The Role of Genetic Counseling & Testing in ALS

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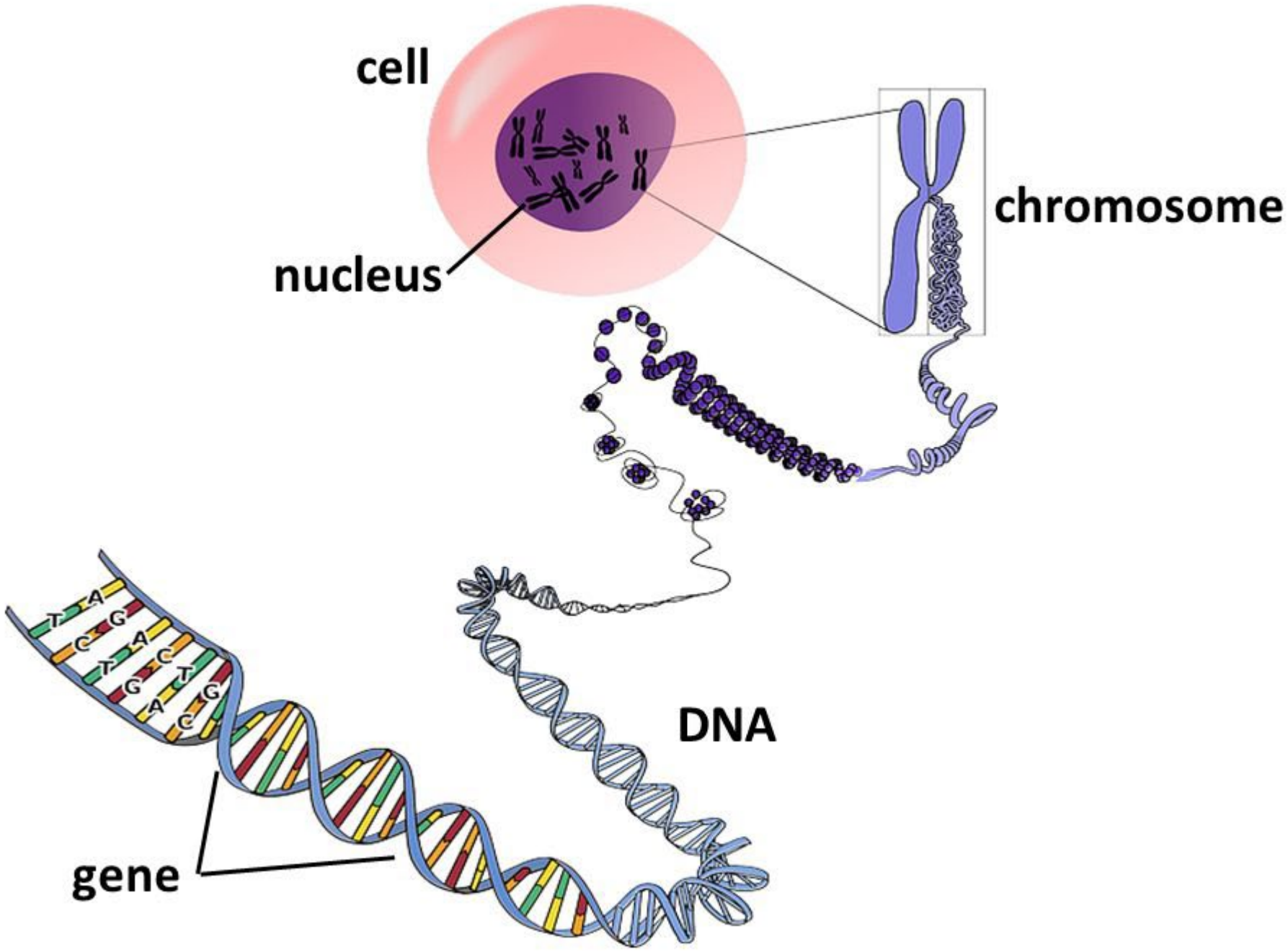
Goals

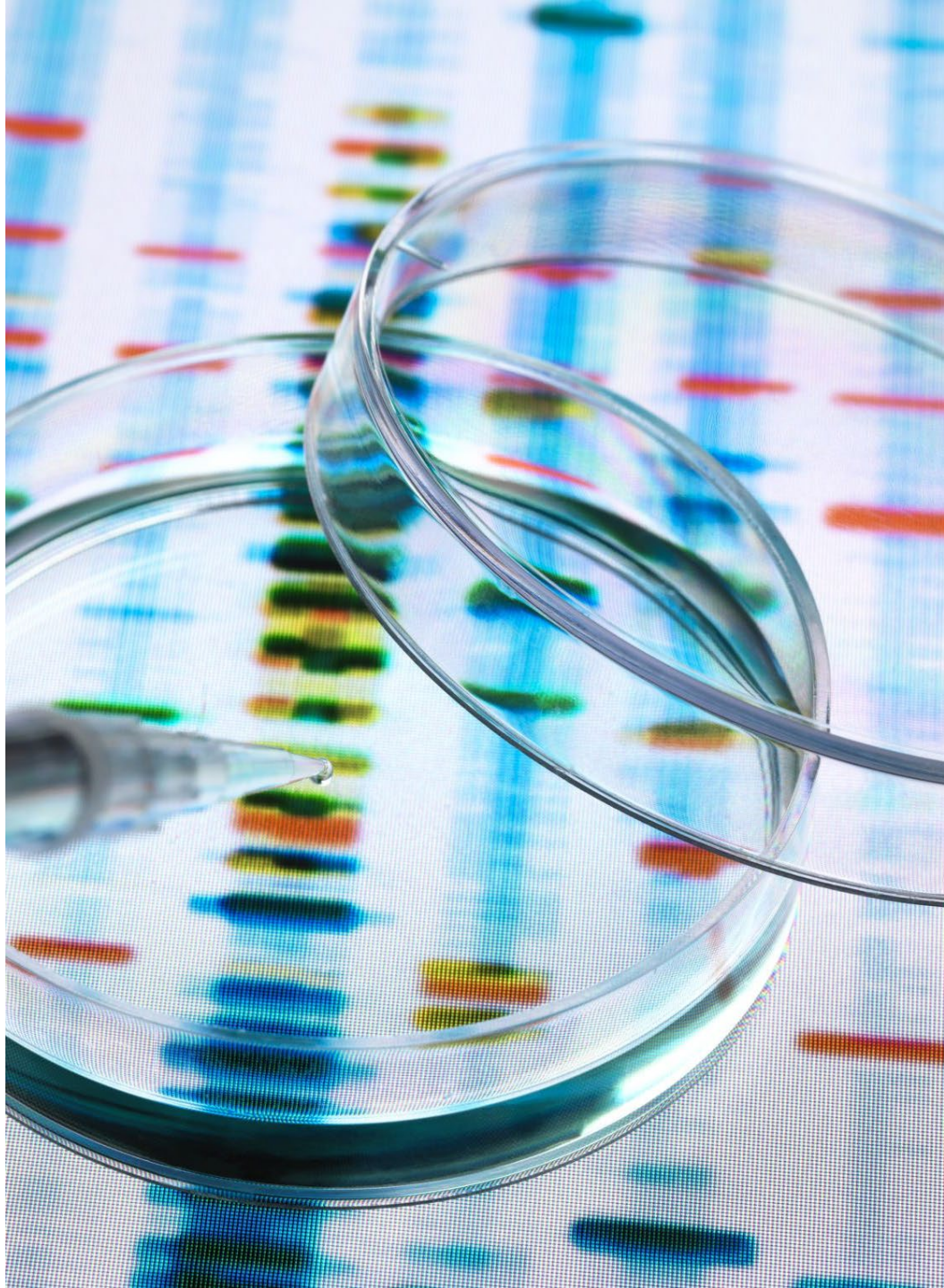
- Provide an overview of the current understanding of ALS genetics and offer insights into the implications for patients and their families who are contemplating genetic testing
- Explore the role of Genetic Counselors in this context, focusing on how they can support and guide patients through this process

Introduction

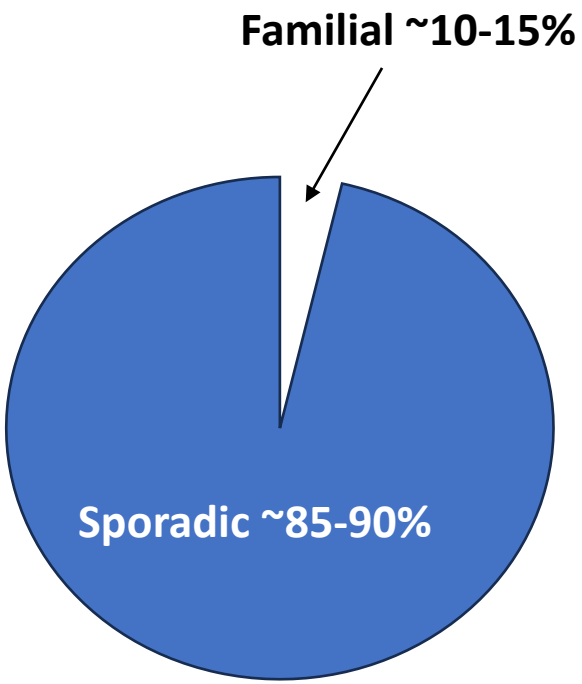

cell
nucleus
chromosome
DNA
gene

Genetics of ALS

- Currently, ~30 genes have been implicated in ALS
  - Some of these genes can also predispose to other neurodegenerative conditions (i.e. frontotemporal dementia)
- ~2/3 of individuals with fALS will have an identifiable genetic explanation while remaining ~1/3 will not
  - C9orf72 – most common genetic cause of fALS cases (~40%)
  - ~11-16% of individuals with sALS will have an identifiable genetic explanation with some studies quoting closer to 20% *(Grassano et al., 2022)*
    - C9orf72 – most common genetic cause of sALS cases (~7-10%)



Genetics of ALS

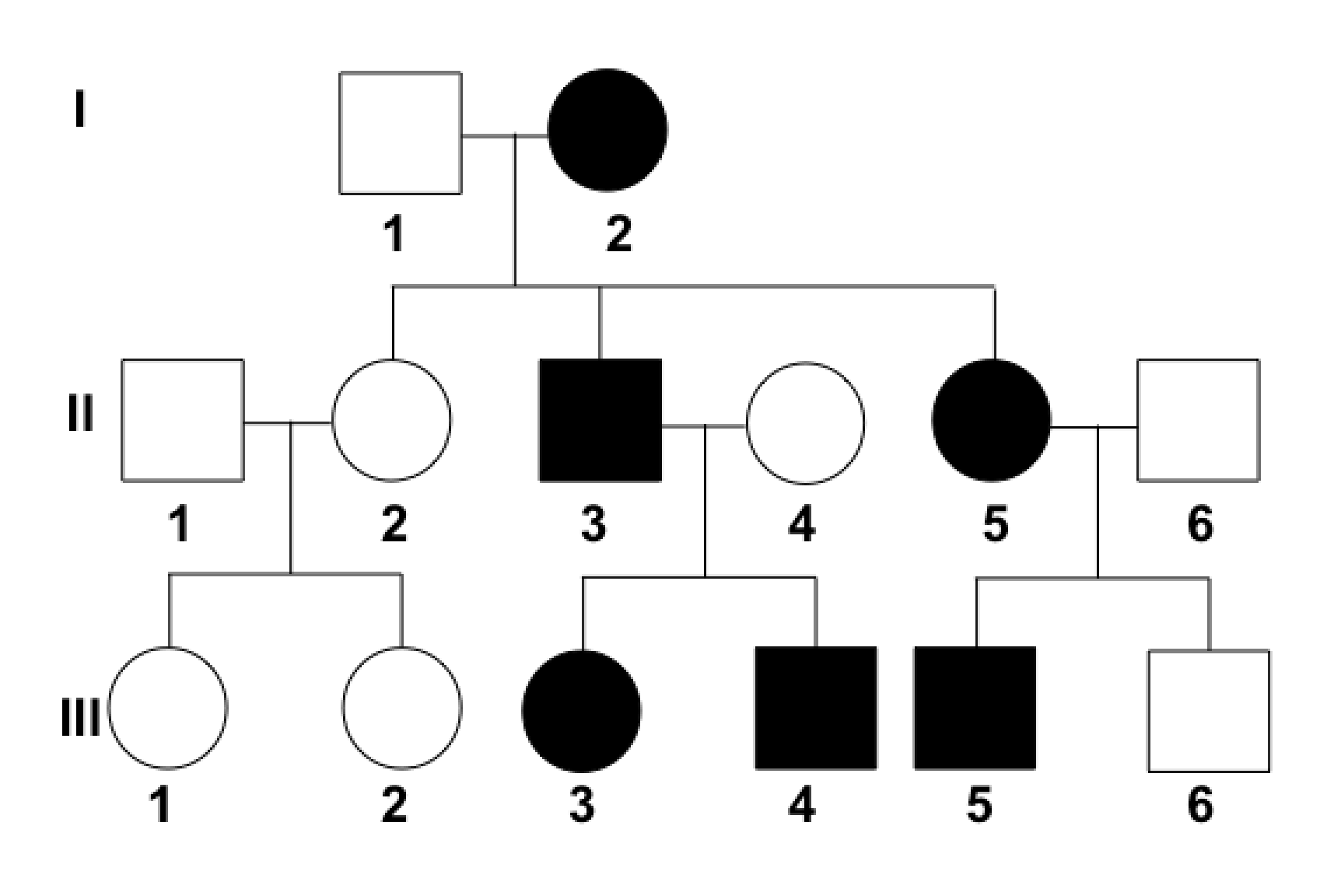


Gene	Reported Incidence: Familial ALS	Sporadic ALS
C9orf72	40%	7-10%
SOD1	20%	2-4%
TARDBP	5%	1%
FUS	4%	<1%
Other	1-2%	1-2%
Total	~70%	~11-16%

Salmon et al., 2022

Inheritance of fALS

- Autosomal dominant (AD)
  - Changes/mutations/variants in one copy of a gene pair is enough to cause disease or to be placed at risk of developing disease
    - Changed copy “dominates” over the typical, working copy
  - 50% risk to all 1st degree relatives



Family Pedigree for an AD Condition

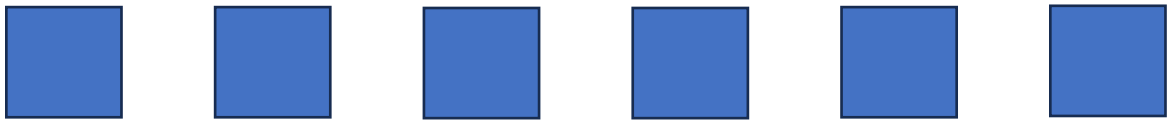
Variable Expression

- Not all individuals with the same gene change will show symptoms in the same way
  - Onset
  - Symptom type
  - Severity
- Can very across AND within families
- We see this with virtually every genetic condition!

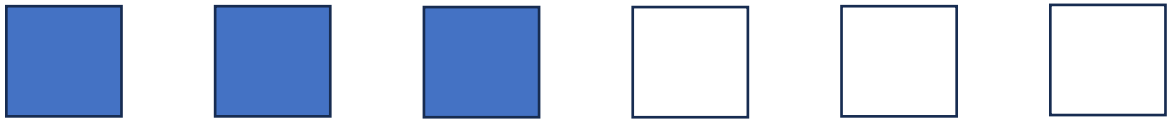
Penetrance

- The % of the time that an individual with a disease-associated gene change will ultimately show symptoms
- Autosomal dominant conditions
  - A possible explanation for the condition appearing to “skip” generations

Penetrance



6 individuals have the same genetic change and all 6 have symptoms = **100% penetrant (complete)**



6 individuals have the same genetic change and 3 have symptoms = **50% penetrant (reduced)**

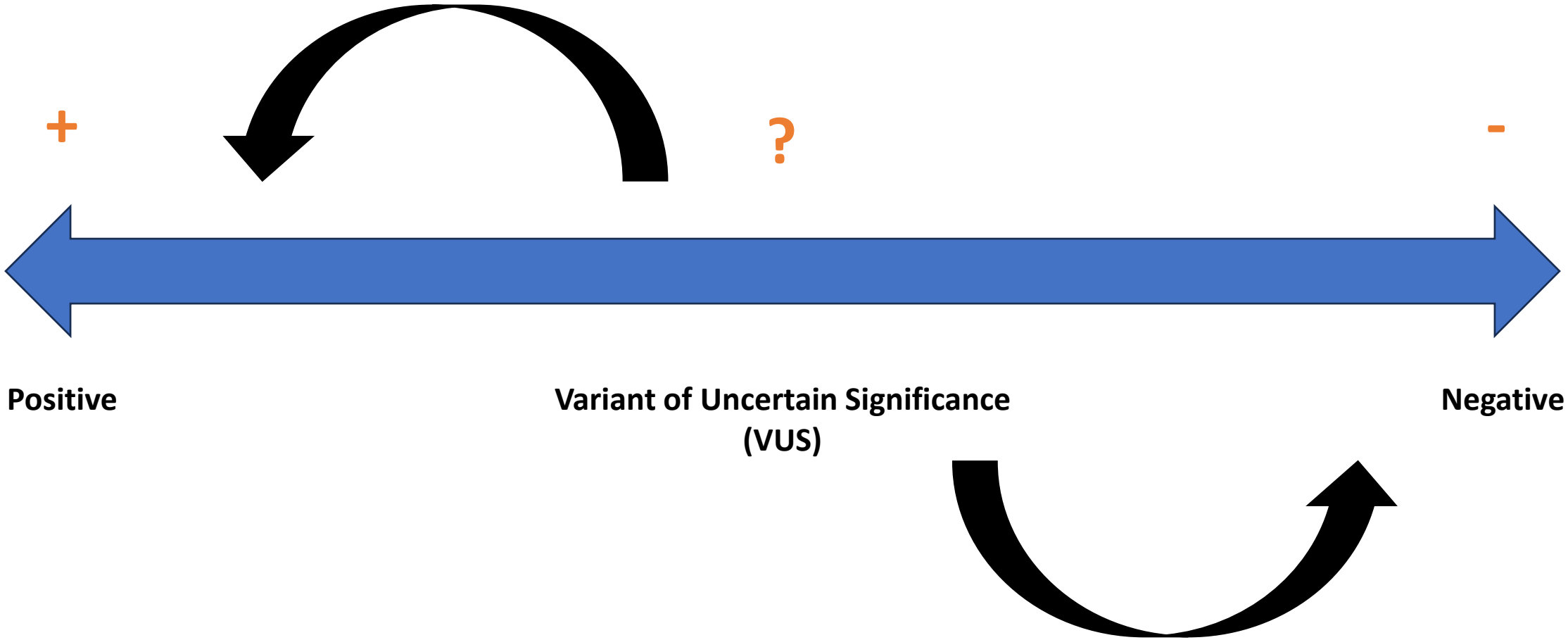
Penetrance

- A non-penetrant individual still has a 50% chance of passing on the gene change to each of their children
- Just because a parent is non-penetrant does NOT mean that will hold true for their children
- The concept of penetrance becomes important when at-risk, asymptomatic family members are considering testing
  - Prior to 2024 felt that penetrance of ALS-related genes was “high”
  - Increasing body of literature suggesting that penetrance of these genes is actually much lower than once thought *(Douglas et al., 2023)*
  - How we counsel at-risk, asymptomatic family members about penetrance should be personalized as much as possible to what is known about the family
  - Possible that seemingly “sporadic” cases are actually familial cases in disguise

Genetic Testing for ALS

- Genetic testing for ALS is becoming more accessible to patients via sponsored testing programs and at-home testing kits
- **Invitae – ALS Identified (Biogen)**
  - Available to individuals 18y and older with ALS OR a family history of ALS (pre-symptomatic or symptomatic)
  - 22 gene panel including C9orf72
    - Option to add-on 9 rare/preliminary evidence genes
- **PreventionGenetics – Ionis no-cost genetic testing for ALS**
  - Available to individuals with a clinical or suspected clinical diagnosis of ALS (with or without a family history), or who are pre-symptomatic WITH a family history of ALS.
  - 32 gene panel including C9orf72 and ATXN2
- Genetic testing for ALS has changed significantly in the past 5-10 years, if you have had genetic testing for ALS previously and it was normal, it is possible you might be eligible for more comprehensive testing.

Types of Results



Benefits & considerations of genetic testing for ALS

Family members can be informed of genetic risk

Coordination of presymptomatic testing, discussions surrounding family planning

Potential access to clinical trials currently underway for gene-specific therapies OR access to currently available gene therapy (i.e. SOD1)

Symptomatic and presymptomatic individuals

Some patients and families might be provided with false reassurance if their results are normal

How do we counsel families with a family history? Without a family history?

Psychological implications

Chances that children or grandchildren could have inherited the same genetic change, informing family members of + results

Variants of uncertain significance (VUS)

How would you handle an uncertain result?

Recommendations for Genetic Testing in pALS

- Historically, there have been differing opinions amongst providers as to who should be offered genetic testing for ALS
  - What constitutes a family history? 1st degree relatives only? 1 person with ALS? 2 or more? What about co-occurring conditions like FTD?
- There are divergent views between ALS providers and patients regarding the value of genetic testing
- Salmon et al. 2022 position that genetic counseling and testing for ALS should be widespread and offered regardless of fALS or sporadic ALS classification

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RESEARCH ARTICLE

Evidence-based consensus guidelines for ALS genetic testing and counseling

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Roggenbuck et al., 2023

- Background:
  - There is a growing recognition of the genetic basis of seemingly sporadic ALS
  - Advances in genetic technologies allowing for the possibility of gene-targeted therapies (i.e. SOD1)
  - Genetic testing for ALS is not yet considered "standard of care" despite people with ALS desiring access to it
  - People with ALS who have undergone genetic testing desire a need for more complete genetic counseling and risk assessment, such as information pertaining to the implications of tests results for family members

"To develop clinical ALS genetic counseling and testing guidelines to improve and standardize genetic counseling and testing practice among neurologists, genetic counselors or any provider carding for persons with ALS"

Roggenbuck et al., 2023

- Results and Discussion:
  - 35 guideline statements were developed
    - All persons with ALS should be offered single-step genetic testing, consisting of C9orf72, SOD1, FUS and TARDBP at a minimum
    - There are key education and genetic risk assessments that should be provided before and after testing are delineated
    - Specific guidance for labs regarding testing methods and reporting for C9orf72 and other ALS-associated genes

Roggenbuck et al., 2023

- Summary of clinical 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]

Figure 4. Summary of clinical testing guidelines. ClinGen, Clinical Genome Resource, https://clinicalgenome.org/affiliation/40096/.

Roggenbuck et al., 2023

- Summary of genetic counseling recommendations

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	

Figure 5. Summary of genetic counseling recommendations.

Genetic testing for at-risk, asymptomatic individuals

- **With a family history AND a known genetic cause to ALS in family member(s)**
  - Model protocols already designed for other adult-onset, neurodegenerative conditions (i.e. Huntington's disease)
    - Multiple conversations and visits with various individuals – GC, neurologist, counselor, family
  - Genetic Information Non-discrimination Act (GINA)
- **With a family history and NO known genetic cause to ALS in family member(s)**
  - No clear guidelines in place
  - Limitations to interpreting significance of a negative result

Accessing Genetic Counseling Services

- Both Invitae and PreventionGenetics offer FREE telehealth genetic counseling services to patients
  - **Invitae**
    - Post-test counseling only
    - Patient-initiated – can contact Invitae Client Services at 1-800-436-3037 or schedule online through your Invitae patient portal
  - **PreventionGenetics**
    - Pre AND post-test counseling
    - Provider-initiated – must select this option on the test requisition form

PREVENTION GENETICS part of EXACT SCIENCES

Test information is available on our website:
PreventionGenetics.com

PREVENTIONGENETICS USE ONLY

GENETIC COUNSELING

No-cost genetic counseling, provided virtually via telephone, with a third party service (provided by GeneMatters LLC, a Genome Medical Affiliate), is available to patients through this sponsored testing program. One no charge pre and/or post genetic counseling appointment is available to patients who are interested in additional information, have questions or would like advice about alternatives before and/or after having this test performed.

By checking the boxes below, I agree to allow PreventionGenetics to facilitate the provision of pre-test and/or post-test genetic counseling services by GeneMatters, a third party telehealth genetic counseling provider.

Check all that apply:

- ☐ Refer to GeneMatters for pre-test genetic counseling.
- ☐ Refer to GeneMatters for post-test genetic counseling.
  - ☐ If results are negative, no referral to GeneMatters is needed.

GeneMatters will contact the patient for scheduling. Please provide the patient's phone number and email address.

PATIENT PHONE NUMBER

U.S. STATE WHERE PATIENT RESIDES (REQUIRED)

Patients will receive a text message to schedule an appointment if they have SMS texting available on their phone.

- If Power of Attorney (POA) for medical decisions/communication is needed, please provide a copy to GeneMatters at (612) 808-5186 (fax) or clinicaladmin@gene-matters.com
- Genetic counseling is typically provided by telephone.

If the patient needs other accommodations for communication please specify below:

- ☐ Video consult requested (via Zoom).

PATIENT EMAIL ADDRESS

- ☐ Other:

PLEASE SPECIFY

Take home points

- All pALS should be offered the option of genetic testing, regardless of family history
- pALS and their families should be offered access to genetic counseling services, to include pre and post-test counseling
- Genetic testing is more than just a “blood draw”
- The landscape of genetics, particularly ALS genetics, is rapidly changing
- Advocate for yourselves and your family

Thank you!