WELCOME!

July 31, 2023

Genetic Counseling in ALS: When and Why

ALS Association
National Office-Care Services
Ph: 800-782-4747 Cynthia.Knoche@als.org

Guest Speaker:
Donna L. Bernstein, MS, CGC
Ionis Pharmaceuticals

ALS Genetic Counseling and Genetic Testing

Donna L. Bernstein, MS, CGC
July, 31st 2023

Genetic Counseling and Genetic Testing- What's it all about?

What is Genetic Counseling?

Who are Genetic Counselors?

What do Genetic Counselors Do?

ALS Genetic Testing- What Can I Learn?

Why Would I Want to Know?

Sponsored Genetic Testing Programs

Who should Have Genetic Counseling?

When Should Genetic Counseling be Done?

Considerations Prior to Genetic Counseling

What is a Genetic Counselor?

Genetic Counselors

American Board of Genetic Counseling, Inc.

ABGC

- Certified Genetic counselors have a graduate degree in human genetics from an accredited program, are required to pass a board certification exam, and in many states are licensed to practice clinical genetic counseling

- Genetic counselors often work in a hospital or medical office or may work at a molecular genetic testing lab or for a biopharma company and many genetic counselors now offer genetic counseling via telemedicine

- Genetic Counselors are often specialized, for example in prenatal, cancer, pediatrics, cardiovascular and neurological genetic conditions

A Few Genetic Counselor Publications

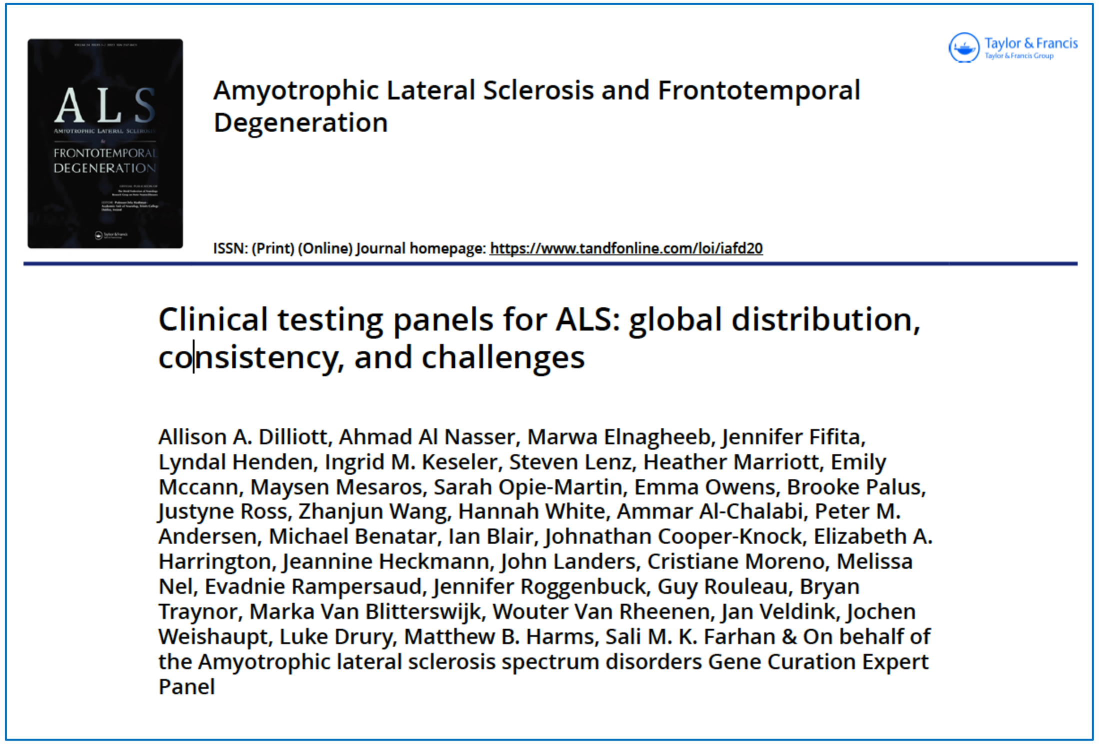
ORIGINAL CONTRIBUTION

When Sporadic Disease Is Not Sporadic

The Potential for Genetic Etiology

Jill S. Goldman, MS, MPhil, CGC; Bruce L. Miller, MD; Jiri Safar, MD; Sunita de Tourreil, MSc; Jennifer L. Martindale, BS, BA; Stanley B. Prusiner, MD; Michael D. Geschwind, MD, PhD

Arch Neurol. 2004;61:213-216



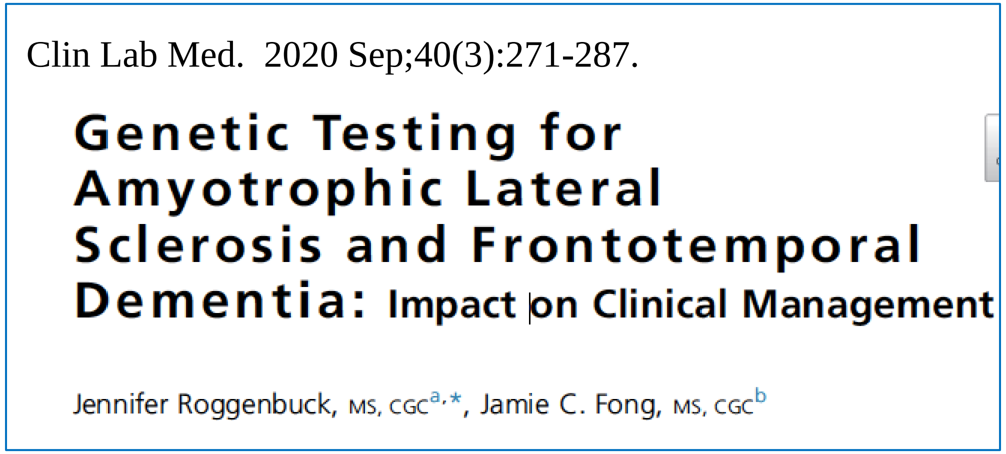
Taylor & Francis

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/iafd20

Clinical testing panels for ALS: global distribution, consistency, and challenges

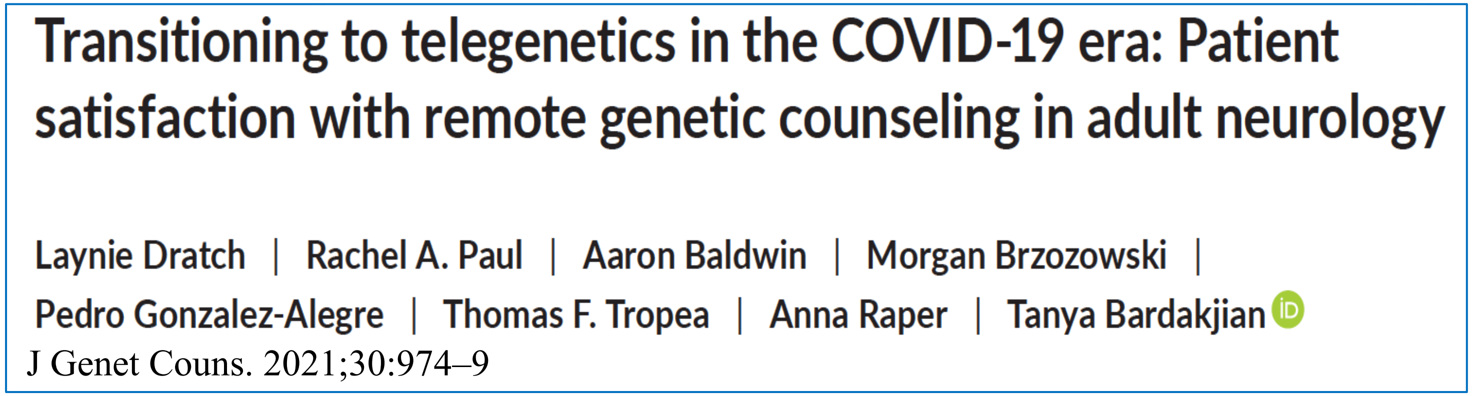
Allison A. Dilliott, Ahmad Al Nasser, Marwa Elnagheeb, Jennifer Fifita, Lyndal Henden, Ingrid M. Keseler, Steven Lenz, Heather Marriott, Emily Mccann, Maysen Mesaros, Sarah Opie-Martin, Emma Owens, Brooke Palus, Justyne Ross, Zhanjun Wang, Hannah White, Ammar Al-Chalabi, Peter M. Andersen, Michael Benatar, Ian Blair, Johnathan Cooper-Knock, Elizabeth A. Harrington, Jeannine Heckmann, John Landers, Cristiane Moreno, Melissa Nel, Evadnie Rampersaud, Jennifer Roggenbuck, Guy Rouleau, Bryan Traynor, Marka Van Blitterswijk, Wouter Van Rheenen, Jan Veldink, Jochen Weishaupt, Luke Drury, Matthew B. Harms, Sali M. K. Farhan & On behalf of the Amyotrophic lateral sclerosis spectrum disorders Gene Curation Expert Panel



Clin Lab Med. 2020 Sep;40(3):271-287.

Genetic Testing for Amyotrophic Lateral Sclerosis and Frontotemporal Dementia: Impact on Clinical Management

Jennifer Roggenbuck, MS, CGC[a,*], Jamie C. Fong, MS, CGC[b]



Transitioning to telegenetics in the COVID-19 era: Patient satisfaction with remote genetic counseling in adult neurology

Laynie Dratch | Rachel A. Paul | Aaron Baldwin | Morgan Brzozowski | Pedro Gonzalez-Alegre | Thomas F. Tropea | Anna Raper | Tanya Bardakjian

J Genet Couns. 2021;30:974–9

Do Genetic Counselors Practice Gene Therapy?

Cartoon by: Dr. Donald J. Davidson

Common to all Genetic Counselors- Bridge between Molecular Lab Physician and Patient

Training- ABGC accredited Human Genetics Graduate Program

Pre-med, A&P, Developmental genetics, molecular and biochemical genetics, Clinical + Molecular

- ABGC Certification
- Code of Ethics
- Rogerian therapeutic techniques
- Nondirective (unless intervention is available)
- Determine appropriate molecular and/or biochemical testing

- Interpret results, variant research, literature review, or other databases
- Determine monitoring, management, treatment
- Results disclosure counseling session
- Follow up- Physician Letter, Physician Education
- Follow up- Patient letter

Who Should Have ALS Genetic Counseling?

2 Kinds of ALS Genetic Counseling- **Diagnostic and Predictive**

- **Diagnostic**– For anyone affected with ALS who is interested in learning about ALS genetic testing
- Including anyone **Suspected of or Diagnosed with ALS even if there is no ALS family history**
- **Predictive**– For any adult with a family member diagnosed with ALS who would like to learn about genetic testing
- Genetic counseling is offered for people with ALS even if there is **no ALS family history**

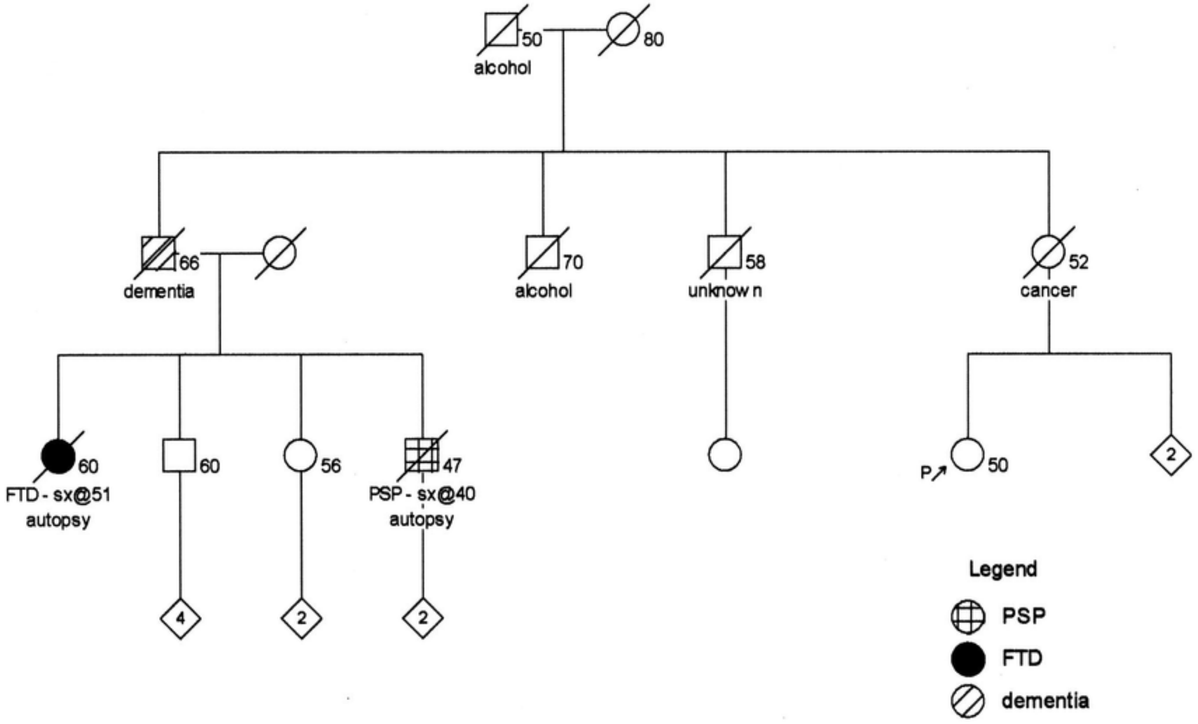
What Happens in a Genetic Counseling Session?

Active Listening-

- What brought you to seek genetic counseling?
- What brought you to medical attention?
- What would you like to learn about your genetics?
- What would you not want to know
- How would you like to learn about your genetic test results if you decide to have genetic testing?
- How would you feel if your genetic test is positive? Negative?
- Who would you tell and how do you imagine they would respond?

Getting to Know You Better

- Review medical records, including laboratory, imaging and pathology results
- Take a medical history
- Take a family history
- Analyze the medical and family histories for inheritance patterns and symptoms that can be part of a genetic condition to assure that the most appropriate genetic testing is ordered

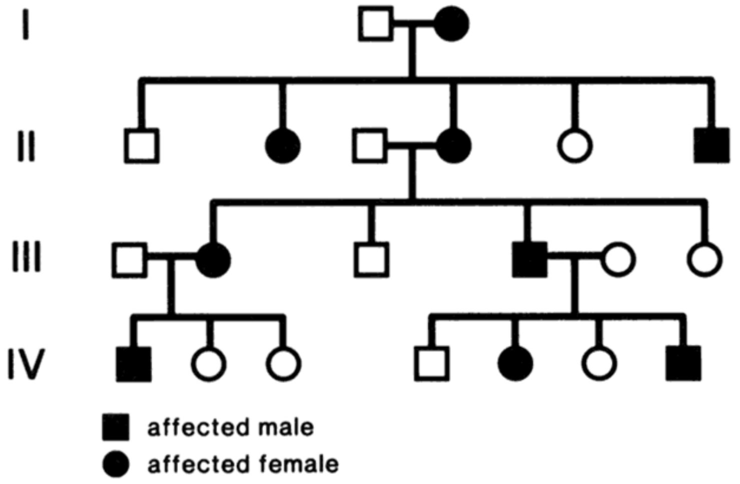


Goldman J, Frontotemporal dementia: genetics and genetic counseling dilemmas October 2004 The Neurologist 10(5):227-34

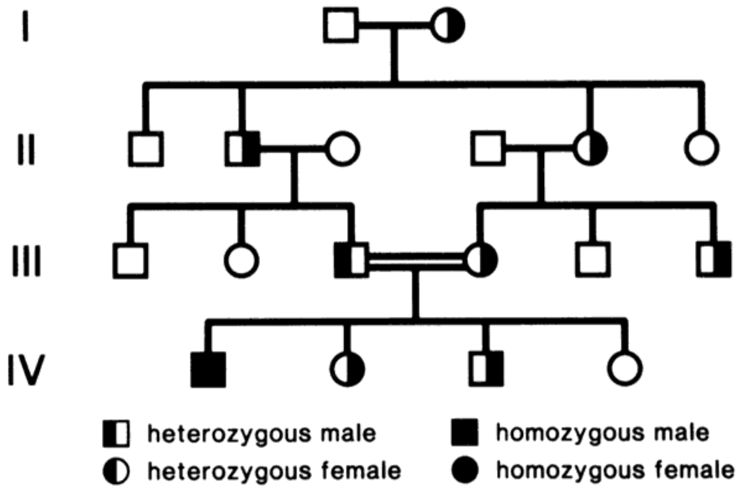
Genetic counselors explain DNA, Genes, Proteins and how they impact health

Family History Can Uncover Dominant, Recessive or X-Linked Inheritance Patterns

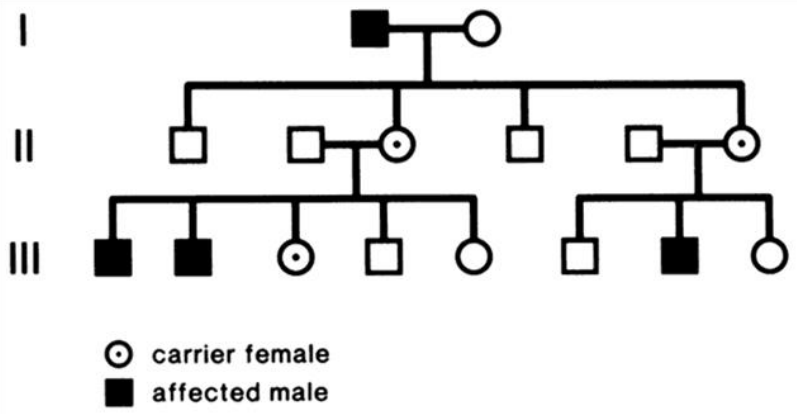
Autosomal Dominant



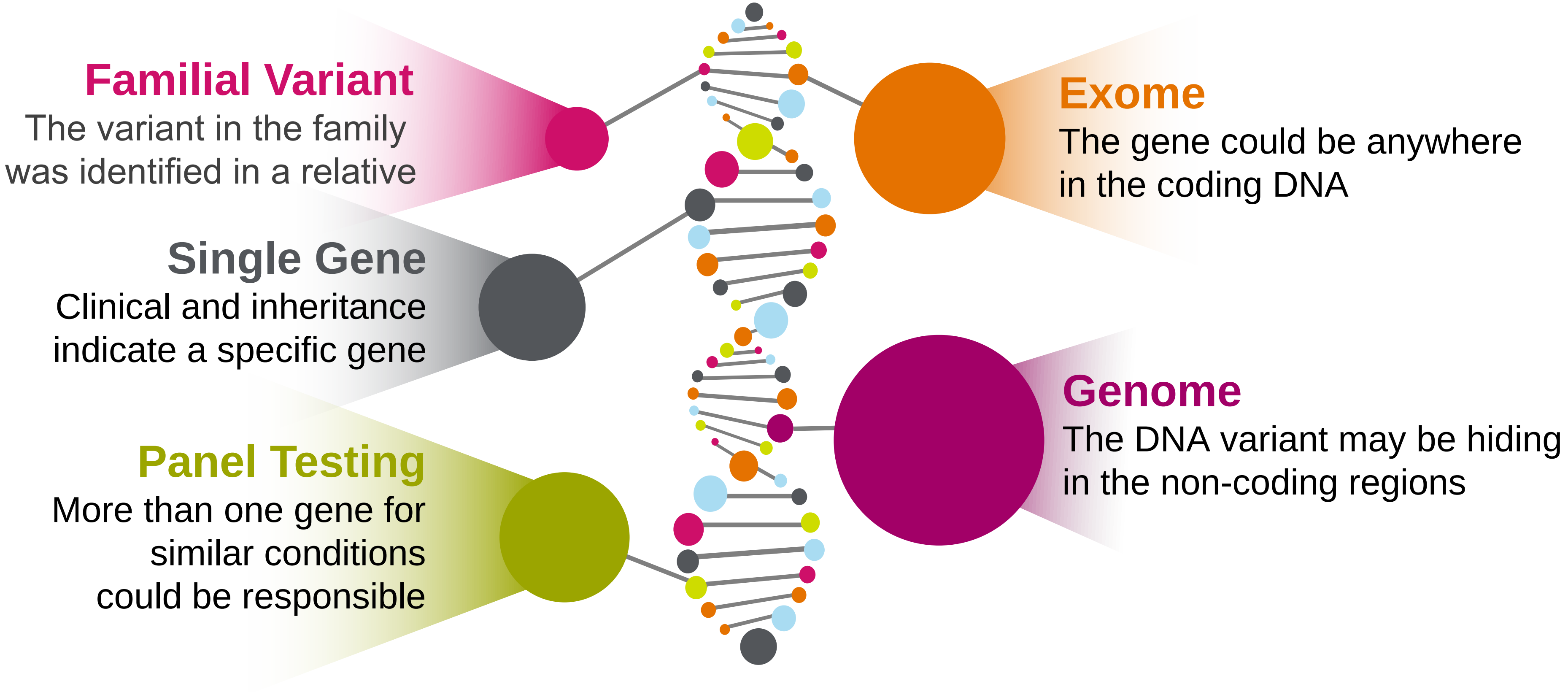
Autosomal Recessive



X-Linked Recessive



A Few of Many Kinds of Genetic Tests- One Test Does Not Fit All



Familial Variant
The variant in the family
was identified in a relative

Single Gene
Clinical and inheritance
indicate a specific gene

Panel Testing
More than one gene for
similar conditions
could be responsible

Exome
The gene could be anywhere
in the coding DNA

Genome
The DNA variant may be hiding
in the non-coding regions

There are at least 33 genes established to cause or increase risk for ALS
The genetic counselor will describe the testing options and the likelihood of detecting a genetic variant

If Undecided about Having Genetic Testing…

- When you have Genetic Counseling, Genetic Testing is not Required
- Genetic Counselors help to weigh the benefits, limitations and possible risks of genetic testing to help you decide if and when genetic testing is right for you based on your values, culture, relationships and life events
- Provide Anticipatory Guidance – Potential for survivor’s guilt if negative, guilt for passing on to children if positive, changes in family dynamics, emotional response
- We do not choose our genes and we do not choose the genes we pass down

Why have ALS Genetic Counseling and Genetic Testing?

- This is an individualized decision
- Genetic Counseling can help clarify the risks, benefits and limitations of genetic testing and help you decide if and when genetic testing is right for you
- There are different reasons for people who have ALS to be tested than for people who have a relative with ALS but no symptoms themselves
- Some people are interested in finding out if they have a genetic form of ALS in case they would be eligible for a gene targeted therapeutic or clinical trial
- Some people want genetic testing for family planning
- Some believe that knowledge is power

When is the Best Time to Have Genetic Counseling?

- Genetic counseling can be done at any time, usually both before and after genetic testing

- Genetic test results informing can be postponed

- Prior to genetic testing it is recommended to have long term care and life insurance in place

- Genetic Counseling ≠ Genetic Testing

- The best time for genetic testing is a topic to discuss with your genetic counselor, especially if you have no ALS signs or symptoms

- If you have ANY ALS signs or symptoms, WAIT is a four letter word

Be Prepared-
Before Genetic Counseling…

- Send medical records, including lab tests and imaging and pathology reports in advance so the genetic counselor can review them
- If genetic testing was done in a relative, request a copy of their results for the genetic counselor
- Gather your family's medical history information, including any health conditions, age and cause of death
- If you have no ALS symptoms, it's best to secure long-term care and life insurance prior to your genetics appointment
- Consider bringing a family member or support person with you to the appointment

Pre-test Genetic Counseling

- Contracting- What will be covered in the genetic counseling session
- How and when and how much to learn about the results? Will a support person be there?
- Medical and family history can inform on inheritance patterns and the appropriate genetic test to order
- The Science: What are genes, proteins, and how do they result in ALS?
- Risks, benefits and limitations of genetic testing
- Anticipatory guidance, expected response to positive, negative or inconclusive result. With whom to communicate results and how? How will family members react? Managing expectations and uncertainty
- Who will see the results? What else may be learned from the genetic test results?

Post-test Genetic Counseling

- Communicate genetic test results interpretation to patients and physicians
- Examine implications to the patient and family members
- Psychosocial support adjusting to the diagnosis and the emotional and psychosocial impact
- Revisit complexities of genetic test results, including limitations, variable expressivity, complete vs incomplete penetrance if applicable
- Explain residual risk or recurrence risks and prenatal options
- Refer for monitoring, management and patient support resources*
- Provide patient and physician summary letters documenting all of the above

*There is a dearth of available patient support services following diagnostic or predictive genetic testing

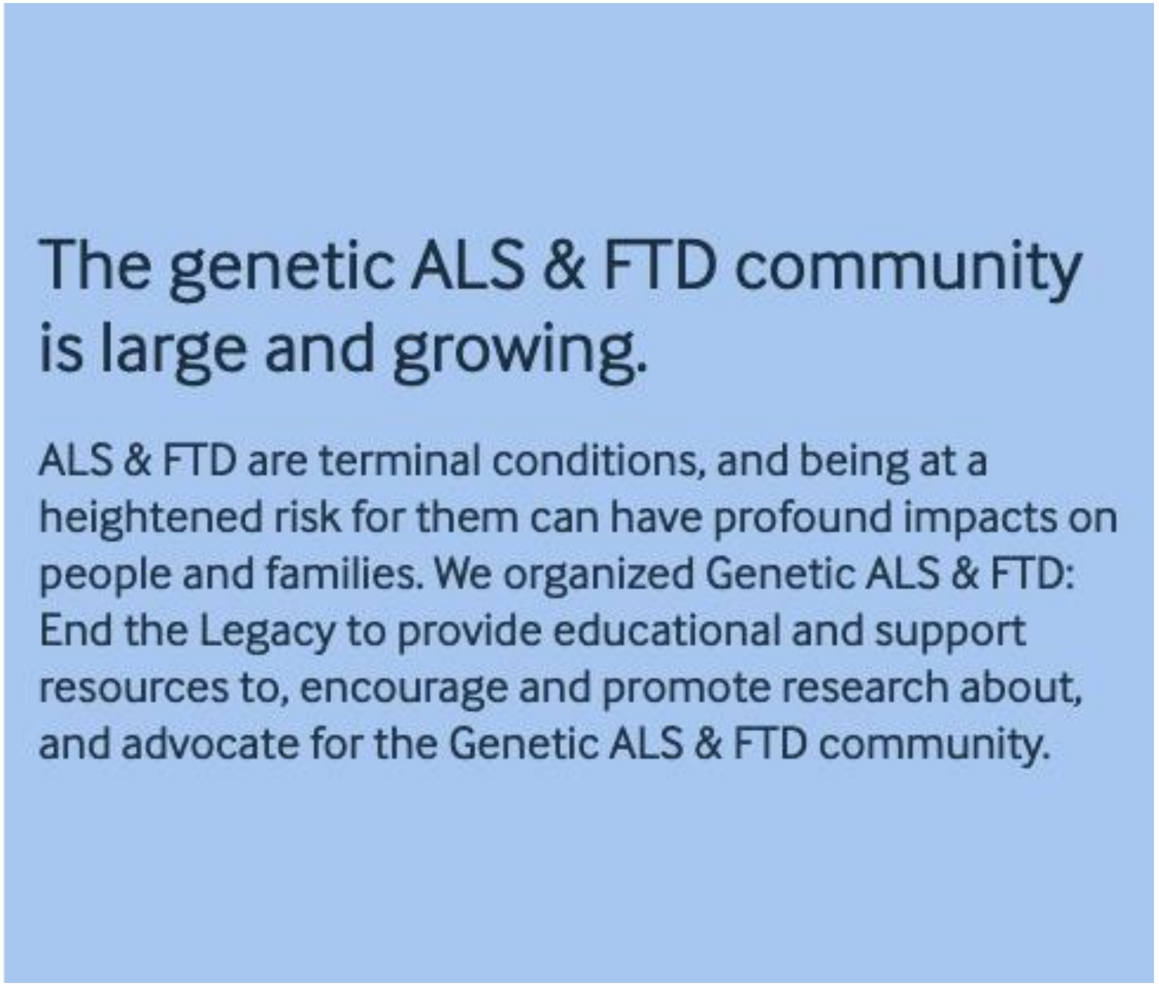
Predictive Genetic Counseling for Adult Onset Neurological Conditions-

- **Predictive genetic testing is not offered to pediatric patients,** which could infringe on their autonomy, privacy and the right to not know as future adults
- Modified, modified Huntington disease protocol, with the need for flexibility
- GINA, discrimination, financial, long-term care and life insurance
- Assess testing motivations, timing and psychosocial context Rogerian therapy/counseling, if needed, refer for emotional and psychotherapeutic support*
- Offer time to opt out or delay genetic testing
- DNA Banking
- Prenatal testing options, Preimplantation Genetic Diagnosis (PGD), including nondisclosure linkage options

What Should Positive Predictive ALS/FTD Genetic Testing Patients Do?

END THE LEGACY

GENETIC ALS & FTD



The genetic ALS & FTD community is large and growing.

ALS & FTD are terminal conditions, and being at a heightened risk for them can have profound impacts on people and families. We organized Genetic ALS & FTD: End the Legacy to provide educational and support resources to, encourage and promote research about, and advocate for the Genetic ALS & FTD community.

geneticalsftd@gmail.com
https://www.alshf.org/end-the-legacy

Jean Swindler- Chair

Presymptomatic ALS and FTD Research Studies

- Amyotrophic Lateral Sclerosis (ALS) Families Project- Columbia University NCT03865420
- The DIALS (Dominant Inherited ALS) Network – Massachusetts General Hospital NCT00317616
- ALLFTD - Longitudinal Frontotemporal Lobar Degeneration: a multisite research consortium
- Biospecimen Collection to Investigate the Causes of ALS- Mayo Clinic
- The Pre-symptomatic Familial Amyotrophic Lateral Sclerosis (Pre-fALS) Study
- ALS Research Collaborative (ARC) Study- ALS Therapy Development Institute –TDI
- AMBRoSIA' project (A Multicentre Biomarker Resource Strategy in ALS) Oxford, Sheffield and Queen Mary's Hospital London
- UPenn Observational Research Repository on Neurodegenerative Disease (UNICORN) University of Pennsylvania
- Emotional Experience of Participating in Research for People at risk of ALS/FTD- Emory University
- Pathogenesis in C9ALS (PICALS) **-** Emory University
- Clinical Manifestations and Biomarkers in Amyotrophic Lateral Sclerosis Type 4 and Other Inherited Neurological Disorders of RNA Processing, NINDS NCT04394871
- The Genetic Frontotemporal dementia Initiative (GENFI), University College London
- **A Study of BIIB067 When Initiated in Clinically Presymptomatic Adults with a confirmed Superoxide Dismutase 1 Mutation (ATLAS), BIOGEN, 29 global sites**

Adapted from the End the Legacy web page

Ionis ALS Sponsored Genetic Testing and Genetic Counseling Program

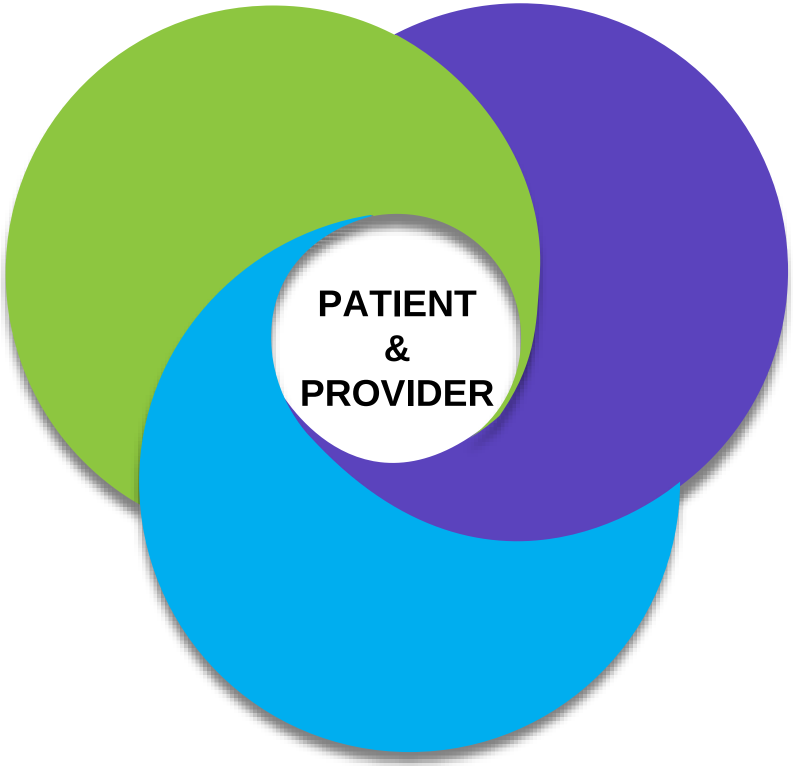
The Most Common Genes

C9ORF72
TARDP
ATXN2
SOD1
FUS

Eligibility for Ionis Sponsored Genetic Testing

- Confirmed or suspected ALS diagnosis at any age
- Family history of ALS with or without genetic confirmation for individuals age 18 and older
- Genetic Counseling is Strongly Encouraged

SPONSORED GENETIC COUNSELING



IONIS

Program Support

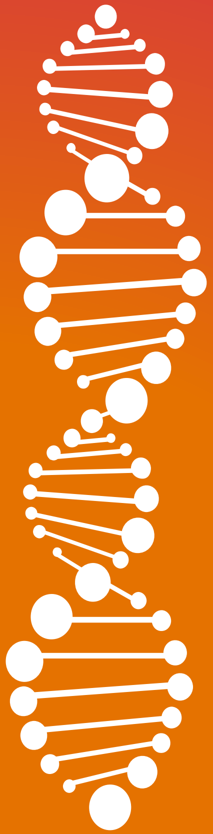
GeneMatters
A Genome Medical Company

Sponsored Genetic Counseling

PREVENTION GENETICS part of EXACT SCIENCES

Sponsored Genetic Testing

ALS Genetic Testing Sponsored by Ionis Pharmaceuticals with PreventionGenetics Clinical Laboratory



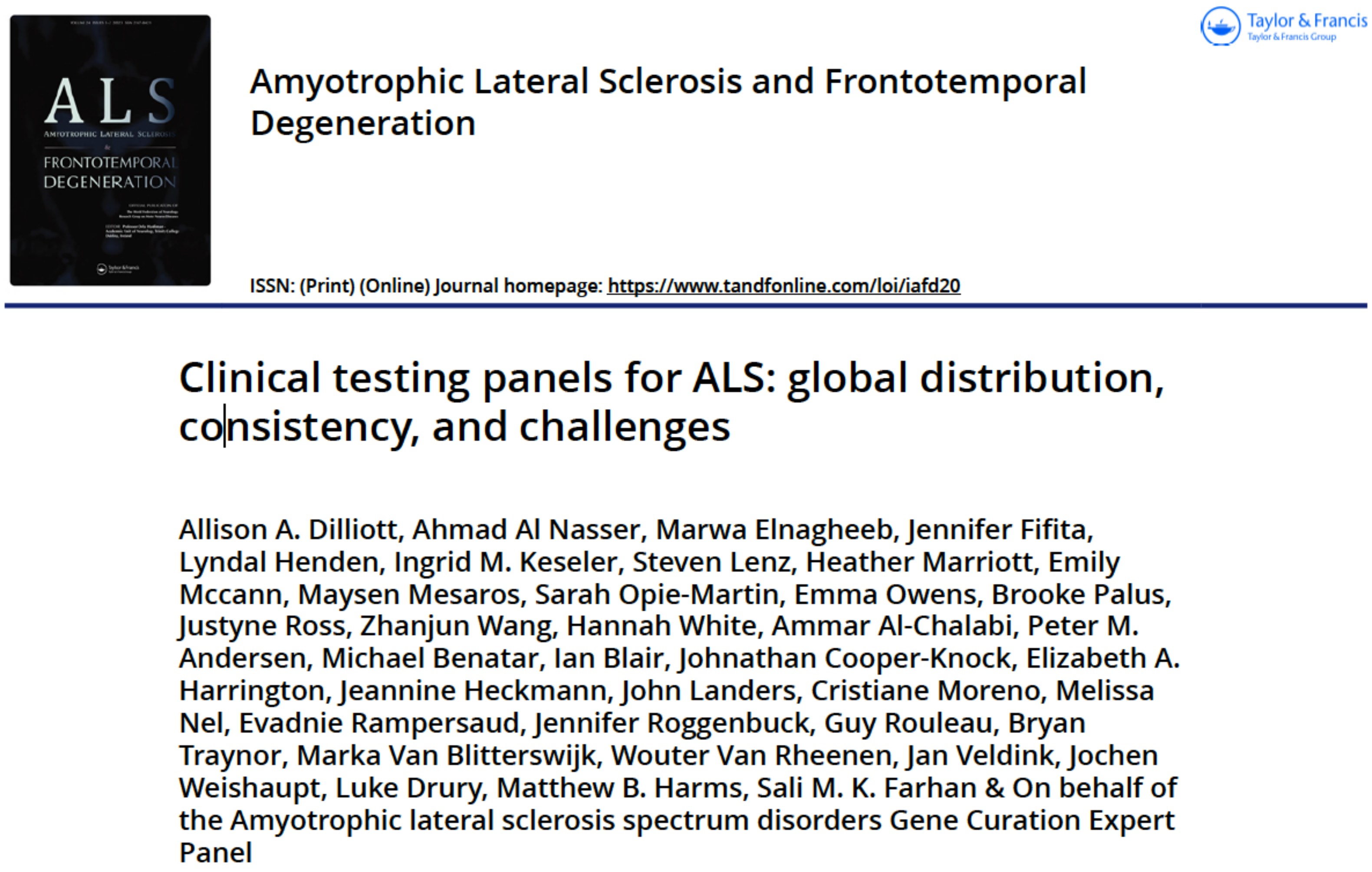
33 Gene Panel:

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

March 2022-July 2023

AMYOTROPHIC LATERAL SCLEROSIS GENE CURATION EXPERT PANEL

Thank you for providing evidence based guidance



Taylor & Francis
Taylor & Francis Group

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration

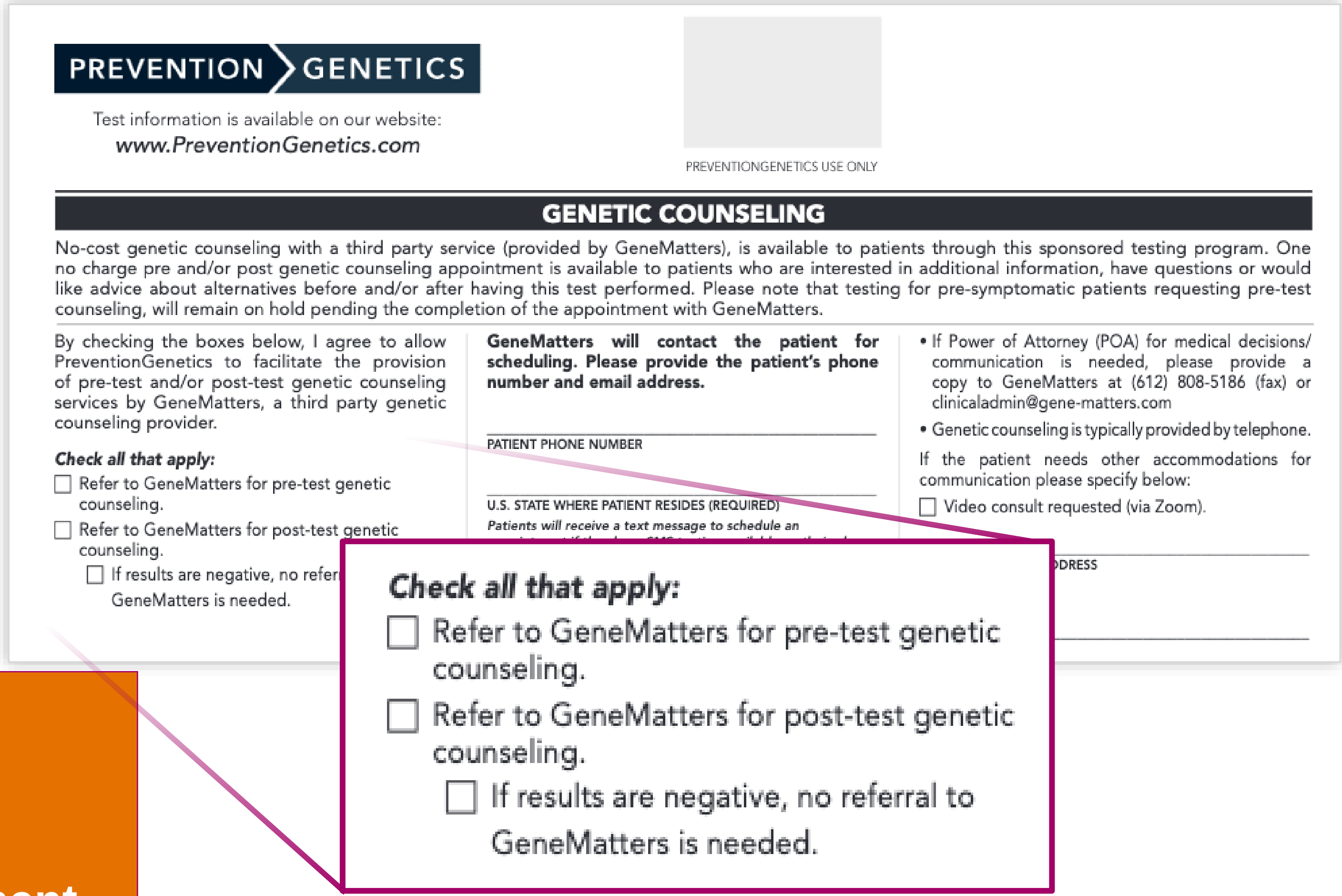
ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/iafd20

Clinical testing panels for ALS: global distribution, consistency, and challenges

Allison A. Dilliott, Ahmad Al Nasser, Marwa Elnagheeb, Jennifer Fifita, Lyndal Henden, Ingrid M. Keseler, Steven Lenz, Heather Marriott, Emily Mccann, Maysen Mesaros, Sarah Opie-Martin, Emma Owens, Brooke Palus, Justyne Ross, Zhanjun Wang, Hannah White, Ammar Al-Chalabi, Peter M. Andersen, Michael Benatar, Ian Blair, Johnathan Cooper-Knock, Elizabeth A. Harrington, Jeannine Heckmann, John Landers, Cristiane Moreno, Melissa Nel, Evadnie Rampersaud, Jennifer Roggenbuck, Guy Rouleau, Bryan Traynor, Marka Van Blitterswijk, Wouter Van Rheenen, Jan Veldink, Jochen Weishaupt, Luke Drury, Matthew B. Harms, Sali M. K. Farhan & On behalf of the Amyotrophic lateral sclerosis spectrum disorders Gene Curation Expert Panel

Sponsored Pre-test and Post Test Third Party TeleGenetic Counseling by GeneMatters can be ordered by your doctor

In the event that timely, local genetic counseling is not available, Ionis Sponsored Genetic Counseling by an ABGC certified genetic counselor via telemedicine is offered through GeneMatters, a GenomeMedical company



PREVENTION GENETICS

Test information is available on our website:
www.PreventionGenetics.com

PREVENTIONGENETICS USE ONLY

GENETIC COUNSELING

No-cost genetic counseling with a third party service (provided by GeneMatters), 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. Please note that testing for pre-symptomatic patients requesting pre-test counseling, will remain on hold pending the completion of the appointment with GeneMatters.

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 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 refer
  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

- 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).

DDRESS

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.

To learn more about genetic counseling and genetic testing for ALS, and to schedule a GeneMatters telegenetic counseling appointment

Please call (888) 460-1891

Data Sharing and Privacy

Working Together to Improve ALS
Diagnoses and Research

Data Sharing and Privacy

- What information is received?
- Information that we do not receive – No PHI
- Permission to share- Clinician Permission, Patient Permission, IRB, GDPR, ICF
- With whom do we share information internally and externally
- What are we interested in learning from the data?
- What are you interested in learning from the data?

De-identified patient data may be used and shared with third parties to support research and improve diagnosis and treatment. No identifiable information is received by Ionis or will be shared. Clinician contact information may be shared, and third parties may contact HCPs regarding products and clinical trials.

With Profuse Thanks

PreventionGenetics – Dr. Luke Drury Kayleigh Avello, Derek Stevens, Chavis Fulmore, Jocelyn Schroeder

GeneMatters a Genome Medical Company- Michelle Hearn and all of the Genetic Counselors who see ALS patients

Ionis Pharmaceuticals- Becky Crean, Chris Yun and the Clinical Development and Clinical Operations Team

Amy Shea, Ionis Pharmaceuticals Diagnostics and Strategic Initiatives Director who made all of this possible

The ALS patients, ALS Carriers and ALS Patient Community who are our raison d’être

ALS Genetic Counseling Resources

- **GeneMatters** Genetic Counseling Information and Appointment line: 888-460-1891
- **National Society of Genetic Counselors**- Find a Genetic Counselor: https://findageneticcounselor.nsgc.org
- **END the LEGACY** :https://www.alshf.org/end-the-legacy
  To register for the ETL Genetic ALS Carrier Support Hour-
  https://forms.gle/1adgSysaaKPebxQg7
- **ALS Research Collaborative** with the ALS Therapy Development Institute, TDI:
  https://www.als.net/arc