Early 1970s
First plasma-derived FVIII and FIX products available[1]

1997
First recombinant FIX replacement product approved[2]

1999
First gene therapy trial in haemophilia[3]

From 2017
Late-stage trials for gene therapy in haemophilia underway[4]

haemevolution

WHAT DOES GENE THERAPY FOR HAEMOPHILIA MEAN FOR ME?

CSL Behring
Biotherapies for Life™

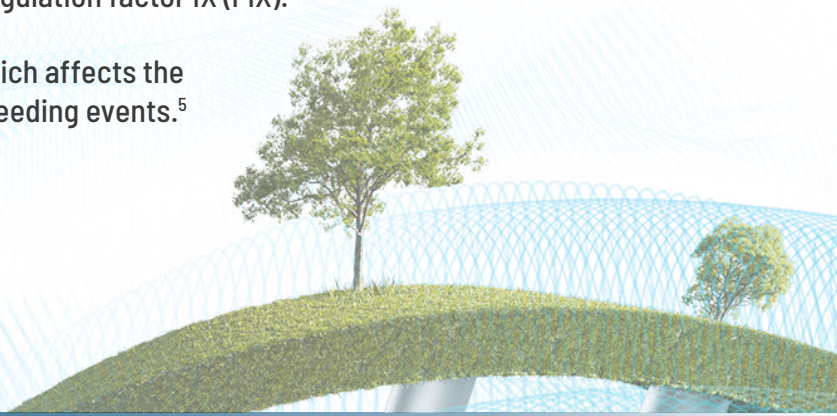
Contents

An introduction to haemophilia

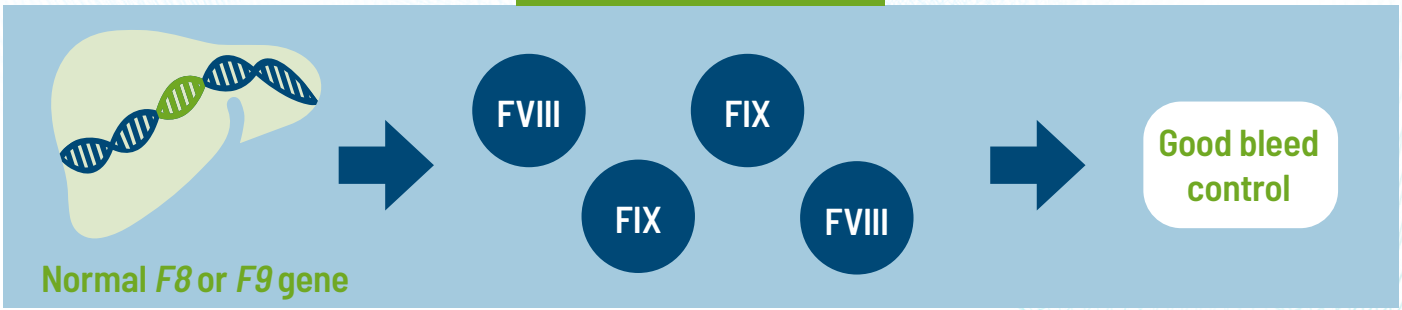
What is haemophilia?

Did you know?
Your liver is the natural producer of coagulation factors and, as long as it has the correct instructions, contains the machinery to produce them.[6]

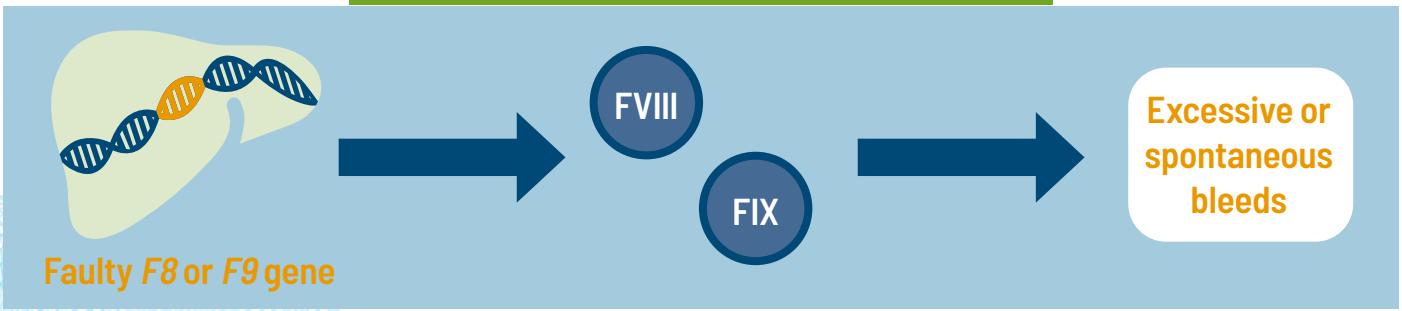
- Haemophilia is a rare, inherited bleeding disorder.[5]
- It is caused by a fault in a single gene.[5]
- There are two types of haemophilia:[5]
  - Haemophilia A refers to a deficiency of coagulation factor VIII (FVIII).
  - Haemophilia B refers to a deficiency of coagulation factor IX (FIX).
- Haemophilia causes low levels of FVIII or FIX, which affects the ability of the blood to clot and this can lead to bleeding events.[5]



Normal coagulation



Poor coagulation in people with haemophilia



What are the symptoms of haemophilia?

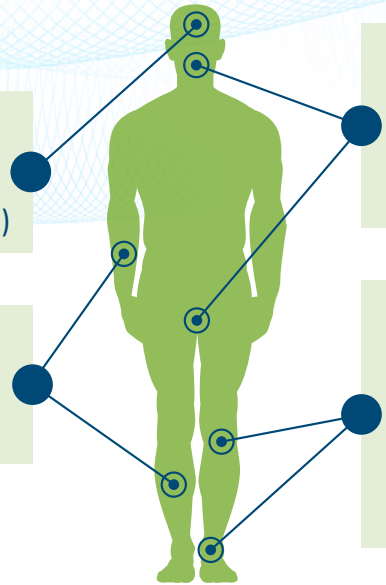
- The main symptom is excessive and sometimes spontaneous bleeds.[5]
- Joints and muscles are the most common locations for bleeds to occur.[5]
- Bleeding can cause chronic pain and joint damage over time.[5,7]

Central nervous system bleeds (<5 %)

- Least common but can be life-threatening (e. g., bleeding in the brain)

Muscle bleeds (10 – 20 %)

- May occur in muscles (e. g. in calf, forearm)



Other major bleeds (5 – 10 %)

- Serious bleeds that occur in other sites (e. g., mouth, nose, genitourinary tract)

Joint bleeds (70 – 80 %)

- Occur most commonly in ankles, knees and elbows
- Negatively impacts quality of life and may lead to disability

How severe are the symptoms of haemophilia?

- The severity of symptoms depends on the level of coagulation factor in the blood.[5]
  - The less coagulation factor there is, the higher the risk of a bleed.[5]

Mild

Coagulation factor level 5 – < 40 % of normal

- Spontaneous bleeding is rare
- Prolonged bleeding with major surgery or trauma

Moderate

Coagulation factor level 1 – < 5 % of normal

- Occasional spontaneous bleeding
- Prolonged bleeding with minor surgery or trauma

Severe

Coagulation factor level < 1 % of normal

- Spontaneous bleeding into joints and muscles

Scientific advances in haemophilia

The aim of any haemophilia treatment is to increase your coagulation ability, to protect you from bleeds.[5]

How are people with haemophilia currently treated?

- Treatment can be given:
  - **"On-demand"** (as and when a bleed occurs)[5]
  - **"Prophylactically"** (on a scheduled regimen e. g., once a week to prevent bleeds)[5]
- Most people with haemophilia are successfully managed with prophylaxis[5]
- Prophylaxis can be adapted to suit your needs, based on your age, weight, joint status, how many bleeds you experience and your lifestyle[5,8,9]

Benefits of regular prophylaxis treatment compared to on-demand treatment are:[10]

- **Bleeding**
- **Joint damage**
- **Disability**
- **Need for orthopaedic surgery**

- **Quality of life**

What are the current unmet needs for people with haemophilia?

While there have been advances in the treatment of haemophilia, there is still a desire for new treatment options which meet the remaining unmet needs of people with the disease.

Even with routine prophylaxis treatment, you may still experience bleeds; this can lead to pain, joint damage, and reduced quality of life.[5,11–13]
Having higher and more consistent FVIII or FIX levels would provide better protection.[5,11]

Regular prophylaxis treatment requires lifelong dedication to receiving a high number of infusions and potential side effects.[14–17]

You, your family and friends may deal with multiple challenges related to the symptoms of haemophilia and the need for repeated infusions. This may affect your ability to regularly attend school or work, to do physical activity or impact your lifestyle and relationships.[12,13,18–20]

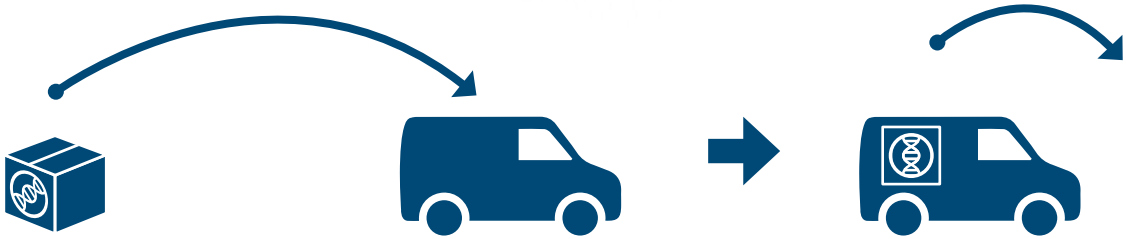
A brief introduction to gene therapy

What is gene therapy?

- Genes contain the genetic instructions to produce proteins which help to build, regulate and maintain your body.[21]
- Genes are inherited – you inherit two copies of each gene, one from each parent.[21]
- Sometimes changes or mutations in genes can happen, many of these mutations are harmless, others can result in genetic conditions such as haemophilia.[21]
- Gene therapy is an innovative approach to treat a genetic condition by introducing a new, working gene into the body, or by turning off or changing the faulty gene that is causing the condition.[21]

- Before the working gene can be delivered to the patient, a method of transporting it is needed.
- Working genes are packaged into modified viruses called “vectors” which protect the gene during the delivery; vectors are non-infectious and do not pose a danger to patients.[25]

Did you know?
Gene therapy has been studied for more than 50 years.[22]
Some gene therapies are already available for people with rare diseases, including retinal dystrophy and spinal muscular atrophy.[23,24]



The working gene
Containing the genetic instructions

The delivery vehicle
The vector

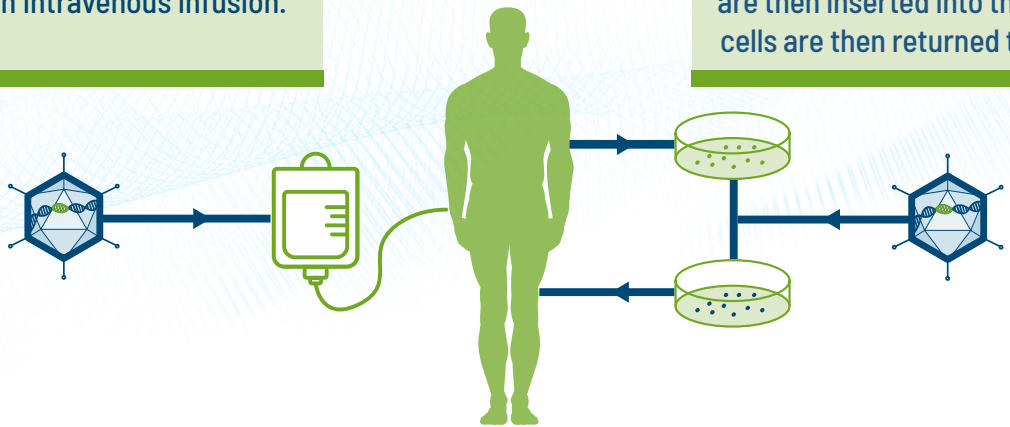
The delivery
The working gene is packaged in the vector, which protects and then delivers the working gene to its destination

Exploring the different ways gene therapy can be administered

- Currently, gene therapy can only be administered as a one-time treatment.[25]
- The working genes are usually delivered to specific target cells in the body by inserting them into a vector.[25]
- Gene therapy is delivered to patients in one of two ways: *in vivo* gene transfer or *ex vivo* gene transfer.[25]

In vivo
The vector containing the working gene is directly delivered into the body using an intravenous infusion.

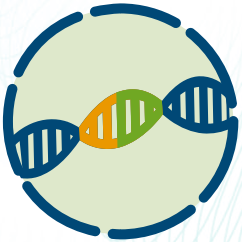
Ex vivo
Cells are taken from the patient. The vectors containing the working gene are then inserted into these cells. The cells are then returned to the patient.



- Once inside the target cell, there are different approaches for gene therapy: gene addition or gene editing.[25]

Target cell containing a non-working gene

Gene addition
Works by adding the working gene into the target cell, alongside the existing non-working gene.



Gene editing
Works by inserting, deleting or modifying the existing gene to work correctly.

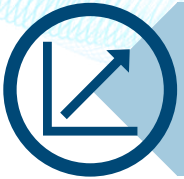
Can I transmit the effect of gene therapy to my children?
No. Gene therapy is designed to correct only the missing or faulty gene of the person who receives it. The effect is not transmissible to your children.

Gene therapy for haemophilia

What makes gene therapy a potential treatment for haemophilia?

Haemophilia is an inherited bleeding disorder that is caused by a fault in a single gene.[6]

Gene therapy can provide a working copy of this gene to you.



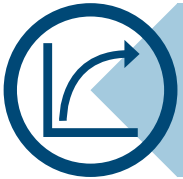
A small increase in coagulation factor levels can reduce the number of bleeds you may experience.[6]

How effective gene therapy is as a treatment can be easily assessed by measuring the level of coagulation factor in your blood.[26]

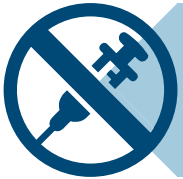
What are the goals of gene therapy?

After a one-time infusion of gene therapy, the goals for treatment are to:

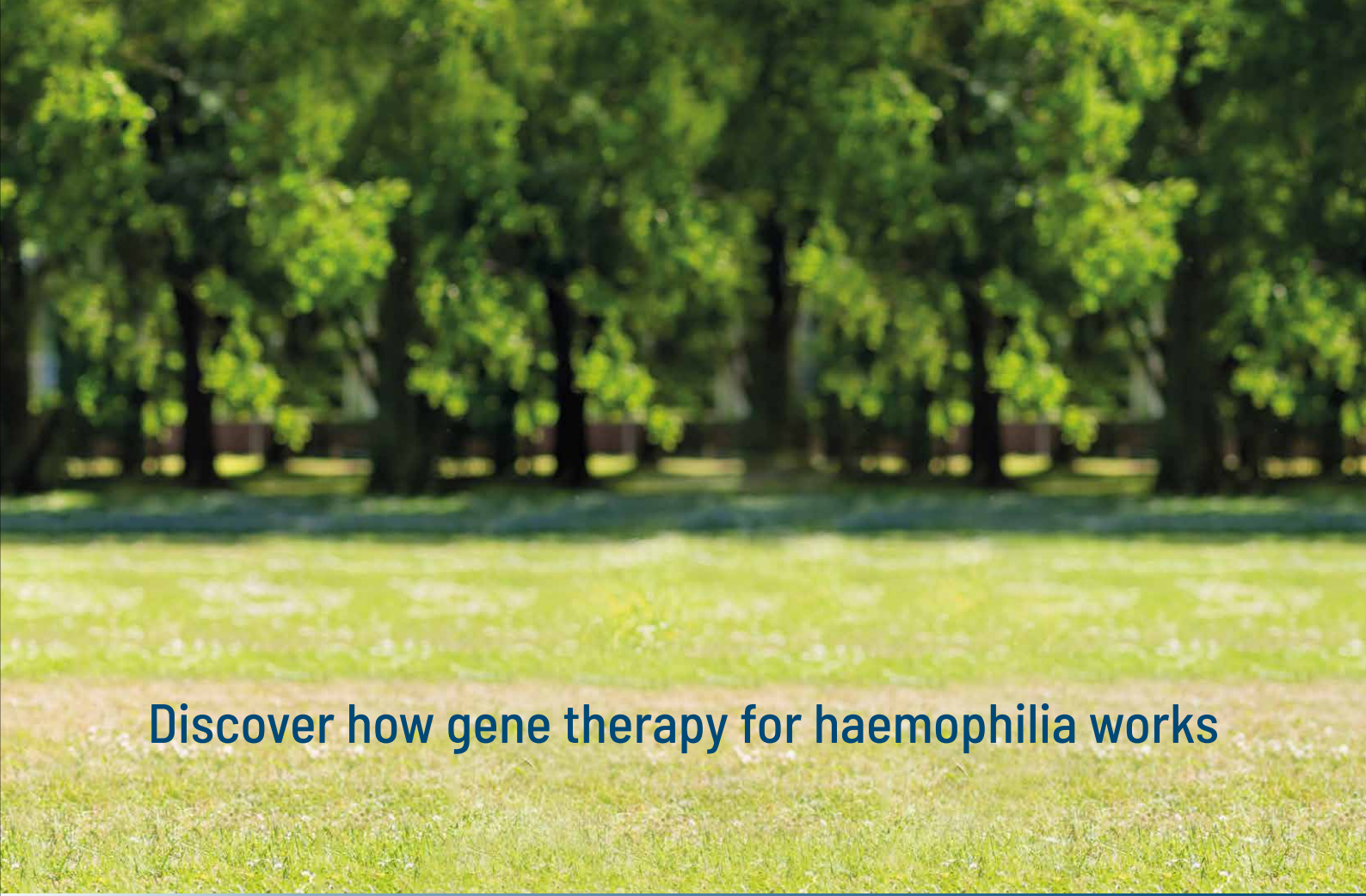
Enable your liver to create its own coagulation factor for a long period of time.[27]



Provide coagulation factor levels which remain stable over a certain period of time, without the "peaks" and "troughs" in levels which occur with regular prophylaxis or on-demand treatment.[27]



Reduce, or even eliminate, spontaneous bleeding and the need for lifelong regular infusions of coagulation factor replacement products.[28]



Discover how gene therapy for haemophilia works

Did you know?

There are many different types of vectors for gene therapy.[27]

In gene therapy for haemophilia, adeno-associated virus (AAV) vectors are used.[30]

AAV vectors are used over other types of vectors because they do not cause any infectious diseases in humans, and they also do not integrate genetic material into one`s own DNA.[30]

Want to know how gene therapy for haemophilia works?[31]

The working coagulation factor gene is packaged within the vector, which acts as a delivery vehicle.[29]

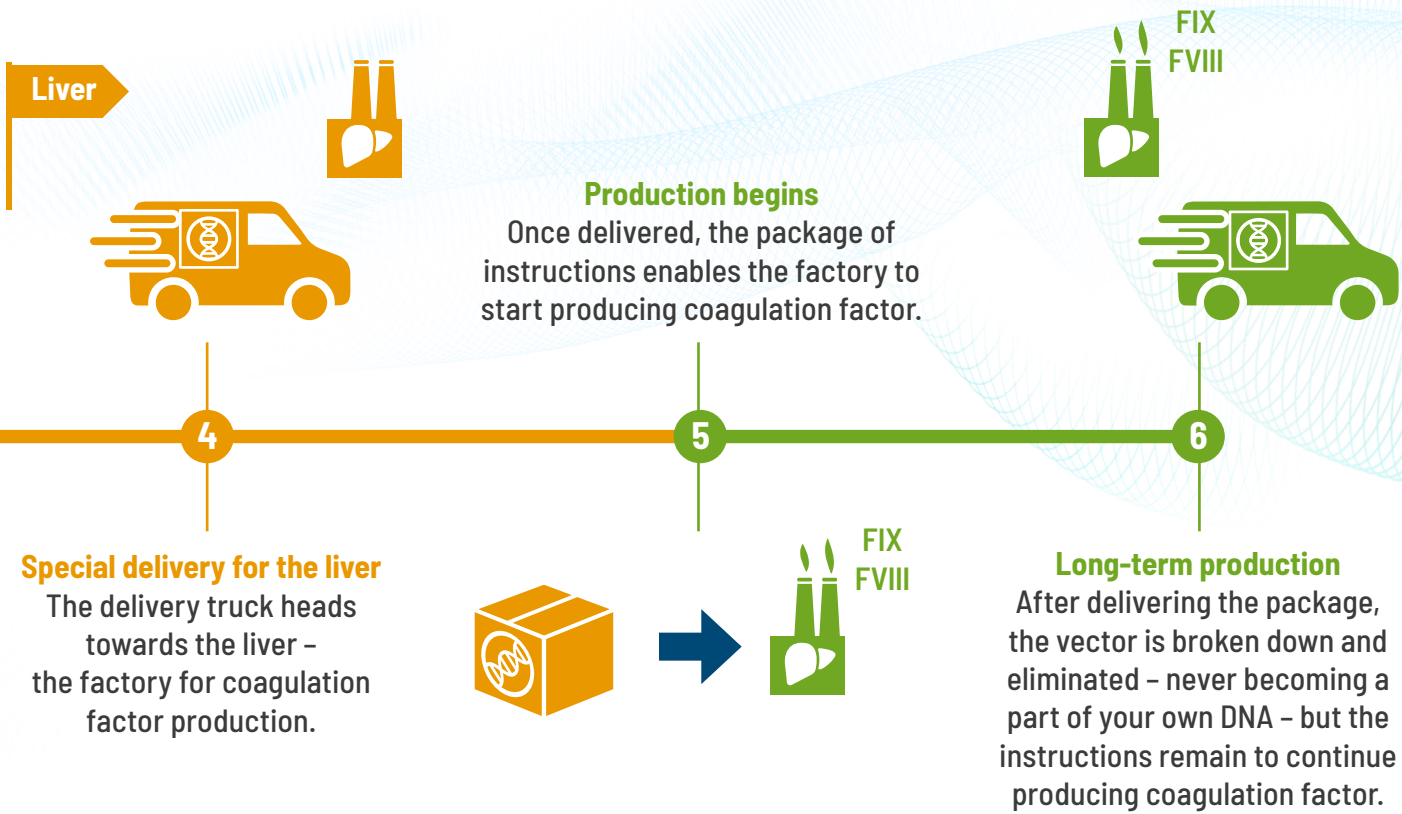
The working gene
It starts by developing a package of genetic instructions – the working coagulation factor gene.

Loading the package
The package of genetic instructions, the working gene, is loaded into a vector, which acts as a delivery truck.

1 2 3

The delivery vehicle
Then the delivery vehicle, the vector, is created, which will eventually enter targeted liver cells.

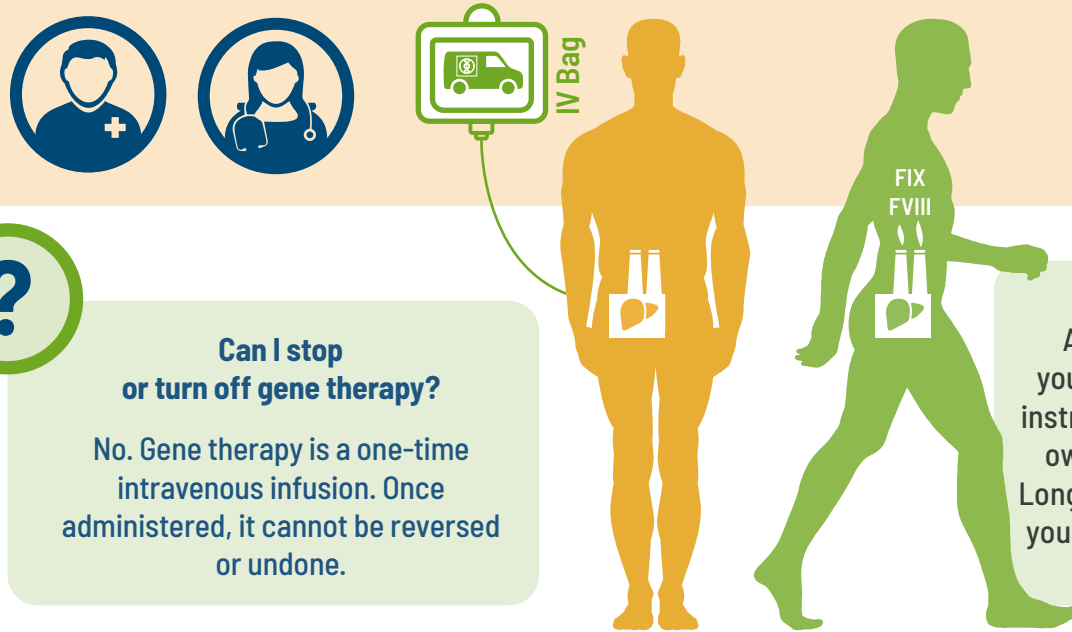
Pharmaceutical production facility


Liver
FIX
FVIII
Production begins
Once delivered, the package of instructions enables the factory to start producing coagulation factor.
4
5
6
Special delivery for the liver
The delivery truck heads towards the liver – the factory for coagulation factor production.
FIX
FVIII
Long-term production
After delivering the package, the vector is broken down and eliminated – never becoming a part of your own DNA – but the instructions remain to continue producing coagulation factor.
Haemophilia Treatment Centre
Home

What can I expect during gene therapy administration?

Hospital/Haemophilia Treatment Centre

Gene therapy is administered *in-vivo* as a one-time intravenous infusion[27], during which you will be closely monitored by your medical doctors and nurses.[27]



Can I stop or turn off gene therapy?

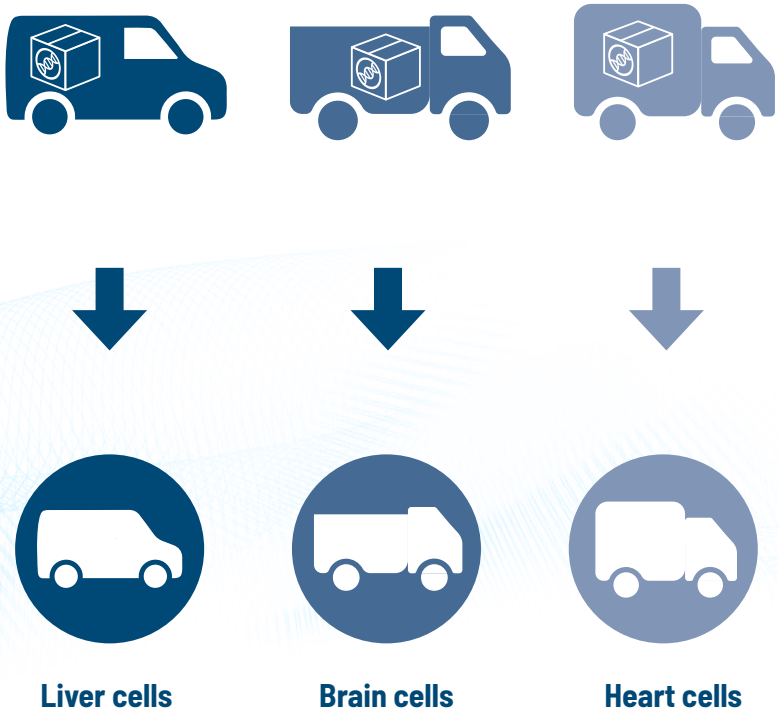
No. Gene therapy is a one-time intravenous infusion. Once administered, it cannot be reversed or undone.

Home

After the infusion, your liver will have the instructions to create its own clotting factor.[27] Long-term follow up with your medical doctor will be required.

How can vectors only target specific cells?

- Vectors have specific elements on their surface which only recognise the matched elements on specific target cells.[30]
- If the elements on a cell do not match those on the vector, the delivery cannot take place.[30]
- The vectors used in gene therapy for haemophilia only target the liver cells.[30]



What is the status of gene therapy for haemophilia?

- Several clinical trials are currently being conducted to investigate the use of adeno-associated virus (AAV) gene therapy in people with haemophilia.[32-36]
- Results have shown:

A strong reduction in the number of bleeding events.[32-37]

Durable coagulation factor levels.[32-37]

A strong reduction in the need for regular infusions of coagulation factor replacement products.[32-37]

A favourable safety profile, with few unexpected adverse events.[32-37]

How durable will my coagulation factor levels be if I receive gene therapy?

This is currently an open question. In clinical trials, there is evidence that coagulation FIX levels remain constant up to 8 years after receiving gene therapy[28].

However, people with haemophilia A have shown a decline in coagulation FVIII levels over the first 4 years after receiving gene therapy.[28]

What coagulation factor levels can I expect if I receive gene therapy?

Currently, it is difficult to predict individual coagulation factor levels after gene therapy. In clinical trials, there is a clear increase in coagulation factor levels, however, there is also significant variability in these levels among individuals.[34,36,37]

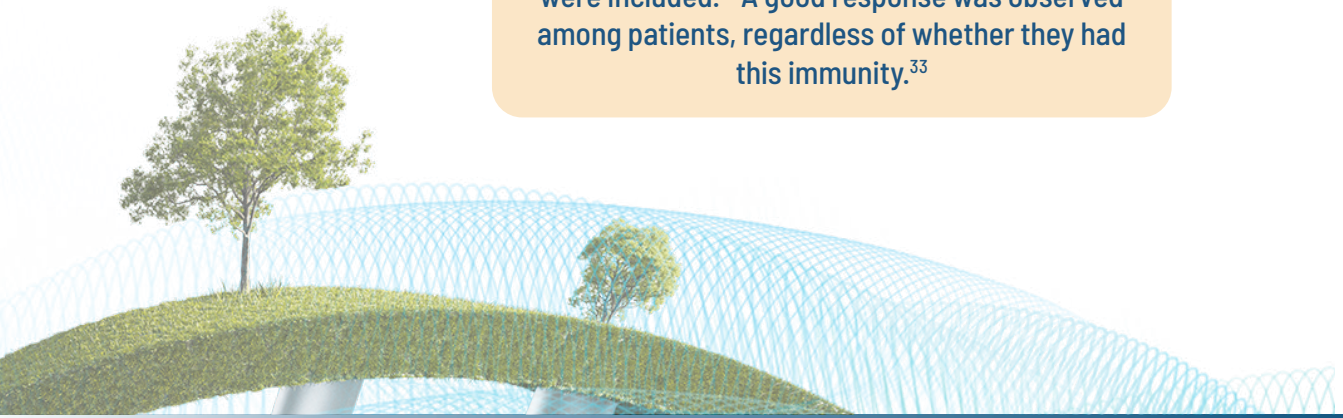
What are the remaining challenges of gene therapy for haemophilia?

Not everyone with haemophilia is eligible to receive gene therapy.[26]

- Some people may have natural "immunity" (i. e., antibodies) against adeno-associated virus (AAV) vectors used for gene therapy – this may stop the genetic information being delivered effectively.
- The potential use of gene therapy in children with haemophilia is still unknown. Currently, all clinical trials have included adult patients with haemophilia.[27]
- The use of gene therapy in patients with inhibitors to coagulation FVIII or coagulation FIX is also unknown. Patients with current or a previous history of inhibitors are also excluded from participating in clinical trials.[24]

Did you know?

Most eligibility criteria for clinical trials exclude people with natural immunity against AAV vectors used in gene therapy.[30]
However, in one clinical trial, patients with and without pre-existing immunity to AAV vectors were included.[33] A good response was observed among patients, regardless of whether they had this immunity.[33]



What are the remaining challenges of gene therapy for haemophilia?

The long-term safety of gene therapy is unknown.[26,27]

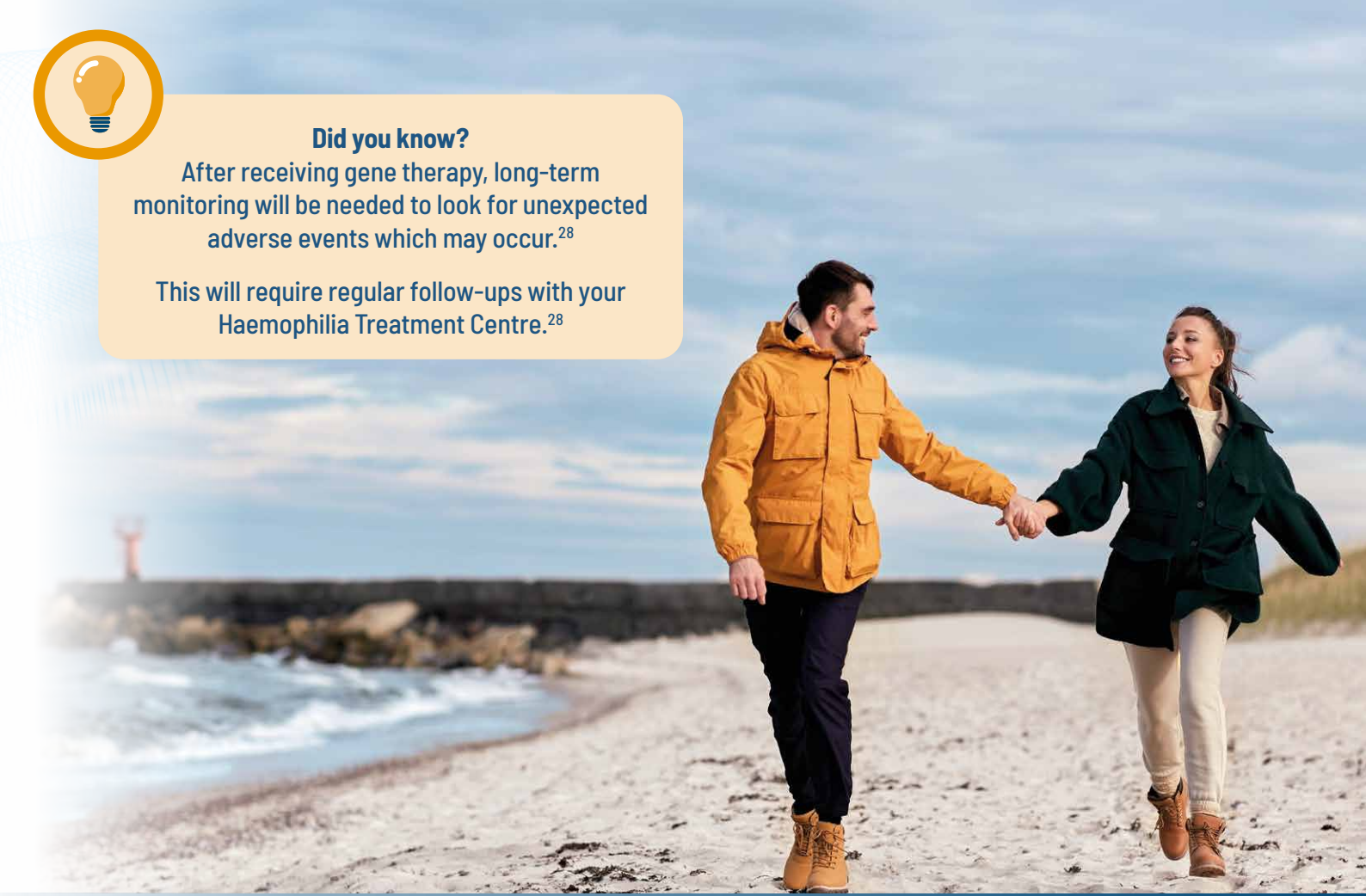
- Adeno-associated virus (AAV) vectors are used in gene therapy for haemophilia because they do not cause any infectious diseases in humans and they do not integrate genetic material inside the host DNA.[30]
- Despite this, there is a potential risk of rare integrations into the host DNA.[26,27,30]
- The exact frequency of these integrations remains unknown.[30]

If I try gene therapy and it stops working, can I try again?
No. At the present time, giving another dose of gene therapy is not permitted.
Gene therapy is viewed as a "one-chance" therapeutic opportunity.
However, research is ongoing to evaluate the possibility of future re-administration.

Did you know?

After receiving gene therapy, long-term monitoring will be needed to look for unexpected adverse events which may occur.[28]

This will require regular follow-ups with your Haemophilia Treatment Centre.[28]

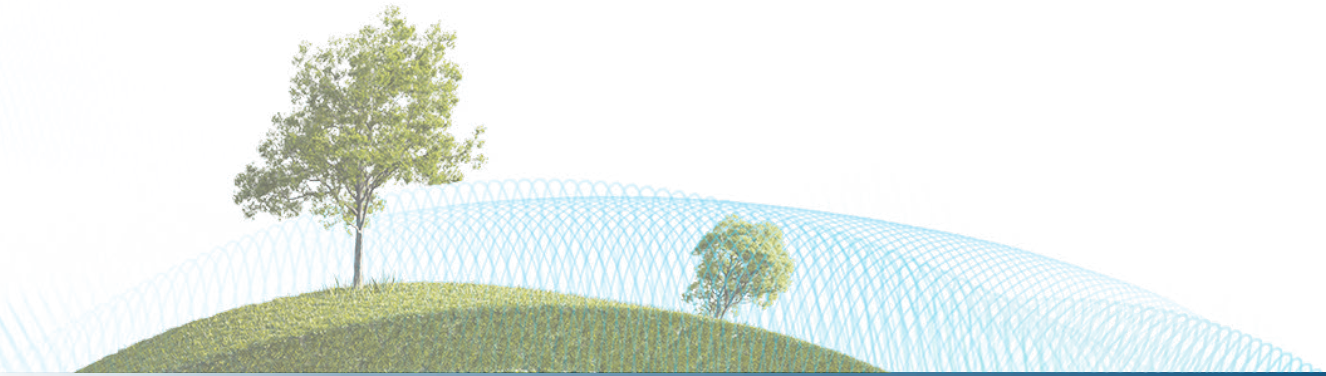



HAEMEVOLUTION

How to get more information

- Reach out to your referring doctors or nurses in your Haemophilia Treatment Centre if you have any questions with regards to gene therapy for haemophilia.
- Shared decision making between yourself, your doctor and the staff at the Haemophilia Treatment Center are key to managing your expectations around gene therapy and navigating the different treatment options which are available.[21,28]
- Explore the science behind gene therapy at

www.HaemEvolution.eu



Glossary

- **Adeno-associated virus (AAV) vector**: One type of delivery vehicle (vector) used in gene therapy to deliver the working gene into the target cell. AAV vectors are currently the most common vector used in gene therapy for haemophilia.[21]
- **Coagulation factors:** Proteins in the blood which help stop excessive bleeding following an injury. People with haemophilia have low levels of coagulation factor in their blood, which makes them more susceptible to excessive or prolonged bleeding episodes.[5]
- ***Ex-vivo*:** One of two methods for delivering gene therapy into the body, the other is *in-vivo*. This is a multi-step process, where cells are first taken from the patient, then the vector containing the working gene is inserted into these cells outside of the patient's body. Finally, the cells, now containing the working gene, are then returned to the patient via an intravenous infusion.[25]
- **Genes:** The written instructions to produce proteins in the body. We each have two copies of each gene, one from each of our parents.[21]
- **Gene addition:** One of two approaches to gene therapy, the other is gene editing. Gene addition works by inserting the working gene into the target cell, alongside the existing non-working gene.[25]
- **Gene editing:** One of two approaches to gene therapy, the other is gene addition. Gene editing works by inserting, deleting or modifying the existing (non-working) gene in order to correct the fault.[25]
- **Immunity:** Our body's natural protection against organisms or diseases. If you have immunity against something, it is less likely to affect you.
- **Inherited:** A trait or condition that is passed down to a child from its parents, via their genes.[21]
- **Inhibitor:** An antibody to coagulation factor replacement treatment. The development of an inhibitor during treatment is currently one of the biggest risk factors associated with coagulation factor replacement therapy.[5]
- **Intravenous:** Administration of treatment into a vein.
- ***In-vivo*:** One of two methods for delivering gene therapy into the body, the other is *ex-vivo*. A one-step process, where the vector containing the working gene is delivered directly into the body using an intravenous infusion.[25] Most gene therapies for haemophilia use *in-vivo* administration.
- **Prophylaxis:** Regular treatment with clotting factor replacement products, which is given on a set regimen e. g., once a week.
- **Replacement product:** The current method of treatment for haemophilia, where the low levels of coagulation factor in the blood of patients with haemophilia are replaced/supplemented by injecting additional coagulation factor. The aim for treatment is to raise the level of coagulation factor in the blood, in order to prevent bleeds. There are two main types of replacement product: plasma-derived and recombinant; both have the same function, but are manufactured in different ways.[5]
- **Vector:** The transporter for a gene being delivered into a cell during gene therapy. A vector is made from an altered virus, which has its viral genes removed before use. This means it can move the working gene without causing diseases.[25]

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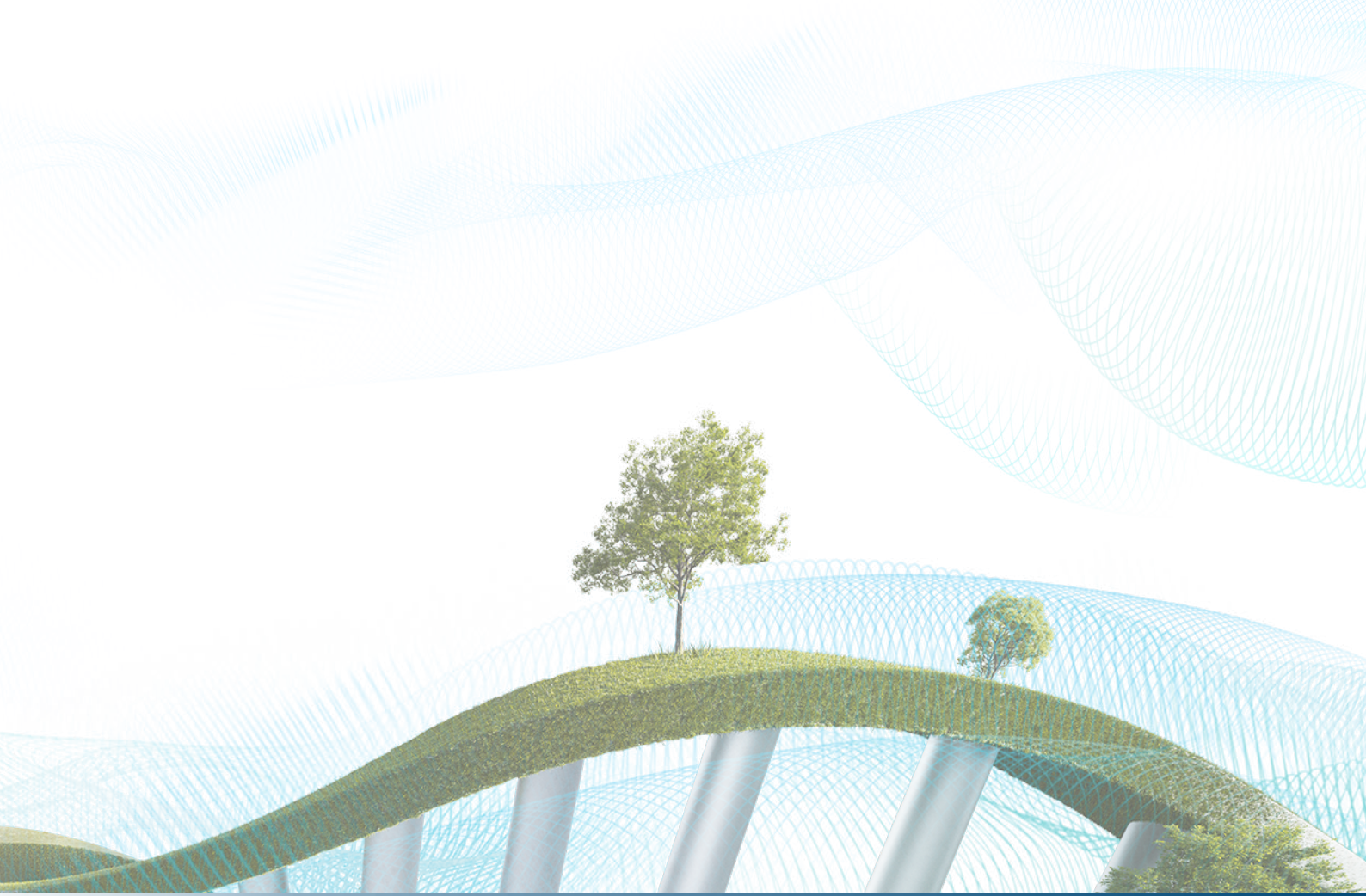

We´re working to make gene therapy in haemophilia a reality for you.

HAEMEVOLUTION

Explore the science behind gene therapy at HaemEvolution.eu

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