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

December 2, 2022
# Today’s Agenda

<table>
<thead>
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<th>Time</th>
<th>Session</th>
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<td>9:00 am</td>
<td><strong>Welcome</strong>: Introduction to the Child Neurology Foundation</td>
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<td>Improving the Patient and Caregiver Experience</td>
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<td>The Impact on Clinical Care</td>
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<td>Long Term Research Gains</td>
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<td><strong>Break</strong></td>
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<td>Testing Considerations</td>
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<td>How to Manage Common Barriers</td>
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<td>12:00 pm</td>
<td><strong>Adjourn</strong></td>
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Welcome: Introduction to the Child Neurology Foundation

Anup D. Patel, MD, FAES, FAAN

December 2, 2022
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?

- 41% for all epilepsy patients
- 23% only for those patients with treatment-resistant epilepsy
- 19% only for patients with possible treatment options based on results
- 11% none

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:
  o Shortening the diagnostic odyssey
  o Transition of Care
  o Finding local resources in their state
  o Getting access to the internet
  o And so much more!
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

What does SCN2A stand for?

- Sodium
- Channel
- Number 2
- Alpha Subunit
A Purpose Driven Life
Leading the Charge

- 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+2T>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
Impacts on Clinical Care

John J Millichap, MD FAES

Date of Presentation
December 2, 2022
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

150k new cases of epilepsy per yr

Genes associated with Epilepsy

Child Neurologist
Pediatrician
Genetic Counselors
Clinical Geneticists
Epilepsy Genetics Paradigm Shift

Two cases over time
Case in 2010

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:

Variant: KCNQ2 c.821 C>T (p.Thr274Met)
WHAT IS RIKEE?

Rational
Intervention for
KcnQ2
Epileptic
Encephalopathy

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

MY EPILEPSY STORY

The Jack Pribaz Foundation

Elizabeth F

Mike and Jack Pribaz.
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.
Epilepsy Genetics in the Clinic
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

Early Genetic Testing

Personalized Testing Algorithm

Family Counseling

Change Treatments

Stop Diagnostic Odyssey

Remember!
onset of focal tonic seizures in the 1st week of life is probably KCNQ2
Bench to Bedside: How basic research informs treatment in genetic epilepsies

Jacy L. Wagnon, PhD

AES
December 2, 2022
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+

Excitatory synapse
Inhibitory synapse
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:

- **a** Action potential
  - Peak or transient current
  - Persistent current
  - 10 ms

- **b** Voltage dependence of activation
  - Fraction of peak
  - Voltage (mV)

- **c** Voltage dependence of inactivation
  - Fraction of peak
  - Voltage (mV)

- **d** Resurgent current
  - +30 mV
  - -100 mV
  - -50 mV
  - Transient current
  - Resurgent current
**SCN8A variants are GOF in DEE**

**Premature activation**

**Impaired inactivation**

**Elevated persistent current**

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 levetiracetam

• **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
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*?

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**

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
Genetic Testing in Epilepsy

Heather C. Mefford, MD, PhD

AES
December 2, 2022
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

Current

- Chromosome microarray

Emerging

- Sequencing: gene panels, exome (genome, RNA)
- RNA sequencing
- 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
<table>
<thead>
<tr>
<th>Test</th>
<th>DD/ID</th>
<th>AUTISM</th>
<th>EPILEPSY</th>
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<tr>
<td>Fragile X</td>
<td>1-2%</td>
<td>1-2%</td>
<td>&lt;1%</td>
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<td>Chromosome microarray</td>
<td>20-30%</td>
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<td>Gene panels</td>
<td>20-30%</td>
<td>&lt;5%</td>
<td>20-30%</td>
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<tr>
<td>Exome seq</td>
<td>30-40%</td>
<td>1-10%</td>
<td>30-50%</td>
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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**
- Benign / likely benign
- Variant of Uncertain Clinical Significance (VUS)
- Likely Pathogenic
- Pathogenic

**TEST RESULT**
- Non-diagnostic / NEGATIVE
- Requires further investigation
- 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

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**Journal of Genetic Counseling**

*Genetic testing and counseling for the unexplained epilepsies: An evidence-based practice guideline of the National Society of Genetic Counselors*

Lacey Smith, Jennifer Malinowski, Sophia Ceulemans, Kaitlin Peck, Nephi Walton, Beth Rosen Sheldley, Natalie Lippa

First published: 24 October 2022 | [https://doi.org/10.1002/jgc4.1646](https://doi.org/10.1002/jgc4.1646)
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)
- Metabolic genetics
  Additional testing (Nondiagnostic)
- 20 mo: parental testing
  VUS x4 inherited
- 24 mo: whole exome seq
  DIAGNOSIS!
  de novo MEF2C
- 30 mo: MEF2C added to panel
Nevertheless...the geneticist persisted

2012
Gene panel (53)
nucSEEK (1100)
Negative

2013
Exome
(patient)
VUS

2014
Exome
(parents)
De novo VUS

2016
Exome
(brother)
Diagnosis: TANGO2 (recessive)

AJHG, Feb 2016
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-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

1. Short Reads
   - Reference Genome
   - Disease Gene
   - Missing sequence data leads to gaps in genome coverage and limits variant detection

2. Long Reads
   - Reference Genome
   - Disease Gene
   - Long reads map uniquely and span large variants providing comprehensive variant detection
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

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

RNA-seq
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

- 16 loci (most GGE)
- ~30% of heritability of GGE
- Genome-wide mega-analysis identifies 16 loci and highlights diverse biological mechanisms in the common epilepsies
Emerging approaches: PRS

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

https://www.medrxiv.org/content/10.1101/2020.04.23.20077099v2
## Current and emerging approaches to detect disease-associated genetic, genomic, and epigenetic variants

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<tr>
<th>Current and Emerging Approaches</th>
<th>Single Nucleotide Variants</th>
<th>Insertions and Deletions</th>
<th>Copy Number Variants</th>
<th>Structural Variants</th>
<th>Mosaic Variants</th>
<th>Repeat Expansions</th>
<th>Non-Coding Variation</th>
<th>Epigenetic Variation</th>
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<td><strong>Cytogenetic Studies</strong></td>
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<td>Chromosomal Microarray</td>
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<td><strong>Current Clinical Approaches</strong></td>
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<td>Next Generation Sequencing (NGS)</td>
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<td>Targeted Single Gene and Gene Panels</td>
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<td><strong>Emerging Approaches for Gene Discovery and Variant Interpretation</strong></td>
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<td>Polygenic Risk Estimates</td>
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✓ - 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”
Managing Common Genetic Testing Barriers

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December 2, 2022
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
- Pretest Counseling/Informed Consent
- Cost/Insurance
- Family Decision-making
- Order Test and Obtain Sample
- Identify patient
- Results Interpretation/Disclosure

The end?
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

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](http://www.hrsa.gov)

• Genetics and social work colleagues

• Sponsored testing
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 interpretation
  - 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