AES 2023 ANNUAL MEETING

Dilemmas in Genetic Testing: Ending the Diagnostic Odyssey in Epilepsy

Child Neurology FOUNDATION
Creating a Community of Support

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Acknowledgements

This educational activity is supported in part by education grants from

- Jazz Pharmaceuticals, Inc.,
- Marinus Pharmaceuticals, Inc., and
- UCB, Inc.

Agenda

9:00 am	**Welcome**
	Patient & Caregiver Dilemmas: What I Would Like Clinicians to Know
	Clinical Dilemmas Related to Genetic Testing
	Genetic Testing in the Transition to Adult Care
	Break
	Dilemmas in Clinical Care Scenarios
	Treatment Dilemmas
	Winding Down
12:00 pm	**Adjourn**

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Welcome:
Introduction to the Child Neurology Foundation

M. Scott Perry, MD
Jane and John Justin Institute for Mind Health
Cook Children's Medical Center

December 1, 2023

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Disclosures

- Speaking: Zogenix/UCB, NobelPharma, Marinus
- Consulting: Zogenix/UCB, Biocodex, Stoke Therapeutics, Marinus, Bright Minds, Eisai, Jazz, and Neurelis
- Research (funds paid to Cook Children's): Zogenix/UCB, Stoke, Encoded, Neurocrine, Takeda)

Learning Objectives

- Determine the right time to conduct a genetic test
- Understand the results of a test and the impact on treatment
- How to discuss results with patients and answer questions from families

Acknowledgements

This educational activity is supported in part by education grants from Jazz Pharmaceuticals, Inc., Marinus Pharmaceuticals, Inc., and UCB, Inc.

Acknowledgements

Advocacy Partners

- Epilepsy Foundation
- International Foundation for CDLK5 Research
- Dravet Syndrome Foundation
- Phelan-McDermid Syndrome Foundation
- Epilepsy Alliance of America
- Pediatric Epilepsy Research Foundation

Navigating life with a neurologic disorder can be an **uncertain and isolating** journey.

The Child Neurology Foundation is here to ensure that **no one has to go it alone.**

Child Neurology Foundation's Mission

To improve the care experiences of children living with neurologic conditions by

building meaningful connections between families and medical professionals

AND

serving as a collaborative center of education, support, and care advancement.

Our Community

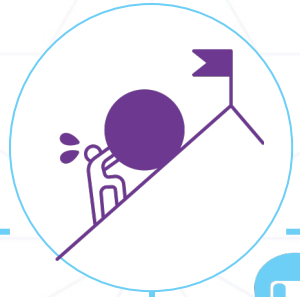
14 million
children live with a neurologic condition (USA)

Thousands of rare and ultra-rare diagnoses
with neurologic components

<3,000
pediatric neurologists

*Source: Federal Interagency Forum on Child and Family Statistics, 2023

Shared Challenges



FAMILIES

Overwhelmed and isolated

Nearly 1/2 of caregivers are very or extremely stressed and report being in crisis daily.

9 in 10 caregivers go to work late, leave early, or take time off during the day to provide care.

Many families are coordinating care across 3-10 medical professionals.

50% of caregivers need 'some or significant' help with finances, treatments, and access to a neurologist.

PROVIDERS

Overworked and siloed

>1/2 of neurologists (56%) feel burned out at least once a week; 10% feel burned out every day

98% of neurologists say they do not get enough time with patients during appointments

7 in 10 neurologists report needing more continuing medical education (CME) than they're currently getting

Top 2 barriers preventing neurologists from providing the highest quality of care are:

1) Insurance/Reimbursement concerns
2) Lack of auxiliary support

Family and Individual Needs for Disability Supports (FINDS) Survey – Community Report 2017
CNF Annual Needs Assessment Survey (2021)

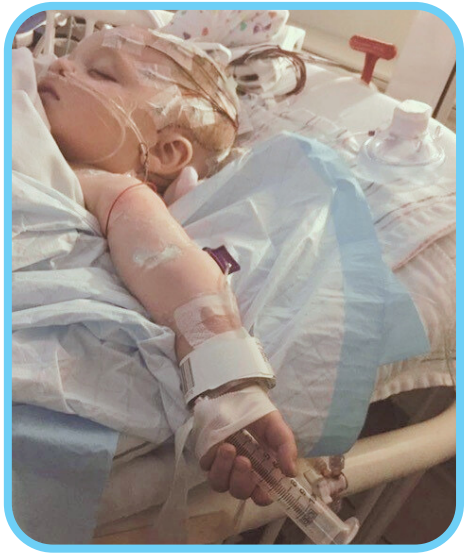
Why Now?

Availability of and access to genetic testing

Overworked and undertrained workforce not adept at neurogenetics

"Living lift" of families without a social services safety net

Exacerbated by COVID-19



Rapidly growing community of diagnosed families at risk of falling through the cracks due to a lack of coordination, education, & social services support

Armed with Compassion

Driven by data,
CNF acts from a
place of understanding.

Annual Needs Assessment Survey
of caregivers and neurologists

Connecting and Collaborating

We work to connect, not replace, all the players across the child neurology community to enable **the rapid sharing of data and information** needed to improve children's experiences and outcomes.

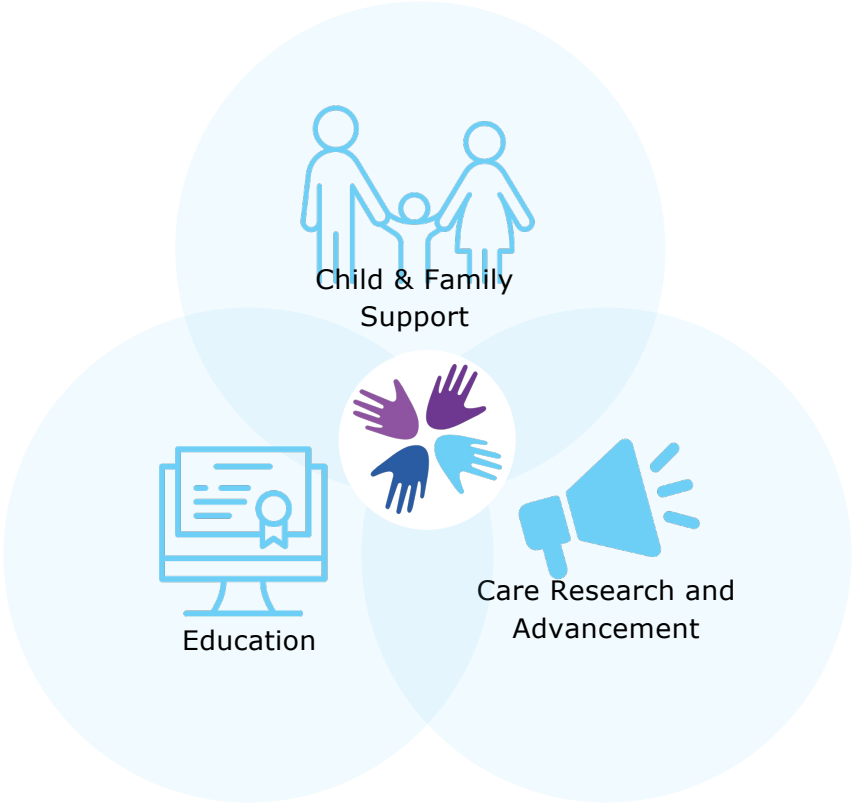
Stronger Together

We work with:

200+ patient organizations and professional societies

Thousands of families and providers

Programs



CHILD & FAMILY SUPPORT

Focused on improving the patient care experience through direct engagement, social services, and partnership with care professionals

EDUCATION

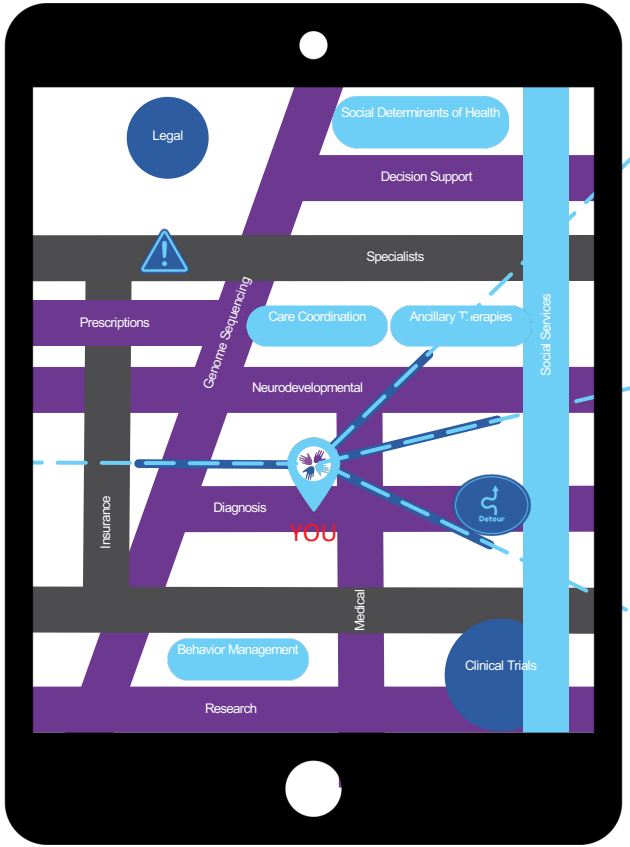
Focused on creating clarity for families and providers through the collection and dissemination of trustworthy information about managing diagnosis, care, and life with a neurologic condition

RESEARCH & CARE ADVANCEMENT

Focused on supporting providers and institutions who care for children with neurologic conditions by building bridges across the neurologic care community

Navigation

Like a GPS system, CNF meets community members where they are and helps them get to where they want to go.



No matter where you are.

CNF will recognize your position.

And empower you for where **YOU** need to go!

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The importance of today's topic

Child Neurology FOUNDATION
Creating a Community of Support

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2022 Assessment Data

CNF collected data using two surveys in March of 2022. The data was collected to better understand the experience of our community and evaluate programming and educational direction. Data was collected about genetic testing for patients with epilepsy.

Families

- 1,513 total responses from 48 states
- 90% of respondents were white
- Household income on average was higher than $100k
- Survey was supported by 53 advocacy organization partners

Child Neurologists (CNs)

- 152 responses from neurologists treating children in 30 states
- 80% of respondents were white, 14% Asian or Asian American
- Survey was supported by CNS and AES

Child Neurology Foundation. “CNF 2022 Needs Assessment & Caregiver Data.” *https://www.childneurologyfoundation.org/2022-caregiver-needs-data/*, August 2022

Causes of Epilepsy are Unknown for Many

Among families

- 40% did not know the reason for the child's epilepsy or seizures
- 1/3 of children without an underlying cause had not had genetic testing

Among child neurologists

- 20% of their epilepsy patients don't know an underlying cause
- 88% report talking about genetic testing to patients without a known cause

Child Neurology Foundation. "CNF 2022 Needs Assessment & Caregiver Data." *https://www.childneurologyfoundation.org/2022-caregiver-needs-data/*, August 2022

Families and Clinicians Differ on WGS

More clinicians are skeptical of WGS's value

- 37% of clinicians believe it won't give a diagnosis or change treatment
- 10% of families believe it won't give a diagnosis or change treatment

More families worry about insurance coverage

- 21% of clinicians believe insurance won't cover WGS
- 60% of families believe insurance won't cover WGS

Some families say they don't want WGS because they *"already have a diagnosis: Epilepsy"*

Child Neurology Foundation. "CNF 2022 Needs Assessment & Caregiver Data." *https://www.childneurologyfoundation.org/2022-caregiver-needs-data/*, August 2022

Genetic Testing leads to diagnosis

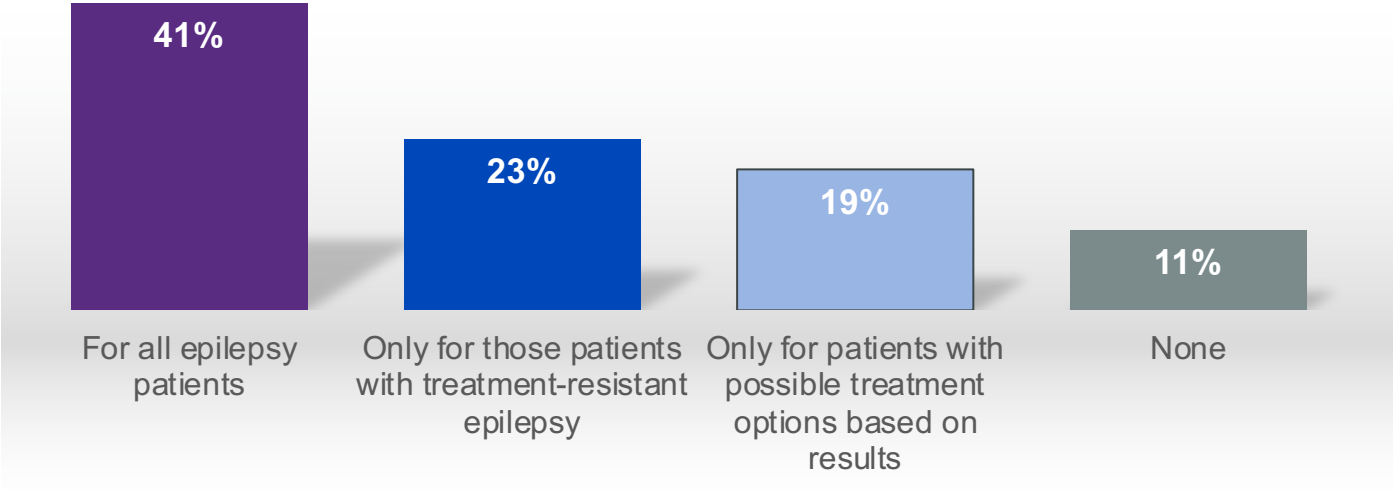
70% of those with a diagnosis had genetic testing

42% children got a diagnosis from WES

30% children got a diagnosis from WGS after all other genetic tests had failed

Child Neurology Foundation. “CNF 2022 Needs Assessment & Caregiver Data.” *https://www.childneurologyfoundation.org/2022-caregiver-needs-data/*, August 2022

For which of your pediatric patients do you consider WGS?



Finding: There is no standard for when to consider genetic testing. Many described specific criteria for their practice in the other category

Child Neurology Foundation. "CNF 2022 Needs Assessment & Caregiver Data." *https://www.childneurologyfoundation.org/2022-caregiver-needs-data/*, August 2022

The search for a diagnosis and genetic testing

- 72% of families without a diagnosis are interested in getting genetic testing
- Only 35% have talked to their neurologist about it
- Of those that talked about it, 32% reported their child's doctor was NOT able to answer all their questions about genetic testing

Child Neurology Foundation. "CNF 2022 Needs Assessment & Caregiver Data." *https://www.childneurologyfoundation.org/2022-caregiver-needs-data/*, August 2022

Families and clinicians agree that testing for a genetic cause would be helpful

92% of families still searching for a diagnosis believe genetic testing would be helpful

42% of families think knowing the reason for their child's epilepsy would be extremely helpful even if there were no known treatments and it wouldn't change the treatment plan

90% of child neurologists think it would be helpful to seek out a genetic cause

Child Neurology Foundation. "CNF 2022 Needs Assessment & Caregiver Data." *https://www.childneurologyfoundation.org/2022-caregiver-needs-data/*, August 2022

A genetic diagnosis mattered

Among families…

39% say it changed the treatment plan

78% say it helped them connect with other families, orgs, and communities

97% say connecting with these groups was helpful

Among clinicians…

31% report always or often being better able to customize the treatment plan

60% report it was always or often helping make diagnosis-specific connections

Child Neurology Foundation. "CNF 2022 Needs Assessment & Caregiver Data." *https://www.childneurologyfoundation.org/2022-caregiver-needs-data/*, August 2022

Impact on clinical care and practice

- There are many dilemmas that medical professionals in epilepsy grapple with when conducting genetic testing for their patients.
- Once an opportunity to do genetic testing is identified, many more questions arise.
- Families and clinicians need to effectively communicate about genetic testing.

CNF is here to help

- Use the QR code at your table to access resources such as:
  - Caregiver webinars about the role of genetic testing
  - 1-page handout for parents explaining genetic testing
  - Epilepsy Education Hub with handouts and webinars for families
  - Links to no cost genetic testing and counseling opportunities
  - Credible disease information in a disorder directory
  - And more

Families can visit **childneurologyfoundation.org,**
call or text 859-551-4977 to be connected to support.

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Caregiver Dilemmas: What I Would Like Clinicians to Know

Tristin West, Parent of Medically Complex Child

Child Neurology Foundation
Patient Experience Bureau

December 1, 2023

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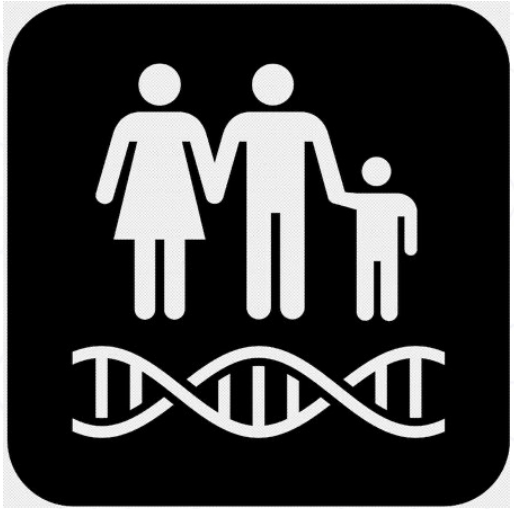
Disclosure

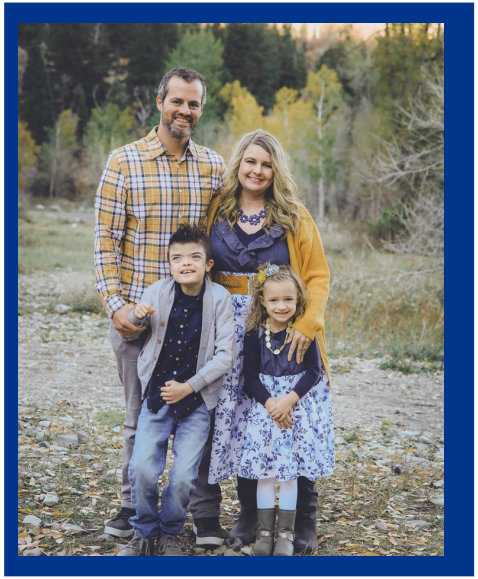
- None

Learning Objectives

- Participants will be able to identify several challenges families may face in when seeking a diagnosis for their children through genetic testing
- Participants will be able to explain ways they can help families with finding resources to help make genetic testing affordable, accessible, understandable and possible

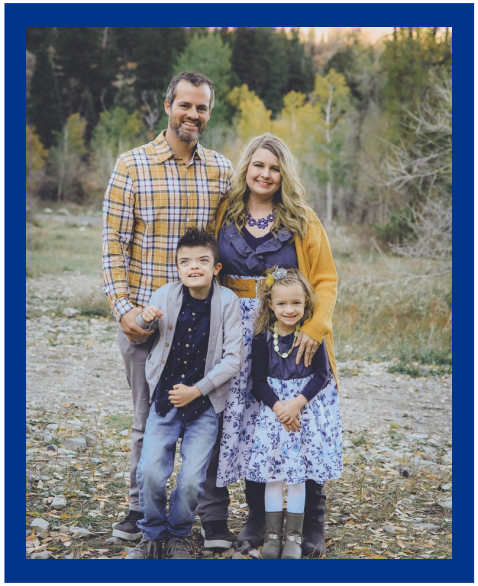


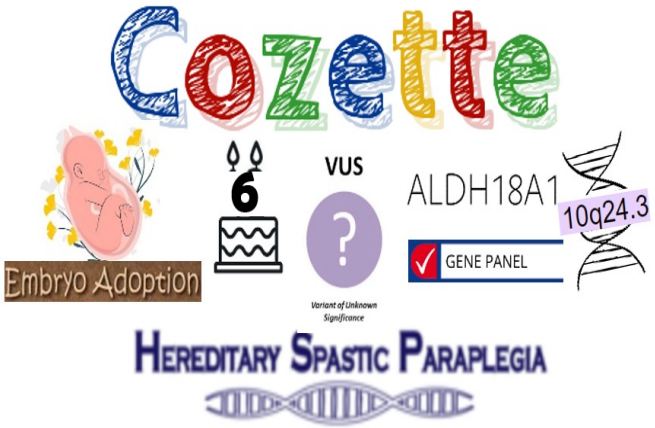
Meet the Wests



Diagnosed using Whole Exome Sequencing
MN1 was found to be pathogenic

Meet the Wests





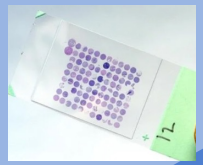
Jayson's Genetic Journey Timeline

2011

Jayson Born
No NICU Stay

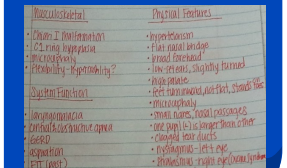
No Knowledge of Any Concerns in Pregnancy

2012



Microarray Genetic Testing & Genetics Appointments

2013



New Genetics Consult

2014

Request Insurance Approval for WES, Denial

2015

WES Directly Through Lab

Jayson's Genetic Journey Timeline

Apr 2016

More Patients Found by Lab

Dec 2016

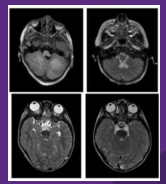
Jay Will Be a Big Brother!

Learned a Publication will be Written

2017

Connection with MN1 Deletion Family

Apr 2018



Rare Brain Abnormality Found- RES

June 2018

Randomly Met Author of First MN1 Deletion Paper

Jayson's Genetic Journey Timeline

Sept 2018

Rhombencephalosynapsis: a hindbrain malformation associated with incomplete separation of midbrain and forebrain, hydrocephalus and a broad spectrum of severity

Part of Hindbrain Study in Seattle

Oct 2018

Hindbrain Malformation Research Program

Seattle Children's

Jay is the Link Researches Were Looking For

Dec 2018

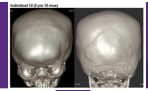
MN1 FOUNDATION

Connected With More MN1 Families

Start of Foundation Website

Dec 2019

MN1 C-terminal truncation syndrome is a novel neurodevelopmental and craniofacial disorder with partial rhombencephalosynapsis



MCTT named, Paper Published

Currently 2023

MN1 C-Terminal Truncation Syndrome MCTT

Private group · 60 members

Community of MCTT and MN1 Families

What I Would Like Clinicians to Know:

Genetic Testing is not <u>Affordable</u> for all Families

Genetic testing can be an expensive cost for families

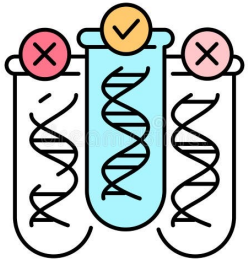
- Many insurance companies will not cover sequencing
- Medicaid does not cover genetic testing in all states
- Are not aware of resources to help with costs
- Costly to see a geneticist/specialist to order testing

What I Would Like Clinicians to Know:
Genetic Testing is not <u>Affordable</u> for all Families

- Cost estimated at $10,000
- Insurance denied WES
- Crowdsourced- Social Media
- Parent told us about a lab
- Lab covered costs of WES

What I Would Like Clinicians to Know:

Genetic Testing is not <u>Affordable</u> for all Families



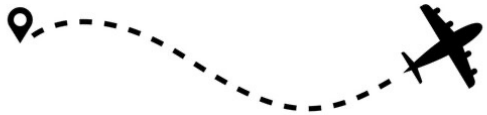
How providers can help:

Provide a list of

- labs with self-pay programs
- local, state, national non-profit organizations that provide financial assistance for testing
- local, state, national resources that assist with medical/travel expenses

What I Would Like Clinicians to Know:

Genetic Testing is not <u>Accessible</u> for all Families



Some areas lack access to geneticists and resources

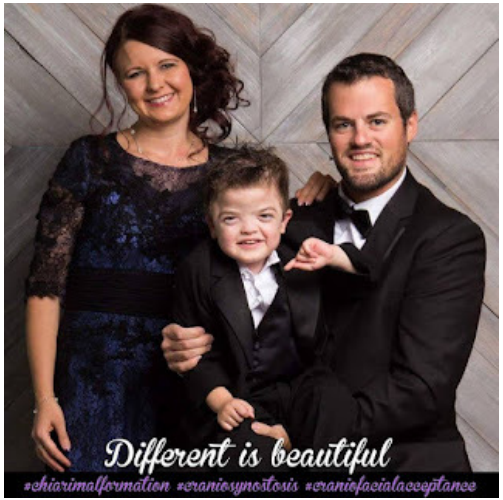
There may be fewer

- supports such as Early Intervention Therapists
- providers and specialists
- docs with experience in referrals/orders for genetic testing

What I Would Like Clinicians to Know:

Genetic Testing is not <u>Accessible</u> for all Families

- Utah has 1-2 year waitlist for genetics
- In 2014 WES was not commonly ordered
- Follow ups in genetics every 3-5 years



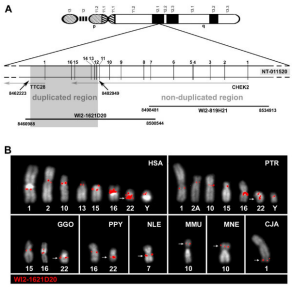
What I Would Like Clinicians to Know:

Genetic Testing is not <u>Accessible</u> for all Families

- **How providers can help:**
- Make sure families
  - work with Early Intervention Specialists and/or School
  - are referred to specialists and can locate them
  - know of organizations for genetic disorders that can offer support

What I Would Like Clinicians to Know:

Genetics and Genetic Testing is not <u>Understandable</u> for all Families



Medical language is complex and difficult to understand

- Typically English only
- Translators not always available
- Genetic Counselors not always available
- New experience, new information

What I Would Like Clinicians to Know:

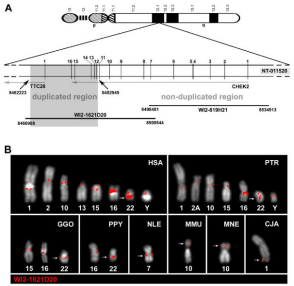
Genetics and Genetic Testing is not <u>Understandable</u> for all Families

- What are the different kinds of genetic tests?
- What resources are available?
- What is a VUS and what does it mean?

*Other parents, social media and non-profit organizations have been a big support for us

What I Would Like Clinicians to Know:

Genetics and Genetic Testing is not <u>Understandable</u> for all Families



- **How providers can help:**
  - schedule a translator
  - Provide medical documents and information in print
  - Share Contact Info
  - Use actions, drawings and diagrams, simplify vocabulary

What I Would Like Clinicians to Know:

Clinicians Can Make Getting a Diagnosis and Treatment <u>Possible</u>

You are a big part of each child's story and diagnostic journey

- You may be the <u>only</u> resource, advocate
- Do not assume others have done it
- If it can help your patient, it is part of <u>your job</u>
- Genetic Testing is life changing and life saving for some patients.

What I Would Like Clinicians to Know:

Clinicians Can Make Getting a Diagnosis and Treatment <u>Possible</u>

- **How providers can help**:
  - Add genetics questions to medical questionnaire/paperwork
  - Provide business cards or contact information of resources
  - Ongoing education on genetics and resources
  - Assign office staff member, a care coordinator or a knowledgeable parent (family liaison) as a support for families with genetic conditions
  - Follow through and follow up

What I Would Like Clinicians to Know:

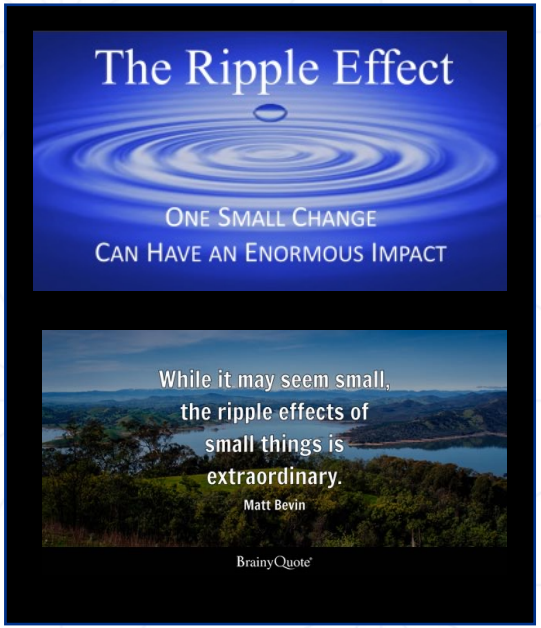
Because of a diagnosis:

- May live long life
- Connections across the world
- Have ideas of how to treat things
- Treated for things that were unknown before
- Credited/Validated with syndrome name
- Doctors now have resources
- Insurance requests and appeals approved easier
- We feel at peace, doing everything we can
- We know so much more and can help other families
- We could have more biological children

Impact on Clinical Care

What is something you can do?

- YOU could be your patient's biggest advocate in getting genetic testing
- You can help make genetic testing affordable, available, understandable and possible for families
- Your patient's family may share their story
- One new genetic diagnosis can
  - Impact/create an entire medical community
  - affect generations
  - leave a medical legacy
  - save lives
  - change EVERYTHING in the lives of many



Tristin West tristintwest@gmail.com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Clinical Dilemmas Related to Genetic Testing

Christa W. Habela, MD, PhD
Krista Schatz, MS, CGC
Johns Hopkins University

December 1, 2023

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Disclosures

Christa W. Habela, MD, PhD

- No conflicts
- Dr. Habela receives research funding from NINDS and the Doris Duke Foundation

Krista Schatz, MS, CGC

- Nothing to disclose

Learning Objectives

- Recognize 2 ways that current genetic testing recommendations may lead to dilemmas in clinical practice
- List 1-2 strategies for resolving a VUS
- Identify 1-2 potential dilemmas related to advances in genetic testing and therapy

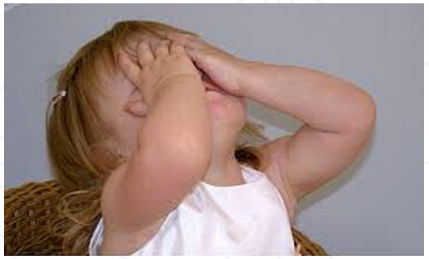
Genetic Testing Strategies

National Society of Genetic Counselors' Practice Guideline endorsed by AES (Smith et al, 2023)

- Genetic testing is strongly recommended for all individuals with unexplained epilepsy, without limitation of age
- WES/WGS and/or a multi-gene panel (>25 genes) as first-tier testing followed by chromosomal microarray
- WES/WGS conditionally recommended over multi-gene panel

A negative genetic test result does not rule out a genetic etiology

Variants of Uncertain Significance



- What is a VUS?
- Can the provider reclassify a VUS? (YES!)
  - Is it necessary?
    - Are there treatment or surgical implications?
    - Is the family considering additional children?
- What if a family doesn’t want to pursue VUS resolution?

Updates on Science and Genetic Testing

- Gene therapy trials
  - Eligibility requires a positive genetic test result
  - Positive genetic test results often cannot predict phenotype
- Genetic testing in focal epilepsy
  - Germline genetic testing for focal epilepsy has a diagnosis rate of ~8%
  - Mosaic/somatic variants detected in ~38% of those with FCDII and HME (Moloney et al, 2022)
- What role will polygenic testing play in clinical care?

Impact on Clinical Care

- Recommendation for genetic testing for all people with epilepsy will create opportunities as well as challenges
  - Changes in management
  - Clinical trials
  - Broadened clinical spectrums
  - VUS interpretation
- VUS resolution is important, particularly when there are clinical care considerations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Genetic Testing in the Transition to Adult Care

Danielle Andrade, MD, MSc, FRCPC, CSCN (EEG)
Professor of Medicine (Neurology), University of Toronto
Medical Director Epilepsy Program
Director, Adult Genetic Epilepsy (AGE) Program, University of Toronto
Co-Chair, ILAE Transition Task Force

December 1, 2023

UNIVERSITY OF TORONTO

AGE ADULT GENETIC EPILEPSY PROGRAM

Child Neurology FOUNDATION
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Disclosures

- Dravet Syndrome Foundation
- Encoded (consultant)
- UCB (consultant)
- Biocodex (consultant)
- Stoke Therapeutics (consultant)
- Jazz (consultant)

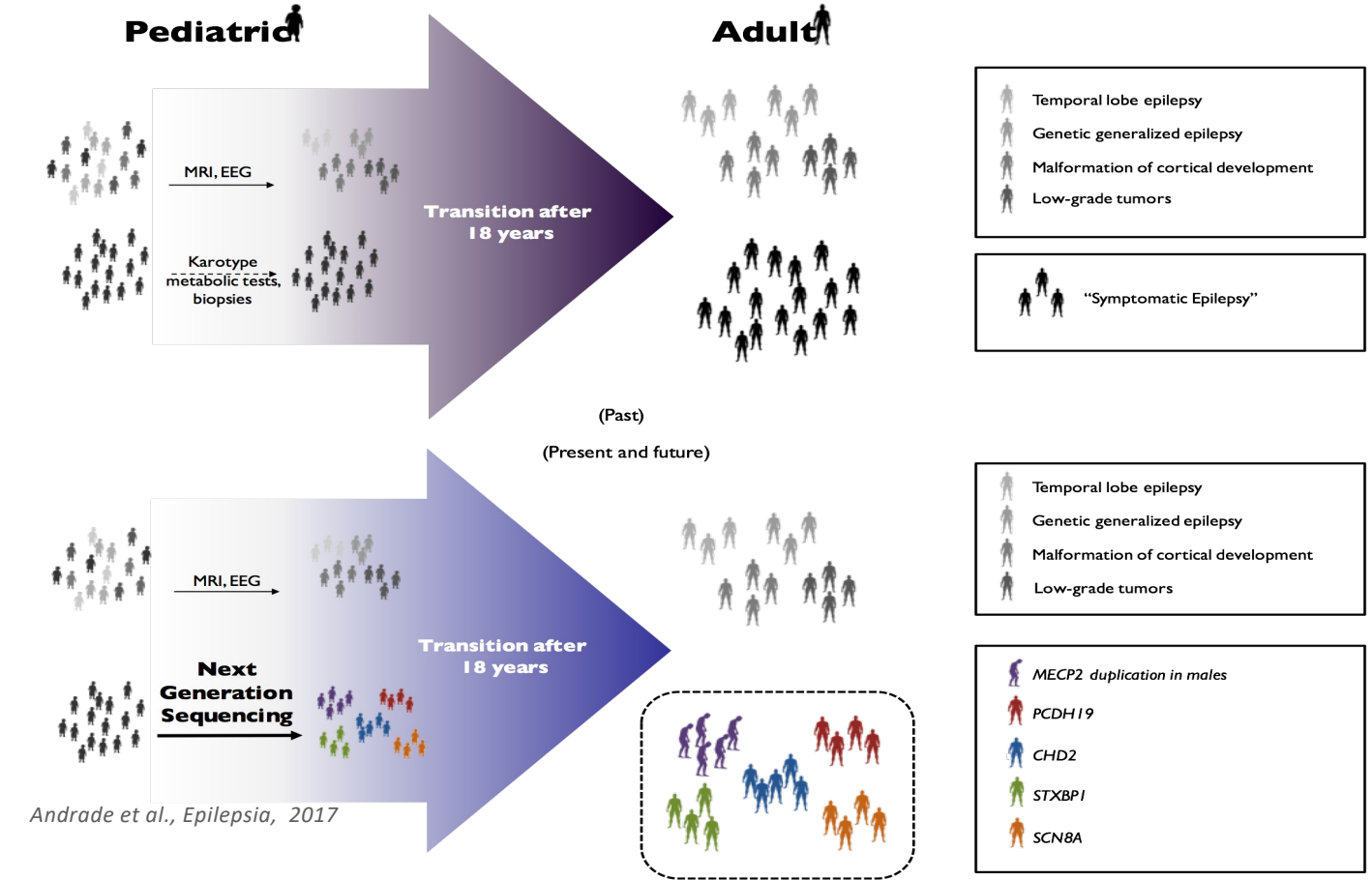
Learning Objectives

- Understand the importance of genetic diagnosis in adults with epilepsy
- Learn how to go about making the diagnosis and supporting the adult patient with a genetic epilepsy as well as their family
- Understand some of the challenges of treating adults with genetic epilepsies

The value of genetic diagnosis for adults

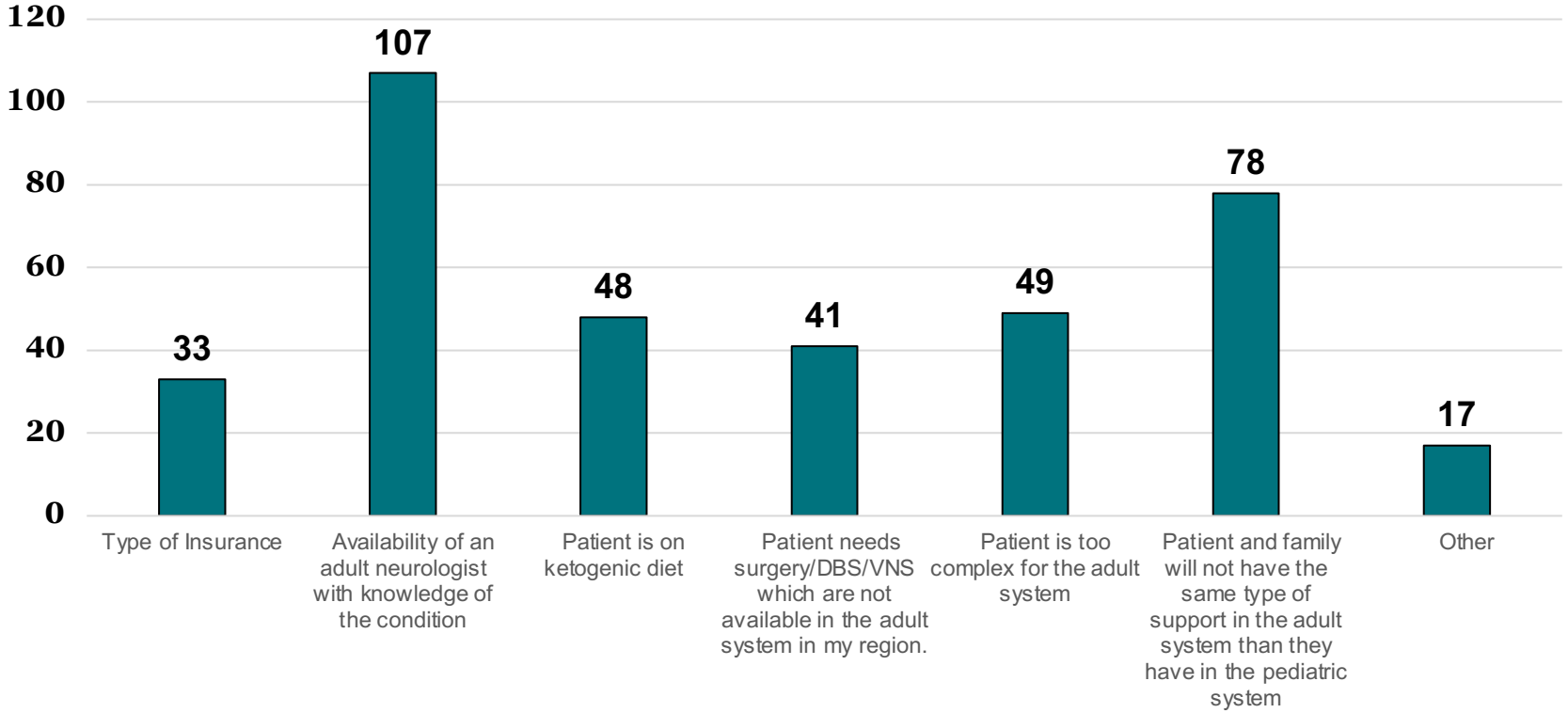
- Clarify the diagnosis and end the diagnostic odyssey
  - Genetic etiology may have been considered early in the disease course but genetic testing at the time (as well as our knowledge of genetic causes) was much more limited
- Changes in treatment of adults recently diagnosed
- Value of understanding genetics in the evaluation of DEE comorbidities
- Genetic counselling for siblings of childbearing age

How testing impacts transition of care



Andrade et al., Epilepsia, 2017

Factors impacting transfer or acceptance into the adult healthcare system



Andrade et al, in preparation

How testing impacts transition of care

- Be prepared to talk about old and new misconceptions such as vaccination encephalopathies and encephalitides
- Discuss pros and cons (likelihood of finding the cause, possibility/need to retest in a few years)

Communication between pediatric & adult providers

- What types of seizures were present in childhood and no longer seen? Clinical diagnosis is mostly based on children's phenotype and very little is known about what changes when these children grow up (adults with Dravet syndrome without myoclonus, absence)
- How did patient respond to specific treatments (keto diet for GLUT1, LMT in DS?)
- If diagnosis not made in pediatric system and you are considering genetic diagnosis
    - Cases of "encephalitis:" What were the LP results? Was there any regression or developmental slowing before the so called "encephalitis?"
    - Obtain DNA for testing in the first visit in the adult system (very unlikely patient and both parents will be present in follow ups with adult neurologist)

Impact on Clinical Care

- If clinically suspicious, always look for genetic diagnosis even if recent genetic investigations were negative
- Think of benefits for patients as well as families
- Opportunity to learn about natural history of genetic DEEs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Dilemmas in Clinical Care: Genetic Case Scenarios

Dalila Lewis, MD, FAAP
Medical University of South Carolina

December 1, 2023

Child Neurology FOUNDATION
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Disclosure

- Speaker’s Bureau - Neurelis

Learning Objectives

- Recognize the role of genetic testing in uncovering developmental and epileptic encephalopathies
- Understand the challenges of prognostication in genetic syndromes with a clinical spectrum
- Acknowledge the importance of literature review with VUS

Case 1

- 8 year-old right-handed female with a history of developmental delay presenting for evaluation for cognitive issues
- She has had global delay requiring therapies throughout her life with previous diagnoses of speech apraxia, motor apraxia, and sensory integration disorder. She has made significant gains in recent years and there is no history of clear regression, but she remains delayed in speech and fine motor skills.
- She was born via C-section at 42 weeks and her perinatal course was complicated by a poor breastfeeding latch. When she was born she was noted to have low tone.
- She had neuropsychological testing at age 6y noting a full scale IQ of 59. Repeat testing at age 7y was 70.
- Prior genetic testing at age 4y was unremarkable

Case 1 continued…

- Routine awake EEG: Spikes, left posterior quadrant, maximal at temporal and parietal regions (F7, T3,P3 and O1)
- 24 hour EEG: Bi-occipital (left maximal) spikes with marked activation during sleep, concerning for electrical status epilepticus of sleep spectrum. Spike-wave index ~93%, calculated via average of 100 sec sample of sleep.
- MRI brain-normal
- Epilepsy genetic panel: pathogenic GNB1 mutation
- Diagnosis: GNB1 encephalopathy

Clinical Findings

- Moderate to profound developmental delay (DD) or intellectual disability (ID); AND
- One or more of the following features presenting in infancy or childhood:
  - Generalized hypotonia of infancy that can evolve to hypertonia and spasticity
  - Feeding disorder and difficulties with weight gain in infancy
  - Movement disorder (dystonia, tics, ataxia, and chorea)
  - Epilepsy (including generalized, focal, and mixed epilepsy and infantile spasms)
  - Behavior problems (repetitive and stereotypic behaviors, attention-deficit/hyperactivity disorder [ADHD], and/or autism spectrum disorder [ASD])
  - Macrocephaly
  - Slow growth
  - Vision impairment (optic atrophy and cortical visual impairment) and/or abnormal eye movements (strabismus, nystagmus)
  - Gastrointestinal issues (chronic constipation, cyclic vomiting, gastroesophageal reflux disease [GERD], and/or abdominal distention with cramps)
  - Craniofacial anomalies (cleft palate, craniosynostosis)

Family Discussion

- Parental testing?
- Implications for siblings (if any)?
- Prognostication?

Case 2

- Nine-month old developmentally normal infant male presenting for evaluation following first-ever seizure episode which presented with afebrile focal status epilepticus
- Birth history and family history unremarkable
- 1 hour awake/asleep EEG: Normal
- Epilepsy genetic panel: Pathogenic mutation in YWHAG
- YWHAG spectrum: Epileptic encephalopathy, childhood myoclonic epilepsy, febrile seizures

Family Discussion

How to approach this clinical discussion with family in a currently developmentally normal infant?

- Literature review
- Limitations of prognostication

Case 3

- 6 year old girl with history of toe-walking, referred to peds PM & R. Examination and history notable for long-standing mild left hemiparesis, early right hand preference, and left limb hypereflexia. Additional history of sporadic left limb shaking lasting minutes, nonsuppressible, without clear associated alteration of awareness.
- Has IEP for unspecified processing disorder
- Birth history: Reported difficult and protracted labor, emergency Cesarean section
- MRI brain: Extensive right hemispheric polymicrogyria
- Genetic epilepsy panel: Heterozygous VUS on LAMC3
- Recessive and complex heterozygous LAMC3 mutations have been associated with malformations of cortical development, particularly in the occipital lobes (occipital cortical malformation- OCCM)

Family Discussion

Genetic etiology versus previously assumed perinatal insult

- Relief vs blame

Impact on Clinical Care

- Genetic testing can uncover as many questions as it answers
- Recognize clinical spectrums and limitations in prognostications thereof
- Thoughtful and empathetic discussions with caregivers with emphasis on shared goals of care is key


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Treatment Dilemmas: When genetic testing leads to potential intervention

Scott Demarest, MD, MSCS

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Associate Professor of Pediatrics and Neurology, University of Colorado

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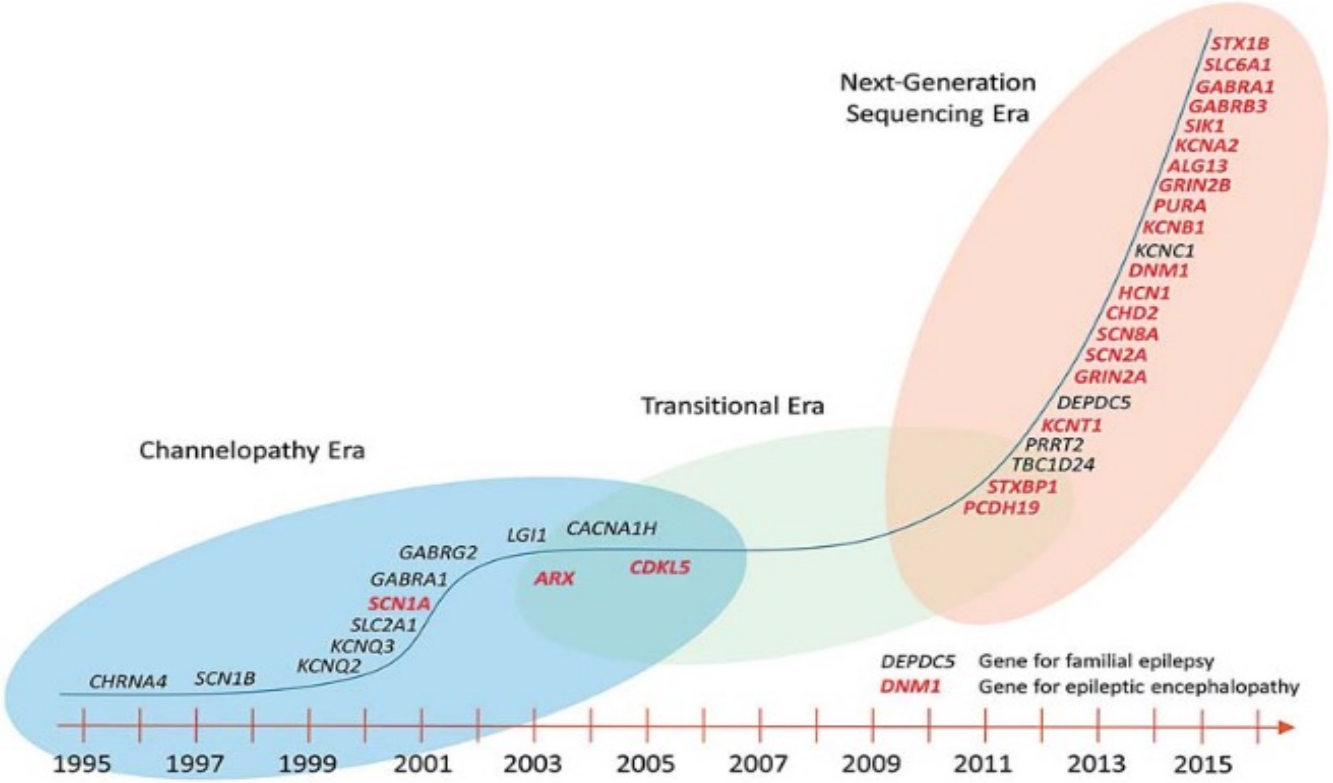
Disclosures

- Consultant for Biomarin, Neurogene, Marinus, Tysha, Ultragenyx, Zogenix (UCB), Capsida, Encoded and Ovid Therapeutics
- Received funding from the NIH, Project 8P and Mila's Miracle Foundation
- Serve on advisory boards for the non-profit foundations Rare X, SLC6A1 Connect, Project 8P, Ring14 USA, FamilieSCN2A and N of 1 Collaborative

Learning Objectives

- To understand the clinical implications and yield of genetic testing
- To consider dilemmas of implementing disease modifying treatments based on genetic testing results
- To understand the role of clinical trials in informing testing and clinical practice
- To discuss how choice of outcome measures can influence clinical trials and availability of disease modifying therapies

History of Genetic Testing in Epilepsy



Helbig, I & Tayoun, A. *Molecular Syndromology.* 2016

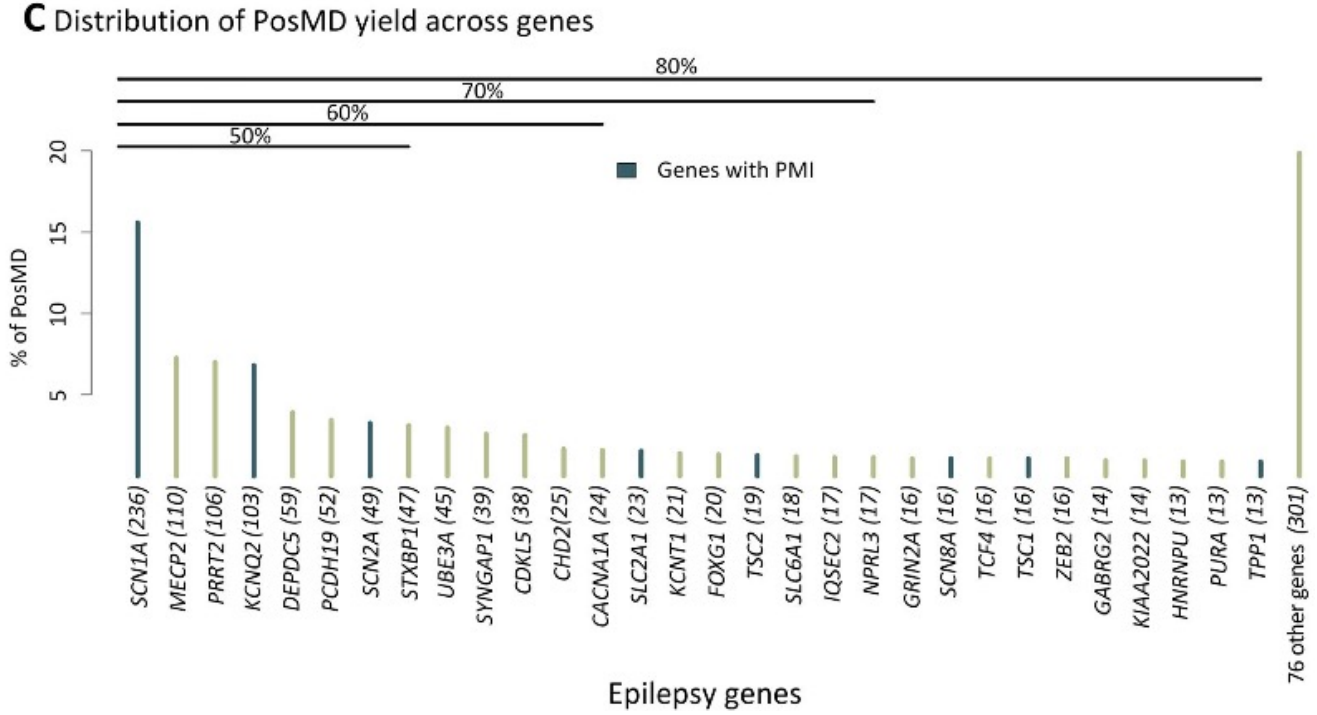
History of Genetic Testing in Epilepsy

Epilepsy Panel Total Yield
>15%

-- but --

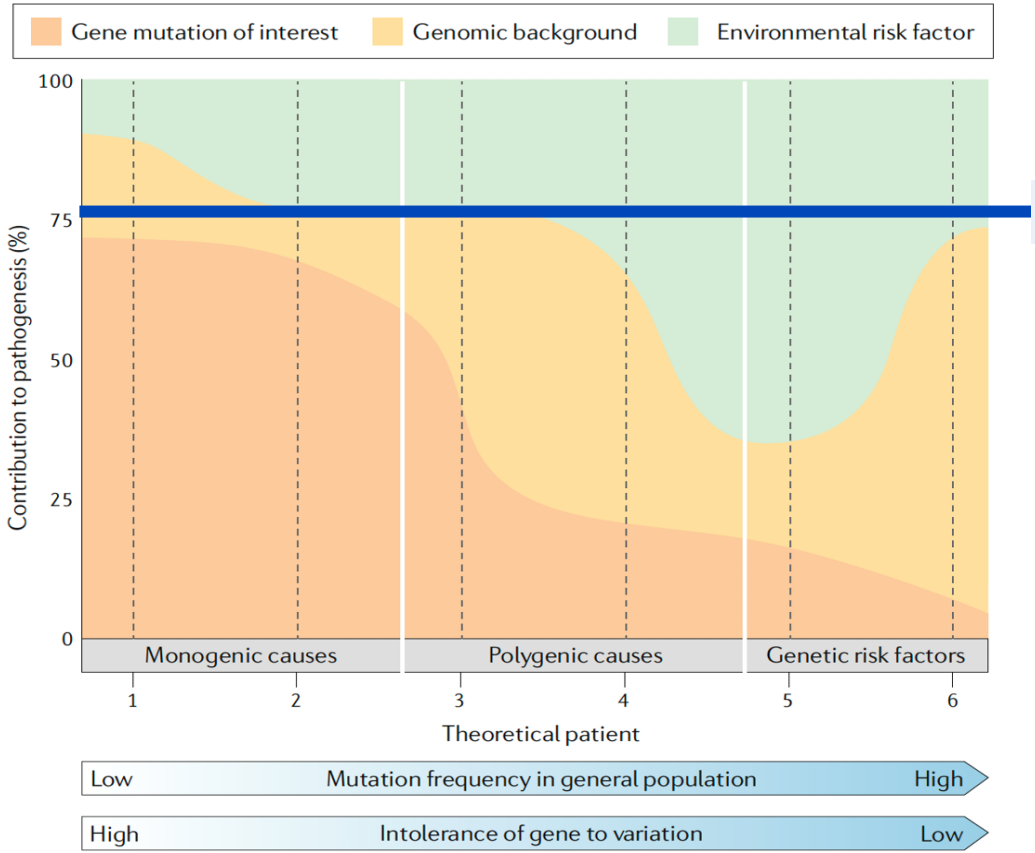
most individual genes have a yield of <1%

>860 genes associated with epilepsy to date



Truty *et al.* Epilepsia Open 2019,
Tumiene *et al*. Clinical Genetics 2018

”Monogenic epilepsies”



Threshold for Disease

Demarest *et al.* Nature Reviews, Neurology 2018

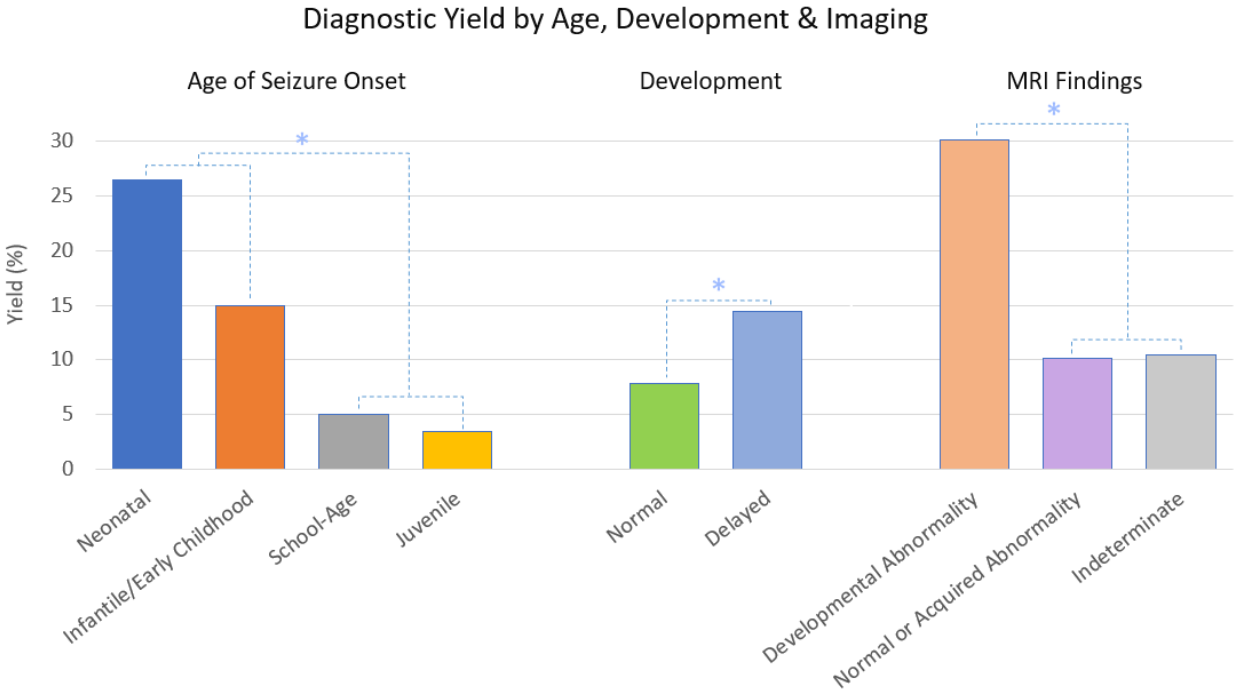
The Value of Genetic Testing in Epilepsy

- Provides families with a specific reason
  - Can provide hope even if there is not current treatment (Reiff *et al. 2017)*
  - Relief of maternal guilt (unpublished data)
- Stops the diagnostic odyssey (Sci Transl Med. 2012)
- Family planning implications
- Prognosis
- Changes Management
  - Precision Medicine Implications
  - Medical Management Implications
    - Screening for potential co-morbidities

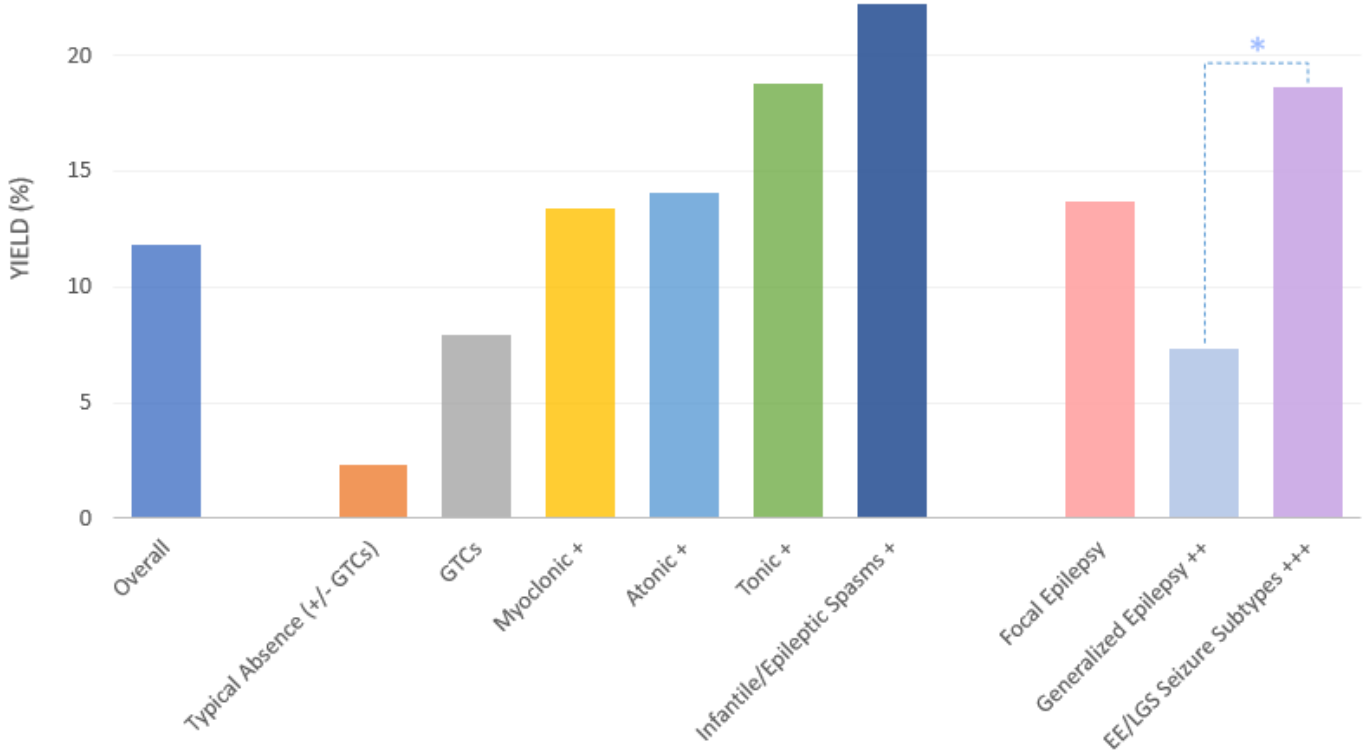
Yield of Genetic Testing

At CHCO we conducted our own review of genetic testing panels Feb 2016 – Feb 2020

Brock DC, Abbott M, Reed L, et al. Epilepsy panels in clinical practice: Yield, variants of uncertain significance, and treatment implications. *Epilepsy Res*. 2023



Diagnostic Yield by Seizure Subtype



Brock DC, Abbott M, Reed L, et al. Epilepsy panels in clinical practice: Yield, variants of uncertain significance, and treatment implications. *Epilepsy Res*. 2023

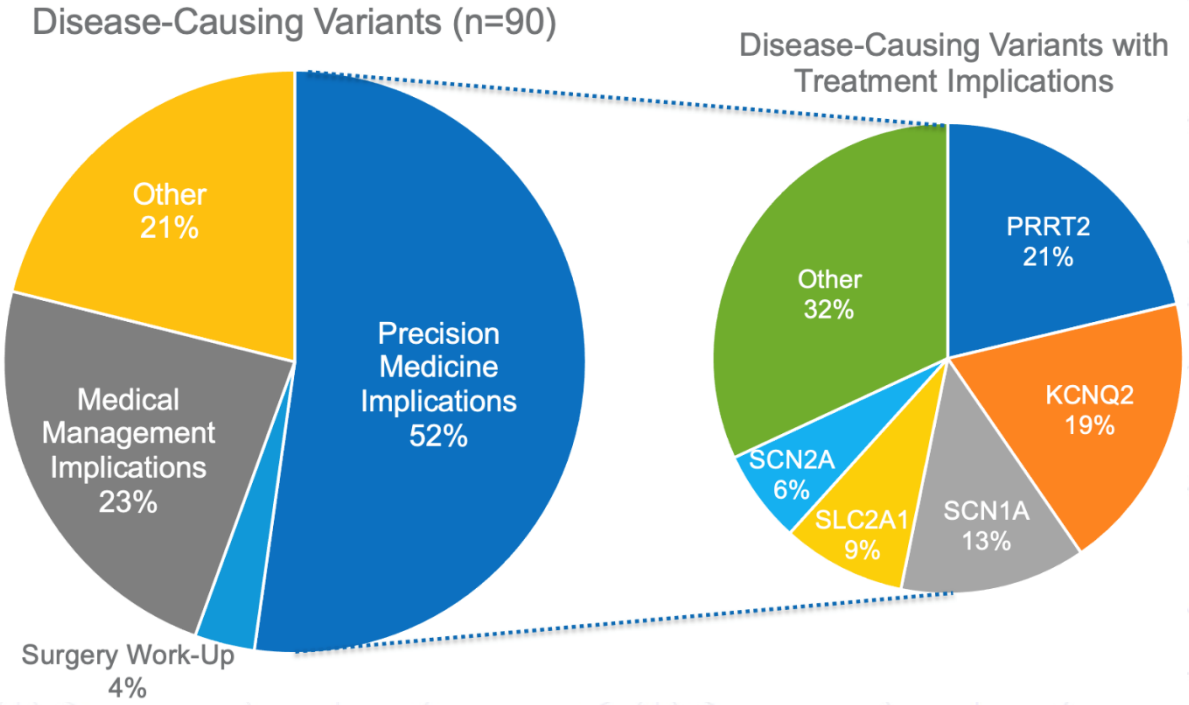
Clinical Impact of Disease-Causing Variants

Precision Medicine Implications

- Per Truty et al study
- 35 epilepsy genes for which there are:
  - Specific or emerging AED indications
  - AED contraindications
  - Biochemical treatment guidelines

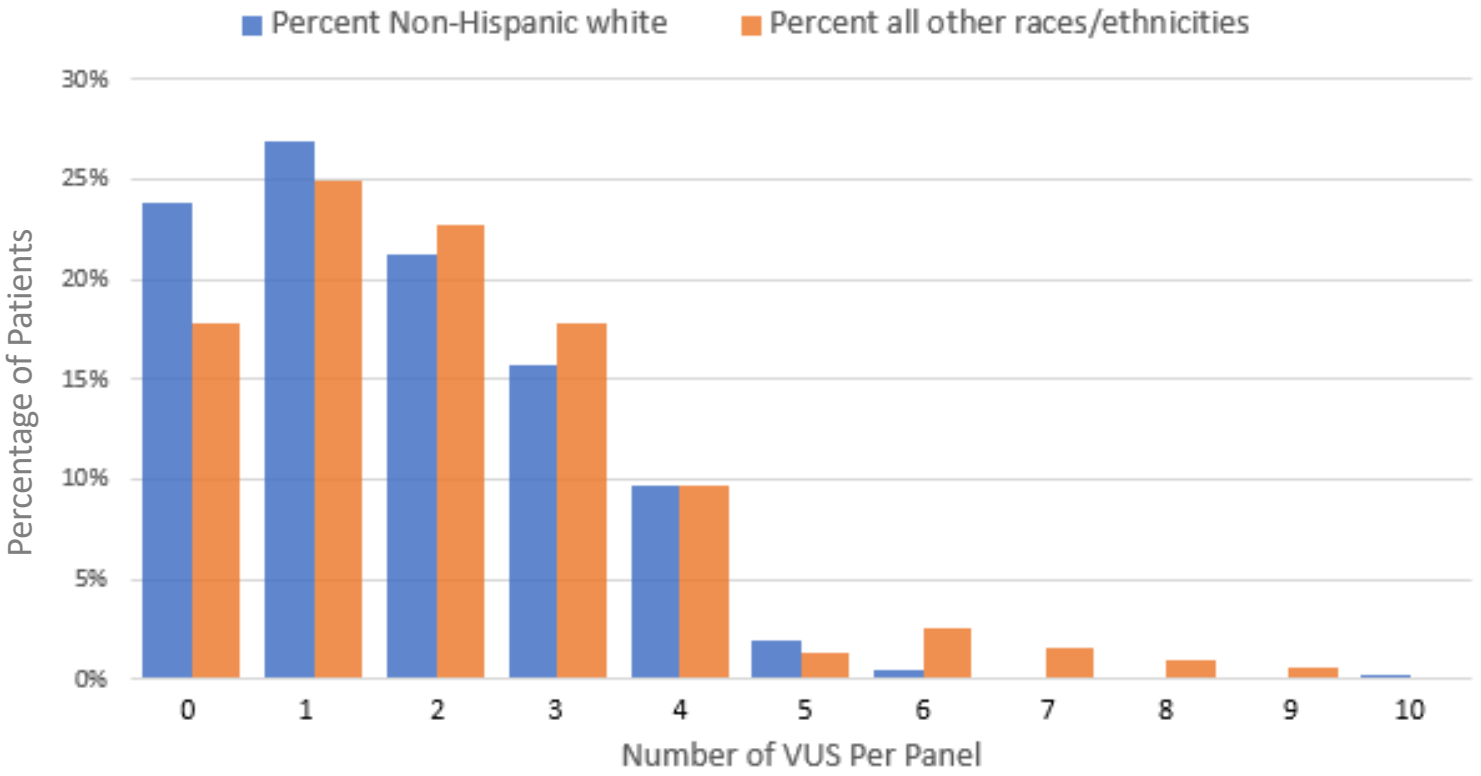
Medical Management Implications

- Referral to specialty or multidisc clinic
- Published care guidelines
- Recommended surveillance



Brock DC, Abbott M, Reed L, et al. Epilepsy panels in clinical practice: Yield, variants of uncertain significance, and treatment implications. *Epilepsy Res*. 2023

Distribution of VUSs by Race/Ethnicity



Brock DC, Abbott M, Reed L, et al. Epilepsy panels in clinical practice: Yield, variants of uncertain significance, and treatment implications. *Epilepsy Res*. 2023

Notes on discussing VUSs with families…

- Our data showed that there were on average 1.2 VUSs per 100 genes on a panel
- For every disease-causing result there were 15.7 VUSs
- This burden of VUSs is exacerbated when looking at races other than Caucasian, with non-Hispanic white patients having 1.7 VUSs per panel when compared to 2.1 VUSs in all other ethnicities
- VUSs can be
  - time consuming to discuss
  - create confusion for families
  - lengthen the diagnostic odyssey
  - hard to know how to treat
- They require skilled genetic counseling to fully discuss results

Brock DC, Abbott M, Reed L, et al. Epilepsy panels in clinical practice: Yield, variants of uncertain significance, and treatment implications. *Epilepsy Res*. 2023

When genetic testing has precision medicine implications: Therapeutic Targets

Disease Modifying Treatments in Development

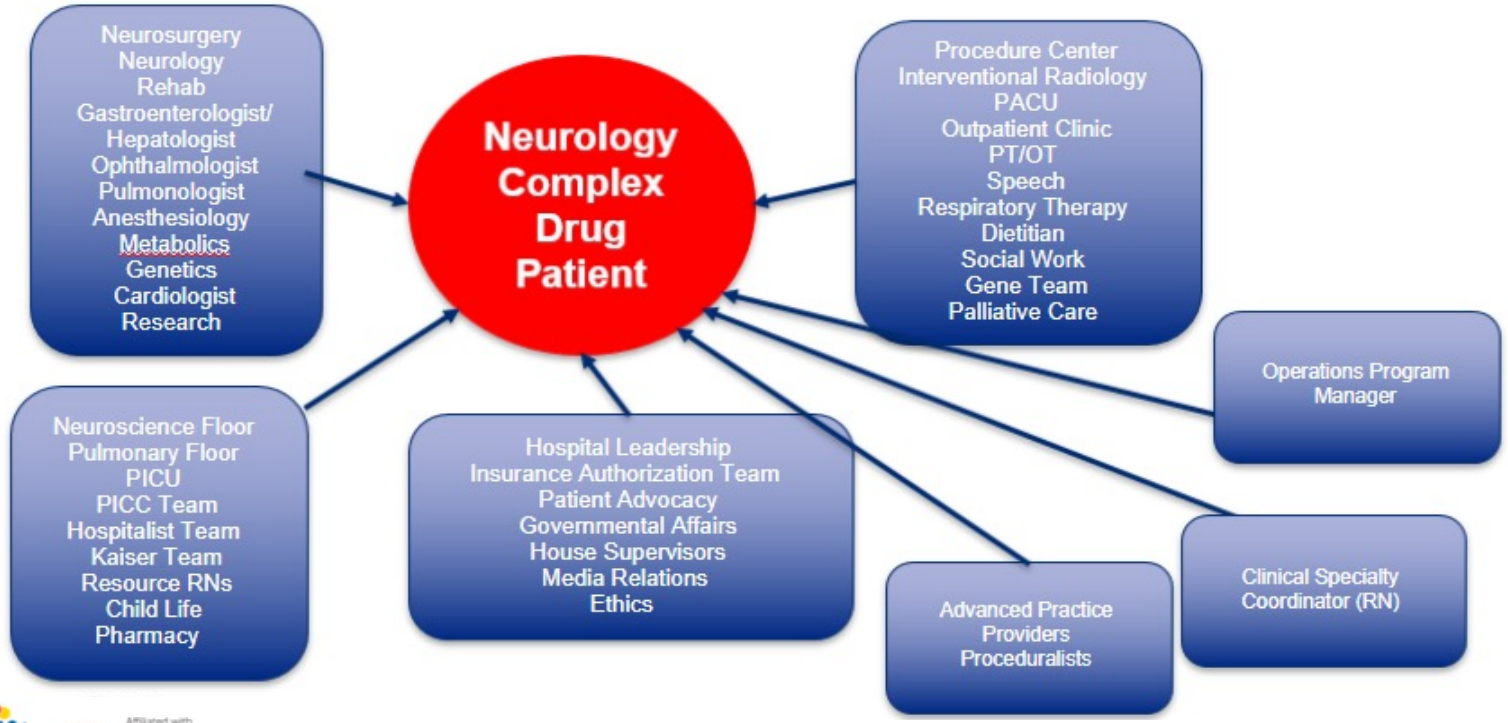
Table 1 DMTs under development for genetic epilepsies

Indication for treatment **(TX) (condition name)**	ICD-10 for condition	Name of drug or device	Status of TX (pre-trial, active trial, approved, off-label)	Type of TX (gene replacement, RNA modulation, biologic, enzyme replacement)
AADC deficiency	E70.81	PTC-AADC	Approval pending	Gene replacement
Angelman Syndrome	Q93.51	TSHA-106	Pre-trial	RNA
Angelman Syndrome	Q93.51	RO7248824	Pre-trial	RNA
Aicardi-Goutières	G31.8	Baricitinib	Off-label	Biologic
CDKL5 disorder	G40.2	REGENXBIO AAV	Pre-trial	Gene replacement
CLN1	E75.4	TSHA-118	Pre-trial	Gene replacement
CLN1	E75.4	ABO-202	Pre-trial	Gene replacement
CLN2	E75.4	AAV2CUhCLN2	Active trial	Gene replacement
CLN2	E75.4	Cerliponase Alfa	Approved	Enzyme replacement
CLN3	E75.4	ABO2-201	Pre-trial	Gene replacement
CLN5	E75.4	Neurogene	Pre-trial	Gene replacement
CLN7	E75.4	Neurogene	Pre-trial	Gene replacement
FOXG1	F84.2	TSHA-117	Pre-trial	Gene replacement
Fragile X syndrome	Q99.2	TSHA-114	Pre-trial	Gene replacement
GM2	E75.00	TSHA-101	Pre-trial	Gene replacement
KCNQ2	Q99.9	TSHA-110	Pre-trial	Gene replacement
MEPC2 duplication	Q92.5	Ionis ASO	Pre-trial	RNA
Prader-Willi syndrome	Q97.11	TSHA-116	Pre-trial	RNA
Rett syndrome	F84.2	OAV201	Pre-trial	Gene replacement
Rett syndrome	F84.2	TSHA-102	Pre-trial	Gene replacement
SCN1A	G40.83	STK-001	Active trial	ASO
SCN1A	G40.83	ETX-DS-001	Pre-trial	RNA
SCN2A	G40.91	Ionis ASO	Pre-trial	RNA
SLC13A5	G40.4	TSHA-105	Pre-trial	Gene replacement
SLC6A1	Z15.89	TSHA-103	Pre-trial	Gene replacement
X-linked developmental encephalopathies	F84.2, G40.2, G40, G40.3, Z15	ACTX-101	Pre-trial	RNA

- Many disease modifying treatments are either in pre-clinical or active trial at this point for various genetic epilepsies
- Multiple therapeutic targets are being investigated including gene replacement, ASO, enzyme replacement

Brock, Dylan C et al. "Clinical Trial Design for Disease-Modifying Therapies for Genetic Epilepsies." *Neurotherapeutics : the journal of the American Society for Experimental NeuroTherapeutics* vol. 18,3 (2021)

Teamwork and Coordination Across a Spectrum of Disciplines



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MD Leads for Neurology Complex Drugs

Battens Disease

Cerliponase Alfa
Lead MD: Dr. Scott Demarest

Spinal Muscular Atrophy (SMA)

Nusinersen
Lead MD: Dr. Julie Parsons

Onasemnogene Abeparvovec-xioi
Lead MD: Dr. Julie Parsons

Risdiplam
Lead MD: Dr. Julie Parsons

Duchenne Muscular Dystrophy (DMD)

Casimersen
Lead MD: Dr. Anne Stratton

Eteplirsen
Lead MD: Dr. Susan Apkon

Golodirsen
Lead MD: Dr. Anne Stratton

Viltolarsen
Lead MD: Dr. Susan Apkon

Total Patients Treated by Complex Drugs Program

Year	CLN2	CLN7	DMD	SMA	Grand Total
2016				5	5
2017			1	17	18
2018	1		3	35	39
2019	2	1	5	39	47
2020	2	1	6	43	52
2021	4	1	8	49	62
2022	5		13	56	74
2023	4		10	43	57
Grand Total	**5**	**1**	**13**	**81**	**100**

As of April 1, 2023

Treatment Dilemma: Shared Decision Making with Families on Therapy Type

- Once a condition has an approved therapy, regardless of type, it will be more likely to have another therapy approved, as it made it through a clinical trial successfully
- Will need to learn from our neuromuscular colleagues on how to navigate choosing a therapy type when multiple options are available for a condition
- Studies are needed to look at how families make these decisions, what can be helpful as the provider team guiding these choices

Many conditions will eventually have multiple options for therapeutic targets

- Currently SMA has this with gene therapy vs ASO
- Other conditions will likely encounter this dilemma based on current pre-clinical and clinical trials on *clinicaltrials.gov* including:
  - SCN1A
  - Rett Syndrome
  - Batten Disease
  - Angelman Syndrome

Therapeutic approach	Gene replacement	Gene editing	ASOs	Protein replacement
Variant-specific		✓	✓	
Gene-specific	✓	✓	✓	✓
Advantages				
One-time dose	✓	✓		
Effective for truncated/deleted genes		✓	✓	
Uses natural cell regulation	✓		✓	
Disadvantages				
Recurrent dosing			✓	✓
Artificial regulation		✓	✓	✓
Vector-based limitations	✓	✓		
Off-target effects	✓		✓	
High manufacturing cost	✓	✓		✓

Carvill GL, Matheny T, Hesselberth J, Demarest S. Haploinsufficiency, Dominant Negative, and Gain-of-Function Mechanisms in Epilepsy: Matching Therapeutic Approach to the Pathophysiology. *Neurotherapeutics*. 2021;18(3):1500-1514. doi:10.1007/s13311-021-01137-z

Clinical Trial Considerations: Discussion with Families on Expectations

- Parents have different priorities & expectations when it comes to a disease modifying therapy vs a small molecule or drug repurposing trial
- In qualitative interviews of *SCN2A* caregivers, there was a considerable difference seen in expectations for a small molecule vs gene therapy trial in terms of outcomes

***SCN2A*-Developmental and Epileptic Encephalopathy: What Does Better Look Like?**

Table: Examples of parent estimates of important differences for trial participation

Impairment	Domain	Small molecule trial	Gene therapy trial
Severe (n=5)	Gross motor	More strength and endurance Move confidently in unfamiliar spaces	Able to bike ride and hike Trajectory of continuing improvement
	Fine motor	Pincer grasp, transfer items, precision Using a pencil or crayon	Using a pencil or crayon Precise manipulation of fasteners
	Communication	Use simple sentences Respond to name	Express needs with words Simple conversations
	ADL*	Chew food / sit for a whole meal More involvement in dressing, toileting	Knowing they need to use the toilet Able to dress, play, manage toileting
Profound (n=3)	Gross motor	Sitting on own Reaching with arm	Head control Motivation to roll Transfer and step to wheelchair
	Fine motor	Able to open hand Reach and grasp	Purposeful grasping Bilateral hand use Trajectory of continuing improvement
	Communication	Point to where it hurts Consistent choice making	*Same* Communicate their needs
	ADL*	Co-operative with toileting Eating orally	Helping to dress Helping to manage toilet needs

* ADL – Activities of Daily Living

Downs J, et al. SCN2A-Developmental and Epileptic Encephalopathy: What Does Better Look Like? American Epilepsy Society 2022. Nashville, TN

Clinical Trial Considerations: Discussion with Families on Expectations

- Disease modifying therapies will aim to **alter** the course of a disease for the better, but at this point are not a cure
- Consider in conversations with families that there may be aspects of a condition that make their child **unique** that they do not necessarily want changed by a gene therapy
- Before enrolling in a clinical trial, a discussion should be had with the family, weighing the **risks and benefits** of an intervention compared to what results a family is hoping for
  - Risk of causing more harm than benefit, especially in the case of neurodegenerative conditions (CLN)
  - Risk of some symptoms improving but other symptoms (e.g., behavior) worsening and impacting quality of life
  - Possibility that receiving a treatment will disqualify you from trials in the future

Unique Challenges of Gene Therapy Trial Design

- Smaller cohorts than traditional anti-seizure medication trials
- Longer durations due to need for developmental outcome endpoints
- Often need historical controls
- More varied outcome measures may be required vs using seizure reduction

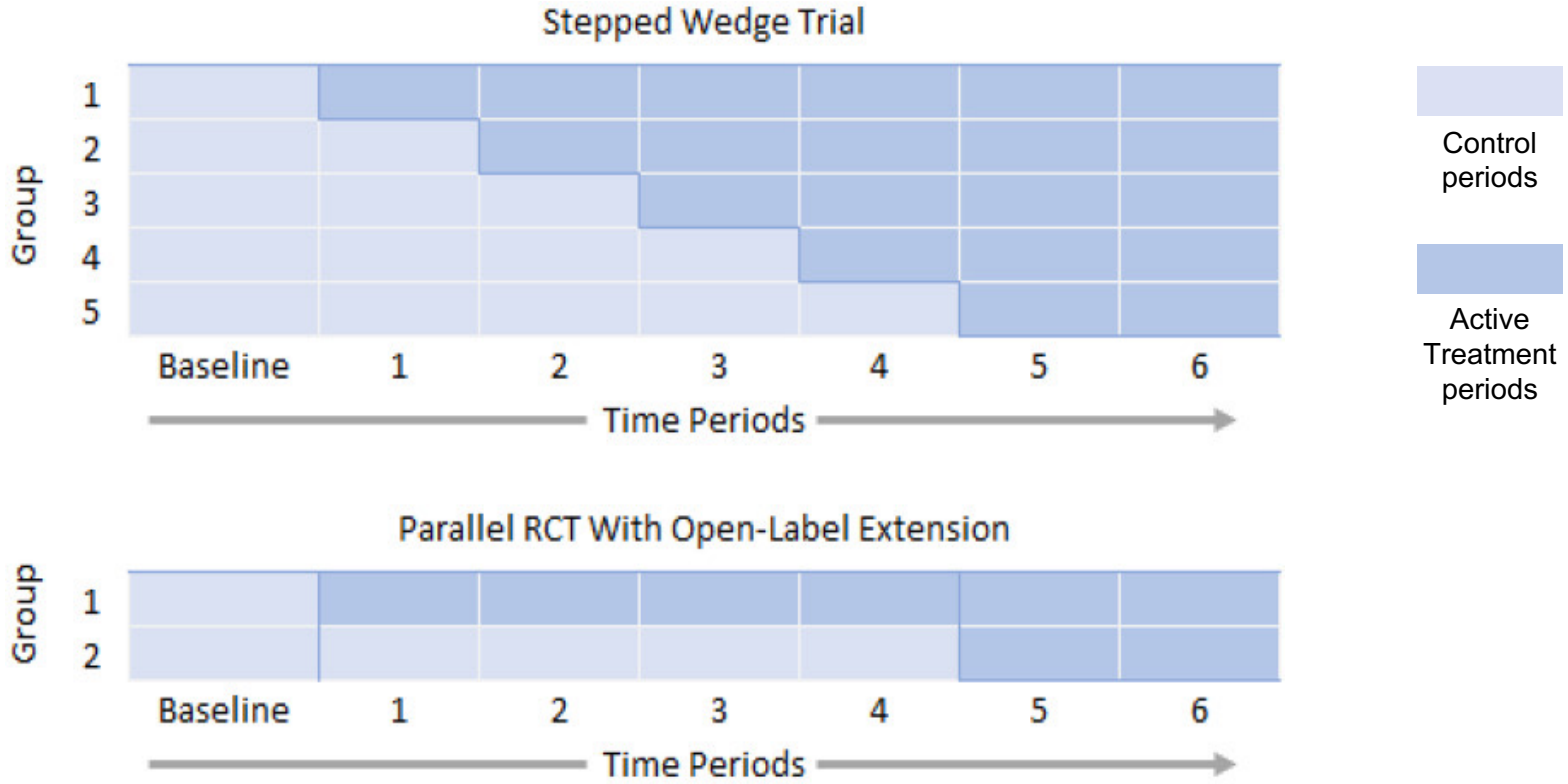
Anti-Seizure Medication trials vs Disease Modifying Therapy trials

Table 3 Trial features of conventional ASM trials and DMT trials

Trial feature	Conventional ASM add-on trials	DMT trial
Population	Small to large (*N*) Heterogeneous population · Drug-resistant epilepsy	Small (N) • Rare and orphan disease More homogenous · Shared genetic diagnosis
Duration	Shorter · 2–6 months	Longer · 1–2 years
Trial design types	Parallel RCT · Conventional trial design Cross-over RCT · Requires wash-out period	Parallel RCT · Open-label phase may be ethically required if benefit expected Stepped-wedge RCT · Practical for rare diseases · May be ethically superior Historical control trial · Comparison to historical controls · Requires robust natural history studies
Outcome measure	Percent seizure reduction · Accepted by FDA · Excellent comparative historic data · Limited disease-modifying relevance Responder rate · ≥ 50% seizure reduction · Accepted by European authorities · Excellent comparative historical data · Limited disease-modifying relevance Time-to-first seizure · May be impractical for DMT Time-to-*N*th seizure · May be impractical for DMTs	Naturalistic functional endpoint · Seizure-reduction efficacy QOL · Tolerability / safety · Limited comparative data Disorder-specific outcome measures · Limited comparative data Time to "X" · "X" = milestone achievement, g-tube placement, or other disease-specific endpoint · Limited comparative data

Brock, Dylan C et al. "Clinical Trial Design for Disease-Modifying Therapies for Genetic Epilepsies." *Neurotherapeutics : the journal of the American Society for Experimental NeuroTherapeutics* vol. 18,3 (2021): 1445-1457. doi:10.1007/s13311-021-01123-5

Clinical Trial Design



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Are we using the correct outcome measures for Disease Modifying Treatment trials?

In CDKL5 Deficiency Disorder, patients reported the following priorities in both a parent report and the natural history study

CDD PFDD Top Concerns	NHS 3 Top Concerns (courtesy of Jeff Neul)
Global developmental delay	Epilepsy/Seizures
Epilepsy/seizures	Communication
Gastrointestinal and feeding problems	Sleep
Limited or absent speech	Lack of hand use
Behavioural disturbances	Abnormal walking/balance issues
Visual impairment	Constipation
Difficulty walking	Vision
Limited hand control	Teeth Grinding
Sleep	Repetitive hand movements
Scoliosis (curvature of the spine)	Poor weight gain

"CDKL5 Patient-Focused Drug Development." *International Foundation for CDKL5 Research*, International Foundation for CDKL5 Research, 19 May 2023, www.cdkl5.com/PFDD.

Are we using the correct outcome measures for Disease Modifying Treatment trials?

In a study of parents of children with Angelman Syndrome, parents identified their top priorities for a clinical trial to focus on

- Neurology/Seizures/Epilepsy
- Communication skills
- Motor Skills
- IQ/Cognitive function
- Expressive speech
- Sleep
- Behavior

Adams, D, Roche, L, Heussler, H. Parent perceptions, beliefs, and fears around genetic treatments and cures for children with Angelman syndrome. *Am J Med Genet Part A*. 2020; 182A: 1716–1724. https://doi.org/10.1002/ajmg.a.61631

Seizure frequency as primary outcome measure: Potential problems

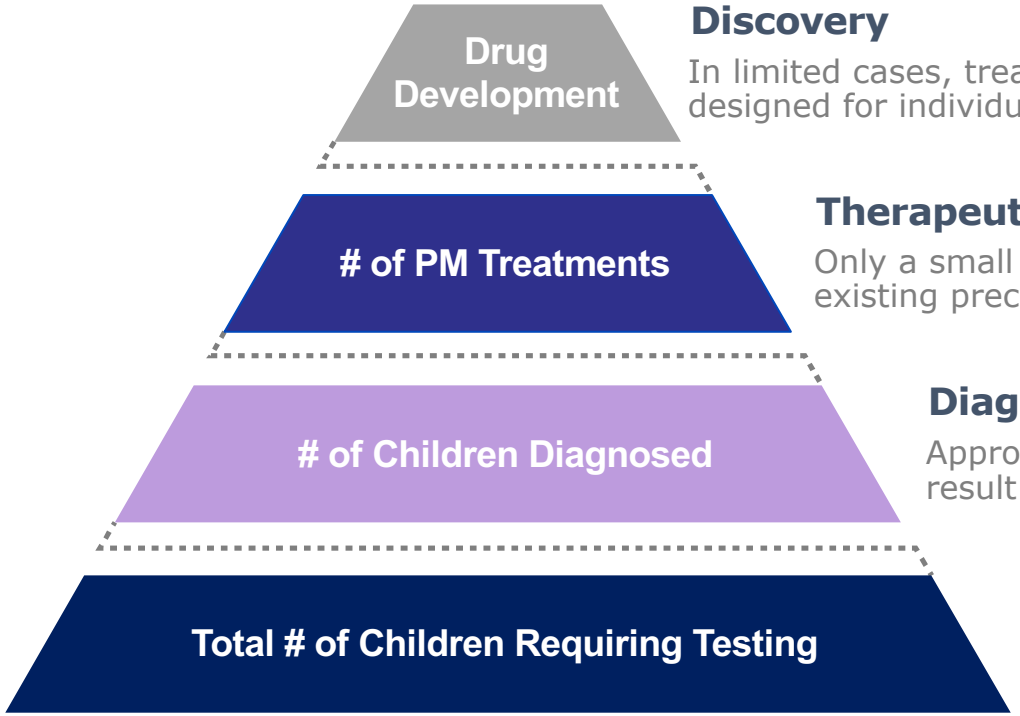
- Many genetic epilepsy syndromes have a range of seizure types and severity
- *STXBP1* often has seizures within the first year of life (89%) however many achieve seizure remission, yet go on to continue to have developmental challenges[4]
- *SCN2A* loss of function patients often do not have seizures but have a neurodevelopmental phenotype
- Vector based treatments often involve immunosuppression (steroids etc.) which can affect seizure frequency

Xian, Julie et al. “Assessing the landscape of STXBP1-related disorders in 534 individuals.” *Brain : a journal of neurology* vol. 145,5 (2022): 1668-1683. doi:10.1093/brain/awab327m

Take-aways for clinical trials and clinical care

- While epilepsy is a major concern, it is not the only concern
- Disease modifying therapies should be aimed at improving the majority of these concerns
- Will need outcome measures which consistently can measure (both for clinical trials and clinical care)
  - Cognition
  - Speech/Motor
  - Sleep
  - Behavior
  - Vision

Precision Medicine: Today's Challenges



Discovery

In limited cases, treatments can be designed for individuals

Therapeutics

Only a small fraction of diagnoses have existing precision medicine treatments

Diagnosis

Approximately 20-60% of tests result in diagnosis

Access to Testing

Not all children who would benefit from genetic testing have access

How to support precision medicine therapy implementation, issues for consideration:

- How do we guide clinical care and learn from every patient?
  - Learning Healthcare Systems
  - Building decision support tools to support diagnostic results
- Similar vectors are being used for different gene therapy treatments
  - Much of the side effects and morbidity come from the vector
  - How do we ensure cross learning and dissemination of serious safety concerns?
  - How do we optimize our immune suppression and side effect management?

My gratitude…

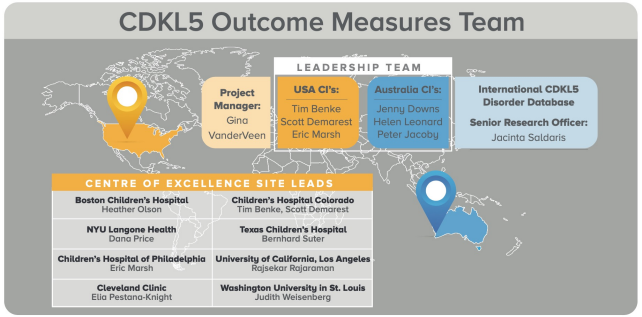
Mila's Miracle Foundation

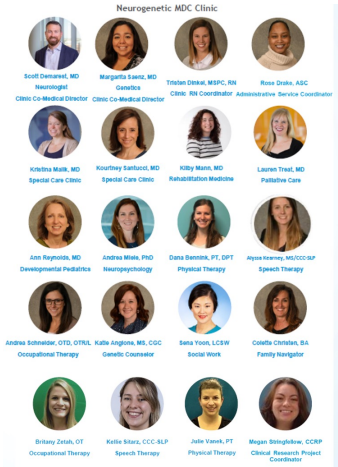
RARE Sisters Batten Foundation

SLC6A1 Connect

International Foundation For CDKL5 Research
HOPE • LOVE • CURE

RARE X





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NIH National Institute of Neurological Disorders and Stroke

STXBP1 disorders
Science + Love = Cure

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PROJECT P

Patients & Families!


AES 2023
ANNUAL
MEETING

AES 2023 ANNUAL MEETING

Winding Down

Sarah Aminoff Kelley, MD, FAES
Associate Professor of Clinical Neurology
Johns Hopkins Hospital

December 1, 2023

AES® AMERICAN EPILEPSY SOCIETY

Disclosures

- I have no relevant disclosures

Take away points

- Difficult questions are abundant in the field genetics and genetic testing
- Questions to answer: How does it affect care of the patient, treatment, trials, prognosis, future research?
- Thinking about VUSs is important
  - Are there treatment/care implications?
  - Can it be reclassified?
- Genetic testing is helpful outside of pediatrics
  - Transition between pediatrics and adult
  - Adulthood
- Navigating difficult discussions is ultimately helpful for families allowing prognostication, understanding underlying causes, and eliminating sense of guilt
- Disease modifying therapy presents opportunity for treatment
  - Difficult questions remain such as choosing the right therapy and weighing risks and benefit

We're with you and your patients every step of the way

Share CNF contact information with families for them to receive:

- 1:1 support from a social worker to find resources in their community
- Education about genetic testing
- Credible disease information in a disorder directory
- Tools to facilitate conversations about things like transition of care, respite care, and a how to prepare for a visit with a child neurologist

Families can visit **ChildNeurologyFoundation.org,**
call or text **859-551-4977** to be connected to support.