Genetic Testing for Epilepsy
A Guide for Patients
Introduction

What is epilepsy?

Epilepsy is a common brain disorder that affects at least 0.8% of the population. It is defined by the occurrence of at least two unprovoked seizures occurring more than 24 hours apart. Seizures are caused by a sudden and abnormal pattern of electrical activity in brain cells. Epilepsy affects over 50 million individuals worldwide, with men, women, and children of all ethnic backgrounds equally at risk. Every year 200,000 new cases of epilepsy are diagnosed in the U.S.

What are the symptoms of epilepsy?

Seizures can be classified into various categories (Figure 1). An individual with epilepsy may have more than one type of seizure. In many cases, seizures result in convulsions and loss of consciousness. Seizures may also present in other ways that affect personality, mood, memory, sensation, and/or movement. Blank stares, lip smacking, intermittent eye movements, and jerking movements of the extremities are all examples of possible manifestations of seizures. In some cases these may not be recognized as a seizure by patients, their family members, or even health care professionals. In many cases, seizures may be isolated and in other cases they may be associated with other neurological problems or health concerns. Some types of epilepsy syndromes are associated with developmental delay or regression, intellectual disability, autism spectrum disorders, movement disorders, or other medical problems.

Reference:

FIGURE 1: Types of seizures.

- Generalized Tonic-Clonic 12-24%
- Complex Partial 8-31%
- Simple Partial 2-12%
- Other Partial 7-29%
- Unclassified/Mixed 4-43%
- Other Generalized <1-3%
- Myoclonic 1-11%
- Infantile Spasms 1-9%
- Absence 5-22%
What causes epilepsy?
There are many different causes of epilepsy, including genetic disorders, metabolic diseases, and structural brain abnormalities. However, in some cases, the cause of epilepsy is not known.

How is epilepsy diagnosed?
Epilepsy is usually diagnosed by an electroencephalogram (EEG). An EEG may provide important information to determine the type of seizures you have and may also help make decisions about your treatment plan (Figure 2). Your EEG, physical examination, medical history, and family history are essential in evaluating the likelihood of a genetic cause for your epilepsy. Genetic testing can be used to confirm a specific type of epilepsy.

How is epilepsy treated?
The management of epilepsy depends on the severity of your disease and symptoms. Epilepsy can often, but not always, be controlled with medication. Other possible treatments include lifestyle changes, ketogenic diet, and surgery. Genetic testing may guide the selection of an optimal treatment plan.
Genetic Testing for Epilepsy

How is genetic testing for epilepsy performed?

The epilepsy genetic test is a blood test ordered by your physician. GeneDx will extract DNA from your blood sample and analyze it by specifically searching for mutations in a large number of genes associated with epilepsy. After the test is finished, your physician will receive the results and explain them to you.

How is genetic testing for epilepsy helpful?

Identifying the genetic cause of your epilepsy is important for several reasons, such as to help with treatment decisions and to provide information for family members about their chance to develop epilepsy. Here is a list of ways that genetic testing for epilepsy may benefit you and your family:

- Confirms your diagnosis of a particular type of epilepsy, especially if the diagnosis is not clear, based on EEG findings or symptoms.
- Assists with decisions about treatment of your epilepsy.
- Provides information about associated neurological or other health problems that you may experience in the future.
- Helps clarify the prognosis for your epilepsy.
- Identifies your family members who are at risk of developing epilepsy or having a child with epilepsy.

Who should have genetic testing for epilepsy?

It is best to do genetic testing on a person with a clinical diagnosis of epilepsy. Genetic testing is appropriate for anyone with a suspected genetic cause of their epilepsy. Genetic forms of epilepsy can present with generalized, focal, or even multiple seizure types. Most genetic forms of epilepsy begin in infancy, childhood, or adolescence. However, a few genes have been identified that can cause seizures starting in adulthood. The chance of finding a genetic cause for epilepsy is higher if you have other family members who have similar symptoms. However, people with no previous family history of epilepsy may also have a disease-causing mutation in an epilepsy gene.

If the GeneDx Epilepsy panel identifies a disease-causing mutation in a person with epilepsy, then other family members can be tested, regardless of whether they have epilepsy or not. Find more information about testing family members on page 5.
What makes the GeneDx test different from others?

GeneDx offers a comprehensive test for genetic causes of epilepsy, as well as smaller panels based on the various ages of onset. The GeneDx Epilepsy panels include multiple genes causing a variety of epilepsy syndromes and types of seizures. Because many genes are included in each of the panels the GeneDx Epilepsy tests provide comprehensive results, which can be useful in clarifying the type and cause of your epilepsy, with a fast turn-around-time.

How long does it take to complete the genetic test?

It usually takes eight to ten weeks to complete the test. This is from the time the lab receives the blood sample to the time your physician receives the results. It can take longer if GeneDx has to test family members to interpret results.

What type of test results can I expect?

Three types of results are possible:

- **A positive result** indicates that the genetic test revealed a disease-causing mutation in a gene associated with epilepsy. This finding confirms the cause of your epilepsy and provides valuable information to your physician and family members. Knowledge of your specific genetic mutation can help your physician clarify the prognosis and assist in treatment and management of epilepsy. All first-degree relatives (children, siblings, parents) may then be offered genetic testing to clarify their risk for epilepsy. If a family member is found to be positive for the familial mutation, this individual may be at risk for epilepsy and should be referred for a neurological evaluation. It is important to note that there is variability in symptoms, age of onset, severity, and response to therapy, even within families.

- **A negative result** indicates that the genetic test did not identify a disease-causing mutation in any of the genes tested. However, this does not mean that you do not have epilepsy, and there may still be a genetic cause of your epilepsy. You should be managed according to your clinical symptoms. Possible reasons for a negative result could be: (1) you may have a mutation in a gene not included in the testing panel, (2) you may have a mutation in a part of an epilepsy gene that was not covered in the test, or (3) you do not have a genetic form of epilepsy. When a genetic test result is negative, predictive genetic testing of family members is not helpful. Careful review of your family history may help determine if your epilepsy is hereditary and whether other family members should be monitored by their doctor(s).

If an asymptomatic individual is negative for a mutation identified in a family member with epilepsy, the result is considered a “true negative.” This indicates that the individual is not at increased genetic risk for the familial epilepsy syndrome and instead has the same risk to develop seizures as a person in the general population. Specific clinical monitoring for the development of seizures is not necessary in individuals with a “true negative” result.
• A variant of unknown significance (VUS) result indicates an inconclusive finding. This happens when the genetic test reveals a DNA abnormality, but it is unclear if that change causes epilepsy because it has never been seen before or there is conflicting information in the medical literature. To further clarify the clinical significance of the VUS, it may be helpful to test other family members. If an affected relative also has the variant, it is more likely that the variant causes epilepsy. The more affected family members who carry the VUS, the greater the likelihood that the VUS is responsible for the epilepsy in your family. If you are the only individual in your family who has epilepsy, testing your parents could reveal that the VUS is de novo (arose new in you and was not inherited from your unaffected parents). Most de novo variants are classified as likely disease-causing.

How will I learn my test results?
Your physician will share your results with you and discuss them in the context of your health care. GeneDx cannot release test results directly to patients or their families.

Will my insurance cover this test?
GeneDx accepts all commercial insurance. GeneDx will bill your insurance company and appeal for payment. Currently, GeneDx does not accept Medicare or Medicaid. For more information, please visit our website at: www.genedx.com/neurology or call us at 301-519-2100, x 6727.

What if I do not have insurance?
If you do not have health insurance or cannot afford to pay the full cost of testing, GeneDx provides a generous financial assistance program, including a significantly discounted price. For more information, call us at 301-519-2100, x 6106.

Do my family members need to be tested?
If you have a disease-causing mutation in one of the genes on the epilepsy panel, then other members of your family might be at risk to also have this mutation. In most cases, your family members can be tested for the specific familial mutation and do not need the full epilepsy panel.

If you do not have a disease-causing mutation in one of the epilepsy genes analyzed, testing of other family members with epilepsy still may be indicated because they may have a different cause for their epilepsy than you do. Therefore, please discuss any genetic test result with your physician or genetic counselor.

Does GeneDx test family members?
Yes, GeneDx offers mutation-specific testing for known familial mutation(s) to family members of anyone who has been shown to have a disease-causing mutation in most genes included in the epilepsy panels. If a family member has been tested at another lab, in most cases we can still test you or other family members at GeneDx, but we require a blood specimen from the previously tested relative to be sent along as positive control. For more information, please call one of our genetic counselors at 301-519-2100.
How does testing of family members differ from full Epilepsy panel testing in a patient?

The first patient with epilepsy in a family to be tested typically requires analysis of all the genes in one or more of the epilepsy panels. Once a disease-causing mutation is identified in a specific gene, family members are tested only for that specific mutation. The cost and turnaround time are significantly reduced when family members get tested for a specific mutation only, instead of the full gene panel.

Does GeneDx perform prenatal testing?

Yes, GeneDx can provide prenatal testing for a known familial mutation in most genes for families who have had previous genetic testing performed in a CLIA laboratory. For more information, please call one of our genetic counselors at 301-519-2100.

Can my health insurer or employer discriminate against me based on my test results?

The Genetic Information Nondiscrimination Act of 2008, also referred to as GINA, is a federal law that protects Americans from discrimination by health insurance companies and employers based on their genetic information. The President signed the act into federal law on May 21, 2008. The parts of the law relating to health insurers took effect on May 2009, and those relating to employers took effect on November 2009. However, this law does not cover life insurance, disability insurance, or long-term care insurance. GINA also does not apply to members of the United States military, to veterans obtaining healthcare through the Department of Veterans Affairs (VA), or to the Indian Health Service. For more information, please visit www.genome.gov/10002328.

How can I order this test?

Your physician can order this test by taking the following steps:

- Download neurology requisition forms from the GeneDx website: www.genedx.com/neurology
- Complete all the forms with the required information
- Ship completed forms along with 2mL–10mL whole blood in EDTA purple/lavender top tube to the following address:
  GeneDx
  207 Perry Parkway
  Gaithersburg, MD 20877

We also provide shipping kits to physicians when requested. To order a neurology shipping kit, you can call us at 301-519-2100, or email us at zebras@genedx.com.
Where can I find more information?

You can find more information at the following websites:

- **GeneDx neurology page**: www.genedx.com/neurology
- **GeneReviews**, a database of genetic diseases: www.geneclinics.org
- **National Society of Genetic Counselors**, to help you find a counselor near you: www.nsgc.org
- **American Epilepsy Society**: www.aesnet.org
- **Epilepsy Foundation**: www.epilepsyfoundation.org
References:


About GeneDx

GeneDx is a highly respected company that specializes in genetic testing for rare inherited disorders. Two scientists from the National Institutes of Health (NIH) founded the company in the year 2000 to address the needs of patients and clinicians concerned with rare inherited disorders. Currently, GeneDx offers testing for more than 350 rare Mendelian disorders, using DNA sequencing and deletion/duplication analysis of the associated gene(s). GeneDx also offers oligonucleotide microarray-based testing for detecting chromosomal abnormalities, and next-gen sequencing based panels for neurological disorders, mitochondrial disorders and inherited cardiac disorders. At GeneDx, our technical services are matched by our scientific expertise and customer support. Our growing staff includes 14 board-certified/eligible geneticists specializing in molecular, cytogenetic, metabolic, and clinical genetics and more than 15 genetic counselors who are just a phone call or email away. We invite you to visit our website: www.genedx.com to learn more about us and the services we offer.