Oculomics: Ocular Biomarkers of Disease

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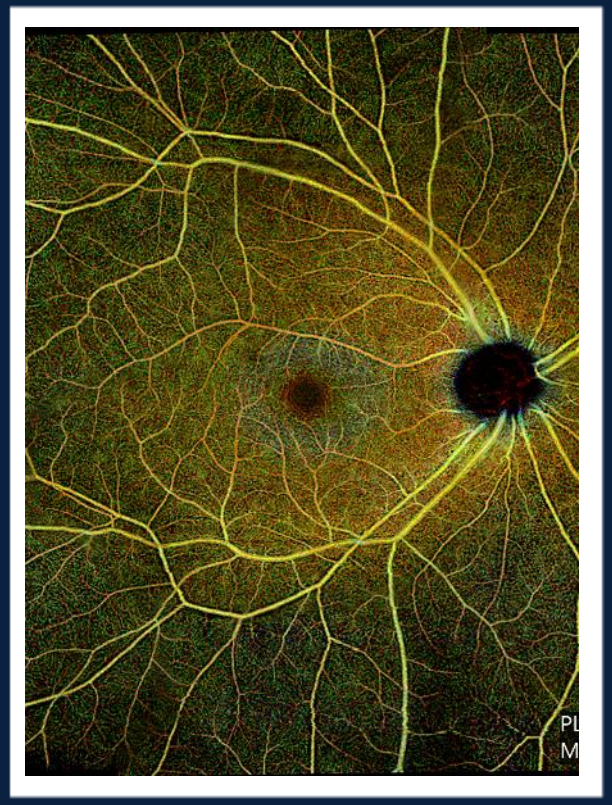
Focus on Eye Health Summit:
Our Changing Vision



Cardiovascular oculomics

Siegfried Wagner

University College London
Moorfields Eye Hospital

Prevent Blindness
Focus on Eye Health National Summit

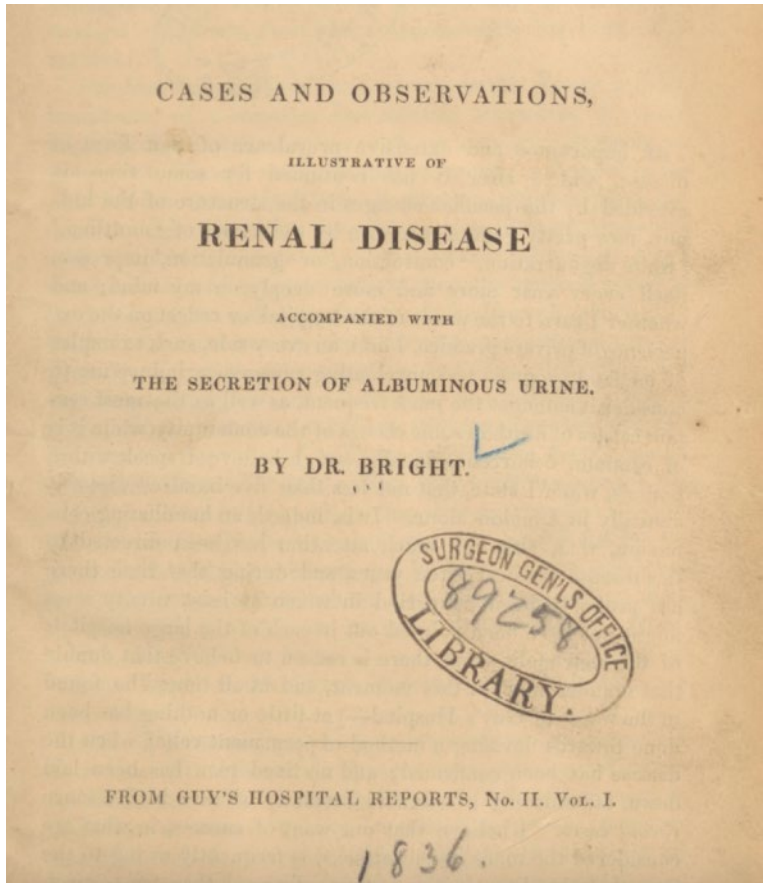
Disclosures

- Employment
  - University College London
  - Moorfields Eye Hospital

- Funding:
  - Medical Research Council
  - National Institute for Health Research

- Grants
  - Moorfields Eye Charity
  - Fight for Sight UK
  - Alzheimer's Research UK
  - University College London

London 1820s



CASES AND OBSERVATIONS,

ILLUSTRATIVE OF

RENAL DISEASE

ACCOMPANIED WITH

THE SECRETION OF ALBUMINOUS URINE.

BY DR. BRIGHT.

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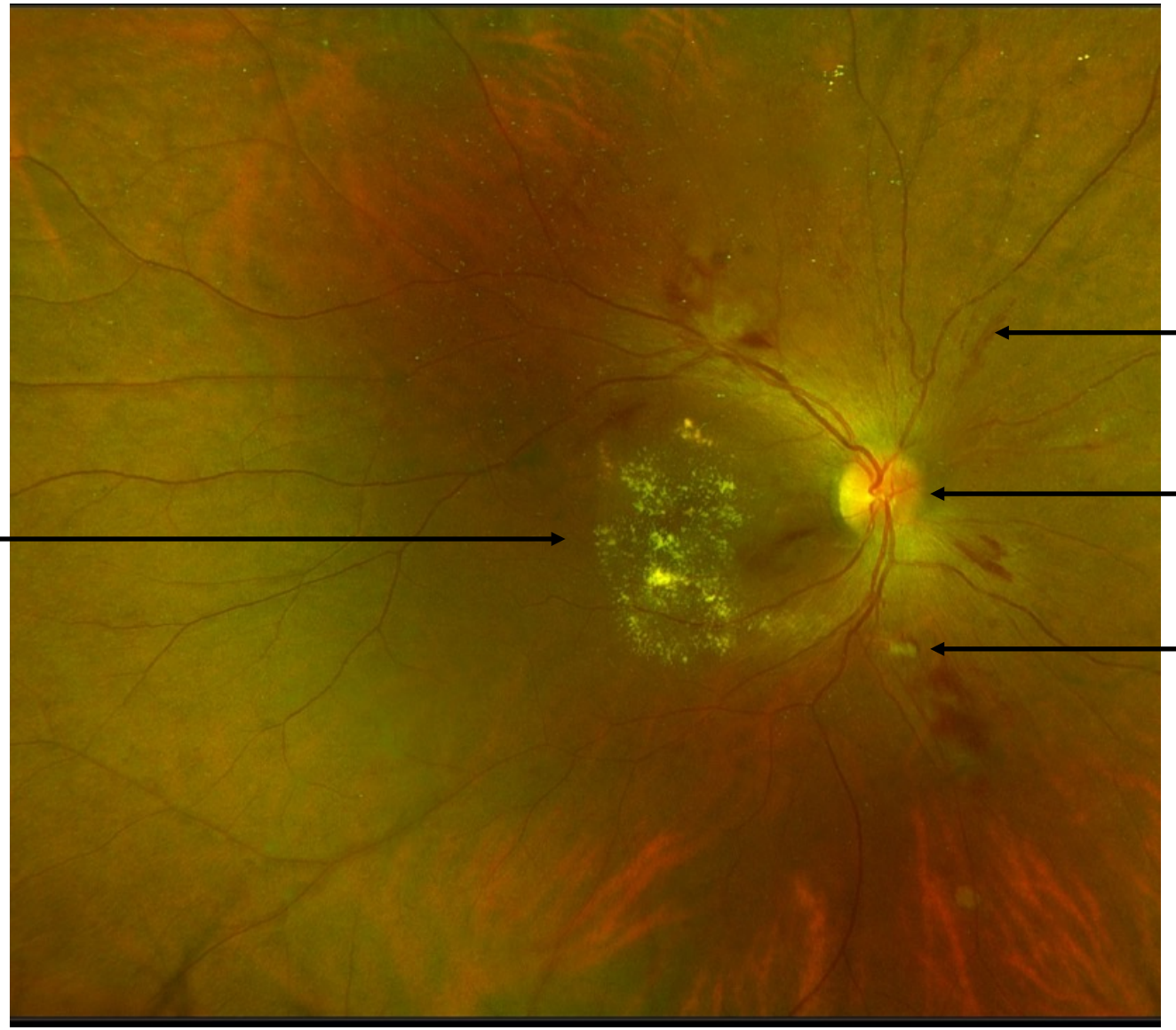
FROM GUY'S HOSPITAL REPORTS, No. II. Vol. I.

1836.

"he is suddenly seized with a convulsive fit, and becomes blind"

"the next day, about two o'clock, having for two hours before his death become apparently blind, he died"


Haemorrhage
Optic nerve swelling
Exudate
Cotton wool spot

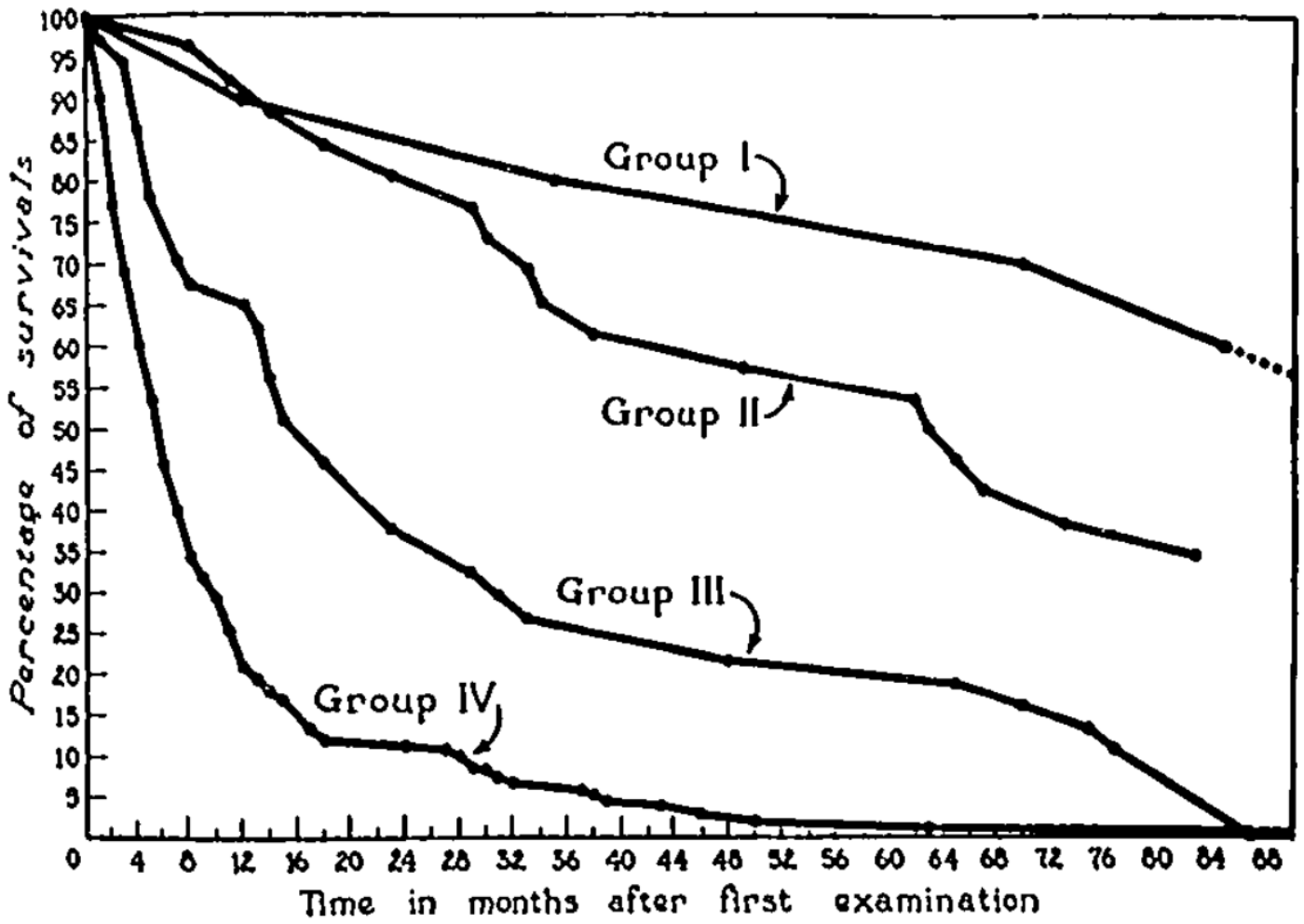
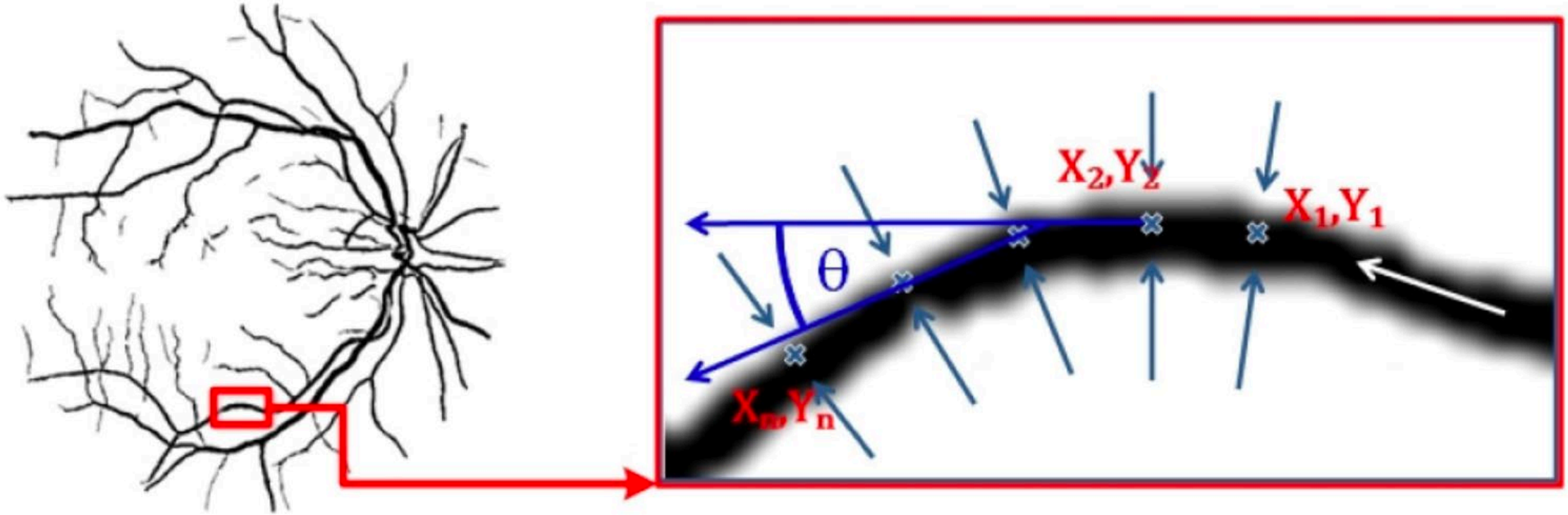


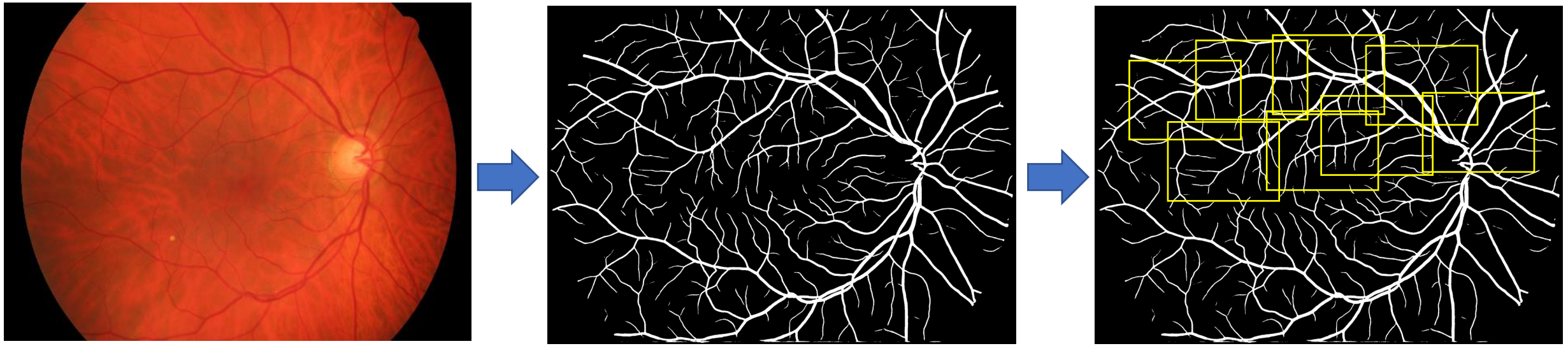
Fig. 1: Survival curves in the four groups.

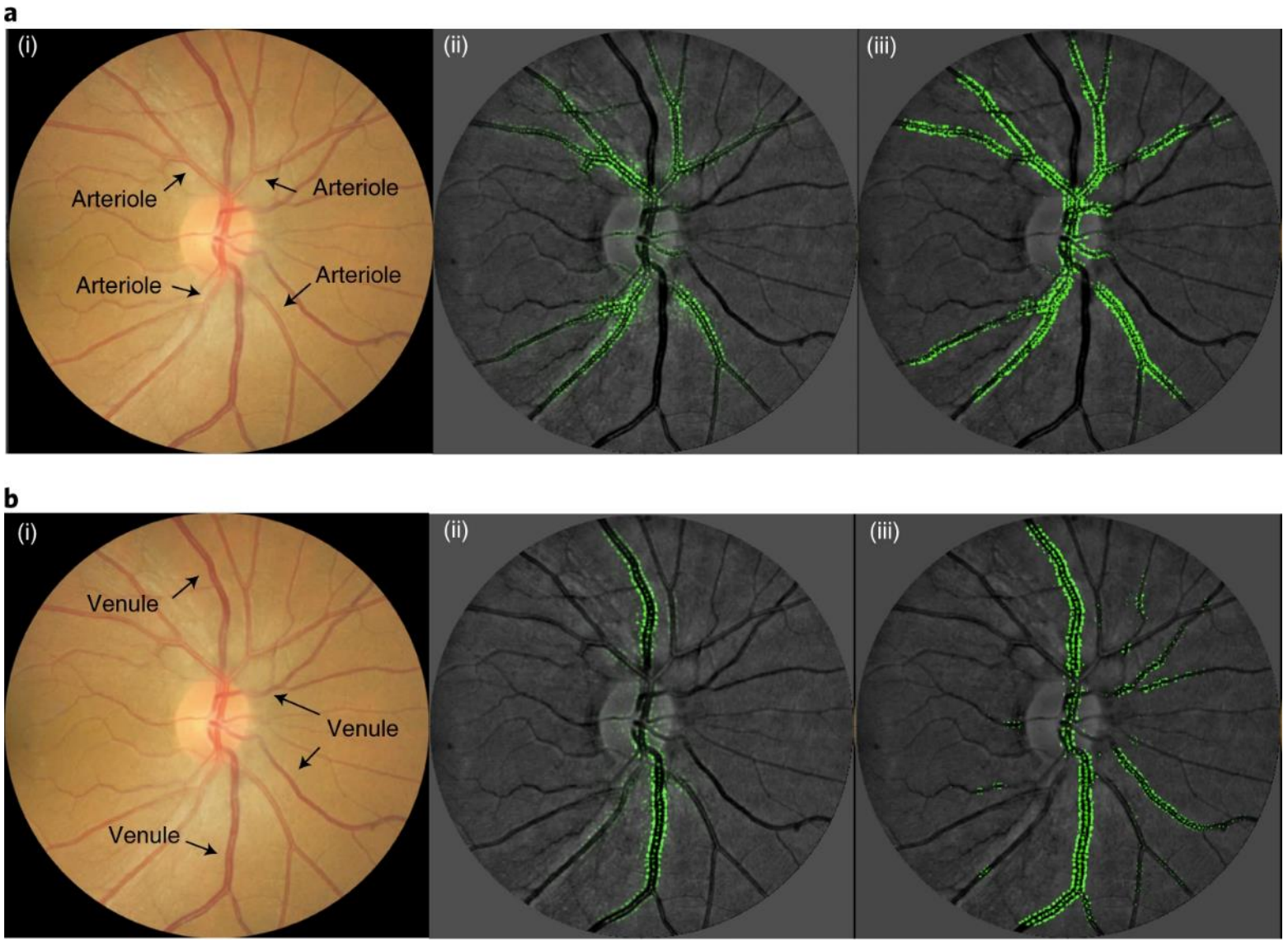


- Calibre
- Tortuosity
- Branching angles

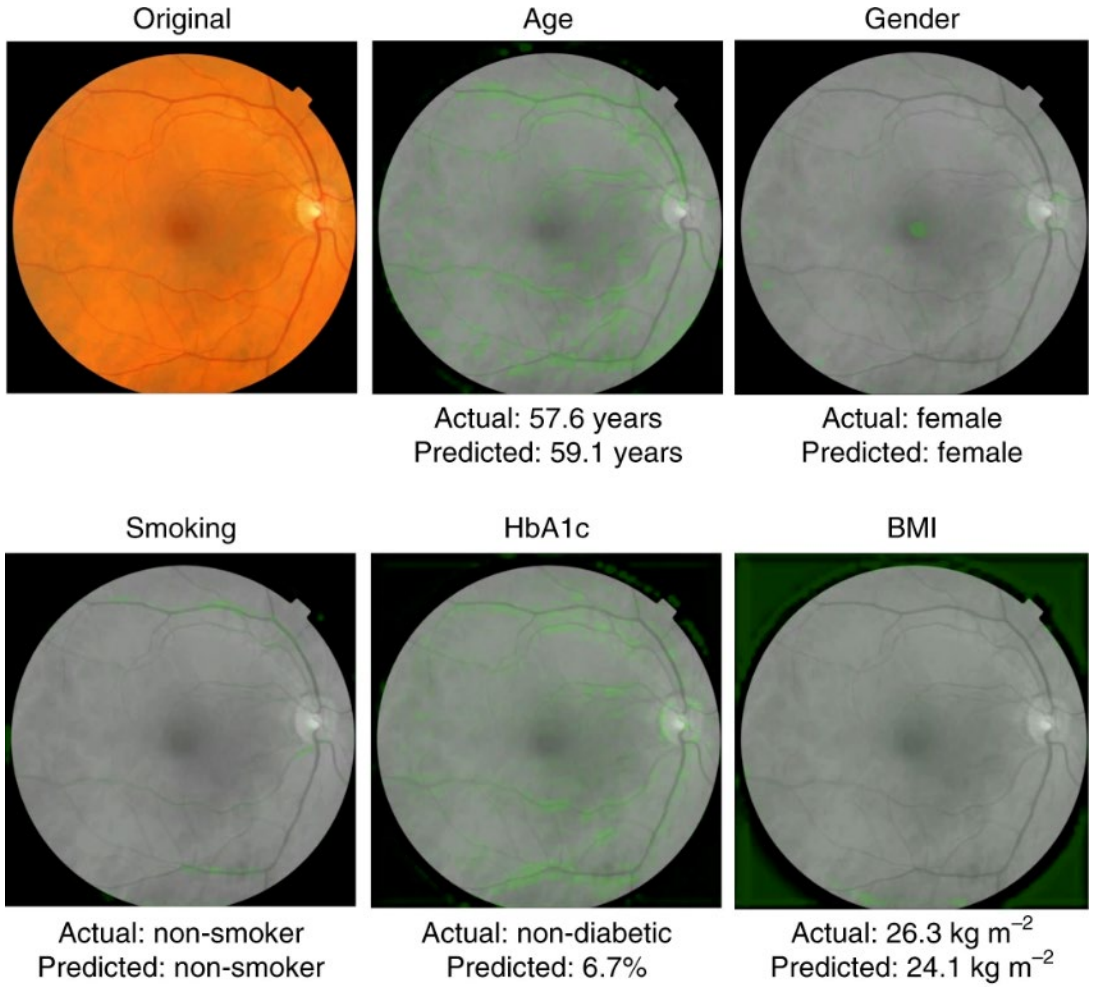
Fraz, M. M., et al. (2015). "QUARTZ: Quantitative Analysis of Retinal Vessel Topology and size – An automated system for quantification of retinal vessels morphology." Expert Systems with Applications **42**(20): 7221-7234.

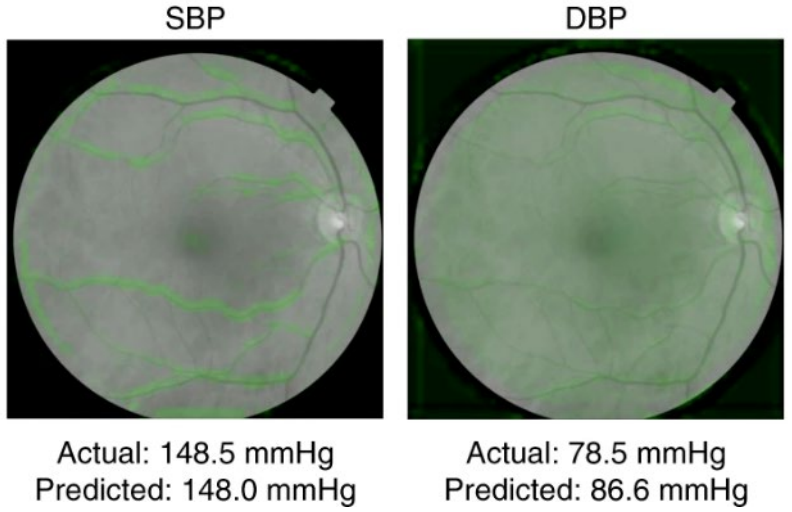
Fractal dimensions





Cheung, C. Y., et al. (2020). "A deep-learning system for the assessment of cardiovascular disease risk via the measurement of retinal-vessel calibre." Nature Biomedical Engineering.





Poplin, R., et al. (2018). "Prediction of cardiovascular risk factors from retinal fundus photographs via deep learning." Nat Biomed Eng **2**(3): 158-164.

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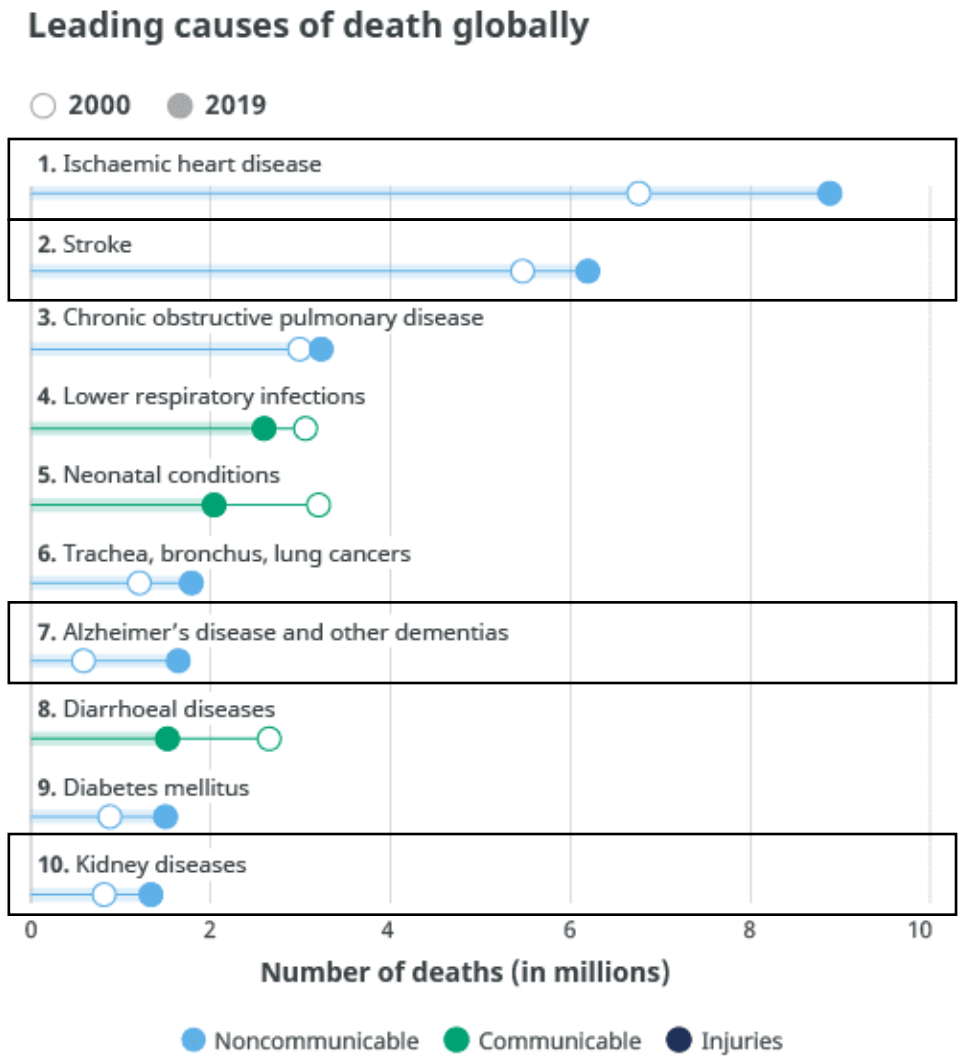

Source: WHO Global Health Estimates.

"The world's biggest killer is ischaemic heart disease, responsible for 16% of the world's total deaths. Since 2000, the largest increase in deaths has been for this disease, rising by more than 2 million to 8.9 million deaths in 2019."

- World Health Organisation

"Adults who are 40 to 75 years of age and are being evaluated for cardiovascular disease prevention should undergo 10-year atherosclerotic cardiovascular disease (ASCVD) risk estimation.."

- American College of Cardiology & American Heart Association Guideline 2019

Prevent Blindness
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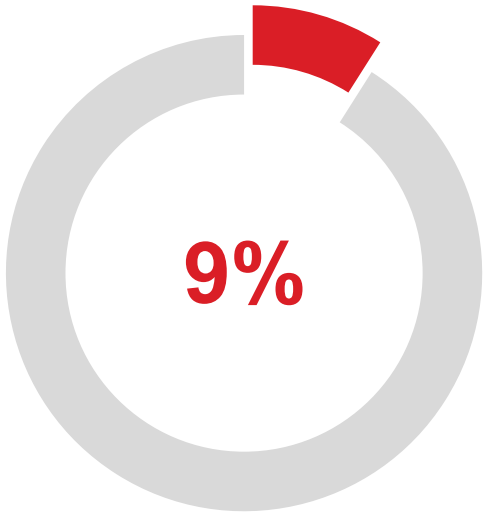
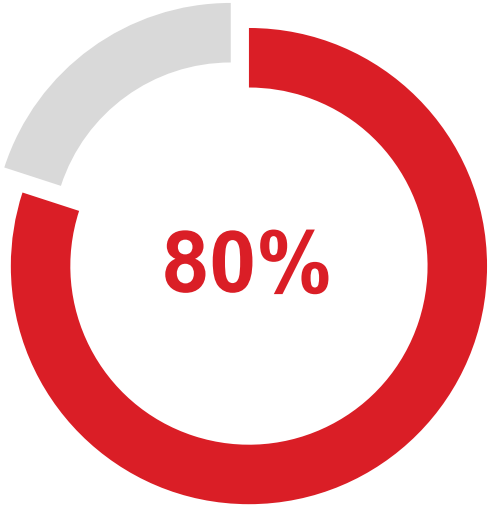
"Our results show that people would prefer to live 5 years in perfect health versus 10 years with complete sight loss"

- *Mr Jamie Enoch, City University*
- *Professor David Crabb, City University*



Attendance at the *NHS Health Check* from 2009-2013

Aged 40-59

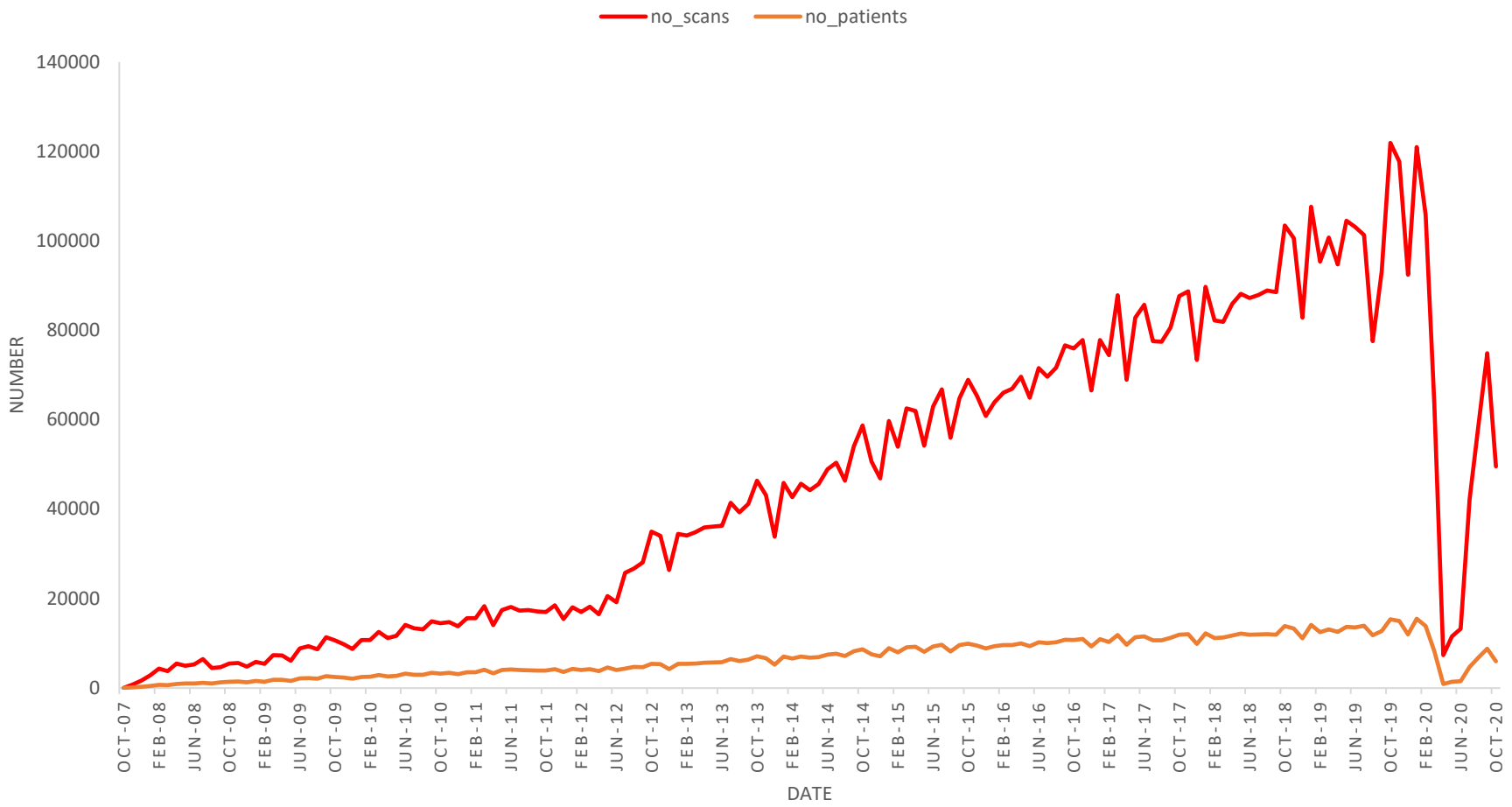


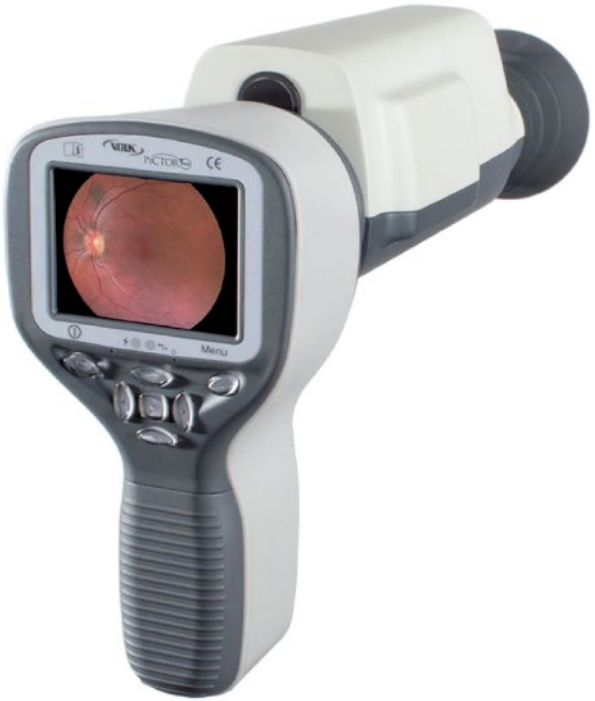
Attendance at the optician every four years in 2011

Aged 45-54

Data Sources: YouGov

NUMBER OF TOPCON IMAGES AT MOORFIELDS 2007-2020





Volk: Pictor Plus

D-EYE

Data Sources: volk.com; d-eyecare.com;

Avenues

- Extensive population screening
- Democratising to low and middle income countries
- Improving current screening strategies
- Clinical trial endpoints

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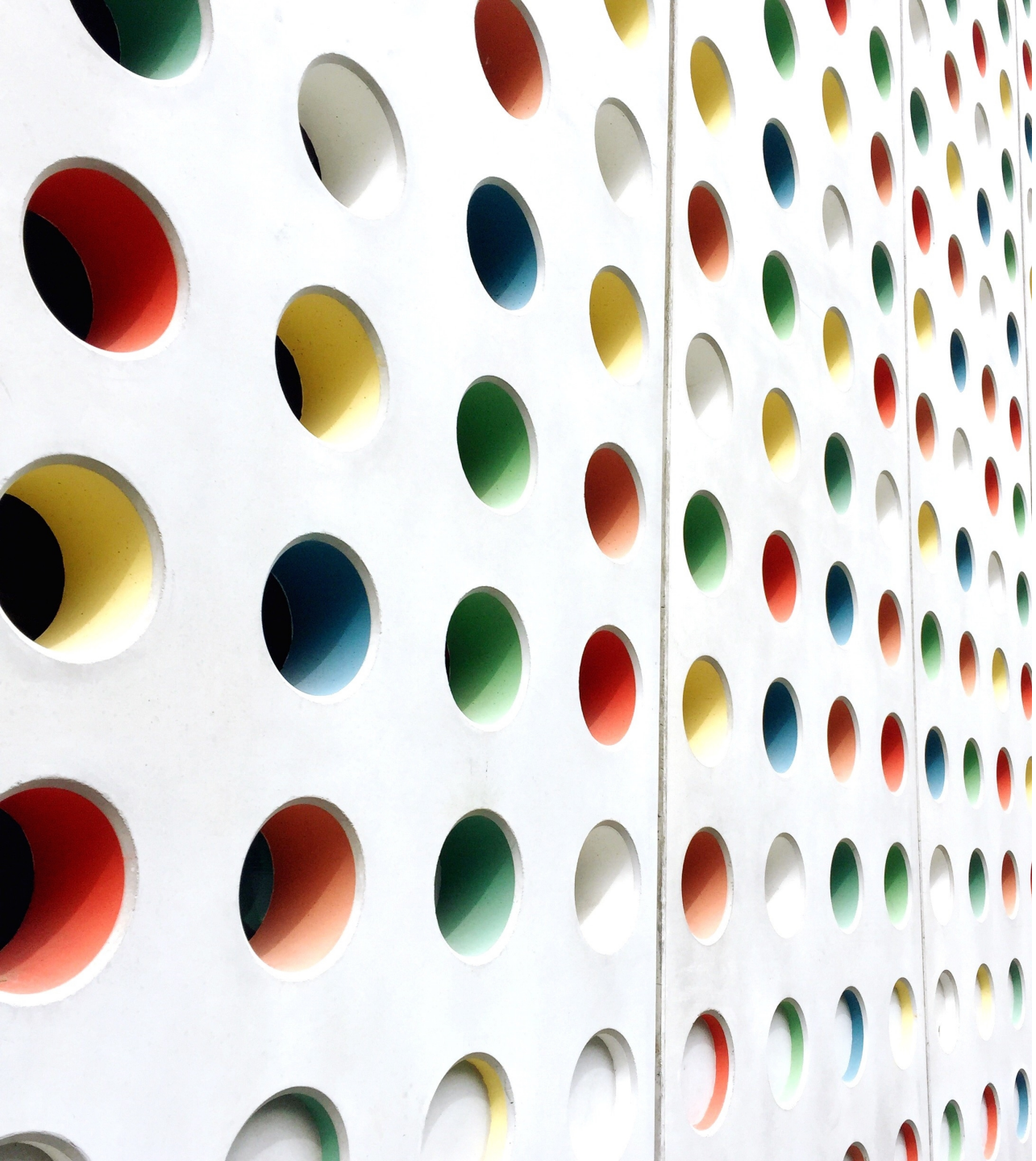
Our Changing Vision



Ocular Biomarkers of Brain Disease

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Outline

The retina as a “window to the brain”

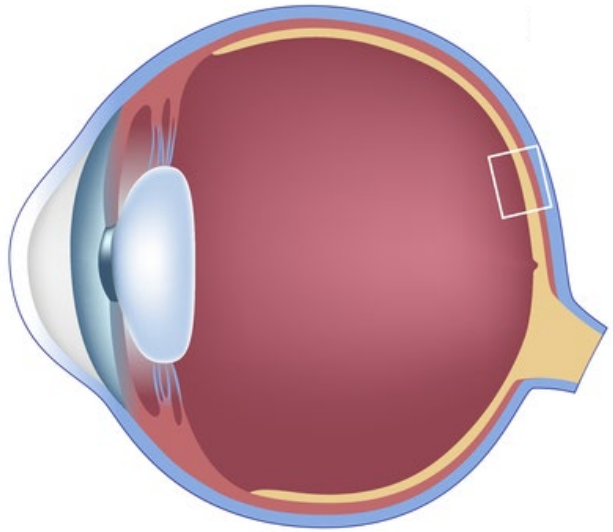
- and a window into brain disease

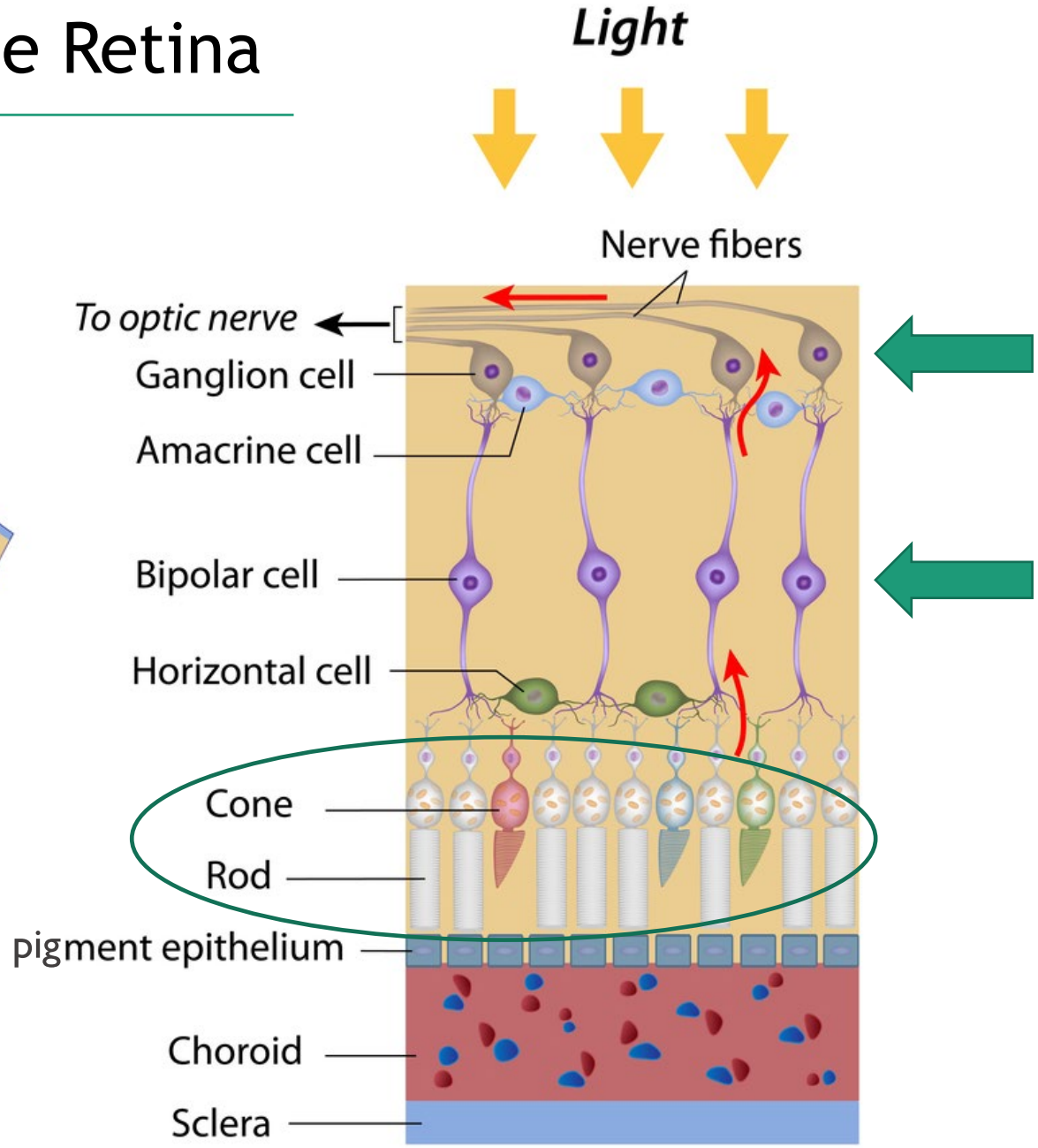
Retinal exam types:

- Imaging of retinal layer thickness
- Imaging of retinal microvasculature
- Electrophysiological recordings of retinal cell activity

Conclusions

Structure of the Retina





The Retina is "A Window to the Brain"

The retina and brain grow out of the same neural tissue during embryonic development

They share important characteristics: neurons, glial cells, layered architecture

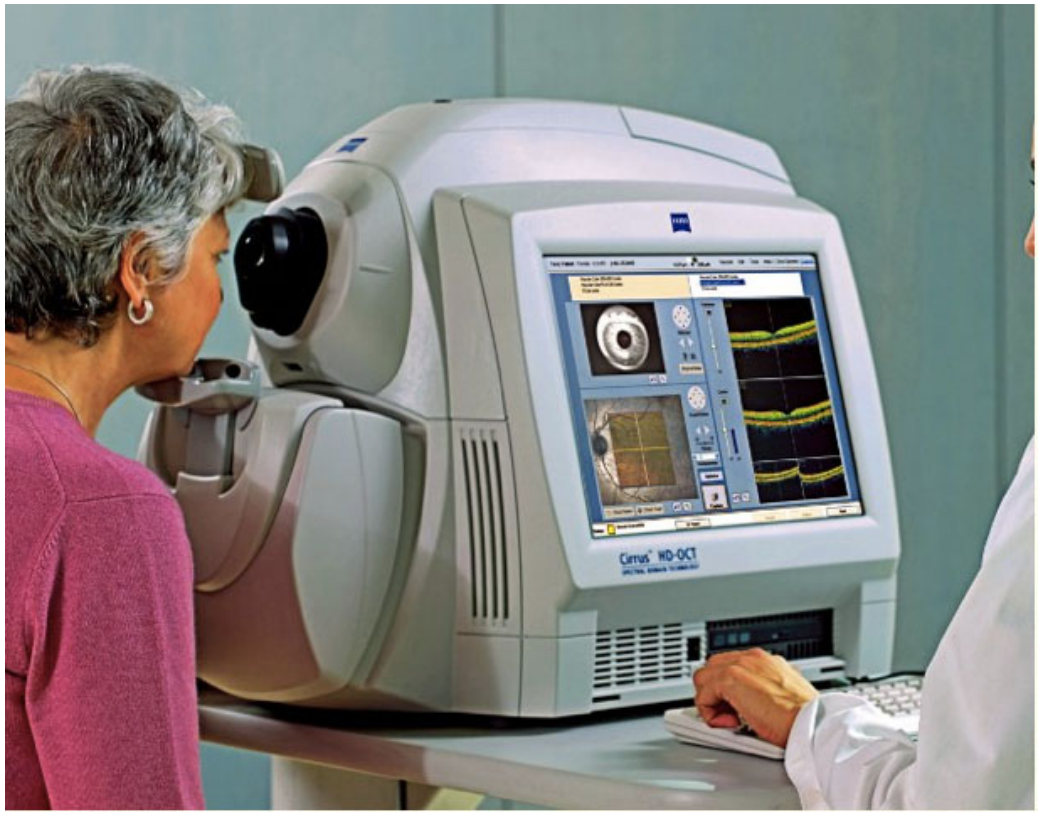
They communicate with each other:

- Retinal ganglion cell axons (retinal nerve fiber layer; RNFL) form the optic nerve
- Neurotransmitter input to retina (Ortiz et al., 2017, Doc Ophthalmol)

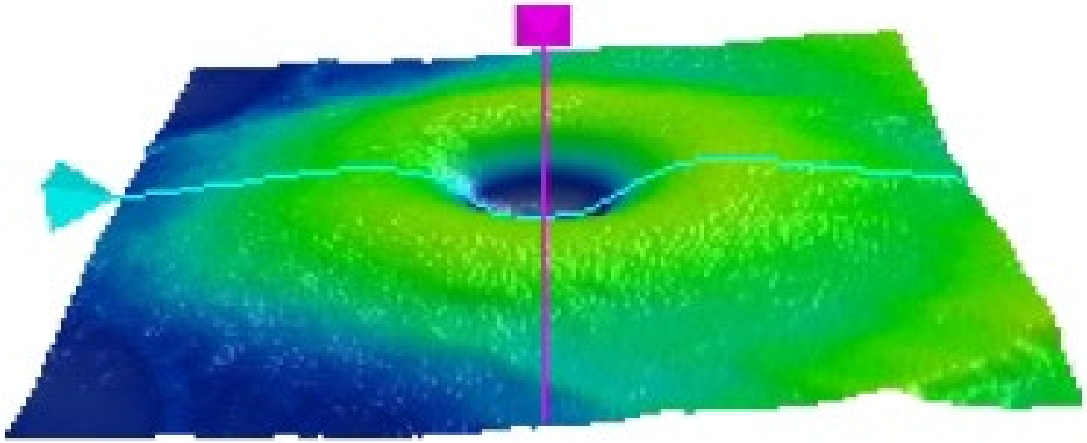
Changes in the retina often indicate changes in the brain:

- RNFL thinning related to illness progression and cognitive decline in MS, Alzheimer's disease, and schizophrenia (Iseri et al., 2006, J Neuroophthalmology; Toledo et al., 2008 Mult Scler; Liu et al., 2015, BMC Neurol; Lai et al., 2020, Biomarkers in Neuropsychiatry)
- RNFL thinning related to visual hallucinations (Lee et al., 2014, Movement Disorders) and functional decline in PD (Satue et al., 2014, Br. J. Ophthalmology)
- RNFL thinning related to brain volume loss in aging (Ong et al., 2015, Neurosci Letters) and MS (Gordon-Lipkin et al., 2007, Neurology)

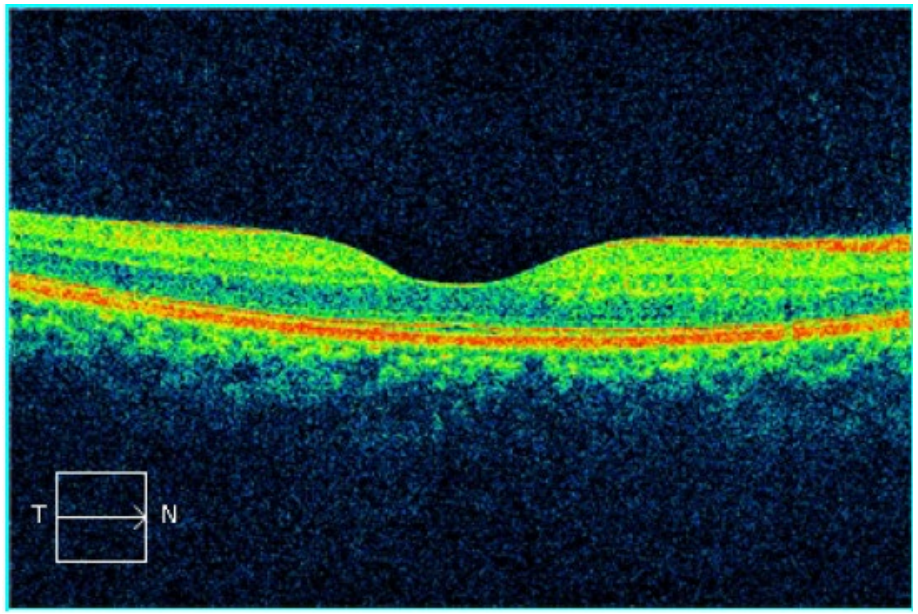
Assessing Retinal Structure with Optical Coherence Tomography (OCT)

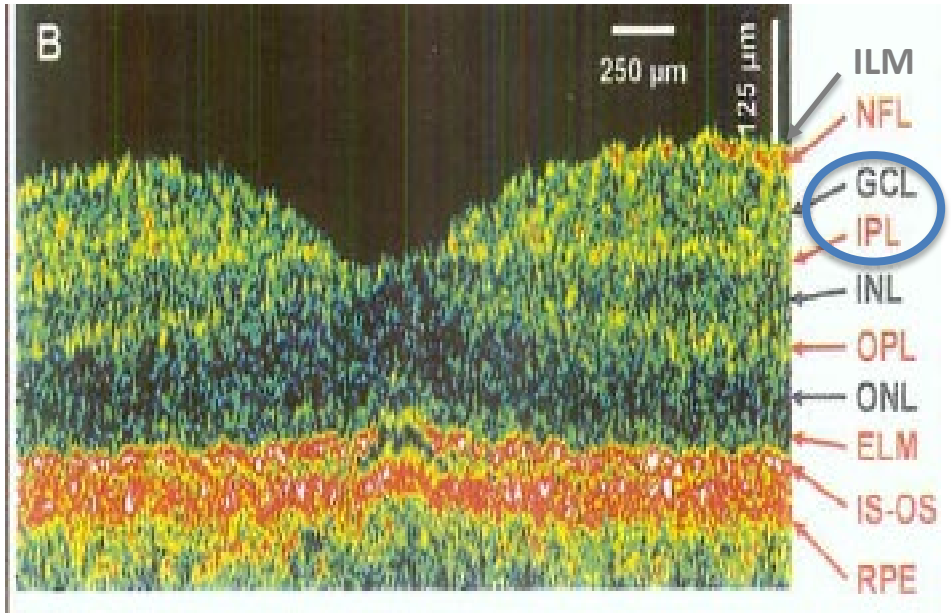


Macula Scan Images

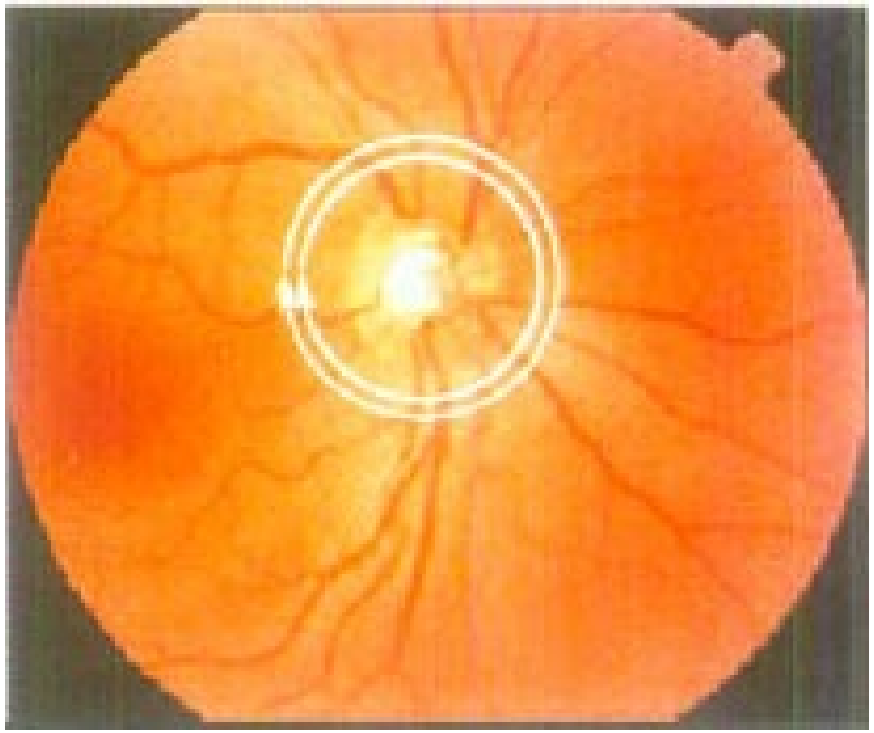


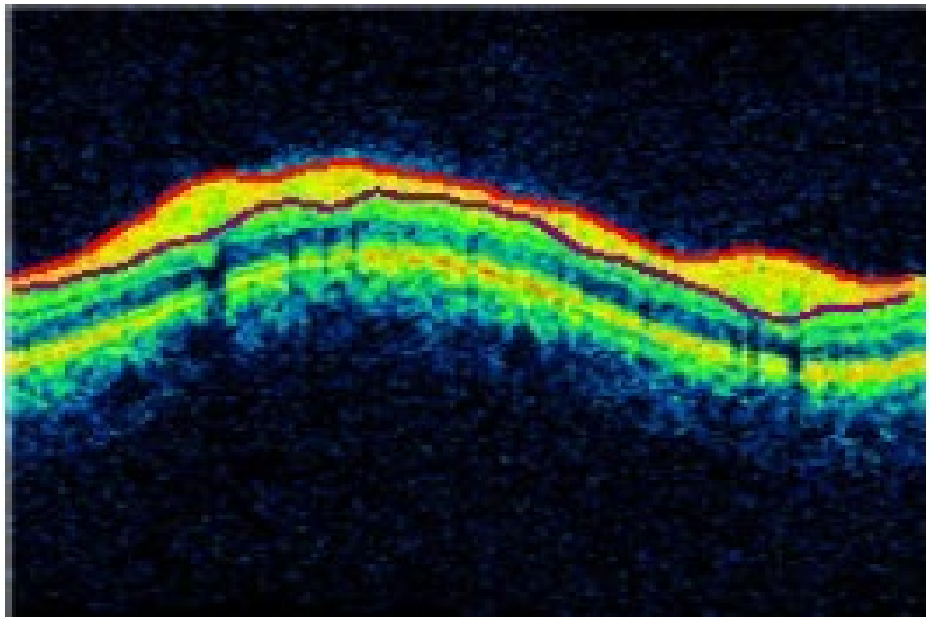
ILM - RPE





Circumpapillary Measurement, for RNFL Thickness, Centered on the Optic Nerve Head





Temporal	Superior	Nasal	Inferior	Temporal

Conditions with Macula or RNFL Thinning

- Autism
- Attention deficit-hyperactivity disorder
- Anorexia nervosa
- Bipolar disorder
- Major depressive disorder
- Schizophrenia
- Multiple sclerosis
- Parkinson’s disease
- Alzheimer’s disease
- Mild cognitive impairment (MCI)
- Huntington’s disease
- Traumatic brain injury (TBI)

Other Conditions and Factors Affecting Eye and Brain Health

- Diabetes
- Hypertension
- Obstructive sleep apnea
- Obesity
- Smoking
- Substance abuse

Biomarkers in Neuropsychiatry 2 (2020) 100018

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Biomarkers in Neuropsychiatry

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

Measures of Retinal Structure and Function as Biomarkers in Neurology and Psychiatry

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[d] Department of Ophthalmology and Flaum Eye Institute, University of Rochester Medical Center
[e] Department of Neuroscience, University of Rochester Medical Center
[f] Center for Visual Science, University of Rochester

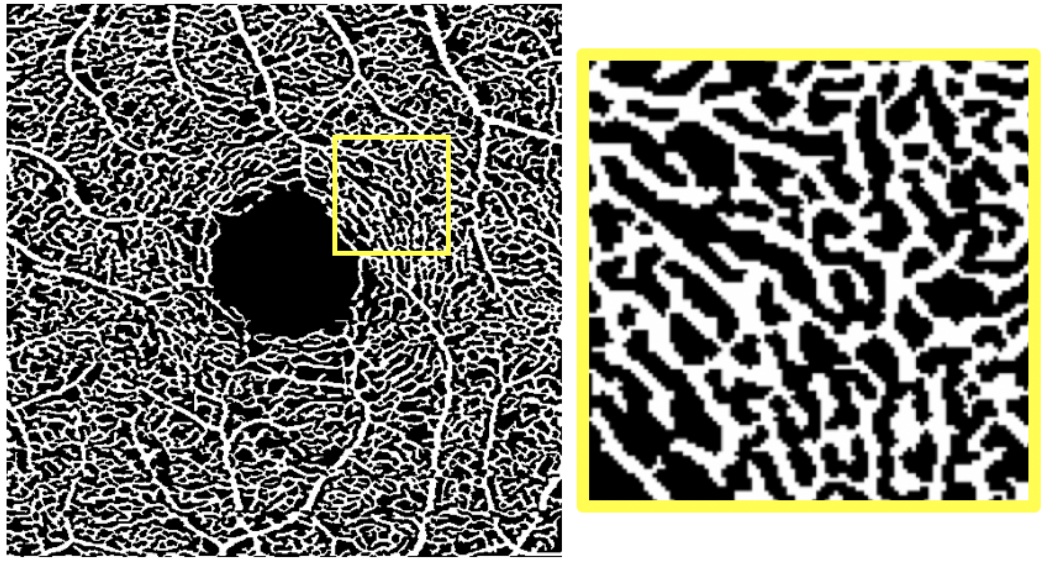
A B S T R A C T

Investigators have increasingly turned to studying the retina as a window into brain structure and function. In neuropsychiatric diseases, retinal anatomy as assessed by optical coherence tomography (OCT) and retinal cell function as assessed by various forms of electroretinography (ERG) demonstrate notable changes. In addition, many studies indicate significant correlations between retinal changes and clinical features such as cognitive decline, overall illness severity, and progression of illness. Here, we review retinal findings in psychiatric (schizophrenia, autism, mood disorders, attention deficit hyperactivity disorder, anorexia nervosa), and neurologic (multiple sclerosis, Parkinson's disease, Alzheimer's disease and mild cognitive impairment, Huntington's disease, traumatic brain injury) conditions, in terms of their potential as biomarkers of disease onset, progression, severity, and outcomes. Consistency and variability in findings across studies are highlighted, and implications for future research are discussed. Potential confounds and methodological issues central to studies of retinal structure and function in neuropsychiatry are also considered. The review concludes with discussions of: a) recent advances in retinal imaging and their potential applications for studying brain disorders; and b) the potential for applications of artificial intelligence to increasing the predictive validity of retinal data.

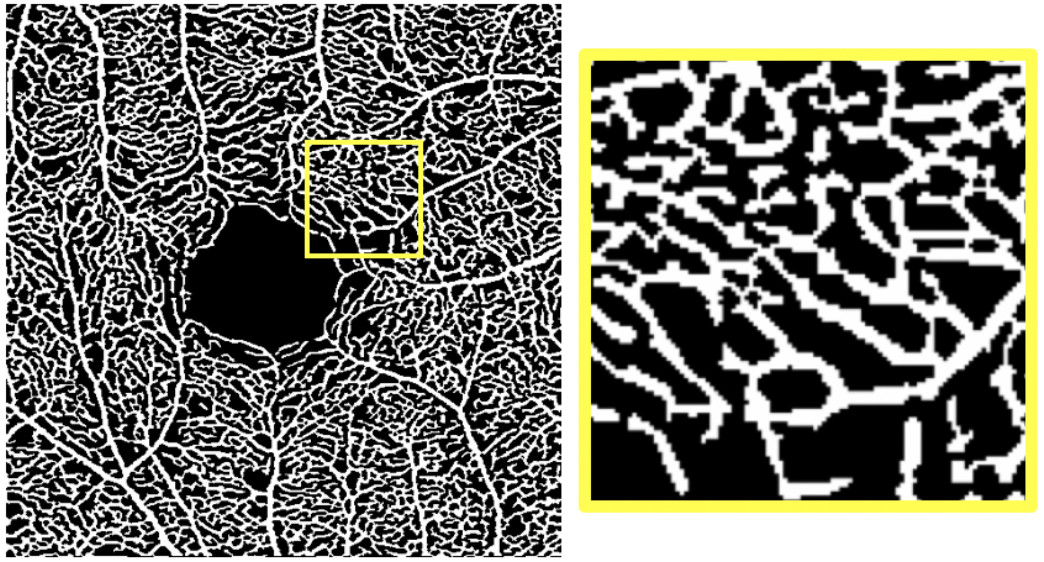
Available at: https://www.sciencedirect.com/science/article/pii/S2666144620300083

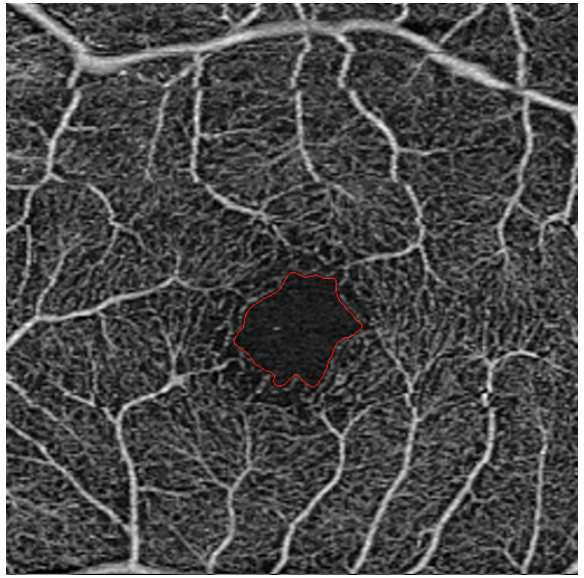
OCT-Angiography (OCT-A)

Control



Schizophrenia





Eye and Brain 2020

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REVIEW

Optical Coherence Tomography Angiography in Neurodegenerative Diseases: A Review

This article was published in the following Dove Press journal:
Eye and Brain

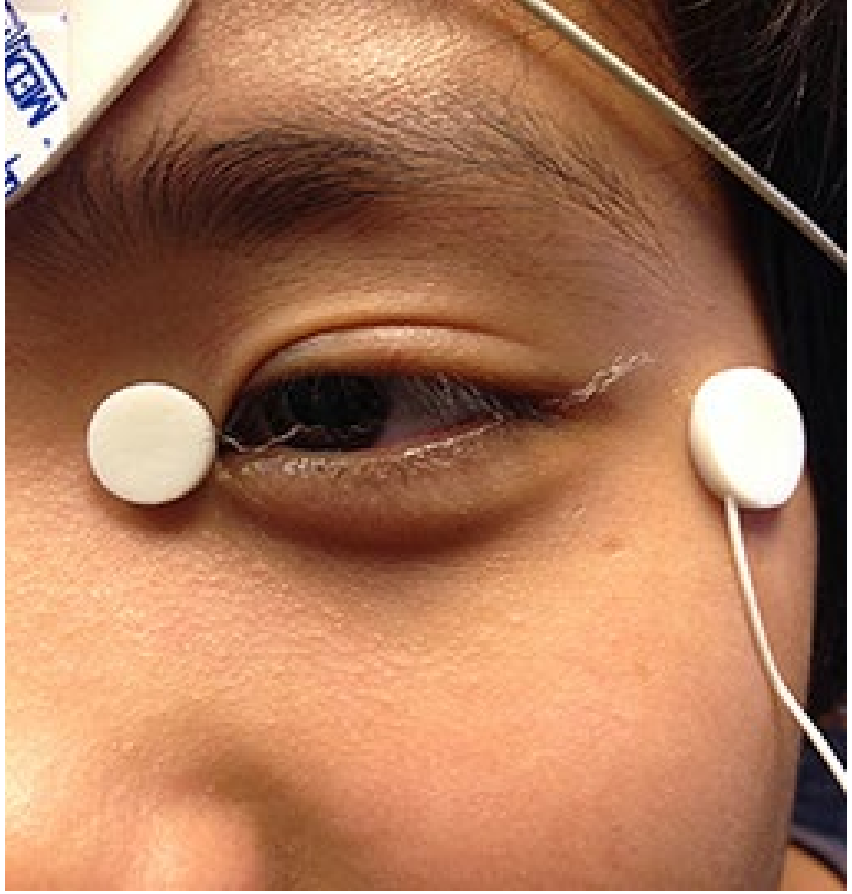
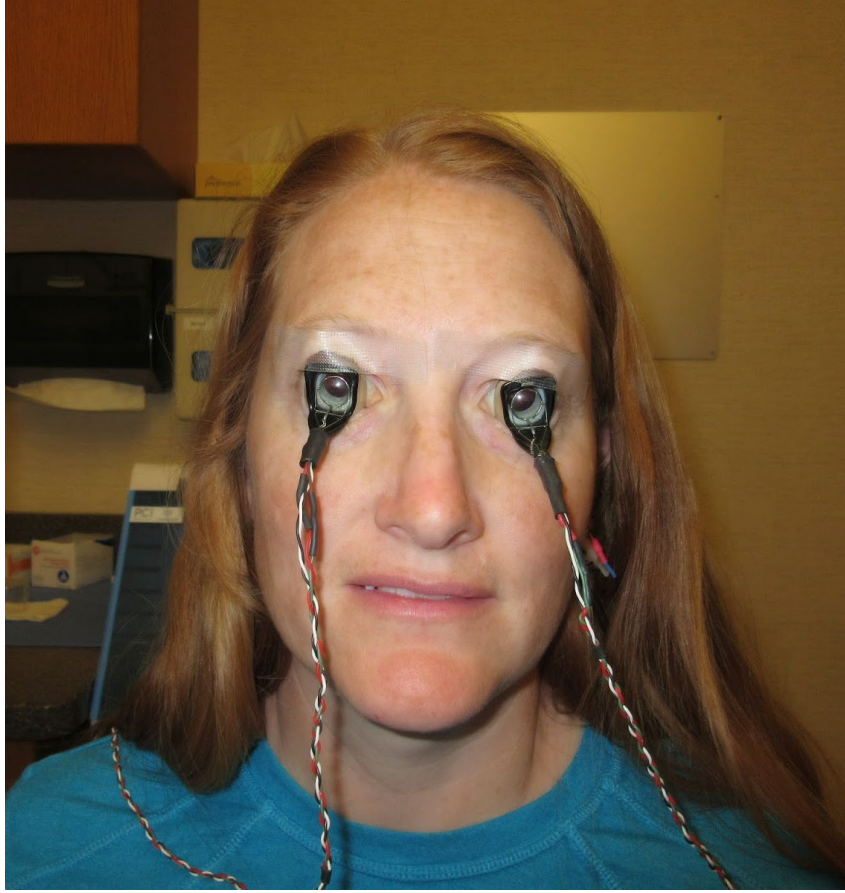
Georgios Tsokolas[1]
Konstantinos T Tsaousis[1]
Vasilios F Diakonis[2]
Artemis Matsou[3]
Straton Tyradellis[1]

[1]Ophthalmology Department, Leicester Royal Infirmary, University Hospitals of Leicester, Leicester, UK; [2]The Eye Institute of West Florida, Largo, FL, USA; [3]Ophthalmology Department, Addenbrooke's Hospital, Cambridge University Hospitals, Cambridge, UK

Background: Optical coherence tomography angiography (OCT-A) has emerged as a novel, fast, safe and non-invasive imaging technique of analyzing the retinal and choroidal microvasculature in vivo. OCT-A captures multiple sequential B-scans performed repeatedly over a specific retinal area at high speed, thus enabling the composition of a vascular map with areas of contrast change (high flow zones) and areas of steady contrast (slow or no flow zones). It therefore provides unique insight into the exact retinal or choroidal layer and location at which abnormal blood flow develops. OCTA has evolved into a useful tool for understanding a number of retinal pathologies such as diabetic retinopathy, age-related macular degeneration, central serous chorioretinopathy, vascular occlusions, macular telangiectasia and choroidal neovascular membranes of other causes. OCT-A technology is also increasingly being used in the evaluation of optic disc perfusion and has been suggested as a valuable tool in the early detection of glaucomatous damage and monitoring progression.

OCT-A has been utilized so far to describe abnormalities in multiple sclerosis (MS), Alzheimer's disease, arteritic and non-arteritic optic neuropathy (AION and NAION), Leber's hereditary optic neuropathy (LHON) papilloedema, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis (ALS), Wolfram syndrome, migraines, lesions of the visual pathway and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). It appears that OCT-A findings correlate quite well with the severity of the aforementioned diseases.

Available at: https://www.dovepress.com/optical-coherence-tomography-angiography-in-neurodegenerative-diseases-peer-reviewed-fulltext-article-EB

Electroretinography (ERG)

Conditions with ERG Anomalies

- Autism
- Attention deficit-hyperactivity disorder
- Major depressive disorder
- Schizophrenia
- Multiple sclerosis
- Parkinson's disease
- Alzheimer's disease

Conclusions

The retina is a window to the brain, and a window into diseases of the brain

Findings are generally not specific to a single disorder

Findings are likely to represent overall changes in central nervous system function that may be useful in monitoring for disease progression and extent of loss of neural tissue and microvasculature over time

Machine learning approaches to retinal imaging (and/or ERG) data – as opposed to using traditional variables (e.g., layer thickness) may reveal patterns of anatomical changes, or aspects of neural activity, that are especially relevant to clinical prediction and monitoring, and possibly to diagnosis.

Thank you

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