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CHAIR SUMMIT

CME Outfitters

Master Class for Neuroscience Professional Development

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CME Outfitters

Epidemiology and Emerging Role of Cannabidiol for Pediatric Epilepsy Syndromes

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Learning Objective 1

Examine the epidemiology of refractory pediatric epilepsy syndromes and the role of genetic testing in early diagnosis.

Learning Objective 2

Recognize the burden of illness of Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS) on patients, caregivers, and families.

Learning Objective 3

Apply safety and efficacy data of cannabidiol to treatment decisions in patients with DS and LGS.

The Facts About Drug-Resistant Epilepsy

- 800,000 Americans have drug-resistant epilepsy
- The chance of seizure freedom declined with successive drug regimens, most markedly from the first to the third and among patients with localization-related epilepsies
- Only 1 in 5 patients seek care at an epilepsy center

Chen Z, et al. *JAMA Neurol*. 2018;75(3):279-286.; Brodie MJ, et al. *Neurology*. 2012;78:1548-1554.

Early Identification of Refractory Pediatric Epilepsy

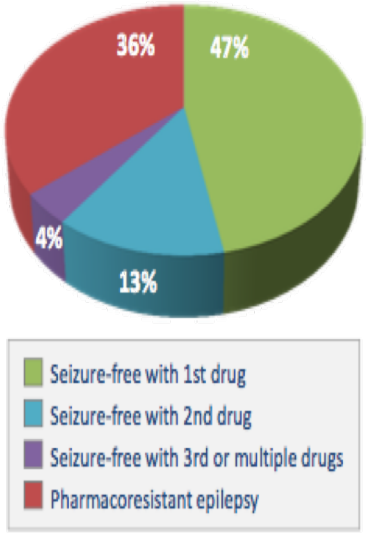
466,000
US CHILDREN WITH EPILEPSY

30%
PHARMACORESISTANT EPILEPTICS[1,4]
SEIZURES THAT PERSIST, DESPITE MULTIPLE AED TREATMENT[2]

140,000
TARGET US POPULATION
REFRACTORY EPILEPSY COMPOSED OF MULTIPLE SYNDROMES

Response to AEDs in patients with newly diagnosed epilepsy[3]

little change to this statistic over last 15 years



Drug-resistant Epilepsy:

- Antiepileptic drugs (AEDs) have little or no effect
- Effects over 30% of epilepsy patients
- Common onset in early childhood
- Increased drug burden
- Decline in cognition and quality of life
- Uncontrolled seizures
- Increased mortality
- Surgery is often the only viable option

1. Sander JW. *Epilepsia*. 1993;34(6):1007-1016. 2. Picot MC, et al. *Epilepsia*. 2008;49:1230-1238. 3. Kwan P, Brodie MJ. *N Engl J Med*. 2000;342:314-319. 4. Kwan P, Brodie MJ. *CNS Spectr*. 2004;9(2);110-119.

Burden of Dravet Syndrome (DS)

- Severe epileptic encephalopathy with onset during the first year of life
- Characterized by the onset of recurrent febrile and/or afebrile generalized or hemiclonic seizures or status epilepticus on a background of normal development, followed by multiple seizure types, including myoclonic, absence, and focal impaired awareness seizures
- Incidence estimates range from 1 in 15,700 to 40,000 infants; early mortality is high, with sudden unexplained death in epilepsy (SUDEP) and status epilepticus as the leading causes of death
- Results from mutations in the gene encoding the α1 subunit of the voltage-gated sodium channel (Nav1.1) encoded by SCN1A in 70% - 80% of cases, whereas mutations in other voltage-gated sodium channel subunits as well as other ion channels can also cause DS
- Seizures in DS are often drug resistant

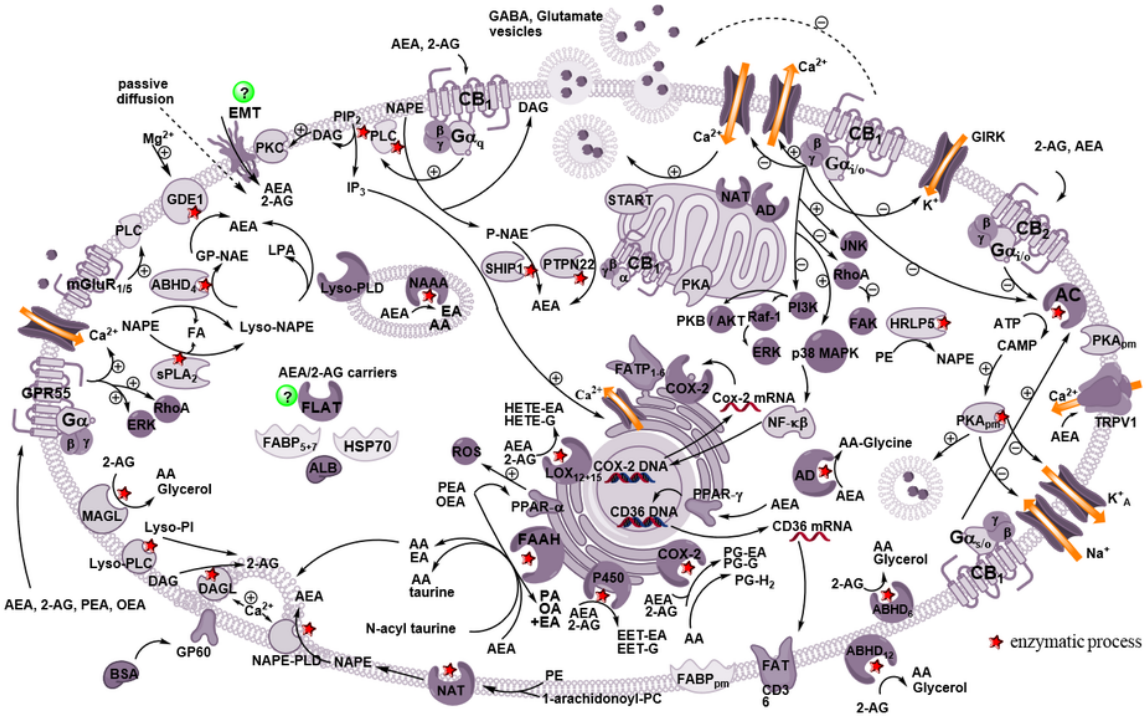
Devinsky O. *Epilepsia*. 2018;1-9.; Catterall WA, in: Ion Channels in Health and Disease, Perspectives in Translational Cell Biology. 2016;85-111.

Burden of Lennox-Gastaut Syndrome (LGS)

- Severe developmental epileptic encephalopathy that has multiple causes
- Incidence of approximately two cases per 100,000 population
- Characterized by several seizure types, severe cognitive impairment, and an abnormal electroencephalographic pattern of slow spike-and-wave complexes
- Seizures usually begin to occur before the age of 8 years and persist into adulthood in more than 90% of patients
- Drop seizures due to an increase in (tonic) or loss of (atonic) motor tone are characteristic of this disorder and often result in serious injury
- Six medications are approved to treat seizures in patients with this syndrome
- Despite treatment, disabling seizures continue to occur in most patients

Trevathan E, et al. *Epilepsia*. 1997;38(12):1283-1288.; Wheless JW. *J Child Neurol*. 2009;24(8 Suppl):24S-32S.

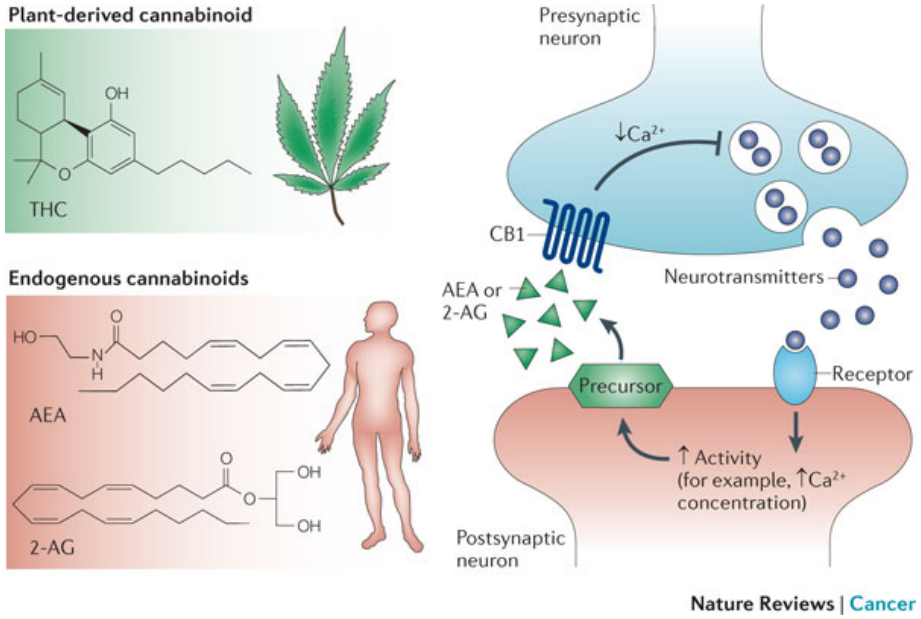
The Endocannabinoid System and Its Components



- The endocannabinoid system in the human body is comprised of three main components: endocannabinoids, receptors, and regulatory enzymes
- **Endocannabinoids:**
  - Two of the most well-studied endocannabinoids are derivatives of arachidonic acid:
    - N-arachidonoylethanolamine (anandamide [AEA])
    - 2-arachidonoylglycerol (2-AG)
- **Receptors:** Two most well-known G-proteins coupled receptors: cannabinoid receptor-1 (CB_1) and cannabinoid receptor-2 (CB_2)
- **Regulatory enzymes:** Fatty acid amidohydrolase (FAAD) is an enzyme that breaks down AEA

Mark R. Gertschgroup. 2017. http://gertschgroup.com/home/laboratory_homepage.

Endogenous Cannabinoids: Anandamide and 2-AG



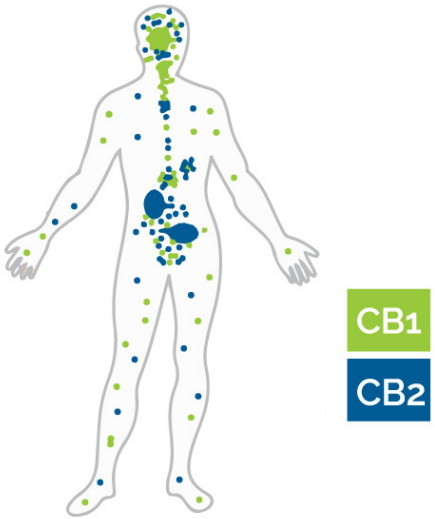
- Both of these endocannabinoids are synthesized on demand
- Travel in a retrograde fashion across a synapse to inhibit neurotransmitter release
  - AEA is a partial agonist of CB1 receptors; its affinity and efficacy at CB2 receptors is low
  - 2-AG is a fully efficacious agonist of both CB1 and CB2 receptors

Velasco G, et al. Nat Rev Cancer. 2012;12:436-444.

CB1 and CB2 Receptors

CB1 Receptor

- Highly expressed in the central nervous system (CNS) and throughout the brain
- **10 times more prevalent in the CNS as compared to the μ-opioid receptor**
- CB1 receptors appear to be the primary psychoactive cannabinoid receptors, and mediate numerous physiological processes, including cardiovascular function, energy homeostasis, emotional behavior, sensory perception, motor control, pain modulation, and reproduction
- CB1 receptors are also found in non-neural tissue, including adipose, liver, pancreas, skeletal muscle and immune cells



CB2 Receptor

- Primarily found in the immune system and are thought to have immunomodulatory effects and to regulate cytokine activity

Institute of Medicine (US); Joy JE, Watson SJ Jr., Benson JA Jr., editors. Marijuana and Medicine: Assessing the Science Base. Washington (DC): National Academies Press (US); 1999. Cannabinoids and Animal Physiology. Available at: https://www.ncbi.nlm.nih.gov/books/NBK230721/

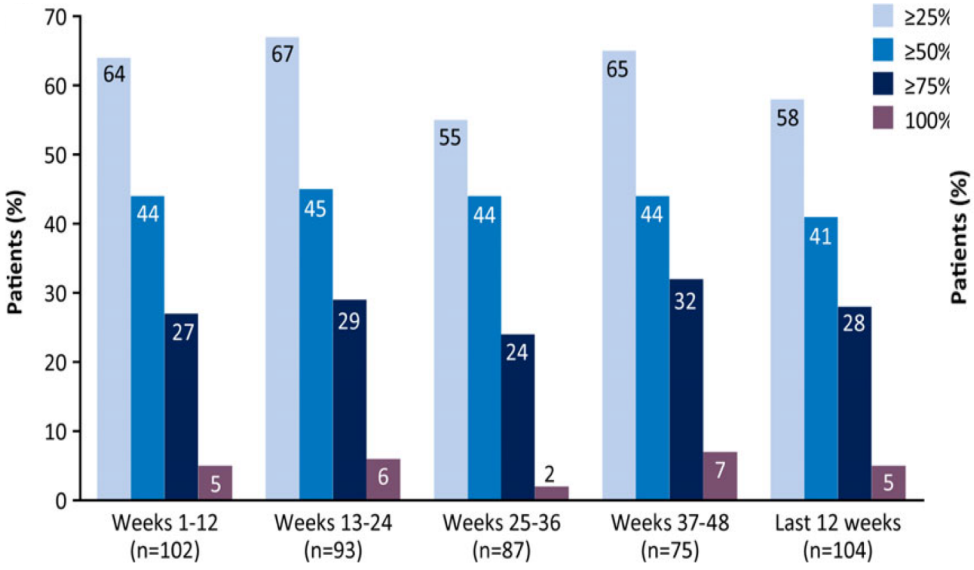
Entourage Effect: Whole Plant Versus Isolated Compounds

- Non-THC *Cannabis* active components may act synergistically and contribute to the pharmacological power and entourage effects of medicinal-based *Cannabis* extract
- Cannabichromene (CBC), Cannabigerol (CBG), Cannabidivarin (CBDV) Cannabigerolic Acid (CBGA), Cannabinol (CBN), Tetrahydrocannabinolic Acid (THCA), Tetrahydrocannabivarin (THCV) and Terpenes all present a wide array of pharmacological properties

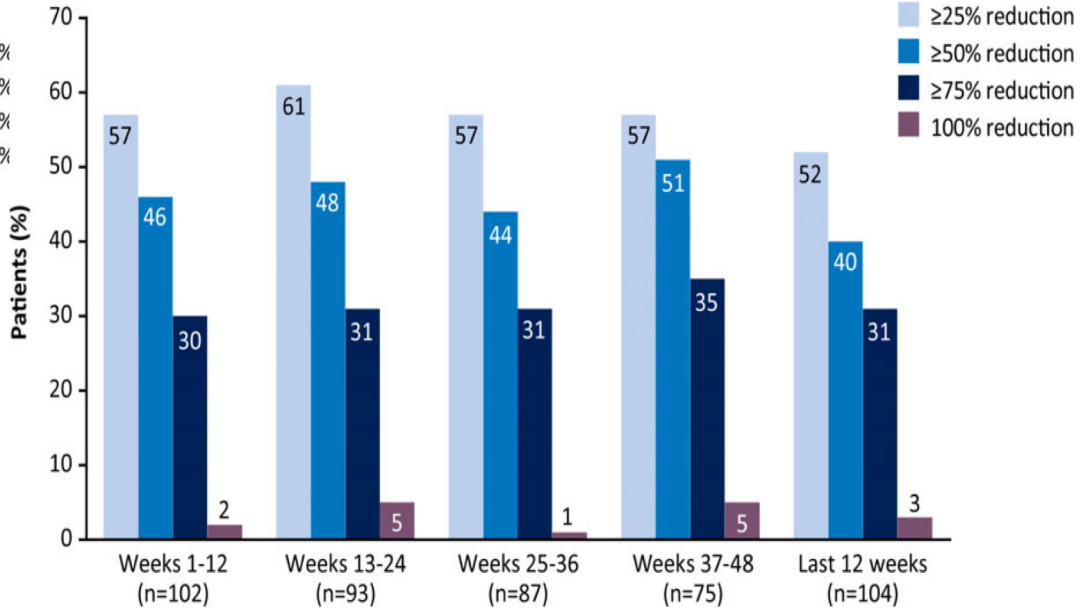
Russo EB. *Br J Pharmacol*. 2011;163(7):1344-1364.

Efficacy and Safety of Cannabidiol in DS

Convulsive Seizures

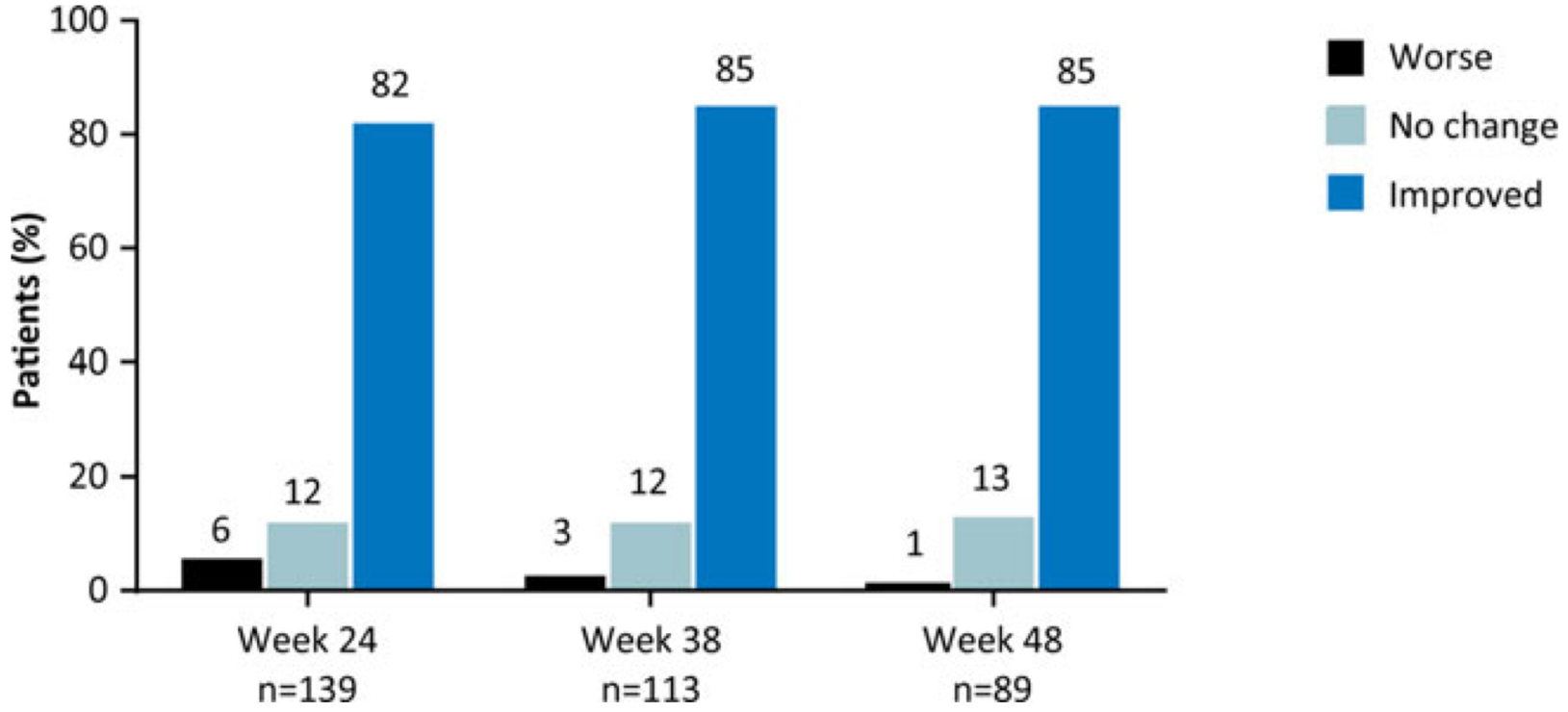


Total Seizures



Devinsky O, et al. *Epilepsy*. 2018;00:1-9.

Patient/Caregiver Ratings of Change in Overall Condition on the S/CGIC Scale

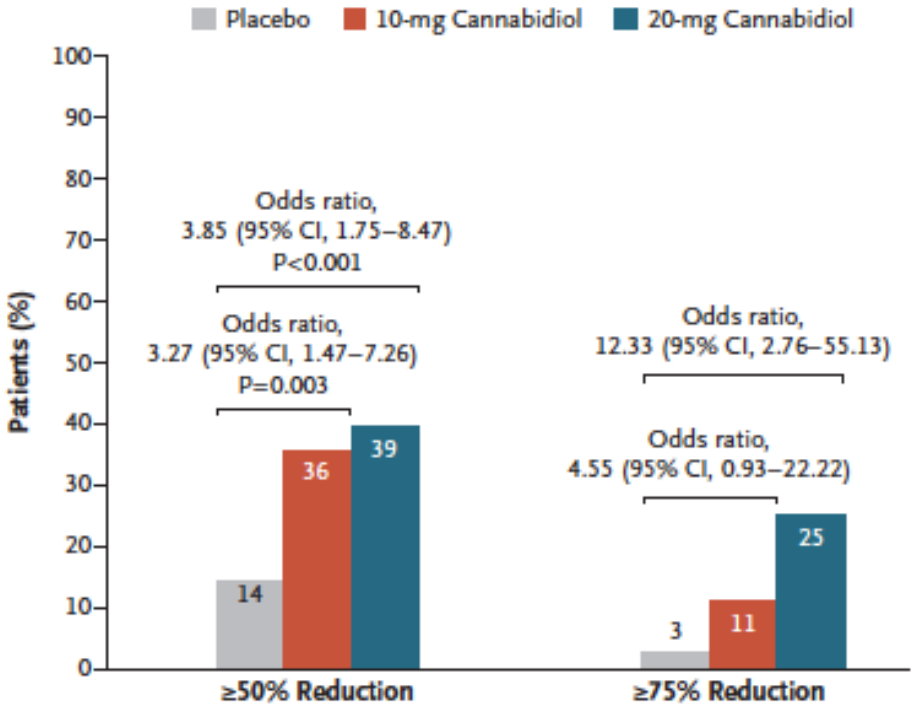


S/CGIC= subject/caregiver global impression of change.

Devinsky O, et al. *Epilepsy*. 2018;00:1-9.

Efficacy and Safety of Cannabidiol in LGS

Reductions in Drop-Seizure Frequency During the Treatment Period



Common adverse events

- Somnolence
- Decreased appetite
- Diarrhea
- Upper respiratory tract infection
- Pyrexia
- Vomiting
- Mild nasopharyngitis
- Status epilepticus

Devinsky O, et al. *N Engl J Med*. 2018;379(8):795.

Behavioral Measures

- Sleep Disruption
- Epworth Daytime Sleepiness Scale (EDSS)
- Quality of Life (QOLCE)
- Caregiver Global Impression (CGIC)
- Neuropsychological Variables
- Differential Ability Scales Preschool Version (DAS-II)
- Social Communication Questionnaire (SCQ)
- Child Development Inventory (CDI)
- Neuropsychological Tests
- Mullen Scales of Early Learning (MSEL)
- Vineland Adaptive Behavior Scale
- Peabody Picture Vocabulary Test III
- Rapid Automatized Naming
- Beery-Buktenica Test of Visual-Motor Integration
- Interhemispheric Transfer of Tactile Information
- Behavior Rating Inventory of Executive Function-Preschool Version (BRIEF-PS)
- Conners' Parent Report Scale-Long Form (CPRS-LF)
- ADOS-2
- Columbia-Suicide Severity Rating Scale (C-SSRS)

- Anticonvulsant Plasma Concentrations
- CBC, LFT, BUN, Creatine Levels, Electrolytes
- Safety
- Physical examination
- Neurologic examination
- 12-lead ECG
- Routine EEG
- MRI Imaging
- Height/weight
- Head Circumference
- Edinburgh Handedness Inventory
- Vital signs (temperature, HR, RR, BP)
- Pregnancy test

BP = blood pressure; BUN = blood urea nitrogen; CBC = complete blood count; ECG = electrocardiogram; EEG = electroencephalogram; HR = heart rate; LFT = liver function test; MRI = magnetic resonance imaging; RR = respiratory rate.

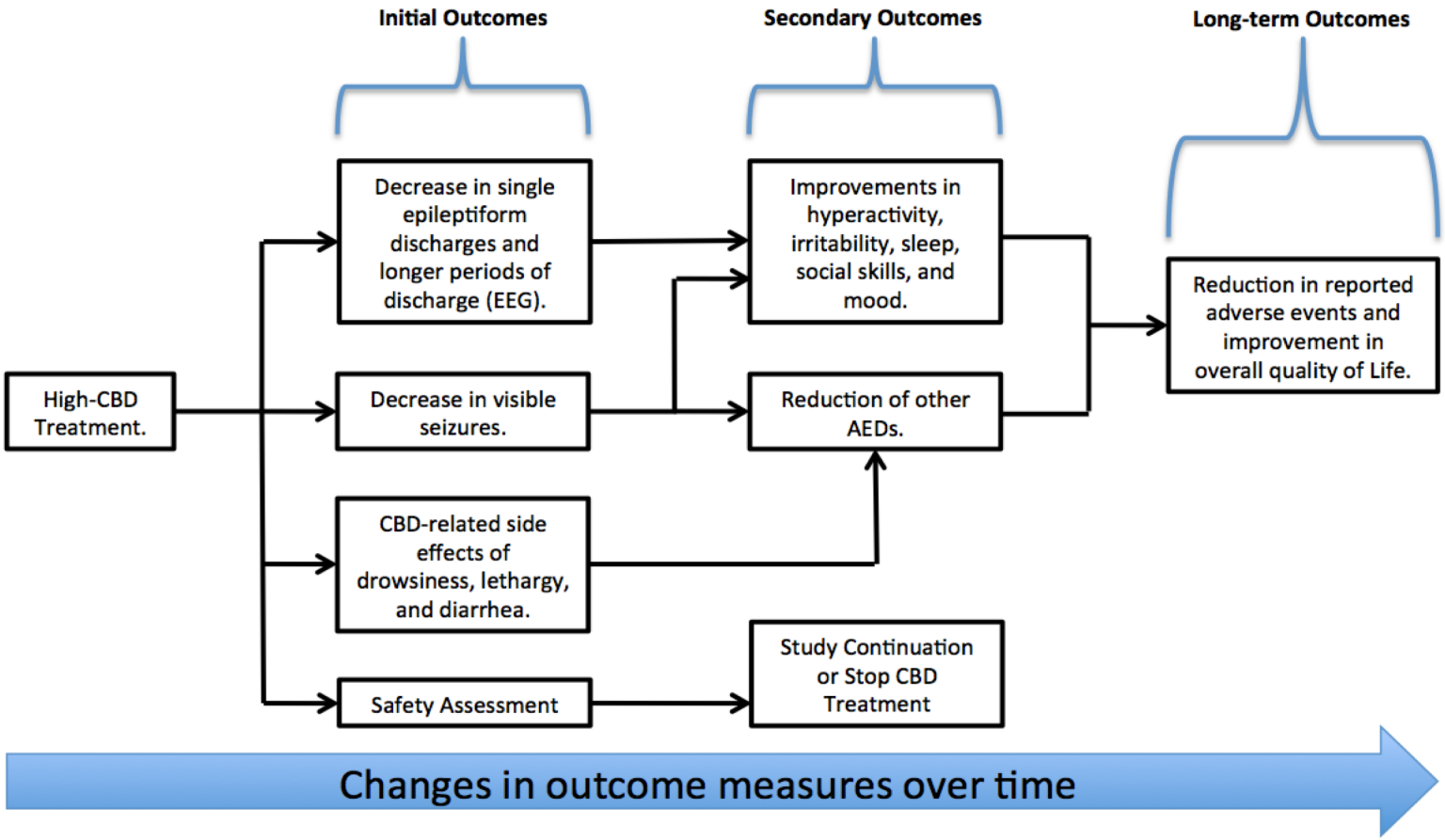
Carney PR, et al. American Epilepsy Society. 2017. Abstract 1.048

Positive and Negative Side Effects from CBD

Positive/Negative Side Effects	n = 33
Seizure Severity Decrease	22 (67%)
Better Mood	14 (42%)
Increased Alertness	11 (33%)
Better Focus	13 (39%)
Improved Social Interaction	15 (45%)
Better Sleep	3 (9%)
Improved Appetite	5 (15%)
Negative Side Effects	n = 33
Drowsiness	11 (33%)
Fatigue	4 (12%)
Diarrhea	4 (12%)
Negative Mood	3 (9%)
Decreased Appetite	2 (6%)

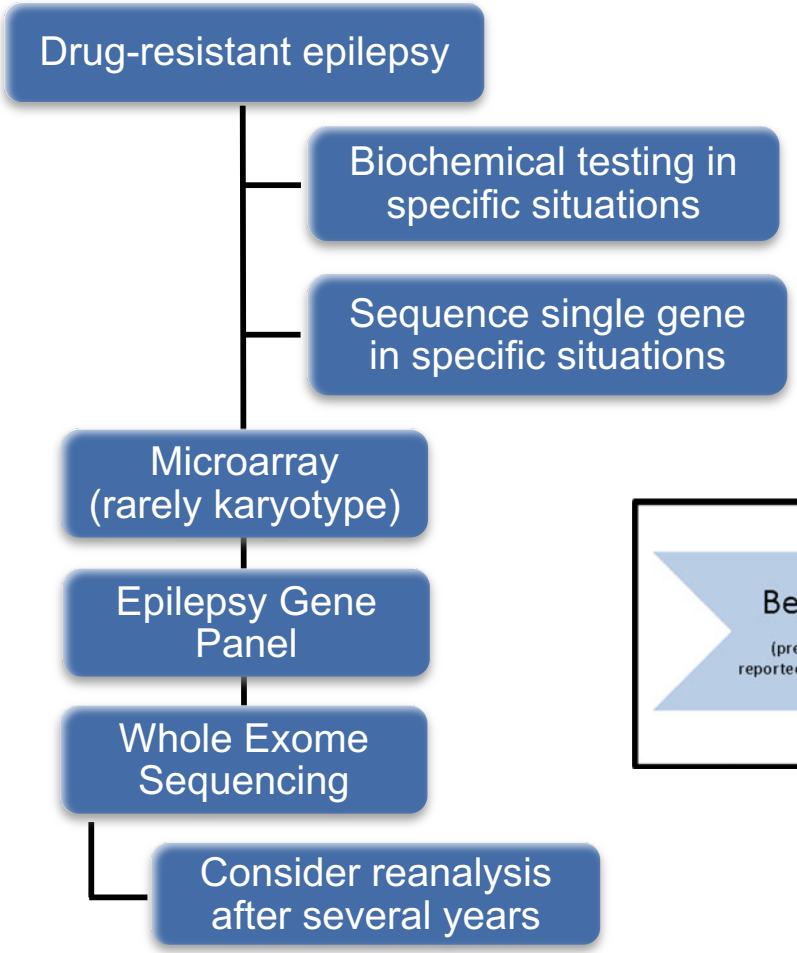
Carney PR, et al. American Epilepsy Society. 2017. Abstract 1.048.

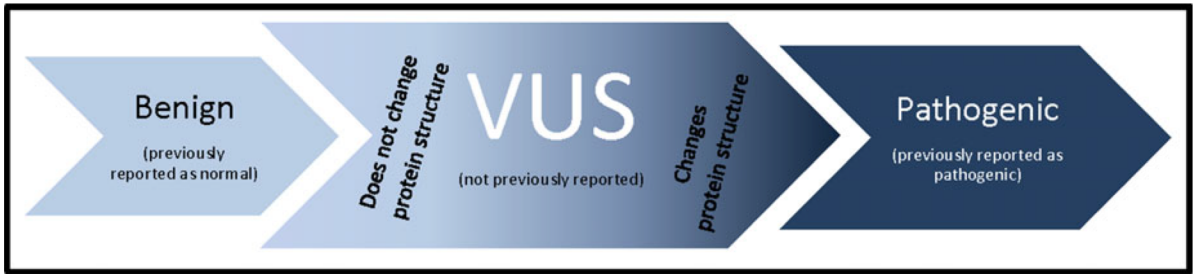
An Evaluation of Effectiveness of Cannabidiol as an Antiepileptic Drug for Children with IGE



Carney PR, et al. American Epilepsy Society. 2017. Abstract 1.048

Genetic Testing in Pediatric Epilepsy

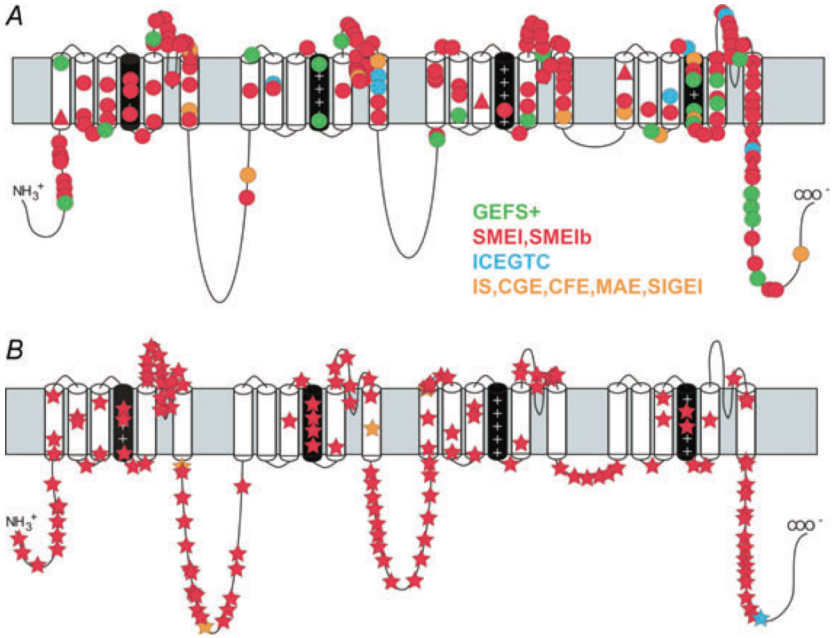




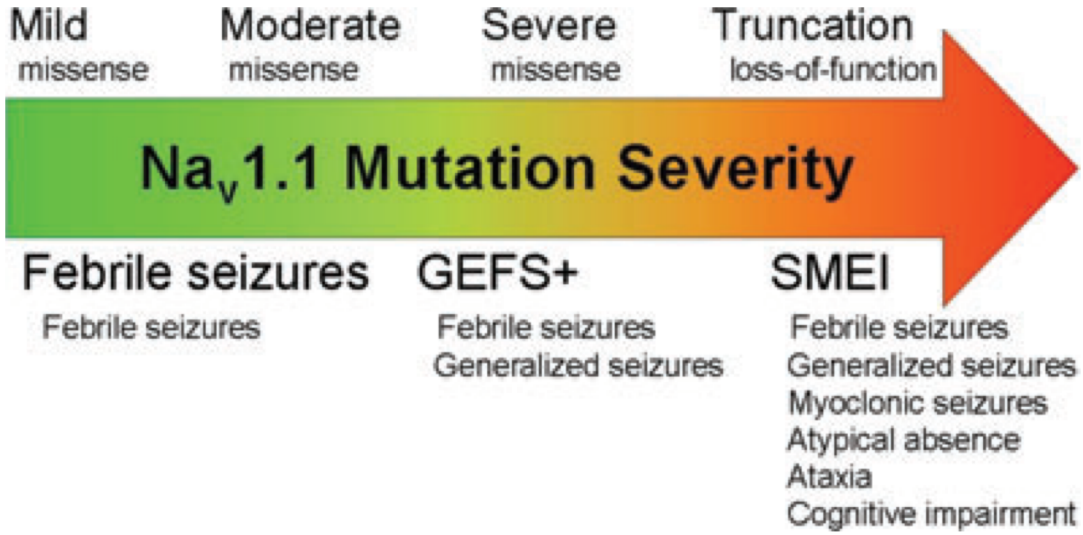
Ream MA, Patel AD. *Epilepsia*. 2015;56(10):1505-1514.

SCN1A Severity

Mutations in NaV1.1 channel



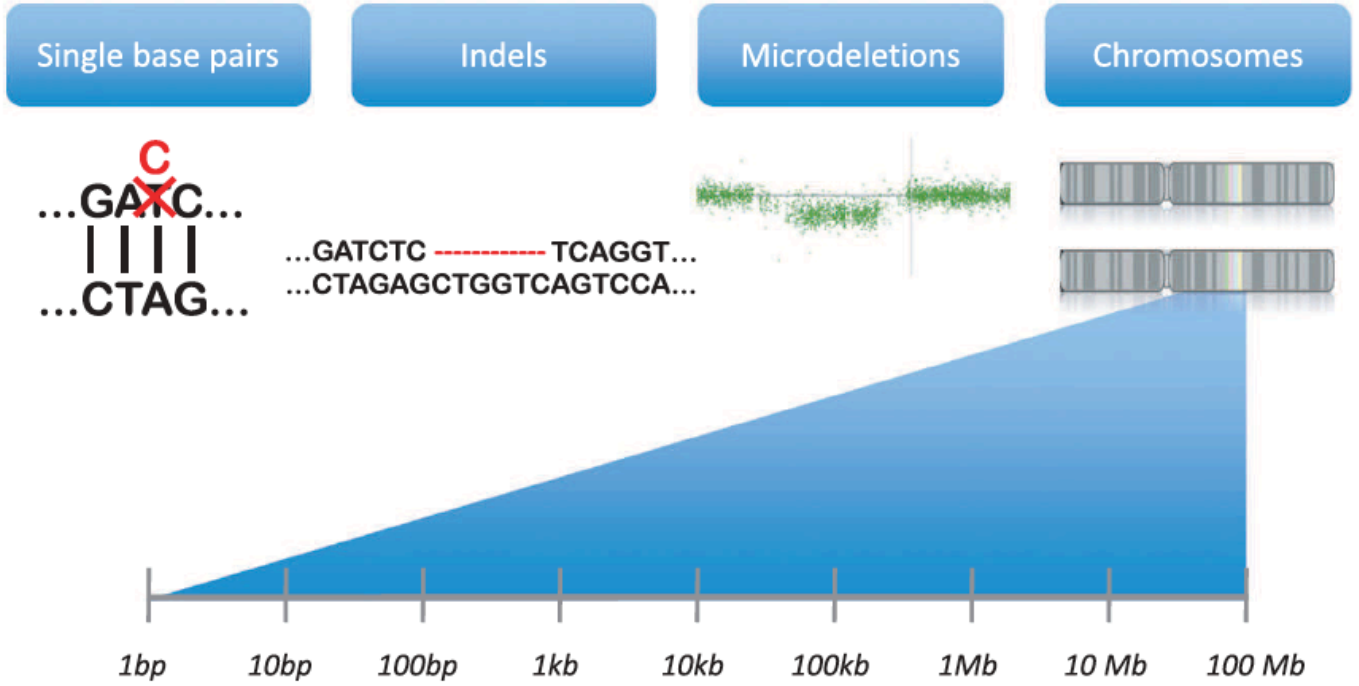
The unified loss-of-function hypothesis for NaV1.1



GEFS = generalized epilepsy with febrile seizures; SMEI = severe myoclonic epilepsy in infancy.

Catterall WA, et al. *J Physiol*. 2010;588(11):1849-1859.

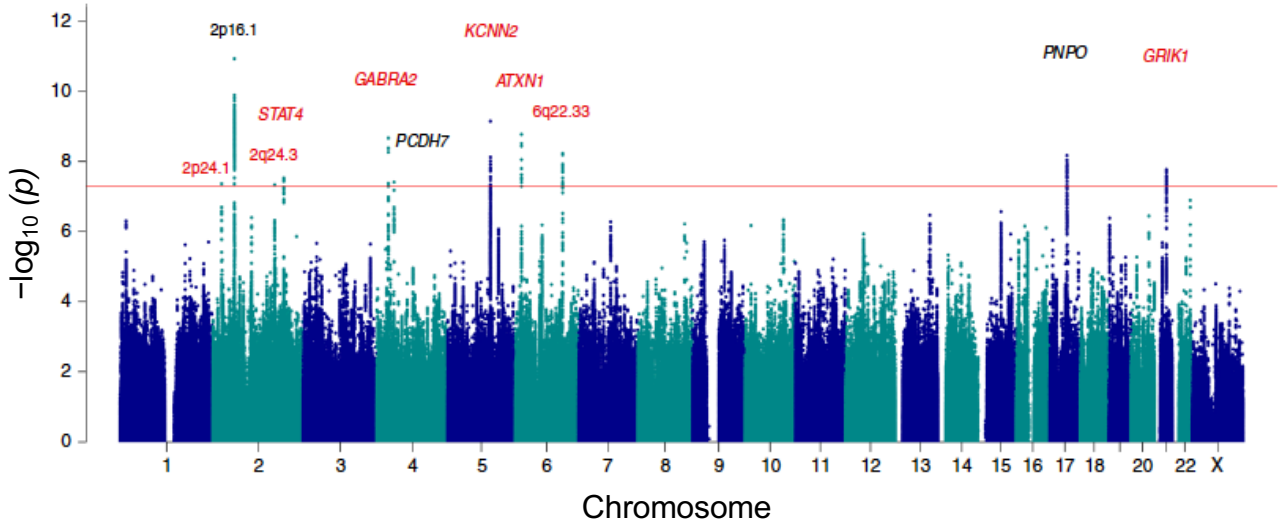
The Range of Variants Predisposing to Epilepsy

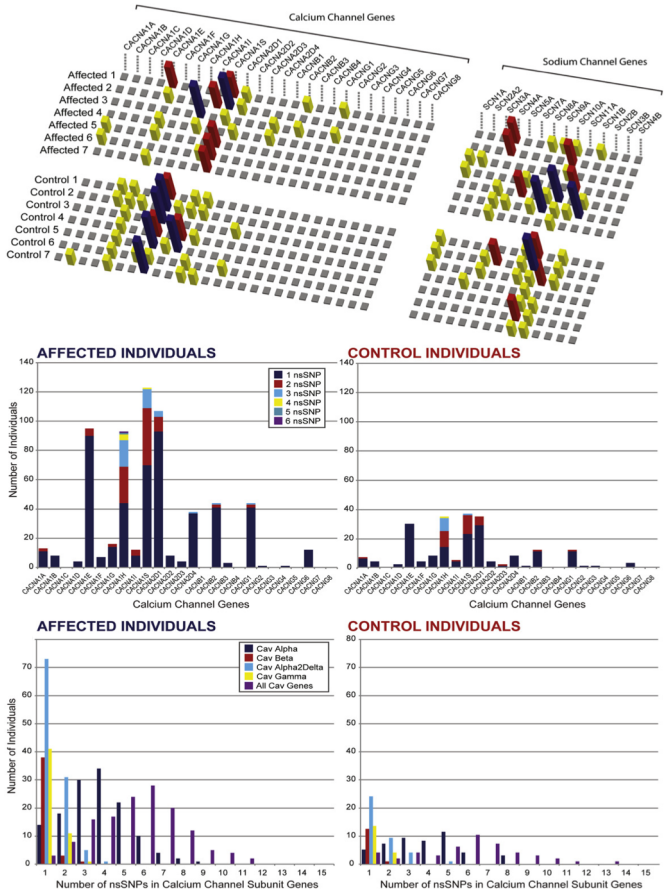


Genetic risk factors for epilepsy can range in size from a single base pair to greater than 1M, although the degree of risk is not necessarily proportionate to the size of the genetic variant

Helbig I, et al. *Epilepsia*. 2016;57(6):861-868.

Genome Wide Association Study of Common Sequence Variants: Exome Sequencing of Ion Channel Genes

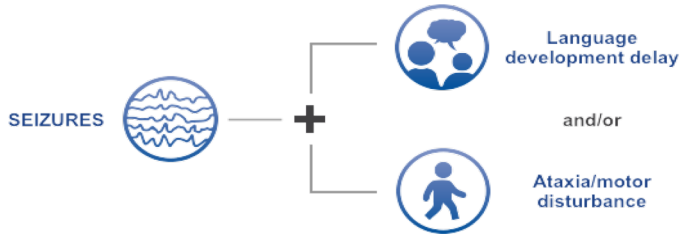




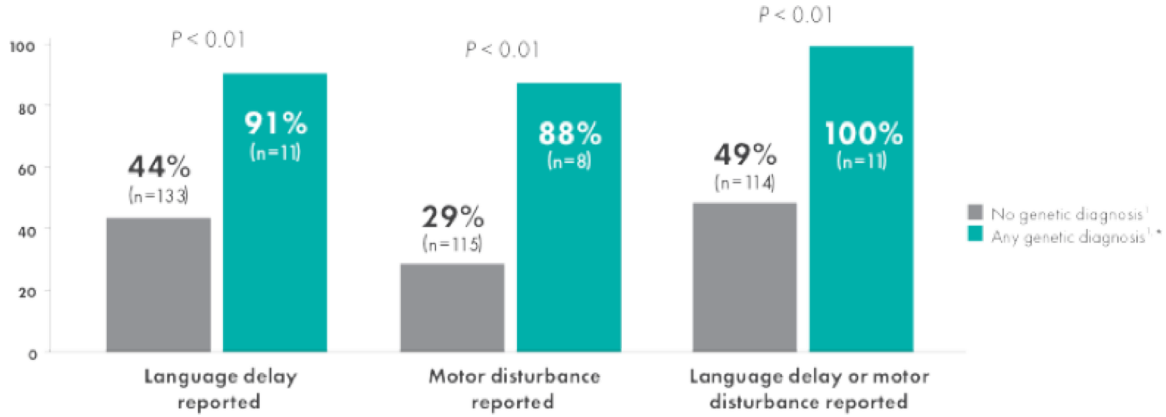
The International League Against Epilepsy Consortium on Complex Epilepsies. *Nature Communication*. 2018;9:5269. Klassen T, et al. *Cell*. 2011;145:1036-1048.

Genetic Epilepsies May Be Hiding Behind Nonspecific Symptoms and Signs

Clinical Presentation by Outcome Group



Language delay and motor disturbance were the best predictors of finding a genetic epilepsy syndrome



Language delay and/or motor disturbance/ataxia are associated with most (92/133) gene panels

Miller N, et al. Behind the Seizure. The ACMG Annual Clinical Genetics Meeting; 2018. Köhler S, et al. *Nucl Acids Res*. 2017;45:D865-D876.

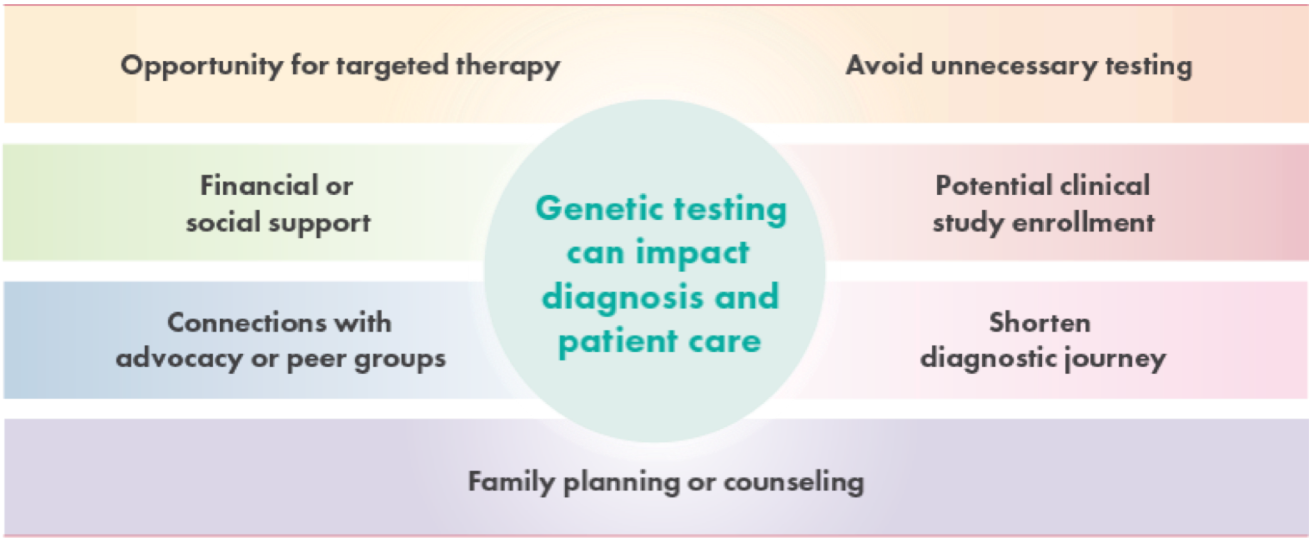
Rationale for Genetic Testing in Pediatric Epilepsy

More than 50% of epilepsies have a genetic basis.

Genetic testing is one of the most direct, accurate, and cost effective diagnostic tools.

Genetic testing can help with definitive diagnosis.

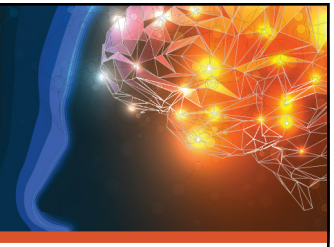
Genetic testing linked 40% of early life epilepsies to a specific genetic factor in a multicenter study (n = 327; 95% CI, 37% - 44%).



Pal DK, et al. *Nat Rev Neurol*. 2010;6:445-453; Berg AT, et al. *JAMA Pediatr*. 2017;171(9):863-871.

SMART Goals

Specific, **M**easurable, **A**ttainable, **R**elevant, **T**imely



- Utilize cannabidiol in appropriate patients with Dravet syndrome and Lennox-Gastaut's syndrome to achieve meaningful reduction in seizures
- Integrate genetic testing into the overall clinical evaluation of a patient with epilepsy

Questions & Answers

Don’t forget to fill out your evaluations to collect your credit.