AES 2022 ANNUAL MEETING

Genetic Testing in Epilepsy: Improving Outcomes and Informing Gaps in Research

December 2, 2022

Child Neurology FOUNDATION
Creating a Community of Support

AES® AMERICAN EPILEPSY SOCIETY

Image Courtesy of Nashville Convention & Visitors Corp.

Today's Agenda

9:00 am	**Welcome**: Introduction to the Child Neurology Foundation
	Improving the Patient and Caregiver Experience
	The Impact on Clinical Care
	Long Term Research Gains
	Break
	Testing Considerations
	How to Manage Common Barriers
12:00 pm	**Adjourn**

AES 2022 ANNUAL MEETING

Welcome: Introduction to the Child Neurology Foundation

Anup D. Patel, MD, FAES, FAAN

December 2, 2022

Child Neurology FOUNDATION
Creating a Community of Support

AES® AMERICAN EPILEPSY SOCIETY

Image Courtesy of Nashville Convention & Visitors Corp.

Disclosures

- Research support: Pediatric Epilepsy Research Foundation (PERF), PCORI, NIH, Encoded, and Stoke
- Webinar Development: Medscape

Learning Objectives

- Determine when a genetic test is appropriate for a patient
- Order or refer patients to genetic testing options more often
- Go beyond seizure management to diagnosis and treatment

Child Neurology Foundation Mission

To serve as a collaborative center of education, resources, and support for children and their families living with neurologic conditions, and facilitate connection with medical professionals who care for them

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

Partner Organizations

Over 30 organizations shared this survey. Special thanks to

- Epilepsy Foundation
- International Foundation for CDKL5 Research
- Dravet Syndrome Foundation
- Phelan-McDermid Syndrome Foundation
- Epilepsy Alliance of America
- NeurAbilities Healthcare
- Pediatric Epilepsy Surgery Alliance

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

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"*

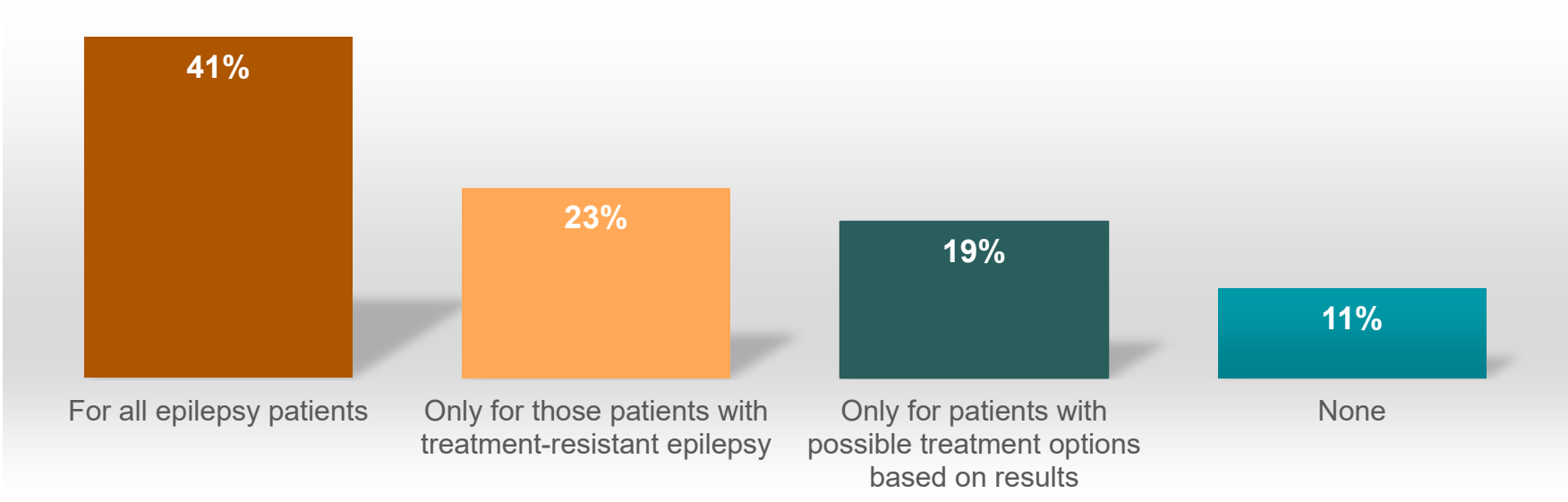
Genetic Testing leads to diagnosis

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

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

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

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

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 these connections

Impact on clinical care and practice

- There is a need in our community to dive deeper into identifying causes for epilepsy
- Families and clinicians need to effectively communicate about options for finding the cause
- CNF is here to help, use the QR code at your table to find a handout you can give to families to contact CNF for support related to things like:
    - Shortening the diagnostic odyssey
    - Transition of Care
    - Finding local resources in their state
    - Getting access to the internet
    - And so much more!

AES 2022 ANNUAL MEETING

Leah Schust Myers, Mom
FamilieSCN2A Foundation

December 2, 2022

Image Courtesy of Nashville Convention & Visitors Corp.

Child Neurology FOUNDATION
Creating a Community of Support

AES®
AMERICAN EPILEPSY SOCIETY

DISCLOSURES

- I have no disclosures to report.

LEARNING OBJECTIVES

- The entire family is affected by a diagnosis of epilepsy
- Discovering the etiology early is critical
- Empowering families with knowledge not only improves the outcome of the child but can have a major ripple effect

Meet Ben, Age 12

Loves

- playing in the pool
- Cheetos
- 4-wheeler rides with his Dad
- Music
- Hugs
- His iPad

Sounds like a typical kid, right?

- Autism Spectrum Disorder
- G-tube dependent
- Cortical Visual Impairment
- Severe Neuromuscular Scoliosis
- Hypotonia and Osteoporosis
- ESES / CSWS
- Intellectually impaired
- Nonverbal
- Incontinent

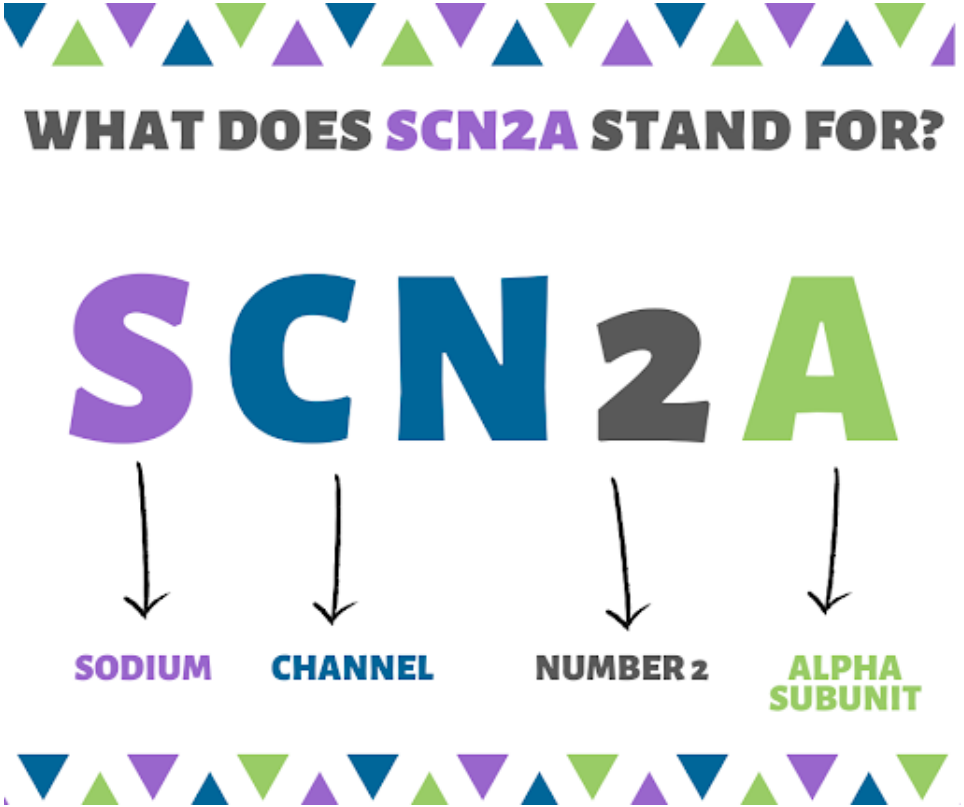
Seizures began at 13 months

Family in Crisis

- World flipped upside down
- Broken dreams
- Feeling alone and hopeless
- Fear of losing our child
- Re-learning how to parent
- Turned to social media

Finally, a Diagnosis

- Diagnostic journey was not smooth
- Learned to challenge and push back
- SCN2A is NOT Dravet
- Knowing the monster
- Tailoring his care



A Purpose Driven Life

Leading the Charge

SCN2A-RELATED AUTISM & EPILEPSY
FAMILIESCN2A®
FOUNDATION
WWW.SCN2A.ORG

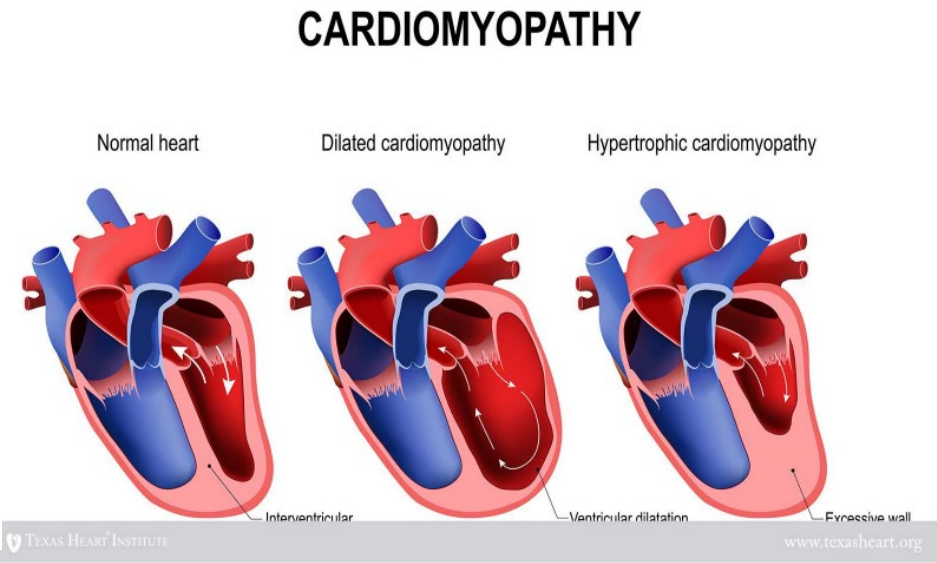
- grown to over 1,000 families
- hosted 4 in-person international educational conferences
- funded over $1M in research
- Contributed to multiple publications
- Become the experts

Still not convinced?

Benjamin's Variant in *TTN*

(c.86821+2 T>A – intron 326)

- Pathogenic Variant = Causative Genetic Change
- Heterozygous: variant was identified in **1** copy of the gene
- Variant type: Splice Site
- Inheritance: Paternally inherited
  - Present in Benjamin's father. Absent in Benjamin's mother.



Impact on Clinical Care and Practice

- Perform genetic testing as early as possible as precision medicine that’s coming down the pipeline now means nothing without a precision diagnosis
- Create a trusting relationship with your patients by addressing the challenges and unknown openly
- Recommended the patient family joins their community NPO to become more informed advocates and find support
- Assemble a list of opportunities for patients to get involved in research
- Connect patients with a multi disciplinary team that can address common comorbidities associated with their genetic disorder to stay ahead of serious problems and avoid surprises

AES 2022 ANNUAL MEETING

Impacts on Clinical Care

John J Millichap, MD FAES

Date of Presentation
December 2, 2022

Child Neurology FOUNDATION
Creating a Community of Support

AES® AMERICAN EPILEPSY SOCIETY

Image Courtesy of Nashville Convention & Visitors Corp.

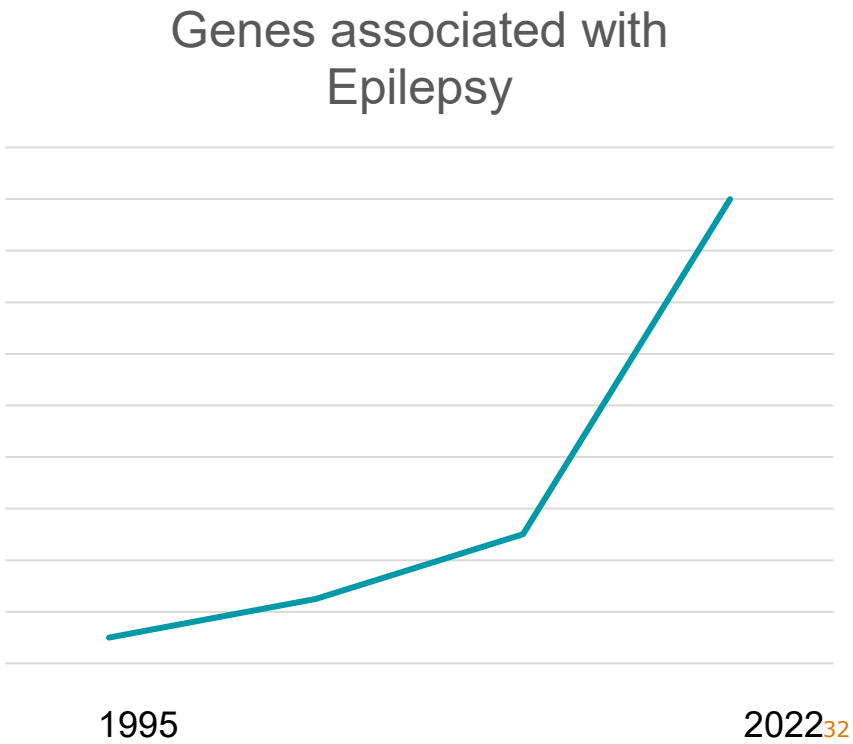
DISCLOSURES

- Dr. Millichap reports royalties from Up-To-Date; consulting fees from Xenon, Biomarin, UCB, Symbiotix, Greenwich, Praxis, Neurelis, Neurocrine, Biohaven; grants from NIH.

LEARNING OBJECTIVES

- Understand how genetic testing in clinical practice has changed over time
- Illustrate how early genetic testing can affect outcomes
- Demonstrate barriers to genetic testing in the clinic and possible solutions

Epilepsy Genetics



Epilepsy Genetics Paradigm Shift

Two cases over time

Case in 2010

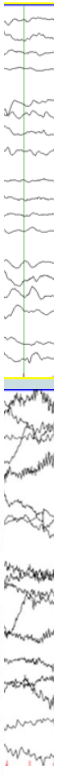
ORIGINAL ARTICLE

KCNQ2 Encephalopathy: Emerging Phenotype of a Neonatal Epileptic Encephalopathy

Sarah Weckhuysen, MD,[1,2,3] Simone Mandelstam, MB ChB,[4,5] Arvid Suls, PhD,[1,2] Dominique Audenaert, PhD,[1,2,6] Tine Deconinck, MSc,[1,2] Lieve R.F. Claes, PhD,[1,2] Liesbet Deprez, PhD,[1,2] Katrien Smets, MD,[1,2,7] Dimitrina Hristova, MD,[8] Iglika Yordanova, MSc,[9] Albena Jordanova, PhD,[1,2] Berten Ceulemans, MD, PhD,[2,10] An Jansen, MD, PhD,[11,12] Danièle Hasaerts, MD,[11] Filip Roelens, MD,[13] Lieven Lagae, MD, PhD,[14] Simone Yendle, BSc (Hons),[15] Thorsten Stanley, MD,[16] Sarah E. Heron, PhD,[17] John C. Mulley, PhD,[18,19] Samuel F. Berkovic, MD, FRS,[15] Ingrid E. Scheffer, MBBS, PhD,[4,15,20] and Peter de Jonghe, MD, PhD[1,2,7]

Objective: *KCNQ2* and *KCNQ3* mutations are known to be responsible for benign familial neonatal seizures (BFNS). A few reports on patients with a *KCNQ2* mutation with a more severe outcome exist, but a definite relationship has not been established. In this study we investigated whether *KCNQ2/3* mutations are a frequent cause of epileptic encephalopathies with an early onset and whether a recognizable phenotype exists.
Methods: We analyzed 80 patients with unexplained neonatal or early-infantile seizures and associated psychomotor retardation for *KCNQ2* and *KCNQ3* mutations. Clinical and imaging data were reviewed in detail.
Results: We found 7 different heterozygous *KCNQ2* mutations in 8 patients (8/80; 10%); 6 mutations arose de novo. One parent with a milder phenotype was mosaic for the mutation. No *KCNQ3* mutations were found. The 8 patients had onset of intractable seizures in the first week of life with a prominent tonic component. Seizures generally resolved by age 3 years but the children had profound, or less frequently severe, intellectual disability with motor impairment. Electroencephalography (EEG) at onset showed a burst-suppression pattern or multifocal epileptiform activity. Early magnetic resonance imaging (MRI) of the brain showed characteristic hyperintensities in the basal ganglia and thalamus that later resolved.
Interpretation: *KCNQ2* mutations are found in a substantial proportion of patients with a neonatal epileptic encephalopathy with a potentially recognizable electroclinical and radiological phenotype. This suggests that *KCNQ2* screening should be included in the diagnostic workup of refractory neonatal seizures of unknown origin.

ANN NEUROL 2012;71:15–25



Interpretation

This test detected a DNA sequence variant whose clinical significance is unknown (see details in Comments section).

Technical Results

DNA Variant 1:	Transition C > T
Nucleotide Position:	821
Codon:	274
Amino Acid Change:	Threonine > Methionine
Variant Type:	Variant of unknown significance

No other abnormal DNA sequence variants were identified in the remainder of the coding sequence or intron/exon junction.

Comments

Most Significant Result: This test detected a DNA sequence variant of unknown clinical significance (KCNQ2 c.821 C>T), but the following data indicate that this variant may be more likely pathogenic than benign:

benign ... unknown ... pathogenic

Variant: KCNQ2 c.821 C>T (p.Thr274Met)

WHAT IS RIKEE?

July 2013: Dr. Cooper and the Pribaz Foundation article featured in BCM Family (Link)

Rational
Intervention for
KcnQ2
Epileptic
Encephalopathy

The RI
by scie
unders
treatm
develo
by defi

ne

MY EPILEPSY STORY

The Jack Pribaz Fo

Elizabeth F

Epilep
doi:

Mike and Jack Pribaz.

2

E. Pribaz and M. Pribaz

The KCNQ2.org debut at the AES meeting in Seattle

Families and physicians together at the KCNQ2 Denver Summit in September 2014.

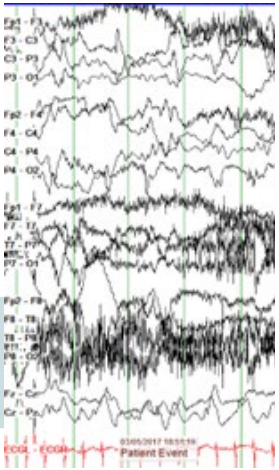
Wheaton, Illinois, got together and helped us start The Jack Pribaz Foundation in December of 2011. Our mission is to raise awareness and fund research of the *KCNQ2* gene.

Liz and I didn't want any other parents to have to feel alone with this diagnosis. We wanted them to have a place

Case in 2017

2 days

- whole body stiffening, head deviation, crying, heavy breathing, and perioral cyanosis
- lasted about 10 seconds and occurred a few times per day



7 days

- Video EEG confirmed seizures at 7 days old
- MRI brain and other tests negative.

Earlier genetic testing would confirm diagnosis and change treatment.

Early and effective treatment of *KCNQ2* encephalopathy

*Tiziana Pisano, †Adam L. Numis, ‡Sinéad B. Heavin, §¶Sarah Weckhuysen, #Marco Angriman, §¶Arvid Suls, **Barbara Podesta, ††Ronald L. Thibert, †Kevin A. Shapiro, *‡‡Renzo Guerrini, ‡Ingrid E. Scheffer, *Carla Marini, and †§§Maria Roberta Cilio

Epilepsia, 56(5):685–691, 2015
doi: 10.1111/epi.12984

Tiziana Pisano is a senior consultant at the pediatric neurology unit of the Meyer Children's Hospital, Florence, Italy.

Summary

Objectives: To describe the antiepileptic drug (AED) treatment of patients with early infantile epileptic encephalopathy due to *KCNQ2* mutations during the neonatal phase and the first year of life.

Methods: We identified 15 patients and reviewed the electroclinical, neuroimaging, and AED treatment data.

Results: Seizure onset was between 1 and 4 days of age with daily tonic asymmetric, focal and clonic seizures in nine patients and status epilepticus in the remaining six. Electroencephalography (EEG) showed multifocal epileptiform abnormalities in nine patients and a burst-suppression pattern in six. All patients were trialed with adequate daily doses of several AEDs before they reached seizure freedom. Six patients (40%) achieved seizure control within 2 weeks of carbamazepine (CBZ) administration and five (33%) were seizure-free with phenytoin (PHT). The last four patients (27%) were successfully treated with topiramate (TPM) (two patients), levetiracetam (LEV) (one), and a combination of LEV with TPM (one). Most patients reached seizure freedom within the first year of life and remained seizure-free thereafter. Twelve patients had moderate-to-severe developmental delay at follow-up. However, the two patients whose seizures ceased within a few days of onset showed only mild cognitive impairment.

Significance: Our findings suggest that drugs acting on sodium channels including CBZ and PHT should be considered as first-line treatment in patients with *KCNQ2* encephalopathy. Voltage-gated sodium and potassium channels co-localize at the neuronal membrane. Therefore, the efficacy of drugs acting as sodium-channel blockers could be linked to their modulating effect on both channels. The type of *KCNQ2* mutation might influence AED response as well as developmental outcome. Early recognition of *KCNQ2* encephalopathy followed by the most appropriate and effective treatment may be important for reducing the neurodevelopmental impairment associated with this disorder.

KEY WORDS: Epilepsy, *KCNQ2* encephalopathy, Antiepileptic drug treatment.

Epilepsy Genetics in the Clinic

AES 2022
ANNUAL
MEETING

Epilepsy Genetics in the Clinic

Early Testing

- de novo, not inherited, mutations most important for epileptic encephalopathy
- Phenotypic heterogeneity

Prognosis and Diagnosis

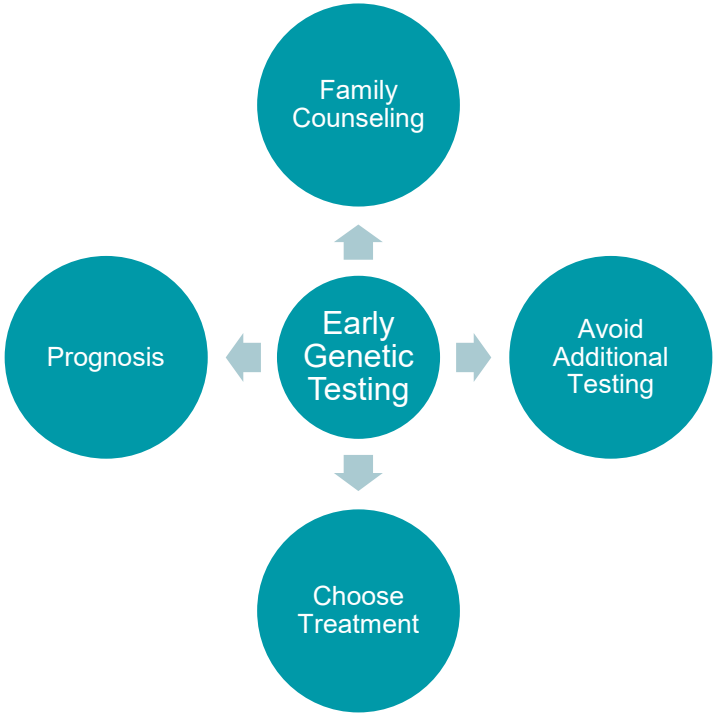
- Counselling parents
- Limit invasive or unnecessary testing

Treatment

- Choosing anticonvulsants

Precision medicine

- Understanding pathogenesis and development of novel treatments



Examples of genes with treatment implications

SCN1A (Dravet syndrome)

- Avoid carbamazepine, phenytoin, etc.

POLG1 (Alper-Huttenlocker syndrome)

- Avoid valproic acid

ALDH7A1

- Use pyridoxine

SLC2A1 (GLUT1-DS)

- Use ketogenic diet

KCNQ2 (Ohtahara syndrome, Lennox-Gastaut syndrome)

- Use carbamazepine, phenytoin, etc.

SCN2A (Ohtahara syndrome, Lennox-Gastaut syndrome)

- Use carbamazepine, phenytoin, etc.

Epilepsy Genetics in 2022

Barriers to Utilizing Epilepsy Genetics

Time

- Pre and post test counseling
- Follow up variant curation

Education

- Not aware of potential for treatment implications
- Primary responsibility for results vs referral to genetics

Cost

- Not expensive compared to EEG and MRI
- Some free testing available
- Potentially saving cost of ongoing standard testing

Dedicated Epilepsy Genetics Clinics

Multidisciplinary

- Genetic counselors, nurses, social worker, epileptologist, geneticist

Referrals from treating neurologists

- Prior to testing: develop personalized testing algorithm, pre-test counseling
- Post testing: counseling, variant (re)analysis

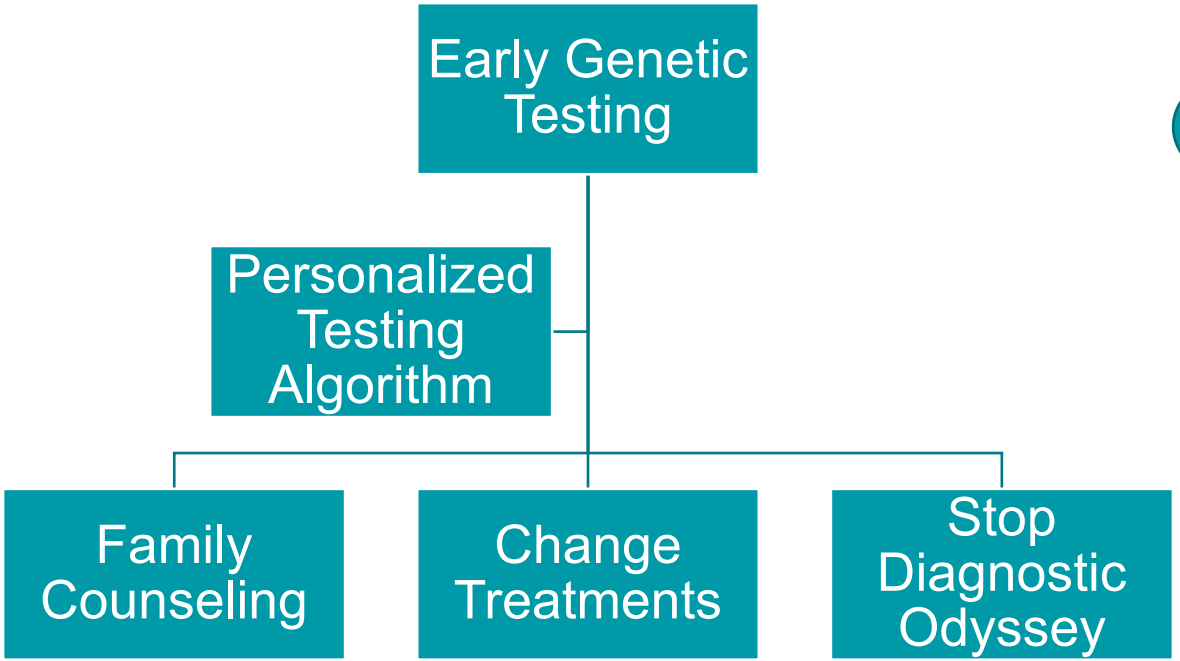
Research

- Genetic studies or gene-specific therapeutic clinical trials

Gene-specific Regional Expertise

- Family foundation supported clinics (Angelman syndrome, Rett syndrome, etc)

IMPACT ON CLINICAL CARE AND PRACTICE



Remember!
onset of focal tonic seizures in the 1st week of life is probably KCNQ2

AES 2022 ANNUAL MEETING

Bench to Bedside: How basic research informs treatment in genetic epilepsies

Jacy L. Wagnon, PhD

AES
December 2, 2022

Child Neurology FOUNDATION
Creating a Community of Support

AES® AMERICAN EPILEPSY SOCIETY

Image Courtesy of Nashville Convention & Visitors Corp.

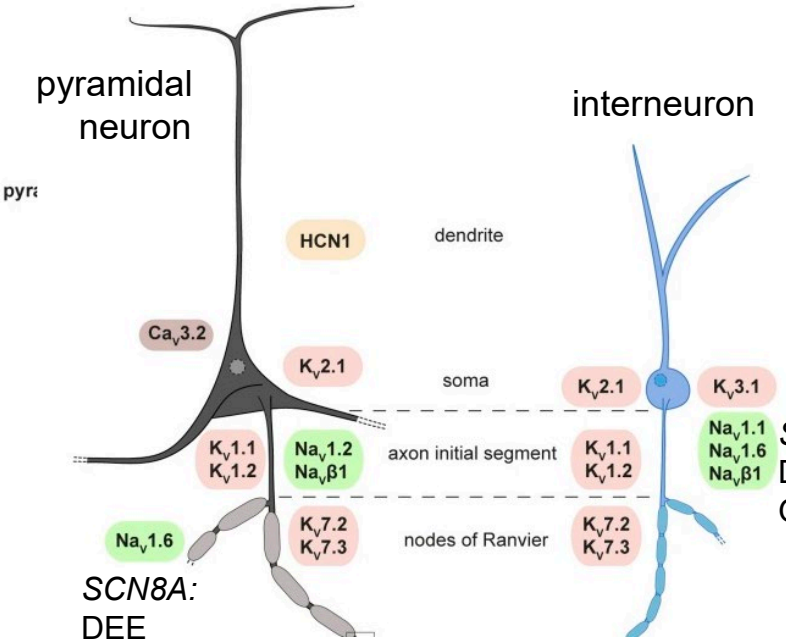
DISCLOSURES

- None

LEARNING OBJECTIVES

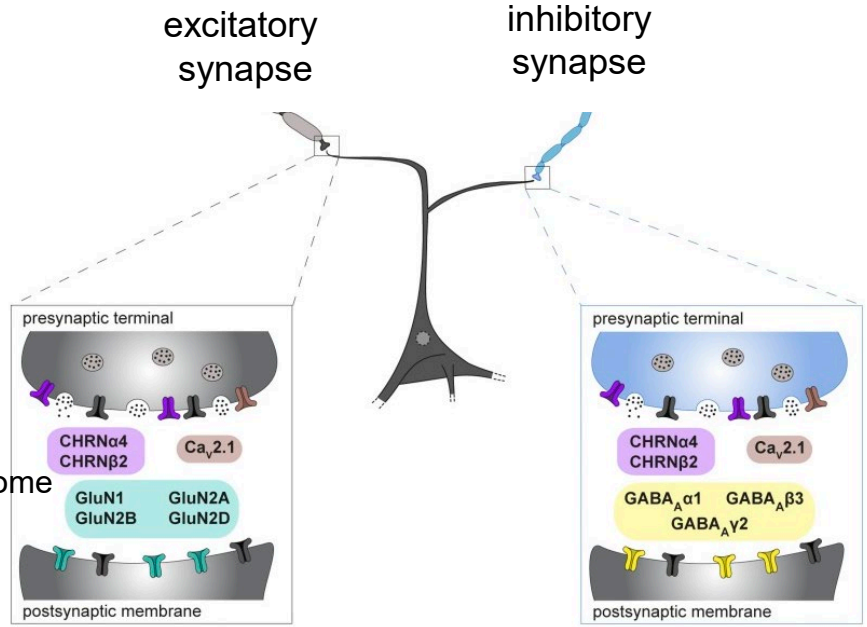
- Utilize functional analyses of genetic variants to understand molecular mechanisms underlying genetic epilepsies
- Design model systems to investigate mechanisms underlying genetic epilepsies *in vitro* and *in vivo*
- Create treatment plans using existing ASMs based on functional data
- Apply knowledge gained from experimental data to develop new treatment strategies for genetic epilepsies

Ion channel dysfunction and channelopathies



SCN8A:
DEE
Intermediate epilepsy
BFIS

SCN1A:
Dravet syndrome
GEFS+



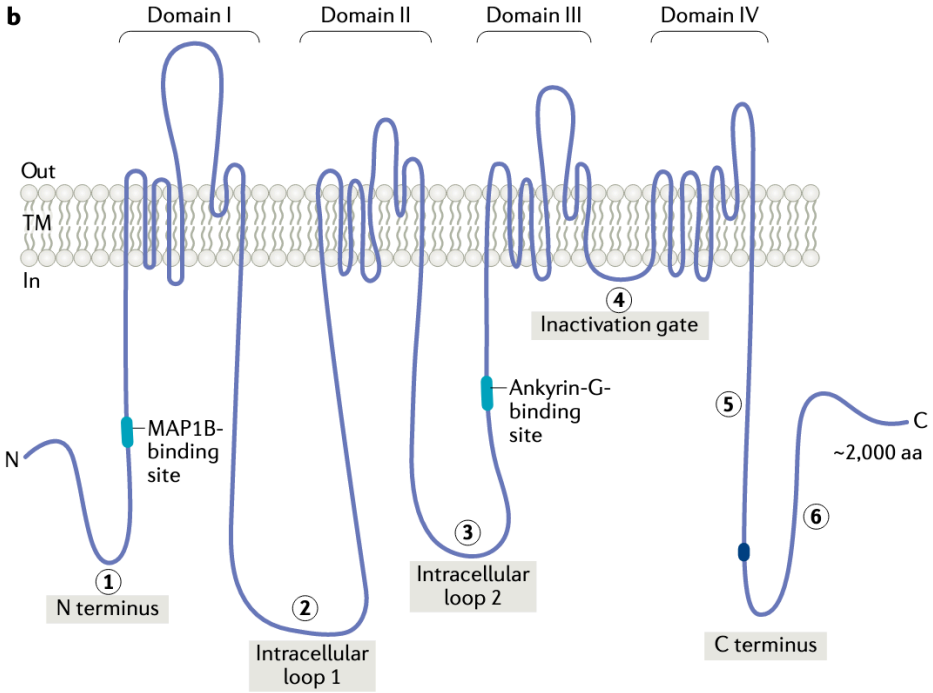
Sodium channel alpha subunits

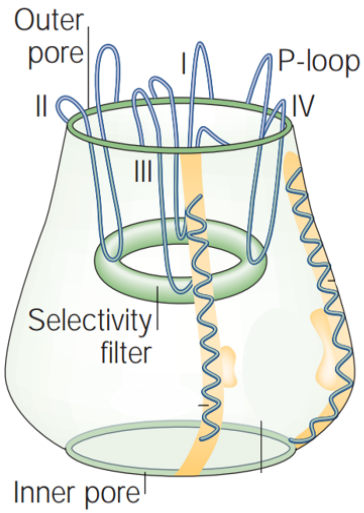
SCN3A, *SCN2A*, *SCN1A*, *SCN9A*, *SCN7A* — 2q23.3

SCN5A, *SCN10A*, *SCN11A* — 3p22.2

SCN8A — 12q13.13

SCN4A — 17q23.3

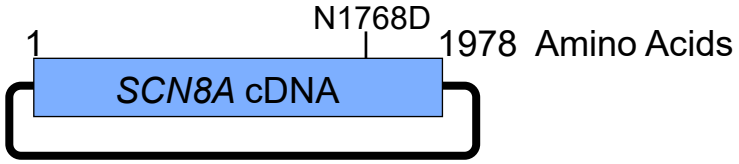


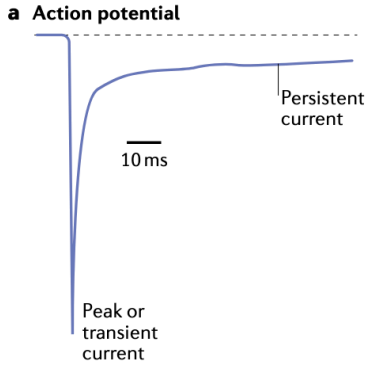


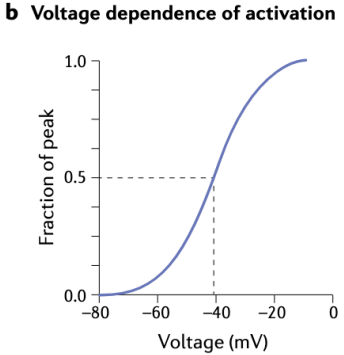
Meisler et al Nat Rev Neurosci 2021

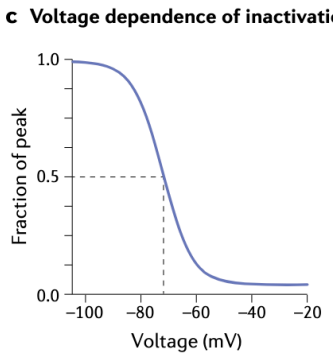
Functional analysis of sodium channel variants

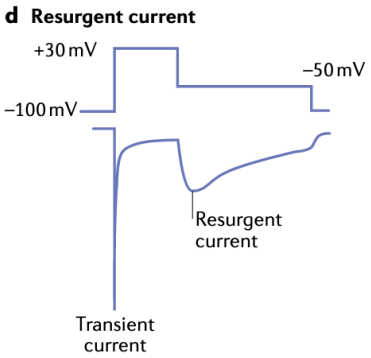
1. cDNA expression system: Tetrodotoxin (TTX) resistant
2. Site-directed mutagenesis to introduce variant (SNP)
3. Sequence 6 kb open reading frame to eliminate errors
4. Recording of currents from transfected heterologous cell (HEK, ND7/23) or hippocampal neurons:



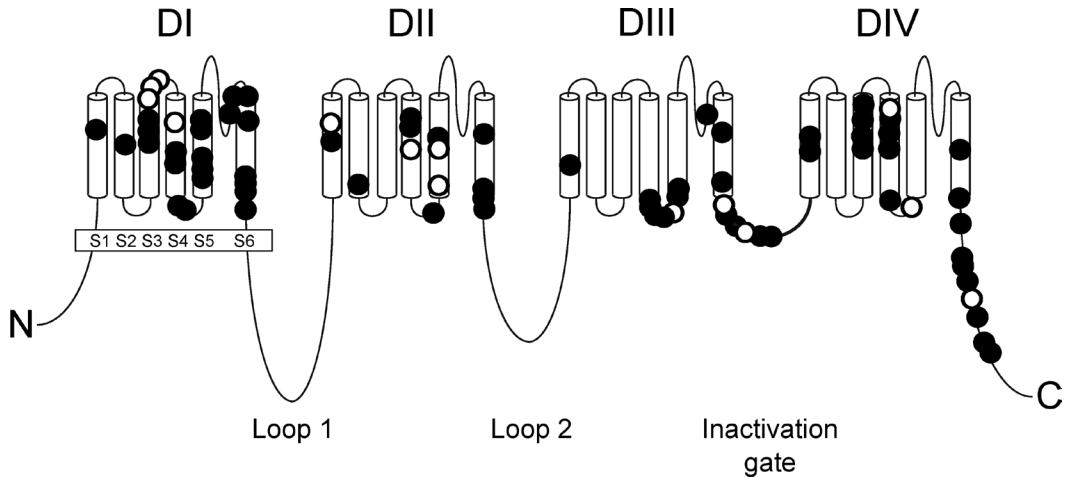




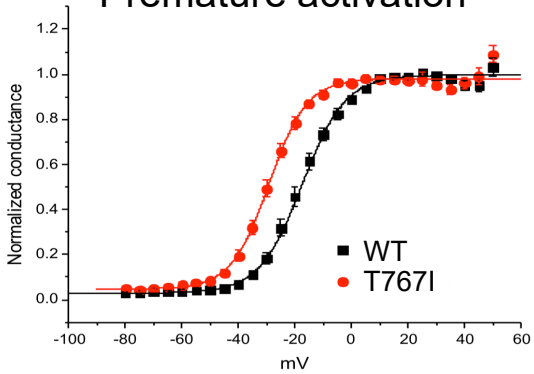




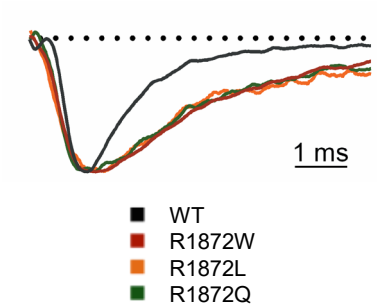
SCN8A variants are GOF in DEE



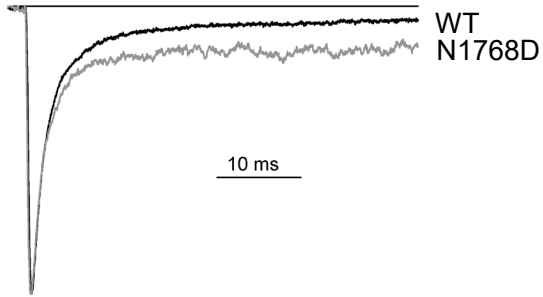
Premature activation



Impaired inactivation

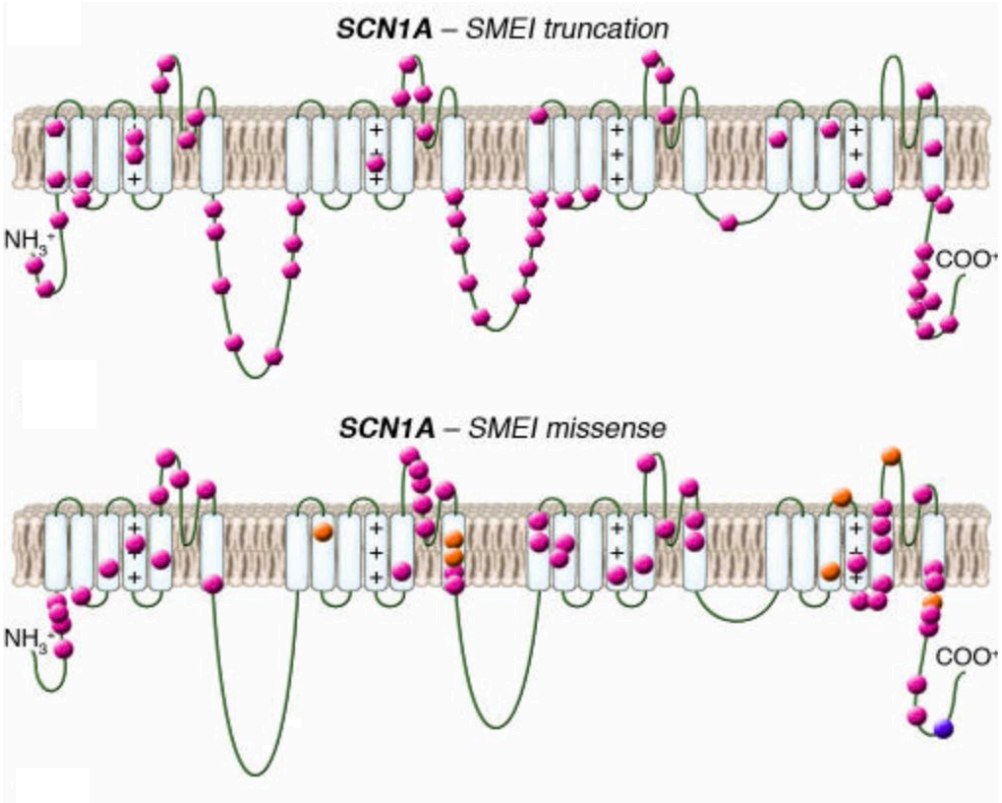


Elevated persistent current



Estacion *Neurobiol Dis* 2014, Wagnon *Ann Clin Transl Neurol* 2015, Lopez-Santiago *PNAS* 2017

SCN1A variants are LOF in Dravet syndrome



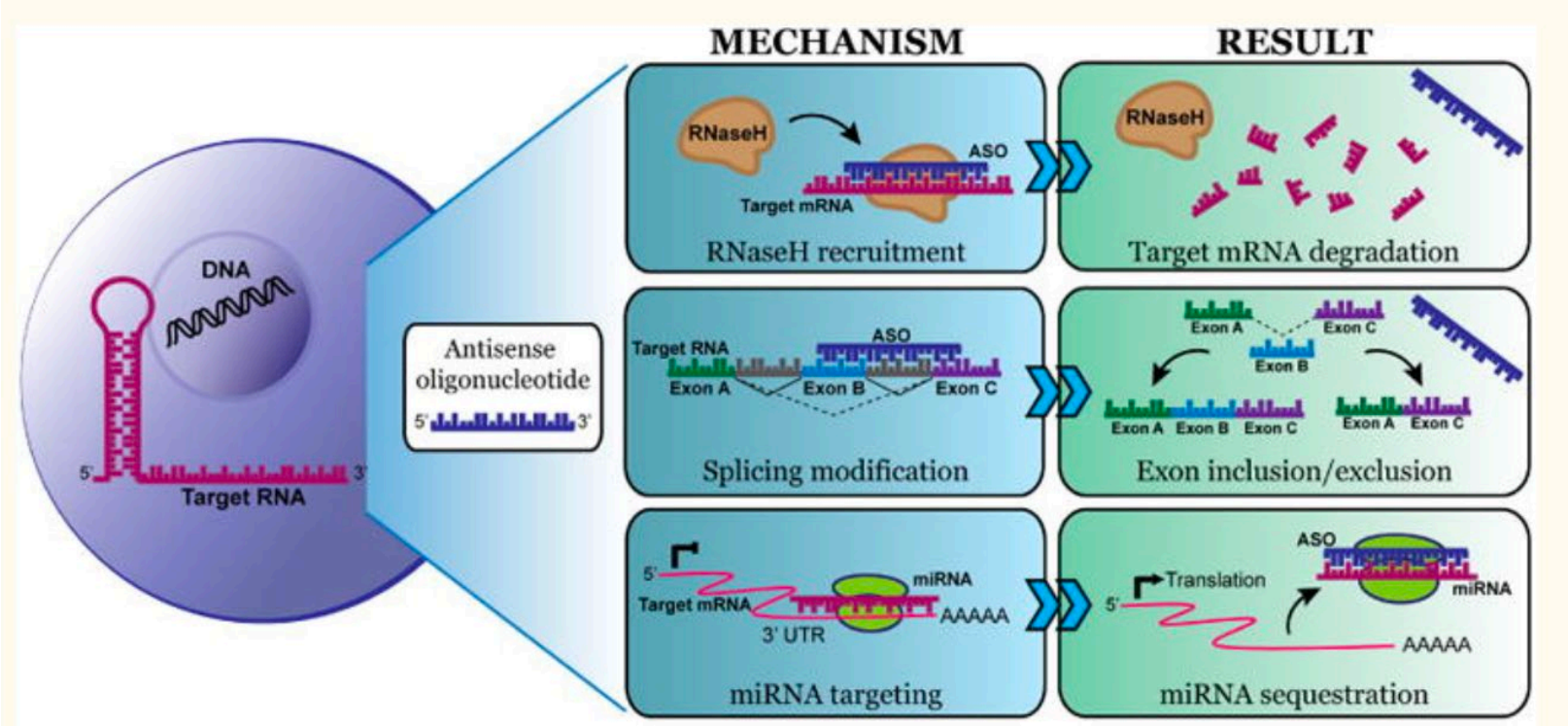
Meisler and Kearney, JCI 2005

Treatment of sodium channel DEE with ASMs

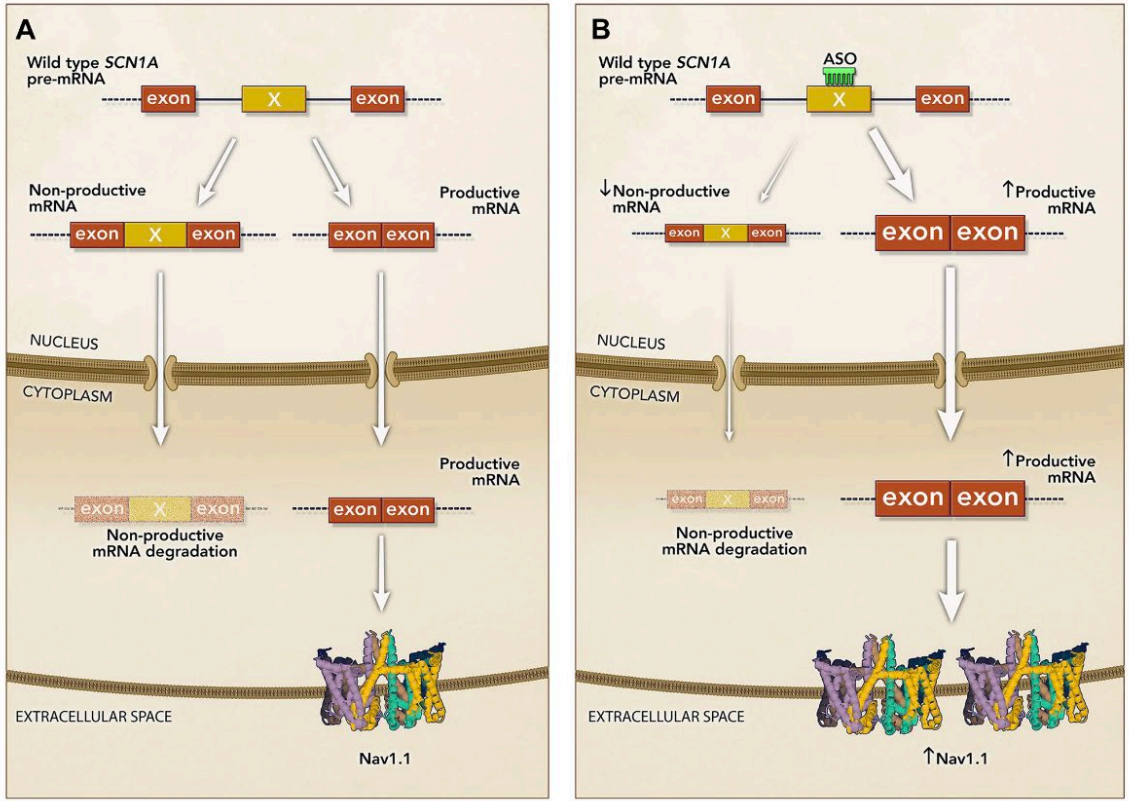
- *SCN8A* (GOF)
- Drug resistant
- Sodium channel blockers recommended
- Majority on 2 or more ASMs
- Most common combo: oxcarbazepine + lacosamide
- Most commonly stopped: topiramate and levertiracetam
- *SCN1A* (LOF)
- Drug resistant
- Sodium channel blockers **not** recommended
    - carbamazepine, oxcarbazepine, lamotrigine, and phenytoin can exacerbate seizures
- Most common: valproic acid and clobazam, also topiramate and levetiracetam

Wirrell and Nabbout, CNS Drugs 2019
Cutts et al, Seizure 2022

Antisense oligonucleotides as potential therapies for genetic epilepsies

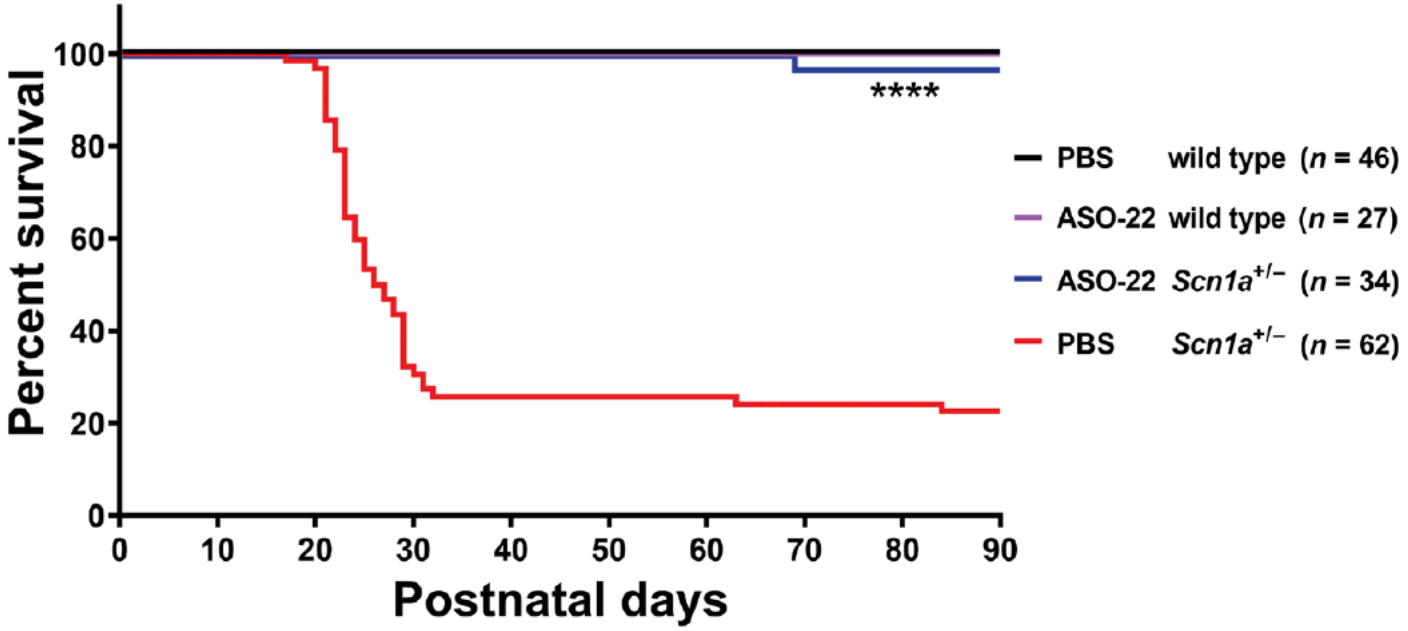


ASO treatment for *SCN1A* epilepsy due to LOF



Isom and Knupp, Neurotherapeutics 2021

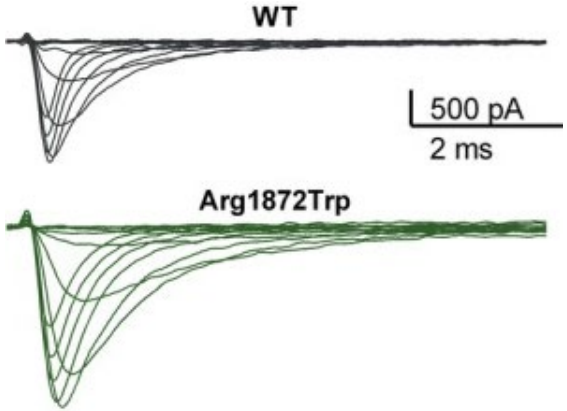
ASO treatment extends survival in mouse model of Dravet syndrome

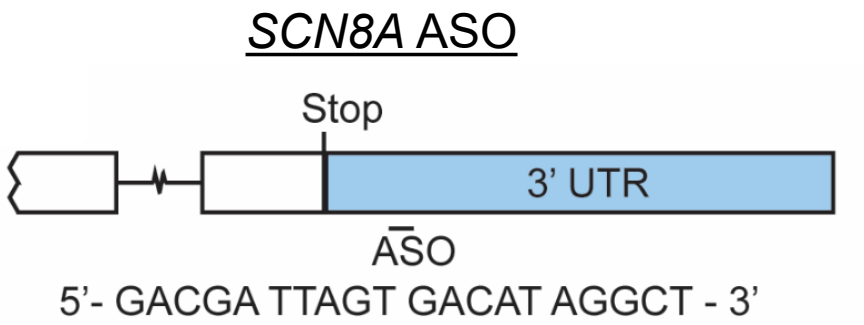


Now in MONARCH phase 1/2a clinical trial
open-label study for ages 2-18 with Dravet syndrome with variant in *SCN1A*

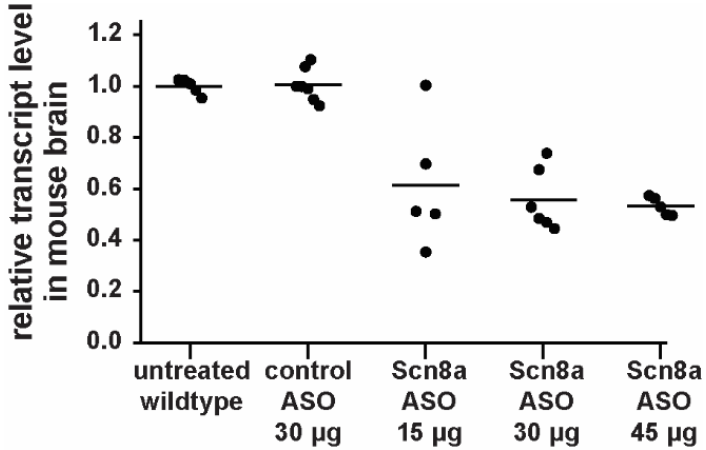
Han et al, *Sci Transl Med* 2020

ASO treatment for *SCN8A* epilepsy due to GOF



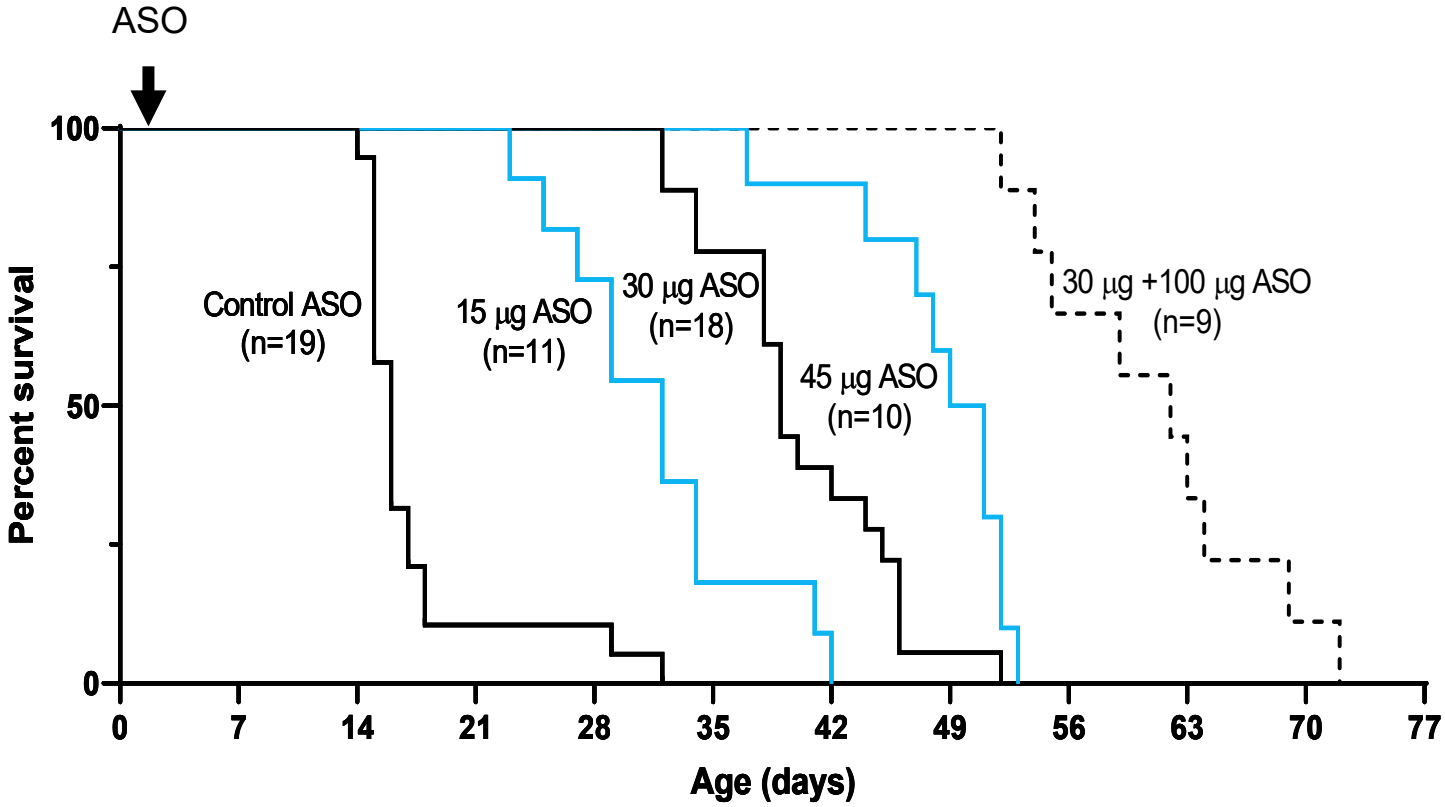


Can we protect against seizures by reducing expression of *SCN8A*?



Lenk et al, *Ann Neurol* 2020

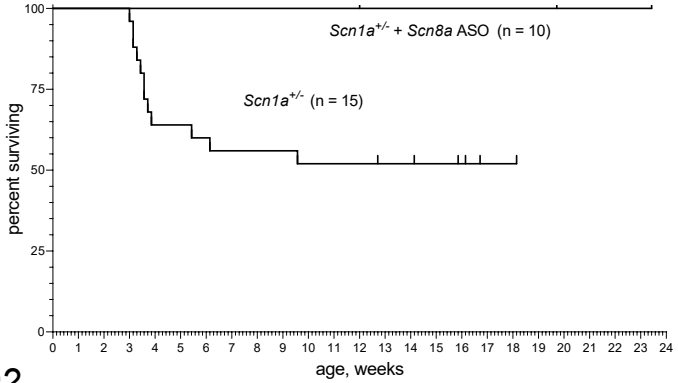
SCN8A ASO extends survival in mouse model of *SCN8A* DEE



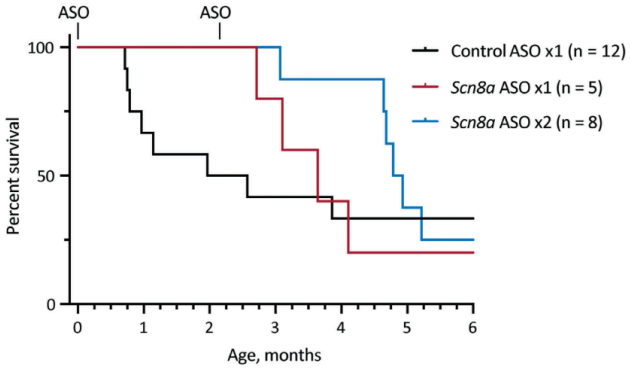
Lenk et al, *Ann Neurol* 2020

SCN8A ASO rescues other mouse models of ion channel-related DEE

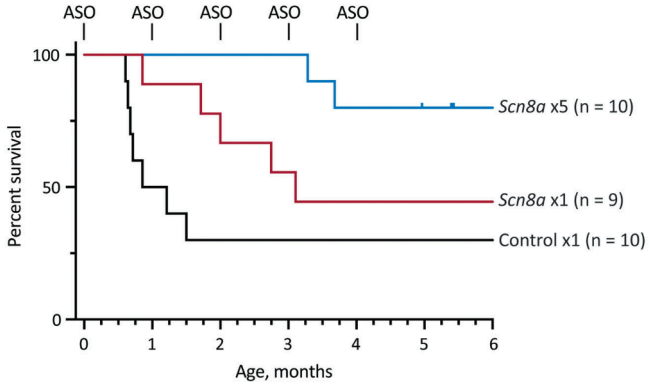
SCN1A



KCNQ2



KCN1A



Lenk et al Ann Neurol 2020, Hill et al, Epilepsia 2022

IMPACT ON CLINICAL CARE AND PRACTICE

- Functional analysis of genetic variants in epilepsy can inform treatment decisions and development of new therapies

- Anti-sense oligonucleotides can be used to regulate gene expression to potentially treat genetic epilepsies

AES 2022 ANNUAL MEETING

Genetic Testing in Epilepsy

Heather C. Mefford, MD, PhD

AES
December 2, 2022

Child Neurology FOUNDATION
Creating a Community of Support

AES® AMERICAN EPILEPSY SOCIETY

Image Courtesy of Nashville Convention & Visitors Corp.

DISCLOSURES

- Scientific Advisory Board
  - Dravet Syndrome Foundation
  - Syngap1 Research Fund
  - Coalition to Cure CHD2
  - KdVS Foundation

LEARNING OBJECTIVES

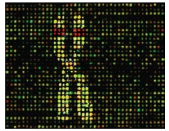
- Outline genetic testing options for patients with epilepsy
- Compare the diagnostic yields of different genetic tests in a patient with epilepsy

Why does a genetic diagnosis matter?

- Improves prognosis counseling
- Facilitates discussion of recurrence risk
- May affect choice of medications
- Connects families with the same genetic diagnosis
- Provides research opportunities: precision therapies

Diagnostic odyssey

Genetic testing menu



Chromosome microarray

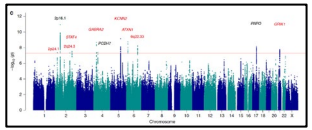
Sequencing: gene panels, exome (genome, RNA)

Current

RNA sequencing

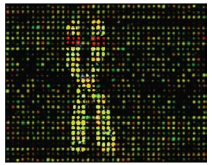
Emerging

Methylation profiling



Polygenic risk scores

Genetic testing menu



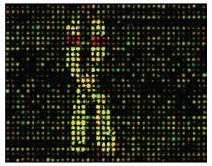
Chromosome microarray

Genome-wide scan for CNVs
deletions, duplications, unbalanced chromosome rearrangements

Sequencing: gene panels, exome (genome)

Looks for sequencing errors in genes
Panel = dozens to thousands of genes
Exome = all 20,000 genes (1% of genome)
Genome = 100% of DNA

These tests DO NOT detect…



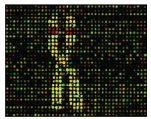
Chromosome microarray

NO sequence information
NO repeat expansions (*e.g.* Fragile X)

Sequencing: gene panels, exome (genome)

NOT good for repeat expansions (Fragile X)
May detect CNVs (depends on test/lab)
Panels test some genes, not all

Which test? Consider diagnostic yield

	DD/ID	AUTISM	EPILEPSY
 Fragile X	1-2%	1-2%	**<1%**
 Chromosome microarray	20-30%	5-10%	**5-10%**
 Gene panels	20-30%	<5%	**20-30%**
 Exome seq	30-40%	1-10%	**30-50%**

Panel vs Exome sequencing

Gene Panels

- Genes that are tested are known to be associated with disease - but few to many genes tested
- Some panels also detect CNVs
- Some panels are actually exomes
- You don’t find what you’re not looking for

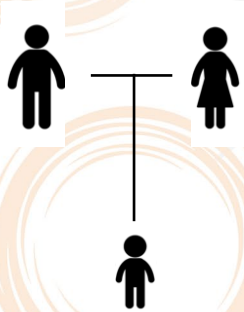
Exome

- “All” genes tested
- Some include CNV analysis
- Data can be reanalyzed
- You may find what you’re not looking for (secondary findings)
- Trio = family relatedness

Genetic testing – interpretation

VARIANT INTERPRETATION	TEST RESULT
• Benign / likely benign • Variant of Uncertain Clinical Significance (VUS)	• Non-diagnostic / NEGATIVE • Requires further investigation
• Likely Pathogenic • Pathogenic	• Diagnostic / POSITIVE

Genetic testing in the clinic



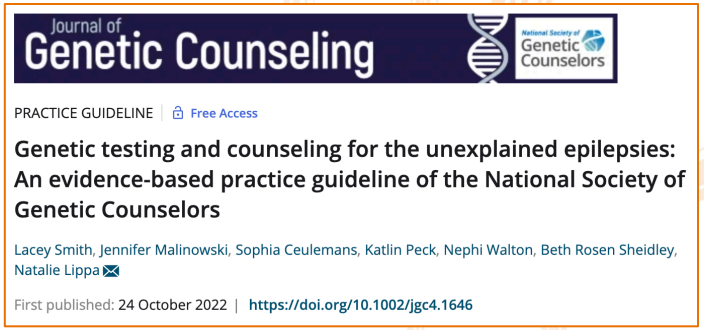
- Early diagnosis is important – avoid the odyssey
- ID, early-onset epilepsy, DEE
  - EXOME > gene panel > array
- Exome is highest yield – trio if possible
- Early onset, severe, syndromic = more likely genetic
- Up to 50% can be diagnosed > **50% remain undiagnosed**

Guidelines for genetic testing & counseling in unexplained epilepsies

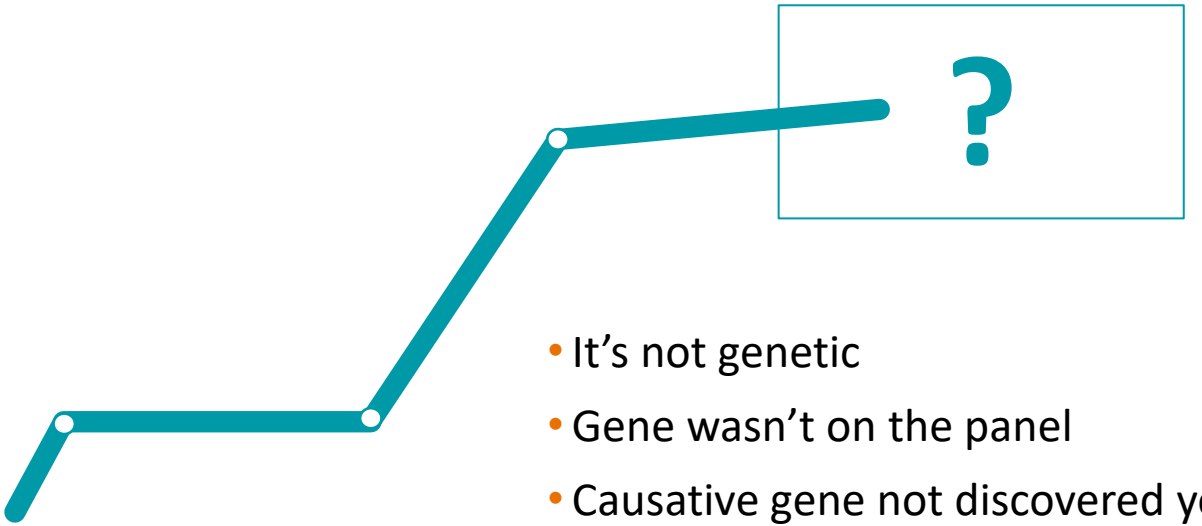
- (1) **Exome/genome** recommended as **first-tier** test
  - Alternative: panel with 25+ genes + CNV

- (2) Testing should include pre- and post-test counseling

- National Society of Genetic Counselors
- Endorsed by AES



Diagnostic odysseys take many forms

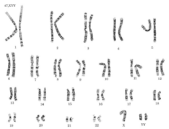


- It’s not genetic
- Gene wasn’t on the panel
- Causative gene not discovered yet
- Variant missed for technical reasons
- Variant misinterpreted

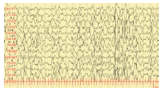
Nevertheless…the geneticist persisted!

6 mo
? delays

9 mo
array
47,XXY



8 mo



+ lots of normal tests

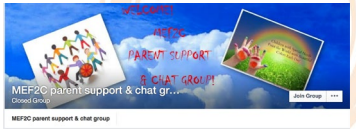
15 mo - 327 gene panel sent
Result: VUS (x4)

20 mo – parental testing
VUS x4 inherited

MEF2C added to panel

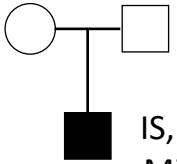
Metabolic genetics
Additional testing
(Nondiagnostic)

24 mo – whole exome seq
26 mo – results
DIAGNOSIS!
de novo MEF2C



30 mo

Nevertheless…the geneticist persisted

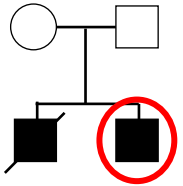


IS, DD at 5 mo
Microcephaly

→ Intractable seizures
Continued delays
Progressive decline

→ Died at 4 yrs

→



IS, DD at 10 mo
Microcephaly

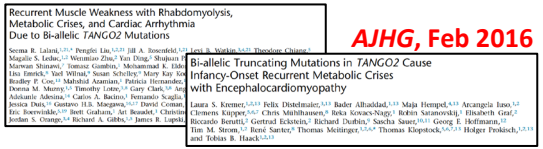
2012
Gene panel (53)
nucSEEK (1100)
Negative

2013
Exome
(patient)
VUS

2014
Exome
(parents)
De novo VUS

2016
Exome
(brother)
Diagnosis: *TANGO2* (recessive)

New knowledge →

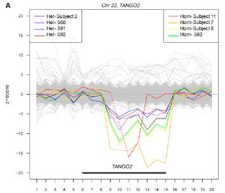


Recurrent Muscle Weakness with Rhabdomyolysis, Metabolic Crises, and Cardiac Arrhythmia Due to Bi-allelic *TANGO2* Mutations

Bi-allelic Truncating Mutations in *TANGO2* Cause Infancy-Onset Recurrent Metabolic Crises with Encephalocardiomyopathy

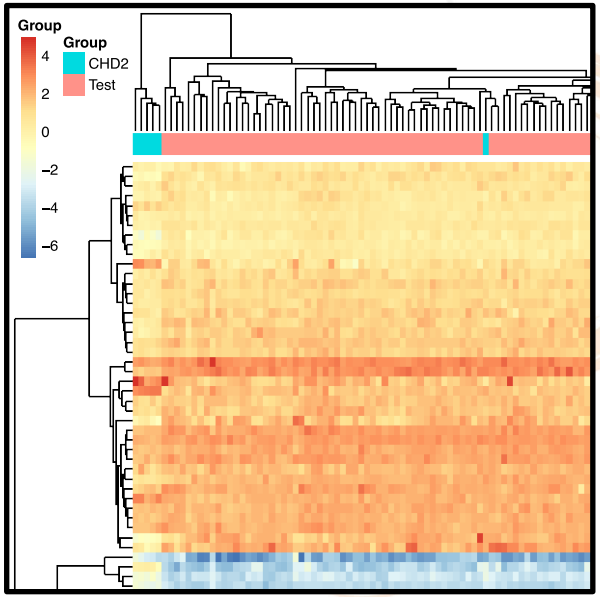
***AJHG*, Feb 2016**

New technology →

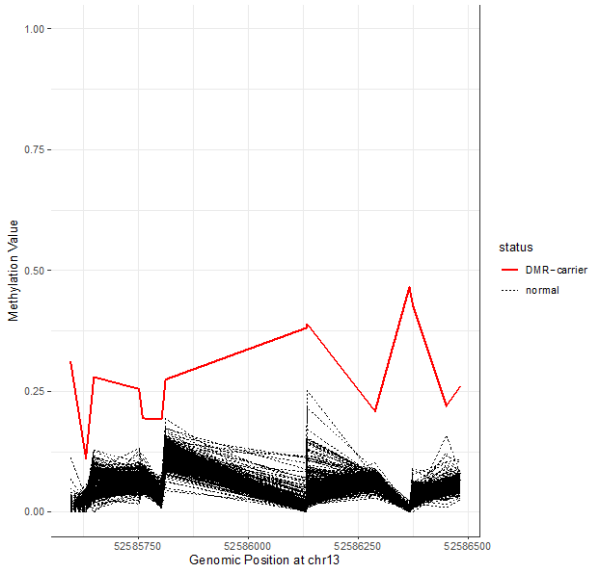


Emerging approaches

- Methylation profiling
  - Genome-wide methylation signatures have been identified for specific genetic disorders
  - EpiSignature can be used to resolve VUS

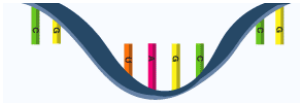


Research: DNA methylation for diagnosis



- Aberrant methylation may be a novel cause of disease
- We are testing this hypothesis in a cohort of unsolved DEE

Emerging approaches



RNA Sequencing

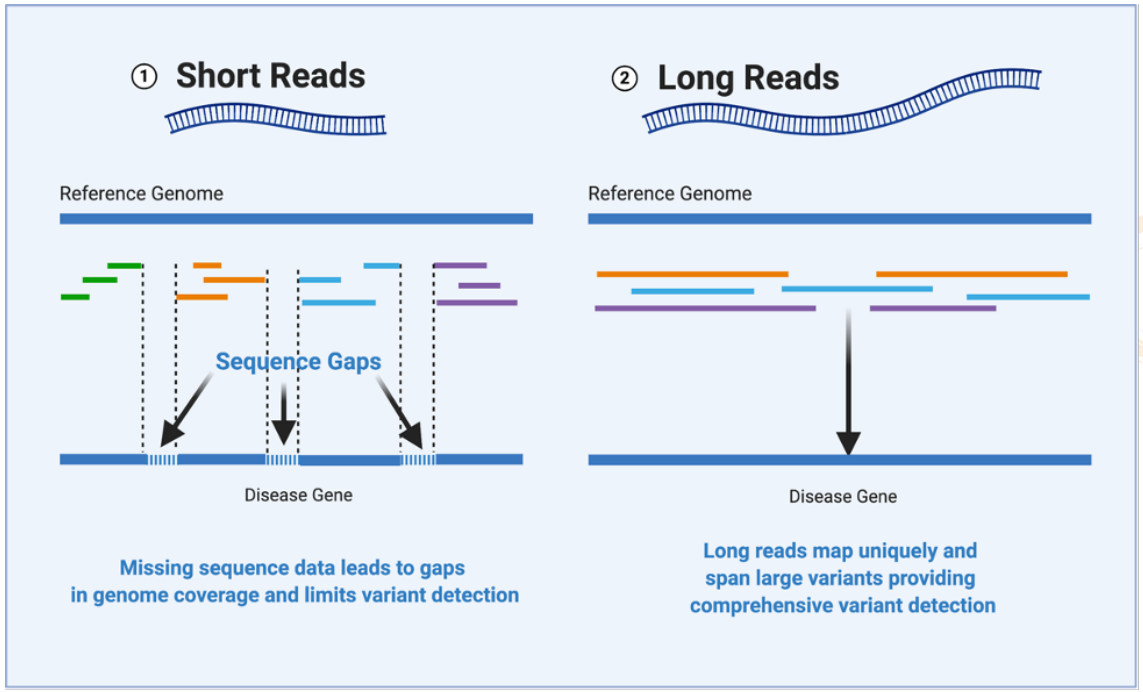
- RNA-seq
  - Can be used to evaluate mono-allelic expression, splicing abnormalities
  - Best when a specific gene is suspected (one-hit)
  - Gene must be expressed in accessible tissue

Emerging approaches

- Whole genome sequencing (WGS)
  - Noncoding variants, repeat expansions, SV
  - Cost $$
  - Interpretation 🤷‍♀️
  - Often require f/u functional studies
  - Clinically available – focuses on exonic variants

Emerging approaches

- Long-read sequencing



Ongoing discovery research

(W)GS + **RNA-seq** + **Methylation**

Short-read trio WGS
40-80 *de novo* / trio
Repeats, SV, etc.

Interpretation…

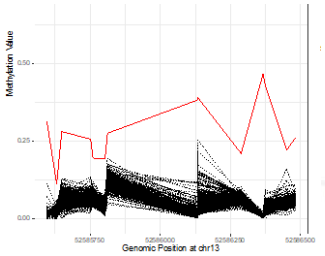
Plan: long-read seq in subset 🤷‍♀️

Fibroblasts > iPSC

Cortical organoids

⬇

RNA-seq



Genome-wide methylation analysis to detect rare, outlier DMRs affecting gene expression

Genetic testing in focal epilepsies

- Familial forms
- Specific phenotypes
- Pre-surgical workup
- Tissue testing in FCD

LGI1

DEPDC5

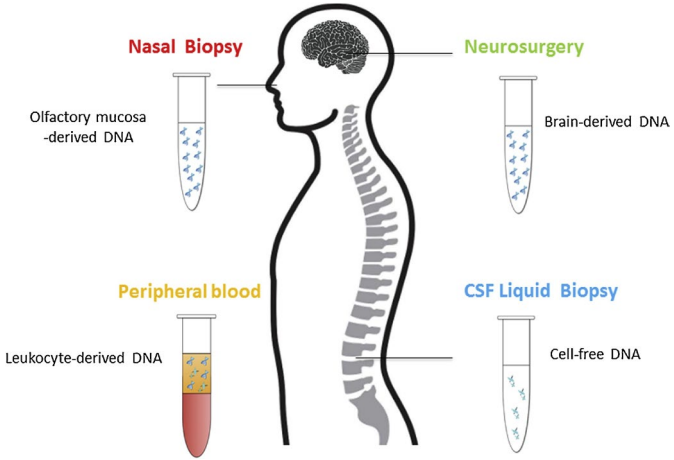
NPRL2/3

TSC1/2

MTOR

Emerging technologies: focal

- Mosaic variants in focal lesions
- Requires deep sequencing
- May require brain tissue
- "Liquid biopsy" of CSF



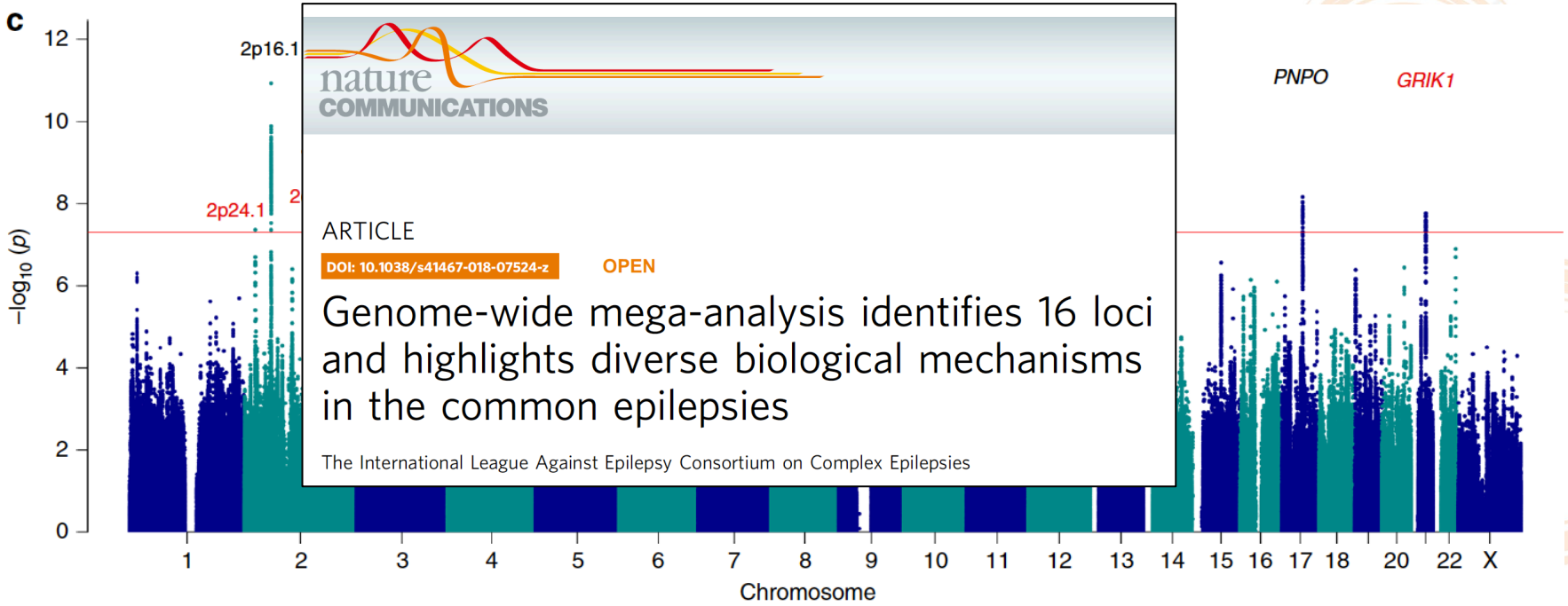
Ye et al (2019)

Genetic testing: GGE

- Rare familial (e.g. GEFS+, FAME)

- GGE+ID consider chromosome array
    - 15q13, other recurrent deletions enriched in GGE+

Emerging approaches: focal, GGE



nature COMMUNICATIONS

ARTICLE

DOI: 10.1038/s41467-018-07524-z OPEN

Genome-wide mega-analysis identifies 16 loci and highlights diverse biological mechanisms in the common epilepsies

The International League Against Epilepsy Consortium on Complex Epilepsies

~15,000 cases
~30,000 controls

16 loci (most GGE)
~30% of heritability of GGE

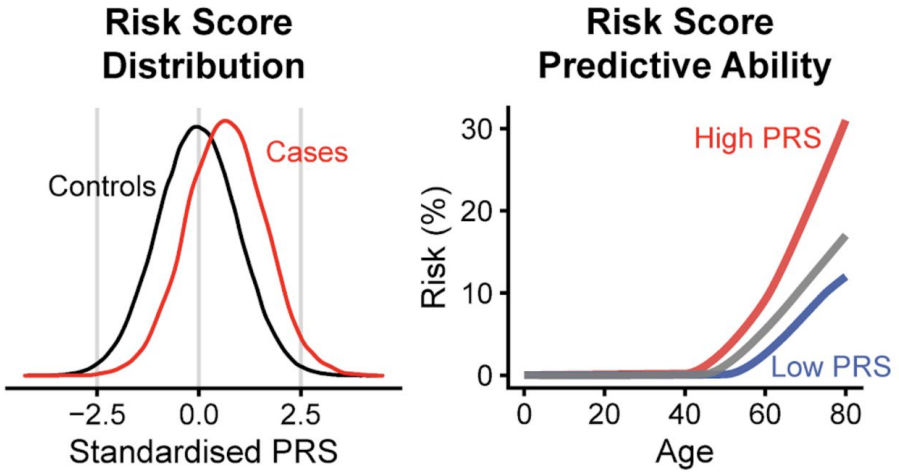
Emerging approaches: PRS

- Polygenic risk scores (PRS)
  - Sum of effect of many risk alleles, each of which confer small increased risk
  - Clinical utility??

BRAIN
A JOURNAL OF NEUROLOGY

Polygenic burden in focal and generalized epilepsies

Costin Leu,[1,2,3] Remi Stevelink,[4] Alexander W. Smith,[2] Slavina B. Goleva,[5,6] Masahiro Kanai,[2,7,8,9,10] Lisa Ferguson,[11,12,13] Ciaran Campbell,[14,15] Yoichiro Kamatani,[10,16] Yukinori Okada,[10,17,18] Sanjay M. Sisodiya,[3,19] Gianpiero L. Cavalleri,[14,15] Bobby P.C. Koeleman,[4] Holger Lerche,[20] Lara Jehi,[11,13] Lea K. Davis,[5,6] Imad M. Najm,[11,13] Aarno Palotie,[2,21] Mark J. Daly,[2,7,21] Robyn M. Busch,[11,12,13] Epi25 Consortium and Dennis Lal[1,2,11,22]



https://www.medrxiv.org/content/10.1101/2020.04.23.20077099v2

Current and emerging approaches to detect disease-associated genetic, genomic, and epigenetic variants

			Single Nucleotide Variants	Insertions and Deletions	Copy Number Variants	Structural Variants	Mosaic Variants	Repeat Expansions	Non-Coding Variation	Epigenetic Variation	Oligo- and Polygenic Variation
Current Clinical Approaches	Cytogenetic Studies	Karyotype			✓	*✓					
		Chromosomal Microarray			*✓						
	Next Generation Sequencing (NGS)	Targeted Single Gene and Gene Panels	✓	✓	(✓)		(✓)				
		Mitochondrial Sequencing	✓ in mtDNA	✓ in mtDNA			✓ in mtDNA				
		Exome Sequencing	✓	✓	(✓)		(✓)				
Emerging Approaches for Gene Discovery and Variant Interpretation		Genome Sequencing	✓	✓	(✓)		(✓)		✓		✓
		Long Read Sequencing	✓	✓				*✓	✓	✓	
		Genome-Wide Methylation								*✓	
		Deep and Ultra Deep Targeted Sequencing	✓	✓	(✓)		*✓				
		Polygenic Risk Estimates									*✓

✓ - variant type detected; (✓) – detection limited and/or validation is developing; *✓ - optimal approach for detection

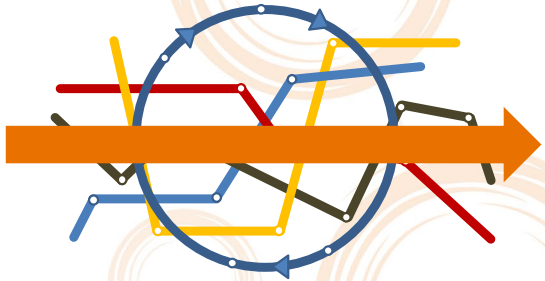
Bonkowski & Mefford for Jaspers, 5th Ed. (Oxford Univ Press, 2022)

Impact on Clinical Care & Practice

WHO: DEE, early-onset epilepsy, epilepsy+ID (40-50%)
Familial focal, GEE
Rare, specific phenotypes

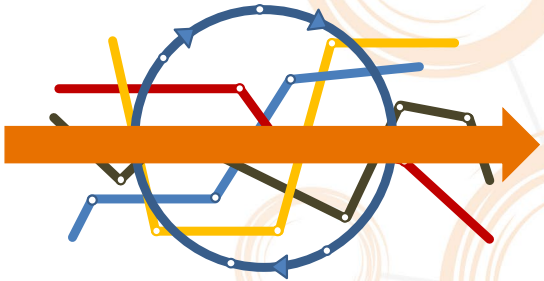
WHEN: Early diagnosis is key, especially in DEE

HOW: EXOME > Gene panel > chromosome array
Specific phenotype – consider targeted panel



The future of genetic testing

- Whole genome sequencing increasingly available
- RNA-seq important in specific cases
- Methylation profiling can help resolve VUS
- Polygenic risk scores may be useful in common epilepsies
- Long-read sequencing may approach “one-test-for-all”



AES 2022 ANNUAL MEETING

Managing Common Genetic Testing Barriers

Tamara Reynolds, MS, CGC

December 2, 2022

Child Neurology FOUNDATION
Creating a Community of Support

AES® AMERICAN EPILEPSY SOCIETY

Image Courtesy of Nashville Convention & Visitors Corp.

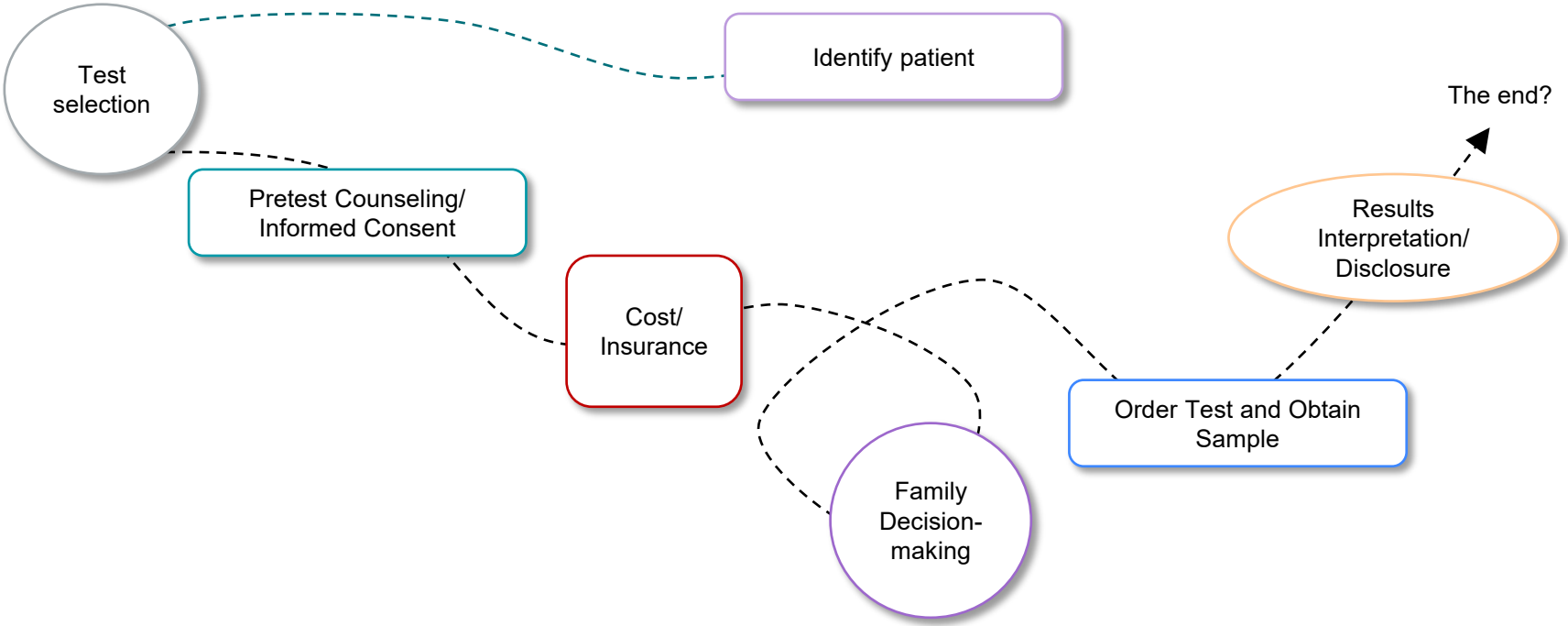
DISCLOSURES

- No disclosures

LEARNING OBJECTIVES

- Identify barriers that delay or prevent access to genetic testing
- Describe strategies and resources to overcome these obstacles

GENTIC TESTING PROCESS



TEST SELECTION

- Provider hesitation: training, support, time
  - Rapid evolution from single gene testing to large panels, exomes, genomes
  - Limited training (30% of PGY1s reported no genetics training), additional allied health support, adjustments to workflows
  - 70% of microarrays ordered outside of genetics
- No guidelines on optimal testing strategy for patients with epilepsy until October 2022
- Group of very heterogeneous phenotypes, family dynamics, family histories, and available resources

Kutscher et al, 2017; Hauser et al, 2018; Salm et al, 2014; Mathew et al, 2022; Sheidley et al, 2022; Smith et al, 2022; Haspel et al, 2021

STRATEGIES

- Liaison-ship with genetics department - at NCH, all departments have two geneticist liaisons and two GC liaisons in addition to some in-clinic support
- Contact the genetic testing lab, most have GCs on staff
- Long-term: Advocate for more genetics support enlisting IS or lab to show increased volume
- Education for Paediatricians: Genomic testing (genetics.edu.au)
- NSGC Practice Guideline
- Review and meta-analysis of diagnostic yield

PRE-TEST GENETIC COUNSELING/CONSENT

- Beneficial to families
- Many insurance companies require pre-test counseling (some require face to face, some require be done by a genetics provider)
- Delays and additional cost with one more provider to see
- Gap between increased volume of genetic testing and number of available genetics providers (2016 46% of genetics residency positions unfilled)

Raspa et al, 2021; Faucett et al, 2019

STRATEGIES

- Embed GC in multi-disciplinary clinic
- On call GC
- Telehealth or in person GC only appointments (faster than seeing geneticist)
- Genetic testing lab may partner with third party GC group
- Neurology provider can provide in some cases
  - National society of genetic counselors (nsgc.org)
  - Genetc Testing Primer
  - Lab consent form as a guide

Lee et al, 2022; Raspa et al, 2021

COST/INSURANCE COVERAGE

- Cost and delays
- Genetic test costs range from a few hundred dollars to several thousand dollars
- Several tests often needed to find diagnosis
- Insurance coverage
  - Prior authorization, LMN, appeal, peer to peer → delays
  - Not a covered benefit; specific test is not covered/considered not medically necessary or experimental; covered but deductible/co-pay

STRATEGIES

- Note evidence based guidelines, change in medical management in PA documentation; has been helpful in the cancer space NSGC Practice Guideline
- Lab may have patient pay OOP max
- State programs
  - In Ohio BCMH: Partially funded by a Federal Title V Block Grant; all states receive a Federal Title V Block grant and use it differently
  - www.hrsa.gov
- Genetics and social work colleagues
- Sponsored testing

Smith et al, 2022
Clemmons et al, 2019;
www.nccn.org

FAMILY DECISION-MAKING/APPREHENSION

- Anxiety about uncertain results, prognosis, secondary findings
- Privacy concerns and general mistrust
- Genetic discrimination (insurance/employment)
- Cultural/religious reasons
- Revealing sensitive family information
- Yield and possibility results will not change medical management

Botkin et al, 2015; Zhong et al, 2021;
Germain et al, 2021

STRATEGIES

- Consider alternate testing strategy around specific concern
- GINA (Genetic Information Non-Discrimination Act)
  - NIH GINA Information
  - GINA Information Sheet
- Defer testing

TEST ORDERING

- Administrative
  - For best test interpretation, the lab needs a completed requisition, consent, clinic notes, and pedigree
- Obtaining sample
  - Family delays

STRATEGIES

- Increased allied health/admin support (GCs, GCAs, prior authorization specialists, administrative assistant training)
- Alternative sample (buccal, saliva)
- Drawing blood at time of visit, sending family home with buccal kits
- Genetic testing lab assistance

Raspa et al, 2021

RESULTS INTERPRETATION AND DISCLOSURE

- Provider hesitation: training, support, and time
- Diagnosis, other body systems, counseling on reproductive recurrence likelihood
- Variants of uncertain significance (VUS)
- Follow up variant testing for parents to resolve a VUS, determine phase, or clarify reproductive recurrence likelihood
- Biochemical testing
- Managing secondary findings
- Non-diagnostic? Is further genetic testing indicated?

Groisman et al, 2017

STRATEGIES

- Reach out to testing lab - genetics professionals on staff (interpretation, next steps, and post-test counseling)
- Liaison-ship with genetics
- Trialing genetics “office hours”
- Regular interdepartmental conference

VARIANT INTERPRETATION SITES AND FAMILY RESOURCES

- **Variant intepretation**
  - ACMG Variant Interpretation Guidelines
  - ClinVar
  - Varsome
- **Prediction tools**
  - POLG Pathogenicity Prediction Server (mitomap.org)
  - Human DNA Polymerase Gamma Mutation Database (nih.gov)
  - GRIN database CFERV
  - Functional Prediction tool
- **Gene/Condition Overviews**
  - Genereviews
  - Omim
  - Beyond the Ion Channel Blog
- **Family Resources**
  - Genetics Fact Sheets for Families
  - Unique – diagnosis specific guides for families
  - Gene specific advocacy sites and Facebook

IMPACT ON CLINICAL CARE AND PRACTICE

- Gap between increased volume and complexity of genetic testing and the number of genetics providers and training for non-genetics provider
- The clinical utility of genetic testing is advancing
- Creating new service delivery models, interdepartmental collaboration, and increased provider support, time, and education is important for patient access