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Genetic Technologies for Hemophilia

Genetic technologies for hemophilia are rapidly evolving.

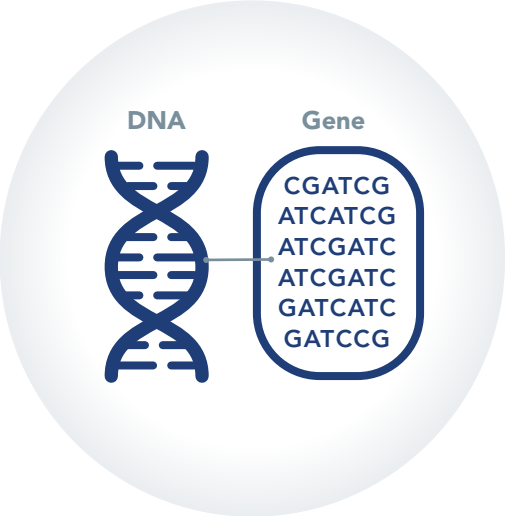
This information sheet is designed to help you understand the similarities, differences, and current state of knowledge for the existing genetic technologies for hemophilia.

What is DNA and what are genes?

The human body is made up of trillions of cells, which are the basic units that perform all the functions needed to keep you alive. Inside of most cells is a chemical called DNA that contains the body's genetic instructions. DNA is made up of four building blocks, or "letters" (A, T, C, and G), that can be "read" like words or sentences in a book.

DNA contains thousands of genes. Genes are the instructions that cells need to make proteins. Proteins control most of the body's essential work, including clotting blood in response to an injury.

Sometimes, genes may have a letter that is incorrect or missing, for example, an A where there should be a G. This causes confusion when reading the instructions and can result in a dysfunctional protein.



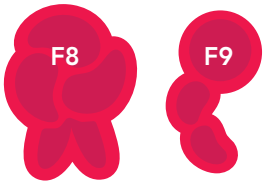
Hemophilia A and Hemophilia B are rare inherited diseases caused by a defect in either the gene for clotting factor VIII (F8) or factor IX (F9), respectively. Therefore, individuals with hemophilia do not produce enough functioning clotting factor proteins and their blood does not clot properly leading to spontaneous bleeding.

People WITHOUT hemophilia

x

F8 gene
F9 gene

Functional F8 and F9 proteins



People WITH hemophilia

x

Hemophilia A
Defect in F8 gene

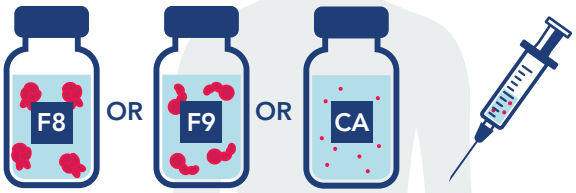
Hemophilia B
Defect in F9 gene

Absent or deficient F8 or F9 proteins

Visit the **WFH eLearning Platform** to learn more about bleeding disorders.

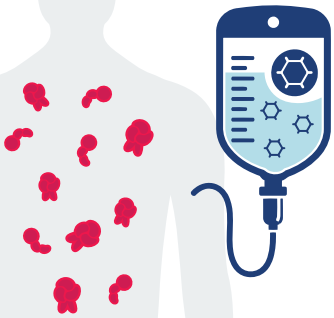
Genetic Technology-Based Therapeutics

Because hemophilia is caused by dysfunction of only one gene, it is a good candidate for genetic technology-based therapeutics.



Preventative Treatment

Standard management of severe hemophilia requires regular preventative treatment (called prophylaxis) and on-demand treatment of bleeds with clotting factor concentrates or other clotting agents (CA). These treatments allow the blood to clot normally, but they require ongoing treatment to remain effective.



Genetic Technologies

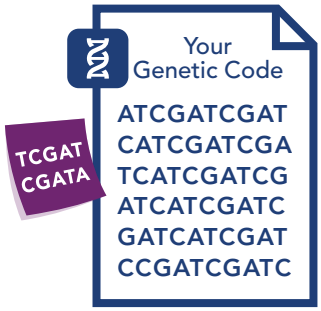
The goal of all genetic technologies for hemophilia is to restore the body's ability to produce its own functional F8 or F9 proteins. If the body can produce its own working F8 and F9 proteins, it could reduce, or possibly eliminate, the need for clotting factor infusions or other hemostatic treatments. These effects cannot be passed on to children.

There are multiple types of genetic technologies being developed for treating hemophilia. These are sometimes collectively referred to as "gene therapy." Each type of genetic technology has key differences that affect how it is administered, how it works, and the known and unknown safety risks, and benefits.

How do genetic technologies change DNA?

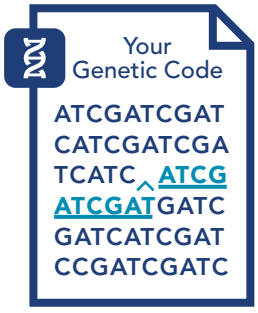
One key difference between genetic technologies is how the cellular DNA is altered.

If you think of your DNA like a book, where every sentence is a gene, all three technologies result in the addition of a complete sentence that can be read and understood.



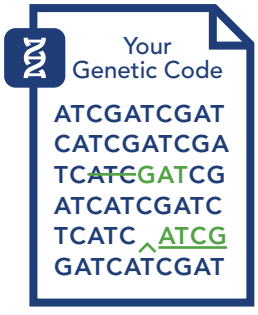
AAV Gene Therapy

is like adding a sticky note containing a new sentence on the outside of the book.



Lentiviral Gene Therapy

is like randomly inserting a new sentence anywhere into the book, even into the middle of an existing sentence.



Gene Editing

is like correcting small grammatical errors in a sentence or inserting a new, grammatically correct clause into the middle of an existing sentence.

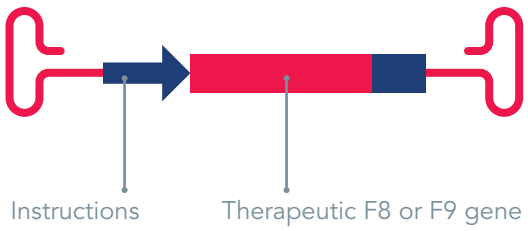
How do genetic technologies work?

Why do genetic technologies use viruses?

Most genetic technologies use viral vectors to deliver the therapeutic gene to the targeted cell. Viruses are naturally good at entering cells, which makes them an effective container for delivering the therapeutic gene. Viral vectors are made up of the outer shell of the virus and have been modified so that all of the disease-causing material is removed.

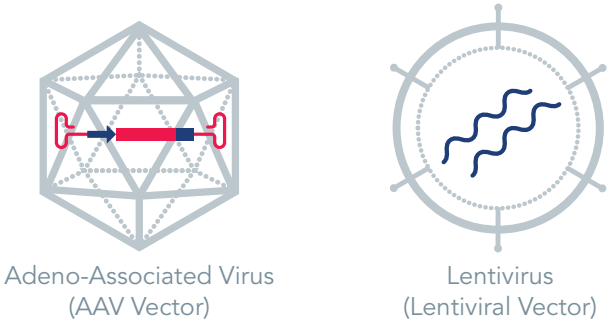
Therapeutic Transgene

The therapeutic gene is often called the "transgene". The therapeutic transgene also contains instructions for where in the body the functional clotting factor proteins should be made.



Viral Vectors

The most commonly used viral vectors are adeno-associated virus (AAV) and lentivirus. Both vector types work to deliver the transgene to your cells, but they may target different cell types and result in different changes to your cellular DNA.



You can think of vectors like shipping boxes
that deliver the therapeutic clotting factor gene to its final destination.

What is AAV gene therapy?

AAV gene therapy is a treatment for hemophilia A or B, that delivers a therapeutic copy of the F8 or F9 gene to the liver, which allows liver cells to produce functional F8 or F9 proteins that are released into the blood stream.

Four AAV gene therapy products have been approved and three are an available treatment in some countries.

Hemophilia A

TREATMENT	SPONSOR
Roctavian® (valoctocogene roxaparvovec-rvox)	**BioMarin**

First approved in 2022

For the treatment of adults with severe hemophilia A without a history of F8 inhibitors and without detectable AAV5 antibodies.

Available in the United States, Germany, and Italy.

Hemophilia B

TREATMENT	SPONSOR
Hemgenix® (etranacogene dezaparvovec-drlb)	**CSL Behring**

First approved in 2022

For the treatment of adults with severe and moderately severe hemophilia B.

Available in the United States, European Union, United Kingdom, Canada, Switzerland, and Australia

TREATMENT	SPONSORS
BBM-H901 (dalnacogene ponparvovec)	**Belief BioMed and Takeda China**

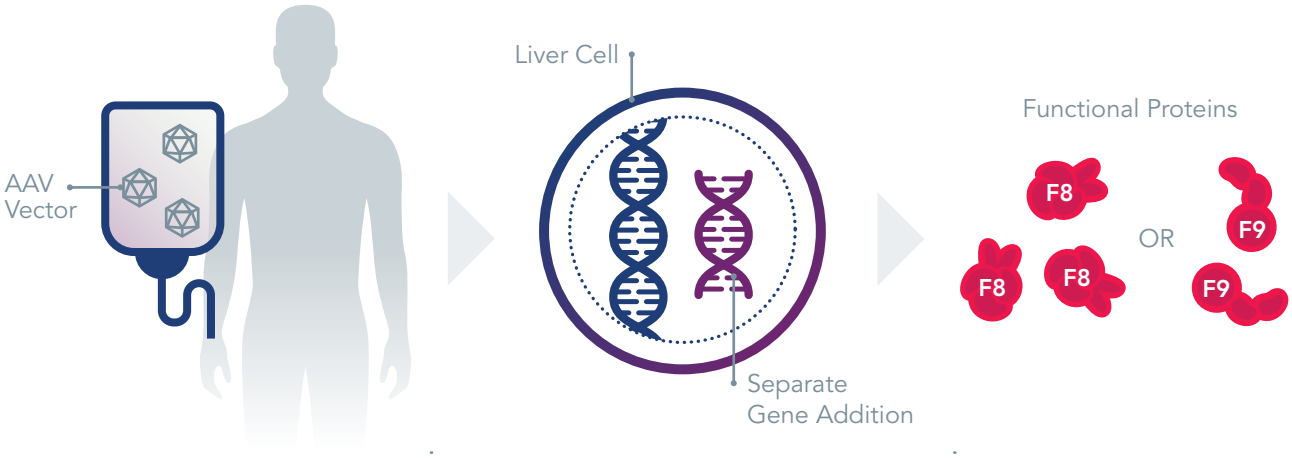
Approved in 2025

For the treatment of adults with moderate to severe hemophilia B.

Available in China.

Disclaimer: Deciding to take AAV gene therapy is potentially long and complex process that should start with a shared-decision making conversation with your health care provider. There are multiple eligibility tests, and rigorous long-term follow-up requirements for up to 15 years.

How does AAV gene therapy work?



AAV gene therapy is administered through a single, one-time infusion.

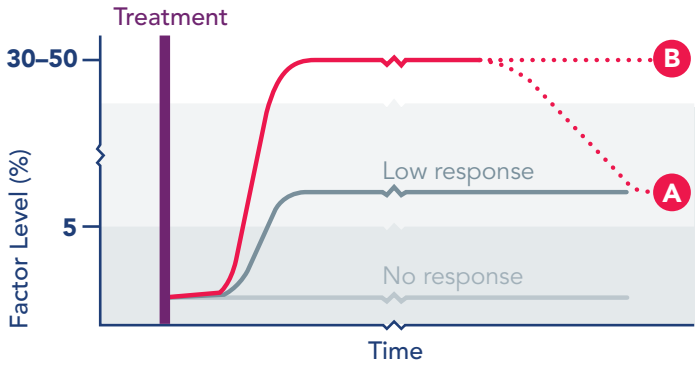
Once inside the body, the AAV vector delivers the therapeutic F8 or F9 gene to the liver.

Now the body can produce its own functional proteins.

AAV gene therapy is like adding a sticky note containing a new sentence outside of the book, meaning the newly added gene remains separate from your cellular DNA.

What will happen to my clotting factor levels?

There is no way to predict how an individual's factor levels will respond to AAV gene therapy or how long the effects will last. AAV gene therapy cannot be re-dosed and cannot be used in children.



In most people with :

– **Hemophilia A** factor levels increase to a mild to normal range, but may decrease with time or may stabilize after an initial decrease.

– **Hemophilia B** factor levels increase to a mild to normal range and are usually sustained long-term.

Some people have a low response, or do not respond to gene therapy.

For more information on AAV gene therapy, please see the WFH **SDM Tool** and the **eLearning Platform**.

What is lentiviral gene therapy?

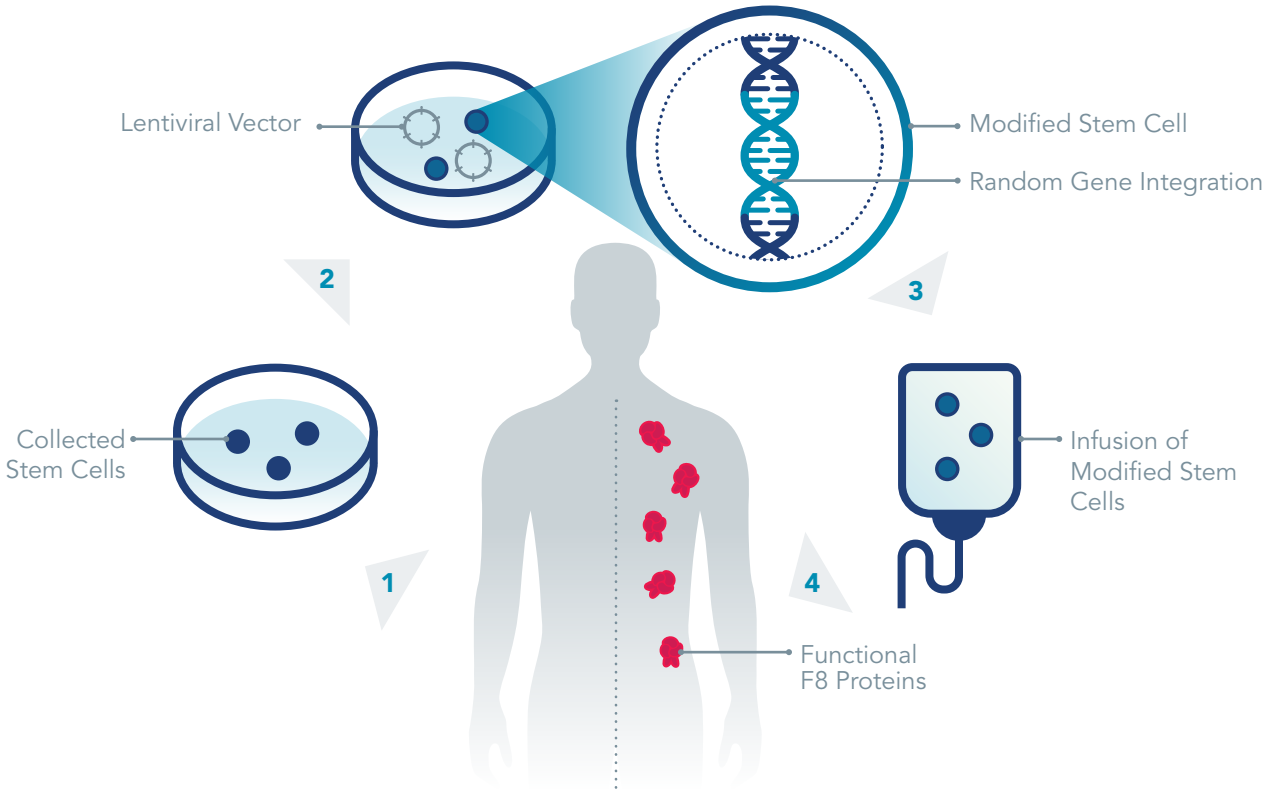
Lentiviral gene therapy is being studied as a potential treatment for hemophilia A that introduces a functional copy of the F8 gene to the person's own blood stem cells. All future blood cells produced by these stem cells will contain a functional copy of the clotting factor gene, enabling the person's body to produce its own clotting factor protein.

Lentiviral gene therapy is still in clinical trials and therefore, there are many unanswered questions, particularly around safety and long-term durability. Lentiviral gene therapy has been approved in two other rare blood diseases, sickle cell disease and β-thalassemia.

There are two lentiviral therapies under investigation for Hemophilia A.

TREATMENT	SPONSOR
CD68-ET3-LV **Under clinical investigation (NCT05265767)**	**Christian Medical College, Vellore, India**
TREATMENT	**SPONSOR**
Pleightlet (MUT6) **Under clinical investigation (NCT03818763)**	**Medical College of Wisconsin**

How does lentiviral gene therapy work?



1. Lentiviral gene therapy is administered through **autologous "self" cell transfer** in which a person's own blood stem cells are collected and modified outside of the body.
2. These stem cells are modified outside of the body with a lentivirus carrying the therapeutic F8 gene.
3. The modified stem cells are then infused back into the body, and the therapeutic F8 gene is passed on to all future blood cells.
4. With the therapeutic gene inserted, the body can produce its own functional F8 proteins.

Lentiviral gene therapy is like randomly inserting a new sentence anywhere into the book, even into the middle of an existing sentence.

This means the therapeutic F8 gene will be passed onto all future blood cells, resulting in sustained treatment effects.

However, random incorporation into the DNA may have unknown safety risks.

What is gene editing?

Gene editing uses specialized machinery, known as CRISPR, to precisely alter specific sections of DNA in specific cell types. Gene editing can correct small genetic errors or it can insert genes into specific safe locations. In hemophilia, all current technologies in development use safe locations to incorporate a therapeutic copy of the F8 or F9 gene into the cellular DNA.

Gene editing is still in clinical trials and therefore, there are many unanswered questions.

There are three gene editing therapies under investigation in hemophilia.

Hemophilia A

TREATMENT	SPONSOR
MGX-001	**Metagenomi**
Under preclinical investigation	

Hemophilia B

TREATMENT	SPONSOR
REGV131-LPN1265	**Regeneron**
Under clinical investigation (NCT06379789)	

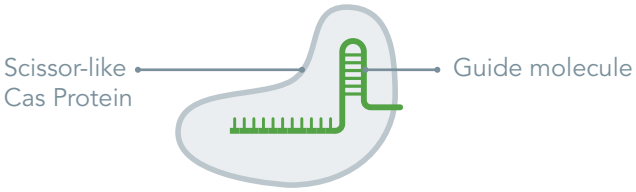
TREATMENT	SPONSOR
BE-101	**Be Biopharma**
Under clinical investigation (NCT06611436)	

How does gene editing work?

Step 1: Delivery of the therapeutic gene and the gene editing machinery

Gene Editing Machinery

The gene editing machinery consists of a scissor-like cas protein and a guide molecule.

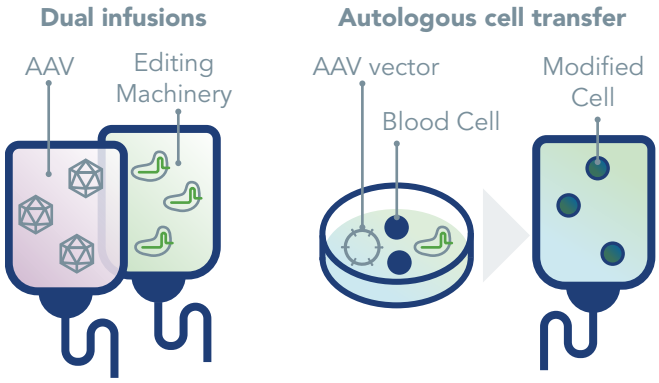


Two methods of delivery

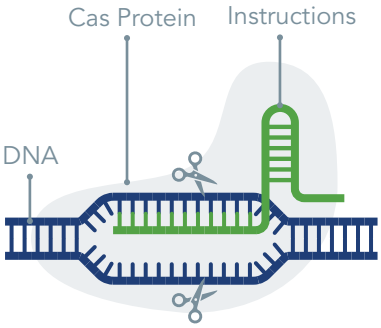
Gene editing technologies can use multiple delivery methods for Step 1, depending on the product type.

Dual infusions: like AAV gene therapy, treatment delivery occur inside the body.

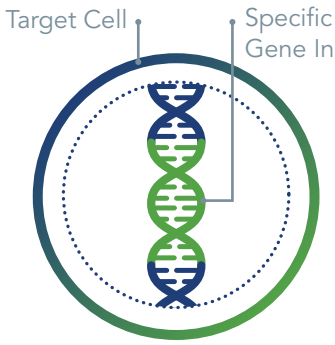
Autologous "self" cell transfer: like lentiviral gene therapy, treatment delivery occur outside of the body after collecting the blood cells.



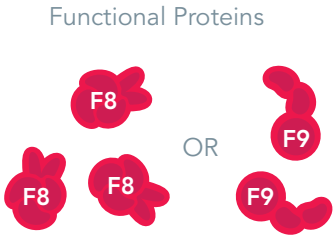
Step 2: Targeted incorporation of the therapeutic F8 or F9 gene



The guide molecule directs the Cas protein to the precise DNA spot where it makes the cut.



The therapeutic F8 or F9 gene is inserted into a precise, safe location in the DNA.



With the therapeutic gene inserted, the body can produce its own functional proteins.

Gene Editing is like adding a grammatically correct clause into the middle of an existing sentence.

Summary of Genetic Technologies for Hemophilia

	AAV Gene Therapy	Lentiviral Gene Therapy	Gene Editing
What stage of clinical development is it in?	1 treatment approved and available for Hem A 3 treatments approved and 2 available for Hem B	2 products in phase 1 for Hem A	1 technology has completed preclinical studies for Hem A 2 products in phase 1/2 clinical trials for Hem B
How is it administered?	**Inside of the body**: single intravenous infusion	**Outside of the body**: stem cell collection, cell modification, and autologous cell transfer.	**Inside of the body**: dual infusion. **Outside of the body**: cell collection, cell modification, and autologous cell transfer.
Can it be used more than once?	All genetic technologies are currently one-time treatments because most of the time the viral vectors can only be introduced to the body once because of the triggered immune response. If treatment is not successful, patients can safely return to their previous treatment routine or consider other non-genetic treatment options.		
	One time treatment	Potential for repeat treatments	Technologies that use AAV inside of the body are one-time treatments. Technologies administered outside of the body have the potential for repeat treatments.
How does it change my DNA?	Most transgenes exist separate from your DNA. However, there can be low levels of DNA integration, typically less than 1%.	All transgenes are randomly inserted into the DNA.	Precisely targets gene insertion into specific sections of DNA.
Are there any liver safety concerns?	Yes, approximately 80% of people with hemophilia A and approximately 20% of people with hemophilia B experience liver enzyme elevations.	Unknown and unlikely	Technologies that use AAV targeted to the liver are likely to cause liver elevations.
How durable are the effects?	For hemophilia A, the increase in factor level shows variable levels of durability. For hemophilia B, the increase in factor levels appears to be long-term.	Durability will depend on the types of cells that are targeted. Durability is currently unknown for these genetic technologies, but they have the potential for long-term durability.	
Can it be used in children?	Gene therapy is not currently approved for use in children with hemophilia.	It is unlikely that lentiviral gene therapy will be available for use in children with hemophilia.	It is possible that gene editing will be available for use in children with hemophilia.
Are the effects heritable?	No. All genetic technologies target non-reproductive cells – therefore, the effects cannot be passed down to children.		
Is the treatment reversible?	No. Once the therapeutic gene has been delivered, the process cannot be stopped or undone.		

References

1. Hermans C, Valentino LA, Thornburg CD, et al. A novel gene editing lexicon strategy for the haemophilia community: Research plan for development and preliminary results. Haemophilia. 2024.
2. Kessler CM, Valentino LA, Thornburg CD, et al. Development of a novel gene editing lexicon for hemophilia: methodology and results. Res Pr Thromb Haemost. 2025.
3. McKeown W, Hermans C, Unzu C, et al. Operationalising a Haemophilia Gene Editing Lexicon for Practical Use. Haemophilia. 2025.

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