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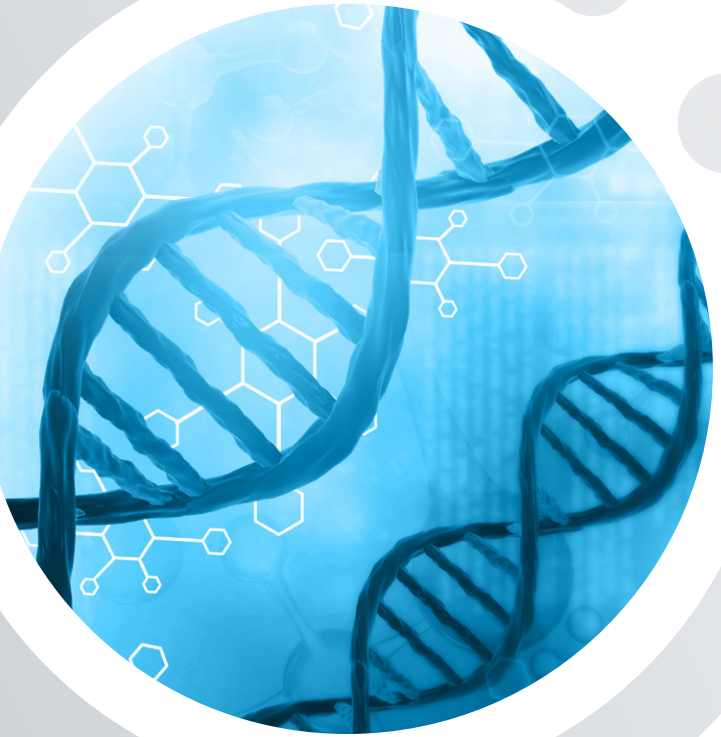

What is **gene therapy?**

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Genes – "The Building Blocks of Life"

Like every other organism on the planet, humans are made up of **cells,** all with their own specialized role. Within each cell are our **genes**, which are the fundamental building blocks of life. Humans inherit one gene from each parent in the form of a **chromosome**. Each chromosome is made up of an organic chemical called deoxyribonucleic acid (**DNA**) and are found in the nucleus of each cell i.e., the cell's "control centre".

Genes are sections of DNA that contain instructions to produce specific molecules in the body, usually a **protein**. These proteins control how our body grows and works. They are also responsible for many of our characteristics, such as eye color, blood type, height etc.

Changes in DNA happen often (known as a **genetic variant**), and they do not always cause a problem. But there are times when the change can result in a protein that does not work, or too much of a protein, or not enough of one, which impacts the body's ability to function properly. Many rare disorders are caused by changes in a gene or genes that change proteins in a way that makes them malfunction. These variants can be inherited from a parent's genes or they can be de novo, meaning the change is new to a person.

Gene therapy as a potential treatment option for hemophilia

People with hemophilia (PWH) cannot clot blood properly because they are deficient, or lacking, in specific **clotting factors** – proteins that circulate in the blood that form clots to prevent excessive bleeding. This is due to a genetic variant in the DNA that typically occurs on either the FVIII (hemophilia A) or FIX (hemophilia B) gene, which prevents their body from making the relevant clotting factor.

The current standard of care for all PWH is regular therapy (**prophylaxis**) with clotting factor replacement therapy or non-factor replacement therapy to prevent bleeding. However, not all prophylaxis regimens achieve zero bleeding for all people with hemophilia, and unmet needs around treatment burden persist.

Gene therapy is a promising technique that uses genetic material, rather than traditional drug development or surgery, to treat rare, genetic disorders, including hemophilia. The most common form of gene therapy involves introducing a working copy of a faulty gene to a target cell to restore normal protein function. Single-gene (monogenic) disorders like hemophilia, whose natural history is well understood, make them ideally suited to gene therapy.

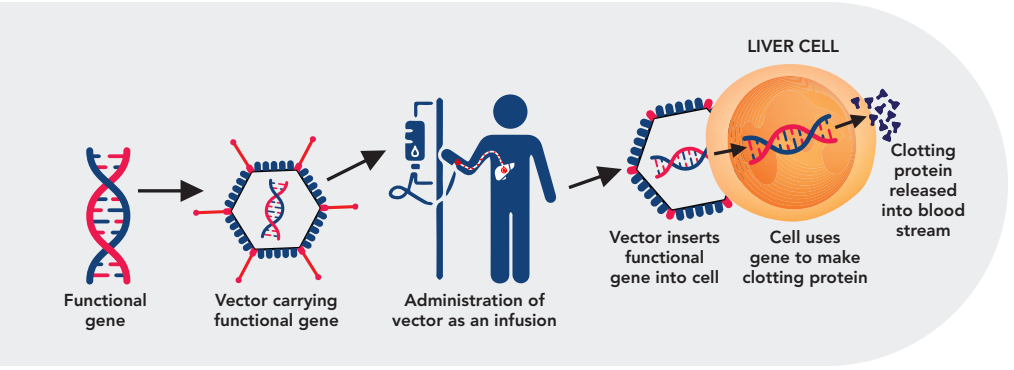
The ultimate goal of gene therapy is to provide sustained protection from bleeding over a much longer duration of time than any other prophylaxis regimen, through a one-time infusion, thereby reducing or removing the need for regular treatment. Gene therapy also offers the prospect for some PWH to achieve better health outcomes and improved quality of life than that attainable with currently available treatments.

How does gene therapy work?

Scientists have "borrowed" a process from nature to deliver a working, or functional, copy of the gene of choice to cells in the body. These are called **viral delivery systems**, which use the natural ability of certain viruses – evolved over billions of years – to infect cells with the new genetic material. The viruses are carefully selected and engineered in a way that avoids causing illness.

For gene therapy in hemophilia, **adeno-associated viruses (AAV)** are currently among the most frequently used viral delivery systems. A modified virus (called a **vector**) is used as a 'vehicle' to carry the functional *F8* or *F9* gene (called a **transgene**) to liver cells (called **hepatocytes**) via a one-time intravenous infusion. The liver plays a key role in blood coagulation as it is where the majority of clotting factors are produced (synthesized), therefore the hepatocytes are the target cells.

Once the transgene is inside the liver cells, two key steps in gene expression known as **transcription** and **translation** occur. These are the processes that cells go through to read the DNA instructions of a gene (transcription) and to produce the protein (translation). The cells will use the new transgene to produce functional clotting FVIII or FIX proteins and release them into the bloodstream.



First-generation gene therapies for hemophilia using AAV do not change a person's existing DNA sequence within the nucleus of the cell. Therefore, whilst PWH who receive gene therapy may no longer experience bleeding symptoms, they can still 'pass on' the faulty gene that causes hemophilia to their children.

Who is eligible to receive gene therapy?

IN CLINICAL TRIALS

Several gene therapy products for hemophilia are currently available as part of a clinical trial. There are several trials ongoing with different AAV-based vectors. Although each trial has its own criteria, in general, eligible participants are:

- Males aged over 18 years old;
- Diagnosed with **moderately severe** (below 2% of normal clotting factor levels) or **severe** (below 1%) hemophilia A or B who are otherwise healthy.

Currently, gene therapy clinical trials do not include females living with hemophilia or participants under 18 years of age. To learn more about gene therapy clinical trials for hemophilia, PWH should discuss participation with their Hemophilia Treatment Centre (HTC).

ONCE APPROVED AS A TREATMENT

Gene therapy treatments for hemophilia A or B have to be approved by a regulatory agency, such as the Food and Drug Administration (FDA) in the United States or European Medicines Agency (EMA) in the European Union. Regulatory agencies evaluate and authorize innovative drugs for use in particular countries/markets. The first gene therapy treatment for hemophilia A was approved by the EMA in August 2022. Regulatory agencies will determine the eligibility criteria for PWH to receive gene therapy as a treatment option, which are expected to be similar to those criteria adopted in clinical trials.

Research and clinical trials continue in the gene therapy field with the ambition of making these treatments available to more people, including children, people with a mild or moderate diagnosis, and those with a history of, or living with, an inhibitor.

Choosing to receive gene therapy

The decision to receive gene therapy can be life-changing and should be considered carefully. First-generation AAV-based gene therapy for hemophilia is an irreversible treatment. There are uncertainties surrounding the long-term safety and efficacy of gene therapies, simply because gene therapies have only been administered within the past 5 years.

As we accumulate data on patients who have received gene therapy, our understanding of the long-term safety and efficacy profile will improve. Therefore, gene therapy has potential ramifications for PWH and their family, now and in the future.

The WFH strongly encourages PWH to discuss the benefits and risks of gene therapy with their treating physician and multidisciplinary care team. The goal is to come to an evidence-informed decision that aligns with the patient's individual preferences, beliefs, and values. Some of the topics that should be discussed as part of the informed decision-making process are:

- Expected effectiveness of gene therapy (i.e., bleed protection)
- Expected durability of gene therapy (i.e., how long transgene expression will last)
- Probability that gene therapy does not work (i.e., loss of transgene expression)
- Possible short- and long-term safety risks (i.e., liver inflammation, developing liver cancer)
- Details about the infusion procedure (i.e., expectations and requirements)
- Short- and long-term monitoring requirements with your HTC (i.e., number of visits, body fluid samples, liver biopsy, period of observation)

PWH should ensure that all their questions and concerns are addressed before making a decision. Please refer to "**Questions to Ask Your Doctor Before Deciding to Take Gene Therapy**" [see page 11] to help PWH discuss gene therapy with their medical team.

What is the process of receiving gene therapy?

Once an evidence-informed decision has been made between PWH and their HTC to proceed with gene therapy, a number of tests will be performed to confirm eligibility. If participating in a clinical trial, specific documents related to the clinical trial will need to be reviewed and signed. If taking gene therapy as an approved treatment, providing informed consent may be required as well.

Gene therapy is given as a one-time intravenous infusion. It takes up to a few hours to administer, and unlike factor infusions, it must be performed by health care personnel at an HTC or another specialized medical facility. Gene therapy recipients will be monitored carefully for an immediate period following the infusion, then over a longer-term for any complications. Each country is likely to have its own clinical protocol (i.e., an agreed procedure) for follow-up after the infusion.

Long-term monitoring and follow-up after gene therapy

After receiving the gene therapy infusion, PWH will be required to keep in close contact with their HTC through regularly scheduled follow-up appointments to check their health status and safety events and determine how well the gene therapy is working. These visits will occur more often at first and then lessen over time, depending on the response to the gene therapy.

It is critically important that PWH who receive gene therapy attend their scheduled follow-up visits and actively participate in the long-term monitoring program. They will be asked to report all hemophilia-related health events, such as bleeding, factor levels, and adverse events. To help discover any unanticipated long-term health effects of the treatment, PWH will also be asked to report any major change in their health status throughout their lifetime.

All PWH who receive gene therapy will be invited by their healthcare team to participate in the WFH Gene Therapy Registry (GTR). The WFH GTR is a global initiative aimed at collecting long-term data on all PWH who receive gene therapy. This data will enhance our understanding of gene therapy and ensure the hemophilia community has access to timely evidence on the long-term safety and efficacy of the specific gene therapy product(s). The registry data will also be used to improve scientific and clinical research on gene therapy and the development of next-generation gene therapies for PWH in the future. Agreeing to participate in the registry does not change the standard of care a PWH will receive at their HTC.

What are the outcomes of gene therapy?

Like all new treatments, the safety and efficacy of gene therapy are tested in human clinical trials. Different types of gene therapies have been investigated for more than two decades in hemophilia. Clinical trials are assessing the safety and efficacy of gene therapy with follow-up ranging from a few years to greater than 10 years, depending on the specific trial.

However, many unresolved questions on the long-term **safety, variability, durability** and **efficacy** remain even at the completion of clinical trial programs. Gene therapy is a novel technology and some of the risks may be unpredictable. Researchers, healthcare institutions and public authorities that regulate the safety and efficacy of medical products are working to ensure that gene therapy is a safe and effective treatment option for patients. Currently, we cannot accurately predict the level of factor protein that will be expressed in a patient, if at all, from the new gene, or how long that factor expression level will last.

Summary

Gene therapy marks an important milestone in the development of treatment for PWH. It offers the potential to improve the health and quality of life through a one-time infusion. However, researchers and clinicians are still gathering data on the long-term safety and effectiveness of this novel treatment approach. Although a specific threshold for factor level expression has not been defined for gene therapy "success", even small increases can substantially improve a person's quality of life, including reducing bleeding episodes and having to treat prophylactically.

Deciding to receive gene therapy is an important treatment decision that may affect health outcomes for patients. Not everyone who might like to receive gene therapy will be eligible to receive it. PWH must be informed about the potential risks and benefits, have regular discussions with their health care team and involve family and loved ones that are important to them in the decision-making process. Continued comprehensive care and engagement with the bleeding disorders community remains important for PWH following gene therapy. Life-long follow-up is crucial to understand the real promise and impact of gene therapy on PWH and to ensure the optimal management of an individual's overall health.

Appendix

GLOSSARY OF TERMS

AAV	A harmless virus used to deliver the transgene to liver cells during gene therapy infusion. When the viral components of the virus are removed and the transgene inserted, it becomes known as a *vector*.
Cells	Tiny units or compartments that circulate in the body. The human body is made of trillions of cells. Each cell contains 23 pairs of chromosomes and the body's hereditary material (DNA).
Chromosome	A thread-like structure found within the nucleus of every cell in our body and made up of DNA. There are 46 chromosomes in each human cell that are inherited from each parent (arranged in 23 pairs).
Clotting factors	Proteins that circulate in the blood to enable a clot to form. Without clotting factor VIII (hemophilia A) or factor IX (hemophilia B), PWH are prone to spontaneous bleeding mainly within the tissues, muscles and joints.
Data	Information collected during medical visits or directly from individuals, including things such as the type of gene therapy or factor level.
DNA	Contains the genetic instructions for the creation and function of life. It is material that people inherit from their parents.
Durability	Relates to how long a gene therapy has a positive effect on a person's clotting factor level.
Efficacy	Describes the ability of a treatment to produce the desired results. For PWH and gene therapy, this relates to elevating clotting factor levels and reducing bleeding events.
Gene therapy	Treating a genetic disease by inserting a corrected copy of the disease-causing gene into a person.
Genes	Sections of DNA that contain instructions to produce specific molecules in the body, usually a protein.

Genetic variant	A change in the DNA instructions of a gene. When the change produces a disease, it may be called a pathogenic variant or a mutation.
Genome	The entire set of DNA instructions in a human body (6.4 billion letters).
Hepatocyte	A type of cell that makes up approximately 60% of total cells found in the liver. For PWH that receive AAV-based gene therapy, hepatocytes are the target cell and will produce new clotting factor once the transgene is inserted.
Prophylaxis	The regular and continued use of a treatment to prevent bleeding events in a PWH.
Protein	Proteins are what cells make and they control how our body grows and works. Proteins are also responsible for many of our characteristics, such as eye color, blood type, and height etc.
Transcription and translation	The processes that cells go through to read the DNA instructions of a gene and express the protein from the target cell.
Transgene	A functional copy of a gene placed inside the vector and inserted into the target cell.
Variability	How clotting factor expression changes in a person over time or between people after gene therapy.
Vector	Delivery vehicle of the functional gene (transgene) into the target cell during gene therapy.

Questions to Ask Your Doctor Before Deciding to Take Gene Therapy

AM I A GOOD CANDIDATE?

- ○ Am I eligible to receive gene therapy?
- ○ Can my child receive gene therapy?
- ○ Is there a difference between gene therapy for Hemophilia A and Hemophilia B?
- ○ Which gene therapy options are currently available to me in clinical trials?
- ○ Which gene therapy options are available to me as an approved treatment?
- ○ Which gene therapy treatment(s) or clinical trial(s) would you recommend for me?
- ○ Can you help me find more information to help me understand my options?
- ○ Can I talk with people who have received gene therapy for hemophilia?

WHAT ARE THE POTENTIAL BENEFITS AND RISKS OF GENE THERAPY?

- ○ How effective is gene therapy for hemophilia?
- ○ Will I still need to use factor after gene therapy?
- ○ What can I expect my factor level to be at after gene therapy?
- ○ How long will the effect on my factor levels last?
- ○ Is it possible that gene therapy will not work for me?
- ○ Can I remove the gene therapy from my body if I no longer want it?
- ○ If gene therapy does not work for me, can I try another gene therapy in the future?
- ○ How might my daily life change after gene therapy?
- ○ What are the potential short-term risks of gene therapy? How often do they occur?
- ○ What are the potential long-term risks of gene therapy? How often do they occur?
- ○ What steps will be taken to monitor my safety?
- ○ Am I at risk of getting an inhibitor after gene therapy?
- ○ Will taking gene therapy affect my ability to have children?
- ○ After receiving gene therapy, can my future children still have hemophilia or be hemophilia carriers?

PROCEDURE

- ○ What are the costs involved with gene therapy?
- ○ What testing do I need to go through before receiving gene therapy?
- ○ How is gene therapy administered?
- ○ Can you describe the steps of the procedure?
- ○ What is the recovery from a gene therapy infusion like?
- ○ What type of support will I need during my recovery?
- ○ How will my safety be monitored during and after treatment?
- ○ How will I know that the treatment is working?
- ○ How long does gene therapy take to work?
- ○ How do I register for the WFH Gene Therapy Registry?

My questions

(write down any questions you might have for your doctor)

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