

Overview

Useful For

Establishing a diagnosis of an epilepsy or seizure disorder associated with known causal genes

Identifying mutations within genes known to be associated with inherited epilepsy or seizure disorders, allowing for predictive testing of at-risk family members

Genetics Test Information

[Epilepsy is a heterogeneous group of disorders that are characterized by recurrent and usually unprovoked seizures.](#)

This test includes the option of performing 1 of several epilepsy/seizure-related panels. Options include the following:

- Early Epileptic Encephalopathy Panel (90 genes)
- Encephalopathy with Seizures Panel (129 genes)
- Epilepsy Expanded Panel (192 genes)
- Epilepsy with Migraine Panel (7 genes)
- Febrile Seizure Panel (9 genes)
- Focal Epilepsy Panel (16 genes)
- Infantile Spasms Panel (17 genes)
- Neuronal Migration Disorders Panel (29 genes)
- Progressive Myoclonic Epilepsy Panel (27 genes)
- Tuberous Sclerosis Panel (2 Genes)
- Custom Gene Panel (https://orders.mayocliniclabs.com/en/tools/gene_panels/)
- Custom Gene Ordering tutorial: <https://vimeo.com/299737728/23d56922f1>

See [Frequently Asked Questions: Custom Gene Ordering Tool](#) in Special Instructions.

See [Targeted Genes and Methodology Details for Epilepsy/Seizure Genetic Panels](#) in Special Instructions for details regarding the targeted genes for each test.

Testing Algorithm

This test includes the option for either 1 of several predefined panel tests or the option to create a custom gene panel.

Pricing for the Custom Gene Panel will be based on the number of genes selected (1, 2-14, 15-49, 50-100, and 101-500).

See [Epilepsy: Unexplained Refractory and/or Familial Testing Algorithm](#) in Special Instructions.

Special Instructions

- [Molecular Genetics: Neurology Patient Information](#)
- [Targeted Genes and Methodology Details for Epilepsy/Seizure Genetic Panels](#)
- [Frequently Asked Questions: Custom Gene Ordering Tool](#)
- [Epilepsy: Unexplained Refractory and/or Familial Testing Algorithm](#)
- [Custom Gene Panel Ordering](#)

Reflex Tests

Test Id	Reporting Name	Available Separately	Always Performed
_G116	Epilepsy Expanded Panel	No	No
_G117	Encephalopathy with Seizures Panel	No	No
_G118	Early Epileptic Encephalopathy Panel	No	No

_G119	Neuronal Migration Disorders Panel	No	No
_G120	Progressive Myoclonic Epilepsy Panel	No	No
_G121	Infantile Spasms Panel	No	No
_G122	Focal Epilepsy Panel	No	No
_G123	Febrile Seizure Panel	No	No
_G124	Epilepsy with Migraine Panel	No	No
_G131	Tuberous Sclerosis Panel	No	No
G145	Hereditary Custom Gene Panel Tier 1	No	No
G146	Hereditary Custom Gene Panel Tier 2	No	No
G147	Hereditary Custom Gene Panel Tier 3	No	No
G148	Hereditary Custom Gene Panel Tier 4	No	No
G149	Hereditary Custom Gene Panel Tier 5	No	No

Method Name

Custom Sequence Capture and Targeted Next-Generation Sequencing (NGS)/Polymerase Chain Reaction (PCR)/qPCR/Sanger Sequencing/or Gene Dosage Analysis by Multiplex Ligation-Dependent Probe Amplification (MLPA)

NY State Available

Yes

Specimen

Specimen Type

Varies

Shipping Instructions

Specimen preferred to arrive within 96 hours of collection.

Necessary Information

The specific epilepsy/seizure panel requested must be provided in order to perform this test.

Specimen Required

Specimen Type: Whole blood

Patient Preparation: A previous bone marrow transplant from an allogenic donor will interfere with testing. Call 800-533-1710 for instructions for testing patients who have received a bone marrow transplant.

Container/Tube:

Preferred: Lavender top (EDTA) or yellow top (ACD)

Acceptable: Any anticoagulant

Specimen Volume: 3 mL

Collection Instructions:

1. Invert several times to mix blood.
2. Send specimen in original tube.

Additional Information: To ensure minimum volume and concentration of DNA is met, the preferred volume of blood must be submitted. Testing may be canceled if DNA requirements are inadequate.

Forms

1. [Molecular Genetics: Neurology Patient Information](#) in Special Instructions
2. [Targeted Genes and Methodology Details for Epilepsy/Seizure Genetic Panels](#) in Special Instructions
3. If not ordering electronically, complete, print, and send a [Neurology Specialty Testing Client Test Request](#) (T732) with the specimen.

Reject Due To

All specimens will be evaluated by Mayo Clinic Laboratories for test suitability.

Specimen Minimum Volume

See Specimen Required.

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Ambient (preferred)		
	Frozen		
	Refrigerated		

Clinical & Interpretive

Clinical Information

Epilepsy is a heterogeneous group of disorders that are characterized by recurrent and usually unprovoked seizures. A comprehensive diagnostic genetic test is useful to help determine a molecular etiology for the heterogeneous epilepsy and seizure disorders and, therefore, establish long-term prognosis.

Early Epileptic Encephalopathy Panel:

Epileptic encephalopathies are neurodevelopmental disorders caused by recurrent clinical seizures usually seen during the early infantile period. Early epileptic encephalopathy is associated with impaired cognitive, sensory, and motor development. The most common causes of early epileptic encephalopathy include structural brain defects and inborn errors of metabolism, but genetic factors have been found to have an increasing role in cases without structural or metabolic causes.

Infantile Spasms Panel:

Infancy is the highest risk period for epileptic seizures, and infantile spasms are the most frequent type of epilepsy in the first year of life. Infantile spasms are characterized by spasms that occur in clusters and usually have an onset before 2 years of age. A spasm involves a brief contraction followed by less intense, but sustained, tonic contraction lasting up to 1 to 2 seconds. Additionally, infantile spasms are associated with a distinguishing electroencephalogram (EEG) pattern called hypsarrhythmia that has random, high-voltage spikes and slow waves. However, hypsarrhythmia is not seen in all cases of infantile spasms.

Infantile spasms seen in addition to hypsarrhythmia and delayed brain development or regression are referred to as West syndrome. Other subgroups of infantile spasms include infantile spasms single-spasm variant (ISSV), in which spasms occur singly rather than in clusters; hypsarrhythmia without infantile spasms (HWIS), when hypsarrhythmia occurs without any evidence of spasms; and infantile spasms without hypsarrhythmia (ISW), when clinical spasms occur without hypsarrhythmia.

Febrile Seizure Panel:

Febrile seizures are the most common convulsive event in childhood, usually occurring between 3 months and 5 years of age, and can be the presenting symptom of many clinical epilepsy syndromes. They are associated with fever, but without evidence of intracranial infection or defined cause. The most significant risk factors for recurrence of febrile seizures are family history of febrile seizures, a relatively low grade of fever, a shorter duration of fever before seizure, and onset of first seizure before 18 months of age.

Most children with febrile seizures do not develop epilepsy. However, the risk to develop unprovoked seizures after a febrile seizure is 2 to 3 times the risk of epilepsy in the general population. The most significant risk factors for the development of epilepsy include developmental delay or an abnormal neurological examination before the onset of the febrile seizure, a history of complex febrile seizures, and a first-degree relative with epilepsy. The most common epilepsy syndromes that present with febrile seizures include genetic epilepsy with febrile seizures plus (GEFS+) and Dravet syndrome. GEFS+ is an epilepsy syndrome in which febrile seizures continue beyond 6 years of age. Dravet syndrome is a neurodevelopment disorder associated with severe myoclonic epilepsy of infancy and often begins with prolonged seizures triggered by fever.

Progressive Myoclonic Epilepsy Panel:

Progressive myoclonic epilepsies are a genetically heterogeneous group of disorders that are characterized by worsening action myoclonus, epileptic seizures, and a progressive neurologic decline. The most common forms of progressive myoclonic epilepsies include Unverricht-Lundborg disease, Lafora disease, neuronal ceroid lipofuscinoses, and sialidoses. The first symptom of Unverricht-Lundborg disease is typically involuntary myoclonic jerks and it presents around 6 to 15 years of age. Lafora disease presents around 12 to 17 years of age, with many individuals having isolated febrile or nonfebrile convulsions in infancy or early childhood. Individuals with a neuronal ceroid lipofuscinosis have progressive decline, an evolving cognitive and motor disorder, and seizures.

Neuronal Migration Disorders Panel:

Neuronal migration disorders are caused by abnormal migration of neurons in the developing brain and nervous system. Neuronal migration disorders include lissencephaly, heterotopia, polymicrogyria, schizencephaly, and focal cortical dysgenesis.

Lissencephaly, which means smooth brain, is characterized by the lack of normal cortical folds or gyria. Severity of the disorder ranges from absence (agyria) to reduction (pachygyria) of normal gyral patterns. Classical lissencephaly, also known as type 1 lissencephaly, consists of early developmental delay, mental retardation, and spastic quadriplegia. Seizures are present in almost all children with early onset, in addition to a high prevalence of infantile spasms. In addition, seizures typically develop with classical lissencephaly in the first 6 to 12 months of life.

Neuronal heterotopia is characterized by a cluster of disorganized neurons in abnormal locations and is divided into periventricular nodule heterotopia and subcortical band heterotopia. Periventricular nodular heterotopia has a wide spectrum of clinical features, which can include developmental delay, microcephaly, and infantile spasms. However, epilepsy is the main feature. Subcortical band heterotopia has a spectrum of cognitive function ranging from normal to severe cognitive impairment, and features intractable epilepsy.

Polymicrogyria is characterized by an irregular brain surface with an excessive number of small and partly fused gyria separated by shallow sulci. Children can present with developmental delay and mild spastic quadriplegia, and almost all affected children have a high risk of developing epilepsy.

Schizencephaly is a disorder of cortical organization and can be divided into closed or fused lips, also known as type I, or open lips, also known as type II. Individuals with unilateral closed-lip schizencephaly generally have mild hemiparesis and

seizures, but no impairment of normal developmental milestones. Individuals with open-lip schizencephaly have mild-to-moderate developmental delay and hemiparesis. Individuals with bilateral clefts typically have more severe cognitive impairment and severe motor abnormalities.

Focal cortical dysgenesis is a congenital abnormality of cortical development that is generally associated with intractable focal epilepsy starting in adolescence. However, seizures associated with focal cortical dysgenesis may arise at any age.

Focal Epilepsy Panel:

Focal epilepsy is a neurological disorder characterized by recurrent seizures with abnormal electrographic activity in localized brain areas. Focal epilepsy can develop at any point during life. However, genetic causes of focal epilepsy are often associated with an earlier onset. They are comprised of autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), familial mesial temporal lobe epilepsy, autosomal dominant lateral temporal lobe epilepsy (ADLTE), and autosomal dominant partial epilepsy with variable loci.

ADNFLE is characterized by frontal lobe seizures occurring during sleep, often in clusters. The seizures are short in duration, fundamentally motor-based, and transmitted in an autosomal dominant pattern. Familial mesial temporal lobe epilepsy has an adolescent or adult onset that consists of seizures with symptoms that are psychic, autonomic, or sensorial. ADLTE is characterized by partial visual or auditory seizures that manifest in the first 2 decades of life and is transmitted in an autosomal dominant pattern. Autosomal dominant partial epilepsy with variable loci is characterized by focal seizures arising from different brain regions in different members of the same family. Most individuals have seizures of frontal or temporal origin and the age of onset is variable.

Epilepsy with Migraine Panel:

Epilepsy, which is multiple unprovoked seizures, is diverse with heterogeneous genetic causes. Additionally, it is one of the most common neurological diseases globally. People with epilepsy are more likely to be diagnosed with migraine than are people in the general population. Epilepsy and migraines share clinical features, and migraines are one of the most common neurologic comorbidities in individuals with epilepsy. The association between migraine and epilepsy is bilateral with either preceding or following the other, or they may occur at the same time.

Encephalopathy with Seizures Panel:

Epileptic encephalopathies are neurodevelopmental disorders caused by recurrent clinical seizures usually seen during the early infantile period. However, this panel is targeted towards those cases of encephalopathy with an onset outside of the neonatal and infantile periods.

Tuberous Sclerosis Panel:

Tuberous sclerosis complex (TSC) is an autosomal dominant neurocutaneous multisystem disorder associated with mutations in the *TSC1* and *TSC2* genes. TSC involves abnormalities of the skin, brain, kidneys, heart, and lungs. Central nervous system tumors are the leading cause of morbidity and mortality. Brain abnormalities can include infantile spasm and hypsarrhythmia syndrome.

Custom Gene Panel:

Custom gene ordering allows the creation of a custom gene list to tailor testing to a patient's exact need. After selection of a specific disease state, the custom gene panel can be modified to add or remove genes. Through this option single gene testing can be performed.

Reference Values

An interpretive report will be provided.

Interpretation

All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.⁽¹⁾ Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Cautions

Clinical Correlations:

Some individuals who are a carrier or have a diagnosis of an epilepsy or seizure disorder may have a mutation that is not identified by the methods performed (eg, promoter mutations or deep intronic mutations). The absence of a mutation, therefore, does not eliminate the possibility of a hereditary epilepsy or seizure disorder. For predictive testing of asymptomatic individuals, it is important to first document the presence of a gene mutation in an affected family member.

Test results should be interpreted in context of clinical findings, family history, and other laboratory data.

Misinterpretation of results may occur if the information provided is inaccurate or incomplete.

Technical Limitations:

In some cases, DNA variants of undetermined significance may be identified.

Due to the limitations of next-generation sequencing, small deletions and insertions may not be detected by this test. If a diagnosis of one of the syndromes on this panel is still suspected, contact a molecular genetic counselor in the Genomics Laboratory at 800-533-1710 for more information regarding follow-up testing options.

Rare polymorphisms exist that could lead to false-negative or false-positive results. If results obtained do not match the clinical findings, additional testing should be considered.

In addition to disease-related probes, the multiplex ligation-dependent probe amplification technique utilizes probes localized to other chromosomal regions as internal controls. In certain circumstances, these control probes may detect other diseases or conditions for which this test was not specifically intended. Results of the control probes are not normally reported. However, in cases where clinically relevant information is identified, the ordering physician will be informed of the result and provided with recommendations for any appropriate follow-up testing.

A previous bone marrow transplant from an allogenic donor will interfere with testing. Call 800-533-1710 for instructions for testing patients who have received a bone marrow transplant.

Evaluation Tools:

Multiple in-silico evaluation tools were used to assist in the interpretation of these results. These tools are updated regularly; therefore, changes to these algorithms may result in different predictions for a given alteration. Additionally, the predictability of these tools for the determination of pathogenicity is currently not validated.

Alterations classified as benign (common polymorphisms) and known pseudodeficiency alleles are not reported but are available upon request. Known pseudodeficiency alleles may lead to false-positive biochemical results, do not cause disease, and will only be reported when identified with a reportable alteration in the same gene.

Reclassification Of Variants-Policy:

All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. At this time, it is not standard practice for the laboratory to systematically review "likely pathogenic" alterations or "variants of uncertain significance" that are detected and reported. The laboratory encourages health care providers to contact the laboratory at any time to learn how the status of a particular variant may have changed over time.

Clinical Reference

1. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* 2015;17:405-423
2. Mameniskiene R, Karmonaite I, Zagorskis R: The burden of headache in people with epilepsy. *Seizure* 2016;41:120-126
3. Auvin S, Cilio MR, Vezzani A: Current understanding and neurobiology of epileptic encephalopathies. *Neurobiol Dis* 2016;92(Pt A):72-89
4. Kalviainen R: Progressive Myoclonus Epilepsies. *Semin Neurol* 2015;35(3):293-299
5. Chung S: Febrile seizures. *Korean J Pediatr* 2014;57(9):384-395

6. Berg AT, Millichap JJ: The 2010 revised classification of seizures and epilepsy. Continuum (Minneapolis Minn) 2013;19(3 Epilepsy):571-597
7. Poza JJ: The genetics of focal epilepsies. Handb Clin Neurol 2012;107:153-161
8. LaRoche SM: Seizures and encephalopathy. Semin Neurol 2011;31(2):194-201
9. Verrotti A, Spalice A, Ursitti F, et al: New trends in neuronal migration disorders. Eur J Paediatr Neurol 2010;14(1):1-12
10. Shields WD: Infantile spasms: little seizures, BIG consequences. Epilepsy Curr 2006;6(3):63-69

Performance

Method Description

Next-generation sequencing (NGS) and/or Sanger sequencing is performed to test for the presence of a mutation and for the presence of large deletions and duplications in the genes analyzed. See [Targeted Genes and Methodology Details for Epilepsy/Seizure Genetic Panels](#) in Special Instructions for details regarding the targeted genes analyzed for each test. There may be regions of genes that cannot be effectively amplified for sequencing or large deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high GC-rich content, and repetitive sequences.

Multiplex ligation-dependent probe amplification (MLPA), PCR, and/or Sanger sequencing is used to confirm alterations detected by NGS when appropriate.(Unpublished Mayo method)

PDF Report

No

Specimen Retention Time

Whole Blood: 2 weeks (if available) Extracted DNA: Indefinitely

Performing Laboratory Location

Rochester

Fees & Codes

Test Classification

This test was developed, and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information

81185 (if appropriate)

81189 (if appropriate)

81302 (if appropriate)

81403 (if appropriate)

81404 (if appropriate)

81405 (if appropriate)

81406 (if appropriate)

81407 (if appropriate)

81408 (if appropriate)

81443 (if appropriate)

81479 (if appropriate)

81419 (if appropriate)