Medical Policy
Genetic Testing for Epilepsy

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- Information Pertaining to All Policies
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Policy Number: 668
BCBSA Reference Number: 2.04.109
NCD/LCD: Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)

Related Policies
- Genetic Testing for Rett Syndrome, #803
- Genetic Testing for FMR1 mutations - including Fragile X Syndrome, #907
- General Approach to Evaluating the Utility of Genetic Panels, #734
- Cytochrome P450 Genotyping, #256
- Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders, #457

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity

Genetic testing for genes associated with infantile and early-childhood-onset epilepsy syndromes in which epilepsy is the core clinical symptom 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.

Single Genes Associated with Epileptic Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Associated Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dravet syndrome</td>
<td>SCN1A, SCN9A, GABRA1, 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</td>
<td>KCNQ2, SLC25A22, STXBP1, CDKL5, ARX</td>
</tr>
<tr>
<td>Condition</td>
<td>Gene(s)</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
<td>----------------------------------------------</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>

Genetic testing for epilepsy is **INVESTIGATIONAL** for all other situations.

**Medicare HMO Blue** and Medicare PPO Blue Members

Medical necessity criteria and coding guidance for Medicare Advantage members living in Massachusetts can be found through the link below.

**Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)**

For medical necessity criteria and coding guidance for Medicare Advantage members **living outside of Massachusetts**, please see the Centers for Medicare and Medicaid Services website for information regarding your specific jurisdiction at [https://www.cms.gov](https://www.cms.gov).

**Prior Authorization Information**

Pre-service approval is required for all inpatient services for all products. See below for situations where prior authorization may be required or may not be required.

- Yes indicates that prior authorization is required.
- No indicates that prior authorization is not required.
- N/A indicates that this service is primarily performed in an inpatient setting.

<table>
<thead>
<tr>
<th>Outpatient</th>
<th>Commercial Managed Care (HMO and POS)</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Commercial PPO and Indemnity</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Medicare HMO Blue**</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Medicare PPO Blue**</td>
<td>No</td>
</tr>
</tbody>
</table>

**CPT Codes / HCPCS Codes / ICD Codes**

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above **medical necessity criteria MUST** be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity:

**CPT Codes**

<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81403</td>
<td>Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of &gt;10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)</td>
</tr>
<tr>
<td>81404</td>
<td>Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or</td>
</tr>
</tbody>
</table>
Epilepsy is defined as the occurrence of 2 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 1 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.

Classification
Epilepsy is heterogeneous in etiology and clinical expression and can be classified in a variety of ways. Most commonly, classification is done by the clinical phenotype, ie, the type of seizures that occur. The International League Against Epilepsy (ILAE) developed the classification system that is widely used for clinical care and research purposes (see Table 1). Classification of seizures can also be done on the basis of age of onset: neonatal, infancy, childhood, and adolescent/adult.

Table 1. Classification of Seizure Disorders by Type (condensed from Berg et al, 2010)

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

More recently, the concept of genetic epilepsies has emerged as a way of classifying epilepsy. Many experts now refer to “genetic generalized epilepsy” as an alternative classification for seizures previously called “idiopathic generalized epilepsies.” The ILAE report, published in 2010, offers the following alternative classification:

- 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 this evidence review, the ILAE classification is most useful. The review focuses 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 herein, but may be included in separate reviews 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. 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 (generalized epilepsies 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 STXBP1 gene in rare cases. West syndrome is an early-onset seizure disorder associated with infantile spasms and the characteristic EEG finding of hypsarrhythmia. Other seizure disorders present early in childhood may have a genetic component, but are characterized by a more benign course, including benign familial neonatal seizures and benign familial infantile seizures.
Genetics

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. This hypothesis arises from the discovery of pathologic variants in small numbers of patients with the disorders. Because of the small amount of research available, the evidence base for these rare syndromes is incomplete, and new variants are currently being discovered frequently.⁷

Some of the most common genes associated with genetic epileptic syndromes are listed in Table 2.

Table 2. Selected Genes Most Commonly Associated with Genetic Epilepsy (adapted from Williams and Battaglia, 2013)¹

<table>
<thead>
<tr>
<th>Genes</th>
<th>Physiologic Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>KCNQ2</td>
<td>Potassium channel</td>
</tr>
<tr>
<td>KCNQ3</td>
<td>Potassium channel</td>
</tr>
<tr>
<td>SCN1A</td>
<td>Sodium channel α subunit</td>
</tr>
<tr>
<td>SCN2A</td>
<td>Sodium channel α subunit</td>
</tr>
<tr>
<td>SCN1B</td>
<td>Sodium channel β subunit</td>
</tr>
<tr>
<td>GABRG2</td>
<td>γ-aminobutyrate A-type subunit</td>
</tr>
<tr>
<td>GABRRA1</td>
<td>γ-aminobutyrate A-type subunit</td>
</tr>
<tr>
<td>GABRD</td>
<td>γ-aminobutyrate subunit</td>
</tr>
<tr>
<td>CHRNA2</td>
<td>Acetylcholine receptor α2 subunit</td>
</tr>
<tr>
<td>CHRNA4</td>
<td>Acetylcholine receptor α2 subunit</td>
</tr>
<tr>
<td>CHRNB2</td>
<td>Acetylcholine receptor β subunit</td>
</tr>
<tr>
<td>STXBP1</td>
<td>Synaptic vesicle release</td>
</tr>
<tr>
<td>ARX</td>
<td>Homeobox gene</td>
</tr>
<tr>
<td>PCDH19</td>
<td>Protocadherin cell-cell adhesion</td>
</tr>
<tr>
<td>EFHC1</td>
<td>Calcium homeostasis</td>
</tr>
<tr>
<td>CACNB4</td>
<td>Calcium channel subunit</td>
</tr>
<tr>
<td>CLCN2</td>
<td>Chloride channel</td>
</tr>
<tr>
<td>LGI1</td>
<td>G-protein component</td>
</tr>
</tbody>
</table>

For the severe early epilepsy syndromes, the disorders most frequently reported to be associated with single-gene variants include GEFS+ syndrome (associated with SCN1A, SCN1B, and GABRG2 variants), Dravet syndrome (associated with SCN1A variants, possibly modified by SCN9A variants), and epilepsy and intellectual disability limited to females (associated with PCDH19 variants). Ohtahara syndrome has been associated with variants in STXBP1 in cases where patients have no structural or metabolic abnormalities. West syndrome is often associated with chromosomal abnormalities or tuberous sclerosis, or may be secondary to an identifiable infectious or metabolic cause, but when there is no underlying cause identified, it is thought to be due to a multifactorial genetic predisposition.⁵

Targeted testing for individual genes is available. Several commercial epilepsy genetic panels are also available. The number of genes included in the tests varies widely, from about 50 to over 450. The panels frequently include genes for other disorders such as neural tube defects, lysosomal storage disorders, cardiac channelopathies, congenital disorders of glycosylation, metabolic disorders, neurologic syndromes and multisystemic genetic syndromes. Some panels are designed to be comprehensive while other panels target specific subtypes of epilepsy Chambers et al (2016) reviewed comprehensive epilepsy panels from 7 U.S.-based clinical laboratories and found that between 1% and 4% of panel
contents were genes not known to be associated with primary epilepsy. Between 1% and 70% of the genes included on an individual panel were not on any other panel.

Pharmacogenomics
Another area of interest for epilepsy is the pharmacogenomics of 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 1 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 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.

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

For individuals who have infantile- or early-childhood-onset epileptic encephalopathy who receive testing for genes associated with epileptic encephalopathies, the evidence includes prospective and retrospective cohort studies describing the testing yield. Relevant outcomes are test accuracy and validity, changes in reproductive decision making, symptoms, quality of life, functional outcomes, medication use, resource utilization, and treatment-related morbidity. For Dravet syndrome, which appears to have the largest body of associated literature, the sensitivity of testing for 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 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.

Policy History

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>4/2017</td>
<td>BCBSA National medical policy review. Policy clarified. Policy statements unchanged. 4/1/2017</td>
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</tbody>
</table>

Information Pertaining to All Blue Cross Blue Shield Medical Policies
Click on any of the following terms to access the relevant information:
Medical Policy Terms of Use
Managed Care Guidelines
Indemnity/PPO Guidelines
Clinical Exception Process
Medical Technology Assessment Guidelines

References


