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Corporate Medical Policy

Genetic Testing for Epilepsy AHS – M2075

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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).

******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

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 not covered when the guidelines listed above are not met.

Policy Guidelines

Epilepsy, defined as having two or more unprovoked seizures, is a common neurologic disorder, affects an estimated 2.2 million people in the United States (England, Liverman, Schultz, & Strawbridge, 2012). The biological mechanisms which can disturb the balance between excitatory and inhibitory neuronal circuits to result in epilepsy are extremely heterogeneous (Williams & Battaglia, 2013). Approximately 20–30 % of epilepsy diagnosis 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).

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)(Myers & Mefford, 2015). 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 epilepsy involves focal seizures which originate in one hemisphere of the brain and include temporal lobe epilepsy, autosomal dominant nocturnal frontal lobe epilepsy, and autosomal dominant epilepsy with auditory features. 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.

The International League Against Epilepsy (ILAE) classifies epilepsies into three broad groups based on underlying cause; genetic, structural-metabolic, and unknown cause (Berg et al., 2010). 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, 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 is meant to be viewed neutrally and to designate that the nature of the underlying cause is unknown; it may have a fundamental genetic defect at its core or it may be the consequence of a separate unrecognized disorder.

Establishing the genetic basis of epilepsy in a given patient is important for counseling with respect to disease prognosis, for determining recurrence risk for future pregnancies and for treatment decisions in select cases (Poduri, Sheidley, Shostak, & Ottman, 2014).

Epilepsy-related genetic variants with implications for clinical management

Gene variant	Syndrome(s)	Change in treatment	Other clinical implications
SCN1A	Dravet syndrome Migrating epilepsy of infancy	Avoidance or removal of some sodium channel agents (for example, phenytoin, lamotrigine) in some patients	Monitoring and management of progressive changes in gait Awareness of risk of sudden unexplained death in epilepsy
SLC2A1	Glucose transporter deficiency (GLUT1 syndrome)	Ketogenic diet should be tried	Monitoring for movement disorder
KCNQ2	Epileptic encephalopathy (also associated with a benign epilepsy syndrome)	Ezogabine specifically targets and modulates opening of the involved potassium channels, but its safety and efficacy in children has not been determined	None
PRRT2	Infantile convulsions (also associated with episodic ataxia, paroxysmal kinesigenic dyskinesia, and hemiplegic migraine)	Carbamazepine or oxcarbazepine might be effective	Surveillance for other neurological manifestations
TSC1 and *TSC2*	Tuberous sclerosis complex, often with infantile spasms	Vigabatrin might be effective Rapamycin and its derivatives might be effective (now in clinical trials)	Surveillance for tumours and non-neurological manifestations
ALDH7A1 and *PNPO*	Severe early-onset epilepsy	Pyridoxine should be used	None

Epilepsy is genetically heterogeneous, extensive phenotypic heterogeneity has been observed even in many monogenic epilepsies. 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. This heterogeneity makes testing one gene at a time not practical. New test modalities have an increased yield of molecular diagnosis, particularly in patients with severe, early-onset epilepsies. Targeted resequencing of 265 candidate genes identified mutations that were presumed to be disease-causing in 16 of 33 patients, many of whom had severe epilepsies associated with intellectual disability (Lemke et al., 2012). Pathogenic mutations were identified in 10% of patients with infantile epileptic encephalopathies through targeted resequencing of 65 genes (Carvill et al., 2013). Most recently, a gene panel targeting 46 epilepsy genes was used on a cohort of 216 patients representing a wide spectrum of epilepsies with age of onset spanning from the neonatal period to adulthood consecutively referred for panel testing. A presumed disease-causing variant was identified in 49 (23%) of the 216 patients. The variants were found in 19 different genes including *SCN1A, STXBP1, CDKL5, SCN2A, SCN8A, GABRA1, KCNA2,* and *STX1B*. 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 epilepsies (Moller et al., 2016). 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 at Cincinnati Children's Hospital Medical Center had an abnormal microarray as defined by laboratory guidelines(Hrabik et al., 2015). Gene panels and exome sequencing for clinical diagnostics provide more comprehensive and affordable options for testing and should be implemented early in the diagnostic process. Chromosome microarrays should be considered in severe cases and in GGE with co-morbid features, where the likelihood of finding a disease-associated CNV is highest. (Myers & Mefford, 2015)

Copy number abnormalities also play an important role in patients with epilepsy. Of 973 patients who had 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 spectrum disorders and in prenatal diagnosis, for which published guidelines recommend testing with CMA, the

implementation of CMA in the evaluation of unexplained epilepsy was recommended (Olson et al., 2014).

Berg et al (2017) recently 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. The study found that "diagnostic yields overall were 40%, with epilepsy gene-sequencing panels and whole-exome sequencing having substantially greater diagnostic yields than chromosomal microarray. In the absence of a clinically identified cause, testing yields were greater than 15% and as high as 47% depending on patient subgroups." They concluded that "Genetic investigations, particularly broad sequencing methods, have high diagnostic yields in newly diagnosed early-life epilepsies regardless of key clinical features. Thorough genetic investigation emphasizing sequencing tests should be incorporated into the initial evaluation of newly presenting early-life epilepsies and not just reserved for those with severe presentations and poor outcomes."

Stosser et al (2017) conducted a "retrospective analysis of 893 probands with epilepsy who had a multigene epilepsy panel or whole-exome sequencing performed in a clinical diagnostic laboratory 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 that "mosaic pathogenic variants were identified at an overall frequency of 3.5% (0.035; 95% CI, 0.024–0.049) 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 previously have not been reported to have mosaicism, and also in KCNQ2 and MECP2. Parental mosaicism was observed for pathogenic variants in multiple genes including KCNQ2, MECP2, SCN1A, and SCN2A." The authors conclude that "individuals with epilepsy who previously tested negative for pathogenic variants in these genes by Sanger sequencing may benefit from a repeat analysis using NGS, which is more sensitive in the detection of mosaic variants. For any proband with a pathogenic variant in these genes, targeted testing of both parents is indicated and should be performed by NGS or another quantitative assay to better evaluate for possible parental mosaicism and more accurately estimate the recurrence risk."

Guidelines and Recommendations

Mutations in several genes have been associated with early onset epilepsy. These genes are outlined in table 1.

Syndrome	**Associated Gene**
Dravet Syndrome	SCN1A, SCN9A, GABRA1, STXBP1, PCDH19, SCN1B, CHD2, HCN1
EFMR syndrome	PCDH19
Epileptic encephalopathy with continuous spike-and-wave during sleep	GRIN2A
GEFS+ syndrome	SCN1A, SCN9A
EIEE 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

Early-onset epilepsy syndromes that may be caused by a single-gene mutation are evaluated by direct gene sequencing, which has an analytic validity >99%. There is limited published literature on the clinical validity of testing for these syndromes. For Dravet syndrome, which appears to have the largest body of evidence, the sensitivity of testing for *SCN1A* mutations is between 70 percent and 80 percent. 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 Dravet Syndrome and PCDH19-related epilepsy (Nascimento & Andrade, 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. There are only a few studies that have evaluated the clinical utility, and this area needs to be further researched.

The common epilepsies are generally evaluated by genetic panel testing, performed by next-generation sequencing. According to Mefford (2015), "the number of new epilepsy genes continues to grow, and the phenotypes associated with mutations in each gene are variable, making gene panel testing very attractive for diagnosing epilepsy patients." This method has an analytic validity between 95 percent to 99 percent. Evidence of clinical validity and clinical utility of testing specific gene mutations to evaluate risk of specific types of epilepsy is insufficient and inconsistent.

Practice Guidelines and Position Statements

International League Against Epilepsy (ILAE) Commission of Pediatrics
In 2015, the ILAE Commission of Pediatrics issued a task force report which included the following related to genetic testing in epilepsy (Wilmshurst et al, 2015)

- "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."

European Federation of Neurological Societies (EFNS)
In 2010, EFNS issued the following recommendations pertaining to epilepsy (Burgunder, 2010):
"Molecular investigations are possible and may help in some cases to diagnose the condition but cannot be considered as a routine procedure with regard to the large number of different mutations in different genes. Furthermore, diagnosis can be made more easily by clinical and physiological investigation (Good Practice Point). One exception of note is the diagnosis of severe myoclonic epilepsy of infancy (SMEI), in which mutations are found in *SCN1A* in 80% of the patients (Level B)."

American Academy of Neurology (AAN) and Child Neurology Society (CNS)
The AAN and CNS have issued evidence-based guideline for clinicians on diagnostic assessment of the child with status epilepticus (SE) in 2006 (Riviello et al, 2006), reaffirmed in 2010, 2013 and 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."

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 service codes:

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

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

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)