



# Help Me Understand Genetics

## Gene Therapy and Other Medical Advances

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# Gene Therapy and Other Medical Advances

## 1 What is gene therapy?

Gene therapy is a medical approach that treats or prevents disease by correcting the underlying genetic problem. Gene therapy techniques allow doctors to treat a disorder by altering a person's genetic makeup instead of using drugs or surgery.

The earliest method of gene therapy, often called gene transfer or gene addition, was developed to:

- Introduce a new gene into cells to help fight a disease.
- Introduce a non-faulty copy of a gene to stand in for the altered copy causing disease.

Later studies led to advances in gene therapy techniques. A newer technique, called genome editing (an example of which is CRISPR-Cas9), uses a different approach to correct genetic differences. Instead of introducing new genetic material into cells, genome editing introduces molecular tools to change the existing DNA in the cell. Genome editing is being studied to:

- Fix a genetic alteration underlying a disorder, so the gene can function properly.
- Turn on a gene to help fight a disease.
- Turn off a gene that is functioning improperly.
- Remove a piece of DNA that is impairing gene function and causing disease.

Gene therapies are being used to treat a small number of diseases, including an eye disorder called Leber congenital amaurosis and a muscle disorder called spinal muscular atrophy. Many more gene therapies are undergoing research to make sure that they will be safe and effective. Genome editing is a promising technique also under study that doctors hope to use soon to treat disorders in people.

### **For general information about gene therapy:**

MedlinePlus offers a list of links to information about genes and gene therapy (<https://medlineplus.gov/genesandgenetherapy.html>).

The Genetic Science Learning Center at the University of Utah provides an interactive introduction to gene therapy (<https://learn.genetics.utah.edu/content/genetherapy/>) and a discussion of several diseases for which gene therapy has been successful (<https://learn.genetics.utah.edu/content/genetherapy/success/>).

The Centre for Genetics Education provides an introduction to gene therapy and other therapeutics (<https://www.genetics.edu.au/SitePages/Gene-therapy-advanced-therapeutics.aspx>), including a discussion of ethical and safety considerations.

The National Heart, Lung, and Blood Institute describes the approaches to gene therapy

and how they work (<https://www.nhlbi.nih.gov/health-topics/genetic-therapies>).

Your Genome from the Wellcome Genome Campus provides an introduction to gene therapy and describes several techniques (<https://www.yourgenome.org/facts/what-is-gene-therapy>).

KidsHealth from Nemours offers a fact sheet called Gene Therapy and Children (<https://kidshealth.org/en/parents/gene-therapy.html>).

## 2 How does gene therapy work?

Gene therapy works by altering the genetic code to recover the functions of critical proteins. Proteins are the workhorses of the cell and the structural basis of the body's tissues. The instructions for making proteins are carried in a person's genetic code, and variants (or mutations) in this code can impact the production or function of proteins that may be critical to how the body works. Fixing or compensating for disease-causing genetic changes may recover the role of these important proteins and allow the body to function as expected.

Gene therapy can compensate for genetic alterations in a couple different ways.

- Gene transfer therapy introduces new genetic material into cells. If an altered gene causes a necessary protein to be faulty or missing, gene transfer therapy can introduce a normal copy of the gene to recover the function of the protein. Alternatively, the therapy can introduce a different gene that provides instructions for a protein that helps the cell function normally, despite the genetic alteration.
- Genome editing is a newer technique that may potentially be used for gene therapy. Instead of adding new genetic material, genome editing introduces gene-editing tools that can change the existing DNA in the cell. Genome editing technologies allow genetic material to be added, removed, or altered at precise locations in the genome. CRISPR-Cas9 is a well-known type of genome editing.

Genetic material or gene-editing tools that are inserted directly into a cell usually do not function. Instead, a carrier called a vector is genetically engineered to carry and deliver the material. Certain viruses are used as vectors because they can deliver the material by infecting the cell. The viruses are modified so they can't cause disease when used in people. Some types of virus, such as retroviruses, integrate their genetic material (including the new gene) into a chromosome in the human cell. Other viruses, such as adenoviruses, introduce their DNA into the nucleus of the cell, but the DNA is not integrated into a chromosome. Viruses can also deliver the gene-editing tools to the nucleus of the cell.

The vector can be injected or given intravenously (by IV) directly into a specific tissue in the body, where it is taken up by individual cells. Alternately, a sample of the patient's cells can be removed and exposed to the vector in a laboratory setting. The cells containing the vector are then returned to the patient. If the treatment is successful, the new gene delivered by the vector will make a functioning protein or the editing molecules will correct a DNA error and restore protein function.

Gene therapy with viral vectors has been successful, but it does carry some risk. Sometimes the virus triggers a dangerous immune response. In addition, vectors that integrate the genetic material into a chromosome can cause errors that lead to cancer. Researchers are developing newer technologies that can deliver genetic material or gene-editing tools without using viruses. One such technique uses special structures called nanoparticles as vectors to deliver the genetic material or gene-editing components into cells. Nanoparticles are incredibly small structures that have been developed for many uses. For gene therapy, these tiny particles are designed with

specific characteristics to target them to particular cell types. Nanoparticles are less likely to cause immune reactions than viral vectors, and they are easier to design and modify for specific purposes.

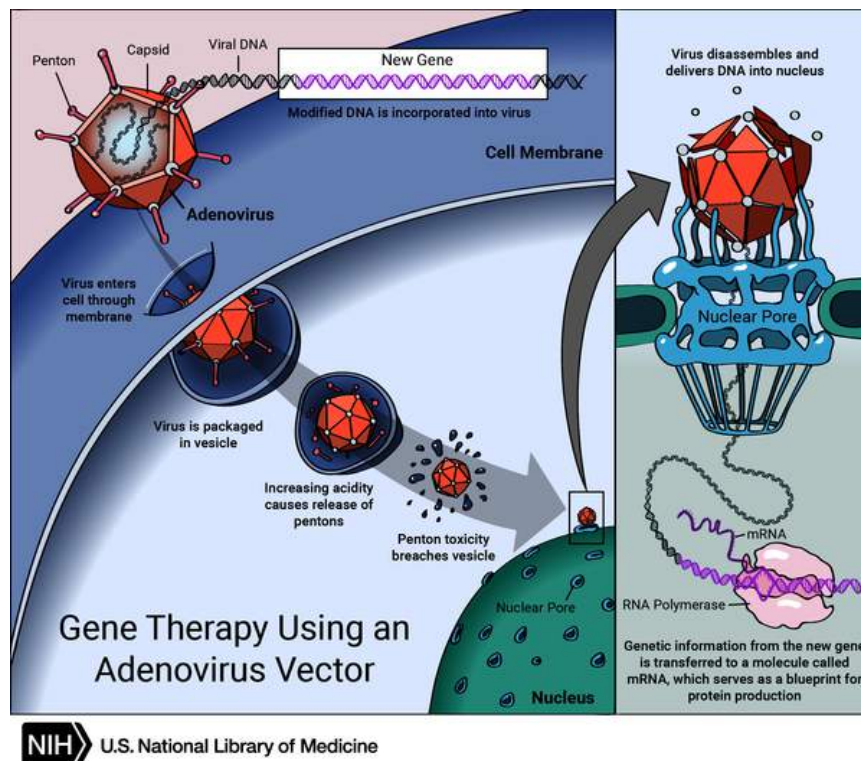
Researchers continue to work to overcome the many technical challenges of gene therapy. For example, scientists are finding better ways to deliver genes or gene-editing tools and target them to particular cells. They are also working to more precisely control when the treatment is functional in the body.

## Scientific journal articles for further reading

Bulcha JT, Wang Y, Ma H, Tai PWL, Gao G. Viral vector platforms within the gene therapy landscape. *Signal Transduct Target Ther.* 2021 Feb 8;6(1):53. doi: 10.1038/s41392-021-00487-6. PMID: 33558455. Free full-text article from PubMed Central: PMC7868676.

Duan L, Ouyang K, Xu X, Xu L, Wen C, Zhou X, Qin Z, Xu Z, Sun W, Liang Y. Nanoparticle Delivery of CRISPR/Cas9 for Genome Editing. *Front Genet.* 2021 May 12; 12:673286. doi: 10.3389/fgene.2021.673286. PubMed: 34054927. Free full-text article from PubMed Central: PMC8149999.

A new gene is inserted directly into a cell. A carrier called a vector is genetically engineered to deliver the gene. An adenovirus introduces the DNA into the nucleus of the cell, but the DNA is not integrated into a chromosome. (Figure 1)



**FIGURE 1:** A new gene is inserted directly into a cell. A carrier called a vector is genetically engineered to deliver the gene. An adenovirus introduces the DNA into the nucleus of the cell, but the DNA is not integrated into a chromosome.

### **For more information about how gene therapy works:**

Boston Children's Hospital summarizes the evolution of gene therapy techniques (<https://answers.childrenshospital.org/gene-therapy-history/>).

The Genetic Science Learning Center at the University of Utah provides information about various technical aspects of gene therapy in Gene Delivery: Tools of the Trade (<https://learn.genetics.utah.edu/content/genetherapy/tools/>). They also discuss other approaches to gene therapy (<https://learn.genetics.utah.edu/content/genetherapy/approaches/>) and offer a related learning activity called Space Doctor (<https://learn.genetics.utah.edu/content/genetherapy/doctor/>).

The American Society of Gene and Cell Therapy offers an in-depth description of the different types of viral vectors used in gene therapy (<https://patienteducation.asgct.org/gene-therapy-101/vectors-101>).

Penn Medicine's OncoLink describes how gene therapy works and how it is administered to patients (<https://www.oncolink.org/cancer-treatment/immunotherapy/what-is-gene-therapy>).

The basics of nanoparticles and their use in medicine (<https://askabiologist.asu.edu/tiny-medicine>) are explained in the Ask a Biologist feature from Arizona State University.

Your Genome from the Wellcome Genome campus explains the first gene therapy trial to treat a condition called severe combined immunodeficiency (SCID) (<https://www.yourgenome.org/stories/treating-the-bubble-babies-gene-therapy-in-use>). It also describes other applications for gene therapy.

### 3 Is gene therapy safe?

The first gene therapy trial was run more than thirty years ago. The earliest studies showed that gene therapy could have very serious health risks, such as toxicity, inflammation, and cancer. Since then, researchers have studied the mechanisms and developed improved techniques that are less likely to cause dangerous immune reactions or cancer. Because gene therapy techniques are relatively new, some risks may be unpredictable; however, medical researchers, institutions, and regulatory agencies are working to ensure that gene therapy research, clinical trials, and approved treatments are as safe as possible.

Comprehensive federal laws, regulations, and guidelines help protect people who participate in research studies (called clinical trials). The U.S. Food and Drug Administration (FDA) regulates all gene therapy products in the United States and oversees research in this area. Researchers who wish to test an approach in a clinical trial must first obtain permission from the FDA. The FDA has the authority to reject or suspend clinical trials that are suspected of being unsafe for participants.

The National Institutes of Health (NIH) also plays an important role in ensuring the safety of gene therapy research. NIH provides guidelines for investigators and institutions (such as universities and hospitals) to follow when conducting clinical trials with gene therapy. These guidelines state that clinical trials at institutions receiving NIH funding for this type of research must be registered with the NIH Office of Biotechnology Activities. The protocol, or plan, for each clinical trial is then reviewed by the NIH Recombinant DNA Advisory Committee (RAC) to determine whether it raises medical, ethical, or safety issues that warrant further discussion at a RAC public meeting.

An Institutional Review Board (IRB) and an Institutional Biosafety Committee (IBC) must approve each gene therapy clinical trial before it can be carried out. An IRB is a committee of scientific and medical advisors and consumers that reviews all research within an institution. An IBC is a group that reviews and approves an institution's potentially hazardous research studies. Multiple levels of evaluation and oversight ensure that safety concerns are a top priority in the planning and carrying out of gene therapy research.

The clinical trial process occurs in three phases. Phase I studies determine if a treatment is safe for people and identify its side effects. Phase II studies determine if the treatment is effective, meaning whether it works. Phase III studies compare the new treatment to the current treatments available. Doctors want to know whether the new treatment works better or has fewer side effects than the standard treatment. The FDA reviews the results of the clinical trial. If it determines that the benefits of the new treatment outweigh the side effects, it approves the therapy, and doctors can use it to treat a disorder.

Successful clinical trials have led to the approval of a small number of gene therapies, including therapies to treat inherited disorders like spinal muscular atrophy and Leber congenital amaurosis.



**For more information about the safety and oversight of gene therapy:**

The Genetic Science Learning Center at the University of Utah explains challenges related to gene therapy (<https://learn.genetics.utah.edu/content/genetherapy/challenges/>).

The NIH's Office of Biotechnology Activities provides NIH guidelines for biosafety (<https://osp.od.nih.gov/biotechnology/nih-guidelines/>).

## 4 What are the ethical issues surrounding gene therapy?

Because gene therapy involves making changes to the body's basic building blocks (DNA), it raises many unique ethical concerns. The ethical questions surrounding gene therapy and genome editing include:

- How can “good” and “bad” uses of these technologies be distinguished?
- Who decides which traits are normal and which constitute a disability or disorder?
- Will the high costs of gene therapy make it available only to the wealthy?
- Could the widespread use of gene therapy make society less accepting of people who are different?
- Should people be allowed to use gene therapy to enhance basic human traits such as height, intelligence, or athletic ability?

Current research on gene therapy treatment has focused on targeting body (somatic) cells such as bone marrow or blood cells. This type of genetic alteration cannot be passed to a person's children. Gene therapy could be targeted to egg and sperm cells (germ cells), however, which would allow the genetic changes to be passed to future generations. This approach is known as germline gene therapy.

The idea of these germline alterations is controversial. While it could spare future generations in a family from having a particular genetic disorder, it might affect the development of a fetus in unexpected ways or have long-term side effects that are not yet known. Because people who would be affected by germline gene therapy are not yet born, they can't choose whether to have the treatment. Because of these ethical concerns, the U.S. Government does not allow federal funds to be used for research on germline gene therapy in people.

### **For more information about the ethical issues raised by gene therapy:**

The National Human Genome Research Institute discusses the ethical concerns of genome editing (<https://www.genome.gov/about-genomics/policy-issues/Genome-Editing/ethical-concerns>).

A debate of the ethics of germline gene therapy (<https://www.yourgenome.org/debates/issues-germline-gene-therapy-ethical>) is presented by yourgenome.org from the Wellcome Genome Campus.

A discussion of the ethics of gene therapy and genetic engineering (<https://medicine.missouri.edu/centers-institutes-labs/health-ethics/faq/gene-therapy>) is available from the University of Missouri Center for Health Ethics.

## 5 Is gene therapy available to treat my disorder?

Gene therapy is currently available primarily in a research setting. The U.S. Food and Drug Administration (FDA) has approved only a small number of gene therapy products for sale in the United States. For example, FDA-approved gene therapies are available for conditions that include a rare eye disorder called Leber congenital amaurosis, a form of skin cancer known as melanoma, and a genetic muscle condition called spinal muscular atrophy. Other genetic therapies have been approved for blood cell cancers such as lymphoma and multiple myeloma. Gene therapies to treat additional conditions have been approved in other countries.

Hundreds of research studies (clinical trials) are under way to test gene therapy as a treatment for genetic conditions, cancer, and HIV/AIDS. If you are interested in participating in a clinical trial, talk with your doctor or a genetics professional about how to participate.

### **For information about gene therapy clinical trials:**

You can also search for clinical trials online. ClinicalTrials.gov (<https://clinicaltrials.gov/>), a service of the National Institutes of Health, provides easy access to information about clinical trials. You can search for a specific clinical trial or browse by health condition or sponsor. You may wish to refer to a list of gene therapy clinical trials (<https://clinicaltrials.gov/search?term=%22gene+therapy%22>) or gene or genome editing clinical trials (<https://clinicaltrials.gov/ct2/results?cond=&term=%22gene+editing%22+OR+%22genome+editing%22>) that are accepting (or will accept) participants.

An explanation of the clinical trial process and how to find a clinical trial is presented by the American Society of Gene and Cell Therapy (<https://patienteducation.asgct.org/gene-therapy-101/clinical-trials-process>).

## 6 What are CAR T cell therapy, RNA therapy, and other genetic therapies?

Several treatments have been developed that involve genetic material but are typically not considered gene therapy. Some of these methods alter DNA for a slightly different use than gene therapy. Others do not alter genes themselves, but they change whether or how a gene's instructions are carried out to make proteins.

### Cell-based gene therapy

CAR T cell therapy (or chimeric antigen receptor T cell therapy) is an example of cell-based gene therapy. This type of treatment combines the technologies of gene therapy and cell therapy. Cell therapy introduces cells to the body that have a particular function to help treat a disease. In cell-based gene therapy, the cells have been genetically altered to give them the special function. CAR T cell therapy introduces a gene to a person's T cells, which are a type of immune cell. This gene provides instructions for making a protein, called the chimeric antigen receptor (CAR), that attaches to cancer cells. The modified immune cells can specifically attack cancer cells.

### RNA therapy

Several techniques, called RNA therapies, use pieces of RNA, which is a type of genetic material similar to DNA, to help treat a disorder. In many of these techniques, the pieces of RNA interact with a molecule called messenger RNA (or mRNA for short). In cells, mRNA uses the information in genes to create a blueprint for making proteins. By interacting with mRNA, these therapies influence how much protein is produced from a gene, which can compensate for the effects of a genetic alteration. Examples of these RNA therapies include antisense oligonucleotide (ASO), small interfering RNA (siRNA), and microRNA (miRNA) therapies. An RNA therapy called RNA aptamer therapy introduces small pieces of RNA that attach directly to proteins to alter their function.

### Epigenetic therapy

Another gene-related therapy, called epigenetic therapy, affects epigenetic changes in cells. Epigenetic changes are specific modifications (often called "tags") attached to DNA that control whether genes are turned on or off. Abnormal patterns of epigenetic modifications alter gene activity and, subsequently, protein production. Epigenetic therapies are used to correct epigenetic errors that underlie genetic disorders.

### Scientific journal articles for further reading

Kim YK. RNA Therapy: Current Status and Future Potential. *Chonnam Med J.* 2020 May;56(2):87-93. doi: 10.4068/cmj.2020.56.2.87. Epub 2020 May 25. PubMed: 32509554. Free full-text article from PubMed Central: PMC7250668.

Lu Y, Chan YT, Tan HY, Li S, Wang N, Feng Y. Epigenetic regulation in human cancer: the potential role of epi-drug in cancer therapy. *Mol Cancer.* 2020 Apr 27;19(1):79. doi: 10.1186/s12943-020-01197-3. 32340605. Free full-text article from PubMed Central:

PMC7184703.

## 7 What are mRNA vaccines and how do they work?

Vaccines help prevent infection by preparing the body to fight foreign invaders (such as bacteria, viruses, or other pathogens). All vaccines introduce into the body a harmless piece of a particular bacteria or virus, triggering an immune response. Most vaccines contain a weakened or dead bacteria or virus. However, scientists have developed a new type of vaccine that uses a molecule called messenger RNA (mRNA) rather than part of an actual bacteria or virus. Messenger RNA is a type of RNA that is necessary for protein production. In cells, mRNA uses the information in genes to create a blueprint for making proteins. Once cells finish making a protein, they quickly break down the mRNA. mRNA from vaccines does not enter the nucleus and does not alter DNA.

mRNA vaccines work by introducing a piece of mRNA that corresponds to a viral protein, usually a small piece of a protein found on the virus's outer membrane. (Individuals who get an mRNA vaccine are not exposed to the virus, nor can they become infected by the vaccine.) Using this mRNA blueprint, cells produce the viral protein. As part of a normal immune response, the immune system recognizes that the protein is foreign and produces specialized proteins called antibodies. Antibodies help protect the body against infection by recognizing individual viruses or other pathogens, attaching to them, and marking the pathogens for destruction. Once produced, antibodies remain in the body, even after the body has rid itself of the pathogen, so that the immune system can quickly respond if exposed again. If a person is exposed to a virus after receiving mRNA vaccination for it, antibodies can quickly recognize it, attach to it, and mark it for destruction before it can cause serious illness.

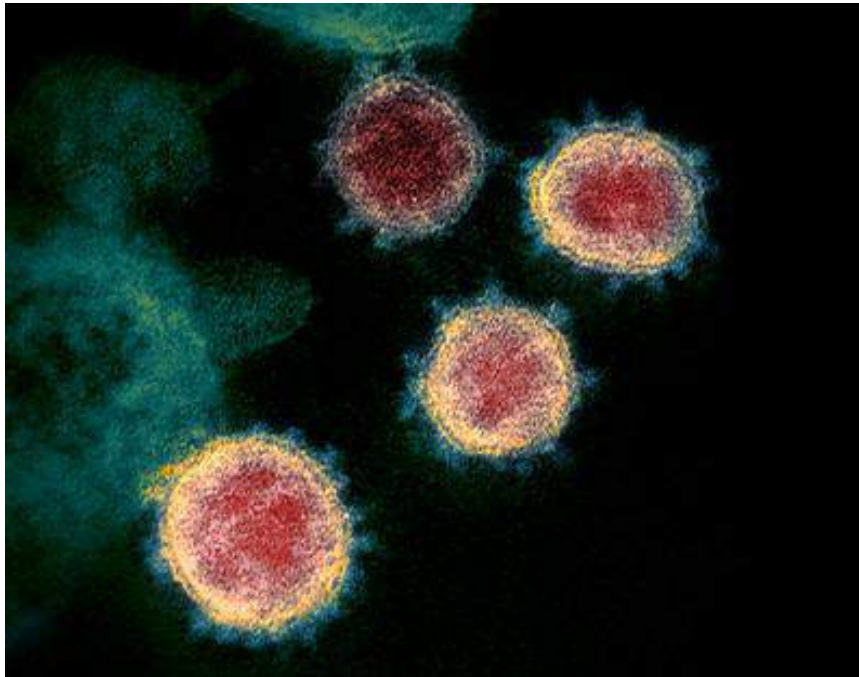
Like all vaccines in the United States, mRNA vaccines require authorization or approval from the Food and Drug Administration (FDA) before they can be used. Currently vaccines for COVID-19, the disease caused by the SARS-CoV-2 coronavirus, are the only authorized or approved mRNA vaccines. These vaccines use mRNA that directs cells to produce copies of a protein on the outside of the coronavirus known as the “spike protein”. Researchers are studying how mRNA might be used to develop vaccines for additional infectious diseases.

### Scientific journal articles for further reading

Jain S, Venkataraman A, Wechsler ME, Peppas NA. Messenger RNA-based vaccines: Past, present, and future directions in the context of the COVID-19 pandemic. *Adv Drug Deliv Rev.* 2021 Oct 9;179:114000. doi: 10.1016/j.addr.2021.114000. Epub ahead of print. PMID: 34637846; PMCID: PMC8502079.

Verbeke R, Lentacker I, De Smedt SC, Dewitte H. The dawn of mRNA vaccines: The COVID-19 case. *J Control Release.* 2021 May 10;333:511-520. doi: 10.1016/j.jconrel.2021.03.043. Epub 2021 Mar 30. PMID: 33798667; PMCID: PMC8008785.

Microscopic image of SARS-CoV-2, the virus that causes COVID-19. Spike proteins are seen surrounding the outer membrane of each virus particle. (Figure 2)



**FIGURE 2:** Microscopic image of four SARS-CoV-2 virus particles, the virus that causes COVID-19. Spike proteins are seen surrounding the outer membrane of each virus particle.

### **For more information about mRNA vaccines:**

MedlinePlus offers many additional resources with information about mRNA vaccines, specifically relating to their use in COVID-19

- MedlinePlus: Health Topic: COVID-19 Vaccines (<https://medlineplus.gov/covid19vaccines.html>)
- MedlinePlus: Encyclopedia: COVID-19 vaccines (<https://medlineplus.gov/ency/article/007775.htm>)
- MedlinePlus: Drugs and Supplements: COVID-19 Vaccine, mRNA (Pfizer-BioNTech) (<https://medlineplus.gov/druginfo/meds/a621003.html>)
- MedlinePlus: Drugs and Supplements: COVID-19 Vaccine, mRNA (Moderna) (<https://medlineplus.gov/druginfo/meds/a621002.html>)

The National Institute of Allergy and Infectious Diseases provides in-depth information (<https://www.niaid.nih.gov/diseases-conditions/coronavirus-vaccines-prevention>) about the COVID-19 vaccines.

The Centers for Disease Control and Prevention has a fact sheet (<https://www.cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines/mRNA.html>) on mRNA vaccines.