MEDICAL POLICY

<table>
<thead>
<tr>
<th>POLICY TITLE</th>
<th>GENETIC TESTING FOR EPILEPSY</th>
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</thead>
<tbody>
<tr>
<td>POLICY NUMBER</td>
<td>MP-2.262</td>
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</tbody>
</table>

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POLICY | PRODUCT VARIATIONS | DESCRIPTION/BACKGROUND
RATIONALE | DEFINITIONS | BENEFIT VARIATIONS
DISCLAIMER | CODING INFORMATION | REFERENCES
POLICY HISTORY

I. POLICY

Genetic testing for epilepsy is considered investigational. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure. (See Policy Guidelines)

Policy Guidelines

This policy statement covers 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 statement also covers 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 mental retardation 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.

This statement does not cover testing for syndromes that have a wider range of symptomatology, of which seizures may be one. Genetic testing for these syndromes may be specifically addressed in other policies (see related policies)

Cross-reference:
MP-2.323 General Approach to Evaluation the Utility of Genetic Panels

II. PRODUCT VARIATIONS

[N] = No product variation, policy applies as stated
[Y] = Standard product coverage varies from application of this policy, see below
### III. DESCRIPTION/BACKGROUND

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. The common epilepsies, also called idiopathic epilepsy, are thought to have a complex, multifactorial genetic basis. There are also numerous rare epileptic syndromes 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.

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 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.(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
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 (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.

For the purposes of this policy review, this classification is most useful. The 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 testing for these syndromes will not be assessed in this policy, but may be included in separate policies that specifically address genetic testing for that syndrome.
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. 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 are syndromes that are characterized by epilepsy as the primary manifestation. 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. A partial list of these 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)

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. 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.

The rare 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.

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.
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 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.

Genetic testing for epilepsy

Commercial testing is available from numerous companies. Testing for individual genes is available for most, or all, or the genes listed in Table 2, as well as for a wider range of genes. 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® offers a number of different epilepsy panels that have overlapping genes in varying combinations. The GeneDx® Comprehensive Epilepsy Panel lists 71 genes. They also offer a Childhood Onset epilepsy panel and an Infancy Panel. The GeneDx® infantile epilepsy panel includes the following 50 genes:

ADSL, ALDH7A1, ARX, ATP6AP2, CDKL5, CHRNA7, CLN3, CLN5, CLN6, CLN8, CNTNAP2, CTSD, FOLR1, FOXG1, GABRG2, GAMT, GRIN2A, KANSL1, KCNJ10, KCNQ2, KCNQ3, KCTD7, LIAS, MAGI2, MBD5, MECP2, MEF2C, MFSD8, NRXN1, PCDH19, PNKP, PNPO, POLG, PPT1, 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® Epilepsy and Seizure Disorders panel offers testing of 123 different genetic mutations by next-generation sequencing.

Regulatory Status

No U.S. Food and Drug Administration (FDA)-cleared genotyping tests were identified. The available commercial genetic tests for epilepsy are offered as laboratory-developed tests. Clinical laboratories may develop and validate tests in-house (“home-brew”) and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA)

IV. RATIONALE

The evaluation of a genetic test focuses on 3 main principles: (1) analytic validity (the technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent); (2) clinical validity (the diagnostic performance of the test [sensitivity, specificity, positive and negative predictive values] in detecting clinical disease); and (3) clinical utility (how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes)

The genetic epilepsies will be discussed in two categories: The rare epileptic syndromes that may be caused by a single-gene mutation and the common epilepsy syndromes that are thought to have a multifactorial genetic basis.

Rare Epilepsy Syndromes Associated With Single-Gene Mutations

There are numerous rare syndromes that have seizures as their primary symptom. These generally present in infancy or early childhood. Many of them are thought to be caused by single-gene mutations. The published literature on these syndromes generally consists of small
cohorts of patients treated in tertiary care centers, with descriptions of genetic mutations that are detected in affected individuals.

The following table lists some of these syndromes, with the putative causative genetic mutations:

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Implicated Gene(s)</th>
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<tr>
<td>Dravet syndrome (severe myoclonic epilepsy of infancy)</td>
<td>SCN1A</td>
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<tr>
<td>Early infantile epileptic encephalopathy</td>
<td>STXBP1</td>
</tr>
<tr>
<td>Generalized epilepsy with febrile seizures plus (GEFS+)</td>
<td>SCN1A, SCN2A, SCN1B, GABRG2</td>
</tr>
<tr>
<td>Epilepsy and mental retardation limited to females</td>
<td>PCDH19</td>
</tr>
<tr>
<td>Nocturnal frontal lobe epilepsy</td>
<td>CHRNA4, CHRN2B, CHRNA2</td>
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**Analytic validity**

These syndromes can be evaluated by single-gene analysis, which is generally performed by direct sequencing. Direct sequencing is the gold standard for identifying specific mutations. This testing method has an analytic validity of greater than 99%. They can also be evaluated by genetic panel testing, which is generally done by next-generation sequencing. This method has a lower analytic validity compared to direct sequencing, but is still considered to be very accurate, in the range of 95 to 99%.

**Clinical validity**

The literature on the clinical validity of these rare syndromes is limited, and for most syndromes, the clinical sensitivity and specificity is not defined. Dravet syndrome is probably
the most well studied, and some evidence on the clinical validity of SCN1A mutations is available. The clinical sensitivity has been reported to be in the 70 to 80% range. (8, 9) In 1 series of 64 patients, 51 (79%) were found to have SCN1A mutations.(9) The false-positive rate and the frequency of variants of uncertain significance, is not well characterized.

For the other syndromes, the associations of the genetic mutations with the syndromes have been reported in case reports or very small numbers of patients. Therefore, it is not possible to determine the clinical validity of the putative causative genetic mutations.

**Clinical utility**

One potential area of clinical utility for genetic testing may be in making a definitive diagnosis and avoiding further testing. For most of these syndromes, the diagnosis is made by clinical criteria, and it is not known how often genetic testing leads to a definitive diagnosis when the diagnosis cannot be made by clinical criteria.

Another potential area of clinical utility may be in directing pharmacologic treatment. For Dravet syndrome, the seizures are often refractory to common medications. Some experts have suggested that diagnosis of Dravet syndrome may therefore prompt more aggressive treatment, and/or avoidance of certain medications that are known to be less effective, such as carbamazepine.(9,10) However, there are no studies that examine the frequency with which genetic testing leads to changes in medication management, and there are no studies that report on whether the efficacy of treatment directed by genetic testing is superior to efficacy of treatment without genetic testing.

**Section Summary**

There are numerous rare epileptic syndromes which may be caused by single-gene mutations, but the evidence on genetic testing for these syndromes is insufficient to form conclusions on the clinical validity and clinical utility of genetic testing. The syndrome with the greatest amount of evidence is Dravet syndrome. The clinical sensitivity of testing patients with clinically defined Dravet syndrome is relatively high in small cohorts of patients. There may be clinical utility in avoiding further testing and directing treatment, but there is only a small amount of evidence to suggest this and no evidence demonstrating that outcomes are improved.

**Common Epilepsies**

The common epilepsy syndromes, also known as idiopathic epilepsy, generally present in childhood, adolescence or early adulthood. They include generalized or focal in nature, and may be convulsant (grand mal) or absence type. They are generally thought to have a multifactorial genetic component.

**Analytic validity**

The common epilepsies are generally evaluated by genetic panel testing. The larger, commercially available panels that include many mutations are generally performed by next-generation sequencing. This method has a lower analytic validity compared to direct sequencing, but is still considered to be very accurate, in the range of 95 to 99%. Less
commonly, deletion/duplication analysis may be performed; this method is also considered to have an analytic validity of greater than 95%.

**Clinical validity**

The literature on clinical validity includes many studies that report the association of various genetic variants with the common epilepsies. There are a large number of case-control studies that compare the frequency of genetic variants in patients with epilepsy to the frequency in patients without epilepsy. There is a smaller number of genome-wide association studies (GWAS) that evaluate the presence of single-nucleotide polymorphisms (SNPs) associated with epilepsy across the entire genome. No studies were identified that reported the clinical sensitivity and specificity of genetic mutations in various clinically defined groups of patients with epilepsy. In addition to these studies on the association of genetic variants with the diagnosis of epilepsy, there are numerous other studies that evaluate the association of genetic variants with pharmacogenomics of anti-epileptic medications.

**Diagnosis of Epilepsy.** The Epilepsy Genetic Association Database (epiGAD) published an overview of genetic association studies in 2010.(11) This review identified 165 case-control studies published between 1985 and 2008. There were 133 studies that examined the association of 77 different genetic variants with the diagnosis of epilepsy. Approximately half of these studies (65/133) focused on patients with genetic generalized epilepsy. Most of these studies had relatively small sample sizes, with a median of 104 cases (range, 8-1361) and 126 controls (range, 22-1390). There were less than 200 case patients in 80% of the studies. The majority of the studies did not show a statistically significant association. Using a cutoff of p<0.01 as the threshold for significance, there were 35 studies (21.2%) that reported a statistically significant association. According to standard definitions for genetic association, all of the associations were in the weak to moderate range, with no associations reported that were considered strong.

The EPICURE Consortium published one of the larger GWAS of genetic generalized epilepsy in 2012.(12) This study included 3,020 patients with genetic generalized epilepsy (GGE) and 3,954 control patients, all of European ancestry. A 2-stage approach was used, with a discovery phase and a replication phase, to evaluate a total of 4.56 million single-nucleotide polymorphisms (SNPs). In the discovery phase, 40 candidate SNPs were identified that exceeded the significance for the screening threshold (1 x 10^{-5}), although none of these reached the threshold defined as statistically significant for genome-wide association (1 x 10^{-8}). After stage 2 analysis, there were 4 SNPs identified that had suggestive associations with GGE on genes *SCN1A, CHRM3, ZEB2*, and *NLE2F1*.

A second GWAS with a relative large sample size of Chinese patients was also published in 2012. (13) Using a similar 2-stage methodology, this study evaluated 1,087 patients with epilepsy and 3,444 matched controls. Two variants were determined to have the strongest association with epilepsy. One of these was on the *CAMSAPlII* gene and the second was on the *GRIK2* gene. There were several other loci on genes that were suggestive of an association on genes that coded for neurotransmitters or other neuron function.
In contrast to the 2 studies, a GWAS published from the UK failed to show any robust associations of SNPs with partial epilepsy. (14) This study included 3,445 patients with partial epilepsies and 6,935 controls of European ancestry. Using a threshold of an odds ratio greater than 1.3, the authors reported that no SNPs were identified that had a statistically significant association at that level.

In 2012, Heinzen et al. used whole exome sequencing to evaluate the association of genetic variants with genetic generalized epilepsy in 118 individuals with the disorder and 242 control patients of European origin. (15) No variants were found that reached the statistical threshold for a statistical association. From this initial data, the researchers selected 3897 candidate genetic variants. These variants were tested in a replication sample of 878 individuals with GGE and 1830 controls. None of the tested variants showed a statistically significant association.

In addition to the individual studies, there are a number of meta-analyses that evaluate the association of particular genetic variants with different types of epilepsy. Most of these have not shown a significant association. For example, Cordoba et al. evaluated the association of SLC6A4 gene variants with temporal lobe epilepsy in a total of 991 case patients and 1202 controls and failed to demonstrate a significant association on combined analysis. (16) Nurmohamed et al. performed a meta-analysis of 9 case-control studies that evaluated the association of the ABC1 gene polymorphisms with epilepsy. (17) There were a total of 2454 patients with epilepsy and 1542 control patients. No significant associations were found. One meta-analysis that did report a significant association was published by Kauffman et al. in 2008. (18) This study evaluated the association of variants in the IL1B gene with temporal lobe epilepsy and febrile seizures, using data from 13 studies of 1866 patients with epilepsy and 1930 controls. Combined analysis showed a significant relationship between one SNP (511T) and temporal lobe epilepsy, with a strength of association that was considered modest (odds ratio [OR]=1.48; 95% confidence interval [CI], 1.1 to 2.0; p=0.01).

Pharmacogenomics of anti-epileptic medications. Numerous case-control studies report on the association of various genetic variants with response to medications in patients with epilepsy. The epiGAD database identified 32 case-control studies of 20 different genes and their association with medication treatment. (11) The most common comparison was between patients who were responders to medication and patients who were nonresponders. Some of the larger representative studies are discussed below.

Kwan et al. compared the frequency of SNPs on the SCN1A, SCN2A, and SCN3A genes in 272 drug responsive patients and 199 drug resistant patients. (19) A total of 27 candidate SNPs were evaluated, selected from a large database of previously identified SNPs. There was one SNP identified on the SCN2A gene (rs2304016) that had a significant association with drug resistance (OR=2.1; 95% CI, 1.2 to 3.7; p<0.007).

Jang et al. compared the frequency of variants on the SCN1A, SCN1B, and SCN2B genes in 200 patients with drug resistant epilepsy and 200 patients with drug responsive epilepsy. (20) None of the individual variants tested showed a significant relationship with drug resistance. In further analysis of whether there were gene-gene interactions that were associated with drug
resistance, the authors reported that there was a possible interaction of 2 variants, one on the
SCN2A gene and the other on the SCN1B gene, that were of borderline statistical significance
(p=0.055).

One meta-analysis evaluating pharmacogenomics was identified.(21) This study examined the
association between SNPs on the ABCB1 gene and drug resistance in 3,231 drug resistant
patients and 3,524 controls from 22 studies. The authors reported no significant relationship
between variants of this gene and drug resistance (combined OR=1.06; 95% CI, 0.98 to 1.14;
p=0.12). There was also no significant association between on subgroup analysis by ethnicity.

**Clinical utility**

There is a lack of evidence on the clinical utility of genetic testing for the common genetic
epilepsies. Association studies are not sufficient evidence to determine whether genetic testing
can improve the clinical diagnosis of GGE. There are no studies that report the accuracy in
terms of sensitivity, specificity, or predictive value; therefore it is not possible to determine the
impact of genetic testing on diagnostic decision making.

The evidence on pharmacogenomics suggests that genetic factors may play a role in the
pharmacokinetics of anti-epileptic medications. However, this evidence does not provide
guidance on how genetic information might be used to tailor medication management in ways
that will improve efficacy, reduce adverse effects, or increase the efficiency of medication
trials.

**Section Summary**

The evidence on genetic testing for the common epilepsies is characterized by a large number
of studies that evaluate associations of many different genetic variants with the various
categories of epilepsy. The evidence on clinical validity is not consistent in showing an
association of any specific genetic mutation with any specific type of epilepsy. Where
associations have been reported, they are not of strong magnitude, and in most cases, have not
been replicated independently or through the available meta-analyses. Because of the lack of
established clinical validity, the clinical utility of genetic testing for the common epilepsies is
also lacking.

**Summary**

Genetic testing for epilepsy covers a wide range of clinical syndromes and possible genetic
defects. For rare epilepsy syndromes, which may be caused by single-gene mutations, there is
only a small body of research, which is insufficient to determine the clinical validity and
clinical utility of genetic testing. 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. There also may be a potential role for genetic testing in identifying
syndromes that are resistant to particular medications, and thereby directing treatment.
However, at the present time, the evidence is limited and the specific way in which genetic
testing leads to improved outcomes is ill-defined.
For the common epilepsies, which are thought to have a complex, multifactorial basis, the role of specific genetic mutations remains uncertain. Despite a large body of literature of 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. This literature does not permit conclusions on the clinical validity of genetic testing. Because of the lack of conclusions on clinical validity, conclusions on clinical utility are also lacking.

For epilepsy pharmacogenomics, there are numerous studies that evaluate the associations of genetic variants with medication response. This body of evidence also does not show consistent or strong relationships between genetic variants and response to medications. Therefore, the clinical utility of pharmacogenomics in epilepsy has not been demonstrated.

As a result of these limitations in the literature, genetic testing for epilepsy is considered investigational.

Practice Guidelines and Position Statements
None identified.

V. DEFINITIONS

N/A

VI. BENEFIT VARIATIONS

The existence of this medical policy does not mean that this service is a covered benefit under the member's contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member’s individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member’s benefit information or contact Capital for benefit information.

VII. DISCLAIMER

Capital’s medical policies are developed to assist in administering a member’s benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member’s benefit information, the benefit information will govern. Capital considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.
VIII. CODING INFORMATION

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Investigational when used for Genetic Testing for Epilepsy:

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<th>CPT Codes®</th>
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Investigational for all diagnoses

<table>
<thead>
<tr>
<th>ICD-9-CM Diagnosis Code*</th>
<th>Description</th>
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*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.

The following ICD-10 diagnosis codes will be effective October 1, 2015:

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<tr>
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IX. REFERENCES


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<td>MP-2.262</td>
<td>CAC 5/20/14 New policy. BCBSA adopted. Genetic testing for epilepsy is considered investigational</td>
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Health care benefit programs issued or administered by Capital BlueCross and/or its subsidiaries, Capital Advantage Insurance Company®, Capital Advantage Assurance Company® and Keystone Health Plan® Central. Independent licensees of the BlueCross BlueShield Association. Communications issued by Capital BlueCross in its capacity as administrator of programs and provider relations for all companies.