



FEP Medical Policy Manual

FEP 2.04.109 Genetic Testing for Epilepsy

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Related Policies:

- 2.04.102 - Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders
- 2.04.38 - Cytochrome P450 Genotype-Guided Treatment Strategy
- 2.04.83 - Genetic Testing for FMR1 Variants (Including Fragile X Syndrome)

Genetic Testing for Epilepsy

Description

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

OBJECTIVE

The objective of this evidence review is to determine whether genetic testing improves the net health outcome in individuals with infantile- or early-childhood-onset epileptic encephalopathy or with presumed genetic epilepsy.

POLICY STATEMENT

Genetic testing for genes 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 (see Policy Guidelines section) may be 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.

Genetic testing for epilepsy is considered **investigational** for all other situations.

POLICY GUIDELINES

Policy Scope

Included Tests and Conditions

This policy addresses testing for epilepsy that might have a genetic etiology. In 2010, the International League Against Epilepsy classified epilepsy as having underlying genetic cause or etiology when, as best understood, the epilepsy is the direct result of a known or presumed genetic defect and seizures are the core symptom of the disorder and for which there is no structural or metabolic defect predisposing to epilepsy. The updated 2017 ILAE classification system does not discuss epilepsy with a genetic cause.

This policy also addresses the rare epilepsy syndromes that present in infancy or early childhood, in which epilepsy is the core clinical symptom (eg, Dravet syndrome, early infantile epileptic encephalopathy, generalized epilepsy with febrile seizures plus, epilepsy and intellectual disability limited to females, nocturnal frontal lobe epilepsy). Other clinical manifestations may be present in these syndromes but are generally secondary to epilepsy itself.

Excluded Tests and Conditions

This policy does not address testing for genetic syndromes that have a wider range of symptomatology, of which seizures may be one, such as the neurocutaneous disorders (eg, neurofibromatosis, tuberous sclerosis) or genetic syndromes associated with cerebral malformations or abnormal cortical development, or metabolic or mitochondrial disorders. Genetic testing for these syndromes may be specifically addressed in other evidence reviews (see Related Policies links).

Testing that is limited to genotyping of cytochrome P450 (*CYP450*) genes is addressed separately (evidence review 2.04.38).

This policy does not address the use of genotyping for the *HLA-B*1502* allelic variant in patients of Asian ancestry prior to considering drug treatment with carbamazepine due to risks of severe dermatologic reactions. This testing is recommended by the U.S. Food and Drug Administration (FDA) labeling for carbamazepine.

This policy also does not address the testing for variants in the mitochondrial DNA polymerase gamma (*POLG*) gene in patients with clinically suspected mitochondrial disorders prior to initiation of therapy with valproate. Valproate's label contains a black box warning related to increased risk of acute liver failure associated with the use of valproate in patients with *POLG* gene-related hereditary neurometabolic syndromes. FDA labeling states that valproate "is contraindicated in patients known to have mitochondrial disorders caused by *POLG* mutations and children under 2 years of age who are clinically suspected of having a *POLG*-related disorder".

For positions on whole exome and whole genome sequencing for the diagnosis of neurodevelopmental disorders refer to evidence review 2.04.102.

Medically Necessary Statement Definitions and Testing Strategy

The medically necessary statement refers to epilepsy syndromes that present in infancy or early childhood, are severe, and are characterized by epilepsy as the primary manifestation, without associated metabolic or brain structural abnormalities. As defined by the International League Against Epilepsy, these include epileptic encephalopathies, which are electroclinical syndromes associated with a high probability of encephalopathic features that present or worsen after the onset of epilepsy. Other clinical manifestations, including developmental delay and/or intellectual disability, may be present secondary to the epilepsy itself. Specific clinical syndromes based on the International League Against Epilepsy classification include:

- Dravet syndrome (also known as severe myoclonic epilepsy in infancy [SMEI] or polymorphic myoclonic epilepsy in infancy)
- EFMR syndrome (epilepsy limited to females with mental retardation)
- Epileptic encephalopathy with continuous spike-and-wave during sleep
- GEFS+ syndrome (generalized epilepsies with febrile seizures plus)
- Ohtahara syndrome (also known as early infantile epileptic encephalopathy with burst suppression pattern)
- Landau-Kleffner syndrome
- West syndrome
- Glucose transporter type 1 deficiency syndrome.

Variants in a large number of genes have been associated with early-onset epilepsies. Some of them are summarized in Table PG1.

Table PG1. Single Genes Associated With Epileptic Syndromes

Syndrome	Associated Genes
Dravet syndrome	SCN1A, SCN9A, GABRA1, STXBP1, PCDH19, SCN1B, CHD2, HCN1
Epilepsy limited to females with mental retardation	PCDH19
Epileptic encephalopathy with continuous spike-and-wave during sleep	GRIN2A
Genetic epilepsy with febrile seizures plus	SCN1A, SCN9A
Early infantile epileptic encephalopathy with suppression burst (Ohtahara 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

Application of the Medically Necessary Policy Statement

Although there is no standard definition of epileptic encephalopathies, they are generally characterized by at least some of the following: (1) onset in early childhood (often in infancy); (2) refractory to therapy; (3) associated with developmental delay or regression; and (4) severe electroencephalogram (EEG) abnormalities. There is a challenge in defining the population appropriate for testing given that specific epileptic syndromes may be associated with different EEG abnormalities, which may change over time, and patients may present with severe seizures prior to the onset or recognition of developmental delay or regression. However, for this policy, the medically necessary policy statement would apply for patients with:

- Onset of seizures in early childhood (ie, before the age of 5 years); AND
- Clinically severe seizures that affect daily functioning and/or interictal EEG abnormalities; AND
- No other clinical syndrome that would potentially better explain the patient's symptoms.

Testing Strategy

There is clinical and genetic overlap for many of the electroclinical syndromes previously discussed. If there is suspicion for a specific syndrome based on history, EEG findings, and other test results, testing should begin with targeted variant testing for the candidate gene most likely to be involved, followed by sequential testing for other candidate genes. In particular, if an *SCN1A*-associated syndrome is suspected (Dravet syndrome, GEFS+), molecular genetic testing of *SCN1A* with sequence analysis of the *SCN1A* coding region, followed by deletion and duplication analysis if a pathogenic variant is not identified, should be obtained.

Given the genetic heterogeneity of early-onset epilepsy syndromes, a testing strategy that uses a multigene panel may be considered reasonable. In these cases, panels should meet the criteria outlined in evidence review 2.04.92 (general approach to evaluating the utility of genetic panels). Criteria for use of whole exome sequencing are outlined in evidence review 2.04.102 (whole exome and whole genome sequencing for diagnosis of genetic disorders).

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (Table PG2). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG3 shows the recommended standard terminology<97>"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"<97>to describe variants identified that cause Mendelian disorders.

Table PG2. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG3. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

State or federal mandates (eg, Federal Employee Program) may dictate that certain U.S. Food and Drug Administration–approved devices, drugs, or biologics may not be considered investigational, and thus these devices may be assessed only by their medical necessity.

FDA REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Commercially available genetic tests for epilepsy are available under the auspices of the CLIA. Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the FDA has chosen not to require any regulatory review of this test.

RATIONALE

Summary of Evidence

For individuals who have infantile- or early-childhood-onset epileptic encephalopathy who receive testing for genes associated with epileptic encephalopathies, the evidence includes a systematic review and meta-analysis, prospective, and retrospective cohort studies describing the testing yield. Relevant outcomes are test validity, symptoms, quality of life, functional outcomes, medication use, resource utilization, and treatment-related morbidity. For Dravet syndrome, which appears to have the largest body of associated literature, the sensitivity of testing for *SCN1A* disease-associated variants is high (up to 80%). For other early-onset epileptic encephalopathies, the true clinical sensitivity and specificity of testing are not well-defined. However, studies reporting on the overall testing yield in populations with epileptic encephalopathies and early-onset epilepsy have reported detection rates for clinically significant variants ranging from 7.5% to 57%. The clinical utility of genetic testing occurs primarily when there is a positive test for a known pathogenic variant. The presence of a pathogenic variant may lead to targeted medication management, avoidance of other diagnostic tests, and/or informed reproductive planning. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have presumed genetic epilepsy who receive testing for genetic variants associated with genetic epilepsies, the evidence includes prospective and retrospective cohort studies describing testing yields. Relevant outcomes are test validity, changes in reproductive decision making, symptoms, quality of life, functional outcomes, medication use, resource utilization, and treatment-related morbidity. For most genetic epilepsies, which are thought to have a complex, multifactorial basis, the association between specific genetic variants and the risk of epilepsy is uncertain. Despite a large body of literature on associations between genetic variants and epilepsies, the clinical validity of genetic testing is poorly understood. Published

literature is characterized by weak and inconsistent associations, which have not been replicated independently or by meta-analyses. A number of studies have also reported associations between genetic variants and antiepileptic drug (AED) treatment response, AED adverse effect risk, epilepsy phenotype, and risk of sudden unexplained death in epilepsy (SUDEP). The largest number of these studies is related to AED pharmacogenomics, which has generally reported some association between variants in a number of genes (including *SCN1A*, *SCN2A*, *ABCC2*, *EPHX1*, *CYP2C9*, *CYP2C19*) and AED response. Similarly, genetic associations between a number of genes and AED-related adverse events have been reported. However, no empirical evidence on the clinical utility of testing for the genetic epilepsies was identified, and the changes in clinical management that might occur as a result of testing are not well-defined. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in "Supplemental Information" if they were issued by, or jointly by, a U.S. professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Academy of Neurology et al.

In 2006, the American Academy of Neurology and Child Neurology Society published joint guidelines on the diagnostic assessment of children with status epilepticus.⁸⁹ These guidelines were reviewed and reaffirmed in 2022. With regard to whether genetic testing should be routinely ordered for children with status epilepticus, the guidelines stated: "There is insufficient evidence to support or refute whether such studies should be done routinely."

In 2000, the American Academy of Neurology, Child Neurology Society, and the American Epilepsy Society published joint guidelines for evaluating a first nonfebrile seizure in children.⁹⁰ This guidance was reviewed and reaffirmed in 2023. Routine electroencephalography was recommended as part of the diagnostic evaluation; genetic testing was not addressed.

International League Against Epilepsy

In 2015, the International League Against Epilepsy issued a report with recommendations on the management of infantile seizures, which included the following related to genetic testing in epilepsy⁴³:

- "Genetic screening should not be undertaken at a primary or secondary level of care, as the screening to identify those in need of specific genetic analysis is based on tertiary settings."
- "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."

National Society of Genetic Counselors

In 2022, the National Society of Genetic Counselors published a practice guideline on genetic testing and counseling for unexplained epilepsies.⁹¹ The Society made the following relevant recommendations:

- "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 exome/genome sequencing or multi-gene panel as a first-tier test.
- We conditionally recommend exome/genome sequencing over multi-gene panel as the first-tier test.
- The multi-gene panel should have a minimum of 25 genes and include copy number analysis."

European Academy of Neurology

In 2010, the European Federation of Neurological Societies (now the European Academy of Neurology) issued guidelines on the molecular diagnosis of channelopathies, epilepsies, migraine, stroke, and dementias.⁹² The guidelines made the following recommendations on epilepsy:

"There is good evidence to suggest that a thorough clinical and electrophysiological investigation may lead to the choice of the gene to be tested in patients with periodic paralysis (Level B). In myotonic disorders, it is recommended to first search for myotonic dystrophy and use clinical and electrophysiological phenotype characterization to guide for molecular genetic testing (Level B).

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 [variants] 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 SMEI, in which mutations [variants] are found in *SCN1A* in 80% of the patients (Level B)."

North American Consensus Panel

In 2017, recommendations were published from a consensus panel of 14 physicians and 5 family members/caregivers of patients with Dravet syndrome.⁹³ There was strong consensus among panel members that genetic testing should be completed in all patients with clinical suspicion for Dravet syndrome since this can lead to earlier diagnosis. Options for testing include *SCN1A* sequencing followed by testing for deletions and duplications if sequencing is negative, or epilepsy gene panel testing, with no consensus among panel members about which option is superior. There was strong consensus that epilepsy gene panel testing is preferred to *SCN1A* testing if the clinical presentation is less clear or if the patient has atypical features, and that karyotyping is not needed. The panel did not reach consensus about the utility of chromosomal microarray in patients with suspected Dravet syndrome (72.2% agreed, 22.2% disagreed, 5.6% did not know) and concluded that this test can be considered. Based on strong consensus, the panel recommended genetic testing in the following circumstances among children with normal development, seizures of unknown etiology, and no evidence of causal lesion in the brain: infants with at least 2 prolonged focal febrile seizures, or children aged 1 to 3 years with at least one prolonged febrile seizure before 18 months of age or myoclonic or atypical absence seizures that are refractory to at least one antiepileptic medication. Infants who experience a single prolonged focal or generalized convulsion do not require genetic testing (strong consensus), but this can be considered in children aged 1 to 3 years who experience multiple brief episodes of febrile seizure activity before 18 months of age or myoclonic or atypical absence seizures that do not respond to antiepileptic medication (moderate consensus). The panel had moderate consensus about the role of genetic testing (epilepsy gene panel) in teens and adults without congenital dysmorphism who have seizure activity resistant to antiepileptic medication and lack an early life history.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
March 2014	New policy	Genetic testing for epilepsy is considered investigational..
June 2015	Replace policy	Policy updated. Policy statement added that genetic testing for early-onset epileptic encephalopathy syndromes may be considered medically necessary with conditions. References 1 and 40 added.
June 2018	Replace policy	Policy updated with literature review through December 21, 2016; references 9, 15-21, 26-29, 31, 35-37, 39, 44, 47, 49-50 and 59-61 added. The policy is revised with updated genetics nomenclature. Policy statements unchanged.
June 2019	Replace policy	Policy updated with literature review through December 6, 2018; references 19-20, and 34-37 added. Policy statements unchanged.
June 2020	Replace policy	Policy updated with literature review through December 9, 2019; no references added. Policy statements unchanged.
June 2021	Replace policy	Policy updated with literature review through December 23, 2020; references added. Policy statements unchanged.
June 2022	Replace policy	Policy updated with literature review through December 29, 2021; references added. Policy statements unchanged.
June 2023	Replace policy	Policy updated with literature review through December 8, 2022; references added. Policy statements unchanged.
June 2024	Replace policy	Policy updated with literature review through December 18, 2023; reference added. Policy statements unchanged.
June 2025	Replace policy	Policy updated with literature review through January 6, 2025; references added. Policy statements unchanged.
June 2026	Replace policy	Policy updated with literature review through January 6, 2026; references added. Policy statements unchanged.

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