2.04.109	Genetic Testing for Epilepsy		
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Section:	2.0 Medicine	**Page:**	Page 1 of 38

Policy Statement

I. Genetic testing for genes associated with infantile- and early-childhood onset epilepsy syndromes in individuals with infantile- and early-childhood-onset epilepsy syndromes in which epilepsy is the core clinical symptom (see Policy Guidelines section) may be considered **medically necessary** if positive test results may lead to changes in **one or more** of the following:
   A. Medication management
   B. Diagnostic testing such that alternative potentially invasive tests are avoided
   C. Reproductive decision making

II. Genetic testing for epilepsy is considered **investigational** for all other situations.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Policy Scope

Included Tests and Conditions

This policy addresses testing for epilepsy that might have a genetic etiology. In 2010, the International League Against Epilepsy classified epilepsy as having underlying genetic cause or etiology when, as best understood, the epilepsy is the direct result of a known or presumed genetic defect and seizures are the core symptom of the disorder and for which there is no structural or metabolic defect predisposing to epilepsy. The updated 2017 ILAE classification system does not discuss epilepsy with a genetic cause.

This policy also addresses the rare epilepsy syndromes that present in infancy or early childhood, in which epilepsy is the core clinical symptom (e.g., Dravet syndrome, early infantile epileptic encephalopathy, generalized epilepsy with febrile seizures plus, epilepsy and intellectual disability limited to females, nocturnal frontal lobe epilepsy). Other clinical manifestations may be present in these syndromes but are generally secondary to epilepsy itself.

Excluded Tests and Conditions

This policy does not address testing for genetic syndromes that have a wider range of symptomatology, of which seizures may be one, such as the neurocutaneous disorders (e.g.,neurofibromatosis, tuberous sclerosis) or genetic syndromes associated with cerebral malformations or abnormal cortical development, or metabolic or mitochondrial disorders. Genetic testing for these syndromes maybe specifically addressed in other Blue Shield of California Medical policies (see Related Policies)

This policy does not address the use of genotyping for the *HLA-B**1502 allelic variant in patients of Asian ancestry prior to considering drug treatment with carbamazepine due to risks of severe dermatologic reactions. This testing is recommended by the U.S. Food and Drug Administration (FDA) labeling for carbamazepine.

This policy also does not address the testing for variants in the mitochondrial DNA polymerase gamma (*POLG*) gene in patients with clinically suspected mitochondrial disorders prior to initiation of therapy with valproate. Valproate's label contains a black box warning related to increased risk of acute liver failure associated with the use of valproate in patients with *POLG* gene-related hereditary neurometabolic syndromes. FDA labeling states that valproate "is contraindicated in patients known to have mitochondrial disorders caused by POLG mutations and children under 2 years of age who are clinically suspected of having a POLG-related disorder".

For positions on whole exome and whole genome sequencing for the diagnosis of neurodevelopmental disorders refer to Blue Shield of California Medical Policy: Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders.

Medically Necessary Statement Definitions and Testing Strategy

The medically necessary statement refers to epilepsy syndromes that present in infancy or early childhood, are severe, and are characterized by epilepsy as the primary manifestation, without associated metabolic or brain structural abnormalities. As defined by the International League Against Epilepsy, these include epileptic encephalopathies, which are electroclinical syndromes associated with a high probability of encephalopathic features that present or worsen after the onset of epilepsy. Other clinical manifestations, including developmental delay and/or intellectual disability, may be present secondary to the epilepsy itself. Specific clinical syndromes based on the International League Against Epilepsy classification include:

- Dravet syndrome (also known as severe myoclonic epilepsy in infancy [SMEI] or polymorphic myoclonic epilepsy in infancy)
- EFMR syndrome (epilepsy limited to females with mental retardation)
- Epileptic encephalopathy with continuous spike-and-wave during sleep
- GEFS+ syndrome (generalized epilepsies with febrile seizures plus)
- Ohtahara syndrome (also known as early infantile epileptic encephalopathy with burst suppression pattern)
- Landau-Kleffner syndrome
- West syndrome
- Glucose transporter type 1 deficiency syndrome.

Variants in a large number of genes have been associated with early-onset epilepsies. Some of them are summarized in Table PG1.

Table PG1. Single Genes Associated With Epileptic Syndromes

Syndrome	Associated Genes
Dravet syndrome	*SCN1A*,*SCN9A*, *GABRA1*, *STXBP1*, *PCDH19*, *SCN1B*, *CHD2*, *HCN1*
Epilepsy limited to females with mental retardation	*PCDH19*
Epileptic encephalopathy with continuous spike-and-wave during sleep	*GRIN2A*
Genetic epilepsy with febrile seizures plus	*SCN1A, SCN9A*
Early infantile epileptic encephalopathy with suppression burst (Ohtahara syndrome)	*KCNQ2*, *SLC25A22*, *STXBP1*, *CDKL5*, *ARX*
Landau-Kleffner syndrome	*GRIN2A*
West syndrome	*ARX*, *TSC1*, *TSC2*, *CDKL5*, *ALG13*, *MAGI2*, *STXBP1*, *SCN1A*, *SCN2A*, *GABA*, *GABRB3*, *DNM1*
Glucose transporter type 1 deficiency syndrome	*SLC2A1*

Application of the Medically Necessary Policy Statement

Although there is no standard definition of epileptic encephalopathies, they are generally characterized by at least some of the following: (1) onset in early childhood (often in infancy); (2) refractory to therapy; (3) associated with developmental delay or regression; and (4) severe electroencephalogram (EEG) abnormalities. There is a challenge in defining the population appropriate for testing given that specific epileptic syndromes may be associated with different EEG abnormalities, which may change over time, and patients may present with severe seizures prior to the onset or recognition of developmental delay or regression. However, for this policy, the medically necessary policy statement would apply for patients with:

- Onset of seizures in early childhood (ie, before the age of 5 years); AND
- Clinically severe seizures that affect daily functioning and/or interictal EEG abnormalities; AND
- No other clinical syndrome that would potentially better explain the patient's symptoms.

Testing Strategy

There is clinical and genetic overlap for many of the electroclinical syndromes previously discussed. If there is suspicion for a specific syndrome based on history, EEG findings, and other test results, testing should begin with targeted variant testing for the candidate gene most likely to be involved, followed by sequential testing for other candidate genes. In particular, if an *SCN1A*-associated syndrome is suspected (Dravet syndrome, GEFS+), molecular genetic testing of *SCN1A* with sequence analysis of the *SCN1A* coding region, followed by deletion and duplication analysis if a pathogenic variant is not identified, should be obtained.

Given the genetic heterogeneity of early-onset epilepsy syndromes, a testing strategy that uses a multigene panel may be considered reasonable. In these cases, panels should meet the criteria outlined in Blue Shield of California Medical Policy: General Approach to Evaluating the Utility of Genetic Panels. Criteria for use of whole exome sequencing are outlined in Blue Shield of California Medical Policy: Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders.

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (Table PG2). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG3 shows the recommended standard terminology—"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.

Table PG2. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG3. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Coding

See the Codes table for details.

Description

Epilepsy is a disorder characterized by unprovoked seizures. It is a heterogeneous condition that encompasses many types of seizures and varies in age of onset and severity. Many genetic epilepsies are thought to have a complex, multifactorial genetic basis. There are also numerous rare epileptic syndromes associated with global developmental delay and/or cognitive impairment that occur in infancy or early childhood, and that may be caused by a single-gene pathogenic variant. Genetic testing is commercially available for a large number of genes that may be related to epilepsy.

Summary of Evidence

For individuals who have infantile- or early-childhood-onset epileptic encephalopathy who receive testing for genes associated with epileptic encephalopathies, the evidence includes a systematic review and meta-analysis, prospective, and retrospective cohort studies describing the testing yield. Relevant outcomes are test validity, symptoms, quality of life, functional outcomes, medication use, resource utilization, and treatment-related morbidity. For Dravet syndrome, which appears to have the largest body of associated literature, the sensitivity of testing for *SCN1A* disease-associated variants is high (up to 80%). For other early-onset epileptic encephalopathies, the true clinical sensitivity and specificity of testing are not well-defined. However, studies reporting on the overall testing yield in populations with epileptic encephalopathies and early-onset epilepsy have reported detection rates for clinically significant variants ranging from 7.5% to 57%. The clinical utility of genetic testing occurs primarily when there is a positive test for a known pathogenic variant. The presence of a pathogenic variant may lead to targeted medication management, avoidance of other diagnostic tests, and/or informed reproductive planning. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have presumed genetic epilepsy who receive testing for genetic variants associated with genetic epilepsies, the evidence includes prospective and retrospective cohort studies describing testing yields. Relevant outcomes are test validity, changes in reproductive decision making, symptoms, quality of life, functional outcomes, medication use, resource utilization, and treatment-related morbidity. For most genetic epilepsies, which are thought to have a complex, multifactorial basis, the association between specific genetic variants and the risk of epilepsy is

uncertain. Despite a large body of literature on associations between genetic variants and epilepsies, the clinical validity of genetic testing is poorly understood. Published literature is characterized by weak and inconsistent associations, which have not been replicated independently or by meta-analyses. A number of studies have also reported associations between genetic variants and antiepileptic drug (AED) treatment response, AED adverse effect risk, epilepsy phenotype, and risk of sudden unexplained death in epilepsy (SUDEP). The largest number of these studies is related to AED pharmacogenomics, which has generally reported some association between variants in a number of genes (including *SCN1A*, *SCN2A*, *ABCC2*, *EPHX1*, *CYP2C9*, *CYP2C19*) and AED response. Similarly, genetic associations between a number of genes and AED-related adverse events have been reported. However, no empirical evidence on the clinical utility of testing for the genetic epilepsies was identified, and the changes in clinical management that might occur as a result of testing are not well-defined. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Additional Information
Not applicable.

Related Policies

- Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

Benefit Application

Benefit determinations should be based in all cases on the applicable member health services contract language. To the extent there are conflicts between this Medical Policy and the member health services contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal law may prohibit health plans from denying FDA-approved Healthcare Services as investigational or experimental. In these instances, Blue Shield of California may be obligated to determine if these FDA-approved Healthcare Services are Medically Necessary.

Regulatory Status

SB 496
SB 496 requires health plans licensed under the Knox-Keene Act ("Plans"), Medi-Cal managed care plans ("MCPS"), and health insurers ("Insurers") to cover biomarker testing for the diagnosis, treatment, appropriate management, or ongoing monitoring of an enrollee's disease or condition to guide treatment decisions, as prescribed. The bill does not require coverage of biomarker testing for screening purposes. Restricted or denied use of biomarker testing for these purposes is subject to state and federal grievance and appeal processes. Where biomarker testing is deemed medically necessary, Plans and Insurers must ensure that the testing is provided in a way that limits disruptions in care.

Clinical Laboratory Improvement Amendments (CLIA) and FDA Regulatory Overview
Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Commercially available genetic tests for epilepsy are available under the auspices of the CLIA. Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the FDA has chosen not to require any regulatory review of this test.

Rationale

Background

Epilepsy

Epilepsy is defined as the occurrence of 2 or more unprovoked seizures. It is a common neurologic disorder, with approximately 3% of the population developing the disorder over their entire lifespan.[1,]

Classification

Epilepsy is heterogeneous in etiology and clinical expression and can be classified in a variety of ways. Most commonly, classification is done by the clinical phenotype, ie, the type of seizures that occur. In 2017, the International League Against Epilepsy (ILAE) updated its classification system that is widely used for clinical care and research purposes (Table 1).[2,]Classification of seizures can also be done on the basis of age of onset: neonatal, infancy, childhood, and adolescent/adult.

Table 1. Classification of Seizure Disorders by Type

Focal Onset (including aware and impaired awareness)	Generalized Onset	Unknown Onset	Unclassified
Motor onset • **automatisms** • **atonic[a]** • **clonic** • **epileptic spasms[a]** • **hyperkinetic** • **myoclonic** • **tonic**	Motor • tonic-clonic • clonic • tonic • myoclonic • myoclonic-tonic-clonic • myoclonic-atonic • atonic • epileptic spams	Motor • tonic-clonic • epileptic spasms	•
Nonmotor Onset • **autonomic** • **behavior arrest** • **cognitive** • **emotional** • **sensory**	Nonmotor (absense) • typical • atypical • myoclonic • eyelid myoclonia	Nonmotor • behavior arrest	
Focal to bilateral tonic-clonic			

Adapted from Fisher et al (2017) [2,][a]Degree of awareness usually is not specified.

Although genetic epilepsies are not discussed in the 2017 ILAE report[2,], a 2010 ILAE report[3,] identified genetic epilepsies as conditions in which the seizures are a direct result of a known or presumed genetic defect(s). Genetic epilepsies are characterized by recurrent unprovoked seizures in patients who do not have demonstrable brain lesions or metabolic abnormalities. In addition, seizures are the core symptom of the disorder, and other symptomatology is not present, except as a direct result of seizures. This is differentiated from genetically determined conditions in which seizures are part of a larger syndrome, such as tuberous sclerosis, fragile X syndrome, or Rett syndrome.

The review focuses on the category of genetic epilepsies in which seizures are the primary clinical manifestation. This category does not include syndromes that have multiple clinical manifestations, of which seizures may be one. Examples of syndromes that include seizures are Rett syndrome and tuberous sclerosis. Genetic testing for these syndromes will not be assessed herein but may be included in separate reviews that specifically address genetic testing for that syndrome.

Genetic epilepsies can be further broken down by type of seizures. For example, genetic generalized epilepsy refers to patients who have convulsive (grand mal) seizures, while genetic absence epilepsy

refers to patients with nonconvulsive (absence) seizures. The disorders are also sometimes classified by the age of onset.

The category of genetic epilepsies includes a number of rare epilepsy syndromes that present in infancy or early childhood.[1,4,] These syndromes are characterized by epilepsy as the primary manifestation, without associated metabolic or brain structural abnormalities. They are often severe and sometimes refractory to medication treatment. They may involve other clinical manifestations such as developmental delay and/or intellectual disability, which in many cases are thought to be caused by frequent uncontrolled seizures. In these cases, the epileptic syndrome may be classified as an epileptic encephalopathy, which is described by ILAE as disorders in which the epileptic activity itself may contribute to severe cognitive and behavioral impairments above and beyond what might be expected from the underlying pathology alone and that these can worsen over time.[3,] A partial list of severe early-onset epilepsy syndromes is as follows:

- Dravet syndrome (also known as severe myoclonic epilepsy in infancy [SMEI] or polymorphic myoclonic epilepsy in infancy)
- EFMR syndrome (epilepsy limited to females with mental retardation)
- Nocturnal frontal lobe epilepsy
- GEFS+ syndrome (generalized epilepsies with febrile seizures plus)
- EIEE syndrome (early infantile epileptic encephalopathy with burst suppression pattern)
- West syndrome
- Ohtahara syndrome.

Dravet syndrome falls on a spectrum of *SCN1A*-related seizure disorders, which includes febrile seizures at the mild end to Dravet syndrome and intractable childhood epilepsy with generalized tonic-clonic seizures at the severe end. The spectrum may be associated with multiple seizure phenotypes, with a broad spectrum of severity; more severe seizure disorders may be associated with cognitive impairment, or deterioration.[5,] Ohtahara syndrome is a severe early-onset epilepsy syndrome characterized by intractable tonic spasms, other seizures, interictal electro-encephalography abnormalities, and developmental delay. It may be secondary to structural abnormalities but has been associated with variants in the *STXBP1* gene in rare cases. West syndrome is an early-onset seizure disorder associated with infantile spasms and the characteristic electroencephalography finding of hypsarrhythmia. Other seizure disorders presenting early in childhood may have a genetic component but are characterized by a more benign course, including benign familial neonatal seizures and benign familial infantile seizures.

Genetic Etiology

Most genetic epilepsies are primarily believed to involve multifactorial inheritance patterns. This follows the concept of a threshold effect, in which any particular genetic defect may increase the risk of epilepsy, but is not by itself causative.[6,] A combination of risk-associated genes, together with environmental factors, determines whether the clinical phenotype of epilepsy occurs. In this model, individual genes that increase the susceptibility to epilepsy have a relatively weak impact. Multiple genetic defects, and/or a particular combination of genes, probably increase the risk by a greater amount. However, it is not well-understood how many abnormal genes are required to exceed the threshold to cause clinical epilepsy, nor is it understood which combination of genes may increase the risk more than others.

Early-onset epilepsy syndromes may be single-gene disorders. Because of the small amount of research available, the evidence base for these rare syndromes is incomplete, and new variants are frequently discovered.[7,]

Some of the most common genes associated with genetic epileptic syndromes are listed in Table 2.

Table 2. Selected Genes Most Commonly Associated With Genetic Epilepsy

Genes	Physiologic Function
KCNQ2	Potassium channel
KCNQ3	Potassium channel
SCN1A	Sodium channel α-subunit
SCN2A	Sodium channel α-subunit
SCN1B	Sodium channel β-subunit
GABRG2	γ-aminobutyrate A-type subunit
GABRRA1	γ-aminobutyrate A-type subunit
GABRD	γ-aminobutyrate subunit
CHRNA2	Acetylcholine receptor α2 subunit
CHRNA4	Acetylcholine receptor α4 subunit
CHRNB2	Acetylcholine receptor β2 subunit
STXBP1	Synaptic vesicle release
ARX	Homeobox gene
PCDH19	Protocadherin cell-cell adhesion
EFHC1	Calcium homeostasis
CACNB4	Calcium channel subunit
CLCN2	Chloride channel
LGI1	G-protein component

Adapted from Williams and Battaglia (2013).[1,]

For the severe early epilepsy syndromes, the disorders most frequently reported to be associated with single-gene variants include generalized epilepsies with febrile seizures plus syndrome (associated with *SCN1A*, *SCN1B*, and *GABRG2* variants), Dravet syndrome (associated with SCN1A variants, possibly modified by *SCN9A* variants), and epilepsy and intellectual disability limited to females (associated with *PCDH19* variants). Ohtahara syndrome has been associated with variants in *STXBP1* in cases where patients have no structural or metabolic abnormalities. West syndrome is often associated with chromosomal abnormalities or tuberous sclerosis or may be secondary to an identifiable infectious or metabolic cause, but when there is no underlying cause identified, it is thought to be due to a multifactorial genetic predisposition.[8,]

Targeted testing for individual genes is available. Several commercial epilepsy genetic panels are also available. The number of genes included in the tests varies widely, from about 50 to over 450. The panels frequently include genes for other disorders such as neural tube defects, lysosomal storage disorders, cardiac channelopathies, congenital disorders of glycosylation, metabolic disorders, neurologic syndromes, and multisystemic genetic syndromes. Some panels are designed to be comprehensive while other panels target specific subtypes of epilepsy. Chambers et al (2016) reviewed comprehensive epilepsy panels from 7 U.S.-based clinical laboratories and found that between 1% and 4% of panel contents were genes not known to be associated with primary epilepsy.[9,] Between 1% and 70% of the genes included on an individual panel were not on any other panel.

Treatment

The condition is generally chronic, requiring treatment with 1 or more medications to adequately control symptoms. Seizures can be controlled by antiepileptic medications in most cases, but some patients are resistant to medications, and further options such as surgery, vagus nerve stimulation, and/or the ketogenic diet can be used.[10,]

Pharmacogenomics

Another area of interest for epilepsy is the pharmacogenomics of antiepileptic medications. There are a wide variety of these medications, from numerous different classes. The choice of medications and the combinations of medications for patients who require treatment with more than 1 agent is complex. Approximately one-third of patients are considered refractory to medications, defined as inadequate control of symptoms with a single medication.[11,] These patients often require escalating doses and/or combinations of different medications. At present, selection of agents is driven by the

clinical phenotype of seizures but has a large trial-and-error component in many refractory cases. The current focus of epilepsy pharmacogenomics is in detecting genetic markers that identify patients likely to be refractory to the most common medications. This may lead to directed treatment that will result in a more efficient process for medication selection, and potentially more effective control of symptoms.

Of note, genotyping for the *HLA-B**1502 allelic variant in patients of Asian ancestry, prior to considering drug treatment with carbamazepine due to risks of severe dermatologic reactions, is recommended by the U.S. Food and Drug Administration (FDA) labeling for carbamazepine.[12,]

Literature Review

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

This evidence review does not address testing for genetic syndromes that have a wider range of symptomatology (e.g., neurofibromatosis, tuberous sclerosis) or genetic syndromes associated with cerebral malformations or abnormal cortical development, or metabolic or mitochondrial disorders.[12,13,]

The genetic epilepsies are discussed in 2 categories: the rare epileptic syndromes that may be caused by a single-gene variant and are classified as epileptic encephalopathies and the epilepsy syndromes that are thought to have a multifactorial genetic basis.

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Early-Onset Epilepsy and Epileptic Encephalopathies

Clinical Context and Test Purpose

Numerous rare syndromes have seizures as their primary symptom, which generally present in infancy or early childhood and may be classified as epileptic encephalopathies. Many are thought to be caused by single-gene variants. The published literature on these syndromes generally consists of small cohorts of individuals treated in tertiary care centers, with descriptions of genetic variants that are detected in affected individuals.

Table 3 lists some of these syndromes, with the putative causative genetic variants.

Table 3. Early-Onset Epilepsy Syndromes Associated With Single-Gene Variants

Syndrome	Implicated Genes
Dravet syndrome (severe myoclonic epilepsy of infancy)	*SCN1A*
Early infantile epileptic encephalopathy	*STXBP1*
Generalized epilepsy with febrile seizures plus	*SCN1A, SCN2A, SCN1B, GABRG2*
Epilepsy and mental retardation limited to females	*PCDH19*
Nocturnal frontal lobe epilepsy	*CHRNA4, CHRNB2, CHRNA2*

Other less commonly reported single-gene variants have been evaluated in childhood-onset epilepsies and early-onset epileptic encephalopathies, including ASAH1, FOLR1, GRIN2A, SCN8A, SYNGAP1, and SYNJ1 variants in families with early-onset epileptic encephalopathies14, and SLC13A5 variants in families with pedigrees consistent with autosomal recessive epileptic encephalopathy.[15,]

The purpose of genetic testing in individuals who have epileptic encephalopathies is to determine the etiology of the epilepsy syndrome and thereby possibly limit further invasive investigation (e.g., epilepsy surgery), to define prognosis, and to help guide therapy.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest are individuals with clinical features (age of onset, seizure semiology, electroencephalography features) consistent with epileptic encephalopathies, including conditions such as Dravet syndrome, Ohtahara syndrome, early-onset myoclonic encephalopathy, and West syndrome, who do not present with evidence of a structural or metabolic condition that increases the likelihood of seizures and for whom seizures are the primary clinical manifestation.

Interventions
The test being considered is genetic testing. Commercial testing is available from numerous companies. Testing for individual genes is available for most, or all of the genes listed in Table 3 , as well as for a wider range of genes. Lists of genes that may lead to genetic epilepsy and testing laboratories in the United States are provided at the GeneTests website funded by BioReference Laboratories and the Genetic Testing Registry of the National Center for Biotechnology Information website. [16,]

Because of the large number of potential genes, panel testing is available from a number of genetic companies. These panels include a variable number of genes implicated in diverse disorders. Some panels are designed to be comprehensive while other panels test for specific subtypes of epilepsy.

Comparators
The following practice is currently being used to make decisions about the care of individuals with epilepsy: standard clinical care without genetic testing.

Outcomes
Specific outcomes in each of these categories are listed in Table 4. The potential beneficial outcomes of primary interest would be an improvement in symptoms (particularly reduction in seizure frequency), functioning, and quality of life. A genetic diagnosis may also limit further invasive investigations into seizure etiology that have associated risks and resource utilization (e.g., a genetic diagnosis may spare individuals the burden and morbidity of unnecessary epilepsy surgery).
The potential harmful outcomes are those resulting from a false test result. False-positive test results can lead to initiation of unnecessary treatment and adverse events from that treatment. False-negative test results could lead to unnecessary surgeries.

The primary outcomes of interest would be related to seizure frequency over a 6-month to 2-year period.

Table 4. Outcomes of Interest for Individuals With Symptomatic Epilepsy

Outcomes	Details
Symptoms	Seizure frequency; reduction in seizure frequency by 50%; proportion seizure-free
Functional outcomes	Measurement of development delays (e.g., Bayley Scales of Infant and Toddler Development)
Quality of life	Validated quality of life assessment tools
Medication use	Number of unsuccessful medication trials, number of medications needed
Resource utilization	Number of surgeries
Treatment-related morbidity	Adverse events of epilepsy medication and surgery

Study Selection Criteria

For the evaluation of clinical validity of genetic testing for epilepsy, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores).
- Included a suitable reference standard.
- Patient/sample clinical characteristics were described.
- Patient/sample selection criteria were described.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Systematic Reviews

Feng et al (2025) conducted a systematic review and meta-analysis of the diagnostic yields of genetic testing in infantile epileptic spasms syndrome.[17,] 30 studies were included (N=2,738), involving whole-exome sequencing (WES), multi-gene panels (MGPs), and chromosomal microarray (CMA). The diagnostic rates for infantile epileptic spasms syndrome were 26% (95% CI: 21% to 31%) for WES (n=799; 13 studies), 20% (95% CI: 15% to 27%) for MGPs (n = 1,117; 13 studies), and 14% (95% CI: 11% to 16%) for CMA (n=629; 13 studies). WES and MGPs showed comparable diagnostic yields (p=.34). The results indicated that 61.6% of individuals with genetic infantile epileptic spasms syndrome could benefit from genetic diagnosis in terms of clinical management. The authors specifically noted the potential of WES and MGPs as first-tier testing approaches for infantile epileptic spasms syndrome cases with suspected genetic or unknown etiologies. The authors note limitations of the analysis, including discrepancies in institution-specific MGPs and varying sample sizes across studies may bias the aggregated results.

Observational Studies

The literature on the clinical validity of genetic testing for these rare syndromes is limited and, for most syndromes, the clinical sensitivity and specificity are not defined. Dravet syndrome is probably the most well studied, and some evidence on the clinical validity of *SCN1A* variants is available. The clinical sensitivity has been reported to be in the 70% to 80% range.[18,19,] In a 2006 series of 64 patients, 51 (79%) were found to have *SCN1A* pathogenic variants.[19,] In a 2015 population-based cohort, among 8 infants who met clinical criteria for Dravet syndrome, 6 had a pathogenic SCN1A variant, all of which were de novo.[20,]

A number of studies have reported on the genetic testing yield in cohorts of pediatric patients with epilepsy, typically in association with other related symptoms. Table 5 summarizes examples of diagnostic yield in children with epileptic encephalopathy.

Esterhuizen et al (2018) analyzed data from 22 South African infants with provisional diagnoses of Dravet syndrome who underwent targeted resequencing of Dravet syndrome-associated genes.[21,] Disease-causing variants (*SCN1A* = 9, *PCDH19* = 1) were identified in 10 children (45.5%), and results suggested that a clinical Dravet syndrome risk score of >6 and seizure onset before age 6 months were highly predictive of *SCN1A*-associated Dravet syndrome. For 10 of the 12 variant-negative children, clinical reassessment resulted in a revised diagnosis. No limitations to the analysis were reported.

Peng et al (2018) published an analysis of 273 pediatric patients with drug-resistant epilepsy who underwent genetic testing using whole exome sequencing (n=74), epilepsy-related gene panel testing (n=141), or clinical whole exome sequencing gene panel testing (n=58).[22,] Ninety-three likely disease-causing mutations in 33 genes were identified in 86 individuals (31.5%). The most frequently mutated geneswere *SCN1A* (24.4%), *TSC2* (8.1%), *SCN8A* (5.8%), *CDKL5* (5.8%), *KCNMA1* (4.6%), *TSC1* (4.6%), *KC*

NQ2 (3.5%), *MECP2* (3.5%), *PCDH19* (3.5%), and *STXBP1* (3.5%). Of the 34 individuals who accepted corrective therapy according to their mutant genes, 52.9% became seizure-free and 38.2% achieved seizure reduction. No limitations to the analysis were reported.

Table 5. Genetic Testing Yields in Pediatric Patients with Epilepsy

Study	Population	Genetic Testing	Results
Scheffer et al (2023)[23,]	103 children and infants with developmental and epileptic encephalopathies	Singleton exome sequencing	Diagnostic yield: • 35% of patients had a genetic etiology • 29% of patients had pathogenic or likely pathogenic variants, 38% had variants of unknown significance, and 33% were negative on exome analysis • *KCNQ2*, *CDKL5*, *SCN1A*, and *STXBP1* were the most frequently identified genes
Jiang et al (2021)[24,]	221 children with epilepsy	Whole exome sequencing	Diagnostic yield: • 64.5% of patients with epilepsy and developmental delay/intellectual disability; 18.9% of patients with only epilepsy (p<.001) • 48 of 87 variants detected were novel (55.2%) • Genes with novel variants: *NCL*, *SEPHS2*, *PA2G4*, *SLC35G2*, *MYO1C*, *GPR158*, and *POU3F1*
Kim et al (2021)[25,]	59 patients with infantile-onset epilepsy and prior negative targeted gene panel testing	Whole exome sequencing	Diagnostic yield: • 8% more patients than with targeted gene panel testing • Genes with pathogenic or likely pathogenic variants: *FARS2, YWHAG, KCNC1, DYRK1A, SMC1A, PIGA, OGT,* and *FGF12* • Genes newly associated with epilepsy: *YWHAG, KCNC1,* and *FGF12*
Palmer et al (2021)[26,]	30 patients with developmental and epileptic encephalopathies with prior negative genetic testing	Whole genome sequencing	Diagnostic yield: • 53% in 15 patients with prior exome sequencing; 20% (3 of 15) had complex structural variants • 68% in 15 patients with prior multigene panel testing
Salinas et al (2021)[27,]	55 patients with developmental and epileptic encephalopathies with prior negative genetic testing	Targeted multigene panel testing, whole exome sequencing	Diagnostic yield: • 38% at baseline • 53% after an average of 29 months using new literature • Genes with novel variants: *CHD2, COL4A1, FOXG1, GABRA1, GRIN2B, HNRNPU, KCNQ2, MECP2, PCDH19, SCN1A, SCN2A, SCN8A, SLC6A1, STXBP1,* and *WWOX*
Sun et al (2021)[28,]	73 infants with epileptic encephalopathies including West syndrome and Dravet syndrome	Whole exome sequencing	Diagnostic yield: • 46.6% (most commonly *SCN1A* variants) • Genes with novel variants: *CACNA1E* and *WDR26*
Lee et al (2020)[29,]	24 patients with Dravet syndrome	Targeted panel with 40 epilepsy genes	Disease-causing variants (*SCN1A* and *PCDH19)* identified in 75% of patients
Lee et al (2021)[30,]	105 children with various seizure types	Whole exome sequencing, microarray, single gene	Diagnostic yield: • 35.71% with whole exome sequencing • 8.33% with microarray

Study	Population	Genetic Testing	Results
		testing, targeted multigene panel testing	• 18.60% with single gene testing • 19.23% with targeted multigene panel testing
Lee et al (2020)[31,]	116 patients with early-onset epilepsy (before age 2 years) and normal brain imaging	Next-generation sequencing targeted gene panel	Disease-causing variants (most commonly *SCN1A* and *PRRT2*) identified in 34.5% of patients
Stodberg et al (2020)[32,]	116 children with epilepsy onset before the age of 2 years	Whole exome sequencing/next-generation sequencing	An epilepsy syndrome was diagnosed in 54% of patients (34% structural causes, 20% genetic causes). Diagnostic yield with whole exome sequencing/next-generation sequencing was 58% (of 26 patients).
Esterhuizen et al (2018)[21,]	22 infants with provisional diagnosis of Dravet syndrome	Target resequencing of Dravet syndrome-associated genes	Disease-causing variants (*SCN1A* and *PCDH*) identified in 45.5% of patients
Peng et al (2018)[22,]	273 pediatric patients with drug-resistant epilepsy	Whole exome sequencing, epilepsy panel, or clinical whole exome sequencing panel	93 likely disease-causing variants found in 31.5% of patients: • *SCN1A* (24.4%) • *TSC2* (8.1%) • *SCN8A* (5.8%) • *CDKL5* (5.8%)
Berg et al (2017)[33,]	327 infants and young children with newly diagnosed with epilepsy	Various forms	Disease-causing variants (*SCN1A* and *PCDH19)* identified in 75% of patients
Moller et al (2016)[34,]	216 patients with epileptic encephalopathy phenotypes or familial epilepsy	Epilepsy panel of 46 genes	Diagnostic yield: • 23% patients overall • 32% of patients with epileptic encephalopathies • 57% of patients with neonatal-onset epilepsies • 3% variants of uncertain significance
Trump et al (2016)[35,]	400 patients with early-onset seizures and/or severe developmental delay	Epilepsy and development delay panel of 46 genes	Diagnostic yield: • 18% patients overall • 39% in patients with seizure onset within first 2 mo of life
Wirrell et al (2015)[36,]	81 patients with infantile spasms and no obvious cause at diagnosis	Various forms	Diagnostic yield: • 0% for karyotyping • 11.3% of 62 for array comparative genomic hybridization • 33.3% of 3 for targeted chromosomal single-nucleotide variant analysis • 11.1% of 9 for targeted single-gene analysis • 30.8% of 26 for epilepsy gene panels
Mercimek-Mahmutoglu et al (2015)[37,]	110 patients with epileptic encephalopathies	Array comparative genomic hybridization, next-generation sequencing	Diagnostic yield: • 2.7% for array comparative genomic hybridization • 12.7% for targeted next-generation sequencing
Hrabik et al (2015)[38,]	147 children with epilepsy	Single-nucleotide	Diagnostic yield: • 7.5% clinically significant abnormal results

Study	Population	Genetic Testing	Results
		variant microarray	

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

For the early-onset epilepsies that may have a genetic component, interventions to reduce the risk of having an affected offspring may be a potential area for clinical utility. Genetic counseling and consideration of preimplantation genetic testing combined with in vitro fertilization are available options. For Dravet syndrome, most pathogenic variants are sporadic, making the clinical utility of testing for the purposes of counseling parents and intervening in future pregnancies low. However, when there is a familial disease with a pathogenic variant present in one parent, then preimplantation genetic testing may reduce the likelihood of having an affected offspring. For other syndromes, the risk in subsequent pregnancies for families with one affected child may be higher, but the utility of genetic counseling is not well-established in the literature.

Another potential area of clinical utility for genetic testing may be in making a definitive diagnosis and avoiding further testing. For most of these syndromes, the diagnosis is made by clinical criteria. However, there may be significant overlap across syndromes regarding seizure types. It is not known how often genetic testing leads to a definitive diagnosis when the diagnosis cannot be made by clinical criteria.

There is no direct evidence of utility, ie, there are no studies that report on whether the efficacy of treatment directed by genetic testing is superior to the efficacy of treatment without genetic testing.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

A chain of evidence could be constructed to demonstrate the utility of genetic testing for epileptic encephalopathies. As mentioned, the differential diagnosis of infants presenting with clinical features of epileptic encephalopathies cannot always be made by phenotype alone; however, treatment may differ depending on the diagnosis. For Dravet syndrome, the seizures are often refractory to common medications. Some experts have suggested that diagnosis of Dravet syndrome may, therefore, prompt more aggressive treatment, and/or avoidance of certain medications known to be less effective and potentially contraindicated due to negative cognitive effect (e.g., ,Also, some experts suggest that patients with Dravet syndrome may be more susceptible to particular antiepileptic drugs (AEDs), including clobazam and stiripentol.[5,] In contrast, the usual medical treatment of infantile spasms is hormonal therapy with corticotropin (adrenocorticotropic hormone),[40,41,42,] and usual first-line treatment of Lennox-Gastaut is sodium valproate.[43,] Therefore, confirming the specific diagnosis leads to changes in therapy expected to improve outcomes.

Ream et al (2014) retrospectively reviewed a single center's use of clinically available genetic tests in the management of pediatric drug-resistant epilepsy.[44,] The study included 25 newly evaluated patients with pediatric drug-resistant epilepsy. Fourteen (56%) tested patients had epileptic

encephalopathies; 17 (68%) had generalized epilepsy syndromes. Of the 25 patients in the newly evaluated group, 15 had positive findings on genetic testing (defined as a "potentially significant" result), with 10 of the 15 considered to be diagnostic (consisting of variants previously described to be disease-causing for epilepsy syndromes or variants predicted to be disease-causing.) The genetic testing yield was higher in patients with epileptic encephalopathies (p=.005) and generalized epilepsy (p=.028). Patients with a clinical phenotype suggestive of an epilepsy syndrome were more likely to have positive results on testing: both patients with Dravet syndrome phenotypes had pathologic variants in *SCN1A*; 3 of 9 patients with Lennox-Gastaut syndrome had identified variants (1 with a *CDKL5* variant, 1 with a *SCL9A6* variant, 1 with both *SCN1A* and *EFHC1* variants). Two (6.9%) patients had diagnostic variants not suspected based on their clinical phenotypes. In 8 (27.6%) patients, genetic test results had potential therapeutic implications. However, only 1 patient had significantly reduced seizure frequency; the patient received stiripentol following a positive *SCN1A* variant test.

Another single-center retrospective study by Hoelz et al (2020) described the effect of next-generation sequencing on clinical decision-making among children with epilepsy.[45,] Testing was performed a mean of 3.6 years after symptom onset. Most of the patients had epileptic encephalopathy (40%) followed by focal epilepsy (33%) and generalized seizures (18%). Sixteen patients (18%) who underwent testing had a pathogenic or likely pathogenic gene identified. Subsequently, 10 of these 16 patients (63%) had changes in their clinical management, including medications (n=7), diagnostic testing (n=8), or avoiding future surgical procedures (n=2).

The study by Scheffer et al (2023) was introduced in Table 6.[23,] Thirteen of 36 patients with a known genetic cause for their condition had management implications. These included treatment for the underlying biochemical abnormality (1 patient with *SLC2A1*), choice of antiseizure medication (4 patients with *KCNQ2*, 3 with *SCN1A*, 2 with *SCN8A*, and 1 with *SCN2A*), choice of other medication (1 patient with *ATP1A3*), and screening for disease-related complications (1 patient with *COL4A1*).

Section Summary: Early-Onset Epilepsy Syndromes and Epileptic Encephalopathies

For early-onset epilepsy syndromes and epileptic encephalopathies, the diagnostic yield is highest for Dravet syndrome (70% to 80%). The yield in epileptic encephalopathies and early infancy onset is between 30% and 60% in the studies reporting in those subsets. There is no direct evidence of the clinical utility of genetic testing. However, a chain of evidence can be constructed to demonstrate the utility of genetic testing for early-onset epilepsy syndromes and epileptic encephalopathies. The differential diagnosis of infants presenting with clinical features of epileptic encephalopathies cannot always be made by phenotype alone, and genetic testing can yield a diagnosis in some cases. Management differs depending on the differential diagnosis so correct diagnosis is expected to improve outcomes.

Presumed Genetic Epilepsy

Clinical Context and Test Purpose

Most genetic epilepsy syndromes present in childhood, adolescence, or early adulthood. They include generalized or focal and may be convulsant (grand mal) or absence type. They are generally thought to have a multifactorial genetic component.

The purpose of genetic testing in individuals who are presumed to have genetic epilepsy is to determine etiology of the epilepsy syndrome and thereby possibly limit further invasive investigation (e.g., epilepsy surgery), define prognosis, and help guide therapy.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest are individuals with clinical features (age of onset, seizure semiology, electroencephalography features) consistent with genetic epilepsies, such as generalized

epilepsy, childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, and epilepsy with tonic-clonic seizures alone, who do not have evidence of a structural or metabolic condition that increases the likelihood of seizures and for whom seizures are the primary clinical manifestation.

Interventions

The test being considered is genetic testing. As mentioned, commercial tests are available from many companies.

Comparators

The following practice is currently being used to make decisions about the care of individuals with epilepsy: standard clinical care without genetic testing.

Outcomes

The outcomes of interest are similar to those described in the previous section. Specific outcomes are listed in Table 6. The National Institute of Neurological Disorders and Stroke Common Data Elements for Epilepsy describes a minimum set of data elements, including outcome measures, that should ideally be collected in research of epilepsy.[46,]

The primary outcomes of interest would be related to seizure frequency over a 6-month to 2-year period.

Table 6. Outcomes of Interest for Individuals With Symptomatic Epilepsy

Outcome	Details
Symptoms	Seizure frequency; reduction in seizure frequency by 50%; proportion seizure-free; Child Symptom Inventory, Adolescent Symptom Inventory
Functional outcomes	Validated measures of cognitive functioning (e.g., Wechsler scales, California Verbal Learning Test)
Quality of life	Validated measure of quality of life (e.g., Quality of Life in Epilepsy Inventory for Adolescents, Quality of Life in Childhood Epilepsy)
Medication use	Number of unsuccessful medication trials, number of medications needed
Resource utilization	Number of surgeries
Treatment-related morbidity	Adverse effects of epilepsy medication and surgery

Study Selection Criteria

For the evaluation of clinical validity of genetic testing for epilepsy, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores).
- Included a suitable reference standard.
- Patient/sample clinical characteristics were described.
- Patient/sample selection criteria were described.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

The literature on clinical validity includes many studies that have reported on the association between various genetic variants and epilepsy. A large number of case-control studies have compared the frequency of genetic variants in patients who have epilepsy with the frequency in patients without epilepsy. There is a smaller number of genome-wide association studies (GWAS) that evaluate the presence of single-nucleotide variants associated with epilepsy across the entire genome. No studies were identified that reported on the clinical sensitivity and specificity of genetic variants in various clinically defined groups of patients with epilepsy. In addition to these

studies on the association of genetic variants with the diagnosis of epilepsy, numerous other studies have evaluated the association between genetic variants and pharmacogenomics of AEDs.

Diagnosis of Epilepsy

Nonrandomized Studies

McKnight et al (2021) conducted targeted gene panel testing (range, 89 to 189 genes) using next-generation sequencing in a cohort of 2008 adults with epilepsy.[47,] Diagnosis occurred in 10.9% of patients, and 55.5% of these diagnoses led to changes in clinical management. Diagnostic yield was highest among individuals who first experienced seizure activity during infancy (29.6%) and among females with developmental delay or intellectual disability (19.6%). Patients with treatment-resistant epilepsy had a diagnostic yield of 13.5% and 57.4% of diagnoses led to changes in clinical management. The most common genes associated with a diagnosis were *SCN1A* and *MECP2*. The most common genes associated with changes in clinical management were SCN1A, DEPDC5, PRRT2, PCDH19, and TSC1. Nondiagnostic and negative genetic findings were common (70.1% and 19.0%, respectively).

Alsubaie et al (2020) evaluated the diagnostic yield of whole exome sequencing among 420 patients at a single center in Saudi Arabia.[48,] Epilepsy was the reason for testing in 15.4% (n=65) of patients. Whole exome sequencing confirmed the diagnosis of epilepsy in 14 patients (positive yield of 21.5%) with variants in the following genes: *ARID1B, UGDH, KCNQ2 ,PAH, PARS2, ARHGEF9, CNA2, CASK, SLC23A3, TBCD, QARS, CBL, GABRB2,* and *SUOX.* Genetic test results were inconclusive in 15 of the 65 patients with epilepsy (23%). Thirty patients with negative whole exome sequencing results underwent comparative genomic hybridization, which identified 4 additional variants (positive yield of 13.3%).

Johannsen et al (2020) published a cohort study of 200 adult patients (range 18 to 80 years) with epilepsy who were referred for genetic testing between 2013 and 2018 in Denmark.[49,] Most of the patients (91%) also had intellectual disability. Various gene panels (range 45 to 580 genes) were used. A genetic cause of epilepsy was identified in 23% of patients (n=46). Pathogenic variants were found in 22 genes (*SCN1A, KCNT1, STXBP1, CDKL5, CHD2, PURA, ATP6V1A, DCX, GABRB3, GABRG2, GRIN2A, HNRNPU, IQSEC2, KCNA2, KIAA2022, MECP2, MEF2C, MTOR, IPF2PBL, PCDH19, SCN8A, SLC2A1, SYNGAP1,* and *IRF2BPL).* Among the 46 patients who received a diagnosis, variants in the SCN1A gene were most prevalent (36%). A change in management occurred in 11 patients after diagnosis, which led to improved seizure control and/or cognitive function.

Minardi et al (2020) published a single-center analysis of 71 adult patients (age range, 21 to 65 years) with developmental and epileptic encephalopathies of unknown etiology who underwent whole exome sequencing.[50,] Almost all patients (90.1%) had prior negative genetic tests. The analysis identified 24 variants that were considered pathogenic or likely pathogenic. The variants were: *DYNC1, ZBTB20, CACNA1, DYRK1A, ANKRD11, GABRG2, KCNB1, KCNH5, SCN1A, GABRB2, YWHAG, STXBP1, PRODH, LAMB1, PNKP, APC2, RARS2, KIAA2022,* and *SMC1A*. No clinical characteristics were significantly different between patients with pathogenic variants and patients with variants of unknown clinical significance; however sample sizes were small. In half of the diagnosed cases (n=9), clinical management changed after diagnosis, including medication selection, additional testing, and reproduction-related decisions.

Hesse et al (2018) published a retrospective analysis of 305 patients (age range, <1 to 69 years of age with 88% <18 years) referred for genetic testing with a targeted epilepsy panel between 2014 and 2016.[51,] Positive yield was 15.1%, with pathogenic, likely pathogenic, and predicted deleterious mutations identified in 46 individuals. Twenty-nine distinct genes were present, and known pathogenic variants were identified in 7 genes (*BRAF*, *DPYD*, *GABRG2*, *PAX6*, *SCN1A*, *SLC2A1*, and *SLC46A1*). No limitations to the analysis were reported.

Lindy et al (2018) published an industry-sponsored analysis of 8565 consecutive individuals with epilepsy and/or neurodevelopmental disorders who underwent genetic testing with multigene panels.[52,] Positive results were reported in 1315 patients (15.4%), and, of 22 genes with high positive yield, *SCN1A* (24.8%) and *KCNQ2* (13.2%) accounted for the greatest number of positive findings. Results found 14 distinct genes with recurrent pathogenic or likely pathogenic variants (most commonly in *MECP2*, *KCNQ2*, *SCN1A*, *SCN2A*, *STXBP1*, and *PRRT2*). More than 30% of positive cases had parental testing performed; all variants found in *CDKL5*, *STXBP1*, *SCN8A, GABRA1*, and *FOXG1* were de novo;, however, 85.7% of variants in *PRRT2* were inherited. No pathogenic or likely pathogenic variants were found in *ATP6AP2*, *CACNB4*, *CHRNA2*, *DNAJC5*, *EFHC1*, *MAGI2*, and *SRPX2*. No limitations to the analysis were reported.

Miao et al (2018) published an analysis of 141 Chinese patients under 14 years of age with epilepsy who underwent genotype and phenotype analysis using an epilepsy-associated gene panel between 2015 and 2017.[53,] Certain diagnoses were obtained in 39 probands (27.7%); these causative variants were related to 21 genes. The most frequently mutated gene was *SCN1A* (5.6%), but others included *KCNQ2*, *KCNT1*, *PCDH19, STXBP1, SCN2A, TSC2,* and *PRRT2*. The treatments for 18 patients (12.8%) were altered based on their genetic diagnosis and on genotype-phenotype analysis. No limitations to the analysis were reported.

Butler et al (2017) published a retrospective analysis of epilepsy patients screened using a 110-gene panel between 2013 and 2016; 339 unselected individuals (age range, 2.5 months to 74 years, with more than 50% <5 years) were included.[54,] Pathogenic or likely pathogenic variants were identified in 62 patients (18%), and another 21 individuals (6%) had potentially causative variants. *SCN1A* (n=15) and *KCNQ2* (n=10) were the frequently identified potentially causative variants. However, other genes in which variants were identified in multiple individuals included *CDKL5, SCN2A, SCN8A, SCN1B, STXBP1, TPP1, PCDH19, CACNA1A, GABRA1, GRIN2A, SLC2A1,* and *TSC2*. The study was limited by the lack of clinical information available for approximately 20% of participants. Tables 7 and 8 provide a summary of these key nonrandomized study characteristics and results.

Table 7. Summary of Key Nonrandomized Study Characteristics

Study	Study Type	Country	Dates	Participants	Treatment 1
McKnight et al (2021)[47,]	Cohort	United States and Canada	2015-2020	Adults with epilepsy referred for genetic testing (n=2008)	Epilepsy-targeted multigene panel (89 to 133 genes)
Alsubaie et al (2020)[48,]	Retrospective	Saudi Arabia	2017-2019	Adults with epilepsy referred for genetic testing (n=420)	Various gene panels (most with at least 100 genes)
Johannesen et al (2020)[49,]	Cohort	Denmark	2013-2018	Patients referred for genetic testing (n=200)	Gene panel testing
Minardi et al (2020)[50,]	Cohort	Italy	2016-2017	Patients with developmental and epileptic encephalopathies (n=71)	Whole exome sequencing
Hesse et al (2018)[51,]	Retrospective	U.S.	2014-2016	Patients referred for genetic testing (n=305)	Targeted epilepsy panel
Lindy et al (2018)[52,]	Cohort	U.S.	2011-2015	Individuals with epilepsy and/or neurodevelopmental disorders (n=8565)	Genetic testing with multiple gene panels
Miao et al (2018)[53,]	Retrospective	China	2015-2017	Patients with epilepsy <14 years of age (n=141)	Epilepsy-associated gene panel
Butler et al (2017)[54,]	Retrospective	U.S.	2013-2016	Patients with epilepsy (n=339)	110-gene epilepsy and seizure disorders panel

Table 8. Summary of Key Nonrandomized Study Results

Study	Positive Yield	Genes with Identified Pathogenic Variants
McKnight et al (2021)[47,]	10.9%	*SCN1A, MECP2, UBE3A, DEPDC5, PRRT2, CHD2, PCDH19, NPRL3, TSC1, KCNQ2, SCN2A, STCBP1, TBC1D24, HNRNPU, KCNA2, CNTNAP2, EEF1A2, GABRB3, UBE3A, KCNC1, KCNT1, SYNGAP1*
Alsubaie et al (2020)[48,]	21.5%	*ARID1B, UGDH, KCNQ2 , PAH, PARS2, ARHGEF9, CNA2, CASK, SLC23A3, TBCD, QARS, CBL, GABRB2, SUOX*
Johannesen et al (2020)[49,]	23%	*SCN1A, KCNT1, STXBP1, CDKL5, CHD2, PURA, ATP6V1A, DCX, GABRB3, GABRG2, GRIN2A, HNRNPU, IQSEC2, KCNA2, KIAA2022, MECP2, MEF2C, MTOR, IPF2PBL, PCDH19, SCN8A, SLC2A1, SYNGAP1, IRF2BPL*
Minardi et al (2020)[50,]	25.3%	*DYNC1, ZBTB20, CACNA1, DYRK1A, ANKRD11, GABRG2, KCNB1, KCNH5, SCN1A, GABRB2, YWHAG, STXBP1, PRODH, LAMB1, PNKP, APC2, RARS2, KIAA2022, SMC1A*
Hesse et al (2018)[51,]	15.1%	*BRAF, DPYD, GABRG2, PAX6, SCN1A, SLC2A1, SLC46A1*
Lindy et al (2018)[52,]	15.4%	*MECP2, KCNQ2, SCN2A, STXBP1, PRRT2*
Miao et al (2018)[53,]	NR	*SCN1A, KCNQ2, KCNT1, PCDH19, STXBP1, SCN2A*
Butler et al (2017)[54,]	NR	*SCN1A, KCNQ2, CDKL5, SCN2A, SCN8A, SCN1B*

NR; not reported.

Tan and Berkovic (2010) published an overview of genetic association studies using records from Epilepsy Genetic Association Database.[55,] Reviewers identified 165 case-control studies published between 1996 and 2008. There were 133 studies that examined the association between 77 different genetic variants and the diagnosis of epilepsy. Approximately half (65/133) focused on patients with genetic generalized epilepsy. Most studies had relatively small sample sizes, with a median of 104 cases (range, 8 to 1361) and 126 controls (range, 22 to 1390). There were fewer than 200 case patients in 80% of the studies. Most did not show a statistically significant association. Using a cutoff of p<.01 as the threshold for significance, 35 studies (21.2%) reported a statistically significant association. According to standard definitions for genetic association, all associations were in the weak-to-moderate range, with no associations considered strong.

In 2014, the International League Against Epilepsy Consortium on Complex Epilepsies published a meta-analysis of GWAS studies for all epilepsy and 2 epilepsy clinical subtypes, genetic generalized epilepsy and focal epilepsy.[56,] The authors combined GWAS data from 12 cohorts of patients with epilepsy and controls (ethnically matched to cases) from population-based datasets, for a total of 8696 cases and 26,157 controls. Cases with epilepsy were categorized as having genetic generalized epilepsy, focal epilepsy, or unclassified epilepsy. For all cases, loci at 2q24.3 (*SCN1A*) and 4p15.1 (*PCDH7*, which encodes a protocadherin molecule) were significantly associated with epilepsy ($p=8.71\times10^{-10}$ and 5.44×10^{-9}, respectively). For those with genetic generalized epilepsy, a locus at 2p16.1 (*VRK2* or *FANCL*) was significantly associated with epilepsy ($p=9.99\times10^{-9}$). No single-nucleotide variants were significantly associated with focal epilepsy.

Some of the larger GWAS are described here. In 2012, the EPICURE Consortium published one of the larger GWAS of genetic generalized epilepsy.[57,] It included 3020 patients with genetic generalized epilepsy and 3954 control patients, all of European ancestry. A 2-stage approach was used, with a discovery phase and a replication phase, to evaluate a total of 4.56 million single-nucleotide variants. In the discovery phase, 40 candidate single-nucleotide variants were identified that exceeded the significance of the screening threshold ($1^{-}10^{-5}$), although none reached the threshold defined as statistically significant for GWAS ($1^{-}10^{-8}$). After stage 2 analysis, 4 single-nucleotide variants identified had suggestive associations with genetic generalized epilepsy on genes *SCN1A*, *CHRM3*, *ZEB2*, and *NLE2F1*.

In 2012, a second GWAS was also published with a relatively large sample size of Chinese patients.[58,] Using a similar 2-stage methodology; this study evaluated 1087 patients with epilepsy and 3444 matched controls. Two variants were determined to have the strongest association with epilepsy. One was on the *CAMSAP1L1* gene and the second was on the *GRIK2* gene. There were several other loci on genes suggestive of an association that coded for neurotransmitters or other neuron function.

Other Analyses

In addition to the individual studies reporting general genetic associations with epilepsy, a number of meta-analyses have evaluated the association of particular genetic variants with different types of epilepsy. Most have not shown a significant association. For example, Cordoba et al (2012) evaluated the association between *SLC6A4* gene variants and temporal lobe epilepsy in 991 case patients and 1202 controls and failed to demonstrate a significant association in a combined analysis.[59,] Nurmohamed et al (2010) performed a meta-analysis of 9 case-control studies that evaluated the association between the *ABC1* gene variants and epilepsy.[60,] It included 2454 patients with epilepsy and 1542 control patients. No significant associations were found.

In 2008, one meta-analysis that did report a significant association was published by Kauffman et al.[61,] They evaluated the association between variants in the *IL1B* gene and temporal lobe epilepsy and febrile seizures, using data from 13 studies (n=1866 patients with epilepsy, n=1930 controls). Combined analysis showed a significant relation between one single-nucleotide variant (511T) and temporal lobe epilepsy, with a strength of association considered modest (odds ratio [OR], 1.48; 95% confidence interval [CI], 1.1 to 2.0; p=.01). In 2014, another meta-analysis reporting a positive association was published by Tang et al.[62,] The authors evaluated the association between the *SCN1A* IVS5N+5GNA variant and susceptibility to epilepsy with febrile seizures. The analysis included 6 studies with 2719 cases and 2317 controls. There was a significant association between the*SCN1A* variant and epilepsy with febrile seizures (A vs. G: OR , 1.5; 95% CI, 1.1 to 2.0).

Prognosis of Epilepsy

A smaller body of literature has evaluated whether specific genetic variants are associated epilepsy phenotypes or prognosis.

Observational Study

Van Podewils et al (2015) evaluated the association between sequence variants in *EFHC1* and phenotypes and outcomes in 38 probands with juvenile myoclonic epilepsy, along with 3 family members.[63,] Several *EFHC1* gene variants, including *F229L*, *R294H*, and *R182H*, were associated with earlier onset of generalized tonic-clonic seizures (66.7% vs. 12.5% ; OR , 13; p=.022), high-risk of status epilepticus (p=.001), and decreased risk of bilateral myoclonic seizures (p=.05).

Pharmacogenomics of Antiepileptic Medications

Pharmacogenomics of Antiepileptic Drug Response

Observational Studies

Numerous case-control studies have reported on the association between various genetic variants and response to medications in patients with epilepsy. The Epilepsy Genetic Association Database

identified 32 case-control studies of 20 different genes and their association with medication treatment.[55,] The most common comparison was between responders to medication and nonresponders. Some of the larger representative studies are discussed next.

Kwan et al (2008) compared the frequency of single-nucleotide variants on the *SCN1A*, *SCN2A*, and *SCN3A* genes in 272 drug-responsive patients and 199 drug-resistant patients.[64,] Twenty-seven candidate single-nucleotide variants were selected from a large database of previously identified single-nucleotide variants. One single-nucleotide variant identified on the *SCN2A* gene (rs2304016) had a significant association with drug resistance (OR, 2.1; 95% CI, 1.2 to 3.7; p<.007).

Jang et al (2009) compared the frequency of variants on the *SCN1A*, *SCN1B*, and *SCN2B* genes in 200 patients with drug-resistant epilepsy and 200 patients with drug-responsive epilepsy.[65,] None of the individual variants tested showed a significant relation with drug resistance. In a further analysis for gene-gene interactions associated with drug resistance, the authors reported a possible interaction of 2 variants, one on the *SCN2A* gene and the other on the *SCN1B* gene, though falling below their cutoff for statistical significance (p=.055).

Other Analyses

Lin et al (2021) conducted a prospective study of 96 children (age <2 years) with epilepsy and neurodevelopmental disability.[66,] A genetic cause of epilepsy was present in 28 children, while the remaining 68 children did not have an identified genetic cause. The incidence of drug-resistant epilepsy was 42.8% in patients with a genetic cause and 13.2% in patients without a genetic cause. Risk of drug-resistant epilepsy was significantly higher in the genetic group compared to the non-genetic group (adjusted OR, 6.50; 95% CI, 2.15 to 19.6; p=.03). Specific genes associated with drug-resistant epilepsy included *TBC1D24*, *SCN1A*, *PIGA*, *PPP1CB*, and *SZT2*.

Li et al (2015) conducted a meta-analysis of 28 articles reporting on 30 case-control studies to evaluate the association between the *ABCB1* gene C3435T variant and AED resistance.[67,] The included studies had a total of 4124 drug-resistant epileptic patients and 4480 control epileptic patients for whom drug treatment was effective. In a pooled random-effects model, the 3435C allele was not significantly associated with drug resistance, with a pooled OR of 1.07 in an allele model (95% CI, 0.95 to 1.19; p=.26) and 1.05 in a genotype model (95% CI, 0.89 to 1.24; p=.55).

Other representative studies that have reported associations between genetic variants and AED response are summarized in Table 9.

Table 9. Genetic Variants and Antiepileptic Drug Response

Study	Population	Genes	Overview of Findings
Song et al (2020)[68,]	83 adults with epilepsy in China receiving sustained-release valproic acid monotherapy	• *CYP2C19*	• Valproic acid concentration to dose ratios were significantly lower in EMs (3.33±1.78) compared to IMs (4.45±1.42) and PMs (6.64±1.06). • Valproic acid concentrations were significantly correlated with CYP2C19*2 and CYP2C19*3, but the CYP2C9*13 allele was not.
Zhao et al (2020)[69,]	245 children with epilepsy in China receiving levetiracetam alone or in combination with other medications (classified as drug-resistant [n=117] or	• *ABCB1* (C1236T, G2677T/A, and C3435T variants)	• Significantly higher levetiracetam concentrations were observed in patients with the following: 2677 genotypes GT, TT, GA, and AT compared to GG carriers (p=.021), and 3435-TT compared to CC and CT carriers (both p<.005).

Study	Population	Genes	Overview of Findings
	drug-responsive [n=128])		• No significant difference in variants among drug-resistant and drug-responsive patients.
Lu et al (2017)[70],	124 epileptic Chinese patients receiving oxcarbazepine monotherapy	• *UGT1A4* 142T>G (rs2011425) • *UGT1A6* 19T>G (rs6759892) • *UGT1A9* 1399C>T (rs2741049) • *UGT2B15*253T>G (rs1902023)	• *UGT1A9* variant allele 1399C>T had significantly lower monohydroxylated derivative plasma concentrations (TT, 13.28 mg/L ; TC, 16.41 mg/L; CC, 22.24 mg/L ; p<.05) and poorer seizure control than noncarriers (p=.01).
Hashi et al (2015)[71],	50 epileptic adults treated with stable clobazam dose	• *CYP2C19*	• Clobazam metabolite N-desmethylclobazam serum concentration: dose ratio was higher in PMs (median, 16,300 [ng/mL]/[mg/kg/d]) than in EMs (median, 1760 [ng/mL]/[mg/kg/d]) or IMs (median, 4640 [ng/mL]/[mg/kg/d]). • Patients with EM or IM status had no change in seizure frequency with clobazam therapy.
Ma et al (2015)[72],	184 epileptic patients receiving oxcarbazepine monotherapy and 156 healthy volunteers	• *SCN1A* c.3184A>G (rs2298771) • *SCN2A* c.56G>A (rs17183814) • *SCN2A* IVS7-32A>G (rs2304016) • *ABCC2* 3972C>T (rs3740066) • *ABCC2* c.1249G>A (rs2273697) • *UGT2B7* c.802T>C (rs7439366)	• *SCN1A* IVS5-91G>A, *UGT2B7* c.802T>C, and *ABCC2* c.1249G>A variants showed significant associations with oxcarbazepine maintenance doses. • Patients with the *ABCC2* c.1249G>A allele variant more likely to require higher oxcarbazepine maintenance doses than noncarriers (p=.002, uncorrected), which remained significant after Bonferroni correction.
Guo et al (2015)[73],	483 Chinese patients with genetic generalized epilepsies	• *KCNJ10*	• Frequency of rs12402969 C allele and the CC+CT genotypes were higher in the drug-responsive patients than that in the drug-resistant patients (9.3% vs. 5.6%; OR , 1.7; 95% CI, 1.1 to 2.9; p=.026).
Ma et al (2014)[74],	453 epileptic patients, classified as drug-responsive (n=207) or drug-resistant (n=246)	• *SCN1A* c.3184A>G (rs2298771) • *SCN2A* c.56G>A (rs17183814) • *SCN2A* IVS7-32A>G (rs2304016) • *ABCC2* 3972C>T (rs3740066) • *ABCC2* c.1249G>A (rs2273697)	• *SCN1A* IVS5-91G>A AA genotype more prevalent in drug-resistant than drug-responsive patients receiving multidrug therapy (OR, 3.41; 95% CI, 1.73 to 6.70; p<.001, uncorrected). • *SCN1A* IVS5-91G>A AA more prevalent in drug-resistant than drug-responsive patients receiving carbamazepine/oxcarbazepine (OR, 3.55; 95% CI, 1.62 to 7.78; p=.002, uncorrected). • *ABCC2* c.1249G>A GA genotype and allele A significantly associated with drug response (OR, 2.14; 95% CI, 1.23 to 3.71; p=.007; OR, 2.05; 95% CI, 1.31

Study	Population	Genes	Overview of Findings
			to 3.19; p=.001, respectively, uncorrected).
Radisch et al (2014)[75,]	229 epileptic patients treated with carbamazepine monotherapy	• *ABCC2:* variant rs717620 (-24G4A), rs2273697 (c.1249G4A), and rs3740067	• *ABCC2* variants not associated with time to first seizure or time to 12-mo remission.
Yun et al (2013)[76,]	38 epileptic patients treated with carbamazepine monotherapy	• *EPHX1* c.337T>C • *EPHX1* c.416A>G • *SCN1A* IVS5-91G>A • *CYP3A4*1G*	• Patients *EPHX1* c.416A>G genotypes had higher adjusted plasma carbamazepine concentrations vs. those with wild-type genotype (p<.05). • Other studied variants not associated with carbamazepine pharmaco-resistance.
Taur et al (2014)[77,]	115 epileptic patients treated with phenytoin, phenobarbital, and/or carbamazepine	• *ABCB1* (c.3435T) • *CYP2C*9 (416C>T) • *CYP2C9* (1061A>T) • *CYP2C19* (681G>A) • *CYP2C19* (636G>A)	• *ABCB1* C3435T genotype and allele variants significantly associated with drug response (OR, 4.5; 95% CI, 1.04 to 20.99; OR, 1.73; 95% CI, 1.02 to 2.95, respectively).

EM: extensive metabolizer; CI: confidence interval; CYP: cytochrome P450; IM: intermediate metabolizer; OR: odds ratio; PM: poor metabolizer.Several meta-analyses evaluating pharmacogenomics were identified.

Haerian et al (2010) examined the association between single-nucleotide variants on the *ABCB1* gene and drug resistance in 3231 drug-resistant patients and 3524 controls from 22 studies.[78,] Reviewers reported no significant relation between variants of this gene and drug resistance (combined OR, 1.06; 95% CI, 0.98 to 1.14; p=.12). There was also no significant association for subgroup analysis by ethnicity.

In a separate meta-analysis, Sun et al (2014) evaluated 8 studies evaluating the association between variants in the multidrug resistance 1 (*MDR1*) gene and childhood medication-refractory epilepsy, including 634 drug-resistant patients, 615 drug-responsive patients, and 1052 healthy controls.[79,] In the pooled analysis, the *MDR1* C3435T variant was not significantly associated with risk of drug resistance.

Table 10. Pharmacogenomics of Antiepileptic Drug Response Systematic Review & Meta-Analysis Characteristics

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Haerian et al (2010)[78,]	2003-2009	22	Individuals with epilepsy	6755 (45-609)	Case-controlled	NR
Sun et al (2014)[79,]	2007-2013	8	Children (<18 years of age) with intractable epilepsy	634 drug-resistant , 615 drug-responsive, and 1052 healthy controls	Case-controlled or cohort studies	NR

NR: not reported.

Table 11. Pharmacogenomics of Antiepileptic Drug Response Systematic Review & Meta-Analysis Results

Study	Association of *ABCB1* C3435T with risk of drug resistance	Association of *MDR1* C3435T with risk of drug resistance
Haerian et al (2010)[78,]		
OR	1.06	
95% CI	0.98-1.14	
p-value	0.12	

Study	Association of *ABCB1* C3435T with risk of drug resistance	Association of *MDR1* C3435T with risk of drug resistance
Sun et al (2014)[79,]		
OR		1.03
95% CI		0.87-1.22
p-value		0.73

CI: confidence interval; OR: odds ratio.

Shazadi et al (2014) assessed the validity of a gene classifier panel consisting of 5 single-nucleotide variants for predicting initial AED response and overall seizure control in 2 cohorts of patients with newly diagnosed epilepsy.[80,] A cohort of 115 Australian patients with newly diagnosed epilepsy was used to develop the classifier from a sample of 4041 single-nucleotide variants in 279 candidate genes via a *k*-nearest neighbor machine learning algorithm, resulting in a 5 single-nucleotide variant classifier. The classifier was validated in 2 separate cohorts. One cohort included 285 newly diagnosed patients in Glasgow, of whom a large proportion had participated in randomized trials of AED monotherapy. Drug-response phenotypes in this cohort were identified by retrospectively reviewing prospectively collected clinical trial and/or hospital notes. The second cohort was drawn from patients who had participated in the Standard and New Epileptic Drugs (SANAD) trial, a multicenter RCT comparing standard with newer AEDs. The trial included 2400 patients, of whom 520 of self-described European ancestry who provided DNA samples were used in the present analysis. The *k*-nearest neighbor machine model derived from the original Australian cohort did not predict treatment response in either the Glasgow or the SANAD cohorts. Investigators redeveloped a *k*-nearest neighbor machine learning algorithm based on single-nucleotide variant genotypes and drug responses in a training dataset (n=343) derived from the SANAD cohort. None of the 5 single-nucleotide variants used in the multigenic classifier was independently associated with AED response in the Glasgow or the SANAD cohort after correction for multiple tests. When applied to a test dataset (n=148) derived from the SANAD cohort, the classifier correctly identified 26 responders and 52 nonresponders but incorrectly identified 26 nonresponders as responders (false-positives) and 44 responders as nonresponders (false-negatives), corresponding to a positive predictive value of 50% (95% CI, 32.8% to 67.2%) and a negative predictive value of 54% (95% CI, 41.1% to 66.7%). In a cross-validation analysis, the 5 single-nucleotide variant classifier was significantly predictive of treatment responses among Glasgow cohort patients initially prescribed either carbamazepine or valproate (positive predictive value, 67%; negative predictive value, 60%; corrected p=.018), but not among those prescribed lamotrigine (corrected p=1.0) or other AEDs (corrected p=1.0). The 5 single-nucleotide variant classifier was significantly predictive of treatment responses among SANAD cohort patients initially prescribed carbamazepine or valproate (positive predictive value, 69%; negative predictive value, 56%; corrected p=.048), but not among those prescribed lamotrigine (corrected p=.36) or other AEDs (corrected p=.36).

Pharmacogenomics of Antiepileptic Drug Adverse Events

Many AEDs have a relatively narrow therapeutic index, with the potential for dose-dependent or idiosyncratic adverse events. Several studies have evaluated genetic predictors of adverse events from AEDs, particularly severe skin reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).

Observational Studies

Chung et al (2014) evaluated genetic variants associated with phenytoin-induced severe cutaneous adverse events (SJS/TEN, drug reactions with eosinophilia and systemic symptoms) and maculopapular exanthema.[81,] This GWAS included 60 cases with phenytoin-related severe cutaneous adverse events and 412 population controls, and was followed by a case-control study of 105 cases with phenytoin-related severe cutaneous adverse events (61 with SJS/TEN, 44 with drug reactions with eosinophilia and systemic symptoms), 78 cases with maculopapular exanthema, 130 phenytoin-tolerant control participants, and 3655 population controls from Taiwan, Japan, and Malaysia. In the GWAS analysis, a missense variant of *CYP2C9*3* (rs1057910) was significantly associated with phenytoin-related severe cutaneous adverse events (OR, 12; 95% CI, 6.6 to 20; $p=1.1^{-17}$). In a case-

control comparison between the subgroups of 168 patients with phenytoin-related cutaneous adverse events and 130 phenytoin-tolerant controls, *CYP2C9*3* variants were significantly associated with SJS/TEN (OR, 30; 95% CI, 8.4 to 109; $p=1.2^{\prime}10^{-19}$), drug reactions with eosinophilia and systemic symptoms (OR, 19; 95% CI, 5.1 to 71; $p=7.0^{\prime}10^{-7}$), and maculopapular exanthema (OR, 5.5; 95% CI, 1.5 to 21; p=.01).

He et al (2014) conducted a case-control study to evaluate the association between carbamazepine-induced SJS/TEN and 10 single-nucleotide variants in the *ABCB1*, *CYP3A4*, *EPHX1*, *FAS*, *SNC1A*, *MICA*, and *BAG6* genes.[82,] The study included 28 cases with carbamazepine-induced SJS/TEN and 200 carbamazepine-tolerant controls. The authors reported statistically significant differences in the allelic and genotypic frequencies of *EPHX1* c.337T>C variants between patients with carbamazepine-induced SJS/TEN and carbamazepine-tolerant controls (p=.011 and p=.007, respectively). There were no significant differences between SJS/TEN cases and carbamazepine-tolerant controls for the remaining single-nucleotide variants evaluated.

Wang et al (2014) evaluated the association between human leukocyte antigen (*HLA)* genes and cross-reactivity of cutaneous adverse drug reactions to aromatic AEDs (carbamazepine, lamotrigine, oxcarbazepine, phenytoin, phenobarbital).[83,] The study included 60 patients with a history of aromatic AED-induced cutaneous adverse drug reactions, including SJS/TEN and maculopapular eruption, who were re-exposed to an aromatic AED, 10 of whom had a recurrence of the cutaneous adverse drug reaction on re-exposure (cross-reactive group). Subjects tolerant to re-exposure were more likely to carry the *HLA-A**2402 allele than cross-reactive subjects (OR, 0.13; 95% CI, 0.015 to 1.108; p=.040). Frequency distributions for testing other *HLA* genes did not differ significantly between groups.

Table 12. Summary of Key Observational Study Characteristics for Pharmacogenomics of Antiepileptic Drug Adverse Events

Study	Study Type	Country	Dates	Participants	Treatment [1]	Treatment [2]	Follow-up
Chung et al (2014)[81,]	Case-control	Taiwan, Malaysia, Japan	2002-2014	Individuals with phenytoin-related severe cutaneous adverse reactions (n=60) and tolerant controls (n=130)	GWAS		NR
He et al (2014)[82,]	Case-control	China	NR	Chinese Han patients with CBZ-SJS/TEN (n=28) and CBZ-tolerant controls (n=200)	Polymerase chain reaction amplification and direct sequencing	Fluorescence polarization immunoassay	NR
Wang et al (2014)[83,]	Cohort	China	2009-2013	Patients with a history of aromatic AED-induced cutaneous adverse drug reactions reexposed to an aromatic AED (n=60)	High-resolution HLA-A, -B, -DRB1 genotyping		NR

AED: antiepileptic drug; CBZ-SJS/TEN: carbamazepine-induced Stevens-Johnson Syndrome/toxic epidermal necrolysis; GWAS: genome-wide association study; NR: not reported.

Table 13. Summary of Key Observational Study Results for Pharmacogenomics of Antiepileptic Drug Adverse Events

Study	Association of rs1057910 (*CYP2C9*3*) with phenytoin-related severe cutaneous adverse reactions	Difference in allelic frequencies of *EPHX1* c.337T>C between groups	Difference in genotypic frequencies of *EPHX1* c.337T>C between groups	Patients carrying *HLA-A*2402* allele
Chung et al (2014)[81,]				

Study	Association of rs1057910 (*CYP2C9*3*) with phenytoin-related severe cutaneous adverse reactions	Difference in allelic frequencies of *EPHX1* c.337T>C between groups	Difference in genotypic frequencies of *EPHX1* c.337T>C between groups	Patients carrying *HLA-A*2402* allele
OR	11			
95% CI	6.2–18.0			
p-value	<.001			
He et al (2014)[82,]				
p-value		.011	.007	
Wang et al (2014)[83,]				
Cross-reactivity group				1 (10%)
Tolerant group				23 (46%)
OR				0.130
95% CI				0.015–1.108
p-value				.040

CI: confidence interval; OR: odds ratio.

Prediction of Sudden Unexplained Death in Epilepsy

Sudden unexplained death in epilepsy (SUDEP) is defined as a sudden, unexpected, nontraumatic, and nondrowning death in patients with epilepsy, excluding documented status epilepticus, with no cause of death identified following comprehensive postmortem evaluation. It is the most common cause of epilepsy-related premature death, accounting for 15% to 20% of deaths in patients with epilepsy.[84,] Given uncertainty related to the underlying causes of SUDEP, there has been interested in identifying genetic associations with SUDEP.

Observational Studies

Bagnall et al (2014) evaluated the prevalence of sequence variations in the *PHOX2B* gene in 68 patients with SUDEP.[84,] Large polyalanine repeat expansions in the *PHOX2B* gene are associated congenital central hypoventilation syndrome, a potentially lethal autonomic dysfunction syndrome, but smaller *PHOX2B* expansions may be associated with nocturnal hypoventilation. In a cohort of patients with SUDEP, 1 patient was found to have a 15-nucleotide deletion in the *PHOX2B* gene, but no *PHOX2B* polyalanine repeat expansions were found.

Coll et al (2016) evaluated the use of a custom resequencing panel including genes related to sudden death, epilepsy, and SUDEP in a cohort of 14 patients with focal or generalized epilepsy and a personal or family history of SUDEP, including 2 postmortem cases.[85,] In 4 cases, rare variants were detected with complete segregation in the *SCN1A*, *FBN1*, *HCN1*, *SCN4A*, and *EFHC1* genes, and in 1 case a rare variant in *KCNQ1* with an incomplete pattern of inheritance was detected. New potential candidate genes for SUDEP were detected: *FBN1*, *HCN1*, *SCN4A*, *EFHC1*, *CACNA1A*, *SCN11A*, and *SCN10A*.

Bagnall et al (2016) performed an exome-based analysis of rare variants related to cardiac arrhythmia, respiratory control, and epilepsy to search for genetic risk factors in 61 SUDEP cases compared with 2936 controls.[86,] Mean epilepsy onset of the SUDEP cases was 10 years and mean age at death was 28 years. De novo variants, previously reported pathogenic variants, or candidate pathogenic variants were identified in 28 (46%) of 61 SUDEP cases. Four (7%) SUDEP cases had variants in common genes responsible for long QT syndrome and a further 9 (15%) cases had candidate pathogenic variants in dominant cardiac arrhythmia genes. Fifteen (25%) cases had variants or candidate pathogenic variants in epilepsy genes; 6 cases had a variant in DEPDC5. DEPDC5 (p=.00015) and *KCNH2* (p=.0037) were highly associated with SUDEP. However, using a rare variant collapsing analysis, no gene reached criteria for genome-wide significance.

Table 14. Summary of Nonrandomized Study Characteristics for Prediction of Sudden Unexplained Death in Epilepsy

Study	Study Type	Country	Dates	Participants	Treatment1
Bagnall et al (2014)[84],	Retrospective	Australia	1993-2009	Patients with SUDEP (N =68)	DNA sequencing analysis of *PHOX2B*
Coll et al (2016)[85],	Cohort	Italy	NR	Patients with focal or generalized epilepsy and a personal or family history of SUDEP (N =14)	Custom resequencing panel
Bagnall et al (2016)[86],	Cohort	Australia	1993-2010	Patients with SUDEP (N =61) and controls (n=2936)	Exome sequencing and rare variant collapsing analysis

NR: not reported; SUDEP: sudden unexplained death in epilepsy.

Table 15. Summary of Key Nonrandomized Study Results for Prediction of Sudden Unexplained Death in Epilepsy

Study	Patients with a 15-nucleotide deletion in *PHOX2B* gene, n/N	Patients with *PHOX2B* polyalanine repeat expansions, n/N	Rare variants detected with complete segregation	New potential candidate genes for SUDEP	Variants highly associated with SUDEP
Bagnall et al (2014)[84],	1/68	0/68			
Coll et al (2016)[85],		4 cases: *SCN1A, FBN1, HCN1, SCN4A, EFHC11case: KCNQ1*		*FBN1, HCN1, SCN4A, EFHC1, CACNA1A, SCN11A, SCN10A*	
Bagnall et al (2016)[86],					*DEPDC5* (p<.001), *KCNH2* (p<.004)

SUDEP: sudden unexplained death in epilepsy.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

There is a lack of evidence on the clinical utility of genetic testing for the genetic epilepsies. Association studies are insufficient evidence to determine whether genetic testing can improve the clinical diagnosis of genetic generalized epilepsy. There are no studies reporting the accuracy regarding sensitivity, specificity, or predictive value; therefore, it is not possible to determine the impact of genetic testing on diagnostic decision making.

The evidence on pharmacogenomics has suggested that genetic factors may play a role in the pharmacokinetics of antiepileptic medications. However, how genetic information might be used to

tailor medication management in ways that will improve efficacy, reduce adverse events, or increase the efficiency of medication trials is not yet well-defined.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Section Summary: Presumed Genetic Epilepsy

The evidence on genetic testing for genetic epilepsies is characterized by a large number of studies that have evaluated associations between many different genetic variants and the various categories of epilepsy. The evidence on the clinical validity of testing for the diagnosis of epilepsy is not consistent in showing an association between any specific genetic variant and any specific type of epilepsy. Where associations have been reported, they are not of strong magnitude and, in most cases, have not been replicated independently or through the available meta-analyses. Because of the lack of established clinical validity, the clinical utility of genetic testing for the diagnosis of genetic epilepsies is also lacking. Several studies have reported associations between a number of genes and response to AEDs or AED adverse events. How this information should be used to tailor medication management is not yet well-defined, and no studies were identified that provide evidence for clinical utility.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 4 specialty societies and 2 academic medical centers, for a total of 8 reviewers, while this policy was under review for 2015. The review was limited to input related to the use of genetic testing for infantile- and early-childhood-onset epileptic encephalopathies. There was a consensus that genetic testing for early-onset epileptic encephalopathies is medically necessary. Particular areas of clinical utility noted by reviewers included making specific treatment decisions in *SCN1A*-related epilepsies and avoiding other diagnostic tests and for reproductive planning for multiple types of early-onset epilepsies.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a U.S. professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Academy of Neurology et al.

In 2006, the American Academy of Neurology and Child Neurology Society published joint guidelines on the diagnostic assessment of children with status epilepticus.[87,] These guidelines were reviewed and reaffirmed in 2022. With regard to whether genetic testing should be routinely ordered for children with status epilepticus, the guidelines stated: "There is insufficient evidence to support or refute whether such studies should be done routinely."

In 2000, the American Academy of Neurology, Child Neurology Society, and the American Epilepsy Society published joint guidelines for evaluating a first nonfebrile seizure in children.[88,] This guidance

was reviewed and reaffirmed in 2023. Routine electroencephalography was recommended as part of the diagnostic evaluation; genetic testing was not addressed.

International League Against Epilepsy

In 2015, the International League Against Epilepsy issued a report with recommendations on the management of infantile seizures, which included the following related to genetic testing in epilepsy[42,]:

- "Genetic screening should not be undertaken at a primary or secondary level of care, as the screening to identify those in need of specific genetic analysis is based on tertiary settings."
- "Standard care should permit genetic counseling by trained personnel to be undertaken at all levels of care (primary to quaternary)."
- "Genetic evaluation for Dravet syndrome and other infantile-onset epileptic encephalopathies should be available at tertiary and quaternary levels of care (optimal intervention would permit an extended genetic evaluation)."
- "Early diagnosis of some mitochondrial conditions may alter long-term outcome, but whether screening at quaternary level is beneficial is unknown."

National Society of Genetic Counselors

In 2022, the National Society of Genetic Counselors published a practice guideline on genetic testing and counseling for unexplained epilepsies.[89,]The Society made the following relevant recommendations:

- "We strongly recommend that individuals with unexplained epilepsy be offered genetic testing, without limitation of age.
- We strongly recommend comprehensive, multi-gene testing, such as exome/genome sequencing or multi-gene panel as a first-tier test.
- We conditionally recommend exome/genome sequencing over multi-gene panel as the first-tier test.
- The multi-gene panel should have a minimum of 25 genes and include copy number analysis."

European Academy of Neurology

In 2010, the European Federation of Neurological Societies (now the European Academy of Neurology) issued guidelines on the molecular diagnosis of channelopathies, epilepsies, migraine, stroke, and dementias.[90,] The guidelines made the following recommendations on epilepsy: "There is good evidence to suggest that a thorough clinical and electrophysiological investigation may lead to the choice of the gene to be tested in patients with periodic paralysis (Level B). In myotonic disorders, it is recommended to first search for myotonic dystrophy and use clinical and electrophysiological phenotype characterization to guide for molecular genetic testing (Level B). Molecular investigations are possible and may help in some cases to diagnose the condition but cannot be considered as a routine procedure with regard to the large number of different mutations [variants] in different genes. Furthermore, diagnosis can be made more easily by clinical and physiological investigation (Good Practice Point). One exception of note is the diagnosis of SMEI , in which mutations [variants] are found in *SCN1A* in 80% of the patients (Level B)."

North American Consensus Panel

In 2017, recommendations were published from a consensus panel of 14 physicians and 5 family members/caregivers of patients with Dravet syndrome.[91,] There was strong consensus among panel members that genetic testing should be completed in all patients with clinical suspicion for Dravet syndrome since this can lead to earlier diagnosis. Options for testing include *SCN1A* sequencing followed by testing for deletions and duplications if sequencing is negative, or epilepsy gene panel testing, with no consensus among panel members about which option is superior. There was strong consensus that epilepsy gene panel testing is preferred to *SCN1A* testing if the clinical presentation is less clear or if the patient has atypical features, and that karyotyping is not needed. The panel did not reach consensus about the utility of chromosomal microarray in patients with suspected Dravet

syndrome (72.2% agreed, 22.2% disagreed, 5.6% did not know) and concluded that this test can be considered. Based on strong consensus, the panel recommended genetic testing in the following circumstances among children with normal development, seizures of unknown etiology, and no evidence of causal lesion in the brain: infants with at least 2 prolonged focal febrile seizures, or children aged 1 to 3 years with at least one prolonged febrile seizure before 18 months of age or myoclonic or atypical absence seizures that are refractory to at least one antiepileptic medication. Infants who experience a single prolonged focal or generalized convulsion do not require genetic testing (strong consensus), but this can be considered in children aged 1 to 3 years who experience multiple brief episodes of febrile seizure activity before 18 months of age or myoclonic or atypical absence seizures that do not respond to antiepileptic medication (moderate consensus). The panel had moderate consensus about the role of genetic testing (epilepsy gene panel) in teens and adults without congenital dysmorphism who have seizure activity resistant to antiepileptic medication and lack an early life history.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
The ongoing trials that might influence this review are listed in Table 16.

Table 16. Summary of Key Trials

NCT No.	*Trial Name*	*Planned Enrollment*	*Completion Date*
Ongoing			
NCT01858285	Genetics of Epilepsy and Related Disorders	5000	Dec 2030

NCT: national clinical trial.

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Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
- Reason for performing test
- Changes in medication management/diagnostic testing/reproductive decision making related to reason for genetic testing
  - Specific clinical syndromes if applicable
  - Family history if applicable
  - How test result will impact clinical decision making
  - Lab results documenting carrier status or genetic disorder
  - Provider order for genetic test • Name and description of genetic test • CPT codes billed for the particular genetic test

Post Service (in addition to the above, please include the following):

- Results/reports of tests performed

Coding

The list of codes in this Medical Policy is intended as a general reference and may not cover all codes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy.

Type	Code	Description
CPT®	0231U	CACNA1A (calcium voltage-gated channel subunit alpha 1A) (e.g., spinocerebellar ataxia), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, short tandem repeat (STR) gene expansions, mobile element insertions, and variants in non-uniquely mappable regions
	81401	Molecular Pathology Procedure Level 2
	81403	Molecular Pathology Procedure Level 4

Type	Code	Description
	81404	Molecular Pathology Procedure Level 5
	81405	Molecular Pathology Procedure Level 6
	81406	Molecular Pathology Procedure Level 7
	81407	Molecular Pathology Procedure Level 8
	81419	Epilepsy genomic sequence analysis panel, must include analyses for ALDH7A1, CACNA1A, CDKL5, CHD2, GABRG2, GRIN2A, KCNQ2, MECP2, PCDH19, POLG, PRRT2, SCN1A, SCN1B, SCN2A, SCN8A, SLC2A1, SLC9A6, STXBP1, SYNGAP1, TCF4, TPP1, TSC1, TSC2, and ZEB2
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
06/30/2015	BCBSA Medical Policy adoption
04/01/2015	Policy revision without position change
04/01/2017	Policy revision without position change
04/01/2018	Policy revision without position change
02/01/2019	Coding update
05/01/2019	Policy revision without position change
10/01/2025	Policy reactivated. Previously archived from 05/01/2020 to 09/30/2025

Definitions of Decision Determinations

Healthcare Services: For the purpose of this Medical Policy, Healthcare Services means procedures, treatments, supplies, devices, and equipment.

Medically Necessary: Healthcare Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield of California, are: (a) consistent with Blue Shield of California medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the member; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the member's illness, injury, or disease.

Investigational or Experimental: Healthcare Services which do not meet ALL of the following five (5) elements are considered investigational or experimental:

A. The technology must have final approval from the appropriate government regulatory bodies.
   - This criterion applies to drugs, biological products, devices and any other product or procedure that must have final approval to market from the U.S. Food and Drug Administration ("FDA") or any other federal governmental body with authority to regulate the use of the technology.
   - Any approval that is granted as an interim step in the FDA's or any other federal governmental body's regulatory process is not sufficient.
   - The indications for which the technology is approved need not be the same as those which Blue Shield of California is evaluating.

B. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.
   - The evidence should consist of well-designed and well-conducted investigations published in peer-reviewed journals. The quality of the body of studies and the consistency of the results are considered in evaluating the evidence.
   - The evidence should demonstrate that the technology can measure or alter the physiological changes related to a disease, injury, illness, or condition. In addition, there should be evidence, or a convincing argument based on established medical facts that such measurement or alteration affects health outcomes.

C. The technology must improve the net health outcome.
   - The technology's beneficial effects on health outcomes should outweigh any harmful effects on health outcomes.

D. The technology must be as beneficial as any established alternatives.
   - The technology should improve the net health outcome as much as, or more than, established alternatives.

E. The improvement must be attainable outside the investigational setting.
   - When used under the usual conditions of medical practice, the technology should be reasonably expected to satisfy Criteria C and D.

Feedback

Blue Shield of California is interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration. Our medical policies are available to view or download at www.blueshieldca.com/provider.

For medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as member health services contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member health services contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE	**AFTER** **Blue font: Verbiage Changes/Additions**
Reactivated Policy **Policy Statement:** N/A	**Genetic Testing for Epilepsy 2.04.109** **Policy Statement:** I. Genetic testing for genes associated with infantile- and early-childhood onset epilepsy syndromes in individuals with infantile- and early-childhood-onset epilepsy syndromes in which epilepsy is the core clinical symptom (see Policy Guidelines section) maybe considered **medically necessary** if positive test results may lead to changes in **one or more** of the following: A. Medication management B. Diagnostic testing such that alternative potentially invasive tests are avoided C. Reproductive decision making II. Genetic testing for epilepsy is considered investigational for all other situations.