Genetic Testing for Epilepsy

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Description of Procedure or Service

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

Background
Epilepsy is defined as the occurrence of two or more unprovoked seizures. It is a common neurologic disorder, with approximately 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 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

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 genetiically determined conditions in which seizures are part of a larger syndrome, such as tuberous sclerosis, fragile X syndrome, or Rett syndrome.
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**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.

This 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 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. These 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 syndromes are characterized by epilepsy as the primary manifestation, without associated metabolic or brain structural abnormalities. They are often severe and sometimes refractory to medication treatment. They may involve other clinical manifestations such as 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 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 burst suppression pattern)
- 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 variants in the STXBPI 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.
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Genetics of epilepsy
Most genetic epilepsies are primarily believed to involve multifactorial inheritance patterns. This follows the concept of a threshold effect, in which any particular genetic defect may increase the risk of epilepsy, but is not by itself causative. A combination of risk-associated genes, together with environmental factors, determines whether the clinical phenotype of epilepsy occurs. In this model, individual genes that increase the susceptibility to epilepsy have a relatively weak impact. Multiple genetic defects, and/or particular combination of genes, probably increase the risk by a greater amount. However, it is not well understood how many abnormal genes are required to exceed the threshold to cause clinical epilepsy, nor is it understood which combination of genes may increase the risk more than others.

Early onset epilepsy syndromes may be single-gene disorders. Because of the small amount of research available, the evidence base for these rare syndromes is incomplete, and new variants are currently being discovered frequently.

Some of the most common genes that have been associated with genetic epileptic syndromes are listed in Table 1.

Table 1. Selected Genes Most Commonly Associated With Genetic Epilepsy (adapted from Williams 2013)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Physiologic function</th>
</tr>
</thead>
<tbody>
<tr>
<td>KCNQ2</td>
<td>Potassium channel</td>
</tr>
<tr>
<td>KCNQ3</td>
<td>Potassium channel</td>
</tr>
<tr>
<td>SCN1A</td>
<td>Sodium channel α-subunit</td>
</tr>
<tr>
<td>SCN2A</td>
<td>Sodium channel α-subunit</td>
</tr>
<tr>
<td>SCN1B</td>
<td>Sodium channel β-subunit</td>
</tr>
<tr>
<td>GABRG2</td>
<td>γ-aminobutyrate A-type subunit</td>
</tr>
<tr>
<td>GABRA1</td>
<td>γ-aminobutyrate A-type subunit</td>
</tr>
<tr>
<td>GABRD</td>
<td>γ-aminobutyrate subunit</td>
</tr>
<tr>
<td>CHRNA2</td>
<td>Acetylcholine receptor α2 subunit</td>
</tr>
<tr>
<td>CHRNA4</td>
<td>Acetylcholine receptor α4 subunit</td>
</tr>
<tr>
<td>CHRNβ2</td>
<td>Acetylcholine receptor β2 subunit</td>
</tr>
<tr>
<td>STXBP1</td>
<td>Synaptic vesicle release</td>
</tr>
<tr>
<td>ARX</td>
<td>Homeobox gene</td>
</tr>
<tr>
<td>PCDH19</td>
<td>Protocadherin cell-cell adhesion</td>
</tr>
<tr>
<td>EFHC1</td>
<td>Calcium homeostasis</td>
</tr>
<tr>
<td>CACNB4</td>
<td>Calcium channel subunit</td>
</tr>
<tr>
<td>CLCN2</td>
<td>Chloride channel</td>
</tr>
<tr>
<td>LGI1</td>
<td>G-Protein component</td>
</tr>
</tbody>
</table>

For the severe early epilepsy syndromes, the disorders most frequently reported to be associated with single-gene variants include GEFS+ syndrome (associated with SCN1A, SCN1B, GABRG2 variants), Dravet syndrome (associated with SCN1A variants, possibly modified by SCN9A variants), and epilepsy and intellectual disability limited to females (associated with PCDH19 variants). Ohtahara syndrome has been associated with variants in STXBP1 in cases where patients have no structural or metabolic abnormalities. West syndrome is often associated with chromosomal abnormalities or tuberous sclerosis, or may be secondary to an identifiable infectious or metabolic cause, but when there is not an underlying cause identified it is thought to be due to a multifactorial genetic predisposition.
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Targeted testing for individual genes is available. Several commercial epilepsy genetic panels are also available. The number of genes included in the tests varies widely, from about 50 to over 450. The panels frequently include genes for other disorders such as neural tube defects, lysosomal storage disorders, cardiac channelopathies, congenital disorders of glycosylation, metabolic disorders, neurologic syndromes and multisystemic genetic syndromes. Some panels are designed to be comprehensive while other panels target specific subtypes of epilepsy. Chambers et al (2016) reviewed comprehensive epilepsy panels from 7 U.S.-based clinical laboratories and found that between 1% and 4% of panel contents were genes not known to be associated with primary epilepsy. Between 1% and 70% of the genes included on an individual panel were not on any other panel.

Pharmacogenomics of epilepsy
Another area of interest for epilepsy is the pharmacogenomics of anti-epileptic medications. There are a wide variety of these medications, from numerous different classes. The choice of medications, and the combinations of medications for patients who require treatment with more than one agent, is complex. Approximately one-third of patients are considered refractory to medications, defined as inadequate control of symptoms with a single medication. These patients often require escalating doses and/or combinations of different medications. At present, selection of agents is driven by the clinical phenotype of seizures, but has a large trial and error component in many refractory cases. The current focus of epilepsy pharmacogenomics is in detecting genetic markers that identify patients who are likely to be refractory to the most common medications. This may lead to directed treatment that will result in a more efficient process for medication selection, and potentially more effective control of symptoms.

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

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

Related Policies:
General Approach to Evaluating the Utility of Genetic Panels
Genetic Testing for Rett Syndrome
Genetic Testing for FMR1 Mutations Including Fragile X Syndrome
Pharmacogenetic Testing for Drug Metabolism
Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy
BCBSNC will cover genetic testing for epilepsy when determined to be medically necessary because the medical criteria and guidelines shown below are met.

Benefits Application
This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit
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design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Genetic Testing for Epilepsy is covered

Genetic testing for genes associated with infantile- and early childhood-onset epilepsy syndromes in individuals with infantile- and early-childhood-onset epilepsy syndromes in which epilepsy is the core clinical symptom (see Policy Guidelines section) 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.

When Genetic Testing for Epilepsy is not covered

Genetic testing for epilepsy is considered investigational for all situations other than those listed above.

Policy Guidelines

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

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

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

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: 81401, 81403, 81404, 81405, 81406, 81407, 81479

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

Senior Medical Director – 1/2014

Specialty Matched Consultant Advisory panel – 10/2015


Specialty Matched Consultant Advisory panel – 10/2017

Specialty Matched Consultant Advisory panel – 10/2018

Policy Implementation/Update Information


Genetic Testing for Epilepsy

4/28/15 Reference added. Policy statement added that genetic testing for early-onset epileptic encephalopathy syndromes may be considered medically necessary when criteria are met. (sk)


1/26/16 Reference added. Policy Guidelines updated. Related policy added. Background section updated. (sk)

11/22/16 Specialty Matched Consultant Advisory panel review 10/26/2016. (sk)

3/31/17 Reference added. Background section updated. Policy revised with updated genetics nomenclature. (sk)


3/29/18 Reference added. (sk)


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