Early Onset Alzheimer's Disease

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www.tmdf.org

TENNESSEE MEMORY DISORDERS FOUNDATION
Genesis Neuroscience Clinic

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Disclosures

- Research support:
  - Biogen, Novonordisk, American College of Radiology and Alzheimer's Association, Roche, Amylx, Avanir
  - Community Collaborations: University of Tennessee-Knoxville, Alzheimer's Tennessee
  - I have no actual or potential conflicts of interest in relation to the contents of this presentation.

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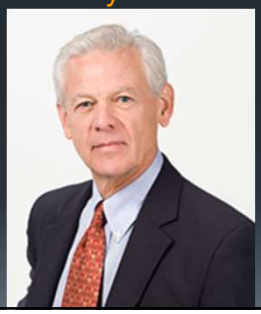
To my mentor



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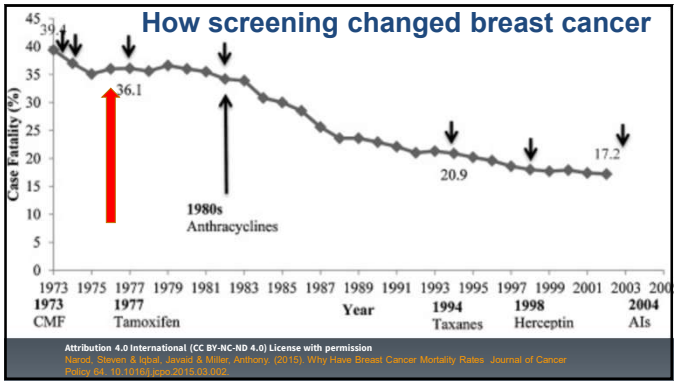
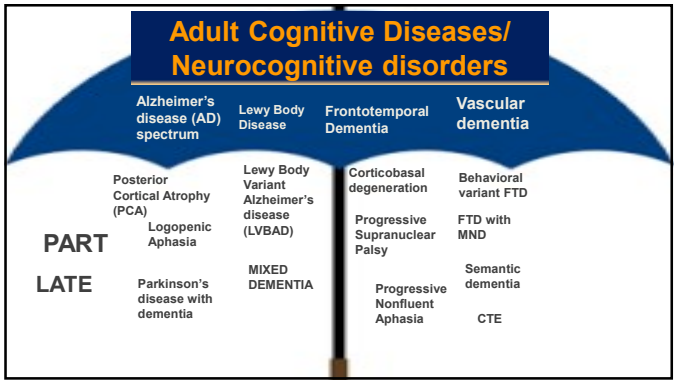

How screening changed breast cancer
Case Fatality (%)
39.4
36.1
20.9
17.2
1980s
Anthracyclines
1973 1975 1977 1979 1981 1983 1985 1987 1989 1991 1993 1995 1997 1999 2001 2003
Year
1973
CMF
1977
Tamoxifen
1994
Taxanes
1998
Herceptin
2004
AIs
Attribution 4.0 International (CC BY-NC-ND 4.0) License with permission
Narod, Steven & Iqbal, Javaid & Miller, Anthony. (2015). Why Have Breast Cancer Mortality Rates Journal of Cancer Policy 64. 10.1016/j.jcpo.2015.03.002.

4


US versus Them
WE

5


Adult Cognitive Diseases/
Neurocognitive disorders
Alzheimer's disease (AD) spectrum
Lewy Body Disease
Frontotemporal Dementia
Vascular dementia
Posterior Cortical Atrophy (PCA)
Logopenic Aphasia
Lewy Body Variant Alzheimer's disease (LVBAD)
MIXED DEMENTIA
Corticobasal degeneration
Progressive Supranuclear Palsy
Progressive Nonfluent Aphasia
Behavioral variant FTD
FTD with MND
Semantic dementia
CTE
PART
LATE
Parkinson's disease with dementia

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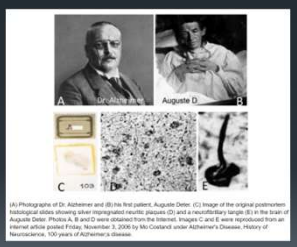
The first case of Alzheimer's disease was Early Onset Alzheimer's disease (EOAD)



- (A) Dr. Alzheimer and his first patient (B) Auguste Deter (1850-1906).
- In 1906, Dr. Alzheimer described postmortem histological slides showing silver impregnated neurtic plaques(D) and a neurofibrillary tangles (E) in Auguste's brain.

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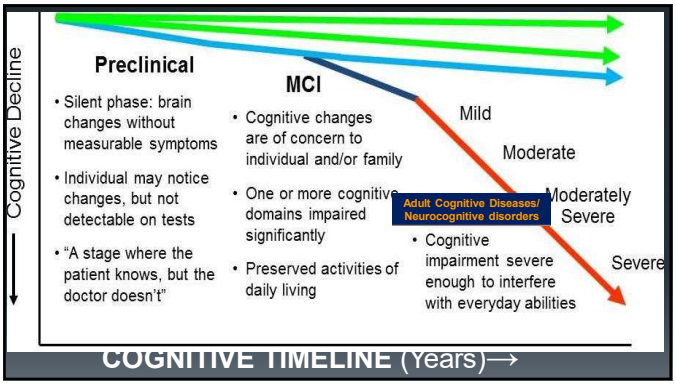

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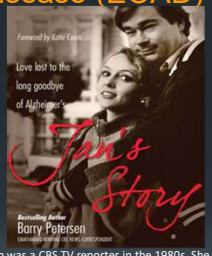
Early-onset Alzheimer's disease (EOAD)

- AD in people younger than age 65
- Includes mendelian (familial) and nonmendelian (typical) AD
- Less common than late onset Alzheimer's disease (LOAD)
- Affects 250,000-700,000 Americans but unclear due to underdiagnosis



Jan Chorlton was a CBS TV reporter in the 1980s. She began to decline in her 40s and was diagnosed at age 55. Her husband, CBS News correspondent Barry Petersen, has written *Jan's Story: Love Lost to the Long Goodbye of Alzheimer's*

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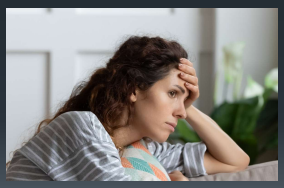
EOAD Diagnostic challenge: atypical symptoms

- Withdrawal from work and social activities
- Changes in mood and personality
- Poor judgement
- Poor cognitive flexibility
- Difficulty in finding words
- Visual problems
- Movement changes
  - Myoclonus,
  - Parkinsonism
- Seizures



Microsoft open stock photo

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Support Needed for EOAD

- Difficulties getting an accurate diagnosis
  - Delayed (1.6 years longer than LOAD)
- Loss of career and income
  - Major financial commitments (mortgage, tuition, etc)
- Loss of household role as a parent or spouse. May have dependent children at home
- Isolation
  - Community programs and living options are geared towards older patients

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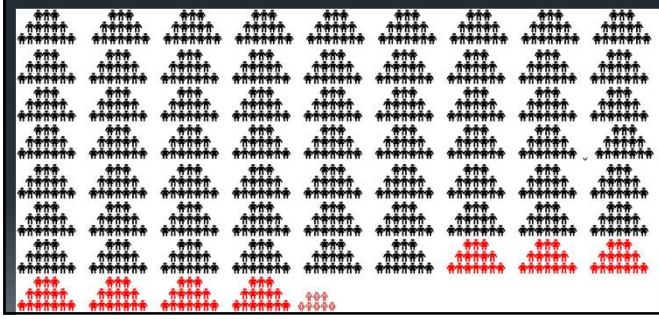
In a random sample of 1000 AD patients, approximately 50-100 will have EOAD and fewer than 10 would have mEOAD (familial AD)



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Genetics and Alzheimer's Disease

	Early-Onset AD (Dominantly Inherited)	Early-Onset AD (Complex Inheritance)	Late-Onset AD (Complex Inheritance)
	Extremely rare	Common	Very Common
Cause:	Inherited Genetic Mutations	Genetic and Environmental Risk Factors	Genetic and Environmental Risk Factors
	"Familial" Mendelian	non-Mendelian	
Age at Onset:	Usually 30-60 years	<65 years	>65 years
Proportion of Cases:	~1%	~4%	~95%

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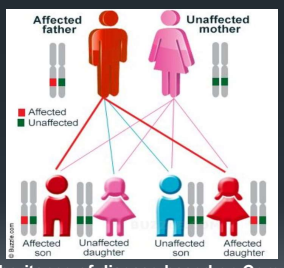
Mendelian EOAD or "Familial" dominantly inherited



Mendelian EOAD is inheritance of disease based on Complete Dominance. You inherit one or two copy of the gene and you will have symptoms

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Non-Mendelian traits: height, weight, hair and eye color, etc.

Non-Mendelian EOAD is complex: some genetics are involved (incomplete inheritance, codominance, multiple alleles, polygenic, sex-linked, etc) AND environmental factors AND lifestyle factors

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Most EOAD is (non-mendelian) a mix of genetic susceptibility and environment

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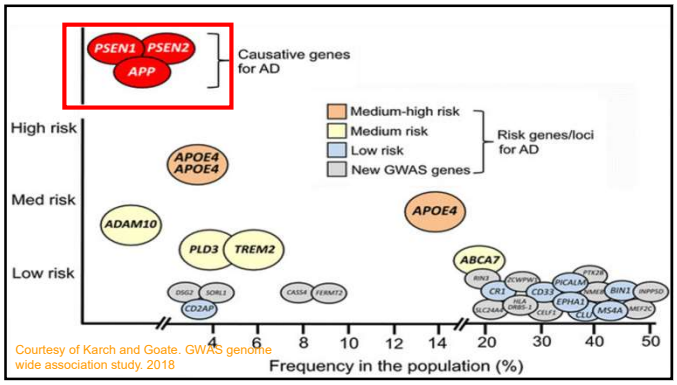

Courtesy of Karch and Goate. GWAS genome wide association study. 2018

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ApoE 4 (Apolipoprotein E4) increases the risk of AD in early and late life but does NOT cause AD.

- *(APOE)* gene on chromosome 19. Each person inherits two *APOE* alleles, one from each biological parent.
- Makes a protein that carries cholesterol and other fats throughout the body including into the brain
- The ApoE gene comes in three different forms – ApoE2, ApoE3, and ApoE4.
- ApoE2 gene is protective but a small percentage of patients with APOE 2/2 and APOE 2/3 still develop Alzheimer's

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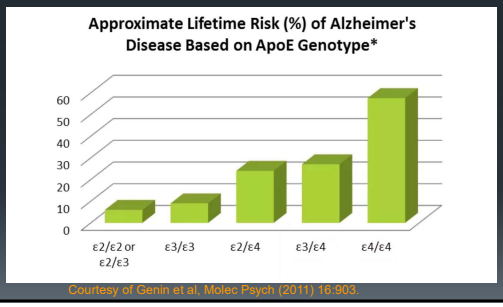
ApoE 4 (Apolipoprotein E4) increases risk of AD



Courtesy of Genin et al, Molec Psych (2011) 16:903.

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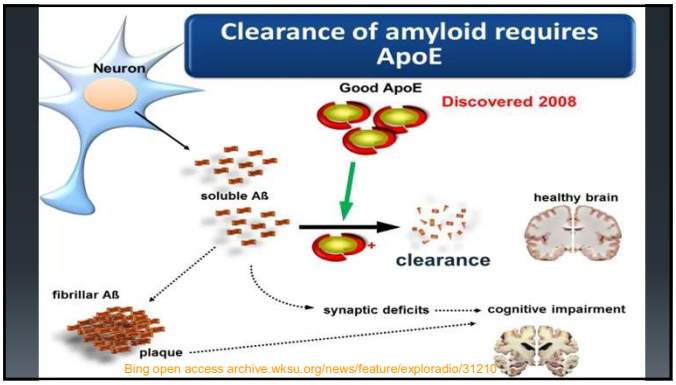

Bing open access archive.wksu.org/news/feature/exploradio/31210

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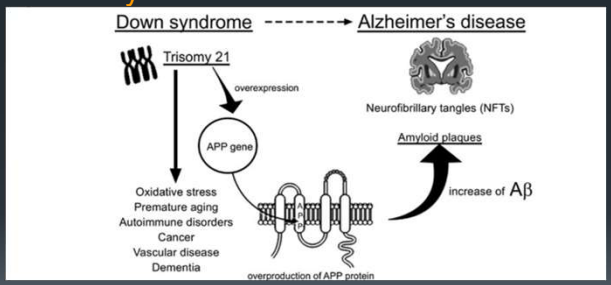
Down Syndrome



Alzheimer's Disease-related Biomarkers in Aging Adults with Down Syndrome: Systematic Review,
Courtesy of Current Psychiatry Research and Reviews 2019 15:1. DOI : 10.2174/1573400515666190122152855

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Alzheimer's disease subtypes

1. Typical Late Onset (*most common*)
2. Mixed
3. Frontal variant AD (nonamnestic)
4. Corticobasal variant AD
5. Logopenic PPA
6. Posterior cortical atrophy (PCA)
7. Typical Non mendelian or typical (nmEOAD)
   common
8. Mendelian (autosomal dominant) (mEOAD)
   extremely rare

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Cognition is not just "memory" but many domains

Episodic memory	Recollection of past events and personal experiences	Executive functions	Organizing one's thinking, eg time management, judgment, planning, awareness, insight, and working memory
Semantic memory	Long-term storage of ideas and concepts	Attention	The capacity to focus and sustain concentration[1]
Working memory	A short-term storage module in which concepts are operated upon to solve problems	Language	Verbal expression, language interpretation, and communication[1]
Visuospatial functions	Concerned with the integration of space and visual form	Praxis	Monitor and process data in the surrounding environment to plan a motor action, eg holding a pen

Harvey PD. Dialogues Clin Neurosci. 2019;21:227–237; 2. Zilli EA, Hasselmo ME. Hippocampus. 2008;18:193–209; 3. Ward M, et al. Dement Neuropsychol. 2015;9:71–75

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Mr. G is a 55 year-old college educated married man who was fired from work due "mental health" problems.

Family History:
Mother with Alzheimer's disease in her 70s and died at age 84

Maternal grandmother with "memory problems" died at age 80

Score	Score		
		ORIENTATION	
5	5	What is the (year), (season), (date), (day), (month)?	2015 fall 30 friday NOV.
5	5	Where are we (country), (state), (county), (city), (clinic)?	USA TN knox knoxville dr. crane
		Text	
3	3	**REGISTRATION** Name 3 objects allotting one second to say each one. Then ask the resident to name all 3 objects after you have said them. Give one point for each correct answer. Repeat them until he/ she hears all 3. Count trials and record number.	
		APPLE BOOK COAT Trials: 1	
5	5	**ATTENTION AND CALCULATION** Begin with 100 and count back by 7 (stop after 5 answers) 93, 86, 79, 72, 65. Score one point for each correct answer. If the resident will not perform this task, ask the resident to spell "WORLD" backwards (DLROW). Record the resident's spelling: dlrow	
-3 0	3	**RECALL** Ask the resident to repeat the objects above (see Registration). Give one point for each correct answer.	X X X w/cues X book @jacket
2	2	**LANGUAGE** Naming: Show a pencil, and a watch and ask the resident to name them.	pen/watch
-1 0	1	Repetition: Repeat the following: "No ifs, ands or buts."	if
3	3	Three Stage Command: Follow the three-stage command. "Take paper in your right hand; fold it in half; and put it on the table."	
1	1	Reading: Read and obey the following: "Close your eyes." Show the resident the item written on the reverse side, or attached.	
1	1	Writing: Write a sentence (on reverse side)	
-1 0	1	Copying: Copy the design of the intersecting pentagons (on reverse side).	
25	30	Total Score Possible	

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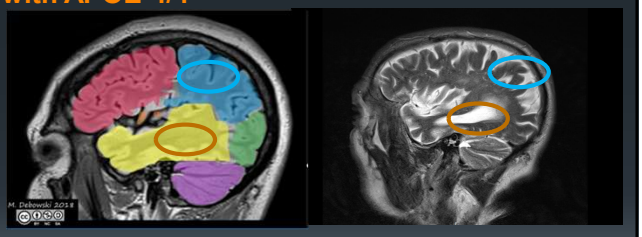
Case 1: Typical (nonmendelian) EOAD with APOE 4/4



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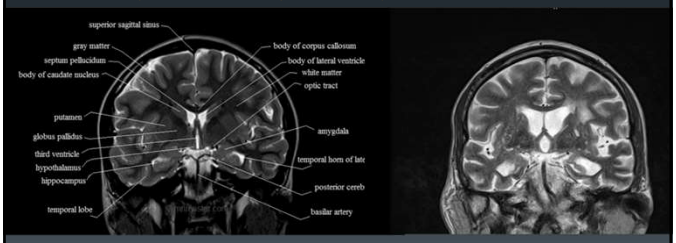
Neuroimaging

- CT vs. MRI (thin coronal cuts through hippocampus)



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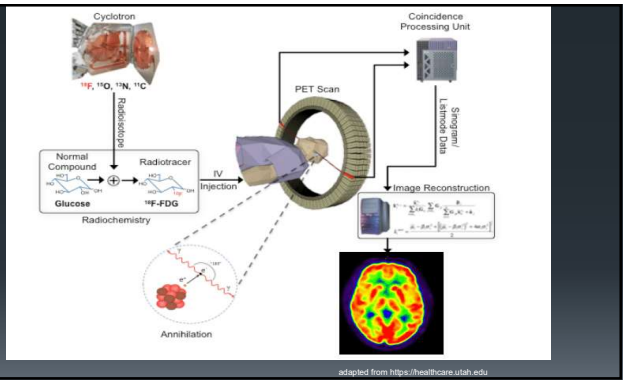

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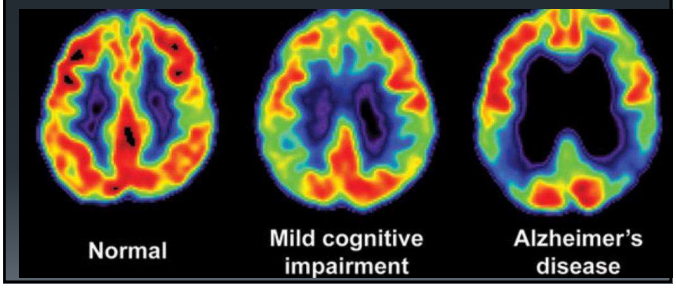
Glucose Metabolism Using ^{18}F-FDG Positron Emission Tomography (PET)



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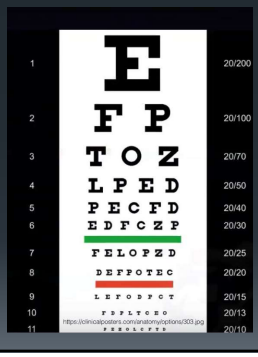
Case 2:

- Ann*, a 53 year-old right handed female who is a CPA presents with difficulty with seeing numbers and doing calculations.
- She and her husband moved to Tennessee three years ago so she could start her own business.
- Two years prior she complained that she vision was blurry. She saw her ophthalmologist many times.
- Her corrected vision was 20/20.

*Ann's family has given us permission to share the actual details of her case including her first name. Her last name has been withheld for privacy.



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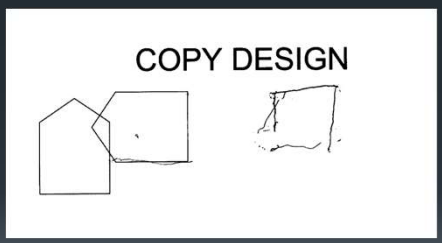
Case 2: Ann's MMSE at her first visit



Ann closed her business after the first visit.

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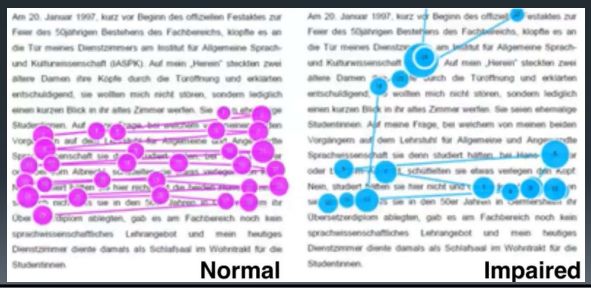
Case 2 Two Months after her first visit:

Ann could not follow a line of text in books or newspapers.
She was unable to calculate simple math.



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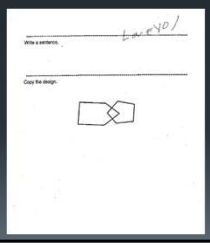
Case 2 after 6 months:

Ann needed help to put the pen to the page to attempt a sentence and she could no longer “see” the intersecting pentagons.



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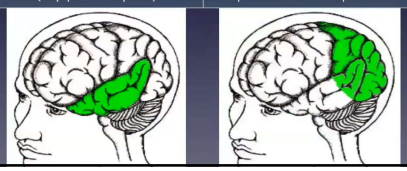
Case 2 Ann’s Diagnosis: Posterior Cortical Atrophy (PCA)

	Alzheimer's Disease (typical)	Posterior Cortical Atrophy
First Noticeable Symptoms	Short-term memory (rapid forgetting)	Visuospatial (visual)
First Area of the Brain Affected	Temporal lobe (hippocampus)	Parietal, occipital, posterior temporal



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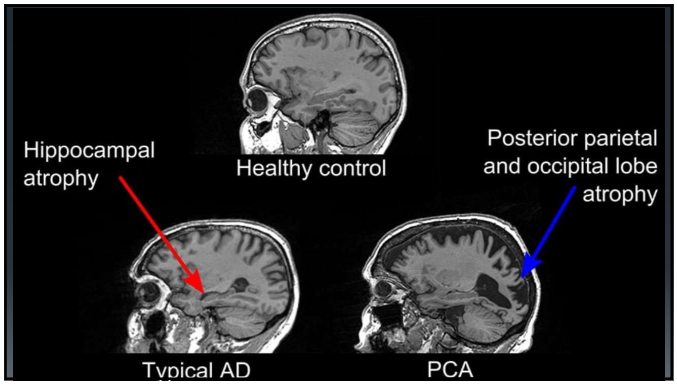
Hippocampal atrophy
Healthy control
Posterior parietal and occipital lobe atrophy
Typical AD
PCA

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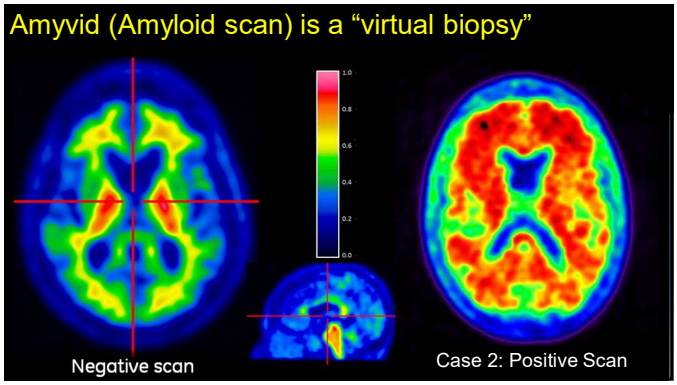
Amyvid (Amyloid scan) is a “virtual biopsy”
Negative scan
Case 2: Positive Scan

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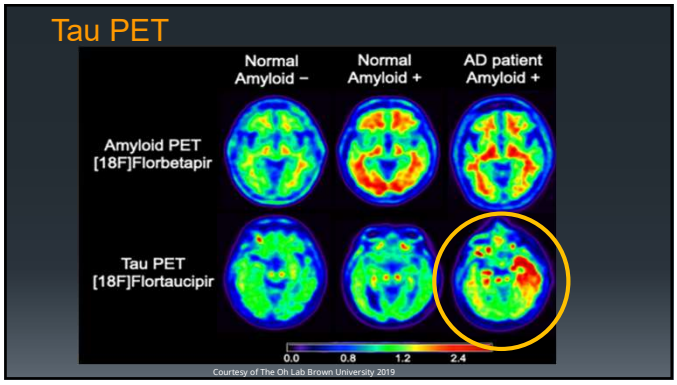
Tau PET
Normal Amyloid –
Normal Amyloid +
AD patient Amyloid +
Amyloid PET [18F]Florbetapir
Tau PET [18F]Flortaucipir
0.0
0.8
1.2
2.4
Courtesy of The Oh Lab Brown University 2019

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How a patient with PCA perceives a visual scene.

Beh SC, et al. Pract Neurol 2015; 15:5-13. doi: 10.1136/practneurol-2014-000883

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Trying to find the fork while eating or finding the handle to open the bathroom was like finding Waldo.

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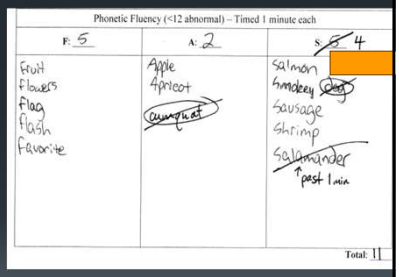
Case 3:

- Mrs. C, a 54 year-old right handed female who is a nursing assistant
- Spouse reports that she has difficulty naming things. She is quieter and prefers to listen.
- She does not lose items and seems to be able to drive without difficulty.



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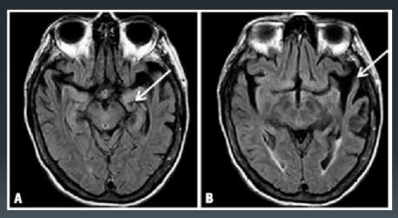
Case 3: Mrs. C was diagnosed with Logopenic Aphasia variant EOAD



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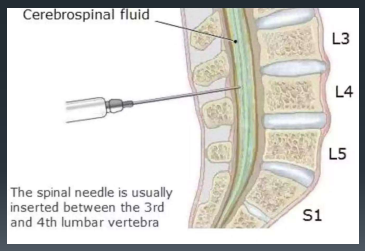
Cerebrospinal Fluid (CSF) for Amyloid, Tau and Phospho-Tau



Open Access Images

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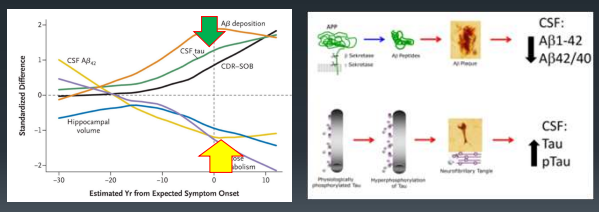
Alzheimer's Biomarker Timeline: CSF



Courtesy of N Engl J Med 2012; 367:795-804 DOI: 10.1056/NEJMoa1202753
Courtesy of Lewczuk, P *et al.* Clinical significance of fluid biomarkers in Alzheimer's Disease. *Pharmacol. Rep* **72**, 528–542 (2020). https://doi.org/10.1007/s43440-020-00107-0

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Case 4: PF is a 54 year-old male with PSEN1 mutation

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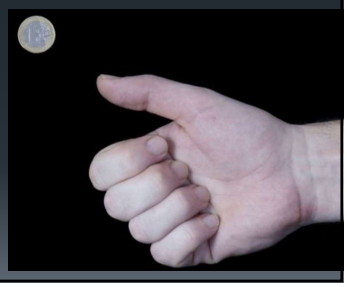
Odds of one of the children in case 3 and 4 inheriting genetic EOAD

- Flip the coin: heads or tails
- 1- (½ x ½ x ½) = .875 = 87.5% chance that one child will have AD
- And a 12.5% chance that all 3 are negative or all 3 are positive



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Courtesy of DIAN and DIAN TU
www.dianexr@wustl.edu and www.dianexr.org

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NEW STAGING SYSTEM

- Stage 1a-7d with ATNIVS biomarkers
- Similar to cancer staging
- Alzheimer's is a disease not a "dementia"
- Help shift awareness and promote screening

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BRAND NEW CRITERIA: ATN to ATNIVS

Biomarker category	fluid	imaging
Core Biomarkers		
A (Ab proteinopathy)	Ab42/40	Amyloid PET
T (AD tau proteinopathy)	ptau 181, 217	Tau PET
Non - specific biomarkers of tissue reaction involved in AD pathophysiology		
N (injury, dysfunction, or degeneration of neuropil)	NfL	Anatomic MR, FDG PET
I (inflammation) Astrocytic activation	GFAP	
Biomarkers of non-AD co-pathology		
V vascular brain injury		Anatomic infarction, WMH, abundant dilated perivascular spaces
S α-synuclein	αSyn-SAA*	

From ATN To ATNIVS. *In the proposed new scheme—which is currently a draft meant to solicit input from the ADRD research community—A and T are the core biomarkers for diagnosis and staging. The draft scheme also recognizes an expanded suite of additional markers that detect non-specific disease responses and co-pathologies. [Courtesy of NIA-AA working group.]*

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New Staging of Alzheimer's disease: 0-7 a, b, c, d

	Initial stage biomarkers	Early stage biomarkers	Intermediate stage biomarkers	Advanced stage biomarkers
	(a)	(b)	(c)	(d)
PET staging	amyloid PET	tau PET medial temporal region	tau PET moderate neocortical uptake	tau PET high neocortical uptake
	A+T-	$A+T_{MTL}+$	$A+T_{MOD}+$	$A+T_{HIGH}+$
Fluid staging	Ab42/40, fluid ptau 181, 217, 231	ptauT205	MTBR-243*	Non-phosphorylated tau fragments*

Parallel Tracks. *The proposed criteria, shown here in draft form dated July 15, allow clinicians to stage disease by either PET or fluid markers; alas, the stages denoted by each are not equivalent, and the modalities cannot be mixed. Late-stage fluid biomarkers are less well-established than the others, with the starred markers meant to be used only in research settings at this time. [Courtesy of NIA-AA working group.]*

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Resources for Patient and Care Partner Support

- Dominantly Inherited Alzheimer's Network (DIAN) https://dian.wustl.edu
- Young Timers www.youngtimers.org
- Alzheimer's Tennessee www.alztennessee.org
- Genesis Neuroscience Clinic/ Tennessee Memory Disorders Foundation www.tmdf.org
- Knoxville Office on Aging www.knoxseniors.org
- Purple Cities www.purplecities.org
- Alzheimer's Association www.alz.org

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