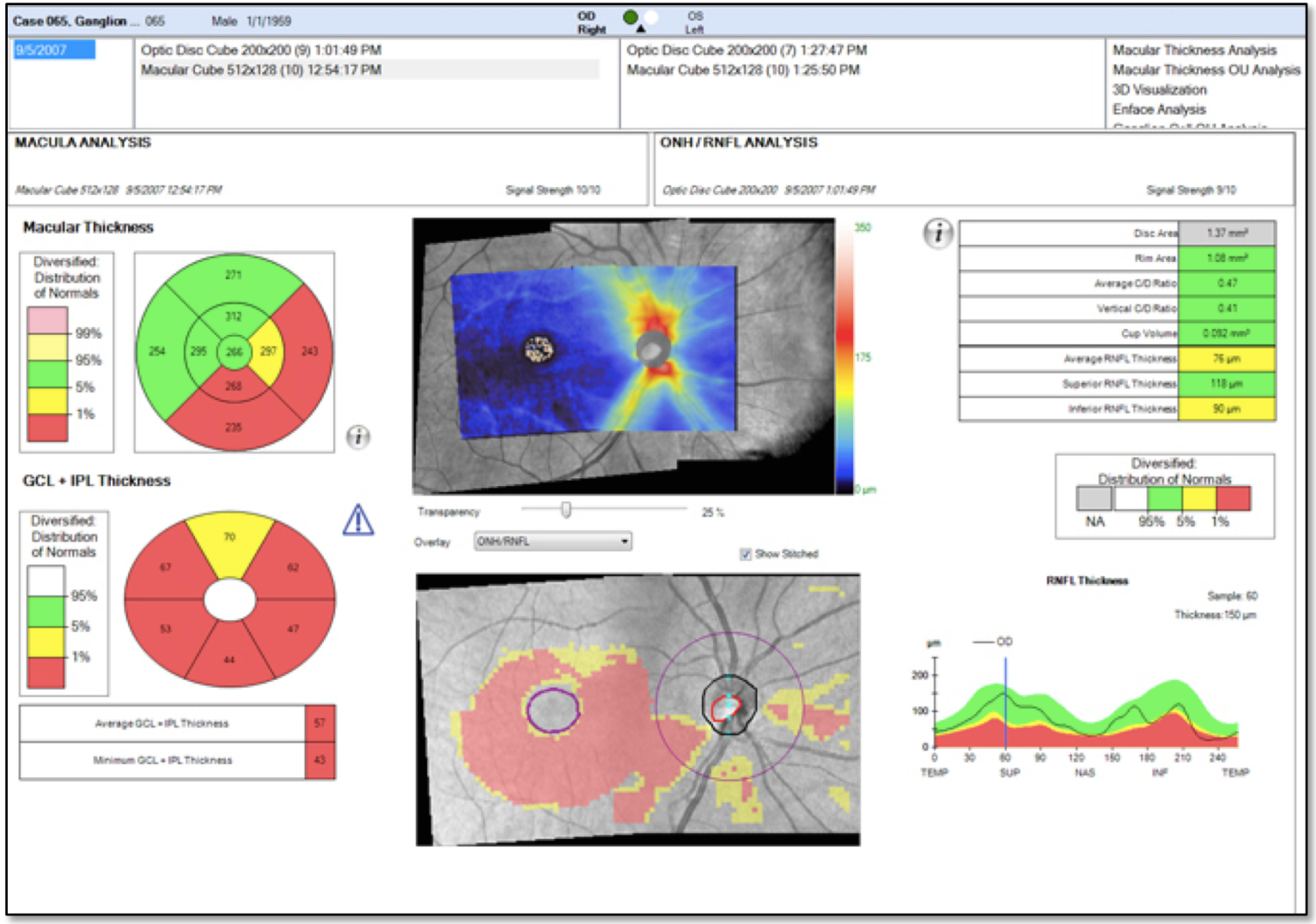
Joong Won Shin, MD,[1] Kyung Rim Sung, MD, PhD,[1] Gary C. Lee, PhD,[2] Mary K. Durbin, PhD,[2] Daniel Cheng, OD[2]





Conclusions: Ganglion cell–inner plexiform layer GPA provides a new approach for evaluating glaucoma progression. It may be more useful for detecting progression in the advanced stages of glaucoma than RNFL GPA. *Ophthalmology 2017;■:1–9* © *2017 by the American Academy of Ophthalmology*

Shin JW et al Ophthalmology 2017


Case 065, Ganglion ... 065 Male 1/1/1959
OD Right
OS Left
9/5/2007
Optic Disc Cube 200x200 (9) 1:01:49 PM
Macular Cube 512x128 (10) 12:54:17 PM
Optic Disc Cube 200x200 (7) 1:27:47 PM
Macular Cube 512x128 (10) 1:25:50 PM
Macular Thickness Analysis
Macular Thickness OU Analysis
3D Visualization
Enface Analysis
MACULA ANALYSIS
Macular Cube 512x128 9/5/2007 12:54:17 PM
Signal Strength 10/10
ONH / RNFL ANALYSIS
Optic Disc Cube 200x200 9/5/2007 1:01:49 PM
Signal Strength 9/10
Macular Thickness
Diversified Distribution of Normals
99%
95%
5%
1%
271
312
254
295
266
297
243
268
235
GCL + IPL Thickness
Diversified Distribution of Normals
95%
5%
1%
70
67
62
53
47
44
Average GCL + IPL Thickness 57
Minimum GCL + IPL Thickness 43
350
175
0 µm
Transparency
25 %
Overlay
ONH/RNFL
Show Stitched
Disc Area 1.37 mm²
Rim Area 1.08 mm²
Average C/D Ratio 0.47
Vertical C/D Ratio 0.41
Cup Volume 0.092 mm³
Average RNFL Thickness 76 µm
Superior RNFL Thickness 118 µm
Inferior RNFL Thickness 90 µm
Diversified Distribution of Normals
NA
95%
5%
1%
RNFL Thickness
Sample: 60
Thickness:150 µm
µm
OD
200
100
0
0
30
60
90
120
150
180
210
240
TEMP
SUP
NAS
INF
TEMP

GLAUCOMA WORKSHOP
APPROCCIO DIGNOSTICO ALLA PATOLOGIA DEL GLAUCOMA

L'importanza della macula nella diagnosi del glaucoma

Francesco Oddone
Responsabile Unità Operativa Glaucoma
Ospedale Britannico
IRCCS Fondazione G.B.Bietti
Roma

Roma, 7 ottobre 2022