



Louisiana

Genetic Testing for Epilepsy

Policy # 00401

Original Effective Date: 02/19/2014

Current Effective Date: 05/16/2018

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Cytochrome p450 Genotyping is addressed separately in medical policy 00169.

Note: Genetic Testing for Rett Syndrome is addressed separately in medical policy 00369.

Note: Genetic Testing for FMR1 Mutations (Including Fragile X Syndrome) is addressed separately in medical policy 00380.

Note: Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders is addressed separately in medical policy 00389.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider genetic testing for genes associated with infantile- and early childhood-onset epilepsy syndromes in individuals with infantile- and early-childhood-onset epilepsy syndromes in which epilepsy is the core clinical symptom (See Policy Guidelines section) to be **eligible for coverage** when patient selection criteria is met.

Patient Selection Criteria

Coverage eligibility will be met if positive test results may:

1. Lead to changes in medication management; AND/OR
2. Lead to changes in diagnostic testing such that alternative potentially invasive tests are avoided; AND/OR
3. Lead to changes in reproductive decision making.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers genetic testing for epilepsy in all other situations to be **investigational**.*

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Policy Guidelines

POLICY SCOPE

Included Tests and Conditions

This policy addresses testing for epilepsy that might have a genetic etiology. The International League Against Epilepsy (ILAE) has classified epilepsy as having underlying genetic cause or etiology when, as best understood, the epilepsy is the direct result of a known or presumed genetic defect and seizures are the core symptom of the disorder and for which there is no structural or metabolic defect predisposing to epilepsy (Berg et al, 2010).

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

Excluded Tests and Conditions

This policy does not address testing for genetic syndromes that have a wider range of symptomatology, of which seizures may be one, such as the neurocutaneous disorders (e.g., neurofibromatosis, tuberous sclerosis) or genetic syndromes associated with cerebral malformations or abnormal cortical development, or metabolic or mitochondrial disorders.

Testing that is limited to genotyping of *CYP450* genes is addressed separately (medical policy 00169).

This policy does not address the use of genotyping for the *HLA-B*1502* allelic variant in patients of Asian ancestry prior to considering drug treatment with carbamazepine due to risks of severe dermatologic reactions. This testing is recommended by the U.S. Food and Drug Administration (FDA) labeling for carbamazepine (Food and Drug Administration, 2014).

This policy also does not address the testing for variants in the mitochondrial deoxyribonucleic acid (DNA) polymerase gamma (*POLG*) gene in patients with clinically suspected mitochondrial disorders prior to initiation of therapy with valproate. Valproate's label contains a black box warning related to increased risk of acute liver failure associated with the use of valproate in patients with *POLG* gene-related hereditary neurometabolic syndromes. FDA labeling states that valproate "is contraindicated in patients known to have mitochondrial disorders caused by *POLG* mutations and children under two years of age who are clinically suspected of having a *POLG*-related disorder" (Food and Drug Administration, 2015).

MEDICALLY NECESSARY STATEMENT DEFINITIONS AND TESTING STRATEGY

The medically necessary statement refers to epilepsy syndromes that present in infancy or early childhood, are severe, and are characterized by epilepsy as the primary manifestation, without associated metabolic or brain structural abnormalities. As defined by the ILAE, these include epileptic encephalopathies, which are electroclinical syndrome associated with a high probability of encephalopathic features that present or worsen after the onset of epilepsy. Other clinical manifestations, including developmental delay and/or

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intellectual disability, may be present secondary to the epilepsy itself. Specific clinical syndromes based on the ILAE classification include:

- 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)
- Epileptic encephalopathy with continuous spike-and-wave during sleep
- GEFS+ syndrome (generalized epilepsies with febrile seizures plus)
- Ohtahara syndrome (also known as early infantile epileptic encephalopathy with burst suppression pattern)
- Landau-Kleffner syndrome
- West syndrome
- Glucose transporter type 1 deficiency syndrome.

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

Table PG1. Single Genes Associated With Epileptic Syndromes

Syndrome	Associated Genes
Dravet syndrome	<i>SCN1A, SCN9A, GABRA1, STXBP1, PCDH19, SCN1B, CHD2, 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>

Application of the Medically Necessary Policy Statement

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

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

Testing Strategy

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

Given the genetic heterogeneity of early-onset epilepsy syndromes, a testing strategy that uses a multigene panel may be considered reasonable. Criteria for use of whole exome sequencing are outlined in medical policy 00389 (whole exome and whole genome sequencing for diagnosis of genetic disorders).

Background/Overview

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.

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 ILAE developed the classification system that is widely used for clinical care and research purposes (see Table 1). 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

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Generalized seizures

Nonconvulsive (absence)

Convulsive

Unclassified seizures

Adapted from Berg et al (2010).

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).

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 for genetic epilepsies 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 (GGE) refers to patients who have convulsive (grand mal) seizures, while genetic absence epilepsy refers to patients with nonconvulsive (absence) seizures. The disorders are also sometimes classified by the age of onset.

The category of genetic epilepsies includes a number of rare epilepsy syndromes that present in infancy or early childhood. 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

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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. A partial list of severe early-onset epilepsy syndromes is as follows:

- Dravet syndrome
- EFMR syndrome
- Nocturnal frontal lobe epilepsy
- GEFS+ syndrome
- 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. 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. A combination of risk-associated genes, together with environmental factors, determines whether the clinical phenotype of epilepsy occurs. In this model, individual genes that increase the susceptibility to epilepsy have a relatively weak impact. Multiple genetic defects, and/or a particular combination of genes, probably increase the risk by a greater amount. However, it is not well-understood how many abnormal genes are required to exceed the threshold to cause clinical epilepsy, nor is it understood which combination of genes may increase the risk more than others.

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

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

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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>CHRN2</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>CLCN2</i>	Chloride channel
<i>LG1</i>	G-protein component

Adapted from Williams and Battaglia (2013).

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.

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. Between 1% and 70% of the genes included on an individual panel were not on any other panel.

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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.

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. 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. FDA labeling for carbamazepine.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

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. FDA has chosen not to require any regulatory review of this test.

Centers for Medicare and Medicaid Services (CMS)

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

Rationale/Source

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

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

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

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 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)	<i>SCN1A</i>
Early infantile epileptic encephalopathy	<i>STXBP1</i>
Generalized epilepsy with febrile seizures plus	<i>SCN1A, SCN2A, SCN1B, GABRG2</i>
Epilepsy and mental retardation limited to females	<i>PCDH19</i>
Nocturnal frontal lobe epilepsy	<i>CHRNA4, CHRNB2, CHRNA2</i>

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

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

The question addressed in this evidence review is: Does genetic testing improve health outcomes in individuals with infantile- or early-childhood-onset epileptic encephalopathy?

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The following PICOTS were used to select literature to inform this review.

Patients

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

Interventions

Commercial testing is available from numerous companies. Testing for individual genes is available for most, or all, or the genes listed in Table 4, as well as for a wider range of genes. Lists of genes that may lead to genetic epilepsy and testing laboratories in the United States are provided at the GeneTests website funded by BioReference Laboratories and the Genetic Testing Registry of the National Center for Biotechnology Information website.

Because of the large number of potential genes, panel testing is available from a number of genetic companies. These panels include a variable number of genes implicated in diverse disorders. Some panels are designed to be comprehensive while other panels test for specific subtypes of epilepsy. Testing using whole exome sequencing is reviewed in medical policy 00389 (whole exome and whole genome sequencing for diagnosis of genetic disorders).

Comparators

The following practice is currently used: standard clinical care without genetic testing.

Outcomes

Specific outcomes in each of these categories are listed in Table 5.

The potential beneficial outcomes of primary interest would be an improvement in symptoms (particularly reduction in seizure frequency), functioning, and quality of life. A genetic diagnosis may also limit further invasive investigations into seizure etiology that have associated risks and resource utilization (e.g., a genetic diagnosis may spare 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 events from that treatment. False-negative test results could lead to unnecessary surgeries.

Table 5. Outcomes of Interest for Individuals With Symptomatic Epilepsy

Outcomes	Details
Symptoms	Seizure frequency; reduction in seizure frequency by 50%; proportion seizure-free
Functional outcomes	Measurement of development delays (e.g., Bayley Scales of Infant and Toddler Development)

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Quality of life	Validated quality of life assessment tools
Medication use	Number of unsuccessful medication trials, number of medications needed
Resource utilization	Number of surgeries
Treatment-related morbidity	Adverse events of epilepsy medication and surgery

Timing

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

Setting

Infants or young children with a first seizure may be initially evaluated by emergency physicians and referred to a primary care physician or neurologist for further diagnosis and management. Patients who are refractory to first-line antiepileptic drugs (AEDs) are frequently referred to a neurologist. Care of patients with medically refractory epilepsy may be managed by an epileptologist. Referral for genetic counseling is important for the explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

Simplifying Test Terms

There are 3 core characteristics for assessing a medical test. Whether imaging, laboratory, or other, all medical tests must be:

- Technically reliable
- Clinically valid
- Clinically useful.

Because different specialties may use different terms for the same concept, we are highlighting the core characteristics. The core characteristics also apply to different uses of tests, such as diagnosis, prognosis, and monitoring treatment.

Diagnostic tests detect presence or absence of a condition. Surveillance and treatment monitoring are essentially diagnostic tests over a time frame. Surveillance to see whether a condition develops or progresses is a type of detection. Treatment monitoring is also a type of detection because the purpose is to see if treatment is associated with the disappearance, regression, or progression of the condition.

Prognostic tests predict the risk of developing a condition in the future. Tests to predict response to therapy are also prognostic. Response to therapy is a type of condition and can be either a beneficial response or adverse response. The term predictive test is often used to refer to response to therapy. To simplify terms, we use prognostic to refer both to predicting a future condition or to predicting a response to therapy.

Technically Reliable

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.

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Clinically Valid

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

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. In a 2006 series of 64 patients, 51 (79%) were found to have *SCN1A* pathogenic variants. Among 8 infants who met clinical criteria for Dravet syndrome in a 2015 population-based cohort, 6 had a pathogenic *SCN1A* variant, all of which were de novo.

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	Population	Genetic Testing	Results
Berg et al (2017)	327 infants and young children with newly diagnosed with epilepsy	Various forms	Diagnostic yield: 40.4% overall <ul style="list-style-type: none"> • 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 et al (2016)	216 patients with epileptic encephalopathy phenotype or familial epilepsy	Epilepsy panel of 46 genes	Diagnostic yield: 23% patients overall <ul style="list-style-type: none"> • 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 <ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> • 0% for karyotyping • 11.3% of 62 for aCGH • 33.3% of 3 for targeted chromosomal SNV 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	aCGH, NGS	Diagnostic yield: <ul style="list-style-type: none"> • 2.7% for aCGH • 12.7% for targeted NGS
Hrabik et al (2015)	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.

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Clinically Useful

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

Direct Evidence

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

For the early-onset epilepsies that may have a genetic component, interventions to reduce the risk of having an affected offspring may be a potential area for clinical utility. Genetic counseling and consideration of preimplantation genetic testing combined with in vitro fertilization are available options. For Dravet syndrome, most pathogenic variants are sporadic, making the clinical utility of testing for the purposes of counseling parents and intervening in future pregnancies low. However, when there is a familial disease with a pathogenic variant present in 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.

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.

Chain of Evidence

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

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

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Ream et al (2014) retrospectively reviewed a single center's use of clinically available genetic tests in the management of pediatric drug-resistant epilepsy. 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*; 3 of 9 patients with Lennox-Gastaut syndrome had identified variants (1 with a *CDKL5* variant, 1 with an *SCL9A6* variant, 1 with both *SCN1A* and *EFHC1* variants). Two (6.9%) patients had diagnostic variants not suspected based on their clinical phenotypes. In 8 (27.6%) patients, genetic test results had potential therapeutic implications. However, only 1 patient had significantly reduced seizure frequency; the patient received stiripentol following a positive *SCN1A* variant test.

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

PRESUMED GENETIC EPILEPSY

Clinical Context and Test Purpose

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

The purpose of genetic testing in 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.

The question addressed in this evidence review is: Does genetic testing improve health outcomes in individuals with presumed genetic epilepsy?

The following PICOTS were used to select literature to inform this review.

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Patients

The relevant population of interest is patients with clinical features (age of onset, seizure semiology, electroencephalography features) consistent with genetic epilepsies, such as generalized epilepsy, childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, and epilepsy with tonic-clonic seizures alone, who do not have evidence of a structural or metabolic condition that increases the likelihood of seizures and for whom seizures are the primary clinical manifestation.

Interventions

As mentioned, commercial tests are available from many companies. Testing using whole exome sequencing is reviewed in medical policy 00389 (whole exome and whole genome sequencing for diagnosis of genetic disorders).

Comparators

The following practice is currently used: standard clinical care without genetic testing.

Outcomes

The outcomes of interest are similar to those described in the previous section. Specific outcomes are listed in Table 7. The National Institute of Neurological Disorders and Stroke Common Data Elements for Epilepsy describes a minimum set of data elements, including outcome measures, that should ideally be collected in research of epilepsy.

Table 7. 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

Timing

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

Setting

Infants or young children with a first seizure may be initially evaluated by emergency physicians and referred to primary care physician or neurologist for further diagnosis and management. Patients who are refractory to first-line AEDs are frequently referred to a neurologist. Care of patients with medically

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refractory epilepsy may be managed by an epileptologist. Referral for genetic counseling is important for the explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

Technically Reliable

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.

Clinically Valid

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

The literature on clinical validity includes many studies that have reported on the association between various genetic variants and epilepsy. A large number of case-control studies have compared the frequency of genetic variants in patients who have epilepsy with the frequency in patients without epilepsy. There is a smaller number of genome-wide association studies (GWAS) that evaluate the presence of single-nucleotide variants (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.

Diagnosis of Epilepsy

Tan and Berkovic (2010) published an overview of genetic association studies using records from Epilepsy Genetic Association Database. 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 GGE. Most studies had relatively small sample sizes, with a median of 104 cases (range, 8-1361) 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 2 epilepsy clinical subtypes, GGE and focal epilepsy. The authors combined GWAS data from 12 cohorts of patients with epilepsy and controls (ethnically matched to cases) from population-based datasets, for a total of 8696 cases and 26,157 controls. Cases with epilepsy were categorized as having 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 ($p=8.71 \times 10^{-10}$ and 5.44×10^{-9} , respectively). For those with GGE, a locus at 2p16.1 (*VRK2* or

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FANCL) was significantly associated with epilepsy ($p=9.99 \times 10^{-9}$). 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. It included 3020 patients with GGE and 3954 control patients, all of European ancestry. A 2-stage approach was used, with a discovery phase and a replication phase, to evaluate a total of 4.56 million 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, 4 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. Using a similar 2-stage methodology; this study evaluated 1087 patients with epilepsy and 3444 matched controls. Two variants were determined to have the strongest association with epilepsy. One was on the *CAMSAP1L1* gene and the second was on the *GRIK2* gene. There were several other loci on genes suggestive of an association that coded for neurotransmitters or other neuron function.

In addition to the individual studies reporting general genetic associations with epilepsy, a number of meta-analyses have evaluated the association of particular genetic variants with different types of epilepsy. Most have not shown a significant association. For example, Cordoba et al (2012) evaluated the association between *SLC6A4* gene variants and temporal lobe epilepsy in 991 case patients and 1202 controls and failed to demonstrate a significant association on combined analysis. Nurmohamed et al (2010) performed a meta-analysis of 9 case-control studies that evaluated the association between the *ABC1* gene variants and epilepsy. 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 et al (2008). 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 1 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 et al (2014). The authors evaluated the association between the *SCN1A* IVS5N+5GNA variant and susceptibility to epilepsy with febrile seizures. The analysis included 6 studies with 2719 cases and 2317 controls. There was a significant association between *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 et al (2015) evaluated the association between sequence variants in *EFHC1* and phenotypes and outcomes in 38 probands with juvenile myoclonic epilepsy, along with 3 family members. 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 ($p=0.05$).

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Pharmacogenomics of Antiepileptic Medications

Pharmacogenomic of AED Response

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

Kwan et al (2008) compared the frequency of SNVs on the *SCN1A*, *SCN2A*, and *SCN3A* genes in 272 drug-responsive patients and 199 drug-resistant patients. 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 et al (2009) compared the frequency of variants on the *SCN1A*, *SCN1B*, and *SCN2B* genes in 200 patients with drug-resistant epilepsy and 200 patients with drug-responsive epilepsy. None of the individual variants tested showed a significant relation with drug resistance. In a further analysis for gene-gene interactions associated with drug resistance, the authors reported a possible interaction of 2 variants, one on the *SCN2A* gene and the other on the *SCN1B* gene, though falling below their cutoff for statistical significance (p=0.055).

Li et al (2015) conducted a meta-analysis of 28 articles reporting on 30 case-control studies to evaluate the association between the *ABCB1* gene C3435T variant and AED resistance. The included studies had a total of 4124 drug-resistant epileptic patients and 4480 control epileptic patients for whom drug treatment was effective. In a pooled random-effects model, the 3435C allele was not significantly associated with drug resistance, with a pooled OR of 1.07 in an allele model (95% CI, 0.95 to 1.19; p=0.26) and 1.05 in a genotype model (95% CI, 0.89 to 1.24; p=0.55).

Other representative studies that have reported associations between genetic variants and AED response are summarized in Table 8.

Table 8. Genetic Variants and Antiepileptic Drug Response

Study	Population	Genes	Overview of Findings
Lu et al (2017) ⁴⁴	124 epileptic Chinese patients receiving OXC monotherapy	<ul style="list-style-type: none"> • <i>UGT1A4</i> 142T>G (rs2011425) • <i>UGT1A6</i> 19T>G (rs6759892) • <i>UGT1A9</i> 1399C>T (rs2741049) • <i>UGT2B15</i> 253T>G (rs1902023) 	<ul style="list-style-type: none"> • <i>UGT1A9</i> 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 et al (2015)	50 epileptic adults treated with stable clobazam dose	<i>CYP2C19</i>	<ul style="list-style-type: none"> • 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

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Study	Population	Genes	Overview of Findings
Ma et al (2015)	184 epileptic patients receiving OXC monotherapy and 156 healthy volunteers	<ul style="list-style-type: none"> • <i>SCN1A</i> c.3184A>G (rs2298771) • <i>SCN2A</i> c.56G>A (rs17183814) • <i>SCN2A</i> IVS7-32A>G (rs2304016) • <i>ABCC2</i> 3972C>T (rs3740066) • <i>ABCC2</i> c.1249G>A (rs2273697) • <i>UGT2B7</i> c.802T>C (rs7439366) 	<ul style="list-style-type: none"> • <i>SCN1A</i> IVS5-91G>A, <i>UGT2B7</i> c.802T>C, and <i>ABCC2</i> c.1249G>A variants showed significant associations with OXC maintenance doses • Patients with the <i>ABCC2</i> c.1249G>A allele variant more likely to require higher OXC maintenance doses than noncarriers (p=0.002, uncorrected), which remained significant after Bonferroni correction • 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)
Guo et al (2015)	483 Chinese patients with genetic generalized epilepsies	<ul style="list-style-type: none"> • <i>KCNJ10</i> 	<ul style="list-style-type: none"> • 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 et al (2014)	453 epileptic patients, classified as drug-responsive (n=207) or drug-resistant (n=246)	<ul style="list-style-type: none"> • <i>SCN1A</i> c.3184A>G (rs2298771) • <i>SCN2A</i> c.56G>A (rs17183814) • <i>SCN2A</i> IVS7-32A>G (rs2304016) • <i>ABCC2</i> 3972C>T (rs3740066) • <i>ABCC2</i> c.1249G>A (rs2273697) 	<ul style="list-style-type: none"> • <i>SCN1A</i> 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) • <i>SCN1A</i> 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) • <i>ABCC2</i> 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 et (2014)	229 epileptic patients treated with carbamazepine monotherapy	<i>ABCC2</i> : variant rs717620 (-24G4A), rs2273697 (c.1249G4A) and rs3740067	<ul style="list-style-type: none"> • <i>ABCC2</i> variants not associated with time to first seizure or time to 12-mo remission
Yun et al (2013)	38 epileptic patients treated with carbamazepine monotherapy	<ul style="list-style-type: none"> • <i>EPHX1</i> c.337T>C • <i>EPHX1</i> c.416A>G • <i>SCN1A</i> IVS5-91G>A • <i>CYP3A4*1G</i> 	<ul style="list-style-type: none"> • Patients <i>EPHX1</i> 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 pharmacoresistance
Taur et al (2014)	115 epileptic patients treated with phenytoin, phenobarbital, and/or carbamazepine	<ul style="list-style-type: none"> • <i>ABCB1</i> (c.3435T) • <i>CYP2C9</i> (416C>T) • <i>CYP2C9</i> (1061A>T) • <i>CYP2C19</i> (681G>A) • <i>CYP2C19</i> (636G>A) 	<ul style="list-style-type: none"> • <i>ABCB1</i> 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 et al (2010) examined the association between SNVs on the *ABCB1* gene and drug resistance in 3231 drug-resistant patients and 3524 controls from 22 studies. 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.

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In a separate meta-analysis, Sun et al (2014) evaluated 8 studies evaluating the association between variants in the multidrug resistance 1 (*MDR1*) gene and childhood medication-refractory epilepsy, including 634 drug-resistant patients, 615 drug-responsive patients, and 1052 healthy controls. In the pooled analysis, the *MDR1* C3435T variant was not significantly associated with risk of 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. 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 2 separate cohorts. One cohort included 285 newly diagnosed patients in Glasgow, of whom a large proportion had participated in randomized trials of AED monotherapy. Drug-response phenotypes in this cohort were identified by retrospectively reviewing prospectively collected clinical trial and/or hospital notes. The second cohort was drawn from patients who had participated in the Standard and New Epileptic Drugs (SANAD) trial, a multicenter RCT comparing standard with newer AEDs. The trial included 2400 patients, of whom 520 of self-described European ancestry who provided DNA samples were used in the present analysis. The *k*-nearest neighbor machine model derived from the original Australian cohort did not predict treatment response in either the Glasgow or the SANAD cohorts. Investigators redeveloped a *k*-nearest neighbor machine learning algorithm based on 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 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 et al (2014) evaluated genetic variants associated with phenytoin-induced severe cutaneous adverse events (SJS/TEN, drug reactions with eosinophilia and systemic symptoms) and maculopapular exanthema. This GWAS included 60 cases with phenytoin-related severe cutaneous adverse events and

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Louisiana

Genetic Testing for Epilepsy

Policy # 00401

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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; $p=1.1 \times 10^{-17}$). 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; $p=1.2 \times 10^{-19}$), drug reactions with eosinophilia and systemic symptoms (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 *ABCB1*, *CYP3A4*, *EPHX1*, *FAS*, *SNC1A*, *MICA*, and *BAG6* genes. 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 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). 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. Given uncertainty related to the underlying causes of SUDEP, there has been interest in identifying genetic associations with SUDEP.

Bagnall et al (2014) evaluated the prevalence of sequence variations in the *PHOX2B* gene in 68 patients with SUDEP. 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.

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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. In 4 cases, rare variants were detected with complete segregation in the *SCN1A*, *FBN1*, *HCN1*, *SCN4A*, and *EFHC1* genes, and in 1 case a rare variant in *KCNQ1* with an incomplete pattern of inheritance was detected. New potential candidate genes for SUDEP were detected: *FBN1*, *HCN1*, *SCN4A*, *EFHC1*, *CACNA1A*, *SCN11A*, and *SCN10A*.

Bagnall et al (2016) performed an exome-based analysis of rare variants related to cardiac arrhythmia, respiratory control, and epilepsy to search for genetic risk factors in 61 SUDEP cases compared with 2936 controls. 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.

Clinically Useful

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

Direct Evidence

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

There is a lack of evidence on the clinical utility of genetic testing for the genetic epilepsies. Association studies are insufficient evidence to determine whether genetic testing can improve the clinical diagnosis of 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

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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 SUDEP. The largest number of these studies is related to AED pharmacogenomics, which has generally reported some association between variants in a number of genes (including *SCN1A*, *SCN2A*, *ABCC2*, *EPHX1*, *CYP2C9*, *CYP2C19*) and AED response. Similarly, genetic associations between a number of genes and AED-related adverse events have been reported. However, no empirical evidence on the clinical utility of testing for the genetic epilepsies was identified, and the changes in clinical management that might occur as a result of testing are not well-defined. The evidence is insufficient to determine the effects of the technology on health outcomes.

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02/06/2014 Medical Policy Committee review

02/19/2014 Medical Policy Implementation Committee approval. New policy.

05/07/2015 Medical Policy Committee review

05/20/2015 Medical Policy Implementation Committee approval. Added new eligibility statement and patient selection criteria. Updated rationale and references.

08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.

05/05/2016 Medical Policy Committee review

05/18/2016 Medical Policy Implementation Committee approval. Coverage statement edited for clarification only.

01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes

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05/04/2017 Medical Policy Committee review

05/17/2017 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

05/03/2018 Medical Policy Committee review

05/16/2018 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 05/2019

Coding

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Code Type	Code
CPT	81401, 81403, 81404, 81405, 81406, 81407, 81479
HCPCS	No codes
ICD-10 Diagnosis	G40.001-G40.019 G40.101-G40.119 G40.201-G40.219 G40.301-G40.319
	G40.401-G40.419 G40.501-G40.509 G40.801-G40.824 G40.89
	G40.901-G40.919 G40.A01-G40.A19 G40.B01-G40.B19

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be law fully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 - 1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
 - 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or

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Louisiana

Genetic Testing for Epilepsy

Policy # 00401

Original Effective Date: 02/19/2014

Current Effective Date: 05/16/2018

3. Reference to federal regulations.

****Medically Necessary (or "Medical Necessity")** - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

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