Retinal Biomarkers of Alzheimer's Disease

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OAO Tech Conference
03/08/2019

CASEY EYE Institute OHSU

Learning Objectives

1. Develop an understanding of the epidemiology, pathology and current diagnostics in Alzheimer's Disease
2. Identify retinal and non-retinal biomarkers of Alzheimer's Disease
3. Explore current and potential imaging techniques for the screening and detection of Alzheimer's Disease

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Agenda

- Epidemiology
- Pathology
- Clinical Course
- Genetics
- Diagnosis
- Retinal Biomarkers
- Other Ocular Markers
- Treatment / Future Directions

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Epidemiology

- Prevalence: 36.5 million worldwide
- Incidence: 5-7 million per year
- 6th leading cause of death in USA
- $215B in 2010
- 13.8 million in USA by 2050
- 15% of population over 65

Number of deaths for leading causes of death

- Heart disease: 635,260
- Cancer: 598,038
- Accidents (unintentional injuries): 161,374
- Chronic lower respiratory diseases: 154,596
- Stroke (cerebrovascular diseases): 142,142
- Alzheimer's disease: 116,103
- Diabetes: 80,058
- Influenza and pneumonia: 51,537
- Nephritis, nephrotic syndrome, and nephrosis: 50,046
- Intentional self-harm (suicide): 44,965

Source: https://www.cdc.gov/nchs/fastats/leading-causes-of-death.htm (2016 data)

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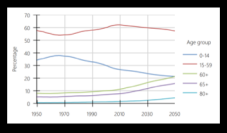
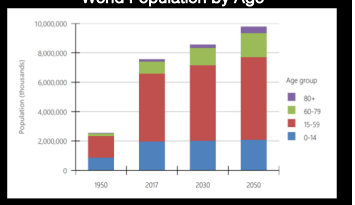
Epidemiology

Population by Age (%)

Age	1950	2017	2030	2050
0-14	34.3	25.9	23.7	21.3
15-59	57.8	61.3	59.9	57.4
60+	8.0	12.7	16.4	21.3
65+	5.1	8.7	11.7	15.8
80+	0.6	1.8	2.4	4.3



World Population by Age



Source: The United Nations 2017 Interactive Data: Profiles in Ageing

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Epidemiology

Protective factors

- Mediterranean diet
- Mentally demanding activities
- Walking

Table 2. Unadjusted and Age-Adjusted Incidence of Dementia According to Distance Walked per Day

	Incidence per 1000 Person-Years (No. of Cases/Men at Risk)							
Dementia	<0.25, mile/d	*P* Value*	0.25 to 1, mile/d	*P* Value*	>1 to 2, mile/d	*P* Value*	>2, mile/d	
Total dementia								
Unadjusted	18.7 (49/600)	.006	18.6 (63/769)	.006	13.5 (27/433)	.18	9.0 (19/455)	
Age-adjusted	17.8	.04	17.6	.04	14.1	.29	10.3	
Alzheimer disease								
Unadjusted	11.5 (30/600)	.02	11.5 (39/769)	.02	10.5 (21/433)	.06	5.2 (11/455)	
Age-adjusted	10.8	.09	10.8	.09	11.0	.11	6.0	
Vascular dementia								
Unadjusted	3.8 (10/600)	.57	3.8 (13/769)	.56	0.5 (1/433)	.11	2.9 (6/455)	
Age-adjusted	3.7	.76	3.7	.76	0.5	.09	3.1	
Mixed and other dementia								
Unadjusted	3.4 (9/600)	.09	3.2 (11/769)	.11	2.5 (5/433)	.25	1.0 (2/455)	
Age-adjusted	3.3	.14	3.1	.17	2.6	.29	1.1	

SI conversion: To convert miles to kilometers, multiply by 1.6.
*P values compare excess of dementia in each category of distance walked per day vs men who walked more than 2 mile/d.

Source: Abbott, R. D., et al. (2004). Walking and dementia in physically capable elderly men. Jama, 292(12), 1447-1453

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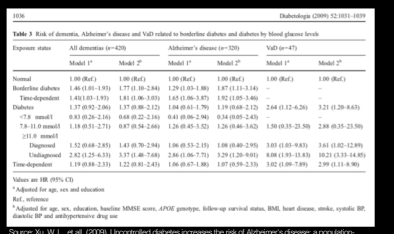
Epidemiology

Risk factors
- Age
- Genetics
- DM, HTN
- Smoking
- Obesity
- Depression
- Cognitive inactivity
- Physical inactivity



1036 Diabetologia (2009) 52:1031–1039

Table 3 Risk of dementia, Alzheimer's disease and VaD related to borderline diabetes and diabetes by blood glucose levels

Exposure status	All dementias (n=420)		Alzheimer's disease (n=320)		VaD (n=47)	
	Model 1[a]	Model 2[b]	Model 1[a]	Model 2[b]	Model 1[a]	Model 2[b]
Normal	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Borderline diabetes	1.46 (1.01–1.93)	1.77 (1.10–2.84)	1.29 (1.03–1.88)	1.87 (1.11–3.14)	–	–
Time-dependent	1.43(1.03–1.93)	1.81 (1.06–3.03)	1.65 (1.06–3.87)	1.92 (1.05–3.46)	–	–
Diabetes	1.37 (0.92–2.06)	1.37 (0.80–2.12)	1.04 (0.61–1.79)	1.19 (0.68–2.12)	2.64 (1.12–6.26)	3.21 (1.20–8.63)
<7.8 mmol/l	0.83 (0.26–2.16)	0.68 (0.22–2.16)	0.41 (0.06–2.94)	0.34 (0.05–2.43)	–	–
7.8–11.0 mmol/l	1.18 (0.51–2.71)	0.87 (0.54–2.66)	1.26 (0.45–3.52)	1.26 (0.46–3.62)	1.50 (0.35–23.50)	2.88 (0.35–23.50)
≥11.0 mmol/l						
Diagnosed	1.52 (0.68–2.85)	1.43 (0.70–2.94)	1.06 (0.53–2.15)	1.08 (0.40–2.95)	3.03 (1.03–9.83)	3.61 (1.02–12.89)
Undiagnosed	2.82 (1.25–6.33)	3.37 (1.48–7.68)	2.86 (1.06–7.71)	3.29 (1.20–9.01)	8.08 (1.93–13.83)	10.21 (3.33–14.85)
Time-dependent	1.19 (0.88–2.33)	1.22 (0.81–2.43)	1.06 (0.67–1.86)	1.07 (0.59–2.33)	3.02 (1.09–7.89)	2.99 (1.11–8.90)

Values are HR (95% CI)
[a] Adjusted for age, sex and education
Ref., reference
[b] Adjusted for age, sex, education, baseline MMSE score, *APOE* genotype, follow-up survival status, BMI, heart disease, stroke, systolic BP, diastolic BP and antihypertensive drug use

Source: Xu, W. L., et al. (2009). Uncontrolled diabetes increases the risk of Alzheimer's disease: a population-based cohort study. Diabetologia, 52(8), 1031–1039

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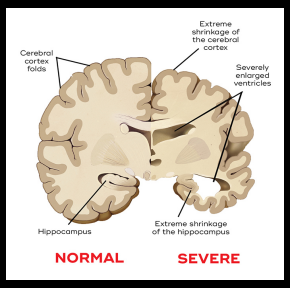
Pathology

Brain structure
positive features: AB, tau, NFT, cerebral amyloid angiopathy

negative features: loss of neurons, synaptic elements

Time Course
AB, tau deposition first
elevated hippocampal activity
loss of hippocampal volume

Neuropathology
synapse loss
neuronal degeneration



Source: https://qbi.uq.edu.au/dementia/dementia-causes-and-treatment

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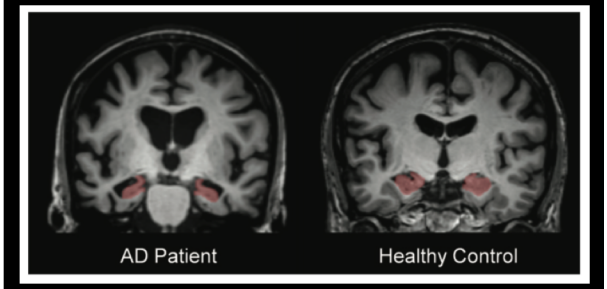
Pathology



Source: Hane, F. T., et al (2017). Recent Progress in Alzheimer's Disease Research, Part 1: Pathology. Journal of Alzheimer's Disease, 57(1), 1–28.

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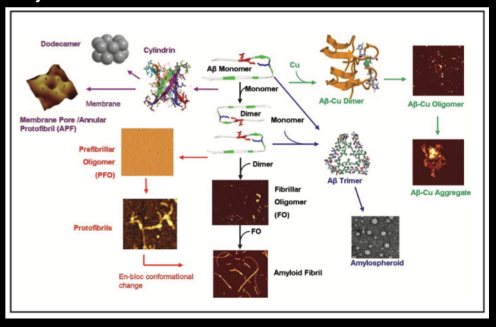
Pathology

Amyloid



Source: Hane, F. T., Lee, B. Y., & Leonenko, Z. (2017). Recent Progress in Alzheimer's Disease Research, Part 1: Pathology. Journal of Alzheimer's Disease, 57(1), 1–28.

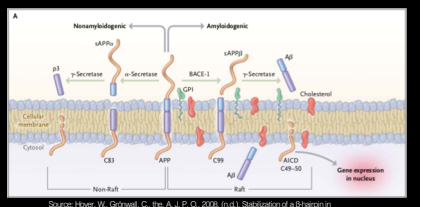
Pathology

AB amyloid

Precursor:
ABPP

Cleavage proteins:
secretases

Amyloid Cascade Hypothesis



Source: Hoyer, W., Grönwall, C., Ihe, A. J. P. O., 2008. (n.d.). Stabilization of a β-hairpin in monomeric Alzheimer's amyloid-β peptide inhibits amyloid formation. National Acad Sciences

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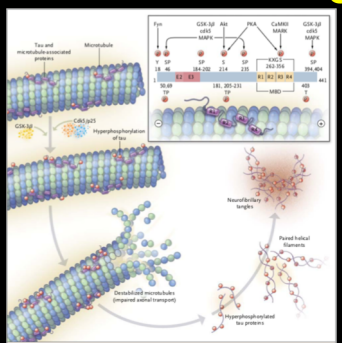
Pathology



Source: Jouanne, M., Rault, S., & Voisin-Chiret, A.-S. (2017). Tau protein aggregation in Alzheimer's disease: An attractive target for the development of novel therapeutic agents. European Journal of Medicinal Chemistry, 139, 153–167.

Tau Protein
in axons of neurons
stabilizes microtubules
interacts with AB

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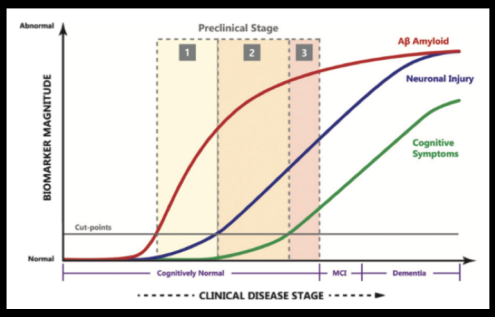
Clinical Course

Phases



Source: Haine, F. T., et al (2017). Recent Progress in Alzheimer's Disease Research, Part 3: Diagnosis and Treatment. *Journal of Alzheimer's Disease*

Genetics

Genes
- early -
ABPP
PSEN1
PSEN2

- late -
APOE

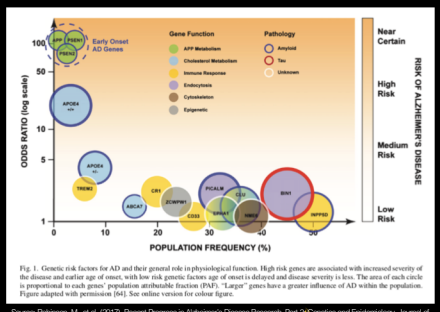


Fig. 1. Genetic risk factors for AD and their general role in physiological function. High risk genes are associated with increased severity of the disease and earlier age of onset, with low risk genetic factors age of onset is delayed and disease severity is less. The area of each circle is proportional to each genes' population attributable fraction (PAF). "Larger" genes have a greater influence of AD within the population. Figure adapted with permission [64]. See online version for colour figure.

Source: Robinson, M., et al. (2017). Recent Progress in Alzheimer's Disease Research, Part 2: Genetics and Epidemiology. Journal of Alzheimer's Disease

Diagnosis

Table 1
Table approximately comparing the major salient points of the classical and proposed updated lexicon

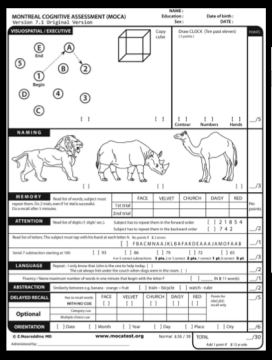
Clinical Criteria	Neuropathological Criteria	Classical Lexicon [2–4]	Revised Lexicon (Dubois) [1]
Cognitively normal	Genetic risk for familial AD		Pre-symptomatic AD
Cognitively normal	Aβ+ Neuro-injury biomarker-	Preclinical AD (Stage 1) [4]	
Cognitively normal	Aβ+ Neuro-injury biomarker+	Preclinical AD (Stage 2) [4]	Asymptomatic at-risk for AD
Subtle cognitive decline	Aβ+ Neuro-injury biomarker+	Preclinical AD (Stage 3) [4]	Prodromal AD
Gradual loss of efficiency with complex functional tasks.	Aβ+ Neuro-injury biomarker+	Mild cognitive Impairment (MCI) [3]	Mild cognitive impairment (MCI)*
Cognitive testing scores 1–1.5 SD below mean for age & education			
Progressive cognitive decline which affects the ability to function and unexplained by other medical etiologies	Aβ+ Neuro-injury biomarker+ Cortical Atrophy	AD dementia [2]	AD dementia

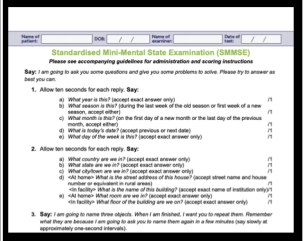
*MCI in updated lexicon may be any etiology- cognitively impaired but biomarker negative. Neuronal Injury biomarkers may be tau or FDG-PET. Aβ+ may be decreased CSF Aβ or PET+.

Source: Haine, F. T., et al (2017). Recent Progress in Alzheimer's Disease Research, Part 3: Diagnosis and Treatment. *Journal of Alzheimer's Disease*

Diagnosis

Cognitive Testing





MMSE source:
https://www.ihpa.gov.au/sites/default/files/publications/smmse-tool-v2.pdf

MoCA source
https://www.mocatest.org/?

Diagnosis

Current biomarkers: CSF AB, CSF tau

Table 2 | Systematic reviews with meta-analyses (AD vs. healthy controls): sensitivity and specificity values.

CSF biomarker and study	Number of studies included	Number of AD patients	Number of healthy controls	Sensitivity (95% CI)	Specificity (95% CI)	LR+	LR−
$A\beta_{42}$							
Bloudek et al. (2011)	14	ns	ns	80 (73–85)	82 (74–88	4	0.2
T-TAU							
Bloudek et al. (2011)	22	ns	ns	82 (76–87)	90 (86–93)	8	0.2
P-TAU							
Mitchell (2009)	19	1329	971	78 (71–84)	88 (84–91)	7	0.3
Bloudek et al. (2011)	14	ns	ns	80 (70–87)	83 (75–88)	5	0.2
COMBINATION OF $A\beta_{42}$ AND T-TAU							
Bloudek et al. (2011)	11	ns	ns	89 (84–92)	87 (83–90)	7	0.1

AD, Alzheimer's disease; CI, confidence interval; LR+, positive likelihood ratio; LR−, negative likelihood ratio; ns, non-specified; sensitivity and specificity values are expressed in percentages.

Source: Ferreira, D., et al. (2014). Meta-Review of CSF Core Biomarkers in Alzheimer's Disease: The State-of-the-Art after the New Revised Diagnostic Criteria. Frontiers in Aging Neuroscience, 6(Suppl. 179), 270.

Diagnosis

Imaging
amyloid/tau PET, MRI, DTI

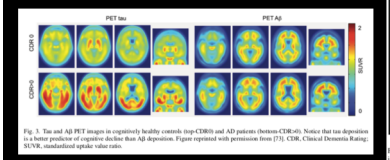


Fig. 3. Tau and Aβ PET images in cognitively healthy controls (top-CDR0) and AD patients (bottom-CDR>0). Notice that tau deposition is a better predictor of cognitive decline than Aβ deposition. Figure reprinted with permission from [73]. CDR, Clinical Dementia Rating; SUVR, standardized uptake value ratio.

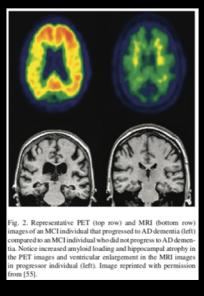
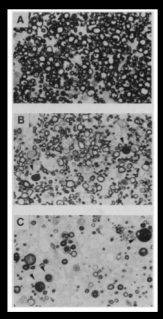


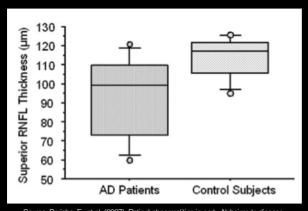
Fig. 2. Representative PET (top row) and MRI (bottom row) images of an MCI individual that progressed to AD dementia (left) compared to an MCI individual who did not progress to AD dementia. Notice increased amyloid loading and hippocampal atrophy in the PET images and ventricular enlargement in the MRI images in progressor individual (left). Image reprinted with permission from [55].

Source: Haine, F. T., et al (2017). Recent Progress in Alzheimer's Disease Research, Part 3: Diagnosis and Treatment. *Journal of Alzheimer's Disease*

Retinal Biomarkers

RNFL and Optic Nerve changes





Source: Berisha, F., et al. (2007). Retinal abnormalities in early Alzheimer's disease. Investigative Ophthalmology & Visual Science, 48(5), 2285–2289.

Source: Hinton, D. R., et al. (1986). Optic-nerve degeneration in Alzheimer's disease. The New England Journal of Medicine, 315(8), 485–487.

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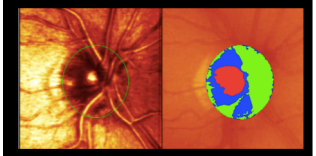
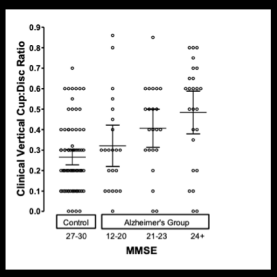
Retinal Biomarkers

RNFL and Optic Nerve changes





Source: Danesh-Meyer, H. V., et al. (2006). Reduction of optic nerve fibers in patients with Alzheimer disease identified by laser imaging. Neurology, 67(10), 1852–1854.

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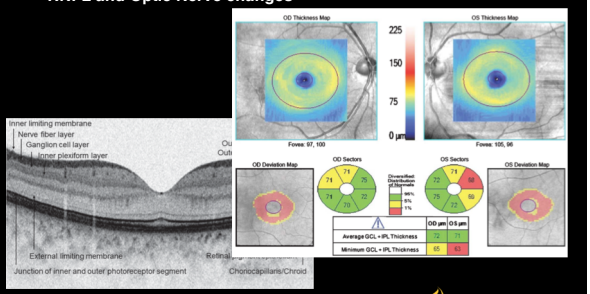
Retinal Biomarkers

RNFL and Optic Nerve changes



Source: Cheung, C. Y.-L., O., et al. (2015). Retinal Ganglion Cell Analysis Using High-Definition Optical Coherence Tomography in Patients with Mild Cognitive Impairment and Alzheimer's Disease. Journal of Alzheimer's Disease, 45(1), 45–56.

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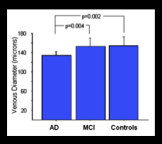
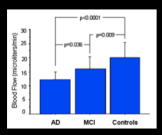
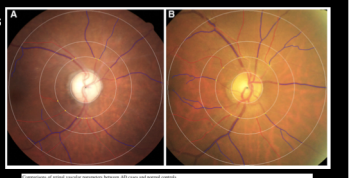
Retinal Biomarkers

Retina vascular changes





Source: Feke, G. T., Hyman, B. T., Stern, R. A., & Pasquale, L. R. (2015). Retinal blood flow in mild cognitive impairment and Alzheimer's disease. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring, 1(2), 144–151.



Source: Williams, M. A., McGowan, A. J., Cardwell, C. R., Cheung, C. Y., Craig, D., Passmore, P., et al. (2015). Retinal microvascular network attenuation in Alzheimer's disease. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*, *1*(2), 229–235.

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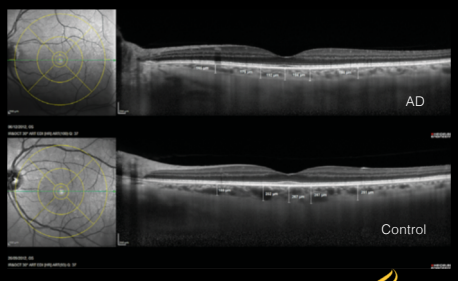
Retinal Biomarkers

Retina vascular changes



Source: Ghanbiya, M., et al. (2014). Choroidal thinning as a new finding in Alzheimer's disease: evidence from enhanced depth imaging spectral domain optical coherence tomography. Journal of Alzheimer's Disease : JAD, 40(4), 907–917.

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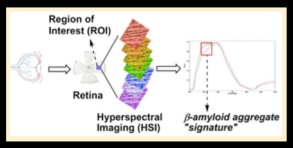
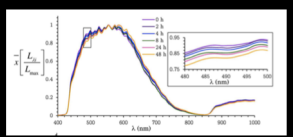
Retinal Biomarkers

AB and tau detection





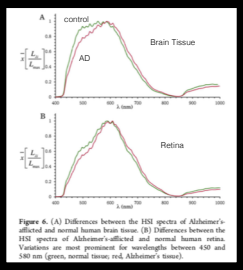


Figure 6. (A) Differences between the HSI spectra of Alzheimer's-afflicted and normal human brain tissue. (B) Differences between the HSI spectra of Alzheimer's-afflicted and normal human retina. Variations are most prominent for wavelengths between 450 and 580 nm (green, normal tissue; red, Alzheimer's tissue).

Source: More, S. S., & Vince, R. (2015). Hyperspectral imaging signatures detect amyloidopathy in Alzheimer's mouse retina well before onset of cognitive decline. ACS Chemical Neuroscience, 6(2).

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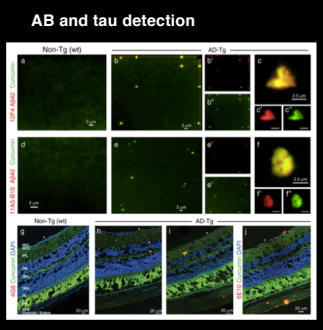
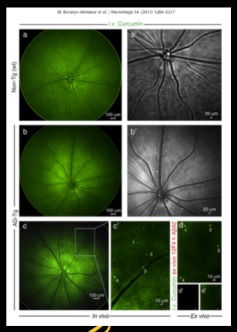
Retinal Biomarkers

AB and tau detection





Source: Koronyo-Hamaoui, M., Koronyo, Y., Ljubimov, A. V., Miller, C. A., Ko, M. K., Black, K. L., et al. (2011). Identification of amyloid plaques in retinas from Alzheimer's patients and noninvasive in vivo optical imaging of retinal plaques in a mouse model. *NeuroImage, 54 Suppl 1*, S204–17.

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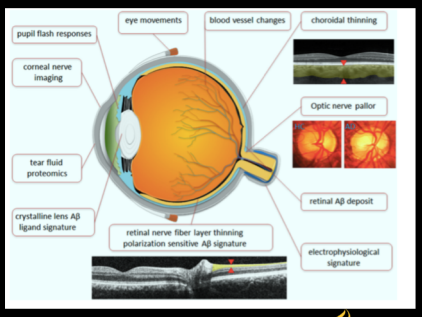
Other Ocular Markers



Source: Lim, J., et al. (2016). The Eye As a Biomarker for Alzheimer's Disease. Frontiers in Neuroscience, 10, 536.

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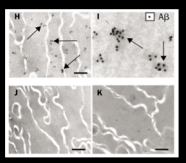
Other Ocular Markers

- Corneal Nerve Imaging
- Ocular Fluid
- Lens
  - Deposits
- Eye Movements
  - Saccades
  - Pupil Responses
- ERG



Goldstein, L. E., et al. (2003). Cytosolic beta-amyloid deposition and supranuclear cataracts in lenses from people with Alzheimer's disease. Lancet (London, England), 361(9365), 1258–1265.

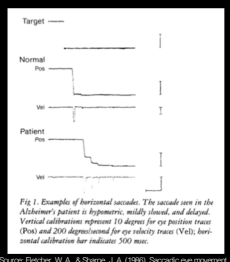


Fig 1. Examples of horizontal saccades. The saccade seen in the Alzheimer's patient is hypometric, mildly slowed, and delayed. Vertical calibrations represent 10 degrees for eye position traces (Pos) and 200 degrees/second for eye velocity traces (Vel); horizontal calibration bar indicates 500 msec.

Source: Fletcher, W. A., & Sharpe, J. A. (1986). Saccadic eye movement dysfunction in Alzheimer's disease. Annals of Neurology, 20(4), 464–471.

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Treatments

Current: Symptom management
- Donepezil: cholinesterase inhibitor
- Memantine: NMDA receptor antagonist

*not disease modifying

Targets
- Amyloid production
- Immunotherapy

Early detection = early treatment

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