Diagnosi precoce del glaucoma: Evidenze scientifiche e ruolo di supporto dell'optometrista.

Riccardo Cheloni, PhD

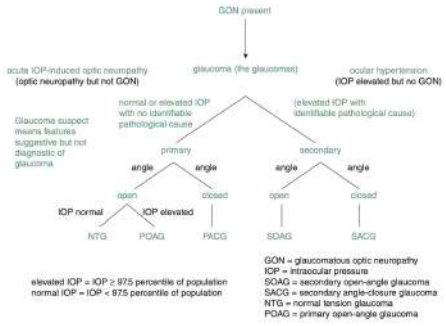
22 Marzo 2024 | Light in Optics and Optometry

University of BRISTOL · Moorfields Eye Hospital NHS Foundation Trust · CITY UNIVERSITY OF LONDON EST 1894

Glaucoma o Glaucomi…

Gruppo eterogeneo di neuropatie ottiche progressive, associate a modifiche strutturali caratteristiche della testa del nervo ottico, e del campo visivo (Foster et al., 2002; Jonas et al., 2017; Weinreb et al., 2016).

- In passato, tendenza ad accomunare glaucoma ad elevata pressione intraoculare (Cedrone et al., 2008);
- Adesso è dimostrato che, sebbene livelli elevati di pressione intraoculare causino glaucoma, in larga parte dei casi è una sinergia di elementi a determinare la patologia, e non la sola pressione intraoculare (Blumberg et al., 2015)



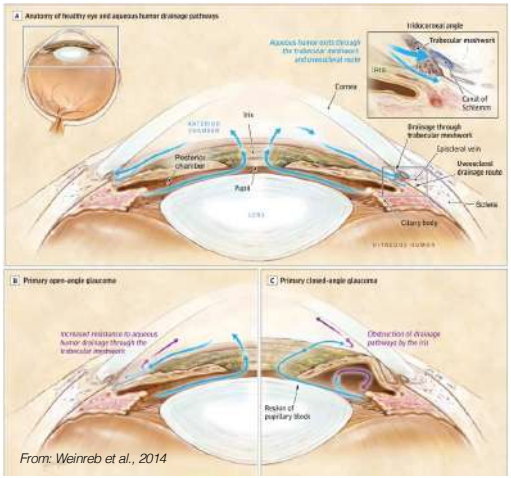
From: Casson et al., 2012

Classificazione

- *Angolo aperto vs chiuso*
  In funzione della conformazione dell'angolo irido-corneale ed accesso al trabecolato.

- *Primario vs secondario*
  In funzione della causa di resistenza al deflusso di umor acqueo, es:
  - Sindrome pseudoesfoliativa
  - Sindrome da dispersione di pigmento

- *Acquisito vs congenito*
  In funzione dell'età di insorgenza della patologia glaucomatosa



From: Weinreb et al., 2014

Glaucoma primario ad angolo aperto

Tipologia più comune di glaucomi riscontrati in paesi occidentali

Primary Open-Angle Glaucoma Preferred Practice Pattern – American Academy of Ophthalmology

European Glaucoma Society Terminology and Guidelines for Glaucoma, 5th Edition

DISEASE DEFINITION

Primary open-angle glaucoma (POAG) is a chronic, progressive optic neuropathy in adults in which there is a characteristic acquired atrophy of the optic nerve and loss of retinal ganglion cells and their axons. This condition is associated with an open anterior chamber angle by gonioscopy. Primary open-angle glaucoma is a potentially blinding eye disease, but early diagnosis and treatment can generally prevent visual disability.

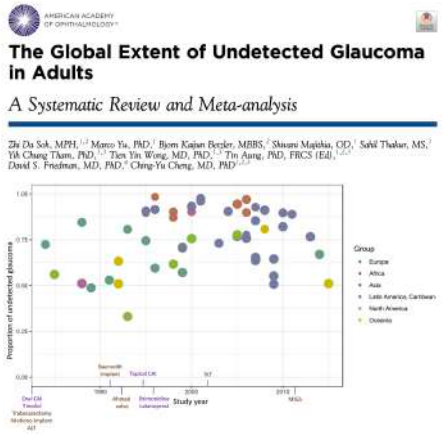
Primary open angle glaucoma is a chronic, progressive, potentially blinding, irreversible eye disease causing optic nerve rim and RNFL loss with related visual field defects. The angle is open with a normal appearance, and major risk factors include the level of IOP and older age. Visual disability is usually prevented by early diagnosis and treatment. See II.2.2

Patologia oculare cronica e progressiva in soggetti adulti caratterizzata da atrofia del nervo ottico e perdita delle cellule gangliari retiniche e delle sue fibre, in presenza di angolo aperto. Il danno è irreversibile, e la patologia può risultare in cecità, ma diagnosi e trattamento precoci possono prevenire la disabilità visiva.

Epidemiologia

- 13% di cecità e danno visivo irreversibile in paesi occidentali (Bourne et al., 2018).
- Prevalenza del 2-3% in Europa, 8 milioni di soggetti affetti (Tham, et al., 2014)
- In larga parte non diagnosticato:
  - 66% dei soggetti con glaucoma non diagnosticato in Europa, 90% in Asia-Africa (Soh et al., 2021).
  - Diagnosi ritardata risulta in significativo danno visivo accumulato
  - Dati UK, ~20% pazienti presenta danno al campo visivo avanzato (MD ≤ -12dB) alla prima visita (Jones et al., 2020, Boodhna and Crabb, 2015).

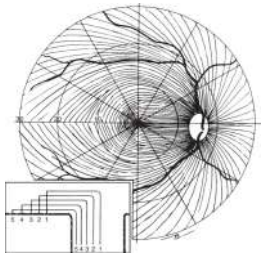
Importanza vitale dello screening oculistico per diagnosi precoce glaucoma.

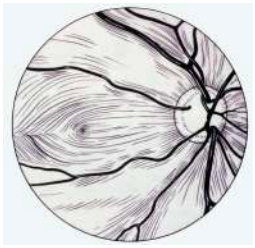


POAG – patofisiologia:

Patologia colpisce gli assoni delle cellule gangliari a livello della testa del nervo ottico:

- **Danno da pressione intraoculare elevata**: danno meccanico (lamina cribrosa), causato da un valore di pressione intraoculare eccessivo
- **Danno indipendente da pressione intraoculare:** danno vascolare, neuro-tossicità, etc.





Glaucoma ≠ pressione elevata

- Proporzione significativa di soggetti sviluppa glaucoma nonostante una ridotta-normale pressione intraoculare, con 30-90% dei soggetti con difetto glaucomatoso che ha pressione normale (Killer, 2018)
- Alcuni soggetti con pressione elevata non sviluppano glaucoma.

A 60 mesi, 4.4% vs 9.5% soggetti con trattamento o controllo sviluppato glaucoma.

A 5 anni, 20% vs 60% soggetti con trattamento o controllo sviluppato progressione glaucoma.

La valutazione del glaucoma, non è sola valutazione della IOP, ma esame oculare complessivo del medico oculista, che include nervo ottico, e campo visivo.

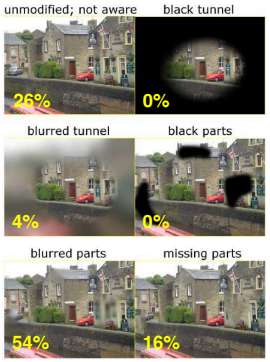
Risk Factor	(Jonas et al., 2017)	(Weinreb et al., 2016)	(Prum et al., 2016)	BMJ Best Practice (Amerasinghe, 2018)	(The College of Optometrists, 2018)
Older Age	O	O	O	O	O
Raised IOP	O	O	O	O	O
Black/African descent	O	O	O	O	O
Positive family history	O	O	O	O	O
Medium/high myopia (>3 - 6 SD)	O	O	O	O	O
Thin CCT (<555µm)	O	O	O	O	O
Male Gender	X	O	X	X	X
Diabetes	X	X	O	X	O
Low Ocular Perfusion	X	X	O	X	X

POAG, presentazione clinica:

1. ~~**Sintomi**~~
2. Nervo ottico e fibre nervose retiniche
3. Campo visivo
4. Pressione intraoculare
5. Esami addizionali

Maggioranza soggetti asintomatici, e sintomi (visione annebbiata, costrizione del vampo visivo) solo con patologia avanzata (Jonas et al., 2017).

Diagnosi molto spesso incidentale, eseguita durante esame oculistico di routine, in soggetti asintomatici.



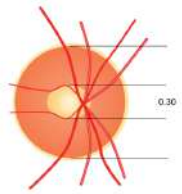
N=50 patients (age 52– 82 years);
Mean deviation -8.7±5.8 dB.

POAG, presentazione clinica:

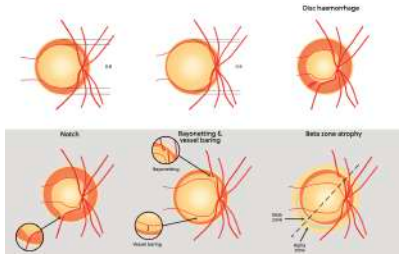
1. Sintomi
2. **Nervo ottico e fibre nervose retiniche**
3. Campo visivo
4. Pressione intraoculare

Esame della testa del nervo ottico, e delle strutture retiniche circostanti: valutazione cardine, che fornisce informazioni essenziali al medico oculista in merito al danno strutturale da glaucoma (Prum et al., 2016).

- Aumento del rapporto coppa:disco; Assottigliamento della rima neurale; Emorragie della rima neurale; Allungamento verticale dell'escavazione



From: The AOP, glaucoma handout

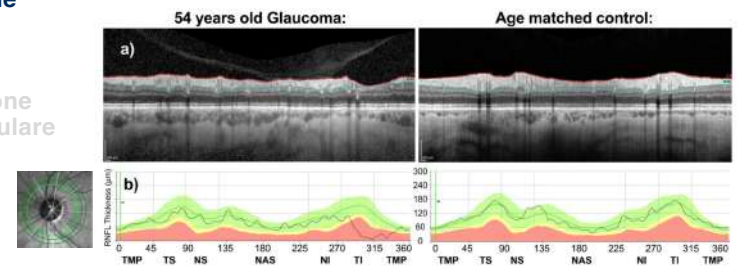


POAG, presentazione clinica:

1. Sintomi
2. **Nervo ottico e fibre nervose retiniche**
3. Campo visivo
4. Pressione intraoculare

Supporto sostanziale nella valutazione nel tempo del danno strutturale derivato da esami strumentali, del nervo ottico, e delle fibre nervose:

- Tomografia a coerenza ottica (OCT) strumento di rifermento per quantificazione accurata e ripetibile delle strutture retiniche danneggiate dal glaucoma (Weinreb et al., 2016, Prum et al., 2016).



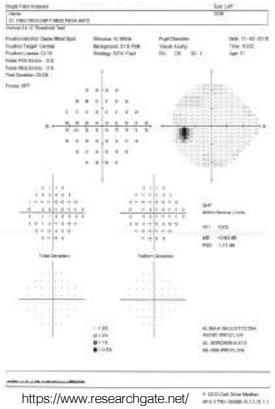
POAG, presentazione clinica:

1. Sintomi
2. Nervo ottico e fibre nervose retiniche
3. **Campo visivo**
4. Pressione intraoculare

Danno della funzione visiva determinato con esame campo visivo con perimetria computerizzata.

Campo visivo permette di quantificare il danno glaucomatoso della funzione visiva, e monitorare la patologia nel tempo (Jonas et al., 2017, Prum et al., 2016).

- Deficit "a scalino" nel settore nasale
- Scotomi arcuati
- Deficit "a cuneo" nel settore temporale
- Scotomi paracentrali
- Danno spesso congruente a quello strutturale



https://www.researchgate.net/

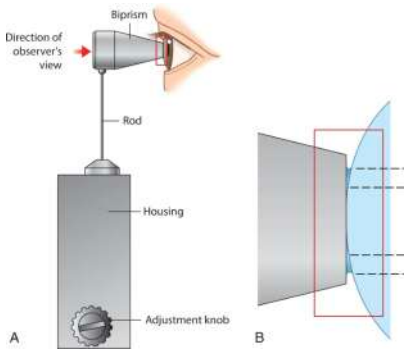
POAG, presentazione clinica:

1. Sintomi
2. Nervo ottico e fibre nervose retiniche
3. Campo visivo
4. **Pressione intraoculare**

Gold standard per questa valutazione è il metodo per applanazione (Tonometro Goldmann);

In congiunzione:

- Valutazione dello spessore corneale (pachimetria)
- Valutazione delle strutture angolari (gonioscopia)



POAG – gestione medica

Finalità del trattamento è preservare qualità della vita dell'individuo tramite preservazione della funzione visiva (Prum et al., 2016).

Riduzione della presssione intraoculare (Jonas et al., 2017, Weinreb et al., 2016).

- Unico trattamento efficace per la riduzione del rischio di progressione del glaucoma, con evidenza dimostrata in RCTs (Prum et al., 2016, Garway-Heath et al., 2015).
- Diminuzione della pressione intraoculare dal 20 al 40%
  - Terapia farmacologica;
  - Chirurgia (trabeculoplastica laser selettiva, MIGS, trabeculectomia, impianto di drenaggio)
- Monitoraggio nel lungo termine e trattamento su base permanente.

Aderenza al trattamento

- Scarsa aderenza al trattamento medico (fino al 50% dei soggetti che non seguono trattamento prescritto), con scarso controllo IOP e rischio di progressione (Tsai 2009).
- Cause:
  - Assenza di sintomi, e assenza di beneficio percepito
  - Costo del trattamento
  - Dimenticanze
  - Effetti collaterali
  - Difficoltà nell'instillazione

Ruolo di supporto per l'optometrista

1. Sensibilizzare sulla necessita di screening e di visite oculistiche

TABLE 2 Comprehensive Medical Eye Evaluation for Adults With No Risk Factors

Age (years)	Frequency of Evaluation*
65 or older	Every 1–2 years
55–64	Every 1–3 years
40–54	Every 2–4 years
Under 40	Every 5–10 years

* Interim eye evaluations, consisting of vision examinations (e.g., refractions, eyeglasses, contact lens evaluations), may be performed during these periods as well.

Ruolo di supporto per l'optometrista

2. Porre attenzione a fattori di rischio, segni clinici incidentali che possono determinare un maggiore rischio per lo sviluppo del glaucoma, e inviare a medico oculista

Fattori di rischio

- Familiarità positiva per glaucoma
- Eta > 50 aa
- Etnia africana
- Miopia > 3-6 D
- Cornea sottile (<550µm)
- *** terapia steroidea a lungo termine

TABLE 3 Comprehensive Medical Eye Evaluation for Patients With Diabetes Mellitus or Risk Factors for Glaucoma

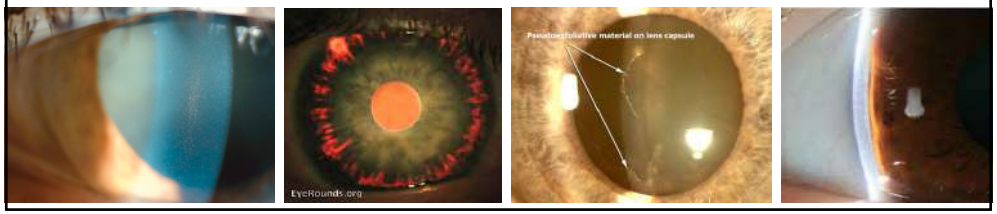
Condition/Risk Factor*	Frequency of Evaluation†	
Diabetes Mellitus	**Recommended Time of First Examination**	**Recommended Follow-up***
Type 1	5 years after onset†	Yearly
Type 2	At time of diagnosis	Yearly
Prior to pregnancy (Type 1 or 2)	Prior to conception and early in the first trimester	See Diabetic Retinopathy PPP for interval recommendations based on findings at first examination
Risk Factors for Glaucoma	**Frequency of Evaluation***	
Age 65 years or older	Every 1–2 years*	
Age 55–64 years	Every 1–2 years	
Age 40–54 years	Every 1–3 years	
Under 40 years	Every 2–5 years	

Ruolo di supporto per l'optometrista

2. Porre attenzione a fattori di rischio, segni clinici incidentali che possono determinare un maggiore rischio per lo sviluppo del glaucoma, e inviare a medico in modo corrispondente

Segni clinici incidentali

- Sindrome da dispersione di pigmento
  - Fusi di Krukenberg
  - Trans-illuminazione iride
- Pseudo esfoliazione
- Camera anteriore bassa



Ruolo di supporto per l'optometrista

2. Porre attenzione a fattori di rischio, segni clinici incidentali che possono determinare un maggiore rischio per lo sviluppo del glaucoma, e inviare a medico in modo corrispondente

Sintomi

- Sintomi di episodi intermittente di chiusura dell'angolo:
  - Fino al 50% di soggetti affetti riporta attacchi intermittenti precedenti: annebbiamento visivo di 1-2h, associato ad aloni intorno alle fonti luminose, dolore oculare, mal di testa frontale.
- Sintomi di glaucoma angolo aperto suggeriscono che danno visivo estremamente avanzato

Ruolo di supporto per l'optometrista

SJOVS, July 2021, Vol. 14, No. 1 – Review article (in English) 1

Referral in a routine Italian optometric examination: towards an evidence-based model.

Riccardo Cheloni[1,2*], Alexander G. Swystun[1], Mauro Frisani[3,4] and Christopher J. Davey[1]

[1] Bradford School of Optometry & Vision Science, University of Bradford, Bradford, United Kingdom.
[2] IRSOO, Institute of Research and Study in Optics and Optometry, Vinci, Italy.
[3] University of Turin, Turin, Italy.
[4] COMiB Research Centre in Optics and Optometry, University of Milano–Bicocca, Milan, Italy.

Received October 20, 2020, accepted May 13, 2021.

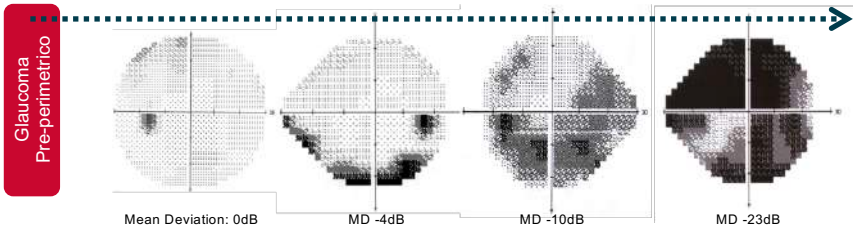
* *Correspondence: r.cheloni@bradford.ac.uk*

Abstract
Whilst Italian optometrists refract patients and prescribe optical appliances, it is ophthalmologists who are responsible for

Italian optometrists have no legal responsibility to detect ocular pathology. In Italy, access to the optometric profession is granted either by a 3-year university-based BSc degree or by professional diplomas implemented by private institutions. Although the duration of diploma courses varies across different institutions, these are usually 1 year long and accessible only by individuals already qualified as opticians (i.e. level 2 from the WCO competences model (Kiely & Chappell, 2015)). Overall, educational programmes mirror the scope of practice, with reduced focus on competencies required for the diagnosis and practical management of eye disease, in favour of skills relevant to optical technology and investigation, and correction of visual function. This is in contrast to other parts of Europe, such as the United Kingdom, where optometrists are also trained in the detection and management of eye disease, both roles that pertain solely to ophthalmologists in Italy. Nevertheless, the relationship between the Italian optometrist and patient is one of assis-

En face OCT imaging for the assessment of glaucoma

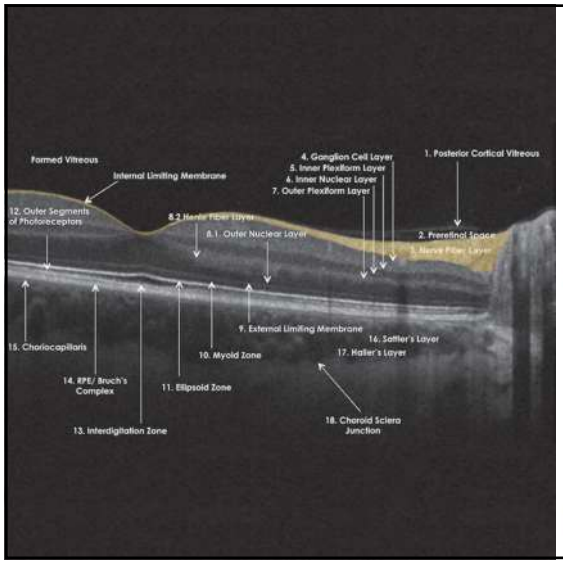
UNIVERSITY of BRADFORD

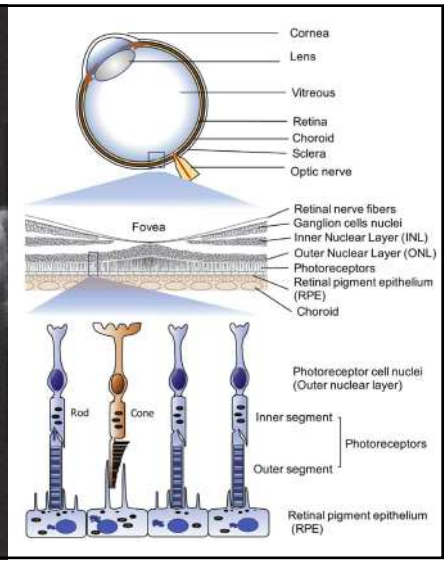


Key clinical moments in glaucoma:

Early diagnosis glaucoma suspects vs early glaucoma (*pre-perimetric?*).

Detection of progression revise treatment regimens, minimise risk of further vision loss.





Clinical science

Accuracy of optical coherence tomography for diagnosing glaucoma: an overview of systematic reviews

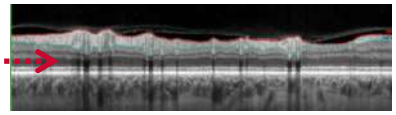
Manuele Michelessi ,[1] Tianjing Li,[2] Alba Miele,[3] Augusto Azuara-Blanco ,[4] Riaz Qureshi ,[5] Gianni Virgili[3]

(n=4 systematic reviews): **Moderate sensitivity (0.69-0.78)** at high specificity for average RNFL thickness in diagnosing **manifest glaucoma**.

Michelessi et al., 2021

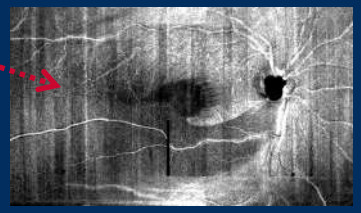
Optical Coherence Tomography - OCT

Key device in glaucoma, mainly used for **cross-sectional** analysis of **cpRNFL thickness** changes

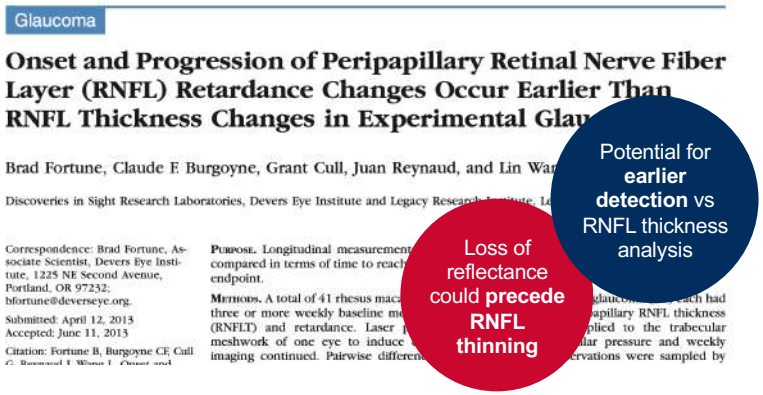


Recent OCTs developments enabled direct visualisation of ganglion cells axon bundles (RNFB): **en face imaging of bundles' reflectivity**

Hood et al., 2015; Ashimatey et al., 2018



Potentials of en face OCT (1):



Glaucoma

Onset and Progression of Peripapillary Retinal Nerve Fiber Layer (RNFL) Retardance Changes Occur Earlier Than RNFL Thickness Changes in Experimental Glau

Brad Fortune, Claude F. Burgoyne, Grant Cull, Juan Reynaud, and Lin Wa

Discoveries in Sight Research Laboratories, Devers Eye Institute and Legacy Research

Correspondence: Brad Fortune, Associate Scientist, Devers Eye Institute, 1225 NE Second Avenue, Portland, OR 97232; bfortune@deverseye.org.

Submitted: April 12, 2013
Accepted: June 11, 2013

Citation: Fortune B, Burgoyne CF, Cull G, Reynaud J, Wang L, Onest and

PURPOSE. Longitudinal measurement compared in terms of time to reach endpoint.

METHODS. A total of 41 rhesus maca three or more weekly baseline m (RNFLT) and retardance. Laser meshwork of one eye to induce imaging continued. Pairwise differen

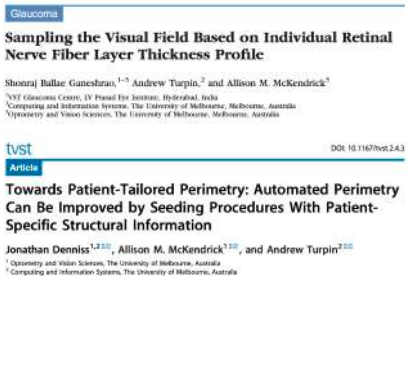
each had apillary RNFL thickness plied to the trabecular ular pressure and weekly ervations were sampled by

Potential for **earlier detection** vs RNFL thickness analysis

Loss of reflectance could **precede RNFL thinning**

Fortune et al., 2013; Huang et al., 2011

Potentials of en face OCT (2):



Glaucoma

Sampling the Visual Field Based on Individual Retinal Nerve Fiber Layer Thickness Profile

Shonaj Ballae Ganeshrao,[1–3] Andrew Turpin,[2] and Allison M. McKendrick[3]

[1]VNT Glaucoma Centre, LV Prasad Eye Institute, Hyderabad, India
[2]Computing and Information Systems, The University of Melbourne, Melbourne, Australia
[3]Optometry and Vision Sciences, The University of Melbourne, Melbourne, Australia

tvst DOI: 10.1167/tvst.2.4.3

Article

Towards Patient-Tailored Perimetry: Automated Perimetry Can Be Improved by Seeding Procedures With Patient-Specific Structural Information

Jonathan Denniss[1,2], Allison M. McKendrick[1], and Andrew Turpin[2]

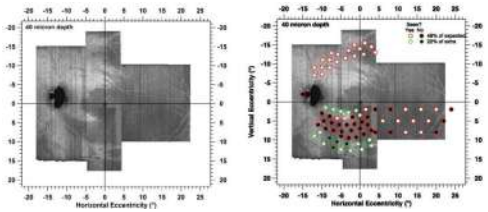
[1] Optometry and Vision Sciences, The University of Melbourne, Australia
[2] Computing and Information Systems, The University of Melbourne, Australia

Structure-driven visual field (VF):

- Reduce errors and testing time
- Region of interest approach

But, requires maps from visual field to optic disc

Independence from ONH to VF maps via en face OCT imaging

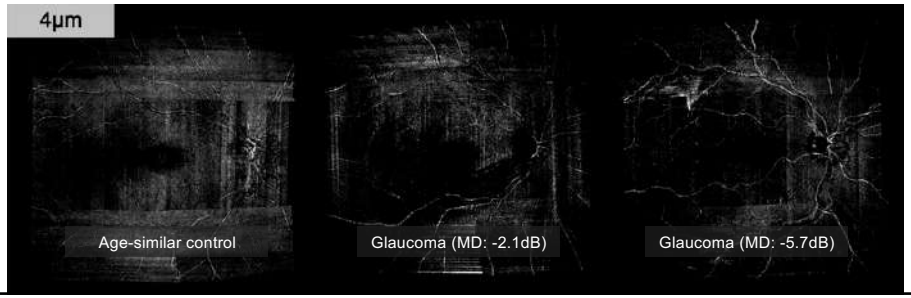


Alluwimi et al., 2018 (TVST)

Gaps of knowledge & limitations:

- Poor understanding of bundles configuration in healthy and glaucoma eyes
- Poor definition of criteria for slab construction and objective extraction of reflectance defects

- Conventional **fixed thickness 50µm slab**
  - **Inconsistent sampling** of bundles through retina
  - **Not examining all depths** with expected bundles



Visible presence of RNFBs

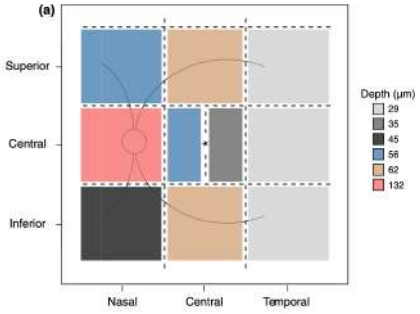
OPO OPHTHALMIC & PHYSIOLOGICAL OPTICS
THE JOURNAL OF THE COLLEGE OF OPTOMETRISTS
Ophthalmic & Physiological Optics ISSN 0275-5408

Depth-resolved variations in visibility of retinal nerve fibre bundles across the retina in enface OCT images of healthy eyes

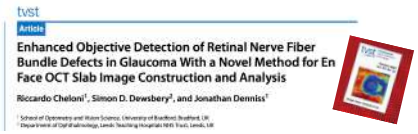
Riccardo Cheloni and Jonathan Denniss
School of Optometry and Vision Science, University of Bradford, Bradford, UK

- 10 healthy adults (median 68.5y, 57 to 75).
- 8 clinicians (median 7y since qualification) rated bundle visibility across the retina

Visible presence of RNFBs changes significantly at different retinal regions and in different eyes.

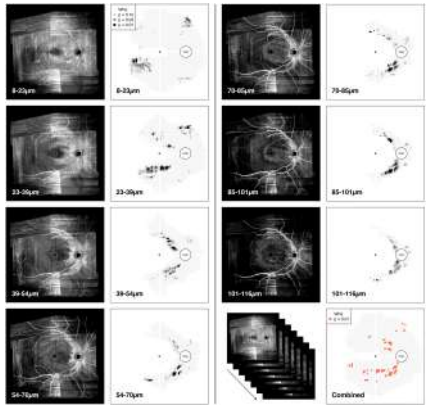


Objective detection of RNFBs defects

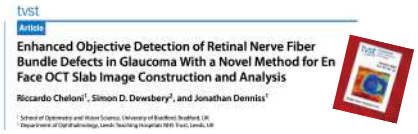


Summary of **M**ultiple **A**natomically-adjusted **S**labs (SMAS)

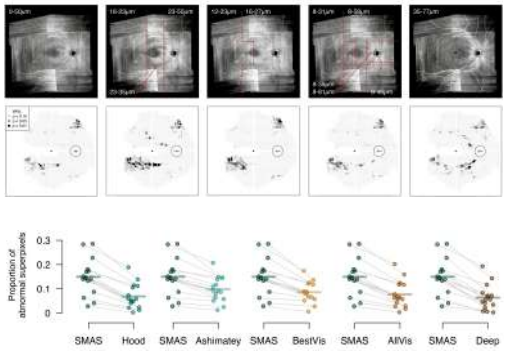
- Montage of 7 dense (30µm btw B-scan) scans over the central ±25° of retina
- Seven 16µm thick slabs from 8 to 116µm below the inner limiting membrane;
- Slabs adjusted for individual position of raphe, fovea, optic disc, to neutralise raphe-disc angle in all eyes;
- Superpixels abnormal if p<1% of controls, at any depth.



Objective detection of RNFBs defects



- 16 glaucoma eyes (median MD: -3.3 dB, IQR: 2.2 dB; age: 70y, range 61-77) and 19 controls
- Single slab methods (n=5) of various thickness and depth VS SMAS
- Ability to detect glaucomatous defects varied significantly among slab methods ($\chi^2_{(5)}$= 120.9, p<0.0001)
- SMAS detected 5-9% more abnormal superpixels than others (all p<0.0001).



Relationship with conventional measures

Concordance of Objectively Detected Retinal Nerve Fiber Bundle Defects in En Face OCT Images with Conventional Structural and Functional Changes in Glaucoma

Riccardo Chaloni, PhD, Jonathan Denniss, PhD

How en face defects relate to conventional measures of glaucoma damage?

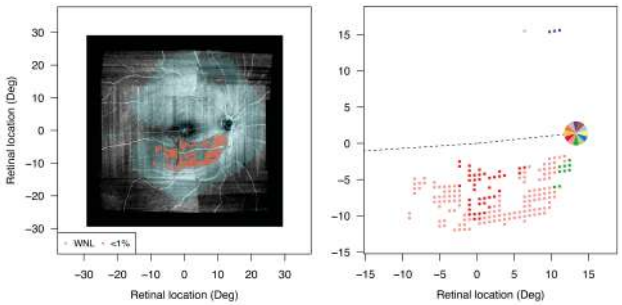
- 16 eyes with early-glaucoma (MD: -3.3db, IQR: 2.2dB) and 29 age-similar controls.
- Conventional examinations:
  - cpRNFL scans (Spectralis OCT, 3.5mm circle);
  - SAP 24-2 SITA Standard (HFA)
- Custom OCT to build SMAS images
- Point-wise examination of concordance:
  - **Structure-structure concordance**
  - **Structure-function agreement**

Methods

Any en face defect mapped to optic disc, according to established model

Defects deemed concordant with cpRNFL when presenting ≥1 point with p<1%, within ±15° of predicted optic disc insertion

Proportion (%) of concordant defects (among all) measured in each eye

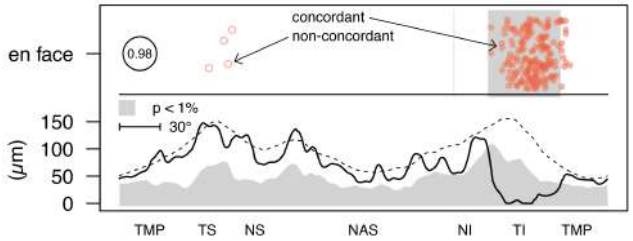


Methods

Any en face defect mapped to optic disc, according to established model

Defects deemed concordant with cpRNFL when presenting ≥1 point with p<1%, within ±15° of predicted optic disc insertion

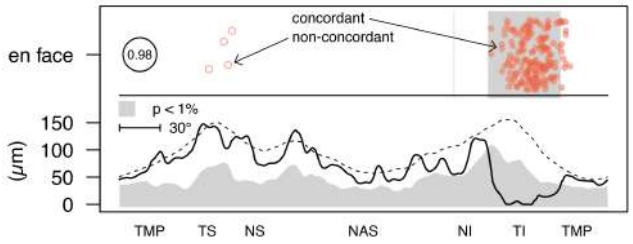
Proportion (%) of concordant defects (among all) measured in each eye



Results

- Concordance ratio*

Median **85%** (IQR: 73-98) of en face reflectance defects had a concordant cpRNFL thickness defect at the mapped location.



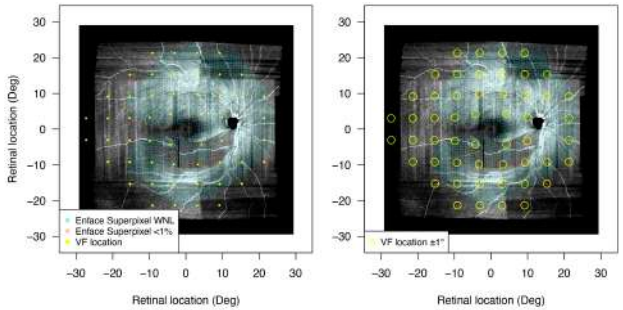
** Turpin & McKendrick, 2021*

Methods

VF locations displaced according to Drasdo model

En face reflectance at any VF location abnormal if ≥1 abnormal en face superpixel lying within ±1° of VF location

VF locations showing total deviation with p<2% considered defects

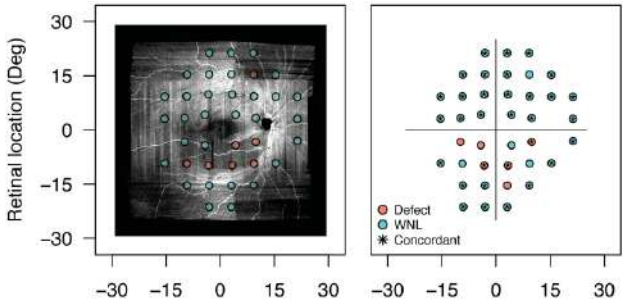


Methods

VF locations displaced according to Drasdo model

En face reflectance at any VF location abnormal if ≥1 abnormal en face superpixel lying within ±1° of VF location

VF locations showing total deviation with p<2% considered defects

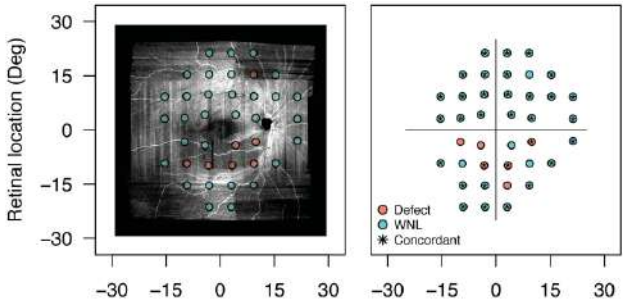


Results

- Overall raw, positive, negative agreement
(Uebersax, 1987)

All eyes showed at least 1 location with corresponding en face & VF defects (median 3 locations, range: 1 to 9)

Moderate raw agreement (median 63%, IQR: 53-73%), stronger on normal locations than defects (77% vs 40%).



PhD work conclusion

- Glaucoma changes of en face reflectance can be assessed objectively
  - & individual anatomy and retinal configuration should be considered
- In established glaucoma, reflectance loss seems well represented in cpRNFL scans
  - Focus on earlier stages of glaucoma?
- Moderate-good agreement with visual field, stronger on preserved regions, but all eyes had some concordant defects.
  - Concordance criteria for diagnosis?
  - Monitoring of progression?

Selected references

Michelessi M, Li T, Miele A, Azuara-Blanco A, Qureshi R, Virgili G. Accuracy of optical coherence tomography for diagnosing glaucoma: an overview of systematic reviews. Br J Ophthalmol. 2021 Apr;105(4):490-495.

Ashimatey, B.S., et al., Evaluating glaucomatous abnormality in peripapillary optical coherence tomography enface visualisation of the retinal nerve fibre layer reflectance. Ophthalmic Physiol Opt, 2018. 38(4): p. 376-388.

Hood, D.C., et al., Details of Glaucomatous Damage Are Better Seen on OCT En Face Images Than on OCT Retinal Nerve Fiber Layer Thickness Maps. Invest Ophthalmol Vis Sci, 2015. 56(11): p. 6208-16. 1.

Huang XR, et al. Reflectance decreases before thickness changes in the retinal nerve fiber layer in glaucomatous retinas. Investigative ophthalmology & visual science. 2011;52(9):6737- 42.

Fortune B, et al. Onset and progression of peripapillary retinal nerve fiber layer (RNFL) retardance changes occur earlier than RNFL thickness changes in experimental glaucoma. Investigative ophthalmology & visual science. 2013;54(8):5653-61

Ganeshrao, S., et al. (2018). "Sampling the Visual Field Based on Individual Retinal Nerve Fiber Layer Thickness Profile." Invest Ophthalmol Vis Sci 59(2): 1066-1074.

Denniss, J., et al. (2013). "Towards Patient-Tailored Perimetry: Automated Perimetry Can Be Improved by Seeding Procedures With Patient-Specific Structural Information." Transl Vis Sci Technol 2(4): 3.

Cheloni, R. and J. Denniss (2021). Use of optical coherence tomography in the detection and diagnosis of glaucoma. Optometry in Practice 21 (1), 1-12

Cheloni, R. and J. Denniss (2021). "Depth-resolved variations in visibility of retinal nerve fibre bundles across the retina in enface OCT images of healthy eyes." Ophthalmic and Physiological Optics 41(1): 179-191.

Cheloni, R., Dewsbery, S. D., & Denniss, J. (2021). A Simple Subjective Evaluation of Enface OCT Reflectance Images Distinguishes Glaucoma From Healthy Eyes. Translational vision science & technology, 10(6), 31-31.

Cheloni, R., Dewsbery, S. D., & Denniss, J. (2021). Enhanced Objective Detection of Retinal Nerve Fiber Bundle Defects in Glaucoma With a Novel Method for En Face OCT Slab Image Construction and Analysis, 10(12), 1-1.

Denniss, J., et al. (2012). "An anatomically customizable computational model relating the visual field to the optic nerve head in individual eyes." Invest Ophthalmol Vis Sci 53(11): 6981-6990.

Turpin, A. and A. M. McKendrick (2021). "Improving Personalized Structure to Function Mapping From Optic Nerve Head to Visual Field." Transl Vis Sci Technol 10(1): 19-19.