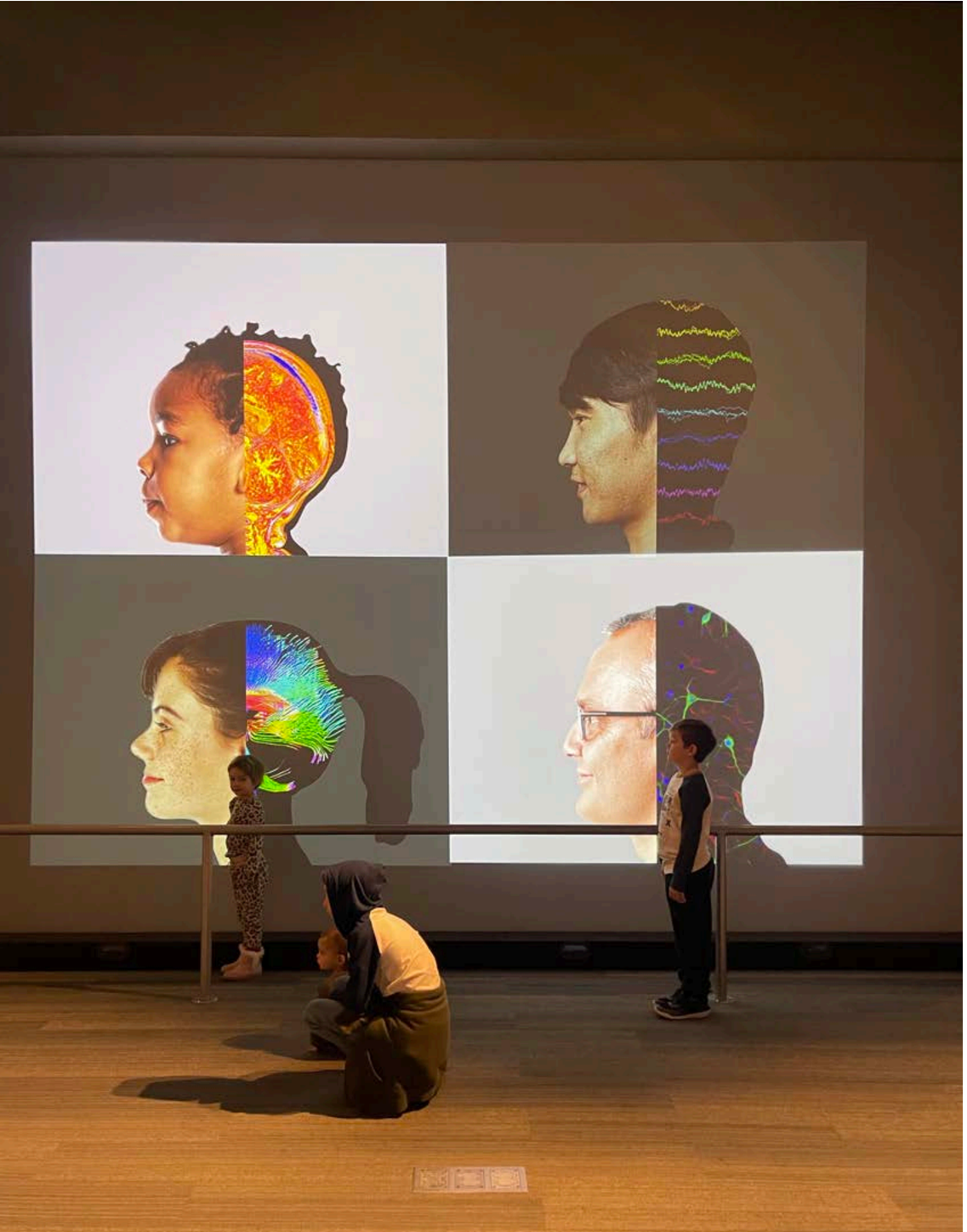


Genetic Counseling for Dementia

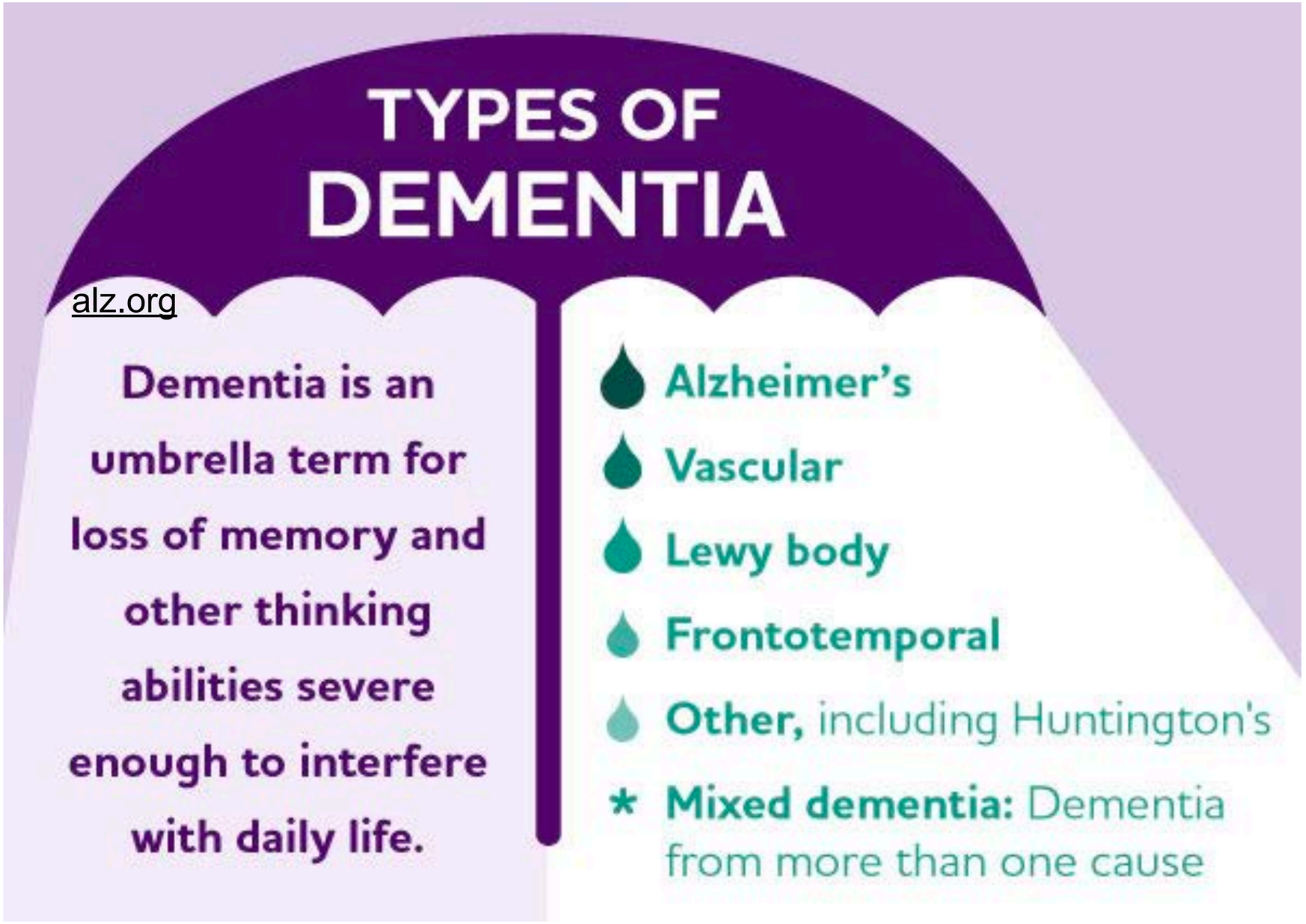
Brain Aging Conference
Mar. 8, 2023

Brook Croke, MS, MPH
Genetic Counselor
Synapticure CARE ND

OBJECTIVES

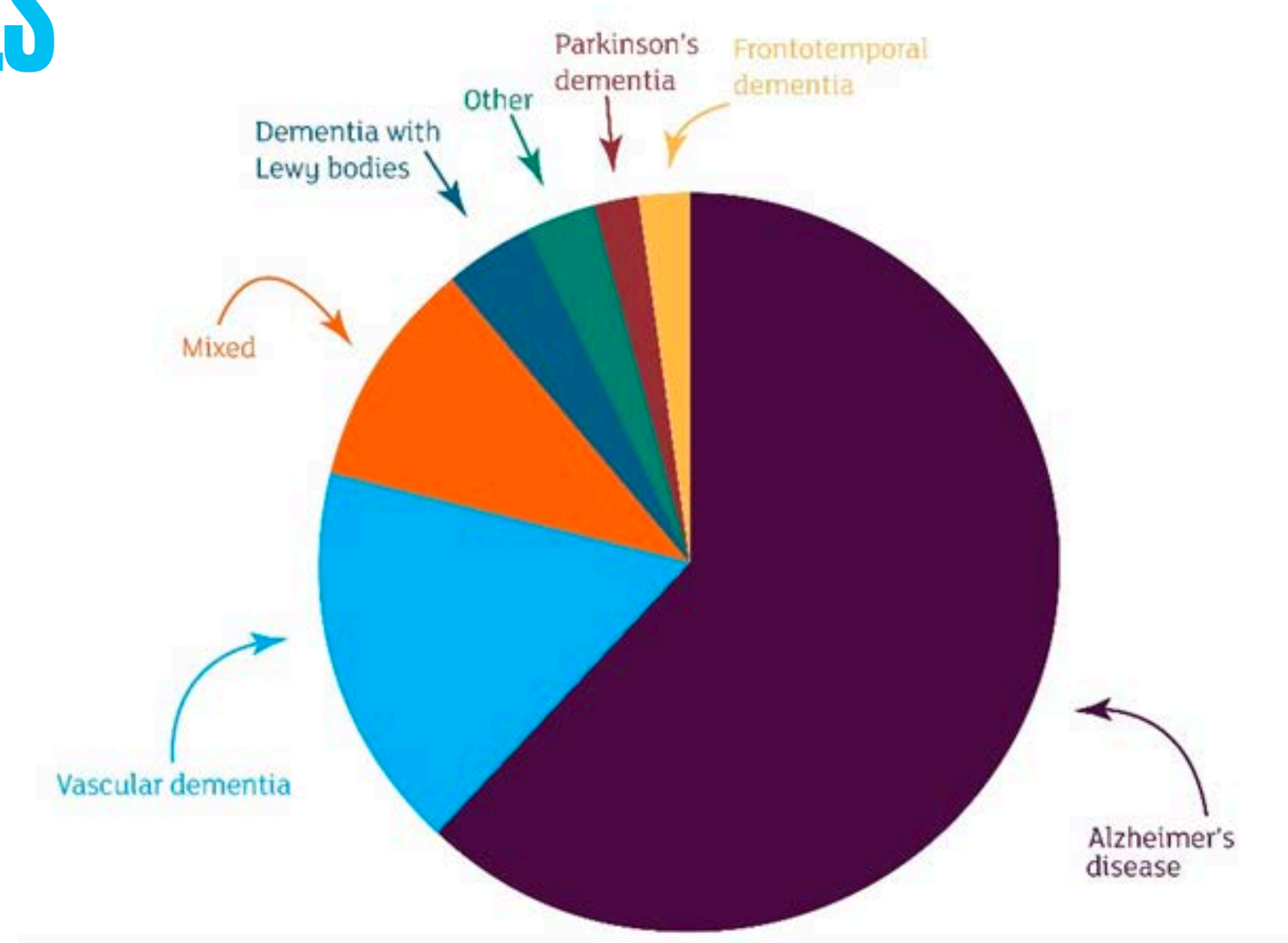
- Define **dementia** and examine the role of **genetics** in the varying dementia subtypes
- Discuss genetic counseling and testing for dementia and other related **neurodegenerative disorders**
- Generally review **clinical trials** for individuals with genetic forms of dementia

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

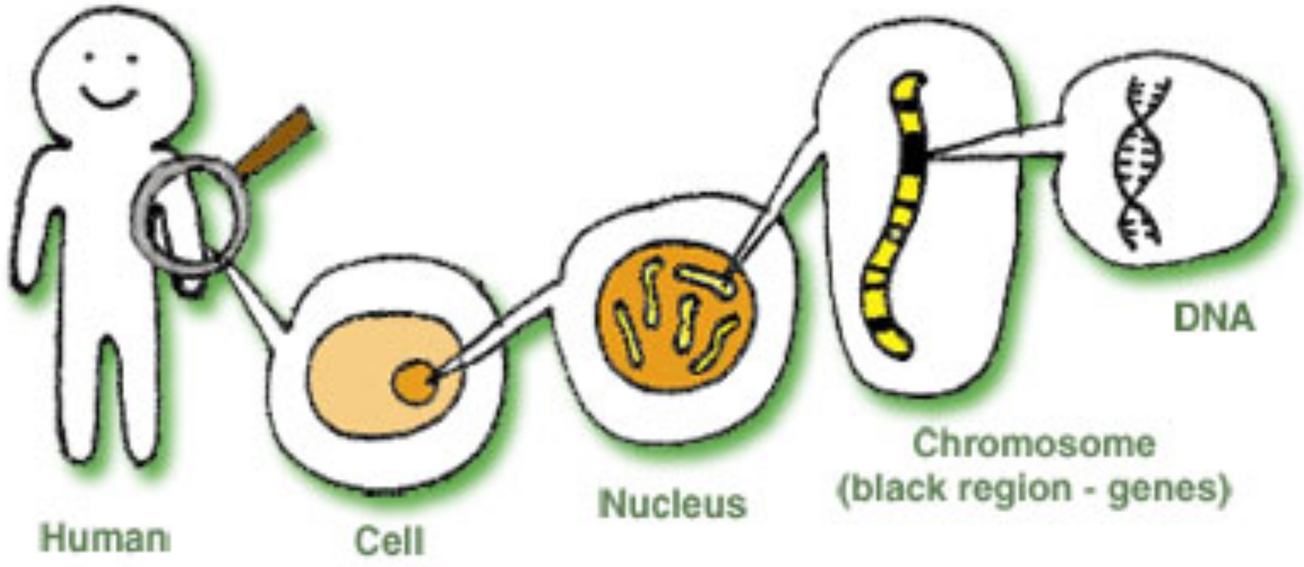
DEMENTIA - SUBTYPES

- **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

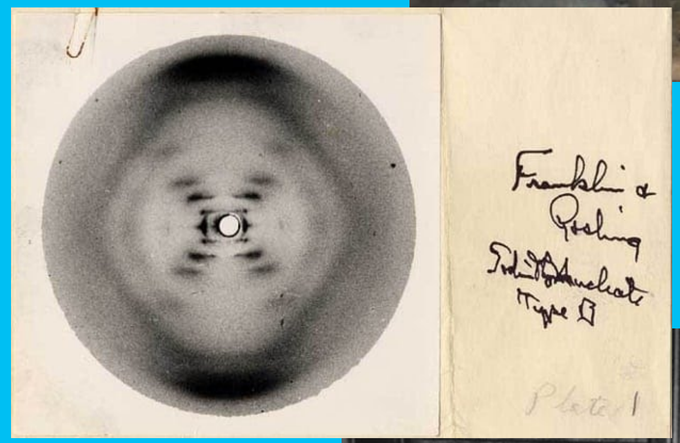
- **Alzheimer's Disease**
  - *APP, PSEN1, PSEN2, PRNP*
- **Vascular Dementia**
  - CADISIL/*NOTCH3*
- **Frontotemporal Dementia***
  - *C9orf72, MAPT, GRN,* others
- **Lewy body**
  - *SNCA, SNCB, GBA, APOE*



- **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



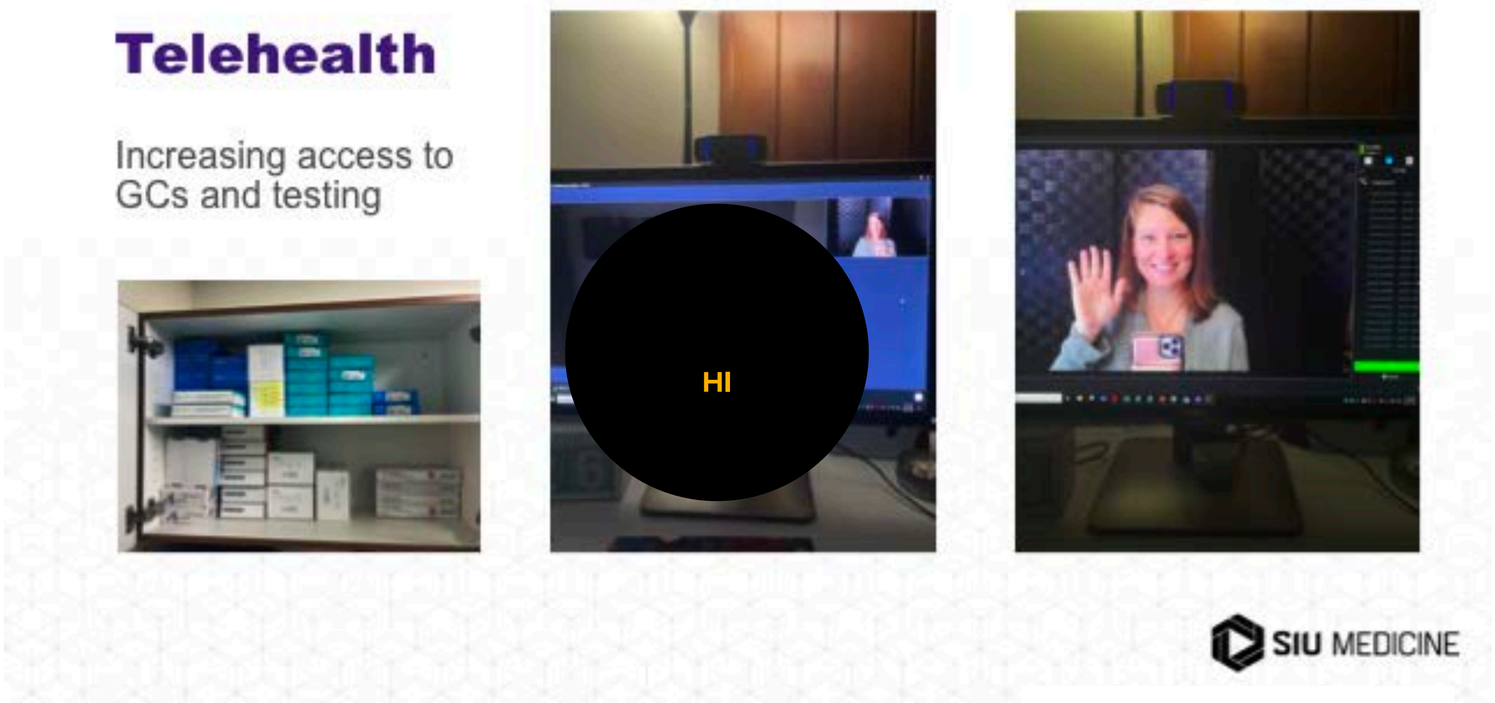
WHO SHOULD PURSUE GENETIC COUNSELING?

- ***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)*

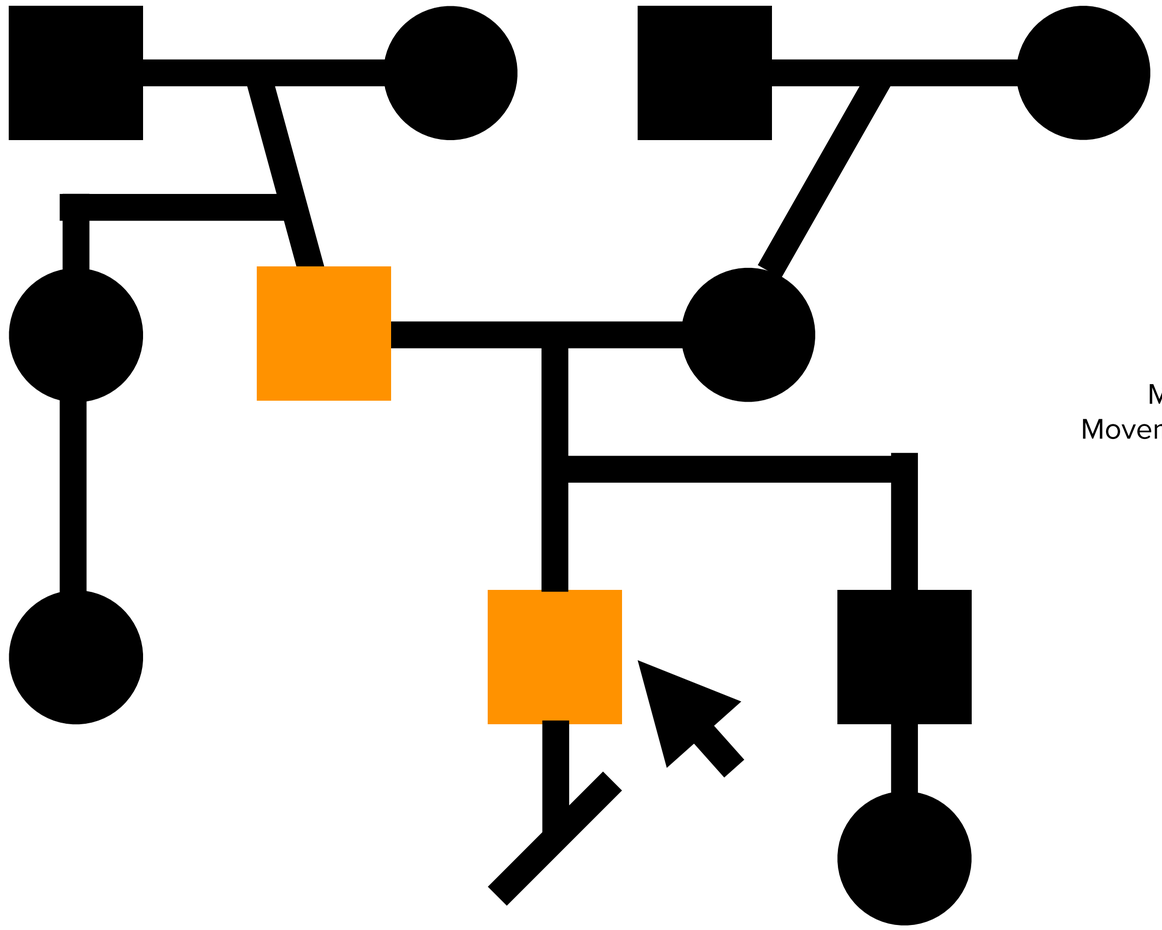
- **Identifying a genetic cause of dementia is very dependent on the subtype of dementia as well as the family history**
  - 40% with FTD
  - 5-10% of those with early onset AD
  - Odds of having a positive genetic result are much higher with a strong family history

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



FAMILY HISTORY ASSESSMENT

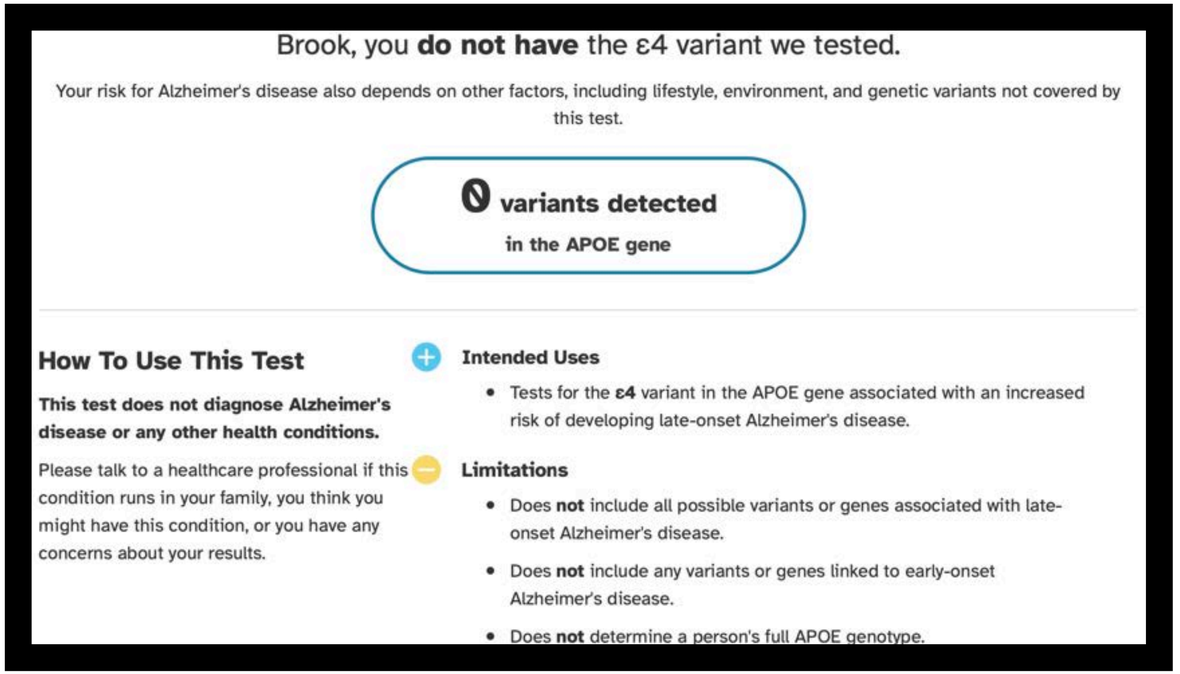


FTD/other dementias
Motor neuron disease (ALS)
Movement disorders (Parkinson’s, HD)
Psychiatric disorders

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**



SPONSORED TESTING PROGRAMS

Amyotrophic Lateral Sclerosis (ALS) Testing Program

Program Overview

In partnership with Ionis Pharmaceuticals, this program provides
erosis (ALS), a
r neuron
ord. No-cost ALS
nosis or family
ered to residents
y criteria.The
vider.

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

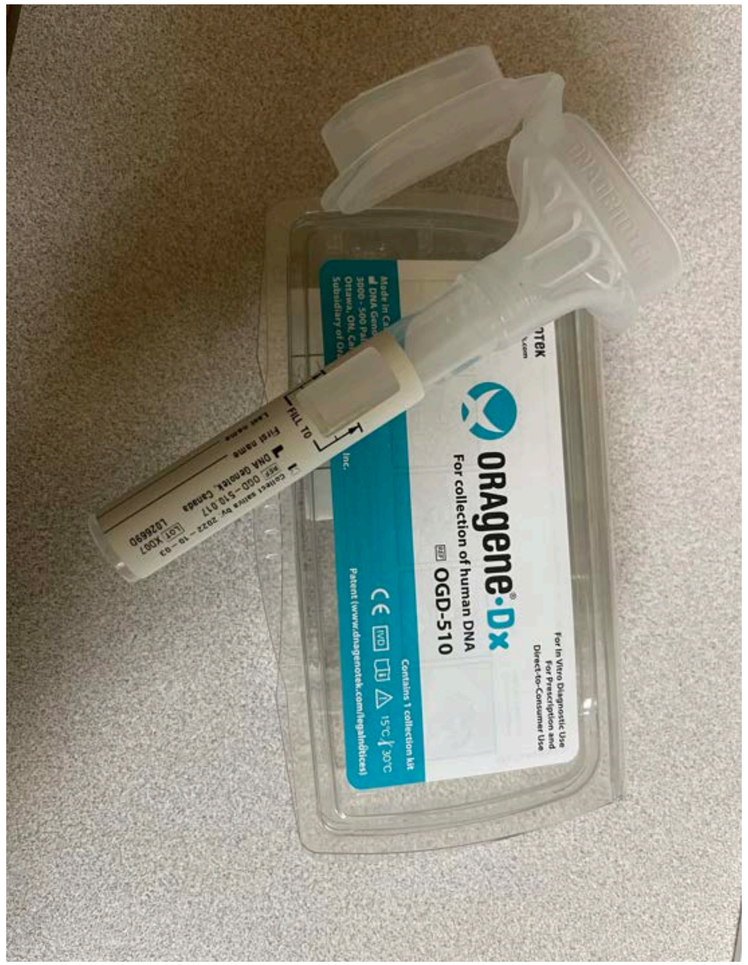
Program Overview

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



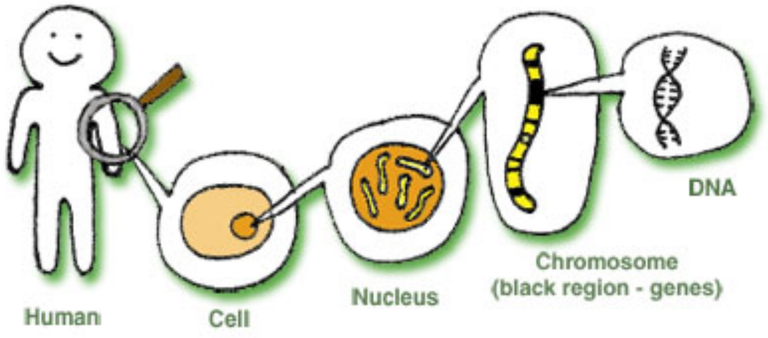
Saliva sample collection

CLINICAL GENETIC TESTING

Place sample in box

Return sample to lab

CLINICAL TESTING - AD



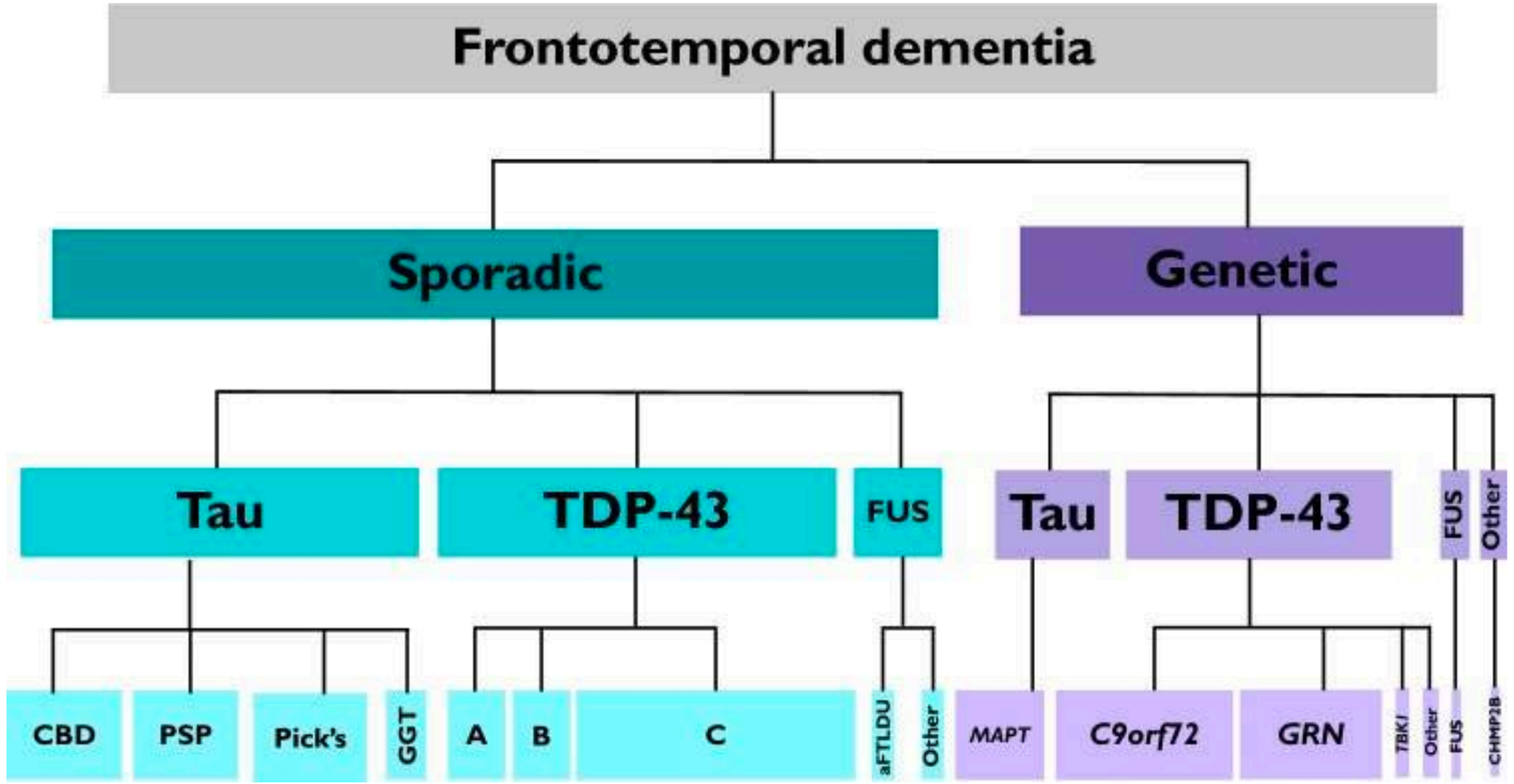
2-3% of AD

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

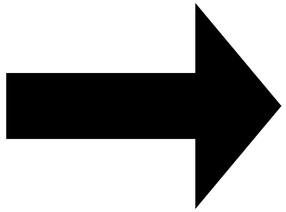


Greaves et al, J Neurol. 2019 Aug;266(8):2075-2086

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

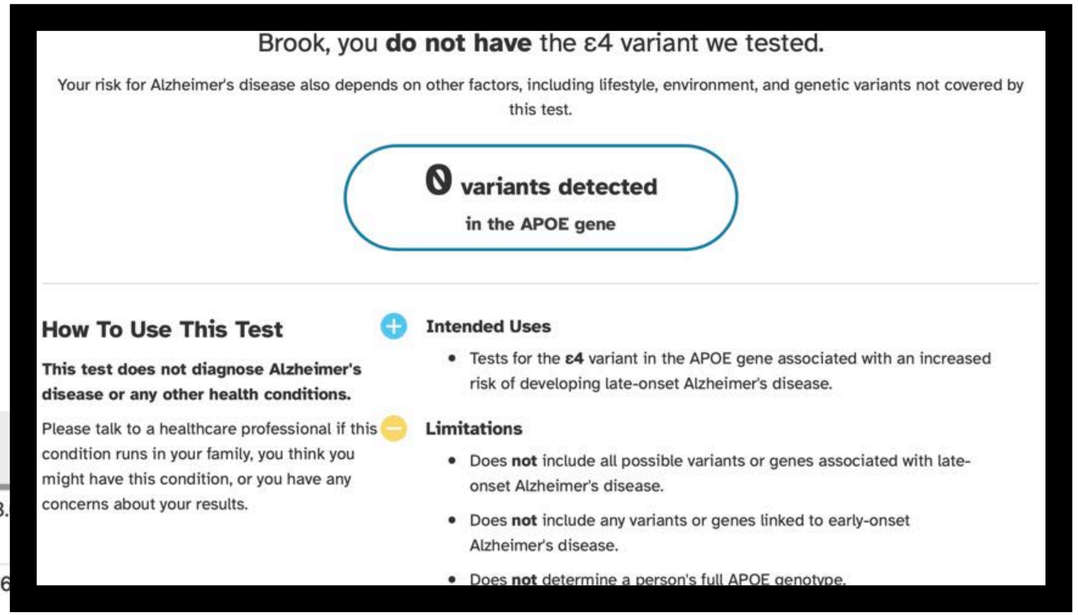
Genes and rare variants identified in sFTD.

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

- *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.
Japanese	NA	0.7 (0.3–1.6)	NA	1.0 (Ref)	3.9 (1.9–8.0)	21.8 (8.6
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)



RESEARCH TESTING

Available through multiple sites across the country

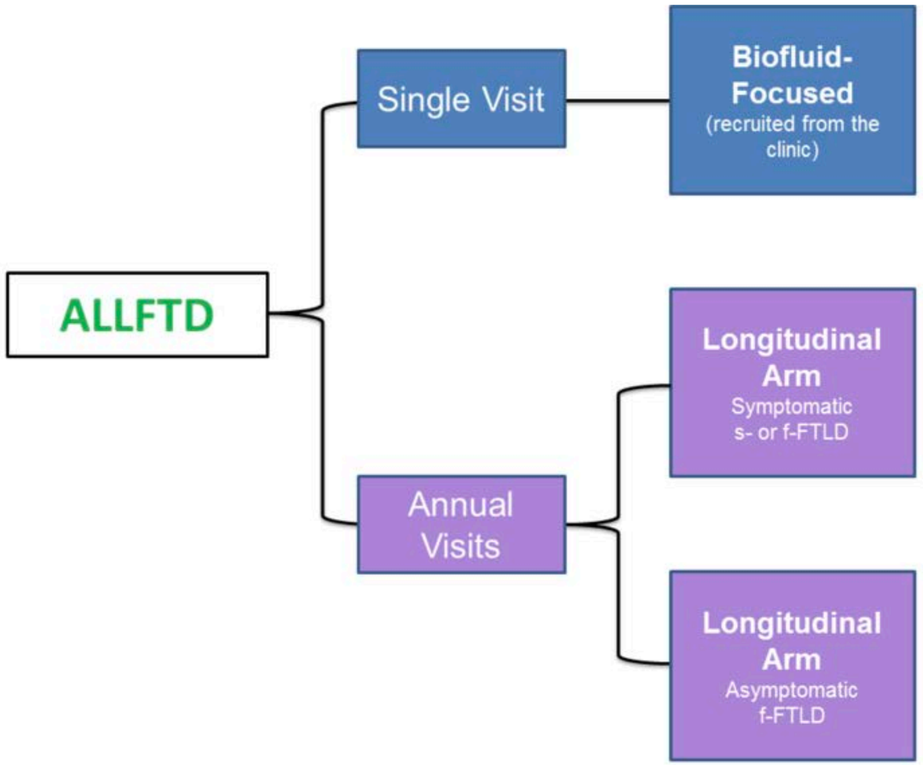
-Family history
-Diagnosis

allftd.org/research

RESEARCH TESTING

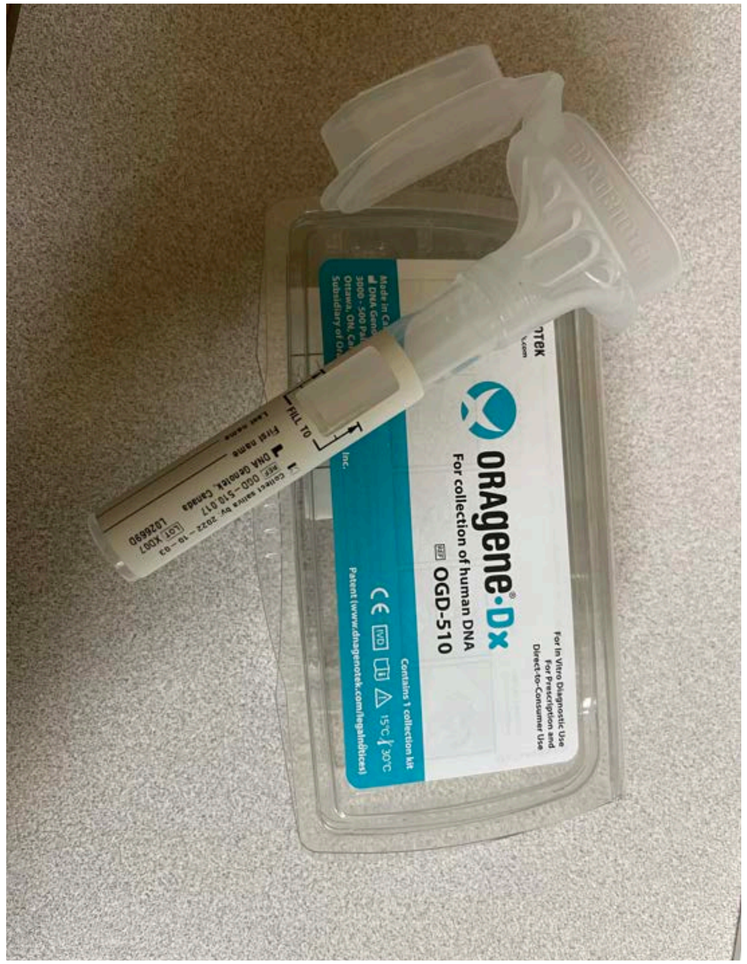
OBSERVATIONAL STUDIES (NATURAL HISTORY OR LONGITUDINAL)

- 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

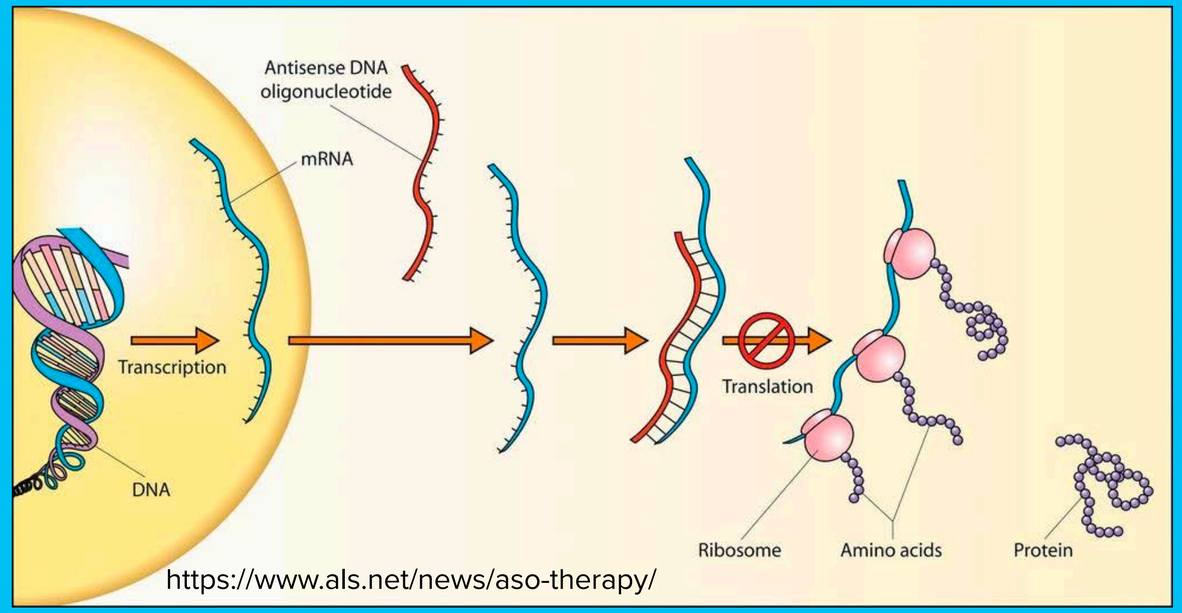
Place sample in box

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*



https://www.als.net/news/aso-therapy/

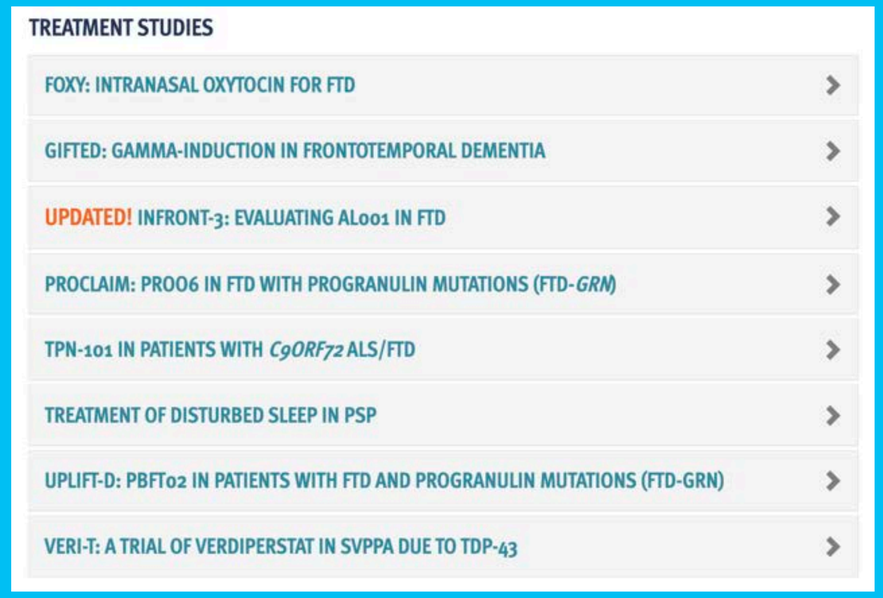
GENE THERAPY

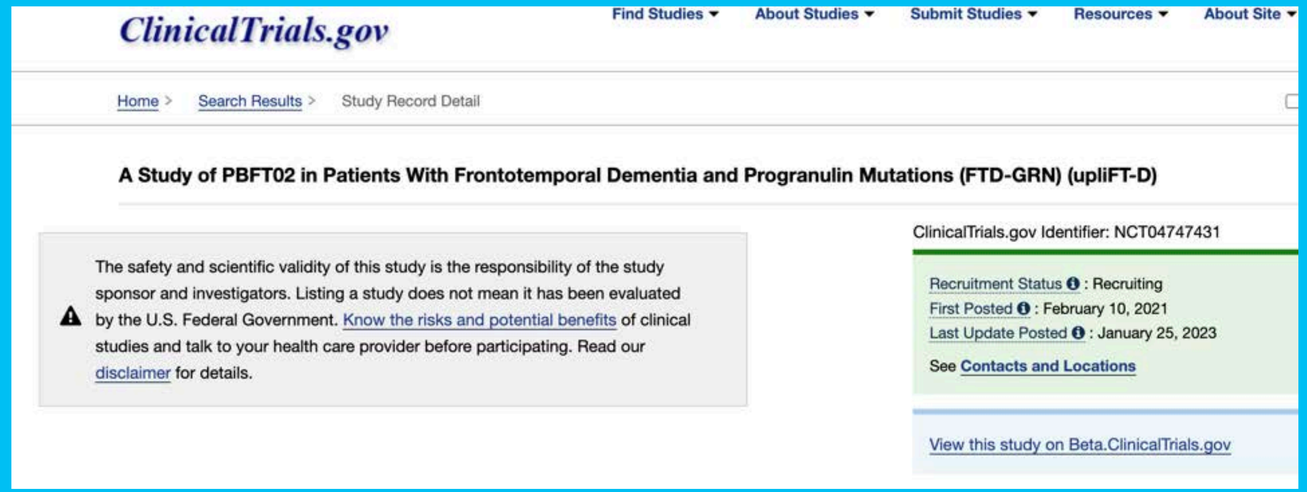
GREAT PROGRESS IN LAST 5 YEARS

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).





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Our amazing team!