
Medical Policy



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(See policy history boxes for previous effective dates)

Title: Genetic Testing for Epilepsy

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.

Medical Policy Statement

Genetic testing for infantile and pediatric epileptic syndromes is established when criteria are met.

Inclusionary and Exclusionary Guidelines

Inclusions:

Genetic testing of genes of individuals with infantile-and pediatric-onset epilepsy syndromes when epilepsy is the core clinical symptom and positive test results may lead to any of the following:

- changes in medication management
- changes in diagnostic testing such that alternative potentially invasive tests are avoided
- changes in reproductive decision making

AND

- Syndrome is severe and is characterized by epilepsy as the primary manifestation without associated metabolic or structural brain abnormalities

Note: Specific clinical syndromes based on the International League against Epilepsy may include, but are not limited to the following infantile and pediatric onset epileptic syndromes:

- 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.

Exclusions:

- Genetic testing for all other epilepsy conditions not related to infantile or pediatric-onset epilepsy syndromes.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

81401	81403	81404	81405	81406	81407
81419	81479				

*A request for panel testing can be considered established, the panel size should be considered reasonable.

Other codes (investigational, not medically necessary, etc.):

0231U*

*This gene (CACNA1A) can be tested in the genetic panel testing code 81419.

Background

EPILEPSY

Epilepsy is defined as the occurrence of two 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, i.e., the type of

seizures that occur. The International League Against Epilepsy (ILAE) developed the classification system that is widely used for clinical care and research purposes (see 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 spasms	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

^aDegree of awareness usually is not specified.

Although genetic epilepsies are not discussed in the 2017 ILAE report², a 2010 ILAE report³ 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 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

Table 2. Single Genes Associated with Epileptic Syndromes

Syndrome	Associated Genes
Dravet syndrome	<i>SCN1A, SCN9A, GABRA1, STXBP1, PCDH19, SCN1B, CACNA1B, HCN1</i>
Epilepsy limited to females with mental retardation	<i>PCDH19</i>
Epileptic encephalopathy with continuous spike-and-wave during sleep	<i>GRIN2A</i>
Genetic epilepsy with febrile seizures plus	<i>SCN1A, SCN9A</i>
Early infantile epileptic encephalopathy with suppression burst (Ohtahara syndrome)	<i>KCNQ2, SLC25A22, STXBP1, CDKL5, ARX</i>
Landau-Kleffner syndrome	<i>GRIN2A</i>
West syndrome	<i>ARX, TSC1, TSC2, CDKL5, ALG13, MAGI2, STXBP1, SCN1A, SCN2A, GABA, GABRB3, DNM1</i>
Glucose transporter type 1 deficiency syndrome	<i>SLC2A1</i>

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 electroencephalography 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 susceptibility to epilepsy have a

relatively weak impact. Multiple genetic defects, and/or 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. This hypothesis arises from the discovery of pathologic variants in small numbers of patients with the disorders. Because of the small amount of research available, the evidence base for these rare syndromes is incomplete, and new variants are discovered frequently.⁷

Some of the most common genes that have been associated with both the common epilepsies and the rare epileptic syndromes are listed in Table 3.

Table 3. Selected Genes Most Commonly Associated with Genetic Epilepsy

Genes	Physiologic Function
<i>KCNQ2</i>	Potassium channel
<i>KCNQ3</i>	Potassium channel
<i>SCN1A</i>	Sodium channel α -subunit
<i>SCN2A</i>	Sodium channel α -subunit
<i>SCN1B</i>	Sodium channel β -subunit
<i>GABRG2</i>	γ -aminobutyrate A-type subunit
<i>GABRA1</i>	γ -aminobutyrate A-type subunit
<i>GABRD</i>	γ -aminobutyrate subunit
<i>CHRNA2</i>	Acetylcholine receptor $\alpha 2$ subunit
<i>CHRNA4</i>	Acetylcholine receptor $\alpha 4$ subunit
<i>CHRNA2</i>	Acetylcholine receptor $\beta 2$ subunit
<i>STXBP1</i>	Synaptic vesicle release
<i>ARX</i>	Homeobox gene
<i>PCDH19</i>	Protocadherin cell-cell adhesion
<i>EFHC1</i>	Calcium homeostasis
<i>CACNB4</i>	Calcium channel subunit
<i>CACNA1A</i>	Calcium channel subunit
<i>CLCN2</i>	Chloride channel
<i>LGII</i>	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 GEFS+ 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 one 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.

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 prospective and retrospective cohort studies describing the testing yield. Relevant outcomes are test accuracy and validity, changes in reproductive decision making, 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 ($\approx 80\%$). For other early-onset epileptic encephalopathies, the true clinical sensitivity and specificity of testing is not well-defined. However, studies reporting on the overall yield of genetic testing in populations with epileptic encephalopathies and early-onset epilepsy report 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 a meaningful improvement in the net health outcomes.

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 accuracy and 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. The largest number of these studies are related to AED pharmacogenomics, which generally report 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 effects have been reported. However, no empirical evidence on the clinical utility of genetic 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 the effects of the technology on health outcomes.

Rationale

Evidence reviews assess clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to individuals and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms. The following is a summary of the key literature to date.

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.

EARLY-ONSET EPILEPSY AND EPILEPTIC ENCEPHALOPATHIES

Clinical Context and Test Purpose

Numerous rare syndromes that 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 4. lists some of these syndromes, with the putative causative genetic variants

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

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

Review of Evidence

Systematic Reviews

Chang et al (2025) performed a systematic review and meta-analysis on 416 studies (N=124,937) to determine the diagnostic yield of chromosomal microarray (CMA) and next-generation sequencing (NGS) methods—including targeted sequencing (TS), whole-exome sequencing (WES), and whole-genome sequencing (WGS)—in individuals with neurodevelopment disorders or epilepsy.¹⁷ Diagnostic yields for epilepsy were 13.3% (95% CI: 11.2% to 15.7%) for CMA, 24% (95% CI: 21.5% to 26.7%) for TS, 34.2% (95% CI: 30.9% to 37.6%) for WES, and 39.1% (95% CI: 32.4% to 46.2%) for WGS. Furthermore, a subgroup analysis was conducted for different types of epilepsy by clinical features including epileptic encephalopathy, West syndrome, and early onset (> 2 years of age). The diagnostic yields for epileptic encephalopathy, West syndrome, and early onset for CMA and TS/WES were 11.7% (95% CI: 8.5% to 16%) and 34.7% (95% CI: 31.8% to 37.7%), 10.7% (95% CI: 7.4% to 15.1%) and 27.7% (95% CI: 22.9% to 33.1%), and 15.4% (95% CI: 8.3% to 26.6%) and 32.9% (95% CI: 29.1% to 36.9%), respectively. The authors specifically noted the potential of NGS methods as first-tier testing approaches for epilepsy, especially for patients with epilepsy associated with onset earlier than 2 years of age, drug-resistant epilepsy, and epileptic encephalopathy may particularly benefit from exome sequencing due to its higher yield. The authors note limitations of the analysis, including discrepancies in institution-specific interpretations of a gene variant, the reporting center, time, bioinformatic pipeline (e.g., CNV calling), genes incorporated in the targeted sequencing, the included participant criteria, and varying sample sizes across studies may bias the aggregated results.

Feng et al (2025) conducted a systematic review and meta-analysis of the diagnostic yields of genetic testing in infantile epileptic spasms syndrome.¹⁸ Thirty 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

A number of studies have reported on the yield of genetic testing 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 (DS) who underwent targeted resequencing of DS-associated genes.²² Disease-causing variants (*SCN1A* = 9, *PCDH19* = 1) were identified in 10 children (45.5%), and results suggested that a clinical DS risk score of >6 and seizure onset before age 6 months were highly predictive of *SCN1A*-associated DS. 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 (WES; n=74), epilepsy-related gene panel testing (n=141), or clinical WES gene panel testing (n=58).²³ Ninety-three likely disease-causing mutations in 33 genes were identified in 86 individuals (31.5%). The most frequently mutated genes were *SCN1A* (24.4%), *TSC2* (8.1%), *SCN8A* (5.8%), *CDKL5* (5.8%), *KCNMA1* (4.6%), *TSC1* (4.6%), *KCNQ2* (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)	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 <i>KCNQ2</i>, <i>CDKL5</i>, <i>SCN1A</i>, and <i>STXBP1</i> were the most frequently identified genes

Jiang et al (2021)	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: <i>NCL</i>, <i>SEPHS2</i>, <i>PA2G4</i>, <i>SLC35G2</i>, <i>MYO1C</i>, <i>GPR158</i>, and <i>POU3F1</i>
Kim et al (2021)	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: <i>FARS2</i>, <i>YWHAG</i>, <i>KCNC1</i>, <i>DYRK1A</i>, <i>SMC1A</i>, <i>PIGA</i>, <i>OGT</i>, and <i>FGF12</i> - Genes newly associated with epilepsy: <i>YWHAG</i>, <i>KCNC1</i>, and <i>FGF12</i>
Palmer et al (2021)	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)	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: <i>CHD2</i>, <i>COL4A1</i>, <i>FOXG1</i>, <i>GABRA1</i>, <i>GRIN2B</i>, <i>HNRNPU</i>, <i>KCNQ2</i>, <i>MECP2</i>, <i>PCDH19</i>, <i>SCN1A</i>, <i>SCN2A</i>, <i>SCN8A</i>, <i>SLC6A1</i>, <i>STXBP1</i>, and <i>WWOX</i>
Sun et al (2021)	73 infants with epileptic encephalopathies including West syndrome and Dravet syndrome	Whole exome sequencing	Diagnostic yield: 46.6% (most commonly <i>SCN1A</i> variants) - Genes with novel variants: <i>CACNA1E</i> and <i>WDR26</i>
Lee et al (2020)	24 patients with Dravet syndrome	Targeted panel with 40 epilepsy genes	Disease-causing variants (<i>SCN1A</i> and <i>PCDH19</i>) identified in 75% of patients
Lee et al (2021)	105 children with various seizure types	Whole exome sequencing, microarray, single gene testing, targeted multigene panel testing	Diagnostic yield: 35.71% with whole exome sequencing 8.33% with microarray 18.60% with single gene testing 19.23% with targeted multigene panel testing
Lee et al (2020)	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 <i>SCN1A</i> and <i>PRRT2</i>) identified in 34.5% of patients

Stodberg et al (2020)	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)	22 infants with provisional diagnosis of Dravet syndrome	Target resequencing of Dravet syndrome-associated genes	Disease-causing variants (<i>SCN1A</i> and <i>PCDH</i>) identified in 45.5% of patients
Peng et al (2018)	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: • <i>SCN1A</i> (24.4%) • <i>TSC2</i> (8.1%) • <i>SCN8A</i> (5.8%) • <i>CDKL5</i> (5.8%)
Berg et al (2017)	327 infants and young children with newly diagnosed with epilepsy	Various forms	Disease-causing variants (<i>SCN1A</i> and <i>PCDH19</i>) identified in 75% of patients
Moller et al (2016)	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)	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)	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)	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)	147 children with epilepsy	Single-nucleotide variant microarray	Diagnostic yield: • 7.5% clinically significant abnormal results

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 1 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 1 affected child may be higher, but the utility of genetic counseling is not well-established in the literature.

Chain of Evidence

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 (e.g., carbamazepine).^{20,40} Also, some experts suggest that patients with Dravet syndrome may be more susceptible to particular AEDs, including clobazam and stiripentol.⁵ In contrast, the usual medical treatment of infantile spasms is hormonal therapy with corticotropin (adrenocorticotrophic hormone),⁴¹⁻⁴³ and usual first-line treatment of Lennox-Gastaut is sodium valproate.⁴⁴ Therefore, confirming the specific diagnosis leads to changes in therapy expected to improve outcomes.

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.⁴⁶ 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 6.²⁴ 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*).

PRESUMED GENETIC EPILEPSY

Clinical Context and Test Purpose

Most genetic epilepsy syndromes are present in childhood, adolescence, or early adulthood. They include generalized or focal in nature 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 a genetic epilepsy is to determine etiology of the epilepsy syndrome and thereby possibly limiting further invasive investigation (e.g., epilepsy surgery), define prognosis, and help guide therapy.

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, which should ideally be collected in research of epilepsy.⁴⁷

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

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 with epilepsy with the frequency in patients without epilepsy. There is a smaller number of genome-wide association studies (GWAS) that evaluate the presence of SNVs associated with epilepsy across the entire genome. No studies were identified that reported 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.⁴⁸ 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.⁴⁹ Epilepsy was the reason for testing in 15.4% (n=65) 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.⁵⁰ 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.⁵¹ 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 <1–69 years old with 88% <18 years old) referred for genetic testing with a targeted epilepsy panel between 2014 and 2016.⁵² Positive yield was 15.1%, with pathogenic, likely pathogenic, 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.⁵³ 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 (P/LP) variants (most commonly in *MECP2*, *KCNQ2*, *SCN1A*, *SCN2A*, *STXBP1*, and *PRRT2*). Greater 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 P/LP 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 2017.⁵⁴ 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 old) were included.⁵⁵ Pathogenic and 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.

Table 7. Summary of Key Nonrandomized Study Characteristics

Study	Study Type	Country	Dates	Participants	Treatment 1
McKnight et al (2021)	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)	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)	Cohort	Denmark	2013-2018	Patients referred for genetic testing (n=200)	Gene panel testing
Minardi et al (2020)	Cohort	Italy	2016-2017	Patients with developmental and epileptic encephalopathies (n=71)	Whole exome sequencing
Hesse et al (2018)	Retrospective	U.S.	2014-2016	Patients referred for genetic testing (n=305)	Targeted epilepsy panel
Lindy et al (2018)	Cohort	U.S.	2011-2015	Individuals with epilepsy and/or neurodevelopmental disorders (n=8565)	Genetic testing with multiple gene panels
Miao et al (2018)	Retrospective	China	2015-2017	Patients with epilepsy <14 years of age-old (n=141)	Epilepsy-associated gene panel
Butler et al (2017)	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)	10.9%	<i>SCN1A, MECP2, UBE3A, DEPDC5, PRRT2, CHD2, PCDH19, NPRL3, TSC1, KCNQ2, SCN2A, STCBP1, TBC1D24, HNRNPU, KCNA2, CNTNAP2, EEF1A2, GABRB3, UBE3A, KCNC1, KCNT1, SYNGAP1</i>
Alsubaie et al (2020)	21.5%	<i>ARID1B, UGDH, KCNQ2, PAH, PARS2, ARHGEF9, CNA2, CASK, SLC23A3, TBCD, QARS, CBL, GABRB2, SUOX</i>
Johannesen et al (2020)	23%	<i>SCN1A, KCNT1, STXBP1, CDKL5, CHD2, PURA, ATP6V1A, DCX, GABRB3, GABRG2, GRIN2A, HNRNPU, IQSEC2, KCNA2, KIAA2022, MECP2, MEF2C, MTOR, IPF2PBL, PCDH19, SCN8A, SLC2A1, SYNGAP1, IRF2BPL</i>
Minardi et al (2020)	25.3%	<i>DYNC1, ZBTB20, CACNA1, DYRK1A, ANKRD11, GABRG2, KCNB1, KCNH5, SCN1A, GABRB2, YWHAG, STXBP1, PRODH, LAMB1, PNKP, APC2, RARS2, KIAA2022, SMC1A</i>
Hesse et al (2018)	15.1%	<i>BRAF, DPYD, GABRG2, PAX6, SCN1A, SLC2A1, SLC46A1</i>
Lindy et al (2018)	15.4%	<i>MECP2, KCNQ2, SCN2A, STXBP1, PRRT2</i>
Miao et al (2018)	NR	<i>SCN1A, KCNQ2, KCNT1, PCDH19, STXBP1, SCN2A</i>
Butler et al (2017)	NR	<i>SCN1A, KCNQ2, CDKL5, SCN2A, SCN8A, SCN1B</i>

NR; not reported.

Other Analyses

Kubota et al (2025) conducted a systematic review and meta-analysis on the predictive value of polygenic risk scores for developing epilepsy.⁶² The meta-analysis only included 2 studies and found that the odds ratios for generalized epilepsy were not statistically significant for the top 20% (2.18, 95 % confidence interval [CI] 1.91 to 2.48), 5% (2.65, 95 % CI 2.07 to 3.39), and 0.5% (4.62 95 % CI 3.45 to 6.20) of the polygenic risk score distribution.

PHARMACOGENOMICS OF ANTI-EPILEPTIC MEDICATIONS

Pharmacogenomics of AED 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 epiGAD database identified 32 case-control studies of 20 different genes and their association with medication treatment.⁵⁶ The most common comparison was between responders to medication and nonresponders. Some of the larger representative studies are discussed next.

Other Analyses

Lin et al (2021) conducted a prospective study of 96 children (age <2 years) with epilepsy and neurodevelopmental disability.⁶⁸ 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*.

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)	83 adults with epilepsy in China receiving sustained-release valproic acid monotherapy	<i>CYP2C19</i>	- 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 <i>CYP2C19</i>*2 and <i>CYP2C19</i>*3, but the <i>CYP2C9</i>*13 allele was not.
Zhao et al (2020)	245 children with epilepsy in China receiving levetiracetam alone or in combination with other medications (classified as drug-resistant [n=117] or drug-responsive [n=128])	<i>ABCB1</i> (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 $p<.005$). - No significant difference in variants among drug-resistant and drug-responsive patients.
Lu et al (2017)	124 epileptic Chinese patients receiving oxcarbazepine monotherapy	<i>UGT1A4</i> 142T>G (rs2011425) <i>UGT1A6</i> 19T>G (rs6759892) <i>UGT1A9</i> 1399C>T (rs2741049) <i>UGT2B15</i> 253T>G (rs1902023)	<i>UGT1A9</i> 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 ($p=.01$).

CI: confidence interval; EM: extensive metabolizer; IM: intermediate metabolizer; OR: odds ratio; OXC: oxcarbazepine; PM: poor metabolizer.

Table 10. Pharmacogenomic of AED Response SR & M-A of Characteristics

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

Table 11. Pharmacogenomic of AED Response SR & M-A Results

Study	Association of <i>ABCB1</i> C3435T with risk of drug resistance	Association of <i>MDR1</i> C3435T with risk of drug resistance
Haerian et al (2010)		
OR	1.06	
95% CI	0.98-1.14	
p-value	0.12	
Sun et al (2014)		
OR		1.03
95% CI		0.87-1.22
p-value		0.73

OR: odds ratio; CI: confidence interval; DR: drug resistance.

Shazadi et al (2014) assessed the validity of a gene classifier panel consisting of 5 SNVs for predicting initial AED response and overall seizure control in 2 cohorts of patients with newly diagnosed epilepsy.⁸² A cohort of 115 Australian patients with newly diagnosed epilepsy was used to develop the classifier from a sample of 4041 SNVs in 279 candidate genes via a k-nearest neighbor machine (kNN) learning algorithm, resulting in a 5-SNV 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 and 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 kNN model derived from the original Australian cohort did not predict treatment response in either the Glasgow or the SANAD cohorts. Investigators redeveloped a kNN learning algorithm based on SNV genotypes and drug responses in a training dataset (n=343) derived from the SANAD cohort. None of the 5 SNVs used in the multigenic classifier were 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 (PPV) of 50% (95% CI, 32.8% to 67.2%) and a negative predictive value (NPV) of 54% (95% CI, 41.1% to 66.7%). In a cross-validation analysis, the 5-SNV classifier was significantly predictive of treatment responses among Glasgow cohort patients initially prescribed either carbamazepine or valproate (PPV=67%, NPV=60%; corrected $p=0.018$), but not among those prescribed lamotrigine (corrected $p=1.0$) or other AEDs (corrected $p=1.0$). The 5-SNV classifier was significantly predictive of treatment responses among SANAD cohort patients initially prescribed carbamazepine or valproate (PPV=69%, NPV=56%; corrected $p=0.048$), but not among those prescribed lamotrigine (corrected $p=0.36$) or other AEDs (corrected $p=0.36$).

Pharmacogenomics of AED Adverse Effects

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 [DRESS]) and maculopapular exanthema.⁸³ The GWAS study included 60 cases with phenytoin-related severe cutaneous AEs and 412 population controls, followed by a case-control study including 105 cases with phenytoin-related severe cutaneous AEs (61 with SJS/TEN, 44 with DRESS) 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 AEs (OR=12; 95% CI, 6.6 to 20; $p=1.1 \times 10^{-17}$). In a case-control comparison between the subgroups of 168 patients with phenytoin-related cutaneous AEs and 130 phenytoin-tolerant controls, *CYP2C9**3 polymorphisms were significantly associated with *SJS/TEN* (OR=30; 95% CI, 8.4 to 109; $p=1.2 \times 10^{-19}$), *DRESS* (OR=19; 95% CI, 5.1 to 71; $p=7.0 \times 10^{-7}$), and maculopapular exanthema (OR=5.5; 95% CI, 1.5 to 21; $p=0.01$).

He et al (2014) conducted a case-control study to evaluate the association between carbamazepine-induced *SJS/TEN* and 10 SNVs in the genes *ABCB1*, *CYP3A4*, *EPHX1*, *FAS*, *SNC1A*, *MICA*, and *BAG6*.⁸⁴ 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 polymorphisms between patients with carbamazepine-induced *SJS/TEN* and carbamazepine-tolerant controls ($p=0.011$ and $p=0.007$, respectively). There were no significant differences between *SJS/TEN* cases and carbamazepine-tolerant controls for the remaining SNPs evaluated.

Wang et al (2014) evaluated the association between HLA genes and cross-reactivity of cutaneous adverse drug reactions to aromatic AEDs (carbamazepine, lamotrigine, oxcarbazepine, phenytoin, phenobarbital).⁸⁵ 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 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=0.040). Frequency distributions for testing other HLA alleles did not differ significantly between groups.

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

Study	Study Type	Country	Dates	Participants	Treatment ¹	Treatment ²	Follow-up
Chung et al (2014)	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)	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)	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

PRSCAR: phenytoin-related severe cutaneous adverse reactions; GWAS: genome-wide association study; NR: not reported; CBZ-SJS/TEN: carbamazepine-induced Stevens-Johnson syndrome/toxic epidermal necrolysis; AED: antiepileptic drug; cADR: cutaneous adverse drug reaction.

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

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

95% CI				0.015–1.108
p-value				.040

PRSCAR: phenytoin-related severe cutaneous adverse reactions; OR: odds ratio; CI: confidence interval; CR: cross reactivity.

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.⁸⁶ Given uncertainty related to the underlying causes of SUDEP, there has been interest 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.⁸⁶ Large polyalanine repeat expansions in the *PHOX2B* gene are associated with 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.⁸⁷ 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 to 2936 controls.⁸⁸ 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=0.00015) and *KCNH2* (p=0.0037) 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	Treatment ¹
Bagnall et al (2014)	Retrospective	Australia	1993-2009	Patients with SUDEP (Nn=68)	DNA sequencing analysis of <i>PHOX2B</i>
Coll et al (2016)	Cohort	Italy	NR	Patients with focal or generalized epilepsy and a	Custom resequencing panel

				personal or family history of SUDEP (Nn=14)	
Bagnall et al (2016)	Cohort	Australia	1993-2010	Patients with SUDEP (Nn=61) and controls (n=2936)	Exome sequencing and rare variant collapsing analysis

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

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

Study	Patients with a 15-nucleotide deletion in <i>PHOX2B</i> gene, n/N	Patients with <i>PHOX2B</i> 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)	1/68	0/68			
Coll et al (2016)			4 cases: <i>SCN1A</i> , <i>FBN1</i> , <i>HCN1</i> , <i>SCN4A</i> , <i>EFHC1</i> case: <i>KCNQ1</i>	<i>FBN1</i> , <i>HCN1</i> , <i>SCN4A</i> , <i>EFHC1</i> , <i>CACNA1A</i> , <i>SCN11A</i> , <i>SCN10A</i>	
Bagnall et al (2016)					<i>DEPDC5</i> (p<.001), <i>KCNH2</i> (p<.004)

SUDEP: sudden unexplained death in epilepsy.

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 clinical validity testing for diagnosis of epilepsy is not consistent in showing an association of any specific genetic variant with 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

CLINICAL INPUT FROM PHYSICIAN SPECIALTY SOCIETIES, ACADEMIC MEDICAL CENTERS AND EXTERNAL STAKEHOLDERS (PRACTICING CLINICIANS AND RESEARCH BASED EXPERTS IN THE FIELD)

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

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, BCBSA received input from 2 academic medical centers and 4 specialty societies, 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 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 are issued by, or jointly by, a US 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 (AAN) and Child Neurology Society (CNS) 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, AAN, CNS, and the American Epilepsy Society published joint guidelines on evaluating a first nonfebrile seizure in children.⁸⁸ This guidance was reviewed and reaffirmed in 2020. 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 Commission of Pediatrics issued a task force 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.”

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.

Ongoing and Unpublished Clinical Trials

Three 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
<i>Ongoing</i>			

NCT01858285	Genetics of Epilepsy and Related Disorders	1000	Dec 2030
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NCT: national clinical trial

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) 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 CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Government Regulations

National:

There is no national coverage determination on this topic. In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Local:

Wisconsin Physicians Service Insurance Corporation MAC - Part B 08202 - MAC B J - 08 Michigan, Local Coverage Article: MolDX: Excluded Test List (A55247), Revision effective 02/16/2017. Retired 01/01/18.

“After a review of the current available literature, WPS GHA has determined that testing for the following genes/gene components does not meet the Medicare criteria for a covered service.”

CPT Code As Gene Descriptor

81401	MT-TK
81403	NHLRC1
81403	ARX, dd
81404	ARX, fgs
81404	EPM2A, fgs
81404	SCN1B, fgs
81405	CDKL5, dup_del
81405	CHRNA4
81405	CHRNA2
81405	GABRG2
81405	PCDH19, fgs
81405	SLC2A1, fgs
81405	TSC1, dup_del
81406	ALDH7A1
81406	CDKL5, fgs
81406	EFHC1
81406	KCNQ2, fgs
81406	STXBP1, fgs
81406	TSC1, fgs
81406	TSC2, dup_del

81407	SCN1A, fgs
81407	TSC2, fgs
81479	ARX, panel
81479	CDKL5, panel
81479	SCN1A, dup_del
81479	SCN1A, panel
81479	TSC1_TSC2

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Genetic Testing for FMR1 mutations (including Fragile X Syndrome)
 - Genetic Testing for HLA-B 1502 before Carbamazepine Therapy
 - Genetic Testing for Rett Syndrome
 - Genetic Testing – Whole Exome and Whole Genome
 - Genetic Testing for Cytochrome P450 Polymorphisms
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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through January 2026, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
5/1/14	2/18/14	2/28/14	Joint policy established
9/1/15	6/16/15	7/16/15	Policy position changed from experimental/investigational to established for the evaluation of infantile- or early-childhood-onset epileptic encephalopathies only.
9/1/16	6/21/16	6/12/16	Routine policy maintenance, updated rationale and references. No change in policy status.
9/1/17	6/20/17	6/20/17	Routine maintenance References and rationale updated. Genetics nomenclature updated throughout policy. Updated Medicare information with excluded tests per Feb 2017 article
9/1/18	6/19/18	6/19/18	Updated rationale, eliminated reference 2, added reference 19. No change in policy status.
9/1/19	6/18/19		Routine policy maintenance, added references 19-20 and 34-37.
9/1/20	6/16/20		Routine policy maintenance, no change in policy status.
7/1/21	4/20/21		Removed “early-childhood” from MPS/Inclusion/Exclusion section. Added asterisk stating, “A request for panel testing can be considered established, the panel size should be considered reasonable.” Added code 81419 as established.
7/1/22	4/19/22		Updated rationale section added references 1-25, 44 and 63. No change in policy status.
7/1/23	4/18/23		Updated rationale section, added references 46 and 67. No change in policy status. Vendor managed: N/A. (ds)
7/1/24	4/16/24		Routine policy maintenance, no change in status. Added reference #90. Code 0231U added as E/I.

			Minor changes in inclusion language for clarity. Vendor managed: N/A (ds)
7/1/25	4/15/25		Removed “safety & effectiveness” removed from MPS. Updated rationale, added reference #17. No change in policy status. Vendor managed: N/A (ds).
7/1/26	4/21/26		Inclusion/exclusion section language changes. Rationale updated two references added, some references deleted. No change in status. Formatting changes made. Vendor managed: N/A (ds, lk).

Next Review Date: 2nd Qtr. 2027

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GENETIC TESTING FOR EPILEPSY

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered for the evaluation of infantile- or early- childhood-onset epileptic encephalopathies only; criteria apply
BCNA (Medicare Advantage)	Refer to Medicare information under Government Regulations
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage