OCULOMICS

THE FUTURE OF HEALTHCARE OR JUST ANOTHER BUZZWORD?

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FINANCIAL DISCLOSURES

- I have no relevant financial relationships to declare.

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COURSE GOAL

- To provide current, clinically relevant information about the emerging field of oculomics.

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COURSE OBJECTIVES

- Define the terms "oculomics" and "biomarker."
- Discuss biomarkers of several ocular diseases.
- Describe ocular biomarkers of various systemic conditions, including cardiovascular, neurodegenerative, and kidney disease.
- Gain familiarity with current concepts and evidence in oculomics, highlighting progress that has been made, remaining challenges, and opportunities for future research.

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THE LANGUAGE OF HEALTH CARE

Terminology	True Meaning
• Precision Medicine	• Customized or individualized medicine (person-specific)
• Social Determinants of Health	• Non-medical factors that influence health (income, education, race, location, access)
• Value Based Healthcare	• Healthcare that centers on patient outcomes and how well clinicians can improve those outcomes
• Integrated Healthcare	• Team-based, interprofessional

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-OMICS OF HUMAN HEALTH

- The suffix "-omics" refers to the large-scale study of molecules like DNA, RNA, proteins, and metabolites and how they function together in a system.
- Genomics: the study of the genome, or all of an organism's DNA, and the way genes influence a person's health. For example, someone with a BRCA1 genetic mutation might undergo earlier and more frequent breast cancer screenings.
- Epigenomics: the study of the complete set of epigenetic modifications (the "epigenome") on a cell's DNA. This regulates gene expression without altering the underlying DNA sequence.

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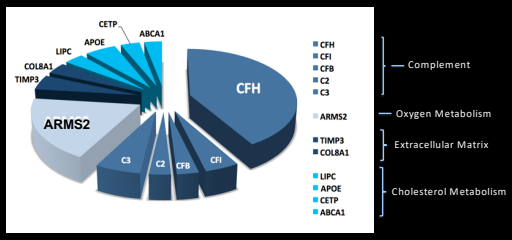
KEY AMD-ASSOCIATED GENES



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Example of Epigenomics

Smoking interacts with CFH Gene variants to increase AMD risk by 5X compared with genetically similar nonsmokers.

Am J Epidemiol. 2009 March 1; 169(5): 633–641.

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-OMICS OF HUMAN HEALTH

- Proteomics: the study of the proteome—the entire set of proteins, their structures, functions, and interactions within a biological system.
  - For example, elevated proteins in the blood might indicate inflammation or an impending heart attack.
  - In the brain, certain protein buildups—like amyloid plaques—are key indicators of diseases like Alzheimer's.
- Transcriptomics: the study of the transcriptome, or all of the RNA messages. Changes in RNA messages directly influence the types and amounts of proteins being produced.

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-OMICS OF HUMAN HEALTH

- Metabolomics: study of the metabolome, the chemical byproducts of metabolism. Metabolic shifts are often a downstream consequence of altered protein activity.
- Phenomics: brings all of this information together by studying the observable characteristics that result from the interaction of genes, proteins, environment, and lifestyle.

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THE EYE IS THE ONLY PART OF THE BODY WHERE NEUROLOGICAL AND VASCULAR TISSUES CAN BE DIRECTLY AND SIMULTANEOUSLY VIEWED IN A NON-INVASIVE MANNER.

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THE EYE IN SYSTEMIC DISEASE

- Inflammatory
- Infectious
- Endocrine
- Vascular
- Neurologic
- Collagen-vascular
- Neoplastic
- Autoimmune

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BIOMARKERS

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WHAT IS A BIOMARKER?

- Biomarkers or "biological markers" are biological indicators that signal disease risk or progression.
- A broad subcategory of medical signs – objective indicatiors observed from outside the patient – which can be measured accurately and reproducibly.
- In 1998, the NIH Biomarkers Definitions Working Group defined a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or responses to a therapeutic intervention."

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WHAT IS A BIOMARKER?

- Examples of biomarkers include everything from pulse and blood pressure to more complex laboratory tests of blood (e.g. CRP, ACE) and other tissues.
- The key issue is determining the relationship between any given measurable biomarker and relevant clinical endpoints.

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WHAT IS OCULOMICS?

- Oculomics is the study of the eye as a "window into overall health", examining the association between ophthalmic biomarkers and systemic health and disease states.
- The development of this field has been accelerated by three major advances:
  - availability and widespread adoption of high-resolution, non-invasive ophthalmic imaging ("hardware")
  - availability of large studies to investigate associations ("big data")
  - development of novel analytical methods, including AI. ("software")

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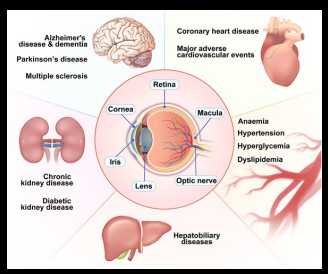

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HISTORY OF THE TERM "OCULOMICS"

- First introduced in a 2020 publication entitled "Insights into Systemic Disease through Retinal Imaging-Based Oculomics" (Wagner et al., 2020).
- The authors suggested the eye could serve as a comprehensive "window into the health of the whole body" by analyzing ocular changes that could be indicative of diseases or conditions elsewhere in the body.
- With advances in technology and research, oculomics has extended beyond observation, diving deep into the combination of ophthalmic imaging, big data and AI.
- We will use a narrow definition - the combination of big data, AI and ocular imaging to identify ocular/retinal biomarkers for systemic disease.

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BIOMARKERS IN OCULOMICS

- Structural and vascular biomarkers—such as retinal thickness, vessel tortuosity, and optic nerve changes—act as early indicators of systemic diseases like Alzheimer's, Parkinson's, cardiovascular disease, and diabetes.
- An ideal biomarker offers a cost-effective, non-invasive real-time method for systemic health screening through ocular evaluation.

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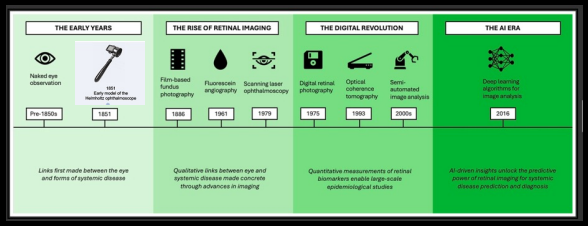
THE TERMINOLOGY IS NEW, BUT THE CONCEPT IS NOT



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FUNDUS BIOMICROSCOPY AND BIO

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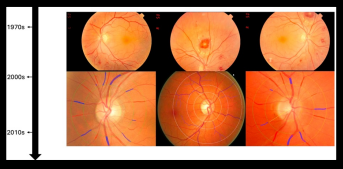
HTN RETINOPATHY

Evolution of retinal images in HR over time, from simple fundus observation to advanced imaging techniques.



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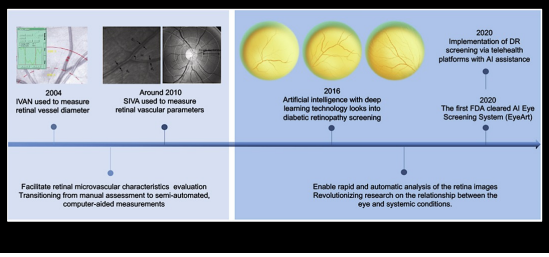
THE DIGITAL AGE HAS ENABLED QUANTITATIVE OCULOMICS



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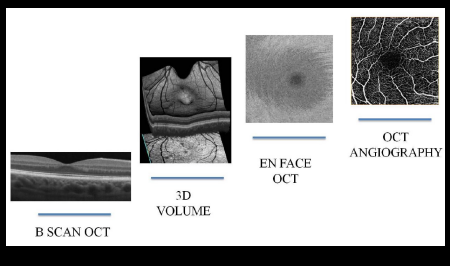
OCT AND OCTA



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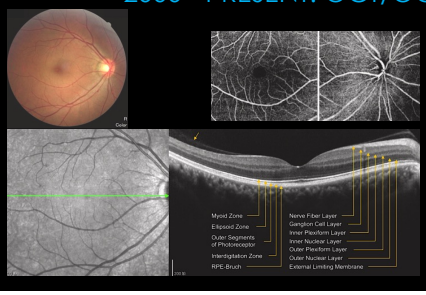
2000 - PRESENT: OCT/OCTA



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MILESTONES IN RETINAL IMAGING

Fundus Photography	1920s
Fluorescein Angiography	1950s
A/B-Scan Ultrasound	1970s
ICG Angiography (Digital)	1980s
CSLO (HRT), SLP (GDX)	1990s
OCT first demonstrated	1991
Time Domain (TD-OCT)	2001
Fourier Domain (SD-OCT)	2006
OCT Angiography (OCTA)	2015
Swept-Source (SS-OCT)	2016

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RETINAL IMAGING: THE "HARDWARE"

INVASIVE

- Fluorescein angiography (FA)
- Indocyanine green angiography (ICGA)

NON-INVASIVE

- Optical coherence tomography (OCT/OCTA)
- A/B scan ultrasonography
- Fundus photography
- Wide field and UWF imaging
- Fundus autofluorescence (FAF)
- Multi-color imaging

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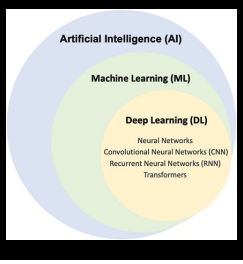
AI: THE "SOFTWARE"



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BIOMARKERS OF OCULAR DISEASE

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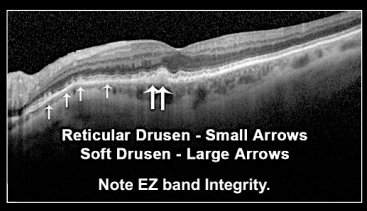
DRY AMD



Presence of RPD is a consistent risk factor for progression to both GA and MNV.

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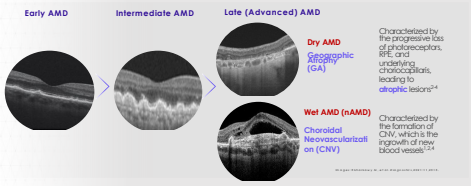
AMD

AMD is a disease spectrum ranging from early to late stages[1,2]



AMD, age-related macular degeneration; RPE, retinal pigmented epithelium.

1. Holz FG, et al. *J Clin Invest*. 2014;124:1430-1438; **2.** Armento A, et al. *Cell Mol Life Sci*. 2021:78;4487-4505; **3.** Fleckenstein M, et al. *Ophthalmology*. 2018;125:369-390; **4.** Elsharkawy M, et al. *Diagnostics*,2021:11,2313.

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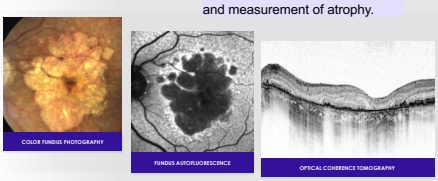
AMD

MMI is used to visualize GA lesions[1,2]

Multimodal imaging is needed to obtain the most reliable detection and measurement of atrophy.



GA, geographic atrophy.

Images: Fleckenstein M, et al. *Ophthalmology*. 2018;125:369-390.

1. Fleckenstein M, et al. *Ophthalmology*. 2018;125:369-390; **2.** Holz FG, et al. *Ophthalmology*. 2017;124:464-478.

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FAF + OCT IN GA

Offers a new perspective of the structure-function relationship within the retina. Note EZ band integrity.

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AMD

Nonfoveal (extrafoveal) GA lesions grow at a significantly greater rate than foveal lesions[1,2]

- GA is a progressive disease, with an average growth rate of 0.33 mm per year or 1.66 mm^2 per year[3]

- Extrafoveal, multifocal, reticular pseudodrusen -→ treat now

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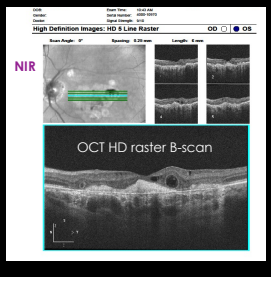
MMI in MNV



OUTER RETINAL TUBULATION IN CNV (OHS)

ORT is a feature of photoreceptor rearrangement after outer retinal insult (MNV scar, GA).

Multimodal imaging with NIR and SD-OCT.

Image credit: Brad Sutton, OD

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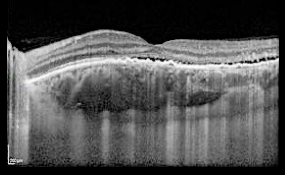
IMAGING THE CHOROID

PACHYCHOROID AND SUBRETINAL FLUID IN CSC



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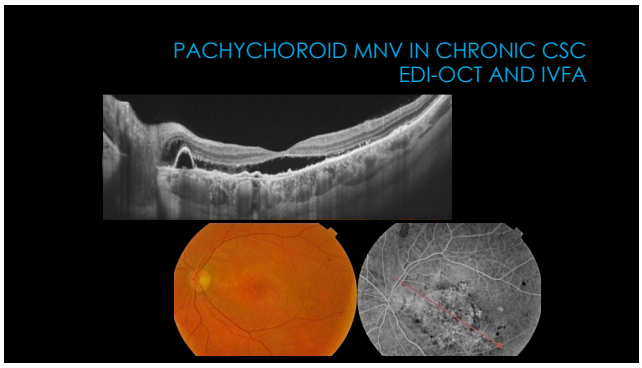

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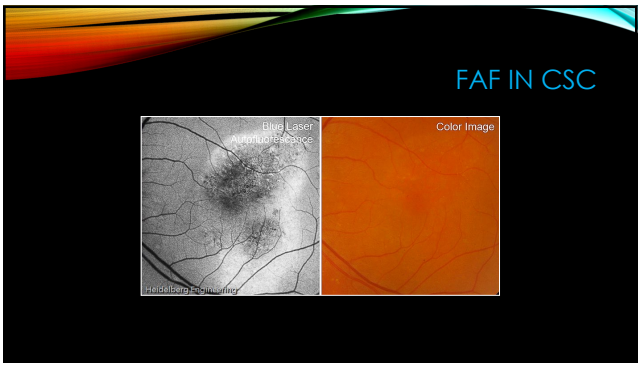

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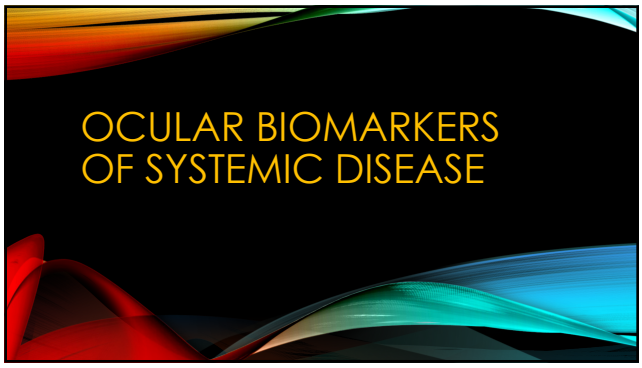

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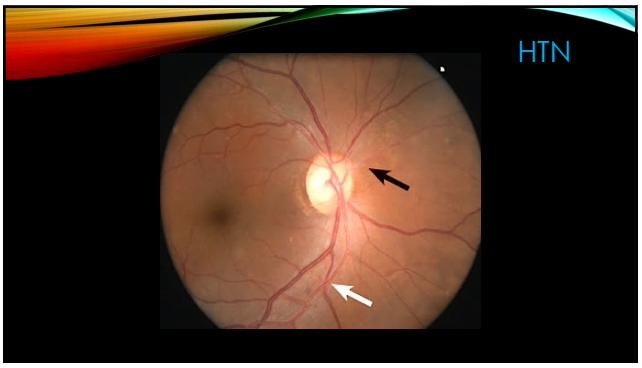

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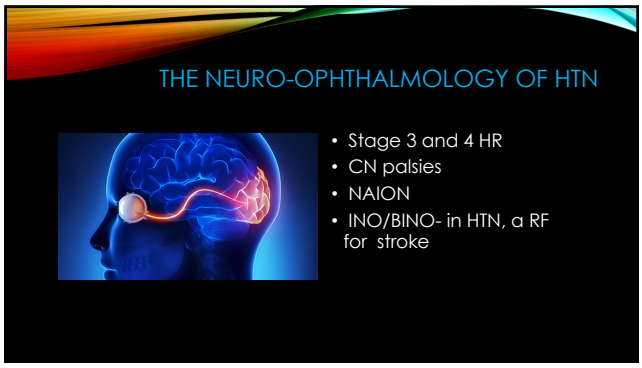

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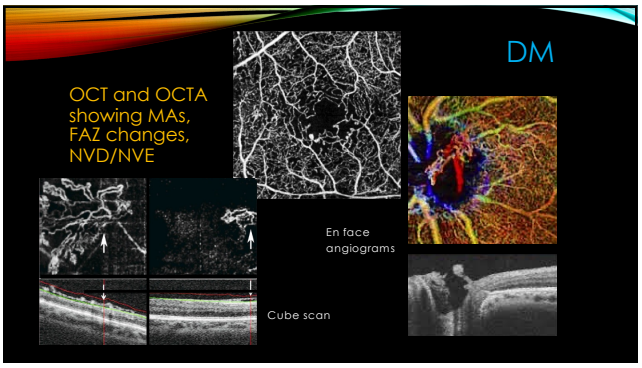

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DR is NOT exclusive to the central retina.

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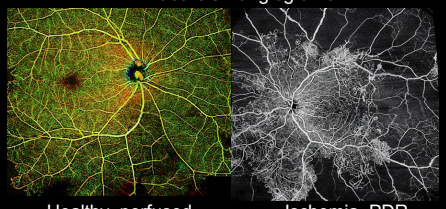
C-SCAN FACILITATES OCTA

En face OCT angiograms



Healthy, perfused

Ischemia, PDR

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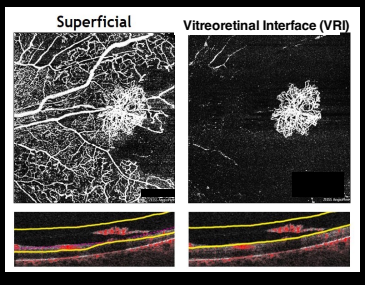
Proper segmentation highlights NVE.



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NEURO-OPHTHALMIC DISEASE

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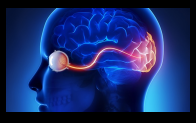
COMMON SYSTEMIC CONDITIONS IN NEURO-EYE DISEASE

- Hypertension
- Diabetes
- Other CV Disease: Carotid
- GCA
- MS
- Alzheimer's Disease
- Parkinson's Disease
- Thyroid Disorders
- Sarcoidosis
- Lupus
- Neoplastic Disease



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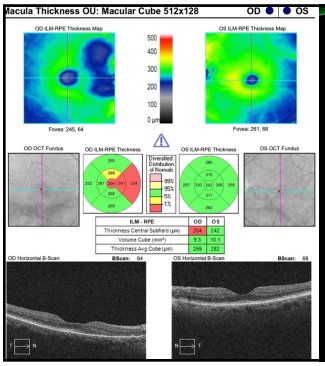

FOVEAL ISCHEMIA IN SCD

- An African American woman in her late 40s with hemoglobin SS disease presented for annual examination.
- She was visually asymptomatic and her VA was 20/30 OD, 20/20 OS.
- Ant segment and DFE were normal in both eyes, without visible SCR.
- SD-OCT shows macular splaying and central macular thinning OD.
- Macular ischemia due to non-perfusion or old PAMM in SCD.

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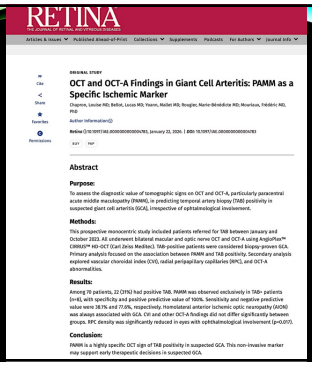
PAMM IN GCA

- The authors found that PAMM is a highly specific sign of TAB positivity in suspected GCA.
- This non-invasive marker may support early therapeutic decisions in suspected cases.



RETINA

OCT and OCT-A Findings in Giant Cell Arteritis: PAMM as a Specific Ischemic Marker

Abstract

Purpose:

To assess the diagnostic value of temporospheric signs on OCT and OCT-A, particularly paracentral acute middle maculopathy (PAMM), in predicting temporal artery biopsy (TAB) positivity in suspected giant cell arteritis (GCA), irrespective of ophtalmological involvement.

Methods:

This prospective monocentric study included patients referred for TAB between January and October 2023. All underwent bilateral macular and optic nerve OCT and OCT-A using AngioPlex™ CIRRUS™ HD-OCT (Carl Zeiss Meditec). TAB-positive patients were considered biopsy-proven GCA. Primary analysis focused on the association between PAMM and TAB positivity. Secondary analysis explored vascular choroidal index (CVI), radial peripapillary capillaries (RPC), and OCT-A abnormalities.

Results:

Among 70 patients, 22 (31%) had positive TAB. PAMM was observed exclusively in TAB+ patients (n=6), with specificity and positive predictive value of 100%. Sensitivity and negative predictive value were 38.5% and 77.6%, respectively. Homolateral anterior ischemic optic neuropathy (AION) was always associated with GCA. CVI and other OCT-A findings did not differ significantly between groups. RPC density was significantly reduced in eyes with ophthalmological involvement (p=0.017).

Conclusion:

PAMM is a highly specific OCT sign of TAB positivity in suspected GCA. This non-invasive marker may support early therapeutic decisions in suspected GCA.

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NEURO-OPHTHALMIC MANIFESTATIONS OF MS

- Optic neuritis
- Brainstem motility disorders
- Nystagmus

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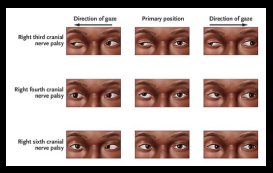
CRANIAL NEUROPATHIES IN MS

- Nuclear or fascicular lesion
  - CN III
  - CN IV
  - CN VI



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MS-RELATED OPTIC NEURITIS

- A focal inflammatory / demyelinating event of the optic nerve that may be idiopathic and localized to the optic nerve or may be or become associated with other systemic illnesses, notably *multiple sclerosis.*
- 90% of all optic neuritis

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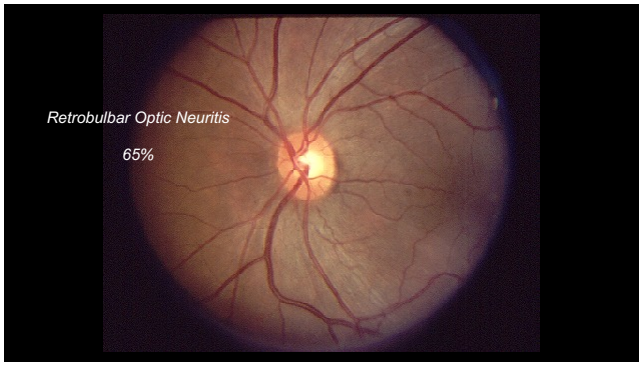

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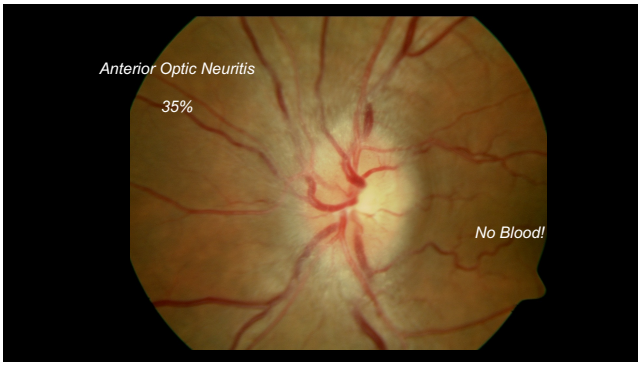

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OCT FINDINGS IN MS

- Acute optic neuritis was associated with RNFL & GCL+IPL thinning of 20% - 40% X 3 months.
- Thinning of RNFL & GCL+IPL occurs over time with MS in the absence of optic neuritis (thinning of 12%).
- OCT RNFL & GCL+IPL, low-contrast VA, vision-specific QOL measures are now incorporated into MS clinical trials.

Balcer LJ. *Neuroophthalmol* 2014
Sakai RE et al. *J Neuroophthalmol* 2011
Fisher JB, et al. *Ophthalmology* 2008

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31 Y/O WOMAN

- 10-year Hx of RRMS
- Meds:
  - Ocrevus (ocrelizumab)
- Prior episode of optic neuritis OD
- BVA:
  - 20/20 -1 OD
  - 20/20 OS

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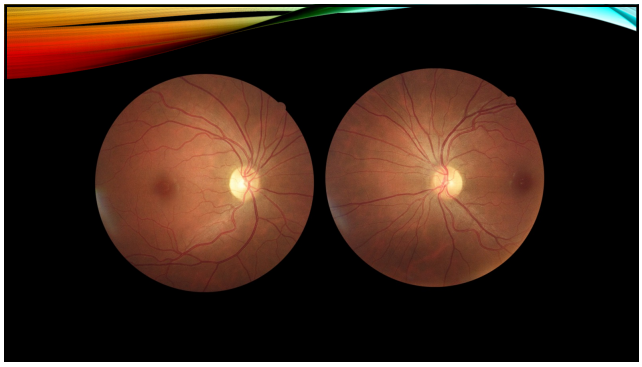

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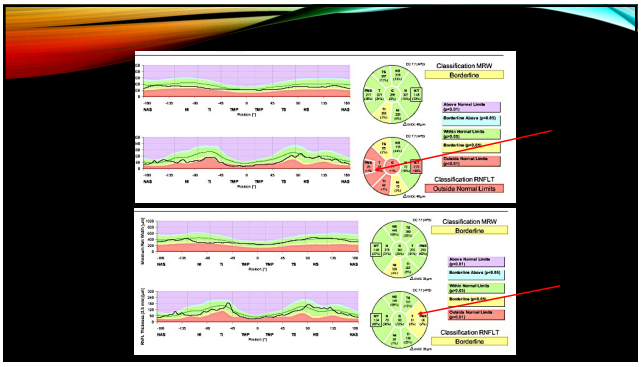

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AMERICAN ACADEMY OF OPHTHALMOLOGY
CrossMark

Retinal and Optic Nerve Degeneration in Patients with Multiple Sclerosis Followed up for 5 Years

Elena Garcia-Martin, PhD,[1,2] Jose R. Ara, PhD,[2,3] Jesus Martin, PhD,[2,3] Carmen Almarcegui, PhD,[2,4] Isabel Dolz, PhD,[2,4] Elisa Vilades, MD,[1,2] Laura Gil-Arribas, PhD,[1,2] Francisco J. Fernandez, PhD,[1,2] Vicente Polo, PhD,[1,2] Jose M. Larrosa, PhD,[1,2] Luis E. Pablo, PhD,[1,2] Maria Satue, PhD[1,2]

- Thinning of RNFL & increased VEP latencies with MS
- Normal standard assessments of vision (VA, color vision & visual fields)
- RNFL thinning greatest temporal and inferior temp
- Thinning correlation with decreased QOL

Garcia-Martin E, et al. *Ophthalmology* 2017

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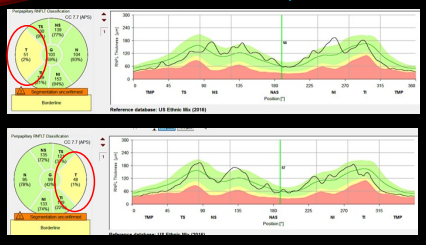
Temporal Predilection



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MS: KEY POINTS

- Neuro-ophthalmic manifestations
  - Afferent system:
    - Optic neuritis
  - Efferent system
    - Brainstem motility disorders
    - Nystagmus
- Visual, OCT biomarkers of disease activity

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WHO WILL USE OCULOMICS?

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POTENTIAL USERS OF OCULOMICS

- Optometrists
- Ophthalmologists
- GPs
- Cardiologists
- Neurologists
- Diabetologists
- Nephrologists
- Other specialists

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PROGRESS

- Rapid gains in retinal imaging (the hardware), AI (the software), and healthcare informatics (big data) are encouraging and will likely continue.
- Oculomics holds immense promise for the future of healthcare.
  - A novel, non-invasive tool for assessing vital organ health
  - Replace invasive, expensive tests
  - Early diagnosis and intervention of major systemic diseases

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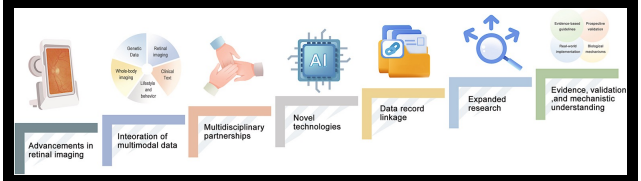
THE FUTURE



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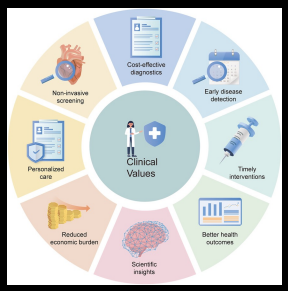
AN OCULOMICS-DRIVEN FUTURE OF HEALTHCARE



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REMAINING CHALLENGES

- Standardization across platforms
- Data security/privacy
- Large datasets are needed to develop and train AI algorithms
- Infrastructure
- Operation and workflow
- Cost-effectiveness

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REMAINING CHALLENGES

- Need continued advancements in retinal imaging, multimodal data integration, automation.
- Retinal measurements are still affected by variability, image quality, artifacts, and technical differences across platforms.
- These limitations highlight the need for faster, more scalable, and fully automated tools.
- Education of all involved
- Communication and collaboration among health professionals is crucial for unlocking the full potential of oculomics.

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REMAINING CHALLENGES

- Data infrastructure advancements such as 6G networks and data record linkage are also essential steps to broaden research and deployment opportunities.

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RESEARCH OPPORTUNITIES

- Future research may focus on:
  - expanding the scope of disease prediction
  - exploring additional imaging modalities such as adaptive optics
  - evidence-based validation that oculomics works in today's (and tomorrow's) healthcare environment
  - Efficient pre-screening for clinical trials

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CONCLUSIONS

- Oculomics is a catchy buzzword, but one that reflects the fact that the eye is an extension of the brain and CNS.
- Just as Helmholtz's ophthalmoscope revolutionized the eye examination, the advent of AI and large-scale data is beginning to transform how we interpret ophthalmic information.
- Indeed, the eye offers a uniquely accessible view into systemic health.

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FURTHER READING

- Evolution of Oculomics: From Naked Eye Observations to Artificial Intelligence over 100 Years. Irodi, Anushka et al. Ophthalmology Science, Volume 0, Issue 0, 101079
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- Zhu, Zhuoting, et al. "Oculomics: Current concepts and evidence." Progress in Retinal and Eye Research 106 (2025): 101350

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THANK YOU

For spending your precious time with me!

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