Molecular Diagnosis from Genetic Testing Guides Clinical Management of Epilepsy and Helps Improve Patient Outcomes

Dianalee McKnight, PhD, FACMG
Medical Affairs Director
Invitae

Learning Objectives

- List examples of patient management changes that can be made by clinicians based on a molecular diagnosis of epilepsy.
- Summarize evidence showing that epilepsy testing can be associated with positive health outcomes.

The state of genetics today

It takes on average 4.8 years for a rare disease patient to receive an accurate diagnosis*

- Cost barriers
- Reimbursement challenges
- Lack of comfort with genetics

*Global Genes website: https://globalgenes.org/rare-facts/?gclid=EAIaIQobChMIupHBhrPr6AIV1BatBh0bCgH6EAAYASAAEgJwzPD_BwE

Benefits of identifying a genetic etiology for patients with early-life epilepsy

- High diagnostic yield[1]
  - Genetic testing of patients with early-life epilepsy has diagnostic yield of 30%–40%
- Direct medical care[2,3]
  - Prevent unnecessary studies/procedures
  - Surveillance for anticipated symptoms
  - Inform medications (indicated vs. contraindicated)
- Avoidance of a diagnostic odyssey[3]
  - Save money and time for family
  - Reduce overall healthcare costs

[1]Berg AT, *et al. JAMA Pediatr.* 2017;171(9):863–71;
[2]Truty R, *et al. Epilepsia Open.* 2019;4(3):397–408.
[3]Oates S, et al. NPJ Genom Med. 2018; 3:13.

Benefits of identifying a genetic etiology for patients with early-life epilepsy (cont.)

- Family planning[1]
  - Determine recurrence risk for parents
  - Determine risk for siblings
- Family support
  - Find advocacy/support groups centered around same rare disease[1]
  - Be part of a community of families with similar concerns
- Clinical trials and research studies[1]
  - Early access to therapies
  - Cutting-edge disease management
  - Natural history studies

⟶ We anticipate that all of these benefits may ultimately result in better outcomes for the patient.

[1]Berg AT, *et al. JAMA Pediatr.* 2017;171(9):863–71;

Many studies demonstrate the clinical utility and costs savings of utilizing a gene panel for patients with epilepsy

Accepted: 3 April 2018
DOI: 10.1111/epi.14087

FULL-LENGTH ORIGINAL RESEARCH

Epilepsia

A population-based cost-effectiveness study of early genetic testing in severe epilepsies of infancy

Katherine B. Howell[1,2,3] | Stefanie Eggers[3] | Kim Dalziel[3,4] | Jessica Riseley[3] | Simone Mandelstam[2,3,5,6,7] | Candace T. Myers[8] | Jacinta M. McMahon[9] | Amy Schneider[9] | Gemma L. Carvill[10] | Heather C. Mefford[8] | the Victorian Severe Epilepsy of Infancy Study Group | Ingrid E. Scheffer[1,2,7,9] | A. Simon Harvey[1,2,3]

FULL-LENGTH ORIGINAL RESEARCH

Diagnostic yield of genetic testing in epileptic encephalopathy in childhood

*†Saadet Mercimek-Mahmutoglu, *Jaina Patel, *Dawn Cordeiro, *Stacy Hewson, ‡David Callen, §Elizabeth J. Donner, §Cecil D. Hahn, *†Peter Kannu, §Jeff Kobayashi, †§¶Berge A. Minassian, §Mahendranath Moharir, *Komudi Siriwardena, §Shelly K. Weiss, *†Rosanna Weksberg, and §O. Carter Snead III

Epilepsia, 56(5):707–716, 2015
doi: 10.1111/epi.12954

ARTICLE

Diagnostic yield of genetic tests in epilepsy

A meta-analysis and cost-effectiveness study

Iván Sánchez Fernández, MD, MPH, Tobias Loddenkemper, MD, Marina Gaínza-Lein, MD, Beth Rosen Sheidley, MS, CGC, and Annapurna Poduri, MD, MPH

Neurology® 2019;92:e1-e11. doi:10.1212/WNL.0000000000006850

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ORIGINAL RESEARCH ARTICLE

Front. Neurol., 13 September 2019 | https://doi.org/10.3389/fneur.2019.00988

Diagnostic Yield of Epilepsy Panel Testing in Patients With Seizure Onset Within the First Year of Life

Se Song Jang[1], Soo Yeon Kim[1], Hunmin Kim[2], Hee Hwang[2], Jong Hee Chae[1], Ki Joong Kim[1], Jong-Il Kim[3,4,5] and Byung Chan Lim[1]*

[1]Department of Pediatrics, Seoul National University College of Medicine, Seoul National University Children's Hospital, Seoul, South Korea
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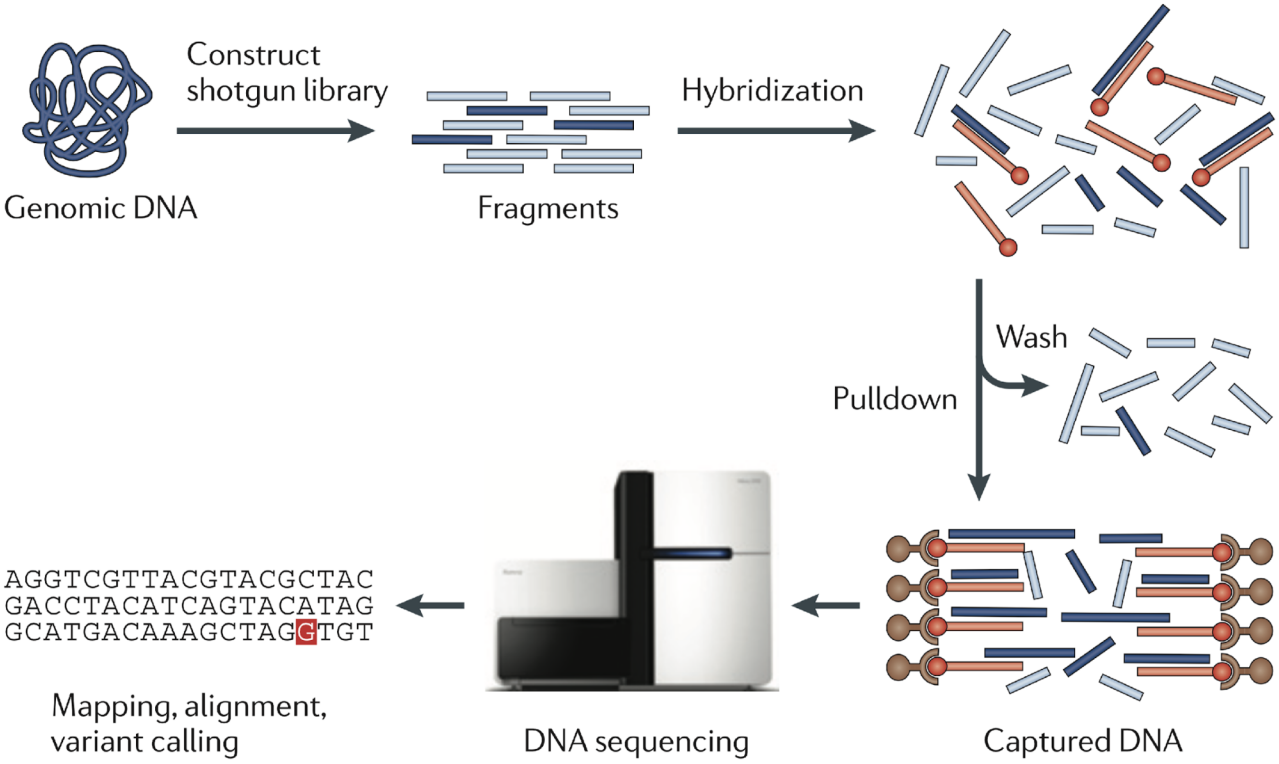
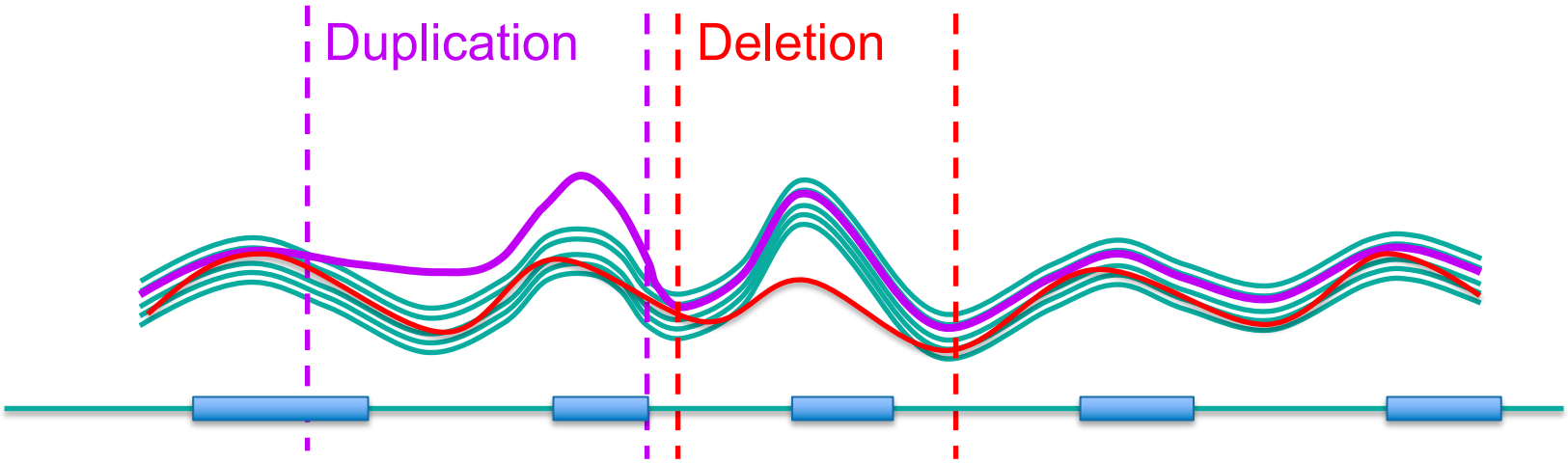
Next Generation Sequencing



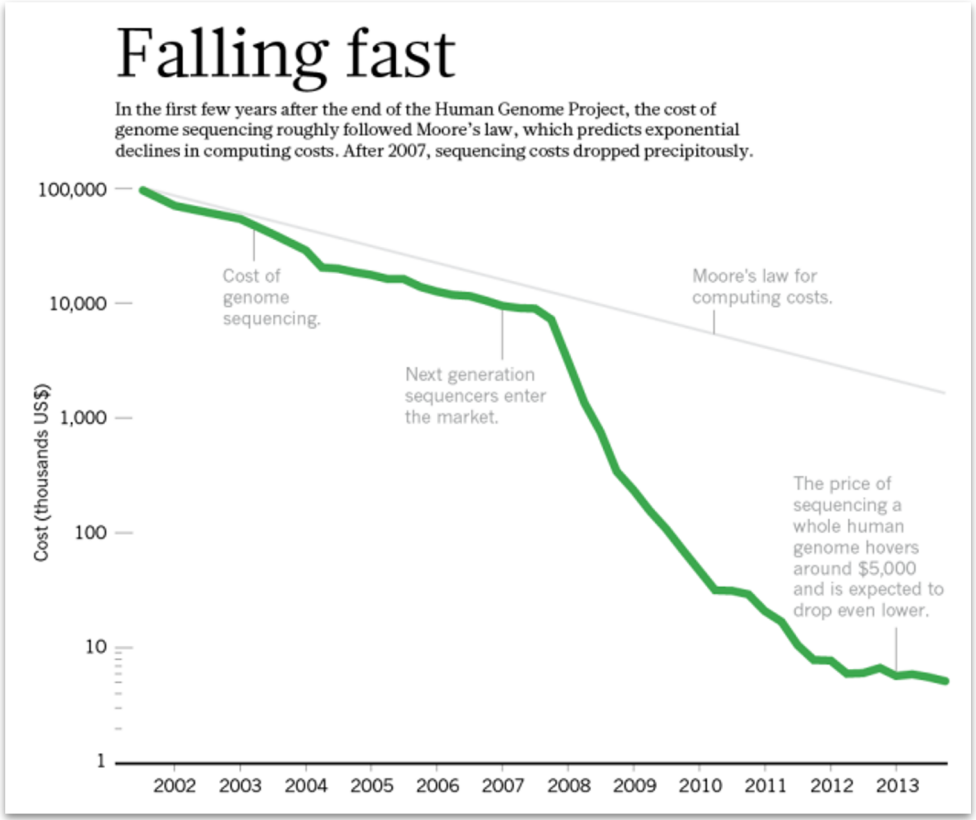
Source: Bamshad MJ, *et al. Nat Rev Genet.* 2011;12(11):745–55.

Copy number detection by next-generation sequencing



- The depth profile is non-uniform but reproducible.
- Look for deviations with respect to *baseline samples.*
- Perform this evaluation at the assay level to be able to detect deletions/duplications down to single-exon resolution across the panel.

Cost of DNA sequencing dropping rapidly



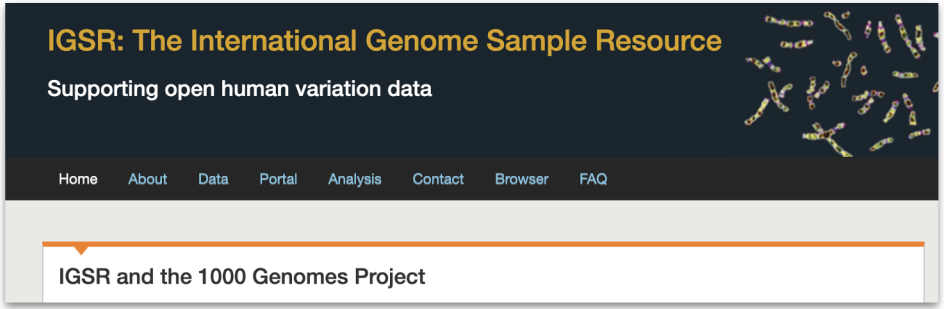
Erika Check Hayden, The $1,000 genome, Nature News, 19 March 2014

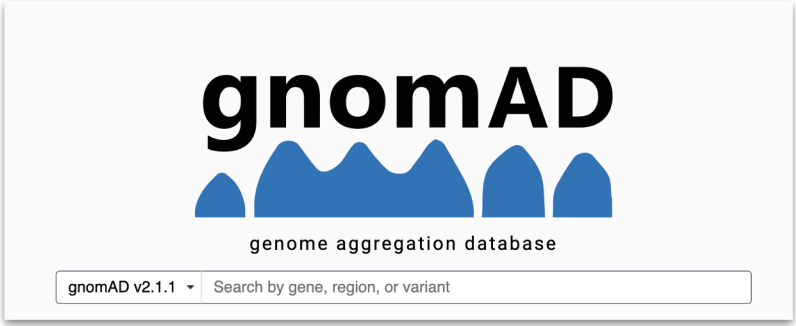
Evolution of large public databases

1000 Genome (2010)
First large public database of genome data from “control” individual

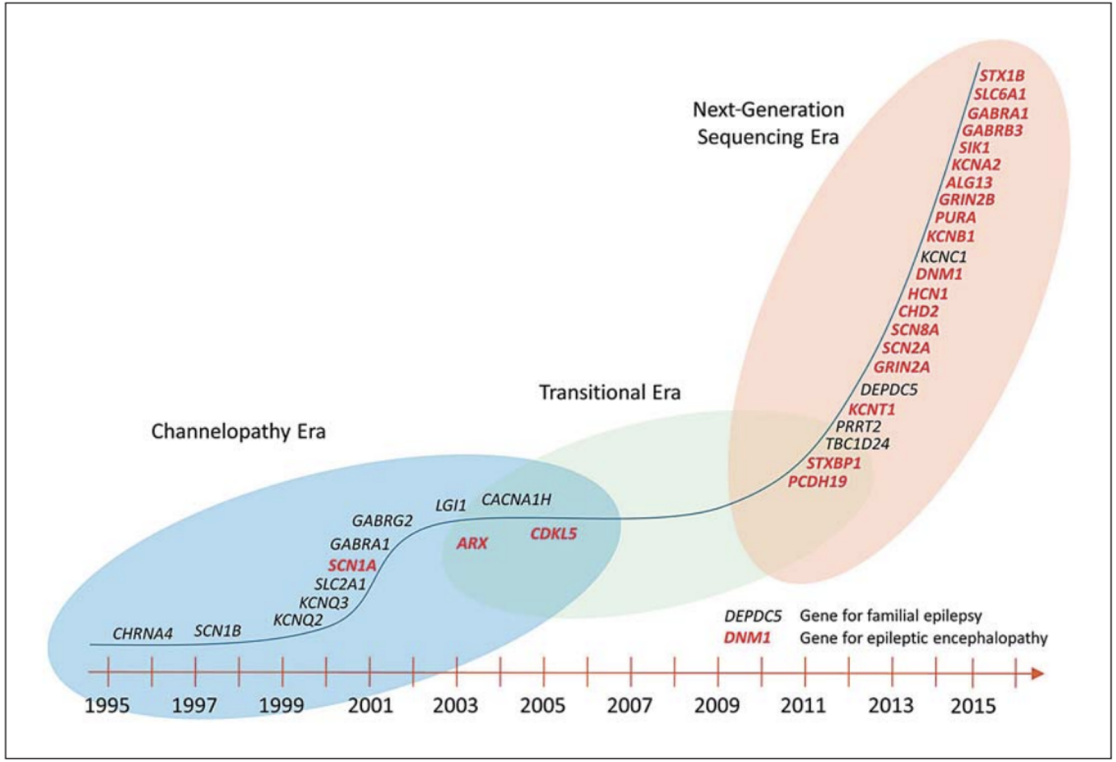
ExAC (2014)
Second large public database
60,000 exomes

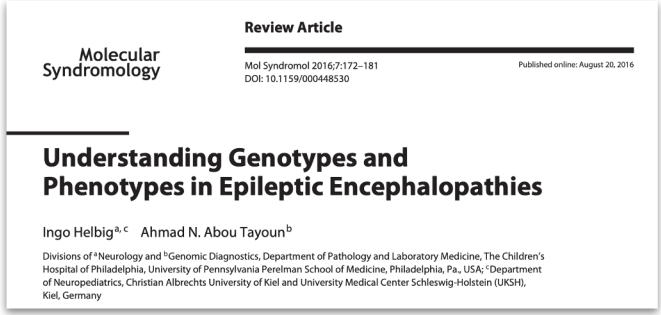
gnomAD (2017)
Current largest public database
v2: 125,748 exomes and 15,708 whole genomes
v3: 71,702 whole genomes





Gene discovery for epilepsy





Molecular Syndromology

Review Article

Mol Syndromol 2016;7:172–181
DOI: 10.1159/000448530

Published online: August 20, 2016

Understanding Genotypes and Phenotypes in Epileptic Encephalopathies

Ingo Helbig[a, c] Ahmad N. Abou Tayoun[b]

Divisions of [a]Neurology and [b]Genomic Diagnostics, Department of Pathology and Laboratory Medicine, The Children's Hospital of Philadelphia, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pa., USA; [c]Department of Neuropediatrics, Christian Albrechts University of Kiel and University Medical Center Schleswig-Holstein (UKSH), Kiel, Germany

Helbig I, Tayoun AA. Understanding Genotypes and Phenotypes in Epileptic Encephalopathies. *Mol Syndromol*. 2016;7(4):172-181.

Study of genetic testing utility in epilepsy

FULL-LENGTH ORIGINAL RESEARCH

Epilepsia Open® Open Access

Possible precision medicine implications from genetic testing using combined detection of sequence and intragenic copy number variants in a large cohort with childhood epilepsy

Rebecca Truty[1] | Nila Patil[2] | Raman Sankar[2] | Joseph Sullivan[3] | John Millichap[4] |
Gemma Carvill[5] | Ali Entezam[1] | Edward D. Esplin[1] | Amy Fuller[1] | Michelle Hogue[1] |
Britt Johnson[1] | Amirah Khouzam[1] | Yuya Kobayashi[1] | Rachel Lewis[1] |
Keith Nykamp[1] | Darlene Riethmaier[1] | Jody Westbrook[1] | Michelle Zeman[1] |
Robert L. Nussbaum[1,6] | Swaroop Aradhya[1]

Truty et al. Epilepsia Open. Jul 2019

Methods

- NGS panel consisting of up to **183 genes**

- Simultaneous detection of sequence variants and exon-level copy number variants (deletions and duplications)

- **~9769 patients** were referred for testing for all genes or a subset (e.g., panels for early infantile epileptic encephalopathy or Rett/Angelman spectrum)
    - Unselected cohort
    - ~90% where under the age of 18 at time of testing

- Definition of **precision medicine implications** based on published literature and curation by expert clinicians with long-standing experience in epilepsy

Truty et al. Epilepsia Open. Jul 2019

Epilepsy genes related to precision medicine

Strong		Emerging	
ALDH7A1	Pyridoxine-dependent epilepsy	*ALDH5A1*	Succinic semialdehyde dehydrogenase deficiency
CSTB	Unverricht and Lundborg PME	*ATP1A3*	Alternating hemiplegia of childhood
EPM2A	Lafora disease	*DEPDC5*	Familial focal epilepsy
FOLR1	Cerebral folate transport deficiency	*GLRA1*	Hyperekplexia
GAMT	Cerebral creatine deficiency syndrome	*GNAO1*	Early infantile epileptic encephalopathy
GATM	Cerebral creatine deficiency syndrome	*GOSR2*	Progressive myoclonic epilepsy
KCNQ2	Early infantile epileptic encephalopathy	*GRIN1*	Epilepsy with ID and hyperkinesis
NHLRC1	Lafora disease	*GRIN2A*	Focal epilepsy, speech impairment & ID
PNPO	Pyridoxamine 5′-PO_4 oxidase deficiency	*GRIN2B*	EIEE & ID
POLG	Mitochondrial DNA depletion; PEO	*KCNQ3*	Benign infantile epilepsy, developmental disability
SCN1A	Dravet syndrome	*KCNT1*	Early infantile epileptic encephalopathy
SCN2A	Early infantile epileptic encephalopathy	*NGLY1*	Congenital disorder of deglycosylation
SCN8A	Early infantile epileptic encephalopathy	*PCDH19*	Sex-limited EIEE
SLC2A1	Glucose transporter deficiency	*PIGA*	Congenital anomalies-hypotonia-seizures syndrome
SLC6A8	Cerebral creatine deficiency syndrome	*PRRT2*	Episodic kinesigenic dyskinesia & seizures
TPP1	Neuronal ceroid lipofuscinosis 2 (CLN2)	*QARS*	Progressive microcephaly with seizures
TSC1	Tuberous sclerosis	*SLC6A1*	Myoclonic-atonic epilepsy
TSC2	Tuberous sclerosis		

Legend:

Genes associated with biochemical disorders

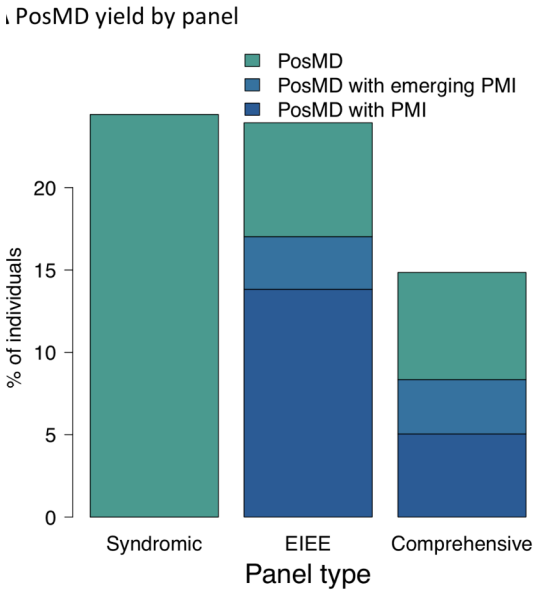
Genes associated with disorders for which there are anti-epileptic drug contraindications

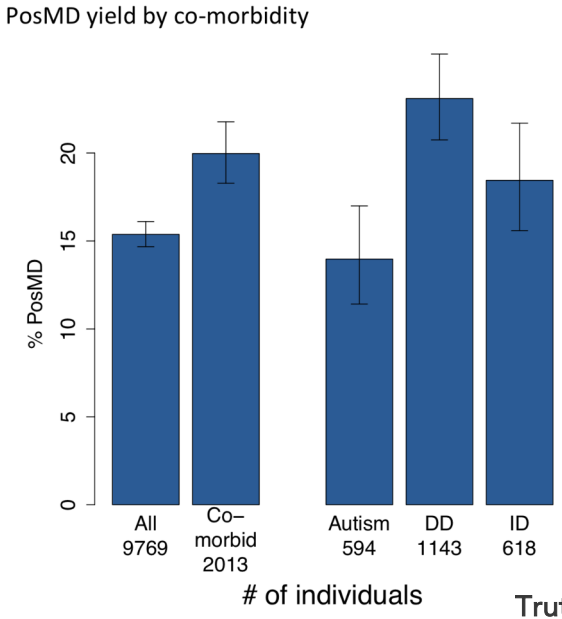
Genes associated with disorders for which there are indications for using specific anti-epileptic drugs.

Truty et al. Epilepsia Open. Jul 2019

Diagnostic yield of genetic testing in epilepsy

- Diagnostic **yield of 15-25%,** depending on panel used
- Syndromic and EIEE have higher yield compared to Comprehensive panel
- **33% of individuals** with positive reports had results with **precision medicine implications**

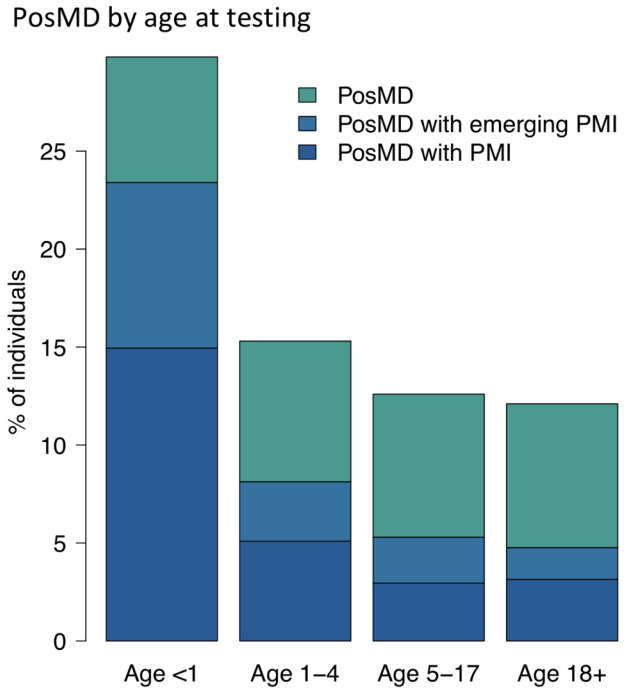




Truty et al. Epilepsia Open. Jul 2019

Early molecular diagnosis is important in epilepsy

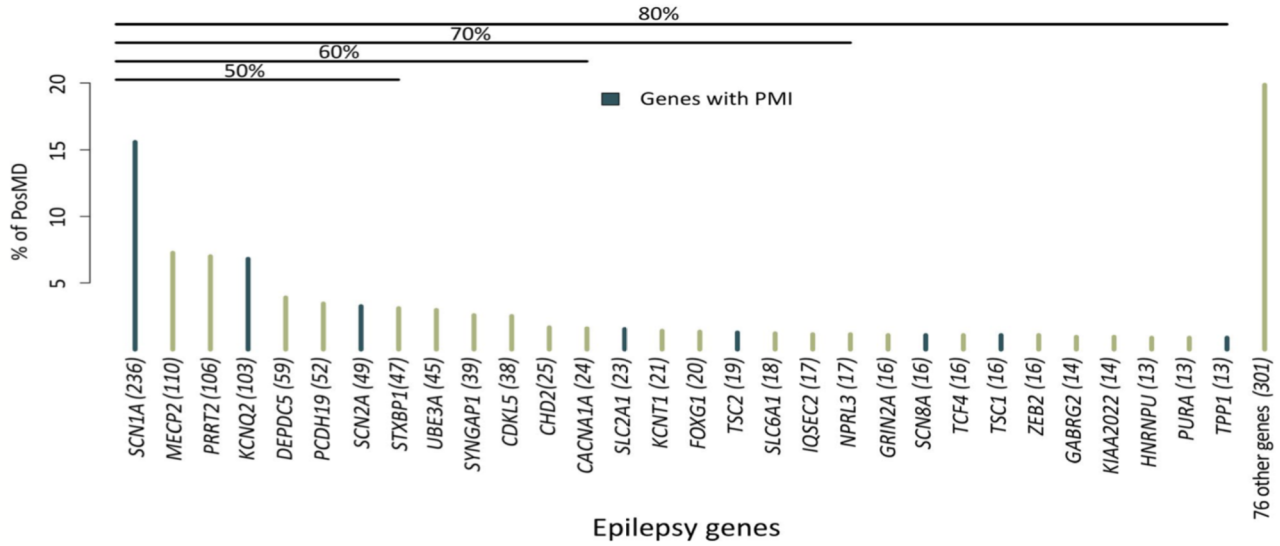
- Children with epilepsy in **first year of life have the highest diagnostic yield, at 30%**
- Nearly **half** of those with seizures in their first year of life and with positive reports have results with **precision medicine implications**
- 66% of all positive results with precision medicine implications were in children **younger than 5 years**



Truty et al. Epilepsia Open. Jul 2019

Critical genes involved in epilepsy

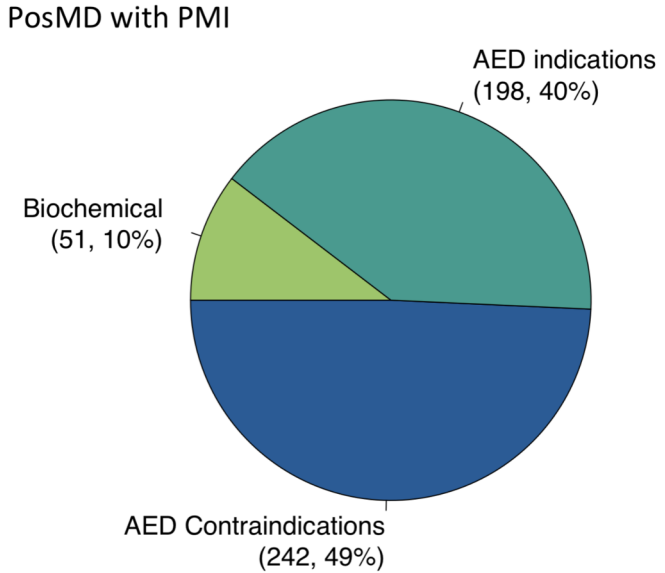
- **80% of positive molecular diagnoses came from only 30 genes** while the remaining 20% were from 76 other genes.
- *SCN1A* has the highest yield
- Corroborated by another large genetic testing study (Lindy et al., Epilepsia 2018)



Truty et al. Epilepsia Open. Jul 2019

Categories of precision medicine implications

- Nearly **half of positive molecular diagnoses** with precision medicine implications were related to **contraindications** for anti-epileptic drugs (AED), largely due to variants in *SCN1A*.
- **10%** of molecular diagnoses were related to **biochemical disorders** with available treatments
- **40%** of molecular diagnoses invoked **indications** for specific AED (e.g., Vigabatrin for spasms in TSC)
- Another **21%** of individuals had positive molecular diagnoses in genes with **emerging associations** with precision medicine implications



Truty et al. Epilepsia Open. Jul 2019

Study of genetic testing utility for epilepsy in adults

ARTICLE OPEN ACCESS

Multigene Panel Testing in a Large Cohort of Adults With Epilepsy

Diagnostic Yield and Clinically Actionable Genetic Findings

Dianalee McKnight, PhD, Sara L. Bristow, PhD, Rebecca M. Truty, PhD, Ana Morales, MS, Molly Stetler, MS, M. Jody Westbrook, PhD, Kristina Robinson, PhD, Darlene Riethmaier, MS, Felippe Borlot, MD, Marissa Kellogg, MD, Sean T. Hwang, MD, Anne Berg, PhD, and Swaroop Aradhya, PhD

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Dr. McKnight
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Neurol Genet 2022;8:e650. doi:10.1212/NXG.0000000000000650

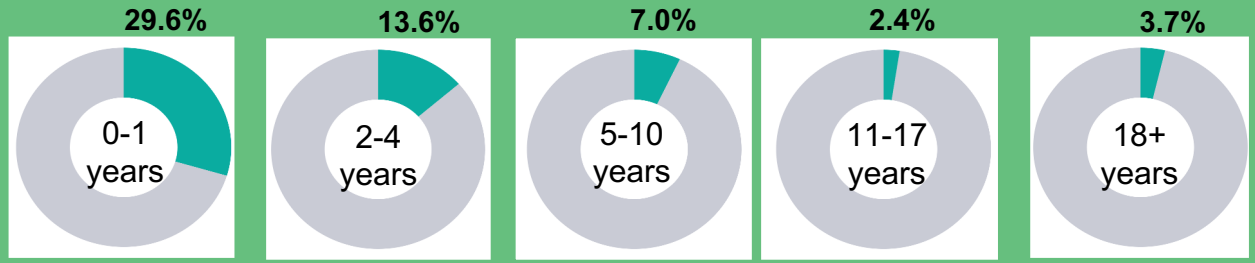
McKnight et al. Neurol Genet. 2022;8:e650

Overall diagnostic yields for genetic testing in adults with epilepsy

2,008 individuals over 18 years of age were tested with multi-gene panels

One in ten adults with epilepsy received a definitive molecular diagnosis

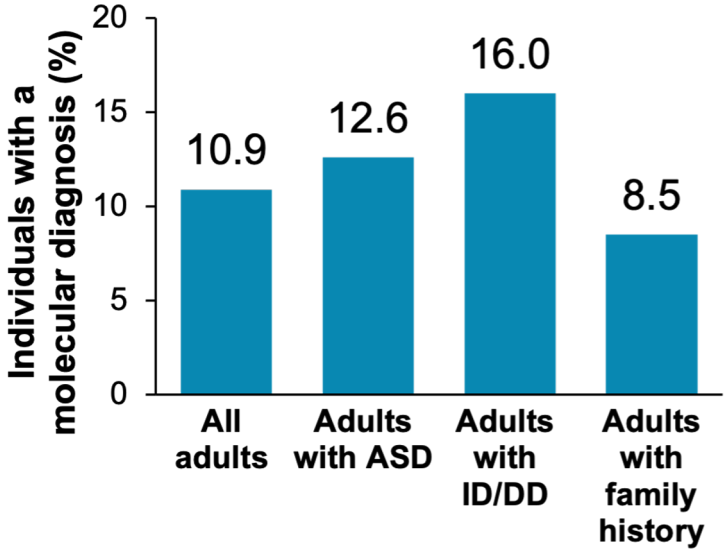
Seizure onset in infancy resulted in the highest diagnostic yield



McKnight et al. Neurol Genet. 2022;8:e650

Adults with epilepsy and comorbidities

Among investigated comorbidities, **adults with reported ID/DD** were most likely to have a molecular diagnosis (16.0%).

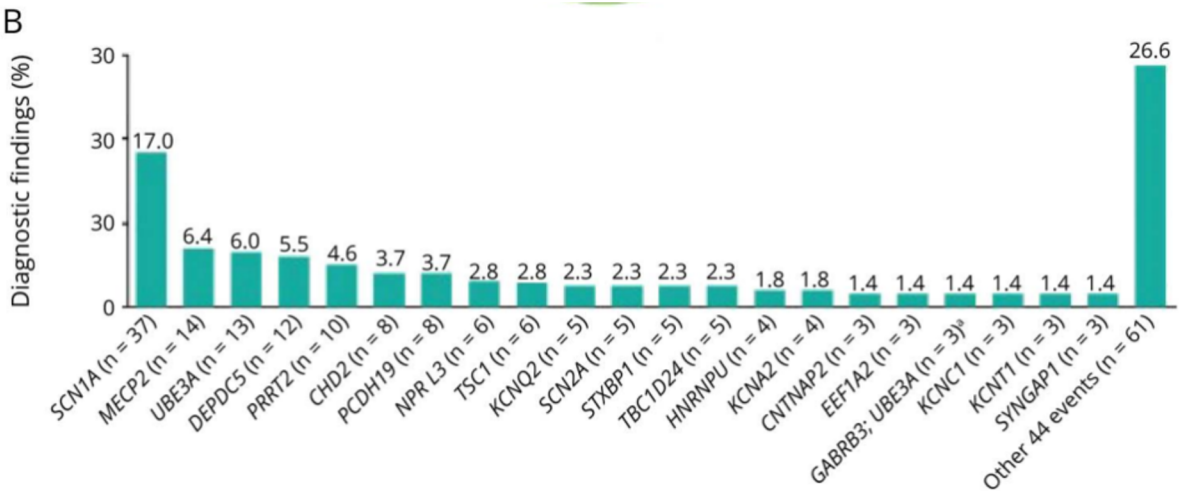


Abbreviations: ASD, autism spectrum disorder; ID/DD, intellectual disability/developmental delay

McKnight et al. Neurol Genet. 2022;8:e650

Critical genes involved in epilepsy

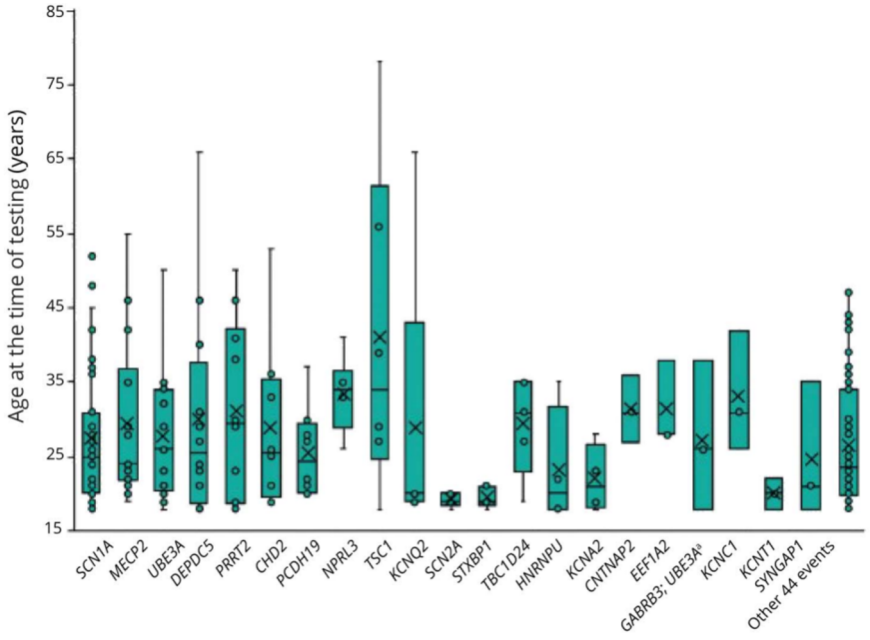
- Just like previous studies, most findings are in under 30 genes
- *SCN1A* has the highest yield
- 11 of the 13 top genes in both the Truty et al. study (90% kids) and this study (100% adults) were the same



McKnight et al. Neurol Genet. 2022;8:e650

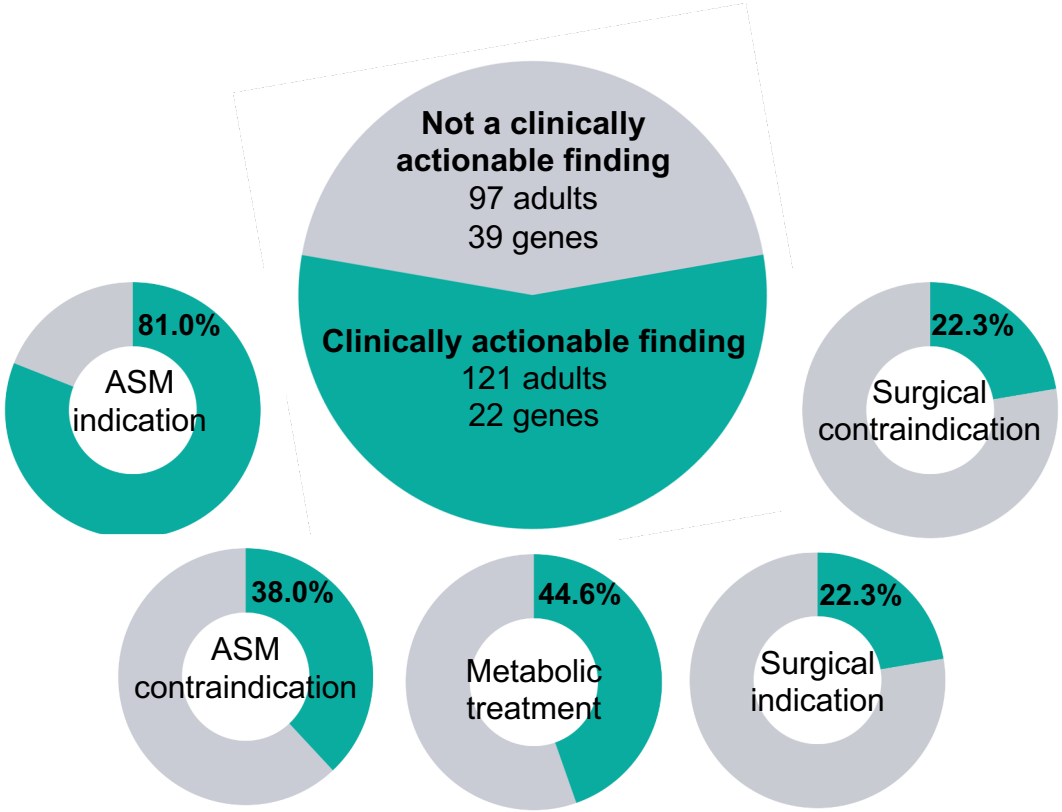
Many adults with genetic epilepsy live well into adulthood

Many adults in their **50s, 60s, 70s and even 80s** were found to have genetic epilepsy



McKnight et al. Neurol Genet. 2022;8:e650

Results with clinically actionable findings



- **Over one-half** of adults with epilepsy had diagnostic findings in genes associated with at least one **specific treatment for seizure control**
- Genetic testing could have a direct impact on clinical management for many adult patients with epilepsy

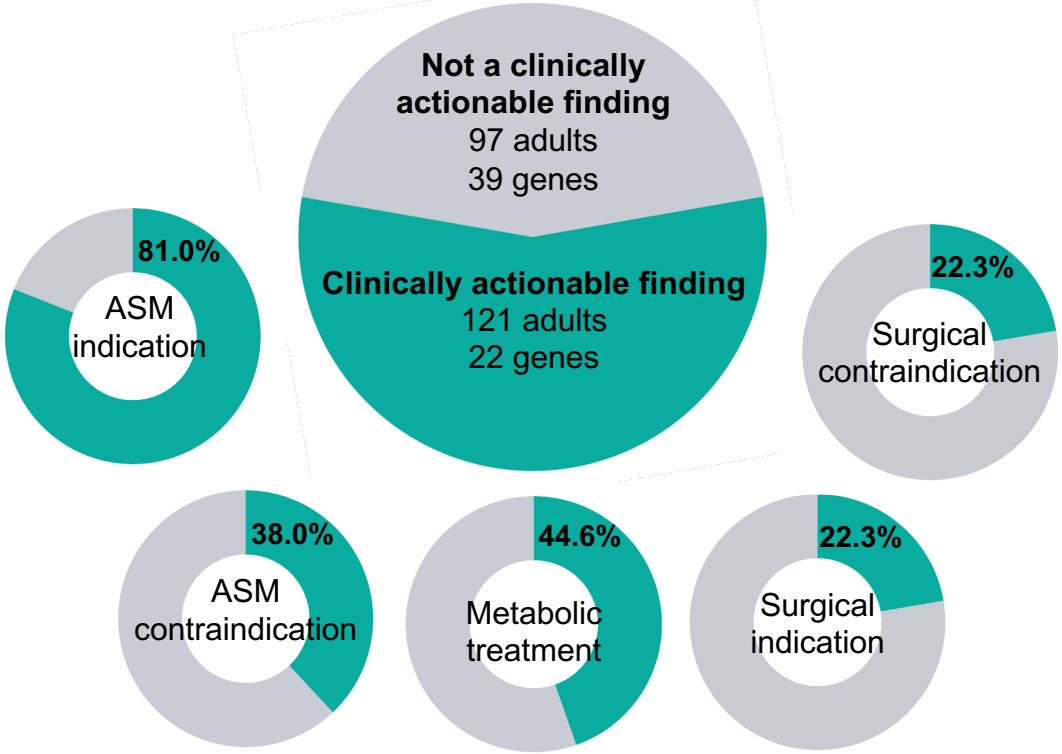
Abbreviations: ASM, antiseizure medication

McKnight et al. Neurol Genet. 2022;8:e650

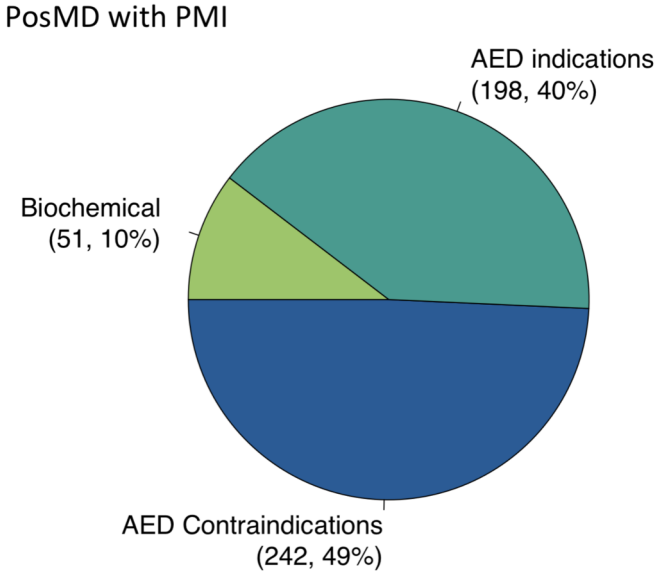
eTable 3. Genes associated with epilepsy that have clinically actionable implications

Gene	Associated syndrome or disorder	Inheritance	Clinical action	Potential clinical management options for daily maintenance of seizures[a]	Potential clinical management options for other manifestations	References (PMIDs)
ALDH7A1	Pyridoxine-dependent epilepsy; folinic acid-responsive seizures	AR				
ATP1A3	Alternating hemiplegia of childhood type 2; dystonia 12; cerebellar ataxia, areflexia, pes cavus, optic atrophy and sensorineural hearing loss	AD				
CACNA1A	Developmental and epileptic encephalopathy; episodic ataxia type 2 (EA2); familial hemiplegic migraine type 1 (FHM1)	AD				
CDKL5	Developmental and epileptic encephalopathy; atypical Rett syndrome; Angelman-like syndrome	XLD				
CHD2	Childhood-onset epileptic encephalopathy	AD				
DEPDC5	Familial focal epilepsy with variable foci; autosomal dominant nocturnal frontal lobe epilepsy	AD	Surgical indications	Indicated: high resolution neuroimaging; epilepsy surgery for identifiable epileptogenic foci		26434565, 30782578, 27683934, 30093711
EPM2A	Progressive myoclonus epilepsy, Lafora type	AR	ASM indicati ASM contraindicati	Indicated: VPA and BZDs as first-line;		
GLRA1	Hyperekplexia 1	AD/AR	ASM indicati			
KCNH2	Long QT syndrome type 2; short QT syndrome	AD	Other			
KCNQ2	Benign familial neonatal seizures; developmental and epileptic encephalopathy	AD	ASM indicati (subject to Gc consideration			
KCNT1	Autosomal dominant nocturnal frontal lobe epilepsy; developmental and epileptic encephalopathy	AD	ASM indications; Metabolic treatment	Indicated: quinidine, KD		26369628, 32167590, 31054119
LGI1	Autosomal dominant lateral temporal lobe epilepsy	AD	ASM indications	Indicated: PHT, CBZ, VPA		20301709, 7647791
NHLRC1	Progressive myoclonus epilepsy, Lafora type	AR	ASM indications; ASM contraindications	Indicated: VPA and BZDs as first-line; LEV, ZNS, TPM, and PER as second-line; primidone, PB, piracetam, and ESM as third-line Contraindicated: PHT, LTG, CBZ, OXC		20301563, 25667898
NPRL3	Familial focal epilepsy with variable foci	AD	Surgical intervention	Indicated: high resolution neuroimaging; epilepsy surgery for identifiable epileptogenic foci		26434565, 26285051
PCDH19	Developmental and epileptic encephalopathy	XLD	ASM indications; Metabolic treatment	Indicated: clobazam, potassium bromide, PHT, KD		26820223, 23712037
PRRT2	Episodic kinesigenic dyskinesia; benign familial infantile seizure 2; familial infantile convulsions with paroxysmal choreoathetosis	AD	ASM indications	Indicated: OXC, CBZ		28056630, 29334453, 32392383

Two studies reported ~50% of positive results should be clinically actionable…..but are they in practice?



McKnight et al. Neurol Genet. 2022;8:e650



Truty et al. Epilepsia Open. Jul 2019

AES 2021 ANNUAL MEETING

Molecular Diagnosis from Genetic Testing Guides Clinical Management of Epilepsy and Helps Improve Patient Outcomes

Dianalee McKnight, PhD, FACMG

Invitae

December 6, 2021

AES 2021 ANNUAL MEETING

Collaborators:

Ana Morales (Invitae)

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Felippe Borlot (University of Calgary)

Kaitlin Angione (Children's Hospital Colorado)

M. Scott Perry (Cook Children's Medical Center)

Joshua Bonkowsky (University of Utah)

Loreto Ríos-Pohl (Clínica Integral de Epilepsia)

Anne Berg (Northwestern-Feinberg School of Medicine)

ELEVIATE consortium

75TH ANNUAL MEETING

Epilepsy Outcomes Study Objectives

- Cite data demonstrating that epilepsy genetic testing can lead to actionable results.
- List examples of patient management changes that are made by clinicians based on a molecular diagnosis of epilepsy.
- Discuss evidence showing that epilepsy testing can be associated with positive health outcomes.

McKnight et al. American Epilepsy Society, Dec 2021

Rationale

- Genetic testing for epilepsy identifies a molecular etiology in up to 40% of cases
- ~50% of positive findings are in clinically actionable genes [1] [2]
- Previous studies have demonstrated reduced healthcare costs for individuals with good versus poor seizure control (~$14,000/year vs. ~$23,000/year, respectively) due to decreased hospitalizations and emergency department visits [3]
- Limited information on how genetic information is used by clinicians to guide management and subsequent patient outcomes

→**AIM**: We investigated changes in clinical management and patient outcomes after a definitive genetic diagnosis of epilepsy was identified

1. Truty R, et al. Epilepsia Open. 2019; 4(3):397–408)

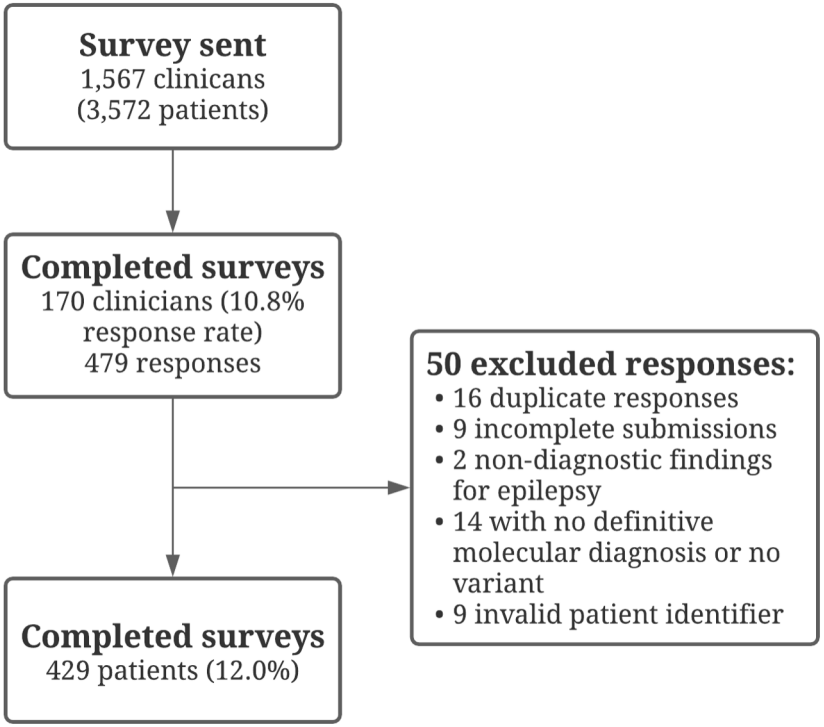
2. McKnight et al. Neurol Genet. 2022;8:e650

3.. Cramer, Joyce A., et al. *Epilepsy & Behavior: E&B* 31 (February): 356–62.

Methods

- 1,567 clinicians who received a positive diagnostic finding for a patient with epilepsy were sent an invitation to participate
- Case report forms were collected between May-November 2020
- 170 clinicians completed case report forms for 429 patients with epilepsy and a genetic diagnosis
- Clinical specialties included:

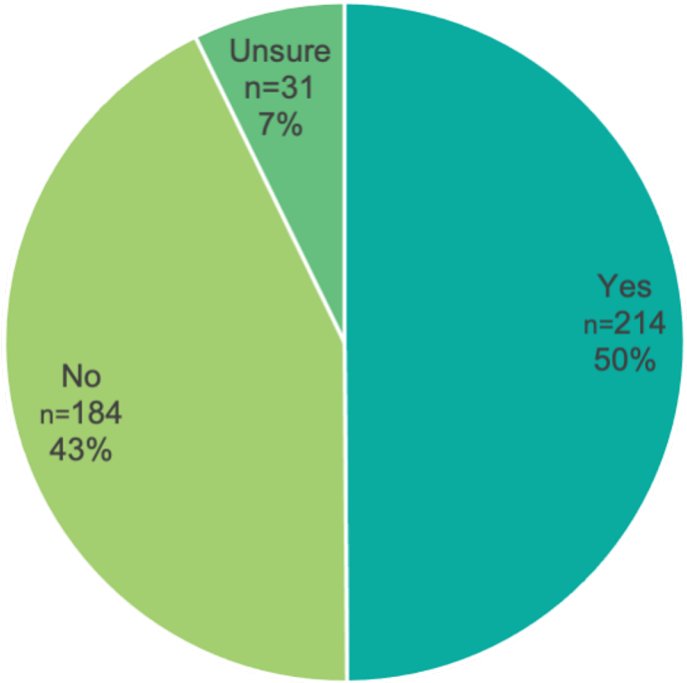
-Genetics (22.4%)
-Pediatric neurology (17.1%)
-Neurology (15.3%)
-Epilepsy (7.6%)
-Internal medicine (0.6%)
-Multiple specialties (37.1%)



McKnight et al. American Epilepsy Society, Dec 2021

Did the genetic finding influence a change in clinical management?

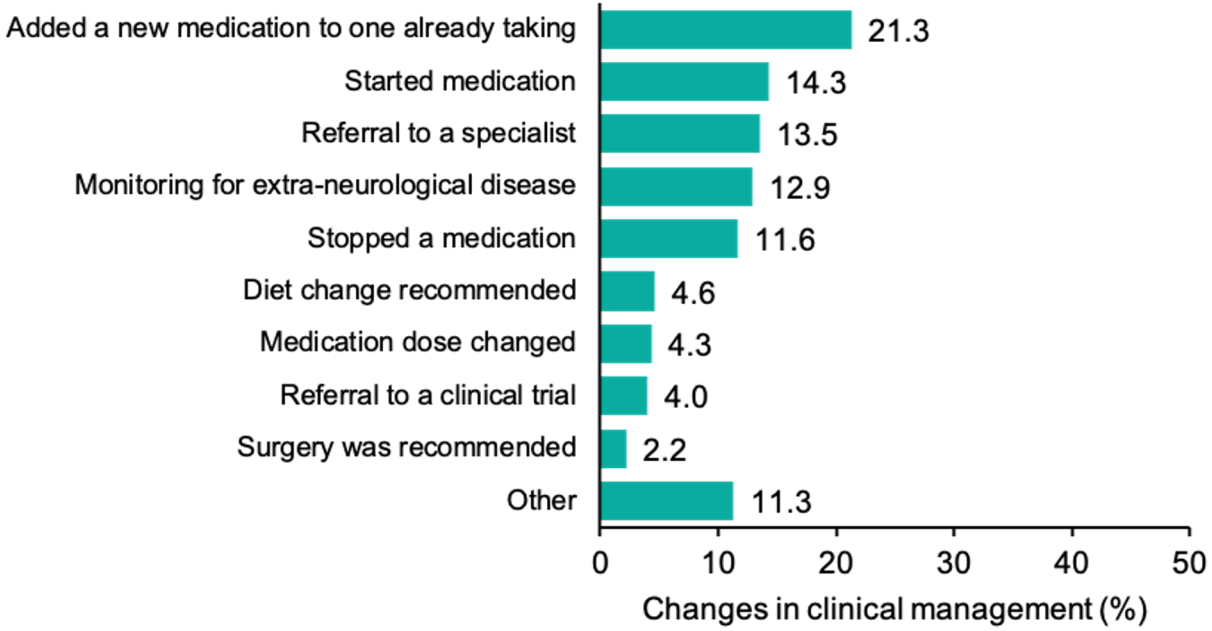
- **Half** of positive genetic diagnoses **led to** a change in clinical management.
- In **81.3%** of cases, providers changed clinical management **within 3 months** of receiving the genetic testing result.



McKnight et al. American Epilepsy Society, Dec 2021

Changes that were implemented due to genetic finding

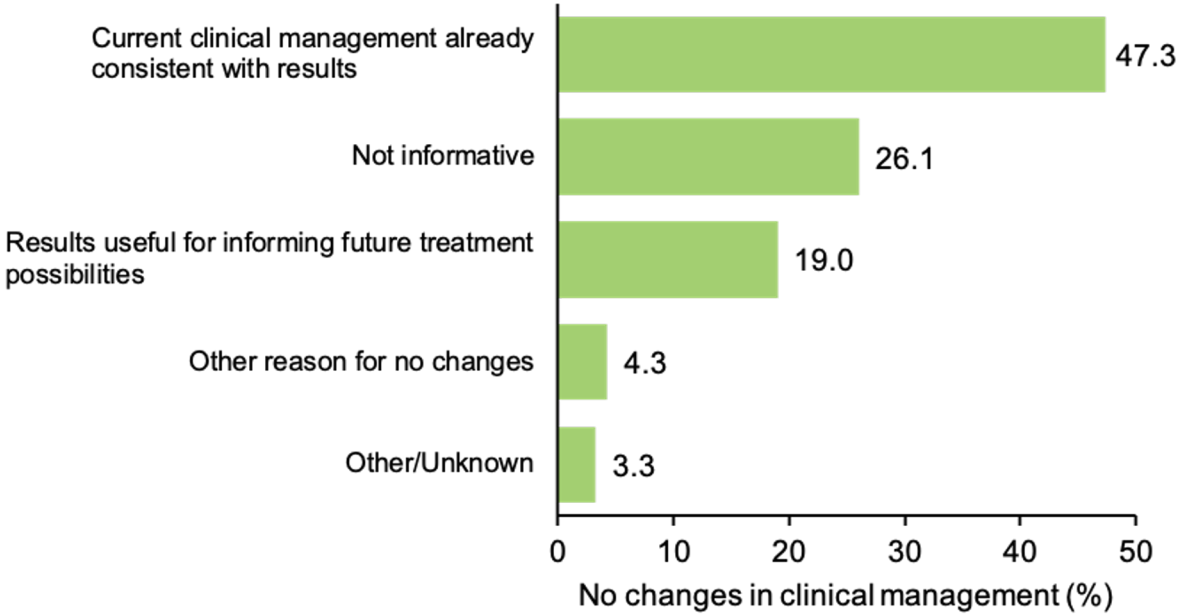
Most common change was to add a new medication.



McKnight et al. American Epilepsy Society, Dec 2021

Reasons for not changing management due to the genetic finding

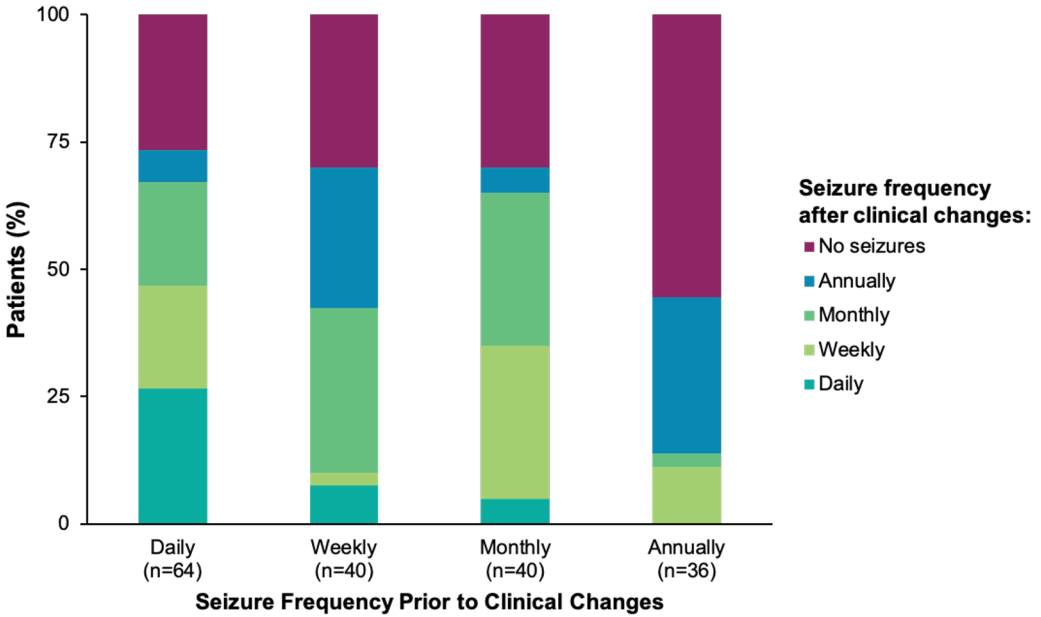
Most common response was that clinical management was already consistent with results.



McKnight et al. American Epilepsy Society, Dec 2021

Patient outcomes after treatment changes due to a molecular finding

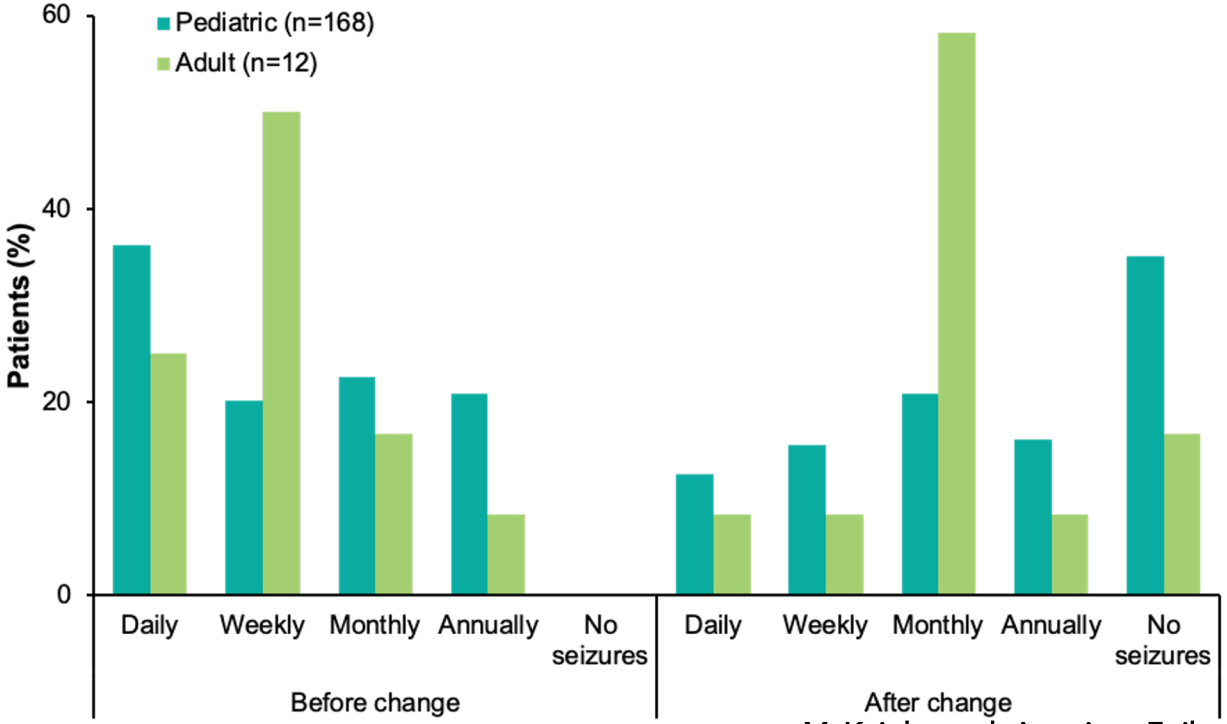
- 75% reported positive outcomes (129/172)
- 65% reported reduced or elimination of seizures
- 23% reported other improvements (i.e. in behavior, development, academics, movement issues)
- 6% reported reduced medication side effects



McKnight et al. American Epilepsy Society, Dec 2021

Positive outcomes observed in both adults and children

Similar trends in increased seizure control after treatment changes due to a diagnostic finding



McKnight et al. American Epilepsy Society, Dec 2021

Conclusions

- **Genetic testing** for epilepsy identifies a genetic diagnosis in **up to 40%** of cases depending on many factors including age of seizure onset and presence of comorbidities.
- **~50%** of positive findings are in **clinically actionable genes**.[1,2]
- A genetic diagnosis appears to inform **changes in clinical management**.[3]
- Management changes informed by genetic information contributes to **improved seizure control** in **65% of cases** and other positive outcomes for many patients.[3]
- These results support growing evidence that genetic testing can **improve health outcomes**, which could also **reduce healthcare costs**.

1.Truty et al. Epilepsia Open. Jul 2019
2.McKnight et al. Neurol Genet. 2022;8:e650
3.McKnight et al. American Epilepsy Society, Dec 2021

Thank you