Protocol

Genetic Testing for Epilepsy

(204109)

Medical Benefit		**Effective Date**: 04/01/16	**Next Review Date**: 11/17
Preauthorization	Yes	**Review Dates**: 01/16, 11/16	

Preauthorization is required.

The following Protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: • With infantile- or early-childhood-onset epileptic encephalopathy	Interventions of interest are: • Testing for genetic mutations associated with epileptic encephalopathies	Comparators of interest are: • Standard management without genetic testing	Relevant outcomes include: • Test accuracy • Test validity • Other test performance measures • Changes in reproductive decision making • Symptoms • Quality of life • Medication use • Resource utilization
Individuals: • With idiopathic epilepsy	Interventions of interest are: • Testing for genetic mutations associated with common epilepsies	Comparators of interest are: • Standard management without genetic testing	Relevant outcomes include: • Test accuracy • Test validity • Other test performance measures • Changes in reproductive decision making • Symptoms • Quality of life • Medication use • Resource utilization

Description

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

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 not been replicated independently or by meta-analyses. A number of studies have also reported associations between genetic polymorphisms and antiepileptic drug (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.

Policy

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 (see Policy Guidelines) may be considered **medically necessary** 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.

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

Policy Guidelines

Policy Scope

Included Tests/Conditions

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

Excluded Tests/Conditions

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

Testing that is limited to genotyping of CYP450 genes is addressed separately in the Cytochrome P450 Genotyping Protocol.

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

This Protocol 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 develop-mental 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 PG1.

Table PG1: Single-Gene Mutations Associated With Epileptic Syndromes

Syndrome	Associated Genes
Dravet syndrome	*SCN1A, SCN9A, GABRA1, STXBP1, PCDH19, SCN1B, CHD2, HCN1*
Epilepsy limited to females with mental retardation	*PCDH19*
Epileptic encephalopathy with continuous spike-and-wave during sleep	*GRIN2A*
Genetic epilepsy with febrile seizures plus	*SCN1A, SCN9A*
Early infantile epileptic encephalopathy with suppression burst (Ohtahara syndrome)	*KCNQ2, SLC25A22, STXBP1, CDKL5, ARX*
Landau-Kleffner syndrome	*GRIN2A*
West syndrome	*ARX, TSC1, TSC2, CDKL5, ALG13, MAGI2, STXBP1, SCN1A, SCN2A, GABA, GABRB3, DNM1*
Glucose transporter type 1 deficiency syndrome	*SLC2A1*

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 Protocol, the medically necessary policy statement would apply for patients with:

1. Onset of seizures in early childhood (i.e., before the age of five 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.

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 the General Approach to Evaluating the Utility of Genetic Panels Protocol.

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

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.[1] The condition is generally chronic, requiring treatment with one or more medications to adequately control symptoms. Seizures can be controlled by antiepileptic medications in most cases, but some patients are resistant to medications, and further options such as surgery, vagus nerve stimulation, and/or the ketogenic diet can be used.[2]

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 1,[3] 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 1. Classification of Seizure Disorders by Type (condensed from Berg et al)[3]

Seizures Disorders
Partial (focal seizures)
Simple partial seizures (consciousness not impaired)
With motor symptoms
With somatosensory or special sensory symptoms
With autonomic symptoms or signs
With psychic symptoms (disturbance of higher cerebral function)
Complex partial (with impairment of consciousness)
Simple partial onset followed by impairment of consciousness
Impairment of consciousness at outset
Partial seizures evolving to secondarily generalized seizures
Generalized seizures
Nonconvulsive (absence)
Convulsive
Unclassified seizures

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[3]:

- 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 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 Protocol, this classification is most useful. The review 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 Protocol, but may be included in separate Protocols that specifically address genetic testing for that syndrome.

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

The category of genetic epilepsies includes a number of rare epilepsy syndromes that present in infancy or early childhood.[1, 4] These are syndromes that are characterized by epilepsy as the primary manifestation, without associated metabolic or brain structural abnormalities. They are often severe and sometimes refractory to medication treatment. They may involve other clinical manifestations such as development delay and/or intellectual disability, which in many cases are thought to be caused by frequent uncontrolled seizures. In these cases, the epileptic syndrome may be classified as an epileptic encephalopathy, which is described by ILAE as disorders in which the epileptic activity itself may contribute to severe cognitive and behavioral impairments above and beyond what might be expected from the underlying pathology alone and that these can worsen over time.[3] A partial list of severe early-onset epilepsy 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.[5] 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.[6] 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.[7]

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 2013)[1]

Gene	Physiologic Function
KCNQ2	Potassium channel
KCNQ3	Potassium channel
SCN1A	Sodium channel α-subunit
SCN2A	Sodium channel α-subunit
SCN1B	Sodium channel β-subunit
GABRG2	GABA A-type subunit
GABRRA1	GABA A-type subunit
GABRD	GABA subunit
CHRNA2	Acetylcholine receptor α2 subunit
CHRNA4	Acetylcholine receptor α4 subunit
CHRNB2	Acetylcholine receptor β2 subunit
STXBP1	Synaptic vesicle release
ARX	Homeobox gene
PCDH19	Protocadherin cell-cell adhesion
EFHC1	Calcium homeostasis
CACNB4	Calcium channel subunit
CLCN2	Chloride channel
LGI1	G-protein component

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.[8]

Pharmacogenomics of Epilepsy

Another area of interest for epilepsy is the pharmacogenomics of antiepileptic medications. There are a wide variety of these medications, from numerous different classes. The choice of medications, and the combinations of medications for patients who require treatment with more than one agent, is complex. Approximately one third of patients are considered refractory to medications, defined as inadequate control of symptoms with a single medication.[9] These patients often require escalating doses and/or combinations of different medications. At present, selection of agents is driven by the clinical phenotype of seizures, but has a large trial and error component in many refractory cases. The current focus of epilepsy pharmacogenomics is in 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.[10] Serious dermatologic reactions, including sometimes fatal dermatologic reactions (including toxic epidermal necrolysis [TEN] and Stevens-Johnson Syndrome [SJS]) may occur in individuals with the HLA-B*1502 allele. HLA-B*1502 is found almost exclusively in patients with ancestry across broad areas of Asia. FDA Labeling on carbamazepine products contains the warning "patients with ancestry in genetically at-risk populations should be screened for the presence of HLA-B*1502 prior to initiating treatment with carbamazepine. Patients testing positive for the allele should not be treated with carbamazepine unless the benefit clearly outweighs the risk."

Genetic Testing for Epilepsy

Commercial testing is available from numerous companies. 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® (Gaithersburg, MD) 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, 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.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (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.

Related Protocols

Cytochrome P450 Genotyping

General Approach to Evaluating the Utility of Genetic Panels

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this Protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

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We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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