Regence

Medical Policy Manual Genetic Testing, Policy No. 80

Genetic Testing for Epilepsy

Effective: January 1, 2024

Next Review: October 2024
Last Review: December 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

There are 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 single-gene pathogenic variants. Genetic testing is commercially available for a large number of genes that may be related to epilepsy.

MEDICAL POLICY CRITERIA

Note: 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., Rett syndrome, neurofibromatosis, tuberous sclerosis) or genetic syndromes associated with cerebral malformations or abnormal cortical development, or metabolic or mitochondrial disorders.

I. Single gene and targeted panel testing for genetic epilepsy syndromes (see Policy Guidelines, Table PG1) may be considered **medically necessary** for individuals suspected of having a genetic epilepsy syndrome when all of the following are met (A. - D.):

   A. Infantile or childhood onset of seizures (younger than 18 years of age at onset); and

B. Clinically severe seizures that affect daily functioning and/or interictal EEG abnormalities; and

C. EEG and neuroimaging by CT or MRI have been performed with no evidence of structural anomalies; and

D. No other clinical syndrome has been identified that would explain the patient's symptoms.

II. Single gene and targeted panel testing for genetic epilepsy syndromes to determine *reproductive carrier status* in prospective parents may be considered **medically necessary** when one or more of the following are met for the epilepsy syndrome being tested:

A. There is at least one first- or second-degree relative diagnosed; or

B. Reproductive partner is known to be a carrier.

III. Epilepsy syndrome genetic testing for reproductive carrier status is considered **not medically necessary** when Criterion II. is not met.

IV. Genetic testing to diagnose genetic epilepsy syndromes is considered **not medically necessary** for patients who do not have severe seizures affecting daily functioning and/or interictal EEG abnormalities, and for patients that have not had EEG and neuroimaging (CT or MRI), or when another clinical syndrome has been identified that would explain a patient's symptoms.

V. Genetic testing to diagnose genetic epilepsy syndromes is considered **investigational** for patients with seizure onset in adulthood (age 18 and older).

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

INFANTILE- AND EARLY-CHILDHOOD-ONSET EPILEPSY SYNDROMES

Variants in a large number of genes have been associated with early-onset epilepsies. Some of these 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*
Neuronal Ceroid-Lipofuscinoses	*PPT1, TPP1, CLN3, CLN5, CLN6, MFSD8, CLN8, CTSD, DNAJC5, CTSF, ATP13A2, GRN, KCTD7*

Syndrome	Associated Genes
Other syndromes	*KCNQ3, GABRG2, GABRD, CHRNA4, CHRNB2, CHRNA2, KCNT1, DEPDC5, CRH, TBC1D24, EFHC1, POLG* *ASAH1, FOLR1, SCN8A, SYNGAP1, SYNJ1, SLC13A5*

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., Rett syndrome, neurofibromatosis, tuberous sclerosis) or genetic syndromes associated with cerebral malformations or abnormal cortical development, or metabolic or mitochondrial disorders.

LIST OF INFORMATION NEEDED FOR REVIEW

SUBMISSION OF DOCUMENTATION

In order to determine the clinical utility of gene test(s), all of the following information must be submitted for review. If any of these items are not submitted, it could impact our review and decision outcome:

- Name of the genetic test(s) or panel test
- Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
- The exact gene(s) and/or mutation(s) being tested
- Relevant billing codes
- Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence testing
- Medical records related to this genetic test:
    - History and physical/chart notes, including *specific* signs and symptoms observed, related to a *specific* epileptic syndrome
    - Known family history related to a specific epileptic syndrome, if applicable
    - Conventional testing and outcomes
    - Conservative treatments, if any

CROSS REFERENCES

1. Cytochrome p450 Genotyping, Genetic Testing, Policy No. 10
2. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20
3. Genetic Testing for Mental Health Conditions, Genetic Testing, Policy No. 53
4. Chromosomal Microarray Analysis (CMA) and Next-generation Sequencing Panels for the Genetic Evaluation of Patients with Developmental Delay, Intellectual Disability, Autism Spectrum Disorder, or Congenital Anomalies, Genetic Testing, Policy No. 58
5. Genetic Testing for Methionine Metabolism Enzymes, including MTHFR, for Indications Other than Thrombophilia, Genetic Testing, Policy No. 65
6. Genetic Testing for Rett Syndrome, Genetic Testing, Policy No. 68
7. Whole Exome and Whole Genome Sequencing, Genetic Testing, Policy No. 76
8. Acthar H.P. Gel, repository corticotropin injection, Medication Policy Manual, Policy No. dru316

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

Seizures Disorders
Partial (focal seizures)
Simple partial seizures (consciousness not impaired)
With motor symptoms
With somatosensory or special sensory symptoms
With autonomic symptoms or signs
With psychic symptoms (disturbance of higher cerebral function)
Complex partial (with impairment of consciousness)
Simple partial onset followed by impairment of consciousness
Impairment of consciousness at outset
Partial seizures evolving to secondarily generalized seizures
Generalized seizures
Nonconvulsive (absence)
Convulsive
Unclassified seizures

Adapted from Berg (2010).[2]

More recently, the concept of genetic epilepsies has emerged as a way of classifying epilepsy. Many experts now refer to “genetic generalized epilepsy” as an alternative classification for seizures previously called “idiopathic generalized epilepsies.” The ILAE report, published in 2010, offers the following alternative classification (see Table 2).[2]

Table 2. Alternative Classifications

Classification	Condition Definition
Genetic epilepsies	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.
Structural/metabolic	Conditions having a distinct structural or metabolic condition that increases the likelihood of seizures. Structural conditions include a variety of central nervous system abnormalities such as stroke, tumor or trauma, and metabolic conditions include a variety of encephalopathic abnormalities that predispose to seizures. These conditions may have a genetic etiology, but the genetic defect is associated with a separate disorder that predisposes to seizures.
Unknown cause	Conditions for which the underlying etiology for the seizures cannot be determined and may include both genetic and nongenetic causes.

For this evidence review, the ILAE classification is most useful. 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 age of onset.

The category of genetic epilepsies includes a number of rare epilepsy syndromes that present in infancy or early childhood.[1 3] 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 development 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.[2] A partial list of severe early-onset epilepsy syndromes is as follows:

- Dravet syndrome (also known as severe myoclonic epilepsy in infancy 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.[4] 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.[5] 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 particular combinations 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 currently being frequently discovered.[6]

Some of the most common genes associated with genetic epileptic syndromes are listed in Table 3.

Table 3. 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.[7]

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 (2016) reviewed comprehensive epilepsy panels from seven 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.[8] 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.[9]

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 one agent is complex. Approximately one-third of patients are considered refractory to medications, defined as inadequate control of symptoms with a single medication.[10] 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 labeling for carbamazepine.[11]

REGULATORY STATUS

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. Commercially available genetic tests for epilepsy are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature[12] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term “variant” is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as “mutation.” Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

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.

The genetic epilepsies are discussed in two 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.

Validation of the clinical use of any genetic test focuses on three main principles:

1. The analytic validity of the test, which refers to the technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent;
2. The clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
3. The clinical utility of the test, i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

EARLY-ONSET EPILEPSY AND EPILEPTIC ENCEPHALOPATHIES

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 patients 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.

Table 4. 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 (GEFS+)	*SCN1A*, *SCN2A*, *SCN1B*, *GABRG2*
Epilepsy and mental retardation limited to females (EFMR)	*PCDH19*
Nocturnal frontal lobe epilepsy	*CHRNA4*, *CHRNB2*, *CHRNA2*

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 encephalopathies[13] and *SLC13A5* variants in families with pedigrees consistent with autosomal recessive epileptic encephalopathy.[14]

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

The potential beneficial outcomes of primary interest would be improvement in symptoms (particularly reduction in seizure frequency), functioning, and quality of life. 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 patients 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 effects from that treatment. False-negative test results could lead to unnecessary surgeries.

Analytic Validity

Assessment of analytic validity focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinical Validity

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.[15 16] In a 2006 series of 64 patients, 51 (79%) were found to have *SCN1A* pathogenic variants.[16] Among eight infants who met clinical criteria for Dravet syndrome in a 2015 population-based cohort, six had a pathogenic *SCN1A* variant, all of which were *de novo*.[17]

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 6 summarizes examples of diagnostic yield in children with epileptic encephalopathy.

Table 6. Genetic Testing Yields in Pediatric Patients with Epilepsy

Study (Year)	Population	Genetic Testing	Results
Bayanova (2023)[18]	20 children with epilepsy onset before age three	Whole genome sequencing	• Diagnostic yield: pathogenic and likely pathogenic variants identified in 70% of patients • Genes with novel variants: *KCNQ2, CASK, WWOX, MT-CO3, GRIN2D, and SLC12A5*
Ko (2023)[19]	1,213 children with neurodevelopmental disorders, 168 of whom had epilepsy	Whole exome sequencing	• Diagnostic yield: 39.3% of patients with neurodevelopmental disorders received genetic diagnosis • Epilepsy-associated variants identified in 77% of patients with epilepsy
Pinto (2023)[20]	110 children with epilepsy	Next-generation sequencing, targeted gene panel	• Diagnostic yield: 34% pathogenic results overall • 54% of pathogenic variants identified in *SCN1A, SCN2A, MECP2, KCNT1, PCDH19, SPTAN1, CACNA1A,* and *UBE3A*
Scheffer (2023)[21]	103 children and infants with developmental and epileptic encephalopathies	Epilepsy panel, singleton exome sequencing	• Diagnostic yield: 35% of patients had 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 (2021)[22]	221 children with epilepsy	Whole exome sequencing	• Diagnostic yield: 64.5% of patients with epilepsy and developmental

Study (Year)	Population	Genetic Testing	Results
			delay/intellectual disability; 18.9% of patients with only epilepsy (p<.0001) • 48 of 87 variants detected were novel • Genes with novel variants: *NCL, SEPHS2, PA2G4, SLC35G2, MYO1C, GPR158,* and *POU3F1*
Kim (2021)[23]	59 patients with infantile-onset epilepsy and prior negative targeted gene panel testing	Whole exome sequencing	• Diagnostic yield: 8% more than with targeted gene panel testing • Genes with pathogenic/likely pathogenic variants: *FARS2, YWHAG, KCNC1, DYRK1A, SMC1A, OGT,* and *FGF12* • Newly associated genes: *YWHAG*, *KCNC1*, and *FGF12*
Palmer (2021)[24]	30 patients with developmental and epileptic encephalopathies with prior negative genetic testing	Whole exome sequencing	Diagnostic yield: • 53% in 15 patients with prior exome sequencing (20% had complex structural variants) • 68% in 15 patients with prior multigene panel testing
Salinas (2021)[25]	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 a mean of 29 months (based on new literature) • Genes with novel variants: *CHD2, COL4A1, FOXG1, GABRA1, GRIN2B, HNRNPU, KCNQ2, MECP2, PCDH19, SCN1A, SCN2A, SCN8A, SLC6A1, STXBP1,* and *WWOX*
Sun (2021)[26]	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*
Gall (2021)[27]	211 patients 24 to 60 months of age with firs unprovoked seizure at/after 24 months and at least one additional finding	Epilepsy panel	• Genetic diagnosis established in 20.4% • Predominant molecular diagnosis was neuronal ceroid lipofuscinosis type 2
Lee (2021)[28]	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
Mitta (2020)[29]	82 children with infantile-onset developmental-epileptic encephalopathies	Epilepsy panel	Diagnostic yield: • 31.7% overall with pathogenic/likely pathogenic variants • 50% for Ohtahara syndrome • 13.3% for West syndrome • 67% for epilepsy of infancy with migrating partial seizures due to CACNA1A and KCNT1 variants

Study (Year)	Population	Genetic Testing	Results
Lee (2020)[30]	24 patients with Dravet syndrome	Targeted panel with 40 epilepsy genes	Disease-causing variants (SCN1A and PCDH19) identified in 75% of patients
Lee (2020)[31]	48 patients with early-onset epileptic encephalopathies with burst suppression	Epilepsy panel	Diagnostic yield was 64.6% overall The most common involved genes were: • STXBP1 (27.1%) • KCNQ2 (10.4%) • SCN2A (10.4%) • DEPDC5 (6.3%) • CASK (2.1%) • CDKL5 (2.1%) • GNAO1 (2.1%) • SLC6A8 (2.1%) • LIS1 (2.1%)
Lee (2020)[32]	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
Stödberg (2020)[33]	116 children with epilepsy onset before the age of 2 years and	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).
Angione (2019)[34]	77 patients with a potential diagnosis of epilepsy with myoclonic-atonic seizures	Microarray, epilepsy panel, or WES	• 6 of 37 microarrays identified copy number variants • 2 of 51 panel tests identified pathogenic or likely pathogenic variants (in SCN1A and GABRG2) • 3 of 6 WES tests identified variants that were believed to explain the phenotype
Balciuniene (2019)[35]	151 patients with idiopathic epilepsy	Sequence and copy number analysis of 100 epilepsy genes; reflex to exome sequencing	Diagnostic yield: • 15.3% overall from initial testing • 17.9% including exome sequencing • 38.6% in patients with epilepsy onset in infancy (age 1-12 months) Diagnostic findings reported in: • SCN1A (n=4) • PRRT2 (n=3) • STXBP1 (n=2) • IQSEC2 (n=2) • ATP1A2, ATP1A3, CACNA1A, GABRA1, KCNQ2, KCNT1, SCN2A, SCN8A, DEPDC5, TPP1, PCDH19, and UBE3A (all n = 1)
Yang (2019)[36]	733 patients with epilepsy onset by one year of age	Exome sequencing or targeted sequencing (2742 gene panel)	Diagnostic yield: • 26.7% for targeted sequencing • 42% for exome sequencing • 48.7% of diagnostic findings related to 12 genes
Jang (2019)[37]	112 patients with seizure onset before 12 months with unknown cause	Deep targeted sequencing with a custom-designed capture probe	Diagnostic yield: • 47.3% overall • 61.5% in patients with neonatal onset • 50.0% in patients with early infantile onset

Study (Year)	Population	Genetic Testing	Results
Symonds (2019)[38]	333 patients presenting with epilepsy by 36 months of age	104-gene epilepsy panel	• 25% of patients had a diagnostic genetic finding. • Most common single-gene epilepsies were PRRT2, SCN1A, KCNQ2, and SLCA1
Esterhuizen (2018)[39]	22 infants with provisional diagnosis of DS	Target resequencing of DS-associated genes	Disease-causing variants (SCN1A and PCDH) identified in 45.5% of patients
Peng (2018)[40]	273 pediatric patients with drug-resistant epilepsy	WES, epilepsy panel, or clinical WES panel	93 likely disease-causing variants found in 31.5% of patients: • SCN1A (24.4%) • TSC2 (8.1%) • SCN8A (5.8%) • CDKL5 (5.8%)
Staněk (2018)[41]	151 unrelated patients with severe childhood epilepsy	Epilepsy panel of 112 genes	Diagnostic yield: 25.8% overall • 61.9% in patients with seizure onset within the first four weeks of life • 35.8% in patients with seizure onset between four weeks and 12 months of age • 11.1% in patients with seizure onset between 12 and 36 months of age • 15.6% in patients with seizure onset after 36 months of age
Kothur (2018)[42]	105 patients with epilepsy of unknown cause	Epilepsy panel of 71 genes or 47 genes	Diagnostic yield: 28.5% overall • 52% of early onset including Ohtahara syndrome patients • 60% of Dravet syndrome patients • 26% of epileptic encephalopathy not otherwise specified • 0% of generalized epilepsy patients
Berg (2017)[43]	327 infants and young children with newly diagnosed with epilepsy	Various forms	Diagnostic yield: 40.4% overall • 44.1% of 59 with karyotyping • 17.0% of 188 with microarrays • 27.2% of 114 with epilepsy panels • 33.3% of 33 with whole exome sequencing • 20% of 20 with mitochondrial panels
Moller (2016)[44]	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 (2016)[45]	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 two mo of life
Wirrell (2015)[46]	81 patients with infantile spasms and no obvious cause at diagnosis	Various forms	Diagnostic yield: • 0% for karyotyping • 11.3% of 62 for aCGH • 33.3% of three for targeted chromosomal SNV analysis • 11.1% of nine for targeted single-gene analysis

Study (Year)	Population	Genetic Testing	Results
			• 30.8% of 26 for epilepsy gene panels
Mercimek-Mahmutoglu (2015)[47]	110 patients with epileptic encephalopathies	aCGH, NGS	Diagnostic yield: • 2.7% for aCGH • 12.7% for targeted NGS
Hrabik (2015)[48]	147 children with epilepsy	SNV microarray	• Diagnostic yield: 7.5% clinically significant abnormal results

aCGH: array comparative genomic hybridization; NGS: next-generation sequencing; SNV: single-nucleotide variant.

Clinical Utility

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 randomized controlled trials.

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, i.e., 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.

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 (e.g., carbamazepine).[16 49] Also, some experts suggest that patients with Dravet syndrome may be more susceptible to particular AEDs, including clobazam and stiripentol.[4] In contrast, the usual medical treatment of infantile spasms is hormonal therapy with corticotropin (adrenocorticotropic hormone),[50-52] and usual first-line treatment of Lennox-Gastaut is sodium valproate.[53] Therefore, confirming the specific diagnosis leads to changes in therapy expected to improve outcomes.

Scheffer (2023) reported diagnostic yield (Table 6) and assessed treatment impact of exome sequencing in 103 children and infants with developmental and epileptic encephalopathies.[21] 13 of 36 patients with a known genetic cause for their condition had management implications. These included treatment for the underlying biochemical abnormality (one patient with *SLC2A1*), choice of antiseizure medication (four patients with *KCNQ2*, three with *SCN1A*, two with *SCN8A*, and one with *SCN2A*), choice of other medication (one patient with *ATP1A3*), and screening for disease-related complications (one patient with *COL4A1*).

In an international, cross-sectional, retrospective study, McKnight (2022) evaluated the association of genetic diagnoses with clinical management and outcomes for epilepsy patients.[54] 418 patients with epilepsy, regardless of sociodemographic features or age, whose genetic test results indicated a pathogenic or likely pathogenic variant in at least one gene were included. Genetic diagnosis was associated with changes in clinical management for 208 patients (49.8%) and usually (81.7% of the time) within three months of receiving the result. The most common clinical management changes were addition of a new medication (78 [21.7%]), initiation of medication (51 [14.2%]), referral of a patient to a specialist (48 [13.4%]), vigilance for subclinical or extra-neurological disease features (46 [12.8%]), and cessation of a medication (42 [11.7%]). Follow-up information was gathered for 167 patients at a mean follow-up time of 584 days. 125 (74.9%) reported positive outcomes, 108 (64.7%) reported reduction or elimination of seizures, 37 (22.2%) had decreases in the severity of other clinical signs, and 11 (6.6%) had reduced medication adverse effects. A few patients reported worsening of outcomes, including a decline in their condition (20 [12.0%]), increased seizure frequency (6 [3.6%]), and adverse medication effects (3 [1.8%]). No clinical management changes were reported for 178 patients (42.6%).

Boonsimma (2022) reported the diagnostic yield and treatment impact of exome sequencing in a cohort of 103 unrelated patients with pharmacoresistant epilepsy presenting during infancy at a center in Thailand.[55] The testing identified a molecular cause in 64 patients (62%) and a partial cause in two patients. Eight of these patients had specific treatment associated with the disorder, including six patients with pyridoxine-dependent epilepsy. Management changes were made for 43% of the patients as a result of the testing.

A single-center retrospective study by Hoelz (2020) described the effect of next-generation sequencing on clinical decision-making among children with epilepsy.[56] 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).

Ream (2014) retrospectively reviewed a single center's use of clinically available genetic tests in the management of pediatric drug-resistant epilepsy.[57] The study included 25 newly evaluated patients with pediatric drug-resistant epilepsy. Fourteen (56%) of 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=0.005) and generalized epilepsy (p=0.028). 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; three of nine patients with Lennox-Gastaut syndrome had identified variants (one with a CDKL5 variant, one with an SCL9A6 variant, one with both SCN1A and EFHC1 variants). Two (6.9%) patients had diagnostic variants not suspected based on their clinical phenotypes. In eight (27.6%) patients, genetic test results had potential therapeutic implications. However, only one patient had significantly reduced seizure frequency; the patient received stiripentol following a positive SCN1A variant test.

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

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 patients 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.

Analytic Validity

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinical Validity

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 SNVs 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.

<u>Diagnosis of Epilepsy</u>

McKnight (2022) conducted targeted gene panel testing (range, 89 to 189 genes) using next-generation sequencing in a cohort of 2,008 adults with epilepsy.[58] 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).

Zacher (2021) reported genetic testing results in 150 adult/elderly individuals (age range 18 to 84 years) with neurodevelopmental disorders with epilepsy.[59] Pathogenic or likely pathogenic variants were identified in 71 individuals (47.3%). The yield was 58.3% in individuals with anecdotal evidence of exogenic early-life events (e.g., nuchal cord, complications at delivery) with alleged/unproven association to the disorder. Causative variants were identified by conventional karyotyping in three individuals (2.0%), CMA in 24 individuals (16%), and NGS in 50 individuals. Causative variants were identified using exome sequencing in 13 of the 71 individuals in whom exome sequencing was performed. The most common diagnosis was 15q13.3 microdeletion syndrome (4 of 150 individuals, 2.7%).

Alsubaie (2020) evaluated the diagnostic yield of whole exome sequencing among 420 patients at a single center in Saudi Arabia.[60] 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 four additional variants (positive yield of 13.3%).

Minardi (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.[61] 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.

Johannesen (2020) reported the diagnostic yield for genetic testing in a group of 200 adult (age 18 to 80 years) epilepsy patients, 91% of whom were comorbid for intellectual disability.[62] A genetic diagnosis was made in 46 patients (23%). Of those, 48% were found to have a variant in *SCN1A, KCNT1,* or *STXBP1*. Variants were also found in *SLC2A1, ATP6A1V, HNRNPU, MEF2C,* and *IRF2BPL*. Treatment changes based on genetic results were made in 17% of patients with a genetic diagnosis.

Borlot (2019) published a single center retrospective study that reported the diagnostic yield of a commercial epilepsy gene panel in adults with chronic epilepsy and intellectual disability.[63]

Of the 64 patients tested, 14 (22%) were found to have pathogenic or likely pathogenic variants in the following genes: *SCN1A, GABRB3, UBE3A, KANSL1, SLC2A1, KCNQ2, SLC6A1, HNRNPU, STX1B, SCN2A, PURA,* and *CHD2*. The results of genetic testing led to a change in diagnosis in 57% of patients with identified pathogenic or likely pathogenic variants.

Hesse (2018) published a retrospective analysis of 305 patients (age range under one to 69 years old with 88% <18 years old) referred for genetic testing with a targeted epilepsy panel between 2014 and 2016.[64] 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 seven genes (*BRAF, DPYD, GABRG2, PAX6, SCN1A, SLC2A1,* and *SLC46A1*).

Lindy (2018) published an industry sponsored analysis of 8,565 consecutive individuals with epilepsy and/or neurodevelopmental disorders who underwent genetic testing with multigene panels.[65] Positive results were reported in 1,315 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*.

Miao (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.[66] 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.

Butler (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% under five years old) were included.[67] 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.

Tan and Berkovic (2010) published an overview of genetic association studies using records from Epilepsy Genetic Association Database.[68] Reviewers identified 165 case-control studies published between 1985 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 (GGE). Most studies had relatively small sample sizes, with a median of 104 cases (range, 8 to 1361) and 126 controls (range, 22-1390). 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 less than 0.01 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 two epilepsy clinical subtypes, GGE and focal epilepsy.[69] 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 8,696 cases and 26,157 controls. Cases with epilepsy were categorized as having GGE, 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 GGE, a locus at 2p16.1 (*VRK2* or *FANCL*) was significantly associated with epilepsy ($p=9.99\times10^{-9}$). No SNVs were significantly associated with focal epilepsy.

Some of the larger GWAS are described here. The EPICURE Consortium published one of the larger GWAS of GGE in 2012.[70] It included 3020 patients with GGE and 3954 control patients, all of European ancestry. A two-stage approach was used, with a discovery phase and a replication phase, to evaluate a total of 4.56 million SNVs. In the discovery phase, 40 candidate SNVs were identified that exceeded the significance for the screening threshold (1×10^{-5}), although none reached the threshold defined as statistically significant for GWAS (1×10^{-8}). After stage 2 analysis, four SNVs identified had suggestive associations with GGE on genes *SCN1A*, *CHRM3*, *ZEB2*, and *NLE2F1*.

A second GWAS with a relatively large sample size of Chinese patients was also published in 2012.[71] Using a similar two-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.

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 (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 on combined analysis.[72] Nurmohamed (2010) performed a meta-analysis of nine case-control studies that evaluated the association between the *ABC1* gene variants and epilepsy.[73] It included 2454 patients with epilepsy and 1542 control patients. No significant associations were found. One meta-analysis that did report a significant association was published by Kauffman (2008).[74] They evaluated the association between variants in the *IL1B* gene and temporal lobe epilepsy and febrile seizures, using data from 13 studies (1866 patients with epilepsy, 1930 controls). Combined analysis showed a significant relation between one SNV (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=0.01). Another meta-analysis reporting a positive association was published by Tang (2014).[75] The authors evaluated the association between the *SCN1A* IVS5N+5GNA variant and susceptibility to epilepsy with febrile seizures. The analysis included six studies with 2719 cases and 2317 controls. There was a significant association between *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. Van Podewils (2015) evaluated the association between sequence variants in *EFHC1* and phenotypes and outcomes in 38 probands with juvenile myoclonic epilepsy, along with three family members.[76] 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=0.022), high risk of status epilepticus (p=0.001), and decreased risk of bilateral myoclonic seizures (p=0.05).

Pharmacogenomics of Antiepileptic Medications

Pharmacogenomic of AED Response

Lin (2021) conducted a prospective study of 96 children less than two years of age with epilepsy and neurodevelopmental disability.[77] 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=0.03). Specific genes associated with drug-resistant epilepsy included *TBC1D24*, *SCN1A*, *PIGA*, *PPP1CB*, and *SZT2*.

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.[68] The most common comparison was between responders to medication and nonresponders. Some of the larger representative studies are discussed next.

Li (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.[78] 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 odds ratio of 1.07 in an allele model (95% CI 0.95 to 1.19; p=0.26) and 1.05 in a genotype model (95% CI 0.89 to 1.24; p=0.55).

Kwan (2008) compared the frequency of SNVs on the *SCN1A*, *SCN2A*, and *SCN3A* genes in 272 drug-responsive patients and 199 drug-resistant patients.[79] Twenty-seven candidate SNVs were evaluated, selected from a large database of previously identified SNVs. One SNV identified on the *SCN2A* gene (rs2304016) had a significant association with drug resistance (OR=2.1; 95% CI 1.2 to 3.7; p<0.007).

Jang (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.[80] 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 two variants, one on the *SCN2A* gene and the other on the *SCN1B* gene, though falling below their cutoff for statistical significance (p=0.055).

Other representative studies that have reported associations between genetic variants and AED response are summarized in Table 7.

Table 7: Genetic Variants and Antiepileptic Drug Response

Study	Population	Genes	Overview of Findings
Feria-Romero[81]	55 children: 32 with controlled epilepsy and 23 with drug-resistant epilepsy	• *SCN1A* • *CYP2C9* • *CYP2C19* • *CYP2D6* • *CYP3A4* • *CYP2B6*	Polymorphisms significantly associated with drug-resistant epilepsy (p=0.021): • *SCN1A*: T1025C (rs10497275), C2177A (rs10198801), and G32431A/C/T, G32432A, G32433A (rs67636132) • *CYP2D6*: C100T (rs1065852) • *CYP3A4*: C313T (rs2242480) • Number of missense variants significantly higher in drug-resistant epilepsy (p=0.014)
Song (2020)[82]	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 (2020)[83]	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])	*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=0.021), and 3435-TT compared to CC and CT carriers (both p<0.005) • No significant difference in variants among drug-resistant and drug-responsive patients
Lu (2017)[84]	124 epileptic Chinese patients receiving OXC 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 vs CC 22.24 mg/L, p<0.05) and poorer seizure control than noncarriers (p=0.01)
Hashi (2015)[85]	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 (2015)[86]	184 epileptic patients receiving OXC 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=0.002,

Study	Population	Genes	Overview of Findings
			uncorrected), which remained significant after Bonferroni correction
Guo (2015)[87]	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=0.026)
Ma (2014)[88]	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<0.001, uncorrected) • *SCN1A* IVS5-91G>A AA more prevalent in drug-resistant than drug-responsive patients receiving carbamazepine/OXC (OR=3.55; 95% CI 1.62 to 7.78; p=0.002, 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=0.007; OR=2.05; 95% CI 1.31 to 3.19; p=0.001, respectively, uncorrected)
Radisch (2014)[89]	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 (2013)[90]	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<0.05) • Other studied variants not associated with carbamazepine pharmaco-resistance
Taur (2014)[91]	115 epileptic patients treated with phenytoin, phenobarbital, and/or carbamazepine	• *ABCB1* (c.3435T) • *CYP2C9* (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)

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

Several meta-analyses evaluating pharmacogenomics were identified. Haerian (2010) examined the association between SNVs on the *ABCB1* gene and drug resistance in 3231 drug-resistant patients and 3524 controls from 22 studies.[92] 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=0.12). There was also no significant association for subgroup analysis by ethnicity.

In a separate meta-analysis, Sun (2014) evaluated eight 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.[93] In the pooled analysis, the *MDR1* C3435T variant was not significantly associated with risk of drug resistance.

Shazadi (2014) assessed the validity of a gene classifier panel consisting of five SNVs for predicting initial AED response and overall seizure control in two cohorts of patients with newly diagnosed epilepsy.[94] 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 learning algorithm, resulting in a 5-SNV classifier. The classifier was validated in two 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 SNV genotypes and drug responses in a training dataset (n=343) derived from the SANAD cohort. None of the five SNVs 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-SNV 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=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 (positive predictive value, 69%; negative predictive value, 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 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).

Chung (2014) evaluated genetic variants associated with phenytoin-induced severe cutaneous adverse events (SJS/TEN, drug reactions with eosinophilia and systemic symptoms) and maculopapular exanthema.[95] 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; $p=1.1\times10^{-17}$). 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; $p=1.2\times10^{-19}$), drug reactions with eosinophilia and systemic symptoms (OR=19; 95% CI 5.1 to 71; $p=7.0\times10^{-7}$), and maculopapular exanthema (OR=5.5; 95% CI 1.5 to 21; p=0.01).

He (2014) conducted a case-control study to evaluate the association between carbamazepine-induced SJS/TEN and 10 SNVs in the *ABCB1*, *CYP3A4*, *EPHX1*, *FAS*, *SNC1A*, *MICA*, and *BAG6* genes.[96] 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=0.011 and p=0.007, respectively). There were no significant differences between SJS/TEN cases and carbamazepine-tolerant controls for the remaining SNVs evaluated.

Wang (2014) evaluated the association between *HLA* genes and cross-reactivity of cutaneous adverse drug reactions to aromatic AEDs (carbamazepine, lamotrigine, oxcarbazepine, phenytoin, phenobarbital).[97] The study included 60 patients with a history of aromatic AED-induced cutaneous adverse drug reactions, including SJS/TEN and maculopapular eruption, who were reexposed 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=0.040). Frequency distributions for testing other *HLA* genes did not differ significantly between groups.

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.[98] Given uncertainty related to the underlying causes of SUDEP, there has been interested in identifying genetic associations with SUDEP.

Bagnall (2014) evaluated the prevalence of sequence variations in the *PHOX2B* gene in 68 patients with SUDEP.[98] 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, one patient was found to have a 15-nucleotide deletion in the *PHOX2B* gene, but no *PHOX2B* polyalanine repeat expansions were found.

Coll (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 two postmortem cases.[99] In four cases, rare variants were detected with complete segregation in the *SCN1A*, *FBN1*, *HCN1*, *SCN4A*, and *EFHC1* genes, and in one 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 (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.[100] 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 nine (15%) cases had candidate pathogenic variants in dominant cardiac arrhythmia genes. Fifteen (25%) cases had variants or candidate pathogenic variants in epilepsy genes; six 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.

Clinical Utility

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 randomized controlled trials.

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 GGE. 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.

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.

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, 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 (≈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 a meaningful 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 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 AED treatment response, AED adverse effect risk, epilepsy phenotype, and risk of sudden unexplained death in epilepsy. 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 the effects of the technology on health outcomes.

PRACTICE GUIDELINE SUMMARY

AMERICAN ACADEMY OF NEUROLOGY AND CHILD NEUROLOGY SOCIETY

The American Academy of Neurology and Child Neurology Society published joint guidelines on the diagnostic assessment of children with status epilepticus.[101] These guidelines were reviewed and reaffirmed in 2016. 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.”

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[52]:

- “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.”

SUMMARY

DIAGNOSIS

Research shows that for patients with infantile- or early-childhood-onset epilepsy genetic testing can aid with diagnosis. For Dravet syndrome, genetic testing for *SCN1A* can identify about 80% of patients. For other early-onset epilepsies, studies report detection rates ranging from 7.5% to 57%. A positive test result may lead to targeted medication management and avoidance of other diagnostic tests. Overall, genetic testing for epilepsy syndromes can improve health outcomes for these patients and therefore may be considered medically necessary when criteria are met.

For patients who do not have severe seizures affecting daily functioning and/or interictal EEG abnormalities, and for patients that have not had EEG and neuroimaging (CT or MRI), or when another clinical syndrome has been identified that would explain a patient’s symptoms, genetic testing is unlikely to be informative. Clinical guidelines based on evidence do not recommend genetic testing in these situations. Therefore, this testing is considered not medically necessary.

While some adult-onset epilepsies may have a genetic component, there is not enough research to show that genetic testing can improve health outcomes for these patients. Evidence linking genetic variants and antiepileptic drug (AED) treatment response, AED adverse effect risk, epilepsy phenotype, and risk of sudden unexplained death in epilepsy is limited. In addition, clinical practice guidelines do not recommend genetic testing for adult-onset epilepsies. Therefore, this testing is considered investigational.

REPRODUCTIVE CARRIER TESTING

There is enough research to show that reproductive carrier testing for patients that are at increased risk of being asymptomatic carriers of genetic epilepsy syndromes can help to inform reproductive decision-making. Therefore, testing in these individuals may be considered medically necessary.

There is enough research to show that targeted reproductive carrier testing for genetic epilepsy syndromes is unlikely to improve health outcomes and inform reproductive decision-making in individuals that are not at increased risk of being carriers of the disorder. Therefore, reproductive carrier testing for genetic epilepsy syndromes is considered not medically necessary when individuals do not have an affected first- or second-degree relative and the reproductive partner is not known to be a carrier.

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CODES

Codes	Number	Description
CPT	0232U	CSTB (cystatin B) (eg, progressive myoclonic epilepsy type 1A, Unverricht-Lundborg disease), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, short tandem repeat (STR) expansions, mobile element insertions, and variants in non-uniquely mappable regions
	81188	CSTB (cystatin B) (eg, Unverricht-Lundborg disease) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
	81189	;full gene sequence
	81190	;known familial variant(s)
	81401	Molecular pathology procedure, Level 2
	81403	Molecular pathology procedure, Level 4
	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
	81479	Unlisted molecular pathology procedure
HCPCS	None	

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