Genetic Testing for Epilepsy

Policy # 00401
Original Effective Date: 02/19/2014
Current Effective Date: 05/17/2017

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.

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 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.*

Scope of the Policy
This policy addresses testing for epilepsy that is possibly genetic. The International League Against Epilepsy 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 (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.
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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 policies.

Testing that is limited to genotyping of CYP450 genes is addressed separately in 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 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 variants in mitochondrial DNA polymerase γ (POLG; e.g., Alpers-Huttenlocher Syndrome) and children under two years of age who are suspected of having a POLG-related disorder (FDA, 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 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 (genetic epilepsy 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 these are summarized in Table PG1.
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Table PG1: Single Genes Associated With Epileptic Syndromes

<table>
<thead>
<tr>
<th>Syndrome Ngoài</th>
<th>Associated Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dravet syndrome</td>
<td>SCN1A, SCN9A, GABRA1, STXBP1, 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>
<tr>
<td>Early infantile epileptic encephalopathy with suppression burst (Ohtahara syndrome)</td>
<td>KCNQ2, SLC2A5A2, STXBP1, DK2L5, ARX</td>
</tr>
<tr>
<td>Landau-Kleffner syndrome</td>
<td>GRIN2A</td>
</tr>
<tr>
<td>West syndrome</td>
<td>ARX, TSC1, TSC2, DK2L5, ALG13, MAGI2, STXBP1, SCN1A, SCN2A, GABA, GABRB3, DNM1</td>
</tr>
<tr>
<td>Glucose transporter type 1 deficiency syndrome</td>
<td>SLC2A1</td>
</tr>
</tbody>
</table>

Application of Medically Necessary Policy Statement

Although there is not standardization in the 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 the purposes of this policy, the medically necessary policy statement would apply for patients with:

1. Onset of seizures in early childhood (ie, 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/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. In these cases, panels should meet the criteria outlined in evidence review 2.04.92 (general approach to evaluating the utility of genetic panels). Criteria for use of whole exome sequencing are outlined in evidence review 2.04.102 (whole exome and whole genome sequencing for diagnosis of genetic disorders).

GENETICS NOMENCLATURE UPDATE

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Human Genome Variation Society (HGVS) 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 (see Table PG2). HGVS nomenclature is recommended by HGVS, the Human Variome Project, and the HUman Genome Organization (HUGO).

The American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) standards and guidelines for interpretation of sequence variants represent expert opinion from ACMG, AMP, and 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**

<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 PG3. 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>

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 is a disorder characterized by unprovoked seizures. It is a heterogeneous condition that encompasses many different 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
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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.

Epilepsy is defined as the occurrence of two or more unprovoked seizures. It is a common neurologic disorder, with approximate 3% of the population developing the disorder over their entire lifespan. The condition is generally chronic, requiring treatment with one or more medications to adequately control symptoms. Seizures can be controlled by anti-epileptic 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.

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. The International League Against Epilepsy (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 (condensed from Berg et al)

<table>
<thead>
<tr>
<th>Seizure 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>Complex partial (with impairment of consciousness)</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>Partial seizures evolving to secondarily generalized seizures</td>
</tr>
<tr>
<td><strong>Generalized seizures</strong></td>
</tr>
<tr>
<td>Nonconvulsive (absence)</td>
</tr>
<tr>
<td>Convulsive</td>
</tr>
<tr>
<td><strong>Unclassified seizures</strong></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 that were previously called “idiopathic generalized epilepsies.” The ILAE report published in 2010 offers the following alternative classification:

- **Genetic epilepsies** – These are 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** – These conditions have a distinct structural or metabolic condition that increases the likelihood of seizures. Structural conditions include a variety of central nervous system (CNS) 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** – These are conditions in which the underlying etiology for the seizures cannot be determined and may include both genetic and nongenetic causes.

For the purposes of this policy review, this 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 (GGE) refers to patients who have convulsive (grand mal) seizures, while genetic absence epilepsy (GAE) 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. These are syndromes that are characterized by epilepsy as the primary manifestation. 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. A partial list of these syndromes is as follows:

- Dravet syndrome
- EFMR syndrome (epilepsy limited to females with mental retardation)
- Nocturnal frontal lobe epilepsy
- GEFS+ syndrome (genetic epilepsy with febrile seizures plus)
- EIEE syndrome (early infantile epileptic encephalopathy with suppression burst)
- West syndrome
- Ohtahara syndrome
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Dravet syndrome (also known as severe myoclonic epilepsy in infancy or polymorphic myoclonic epilepsy in infancy) 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.

Genetics

The common 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 particular combination of genes, probably increase the risk by a greater amount. However, it is not well understood how many abnormal genes are required to exceed the threshold to cause clinical epilepsy, nor is it understood which combination of genes may increase the risk more than others.

Early onset epilepsy syndromes may be single-gene disorders. This hypothesis arises from the discovery of pathologic variants in small numbers of patients with the disorders. Because of the small amount of research available, the evidence base for these rare syndromes is incomplete, and new variants are currently being discovered frequently.

Some of the most common genes that have been associated with both the common epilepsies and the rare epileptic syndromes are listed in Table 2.

### Table 2. Selected Genes Most Commonly Associated With Genetic Epilepsy (adapted from Williams and Battaglia, 2013)

<table>
<thead>
<tr>
<th>Genes</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>γ-aminobutyrate A-type subunit</td>
</tr>
<tr>
<td>GABRRA1</td>
<td>γ-aminobutyrate A-type subunit</td>
</tr>
<tr>
<td>GABRD</td>
<td>γ-aminobutyrate 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>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Genes</th>
<th>Physiologic Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHRNB2</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>

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.

Pharmacogenomics
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 pharmogenomics is in identifying 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 labeling for carbamazepine.
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FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration
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.

Centers for Medicare and Medicaid Services (CMS)
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.

Rationale/Source

This policy was originally created in 2014 and has been updated regularly with literature reviews, most recently covering the period through December 21, 2016. Criteria for use of whole exome sequencing are outlined in policy 00389 (whole exome and whole genome sequencing for diagnosis of genetic disorders). This policy does not address testing for genetic syndromes that have a wider range of symptomatology (eg, neurofibromatosis, tuberous sclerosis) or genetic syndromes associated with cerebral malformations or abnormal cortical development, or metabolic or mitochondrial disorders.

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

The genetic epilepsies will be discussed in two categories: The rare epileptic syndromes that may be caused by a single-gene mutation and the common epilepsy syndromes that are thought to have a multifactorial genetic basis.

Early Onset Epilepsy and Epileptic Encephalopathies
There are numerous rare syndromes that have seizures as their primary symptom which generally present in infancy or early childhood and may be classified as epileptic encephalopathies. Many of them 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.

The following table lists some of these syndromes, with the putative causative genetic variants:

Table 3. Early-Onset Epilepsy Syndromes Associated With Single-Gene Variants

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Implicated Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dravet syndrome (severe myoclonic epilepsy of infancy)</td>
<td>SCN1A</td>
</tr>
</tbody>
</table>
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Early infantile epileptic encephalopathy
- STXBP1

Generalized epilepsy with febrile seizures plus (GEFS+)
- SCN1A, SCN2A, SCN1B, GABRG2

Epilepsy and mental retardation limited to females (EFMR)
- PCDH19

Nocturnal frontal lobe epilepsy
- CHRNA4, CHRNB2, CHRNA2

Other less commonly reported single-gene mutations have been evaluated in childhood-onset epilepsies and in early-onset epileptic encephalopathies, including ASAH1, FOLR1, GRIN2A, SCN8A, SYNGAP1, and SYNJ1 variants in families with early-onset epileptic encephalopathies 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 thereby possibly limiting further invasive investigation (eg, 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 infantile- or early-childhood-onset epileptic encephalopathy?

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, EEG features) consistent with epileptic encephalopathies, including conditions such as Dravet syndrome, Ohtahara syndrome, early-onset myoclonic encephalopathy, and West syndrome, 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
Commercial testing is available from numerous companies. Testing for individual genes is available for most, or all, or the genes listed in Table 3, 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. Examples of commercially available genetic panels for epileptic encephalopathies are listed in Table 4. Testing using whole exome sequencing is reviewed in policy 00389 (whole exome and whole genome sequencing for diagnosis of genetic disorders).

Table 4. Commercially Available Genetic Panels for Epileptic Encephalopathies

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Panel Name</th>
<th>No. of Genes Tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>GeneDx</td>
<td>Infantile Epilepsy Panel</td>
<td>53</td>
</tr>
</tbody>
</table>
Comparators
The comparator of interest is standard clinical care without genetic testing.

Outcomes
The general outcomes of interest are symptoms, quality of life, functional outcomes, medication use, resource utilization, and treatment-related morbidity. Specific outcomes in each of these categories are listed in Table 5.

The potential beneficial outcomes of primary interest would be improvement in symptoms (particularly reduction in seizure frequency), functioning, and quality of life. Genetic diagnosis may also limit further invasive investigations into seizure etiology that have associated risks and resource utilization, eg, a genetic diagnosis may spare patients the burden and morbidity of unnecessary epilepsy surgery.

The potential harmful outcomes are those resulting from a false test result. False-positive test results can lead to initiation of unnecessary treatment and adverse effects from that treatment. False-negative test results could lead to unnecessary surgeries.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>Seizure frequency; reduction in seizure frequency by 50%; proportion seizure-free</td>
</tr>
<tr>
<td>Functional outcomes</td>
<td>Measurement of development delays (eg, Bayley Scales of Infant and Toddler Development)</td>
</tr>
<tr>
<td>Quality of life</td>
<td>Validated quality of life assessment tools</td>
</tr>
<tr>
<td>Medication use</td>
<td>Number of unsuccessful medication trials, number of medications needed</td>
</tr>
<tr>
<td>Resource utilization</td>
<td>Number of surgeries</td>
</tr>
<tr>
<td>Treatment-related morbidity</td>
<td>Adverse events of epilepsy medication and surgery</td>
</tr>
</tbody>
</table>

Time
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 first seizure may be initially evaluated by emergency physicians and referred to primary care or neurologist for further diagnosis and management. Patient 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 explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.
Analytic Validity
Epileptic encephalopathies can be evaluated by single-gene analysis, which is generally performed by direct sequencing. Direct sequencing is the criterion standard for identifying specific pathogenic variants. This testing method has an analytic validity of greater than 99%. These encephalopathies can also be evaluated by individual variant testing or panel testing by next-generation sequencing. This method has a lower analytic validity compared with direct sequencing, but is still considered to be very accurate, in the range of 95% to 99%.

Clinical Validity
The literature on the clinical validity of genetic testing for these rare syndromes is limited and, for most syndromes, the clinical sensitivity and specificity is not defined. Dravet syndrome is probably the most well studied, and some evidence on the clinical validity of \textit{SCN1A} variants is available. The clinical sensitivity has been reported to be in the 70% to 80% range. In 1 series (2006) of 64 patients, 51 (79%) were found to have \textit{SCN1A} pathogenic variants. Among 8 infants who met clinical criteria for Dravet syndrome in a 2015 population-based cohort, 6 had a pathogenic \textit{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 results of recent studies and details are described hereinafter.

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Population</th>
<th>Genetic Testing</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moller et al (2016)</td>
<td>216 patients with epileptic encephalopathies phenotypes or familial epilepsy</td>
<td>Epilepsy panel of 46 genes</td>
<td>Diagnostic yield:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 23% patients overall</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 32% of patients with epileptic encephalopathies</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 57% of patients with neonatal-onset epilepsies</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Variant of uncertain significance found in 3%</td>
</tr>
<tr>
<td>Trump et al (2016)</td>
<td>400 patients with early-onset seizures and/or severe developmental delay</td>
<td>Epilepsy and development delay panel of 46 genes</td>
<td>Diagnostic yield:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 18% patients overall</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 39% in patients with seizure onset within first 2 mo of life</td>
</tr>
<tr>
<td>Wirrell et al (2015)</td>
<td>81 patients with infantile spasms and no obvious cause at diagnosis</td>
<td>Karyotyping, aCGH, chromosomal SNV analysis, targeted single-gene testing, gene panels</td>
<td>Diagnostic yield:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 10 (0%) for karyotyping</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 7 (11.3%) of 62 for aCGH</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 1 (33.3%) of 3 for targeted chromosomal SNV analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 1 (11.1%) of 9 for targeted single-gene analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 8 (30.8%) of 26 for epilepsy gene panels</td>
</tr>
<tr>
<td>Mercimek-Mahmutoglu et al (2015)</td>
<td>110 patients with epileptic encephalopathies</td>
<td>aCGH, NGS</td>
<td>Diagnostic yield:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 2.7% for aCGH</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 12.7% for targeted NGS</td>
</tr>
<tr>
<td>Hrabik et al (2015)</td>
<td>147 children with epilepsy</td>
<td>SNV microarray</td>
<td>Diagnostic yield:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 7.5% clinically significant abnormal results</td>
</tr>
</tbody>
</table>
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Moller et al (2016) reported the testing yield with an epilepsy gene panel including 46 genes in a cohort of 216 consecutive patients referred for genetic testing with epileptic encephalopathies phenotypes or familial epilepsy. The patients ranged in age from 2 weeks to 74 years; the majority (52%) had epileptic encephalopathies. The criterion for including a gene in the panel was that it had been reported more than once in patients with monogenic epilepsies as of January 2014. Overall, a presumed disease-causing variant was found in 49 (23%) patients and a variant of uncertain significance (VUS) was found in 3%. The yield was highest in patients with epileptic encephalopathies (32%) and neonatal-onset epilepsies (57%). Variants were found in 19 genes, including SCN1A, STXBP1, CDKL5, SCN2A, SCN8A, GABRA1, KCNA2, and STX1B.

Trump et al (2016) also reported the yield of a gene panel including 46 genes in 400 patients with early-onset seizure disorders and/or severe developmental delay who were referred for gene panel testing in the United Kingdom. Patients with major structural brain malformations or clinically significant copy number defects on microarray were not included. Authors reported that genes were included in the panel if they had been “established” as causes of early-onset seizures and/or severe developmental delay in patients without frequent major structural brain anomalies. Approximately half of the included genes overlapped with genes on the panel from Moller et al. Genes were added to the panel over time so that the original panel used in the first 48 patients included 29 genes, a second panel used in 94 patients included 39 genes, and the final panel used in the remaining 258 patients included 46 genes. Variants were found in 21 genes, most commonly SCN2A, CDKL5, KCNQ2, SCN8A, FOXL1, MECP2, SCNA1, STXBP1, KCNT1, PCDH19, and TCF4.

Wirrell et al (2015) reported on the genetic and metabolic testing yield among patients with newly diagnosed infantile spasms enrolled in a multicenter prospective cohort study. Among 251 patients enrolled, 112 had no obvious cause at diagnosis. Of those without an obvious cause at diagnosis, 81 (72.3%) underwent genetic testing, which demonstrated a causal abnormality in 19 (23.5%) and a VUS in 12 (14.8%). The diagnostic yield was 0 (0%) of 10 for karyotyping, 7 (11.3%) of 62 for array comparative genomic hybridization (aCGH), 1 (33.3%) of 3 for targeted chromosomal single-nucleotide variant (SNV) analysis, 1 (11.1%) of 9 for targeted single-gene analysis, 8 (30.8%) of 26 for epilepsy gene panels, 0 (0%) of 3 for whole exome or whole genome sequencing, 0 (0%) of 2 for mitochondrial SNV panels, and 2 (28.6%) of 7 for mitochondrial gene panels.

Mercimek-Mahmutoglu et al (2015) reported on the genetic testing yield in children with epileptic encephalopathies in a retrospective, single-center cohort study. All subjects included had intractable epilepsy and global developmental delay and cognitive dysfunction, and were seen at an epilepsy genetics clinic from January 2012 to June 2014 (N=110). Among all patients, 31 (28%) had an identifiable genetic disorder, including 8 with an inherited metabolic disorder leading to epileptic encephalopathy and 23 with other genetic causes of epileptic encephalopathy. Overall, a specific genetic cause was identified based on suggestive clinical features in 4.5%, pathogenic copy number variants on aCGH in 2.7%, brain magnetic resonance imaging in 1.8%, metabolic studies in 7%, and targeted next-generation sequencing (NGS) in 12.7%.
Another single-center study reported on the yield of aCGH results among a group of 147 children with epilepsy, which, although not comprised exclusively of children with epileptic encephalopathies, had a high proportion (79.9%) of patients with intellectual disability or developmental delay. Overall, 17.7% (n=26) had abnormal microarray results, 11 (7.5% of the overall population) of which were considered to be clinically significant.

The false-positive rate and the VUS frequency in testing for genes associated with early-onset epileptic encephalopathies are not well-characterized.

**Clinical Utility**

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 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 in terms of 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, ie, there are no studies that report on whether the efficacy of treatment directed by genetic testing is superior to efficacy of treatment without genetic testing. However, a chain of evidence might be constructed to demonstrate the utility of genetic testing for epileptic encephalopathies. As mentioned above, the differential diagnosis for 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 (eg, carbamazepine). In addition, 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.

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

The purpose of genetic testing in patients who are presumed to have a genetic epilepsy is to determine etiology of the epilepsy syndrome and thereby possibly limiting further invasive investigation (eg, 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.

Patients
The relevant population of interest is patients with clinical features (age of onset, seizure semiology, EEG 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 above, commercial tests are available from many companies. Examples are listed in Table 7. Testing using whole exome sequencing is reviewed in policy 00389 (whole exome and whole genome sequencing for diagnosis of genetic disorders).

Table 7. Commercially Available Comprehensive Genetic Panels for Epilepsy

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Panel Name</th>
<th>No. of Genes Tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>GeneDx</td>
<td>Comprehensive Epilepsy Panel</td>
<td>87</td>
</tr>
<tr>
<td>GeneDx</td>
<td>Childhood Onset Epilepsy</td>
<td>58</td>
</tr>
<tr>
<td>MNG</td>
<td>Comprehensive Epilepsy</td>
<td>165</td>
</tr>
<tr>
<td>Athena Diagnostics</td>
<td>Epilepsy Advanced Sequencing Evaluation</td>
<td>141</td>
</tr>
<tr>
<td>University of Chicago Genetic</td>
<td>Infantile and Childhood Epilepsy sequencing</td>
<td>75</td>
</tr>
<tr>
<td>Services</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Courtagen</td>
<td>epiSEEK Comprehensive</td>
<td>471</td>
</tr>
<tr>
<td>Courtagen</td>
<td>epiSEEK Focus</td>
<td>76</td>
</tr>
</tbody>
</table>

Comparators
The comparator of interest is 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 8. 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 8. Outcomes of Interest for Individuals With Symptomatic Epilepsy

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>Seizure frequency; reduction in seizure frequency by 50%; proportion seizure-free; Child Symptom Inventory, Adolescent Symptom Inventory</td>
</tr>
<tr>
<td>Functional outcomes</td>
<td>Validated measures of cognitive functioning (eg, Wechsler scales, California Verbal Learning Test)</td>
</tr>
<tr>
<td>Quality of life</td>
<td>Validated measure of quality of life (eg, Quality of Life in Epilepsy Inventory for Adolescents, Quality of Life in Childhood Epilepsy)</td>
</tr>
<tr>
<td>Medication use</td>
<td>Number of unsuccessful medication trials, number of medications needed</td>
</tr>
<tr>
<td>Resource utilization</td>
<td>Number of surgeries</td>
</tr>
<tr>
<td>Treatment-related morbidity</td>
<td>Adverse effects of epilepsy medication and surgery</td>
</tr>
</tbody>
</table>

Time
As described in the previous section.

Setting
As described in the previous section.

Analytic Validity
The genetic epilepsies are generally evaluated by genetic panel testing. The larger, commercially available panels that include many variants are generally performed by next-generation sequencing. This method has
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a lower analytic validity compared with direct sequencing but is still considered to be very accurate, in the range of 95% to 99%. Less commonly, deletion/duplication analysis may be performed; this method is also considered to have an analytic validity of greater than 95%.

Clinical Validity
The literature on clinical validity includes many studies that have reported on the association between various genetic variants and epilepsy. A large number of case-control studies have compared the frequency of genetic variants in patients with epilepsy with the frequency in patients without epilepsy. There is a smaller number of genome-wide association studies (GWAS) that evaluate the presence of SNVs associated with epilepsy across the entire genome. No studies were identified that reported the clinical sensitivity and specificity of genetic variants in various clinically defined groups of patients with epilepsy. In addition to these studies on the association of genetic variants with the diagnosis of epilepsy, numerous other studies have evaluated the association between genetic variants and pharmacogenomics of AEDs.

Diagnosis of Epilepsy
The Epilepsy Genetic Association Database (epiGAD) published an overview of genetic association studies in 2010. This review identified 165 case-control studies published between 1985 and 2008. There were 133 studies that examined the association of 77 different genetic variants with the diagnosis of epilepsy. Approximately half of these studies (65/133) focused on patients with genetic generalized epilepsy. Most of these studies had relatively small sample sizes, with a median of 104 cases (range, 8-1361) and 126 controls (range, 22-1390). There were less than 200 case patients in 80% of the studies. The majority of the studies did not show a statistically significant association. Using a cutoff of p<0.01 as the threshold for significance, there were 35 studies (21.2%) that reported a statistically significant association. According to standard definitions for genetic association, all of the associations were in the weak to moderate range, with no associations reported that were 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, genetic generalized epilepsy 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 genetic generalized epilepsy, 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=8.71×10^{-10} and 5.44×10^{-9}, respectively). For those with genetic generalized epilepsy, a locus at 2p16.1 (VRK2 or FANCL) was significantly associated with epilepsy (p=9.99×10^{-5}). No SNPs were significantly associated with focal epilepsy.

Some of the larger GWAS studies are described here. The EPICURE Consortium published one of the larger GWAS of genetic generalized epilepsy in 2012. This study included 3020 patients with genetic generalized epilepsy (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 SNPs. In the discovery phase, 40 candidate SNPs were identified that exceeded the significance for the screening threshold (1×10^{-5}), although none of these reached the threshold defined as statistically significant for GWA.
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After stage 2 analysis, there were 4 SNPs identified that had suggestive associations with GGE on genes SCN1A, CHRM3, ZEB2, and NLE2F1.

A second GWAS with a relative large sample size of Chinese patients was also published in 2012. Using a similar 2-stage methodology, this study evaluated 1,087 patients with epilepsy and 3,444 matched controls. Two variants were determined to have the strongest association with epilepsy. One of these was on the CAMSAP1L1 gene and the second was on the GRIK2 gene. There were several other loci on genes that were suggestive of an association on genes 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 of SLC6A4 gene variants with 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 a total of 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 (OR=1.48; 95% 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 SCN1A IVS5N+5GNA polymorphism and susceptibility to epilepsy with febrile seizures. The analysis included 6 studies with 2719 cases and 2317 controls. There was a found significant association between SCN1A polymorphism and EFS (A versus. G: OR = 1.5; 95%CI, 1.1–2.0).

Prognosis of Epilepsy

A smaller body of literature has evaluated whether specific genetic variants are associated epilepsy phenotypes or prognosis. Van Podewils et al evaluated the association of sequence variants in EFHC1 and phenotypes and outcomes in 38 probands with juvenile myoclonic epilepsy, along with 3 family members. Several EFHC1 variants, including F229L, R294H, and R182H, were associated with earlier onset of generalized tonic clonic seizures (66.7% vs 12.5%, OR=13, p=0.022), high risk of status epilepticus (p=0.001), and decreased risk of bilateral myoclonic seizures (p=0.05).

Pharmacogenomics of Antiepileptic Medications

Numerous case-control studies report on the association of various genetic variants with response to medications in patients with epilepsy. The epiGAD database identified 32 case-control studies of 20 different genes and their association with medication treatment. The most common comparison was between patients who were responders to medication and patients who were nonresponders. Some of the larger representative studies are discussed below.
Kwan et al. compared the frequency of SNVs on the SCN1A, SCN2A, and SCN3A genes in 272 drug responsive patients and 199 drug resistant patients. A total of 27 candidate SNVs were evaluated, selected from a large database of previously identified SNPs. There was one SNV identified on the SCN2A gene (rs2304016) that had a significant association with drug resistance (OR=2.1; 95% CI, 1.2 to 3.7; p<0.007).

Jang et al. 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 relationship with drug resistance. In further analysis of whether there were gene-gene interactions that were associated with drug resistance, the authors reported that there was a possible interaction of 2 variants, one on the SCN2A gene and the other on the SCN1B gene, that were of borderline statistical significance (p=0.055).

Li et al conducted a meta-analysis of 28 articles reporting on 30 case-control studies to evaluate the association between the ABCB1 gene C3435T polymorphism 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: 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 report associations between genetic polymorphisms and antiepileptic drug response are summarized in Table 9.

Table 9: Genetic Variants and Antiepileptic Drug Response

<table>
<thead>
<tr>
<th>Study</th>
<th>Population Description</th>
<th>Genes</th>
<th>Overview of Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lu et al (2016)</td>
<td>124 epileptic Chinese patients receiving oxcarbazepine monotherapy</td>
<td>UGT1A4 142T&gt;G (rs2011425)</td>
<td>UGT1A9 variant allele 1399C&gt;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&lt;0.05) and poorer seizure control than noncarriers (p=0.01)</td>
</tr>
<tr>
<td>Hashi et al (2015)</td>
<td>50 epileptic adults treated with stable clobazam dose</td>
<td>CYP2C19</td>
<td>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])</td>
</tr>
<tr>
<td>Ma et al (2015)</td>
<td>184 epileptic patients receiving OXC monotherapy and 156 healthy volunteers</td>
<td>SCN1A c.3184A&gt;G (rs2298771)</td>
<td>Patients with EM or IM status had no change in seizure frequency with clobazam therapy</td>
</tr>
<tr>
<td>Ma et al (2015)</td>
<td></td>
<td>SCN2A c.56G&gt;A (rs17183814)</td>
<td></td>
</tr>
<tr>
<td>Ma et al (2015)</td>
<td></td>
<td>SCN2A IVS7-32A&gt;G (rs2304016)</td>
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</tr>
<tr>
<td>Ma et al (2015)</td>
<td></td>
<td>ABCC2 3972C&gt;T (rs3740066)</td>
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</tr>
<tr>
<td>Ma et al (2015)</td>
<td></td>
<td>ABCC2 c.1249G&gt;A (rs2273697)</td>
<td></td>
</tr>
<tr>
<td>Ma et al (2015)</td>
<td></td>
<td>UGT2B7 c.802T&gt;C (rs7439366)</td>
<td></td>
</tr>
<tr>
<td>Guo et al (2016)</td>
<td>483 Chinese patients</td>
<td>KCNJ10</td>
<td>Frequency of rs12402969 C allele and the CC+CT</td>
</tr>
</tbody>
</table>

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### Study Population Genes Overview of Findings

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Genes</th>
<th>Overview of Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>(2015)</td>
<td>with genetic generalized epilepsies</td>
<td></td>
<td>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)</td>
</tr>
<tr>
<td>Ma et al (2014)</td>
<td>453 epileptic patients, classified as drug-responsive (n=207) or drug-resistant (n=246)</td>
<td>SCN1A c.3184A&gt;G (rs2298771)</td>
<td>• SCN1A IVS5-91G&gt;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&lt;0.001, uncorrected)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SCN2A c.56G&gt;A (rs17183814)</td>
<td>• SCN1A IVS5-91G&gt;A AA more prevalent in drug-resistant than drug-responsive patients receiving carbamazepine/oxcarbazepine (OR=3.55; 95% CI, 1.62 to 7.78; p=0.002, uncorrected)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SCN2A IVS7-32A&gt;G (rs2304016)</td>
<td>• ABC2C 3972C&gt;T (rs3740066) GA genotype and allele A significantly associated with drug response (OR=2.14; 95% CI. 1.62 to 2.51; p=0.007)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ABCC2 c.1249G&gt;A (rs2273697)</td>
<td>• ABC2 variants not associated with time to first seizure or time to 12-mo remission</td>
</tr>
<tr>
<td>Radisch et al (2014)</td>
<td>229 epileptic patients treated with carbamazepine monotherapy</td>
<td>ABCC2: variant rs717620 (-24G4A), rs2273697 (c.1249G4A) and rs3740067</td>
<td>Patients EPHX1 c.416A&gt;G genotypes had higher adjusted plasma carbamazepine concentrations vs those with wild-type genotype (p&lt;0.05)</td>
</tr>
<tr>
<td>Yun et al (2014)</td>
<td>38 epileptic patients treated with carbamazepine monotherapy</td>
<td>EPHX1 c.337T&gt;C</td>
<td>• Other studied variants not associated with carbamazepine pharmacore-sistance</td>
</tr>
<tr>
<td>Taur et al (2014)</td>
<td>115 epileptic patients treated with phenytoin, phenobarbital, and/or carbamazepine</td>
<td>ABCB1 (c.3435T)</td>
<td>• ABCB1 C3435T genotype and allele variants significantly associated with drug response (OR=4.5; 95% CI, 1.04 to 20.99; OR=1.73; 95% CI, 1.02 to 2.95, respectively)</td>
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<tr>
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<td>CYP2C9 (416C&gt;T)</td>
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<td>CYP2C9 (1061A&gt;T)</td>
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<td>CYP2C19 (681G&gt;A)</td>
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<tr>
<td></td>
<td></td>
<td>CYP2C19 (636G&gt;A)</td>
<td></td>
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</tbody>
</table>

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 examined the association between SNVs on the ABCB1 gene and drug resistance in 3231 drug resistant patients and 3524 controls from 22 studies. The authors reported no significant relationship 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 between on subgroup analysis by ethnicity.

In a separate meta-analysis, Sun et al 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 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, including 634 drug-resistant patients, 615 drug-responsive patients, and 1052 healthy controls. In pooled analysis, the MDR1 C3435T variant was not significantly associated with a risk of drug resistance.
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newly diagnosed patients in Glasgow, of whom a large proportion had participated in randomized trials of AED monotherapy. Drug response phenotypes in this cohort were identified by retrospectively reviewing prospectively collected clinical trial and/or hospital notes. The second cohort was drawn from patients who had participated in the Standard and New Epileptic Drugs (SANAD) trial, a multicenter RCT comparing standard and newer AEDs. The trial included 2400 patients, of whom 520 of self-described European ancestry who provided DNA samples were used in the present analysis. The kNN model derived from the original Australian cohort did not predict treatment response in either the Glasgow or the SANAD cohorts. Investigators redeveloped a kNN learning algorithm based on SNV genotypes and drug responses in a training dataset (n=343) derived from the SANAD cohort. None of the 5 SNVs used in the multigenic classifier 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 (PPV) of 50% (95% CI, 32.8% to 67.2%) and a negative predictive value (NPV) of 54% (95% CI, 41.1% to 66.7%). In a cross-validation analysis, the 5-SNV classifier was significantly predictive of treatment responses among Glasgow cohort patients initially prescribed either carbamazepine or valproate (PPV=67%, NPV=60%; corrected p=0.018), but not among those prescribed lamotrigine (corrected p=1.0) or other AEDs (corrected p=1.0). The 5-SNV classifier was significantly predictive of treatment responses among SANAD cohort patients initially prescribed carbamazepine or valproate (PPV=69%, NPV=56%; corrected p=0.048), but not among those prescribed lamotrigine (corrected p=0.36) or other AEDs (corrected p=0.36).

Pharmacogenomics of AED Adverse 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 [DRESS]) and maculopapular exanthema. This GWAS study included 60 cases with phenytoin-related severe cutaneous adverse events and 412 population controls, and was followed by a case-control study of 105 cases with phenytoin-related severe cutaneous adverse events (61 with SJS/TEN, 44 with DRESS) 78 cases with maculopapular exanthema, 130 phenytoin-tolerant control participants, and 3655 population controls from Taiwan, Japan, and Malaysia. In the GWAS analysis, a missense variant of CYP2C9*3 (rs1057910) was significantly associated with phenytoin-related severe cutaneous adverse events (OR=12; 95% CI, 6.6 to 20; p=1.1x10^-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=1.2x10^-19), DRESS (OR=19; 95% CI, 5.1 to 71; p=7.0x10^-7), and maculopapular exanthema (OR=5.5; 95% CI, 1.5 to 21; p=0.01).

He et al (2014) conducted a case-control study to evaluate the association between carbamazepine-induced SJS/TEN and 10 SNVs in the genes ABCB1, CYP3A4, EPHX1, FAS, SNC1A, MICA, and BAG6.
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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 recurrence of the cutaneous adverse drug reaction on re-exposure (cross-reactive group). Subjects tolerant to re-exposure were more likely to carry the HLA-A*2402 allele than cross-reactive subjects (OR=0.13; 95% CI, 0.015 to 1.108; p=0.040). Frequency distributions for testing other HLA alleles did not differ significantly between groups.

**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.

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 to 2936 controls. Mean epilepsy onset of the SUDEP cases was 10 years and mean age at death was 28 years. In 28 (46%) of 61 SUDEP cases, previously reported pathogenic variants, or candidate pathogenic variants were identified in common genes responsible for long QT syndrome and in 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.

Clinical Utility
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 in terms of 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 clinical validity of testing for diagnosis of epilepsy is not consistent in showing an association of any specific genetic variant with any specific type of epilepsy. Where associations have been reported, they are not of strong magnitude and, in most cases, have not been replicated independently or through the available meta-analyses. Because of the lack of established clinical validity, the clinical utility of genetic testing for the diagnosis of genetic epilepsies is also lacking. Several studies have reported associations between a number of genes and response to AEDs or AED adverse events. How this information should be used to tailor medication management is not yet well-defined, and no studies were identified that provide evidence for clinical utility.

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 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 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.
Summary of Evidence
For individuals who have infantile- or early-childhood-onset epileptic encephalopathy who receive testing for genes associated with epileptic encephalopathies, the evidence includes prospective and retrospective cohort studies describing the testing yield. Relevant outcomes are test accuracy and validity, changes in reproductive decision making, symptoms, quality of life, functional outcomes, medication use, resource utilization, and treatment-related morbidity. For Dravet syndrome, which appears to have the largest body of associated literature, the sensitivity of testing for \textit{SCN1A} disease-associated variants is high (~80%). For other early-onset epileptic encephalopathies, the true clinical sensitivity and specificity of testing is not well-defined. However, studies reporting on the overall yield of genetic testing in populations with epileptic encephalopathies and early-onset epilepsy report detection rates for clinically significant variants ranging from 7.5% to 57%. The clinical utility of genetic testing occurs primarily when there is a positive test for a known pathogenic variant. The presence of a pathogenic variant may lead to targeted medication management, avoidance of other diagnostic tests, and/or informed reproductive planning. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health 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 generally report some association between variants in a number of genes (including \textit{SCN1A}, \textit{SCN2A}, \textit{ABCC2}, \textit{EPHX1}, \textit{CYP2C9}, \textit{CYP2C19}), and AED response. Similarly, genetic associations between a number of genes and AED-related adverse effects have been reported. However, no empirical evidence on the clinical utility of genetic testing for the genetic epilepsies was identified, and the changes in clinical management that might occur as a result of testing are not well-defined. The evidence is insufficient to determine the effects of the technology on health outcomes.

References
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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
05/04/2017 Medical Policy Committee review
05/17/2017 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
Next Scheduled Review Date: 05/2018

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**ICD-10 Diagnosis**

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A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. 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:

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2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or

3. Reference to federal regulations.

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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.

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