

Corporate Medical Policy

Genetic Testing for Epilepsy AHS – M2075

File Name: genetic_testing_for_epilepsy
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Description of Procedure or Service

Epilepsy is a group of disorders characterized by recurrent, unprovoked seizures due to abnormal, synchronized neuronal firing in the brain that can be distinguished by seizure type, age of onset, developmental status, co-morbid features and etiology (Berg et al., 2010; Myers & Mefford, 2015).

Related Policies

General Genetic Testing Germline Disorders
General Genetic Testing Somatic Disorders
Genetic Testing of Mitochondrial Disorders

Regulatory Status

Numerous methods for genetic sequencing have been well-validated. Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

*****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 provide coverage for genetic testing for epilepsy when it is 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 design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Genetic Testing for Epilepsy is covered

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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 is considered medically necessary if positive test results may:

- Lead to changes in medication management; AND/OR
- Lead to changes in diagnostic testing such that alternative potentially invasive tests are avoided; AND/OR
- Lead to changes in reproductive decision making.

Current mutation testing is considered medically necessary in the following clinical situations:

- SCN1A testing in assessment for SCN1A-Related Seizure Disorders; or
- ALDH7A1 testing in assessment of Pyridoxine-Related Epilepsy; or
- SLC2A1 testing in assessment of Glucose Transporter Type 1 Deficiency Syndrome.
- PCDH19 testing for evaluation of epilepsy female-restricted with mental retardation (EFMR)

When Genetic Testing for Epilepsy is not covered

Genetic testing for epilepsy is considered investigational in all other clinical situations not described above and for any other mutations not listed above.

Policy Guidelines

Epilepsy, defined as having two or more unprovoked seizures, is a common neurologic disorder, affecting an estimated 2.2 million people in the United States (England, Liverman, Schultz, & Strawbridge, 2012). The biological and genetic mechanisms that disturb the balance between excitatory and inhibitory neuronal circuits to result in epilepsy are extremely heterogeneous (Ottman et al., 2010; Williams & Battaglia, 2013). Approximately 20–30 % of epilepsy diagnoses can be attributed to other primary conditions such as stroke, tumor or head injury, but the remaining 70–80 % of cases are believed to be due to one or more genetic factors (Hildebrand et al., 2013; Myers & Mefford, 2015).

The epilepsies can be classified by multiple approaches. Clinically, they can be broadly grouped into three classes: genetic generalized epilepsy (GGE); focal epilepsy; and epileptic encephalopathy (EE). GGE is characterized by generalized seizures that involve both sides of the brain, start in childhood or adolescence, are usually associated with normal development and intellect, and include juvenile myoclonic epilepsy and childhood absence epilepsy among others. Focal seizures originate in one hemisphere of the brain and include temporal lobe epilepsy and autosomal dominant nocturnal frontal lobe epilepsy. EE are severe, early onset conditions characterized by refractory seizures, developmental delay or regression associated with ongoing epileptic activity, and generally poor prognosis such as Dravet, Ohtahara and West syndromes. Epilepsy is often a co-morbid condition with intellectual disability (ID), autism or schizophrenia and may be a feature of many metabolic conditions and genetic syndromes (Myers & Mefford, 2015).

The International League Against Epilepsy (ILAE) classifies epilepsies into three broad groups based on underlying cause; genetic, structural-metabolic, and unknown cause. The genetic type includes conditions of known gene causation without structural brain anomalies or other syndrome associations. Seizures are the core symptom of the disorder and other symptomatology is not present, except as a direct result of seizures. Structural-metabolic types are generally applied to many conditions which 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 or trauma, and metabolic conditions, including a variety of encephalopathic abnormalities that predispose to seizures. These conditions may have a genetic

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etiology, but the genetic defect is associated with a separate disorder that predisposes to seizures. The unknown class is meant to be viewed neutrally and to designate that the underlying cause is unknown; it may be genetic or caused by a separate unrecognized disorder (Berg et al., 2010).

Epilepsy is genetically heterogeneous, and extensive phenotypic heterogeneity has been observed even in many monogenic epilepsies. This heterogeneity makes testing each gene individually through Sanger sequencing impractical despite its status as the gold standard (Lemke et al., 2012). Mutations in ion channels, chromatin remodeling, transcriptional regulation and regulation of the mammalian target of rapamycin (mTOR) protein have been implicated in the etiology of epilepsy (Moller et al., 2016).

Clinical Validity and Utility

The DNA sequencing methods have high analytic validity; the methods are well-established in laboratories. Sequencing bi-directionally has been evaluated at over 98% sensitivity (Stenhouse, Ellis, & Zuberi, 2013). Next generation sequencing (NGS) allows for parallel sequencing of any number of genes, thereby allowing for far superior testing of heterogeneous conditions such as epilepsy. Since the number of new epilepsy genes continues to grow and the phenotypes associated with mutations in each gene are so variable, NGS is a desirable option to diagnose epilepsy patients (Mefford, 2015).

New test options have an increased yield of molecular diagnosis, particularly in patients with severe, early-onset epilepsies. For example, a study by Lemke et al focused on targeted resequencing of 265 candidate genes, which identified mutations that were presumed to be pathogenic in 16 of 33 patients. Many of these patients had severe epilepsies associated with intellectual disability. This NGS method detected mutations that had been missed by the previous gold standard of Sanger sequencing (with at least one mutation missed due to artifacts from Sanger sequencing). Furthermore, the authors concluded that a patient with more than one possible gene responsible for their phenotype would benefit from this sequencing method compared to Sanger. The authors noted that NGS is only suited for conditions with at least one major gene effect and that whole exome sequencing (WES) would be a better option for more complex genetic conditions (Lemke et al., 2012).

Most recently, a gene panel targeting 46 epilepsy genes was used on 216 patients representing a wide spectrum of epilepsies with age of onset spanning from the neonatal period to adulthood. A presumed pathogenic variant was identified in 49 (23%) patients. The variants were found in 19 different genes including *SCN1A*, *STXBPI*, and *CDKL5*. Patients with neonatal-onset epilepsies had the highest rate of positive findings (57%). The overall yield for patients with EEs was 32%, compared to 17% among patients with generalized epilepsies and 16% in patients with focal or multifocal (Moller et al., 2016). Another study focusing on the diagnostic use of microarray was performed by Hrabik et al. Approximately 17.7% (26/147) of participants between the ages of birth to 23 years who were diagnosed with epilepsy and had a SNP microarray performed had an abnormal microarray as defined by laboratory guidelines (Hrabik et al., 2015). Gene panels and exome sequencing for clinical diagnostics provide better and less expensive options for testing and could be implemented early in the diagnostic process. Chromosome microarrays may be considered in severe cases and in GGE with co-morbid features (Myers & Mefford, 2015). Overall, sequencing of many genes at once may provide major benefits to those with epilepsy as epilepsy's genetic profile is widespread.

Copy number abnormalities also play an important role in patients with epilepsy. Of 973 patients who had chromosomal microarray (CMA) and ICD-9 codes for epilepsy or seizures, 805 patients satisfied criteria for epilepsy. 437 copy number variants (CNVs) in 323 patients (1-4 per patient), including 185 (42%) deletions and 252 (58%) duplications were observed. Forty (9%) were confirmed de novo, 186 (43%) were inherited, and parental data were unavailable for 211 (48%). Because the diagnostic yield of CMA for epilepsy patients is similar to the yield in autism

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spectrum disorders and in prenatal diagnosis (which published guidelines recommending testing with CMA), the authors recommended implementation of CMA in the evaluation of unexplained epilepsy (Olson et al., 2014).

Berg et al conducted a prospective cohort study of 775 children with newly diagnosed epilepsy with an onset at less than 3 years of age to determine the role of genetic testing in the initial evaluation of early life epilepsies. 95 children had brain injury, and of the other 680, 327 underwent genetic testing, such as microarrays, WES, and gene panels. 132 (40.4%) children were found to have pathogenic variants. A total of 446 children were deemed to have an unknown etiology without genetic testing, and 180 of these children were tested. Pathogenic variants were found in 48 or 26.7% of the children. However, epilepsy gene-sequencing panels and whole-exome sequencing (WES) had substantially greater diagnostic yields than CMA. 28 of 96 or 29.2% were detected by epilepsy panels, 5 of 18 or 27.8% for WES, and 8 for 101 or 7.9% for CMA. Without a clinically identified cause, testing yields were greater than 15% and as high as 47% depending on patient subgroups. The authors concluded that broad genetic sequencing methods have high diagnostic yields in diagnosing early-life epilepsies regardless of clinical features. Sequencing tests should be incorporated into the initial evaluation of newly presenting early-life epilepsies and not just reserved for those with severe presentations (Berg et al., 2017). Gene panels including the most commonly mutated genes have a 10%-50% diagnostic rate (depending on the panel used and the population) although it is possible that a greater number of genes in the panel does not necessarily equate to a higher diagnostic rate. A 67 gene panel and a 265 gene panel were found to have nearly equivalent diagnostic rates; however, the study using the 67 gene panel only included nineteen patients (Dunn et al., 2018; Mefford, 2015). Exome sequencing has been evaluated at a 25% diagnostic rate (without a prior diagnosis), and whole-genome sequencing (WGS) has been evaluated at as high as 60% with smaller studies and known phenotypes. The weaker sequencing depth contributes to the difficulty of locating copy number variants, which are a significant cause of epilepsy-related conditions. Nonetheless, the authors conclude that WES and WGS will become part of the regularly used tools for clinicians once their cost decreases (Dunn et al., 2018).

Stosser et al conducted a retrospective analysis of “893 probands with epilepsy who had an epilepsy panel or WES performed and were positive for a pathogenic or likely pathogenic variant in one of nine genes (CDKL5, GABRA1, GABRG2, GRIN2B, KCNQ2, MECP2, PCDH19, SCN1A, or SCN2A),” which found “mosaic pathogenic variants... at an overall frequency of 3.5% (95% CI, 2.4%-4.9%) in nine genes associated with epilepsy-related disorders.... Mosaicism was most common in the CDKL5, PCDH19, SCN2A, and SCN1A genes. Mosaicism was observed in GABRA1, GABRG2, and GRIN2B, which were not reported to have mosaicism prior to this study, and in KCNQ2 and MECP2. Parental mosaicism was observed for pathogenic variants in multiple genes including KCNQ2, MECP2, SCN1A, and SCN2A.” The authors concluded that patients with epilepsy who previously tested negative for pathogenic variants may benefit from an NGS test, which is superior at detecting mosaic variants. The authors also noted that targeted testing of parents of probands may use NGS to better assess risk and mosaicism (Stosser et al., 2017).

Some conditions have well-known mutations caused by a singular gene. For example, in Dravet syndrome, (DS, previously known as SMEI) the occurrence of *SCN1A* mutations is 70%-80%. About 90% of these mutations are de novo. Truncating mutations have found to be more severe (earlier onset of symptoms, faster cognitive decline) compared to missense mutations. *PCDH19*-related epilepsy is a rare syndrome characterized by focal and/or generalized seizures, which are commonly fever-induced and in clusters. Previously referred to as EFMR, *PCDH19*-related epilepsy occurs primarily in females and has an early onset. A mutation in *PCDH19* can cause both DS and *PCDH19*-related epilepsy as *PCDH19* is thought to account for 5% of patients with DS (Nascimento, 2018). Another example is tuberous sclerosis complex; as many as 89% of cases have mutations in either the *TSC1* or *TSC2* gene (Randle, 2017). Other mutations include *KCNQ2* with EE, *SLC2A1* with glucose transporter deficiency syndrome, *PRRT2* with general

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infantile convulsions, and *ALDH7A1* and *PNPO* with severe early-onset epilepsy (Poduri, Sheidley, Shostak, & Ottman, 2014).

“Epilepsy-plus” patients tend to have highest yield for diagnostic testing; that is, patients with other symptoms such as autism in addition to their epilepsy. Still, even the diagnostic yield of these individuals only reached 50% with panel or exome sequencing (Poduri, 2017). The potential clinical utility of genetic testing for these syndromes is in avoiding further diagnostic testing, directing medication management, and assisting in reproductive decision making. Establishing the genetic basis of epilepsy in a given patient will help in making treatment decisions, genetic counseling, and more (Poduri et al., 2014). For instance, mutations in *ALDH7A1* or in the *PNPO* gene may lead to seizures not treated with typical antiepileptic drugs, but with pyridoxine (Falsaperla & Corsello, 2017). On the other hand, sodium channel agents may be avoided in patients with an *SCNA1* mutation. Genetic counseling revolving around topics such as recurrence or heritability risk for pregnancies or testing of relatives is also helpful, and proper care must be taken to ensure that the information is clearly explained to the patient and their family (Poduri et al., 2014).

Guidelines and Recommendations

International League Against Epilepsy (ILAE)

In 2015, the ILAE Commission of Pediatrics issued a task force report which included the following related to genetic testing in epilepsy.

- “Genetic screening should not be undertaken at a primary or secondary level of care.”
- “Standard care should permit genetic counseling by trained personnel to be undertaken at all levels of care (primary to quaternary).”
- “Genetic evaluation for Dravet syndrome and other infantile-onset epileptic encephalopathies should be available at tertiary and quaternary levels of care (optimal intervention would permit an extended genetic evaluation).”
- “Early diagnosis of some mitochondrial conditions may alter long-term outcome, but whether screening at quaternary level is beneficial is unknown. (Wilmshurst et al, 2015)”

In 2017, the ILAE released a position paper containing a stance on the genetic etiologies of epilepsies. The ILAE states that “the epilepsies in which a genetic etiology has been implicated are quite diverse and, in most cases, the underlying genes are not yet known”. The ILAE also notes that genetic is not equivalent to inherited; de novo mutations are being identified with increasing frequency, thereby making an epileptic syndrome not inherited. Furthermore, the ILAE states that environmental contributions to an epileptic syndrome should not be minimized and that a genetic etiology should be of significant effect in causing epilepsy (Scheffer et al., 2017).

European Federation of Neurological Societies (EFNS)

In 2010, EFNS issued the following recommendations pertaining to epilepsy. The EFNS noted that molecular investigations may be useful for diagnosis but cannot be considered routine with the large amount of mutations present and state that clinical or physiological methods are generally superior. However, they note severe myoclonic epilepsy of infancy (SMEI) has a mutation in the gene *SCN1A* in 80% of patients. Since 2010, this organization has been renamed to the European Academy of Neurology, but no new updates on epilepsy have been released (Burgunder et al., 2010).

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American Academy of Neurology (AAN) and Child Neurology Society (CNS)

The AAN and CNS issued guidelines for clinicians on diagnostic assessment of the child with status epilepticus (SE) in 2006, reaffirmed 2016. The recommendations provided guidance for the assessment of laboratory studies, metabolic and genetic studies, electroencephalography and neuroimaging in children with SE. The expert panel concluded that “there are insufficient data to support or refute whether genetic testing (chromosomal or molecular studies) should be done routinely in children with SE (Riviello et al., 2006).”

North American Consensus Panel on Dravet Syndrome (2017)

This panel was convened to establish standards for evaluation of Dravet Syndrome. The panel recommended that genetic testing be performed in patients whose symptoms indicated Dravet syndrome; the panel noted that either specific *SCN1A* sequencing or a larger gene panel may be performed, and a chromosomal microarray was not necessary.

The panel also notes that genetic testing should be pursued in a child <12 months and with ≥ 2 febrile seizures >15 minutes as well as a child 12-35 months old with at least 1 febrile seizure over 15 minutes. However, genetic testing should not be performed for a child <12 months with only one focal or generalized febrile seizure.

Genetic counseling should be provided, particularly information about heritability and risk of epilepsy in siblings. Other information about *SCN1A* mutations may also be provided (Wirrell et al., 2017).

Scottish Intercollegiate Guidelines Network (SIGN, revised 2018)

SIGN lists features suggesting genetic generalized epilepsies, which are as follows:

- childhood or teenage onset
- triggered by sleep deprivation and alcohol
- early morning tonic-clonic seizures or myoclonic jerks
- short absence seizures
- photoparoxysmal response on electroencephalography (EEG)
- generalised 3 per second spike and wave or polyspike and wave on EEG.

Genetics services are recommended for patients with a “very strong” family history of epilepsy, or with “a clinical phenotype suggestive of a monogenic epilepsy syndrome” (SIGN, 2018).

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.bcsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes:

| Code Number | PA Required | PA Not Required | Not Covered |
|-------------|-------------|-----------------|-------------|
| 81405 | X | | |
| 81406 | X | | |
| 81407 | X | | |
| 81479 | X | | |

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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

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Policy Implementation/Update Information

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| 1/1/19 | New policy developed. BCBSNC will provide coverage for genetic testing for epilepsy when it is determined to be medically necessary because the medical criteria and guidelines are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (sk) |
| 5/14/19 | Reviewed by Avalon 1st Quarter 2019 CAB. Related policies added. Regulatory Status added. Not Covered statement reworded. Intent unchanged. Background section updated. Clinical Utility and Validity section added. Policy Guidelines updated. Medical Director review 4/2019. References added. (sk) |

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.