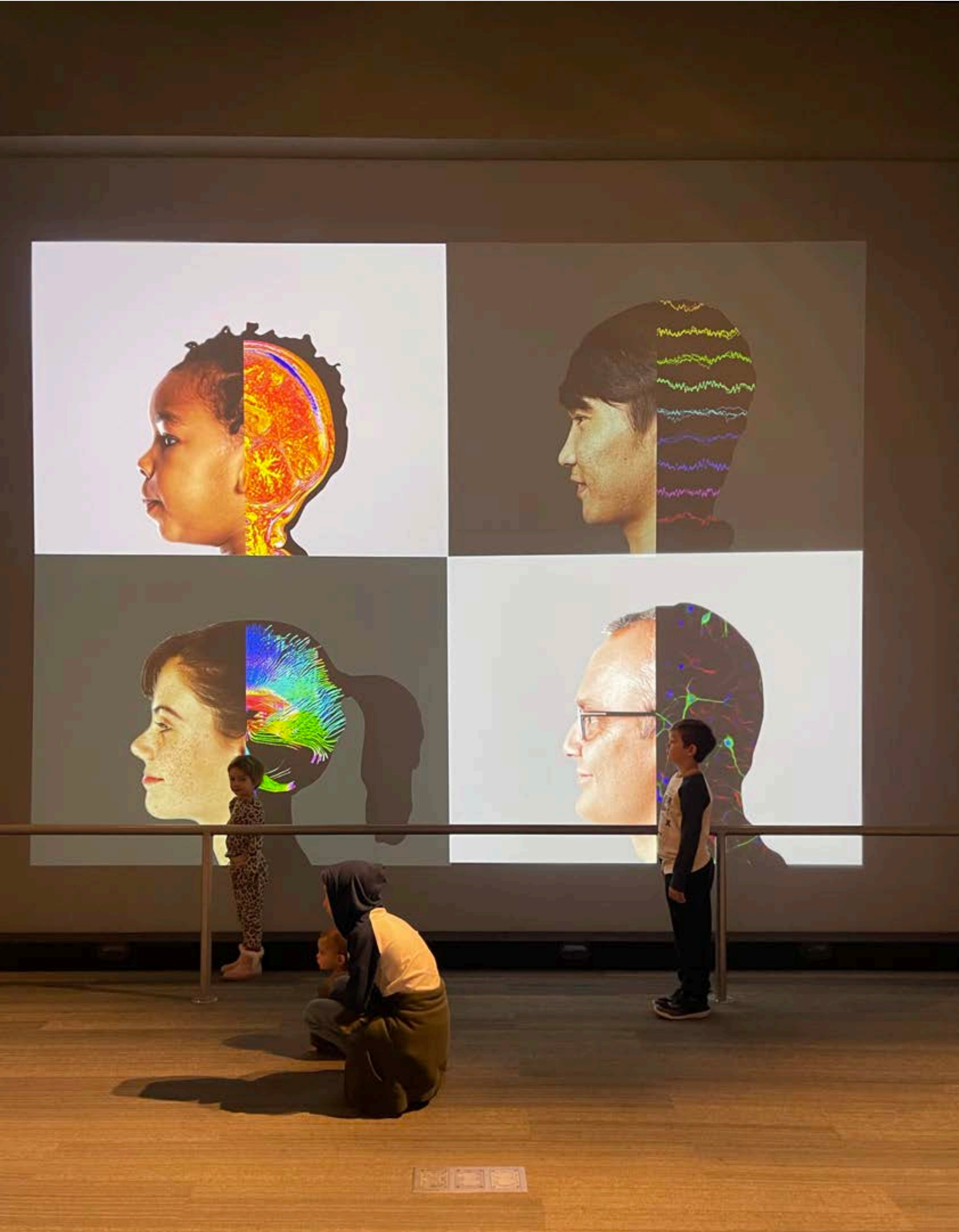


Genetic Counseling for Dementia

Brain Aging Conference
Mar. 8, 2023

Brook Croke, MS, MPH
Genetic Counselor
Synapticure CAREND



OBJECTIVES

- Define **dementia** and examine the role of **genetics** in the varying dementia subtypes
- Discuss genetic counseling and testing for dementia and other related **neurodegenerative disorders**
- Generally review clinical trials for individuals with genetic forms of dementia



DEFINITION:

TYPES OF DEMENTIA

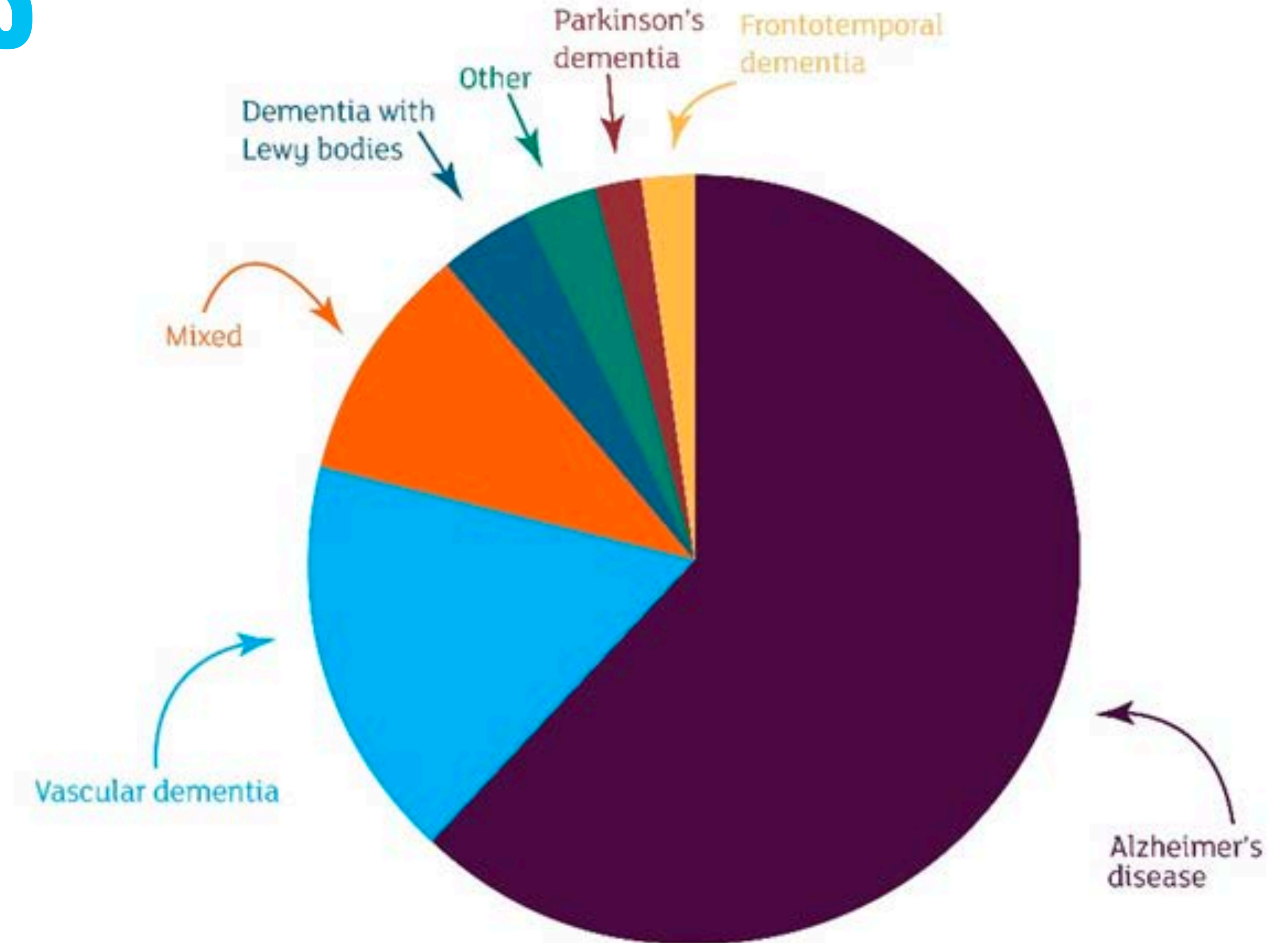
alz.org

Dementia is an umbrella term for loss of memory and other thinking abilities severe enough to interfere with daily life.

- Alzheimer's
- Vascular
- Lewy body
- Frontotemporal
- Other, including Huntington's
- * **Mixed dementia:** Dementia from more than one cause

DEMENTIA - SUBTYPES

- **Alzheimer's disease**
 - 60-70% of dementia
- **Vascular dementia**
 - 5-10% of dementia
- **Frontotemporal dementia**
 - 5-10% of dementia
- **Dementia with Lewy bodies**
 - <5%
- **Parkinson's disease dementia**
- **Huntington's disease**



GENETICS OF DEMENTIA

- **Alzheimer's Disease**

- *APP, PSEN1, PSEN2, PRNP*

- **Vascular Dementia**

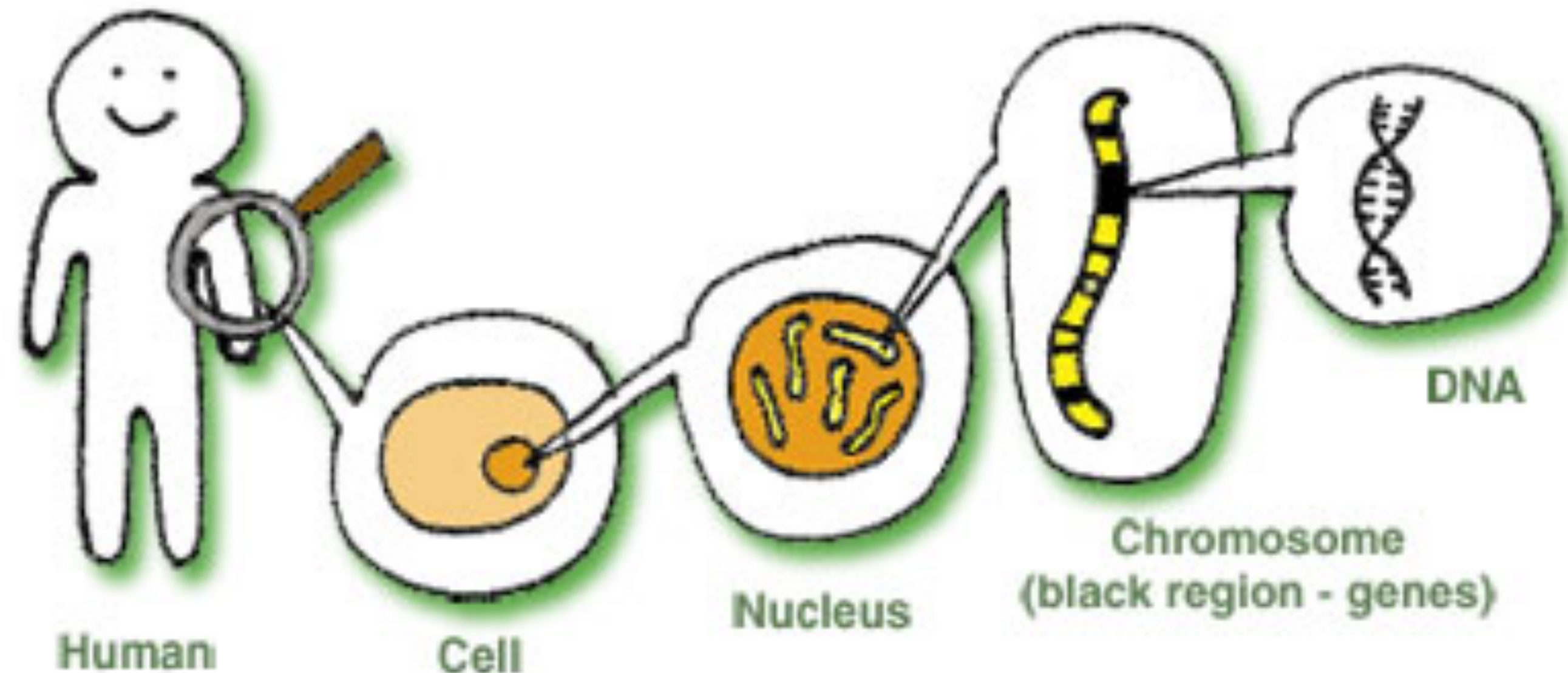
- *CADASIL/NOTCH3*

- **Frontotemporal Dementia***

- *C9orf72, MAPT, GRN, others*

- **Lewy body**

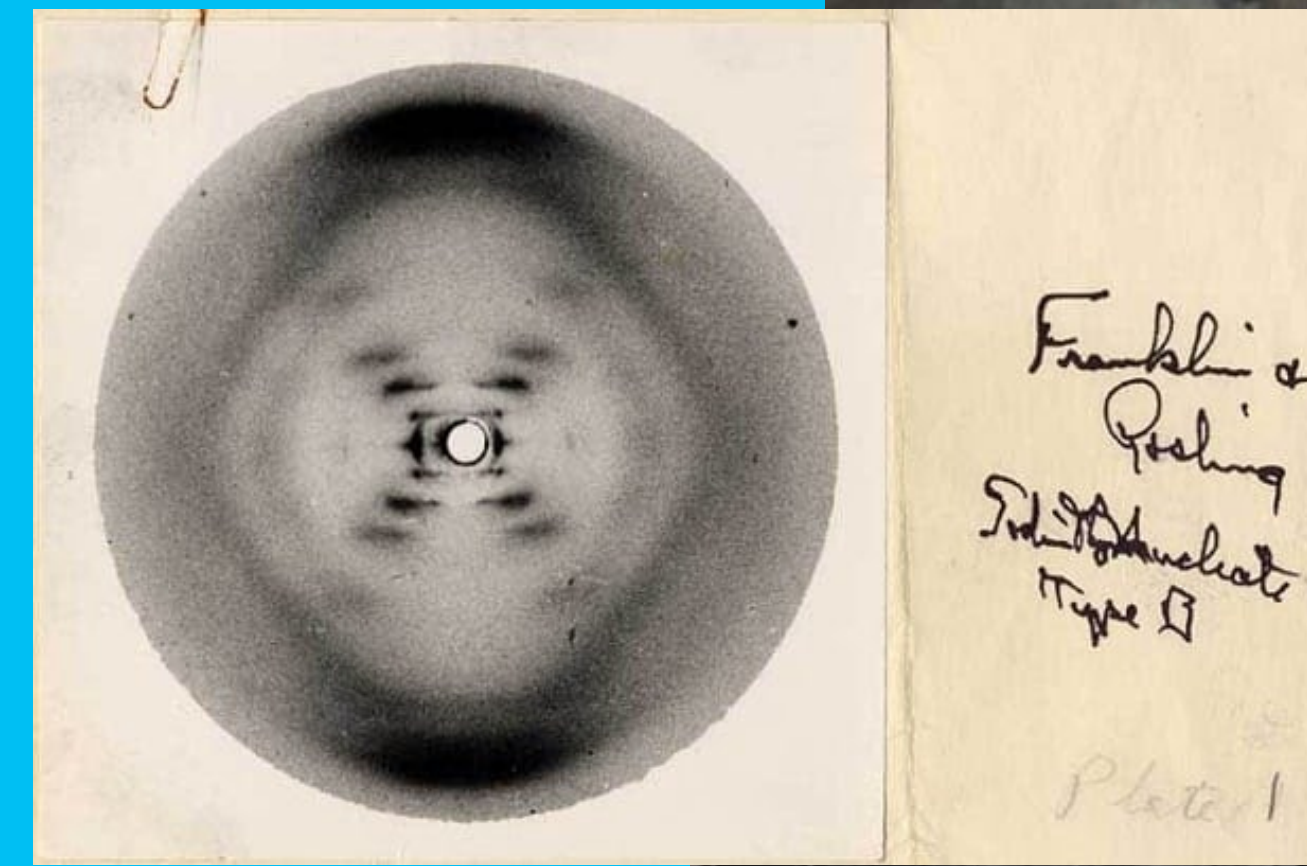
- *SNCA, SNCB, GBA, APOE*



- Now well established that genes initially discovered to cause one subtype of dementia can cause multiple phenotypes (gene pleiotropy)

HISTORY

- Late 1890s - Arnold Pick: FTD
- 1906 - Alois Alzheimer - AD
- 1922 - Pick's Disease (FTD) coined
- 1953 - DNA discovered!
- 1987 - **PSEN1/APP** linked to EOAD
- 1993 - **APOE4**: risk variant for LOAD; **MAPT** linked to FTD
- 2003 - **GRN** linked to FTD
- 2008 **TARDBP** discovered - encodes TDP-43
- 2011 - **C9orf72** identified as top cause of FTD/ALS (European descent)
- Current- Gene pleiotropy seen with major neurodegenerative disorders



WHO SHOULD PURSUE GENETIC COUNSELING?

- ***Anyone with a diagnosis or family history of dementia***
 - Learn whether you may be eligible for a clinical trial
 - Increase knowledge - benefit to family and community as a whole
- ***Family members of individuals with known genetic cause of dementia***
 - *Eligibility for gene-specific trials*
 - *Family planning (IVF with PGT)*
- **Identifying a genetic cause of dementia is very dependent on the subtype of dementia as well as the family history**
 - 40% with FTD
 - 5-10% of those with early onset AD
 - Odds of having a positive genetic result are much higher with a strong family history

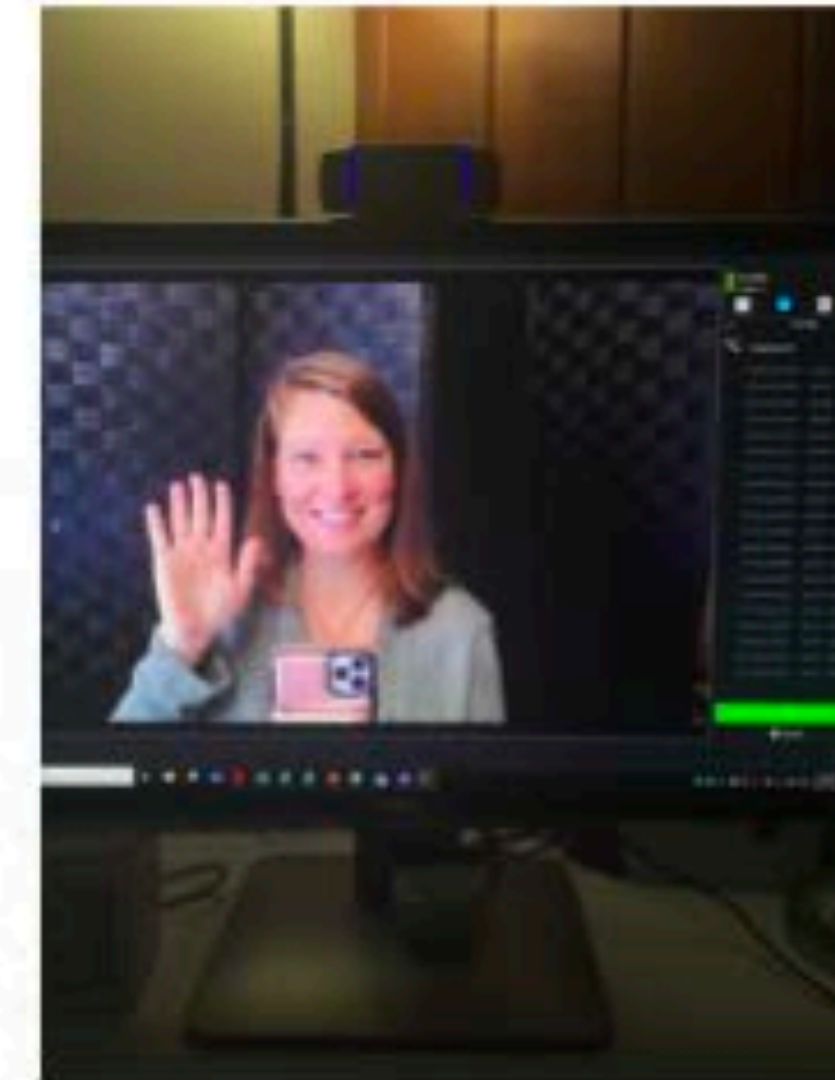
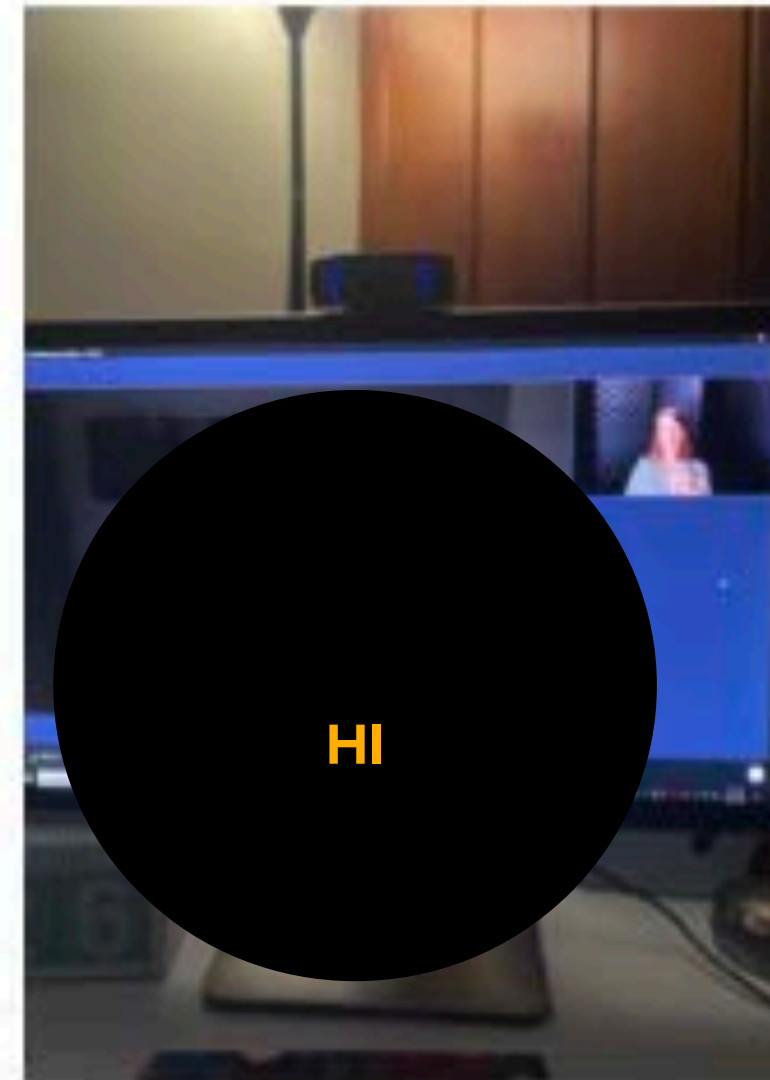


GENETIC COUNSELING

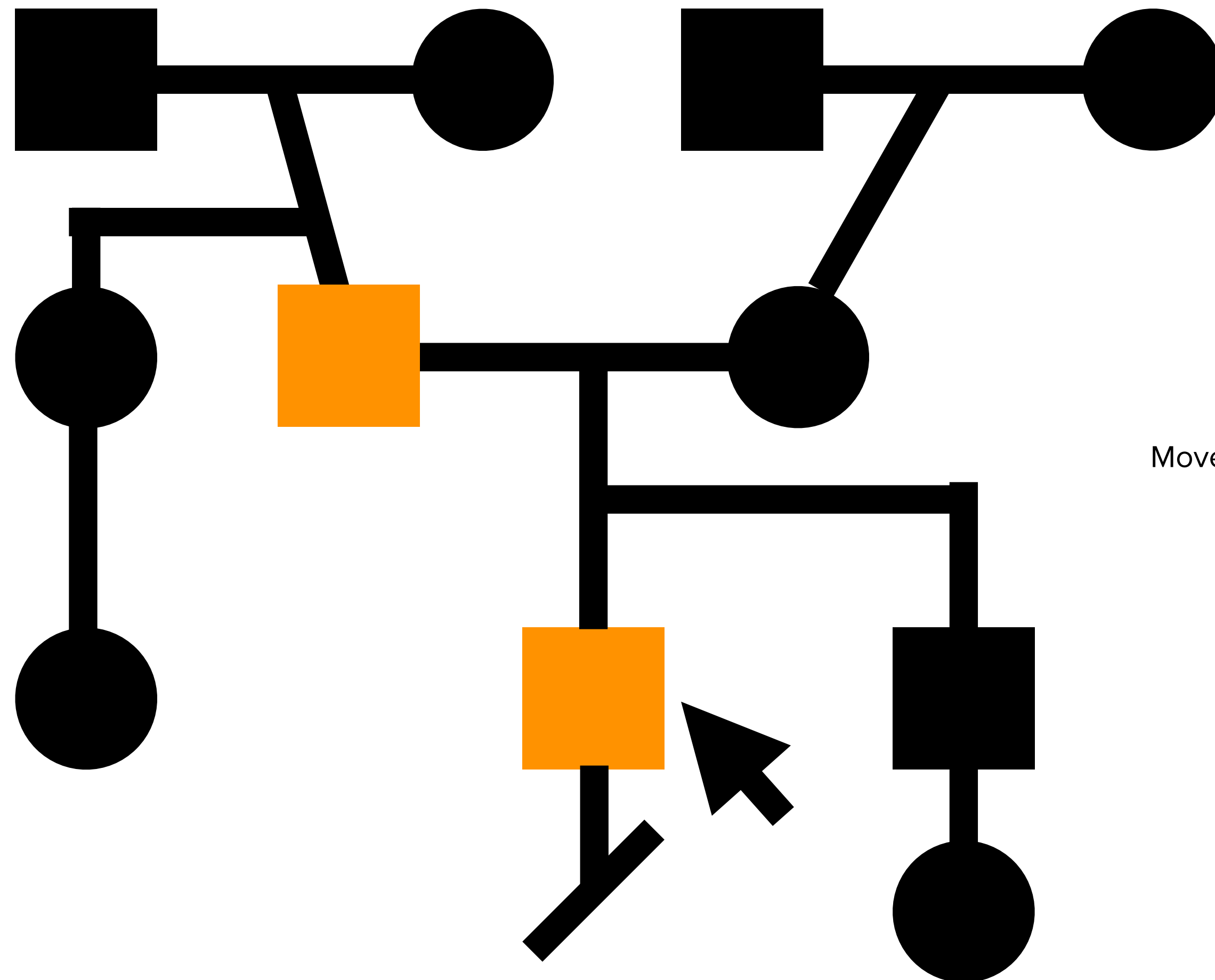
- **Genetic Counselor**
 - Reviews records and any prior genetic testing results
 - Obtains three generation family health history
 - Discusses testing options
 - Gene panel
 - WES or WGS
 - Mitochondrial testing
 - Other

Telehealth

Increasing access to GCs and testing



FAMILY HISTORY ASSESSMENT



FTD/other dementias
Motor neuron disease (ALS)
Movement disorders (Parkinson's, HD)
Psychiatric disorders
Other genetic conditions

GENETIC TESTING OPTIONS

— Clinical testing

- *Genetic testing that must be ordered by a provider, typically focused on a specific diagnosis*

— Direct to consumer testing

- See example on right

— Research testing

- Option to opt in/out of knowing results if desired for some studies, less likely to have implications on insurance

— DNA Banking

Brook, you **do not have** the ε4 variant we tested.

Your risk for Alzheimer's disease also depends on other factors, including lifestyle, environment, and genetic variants not covered by this test.

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.

+ Intended Uses

- Tests for the ε4 variant in the APOE gene 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.

SPONSORED TESTING PROGRAMS

Amyotrophic Lateral Sclerosis (ALS) Testing Program

Program Overview

In partnership with Ionis Pharmaceuticals, this program provides genetic testing for Amyotrophic Lateral Sclerosis (ALS), a neurodegenerative disorder. No-cost ALS testing is available for patients with a family history of ALS or who meet the program's eligibility criteria. Testing is available to residents of the following states: AL, AR, AZ, CA, CO, CT, DC, DE, FL, GA, HI, IL, IN, IA, KS, KY, LA, MA, MD, ME, MI, MN, MO, MS, MT, NC, ND, NH, NJ, NY, OH, OK, OR, PA, RI, SC, SD, TN, TX, VA, VT, WA, WI, WY.

Test Code: 15479 33 Genes

ANG, ANXA11, ARHGEF28, ATXN2, C9orf72, CFAP410, CHCHD10, CHMP2B, DAO, DCTN1, ERBB4, FIG4, FUS, HNRNPA1, HNRNPA2B1, KIF5A, MATR3, MOBP, NEFH, NEK1, OPTN, PFN1, SETX, SOD1, SQSTM1, TAF15, TARDBP, TBK1, TUBA4A, UBQLN2, UNC13A, VAPB, VCP

Frontotemporal Dementia Sponsored Testing Program

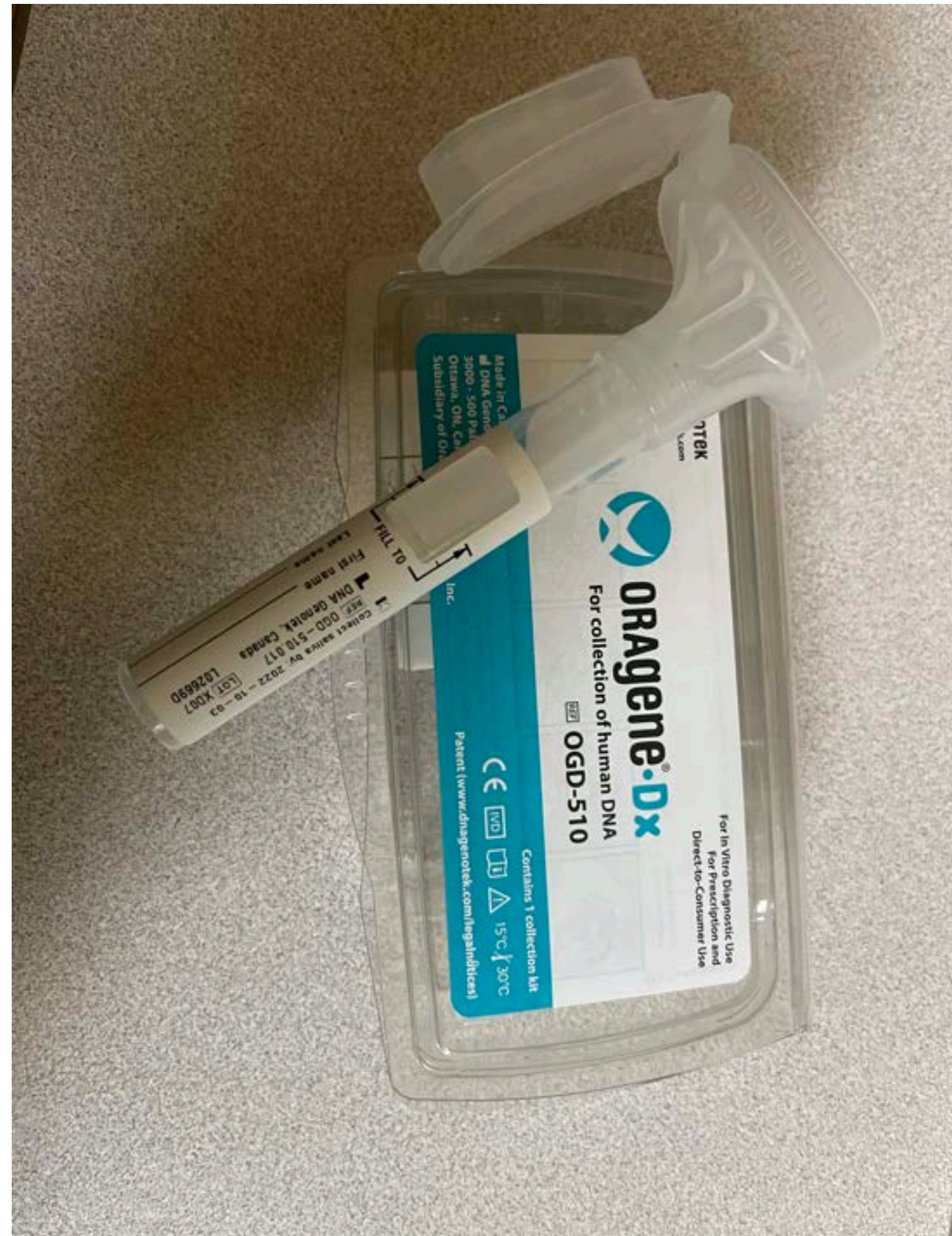
Program Overview

In partnership with Passage Bio, this program provides physicians access to no-cost genetic testing for patients, who are suspected of having frontotemporal dementia (FTD), a clinically heterogeneous syndrome due to the progressive degeneration and atrophy of various regions of the frontal and temporal lobes of the brain.

Test Code: 5265 18 Genes

APP, C9orf72, CHCHD10, CHMP2B, CSF1R, DCTN1, FUS, GRN, ITM2B, MAPT, PSEN1, PSEN2, SQSTM1, TARDBP, TBK1, TREM2, UBQLN2, VCP

CLINICAL GENETIC TESTING



Saliva sample collection

CLINICAL GENETIC TESTING

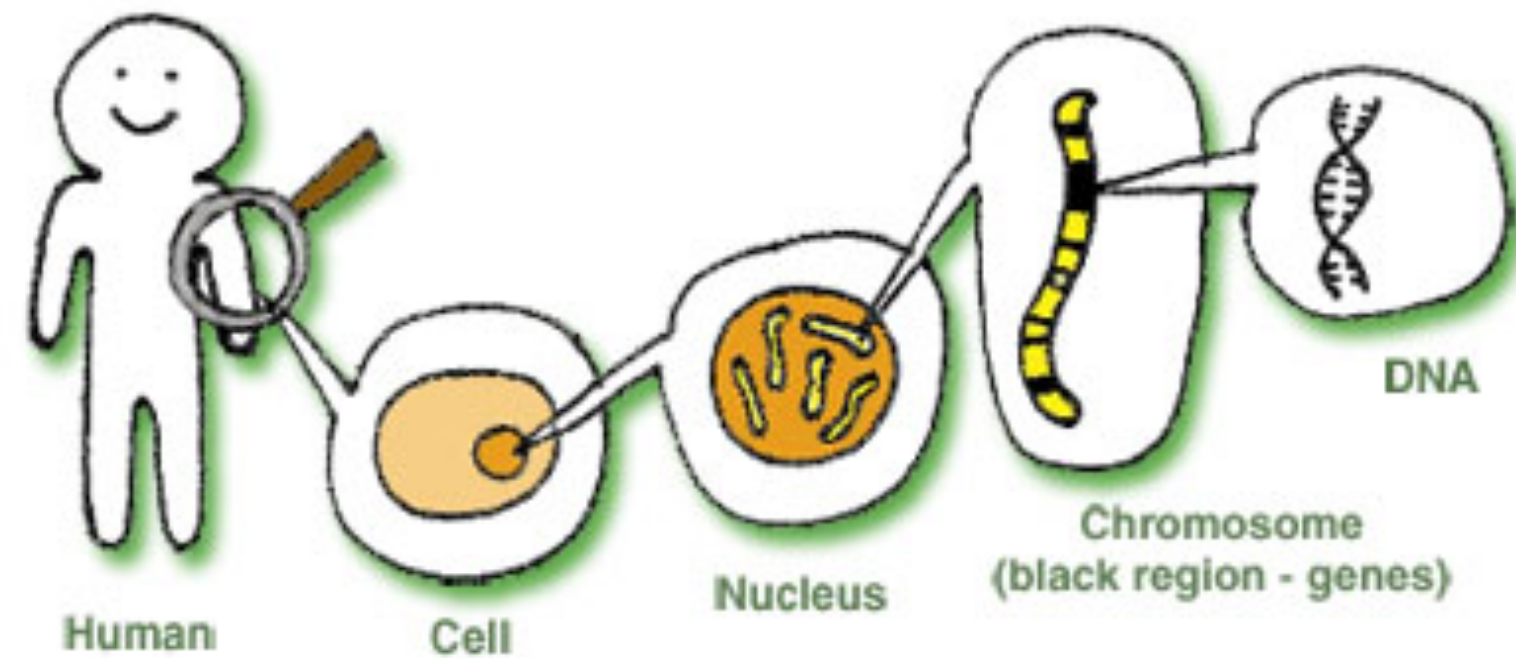


Place sample in box



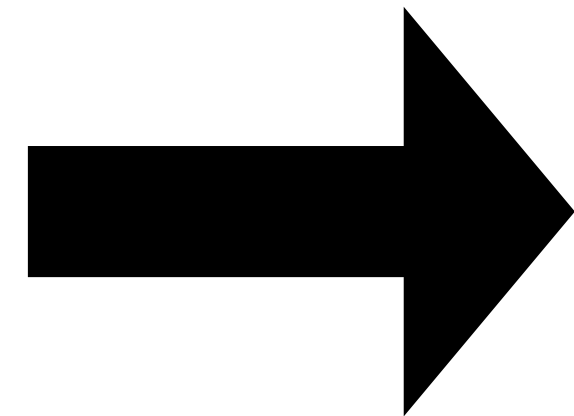
Return sample to lab

CLINICAL TESTING - AD



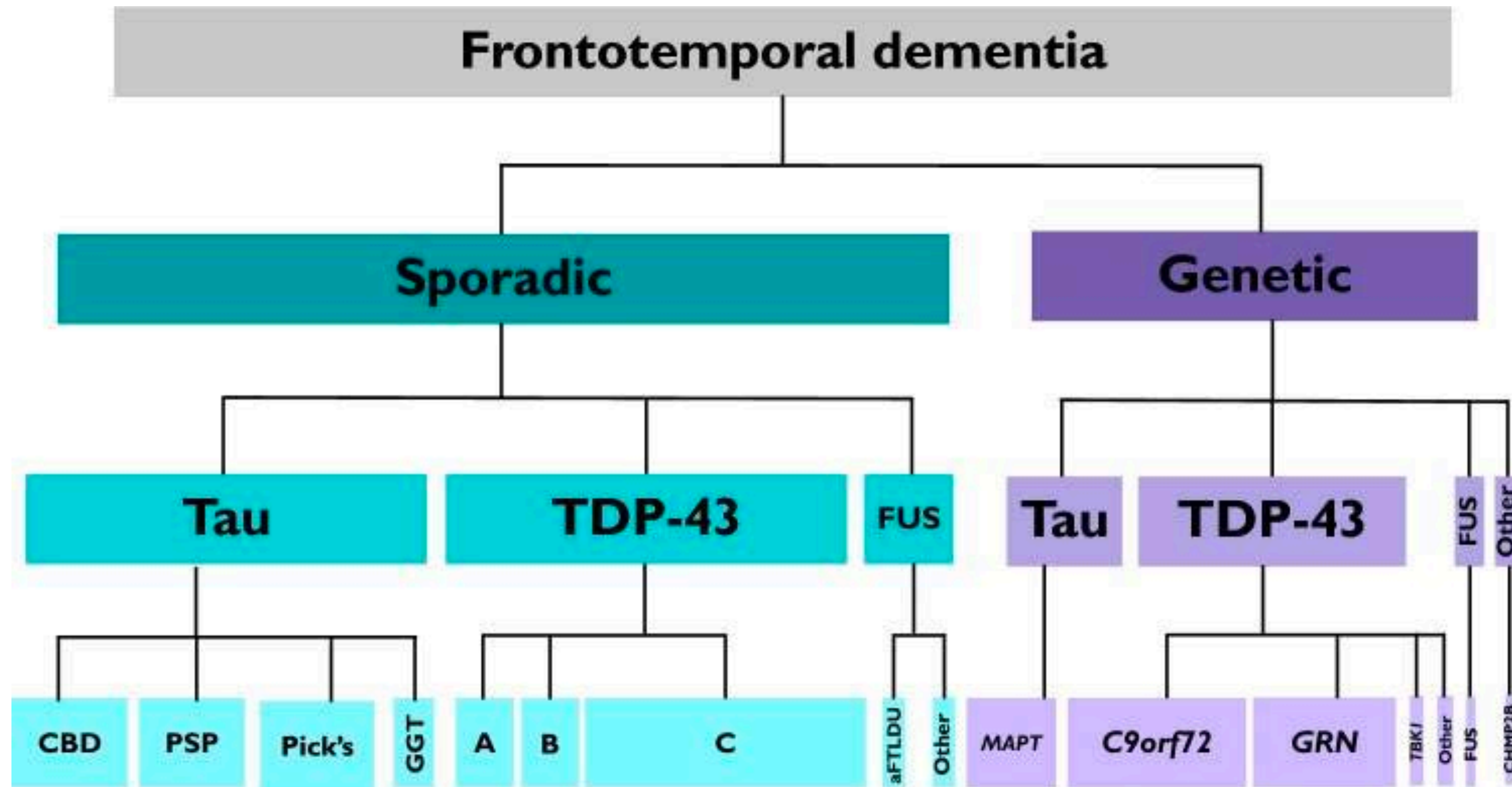
2-3% of AD

DNA BANKING should also be considered



- **PSEN1**
 - 70% of EOAD
- **APP**
 - 15% of EOAD
- **PSEN2**
 - 5% of EOAD
- *APOE - risk factor for late-onset AD*

CLINICAL TESTING - FTD

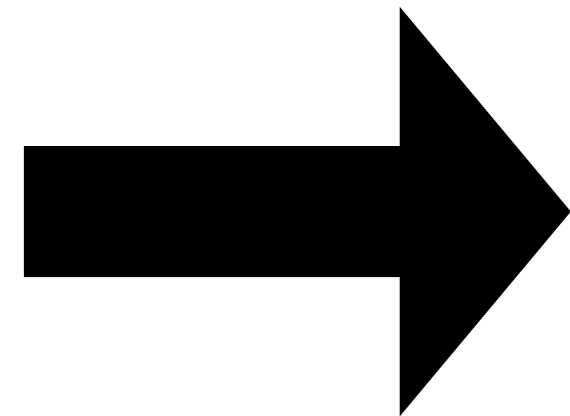


Greaves et al, J Neurol. 2019
Aug;266(8):2075-2086

CLINICAL TESTING - FTD

Sponsored genetic testing (18 genes)

40% of FTD is genetic



- **C9orf72 repeat expansion**
 - Over 30% of fALS/FTD (Europeans)
 - Less common in other populations
- **GRN**
 - 25% of FTD
- **MAPT**
 - 15% of FTD
- *Additional genes with that are more rare causes of FTD are on the panel. The genes that cause EOAD are also often on such panels.*

CLINICAL TESTING - GENE PLEIOTROPY

Genes and rare variants identified in sFTD.

Subject	Chromosome	Reference Sequence	Gene
1	1	NM_001171811	<i>GBA</i>
5	19	NM_019112	<i>ABCA7</i>
6	1	NM_001123377	<i>PARK7</i>
	19	NM_019112	<i>ABCA7</i>
	16	NM_001170634	<i>FUS</i>
7	11	NM_003105	<i>SORL1</i>
	12	NM_198578	<i>LRRK2</i>
	2	NM_020919	<i>ALS2</i>

- *sFTD patients who were negative for common FTD genes*
- *50% showed at least one rare missense variant in genes associated with:*
 - *Alzheimer's disease*
 - *Parkinson's disease*
 - *Lewy body dementia*
- *Confirmation of the **genetic pleiotropy** of neurodegenerative diseases.*

DTC TESTING

	ε2*2	ε2*3	ε2*4	ε3*3	ε3*4	ε4*4
Japanese	1.1 (0.1–17.2)	0.9 (0.4–2.5)	2.4 (0.4–15.4)	1.0 (Ref)	5.6 (3.9–8.0)	33.1 (13.1–83.3)
Japanese	NA	0.7 (0.3–1.6)	NA	1.0 (Ref)	3.9 (1.9–8.0)	21.8 (8.6–55.1)
Caucasians: clinic/autopsy	0.6 (0.2–2.0)	0.6 (0.5–0.8)	2.6 (1.6–4.0)	1.0 (Ref)	3.2 (2.8–3.8)	14.9 (10.8–20.6)
Caucasians: clinic/autopsy	NA	0.6 (0.3–1.2)	NA	1.0 (Ref)	4.3 (3.3–5.5)	15.6 (10.9–22.5)
Caucasians: autopsy	0.1 (0.1–0.4)	0.4 (0.3–0.5)	2.7 (1.7–4.4)	1.0 (Ref)	6.1 (5.–7.4)	31.2 (16.6–58.8)
Caucasians: population-based	0.9 (0.3–2.8)	0.6 (0.5–0.9)	1.2 (0.8–2.0)	1.0 (Ref)	2.7 (2.2–3.2)	12.5 (8.8–17.7)
Caucasians: population-based	NA	0.3 (0.2–0.6)	NA	1.0 (Ref)	2.8 (2.3–3.5)	11.8 (7.0–19.8)
African Americans	2.4 (0.3–22.7)	0.6 (0.4–1.7)	1.8 (0.4–8.1)	1.0 (Ref)	1.1 (0.7–1.8)	5.7 (2.3–14.1)
Hispanics	2.6 (0.2–33.3)	0.6 (0.3–1.3)	3.2 (0.9–11.6)	1.0 (Ref)	2.2 (1.3–3.4)	2.2 (0.7–6.7)

Brook, you **do not have** the ε4 variant we tested.

Your risk for Alzheimer's disease also depends on other factors, including lifestyle, environment, and genetic variants not covered by this test.

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.

+ Intended Uses

- Tests for the ε4 variant in the APOE gene 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.

RESEARCH TESTING

Available through
multiple sites
across the country

- Family history
- Diagnosis

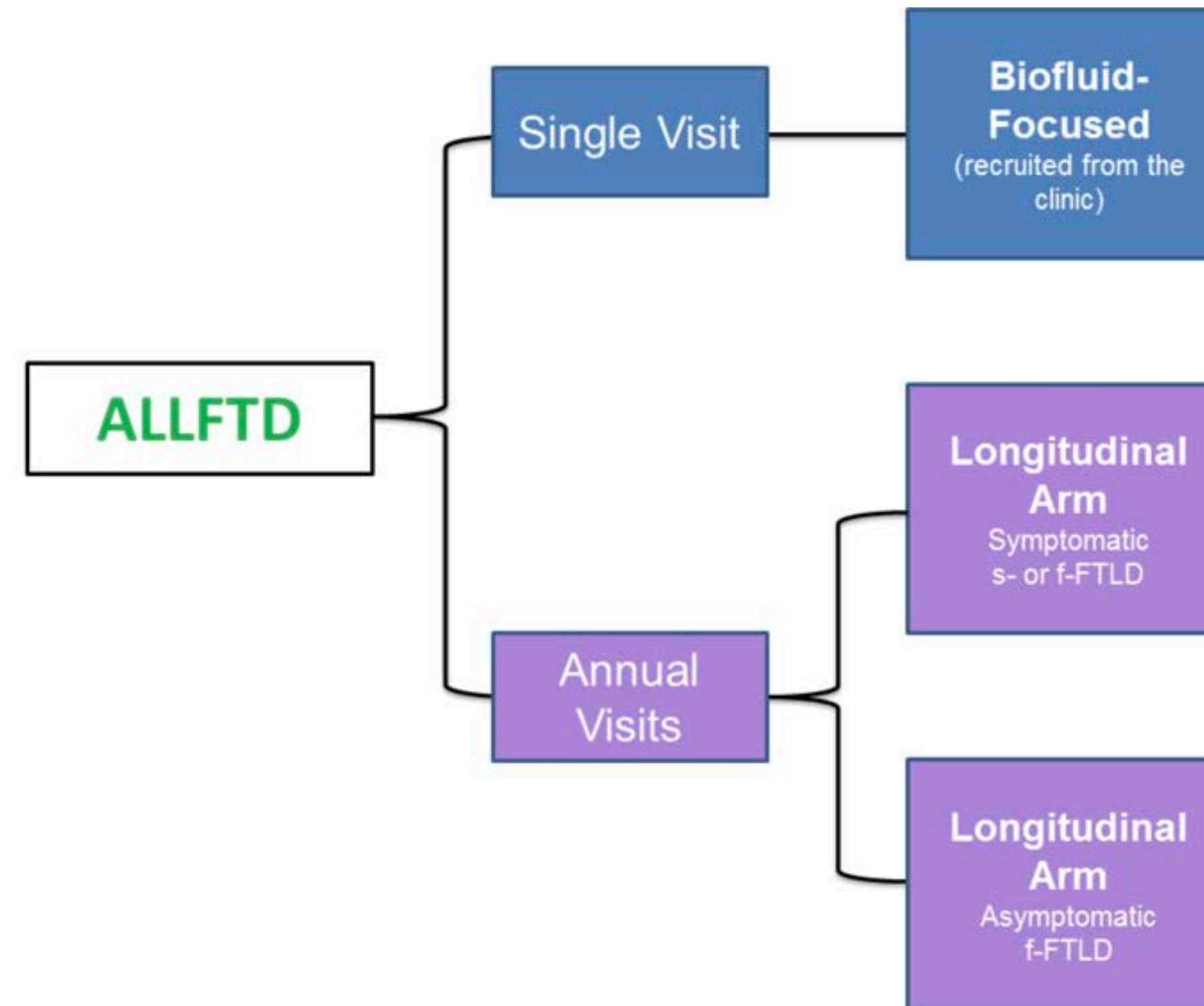
allftd.org/research



RESEARCH TESTING

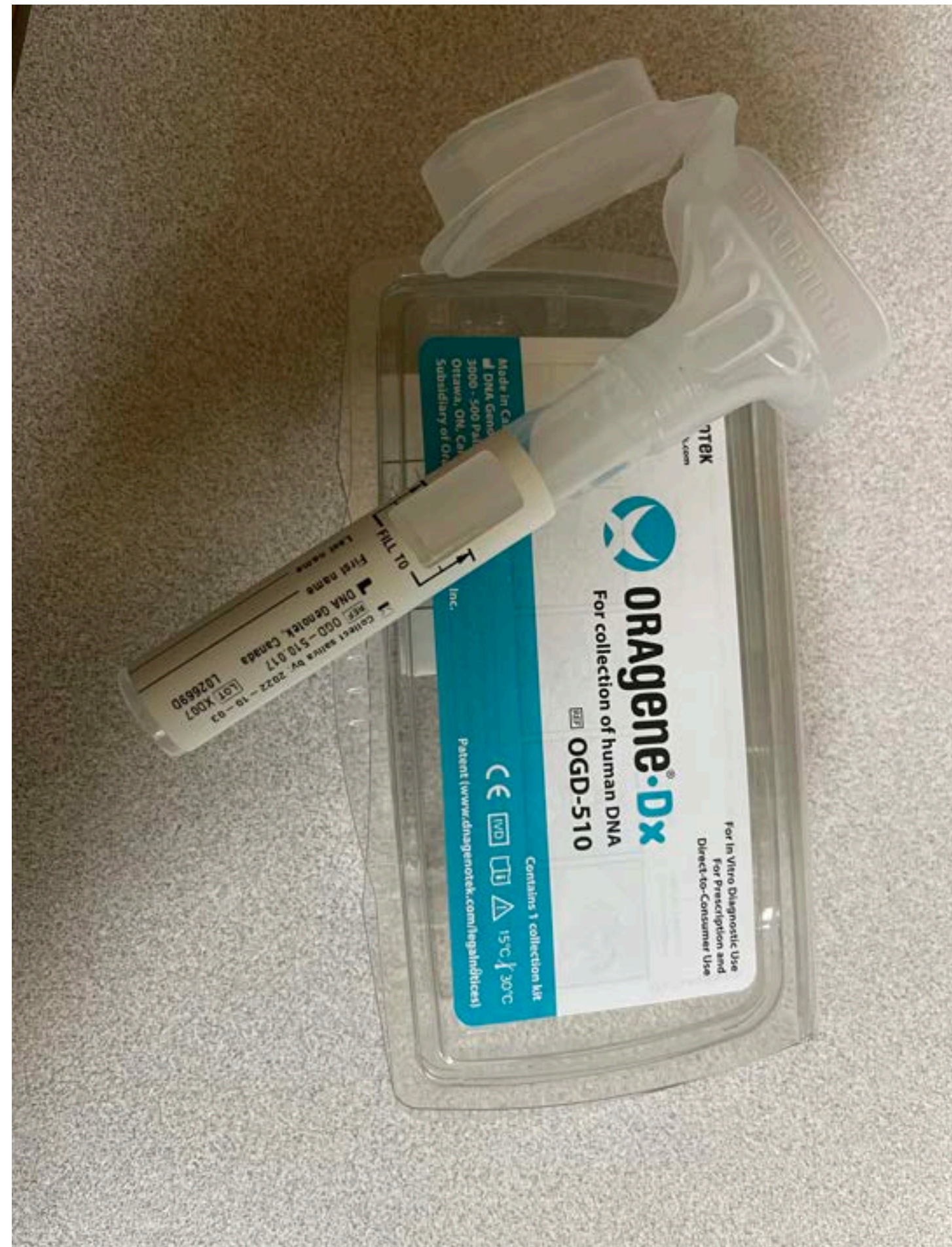
OBSERVATIONAL STUDIES (NATURAL HISTORY OR LONGITUDINAL)

ALLFTD (ARTFL LEFFTDS LONGITUDINAL FRONTOTEMPORAL DEMENTIA)	>
BLUEFIELD NEUROFILAMENT SURVEILLANCE PROJECT (NSP) STUDY	>
UPDATED! DEVELOPMENT IN FAMILIES WITH NEURODEGENERATIVE DISEASE	>
GENES, BRAINS, AND DECISIONS	>
GENETICS OF FTD IN DIVERSE POPULATIONS	>
IMAGING STUDY IN BVFTD	>
LANGUAGE IN PRIMARY PROGRESSIVE APHASIA (PPA)	>
UPDATED! PROGRANULIN GENE FTD (PG FTD) GENETIC COUNSELING & TESTING	>



DNA BANKING

Typically <\$200 for lifetime storage of a DNA sample



Saliva sample collection

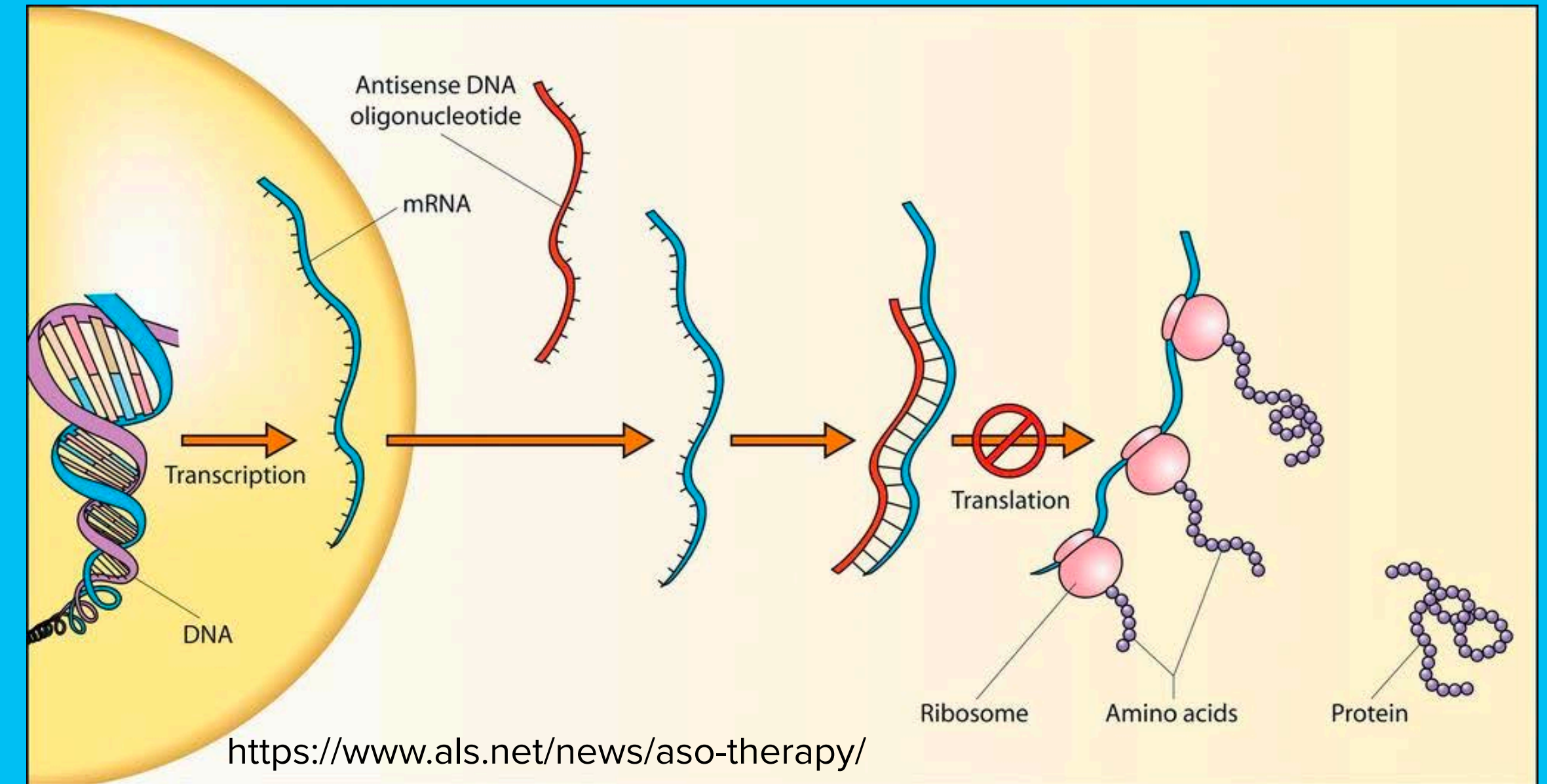


Place sample in box

TARGETED THERAPIES

Antisense Oligonucleotide (ASO)

- Gene-specific targets
 - Typically the RNA encoded by the DNA
- **Current ASO Clinical trials for FTD and ALS**
 - *C9orf72*, *SOD1* *phase III*, *FUS*, *ATXN2*



GENE THERAPY

GREAT PROGRESS IN LAST 5 YEARS

Adeno-associated virus (AAV) delivery for patients w/*GRN*-associated FTD.

Recruitment through sponsored genetic testing program

- Documentation of as a pathogenic *GRN* mutation carrier
- Clinical diagnosis of FTD
- Ages of 35-75
- Have a reliable informant / caregiver who personally speaks with or sees the subject at least weekly
- Live in the community (i.e., not in a nursing home; assisted living may be permitted at the discretion of the investigator).

TREATMENT STUDIES	
FOXY: INTRANASAL OXYTOCIN FOR FTD	>
GIFTED: GAMMA-INDUCTION IN FRONTOTEMPORAL DEMENTIA	>
UPDATED! INFRONT-3: EVALUATING AL001 IN FTD	>
PROCLAIM: PRO06 IN FTD WITH PROGRANULIN MUTATIONS (FTD-GRN)	>
TPN-101 IN PATIENTS WITH <i>C9ORF72</i> ALS/FTD	>
TREATMENT OF DISTURBED SLEEP IN PSP	>
UPLIFT-D: PBFT02 IN PATIENTS WITH FTD AND PROGRANULIN MUTATIONS (FTD-GRN)	>
VERI-T: A TRIAL OF VERDIPERSTAT IN SVPPA DUE TO TDP-43	>

ClinicalTrials.gov Find Studies ▾ About Studies ▾ Submit Studies ▾ Resources ▾ About Site ▾

Home > Search Results > Study Record Detail

A Study of PBFT02 in Patients With Frontotemporal Dementia and Progranulin Mutations (FTD-GRN) (upliFT-D)

ClinicalTrials.gov Identifier: NCT04747431

Recruitment Status ⓘ : Recruiting
First Posted ⓘ : February 10, 2021
Last Update Posted ⓘ : January 25, 2023
See [Contacts and Locations](#)

[View this study on Beta.ClinicalTrials.gov](#)

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. [Know the risks and potential benefits](#) of clinical studies and talk to your health care provider before participating. Read our [disclaimer](#) for details.

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- The Missing Heritability of Sporadic Frontotemporal Dementia: New Insights from Rare Variants in Neurodegenerative Candidate Genes *Int J Mol Sci*. 2019 Aug; 20(16): 3903. Published online 2019 Aug 10. doi: 10.3390/ijms20163903 PMCID: PMC6721049 PMID: 31405128

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Our amazing team!