Genetic Testing for Mitochondrial Disorders: A Guide for Patients
Mitochondrial Disorders

What are mitochondria?

Mitochondria are small structures that are found within almost every cell of the body. They are considered the power plants of the cell because they use nutrients and oxygen to produce chemical energy called ATP. Approximately 90% of the energy the body needs is provided by mitochondria. In some cells there are only a few mitochondria while in others there are thousands. Generally, cells that need more energy to function, such as those in the brain, heart, and skeletal muscle, have a greater number of mitochondria.

What are mitochondrial disorders?

Disorders that are caused by dysfunction of the mitochondria are referred to as mitochondrial disorders. If the mitochondria aren’t functioning properly, any organ system may be affected because all require energy for growth and maintenance. The organ systems that are more likely to be affected are typically those requiring a lot of energy to function, such as the brain, heart, and skeletal muscles (see Figure 1). Some mitochondrial disorders affect only one organ, but many affect multiple organs, so patients with mitochondrial disorders often exhibit groups of symptoms. Some of the common symptoms are listed below.

Common Symptoms of Mitochondrial Disorders

- Neurological problems
- Muscle weakness
- Exercise intolerance
- Diabetes
- Drooping eyelids
- Paralysis of the muscles that control eye movement
- Seizures
- Dementia
- Stroke-like episodes
- Hearing loss
- Migraines
- Heart muscle weakness
- Liver failure
- Recurrent vomiting
- Gastrointestinal reflux
- Delayed gastric emptying
- Chronic diarrhea or constipation

What causes mitochondrial disorders?

Mitochondrial disorders occur in approximately 1 of every 4,000 to 5,000 individuals and are caused by errors in DNA. DNA is the blueprint that instructs the body’s growth, development, and maintenance. Most DNA is found within the nucleus of the cell; however, a smaller amount of DNA is found within the cell’s mitochondria. Both nuclear and mitochondrial DNA are comprised of functional units called genes. If there is an error or mutation in a gene, the
instructions in the DNA are no longer correct and the result is that the mitochondria will not be able to work properly. Most mitochondrial disorders are inherited (passed from generation to generation in a family); however, some mitochondrial disorders may appear for the first time in an individual, with no family history of the disorder.

How are mitochondrial disorders inherited?
Mitochondrial disorders can be due to errors in nuclear DNA or mitochondrial DNA. Nuclear DNA is inherited from both the mother and the father in the egg and sperm, whereas mitochondrial DNA is only inherited from the mother in the egg. Therefore, mutations in nuclear DNA can be inherited from either the mother or father and sometimes from both, whereas mutations in mitochondrial DNA are inherited only from the mother. Mutations in mitochondrial DNA have a higher chance to occur as a new mutation in the fetus (i.e., not inherited from the mother).

How are mitochondrial disorders diagnosed?
Physicians will likely consider a mitochondrial disorder when they encounter a patient with a progressive disorder that involves multiple organ systems. Sometimes physicians may be able to diagnose a mitochondrial disorder based on the specific set of symptoms a patient exhibits. However, classifying mitochondrial diseases can be difficult since the specific cause and the symptoms are often extremely variable from person to person. Testing is initially performed on the symptomatic family member. Testing options include biochemical testing.
and/or DNA testing. Biochemical testing examines whether mitochondria are functioning properly, and these tests often require an invasive procedure such as a muscle or liver biopsy. Unfortunately, biochemical test results for mitochondrial disorders may not be reliable or reproducible. DNA tests can be performed on most tissues, for example, from a blood sample or muscle/liver biopsy. DNA tests can examine both the nuclear and mitochondrial DNA for mutations in genes that are associated with mitochondrial disorders.

**What tests does GeneDx offer?**

GeneDx offers extensive testing for mitochondrial disorders. Comprehensive testing for many types of mitochondrial disorders include:

- Full sequence analysis and deletion testing of the mitochondrial genome
- Next-generation sequence analysis of 101 nuclear genes important for normal mitochondrial function
- Deletion/duplication testing of nuclear genes important for normal mitochondrial function
- Deletion/duplication analysis of the mitochondrial genome
- Multiple disease-specific mitochondrial disorder panels

**What makes the GeneDx tests different from others?**

- Highly sensitive genetic testing is provided using new technologies:
  - Next-generation sequence analysis
  - Deletion/duplication analysis by gene-specific array CGH
  - Mitochondrial DNA point mutation analysis by real-time ARMS qPCR
- Multiple genes can be tested at the same time, leading to:
  - A more cost-effective test
  - A faster turn around-time
- Mutation-specific carrier testing
- A Mitochondrial program led by an expert in mitochondrial disorders with over 12 years experience
- Carefully researched reports written by geneticists and genetic counselors
- Over 12 years of experience in genetic testing for rare disorders
- Access to board certified geneticists and genetic counselors to answer your questions
- A comprehensive, easy-to-use website with detailed information about testing options

**How long does it take to complete the genetic test?**

Depending on the specific test ordered by the physician, it may take 2 to 10 weeks to complete a test. Please refer to the GeneDx website (www.genedx.com/mito) to find out the appropriate turn-around-time for the test(s) your physician is ordering.
How is genetic testing helpful?

Genetic tests may identify a known disease-causing mutation(s) in the nuclear DNA or in the mitochondrial DNA. If a mutation is identified and a diagnosis is confirmed, this information may provide knowledge about the progression of the disease, determine possible treatments for specific associated symptoms, and whether other family members should be tested. When a disease-causing mutation(s) is identified, information, such as the possibility of having another affected child can be provided to the family.

What type of test results can I expect?

Genetic test results can be complex. It is important that your physician and/or genetic counselor discuss your test results with you based on the type of test performed and in the context of your medical and family history. Possible results include:

- **A positive result** indicates that a previously understood disease-causing mutation was identified in the individual undergoing the test. Knowledge of a disease-causing mutation can help the physician assess the patient’s risk of experiencing certain symptoms, and may influence decisions about how to manage the condition. A positive result may also identify certain family members as being at-risk for having the mutation, and carrier testing may be recommended to those individuals.

- **A negative result** in an affected individual does not necessarily rule out a mitochondrial disorder, and the patient should be managed according to his/her clinical symptoms. Possible reasons for a negative result could be: (1) the patient may have a mutation in a gene not covered in the testing panel, (2) the patient may have a type of mutation which would not be detected by the test method performed, or (3) the patient does not have a mitochondrial disorder.

- **A variant of unknown clinical significance (VUS)** indicates that a change in the DNA was identified in the individual undergoing the test, however, the change is not known to be associated with a disorder. To clarify the clinical significance of the variant, testing other family members may be helpful. Sometimes the test results may remain uncertain until additional information is obtained from research studies.

Do my family members need to be tested?

If a disease-causing mutation is identified in one of the mitochondrial or nuclear genes, at-risk family members can be tested at GeneDx for that specific mutation. If a VUS is identified, GeneDx may recommend testing family members to help in interpreting the test results. For more information, please call one of our genetic counselors at 301-519-2100.

Does GeneDx perform prenatal testing?

GeneDx can provide prenatal testing only for a known familial mutation(s) identified in a nuclear gene. GeneDx does not offer prenatal testing for mutations identified in the mitochondrial genome. For more information, please call one of our genetic counselors at 301-519-2100.
How will test results be provided?
GeneDx will send test results directly to the ordering physician when they are completed. Your physician will provide results to you and your family and discuss them in the context of your health care.

Will 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/mito 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.

Can a health insurer or employer discriminate against a person based on his/her test results?
No, 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. For more information, please visit http://www.genome.gov/10002328

Where can I find more information?
More information about mitochondrial disorders can be found at the following websites:
- GeneDx mitochondrial disorders page: www.genedx.com/mito
- United Mitochondrial Disease Foundation, a patient organization that promotes research and education for the diagnosis, treatment, and cure of mitochondrial disorders: www.umdf.org
- Gene Reviews, a database of genetic diseases: www.geneclinics.org
- National Society of Genetic Counselors, an organization that can help you find a counselor near you: www.nsgc.org
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, testing for autism spectrum disorders, and testing for various inherited cardiac disorders. At GeneDx, our technical services are matched by our scientific expertise and customer support. Our growing staff includes more than 14 experts in molecular and clinical genetics as well as 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.