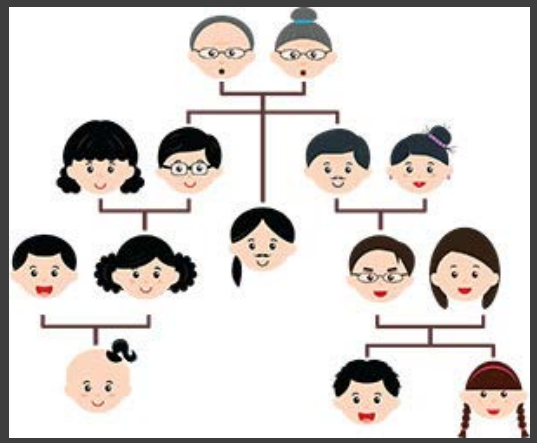


Is Alzheimer's in My Genes?

JILL GOLDMAN, MS, MPHIL, CGC

TAUB INSTITUTE, COLUMBIA UNIVERSITY

Some of the questions that we will address: ??????

- How do you define “dementia”?
- How genetic is Alzheimer’s Disease (AD) (and other dementias)?
- How do you know if hereditary AD is what’s in the family?
- What are the different genes involved in AD risk?
- Should I take a genetic test?
- Is there anything I can do to prevent AD?

THE big question: Am I going to get it?

2017 Facts and Figures:

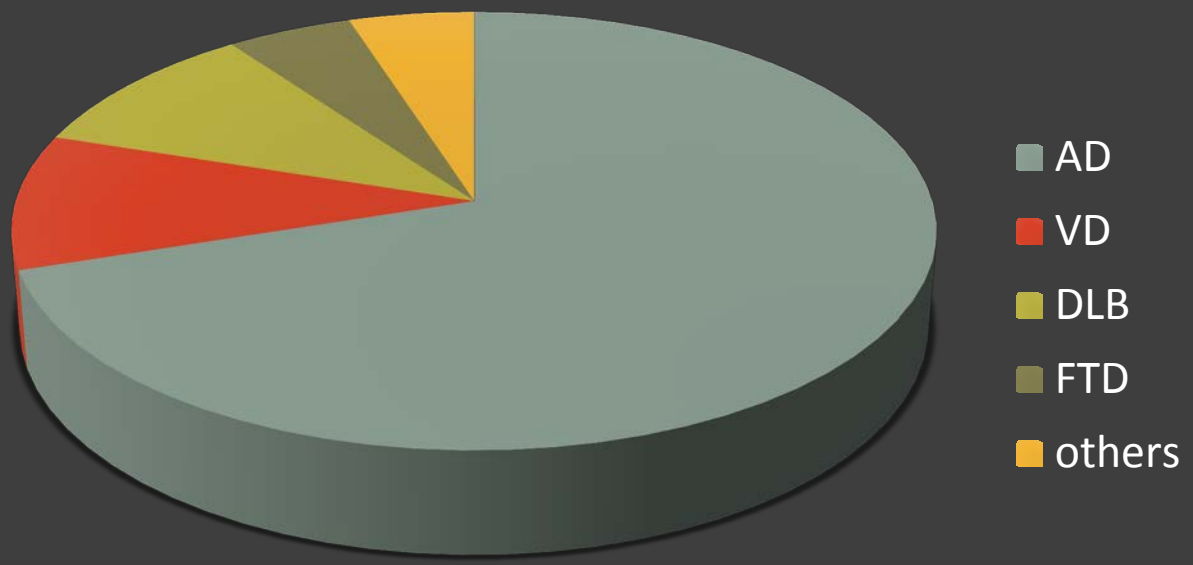
- 5.5 million Americans have AD
- **200,000 have AD <65 yrs.: Early onset AD (EOAD)**

< 20% of EOAD is fully genetic!!

<1% of ALL AD is fully genetic… but much more has genetic risk factors

Lifetime Risk to 1º relative: 20-38% (2-3 times background risk)

Dementia: the umbrella

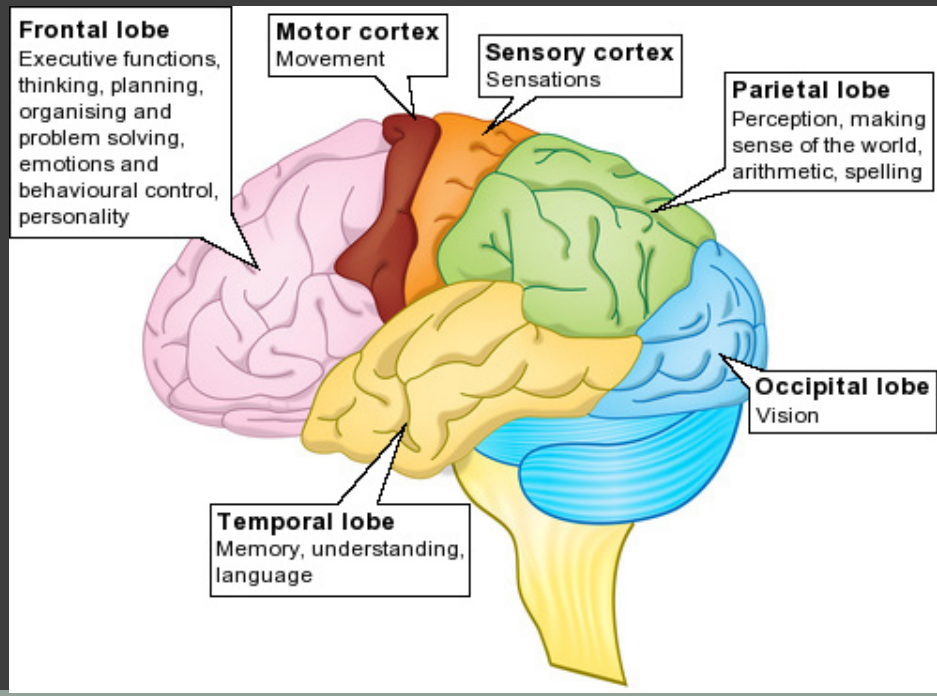


Definition of dementia

Progressive cognitive impairment that interferes with activities of daily living in the home, at work, or in social activities.

Must involves at least two cognitive domains:

- Memory
- Executive function
- Visuospatial abilities
- Language
- Personality, behavior.



Diagnosis

Symptom history
- onset
- types and duration symptoms
- other medical history
- drug/alcohol use
- environmental exposure

Family history
- age of onset
- # affected family members
- degree of relationship

Neurological exam

Neuropsychological testing

Neuroimaging

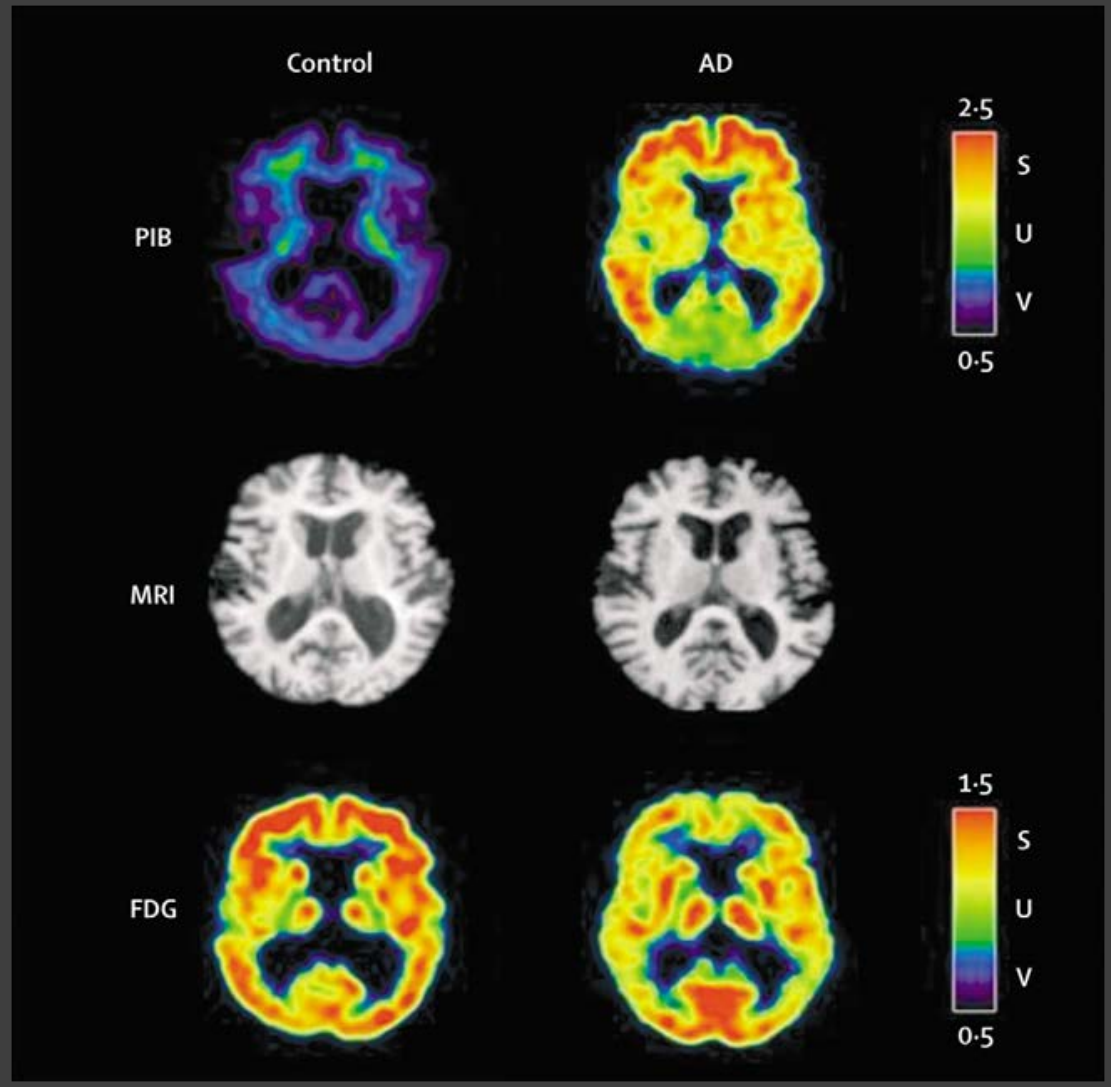
Laboratory testing

Lumbar puncture

Genetic testing (appropriate if only!!!)

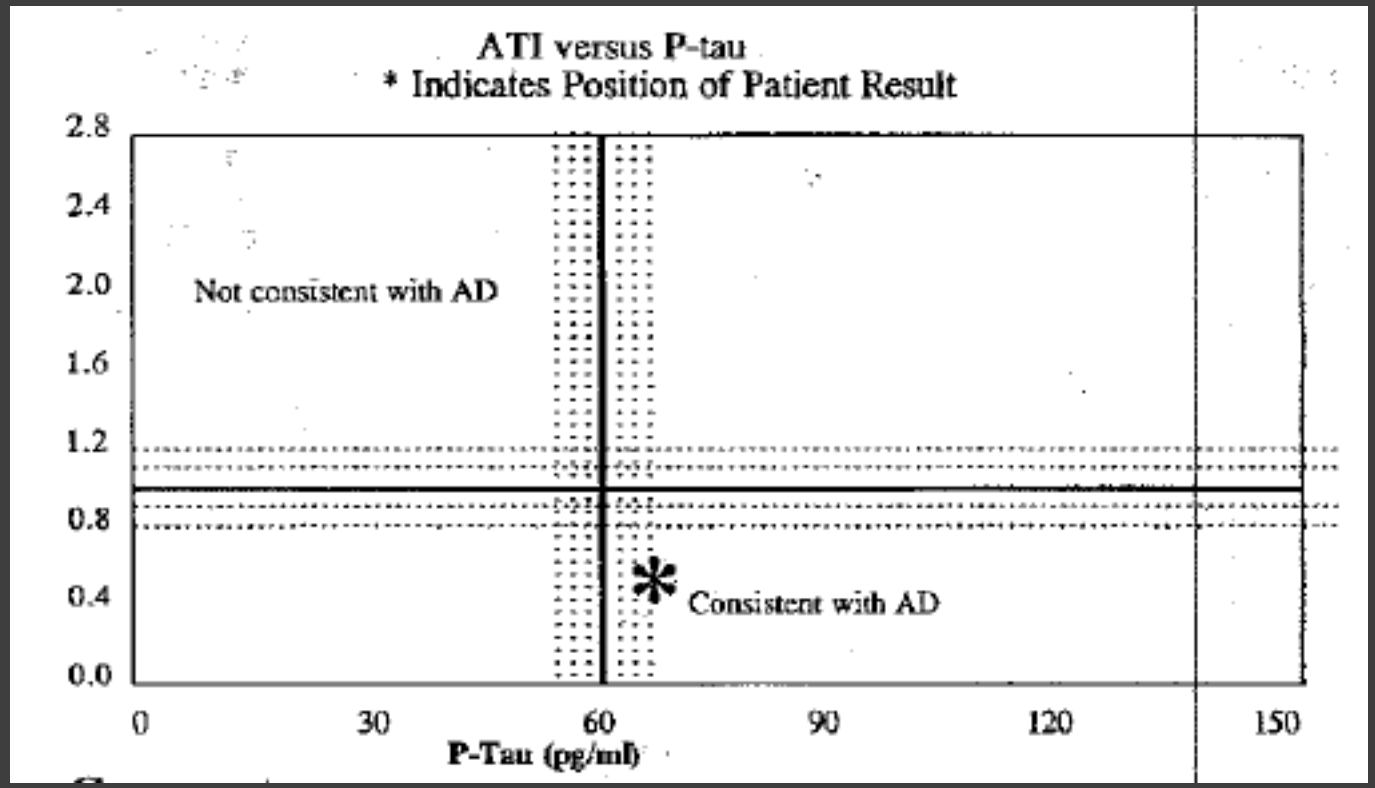
"If you're stumped, why not write an illegible prescription and hope the pharmacist comes up with something?"

Imaging

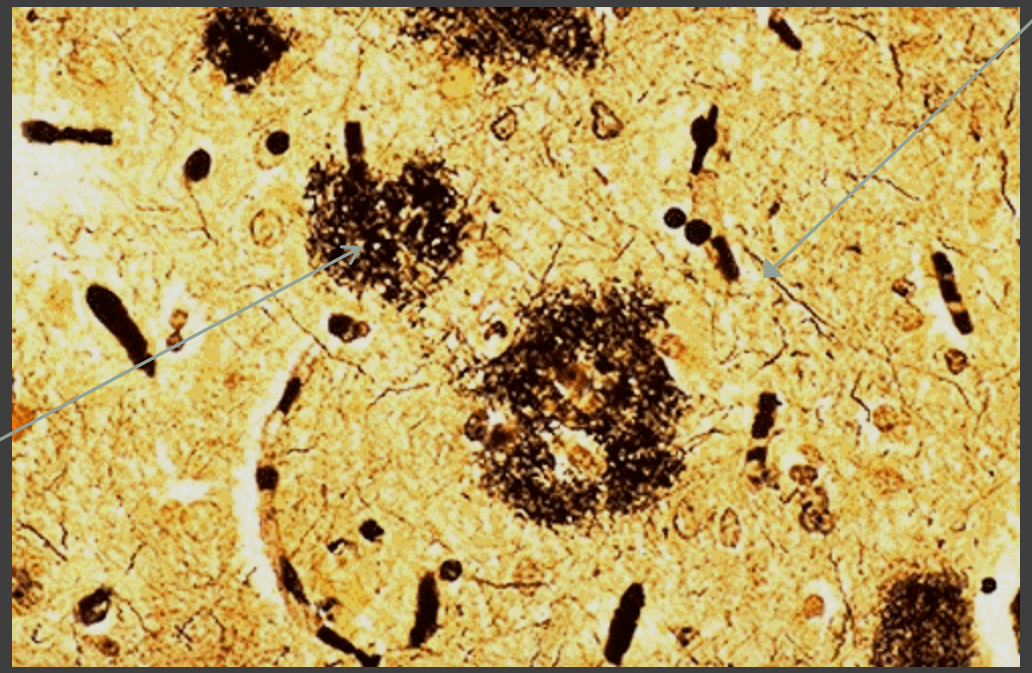


Blennow K, de Leon MJ, Zetterberg . Alzheimer's disease. *Lancet*. 2006; 368: 387-403.

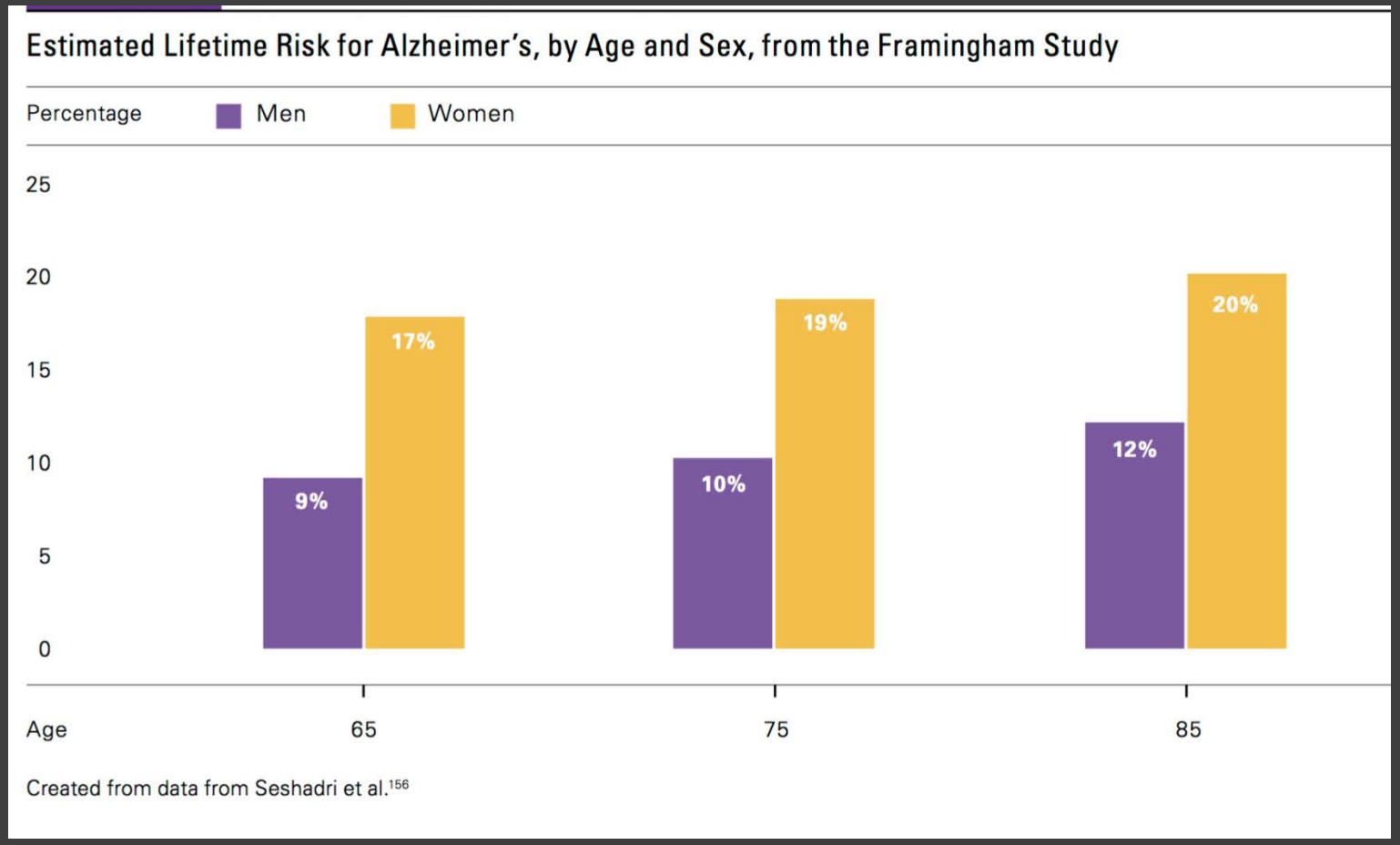
CSF results


ATI versus P-tau
* Indicates Position of Patient Result
2.8
2.4
2.0
1.6
1.2
0.8
0.4
0.0
Not consistent with AD
Consistent with AD
0
30
60
90
120
150
P-Tau (pg/ml)

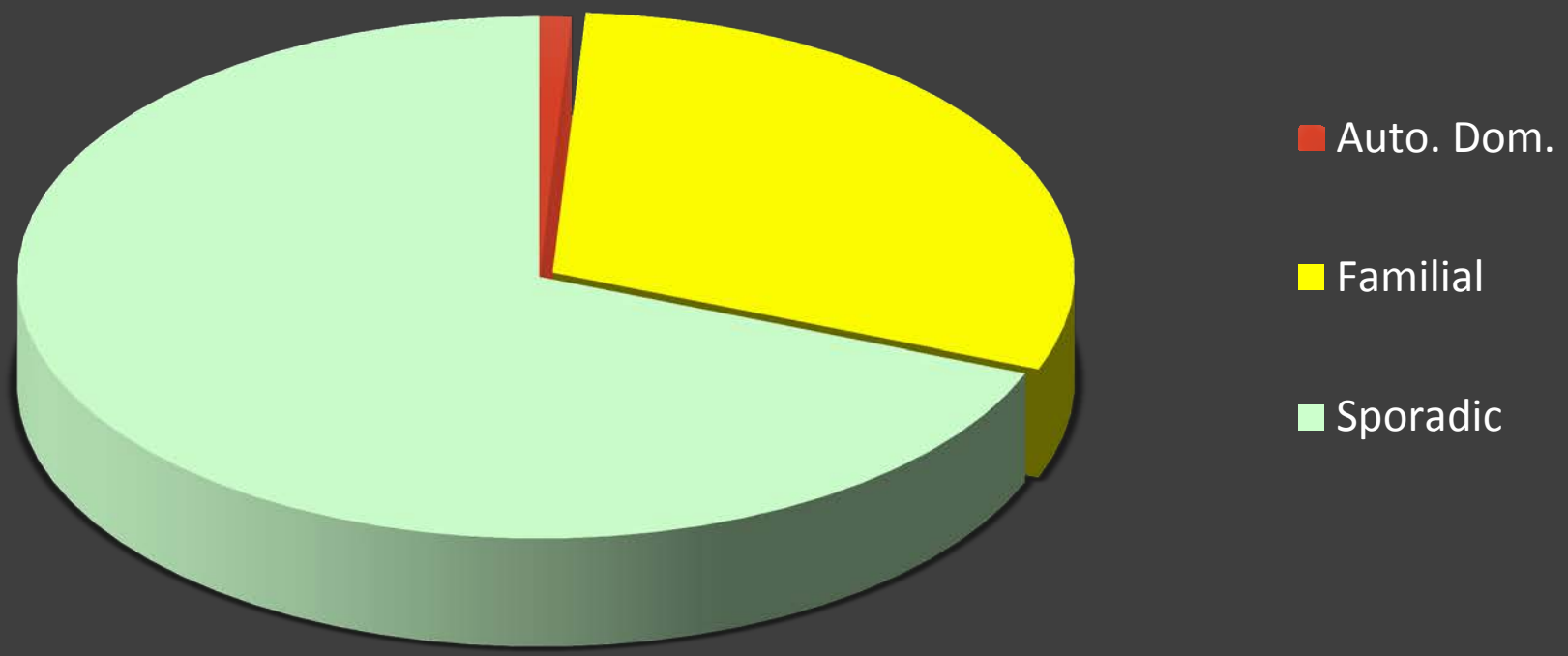
Definitive Diagnosis: Autopsy



Etiology 1: Age- greatest risk factor

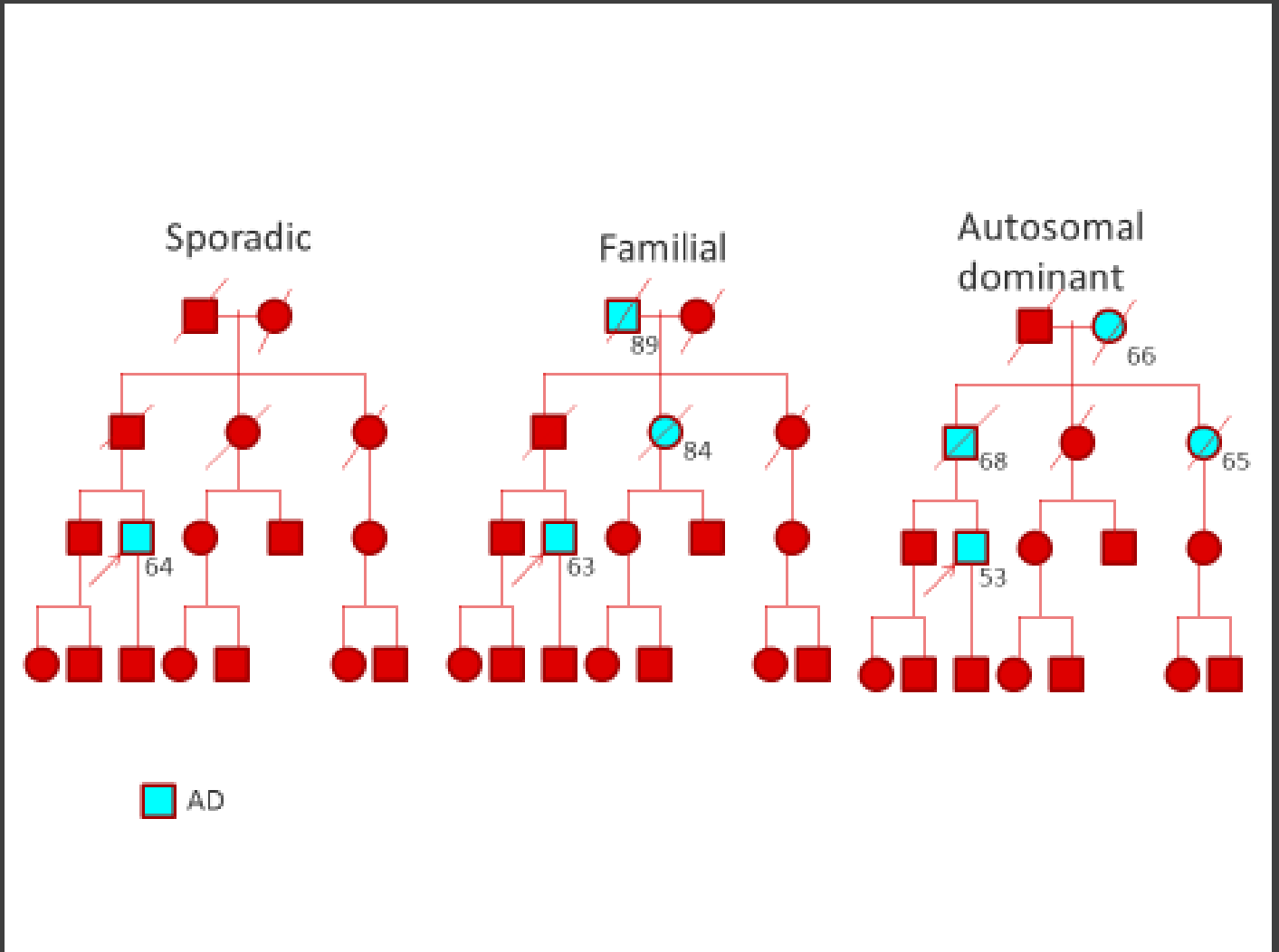


Etiology 2: Genetics

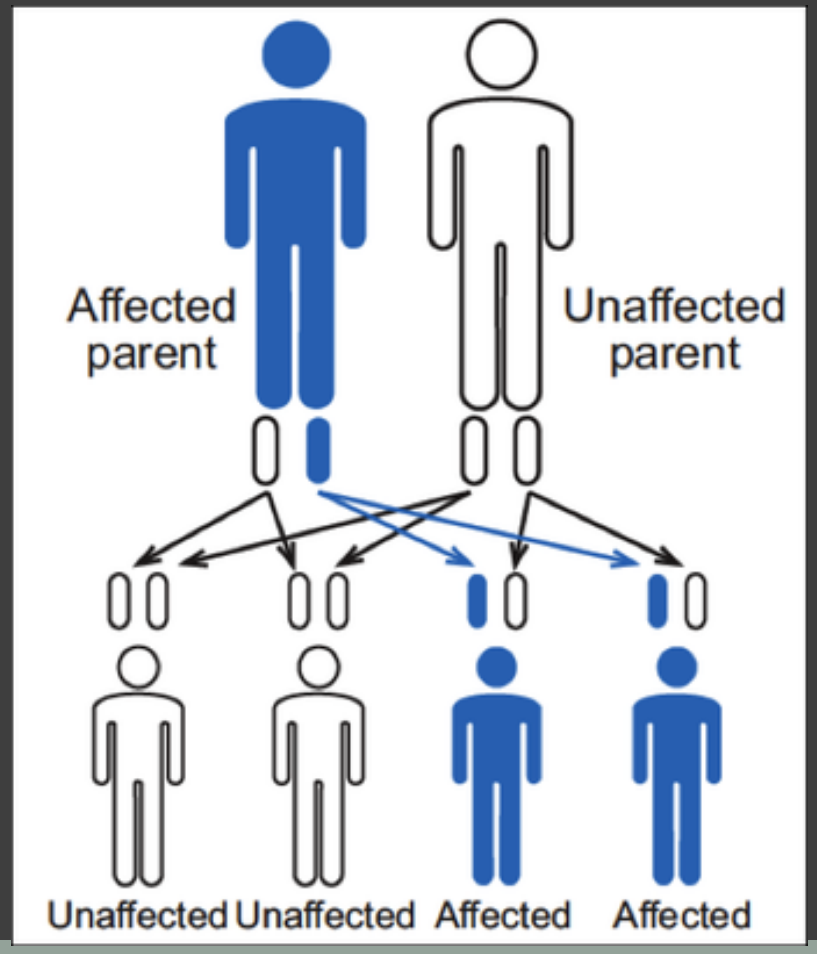


So how do you know if it is genetic?

Step 1 : look at Family History:



Autosomal dominant inheritance



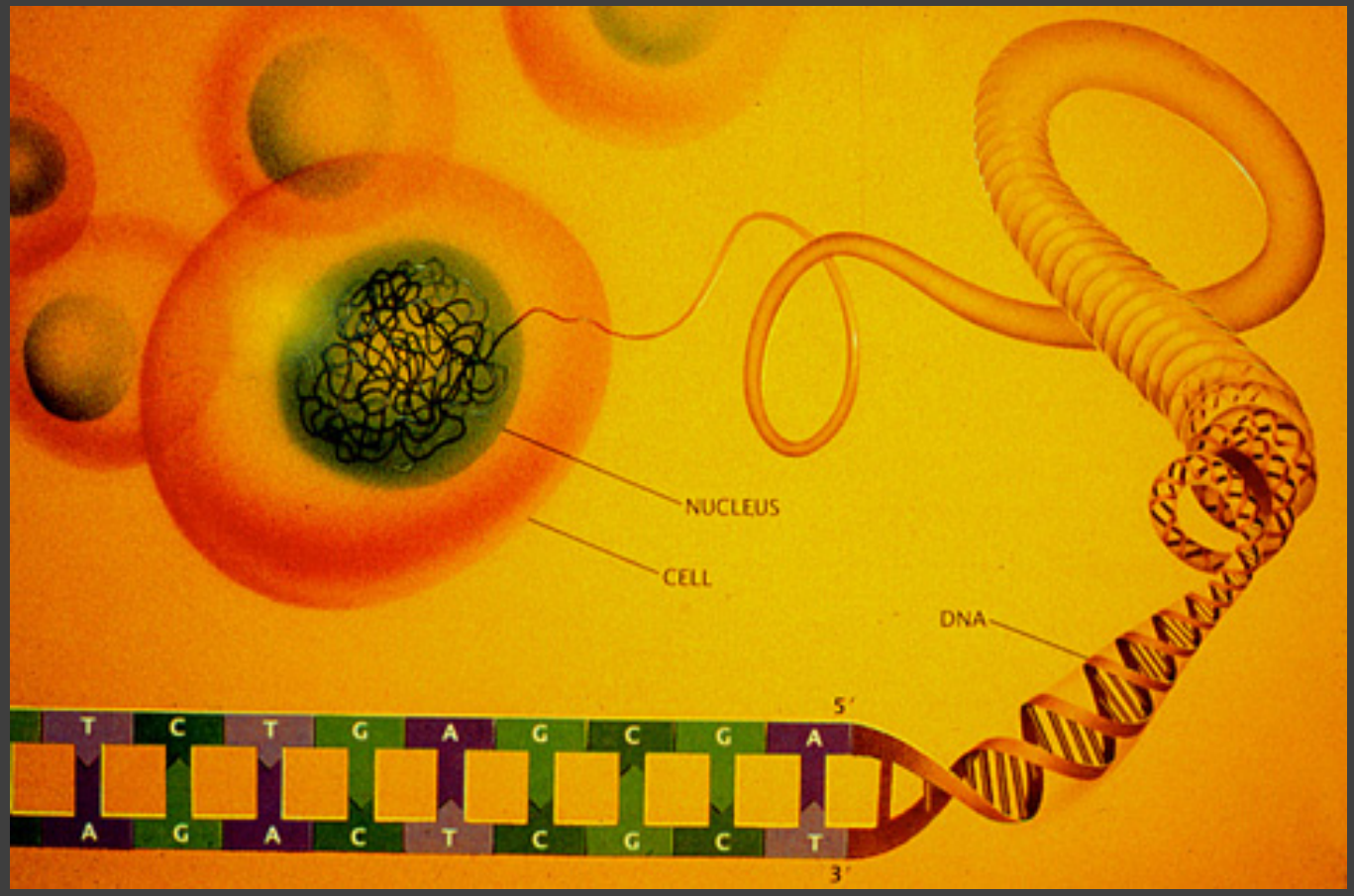
Highly unlikely to find a mutation in EOAD individual without an autosomal dominant family history (but sometimes family history is lost or adoption, non-paternity

How do we know for sure whether the dementia in the family is genetic?

Do genetic testing:

Look for mutations (alterations) in genes known to be associated with the disease in the family.

Genetics 101
Chromosomes are made of DNA



Mutations

Mistakes in the DNA sequence

e.g.

Normal gene: CA**T**GAT,

Mutated gene: CA**G**GAT, CAGAT, CAT**T**GAT, CATGAT**CATGAT**

Result of mutation: change in amino acid sequence of protein, hence change in function of protein OR inability to produce protein or production of a toxic molecule

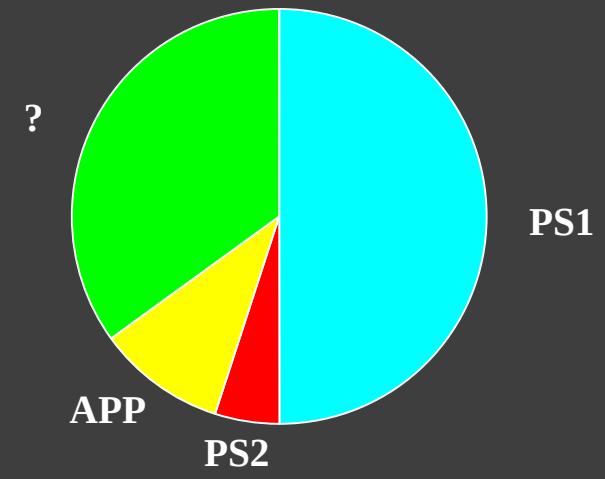
Autosomal Dominant Predisposition Genes

Result in early onset:

- Presenilin 1 (PS1): 30s-60s usually 40s,50s
- Presenilin 2 (PS2): 40-75, < 100% penetrant
- Amyloid precursor protein (APP):

40s-50s

Rapid progression (usually 8-10 yrs)



Gold standard for genetic testing

- Test an affected family member first to determine a specific mutation
- But genetic counseling is step 1

Interpretation of Autosomal Dominant Gene Test Results

True Positive: previously identified pathogenic mutation found

True negative: affected family member's mutation not found

Positive with variant of unknown significance: new mutation found: polymorphism or pathogenic?

Negative with unknown significance: affected family member not previously tested-is there some other gene?

Predictive testing:
finding out if you carry the family gene

Motivation:

- Reproductive
- Life planning
- End uncertainty

Approach to genetic testing: Step 1

Questions:

- Has anyone in the family had an autopsy to confirm AD?
- Is the family history consistent with an amnestic disorder?
- What are the atypical symptoms? Spastic paraparesis, seizures, behavioral change, parkinsonism, ALS, etc.
- What are the family finances and will insurance pay?

How do you do predictive testing?

Modified HD predictive testing protocol should be followed

- Genetic counseling with support person present
- Psychiatric/Cognitive evaluation
- Result session with support person present

Testing protocol

- *Known family mutation
- Next-gen dementia panel?

What do you need to think about?

- If I knew my genetic status, is there anything I could do to prevent or delay the disease?
- How would learning my results help or harm my life?
- With whom would I share my results?
- How would my results effect my family?

Predictive genetic counseling

Experience with AD and feelings about it

Family hx

Symptom variability and course

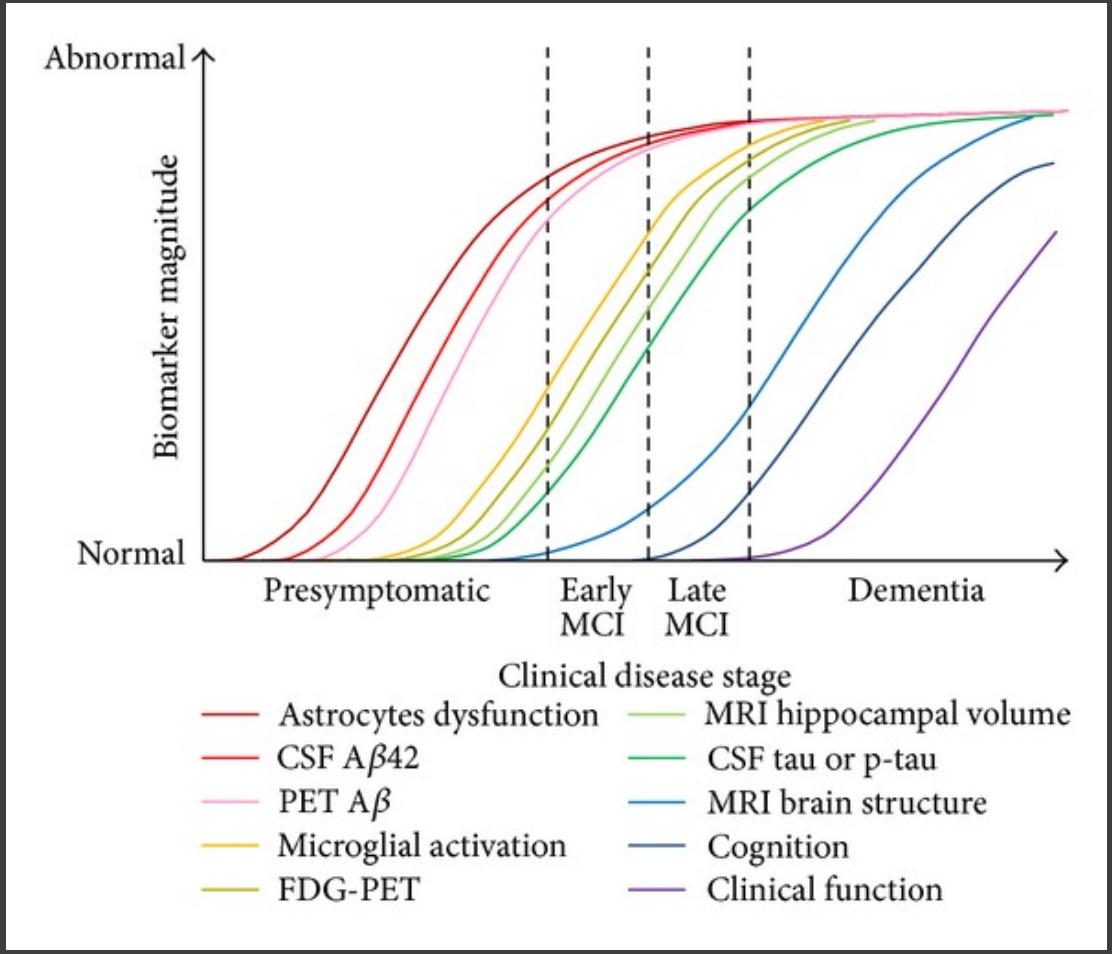
Genetics of AD

Possible results of testing and implications

Anticipatory guidance for positive and negative result

- How will you react over the short term and long term?
- What would you do differently with life plans?
- Will the result make your quality of life better or worse?
- How will it impact your partner/ family?
- With whom will you share results and do they want to know?
- Have you gotten long-term care, life insurance?
- What does the support person think?

DIAN Study: Dominantly Inherited Alzheimer's Network



It's one thing to know that you will eventually get the disease but another to know that you are already showing signs.

Will early biomarker testing (now used in research only) become standard of care?

If so, this can be as predictive as genetic testing.

Risacher S, Saykin AJ. Annu Rev Clin Psychol. 2013;9:621-48.

The New York Times

Sunday Review

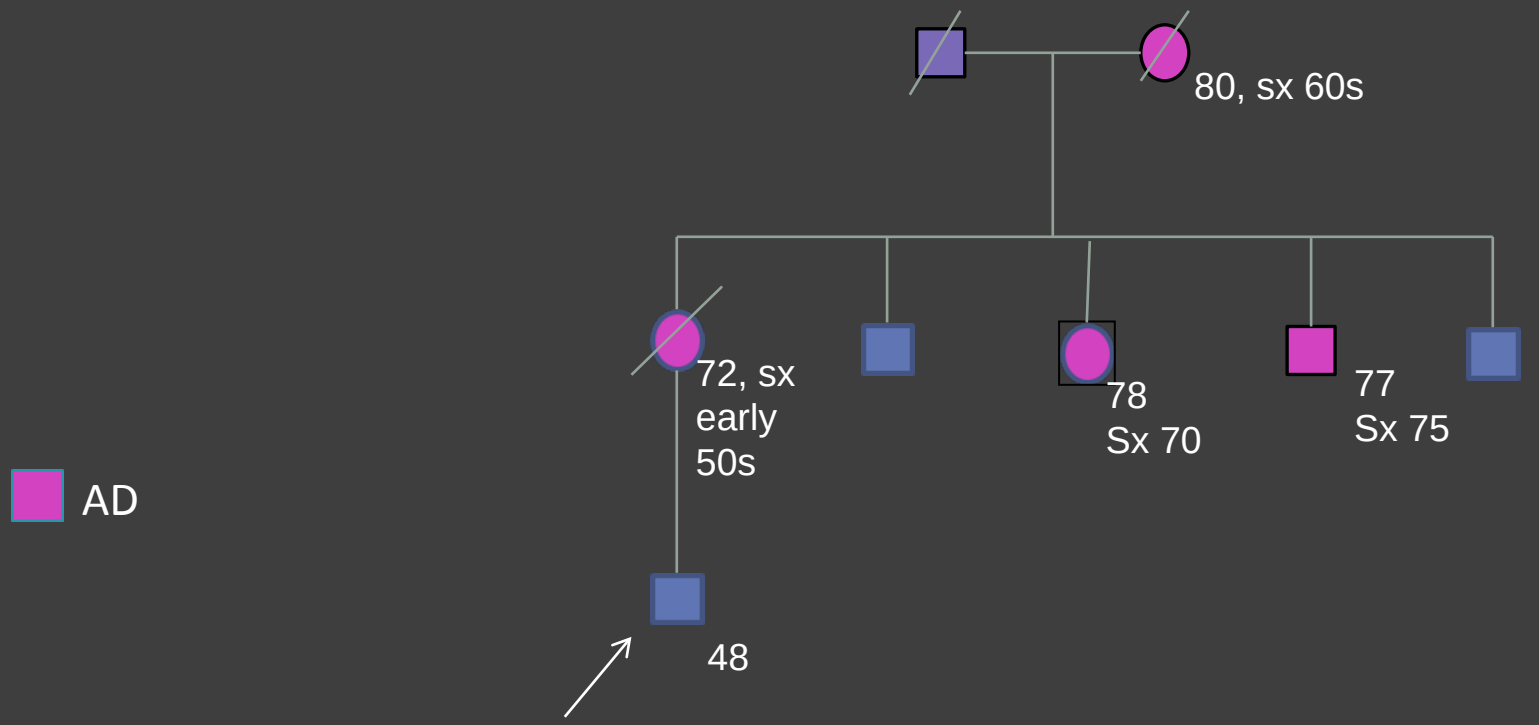
What if You Knew Alzheimer's Was Coming for You?

Simple blood tests may soon be able to deliver alarming news about your cognitive health.

By PAGAN KENNEDY NOV. 17, 2017

Illustration by Mike McQuade; Photograph by FangXiaNuo/Getty Images

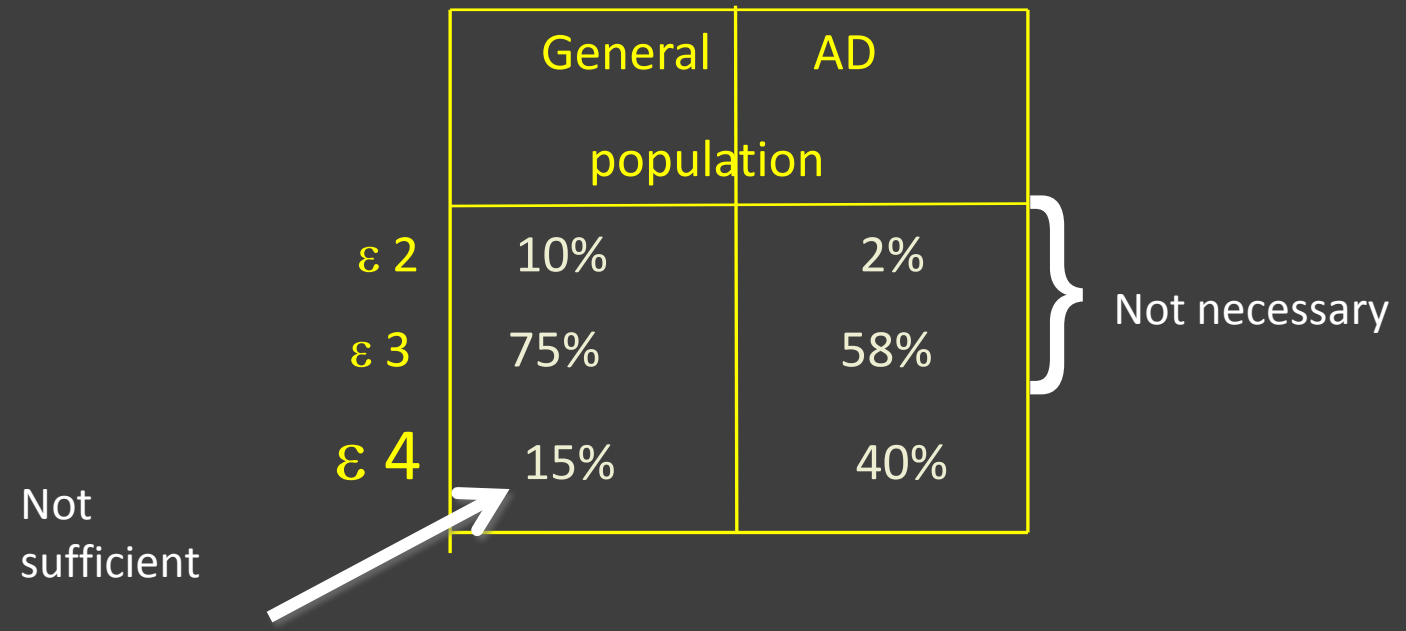
“I want to be tested for the Alzheimer’s gene”



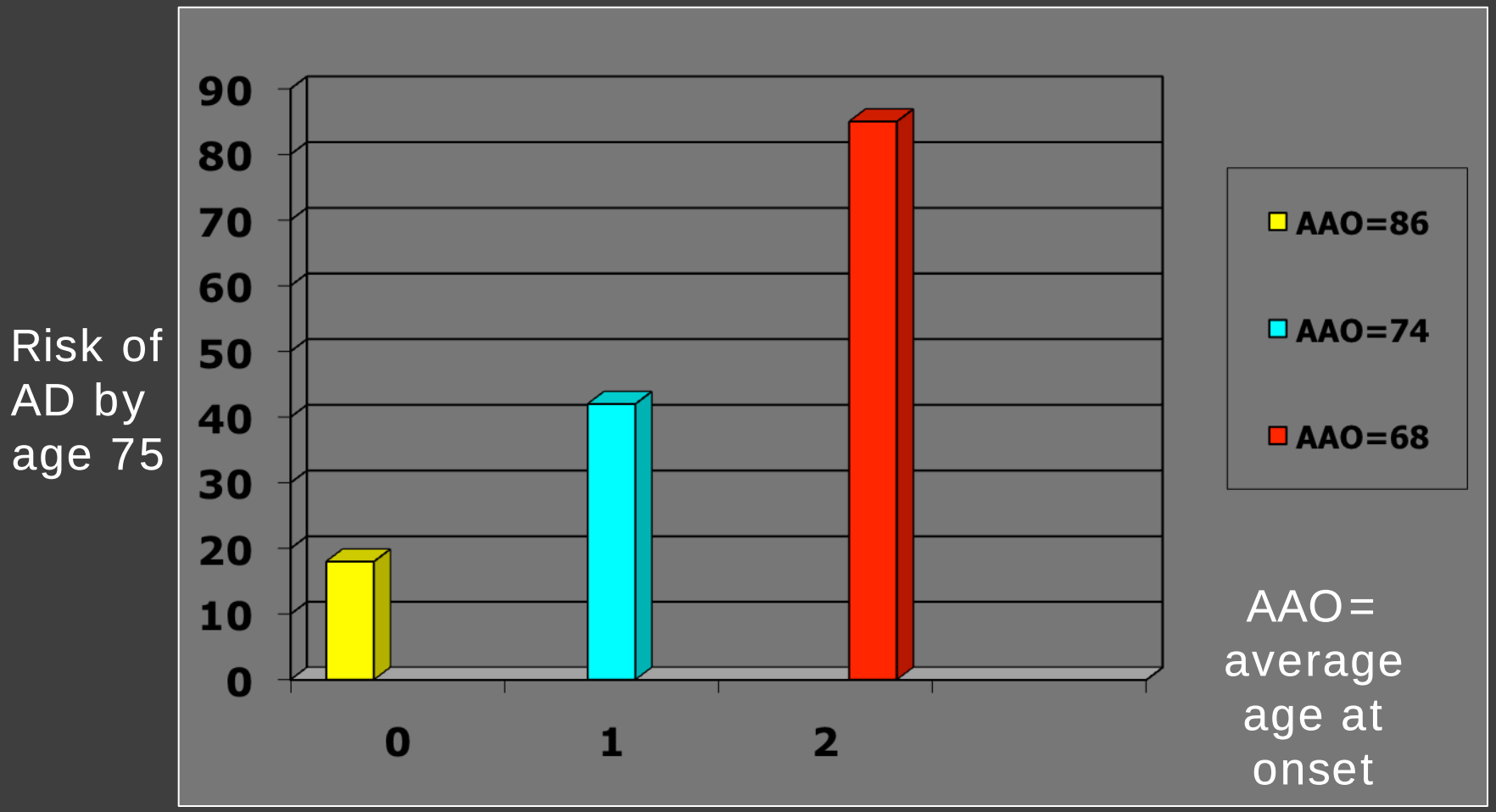
Why? “I want to do everything I can to stave it off”.

Susceptibility Gene: APOE

The 3 ApoE alleles: ε2, ε3, & ε4



Risk and Age of Onset of AD
Depends on APOE allele dosage



Problems with APOE testing

Neither necessary or sufficient for developing disease

also > cardiovascular risk

AD risk depends on ethnicity

Overall risk depends on combination of all risk alleles

- Lifetime risk is still associated with family history: e4 negative does not remove 2-3X increased risk

Yet, APOE testing may be useful for inclusion in clinical trials

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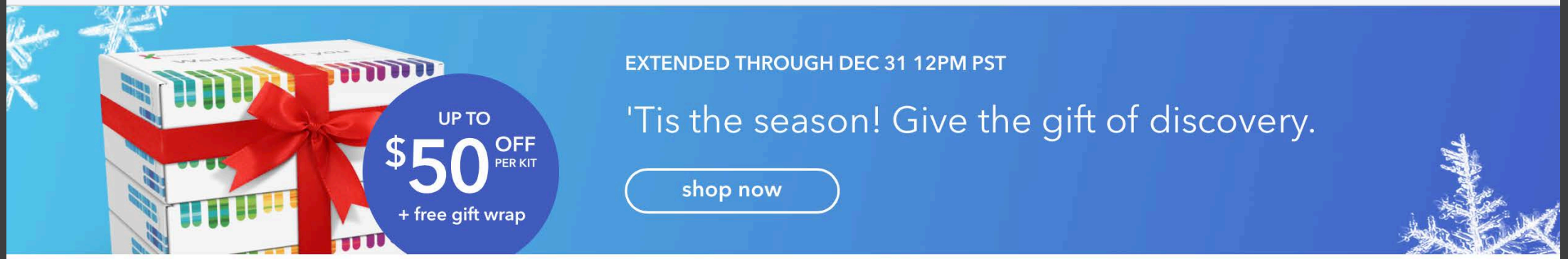

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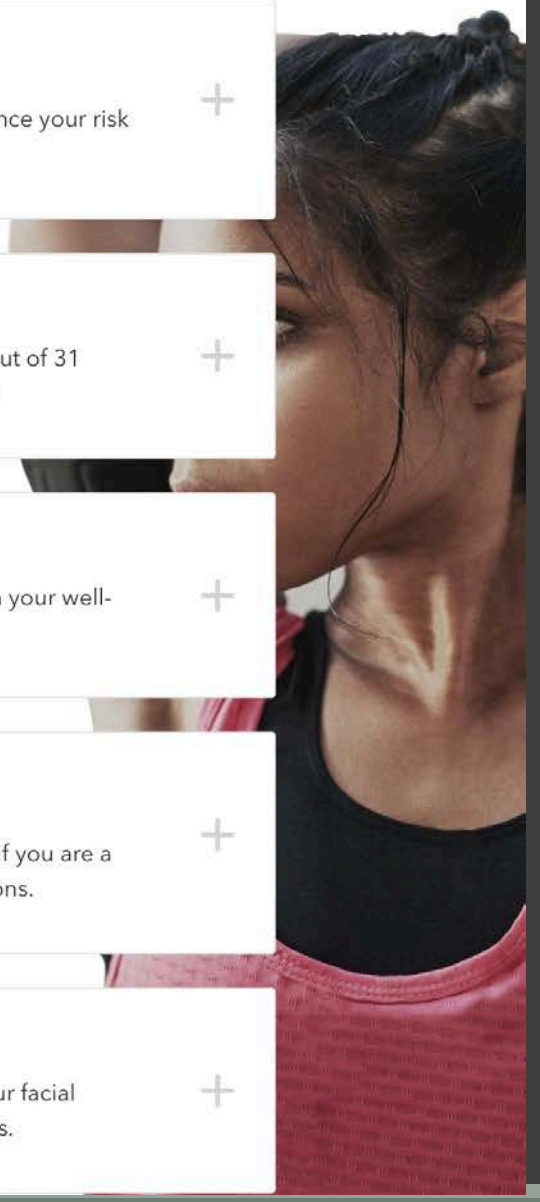
see all reports



MEETS FDA REQUIREMENTS

Genetic Health Risks**

Learn how your genetics can influence your risk for certain diseases.

Ancestry

Discover where your DNA is from out of 31 populations worldwide - and more.

Wellness

Learn how your genes play a role in your well-being and lifestyle choices.

MEETS FDA REQUIREMENTS

Carrier Status**

If you are starting a family, find out if you are a carrier for certain inherited conditions.

Traits

Learn how your DNA influences your facial features, taste, smell and other traits.

Wellness reports

5+ reports

Alcohol Flush Reaction
Caffeine Consumption
Deep Sleep
Genetic Weight
Lactose Intolerance
Muscle Composition
Saturated Fat and Weight
Sleep Movement

See sample report

Traits reports

15+ traits

Asparagus Odor Detection
Back Hair (available for men only)
Bald Spot (available for men only)
Bitter Taste Perception
Cheek Dimples
Cleft Chin
Earlobe Type
Earwax Type
Eye Color
Finger Length Ratio
Freckles
Hair Curliness
Light or Dark Hair
Male Hair Loss (available for men only)

Carrier Status reports*

40+ reports

ARSACS
1 variant in the SACS gene; relevant for French Canadian descent

Agenesis of the Corpus Callosum with Peripheral Neuropathy
1 variant in the SLC12A6 gene; relevant for French Canadian descent

Autosomal Recessive Polycystic Kidney Disease
3 variants in the PKHD1 gene

Beta Thalassemia and Related Hemoglobinopathies
10 variants in the HBB gene; relevant for Cypriot, Greek, Italian, Sardinian descent

Bloom Syndrome
1 variant in the BLM gene; relevant for Ashkenazi Jewish descent

Canavan Disease
3 variants in the ASPA gene; relevant for Ashkenazi Jewish descent

Congenital Disorder of Glycosylation Type 1a (PMM2-CDG)
2 variants in the PMM2 gene; relevant for Danish descent

Cystic Fibrosis
28 variants in the CFTR gene; relevant for European, Hispanic/Latino, Ashkenazi Jewish descent

D-Bifunctional Protein Deficiency
2 variants in the HSD17B4 gene

Dihydrolipoamide Dehydrogenase Deficiency
1 variant in the DLD gene; relevant for Ashkenazi Jewish descent

Familial Dysautonomia
1 variant in the IKBKAP gene; relevant for Ashkenazi Jewish descent

Genetic Health Risk reports*

5+ reports

Age-Related Macular Degeneration
2 variants in the ARMS2 and CFH genes; relevant for European descent

Alpha-1 Antitrypsin Deficiency
2 variants in the SERPINA1 gene; relevant for European descent

Celiac Disease
2 variants near the HLA-DQA1 and HLA-DQB1 genes; relevant for European descent

Hereditary Hemochromatosis (HFE-Related)
2 variants in the HFE gene; relevant for European descent

Hereditary Thrombophilia
2 variants in the F2 and F5 genes; relevant for European descent

Late-Onset Alzheimer's Disease
1 variant in the APOE gene; variant found and studied in many ethnicities

Parkinson's Disease
2 variants in the LRRK2 and GBA genes; relevant for European, Ashkenazi Jewish, North African Berber descent

0 variants detected

in the APOE gene

How To Use This Test

This test does not diagnose Alzheimer's disease or any other health conditions.

Please talk to a healthcare professional if this condition runs in your family, you think you might have this condition, or you have any concerns about your results.

Review the Genetic Health Risk tutorial

See Scientific Details

See Frequently Asked Questions

Intended Uses

- Tests for the **ε4** variant in the APOE gene.
- Identifies if someone has the ε4 variant associated with an increased risk of developing late-onset Alzheimer's disease.

Limitations

- Does **not** include all possible variants or genes associated with late-onset Alzheimer's disease.
- Does **not** include any variants or genes linked to early-onset Alzheimer's disease.
- Does **not** determine a person's full APOE genotype.

Important Ethnicities

- The ε4 variant included in this test is found and has been studied in many ethnicities. Detailed risk estimates have been studied the most in people of **European** descent.

Everyone's talking about doing their genomes-should I?

- Know what you are getting into!!
- Think about consequences of knowing your status.
- Think about implications for other family members and whether they want to know.

- An interesting story…..

Genetic testing for risk factors can only say, “You are at greater risk” not “You are going to get the disease”

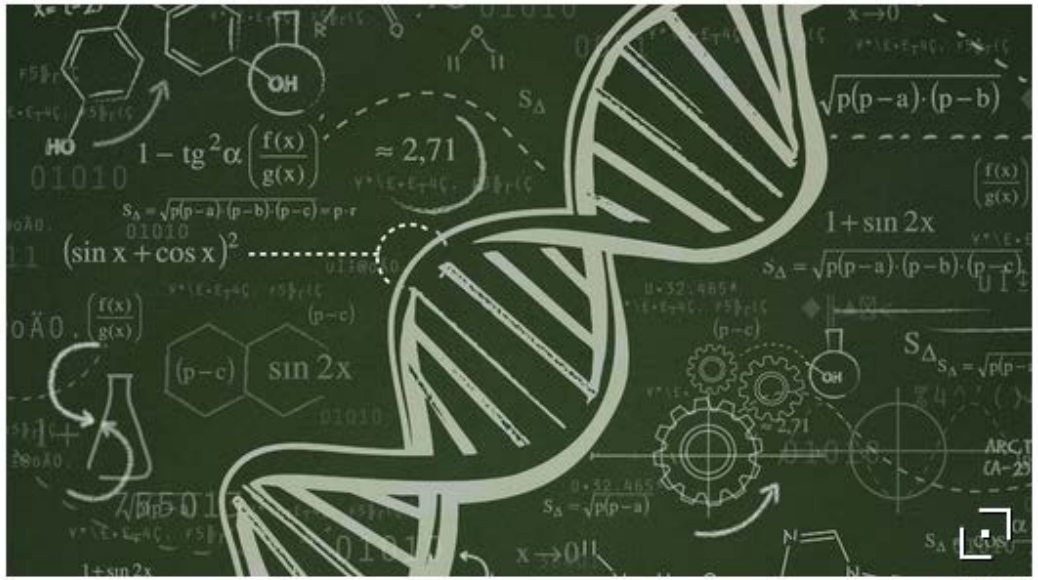
Will more genetic testing lead to heightened anxiety, inappropriate use of health care, unnecessary testing, change of interpretation of biomarkers?

THE GOOD LIFE

Genetic testing for Alzheimer's chances carries risks of its own

Testing for Alzheimer’s risk is possible, but some experts say the tests carry risks of their own.

By Katy Read Star Tribune | MARCH 30, 2015 — 10:09AM



ISTOCK

Can we change our risk factors?

HUFF/POST50

Edition: US

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Too Much TV May Raise The Risk Of Alzheimer's, Study Says

Binge-watchers alert! Lose the sedentary lifestyle.

Ann Brenoff
Senior Writer/Columnist, The Huffington Post

Better Sleep May Be Incredibly Important to Alzheimer's Risk

The Associated Press
July 21, 2015

Disrupted sleep may be one of the missing pieces in explaining how Alzheimer's starts its damage long before people have trouble with memory. *(Photo:*

A reason to know genetic status!!!

SCIENTIFIC AMERICAN™

Exercise Counteracts Genetic Risk for Alzheimer's

Regular physical activity may correct the brain's metabolism to stave off dementia

By Emilie Reas | Oct 16, 2014

THINKSTOCK

If you carried a gene that doubled your likelihood of getting Alzheimer's disease, would you want to know? What if there was a simple lifestyle change that virtually abolished that elevated risk? People with a gene known as *APOE* e4 have a higher risk of cognitive impairment and dementia in old age. Even before behavioral symptoms appear, their brains show reduced metabolism, altered activity and more deterioration than those without the high-risk gene. Yet accumulating research is showing that carrying this gene is not necessarily a sentence for memory loss and confusion—if you know how to work it to your advantage with exercise.

Scientists have long known that exercise can help stave off cognitive decline. Over the past decade evidence has mounted suggesting that this benefit is even greater for those at higher genetic risk for Alzheimer's. For example, two studies by a team in Finland and Sweden found that exercising at least twice a week in midlife lowers one's chance of getting dementia more than 20 years later, and this protective effect is stronger in people with the *APOE* e4 gene. Several others reported that frequent

sociation between dementia and leisure time physical activity over an expanded range.

- We did not analyze other types of physical activity (PA), such as housework, occupational PA or commuting -related PA.

r Demen. 2014 June ; 29(4): 372–378. doi:10.1177/1533317513518646.

The Impact of Exercise, Cognitive Activities, and Socialization on Cognitive Function: Results From the National Long-Term Care Survey

M. Kathryn Jedrziewski, PhD[1,2,3,4], **Douglas C. Ewbank, PhD**[5], **Haidong Wang, PhD**[6], and **John Q. Trojanowski, MD, PhD**[1,2,3,4,7]

[1]The Institute on Aging, University of Pennsylvania, Philadelphia, PA, USA

[2]Marian S. Ware Alzheimer Program, University of Pennsylvania, Philadelphia, PA, USA

[3]Alzheimer's Disease Core Center, University of Pennsylvania, Philadelphia, PA, USA

[4]Department of Pathology and Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

[5]Population Studies Center, University of Pennsylvania, Philadelphia, PA, USA

[6]Institute for Health Metrics and Evaluation, University of Washington, Seattle, WA, USA

[7]Center for Neurodegenerative Disease Research, University of Pennsylvania, Philadelphia, PA, USA

Abstract

Currently, there are no effective treatments for Alzheimer's disease and related disorders and age continues to be a robust risk factor. Thus, population aging in the United States may have catastrophic results if interventions are not found and implemented. This study examines possible associations between cognitive impairment and exercise, cognitive activities, and socialization. Cognitive activities, socialization, and exercise were assessed at baseline, and cognitive function was measured at baseline, 5-year, and 10-year follow-up. Controlling for baseline cognitive function, age, sex, education, diabetes, and hypertension, linear regression was performed. Engagement in cognitive activities was inversely associated with the onset of cognitive impairment at 5-year follow-up but was no longer significant at 10-year follow-up. Exercise was associated with a lower risk of cognitive impairment at 10-year follow-up but was not significant at 5-year follow-up. Associations with socialization were not statistically significant at either follow-up.

Bottom line

What's good for your heart is good for your brain

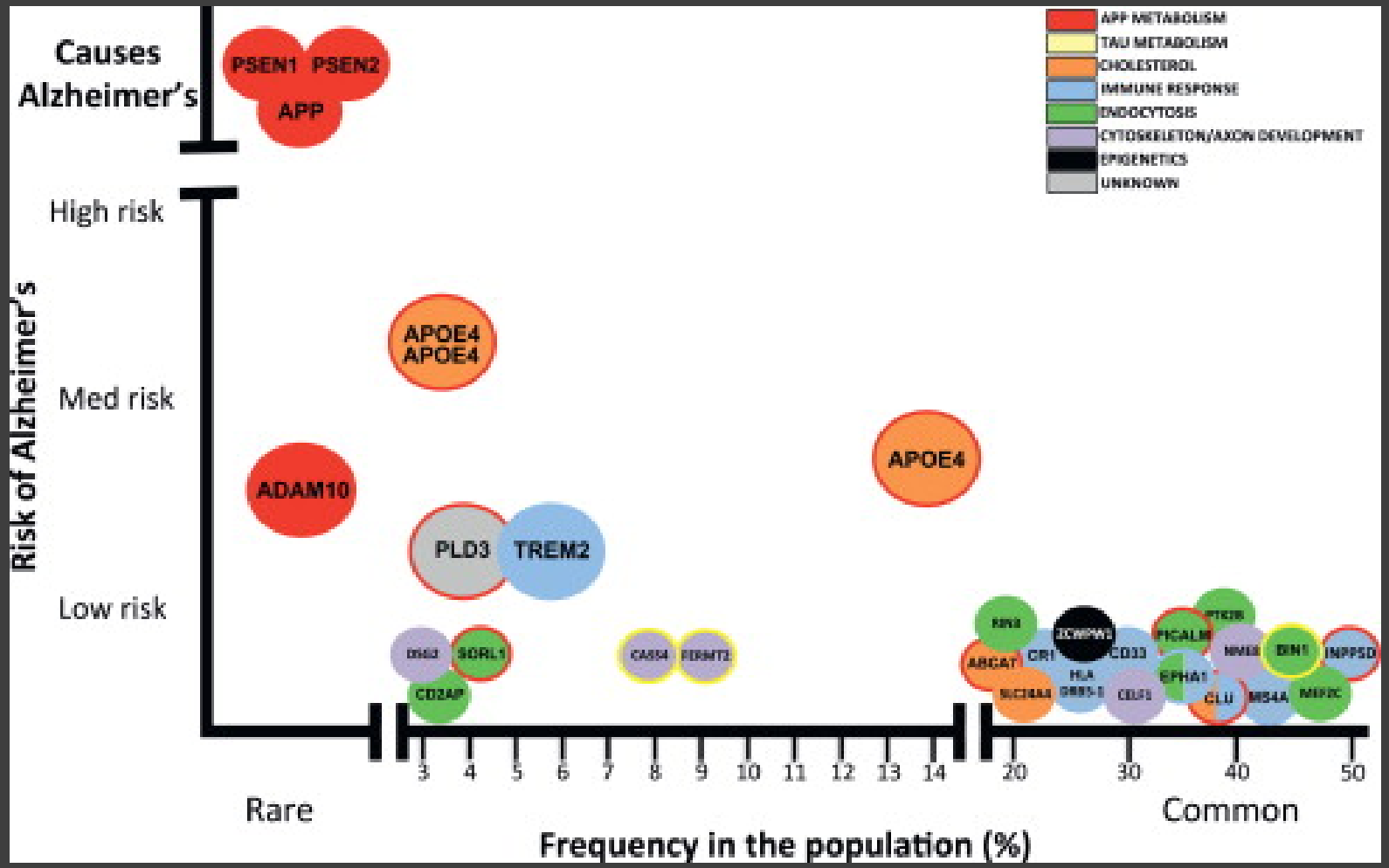
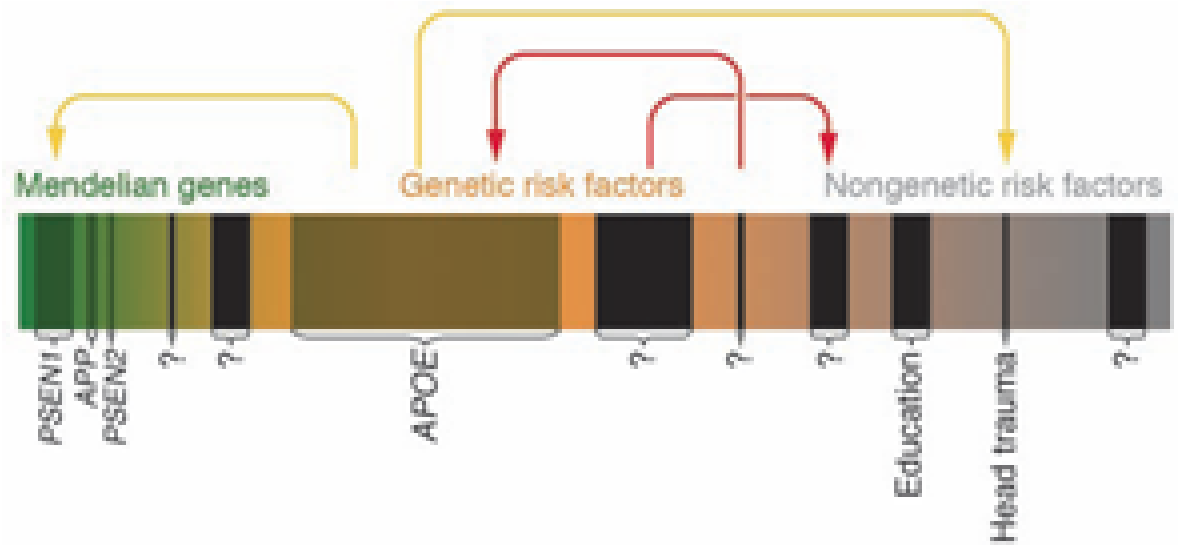


Figure 1. Rare and common variants contribute to Alzheimer's disease risk. GWAS, genome-wide associated studies.

Karch CM, Goate AM. Biological Psychiatry, 2015, 77(1) :43–51

Overall Risk for AD…Multifactorial!!



Lars Bertram,L and Tanzi RE. The genetic epidemiology of neurodegenerative disease
JCI. 2005; 115(6):1449-1457

Frontotemporal Degeneration (FTD)

25-50% of presenile dementias

- (5-15% of all dementias reported on autopsy)

Presents as bvFTD or PPA

Often misdiagnosed as AD or psychiatric disorder

Or AD is misdiagnosed as FTD

Age of Onset: 40-75 (Avg.=56)

10-30% Autosomal dominant

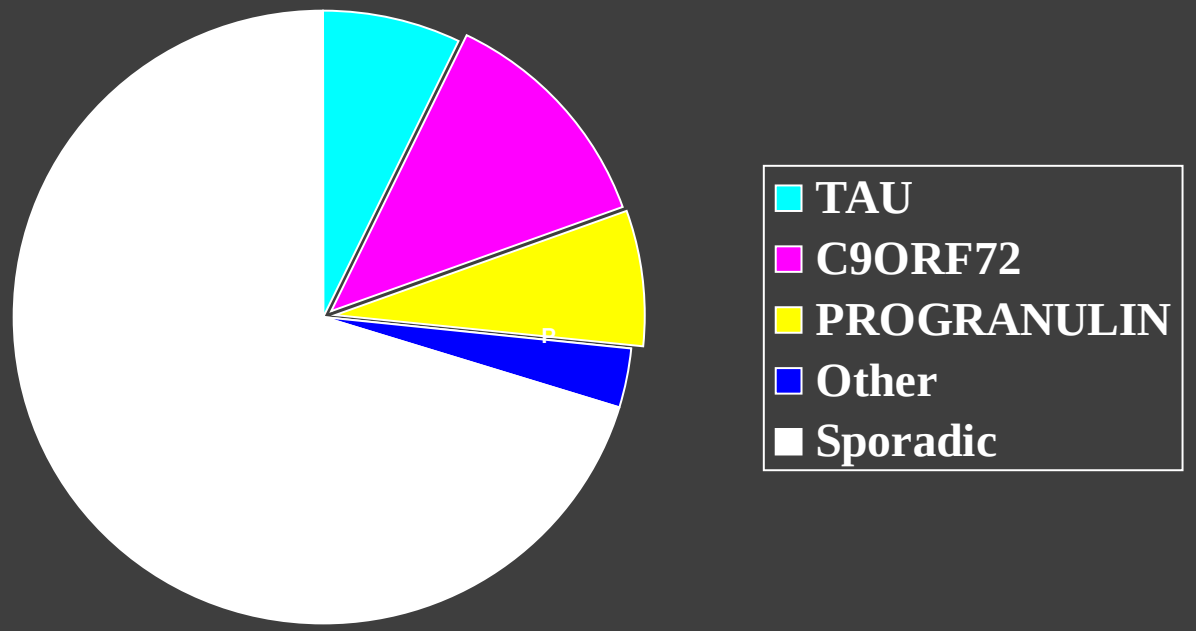
Autosomal dominant FTD

MAPT

PGRN

C9ORF72: FTD/ALS

Other rare genes

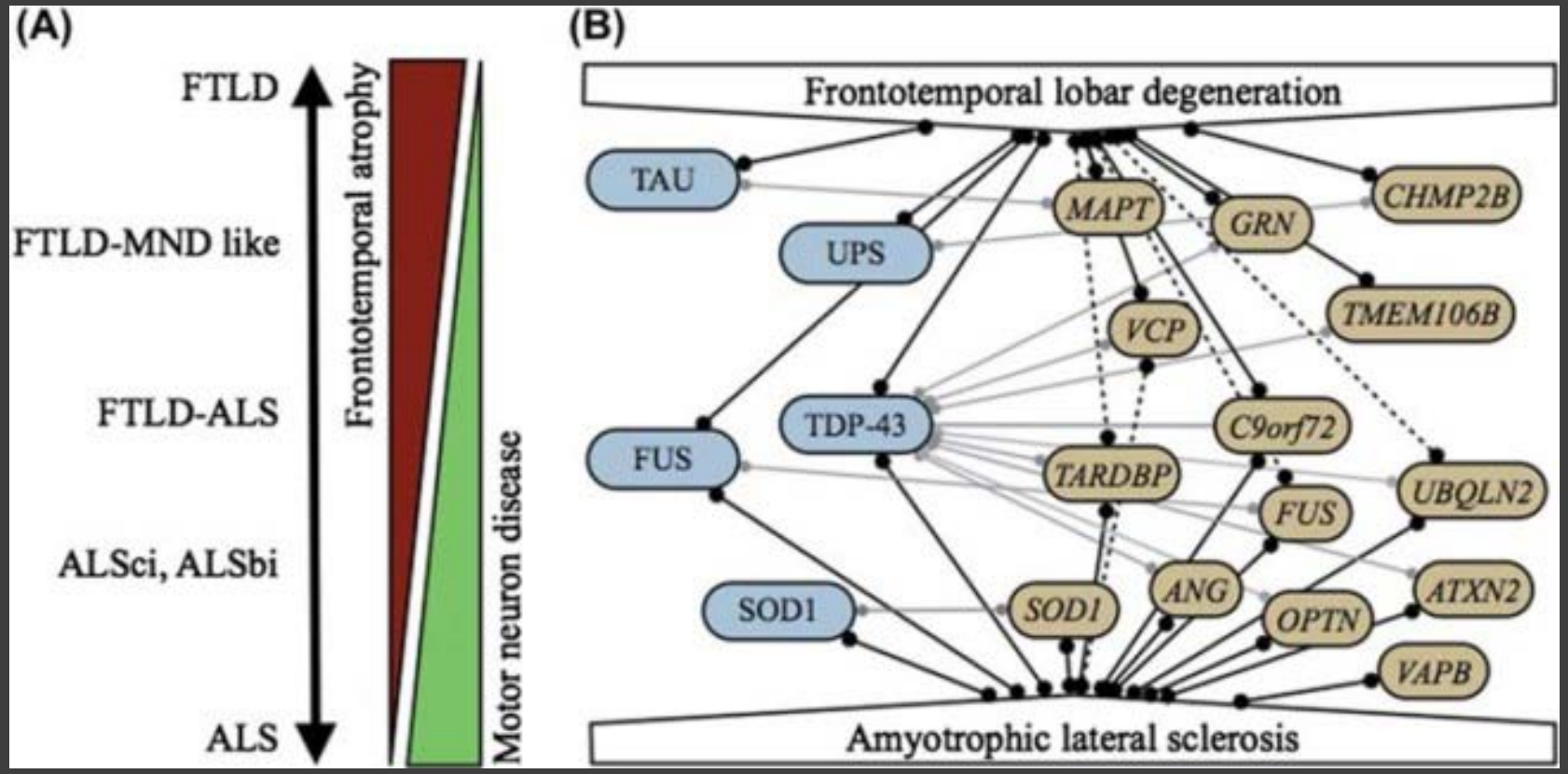


C9orf72

	FTD	ALS
Familial	12-18%	24-38%
All	7-9%	7-11%
Sporadic	3%	4%

A. FTLD and ALS form a clinical disease continuum.

B. Molecular relationships between FTLD and ALS. Pathological proteins are indicated in blue, causal genes in yellow. Full lines indicate strong correlations; dotted lines represent putative correlations. Correlations between genes and pathological proteins are indicated by light gray lines.



Van Langenhove T1, van der Zee J, Van Broeckhoven C. Ann Med. 2012 Dec;44(8):817-28.

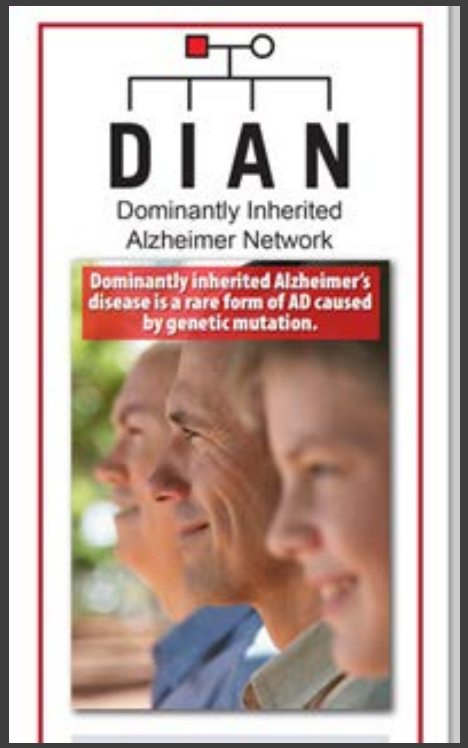
In conclusion: genetic testing for AD and other dementias

- Single gene testing: known family mutation or autosomal dominant family hx
- Panel testing: dx with possible related diseases
- WES: unknown dx or negative findings in above

And back to the questions…..

- How do you define “dementia”?
  - When 2 or more cognitve domains are impaired enough to impact ADLs
- How genetic is Alzheimer’s Disease (AD) (and other dementias)?
  - It depends on the specific dementia and on family history
- How do you know if hereditary AD is what’s in the family?
  - Draw a family tree with **ages** and causes of death and any dementia-related symptoms.
- What are the different genes involved in AD risk?
  - Autosomal dominant genes: *PSEN1, PSEN2, APP*
  - Risk factor genes: *APOE* and many more
- Should I take a genetic test?
  - Depends on specific family history
  - risk for depression, anxiety and family factors
- Is there anything I can do to prevent AD?
  - What’s good for your heart is good for your brain

Through research there is hope….Learning that you have a gene may mean eligibility for a clinical trial



Longitudinal Evaluation of Familial FrontoTemporal Dementia Subjects
LEFFTDS
A·R·T·F·L
Advancing Research & Treatment for Frontotemporal Lobar Degeneration

Researchers need all of you!

Volunteer for research studies

Fund raise

Advocate