



Genetics  
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Reference

Help Me Understand Genetics

# Genetic Testing

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# Genetic Testing

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## What is genetic testing?

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. More than 1,000 genetic tests are currently in use, and more are being developed.

Several methods can be used for genetic testing:

- 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.
- 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.
- 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.

Genetic testing is voluntary. Because testing has benefits as well as limitations and risks, the decision about whether to be tested is a personal and complex one. A geneticist or genetic counselor can help by providing information about the pros and cons of the test and discussing the social and emotional aspects of testing.

### **For general information about genetic testing:**

MedlinePlus offers a list of links to information about genetic testing (<https://medlineplus.gov/genetictesting.html>).

The National Human Genome Research Institute provides an overview of this topic in its Frequently Asked Questions About Genetic Testing (<https://www.genome.gov/19516567/>). Additional information about genetic testing legislation, policy, and oversight (<https://www.genome.gov/10002335/>) is available from the Institute.

The National Institutes of Health fact sheet Genetic Testing: What It Means for Your Health and for Your Family's Health (<https://www.genome.gov/pages/health/patientpublicinfo/genetictestingfactsheet.pdf>) provides a brief overview for people considering genetic testing.

You can also search for clinical trials involving genetic testing. ClinicalTrials.gov (<https://clinicaltrials.gov/>), a service of the National Institutes of Health, provides easy access to information on clinical trials. You can search for specific trials or

browse by condition or trial sponsor. You may wish to refer to a list of studies related to genetic testing (<https://clinicaltrials.gov/search?term=%22genetic+testing%22>) that are accepting (or will accept) participants.

## What are the types of genetic tests?

Genetic testing can provide information about a person's genes and chromosomes. Available types of testing include:

### **Newborn screening**

Newborn screening is used just after birth to identify genetic disorders that can be treated early in life. Millions of babies are tested each year in the United States. All states currently test infants for phenylketonuria (a genetic disorder that causes intellectual disability if left untreated) and congenital hypothyroidism (a disorder of the thyroid gland). Most states also test for other genetic disorders.

### **Diagnostic testing**

Diagnostic testing is used to identify or rule out a specific genetic or chromosomal condition. In many cases, genetic testing is used to confirm a diagnosis when a particular condition is suspected based on physical signs and symptoms. Diagnostic testing can be performed before birth or at any time during a person's life, but is not available for all genes or all genetic conditions. The results of a diagnostic test can influence a person's choices about health care and the management of the disorder.

### **Carrier testing**

Carrier testing is used to identify people who carry one copy of a gene mutation that, when present in two copies, causes a genetic disorder. This type of testing is offered to individuals who have a family history of a genetic disorder and to people in certain ethnic groups with an increased risk of specific genetic conditions. If both parents are tested, the test can provide information about a couple's risk of having a child with a genetic condition.

### **Prenatal testing**

Prenatal testing is used to detect changes in a fetus's genes or chromosomes before birth. This type of testing is offered during pregnancy if there is an increased risk that the baby will have a genetic or chromosomal disorder. In some cases, prenatal testing can lessen a couple's uncertainty or help them make decisions about a pregnancy. It cannot identify all possible inherited disorders and birth defects, however.

### **Preimplantation testing**

Preimplantation testing, also called preimplantation genetic diagnosis (PGD), is a specialized technique that can reduce the risk of having a child with a particular genetic or chromosomal disorder. It is used to detect genetic changes in embryos that were created using assisted reproductive techniques such as in-vitro fertilization. In-vitro fertilization involves removing egg cells from a woman's ovaries and fertilizing them with sperm cells outside the body. To perform preimplantation testing, a small number of cells are taken from these embryos and tested for certain genetic changes. Only embryos without these changes are implanted in the uterus to initiate a pregnancy.

### **Predictive and presymptomatic testing**

Predictive and presymptomatic types of testing are used to detect gene mutations associated with disorders that appear after birth, often later in life. These tests can be helpful to people who have a family member with a genetic disorder, but who have no features of the disorder themselves at the time of testing. Predictive testing can identify mutations that increase a person's risk of developing disorders with a genetic basis, such as certain types of cancer. Presymptomatic testing can determine whether a person will develop a genetic disorder, such as hereditary hemochromatosis (an iron overload disorder), before any signs or symptoms appear. The results of predictive and presymptomatic testing can provide information about a person's risk of developing a specific disorder and help with making decisions about medical care.

### **Forensic testing**

Forensic testing uses DNA sequences to identify an individual for legal purposes. Unlike the tests described above, forensic testing is not used to detect gene mutations associated with disease. This type of testing can identify crime or catastrophe victims, rule out or implicate a crime suspect, or establish biological relationships between people (for example, paternity).

### **For more information about the uses of genetic testing:**

A Brief Primer on Genetic Testing (<https://www.genome.gov/10506784/>), which outlines the different kinds of genetic tests, is available from the National Human Genome Research Institute.

Educational resources related to patient genetic testing/carrier screening ([https://geneed.nlm.nih.gov/topic\\_subtopic.php?tid=52&sid=55](https://geneed.nlm.nih.gov/topic_subtopic.php?tid=52&sid=55)) are available from GeneEd. Johns Hopkins Medicine provides additional information about genetic

carrier screening ([https://www.hopkinsmedicine.org/gynecology\\_obstetrics/specialty\\_areas/fertility-center/infertility-services/genetic-screening.html](https://www.hopkinsmedicine.org/gynecology_obstetrics/specialty_areas/fertility-center/infertility-services/genetic-screening.html)).

The National Society of Genetic Counselors provides an overview of the different types of genetic testing (<http://aboutgeneticcounselors.com/Genetic-Testing>) that are available.

The Centre for Genetics Education offers an overview of prenatal testing (<https://www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-24-prenatal-testing-overview>), as well as fact sheets about preimplantation genetic diagnosis (<https://www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-29-preimplantation-genetic-diagnosis-pgd>), screening tests during pregnancy, (<https://www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-25-screening-tests-during-pregnancy>) and diagnostic tests during pregnancy (<https://www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-26-diagnostic-tests-during-pregnancy>).

EuroGentest provides fact sheets about predictive testing (<http://www.eurogentest.org/index.php?id=617>) and carrier testing (<http://www.eurogentest.org/index.php?id=610>).

The University of Pennsylvania offers an explanation of preimplantation genetic diagnosis (<https://www.pennmedicine.org/for-patients-and-visitors/find-a-program-or-service/penn-fertility-care/embryo-screening>).

Genetics Home Reference provides information and links related to newborn screening (<https://ghr.nlm.nih.gov/primer#newbornscreening>).

The National Newborn Screening and Genetics Resource Center (<http://genes-r-us.uthscsa.edu/>) offers detailed information about newborn screening.

For information about forensic DNA testing, refer to the fact sheet about forensic genetic testing (<https://www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-17-forensic-paternity-and-ancestry-dna-testing>) from the Centre for Genetics Education and a page about forensic DNA analysis (<https://learn.genetics.utah.edu/content/science/forensics/>) from the Genetic Science Learning Center at the University of Utah.



## How is genetic testing done?

Once a person decides to proceed with genetic testing, a medical geneticist, primary care doctor, specialist, or nurse practitioner can order the test. Genetic testing is often done as part of a genetic consultation.

Genetic tests are performed on a sample of blood, hair, skin, amniotic fluid (the fluid that surrounds a fetus during pregnancy), or other tissue. For example, a procedure called a buccal smear uses a small brush or cotton swab to collect a sample of cells from the inside surface of the cheek. The sample is sent to a laboratory where technicians look for specific changes in chromosomes, DNA, or proteins, depending on the suspected disorder. The laboratory reports the test results in writing to a person's doctor or genetic counselor, or directly to the patient if requested.

Newborn screening tests are done on a small blood sample, which is taken by pricking the baby's heel. Unlike other types of genetic testing, a parent will usually only receive the result if it is positive. If the test result is positive, additional testing is needed to determine whether the baby has a genetic disorder.

Before a person has a genetic test, it is important that he or she 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 is called informed consent on page 10.

### **For more information about genetic testing procedures:**

The National Society of Genetic Counselors offers an overview of the genetic testing process (<http://aboutgeneticcounselors.com/Genetic-Testing/How-Does-the-Testing-Process-Work>).

A brief overview of how genetic testing is done (<https://www.cancer.gov/about-cancer/causes-prevention/genetics/genetic-testing-fact-sheet#q5>) is also available from The National Cancer Institute.

The Genetic Science Learning Center at the University of Utah provides an interactive animation of DNA extraction techniques (<https://learn.genetics.utah.edu/content/labs/extraction/>).

## What is 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. "Informed" means that the person has enough information to make an educated decision about testing; "consent" refers to a person's voluntary agreement to have the test done.

In general, informed consent can only be given by adults who are competent to make medical decisions for themselves. For children and others who are unable to make their own medical decisions (such as people with impaired mental status), informed consent can be given by a parent, guardian, or other person legally responsible for making decisions on that person's behalf.

Informed consent for genetic testing is generally obtained by a doctor or genetic counselor during an office visit. The healthcare provider will discuss the test and answer any questions. If the person wishes to have the test, he or she will then usually read and sign a consent form.

Several factors are commonly included on an informed consent form:

- A general description of the test, including the purpose of the test and the condition for which the testing is being performed.
- How the test will be carried out on page 9 (for example, a blood sample).
- What the test results mean on page 14, including positive and negative results, and the potential for uninformative results or incorrect results such as false positives or false negatives.
- Any physical or emotional risks associated with the test on page 19.
- Whether the results can be used for research purposes on page 23.
- Whether the results might provide information about other family members' health, including the risk of developing a particular condition or the possibility of having affected children.
- How and to whom test results will be reported and under what circumstances results can be disclosed (for example, to health insurance providers).
- What will happen to the test specimen after the test is complete.

- Acknowledgement that the person requesting testing has had the opportunity to discuss the test with a healthcare professional.
- The individual's signature, and possibly that of a witness.

The elements of informed consent may vary, because some states have laws that specify factors that must be included. (For example, some states require disclosure that the test specimen will be destroyed within a certain period of time after the test is complete.)

Informed consent is not a contract, so a person can change his or her mind at any time after giving initial consent. A person may choose not to go through with genetic testing even after the test sample has been collected. A person simply needs to notify the healthcare provider if he or she decides not to continue with the testing process.

**For more information about informed consent:**

MedlinePlus offers general information about informed consent by adults (<https://medlineplus.gov/ency/patientinstructions/000445.htm>).

The National Cancer Institute discusses informed consent for genetic testing in the context of inherited cancer syndromes (<https://www.cancer.gov/about-cancer/causes-prevention/genetics/risk-assessment-pdq>).

The National Human Genome Research Institute provides information about informed consent in genomics research (<https://www.genome.gov/27026588/>) and policies and legislation related to informed consent for genetic research studies and testing (<https://www.genome.gov/10002332/>).

The Centers for Disease Control and Prevention offers several examples of state-required components of informed consent for genetic testing (<https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5806a3.htm>).

## How can consumers be sure a genetic test is valid and useful?

Before undergoing genetic testing, it is important to be sure that the test is valid and useful. A genetic test is valid if it provides an accurate result. Two main measures of accuracy apply to genetic tests: analytical validity and clinical validity. Another measure of the quality of a genetic test is its usefulness, or clinical utility.

- Analytical validity refers to how well the test predicts the presence or absence of a particular gene or genetic change. In other words, can the test accurately detect whether a specific genetic variant is present or absent?
- Clinical validity refers to how well the genetic variant being analyzed is related to the presence, absence, or risk of a specific disease.
- Clinical utility refers to whether the test can provide information about diagnosis, treatment, management, or prevention of a disease that will be helpful to a consumer.

All laboratories that perform health-related testing, including genetic testing, are subject to federal regulatory standards called the Clinical Laboratory Improvement Amendments (CLIA) or even stricter state requirements. CLIA standards cover how tests are performed, the qualifications of laboratory personnel, and quality control and testing procedures for each laboratory. By controlling the quality of laboratory practices, CLIA standards are designed to ensure the analytical validity of genetic tests.

CLIA standards do not address the clinical validity or clinical utility of genetic tests. The Food and Drug Administration (FDA) requires information about clinical validity for some genetic tests. Additionally, the state of New York requires information on clinical validity for all laboratory tests performed for people living in that state. Consumers, health providers, and health insurance companies are often the ones who determine the clinical utility of a genetic test.

It can be difficult to determine the quality of a genetic test sold directly to the public. Some providers of direct-to-consumer genetic tests are not CLIA-certified, so it can be difficult to tell whether their tests are valid. If providers of direct-to-consumer genetic tests offer easy-to-understand information about the scientific basis of their tests, it can help consumers make more informed decisions. It may also be helpful to discuss any concerns with a health professional before ordering a direct-to-consumer genetic test.

**For more information about determining the quality of genetic tests:**

The Centers for Disease Control and Prevention (CDC) provides an explanation of the factors used to evaluate genetic tests (<https://www.cdc.gov/genomics/gtesting/ACCE/>), including analytical validity, clinical validity, and clinical utility, as part of their ACCE project.

The Genetic Alliance offers information about the quality of genetic tests and current public policy issues (<http://www.geneticalliance.org/advocacy/policyissues/genetictesting>) surrounding their regulation.

The World Health Organization discusses quality and safety in genetic testing ([https://www.who.int/genomics/policy/quality\\_safety/en/index1.html](https://www.who.int/genomics/policy/quality_safety/en/index1.html)).

The U.S. Centers for Medicare and Medicaid Services (CMS) provide an overview of the Clinical Laboratory Improvement Amendments (CLIA) (<https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/>).

## What do the results of genetic tests mean?

The results of genetic tests are not always straightforward, which often makes them challenging to interpret and explain. Therefore, it is important for patients and their families to ask questions about the potential meaning of genetic test results both before and after the test is performed. When interpreting test results, healthcare professionals consider a person's medical history, family history, and the type of genetic test that was done.

A positive test result means that the laboratory found a change in a particular gene, chromosome, or protein of interest. Depending on the purpose of the test, this result may confirm a diagnosis, indicate that a person is a carrier of a particular genetic mutation, identify an increased risk of developing a disease (such as cancer) in the future, or suggest a need for further testing. Because family members have some genetic material in common, a positive test result may also have implications for certain blood relatives of the person undergoing testing. It is important to note that a positive result of a predictive or presymptomatic genetic test usually cannot establish the exact risk of developing a disorder. Also, health professionals typically cannot use a positive test result to predict the course or severity of a condition.

A negative test result means that the laboratory did not find a change in the gene, chromosome, or protein under consideration. This result can indicate that a person is not affected by a particular disorder, is not a carrier of a specific genetic mutation, or does not have an increased risk of developing a certain disease. It is possible, however, that the test missed a disease-causing genetic alteration because many tests cannot detect all genetic changes that can cause a particular disorder. Further testing may be required to confirm a negative result.

In some cases, a test result might not give any useful information. This type of result is called uninformative, indeterminate, inconclusive, or ambiguous. Uninformative test results sometimes occur because everyone has common, natural variations in their DNA, called polymorphisms, that do not affect health. If a genetic test finds a change in DNA that has not been associated with a disorder in other people, it can be difficult to tell whether it is a natural polymorphism or a disease-causing mutation. An uninformative result cannot confirm or rule out a specific diagnosis, and it cannot indicate whether a person has an increased risk of developing a disorder. In some cases, testing other affected and unaffected family members can help clarify this type of result.

### **For more information about interpreting genetic test results:**

The National Cancer Institute fact sheet Genetic Testing for Hereditary Cancer Syndromes (<https://www.cancer.gov/about-cancer/causes-prevention/genetics/>)

[genetic-testing-fact-sheet#q6](#)) provides an explanation of positive and negative genetic test results.

Fact sheets including "What can genetic testing tell you and how can it help? (<http://aboutgeneticcounselors.com/Genetic-Testing/What-Can-Genetic-Testing-Tell-You-and-How-Can-It-Help>)" and "How do I understand my test results? (<http://aboutgeneticcounselors.com/Genetic-Testing/How-Do-I-Understand-My-Test-Results>)" are available from the National Society of Genetic Counselors.

## What is the cost of genetic testing, and how long does it take to get the results?

The cost of genetic testing can range from under \$100 to more than \$2,000, depending on the nature and complexity of the test. The cost increases if more than one test is necessary or if multiple family members must be tested to obtain a meaningful result. For newborn screening, costs vary by state. Some states cover part of the total cost, but most charge a fee of \$15 to \$60 per infant.

From the date that a sample is taken, it may take a few weeks to several months to receive the test results. Results for prenatal testing are usually available more quickly because time is an important consideration in making decisions about a pregnancy. The doctor or genetic counselor who orders a particular test can provide specific information about the cost and time frame associated with that test.

### **For more information about the logistics of genetic testing:**

The National Human Genome Research Institute discusses the coverage and reimbursement of genetic tests (<https://www.genome.gov/19016729/coverage-and-reimbursement-of-genetic-tests/>).

EuroGentest offers a fact sheet about genetic testing laboratories (<http://www.eurogentest.org/index.php?id=621>), including the reasons why some genetic test results take longer than others.



## Will health insurance cover the costs of genetic testing?

In many cases, health insurance plans will cover the costs of genetic testing when it is recommended by a person's doctor. Health insurance providers have different policies about which tests are covered, however. A person interested in submitting the costs of testing may wish to contact his or her insurance company beforehand to ask about coverage.

Some people may choose not to use their insurance to pay for testing because the results of a genetic test can affect a person's insurance coverage. Instead, they may opt to pay out-of-pocket for the test. People considering genetic testing may want to find out more about their state's privacy protection laws before they ask their insurance company to cover the costs. (Refer to [What is genetic discrimination?](#) on page 20 for more information.)

### **For more information about insurance coverage of genetic testing:**

The National Human Genome Research Institute provides information about Coverage and Reimbursement of Genetic Tests (<https://www.genome.gov/19016729/>).

Genes In Life discusses insurance coverage (<http://www.genesinlife.org/after-diagnosis/plan-future/insurance-and-financial-planning>) and reimbursement (<http://www.genesinlife.org/testing-services/testing-genetic-conditions/reimbursement-genetic-testing>) for genetic testing.

## What are the benefits of genetic testing?

Genetic testing has potential benefits whether the results are positive or negative for a gene mutation. Test results can provide a sense of relief from uncertainty and help people make informed decisions about managing their health care. For example, a negative result can eliminate the need for unnecessary checkups and screening tests in some cases. A positive result can direct a person toward available prevention, monitoring, and treatment options. Some test results can also help people make decisions about having children. Newborn screening can identify genetic disorders early in life so treatment can be started as early as possible.

### **For more information about the benefits of genetic testing:**

EuroGentest offers a fact sheet about genetic testing (<http://www.eurogentest.org/index.php?id=622>), including a section on its benefits.

## What are the risks and limitations of genetic testing?

The physical risks associated with most genetic tests are very small, particularly for those tests that require only a blood sample or buccal smear (a method that samples cells from the inside surface of the cheek). The procedures used for prenatal testing carry a small but real risk of losing the pregnancy (miscarriage) because they require a sample of amniotic fluid or tissue from around the fetus.

Many of the risks associated with genetic testing involve the emotional, social, or financial consequences of the test results. People may feel angry, depressed, anxious, or guilty about their results. In some cases, genetic testing creates tension within a family because the results can reveal information about other family members in addition to the person who is tested. The possibility of genetic discrimination in employment or insurance is also a concern. (Refer to What is genetic discrimination? on page 20 for additional information.)

Genetic testing can provide only limited information about an inherited condition. The test often can't determine if a person will show symptoms of a disorder, how severe the symptoms will be, or whether the disorder will progress over time. Another major limitation is the lack of treatment strategies for many genetic disorders once they are diagnosed.

A genetics professional can explain in detail the benefits, risks, and limitations of a particular test. It is important that any person who is considering genetic testing understand and weigh these factors before making a decision.

### **For more information about the risks and limitations of genetic testing:**

The American College of Medical Genetics and Genomics (ACMG) published a policy statement about the risks associated with incorrect genetic test results or interpretation ([https://www.acmg.net/docs/LDT\\_Release.pdf](https://www.acmg.net/docs/LDT_Release.pdf)).

EuroGentest offers a fact sheet about genetic testing (<http://www.eurogentest.org/index.php?id=622>), including a section on its possible risks and limitations.

## What is genetic discrimination?

Genetic discrimination occurs when people are treated differently by their employer or insurance company because they have a gene mutation that causes or increases the risk of an inherited disorder. Fear of discrimination is a common concern among people considering genetic testing.

Several laws at the federal and state levels help protect people against genetic discrimination. In particular, a federal law called the Genetic Information Nondiscrimination Act (GINA) is designed to protect people from this form of discrimination.

GINA has two parts: Title I, which prohibits genetic discrimination in health insurance, and Title II, which prohibits genetic discrimination in employment. Title I makes it illegal for health insurance providers to use or require genetic information to make decisions about a person's insurance eligibility or coverage. This part of the law went into effect on May 21, 2009. Title II makes it illegal for employers to use a person's genetic information when making decisions about hiring, promotion, and several other terms of employment. This part of the law went into effect on November 21, 2009.

GINA and other laws do not protect people from genetic discrimination in every circumstance. For example, GINA does not apply when an employer has fewer than 15 employees. It does not cover people in the U.S. military or those receiving health benefits through the Veterans Health Administration or Indian Health Service. GINA also does not protect against genetic discrimination in forms of insurance other than health insurance, such as life, disability, or long-term care insurance.

### **For more information about genetic discrimination and GINA:**

The National Human Genome Research Institute provides detailed discussions of genetic discrimination and current laws that address this issue:

- Genetic Discrimination (<https://www.genome.gov/10002077/>)
- NHGRI Genome Statute and Legislation Database (<https://www.genome.gov/policyethics/legdatabase/pubsearch.cfm>)
- Genetic Information Nondiscrimination Act (GINA) of 2008 (<https://www.genome.gov/24519851/>)

The Genetic Alliance offers links to resources and policy statements on genetic discrimination (<http://www.geneticalliance.org/advocacy/policyissues/geneticdiscrimination>).

The Smithsonian National Museum of Natural History's exhibit 'Genome: Unlocking Life's Code' discusses GINA's implementation (<https://unlockinglifescode.org/explore/genomics-society/feature-story-gina-protection-misuse-genetic-information>).

More detailed information about GINA is available from these resources

- Coalition for Genetic Fairness (<http://www.geneticfairness.org/ginaresource.html>)
- GINAHelp.org (<http://www.ginahelp.org/>)

## Can genes be patented?

A gene patent is the exclusive rights to a specific sequence of DNA (a gene) given by a government to the individual, organization, or corporation who claims to have first identified the gene. Once granted a gene patent, the holder of the patent dictates how the gene can be used, in both commercial settings, such as clinical genetic testing, and in noncommercial settings, including research, for 20 years from the date of the patent. Gene patents have often resulted in companies having sole ownership of genetic testing for patented genes.

On June 13, 2013, in the case of the Association for Molecular Pathology v. Myriad Genetics, Inc., the Supreme Court of the United States ruled that human genes cannot be patented in the U.S. because DNA is a "product of nature." The Court decided that because nothing new is created when discovering a gene, there is no intellectual property to protect, so patents cannot be granted. Prior to this ruling, more than 4,300 human genes were patented. The Supreme Court's decision invalidated those gene patents, making the genes accessible for research and for commercial genetic testing.

The Supreme Court's ruling did allow that DNA manipulated in a lab is eligible to be patented because DNA sequences altered by humans are not found in nature. The Court specifically mentioned the ability to patent a type of DNA known as complementary DNA (cDNA). This synthetic DNA is produced from the molecule that serves as the instructions for making proteins (called messenger RNA).

### **For more information about gene patenting and the Supreme Court ruling:**

Read the Supreme Court ruling ([https://www.supremecourt.gov/opinions/12pdf/12-398\\_1b7d.pdf](https://www.supremecourt.gov/opinions/12pdf/12-398_1b7d.pdf)) against gene patenting.

The National Institutes of Health (<https://www.nih.gov/about-nih/who-we-are/nih-director/statements/statement-nih-director-francis-collins-us-supreme-court-ruling-gene-patenting>), the American College of Medical Genetics and Genomics (<https://www.acmg.net/docs/GenePatientsDecision.pdf>), and the American Medical Association (<https://www.ama-assn.org/delivering-care/precision-medicine/gene-patenting>) voice their support for the Supreme Court's ruling on gene patents.

The National Human Genome Research Institute discusses the relationship between Intellectual Property and Genomics (<https://www.genome.gov/19016590/>)

## How does genetic testing in a research setting differ from clinical genetic testing?

The main differences between clinical genetic testing and research testing are the purpose of the test and who receives the results. The goals of research testing include finding unknown genes, learning how genes work, developing tests for future clinical use, and advancing our understanding of genetic conditions. The results of testing done as part of a research study are usually not available to patients or their healthcare providers. Clinical testing, on the other hand, is done to find out about an inherited disorder in an individual patient or family. People receive the results of a clinical test and can use them to help them make decisions about medical care or reproductive issues.

It is important for people considering genetic testing to know whether the test is available on a clinical or research basis. Clinical and research testing both involve a process of informed consent on page 10 in which patients learn about the testing procedure, the risks and benefits of the test, and the potential consequences of testing.

### **For more information about the differences between clinical and research testing:**

The Ohio State University's Wexner Medical Center describes the difference between clinical and research genetic testing (<https://wexnermedical.osu.edu/genetics/facts-about-testing>).

The Sudden Arrhythmia Death Syndromes (SADS) Foundation also outlines the major differences between clinical tests and research tests (<https://www.sads.org/Living-with-SADS/Genetic-Testing/Genetic-Testing---Clinical-vs--Research>).

The Columbia University Medical Center offers a table that summarizes the major differences between clinical genetic testing and genetic research (<http://www.columbianeurology.org/research/divisions-and-programs/movement-disorders/genetic-research>).

Additional information about clinical and research tests (<https://www.ncbi.nlm.nih.gov/gtr/docs/about/#tests>) is available from the Genetic Testing Registry.

## What are whole exome sequencing and whole genome sequencing?

Determining the order of DNA building blocks (nucleotides) in an individual's genetic code, called DNA sequencing, has advanced the study of genetics and is one technique used to test for genetic disorders. Two methods, whole exome sequencing and whole genome sequencing, are increasingly used in healthcare and research to identify genetic variations; both methods rely on new technologies that allow rapid sequencing of large amounts of DNA. These approaches are known as next-generation sequencing (or next-gen sequencing).

The original sequencing technology, called Sanger sequencing (named after the scientist who developed it, Frederick Sanger), was a breakthrough that helped scientists determine the human genetic code, but it is time-consuming and expensive. The Sanger method has been automated to make it faster and is still used in laboratories today to sequence short pieces of DNA, but it would take years to sequence all of a person's DNA (known as the person's genome). Next-generation sequencing has sped up the process (taking only days to weeks to sequence a human genome) while reducing the cost.

With next-generation sequencing, it is now feasible to sequence large amounts of DNA, for instance all the pieces of an individual's DNA that provide instructions for making proteins. These pieces, called exons, are thought to make up 1 percent of a person's genome. Together, all the exons in a genome are known as the exome, and the method of sequencing them is known as whole exome sequencing. This method allows variations in the protein-coding region of any gene to be identified, rather than in only a select few genes. Because most known mutations that cause disease occur in exons, whole exome sequencing is thought to be an efficient method to identify possible disease-causing mutations.

However, researchers have found that DNA variations outside the exons can affect gene activity and protein production and lead to genetic disorders--variations that whole exome sequencing would miss. Another method, called 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.

While 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. Because not all genetic changes affect health, it is difficult to know whether identified variants are involved in the condition of interest. Sometimes, an identified variant is associated with a different genetic disorder that has not yet been diagnosed (these are called incidental or secondary findings on page 26).



In addition to being used in the clinic, whole exome and whole genome sequencing are valuable methods for researchers. Continued study of exome and genome sequences can help determine whether new genetic variations are associated with health conditions, which will aid disease diagnosis in the future.

**For more information about DNA sequencing technologies and their use:**

Genetics Home Reference discusses whether all genetic changes affect health and development.

An illustration of the decline in the cost of DNA sequencing (<https://www.genome.gov/sequencingcosts/>), including that caused by the introduction of new technologies, is provided by the National Human Genome Research Institute.

The American College of Medical Genetics and Genomics has laid out their policies regarding whole exome and whole genome sequencing (<https://www.acmg.net/PDFLibrary/Genomic-Sequencing-Clinical-Application.pdf>), including when these methods should be used, what results may arise, and what the results might indicate.

GeneReviews compares whole genome sequencing, whole exome sequencing, and the sequencing of a selection of individual genes (<https://www.ncbi.nlm.nih.gov/books/NBK279899/>), particularly their use in the diagnosis of genetic conditions.

The PHG Foundation provides an overview of whole genome sequencing ([http://www.phgfoundation.org/documents/279\\_1319536722.pdf](http://www.phgfoundation.org/documents/279_1319536722.pdf)) and how it can be used in healthcare.

The Mount Sinai School of Medicine Genomics Core Facility describes the techniques used in whole exome sequencing (<https://icahn.mssm.edu/research/genomics/core-facility/whole-exome>).

The Smithsonian National Museum of Natural History's exhibit 'Genome: Unlocking Life's Code' discusses the advancements (<https://unlockinglifescode.org/explore/genome-within-us/reading-life%E2%80%99s-code>) made in DNA sequencing.

## What are secondary findings from genetic testing?

Secondary findings are genetic test results that provide information about changes (variants) in a gene unrelated to the primary purpose for the testing.

When a clinician orders a genetic test on page 4 to discover the genetic cause of a particular condition, the test will often sequence one or a few genes that seem most likely to be associated with that individual's set of signs and symptoms. However, if the individual's signs and symptoms do not have an obvious genetic cause, a clinician might order a test that sequences all of the pieces of an individual's DNA that provide instructions for making proteins (called an exome) or a test that sequences all of an individual's DNA building blocks (nucleotides), called a genome. These tests are called whole exome sequencing and whole genome sequencing on page 24, respectively.

Many more genetic changes can be identified with whole exome and whole genome sequencing than by sequencing just one or a few genes. Sometimes, testing finds a variant that is associated with a condition other than the one for which testing was originally indicated. This is called a secondary finding. Some individuals with a secondary finding may not yet have any of the symptoms associated with the condition, but may be at risk of developing it later in life. For example, a person with a variant in the *BRCA1* gene, which is associated with an increased risk of breast and ovarian cancer, may not have developed cancer. Other individuals with secondary findings may have a known medical condition, such as extremely high cholesterol, but receive results that indicate a genetic cause for that condition, such as a variant in the *LDLR* gene.

In 2013 (and again in 2017), the American College of Medical Genetics and Genomics (ACMG) recommended that all labs performing whole exome and whole genome sequencing tests include the reporting of secondary findings, in addition to any variants that are found related to the primary purpose of the testing. The ACMG proposed a list of 59 genes that are associated with a variety of conditions, from cancer to heart disease. The 59 genes for which secondary findings are reported were chosen because they are associated with conditions that have a definable set of clinical features, the possibility of early diagnosis, a reliable clinical genetic test, and effective intervention or treatment. The goal of reporting these secondary findings to an individual is to provide medical benefit by preventing or better managing health conditions. The variants that are reported are known to cause disease. Variants of unknown significance, whose involvement in disease at the current time is unclear, are not reported.

The information provided by secondary findings can be very important because it may help prevent a disease from occurring or guide the management of signs and symptoms if the disease develops or is already present. However, as with

any type of medical diagnosis, the news of an unexpected potential health problem may lead to additional health costs and stress for individuals and their families. On the basis of secondary findings, additional testing to confirm results, ongoing screening tests, or preventive care may be advised. Individuals receiving whole exome or whole genome sequencing can choose to “opt out” of analysis of the 59 secondary finding genes and not receive variant results. As whole exome and whole genome sequencing become more common, it is important for individuals to understand what type of information they may learn and how it can impact their medical care.

### **Scientific journal articles for further reading**

Robert C. Green MD, MPH, Jonathan S. Berg MD, PhD, Wayne W. Grody MD, PhD, Sarah S. Kalia ScM, CGC, Bruce R. Korf MD, PhD, Christa L. Martin PhD, FACMG, Amy L. McGuire JD, PhD, Robert L. Nussbaum MD, Julianne M. O’Daniel MS, CGC, Kelly E. Ormond MS, CGC, Heidi L. Rehm PhD, FACMG, Michael S. Watson PhD, FACMG, Marc S. Williams MD, FACMG & Leslie G. Biesecker MD. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. *Genet Med.* 2013 Jul;15(7):565-74. doi: 10.1038/gim.2013.73. Epub 2013 Jun 20. PubMed: 23788249 (<https://www.ncbi.nlm.nih.gov/pubmed/23788249>). Free full-text article from PubMed Central: 3727274 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3727274/>).

Sarah S. Kalia ScM, Kathy Adelman, Sherri J. Bale PhD, Wendy K. Chung MD, PhD, Christine Eng MD, James P. Evans MD, PhD, Gail E. Herman MD, PhD, Sophia B. Hufnagel MD, Teri E. Klein PhD, Bruce R. Korf MD, PhD, Kent D. McKelvey MD, Kelly E. Ormond MS, C. Sue Richards PhD, Christopher N. Vlangos PhD, Michael Watson PhD, Christa L. Martin PhD & David T. Miller MD, PhD ; on behalf of the ACMG Secondary Findings Maintenance Working Group. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. *Genet Med.* 2017 Feb;19(2):249-255. doi: 10.1038/gim.2016.190. Epub 2016 Nov 17. PubMed: 27854360 (<https://www.ncbi.nlm.nih.gov/pubmed/27854360>).

### **Learn more about secondary genetic findings:**

The Hospital for Sick Children in Toronto, Canada, provides a video that explains the process of receiving secondary findings (<http://www.sickkids.ca/CGM/education/secondary-findings.html>) from whole exome sequencing.

The Columbia University Medical Center has videos giving an Introduction to Secondary Findings (<http://www.learninggenetics.org/secondary-findings.html>) as well as discussing the Pros and Cons of Secondary Findings (<http://>

[www.learninggenetics.org/pros-cons.html](http://www.learninggenetics.org/pros-cons.html)) and Decisions about Secondary Findings (<http://www.learninggenetics.org/decisions.html>).

The U.S. National Library of Medicine provides a list of the ACMG-recommended secondary finding genes and their associated conditions (<https://www.ncbi.nlm.nih.gov/clinvar/docs/acmg/>).

Genetics Home Reference has information on the genetic conditions (<https://ghr.nlm.nih.gov/search?query=acmg&tab=condition>) that are associated with the 59 ACMG-recommended secondary finding genes.

## What is noninvasive prenatal testing (NIPT) and what disorders can it screen for?

Noninvasive prenatal testing (NIPT), sometimes called noninvasive prenatal screening (NIPS), is a method of determining the risk that the fetus will be born with certain genetic abnormalities. This testing analyzes small fragments of DNA that are circulating in a pregnant woman's blood. Unlike most DNA, which is found inside a cell's nucleus, these fragments are free-floating and not within cells, and so are called cell-free DNA (cfDNA). These small fragments usually contain fewer than 200 DNA building blocks (base pairs) and arise when cells die off and get broken down and their contents, including DNA, are released into the bloodstream.

During pregnancy, the mother's bloodstream contains a mix of cfDNA that comes from her cells and cells from the placenta. The placenta is tissue in the uterus that links the fetus and the mother's blood supply. These cells are shed into the mother's bloodstream throughout pregnancy. The DNA in placental cells is usually identical to the DNA of the fetus. Analyzing cfDNA from the placenta provides an opportunity for early detection of certain genetic abnormalities without harming the fetus.

NIPT is most often used to look for chromosomal disorders that are caused by the presence of an extra or missing copy (aneuploidy) of a chromosome. NIPT primarily looks for Down syndrome (trisomy 21, caused by an extra chromosome 21), trisomy 18 (caused by an extra chromosome 18), trisomy 13 (caused by an extra chromosome 13), and extra or missing copies of the X chromosome and Y chromosome (the sex chromosomes). The accuracy of the test varies by disorder.

NIPT may include screening for additional chromosomal disorders that are caused by missing (deleted) or copied (duplicated) sections of a chromosome. NIPT is beginning to be used to test for genetic disorders that are caused by changes (variants) in single genes. As technology improves and the cost of genetic testing decreases, researchers expect that NIPT will become available for many more genetic conditions.

NIPT is considered noninvasive because it requires drawing blood only from the pregnant woman and does not pose any risk to the fetus. NIPT is a screening test, which means that it will not give a definitive answer about whether or not a fetus has a genetic condition. The test can only estimate whether the risk of having certain conditions is increased or decreased. In some cases, NIPT results indicate an increased risk for a genetic abnormality when the fetus is actually unaffected (false positive), or the results indicate a decreased risk for a genetic

abnormality when the fetus is actually affected (false negative). Because NIPT analyzes both fetal and maternal cfDNA, the test may detect a genetic condition in the mother.

There must be enough fetal cfDNA in the mother's bloodstream to be able to identify fetal chromosome abnormalities. The proportion of cfDNA in maternal blood that comes from the placenta is known as the fetal fraction. Generally, the fetal fraction must be above 4 percent, which typically occurs around the tenth week of pregnancy. Low fetal fractions can lead to an inability to perform the test or a false negative result. Reasons for low fetal fractions include testing too early in the pregnancy, sampling errors, maternal obesity, and fetal abnormality.

There are multiple NIPT methods to analyze fetal cfDNA. To determine chromosomal aneuploidy, the most common method is to count all cfDNA fragments (both fetal and maternal). If the percentage of cfDNA fragments from each chromosome is as expected, then the fetus has a decreased risk of having a chromosomal condition (negative test result). If the percentage of cfDNA fragments from a particular chromosome is more than expected, then the fetus has an increased likelihood of having a trisomy condition (positive test result). A positive screening result indicates that further testing (called diagnostic testing, because it is used to diagnose a disease) should be performed to confirm the result.

### **Scientific journal articles for further reading**

Committee Opinion No. 640: Cell-Free DNA Screening For Fetal Aneuploidy. *Obstet Gynecol.* 2015 Sep;126(3):e31-7. doi: 10.1097/AOG.0000000000001051. PubMed: 26287791 (<https://www.ncbi.nlm.nih.gov/pubmed/26287791>).

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Goldwaser T, Klugman S. Cell-free DNA for the detection of fetal aneuploidy. *Fertil Steril.* 2018 Feb;109(2):195-200. doi: 10.1016/j.fertnstert.2017.12.019. PubMed: 29447662 (<https://www.ncbi.nlm.nih.gov/pubmed/29447662>).

Gregg AR, Skotko BG, Benkendorf JL, Monaghan KG, Bajaj K, Best RG, Klugman S, Watson MS. Noninvasive prenatal screening for fetal aneuploidy, 2016 update: a position statement of the American College of Medical Genetics

and Genomics. *Genet Med.* 2016 Oct;18(10):1056-65. doi: 10.1038/gim.2016.97. Epub 2016 Jul 28. PubMed: 27467454 (<https://www.ncbi.nlm.nih.gov/pubmed/27467454>).

Skrzypek H, Hui L. Noninvasive prenatal testing for fetal aneuploidy and single gene disorders. *Best Pract Res Clin Obstet Gynaecol.* 2017 Jul;42:26-38. doi: 10.1016/j.bpobgyn.2017.02.007. Epub 2017 Feb 28. PubMed: 28342726 (<https://www.ncbi.nlm.nih.gov/pubmed/28342726>).

**For more information about NIPT:**

Dana-Farber Cancer Institute: Cell-free DNA (<https://www.dana-farber.org/research/departments-centers-and-labs/integrative-research-centers/center-for-cancer-genome-discovery/cell-free-dna/>)

Genomics Education Programme (UK): What is NIPT? (<https://www.genomicseducation.hee.nhs.uk/news/item/403-what-is-nipt/>)

National Human Genome Research Institute: Noninvasive Prenatal Genetic Testing (<https://www.genome.gov/27570937/april-17-noninvasive-prenatal-genetic-testing/>)

Centre for Genetics Education (Australia): Fact Sheet: Non-Invasive Prenatal Testing (NIPT) (<https://www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-27-non-invasive-prenatal-testing-nipt/view>)

National Society of Genetic Counselors: Questions Expectant Mothers Should Ask Before Prenatal Screening (<http://www.aboutgeneticcounselors.com/Genetic-Conditions/Questions-Expectant-Mothers-Should-Ask-Before-Prenatal-Screening>)

Eunice Kennedy Shriver National Institute of Child Health and Human Development: How do Health Care Providers Diagnose Birth Defects? (<https://www.nichd.nih.gov/health/topics/birthdefects/conditioninfo/diagnosed>)

American College of Obstetricians and Gynecologists: Cell-free DNA Prenatal Screening Test Infographic (<https://www.acog.org/-/media/For-Patients/pfsi008.pdf?dmc=1&ts=20180613T1631181843>)

Genetic Support Foundation: Prenatal Cell-free DNA (cfDNA) Screening (<https://www.geneticsupport.org/genetics-pregnancy/prenatal-screening-tests/cell-free-dna-screening/>)

## What is circulating tumor DNA and how is it used to diagnose and manage cancer?

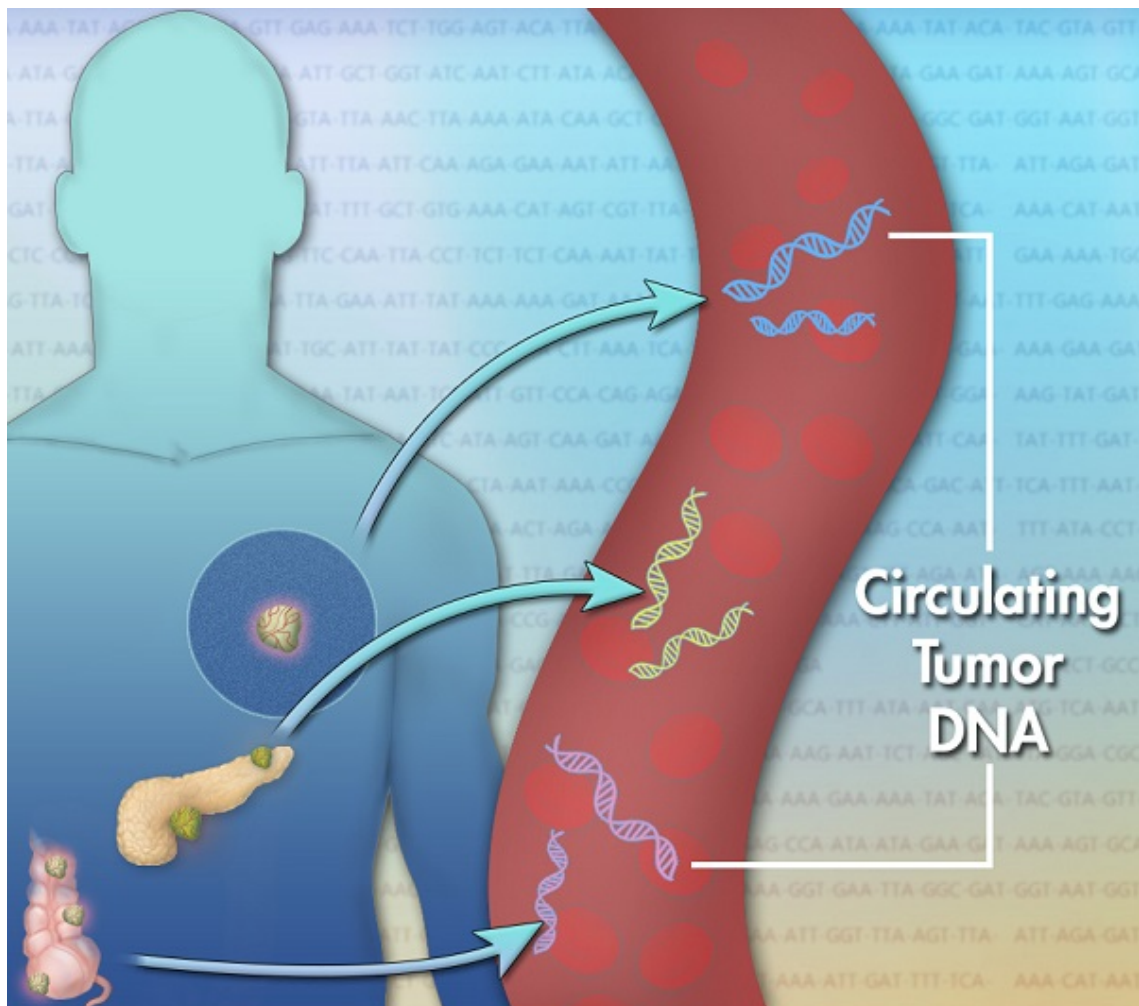
Circulating tumor DNA (ctDNA) is found in the bloodstream and refers to DNA that comes from cancerous cells and tumors. Most DNA is inside a cell's nucleus. As a tumor grows, cells die and are replaced by new ones. The dead cells get broken down and their contents, including DNA, are released into the bloodstream. ctDNA are small pieces of DNA, usually comprising fewer than 200 building blocks (nucleotides) in length.

The quantity of ctDNA varies among individuals and depends on the type of tumor, its location, and for cancerous tumors, the cancer stage.

Detection of ctDNA can be helpful in the following cases:

- Detecting and diagnosing a tumor. Because tumor DNA has acquired multiple genetic mutations, leading to tumor development, ctDNA is not an exact match to the individual's DNA. Finding DNA with genetic differences aids in tumor detection. Diagnosing the type of tumor using ctDNA can reduce the need for getting a sample of the tumor tissue (tumor biopsy), which can be challenging when a tumor is difficult to access, such as a tumor in the brain or lung.
- Guiding tumor-specific treatment. Analyzing the genome of tumor cells using ctDNA can help doctors determine which treatment will be most effective. Currently, however, approval from the U.S. Food and Drug Administration for ctDNA testing to personalize cancer treatment is limited.
- Monitoring treatment. A decrease in the quantity of ctDNA suggests the tumor is shrinking and treatment is successful.
- Monitoring periods with no symptoms (remission of cancer). A lack of ctDNA in the bloodstream indicates that the cancer has not returned.





Scientists have discovered that dying tumor cells release small pieces of their DNA into the bloodstream. These pieces are called cell-free circulating tumor DNA (ctDNA).

### Scientific journal articles for further reading

Merker JD, Oxnard GR, Compton C, Diehn M, Hurley P, Lazar AJ, Lindeman N, Lockwood CM, Rai AJ, Schilsky RL, Tsimberidou AM, Vasalos P, Billman BL, Oliver TK, Bruinooge SS, Hayes DF, Turner NC. Circulating Tumor DNA Analysis in Patients With Cancer: American Society of Clinical Oncology and College of American Pathologists Joint Review. *J Clin Oncol*. 2018 Jun 1;36(16):1631-1641. doi: 10.1200/JCO.2017.76.8671. Epub 2018 Mar 5. PubMed: 29504847 (<https://www.ncbi.nlm.nih.gov/pubmed/29504847>).

Stewart CM, Kothari PD, Mouliere F, Mair R, Somnay S, Benayed R, Zehir A, Weigelt B, Dawson SJ, Arcila ME, Berger MF, Tsui DW. The value of cell-free DNA for molecular pathology. *J Pathol*. 2018 Apr;244(5):616-627.

doi: 10.1002/path.5048. Epub 2018 Mar 12. PubMed: 29380875 (<https://www.ncbi.nlm.nih.gov/pubmed/29380875>).

**For more information about ctDNA:**

National Human Genome Research Institute: Circulating Tumor DNA: A New Generation of Cancer Biomarkers (<https://www.genome.gov/27556716/circulating-tumor-dna-a-new-generation-of-cancer-biomarkers/>)

My Cancer Genome: Circulating Tumor DNA (<https://www.mycancergenome.org/content/molecular-medicine/circulating-tumor-dna/>)

PHG Foundation (UK): Circulating Tumour DNA Technology: The Future of Cancer Management? (<http://www.phgfoundation.org/briefing/ctDNA-the-future-of-cancer-management>)



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