



# Retinal Biomarkers of Alzheimer's Disease

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# 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



# Agenda

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




# Epidemiology

- Prevalence: 36.5 million worldwide
- Incidence: 5-7 million per year
- 6<sup>th</sup> 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/healthdata/leading-causes-of-death.htm> (2016 data)

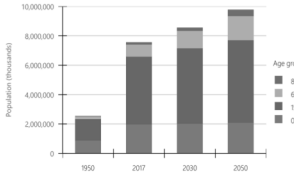


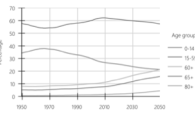
# Epidemiology

**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



# Epidemiology


**Protective factors**  
 Mediterranean diet  
 Mentally demanding activities  
 Walking

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

Dementia	Incidence per 1000 Person-Years (No. of Cases/Men at Risk)					
	<0.25, mild	p Value*	0.25 to 1, mild	p Value*	>1 to 2, mild	p Value*
<b>Total dementia</b>						
Unadjusted	18.7 (49/603)	.006	18.6 (83/769)	.006	13.5 (27/433)	.18
Age-adjusted	17.8	.04	17.6	.04	14.1	.29
<b>Alzheimer disease</b>						
Unadjusted	11.5 (20/603)	.02	11.5 (39/769)	.02	10.5 (21/433)	.06
Age-adjusted	10.8	.09	10.8	.09	11.0	.11
<b>Vascular dementia</b>						
Unadjusted	3.8 (10/603)	.57	3.8 (13/769)	.56	0.5 (1/433)	.11
Age-adjusted	3.7	.76	3.7	.76	0.5	.09
<b>Mixed and other dementia</b>						
Unadjusted	3.4 (6/603)	.09	3.2 (11/769)	.11	2.5 (5/433)	.25
Age-adjusted	3.3	.14	3.1	.17	2.6	.29

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 miles.

Source: Abbott, R. D., et al. (2016). Walking and dementia in physically capable elderly men. *Jama*, 316(12), 1447-1455



## Epidemiology

**Risk factors**


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

Diabetologia (2009) 52:1001–1009

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

Exposure status	All dementia (n=426)		Alzheimer's disease (n=320)		VaD (n=47)	
	Model 1*	Model 2*	Model 1*	Model 2*	Model 1*	Model 2*
Normal	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Hemodialysis diabetes	1.66 (1.01–2.73)	1.75 (1.02–2.94)	1.29 (0.65–2.80)	1.87 (1.13–3.14)	–	–
Tau-dependent	1.83 (1.03–3.30)	1.83 (1.06–3.07)	1.03 (0.36–2.87)	1.92 (1.05–3.48)	–	–
Diabetes	1.07 (0.62–1.86)	1.07 (0.62–1.52)	1.06 (0.61–1.76)	1.09 (0.68–1.72)	2.64 (1.12–6.26)	3.21 (1.28–8.63)
<7.8 mmol/l	0.83 (0.26–2.64)	0.68 (0.22–2.04)	0.41 (0.06–2.94)	0.34 (0.05–2.43)	–	–
7.8–11.0 mmol/l	1.18 (0.31–2.71)	0.87 (0.34–2.26)	1.26 (0.45–3.52)	1.26 (0.66–2.42)	3.98 (0.39–20.98)	2.88 (0.35–23.95)
>11.0 mmol/l	–	–	–	–	–	–
Diagnosed	1.32 (0.68–2.61)	1.43 (0.76–2.74)	1.06 (0.52–2.15)	1.88 (0.80–4.43)	3.03 (1.03–9.43)	3.61 (1.42–12.89)
Undiagnosed	1.62 (1.21–4.31)	1.37 (0.48–3.86)	1.86 (1.06–3.27)	1.29 (1.28–10.01)	0.68 (0.19–2.63)	10.21 (1.33–81.85)
Time-dependent	1.19 (0.88–2.13)	1.22 (0.81–2.41)	1.06 (0.67–1.68)	1.07 (0.59–2.33)	3.62 (1.09–7.89)	2.99 (1.11–8.96)

Values are HR (95% CI)  
\*Adjusted for age, sex, and education  
Ref. reference  
\*Adjusted for age, sex, education, baseline MMSE score, APOE genotype, follow-up survival status, BMI, heart disease, stroke, systolic BP, diabetes (if not antidiabetic 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



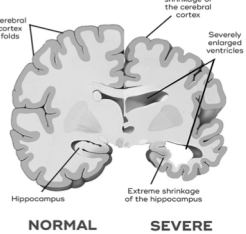
## Pathology

**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

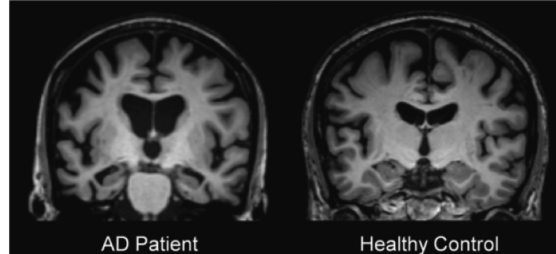
**Neuropathology**  
synapse loss  
neuronal degeneration




Source: <https://pubs.un.edu/alzheimer/dementia/causes-and-treatment>



## Pathology

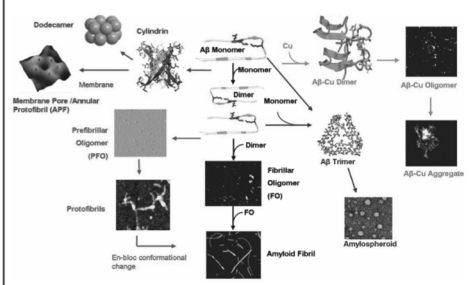


Source: Henz, F. T., et al. (2017). Recent Progress in Alzheimer's Disease Research, Part 1: Pathology. Journal of Alzheimer's Disease, 57(1), 1–26.




## Pathology

**Amyloid**



Source: Henz, F. T., Lee, B. Y., & Lesniewski, Z. (2017). Recent Progress in Alzheimer's Disease Research, Part 1: Pathology. Journal of Alzheimer's Disease, 57(1), 1–26.



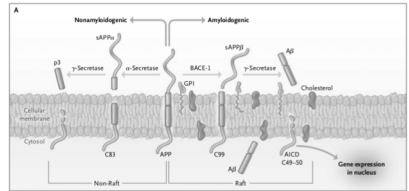
## Pathology

**AB amyloid**


Precursor: ABPP

Cleavage proteins: secretases

Amyloid Cascade Hypothesis

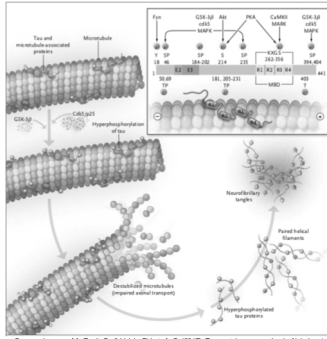


Source: Hoyer, W., Grimwell, C., & A. J. P. O., 2008. (n.d.). Stabilization of a β-secretase in monomeric Alzheimer's amyloid-β peptide inhibits amyloid formation. National Acad Sciences




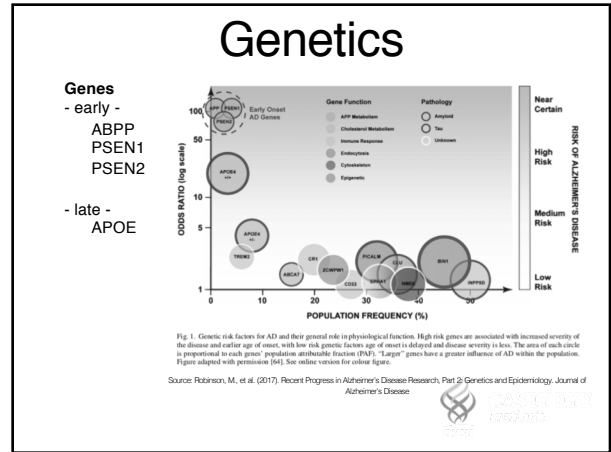
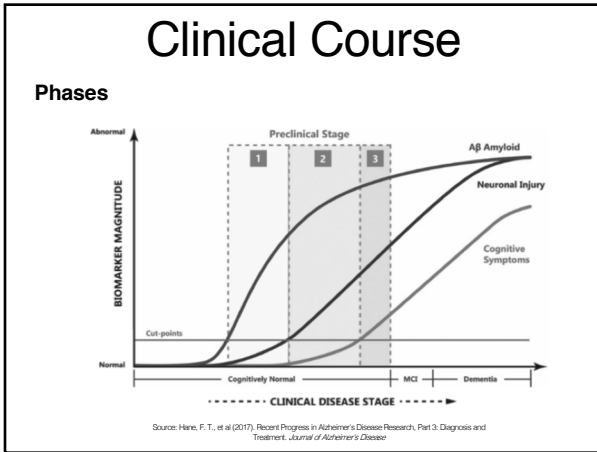
## Pathology

**Tau Protein**  
in axons of neurons  
stabilizes microtubules  
interacts with AB



Source: Joannice, M., Rault, S., & Voinchet, 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, 136, 103–107.





# 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: Hariri, 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

The MoCA test interface shows various cognitive tasks including clock drawing, trail making, and word recall. It includes instructions for the patient and a scoring system.

The 3MMSE test interface includes instructions for the patient and a list of questions to be asked, such as 'What year is this?' and 'What month is this?'.

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

# Diagnosis

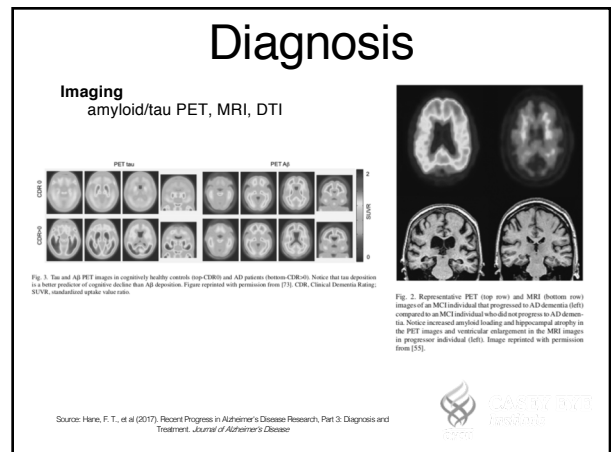
## Current biomarkers: CSF AB, CSF tau

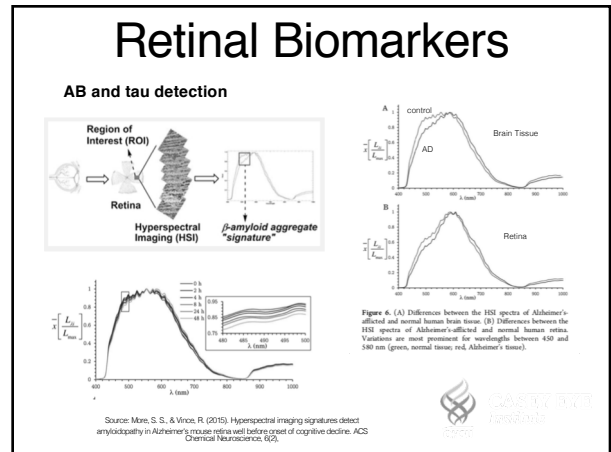
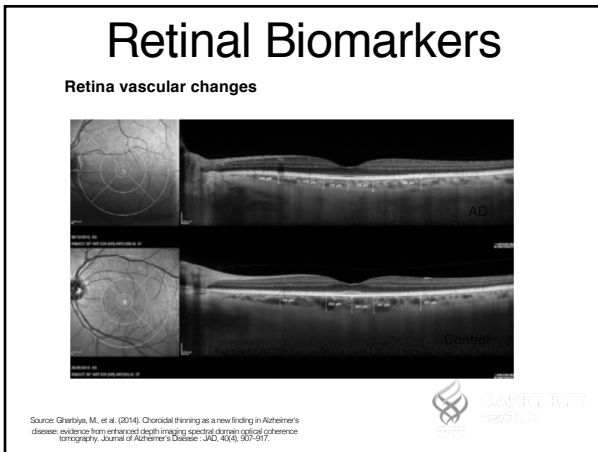
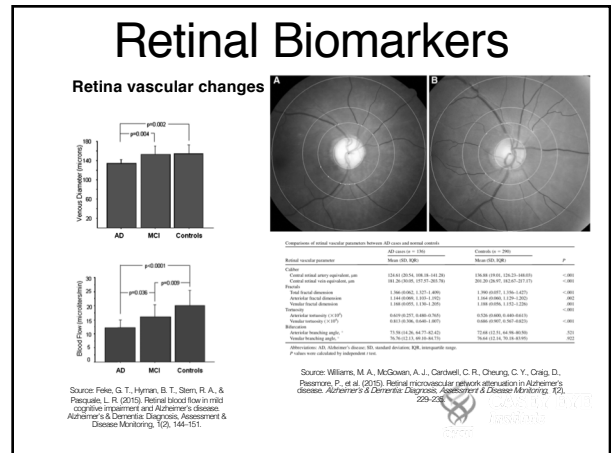
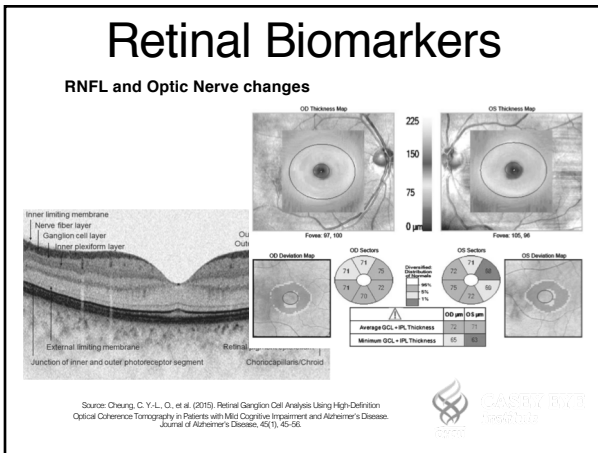
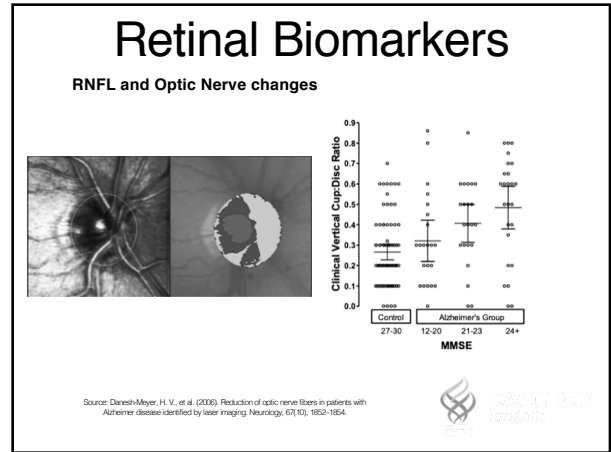
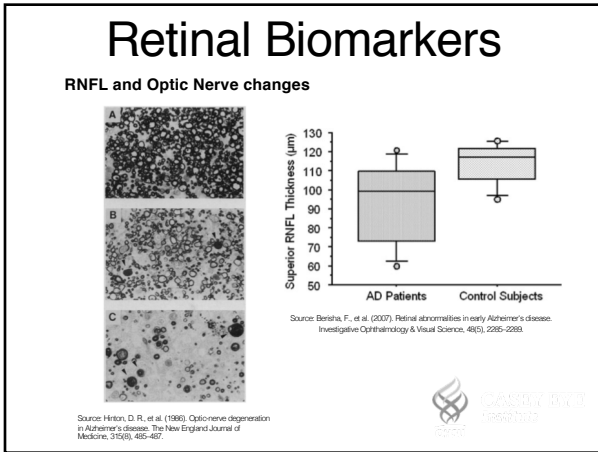
**Table 2 | Systematic reviews with meta-analyses (AD vs. healthy controls): sensitivity and specificity values.**

CSF biomarker and study	Number of studies included	Number of AD patients	Number of healthy controls	Sensitivity (95% CI)	Specificity (95% CI)	LR+	LR-
<b>Aβ</b>							
Bloudek et al. (2011)	14	ns	ns	80 (73-85)	82 (74-88)	4	0.2
<b>T.TAU</b>							
Bloudek et al. (2011)	22	ns	ns	82 (76-87)	90 (86-93)	8	0.2
<b>Aβ/TAU</b>							
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
<b>COMBINATION OF Aβ AND TAU</b>							
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. 1):79, 270.





## Retinal Biomarkers

### AB and tau detection

Source: Korony-Hamzaoui, M., Koronyo, Y., Lubimov, 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 nontransgenic in vivo optical imaging of retinal plaques in a mouse model. *NeuroImage*, 54(Suppl 1), S204-17.

## Other Ocular Markers

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

## Other Ocular Markers

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

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

Source: 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(9363), 1256-1260.

## 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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- <https://www.mocbaoc.org/>