

# Epilepsy Genetic Testing

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**Procedures addressed**

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures covered by this guideline	Procedure codes
CACNA1A full gene sequence	81185
CSTB full gene sequence	81189
CSTB gene analysis; evaluation to detect abnormal alleles	81188
Epilepsy gene analysis	81400 81401 81402 81403 81404 81405 81406 81407 81408 81479
Epilepsy gene known familial mutation analysis	81403

Epilepsy Genetic Testing

Procedures covered by this guideline	Procedure codes
Epilepsy gene panel (must include analyses for ALDH7A1, CACNA1A, CDKL5, CHD2, GABRG2, GRIN2A, KCNQ2, MECP2, PCDH19, POLG, PRRT2, SCN1A, SCN1B, SCN2A, SCN8A, SLC2A1, SLC9A6, STXBP1, SYNGAP1, TCF4, TPP1, TSC1, TSC2, and ZEB2)	81419
Genomic Unity CACNA1A Analysis	0231U
Genomic Unity CSTB Analysis	0232U

## Criteria

This guideline applies to all epilepsy testing, including single gene analysis and multi-gene panels, which are defined as assays that simultaneously test for more than one epilepsy gene. Coverage criteria differ based on the type of testing being performed (i.e., individual epilepsy genes separately chosen versus pre-defined panels of epilepsy genes).

### Epilepsy single gene tests

Epilepsy single gene tests are considered medically necessary when the following criteria are met:

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous genetic testing inclusive of the gene(s) requested, AND
- Diagnostic Testing in Symptomatic Individuals:
  - The member has a condition that will benefit from information provided by the requested epilepsy gene testing based on at least one of the following criteria:
    - The member displays clinical features of the condition for which testing is being requested and a particular treatment is being considered for the member that requires a genetic diagnosis, OR
    - A particular antiepileptic drug (AED) is being considered for the member and the AED is contraindicated for individuals with mutations in the requested gene, defined by ONE of the following criteria:

- A neurology therapy FDA label requires results from the genetic test to effectively or safely use or avoidance of the therapy for the member's epilepsy type, and the member has not previously had a trial of the therapy, or
- An American neurological society specifically recommends the testing for the safe and effective use or avoidance of a therapy, and the member has not previously had a trial of the therapy, OR
- The member meets all criteria in a test-specific guideline, if available (see Table: *Select Epilepsy Conditions, Associated Genes, and Applicable Guidelines*), AND
- The member does not have a known underlying cause for their seizures (e.g. tumor, head trauma, known genetic condition), AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy

### Epilepsy multi-gene panels

Epilepsy multigene panels are considered medically necessary when all of the following criteria are met:

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous epilepsy multigene panel testing, AND
- Diagnostic Testing in Symptomatic Individuals:
  - The member has a diagnosis of early infantile epileptic encephalopathy, OR
  - The member has a diagnosis of infantile spasms, OR
  - The member has a diagnosis of intractable, neonatal seizures, OR
  - The member has drug-resistant focal epilepsy, OR
  - The member has focal epilepsy with a positive family history suggestive of monogenic inheritance, OR
  - The member has a diagnosis of febrile seizures with at least one episode of status epilepticus, OR
  - The member has a progressive neurological disease defined by the following:
    - Member has epilepsy with persistent loss of developmental milestones, and
    - Member's seizures are worsening in severity and/or frequency despite treatment, OR
  - A particular antiepileptic drug (AED) is being considered for the member and there are 2 or more genes on the panel for which the AED is contraindicated for individuals with mutations in that gene by ONE of the following:

- A neurology therapy FDA label requires results from the genetic test to effectively or safely use or avoidance of the therapy for the member's epilepsy type and the member has not previously had a trial of the therapy, or
- An American neurological society specifically recommends the testing for the safe and effective use or avoidance of a therapy and the member has not previously had a trial of the therapy, AND
  - The member does not display clinical features of a specific condition for which testing is available (e.g. Tuberous Sclerosis, Angelman Syndrome, Rett Syndrome, etc.), AND
  - The member does not have a known underlying cause for their seizures (e.g. tumor, head trauma, known genetic condition), AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

### Other considerations

This guideline may not apply to genetic testing for indications that are addressed in test-specific guidelines. Please see the test-specific list of guidelines for a complete list of test-specific panel guidelines.

Genetic testing for a specific gene is medically necessary only once per lifetime. Therefore, a single gene included in a panel or a multi-gene panel may not be reimbursed if testing has been performed previously. Exceptions may be considered if technical advances in testing demonstrate significant advantages that would support a medical need to retest. Further, given rapidly advancing knowledge regarding genetic variations in epilepsy and in normal or healthy populations, re-analysis of genetic tests may be warranted at regular intervals.

## Billing and Reimbursement

### Introduction

This section outlines the billing requirements for tests addressed in this guideline. These requirements will be enforced during the case review process whenever appropriate. Examples of requirements may include specific coding scenarios, limits on allowable test combinations or frequency and/or information that must be provided on a claim for automated processing. Any claims submitted without the necessary information to allow for automated processing (e.g. ICD code, place of service, etc.) will not be reimbursable as billed. Any claim may require submission of medical records for post service review.

- Any individual gene or multi-gene panel is only reimbursable once per lifetime.
- When otherwise reimbursable, the following limitations apply:
  - When a panel is being performed, it is only reimbursable when billed with a single, appropriate panel procedure code (e.g., 81419\*).

- When use of a panel code is not possible, each billed component procedure will be assessed independently.
- In general, only a limited number of panel components that are most likely to explain the member's presentation will be reimbursable. The remaining panel components will not be reimbursable.

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**Note:** \*The panel code(s) listed here may not be all-inclusive. For further discussion of what is considered an appropriate panel code, please refer to the guideline *Laboratory Billing and Reimbursement*.

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## What is epilepsy?

Epilepsy is a neurological condition that causes seizures.

### Prevalence

Epilepsy is one of the most common disorders, with an estimated prevalence of 6 in 1000 people worldwide.<sup>1</sup>

### Symptoms

Epilepsy can manifest in different ways, including different types of seizures or with multiple neurodevelopmental and medical complications besides seizures. Seizure types include generalized seizures (absence seizures, tonic-clonic seizures, myoclonic seizures), focal seizures (simple focal seizures, complex focal seizures, secondary generalized seizures, among others), and seizures for which the type is unknown.

Epilepsy syndromes can be associated with generalized, focal, or combined generalized and focal seizures, and can have onset in childhood or adulthood.<sup>2</sup> Epilepsy syndromes may be associated with developmental and/or epileptic encephalopathy (childhood onset) or progressive neurological deterioration (later onset).<sup>2</sup>

### Cause

Epilepsy has multiple causes, including central nervous system infection, autoimmune disease, structural brain abnormalities, brain tumors, and head trauma.<sup>3</sup> There are also numerous genetic conditions associated with epilepsy. It is estimated that approximately 40% of individuals with seizures have an underlying genetic basis for their condition (see Table for a list of common genetic causes).<sup>4</sup> Factors that contribute to the likelihood of a genetic basis includes type of seizures (focal or generalized) or epilepsy syndromes (such as epileptic encephalopathy), age of onset, family history, and presence of other clinical features.

Through Next Generation Sequencing (NGS)-based testing, including multi-gene panels, whole exome and genome sequencing as well as whole-genome screening for CNVs, pathogenic sequence variants have been identified in about 30-40% and deletions or duplications in ~5-10% of patients with a range of epilepsy phenotypes, including focal epilepsy, generalized epilepsies, epileptic encephalopathies, fever-associated epilepsy syndromes, other epilepsy syndromes, and patients with neurodevelopmental disorders and epilepsy.<sup>5,6</sup>

There are many different epilepsy syndromes, including generalized epilepsy syndromes, focal epilepsy syndromes, combined generalized and focal epilepsy syndromes, epilepsy syndromes with developmental and/or epileptic encephalopathy (DEE). These syndromes can present at variable ages ranging from neonatal to adulthood.<sup>2,7</sup>

DEE is a group of disorders in which seizures are accompanied by developmental delays, cognitive impairment, or a host of other neurological issues such as feeding difficulties, sleep dysregulation, and behavioral problems.<sup>8</sup> Knowledge regarding the genetic basis of these disorders has increased significantly in the last decade due to the advent of high throughput NGS methods, resulting in a growing list of known associated genes and wider availability of multi-gene panel testing. The following are examples of epileptic encephalopathies:

- Ohtahara Syndrome (Early Infantile Epileptic Encephalopathy)
  - "Characterized by early onset intractable tonic spasms, suppression-burst pattern on interictal EEG, and poor prognosis."<sup>9</sup>
  - "To date various genes, which have essential roles in the brain's neuronal and interneuronal functions, have been reported to be associated with Ohtahara syndrome. For instance, syntaxin binding protein 1 (STXBP1) regulates synaptic vesicle release; aristaless-related homeobox (ARX) acts as a regulator of proliferation and differentiation of neuronal progenitors; solute carrier family 25 member 22 (SLC25A22) encodes a mitochondrial glutamate transporter<sup>13</sup>; and potassium voltage-gated channel, KQT-like subfamily, member 2 (KCNQ2) plays a key role in a cell's ability to generate and transmit electrical signals."<sup>10</sup>
- Dravet Syndrome (Severe Myoclonic Epilepsy of Infancy)
  - "Clinical cardinal features include febrile or afebrile generalized or hemiconvulsions starting in the first year of life, seizure evolution to a mixture of intractable generalized (myoclonic or atonic seizures, atypical absences) and focal seizures, normal early development, subsequent psychomotor retardation, and normal brain imaging at onset."<sup>9</sup>
  - "In most of the cases with Dravet syndrome, one single gene has been involved, in contrast to other epileptic encephalopathy syndromes. SCN1A mutations have been shown in at least 80% of patients with Dravet syndrome."<sup>10</sup>
- Infantile Spasms (West Syndrome and X-linked Infantile Spasms)

- "West syndrome is characterized by a specific seizure type, i.e., epileptic spasms, a unique interictal EEG pattern termed hypsarrhythmia, and psychomotor retardation. Spasms start within the first year of life, mainly between 4 and 6 months of age."<sup>9</sup>
- "There are multiple genetic determinants of infantile spasms, which are usually explained by mutations in distinct genes. Genetic analysis of children with unexplained infantile spasms have demonstrated mutations on the X chromosome in genes such as ARX, cyclin-dependent kinase-like 5 (CDKL5), and UDP-N-acetylglucosaminyltransferase subunit (ALG13) as well as de novo mutations in autosomal genes, including membrane-associated guanylate kinase, WW and PDZ domain containing protein 2 (MAGI2), STXBP1, sodium channel alpha 1 subunit (SCN1A), sodium channel protein type 2 subunit alpha (SCN2A), g-aminobutyric acid (GABA) A receptor, beta 3 (GABRB3), and dynamin 1 (DNM1)."<sup>10</sup>
- Epilepsy and Intellectual Disability Limited to Females
  - "Epilepsy and intellectual disability limited to females (EFMR) is an underrecognized disorder with X-linked inheritance but surprisingly only affecting females while sparing transmitting males. Seizure, cognitive, and psychiatric phenotypes show heterogeneity. Seizures start from the age of 6 to 36 months and may be precipitated by fever. Seizure types include GTCS, myoclonic and tonic seizures, absences, and focal."<sup>9</sup>
  - "Different mutations of PCDH19 (protocadherin 19), including missense, nonsense, and frameshift mutations, have been reported as the cause of EFMR."<sup>9</sup>

**Table: Select Epilepsy Conditions, Associated Genes, and Applicable Guidelines**

Condition*	Associated genes*	Applicable guideline	Guideline number
Angelman syndrome	UBE3A	Angelman Syndrome Genetic Testing	MOL.TS.126
Biotin-thiamine-responsive basal ganglia disease	SLC19A3	Epilepsy Genetic Testing	MOL.TS.257
Cerebral folate transport deficiency	FOLR1	Epilepsy Genetic Testing	MOL.TS.257



Condition*	Associated genes*	Applicable guideline	Guideline number
Classic Rett syndrome (females); MECP2-Related Epileptic Encephalopathy (males)	MECP2	Rett Syndrome Genetic Testing	MOL.TS.224
Creatine deficiency syndromes	GAMT, GATM, SLC6A8	Epilepsy Genetic Testing	MOL.TS.257
Developmental and epileptic encephalopathy (DEE)	ARGHEF9, ARX, CDKL5, CHD2, PCDH19, GABRA1, GABR2, GABRB3, GRIN2A, KCNQ2, KCNT1, PNKP, SCN1A, SCN1B, SCN2A, SCN8A, SLC25A22, SPTAN1, STXBP1, TBC1D24	Epilepsy Genetic Testing	MOL.TS.257
Familial hemiplegic migraine	ATP1A2, CACNA1A, PRRT2	Epilepsy Genetic Testing	MOL.TS.257
GLUT1 Deficiency	SLC2A1	Epilepsy Genetic Testing	MOL.TS.257
POLG-related disorders	POLG	Polymerase Gamma (POLG) Related Disorders Genetic Testing	MOL.TS.276
Progressive myoclonic epilepsy	CSTB, EPM2A, GOSR2, KCNC1, KCTD7, NHLRC1, PRICKLE1, SCARB2	Epilepsy Genetic Testing	MOL.TS.257
Pyridoxine-dependent epilepsy	ALDH7A1, PNPO	Epilepsy Genetic Testing	MOL.TS.257



Condition*	Associated genes*	Applicable guideline	Guideline number
Tuberous sclerosis	TSC1, TSC2	Epilepsy Genetic Testing	MOL.TS.257

\*This list of conditions and their associated genes is not all-inclusive. Many genes can be associated with multiple types of seizure disorders, including some milder disorders not listed here (e.g., generalized epilepsy with febrile seizures or self-limited familial neonatal/infantile epilepsy).

### Inheritance

Inheritance patterns differ between various epilepsy syndromes, and include monogenic inheritance patterns such as dominant, X-linked, recessive, and mitochondrial, in addition to epilepsy caused by de novo (i.e. new) genetic mutations. Clinical heterogeneity is also seen in these conditions.

### Diagnosis

An electroencephalograph (EEG) can be used to help diagnose epilepsy and possibly give information as to the seizure type. A brain magnetic resonance imaging (MRI) scan can further help define whether epilepsy is caused by a structural brain abnormality or help determine the origin of epilepsy.

Genetic testing for epilepsy is complicated by many factors. Epilepsy syndromes frequently have overlapping features, such as the types of seizures involved, ages of onset, and/or additional clinical findings. Reduced penetrance, with not all individuals carrying a pathogenic genetic change developing seizures, also complicates the family history assessment. Many (if not most) epilepsy syndromes, including epileptic encephalopathy, are genetically heterogeneous, and can be caused by mutations in a number of different genes. Sometimes, the inheritance pattern or the presence of pathognomonic features makes the underlying syndrome clear. However, in many cases, it can be difficult to reliably diagnose a genetic epilepsy syndrome based on clinical and family history alone.

NGS-based testing has been shown to dramatically improve the diagnostic rate for children and adults with epilepsy, as well as significantly shorten the time from assessment to diagnosis.<sup>11-13</sup> The diagnostic yield of NGS in patients with epilepsy is estimated to be 20-40%.<sup>6,14,15</sup>

Clinical information (e.g. age of onset, seizure type, EEG results, etc.) or family history may be used in some cases to help narrow down the suspected cause. In these cases, it may be possible to identify a narrow subset of genes that may be responsible for an individual's epilepsy.<sup>9,10</sup>

## Management

Treatment for epilepsy ranges from antiepileptic drugs (AEDs) to the ketogenic diet to vagal nerve stimulation to epilepsy surgery in the most severe situations. Not all treatments will work for everyone and often, it takes multiple treatment trials to find a regimen that is successful. Refractory epilepsy is diagnosed after two or more AEDs have failed to control seizures. Drug-resistant epilepsy is defined as "failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom".<sup>16</sup>

In a rapidly growing number of epilepsy disorders, knowing the genetic mutation that is responsible for the epilepsy has been shown to help guide management and provide more disease-specific treatment.<sup>17,18</sup>

## Survival

Lifespan is dependent upon seizure control and the underlying cause of the individual's epilepsy.

## Test information

### Introduction

Genetic testing for epilepsy may consist of next-generation sequencing or multigene panels.

### Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

### Multi-Gene Testing Panels

The efficiency of NGS has led to an increasing number of large, multi-gene testing panels. NGS panels that test several genes at once are particularly well-suited to conditions caused by more than one gene or where there is considerable clinical overlap between conditions making it difficult to reliably narrow down likely causes. Additionally, tests should be chosen to maximize the likelihood of identifying mutations in the genes

of interest, contribute to alterations in management for an individual, and/or minimize the chance of finding variants of uncertain clinical significance.

## Guidelines and evidence

### International League Against Epilepsy

A Task Force for the International League Against Epilepsy (ILAE, 2015) Commission of Pediatrics published recommendations for the management of infantile seizures that stated:<sup>19</sup>

- "[F]or Dravet syndrome, strong evidence supports that stiripentol is effective (in combination with valproate and clobazam), whereas weak evidence supports that topiramate, zonisamide, valproate, bromide, and the ketogenic diet are possibly effective; and for Ohtahara syndrome, there is weak evidence that most antiepileptic drugs are poorly effective."
- "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) (level of evidence —weak recommendation, level C)."
- "Early diagnosis of some mitochondrial conditions may alter long-term outcome, but whether screening at quaternary level is beneficial is unknown (level of evidence U)."

The ILAE (2022) Task Force on Clinical Genetic Testing in the Epilepsies provided an updated review of the role of genetic testing for those with epilepsy that stated:<sup>20</sup>

- "A precise epilepsy genetic diagnosis is important for individuals and their families as it has both clinical and personal utility."
- "Testing should be considered in epilepsy types with a reasonably high pre-test probability of a genetic cause being identified and, especially, if the results may lead to improved care for the individual."
- "Overall, the likelihood of identifying a genetic cause decreases with increasing age at onset of the epilepsy; the greatest proportion of genetic epilepsies manifests in the neonatal period, followed by infancy. In this age period, the diagnostic yield of genetic testing may reach up to 60%. However, age at testing (as opposed to the age at onset of epilepsy) should not influence the decision to test or the type of test chosen. Individuals who are now adults who had early-onset epilepsy likely presented in the era before genetic testing was widely available, and should be considered candidates for testing."
- "Clinical utility of genetic testing is highest in the more severe, drug-resistant epilepsies. Overall, the most obvious indication, in terms of clinical utility and diagnostic yield, is for people with early-onset DEE or neurodevelopmental disorders with epilepsy. The presence of comorbid conditions, such as intellectual disability, autism, dysmorphic features or multi-system symptoms increases the likelihood of

a genetic finding. Testing of individuals with drug-resistant non-acquired epilepsy without such comorbidities could be useful as identification of an underlying genetic cause might lead to a more targeted treatment."

### National Society of Genetic Counselors

The National Society of Genetic Counselors practice guideline on epilepsy (2022), which was endorsed by the American Epilepsy Society (AES), stated:<sup>7</sup>

- "We strongly recommend that individuals with unexplained epilepsy be offered genetic testing, without limitation of age."
- "We strongly recommend comprehensive, multi-gene testing, such as ES/GS [exome sequencing/genome sequencing] or MGP [multigene panels] as a first-tier test. We conditionally recommend ES/GS over MGP as the first-tier test."
- "The MGP panel should have a minimum of 25 genes and include copy number analysis."
- "MGPs are valuable clinical tools that can be employed in a number of clinical scenarios, for example, when an individual presents with a defined epilepsy syndrome for which a subset of genes should be interrogated more robustly than through ES when GS is unavailable. Additionally, if urgent results are required and rapid ES/GS is unavailable, a targeted MGP may be considered. MGPs may also be utilized as a first-tier test when access to ES/GS, or the additional genetic counseling required to implement such testing, may be limited."

### Selected Relevant Publications

Peer reviewed and expert authored articles are presented below.

- In 2016, a peer reviewed article on genetic testing for epileptic encephalopathy stated the following:
  - "Second line investigations: Targeted next generation sequencing panels of epileptic encephalopathy genes for individuals with epileptic encephalopathy."<sup>8</sup>
- In 2016, a peer reviewed article on genetic causes of early-onset epileptic encephalopathy stated the following:<sup>10</sup>
  - "Molecular-based studies on early-onset epileptic encephalopathies should be performed, necessitating programmed genetical algorithms. If the phenotype could be determined with clinical findings, specific gene testing would be helpful in diagnosis. However, if the phenotype could not be determined because of overlapping phenotypes of different syndromes and the spectrum of phenotypes seen in different mutations, the use of gene panels for epilepsy would increase the probability of correct diagnosis. In a recent study, the rate of diagnosis with targeted single gene sequencing has been reported as 15.4%, whereas the rate has increased to 46.2% with the utility of epilepsy gene panels."

- A systematic evidence review and meta-analyses of the diagnostic yield of genetic tests commonly utilized for patients with epilepsy was conducted in 2022.<sup>6</sup> Studies that utilized genome sequencing, exome sequencing, multigene panel, and/or genome-wide comparative genomic hybridization/chromosomal microarray (CGH/CMA) in cohorts (n ≥ 10) ascertained for epilepsy were included.
  - Overall diagnostic yield across all test modalities was 17%, with the highest yield for GS (48%), followed by ES (24%), MGP (19%), and CGH/CMA (9%).
  - The number of genes included on MGP increases the diagnostic yield. Panels with 26-500 genes had a yield of 20-25% and >500 genes had a yield of about 35% (26-45%).
  - Phenotypic factors that were significantly associated with increased diagnostic yield included the presence of:
    - developmental and epileptic encephalopathy, and/or
    - neurodevelopmental comorbidities.
- Multiple peer-reviewed articles have shown that epilepsy multi-gene panels have a significant diagnostic yield when seizure onset is in infancy or early childhood.<sup>13,21-23</sup> The diagnostic yields in adults with epilepsy tend to be lower.<sup>24,25</sup>
- A 2023 peer reviewed article on the genetics of nonlesional focal epilepsy stated:<sup>26</sup>
  - "Genetic testing should be performed on individuals with a family history suggestive of monogenic inheritance, patients with defined syndromes (e.g., epilepsy with auditory features), and individuals with additive symptoms (intellectual impairment, autism, dysmorphic features)."
  - "Genetic testing should be considered during presurgical evaluation of patients with drug-resistant focal epilepsy."

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#### Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for epilepsy genetic testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

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