Mile High Masters of Retina 2026
Retinal Manifestations of Alzheimer's disease

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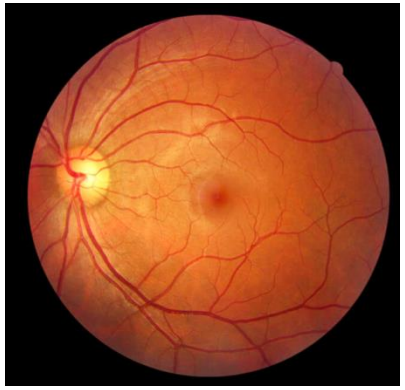

Disclosures

- Esai
- Lilly
- Alzheimer's Association
- NIH Grant Funding

Objectives

- Update the current definition of Alzheimer's disease (AD) and available biomarkers for AD
- Provide background of retinal pathology and optical coherence tomography (OCT) retinal imaging findings in AD
- Understand the potential future use of retinal OCT and other retinal imaging biomarkers in AD

Define Alzheimer's disease biologically

- **Hallmarks of AD Pathology:** amyloid and tau proteinopathy
- **Biomarkers**
  - amyloid PET imaging
  - CSF amyloid beta (Aβ) 42/40
  - CSF p-tau 181/Aβ 42
  - Plasma p-tau 217

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Alzheimer's & Dementia®
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RESEARCH ARTICLE

Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup

- **Stage: Severity of Cognitive Impairment**
  - Mild Cognitive Impairment
  - Dementia (mild, moderate, severe)

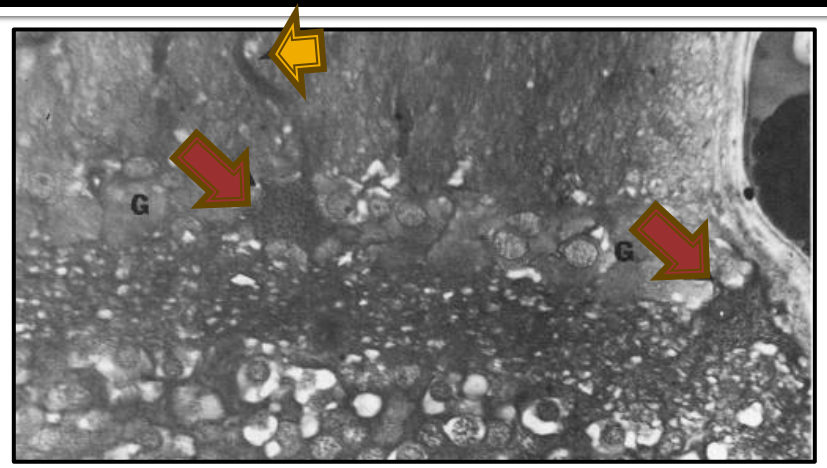
Treatment is only for those with cognitive impairment

- **<u>Do not order</u> biomarkers on asymptomatic people**
- **Disease-modifying anti-amyloid antibody therapy**: IV infusion
  - FDA-approved
  - lecanemab (2023)
  - donanemab (2024)
- **Cognitive support:** oral
  - FDA-approved
  - Multiple acetylcholinesterase inhibitors

Retinal pathology in Alzheimer's disease (AD)

I. Human post-mortem retinal tissue: AD v. Healthy

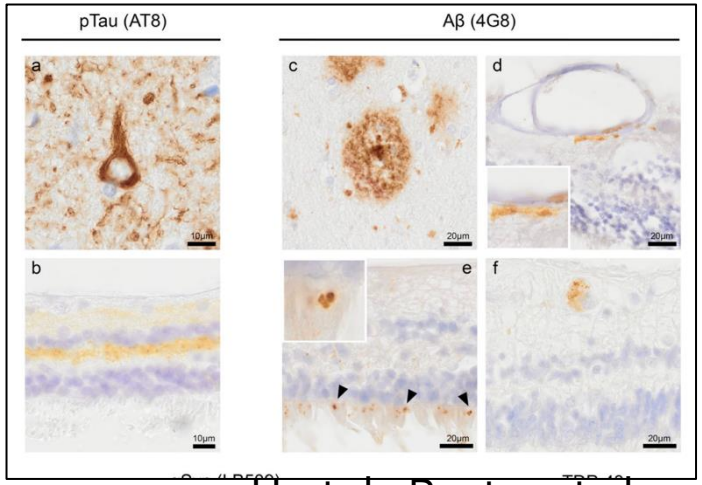
- **1990: histopathology**
  - Loss and degenerating retinal ganglion cells and axons (inner retina)
- **1980-present: amyloid and tau protein deposits**
  - 2024 - amyloid and tau deposits (Hart de Ruyter et al.)
  - retinal protein morphology differs from that in the brain



A. Sadun 1990

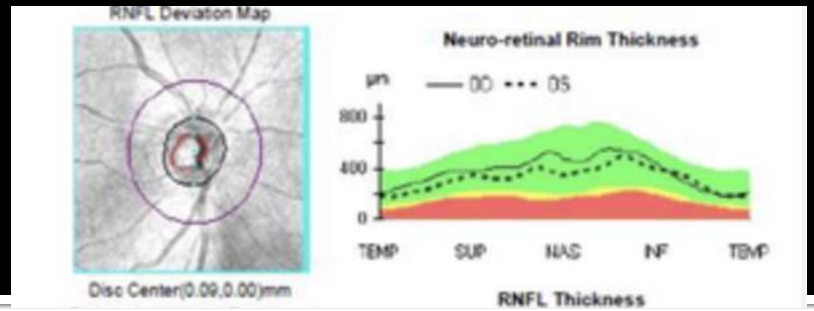
II. In vivo human retinal imaging: AD v. Healthy

- **2001: retinal imaging with optical coherence tomography (OCT)**
  - thinning of retinal ganglion cell and axonal layers (inner retina)
- **2005-present: imaging amyloid and tau protein deposits**
  - Using labeling - but replication of findings has been poor



Hart de Ruyter et al. 2024

In Vivo Retinal OCT and AD: Not for clinical practice



Area under the curve (AUC)
AD v. Healthy:

- Ganglion cell and axon thickness
  Low AUC = 0.7
- Foveal avascular zone size (OCT-A)
  Low AUC = 0.73

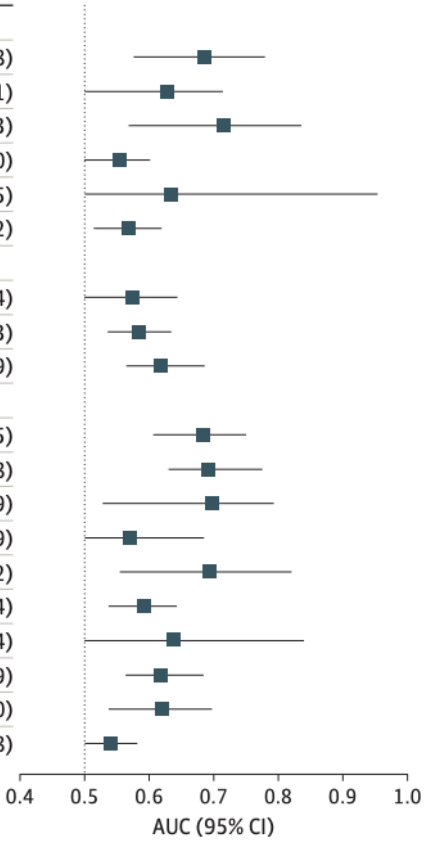
Not appropriate for individual screening (2-7% difference thickness)

Study populations: excluded glaucoma, macular degeneration

- Ganglion cell and axon thickness

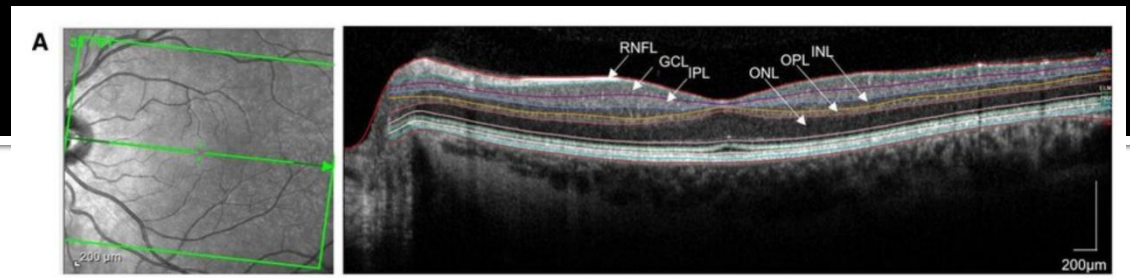
Figure 2. Optical Coherence Tomography Parameters

Parameter and source	Study population	No. of studies (No. of patients)	Risk of bias	AUC (95% CI)
GC-IPL				
Ge et al,[6] 2021	AD vs HC	11 (1900)	Low	0.69 (0.58-0.78)
Chan et al,[10] 2019	AD vs HC	5 (540)	Low	0.63 (0.50-0.71)
Chan et al,[10] 2019	MCI vs HC	4 (350)	Low	0.72 (0.57-0.83)
Ge et al,[6] 2021	MCI vs HC	8 (1377)	Low	0.55 (0.50-0.60)
→ Mejia-Vergara et al,[15] 2020	MCI vs HC	5 (375)	High	0.63 (0.50-0.95)
Ge et al,[6] 2021	AD vs MCI	7 (971)	Low	0.57 (0.51-0.62)
mRNFL				
Ge et al,[6] 2021	AD vs HC	5 (967)	Low	0.57 (0.50-0.64)
Ge et al,[6] 2021	MCI vs HC	3 (756)	Low	0.58 (0.54-0.63)
Noah et al,[16] 2020	MCI vs HC	17 (1776)	Low	0.62 (0.56-0.69)
pRNFL				
Chan et al,[10] 2019	AD vs HC	24 (2219)	Low	0.68 (0.61-0.75)
den Haan et al,[12] 2017	AD vs HC	24 (1715)	Unclear	0.69 (0.63-0.78)
Ge et al,[6] 2021	AD vs HC	38 (4393)	Low	0.70 (0.53-0.79)
Chan et al,[10] 2019	MCI vs HC	7 (507)	Low	0.57 (0.50-0.69)
den Haan et al,[12] 2017	MCI vs HC	8 (582)	Unclear	0.69 (0.55-0.82)
Ge et al,[6] 2021	MCI vs HC	21 (3454)	Low	0.59 (0.54-0.64)
→ Mejia-Vergara et al,[15] 2020	MCI vs HC	NA	High	0.64 (0.50-0.84)
Noah et al,[16] 2020	MCI vs HC	17 (1776)	Low	0.62 (0.56-0.69)
den Haan et al,[12] 2017	AD vs MCI	8 (538)	Unclear	0.62 (0.54-0.70)
Ge et al,[6] 2021	AD vs MCI	14 (1503)	Low	0.54 (0.50-0.58)



Costanzo E et al. *JAMA Ophthalmol.* 2023;141(1):84–91.

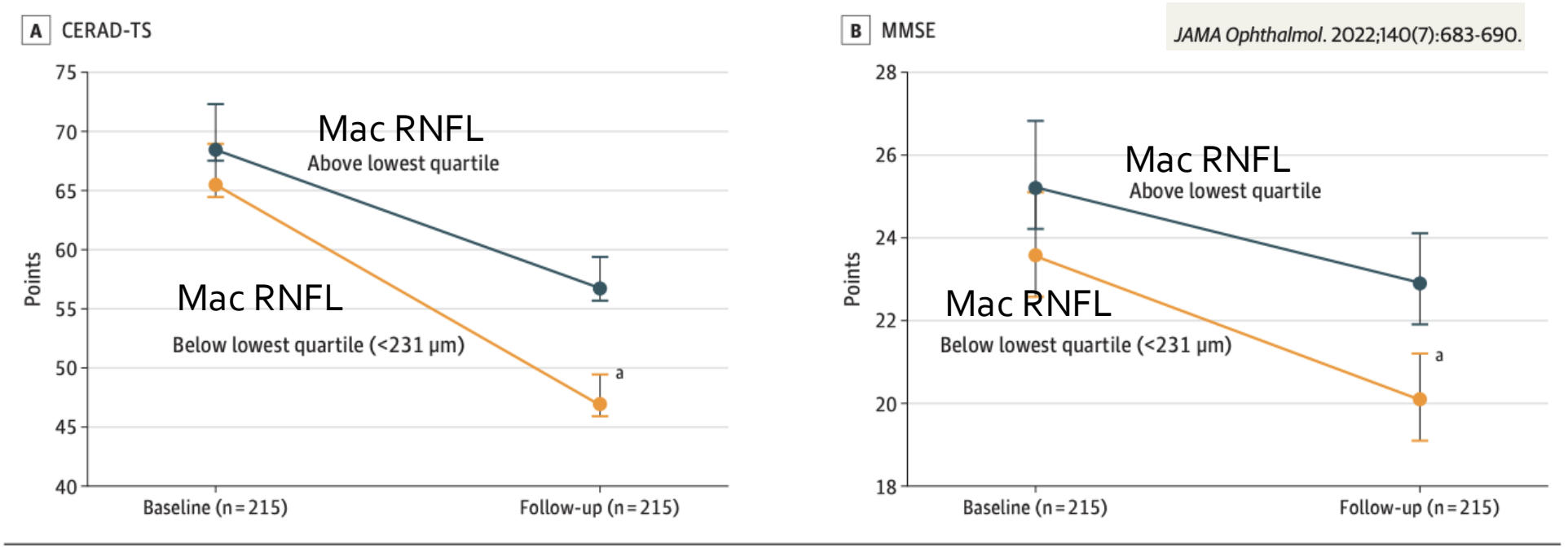
Cognition community-dwelling populations associated with inner retinal thinning by OCT



Macula retinal nerve fiber layer
(retinal ganglion cell axons)

Cog testing

Figure 2. Cognitive Performance Scores According to the Baseline Total Macular Retinal Nerve Fiber Layer (RNFL) Quartile Groups

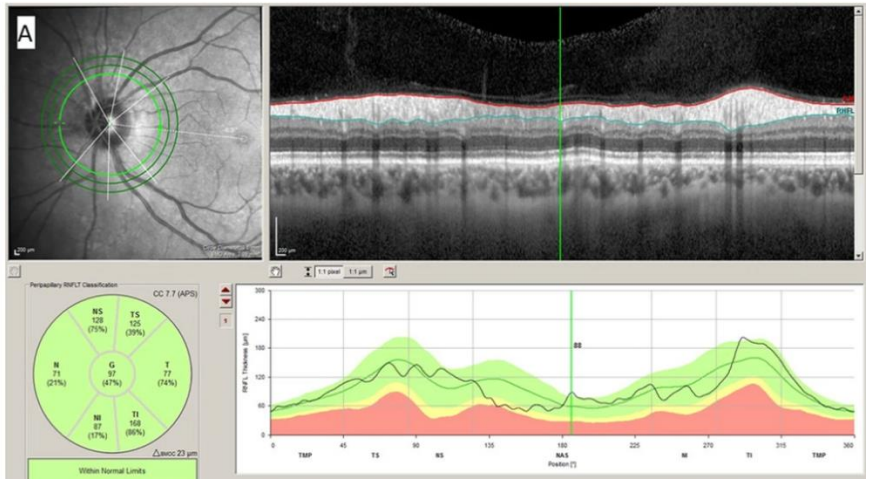


JAMA Ophthalmol. 2022;140(7):683-690.

Summary: Retinal OCT and AD

Retinal ganglion cell and axon layers

- Thinning in AD v. healthy controls
- Thinning in community populations is tied to future cognition decline
- <u>Can't use retinal OCT for diagnostic</u> purposes



Future: hyper- or tri-spectral retinal imaging

In vivo imaging mice models of AD

More et al. IOVS June 2016
Hyperspectral endoscopic amyloid imaging

Human: hyperspectral imaging detected wavelength-dependent (450-585 nm) **differences in retinal reflectance in those with amyloid beta brain biomarkers:**

- AUC: 0.8 (+) Amyloid PET v. (-) Amyloid PET

J Alzheimers Dis. 2024;100(s1):S131-S152.

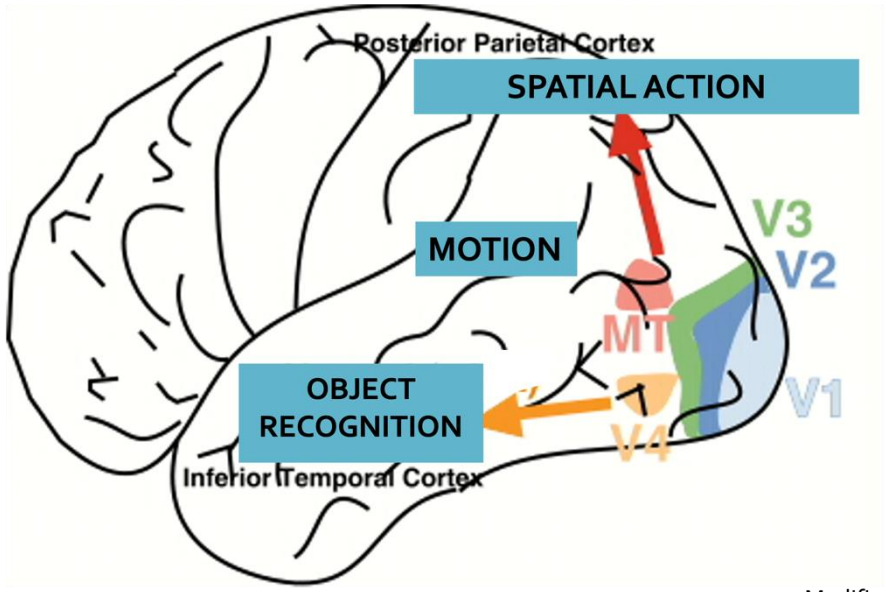
Tri-spectral retinal imaging + clinical + demographic data + machine learning models

- AUC: 0.91 (+)AD brain biomarker v. healthy (no biomarker tested)

Sci Rep. 2026 Jan 13;16(1):5083

Visual symptoms and Alzheimer's disease

Caused by:
Visual Brain Dysfunction



Modified from Pelak 2009

Rapid Eye Clinic Screening Battery for Visual Cortical Dysfunction (VisCorD) & Visual Field Perimetry

The VisCorD screening battery is designed for use in eye clinics along with the Visual Field Perimetry to identify potential posterior cortical visual dysfunction in patients who have **unexplained visual complaints following a comprehensive eye exam* see disclaimer.**

Click here to take the survey to help the designers know more about who is utilizing this screening assessment. This information will only be accessible by the team base at University of Colorado School of Medicine.DV

Web-based Visual Cortical Screening Battery (VisCorD)

Summary: Retina and Alzheimer's Disease

- AD: biologically defined by biomarkers for symptomatic people
- AD: associated with post-mortem inner retinal degeneration (retinal ganglion cells and their axons) and AD proteinopathies
- AD: in vivo OCT retinal imaging can detect inner retinal thinning but lacks diagnostic accuracy
- Community populations (unknown biomarker status): associations between OCT inner retinal thinning and future cognitive decline
- Future: spectral retinal imaging promising to detect AD proteinopathies
- Visual symptoms due to AD stem from visual brain dysfunction

Thank you