

# Gene therapy: what to know

The purpose of this site is to provide information to patients and caregivers about the field of gene therapy and how it is being investigated for use in hemophilia.

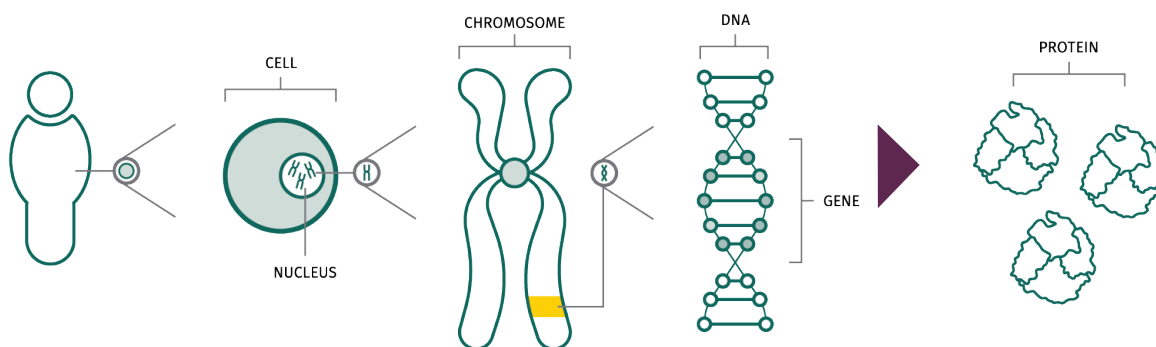
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## About genetic disease

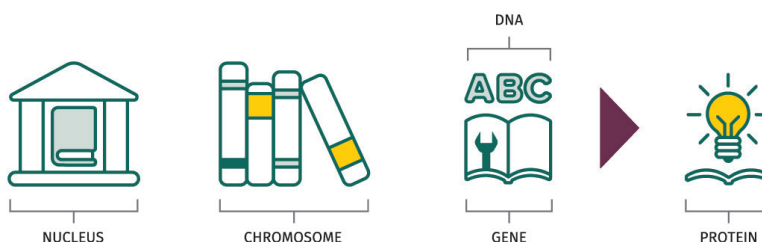
### Genes: the body's instruction manual

The human body is made up of trillions of **cells**. At the center of each cell is the **nucleus**, which contains all of the instructions the body needs to function.

These instructions are stored on **chromosomes**, which are made up of **DNA** (deoxyribonucleic acid). DNA is organized into **genes**, which provide instructions to make **proteins**—molecules that build, regulate, and maintain the body. Clotting factors are an example of proteins.



Another way to think about this is like a reference library.

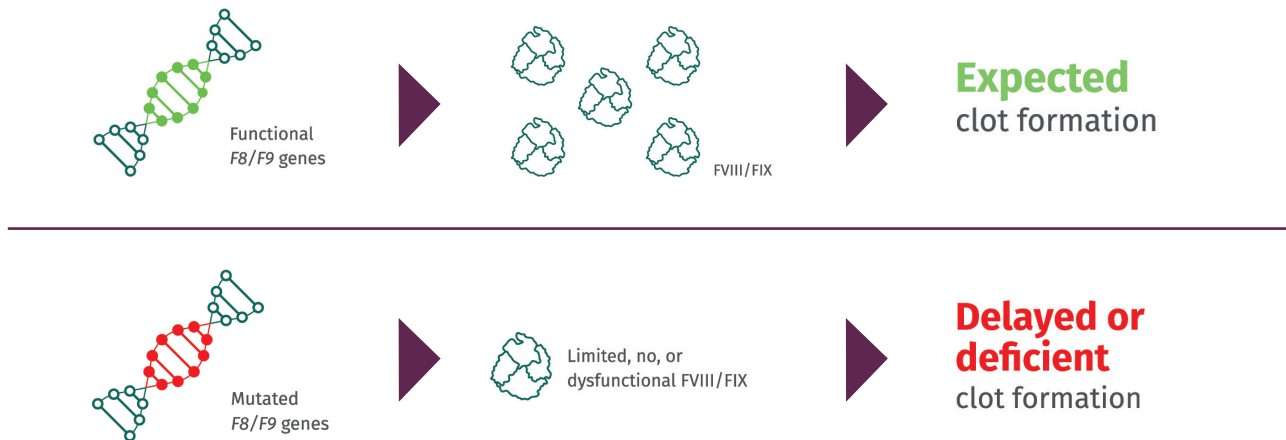


The library (nucleus) contains a bunch of “how to” encyclopedias (chromosomes) that are written in their own special alphabet (DNA). The encyclopedias (chromosomes) are organized into specific chapters (genes), which provide the instructions the body needs to build proteins.

## Genes and hemophilia

Hemophilia is a rare genetic bleeding disorder that causes a delay in clot formation. In hemophilia, there is a mutation in the gene that contains the body's instructions for creating one of several important blood-clotting proteins called "factors." There are two main types of hemophilia: A and B.

- Hemophilia A, or factor VIII deficiency, affects approximately 1 in 5,000 males
- Hemophilia B, or factor IX deficiency, affects approximately 1 in 25,000 males



Hemophilia is most often inherited, meaning it's passed down through a mutation in the parents' genes or DNA. However, in one-third of cases, hemophilia is caused by a new or spontaneous mutation. Because of how hemophilia is passed from parents to children, it primarily affects men. However, in rare cases, women can have hemophilia too.

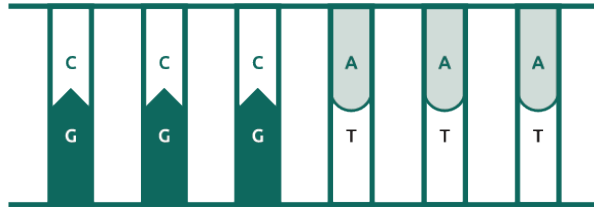
Hemophilia severity is classified based on a person's factor level in the blood:

- Mild (>5% to 40%)
- Moderate (1% to 5%)
- Severe (<1%)

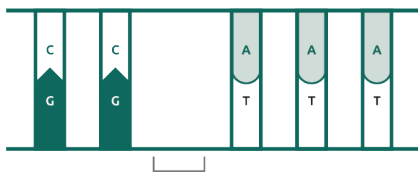
Individuals with hemophilia may bleed spontaneously (without a known cause) from an injury, inside or outside of the body, and longer than those without hemophilia. Common sites of internal bleeding are joints and muscles; bleeding in these locations can lead to joint damage and arthritis. External bleeding may also occur, including nose bleeds, prolonged bleeding from minor cuts and dental work, and unexplained bruising.

## Understanding genetic disease

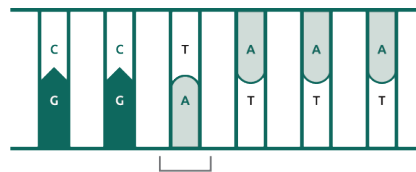
DNA has its own alphabet: A, C, G, T. The letters stand for the 4 nucleotides, which are the building blocks of DNA. Unique combinations of adenine (A), cytosine (C), guanine (G), and thymine (T) make up all of the genes in the body.



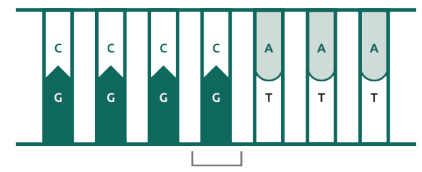
A **gene mutation** is a change in the sequence of DNA that makes up a gene. There are different types of gene mutations including:



**Deletion:** A segment of DNA is deleted or lost



**Substitution:** A segment of DNA is replaced with a different segment



**Duplication:** A segment of DNA is repeated, resulting in multiple copies of that genetic information

Gene mutations can cause:

- A protein to not work properly or stop working altogether
- An insufficient amount of protein or no protein to be made at all

When a protein is missing or not working properly, the function in the body that protein controls will be affected, resulting in a genetic disease.

# What is investigational gene therapy?

## Introduction to gene therapy research

Gene therapy is a potential approach to treating or preventing genetic diseases. The goal of gene therapy is to address a genetic disease at its source—the gene. This can be done by modifying (changing) genes or creating new functional genes in a laboratory and delivering them to specific cells in the body.

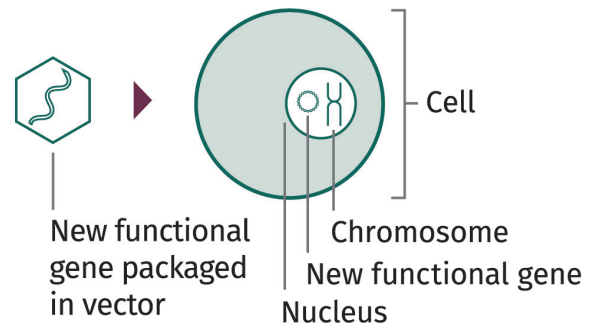


Scientists have been investigating gene therapy for more than 50 years, and the science around gene therapy continues to evolve. To date, more than 2,600 gene therapy clinical trials are planned, ongoing, or have been completed for different genetic diseases.

Gene therapy is the approach being most broadly investigated for use in hemophilia. This approach introduces a *new* functional copy of a gene with the aim of restoring or enhancing its original function. It is sometimes referred to as gene augmentation, gene transfer, or gene replacement.

### Gene therapy

Creating new functional genes in a laboratory and delivering them to specific cells in the body



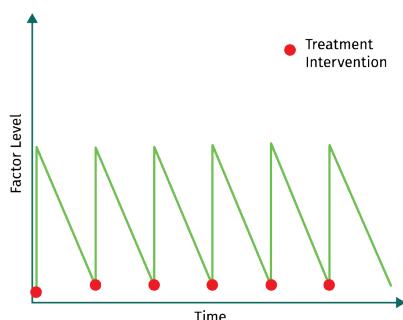
What is investigational gene therapy?

## NEXT LEVEL

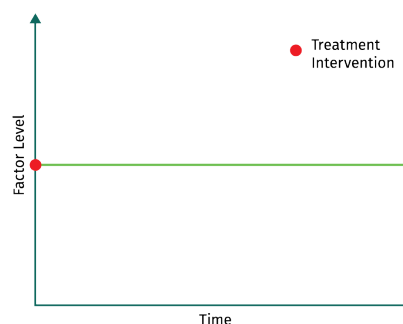
## Aim of gene therapy research in hemophilia

Why have scientists continued to research gene therapy for so long? Their efforts are aimed at finding a potential one-time or infrequent treatment as an additional treatment option to replace ongoing, recurring treatments for hemophilia. The hope is to move from the highs and lows in clotting factor levels (often called “peaks and troughs”) to a continuously expressed factor level.

### Current therapy for hemophilia



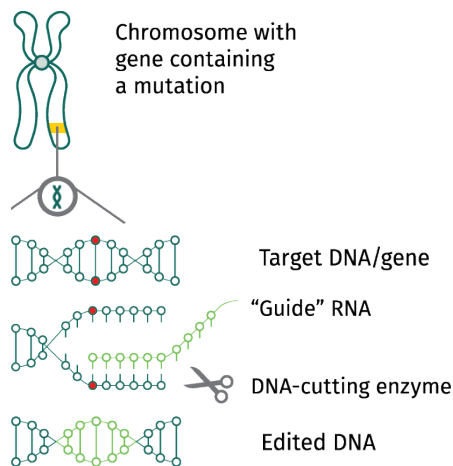
### Aim: continuously expressed factor level



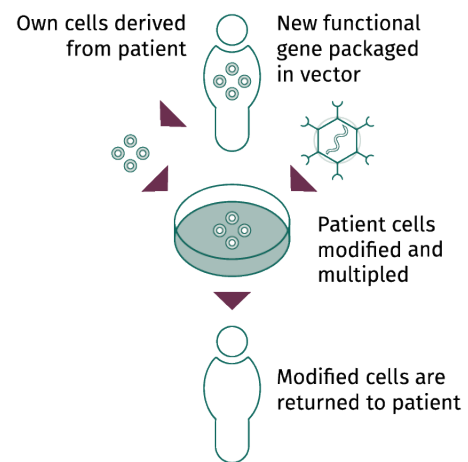
## Other techniques being investigated to treat or prevent disease at the gene level

Scientists are studying other approaches for treating or preventing genetic disease at its source—the gene.

**Gene editing**, sometimes called genome editing or genomic editing, modifies *existing* genes in a person's DNA to correct specific mutations. Some examples of investigational gene editing technologies include CRISPR and Zinc Finger Nucleases.



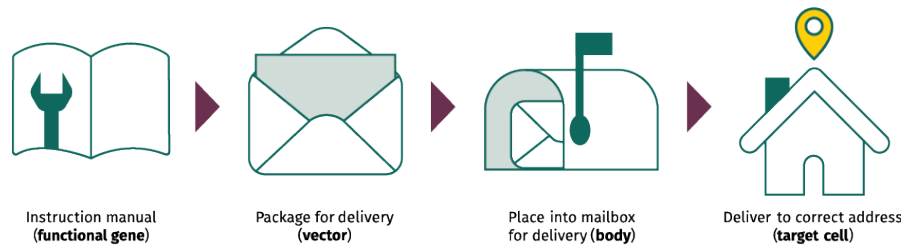
**Cell therapy** transplants *whole cells* capable of adding a new or desired function into a person. The genes in the cells may or may not be modified by gene therapy or gene editing while outside the body before being returned to the patient.



# What is investigational gene therapy meant to do?

## Step by step

The overall goal of investigational gene therapy is to deliver a functional gene to a specific, or target, cell.



Think of the **functional gene** as the instruction manual that tells the body how to make a desired protein.

Once a functional gene is created, there must be a way to deliver it to the right address, or target cells. The functional gene can be inserted into a viral-based shell, creating a delivery package known as a **vector**.

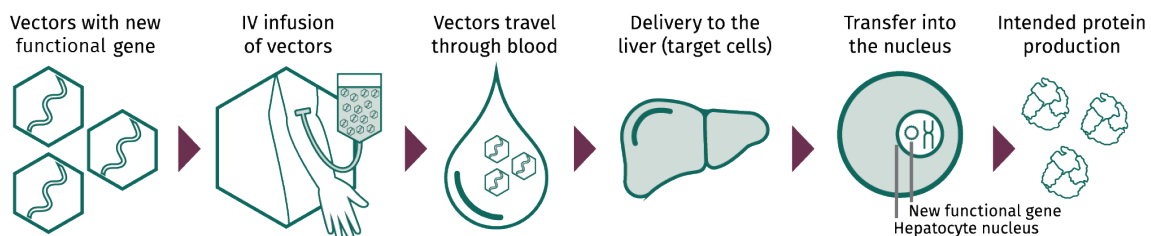
The vector's sole purpose is to deliver the functional gene to the correct target cell type—just like an envelope that ensures the instruction manual gets to the right address. The envelope (vector) is then placed into the mailbox (body) and mailed to the correct address (target cell type) to deliver the instruction manual (functional gene).

Vectors are chosen because they have an affinity, or preference, for a specific cell type or types, allowing the functional gene to get to the right place. They're sort of like a pre-addressed envelope that can only be sent to a particular address.

What is gene therapy meant to do?

## NEXT LEVEL

## Goals for gene therapy research in hemophilia



The primary research goal is to evaluate the safety and effectiveness of gene therapy intended to deliver a functional gene. Secondary goals include determining dosage of a potential gene therapy (eg, how many times it is administered and the appropriate dose needed to balance benefits and risks).

Investigational gene therapy for hemophilia is designed to add a functional copy of the factor VIII or factor IX gene to the cell's command center (nucleus). If transferred successfully, the functional gene is intended to provide the correct instructions for the cell to make factor VIII or factor IX clotting protein.

In this case, a virus is used as the delivery vehicle or vector. First the viral genetic information is removed. The new DNA (functional gene) is placed inside the viral-based shell, which can carry the new gene into the body. The vector is delivered into the body via intravenous (IV) infusion into the blood.

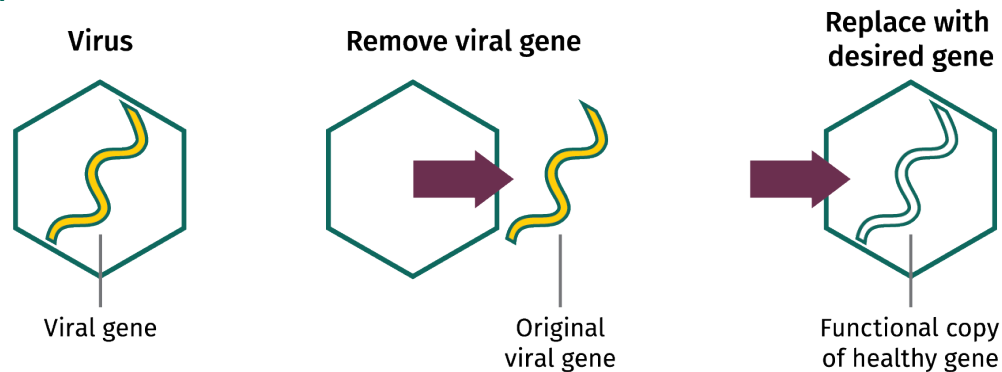
The vector used in hemophilia gene therapy research has a preference to travel to liver cells (hepatocytes).

## Modified viruses as vectors

In gene therapy research, modified viruses are the most commonly used method for the delivery of genetic material. Over millions of years, viruses evolved to be very good at placing genetic information into other cells. They also have a natural ability to target specific cell types in the body.

To modify a virus for use in gene therapy research, its own genetic information is replaced by the functional gene. It's now no longer a virus, but a vector, or transporter. Vectors are modified to be nonpathogenic, meaning they cannot reproduce the virus and cause disease.

### Creating a vector



Adeno-associated virus (AAV) is commonly used as a vector in gene therapy research overall and specifically in gene therapy research for hemophilia.

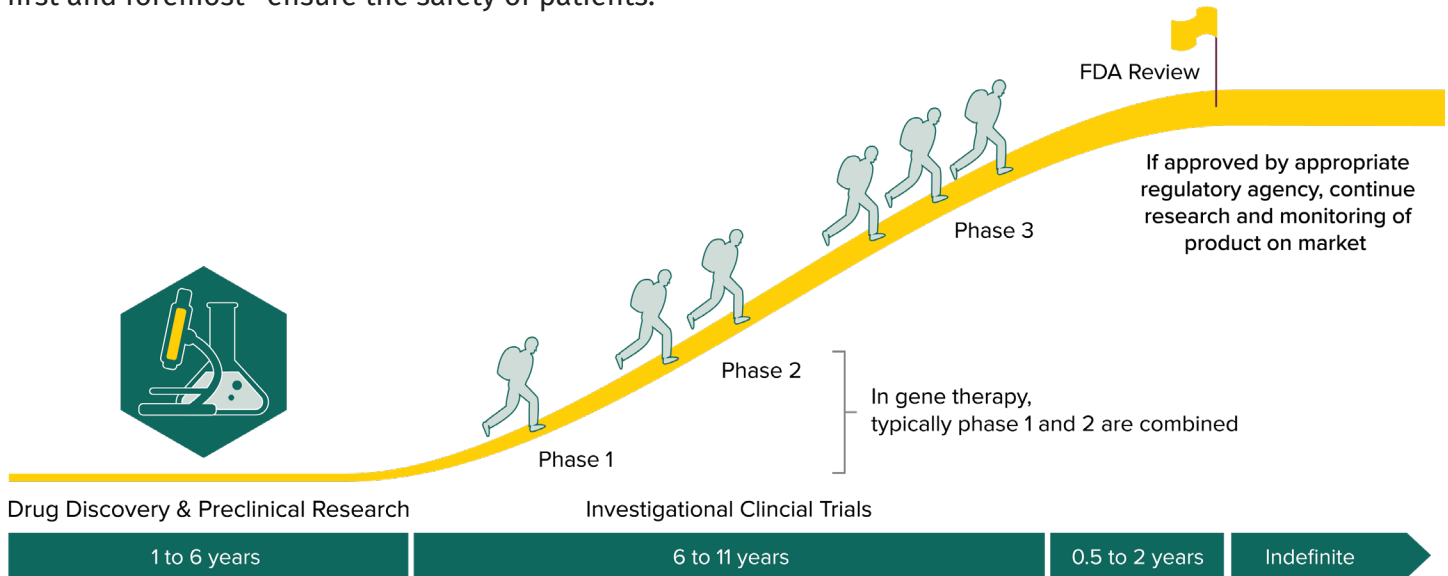
There are a few reasons why AAV is used:

- It is not known to cause human disease.
- It has relatively low pre-existing antibodies (immunogenicity). This means there is a lower chance a patient would have previously been exposed to it. The immune system would, therefore, not recognize it and not attempt to destroy the vector before it had its chance to reach the target cells.
- It can fit the functional factor gene inside.
- There are a variety of naturally occurring versions of AAV, which prefer, or have an affinity for, different cell types (tropism).

# How investigational therapies are studied

## Safety and well-being of patients are top priorities

Following many years of initial (preclinical) research, which includes laboratory, manufacturing, and animal studies, investigational new therapies may then be reviewed and approved by the FDA for research studies in humans, known as clinical trials. Clinical trials include multiple phases and extensive review of data to—first and foremost—ensure the safety of patients.



Results from clinical trials provide insights into the safety, effectiveness, and appropriate use of the gene therapy being studied.

## Potential risks of gene therapy

As with any new treatment being researched, there is the potential for unintended effects. To help identify these risks, gene therapies are studied in clinical trials under controlled conditions. While the safety of investigational gene therapy is still being studied, research to date has helped scientists learn important lessons.

Potential risks identified in gene therapy research so far include the following:

### **The body's immune system could respond in unintended ways.**

The job of the immune system is to defend against outside pathogens—things, such as viruses, from outside the body that could cause harm or sickness when inside the body. While this defense mechanism is normal and expected, it could cause the immune system to resist or attempt to fight off the gene therapy. This is because the immune system may see the vector, acting as the delivery vehicle for gene therapy, as something that isn't supposed to be there, an "invader." This may lead to immune responses in the body, such as:

- Swelling of the liver, which, if not controlled, could lead to a decrease or loss of the factor protein made from investigational gene therapy. Treatment, such as a short course of steroids, may be required to calm the immune system.
- The development of antibodies in response to AAV gene therapy, which could make someone ineligible for AAV gene therapy research and potential future treatments. This is because the antibodies would recognize the previously identified AAV gene therapy and escort it out of the body.
- The development of antibodies against FVIII or FIX (also called inhibitors), which would limit the ability of gene therapy to work as desired.
- Allergic reactions ranging from mild to severe



# How investigational therapies are studied (continued)

## Other potential risks could occur related to the gene transfer itself

- The functional gene carried by a vector may be delivered to the wrong cells. While vectors tend to be specific in the cells they target, there is still a risk that vectors could find their way into unintended cells. This could damage those cells or cause inappropriate cell growth, leading to tumors or cancer.
- Once the AAV vector has placed the functional gene inside the nucleus, the vector's empty shell (the "envelope") is removed (or shed) from the body. This "vector shedding" occurs in fluids such as urine, semen, or saliva. While rare, this could lead to the formation of antibodies to the AAV vector in people who come in contact with these fluids. This could unintentionally make someone ineligible for AAV gene therapy in the future.

Studies are ongoing and participants continue to be followed. Additional risks may be identified in the future.

## Learning more

If you're interested in learning more about gene therapy clinical trials for hemophilia, speak with your physician and visit [ClinicalTrials.gov](https://clinicaltrials.gov).



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