



Genetic Testing for Epilepsy

Policy # 00401

Original Effective Date: 02/19/2014

Current Effective Date: 06/12/2023

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 are met:

Patient Selection Criteria

Coverage eligibility will be met if positive test results may:

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

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When Services Are Considered Investigational

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

The use of genetic testing for epilepsy when patient selection criteria are not met is considered to be **investigational**.*

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

Policy Guidelines

Policy Scope

Included Tests and Conditions

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

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

Excluded Tests and Conditions

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

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syndromes may be specifically addressed in other medical policies (see medical policies 00169, 00369, 00380 and 00389).

Testing that is limited to genotyping of cytochrome P450 (*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.

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

Medically Necessary Statement Definitions and Testing Strategy

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

- Dravet syndrome (also known as severe myoclonic epilepsy in infancy [SMEI] or polymorphic myoclonic epilepsy in infancy)
- EFMR syndrome (epilepsy limited to females with mental retardation)
- Epileptic encephalopathy with continuous spike-and-wave during sleep
- GEFS+ syndrome (generalized epilepsies with febrile seizures plus)

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- 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>

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Landau-Kleffner syndrome	<i>GRIN2A</i>
West syndrome	<i>ARX, TSC1, TSC2, CDKL5, ALG13, MAGI2, STXBPI, SCN1A, SCN2A, GABA, GABRB3, DNMI</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:

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

Testing Strategy

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

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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.

Genetics Nomenclature Update

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

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

Table PG2. Nomenclature to Report on Variants Found in DNA

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

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



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

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

Genetic Counseling

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

Background/Overview

Epilepsy

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

Classification

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

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Table 1. Classification of Seizure Disorders by Type

Focal Onset (including aware and impaired awareness)	Generalized Onset	Unknown Onset	Unclassified
Motor onset <ul style="list-style-type: none">• automatisms• atonic^a• clonic• epileptic spasms^a• hyperkinetic• myoclonic• tonic	Motor <ul style="list-style-type: none">• tonic-clonic• clonic• tonic• myoclonic• myoclonic-tonic-clonic• myoclonic-atonic• atonic• epileptic spasms	Motor <ul style="list-style-type: none">• tonic-clonic• epileptic spasms	
Nonmotor Onset <ul style="list-style-type: none">• autonomic• behavior arrest• cognitive• emotional• sensory	Nonmotor (absense) <ul style="list-style-type: none">• typical• atypical• myoclonic• eyelid myoclonia	Nonmotor <ul style="list-style-type: none">• behavior arrest	
Focal to bilateral tonic-clonic			

Adapted from Fisher et al (2017).^aDegree of awareness usually is not specified.

Although genetic epilepsies are not discussed in the 2017 ILAE report, a 2010 ILAE report identified genetic epilepsies as conditions in which the seizures are a direct result of a known or presumed genetic defect(s). Genetic epilepsies are characterized by recurrent unprovoked seizures

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in patients who do not have demonstrable brain lesions or metabolic abnormalities. In addition, seizures are the core symptom of the disorder, and other symptomatology is not present, except as a direct result of seizures. This is differentiated from genetically determined conditions in which seizures are part of a larger syndrome, such as tuberous sclerosis, fragile X syndrome, or Rett syndrome.

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

Genetic epilepsies can be further broken down by type of seizures. For example, genetic generalized epilepsy refers to patients who have convulsive (grand mal) seizures, while genetic absence epilepsy refers to patients with nonconvulsive (absence) seizures. The disorders are also sometimes classified by the age of onset.

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

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

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- 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 *STXBPI* 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 frequently discovered.

Some of the most common genes associated with genetic epileptic syndromes are listed in Table 2.
Table 2. Selected Genes Most Commonly Associated With Genetic Epilepsy

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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>GABRR1</i>	γ -aminobutyrate A-type subunit
<i>GABRD</i>	γ -aminobutyrate subunit
<i>CHRNA2</i>	Acetylcholine receptor $\alpha 2$ subunit
<i>CHRNA4</i>	Acetylcholine receptor $\alpha 4$ subunit
<i>CHRNA2</i>	Acetylcholine receptor $\beta 2$ subunit
<i>STXB1</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>LGII</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 generalized epilepsies with febrile seizures plus syndrome (associated with *SCN1A*, *SCN1B*, and *GABRG2* variants), Dravet syndrome (associated with *SCN1A*

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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 *STXBPI* 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.

Treatment

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

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

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that will result in a more efficient process for medication selection, and potentially more effective control of symptoms.

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

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 (CLIA). Commercially available genetic tests for epilepsy are available under the auspices of the CLIA. Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the FDA has chosen not to require any regulatory review of this test.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

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

Summary of Evidence

For individuals who have infantile- or early-childhood-onset epileptic encephalopathy who receive testing for genes associated with epileptic encephalopathies, the evidence includes prospective and

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

For individuals who have presumed genetic epilepsy who receive testing for genetic variants associated with genetic epilepsies, the evidence includes prospective and retrospective cohort studies describing testing yields. Relevant outcomes are test validity, changes in reproductive decision making, symptoms, quality of life, functional outcomes, medication use, resource utilization, and treatment-related morbidity. For most genetic epilepsies, which are thought to have a complex, multifactorial basis, the association between specific genetic variants and the risk of epilepsy is uncertain. Despite a large body of literature on associations between genetic variants and epilepsies, the clinical validity of genetic testing is poorly understood. Published literature is characterized by weak and inconsistent associations, which have not been replicated independently or by meta-analyses. A number of studies have also reported associations between genetic variants and antiepileptic drug (AED) treatment response, AED adverse effect risk, epilepsy phenotype, and risk of sudden unexplained death in epilepsy (SUDEP). The largest number of these studies is related to AED pharmacogenomics, which has generally reported some association between variants in a number of genes (including *SCN1A*, *SCN2A*, *ABCC2*, *EPHX1*, *CYP2C9*, *CYP2C19*) and AED response. Similarly, genetic associations between a number of genes and AED-related adverse events have been reported. However, no empirical evidence on the clinical utility of testing for the genetic epilepsies was identified, and the changes in clinical management that might occur as a result of testing are not well-defined. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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Supplemental Information

Clinical Input From Physician Specialty Societies and Academic Medical Centers

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

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

Practice Guidelines and Position Statements

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

American Academy of Neurology et al.

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

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

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was reviewed and reaffirmed in 2020. Routine electroencephalography was recommended as part of the diagnostic evaluation; genetic testing was not addressed.

International League Against Epilepsy

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

- “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.”

European Academy of Neurology

In 2010, the European Federation of Neurological Societies (now the European Academy of Neurology) issued guidelines on the molecular diagnosis of channelopathies, epilepsies, migraine, stroke, and dementias. The guidelines made the following recommendations on epilepsy:

“There is good evidence to suggest that a thorough clinical and electrophysiological investigation may lead to the choice of the gene to be tested in patients with periodic paralysis (Level B). In myotonic disorders, it is recommended to first search for myotonic dystrophy and use clinical and electrophysiological phenotype characterization to guide for molecular genetic testing (Level B).

Molecular investigations are possible and may help in some cases to diagnose the condition but cannot be considered as a routine procedure with regard to the large number of different mutations [variants] in different genes. Furthermore, diagnosis can be made more easily by clinical and physiological investigation (Good Practice Point). One exception of note is the diagnosis of SMEI , in which mutations [variants] are found in *SCN1A* in 80% of the patients (Level B).”

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North American Consensus Panel

In 2017, recommendations were published from a consensus panel of 14 physicians and 5 family members/caregivers of patients with Dravet syndrome. There was strong consensus among panel members that genetic testing should be completed in all patients with clinical suspicion for Dravet syndrome since this can lead to earlier diagnosis. Options for testing include *SCN1A* sequencing followed by testing for deletions and duplications if sequencing is negative, or epilepsy gene panel testing, with no consensus among panel members about which option is superior. There was strong consensus that epilepsy gene panel testing is preferred to *SCN1A* testing if the clinical presentation is less clear or if the patient has atypical features, and that karyotyping is not needed. The panel did not reach consensus about the utility of chromosomal microarray in patients with suspected Dravet syndrome (72.2% agreed, 22.2% disagreed, 5.6% did not know) and concluded that this test can be considered. Based on strong consensus, the panel recommended genetic testing in the following circumstances among children with normal development, seizures of unknown etiology, and no evidence of causal lesion in the brain: infants with at least 2 prolonged focal febrile seizures, or children aged 1 to 3 years with at least one prolonged febrile seizure before 18 months of age or myoclonic or atypical absence seizures that are refractory to at least one antiepileptic medication. Infants who experience a single prolonged focal or generalized convulsion do not require genetic testing (strong consensus), but this can be considered in children aged 1 to 3 years who experience multiple brief episodes of febrile seizure activity before 18 months of age or myoclonic or atypical absence seizures that do not respond to antiepileptic medication (moderate consensus). The panel had moderate consensus about the role of genetic testing (epilepsy gene panel) in teens and adults without congenital dysmorphism who have seizure activity resistant to antiepileptic medication and lack an early life history.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

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

Ongoing and Unpublished Clinical Trials

The ongoing trials that might influence this review are listed in Table 3.

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Table 3. Summary of Key Trials

<i>NCT No.</i>	<i>Trial Name</i>	<i>Planned Enrollment</i>	<i>Completion Date</i>
<i>Ongoing</i>			
NCT01858285	Genetics of Epilepsy and Related Disorders	1000	Dec 2030

NCT: national clinical trial.

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Policy History

Original Effective Date: 02/19/2014

Current Effective Date: 06/12/2023

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.

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Louisiana

Genetic Testing for Epilepsy

Policy # 00401

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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
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.
05/02/2019	Medical Policy Committee review
05/15/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/07/2020	Medical Policy Committee review
05/13/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/16/2020	Coding update
12/11/2020	Coding update
05/06/2021	Medical Policy Committee review
05/12/2021	Medical Policy Implementation Committee approval. Added an investigational statement for the use of genetic testing for epilepsy when patient selection criteria are not met for clarity. Coverage eligibility unchanged.
06/02/2022	Medical Policy Committee review
06/08/2022	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/04/2023	Medical Policy Committee review
05/10/2023	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 05/2024

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Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)†, copyright 2022 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	0231U, 0232U, 81401, 81403, 81404, 81405, 81406, 81407, 81419, 81479
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

*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

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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 lawfully 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 technology evaluation center(s);
 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 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: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

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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