Genetic Testing for Epilepsy

Policy #  00401
Original Effective Date:  02/19/2014
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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 mutations 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 the common epilepsies, which are also called idiopathic epilepsies. These are defined as epilepsy syndromes that present in childhood, adolescence, or early adulthood, in which epilepsy is the only clinical manifestation and for which there is not a structural or metabolic defect predisposing to epilepsy.

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.

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.

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 mutations 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 mutations 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)
- EIEE syndrome (early infantile epileptic encephalopathy with suppression burst; also known as Ohtahara syndrome)
- Landau-Kleffner syndrome
- West syndrome
- Glucose transporter type 1 deficiency syndrome

Mutations in a large number of genes have been associated with early onset epilepsies. Some of these are summarized in Table 1.
Table 1: Single-Gene Mutations Associated With Epileptic Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Associated Genes</th>
</tr>
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<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, SLC25A22, STXBP1, CDKL5, ARX</td>
</tr>
<tr>
<td>Landau-Kleffner syndrome</td>
<td>GRIN2A</td>
</tr>
<tr>
<td>West syndrome</td>
<td>ARX, TSC1, TSC2, CDKL5, 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 mutation 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.

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. The common epilepsies, also called idiopathic epilepsy, are thought to have a complex, multifactorial genetic basis. There are also numerous rare epileptic syndromes that occur in infancy or early childhood and that may be caused by a single gene mutation. Genetic testing is commercially available for a large number of genetic mutations 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.

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 shown in Table 2, which is widely used for clinical care and research purposes. Classification of seizures can also be done on the basis of age of onset:

- Neonatal
- Infancy
- Childhood
- Adolescent/Adult

Table 2. Classification of Seizure Disorders by Type (condensed from Berg et al)

<table>
<thead>
<tr>
<th>Seizures Disorders</th>
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</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>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
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 mutations 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 of Epilepsy**

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 mutations 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 mutations 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 3.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Physiologic Function</th>
</tr>
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<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>GABRR1</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>
</tbody>
</table>
For the severe early epilepsy syndromes, the disorders most frequently reported to be associated with single-gene mutations include GEFS+ syndrome (associated with SCN1A, SCN1B, GABRG2 mutations), Dravet syndrome (associated with SCN1A mutations, possibly modified by SCN9A mutations), and epilepsy and intellectual disability limited to females (associated with PCDH19 mutations). Ohtahara syndrome has been associated with mutations 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 not an underlying cause identified it is thought to be due to a multifactorial genetic predisposition.

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 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.

Genetic Testing for Epilepsy
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. Because of the large number of potential genes, panel testing is available from a number of genetic companies. These panels typically include large numbers of genes that have been implicated in diverse disorders.

GeneDx offers a number of different epilepsy panels that have overlapping genes in varying combinations. The GeneDx Comprehensive Epilepsy Panel lists 70 genes. GeneDx also offers a childhood-onset epilepsy panel and an infantile epilepsy panel. The GeneDx Infantile Epilepsy Panel includes the following 53 genes:

- ADSL
- ALDH7A1
- ARX
- ATP6AP2
- CDKL5
- CHRNA7
- CLN3
- CLN5
- CLN6
- CLN8
- CNTNAP2
- CTSD
- FOLR1
- FOXG1
- GABRA1
- GABRG2
- GAMT
- GRIN2A
- GRIN2B
- KANSL1
- KCNJ10
- KCNQ2
- KCNQ3
- KCTD7
- LIAS
- MAGI2
- MBD5
- MECP2
- MEF2C
- MFSD8
- NRXN1
- PCDH19
- PNKP
- PNPO
- POLG
- PPT1

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PRRT2, SCN1A, SCN1B, SCN2A, SCN8A, SLC25A22, SLC2A1, SLC9A6, SPTAN1, STXBP1, TBC1D24, TCF4, TPP1 (CLN2), TSC1, TSC2, UBE3A, ZEB2

The Courtagen epiSEEK® gene panel includes over 200 genes in its panel.

Emory Genetics Laboratory’s Epilepsy and Seizure Disorders Sequencing Panel is a next-generation sequencing panel that includes 110 genes.

FDA or Other Governmental Regulatory Approval
U.S. Food and Drug Administration
No U.S. FDA-cleared genotyping tests were identified. The available commercial genetic tests for epilepsy are offered as laboratory-developed tests. Clinical laboratories may develop and validate tests in-house ("home-brew") and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA).

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
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 Syndromes Associated With Single-Gene Mutations
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 mutations. The published literature on these syndromes generally consists of small cohorts of patients treated in tertiary care centers, with descriptions of genetic mutations that are detected in affected individuals.

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

| Table 4. Early-Onset Epilepsy Syndromes Associated With Single-Gene Mutations |
|-----------------------------|-----------------------------|
| Syndrome                    | Implicated Genes            |
| Dravet syndrome (severe myoclonic epilepsy of infancy) | SCN1A |

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Early infantile epileptic encephalopathy

Generalized epilepsy with febrile seizures plus (GEFS+)

Epilepsy and mental retardation limited to females (EFMR)

Nocturnal frontal lobe epilepsy

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 mutations in families with early-onset epileptic encephalopathies and SLC13A5 mutations in families with pedigrees consistent with autosomal recessive epileptic encephalopathy.

**Analytic validity**

These syndromes can be evaluated by single-gene analysis, which is generally performed by direct sequencing. Direct sequencing is the gold standard for identifying specific mutations. This testing method has an analytic validity of greater than 99%. They can also be evaluated by genetic panel testing, which is generally done by next-generation sequencing. This method has a lower analytic validity compared to 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 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 SCN1A mutations is available. The clinical sensitivity has been reported to be in the 70 to 80% range. In 1 series of 64 patients, 51 (79%) were found to have SCN1A mutations. Among 8 infants who met clinical criteria for Dravet syndrome in a population-based cohort, 6 had a pathogenic SCN1A mutation, all of which were de novo.

A number of studies have reported on the yield of genetic testing in cohorts of pediatric patients with epilepsy, typically in association with other related symptoms.

Wirrell et al reported the yield of genetic and metabolic testing 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 variant of uncertain significance (VOUS) in 12 (14.8%). The diagnostic yield was 0 of 10 (0%) for karyotyping, 7 of 62 (11.3%) for array comparative genomic hybridization (aCGH), 1 of 3 (33.3%) for targeted chromosomal single nucleotide polymorphism (SNP) analysis, 1 of 9 (11.1%) for targeted single-gene analysis, 8 of 26 (30.8%) for epilepsy gene panels, 0 of 3 (0%) for whole exome or whole genome sequencing, 0 of 2 (0%) for mitochondrial SNP panels, and 2 of 7 (28.6%) for mitochondrial gene panels.

Mercimek-Mahmutoglu et al reported on the yield of genetic testing 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
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suggestive clinical features in 4.5%, pathogenic copy number variants on aCGH in 2.7%, brain MRI 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 frequency of VOUS in testing for genes associated with early-onset epileptic encephalopathies are not well characterized.

Clinical Utility
One 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, and it is not known how often genetic testing leads to a definitive diagnosis when the diagnosis cannot be 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.

Another potential area of clinical utility may be in directing pharmacologic treatment. 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 that are known to be less effective, such as carbamazepine. However, there are no studies that examine the frequency with which genetic testing leads to changes in medication management, and 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.

For the early-onset epilepsies that may have a genetic component, interventions to reduce the risk of having an affected offspring may be another 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 mutations 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 mutation 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.

Evidence of Clinical Utility of Genetic Testing for Early-Onset Epilepsy Syndromes
The evidence related to the clinical utility of genetic testing in patients with early-onset epileptic encephalopathies is limited. One study was identified that described the use of genetic testing in practice, including changes in management that occurred following testing. Ream et al reported a retrospective review of 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.
(out of a total of 175 new patients seen at the authors’ center, of whom 37 had drug-resistant epilepsy) who underwent genetic testing with 1 or more of the following: karyotype, chromosomal microarray, gene sequencing of specific single genes, gene sequencing using a panel, and/or whole exome sequencing (WES). Genetic testing was obtained based on the clinical judgment of treating providers due to the lack of an alternative nongenetic etiology and clinical suspicion for a genetic cause. Fourteen (56%) of tested patients had epileptic encephalopathies; 17 (68%) had generalized epilepsy syndromes. Compared with those who had no genetic testing, patients who underwent genetic testing were more likely to have generalized epilepsy (68% vs 17%, p=0.005), developmental delay (96% vs 42%, p=0.001), or epileptic encephalopathy (56% vs 0%, p=0.002). Of the 25 patients in the newly evaluated group, 15 had positive findings on genetic testing (defined as a “potentially significant” result), while 10 of those were considered to be diagnostic (consisting of mutations previously described to be disease-causing for epilepsy syndromes or variants predicted to be disease-causing.) The yield of a diagnostic result for the various testing modalities were as follows: 1 of 7 tested (14.3%) for karyotype; 2 of 12 tested (16.7%) for microarray; 2 of 13 tested (15.4%) for targeted single-gene sequencing; 6 of 13 (46.2%) for epilepsy gene panel testing; 1 of 6 tested (16.7%) for WES (confirmatory of a variant detected on an epilepsy panel). The yield of genetic testing 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: 2 of 2 patients with Dravet syndrome phenotype had pathologic mutations in SCN1A; 3 of 9 patients with Lennox-Gastaut syndrome had identified mutations (1 with a CDKL5 mutation, 1 with an SCL9A6 mutation, 1 with both SCN1A and EFHC1 mutations). Two patients (6.9%) had diagnostic mutations that were not suspected based on their clinical phenotypes. In 8 patients (27.6%), genetic test results had potential therapeutic implications. However, only 1 patient had significantly reduced seizure frequency, in the case of a patient who received stiripentol following a positive SCN1A mutation test.

Section Summary
There are numerous rare epileptic syndromes which may be caused by single-gene mutations, but the evidence on genetic testing for these syndromes is insufficient to form conclusions on the clinical validity and clinical utility of genetic testing. The syndrome with the greatest amount of evidence is Dravet syndrome. The clinical sensitivity of testing patients with clinically defined Dravet syndrome is relatively high in small cohorts of patients. There may be clinical utility in avoiding further testing and directing treatment in probands, and for reproductive planning, but there is only a small amount of empiric evidence to suggest this and no evidence demonstrating that outcomes are improved.

Common Epilepsies
The common epilepsy syndromes, also known as idiopathic epilepsy, generally 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.

Analytic validity
The common epilepsies are generally evaluated by genetic panel testing. The larger, commercially available panels that include many mutations are generally performed by next-generation sequencing. This method has a lower analytic validity compared to direct sequencing, but is still considered to be very
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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 report the association of various genetic variants with the common epilepsies. There are a large number of case-control studies that compare the frequency of genetic variants in patients with epilepsy to the frequency in patients without epilepsy. There is a smaller number of genome-wide association studies (GWAS) that evaluate the presence of SNPs associated with epilepsy across the entire genome. No studies were identified that reported the clinical sensitivity and specificity of genetic mutations 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, there are numerous other studies that evaluate the association of genetic variants with pharmacogenomics of antiepileptic medications.

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
(1×10^3). 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 contrast to the 2 studies, a GWAS published from the UK failed to show any robust associations of SNPs with partial epilepsy. This study included 3,445 patients with partial epilepsies and 6,935 controls of European ancestry. Using a threshold of an odds ratio greater than 1.3, the authors reported that no SNPs were identified that had a statistically significant association at that level.

In 2012, Heinzen et al. used whole exome sequencing to evaluate the association of genetic variants with genetic generalized epilepsy in 118 individuals with the disorder and 242 control patients of European origin. No variants were found that reached the statistical threshold for a statistical association. From this initial data, the researchers selected 3897 candidate genetic variants. These variants were tested in a replication sample of 878 individuals with GGE and 1830 controls. None of the tested variants showed a statistically significant association.

In 2014, Baum et al conducted a case-control study to evaluate the association of polymorphisms in SCN1A, SCN2A, SCN3A, SCN1B, and SCN2B genes and epilepsy. The analysis included 1529 epilepsy patients and 1935 controls from 4 ethnicities or locations. The SCN1A IVS5N+5G>A polymorphism showed the strongest associated with epilepsy, with an OR of 0.85 for allele G (p<0.000) and 0.73 for genotype GG versus AA (p=0.003). Other gene polymorphisms significantly associated with epilepsy included SCN1A (rs10188577, OR=1.20 for the C allele, p=0.003) and SCN2A (rs12467383, OR=1.16 for the A allele, p<0.009).

In a case-control study that included 441 epilepsy patients (240 with mesial temporal lobe epilepsy with hippocampal sclerosis, 201 with juvenile myoclonic epilepsy) and 267 nonepileptic controls, Balan et al reported that the GABA_A receptor subunit gene GABARG2 (rs211037) is significantly associated with both types of epilepsy (OR=1.6; 95% confidence interval [CI], 1.22 to 2.08; p<0.000).

In addition to the individual studies, there are a number of meta-analyses that evaluate the association of particular genetic variants with different types of epilepsy. Most of these have not shown a significant association. For example, Cordoba et al. evaluated the association of SLC6A4 gene variants with temporal lobe epilepsy in a total of 991 case patients and 1202 controls and failed to demonstrate a significant association on combined analysis. Nurmohamed et al. performed a meta-analysis of 9 case-control studies that evaluated the association of the ABC1 gene polymorphisms with epilepsy. There were 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. in 2008. This study evaluated the association of variants in the IL1B gene with temporal lobe epilepsy and febrile seizures, using data from 13
studies of 1866 patients with epilepsy and 1930 controls. Combined analysis showed a significant relationship between one SNP (511T) and temporal lobe epilepsy, with a strength of association that was considered modest (odds ratio [OR]=1.48; 95% confidence interval [CI], 1.1 to 2.0; p=0.01).

**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**

*Pharmacogenomic of Antiepileptic Drug Response*

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 SNPs on the *SCN1A*, *SCN2A*, and *SCN3A* genes in 272 drug responsive patients and 199 drug resistant patients. A total of 27 candidate SNPs were evaluated, selected from a large database of previously identified SNPs. There was one SNP 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 5.
### Table 5: Genetic Polymorphisms and Antiepileptic Drug Response

<table>
<thead>
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<th>Study</th>
<th>Population</th>
<th>Genes</th>
<th>Overview of Findings</th>
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| Hashi et al (2015)     | 50 adults with epilepsy treated with stable clobazam dose                    | CYP2C19                                                              | - Clobazam metabolite N-desmethyloclobazam serum concentration:dose ratio was higher in PMs (median, 16,300 [ng/mL]/[mg/kg/d]) than in EMs (median, 1760 [ng/mL]/[mg/kg/d]) or IMs (median, 4640 [ng/mL]/[mg/kg/d])  
- Patients with EM or IM status had no change in seizure frequency with clobazam therapy. |
| Ma et al (2015)        | 184 epileptic patients receiving OXC monotherapy and 156 healthy volunteers | SCN1A c.3184A>G, SCN2A c.56G>A, SCN2A IVS7-32A>G, ABCC2 3972C>T, ABCC2 c.1249G>A, UGT2B7 c.802T>C | - SCN1A IVS5-91G>A, UGT2B7 c.802T>C, and ABCC2 c.1249G>A polymorphisms showed significant associations with OXC maintenance doses  
- Patients with the variant ABCC2 c.1249G>A allele were more likely to require higher OXC maintenance doses than noncarriers (p=0.002, uncorrected), which remained significant after Bonferroni correction |
| Ma et al (2014)        | 453 patients with epilepsy, classified as drug-responsive (n=207) or drug-resistant (n=246) | SCN1A c.3184A>G, SCN2A c.56G>A, SCN2A IVS7-32A>G, ABCC2 3972C>T, ABCC2 c.1249G>A, UGT2B7 c.802T>C | - SCN1A IVS5-91G>A AA genotype more prevalent in drug-resistant than drug-responsive patients receiving multidrug therapy (OR=3.41; 95% CI, 1.73 to 6.70; p<0.001, uncorrected)  
- SCN1A IVS5-91G>A AA more prevalent in drug-resistant than drug-responsive patients receiving carbamazepine/oxcarbazepine (OR=3.55; 95% CI, 1.62 to 7.78; p=0.002, uncorrected)  
- ABCC2 c.1249G>A GA genotype and allele A significantly associated with drug response (OR=2.14, 95% CI, 1.23 to 3.71, p=0.007; OR=2.05, 95% CI, 1.31 to 3.19, p=0.001, respectively, uncorrected) |
| Radisch et al (2014)   | 229 patients treated with carbamazepine monotherapy                         | ABCC2: polymorphisms rs717620 (-24G4A), rs2236397 (c.1249G4A) and rs3740067 | - ABCC2 polymorphisms not associated with time to first seizure or time to 12-mo remission |
| Yun et al (2014)       | 38 patients with epilepsy treated with carbamazepine monotherapy            | EPHX1 c.337T>C, EPHX1 c.416A>G, SCN1A IVS5-91G>A, CYP3A4*1G           | - Patients EPHX1 c.416A>G genotypes had higher adjusted plasma carbamazepine concentrations vs those with wild-type genotype (p<0.05)  
- Other studied polymorphisms not associated with carbamazepine pharmacoresistance |
| Taur et al (2014)      | 115 patients with epilepsy treated                                           | ABCB1 (C3435T), CYP2C9 (416 C>T)                                     | - ABCB1 C3435T genotype and allele polymorphisms significantly associated with drug |
Study Population | Genes | Overview of Findings
--- | --- | ---
with phenytoin, phenobarbital, and/or carbamazepine | • CYP2C9 (1061 A>T) <br>• CYP2C19 (681 G>A) <br>• CYP2C19 (636 G>A) | response (OR=4.5, 95% CI, 1.04 to 20.99; OR=1.73, 95% CI, 1.02 to 2.95, respectively)

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

Several meta-analyses evaluating pharmacogenomics were identified. Haerian et al examined the association between SNPs 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 polymorphisms 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 polymorphism was not significantly associated with risk of drug resistance.

Shazadi et al assessed the validity of a gene classifier panel consisting of 5 SNPs for predicting initial AED response and overall seizure control in 2 cohorts of patients with newly diagnosed epilepsy. A cohort of 115 Australian patients with newly diagnosed epilepsy was used to develop the classifier from a sample of 4041 SNPs in 279 candidate genes via a k-nearest neighbor machine (kNN) learning algorithm, resulting in a 5-SNP classifier. The classifier was validated in 2 separate cohorts. One cohort included 285 newly diagnosed patients in Glasgow, of whom a large proportion had participated in randomized trials of AED monotherapy. Drug response phenotypes in this cohort were identified by retrospectively reviewing prospectively collected clinical trial and/or hospital notes. The second cohort was drawn from patients who had participated in the Standard and New Epileptic Drugs (SANAD) trial, a multicenter RCT comparing standard 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 SNP genotypes and drug responses in a training dataset (\( n=343 \)) derived from the SANAD cohort. None of the 5 SNPs used in the multigenic classifier was independently associated with AED response in the Glasgow or the SANAD cohorts. 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-SNP 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-SNP 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 Antiepileptic Drug Adverse Effects

Many antiepileptic drugs have a relatively narrow therapeutic index, with the potential for dose-dependent or idiosyncratic adverse effects (AEs). Several studies have evaluated genetic predictors of AEs from antiepileptic drugs, particularly severe skin reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).

Chung et al evaluated genetic variants associated with phenytoin-induced severe cutaneous AEs (SJS/TEN, drug reactions with eosinophilia and systemic symptoms [DRESS]) and maculopapular exanthema. The study entailed a GWAS study including 60 cases with phenytoin-related severe cutaneous AEs and 412 population controls, followed by a case-control study including 105 cases with phenytoin-related severe cutaneous AEs (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 \( \text{CYP2C9}^{*3} \) (rs1057910) was significantly associated with phenytoin-related severe cutaneous AEs (OR=12; 95% CI, 6.6 to 20; \( p=1.1 \times 10^{-17} \)). In a case-control comparison between the subgroups of 168 patients with phenytoin-related cutaneous AEs and 130 phenytoin-tolerant controls, \( \text{CYP2C9}^{*3} \) polymorphisms were significantly associated with SJS/TEN (OR=30; 95% CI, 8.4 to 109; \( p=1.2 \times 10^{-15} \)), DRESS (OR=19; 95% CI, 5.1 to 71; \( p=7.0 \times 10^{-7} \)), and maculopapular exanthema (OR=5.5; 95% CI, 1.5 to 21; \( p=0.01 \)).

He et al conducted a case-control study to evaluate the association between carbamazepine-induced SJS/TEN and 10 SNPs in the genes \( \text{ABCB1}, \text{CYP3A4}, \text{EPHX1}, \text{FAS}, \text{SNC1A}, \text{MICA}, \text{and BAG6} \). 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 \( \text{EPHX1} \ c.337T>C \) polymorphisms 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 SNPs evaluated.

Wang et al evaluated the association between HLA genes and cross-reactivity of cutaneous adverse drug reactions to aromatic antiepileptic drugs (carbamazepine, lamotrigine, oxcarbazepine, phenytoin, phenobarbital). The study included 60 patients with a history of aromatic antiepileptic drug-induced cutaneous adverse drug reactions, including SJS/TEN and maculopapular eruption, who were reexposed to an aromatic antiepileptic drug, 10 of whom had recurrence of the cutaneous adverse drug reaction on re-exposure (cross-reactive group). Subjects who were 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 other HLA alleles testing were not significantly different 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 interested in identifying genetic associations with SUDEP.

Bagnall et al evaluated the prevalence of sequence variations in the \textit{PHOX2B} gene in 68 patients with SUDEP. Large polyalanine repeat expansions in the \textit{PHOX2B} gene are associated congenital central hypoventilation syndrome, a potentially lethal autonomic dysfunction syndrome, but smaller \textit{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 \textit{PHOX2B} gene, but no \textit{PHOX2B} polyalanine repeat expansions were found.

Coll et al 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 \textit{SCN1A}, \textit{FBN1}, \textit{HCN1}, \textit{SCN4A}, and \textit{EFHC1} genes, and in 1 case a rare variant in \textit{KCNQ1} with an incomplete pattern of inheritance was detected. New potential candidate genes for SUDEP were detected: \textit{FBN1}, \textit{HCN1}, \textit{SCN4A}, \textit{EFHC1}, \textit{CACNA1A}, \textit{SCN11A}, and \textit{SCN10A}.

**Clinical Utility**

There is a lack of evidence on the clinical utility of genetic testing for the common genetic epilepsies. Association studies are not sufficient evidence to determine whether genetic testing can improve the clinical diagnosis of GGE. There are no studies that report 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 suggests 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 AEs, or increase the efficiency of medication trials is not yet well-defined.

**Section Summary**

The evidence on genetic testing for the common epilepsies is characterized by a large number of studies that evaluate associations of many different genetic variants with 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 mutation 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 common epilepsies is also lacking. Several studies have reported associations between a number of genes and response to AEDs or AED adverse effects. 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.
Ongoing and Unpublished Clinical Trials
A search of ClinicalTrials.gov in October 2015 did not identify any ongoing or unpublished trials that would likely influence this review.

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.

Summary of Evidence
The evidence for testing for genetic mutations associated with epileptic encephalopathies in individuals who have infantile- or early-childhood-onset epileptic encephalopathy includes prospective and retrospective cohort studies describing the yield of testing. Relevant outcomes are test accuracy and validity, other test performance measures, changes in reproductive decision making, symptoms, quality of life, medication use, and resource utilization. For Dravet syndrome, which appears to have the largest body of associated literature, the sensitivity of testing for SCN1A mutations 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 report detection rates for clinically significant mutations ranging from 7.5% to 28%. The clinical utility of genetic testing occurs primarily when there is a positive test for a known pathogenic mutation. The presence of a pathogenic mutation may lead to targeted medication management, avoidance of other diagnostic tests, and/or informed reproductive planning. There may be a potential role in differentiating these syndromes from the common epilepsies and from each other, and in improving the efficiency of the diagnostic work-up. However, there is limited empirical evidence about the clinical utility of genetic testing for these epilepsy syndromes. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for testing for genetic mutations associated with common epilepsies in individuals who have idiopathic epilepsy includes prospective and retrospective cohort studies describing the yield of testing. Relevant outcomes are test accuracy and validity, other test performance measures, changes in reproductive decision making, symptoms, quality of life, medication use, and resource utilization. For common epilepsies, which are thought to have a complex, multifactorial basis, the association between specific genetic mutations and the risk of epilepsy is uncertain. Despite a large body of literature on associations between genetic variants and common epilepsies, the clinical validity of genetic testing is poorly understood. Published literature is characterized by weak and inconsistent associations, which have
Clinical utility of genetic testing for the common epilepsies

The evidence is insufficient to determine the effects of the technology on health outcomes. A number of studies have also reported associations between genetic polymorphisms 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 polymorphisms 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 effects have been reported. However, no empirical evidence on the clinical utility of genetic testing for the common 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

Genetic Testing for Epilepsy

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02/19/2014 Medical Policy Implementation Committee approval. New policy.
05/07/2015 Medical Policy Committee review
05/20/2015 Medical Policy Implementation Committee approval. Added new eligibility statement and patient selection criteria. Updated rationale and references.
08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
05/05/2016 Medical Policy Committee review
05/18/2016 Medical Policy Implementation Committee approval. Coverage statement edited for clarification only.
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes

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Genetic Testing for Epilepsy

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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.

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

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