



AUGUST 2021

# Genetic Testing: Getting to a Diagnosis



# About **Global Genes**®

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Global Genes is a 501(c)(3) non-profit organization dedicated to eliminating the burdens and challenges of rare diseases for patients and families globally. In pursuit of our mission we connect, empower, and inspire the rare disease community to stand up, stand out, and become more effective on their own behalf—helping to spur innovation, meet essential needs, build capacity and knowledge, and drive progress within and across rare diseases. We serve the more than 400 million people around the globe and nearly 1 in 10 Americans affected by rare diseases. If you or someone you love has a rare disease or are searching for a diagnosis, contact Global Genes at 949-248-RARE or visit our resource hub at [www.globalgenes.org](http://www.globalgenes.org).

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***Supported by charitable contributions from Applied Therapeutics, Taysha Gene Therapies, and Traverre Therapeutics***



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# Introduction

## Understanding Genetic Testing

**Genetic testing** can be a great path forward for patients and family members who are desperately seeking answers. This is especially true for patients with rare diseases. There are more than 7000 of these little-known diseases and 80 percent of them are caused by **genetic mutations**. These are also known as **variants**.

80% of all Rare Diseases are genetic



Many rare diseases are chronic, progressive, and life-limiting. Rapid diagnosis is essential. The stakes are high. The need for treatment is urgent. Genetic testing may shed light on these dark corners. *It can even be lifesaving.*

Even if there is currently no treatment, a diagnosis can lead to more effective disease management. It can be a cue to keep an eye out for symptoms that could appear over time and other body systems that may be impacted. Having a name for your disease connects you to social support and allows you to inform other family members about any risks.

Not everyone who has a genetic test will receive a diagnosis. For some people, multiple tests may be needed. There may be signs that tell your doctor something is wrong, but you may have to wait for science to progress before you receive a clear diagnosis.

What is clear is that every genetic test adds to the sum total of knowledge that researchers and physicians are able to draw from as they push forward to find the answers that you—and others like you—so deeply desire.

## How to Use This Genetic Testing Toolkit

Technology has advanced tremendously over the last decade. The costs of tests are decreasing. Genetic testing is on the rise, but it is still unfamiliar territory for most patients and caregivers and even many physicians.

We wrote this guide to help you understand your options and make good decisions. Only you can decide what's best for you and your family!

If you have a child in the **neonatal intensive care unit (NICU)** or **pediatric intensive care unit (PICU)** who is undergoing testing—or if you are considering asking your doctor or a **genetic counselor** if testing could help you get to a diagnosis you've been seeking for days, months, or years—you'll find the information you need here to prepare you for some of the most important conversations of your life.

### ***Help from RARE Concierge ([www.globalgenes.org/rare-concierge](http://www.globalgenes.org/rare-concierge))***

Global Genes offers a free service for people seeking a rare disease diagnosis and those who have questions about a diagnosis they have already received. Reach out through our RARE Concierge portal to be connected to resources, support and advice on accessing care.

### ***Support from GARD: ([www.rarediseases.info.nih.gov](http://www.rarediseases.info.nih.gov))***

The National Institutes of Health (NIH) Genetic and Rare Disease Information Center (GARD) provides easy-to-understand information in English and Spanish as well as online phone support.

# Genetics 101

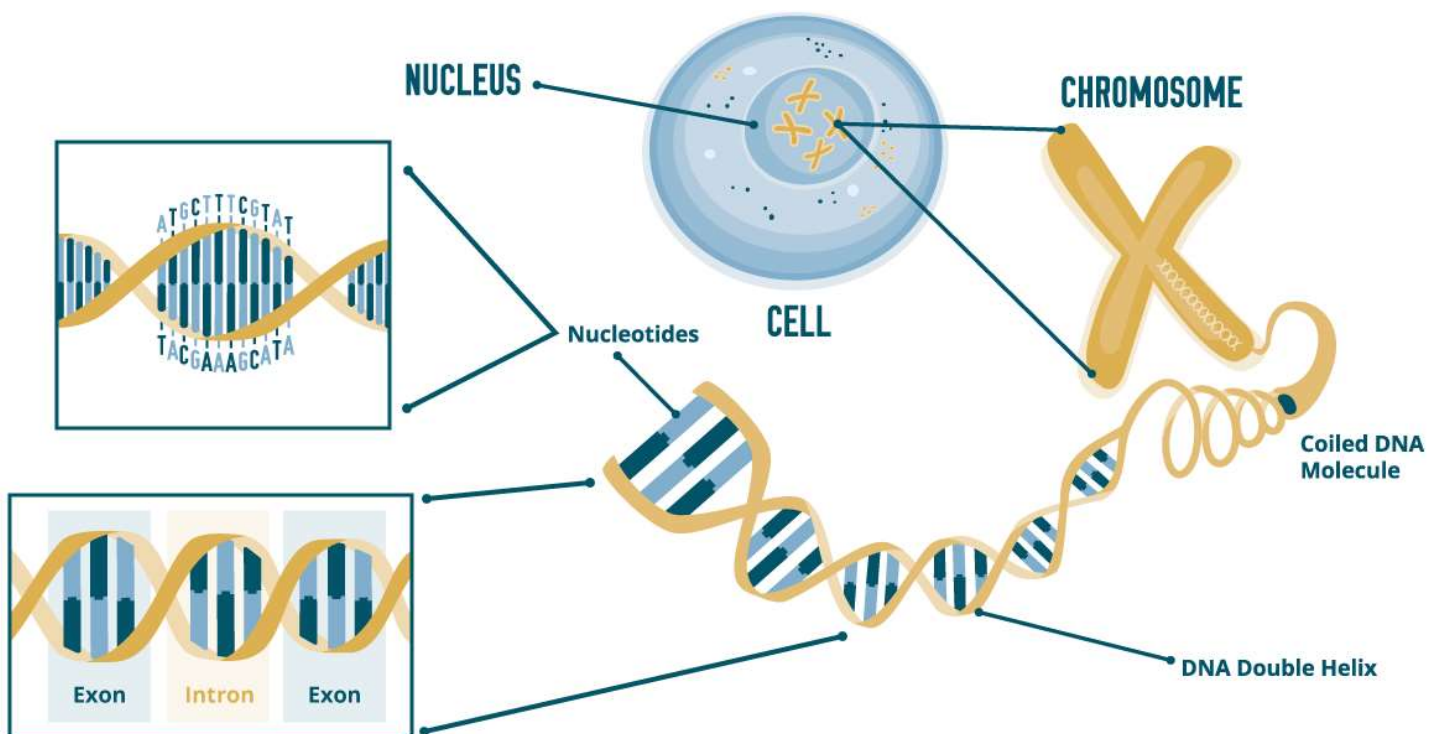
In order to understand the role of genetic testing in your care, it's helpful to know a bit about genes.

## What (and Where) Are Genes?

**Genes** are the basic units of **inheritance**. They are made up of **DNA (deoxyribonucleic acid)**, a molecule that contains a 'blueprint' or 'instruction manual' for building and maintaining your own individual body. There are about 20,000-25,000 genes in human DNA.

Your body has trillions of cells. Nearly all cells get their own copy of your DNA which they keep in a special part of the cell called the nucleus.

DNA is bundled up as a double helix and organized into structures called **chromosomes**. Chromosomes are made up of lots of genes that give specific instructions from the DNA. Within each cell nucleus, the DNA double helix will unwind and send specific instructions to each individual cell to give its function and purpose. For example, muscle cells get different instructions than skin or blood cells but almost all cells carry a complete set of DNA in the nucleus.



## Why Are Genes Important?

Most genes act as instructions for making molecules called proteins. These proteins are the building blocks for muscles, tissues, skin, and organs. Genes are also needed to make enzymes, the complex proteins that control and carry out nearly all chemical processes and reactions within the body. A geneticist will use a variety of genetic testing to look at a patient's **genotype**—the exact copy of each individual's DNA to look at variants within specific genes. They will then compare the **genotype** to the patient's **phenotype**—the physical attributes of a person. Phenotypical characteristics can include neuromuscular or cognitive delays, seizures, dysmorphia, etc. Not all of your DNA gives instructions for creating proteins. In between your genes, there are large parts of DNA that are not known to have a function (non-coding DNA).

Within the genes themselves, there are sections of DNA that contain information that is important for the genes to function (**exons**) and there are sections that are not used directly by the gene to function (**introns**). These protein coding regions (exons) and non-coding sections (introns) alternate along the genes.

## What are Genomes and Exomes?

Quite simply, your **genome** is your complete set of DNA. It includes not only your genes, but also non-coding DNA, and **mitochondrial** DNA (responsible for producing energy for

cells and human body functions). The human genome contains more than 3 billion DNA base pairs.

Your **exome** is all of the exons in all of your genes. That's around one percent of your entire genome, but it's an important one percent!

There is still a lot we do not understand about the exome and genome, but as technological advancements increase our ability to analyze large data sets, genomic knowledge is rapidly increasing.

## How Do We Get Our Genes?

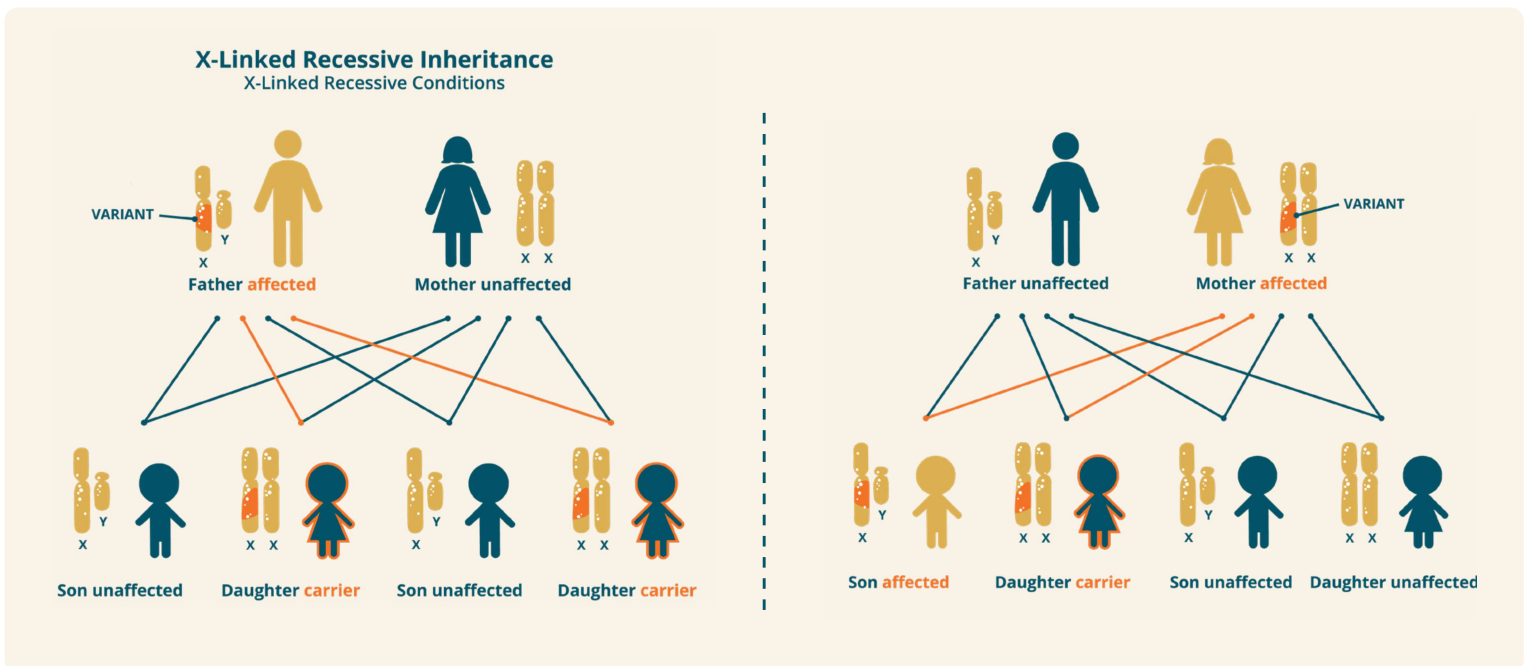
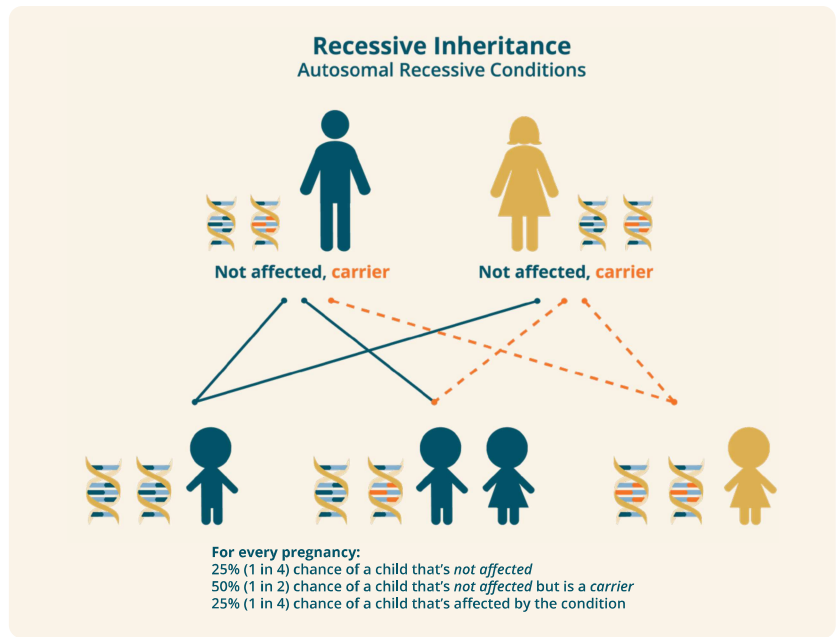
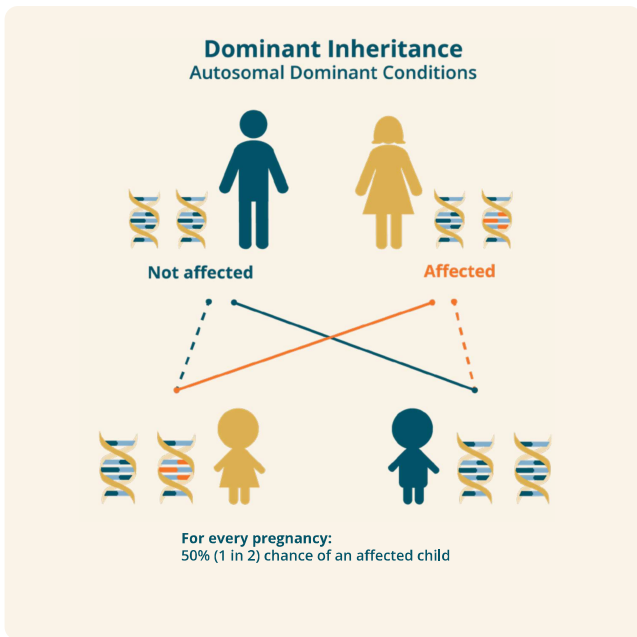
There is a reason that people resemble their parents. Each of us gets our genes from our biological parents. We typically get 23 chromosomes from the biological mother and 23 chromosomes from the biological father to make 23 pairs or 46 chromosomes. Each of these chromosomes contains hundreds or even thousands of genes.

The first cell that combines the two sets of chromosomes is called a **zygote**. The zygote is created when a sperm cell and an egg cell combine, bringing together genes from your biological mother and biological father. This mixing and matching of genes makes you similar to your parents and others in your family's **gene pool**—but also uniquely you.

## What Causes Genetic Conditions?

Genetic information is encoded in genes using a four-letter alphabet made up of the letters A, T, C, and G. The letters stand for the molecules **adenine**, **thymine**, **cytosine**, and **guanine**. These molecules form complementary **base pairs** that make-up each of the 3 billion rungs of the twisted ladder that is DNA.

When there are mistakes in the sequence of letters, called **variants**, this can affect the production of the specific protein that the gene normally encodes. These mutations can be passed down from a parent to a child or occur randomly in the egg or sperm.





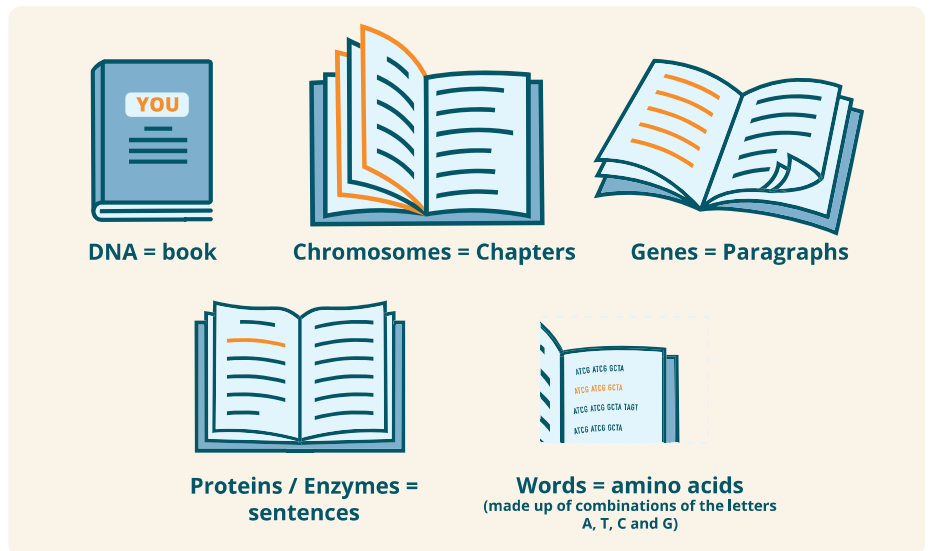
## The Book of You

One way to understand genetic conditions is by imagining that your genome is an instruction manual for creating and maintaining your body.

Genetic testing looks for errors in any of these sections. Sometimes there are errors in the letters, genes, or chromosomes.

One might be deleted, added, misspelled or misplaced. Just as the order of letters can change the meaning of a word (think of T-E-A compared to E-A-T) **variants** that change the order, or sequence, of letters in a gene's code can change how it works, for better or for worse.

Although variants can occasionally be beneficial, often they can cause disease if the error happens in parts of genes that are important for regular bodily functions.



## Going Deeper into Genetics

Here are some recommendations for learning more about genetics, inheritance, DNA, and genes.

### **[Genetics Home Reference \(www.medlineplus.gov/genetics\)](http://www.medlineplus.gov/genetics)**

Guide to genetic conditions, genes, and research

### **[Genetics Concepts for Rare Disease Patients and Families \(www.rareuniversity.com/\)](http://www.rareuniversity.com/)**

A RARE University online course from Global Genes that you can take at your own pace.

### **[Genetics Alive \(www.geneticsalive.com/GandG.html\)](http://www.geneticsalive.com/GandG.html)**

Student-friendly, interactive instruction on genes and genetics

# Genetic Testing Options

**Genetic testing** is a type of medical test that identifies changes in chromosomes, genes, or proteins. The results of these tests can confirm or rule out suspected genetic conditions.

## Why Do Physicians Order Genetic Tests?

Identifying the cause of the condition may help your doctor treat it and prevent further deterioration. It may allow you to inform other family members or help with family planning. Sometimes just having a name for your condition helps, even if there is not yet a treatment. It will allow you to connect to others who know just what you are going through and will work alongside you toward a better future.

## What Types of Genetic Tests May be Ordered?

There are several different types of genetic tests available to physicians, including **molecular tests (gene sequencing)**, **chromosome tests**, and **biochemical** genetic tests. A patient's symptoms and results from prior tests will determine which one to use. Your provider or genetic counselor can support you in deciding which testing options are best for you.

In the past, genetic tests were usually targeted at just one gene. This meant that your doctor either had to have a good idea of what the condition was, then test a single gene, or order multiple tests of several genes over a long period of time.

## Find an Organization

The Global Genes RARE Foundation Alliance is a coalition of more than 800 rare disease organizations that offer information, support, and connection for rare disease patients and families. Request contacts for organizations [here](#).

There are two technologies that are increasingly used to sequence large amounts of DNA: **whole exome sequencing (WES)** and **whole genome sequencing (WGS)**. Together, they are referred to as next generation sequencing (NGS) sequencing.

## Whole Exome Sequencing (WES)

WES sequences the exons (the protein coding regions) of about 20,000 genes. The exons are currently thought to be responsible for 85 percent of all known disease-causing variants. This test may be recommended as a first step. It may also be recommended if prior tests have not revealed conclusive results.



### PRO TIP

“Many of our patients have come in with other genetic tests that have been inconclusive or negative. Sometimes families went on a diagnostic odyssey looking for answers for years.

Now we have that ability with exome sequencing. We needed a technology to say, ‘Aha, this is the diagnosis!’, which this does in many cases.”



- ADA HAMOSH, PHYSICIAN, DEPARTMENT OF GENETIC MEDICINE AT JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE

To begin the process, DNA is collected, typically by a blood draw. If a blood draw is difficult, DNA can also be extracted from saliva or a cheek swab.

Prior to sample collection, be sure to ask your doctor about preserving the donated sample for future testing. This could help reduce the amount of blood draws and allow the sample to be used for multiple purposes. Also, inquire as to your rights to a copy of your exome – you should be able to get a copy for your own use later.

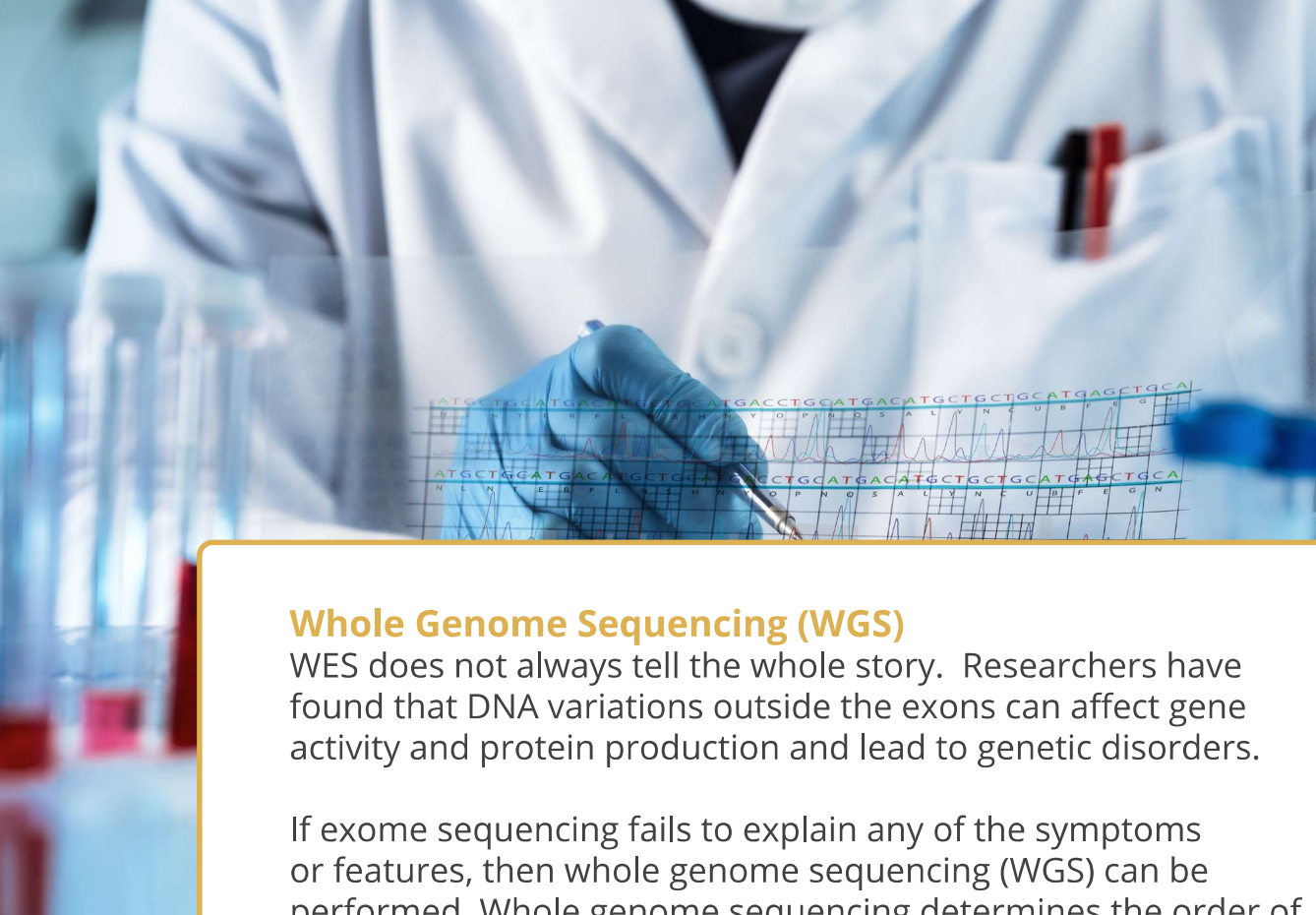


### PRO TIP

“People are very generous when they are asked to provide samples for researchers, especially in the rare disease community. However, donating a biological sample such as blood or tissue multiple times can become challenging; it can be a hassle. Through biobanks, biorepositories that store various biological samples and associated information, these samples can be held and used in current and future research studies. It’s a more efficient way to conduct research, and it minimizes the burden on the person donating the sample.”



- LIZ HORN, PRINCIPAL OF LHC BIOSOLUTIONS



### Whole Genome Sequencing (WGS)

WES does not always tell the whole story. Researchers have found that DNA variations outside the exons can affect gene activity and protein production and lead to genetic disorders.

If exome sequencing fails to explain any of the symptoms or features, then whole genome sequencing (WGS) can be performed. Whole genome sequencing determines the order of all 3 billion base pairs in the human genome.







Physicians sometimes order this test for patients who have exhausted all other forms of genetic testing. Or they may begin with WGS knowing it will provide a complete picture. If no diagnosis is reached, your data can be reanalyzed at a later time.

One should note that getting insurance reimbursement for this test is often more difficult than for exome sequencing. But it is also possible to appeal if your claim is denied.







As with exome sequencing, make sure to ask if you can have a copy of your genome.

The chart on the next page (Table 1) compares various types of genetic testing options for individuals with rare diseases, along with their cost and recommended uses.

**Table 1. Types of Genetic Testing**

 <b>TYPE OF GENETIC TESTING</b>	 <b>BASIC DEFINITION</b>	 <b>RECOMMENDED USES</b>	 <b>APPROXIMATE TIME IT TAKES</b>	 <b>LIMITATIONS</b>	 <b>ESTIMATED COST</b>
<b>FISH</b>	A genetic test used to find small deletions or duplications in an individual's chromosomes.	To assess for deletions/duplications for a suspected genetic syndrome, aneuploidy (extra or missing chromosomes), and sex chromosomes	Rapid FISH (chromosomes 13, 18, 21, X, and Y): 24-48 hours.  For deletion syndromes: 7-10 days.	Limited to the specific disease/chromosome being studied. Not able to detect point mutations (single-base changes) for the disorder being studied.	Aneuploidy: \$300-\$350.  Single probe FISH: \$250-\$500 per probe.
<b>KARYOTYPE</b>	A genetic test used to examine an individual's chromosome structure.	To rule out chromosomal abnormalities, including aneuploidy (extra or missing chromosomes), larger deletions/duplications, and translocations	1-2 weeks	Not able to detect small deletions and duplications or single-gene genetic disorders	\$600-\$1,200
<b>CHROMOSOMAL MICROARRAY</b>	A genetic test used to examine or quantify an individual's amount of genetic material; it can detect changes smaller than those found through FISH or karyotype.	To possibly identify causes of autism, developmental delay, intellectual disability, and/or abnormal ultrasound findings in the prenatal period	1 week	Cannot detect balanced chromosome rearrangements; also has a 5% risk of uncertain results	Price based on specimen type.  Blood: \$1,800-\$3,000 (max out of pocket: \$500).  Amnio: \$1,900-\$3,000 (not covering the cost of amnio procedure).
<b>TARGETED MUTATION ANALYSIS</b>	A genetic test used to examine for a specific or a few specific genetic mutations within a single gene.	Used when there is a known familial mutation, there are specific mutations that commonly cause a particular disease, and/or there are specific mutations that are more common in certain ethnic groups for a specific disease	10-14 days	Limited to the specific mutations being tested	\$250-\$600



 TYPE OF GENETIC TESTING	 BASIC DEFINITION	 RECOMMENDED USES	 APPROXIMATE TIME IT TAKES	 LIMITATIONS	 ESTIMATED COST
<b>SINGLE GENE SEQUENCING</b>	A genetic test used to examine a single gene's entire sequence at a high level of detail.	Used for diagnostic purposes when a specific genetic syndrome is suspected	2-3 weeks	Possible risk of an uncertain result; does not detect deletions or duplications	\$500-\$6,000 (depends on the gene).
<b>MULTIPLE GENE SEQUENCING PANEL</b>	A genetic test used to examine the sequence of several genes at a high level of detail.	Used for diagnostic purposes when there are several genes that can cause similar symptoms (i.e. cancer syndrome, intellectual disability, neurodegenerative disorders)	2-3 weeks	Possible risk of uncertain results; does not detect deletions or duplications	\$2,000-\$6,000
<b>WHOLE EXOME SEQUENCING</b>	A genetic test used to sequence all of the exons (i.e. coding regions) within all of the genes in an individual's genome. May or may not sequence the mitochondrial genome.	Used in individuals suspected of having an underlying genetic cause for their symptoms, typically when all other genetic testing has not identified a cause	2-6 weeks	Results in a large amount of data, some of which will be of uncertain significance; also can get results for other genetic diseases that are not related to the initial reason for testing	Variable, up to \$5,000
<b>WHOLE GENOME SEQUENCING</b>	A genetic test used to sequence an individual's entire genome (both coding and non-coding regions). May or may not sequence mitochondrial genome.	Primarily used in a research setting for individuals suspected of having an underlying genetic cause for their symptoms, typically when all other genetic testing has not identified a cause	Variable, depending on the research study and/or institution	Results in a large amount of data, some of which will be of uncertain significance; also can get results for other genetic diseases that are not related to the initial reason for testing	Variable, up to \$10,000



## What Results Can Be Expected?

Your physician or genetics professional will receive a report from the lab. The results could show a **variant**, or change in the sequence of your genetic material.

If a variant is found, the lab or physician will check to see if other people who have a similar condition to you also have this variant. For the sake of comparison, they may ask both biological parents to undergo genetic testing. This is called **trio testing**.

Sometimes, an identified variant is associated with a different genetic disorder that has not yet been diagnosed. These are called **secondary findings**.

Everyone has variants and many of them have no effect on our health. If the lab or physician has no evidence showing that it is either harmful or harmless, they will classify it as a variant of uncertain significance.

Even though many more genetic changes can be identified with whole exome and whole genome sequencing than with select gene sequencing, the significance of much of this information is unknown.



# Making Decisions

The choice of whether or not to pursue clinical genetic testing is a personal one and is never mandatory. To help you make this decision, your physician, genetic counselor or geneticist can provide information on when genetic testing is appropriate and how testing results may impact treatment or other life decisions.

Genetic testing may be considered if there are:

- People in your family with a genetic disease
- Multiple family members with similar symptoms/features but no diagnosis
- Symptoms that can't be diagnosed through continuous testing
- Multiple **congenital anomalies/** birth defects
- Indications on newborn screening of a possible genetic disease
- Multiple miscarriages, stillbirths or unexplained infant death
- General developmental delays/ intellectual disability

## Your Right to Ask

If your hospital or physician's practice does not provide you with professional genetic services, you have the right to ask for a referral to a specialist who can discuss your options in more detail. If finances are a concern, you should also feel empowered to ask to speak to a financial navigator, patient navigator, nurse navigator, financial counselor, insurance advisor or social worker who can direct you to services. **Don't be afraid to ask questions! You are a key member of your own—and your child's—healthcare team.**

## Working with a Genetic Counselor

Having a conversation with a genetic counselor before testing may help you make the right choice for you or a family member. You may also want to consult a genetic counselor

after testing to help you understand your results and possible next steps, whether or not you are diagnosed.



## PRO TIP

“Genetic counselors provide non-directive counseling. This means that they help patients understand the information and options available, but they do not advise patients on their decisions. Ultimately, the patient makes their own decisions regarding testing. The genetic counselor is there to provide information, options, and support.”



- ANDREA KNOB, GENETIC COUNSELOR AND COORDINATOR, BETH ISRAEL DEACONESS MEDICAL CENTER

## Where Can I Find A Genetic Counselor?

Here are websites to help you. Be sure to check with your insurance company to verify coverage of genetic counseling, testing and authorized providers.

***[Find a Genetic Counselor \(NSGC\)](http://www.findageneticcounselor.nsgc.org)***  
***[www.findageneticcounselor.nsgc.org](http://www.findageneticcounselor.nsgc.org)***

***[ABGC Find a Genetic Counselor](http://www.abgc.net/about-genetic-counseling/find-a-certified-counselor)***  
***[www.abgc.net/about-genetic-counseling/find-a-certified-counselor](http://www.abgc.net/about-genetic-counseling/find-a-certified-counselor)***

The National Society of Genetics Counselors defines **genetic counseling** as “the process of helping people understand and adapt to the medical, psychological, and familial implications of genetic contributions to disease.” People can consult with genetic counselors to understand the scientific, emotional, and ethical factors surrounding the decision to have genetic testing and how to deal with the results of those tests.

Genetic counselors are trained to use **shared decision-making**, a collaborative approach focused on educating, supporting and guiding patients and families as they make choices in line with their values.

If a genetic counselor is not easily available, you may be able to work with a geneticist, a genetics nurse or another specialized healthcare provider. There are also telehealth services available, so you can access a genetic counselor over the phone.

## Partnering with a Genetic Counselor

Find more discussion topics and hints on how a genetic counselor can help you in this [\*Global Genes\*](#) toolkit.

## Informed Consent

Genetic testing has risks and benefits, just like any medical procedure. The process of educating you about the test and obtaining permission is called **informed consent**. This is often conducted by a medical professional (a physician, genetic counselor, genetic nurse, etc.) who will talk to you about potential outcomes, limitations of the test, and the possible consequences of the test results.

The following subsections break down the elements of informed consent, but to learn even more about informed consent, the National Human Genome Research Institute's "*Elements of Informed Consent*" further explains the elements of this process.

### Risks and Benefits

Test results can provide a sense of relief from uncertainty, helping people make informed decisions about managing their healthcare. Genetic testing can:

- reveal a diagnosis, if one has symptoms
- establish whether or not someone is a **carrier** of a genetic disease (Carriers have an altered gene but will not display symptoms of the disease; they may, however, pass this altered gene to their children.)
- alert people to the possibility of an inherited disease before symptoms start

But along with beneficial aspects, there are also potential emotional, social, and financial consequences that come with genetic testing. People may feel angry, depressed, anxious, or guilty about their results.

Sometimes patients and caregivers are concerned about the possibility of genetic discrimination. The ***Genetic Information Nondiscrimination Act***, or GINA, was passed in 2008 to protect individuals from employment or health insurance discrimination. Unfortunately, GINA does not apply to life insurance, long term care insurance, or military personnel.

There can also be unintended consequences of genetic testing, such as learning about potential risks for other diseases or information about ancestry that people may not want to know.



## PRO TIP

“The key in any genetic testing is to understand the choice before deciding whether or not to get the test. Informed consent is not about the absence of risk, but the conscious decision that the benefits are worth accepting them. Most genetic testing today is very low risk to most people, and there is a robust genetic counseling community to help you navigate a specific test’s particular benefits and outcomes. Informed consent processes should always help you understand the test at hand and connect to experts who can give even more detail.”



- JOHN WILBANKS, CHIEF COMMONS OFFICER OF SAGE BIONETWORKS

### Limitations

Genetic testing can provide only certain kinds of information about an inherited condition: the existence of a variant, or the number of repeats of a mutation, and so forth. But the genotype is not usually a perfect forecast of the body – the test results may not be able to determine if and when a person will show symptoms of a disorder and how severe the symptoms will be.

Another major limitation is the lack of treatment strategies for many genetic disorders once they are diagnosed. In many cases, there are no treatment options for these conditions. However, research is ongoing and our knowledge of genetics is growing rapidly.

A truly informed consent should emphasize understanding these profound limitations.

### Opportunities

In very rare cases, treatments already on the market can be rapidly targeted at newly found genetic illnesses. But even if there are currently no treatments available, your genetic test data adds to our collective knowledge. This is why it is so important to ask for a copy of your data at all times – it allows you, later, to connect with others to create pooled data for “data scientists” who are conducting research.



## Getting Access to Testing

Genetic testing for rare and undiagnosed conditions should be ordered by a qualified healthcare provider. Many insurance companies including commercial plans, Medicare and Medicaid will cover genetic testing.

But not all tests are covered. It's important to talk to your healthcare team and health insurance company for details. Prior authorizations may also need to be obtained.

Before contacting the health insurance company, be prepared to have:

- The name of the test
- The name of the laboratory the test will be performed at
- The CPT (current procedural terminology) codes

In addition to asking about the insurance coverage of the test, consider asking about deductibles and co-pays which may be expenses that are the responsibility of the member to pay. The use of an in-network laboratory also reduces the risk of receiving a bill for services not covered by insurance.

## Selecting a Lab

When selecting a laboratory to use for genetic testing, it is important to consider patient financial assistance programs, insurance coverage, and cash-pay options. Many laboratories

offer both financial assistance programs and patient-pay (out-of-pocket) prices that are significantly reduced.

## Navigating Health Insurance

Find information about understanding coverage in this Global Genes toolkit.

[Navigating Health Insurance](#)





# Glossary

**Biochemical tests** Biochemical genetic tests study the amount or activity level of proteins; abnormalities in either can indicate changes to the DNA that result in a genetic disorder. <https://medlineplus.gov/genetics/understanding/testing/genetic-testing/>

**Carrier** A carrier is an individual who carries and is capable of passing on a genetic mutation associated with a disease and may or may not display disease symptoms. Carriers are associated with diseases inherited as recessive traits. <https://www.genome.gov/genetics-glossary/Carrier>

**Chromosome tests** Chromosomal genetic tests analyze whole chromosomes or long lengths of DNA to see if there are large genetic changes, such as an extra copy of a chromosome, that cause a genetic condition. <https://medlineplus.gov/genetics/understanding/testing/genetic-testing/>

**Congenital anomalies** Structural or functional anomalies (for example, metabolic disorders) that occur during intrauterine life and can be identified prenatally, at birth, or sometimes may only be detected later in infancy, such as hearing defects. <https://www.who.int/news-room/fact-sheets/detail/congenital-anomalies>

**DNA (deoxyribonucleic acid)** A long, winding molecule contained within each of your cells that carries the instructions needed to build and maintain provide the many different types of cells that make you, you. <https://www.genome.gov/Pages/Education/AllAbouttheHumanGenomeProject/GuidetoYourGenome07.pdf>

**Exome** The exome consists of all of the genome's exons, which are the coding portions of genes. <https://www.broadinstitute.org/blog/what-exome-sequencing>

**Failure to thrive** Failure to thrive refers to children whose current weight or rate of weight gain is much lower than that of other children of similar age and sex. <https://medlineplus.gov/ency/article/000991.htm>

**FISH** Fluorescence in situ hybridization (FISH) provides researchers with a way to visualize and map the genetic material in an individual's cells, including specific genes or portions of genes. This may be used for understanding a variety of chromosomal abnormalities and other genetic mutations. <https://www.genome.gov/about-genomics/fact-sheets/Fluorescence-In-Situ-Hybridization>

**Gene** The gene is the basic physical unit of inheritance. Genes are passed from parents to offspring and contain the information needed to specify traits. Genes are arranged, one after another, on structures called chromosomes. A chromosome contains a single, long DNA molecule, only a portion of which corresponds to a single gene. Humans have approximately 20,000 genes arranged on their chromosomes. <https://www.genome.gov/genetics-glossary/Gene>

**Geneticist** A geneticist is a doctor who studies genes and heredity. <http://www.genesinlife.org/testing-services/working-healthcare-professionals/geneticists>

**Genetics** Human genetics is a branch of biology that studies how human traits are determined and passed down among generations. <https://www.ashg.org/discover-genetics/genetics-basics/>

**Genetic counselor** Genetic counselors are professionals who have specialized education in genetics and counseling to provide personalized help to patients who need to make decisions about their genetic health. <https://www.nsgc.org/page/whoaregeneticcounselors-473>

**Genetic counseling** Genetic counseling gives you information about how a genetic condition might affect you or your family. [https://www.cdc.gov/genomics/gtesting/genetic\\_counseling.htm](https://www.cdc.gov/genomics/gtesting/genetic_counseling.htm)

**Genetic information non-discrimination act (GINA)** The Genetic Information Nondiscrimination Act (GINA) of 2008 protects Americans from discrimination based on their genetic information in both health insurance (Title I) and employment (Title II) <https://www.genome.gov/about-genomics/policy-issues/Genetic-Discrimination>

**Genetic mutation (see variant)** A gene mutation is a permanent alteration in the DNA sequence that makes up a gene, such that the sequence differs from what is found in most people. <https://medlineplus.gov/genetics/understanding/mutationsand-disorders/genemutation/>

**Genetic test** Genetic testing is a type of medical test that identifies changes in chromosomes, genes, or proteins. The results of a genetic test can confirm or rule out a suspected genetic condition or help determine a person's chance of developing or passing on a genetic disorder. <https://medlineplus.gov/genetics/understanding/testing/genetic-testing/>

**Genetic variant**

Historically, disease causing variants were called mutations. To reduce confusion, all genetic changes—whether they cause a medical condition or have no impact at all—are now called variants. Genetic variants are classified on a 5-point scale: Pathogenic, Likely Pathogenic, Variant of Uncertain Significance, Likely Benign, Benign.

Pathogenic variants are proven to be disease causing. Likely pathogenic variants are suspected to be disease causing with ~90% certainty. Variants of Uncertain Significance do not have enough scientific evidence to know for certain if the variant is disease causing or not. Likely Benign variants are suspected to be Benign with ~90% certainty. Benign variants have been proven not to be disease causing, often because they are seen in many other individuals in the general population who do not have the health condition associated with the gene. [https://cser-consortium.org/system/files/attachments/cser\\_provider\\_toolkit.pdf](https://cser-consortium.org/system/files/attachments/cser_provider_toolkit.pdf)

**Genome** Your complete set of DNA instructions. <https://www.genome.gov/Pages/Education/AllAbouttheHumanGenomeProject/GuidetoYourGenome07.pdf>

**Genotype** A genotype is an individual's collection of genes. The term also can refer to the two alleles inherited for a particular gene. The genotype is expressed when the information encoded in the genes' DNA is used to make protein and RNA molecules. The expression of the genotype contributes to the individual's observable traits, called the phenotype. <https://www.genome.gov/genetics-glossary/genotype>

**Informed consent** Before a person has a genetic test, it is important that he or she fully understands the testing procedure, the benefits and limitations of the test, and the possible consequences of the test results. The process of educating a person about the test and obtaining permission to carry out testing is called informed consent. <https://medlineplus.gov/genetics/understanding/testing/informed-consent/>

**Inheritance** The process by which genetic material is handed on from parent to child. It's why members of the same family tend to have similar characteristics. <https://www.yourgenome.org/facts/what-is-inheritance>

**Karyotype** A karyotype is an individual's collection of chromosomes. The term also refers to a laboratory technique that produces an image of an individual's chromosomes. The karyotype is used to look for abnormal numbers or structures of chromosomes. <https://www.genome.gov/genetics-glossary/Karyotype>

**Molecular tests** Molecular genetic tests (or gene tests) study single genes or short lengths of DNA to identify variations or mutations that lead to a genetic disorder. <https://medlineplus.gov/genetics/understanding/testing/genetic-testing/>

**Multiple gene sequencing panel** Genetic tests that use next-generation sequencing to test multiple genes at once. <https://www.cancer.gov/publications/dictionaries/genetics-dictionary/def/multiple-gene-panel-test>

**Neonatal intensive care unit (NICU)** Newborn babies who need intensive medical care are often put in a special area of the hospital called the neonatal intensive care unit (NICU). The NICU has advanced technology and trained healthcare professionals to give special care for the tiniest patients. <https://www.urmc.rochester.edu/encyclopedia/content.aspx?contenttypeid=90&contentid=P02389>

**Pediatric intensive care unit (PICU)** The pediatric intensive care unit (PICU) is a specialized unit of the hospital where the sickest pediatric patients are admitted. <https://medicine.iu.edu/blogs/pediatrics/what-is-the-pediatric-intensive-care-unit-an-introduction>

**Phenotype** A phenotype is an individual's observable traits, such as height, eye color, and blood type. The genetic contribution to the phenotype is called the genotype. Some traits are largely determined by the genotype, while other traits are largely determined by environmental factors. <https://www.genome.gov/genetics-glossary/Phenotype>

**Secondary findings** Secondary findings are genetic test results that provide information about changes (variants) in a gene unrelated to the primary purpose for the testing. <https://medlineplus.gov/genetics/understanding/testing/secondaryfindings/>

**Shared decision making** Shared decision making is a model of patient-centered care that enables and encourages people to play a role in the medical decisions that affect their health. <https://www.ahrq.gov/cahps/quality-improvement/improvement-guide/6-strategies-for-improving-communication/strategy6i-shared-decisionmaking.html>

**Single gene sequencing** Single gene tests look for changes in only one gene. Single gene testing is done when your doctor believes you or your child have symptoms of a specific condition or syndrome. [https://www.cdc.gov/genomics/gtesting/genetic\\_testing.htm](https://www.cdc.gov/genomics/gtesting/genetic_testing.htm)

**Trio testing** In trio testing, the parents' exomes are sequenced, along with the child's. The results are compared to normal reference sequence. Variations in an individual's DNA sequence can be identified and related back to the individual's medical concerns. [https://www.bcm.edu/research/medical-genetics-labs/test\\_detail.cfm?testcode=1600](https://www.bcm.edu/research/medical-genetics-labs/test_detail.cfm?testcode=1600)

### **Whole exome sequencing (WES)**

Each organism has a unique DNA sequence which is composed of bases (A, T, C, and G). If you know the sequence of the bases in an organism, you have identified its unique DNA fingerprint, or pattern. Determining the order of bases is called sequencing. Whole genome sequencing is a laboratory procedure that determines the order of bases in the genome of an organism in one process. <https://medlineplus.gov/genetics/understanding/testing/sequencing/>

### **Whole genome sequencing (WGS)**

Whole genome sequencing, determines the order of all the nucleotides in an individual's DNA and can determine variations in any part of the genome. <https://medlineplus.gov/genetics/understanding/testing/sequencing/>

**For more definitions, see:** <https://rarediseases.info.nih.gov/guides/pages/48/medical-and-science-glossaries>

# Resources

## Understanding Genetics

**[American Society of Human Genetics](#)**. Basic materials on genetics, DNA, family history, privacy and medical genetics, suitable for educators.

**[Centers for Disease Control and Prevention: Genetics 101](#)** Brief overview with links to many more educational resources

**[Centers for Disease Control and Prevention Family History Tool](#)** An online tool to help you track and share your risk for conditions that run in families.

**[Genetic and Rare Diseases Information Center \(GARD\)](#)** Online and phone support

**[Genetics Alive](#)** Student-friendly, interactive instruction on genes and genetics

**[Genetic Alliance](#)** Wide assortment of resources related to genetics.

**[Help Me Understand Genetics Handbook](#)** This Genetics Home Reference website presents basic information on genetics with additional links to resources.

**[National Organization for Rare Disorders \(NORD\)](#)** Resources for undiagnosed patients

**[National Human Genome Research Institute: Genomics Education Websites](#)** Comprehensive listing across all topics.



## General Information on Genetic Testing

**[Centers for Disease Control and Prevention \(CDC\) Genetic Testing: What You Need to Know.](#)** An excellent general explanation of the topic which includes types of tests and results and reasons for testing.

**[U.S. National Library of Medicine Medline Plus. What is Genetic Testing?](#)** Frequently asked questions on a variety of genetic testing topics.

## Understanding Shared Decision Making

**[Agency for Healthcare Research and Quality.](#)** Consumer Assessment of Healthcare Providers and Systems (CAHPS) Strategies for Shared Decision Making

**[Center for Shared Decision-Making Dartmouth.](#)** Decision Support Toolkit.:

**[Shared Decision Making: A Model for Clinical Practice.](#)** Elwyn G; Frosch D; Thompson R; Joseph-Williams N; Lloyd A; Kin C; Rollnick S; Edwards A; Barry M.

## Learning About Informed Consent

**[National Human Genome Research Institute](#)**

**[U.S. National Library of Medicine Medline Plus.](#)** "What is Informed Consent" This breakdown describes the process of informed consent as it applies to genetic testing.

## Information on GINA

**[Protections Provided by the Genetic Information Non-Discrimination Act \(GINA\).](#)** A resource from the Genetic Alliance that explains the laws that protect your genetic information from employment or insurance discrimination.

## Locating and Working with Genetic Counselors

**American Board of Medical Genetics.** The ABMG serves the public and the medical profession by promoting and assuring standards of excellence in medical genetics. It also provides a free online searchable database to find and verify the status of board-certified individuals.

**American College of Medical Genetics and Genomics** The organization's Genetics Clinics Database is a service for individuals who wish to locate genetics centers. The database contains the locations of genetics clinics that have requested to be listed.

**The American Society of Human Genetics:** The society is the primary professional membership organization for human genetics specialists worldwide.

**Centers for Disease Control and Prevention.** Overview of reasons for seeking genetic counseling and what to expect.

**Find a Genetic Counselor Tool.** The National Society of Genetic Counselors provides a tool to help you find a professional in your area.

**Find a Certified Genetic Counselor.** This search tool is provided by the American Board of Genetic Counselors.

**Genetic Counselors: Personalized Care for Your Genetic Health.** Information for the public on what genetics counselors do and when you should see one, from the National Society of Genetic Counselors.

**RARE Concierge.** Global Genes offers a free service for people seeking a rare disease diagnosis and those who have questions about a diagnosis they have already received. Reach out through our Rare Concierge portal to be connected to resources, support and advice on accessing care.

## Funding Sources

**National Institutes of Health (NIH) Genetic and Rare Disease Information Center (GARD).** A comprehensive list of resources that offer financial assistance for rare disease patients and families with a variety of needs.

GARD also *provides phone support* for rare disease patients and families.

## Videos

**Genome TV's "How to Sequence a Genome"**: This animated video presents all the essential steps in sequencing a genome.

### **Human Nature**

An *exploration of CRISPR's implications* through the eyes of the scientists who discovered it, the families it is affecting and the bioengineers who are testing its limits.

**Jeans for Genes UK, "What are Genes?"**: This fun and easy to understand animation shows the influence that genes have on our everyday lives, from the color of our eyes to the way our body works, grows, and develops.

**Rady Children's Institute Genomic Medicine**. Sebastiana's story.

**Searching for a Diagnosis**. Colleen Olson, Co-Founder and President of the DHPS Foundation, tells how genetic testing helped physicians identify the rare condition that affects two of her three children.

**The Gene: An Intimate History**. This PBS documentary was produced by Ken Burns. It includes segments on the history of genetic science and medicine and the current revolution in treatment.

**TGen Center for Rare Childhood Disorders' "Personalized Medicine Helps Girl Walk Again"**: This is the story of Shelby, a 12-year-old girl who was wheelchair-bound for nearly a decade due to a rare disease of unknown cause. TGen sequenced Shelby's genome and were able to provide clues to the genetic basis of her rare disorder and empower her physician to prescribe a medicine based on this new information that resulted in changes to Shelby that were nothing short of a miracle.

**Unconditional: Raising a Glass Child with a PACS1 Sibling** Explores how a genetic diagnosis helped a family find a supportive community.

# A Patient's Story

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Finding Answers Through Genetic Testing  
Kim Miller, Mother of Jasey

When our daughter Jasey was born, like most parents, it was a time of joy and excitement. However, happiness was quickly overshadowed by tears, questions, and prayer early in her life. When she was just a week old, Jasey stopped breathing and had to be hospitalized.

We spent a few weeks in the hospital as the doctors worked to determine why she continued to stop breathing. She would be released from the hospital—only to return a few days later and stay for a month. Jasey stopped breathing nine times within the first two weeks of her life. She was diagnosed with seizures and was placed on a seizure medication and a breathing monitor.

As Jasey continued to get older, we noticed that she was not hitting milestones that other children her age were reaching. She began physical therapy and then added speech and occupational therapies to help with her developmental delays. In addition to developmental delays, she was diagnosed with failure to thrive, meaning her growth and weight gain were not what they should be.

Her pediatrician referred us to a local hospital for genetic testing. Jasey went through numerous genetic tests over the next few years of her life. Nevertheless, we were still without an answer. I started researching children's hospitals that specialized in genetic research.

I contacted Cincinnati Children's Hospital, where they performed an MRI on Jasey's brain and whole exome sequencing. Exome

sequencing identified a variant in the gene known as PACS1, a rare genetic mutation—so rare, in fact, that Jasey was only the third person in the world to be diagnosed with this mutation at the time. Jasey continues to receive physical therapy, speech therapy, and occupational therapy. She is making great progress. She is a walking miracle. We are continuing to work with Cincinnati's Genetics Department in our quest to learn more about this mutation.

## Takeaways from the Author:



1. Exome sequencing made **diagnosis possible**. Without this test, we would still be searching for answers and constantly justifying why Jasey needs various therapies.
2. Exome sequencing can be very time consuming, but it is well **worth the wait**. Since receiving Jasey's diagnosis, we have been able to communicate with other parents whose children have recently been diagnosed with the same variant. Communicating with others in similar situations has been very helpful and invaluable.
3. Prior to receiving a diagnosis, most of Jasey's doctor appointments required blood draws and tests. Now we can focus on learning more about the genetic variant and how to best help her.

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**Hope.** It's in our genes.



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