A conversation with a genetic counselor: Could the ALS in my family be genetic?

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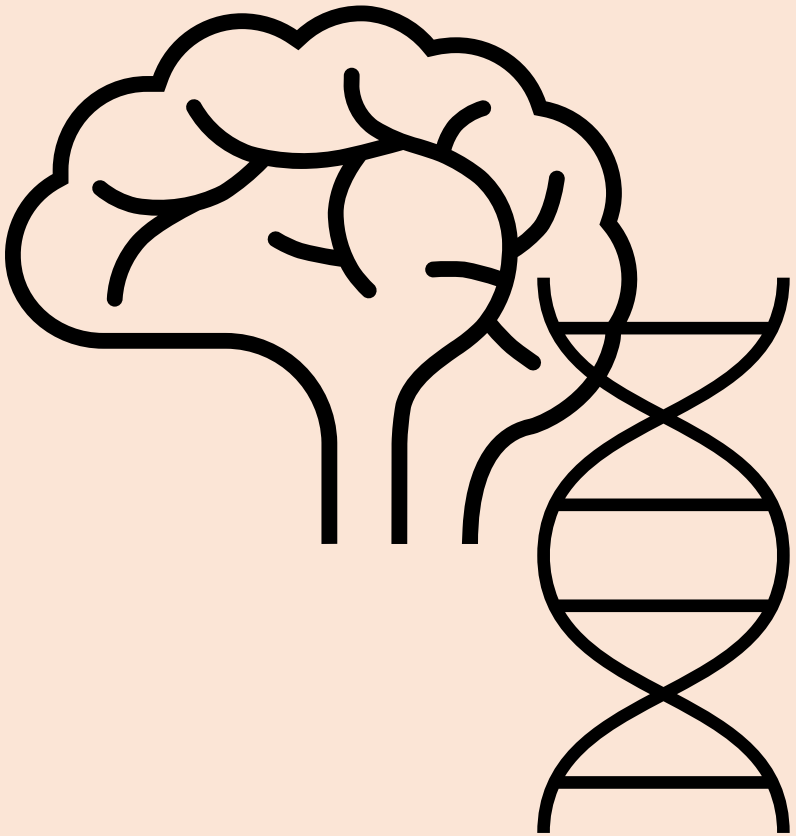


January 31, 2024

Disclosures

Laynie Dratch is an employee of Penn Medicine. She has current or former consulting/advisory relationships with Sano Genetics, Passage Bio, and Biogen.

Outline

- Genetics of ALS
- Diagnostic & predictive genetic counseling and testing
- Logistics & other FAQs
- Resources
- Q&A

Defining some terms…

ALS = Amyotrophic Lateral Sclerosis (Lou Gehrig's disease)

FTD = Frontotemporal dementia or frontotemporal degeneration

AD = Alzheimer disease

PD = Parkinson’s disease

The big question: Is ALS genetic?

Most often not due to a single genetic cause

Multifactorial

Depends on certain characteristics (mainly family history, but to some extent also age of onset, rate of progression)

Importance of an accurate diagnosis

Genes are the Instruction Manual of the Body

THE HIP
AND THE
LEG

→

THE HIP
AND THE
PEG

ALS Genetics

- Approximately 10% of persons with ALS have a family history of ALS or related conditions
  - We can identify a genetic cause in about ~75% of these individuals
- The vast majority of people with ALS do NOT have a known family history of ALS or related conditions
  - We can still identify a genetic cause in >10% of these individuals

So what do we mean by "related conditions"

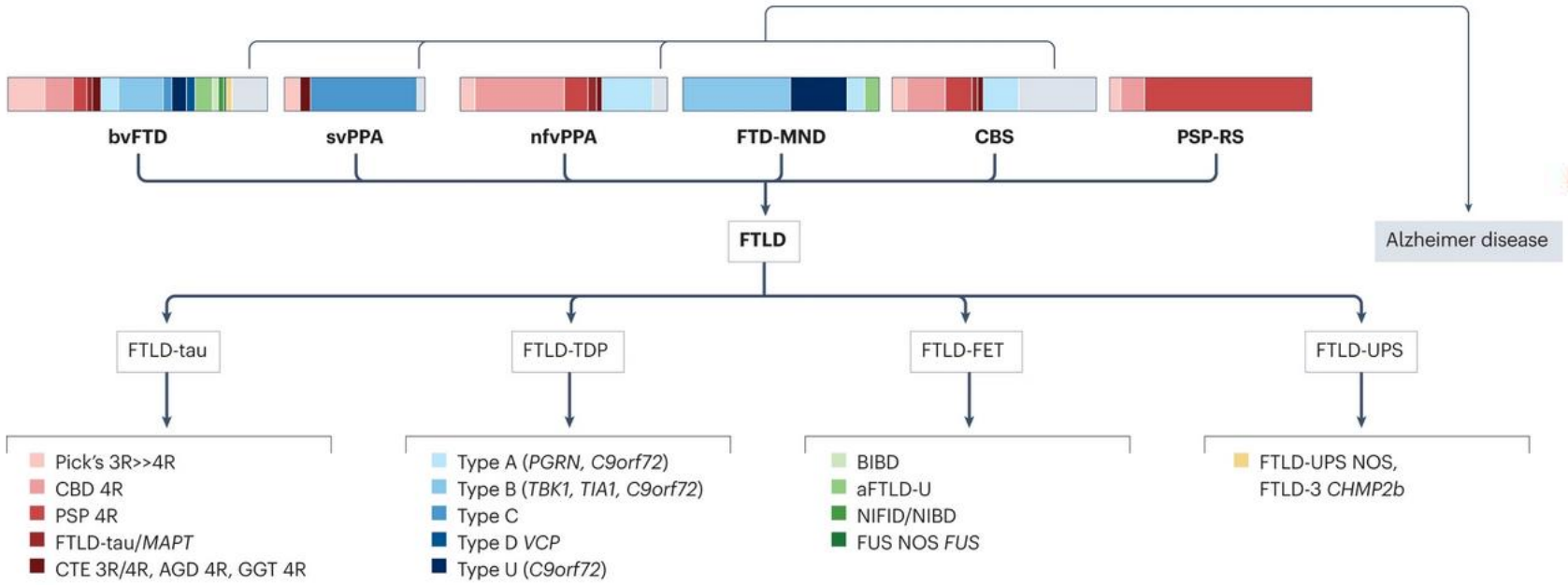
Shepheard et al. (2021)

Defining the ALS-FTD Spectrum

Grossman et al. (2023)

Fig. 1: FTD syndromes and associated pathology.

From: Frontotemporal lobar degeneration



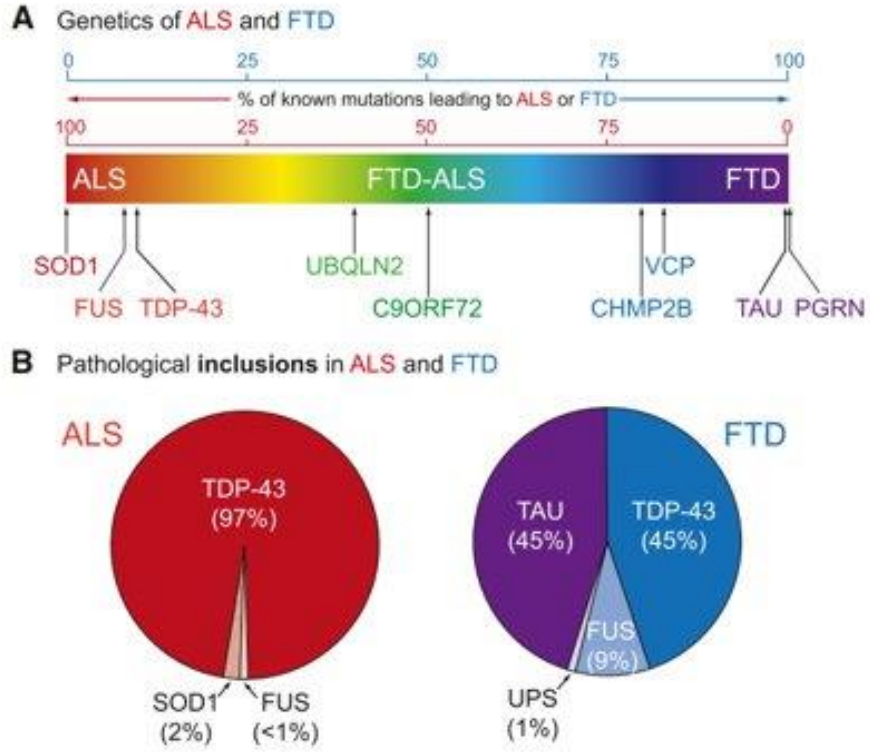


Figure 1. Clinical, Genetic, and Pathological Overlap of ALS and FTD

Ling et al. (2013)

Frontotemporal dementia (FTD)

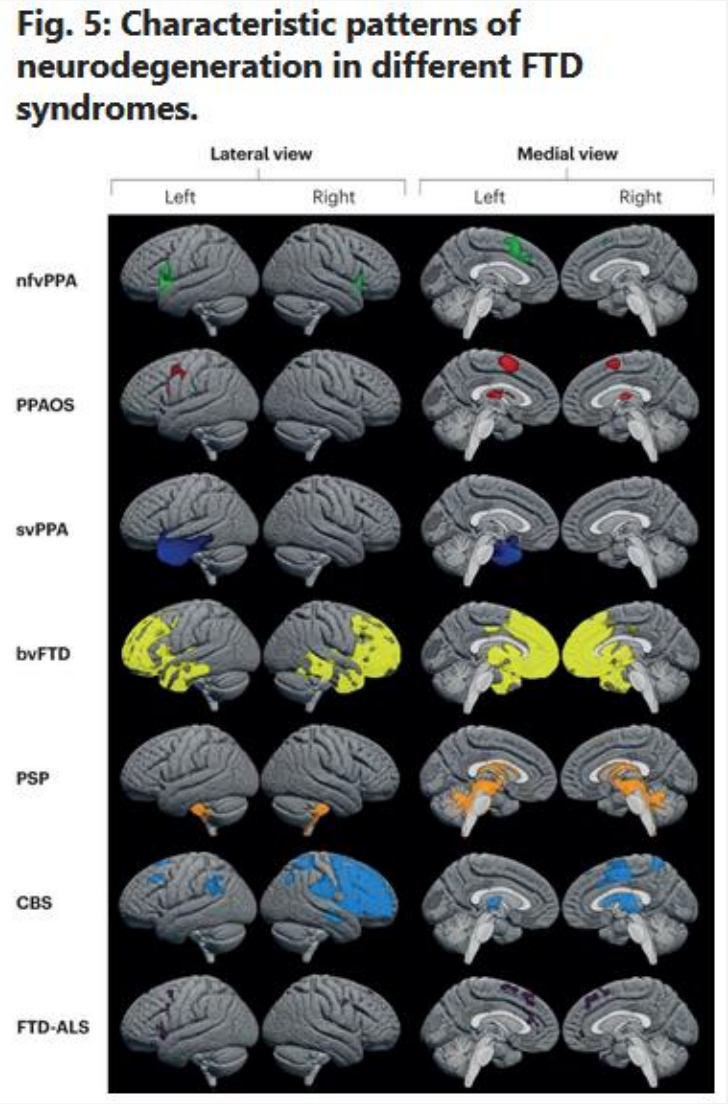
- Age-associated neurodegenerative disease that is a common cause of "young-onset dementia."
- Average disease duration ~7 years

<u>Spectrum of non-amnestic dementia syndromes</u>

- Social disorder
- Executive impairments > Memory Loss
- Language disorder (Aphasia)

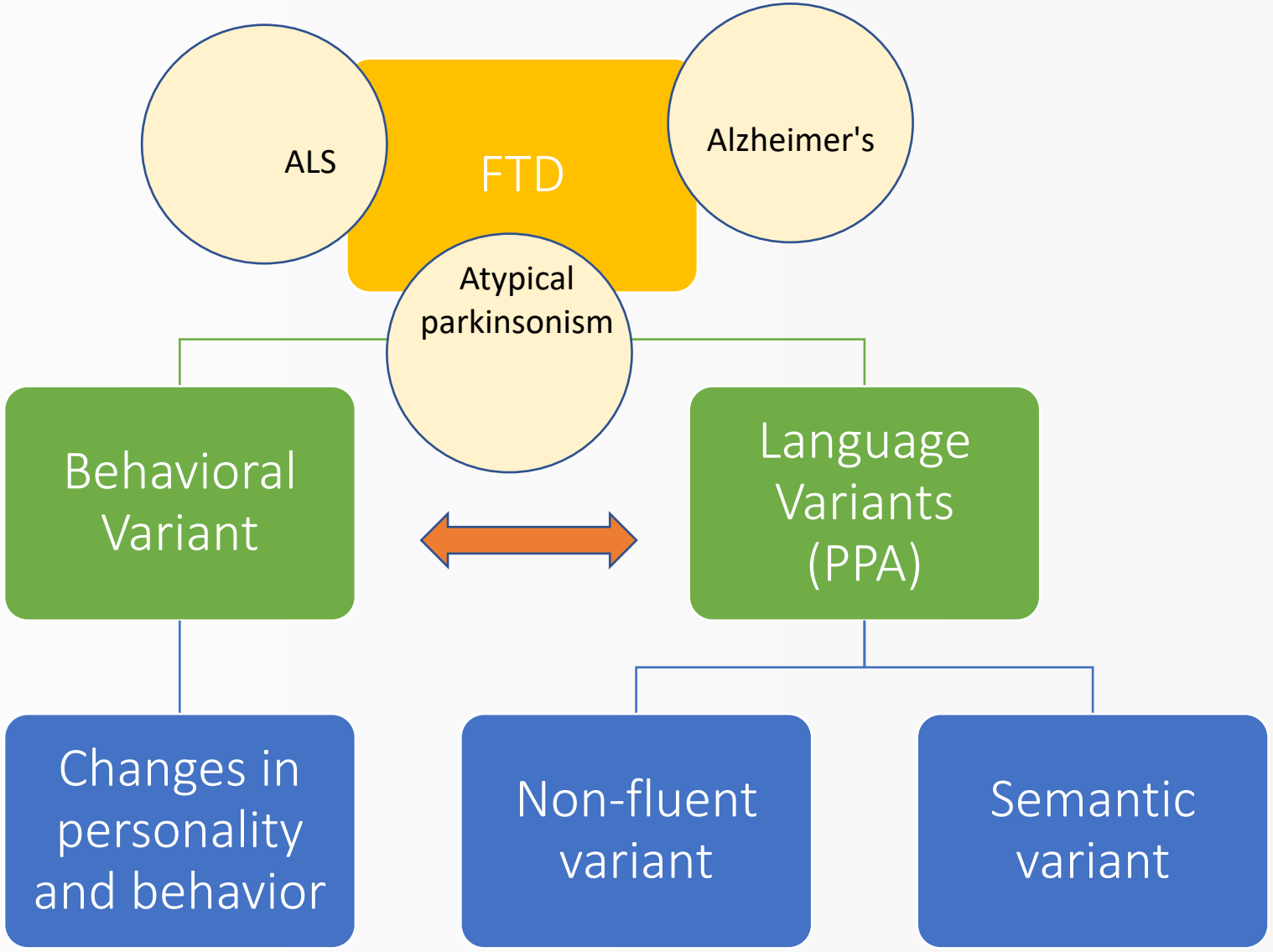
<u>Often can overlap with motor symptoms</u>

- Parkinsonism (extra-pyramidal)
  - Tremor, balance difficulty, slowness, rigidity
- Motor Neuron Disease (pyramidal)
  - Weakness, muscle atrophy, spasticity



Grossman et al. (2023)

Frontotemporal Degeneration (FTD)



Why does family history matter?

- Family history of neurodegenerative disease increases chances of genetic cause, but imperfect tool
- High, but not always completely penetrant genetic variants

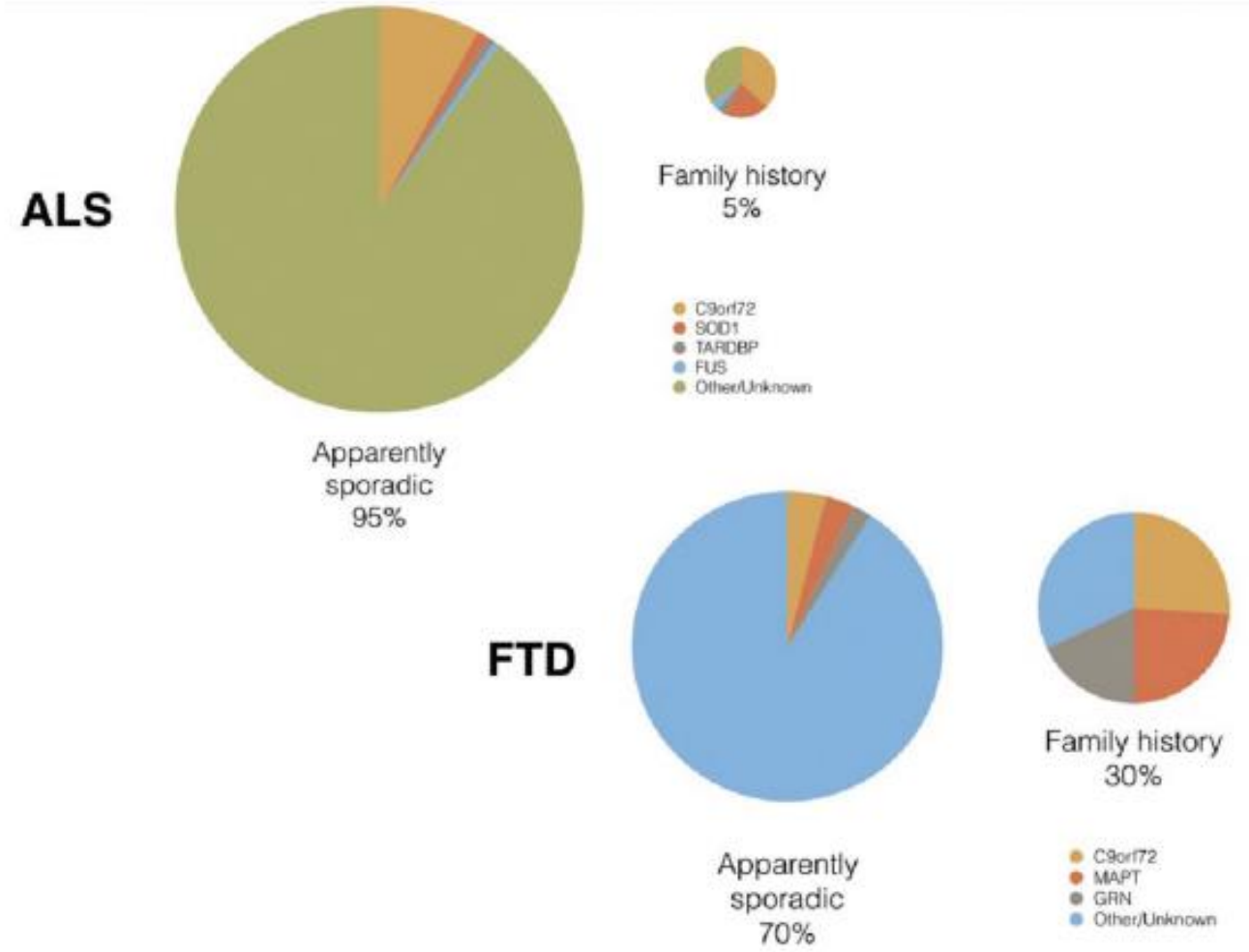
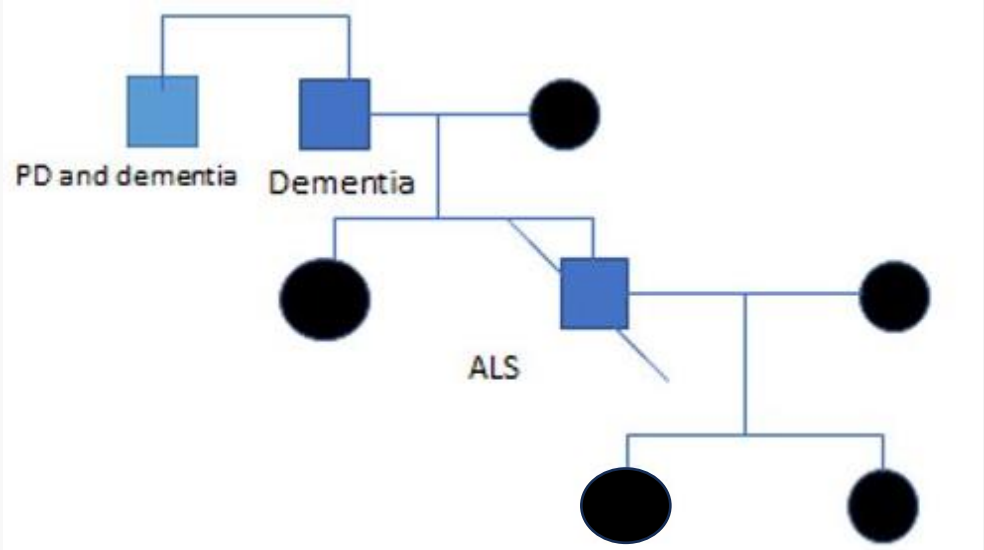


Figure 1 Upper panel: Comparison of proportions of monogenic causes of ALS in those reporting a family history of ALS versus apparently sporadic cases. Lower panel: Comparison of proportions of monogenic causes of FTD in those reporting a family history of dementia versus apparently sporadic cases. ALS, amyotrophic lateral sclerosis; FTD, frontotemporal dementia.

Turner et al., 2017

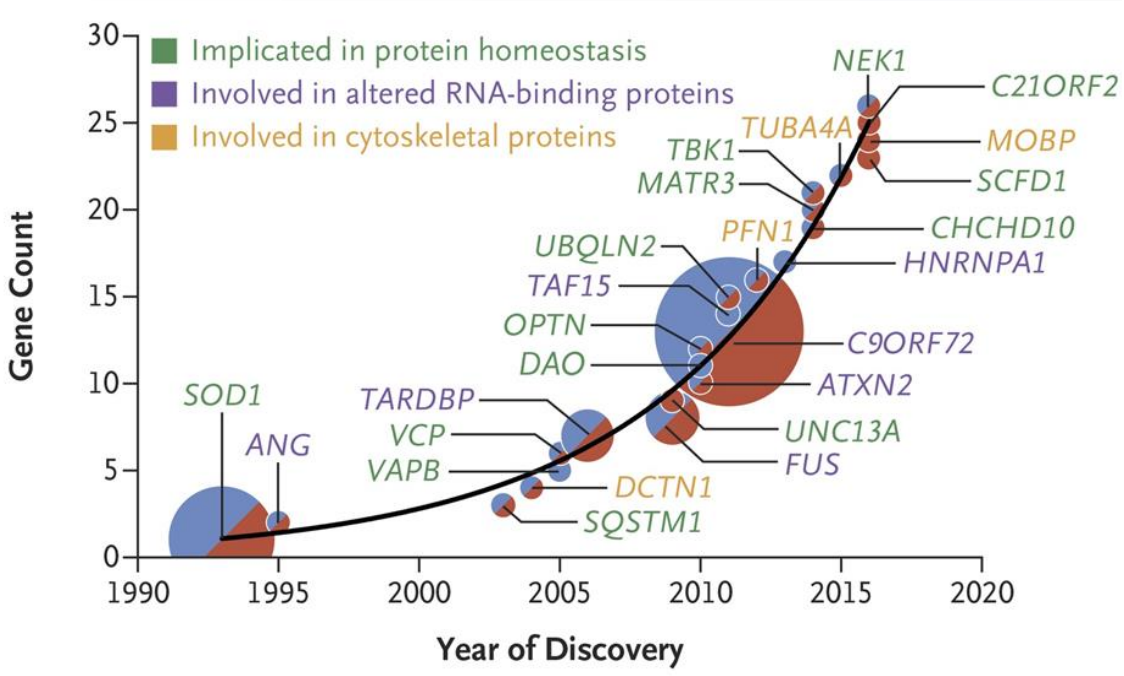
The Pitfalls of Family History

- Challenges in diagnosis
  - Misdiagnosis and missed diagnoses
- Limited family health information sharing or available
  - Strained relationships / lack of communication
  - Stigma
  - Adoption or displacement
- Lack of data within the family
  - Small family size
  - Young ages at death due to other causes
- Variable Presentations
  - Pattern finding

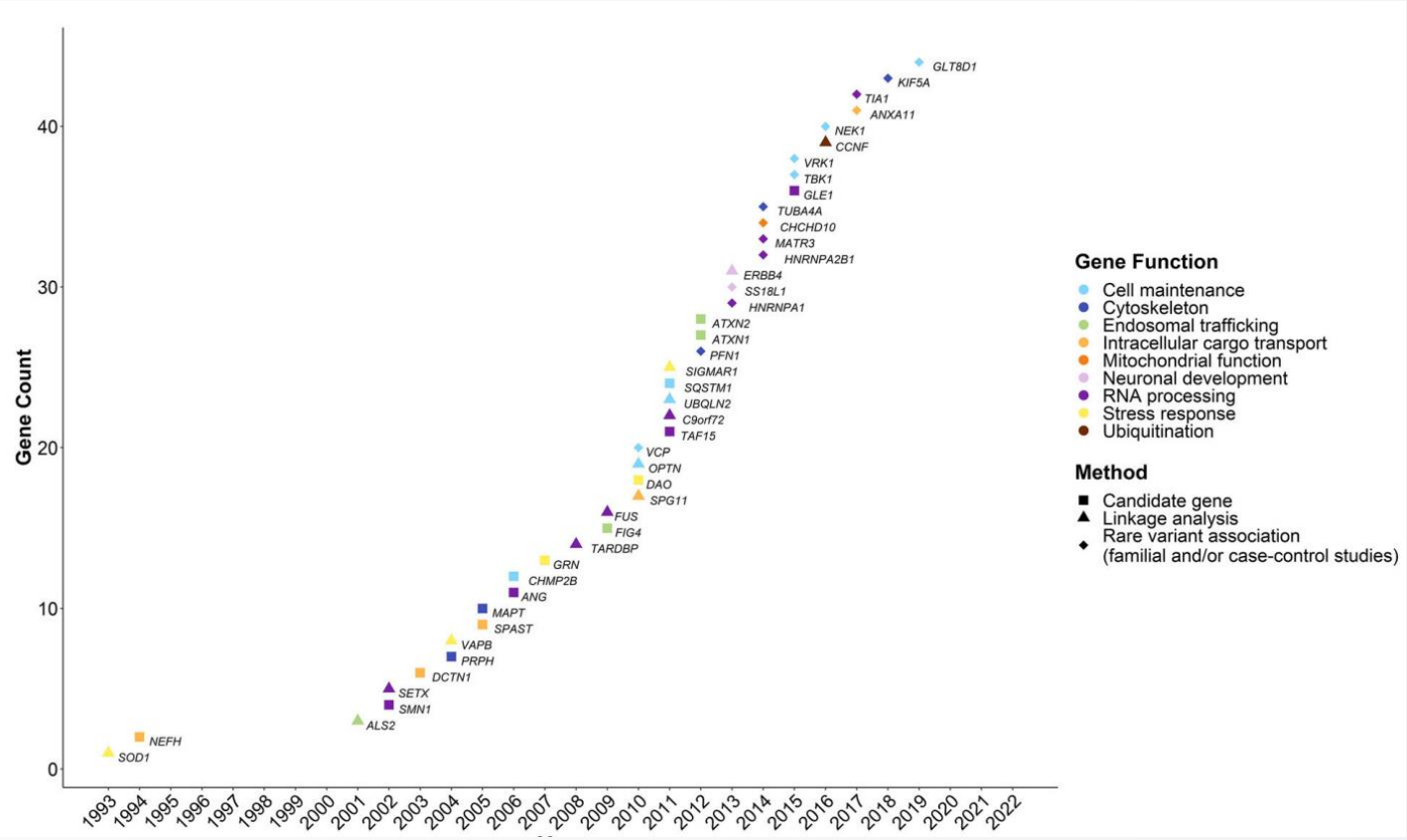


Chambers et al. (2023)

Over 30 Genes Implicated in ALS Spectrum Disorders



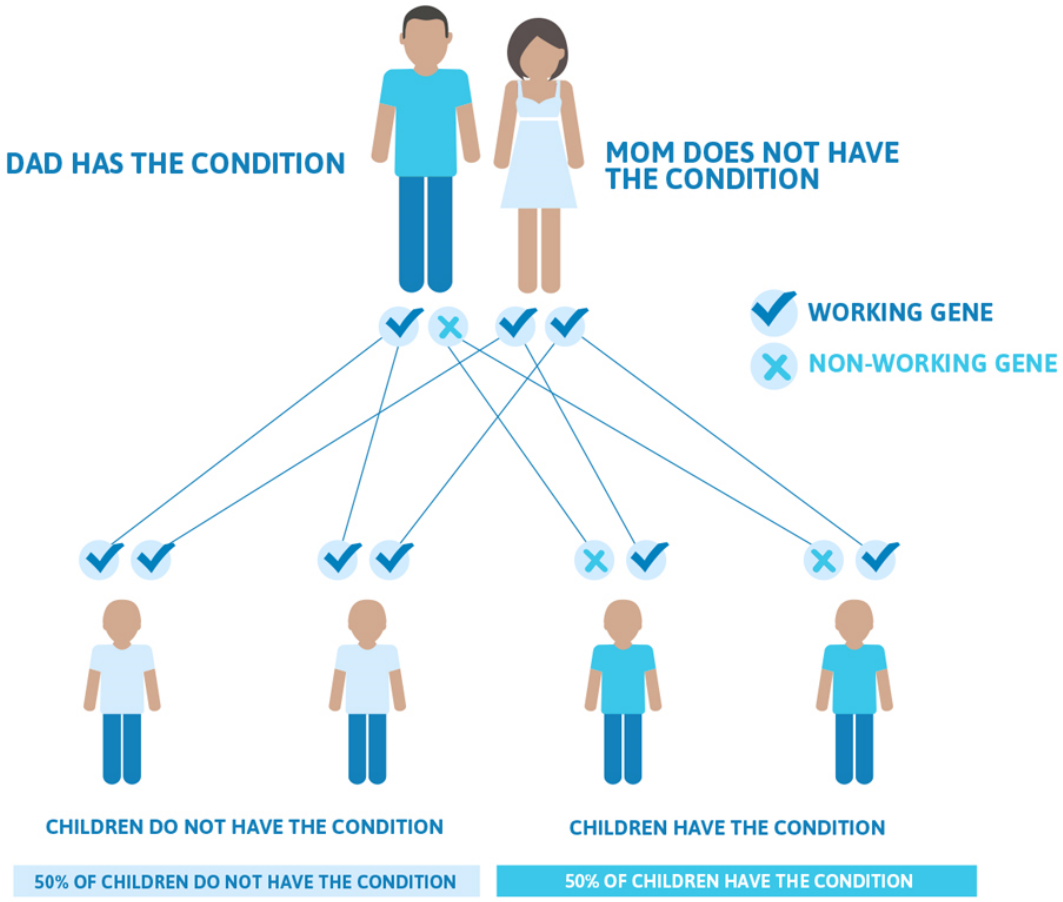
Brown & Al-Chalabi (2017)



Dilliott et al. (2023)

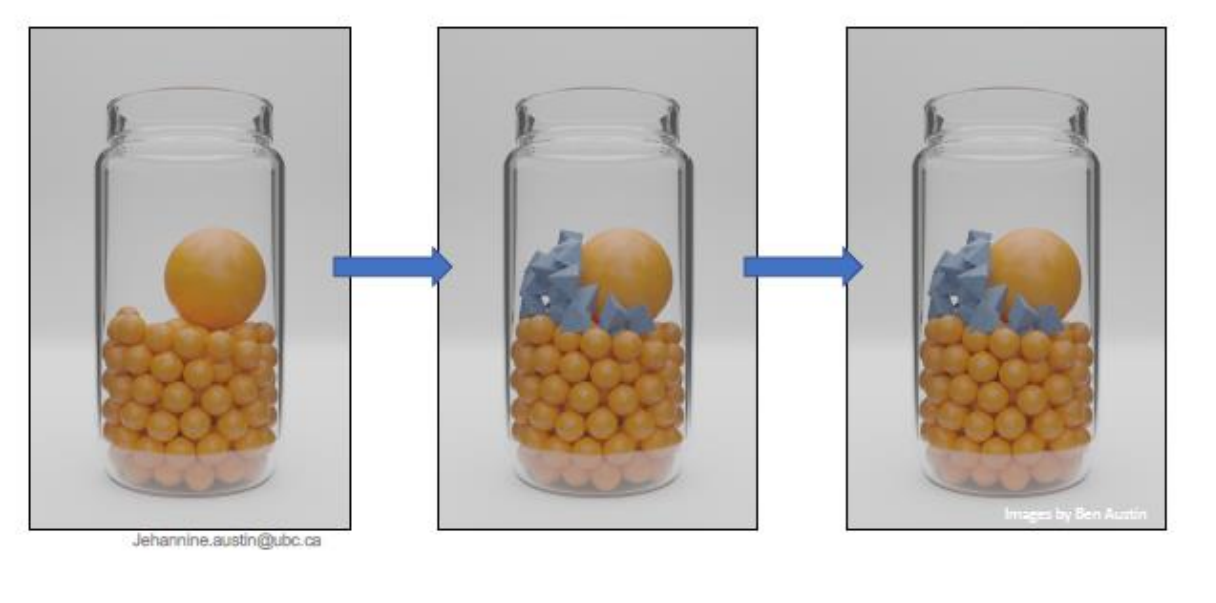
Inheritance Patterns

Autosomal Dominant Inheritance Pattern



https://edsociety.co.uk/what-is-ed/genetics/inheritance-patterns/

Multifactorial Inheritance



Images from the Translational Psychiatric Genetics Group

What is sporadic versus familial versus genetic ALS?

Can specific symptoms help differentiate?	No – they have similar/overlapping symptoms
What about autopsy findings?	Some rare autopsy findings indicate familial (genetic) BUT many autopsy findings can be seen in both Results may not be available, or from many years ago
Is it just about family history?	Family history can help guide us, but can be unreliable

How can I find out if the ALS in my family is genetic?

- Let’s discuss genetic counseling and testing!

What is Genetic Counseling?

THE PROCESS OF HELPING PEOPLE UNDERSTAND AND ADAPT TO THE MEDICAL, PSYCHOLOGICAL AND FAMILIAL IMPLICATIONS OF GENETIC CONTRIBUTIONS TO DISEASE.

THIS PROCESS INTEGRATES THE FOLLOWING:

INTERPRETATION OF FAMILY AND MEDICAL HISTORIES TO ASSESS THE CHANCE OF DISEASE OCCURRENCE OR RECURRENCE.

EDUCATION ABOUT INHERITANCE, TESTING, MANAGEMENT, PREVENTION, RESOURCES AND RESEARCH.

COUNSELING TO PROMOTE INFORMED CHOICES AND ADAPTATION TO THE RISK OR CONDITION.

***Genetic Counseling is not the same as genetic testing!**

Resta et al. (2006)

Two Types of Genetic Testing

DIAGNOSTIC

PREDICTIVE

Determining whether a genetic cause can be identified as the reason that a person developed a condition

The Importance of Offering Genetic Counseling and Testing in ALS

The importance of offering early genetic testing in everyone with amyotrophic lateral sclerosis

Kristiana Salmon, Matthew C. Kiernan, Seung H. Kim, Peter M. Andersen, Adriano Chio, Leonard H. van den Berg, Philip Van Damme, Ammar Al-Chalabi, Patricia Lillo, Jinsy A. Andrews ... Show more

Author Notes

Brain, Volume 145, Issue 4, April 2022, Pages 1207–1210,
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Evidence-based consensus guidelines for ALS genetic testing and counseling

Jennifer Roggenbuck ✉, Breda H. F. Eubank, Joshua Wright, Matthew B. Harms, Stephen J. Kolb, the ALS Genetic Testing and Counseling Guidelines Expert Panel

First published: 10 September 2023 | https://doi.org/10.1002/acn3.51895

INNOVATIONS IN NEUROLOGIC PRACTICE

Incorporating Genetic Testing Into the Care of Patients With Amyotrophic Lateral Sclerosis/Frontotemporal Degeneration Spectrum Disorders

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Neurology: Clinical Practice 2023;13:e200201. doi:10.1212/CPJ.0000000000200201

ALS Genetic Counseling and Testing Guidelines

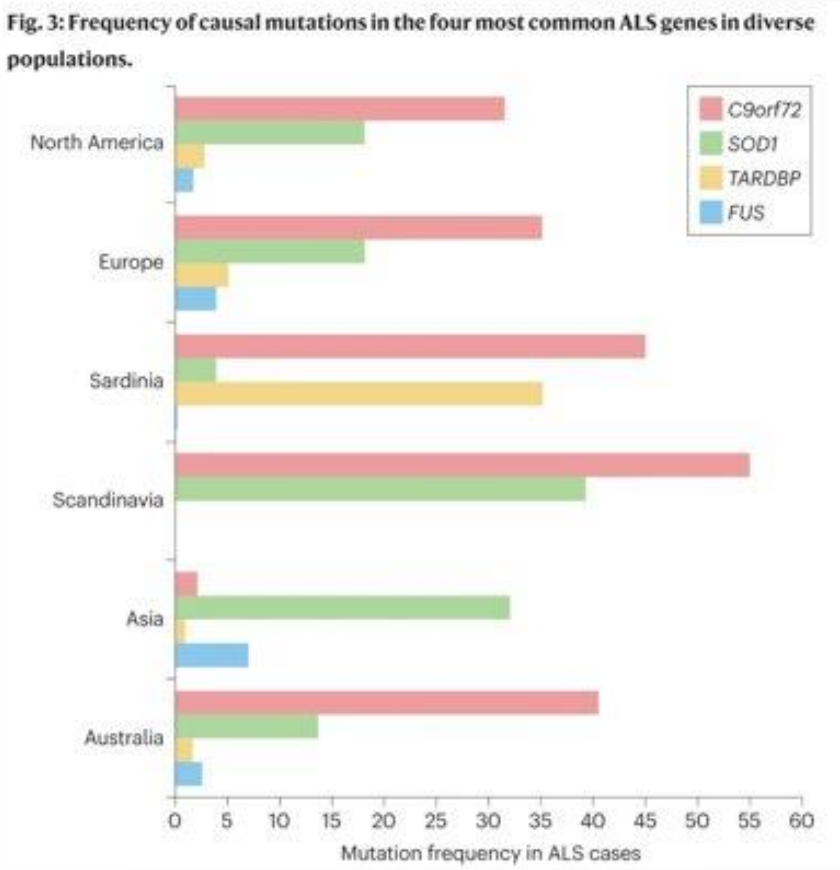
All persons with ALS should be offered genetic testing with an ALS gene panel that includes at minimum:

- *C9ORF72*
- *SOD1*
- *FUS*
- *TARDBP*
- Any gene for which the FDA approves a targeted therapy
- Genes rated as "strong" or "definitively" associated with ALS by ClinGen[1]

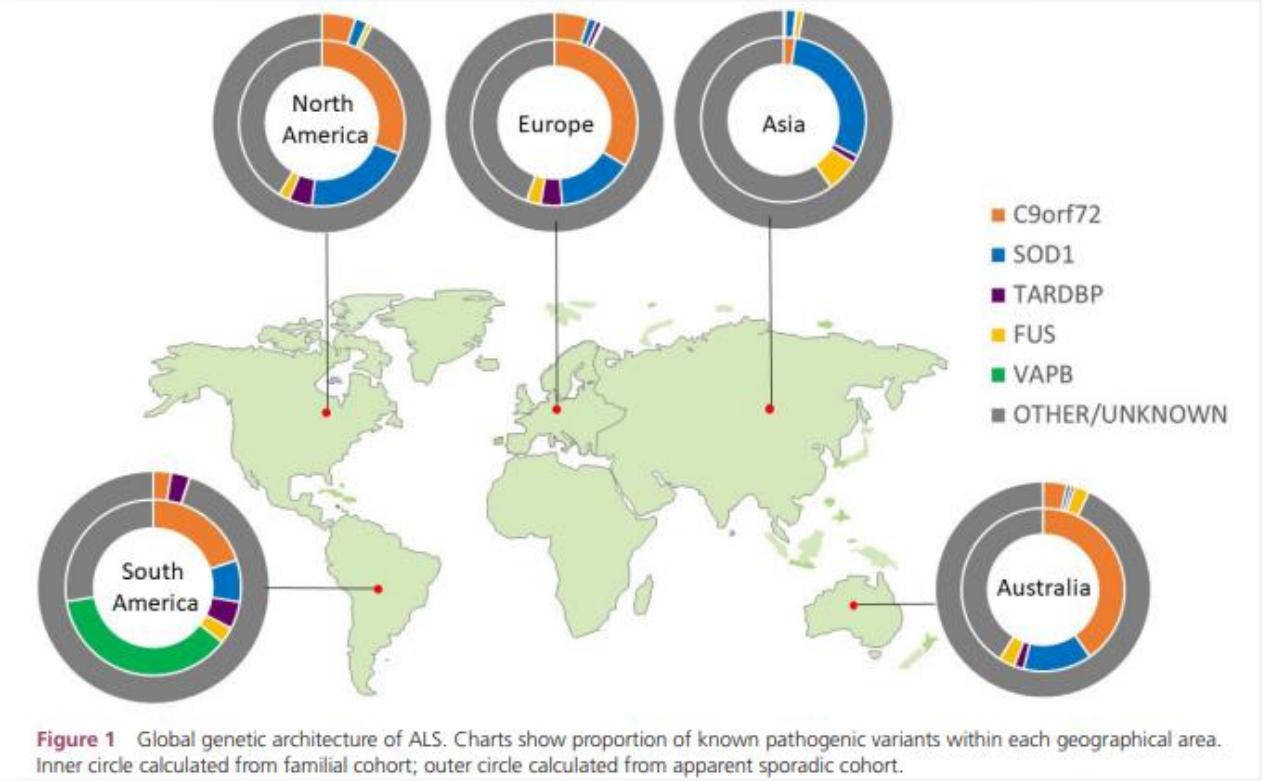
Pre-test genetic counseling should include:	
• Collecting a three-generation pedigree that ascertains:	❑ MND of all flavors ❑ FTD ❑ Other dementias ❑ Movement disorders ❑ Psychiatric disease
• Discussion of:	❑ Genetic heterogeneity ❑ Inheritance patterns ❑ Penetrance
• Personalized risk assessments for:	❑ Likelihood of a genetic etiology ❑ Likelihood of positive results on testing of currently known genes ❑ Recurrence in relatives
• Preparing individuals for possible personal, psychological, and economic impacts of testing:	❑ For themselves ❑ For family members
• Covering the range of possible testing outcomes: positive, negative or uncertain	
• Covering testing methodology limitations	
Post-test genetic counseling should include:	
• For those with Pathogenic (P) or Likely Pathogenic (LP) test outcomes:	❑ Result may or may not allow prediction of disease course ❑ Genetic risks and implications for specific family members, including the availability of pre-symptomatic testing ❑ Availability of relevant observational studies, FDA approved therapies and clinical trials
• For those with a negative outcome, result does not exclude a genetic form of ALS	
• For those with uncertain result, variant(s) may not be contributing to ALS	
• Discussion that periodic reevaluation of results may be appropriate, and the interpretation of results could change over time	

Roggenbuck et al. (2023)

Geographic Diversity in ALS Genetics

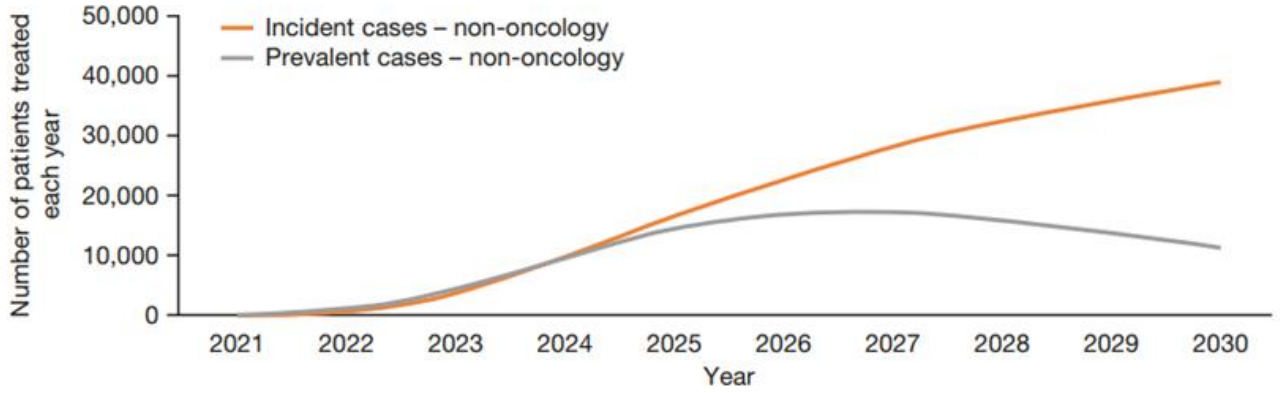


Akçimen et al. (2023)



Dharmadasa et al. (2022)

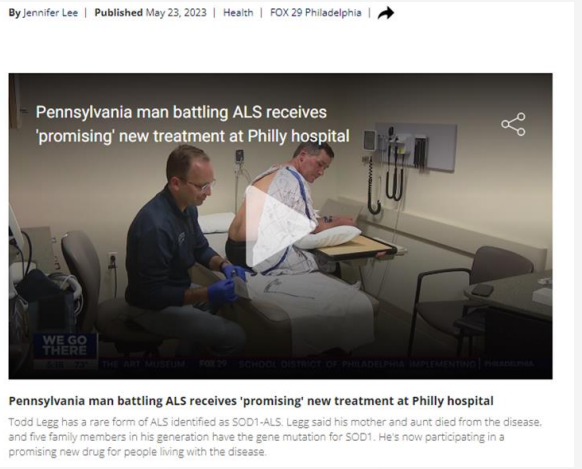
Genomic Medicine is HERE!



Incident cases	251	609	3,995	9,982	16,679		39,226
Prevalent cases	140	917	4,408	9,731	14,966		11,592
Total addressable cases	391	1,526	8,403	19,713	31,675		50,818

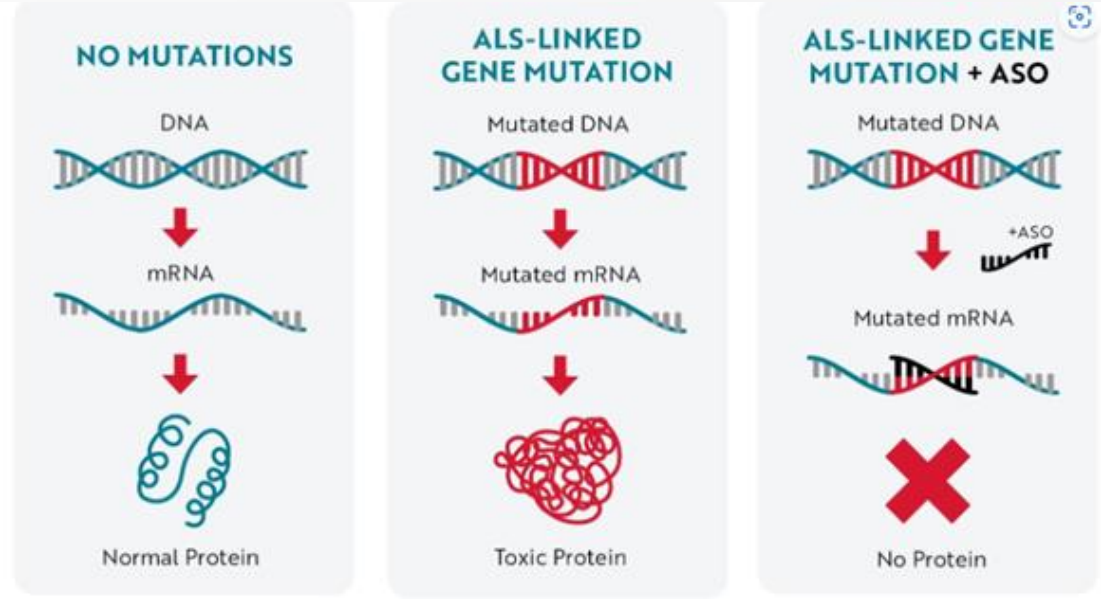
Figure 1 Estimated number of patients in the United States treated each year with durable nononcology gene and cell therapies. This figure assumes that the gene therapy pipeline is not replenished over time. (Adapted from Young et al[7]).

Vockley et al. (2023)



https://www.fox29.com/news/pennsylvania-man-battling-als-receives-promising-new-treatment-at-philly-hospital

April 25, 2023 FDA approved an antisense oligonucleotide therapy (tofersen) via the accelerated approval pathway for persons with *SOD1*-ALS in the USA



https://www.als.org/navigating-als/living-with-als/fda-approved-drugs/tofersen

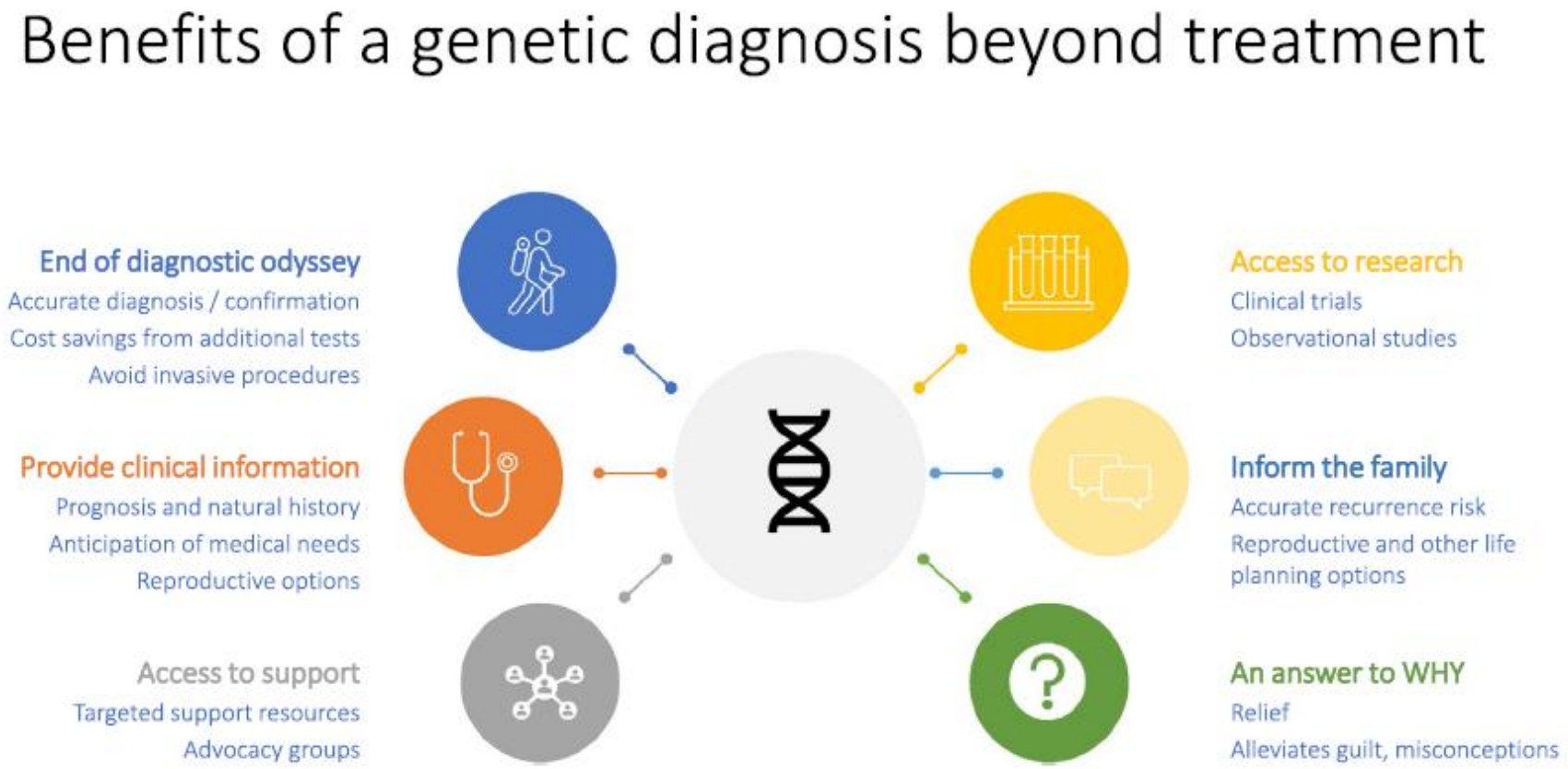


Fig. 1 Benefits of a genetic diagnosis beyond treatment. For many patients and families, a genetic diagnosis has multiple important benefits. A genetic diagnosis can end the diagnostic odyssey, confirm a clinical diagnosis, clarify prognosis, impact family planning, and identify at-risk relatives. Connections with support networks such as family foundations are important sources of advocacy and research

Dratch et al. (2023)

Nuances of Genetic Testing in ALS

Panel of genes including or in addition to *C9orf72* and *ATXN2* Repeat Expansion Analysis	• Start with genes that are known to be able to cause ALS and related conditions • Unique testing methodology for repeat expansions

Exome or Genome Sequencing	• Consider reflex to exome or genome
	  • Broader testing to identify rarer genetic causes
	  • Continued access to data to reevaluate as new genes are found

Consideration of DNA Banking	• The secure storage of a person's DNA to ensure future access for testing if desired [if available]

Types of Results from Genetic Testing

Positive

- Cause of diagnosis identified
- May allow for anticipation of other symptoms / prognostic info
- May allow for clinical trial enrollment and/or access to therapies
- Gives information about risk to family members

Negative

- Cause of diagnosis not identified
- No changes to management, can revisit over time
- More nuances for family member testing/implications

Uncertain

- Cause of diagnosis not clearly identified but a variant was found
- No changes to management, can revisit over time
- Would not do predictive testing for family based on this
- May be steps taken to try to clarify

A genetic cause of ALS was found for me or my loved one…

Should I share this information with family members?

- Being proactive when possible
- Penetrance considerations
- Providing information does not mean people have to do anything with it
- Access to resources
- Avoiding anger/resentment

Two Types of Genetic Testing

DIAGNOSTIC

PREDICTIVE

Predictive Genetic Testing

- Testing of a person that does not have neurologic symptoms but is at-risk of having a pathogenic variant
  - Should only be performed in a CLIA-approved genetic testing lab

- Much more straightforward testing/results if the genetic variant that is causing symptoms in the family has already been identified
  - We start with the person with a diagnosis!

- Individual & personal choice that is made after having genetic counseling that includes the discussion of risks, benefits, motivations, and limitations
  - Neuro exam
  - Psychiatric assessment

Predictive Genetic Testing

What do some asymptomatic individuals consider when thinking about genetic testing?

Reproductive options	Reducing uncertainty	Life planning (career, financial, family goals, etc.)
Information for children	Clinical trials and or research participation	Impact on relationship with family, partner, willingness to date, etc.
Insurance / GINA	Anxiety regarding symptom development	No current treatments, but can meet with neurologist for monitoring

Genetic discrimination

Existing protections and their limitations (in the USA)

- Genetic Information Nondiscrimination Act (GINA)
  - Federal law signed in 2008
  - Protects most people from employment and health insurance discrimination based on genetic testing results
    - Not people in the military or working for employers with less than 15 employees
  - Does NOT protect against:
    - Long term insurance
    - Life insurance
    - Disability insurance
- Some states may also have additional laws
- Proven cases of discrimination are rare but this is very important for people considering predictive testing

What is my likelihood of developing ALS?

- Baseline / general population risk
- If ALS has been found in a relative
  - Depends on the age of onset and family history
  - Penetrance of identified variants
- Protective and risk factors
  - Genetic, environmental, etc.

<u>Example question for us to think through:</u>

Are children of ALS patients more likely to get the disease even if the patient does not have a genetic disposition?

What if my family does not have a known genetic cause?

Not all genes that can cause ALS have been identified

Always making advances...important to stay in touch!

Keep track of your family's genetics reports; depending on when testing was completed, additional testing may be available/recommended

Options for broad testing and/or DNA banking

You can always request to meet with a genetic counselor

If my parent had ALS without a known cause…

Can I and should I get tested?

- Likelihood of the parent's form being genetic depends on subtype, age of onset, family history
- Broad testing is available, but need to consider:
  - Regular predictive testing issues
  - Uninformative negative
  - Unresolvable VUS
- What are the goals for this testing?
  - How would you use this information?
  - What would this change for you?
- Family considerations

Who Should Have a Genetic Counseling Appointment?

Individuals and families who are concerned about a genetic condition may benefit from a genetic counseling visit regardless of whether testing is available or desired

Many people seek information and coping strategies as much as test results

Genetic counseling does NOT always mean genetic testing

Does everyone with ALS have access to a genetic counselor?

- Sadly, this is unlikely to be the case
- Alternative education tools may help you get started, like the Les Turner ALS Foundation My ALS Decision Tool™
  - https://lesturnerals.org/genetic/about-this-decision-tool/
- Ask your provider for a genetic counseling referral
- You can also locate a genetic counselor using https://findageneticcounselor.nsgc.org/
  - There are some telehealth genetic counseling companies
  - There are some sponsored programs offering genetic counseling if the testing is ordered by your provider

PLEASE DO NOT SEEK PREDICTIVE GENETIC TESTING WITHOUT SEEING A GENETIC COUNSELOR!!

How does genetic counseling and testing actually happen?

- Let’s discuss some logistics!

How do I prepare for a genetic counseling visit?

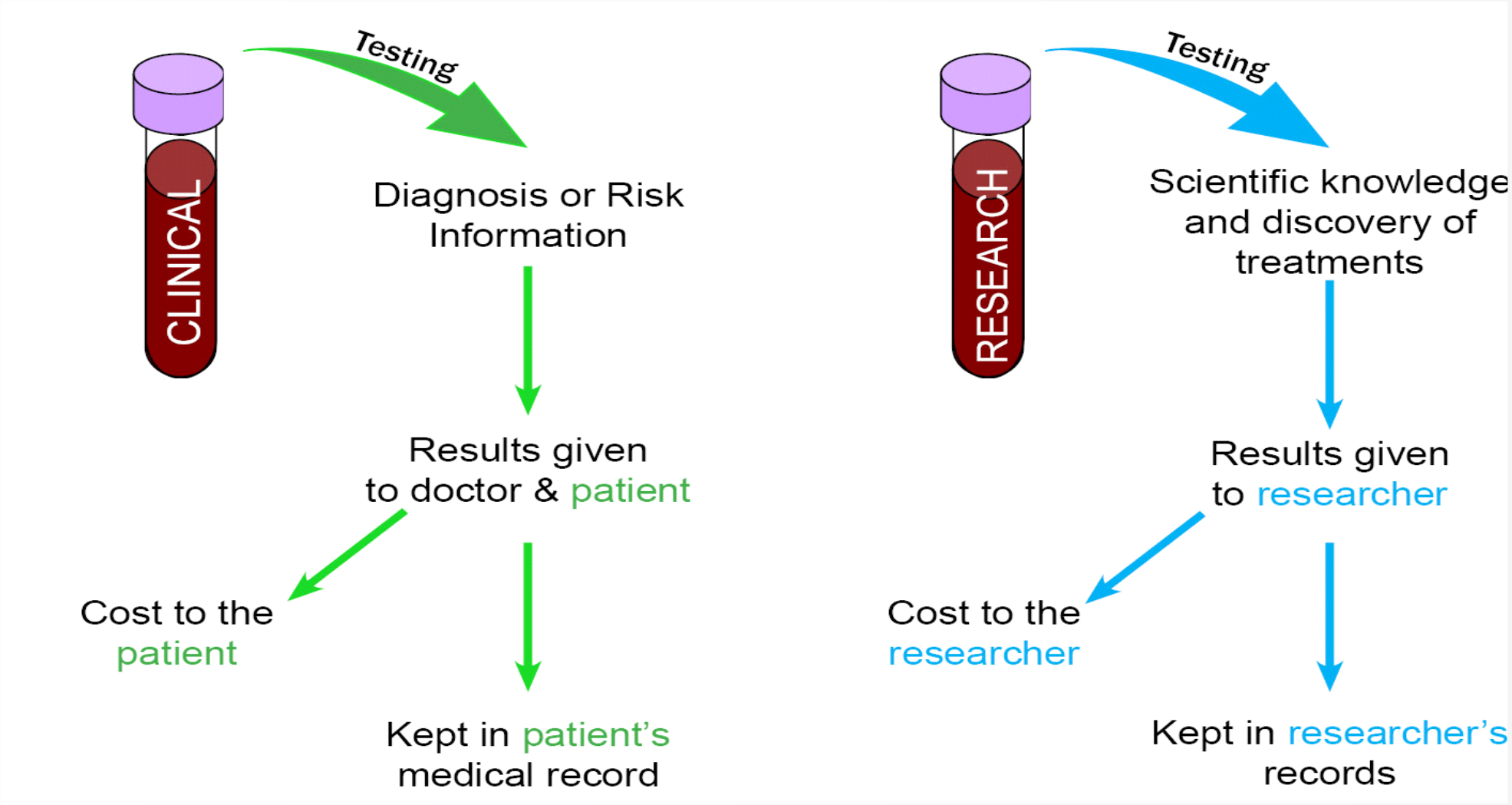
What to bring:

- Results from any genetic test you or your relatives have had
- Questions for the genetic counselor
- Family history information

<u>Questions to ask about family history include:</u>

- Who in the family has had neurologic or psychiatric conditions?
- What is their diagnosis or name of their condition? Or what are their symptoms?
- Does/did they have any other health problems?
- What age did they start having symptoms?
- Have they had genetic testing done for that condition?
- What age did they pass away, and what was the cause of death?

Genetic Testing Options: Clinical vs. Research



Testing Logistics

FAQs

How do we collect a sample?

Blood, buccal, saliva

How long does it take to get results?

In clinical care: most tests are 2-4 weeks, broader tests can be up to several months

In research: depends on the study protocol

How much does testing cost?

In clinical care: often well-covered by insurance; can be several hundred dollars if not

In research: covered by the study

How can genetic testing help with research?

…and does genetic testing as part of research help?

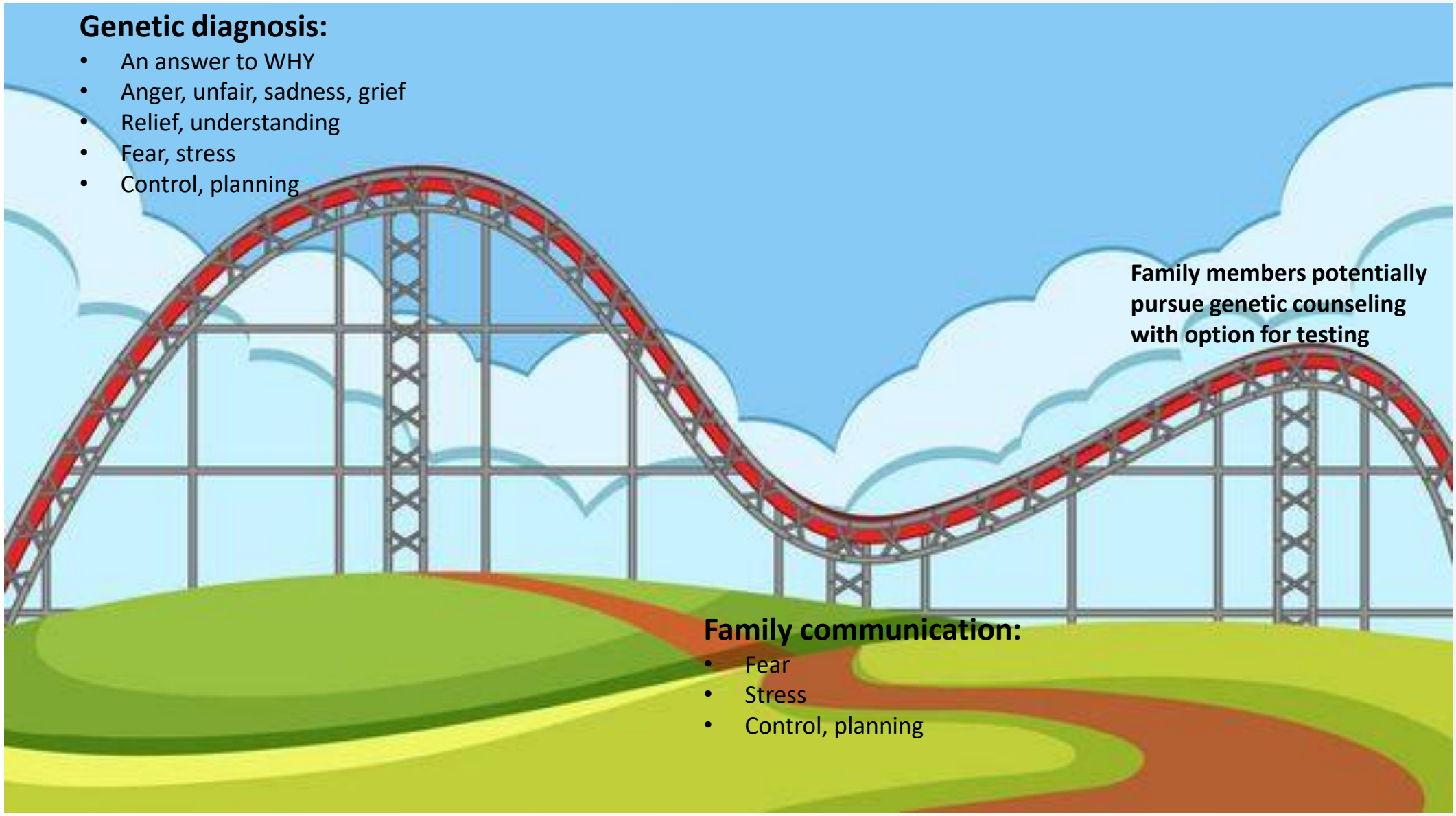
How your genetic testing results can help research:

- For the patient with ALS:
  - Access to studies (observational, interventional)
- For the family members of the patient with ALS:
  - Access to studies (observational, interventional)
- For the research community:
  - Better scientific understanding of the condition, which informs therapeutic development

How genetic testing through research participation helps the community:

- Identifying new genetic links to ALS
- Better understanding what symptoms are linked to which variants
- Guiding therapeutic development

A genetic diagnosis can feel like a new journey...



Summary

Majority of ALS does not have a single genetic cause

Variants in *C9orf72, SOD1, FUS, TARDBP* are some of the most common genetic culprits, and are associated with autosomal dominant inheritance

A family history of other individuals with ALS, FTD, early onset dementia, PD, or other neurodegenerative disorders increases the chance to find a genetic cause

Genetic testing is available

Testing someone with the diagnosis is the best place to start in the family, if possible

Talk with a genetic counselor or a genetics-wise clinician for guidance on genetic testing

Genetic counseling does NOT have to result in genetic testing

Thank You & Let's Chat!

Resources:

- Find a genetic counselor near you - https://findageneticcounselor.nsgc.org/
- Les Turner ALS Foundation My ALS Decision Tool™ https://lesturnerals.org/genetic/about-this-decision-tool/
- ALS Hope Foundation, & subgroup End the Legacy: https://www.alshf.org/end-the-legacy
- ALS Association website: http://www.alsa.org/
- I AM ALS: https://iamals.org/
- EverythingALS: https://www.everythingals.org/
- Penn Familial FTD/ALS Conference https://www.pennftdcenter.org/familial-conference
- AFTD genetics page: https://www.theaftd.org/ftd-genetics/ftd-genetics-and-you-learning-more/
- FTD Disorders Registry genetics page: https://ftdregistry.org/genetics-ftd
- Clinical trials and observational research search tool: http://clinicaltrials.gov/