Introduction

Epilepsy is a problem with the electrical activity in the brain. There are many causes of epilepsy, including abnormalities in the brain structure, diseases of the metabolism, or a problem with certain genes. Medical and family history, blood tests, an EEG (a test that records electrical activity in the brain), or possibly imaging like a CT scan or MRI, can be used to diagnose epilepsy. While epilepsy often develops for no known reason, in some cases it can be inherited. Genetic tests are available to see if a person has an inherited form of epilepsy. This policy describes the specific situations in which the plan may cover genetic testing for epilepsy.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

<table>
<thead>
<tr>
<th>Reason for Testing</th>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic testing for infantile and</td>
<td>Genetic testing for genes associated with infantile- and early childhood-onset</td>
</tr>
<tr>
<td>early</td>
<td>epilepsy syndromes in which epilepsy is the</td>
</tr>
</tbody>
</table>
Reason for Testing | Medical Necessity
--- | ---
**childhood-onset epilepsy**  
- Emory Genetics® Epilepsy and Seizure Disorders Sequencing panel  
- GeneDx® Childhood-Onset Epilepsy Panel  
- GeneDx® Comprehensive Epilepsy Panel  
- GeneDx® Infantile Epilepsy Panel  
- Invitae Epilepsy Panel | core clinical symptom may be considered medically necessary for individuals age 5 and younger 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

**Note:** See Application of Medical Necessity Policy Statement for more information.

**All other situations** | Genetic testing for epilepsy is considered investigational in all other situations.

---

**Included Tests/Conditions**

- This policy addresses testing for epilepsy that possibly has a 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 (Dravet syndrome, early infantile epileptic encephalopathy, generalized epilepsy with febrile seizures plus, epilepsy and intellectual disability limited to females, nocturnal frontal lobe epilepsy, and others). Other clinical manifestations may be present in these syndromes, but are generally secondary to the epilepsy itself.

---

**Excluded Tests/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 syndromes may be specifically addressed in other medical policies.
**Excluded Tests/Conditions**

(see Related Policies).

- Testing that is limited to genotyping of CYP450 genes is addressed in a separate policy (see Related Policies).

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

- This policy also does not address the use of 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, “Valproate is contraindicated in patients known to have mitochondrial disorders caused by POLG mutations and children under two years of age who are suspected of having a POLG-related disorder,”(FDA. 2015#137).

---

**Medical Necessity Statement Definitions and Testing Strategy**

- The medical necessity 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 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 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 [PMEI])
  - 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)
Medical Necessity Statement Definitions and Testing Strategy

- Landau-Kleffner syndrome
- West syndrome Glucose transporter type 1 deficiency syndrome

Application of Medical Necessity Policy Statement

Although there is no standard definition of epileptic encephalopathies, they are generally characterized by at least some of the following:

- Onset in early childhood (often in infancy)
- Refractory to therapy
- Associated with developmental delay or regression
- 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 the purposes of this policy, the medically necessary policy statement would apply for patients with:

- Onset of seizures in early childhood (i.e., before the age of 5 years)
- Have clinically severe seizures that affect daily functioning and/or interictal EEG abnormalities
- No other clinical syndrome that would potentially better explain the patient’s symptoms.

Variants in a large number of genes have been associated with early onset epilepsies. Some of these are summarized in Table 1.

Table 1: Single Genes Associated With Epileptic Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Associated Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dravet syndrome</td>
<td>( SCN1A, SCN9A, GABRA1, STXB1, )</td>
</tr>
<tr>
<td></td>
<td>( PCDH19, SCN1B, CHD2, HCN1 )</td>
</tr>
<tr>
<td>Epilepsy limited to females with mental retardation</td>
<td>( PCDH19 )</td>
</tr>
<tr>
<td>Epileptic encephalopathy with continuous spike-and-wave during sleep</td>
<td>( GRIN2A )</td>
</tr>
<tr>
<td>Genetic epilepsy with febrile seizures plus</td>
<td>( SCN1A, SCN9A )</td>
</tr>
</tbody>
</table>
### Syndrome

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Associated Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early infantile epileptic encephalopathy with suppression burst (Ohtahara syndrome)</td>
<td><em>KCNQ2, SLC25A22, STXBP1, CDKL5, ARX</em></td>
</tr>
<tr>
<td>Landau-Kleffner syndrome</td>
<td><em>GRIN2A</em></td>
</tr>
<tr>
<td>West syndrome</td>
<td><em>ARX, TSC1, TSC2, CDKL5, ALG13, MAGI2, STXBP1, SCN1A, SCN2A, GABA, GABRB3, DNM1</em></td>
</tr>
<tr>
<td>Glucose transporter type 1 deficiency syndrome</td>
<td><em>SLC2A1</em></td>
</tr>
</tbody>
</table>

### Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td></td>
</tr>
<tr>
<td>81401</td>
<td>MT-TK (mitochondrially encoded tRNA lysine) (eg, myoclonic epilepsy with ragged-red fibers [MERRF]), common variants (eg, m.8344A&gt;G, m.8356T&gt;C)</td>
</tr>
<tr>
<td>81403</td>
<td>NHLRC1 (NHL repeat containing 1) (eg, progressive myoclonus epilepsy), full gene sequence</td>
</tr>
<tr>
<td>81404</td>
<td>ARX (aristaless related homeobox) (eg, X-linked lissencephaly with ambiguous genitalia, X-linked mental retardation), full gene sequence</td>
</tr>
<tr>
<td>81405</td>
<td>CHRNA4 (cholinergic receptor, nicotinic, alpha 4) (eg, nocturnal frontal lobe epilepsy), full gene sequence CHRNβ2 (cholinergic receptor, nicotinic, beta 2 [neuronal]) (e.g., nocturnal frontal lobe epilepsy), full gene sequence</td>
</tr>
<tr>
<td>81406</td>
<td>ALDH7A1 (aldehyde dehydrogenase 7 family, member A1) (eg, pyridoxine-dependent epilepsy), full gene sequence</td>
</tr>
<tr>
<td>81407</td>
<td>SCN1A (sodium channel, voltage-gated, type 1, alpha subunit) (eg, generalized epilepsy with epilepsy with febrile seizures), full gene sequence</td>
</tr>
<tr>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
</tr>
</tbody>
</table>

**Note:** CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).
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.

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 (see Table 2). 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 3 shows the recommended standard terminology—“pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign”—to describe variants identified that cause Mendelian disorders.

Table 2. Nomenclature to Report on Variants Found in DNA

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
<td></td>
</tr>
</tbody>
</table>
**Table 3. ACMG-AMP Standards and Guidelines for Variant Classification**

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

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

**Consideration of Age**

The age at which genetic testing for infantile- and early childhood-onset epilepsy syndromes is considered to be medically necessary in this policy is age 5 and younger for the following reasons: There are rare epilepsy syndromes that present in infancy or early childhood (first couple years of life), in which epilepsy is the core clinical symptom (Dravet syndrome, early infantile epileptic encephalopathy, generalized epilepsy with febrile seizures plus, epilepsy and intellectual disability limited to females, Nocturnal frontal lobe epilepsy, and others). The evidence for testing for mutations associated with infantile- or early childhood-onset epileptic encephalopathies in individuals with infantile- or early childhood-onset epileptic encephalopathy includes prospective and retrospective cohort studies describing the yield of testing.

Clinical input was sought and indicated strong support for the use of genetic testing in the evaluation of infantile- and early-childhood-onset epilepsy syndromes associated with encephalopathy. Reviewers noted that the presence of a pathogenic mutation may lead to targeted medication management, avoidance of other diagnostic tests, and/or informed reproductive planning.

**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/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.

**Evidence Review**

**Description**

Epilepsy is a disorder characterized by unprovoked seizures. It is a heterogeneous condition that encompasses many types of seizures, and that 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 variants. Genetic testing is commercially available for a large number of genes that may be related to epilepsy.

**Background**

*Epilepsy*

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

*Classification*

Epilepsy is heterogeneous in etiology and clinical expression and can be classified in a variety of ways. Most commonly, classification is done by the clinical phenotype, i.e., the type of seizures that occur. The International League Against Epilepsy (ILAE) developed the classification system that is widely used for clinical care and research purposes (see Table 4).² Classification of seizures can also be done on the basis of age of onset:
- Neonatal
- Infancy
- Childhood
- Adolescent/Adult

### Table 4. Classification of Seizure Disorders by Type

<table>
<thead>
<tr>
<th>Seizures Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Partial (focal seizures)</strong></td>
</tr>
<tr>
<td>Simple partial seizures (consciousness not impaired)</td>
</tr>
<tr>
<td>With motor symptoms</td>
</tr>
<tr>
<td>With somatosensory or special sensory symptoms</td>
</tr>
<tr>
<td>With autonomic symptoms or signs</td>
</tr>
<tr>
<td>With psychic symptoms (disturbance of higher cerebral function)</td>
</tr>
<tr>
<td><strong>Complex partial (with impairment of consciousness)</strong></td>
</tr>
<tr>
<td>Simple partial onset followed by impairment of consciousness</td>
</tr>
<tr>
<td>Impairment of consciousness at outset</td>
</tr>
<tr>
<td><strong>Partial seizures evolving to secondarily generalized seizures</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Generalized seizures</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonconvulsive (absence)</td>
</tr>
<tr>
<td>Convulsive</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Unclassified seizures</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Adapted from Berg et al (2010).²</td>
</tr>
</tbody>
</table>

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 5).²
Table 5. Alternative Classifications

<table>
<thead>
<tr>
<th>Classification</th>
<th>Condition Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic epilepsies</td>
<td>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.</td>
</tr>
<tr>
<td>Structural/metabolic</td>
<td>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.</td>
</tr>
<tr>
<td>Unknown cause</td>
<td>Conditions for which the underlying etiology for the seizures cannot be determined and may include both genetic and nongenetic causes.</td>
</tr>
</tbody>
</table>

For the purposes of this policy review, the ILAE classification is most useful. The policy will focus 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 in this policy, but may be included in separate policies that specifically address genetic testing for that syndrome.

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

The category of genetic epilepsies includes a number of rare epilepsy syndromes that present in infancy or early childhood.¹,³ These are syndromes that are characterized by epilepsy as the primary manifestation, without associated metabolic or brain structural abnormalities. They are often severe and sometimes refractory to medication treatment. They may involve other clinical manifestations such as development delay and/or intellectual disability, which in many cases are thought to be caused by frequent uncontrolled seizures. In these cases, the epileptic syndrome may be classified as an epileptic encephalopathy, which is described by ILAE as disorders in which the epileptic activity itself may contribute to severe cognitive and behavioral impairments above and beyond what might be expected from the underlying pathology alone and that these can worsen over time.² A partial list of severe early-onset epilepsy syndromes is as follows:
• Dravet syndrome (also known as severe myoclonic epilepsy in infancy or polymorphic myoclonic epilepsy in infancy)

• EFMR syndrome (epilepsy limited to females with mental retardation)

• Nocturnal frontal lobe epilepsy

• GEFS+ syndrome (generalized epilepsies with febrile seizures plus)

• EIEE syndrome (early infantile epileptic encephalopathy with burst suppression pattern)

• West syndrome

• Ohtahara syndrome

Dravet syndrome falls on a spectrum of SCN1A-related seizure disorders, which includes febrile seizures at the mild end to Dravet syndrome and intractable childhood epilepsy with generalized tonic-clonic seizures at the severe end. The spectrum may be associated with multiple seizure phenotypes, with a broad spectrum of severity; more severe seizure disorders may be associated with cognitive impairment or deterioration. Ohtahara syndrome is a severe early-onset epilepsy syndrome characterized by intractable tonic spasms, other seizures, interictal EEG 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 EEG finding of hypsarrhythmia. There are other seizure disorders that present early in childhood and may have a genetic component but which 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.\textsuperscript{6}

Some of the most common genes associated with genetic epileptic syndromes are listed in Table 6.

### Table 6. Selected Genes Most Commonly Associated with Genetic Epilepsy

<table>
<thead>
<tr>
<th>Gene</th>
<th>Physiologic function</th>
</tr>
</thead>
<tbody>
<tr>
<td>KCNQ2</td>
<td>Potassium channel</td>
</tr>
<tr>
<td>KCNQ3</td>
<td>Potassium channel</td>
</tr>
<tr>
<td>SCN1A</td>
<td>Sodium channel α-subunit</td>
</tr>
<tr>
<td>SCN2A</td>
<td>Sodium channel α-subunit</td>
</tr>
<tr>
<td>SCN1B</td>
<td>Sodium channel β-subunit</td>
</tr>
<tr>
<td>GABRG2</td>
<td>GABA A-type subunit</td>
</tr>
<tr>
<td>GABRRA1</td>
<td>GABA A-type subunit</td>
</tr>
<tr>
<td>GABRD</td>
<td>GABA subunit</td>
</tr>
<tr>
<td>CHRNA2</td>
<td>Acetylcholine receptor α2 subunit</td>
</tr>
<tr>
<td>CHRNA4</td>
<td>Acetylcholine receptor α4 subunit</td>
</tr>
<tr>
<td>CHRN82</td>
<td>Acetylcholine receptor β2 subunit</td>
</tr>
<tr>
<td>STXBP1</td>
<td>Synaptic vesicle release</td>
</tr>
<tr>
<td>ARX</td>
<td>Homeobox gene</td>
</tr>
<tr>
<td>PCDH19</td>
<td>Protocadherin cell-cell adhesion</td>
</tr>
<tr>
<td>EFHC1</td>
<td>Calcium Homeostasis</td>
</tr>
<tr>
<td>CACNB4</td>
<td>Calcium channel subunit</td>
</tr>
<tr>
<td>CLCN2</td>
<td>Chloride channel</td>
</tr>
<tr>
<td>LGI1</td>
<td>G-protein component</td>
</tr>
</tbody>
</table>

Adapted from Williams (2013)\textsuperscript{1}
For the severe early epilepsy syndromes, the disorders most frequently reported to be associated with single-gene variants include GEFS+ syndrome (associated with SCN1A, SCN1B, GABRG2 variants), Dravet syndrome (associated with SCN1A variants, possibly modified by SCN9A variants), and epilepsy and intellectual disability limited to females (associated with PCDH19 mutations). 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 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, neurological 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 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 of Epilepsy**

Another area of interest for epilepsy is the pharmacogenomics of anti-epileptic medications. There are a wide variety of these medications, from numerous different classes. The choice of medications, and the combinations of medications for patients who require treatment with more than one agent, is complex. Approximately one-third of patients are considered refractory to medications, defined as inadequate control of symptoms with a single medication. 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 who are likely to be refractory to the most common medications. This may lead to directed treatment that will result in a more efficient process for medication selection, and potentially more effective control of symptoms.

Of note, genotyping for the HLA-B*1502 allelic variant in patients of Asian ancestry, prior to considering drug treatment with carbamazepine due to risks of severe dermatologic reactions is recommended by the U.S. Food and Drug Administration (FDA) labeling for carbamazepine.11

**Ongoing and Unpublished Clinical Trials**

Three ongoing trials that might influence this review are listed in Table 7.

### Table 7. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02883712</td>
<td>Study of Predictors of Response to Anti-Epilepsy in Epilepsy (RESISTANT)</td>
<td>1000</td>
<td>Dec 2019</td>
</tr>
<tr>
<td>NCT01858285</td>
<td>Genetics of Epilepsy and Related Disorders</td>
<td>500</td>
<td>Dec 2020</td>
</tr>
<tr>
<td></td>
<td><strong>Unpublished</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT00552045</td>
<td>Epilepsy Phenome/Genome Project: a Phenotype/Genotype Analysis of Epilepsy</td>
<td>4150</td>
<td>Apr 2014 (unknown)</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

**Summary of Evidence**

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

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

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

Practice Guidelines and Position Statements

**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 2016. With regard to whether genetic testing should be routinely ordered for children with status epilepticus, the guidelines stated: “There is insufficient evidence to support or refute whether such studies should be done routinely.”

In 2000, 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 was reviewed and reaffirmed in 2014. 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 (ILAE) issued a report with recommendations on the management of infantile seizures, which included the following recommendations 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 Federation of Neurological Societies**

In 2010, the European Federation of Neurological Societies issued guidelines on the molecular diagnosis of channelopathies, epilepsies, migraine, stroke, and dementias. The guidelines made the following recommendations pertaining to 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 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 severe myoclonic epilepsy of infancy (SMEI), in which variants are found in SCN1A in 80% of the patients (Level B).

**Medicare National Coverage**

There is no national coverage determination (NCD) for genetic testing for epilepsy. In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

**Regulatory Status**

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


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