

Hemophilia
gene therapy:
**your questions
answered**

Pre-gene therapy information seeking

Questions	Answers
What is gene therapy?	<p>Gene therapy provides a corrected version of a missing or defective gene, such as the <i>F8</i> gene for hemophilia A, and the <i>F9</i> gene for hemophilia B. The most common method to introduce the treatment into your body is to use a neutralized virus. This modified virus, called a vector, can target certain cells in your body (for example the liver) and deliver a correct version.</p> <p>The instructions in this newly introduced gene are then processed, just like any other gene, to produce the clotting factor.¹ Gene therapy provides a healthy copy of a gene but does not build it into your DNA. It is different to gene editing, which aims to directly change the defective gene within your DNA.</p>
How does gene therapy work in my body as compared to how my usual treatment works in my body?	<p>Gene therapy and regular factor replacement therapy both help your blood to clot but work in different ways. Gene therapy is designed to enter your cells and enable your body to produce clotting factor on its own.¹</p> <p>Although regular therapy replaces the missing factor in the blood, the factor is not produced by your body and needs to be given regularly to maintain effective levels. Historically, it was produced from donated blood, which carried risk of infections. Nowadays it is industrially manufactured.²</p>
How is gene therapy given to patients?	<p>Gene therapy is administered at a specialist center by a single infusion into a vein. The infusion should take about an hour.</p>
What information is currently available on how safe and effective gene therapy is?	<p>Gene therapy is a new form of therapy for hemophilia. Researchers are testing different gene therapy products in clinical trials. No products are on the market because there is not enough information available yet.³⁻¹³</p>
What does a clinical trial involve?	<p>To take part in a gene therapy clinical trial, you will first need to meet the criteria, such as being older than age 18, and having good liver health. Regular clinic visits will be required before and after treatment. The most frequent follow-up will be expected the first year after gene therapy infusion. Afterward, the number of appointments will be based on your body's response to the treatment. During the clinical trial, measurements and samples will be taken (ie, blood tests, semen samples, etc.). After the trial has finished, the World Federation of Hemophilia (WFH) gene therapy registry will continue to collect long-term information, preferably over your lifetime. This is often via a mobile app.^{10,14}</p>
Who is eligible for gene therapy? Am I a good candidate for gene therapy?	<p>Currently, you can only receive gene therapy as part of clinical trials, which have strict criteria.¹⁵ Once gene therapy is on the market, it could be, in theory, accessible to most adult patients with hemophilia. All hemophilia gene therapy products have the same goal (to replace the missing factor), but they are not identical. Your doctor will be able to let you know if you can receive gene therapy. They will also help you select the best treatment for you.</p>
What are the differences between the various gene therapies in development?	<p>Each of the gene therapy products has different design features, such as the constituent parts or how it is manufactured. These features can influence which product may be suitable for you. There may also be differences in the length of time other medication (eg, steroids) may be required, and how the treatment works.</p>

Pre-gene therapy information seeking (continued)

Questions	Answers
How will my quality of life be affected after gene therapy?	<p>After gene therapy you may enjoy increased freedom. You may not need regular prophylaxis, and you may be able to do more physical activity.¹⁶ In the short-term you will need to use condoms for as long as the treatment by-products are detectable in your semen. This is less than a year for most patients but may be longer and family planning could be delayed.</p> <p>Although you might no longer need weekly treatment, you will need to be prepared for long-term monitoring. You will also need to reduce alcohol consumption to protect your liver.</p>
Will I still need regular treatment for hemophilia after gene therapy?	<p>The response to gene therapy is expected to be different from patient-to-patient. Regular factor/non-factor replacement therapy will stop once your factor levels after gene therapy reach a level where most bleeds would stop.^{17,18} How long gene therapy lasts is still an open question. At some point in the future, you may need to restart your regular medicine.</p>
How long are the effects of gene therapy likely to last?	<p>The goal of gene therapy is to last for a lifetime. However, this will depend on each individual, and which gene therapy product is given. A small number of patients have shown lasting levels of factor for about 5 years for hemophilia A and 8 years for hemophilia B.^{19,20} However, a decline in factor levels has been reported in some early hemophilia clinical trials. Currently, re-treatment is not possible with gene or cell therapy.</p>
Where can I go for more information? Who do I call if I have more questions?	<p>There are many helpful online resources. The World Federation of Hemophilia (wfh.org), European Haemophilia Consortium (ehc.eu), or National Hemophilia Foundation (hemophilia.org) websites are good places to look for additional information. For more specific and personalized information, please contact your local hemophilia treatment center (HTC) and care team.</p>

Pre-gene therapy decision-making

Questions	Answers
What is the experience of other people with hemophilia who have undergone gene therapy?	<p>Many patients treated with hemophilia gene therapy in clinical trials have reported a reduction in bleeds and have been able to stop taking their regular prophylaxis. However, patients have also experienced some short-term side effects, particularly related to steroids (given to control the immune response and treat potential liver problems). So far, there is not a lot of published research on the experience and quality of life of patients with hemophilia A or B who have undergone gene therapy. A small study found patients treated with gene therapy for hemophilia B have greater freedom to participate in sports.¹⁶</p> <p>Following treatment, some patients have had improved feelings about their future. Some patients were worried about how long the treatment will last.¹⁶</p>
How likely is it the therapy will work?	<p>Early clinical trials in a small number of patients with severe hemophilia A and hemophilia B report that gene therapy can prevent bleeds in most patients. It is currently unknown whether enough factor will be produced by all patients, and whether factor levels will drop over time. Long-term information is needed to fully answer this question.¹</p>
What are the potential risks and side effects?	<p>More information from clinical trials is needed to understand the potential risks. Short-term risks include immediate reactions to infusion or possible temporary liver changes. Steroids (a medication you need to take alongside gene therapy) are associated with side effects such as weight gain, nausea, or trouble sleeping.²¹ Steroid use can usually stop once any liver changes return to normal. This is usually within a few weeks or months but could be longer for some patients.²²</p> <p>Long-term risks may include lasting impacts on liver health.¹⁸ Hemophilia gene therapy is not thought to contribute to a risk of cancer²³ but this will need to be carefully monitored.</p>
Will my day-to-day life be affected?	<p>Yes, your day-to-day life may be affected in a few ways. Some of these will be positive changes. You may be able to participate in more or different types of sports/activities and you will not need to have regular factor infusions. With a reduction in chronic joint bleeding, your joint health could be maintained as you grow older.</p> <p>You will need to be prepared to undergo regular visits and tests in the first year after therapy. You will also need treatment for any side effects if these occur. After the first year, you can expect follow-up visits and tests at least twice per year. If you enroll in the WFH Gene Therapy registry, this requires follow-up for at least 15 years, and potentially lifelong monitoring.^{10,14} You will need to wear a condom for contraception for up to a year after treatment. You will need to reduce alcohol consumption.</p>
I have heard I might need to take steroids – what does this mean?	<p>Steroids are a type of medicine that reduce your body's ability to reject an unknown substance and are given to most patients undergoing gene therapy to manage possible side effects.²² Possible steroid side effects can include nausea, weight gain, high blood pressure or increased risk of infection.^{21,24} Steroid treatment should be temporary. It should be for a few weeks or months, but it could be longer in certain circumstances. How long you will need to take it will depend on your individual response and liver health.</p>

Pre-gene therapy decision-making (continued)

Questions	Answers
Will gene therapy heal existing joint damage?	No, gene therapy does not heal existing joint damage. However, by achieving and maintaining sufficient factor levels to prevent bleeds, joint health may be maintained. ²⁵
Will I still have hemophilia after treatment?	Yes, you will still have hemophilia as gene therapy does not change your body's DNA. Gene therapy is not the same as gene editing. Although you will still have hemophilia, and it could still be passed on to your children, gene therapy should improve factor levels to moderate or mild or even normal levels.
What do we not know about gene therapy?	Long-term experience with gene therapy in hemophilia is limited. ^{20,26} We cannot say how long gene therapy can continue to work, the long-term risks, or how long protection from bleeds will last. We are still learning about how gene therapy interacts with your body's immune system, and what this will mean for future treatment options if gene therapy stops working.
Where will treatment be administered; where and how will follow-up be undertaken? How often will I need to visit the hospital?	Gene therapy will likely be administered at an HTC that has the expertise to safely administer a gene therapy vector. Depending on your gene therapy vector and your prior health, you and your HTC care team will determine how frequently you need to be seen in person, and how often labs need to be drawn after vector infusion.

Treatment initiation

Questions	Answers
What do I need to do to prepare for treatment?	You should talk with your care team about gene therapy and develop strategies for your education and a roadmap to guide your safe care before, during and after gene therapy. Being well informed and having a care team you trust is essential for maximizing your understanding of the process and to prepare for any lifestyle changes that may be required.
When does regular prophylaxis stop?	Your regular prophylaxis treatment should stop once you have a measurable, protective level of factor from your gene therapy. ³⁻¹³ Your HTC care team will discuss this target range with you based on aspects such as previous bleeding pattern and joint health.
How will I know if my treatment has worked?	<p>Initially, you will have regular (weekly) evaluation of factor levels. You and your team will discuss these levels and what they mean.</p> <p>Until you are treated, it will not be known what factor level you will achieve, how soon you will get to that level, or how long that will last. Over time, the frequency of factor testing will be reduced.</p>
How does bleeding risk change after gene therapy?	Bleeding risk is related to factor levels. There is good evidence that higher factor activity levels are associated with less bleeding. ²⁷ Every patient is different and there may be other aspects that affect protection such as previous joint health, weight, and physical activity level. Your HTC team should discuss this with you before your gene therapy starts.
How long will monitoring continue for?	Lifelong monitoring is recommended. This enables tracking your factor level over time and careful monitoring of general health.
Can I drink alcohol after gene therapy?	<p>It is currently recommended that you abstain from alcohol for at least 6–12 months. It is likely this guidance will also be given to patients once gene therapy is more widely available.</p> <p>There is not very much information on the impact of alcohol intake after gene therapy.²⁴ However, because the liver is the target for hemophilia gene therapy, liver health must be carefully monitored and maintained. Long-term reduction in alcohol consumption may be recommended after gene therapy.</p>
Do I need to use a condom after gene therapy?	Condom use for contraception is required until no gene therapy by-products are detectable (determined by semen samples, usually up to 9–10 months post-infusion but may be longer for some patients). ²⁴
Will I need liver tests (biopsies)?	The need for liver tissue (by biopsy) or function tests, liver ultrasounds, or other liver health tests will vary between patients. Previous liver problems or any hepatitis will likely mean that you will be monitored more closely. If you have abnormal imaging or worsening liver function, your care team will discuss whether a small tissue sample should be taken for closer examination.

Short-term post-gene therapy follow-up (≤1 year)

Questions	Answers
What are the immediate follow-up requirements?	The most frequent monitoring will be in the first 3 months, but regular monitoring will continue through the first year. Assessments will include measurements to monitor temperature, pulse rate, breathing rate and weight, laboratory tests (eg, blood, urine, and semen samples), heart health and joint assessments, recording of any side effects, patient questionnaires, and your patient bleed diary will be reviewed (for bleeding episodes and use of factor replacement therapy).
What are the World Federation of Hemophilia Gene Therapy (WFH GT) Registry follow-up requirements?	<p>Participation in the registry is voluntary; if you consent to participating, in collaboration with your HTC, the registry will collect your baseline information (ie, your physical status and background information) prior to commencing gene therapy. Information from follow-up visits at months 3, 6, 12, 18, 24, and annually thereafter.</p> <p>The core data collected will include:</p> <ul style="list-style-type: none"> • Your age, gender, race, occupation, and diagnosis • Your medical/clinical history • Gene therapy infusion details • Safety data (any side effects you may report, as well as any other illnesses that occur or other medications you need to take. Even things that may seem unrelated will all need to be recorded) • Efficacy data (your FVIII/FIX level after treatment and any bleeds) • Questionnaires on your quality of life after treatment and other patient-reported outcome measures (usually collected using a mobile application).
Can I exercise/play sports whenever I want?	<p>Exercise is good for general health and well-being^{28,29}; however, participation in contact sports and other kinds of high intensity sports will be an individual decision in consultation with your healthcare professional (HCP). This decision will be based on your treatment response and other relevant information such as existing joint damage.</p> <p>As with any hemophilia treatment, the ability to play sports and exercise will depend on the factor levels achieved after gene therapy. This will be a lifelong consideration.</p>
What are quality of life questionnaires and what aspects of my life will they inquire about?	<p>Quality of life questionnaires capture views and feedback on the various aspects of treatment from patient's point of view. The aim is to ask patients about their perceptions of their health and treatment, and you may be asked to rate your answer on a scale. These measures evaluate different aspects such as feelings about your future, work and social life, pain, fatigue, and sexual dysfunction. They also assess other aspects of physical or mental health, such as anxiety.</p> <p>Your answers are confidential and will be very helpful to your HCP to assess your response to the treatment and to support future research.</p>
What happens in the event of a bleed?	Gene therapy may not prevent bleeds in the first few weeks after treatment. It takes a little while for the factor levels to reach a protective level. There can be no guarantee that gene therapy will offer protection from all bleeds because each individual response will be different. If a bleed occurs at any time after gene therapy treatment, you will be advised to treat it in the usual way and administer your usual replacement therapy products. You will be asked to record all the details of any bleed and any factor replacement treatment in an infusion log.

*The World Federation of Hemophilia Gene Therapy (WFH GT) Registry aims to collect standardized core data on patients receiving hemophilia GT, available to all healthcare professionals treating patients with GT.¹⁴

Short-term post-gene therapy follow-up (≤ 1 year)

(continued)

Questions	Answers
What happens if surgery is required?	After gene therapy, in case of emergency surgeries, additional factor replacement treatment might be needed. At the current time, if you need planned surgery this would exclude you from participating in a gene therapy clinical trial. If you have a surgery after gene therapy, factor activity levels will be assessed and follow-up and treatment information will be provided.
Who do I contact for information/support if I am unsure about anything?	Your HTC care team will be your first point of contact when you have any questions or concerns. After receiving gene therapy at an HTC, you may find that follow-up tests are carried out at a different center. You will be given details and contact information to help you keep track of your appointments and know who to approach to answer questions. However, additional online educational resources are available, eg, those provided by the National Hemophilia Foundation.
What happens if I need other medications at the same time as gene therapy (either related to my hemophilia or not)?	<p>To be eligible for a gene therapy clinical trial, you should have been taking any existing medications according to the same regimen/dose for more than 3 weeks, with no dose changes expected in the near future.</p> <p>For any new medication, your doctor will record the drug name, dates of administration, and reason for use. This information will be recorded for all prescription drugs, herbal products, vitamins, minerals, vaccines, and over-the-counter medications.</p>

Long-term post-gene therapy follow-up (>1 year)

Questions	Answers
What is known about long-term safety?	Limited long-term safety information exists for hemophilia gene therapy, with the longest clinical trial data follow-up of 5 years for hemophilia A ³⁰ and up to 8 years for hemophilia B. ¹⁹ Researchers have found no major safety concerns to date in hemophilia gene therapy trials, but there have been safety concerns related to gene therapies for other conditions. ^{31,32} Consequently, more safety data are needed. ^{10,14} Long-term safety information will include number of patients experiencing side effects and details of these effects, illnesses, and deaths (even if unrelated to treatment) after gene therapy.
What are the requirements for long-term follow-up?	Lifetime follow-up and continued monitoring after initial gene therapy treatment is recommended and will involve various measurements, eg, blood tests, semen samples, and questionnaires.
What are the requirements for registry participation and other long-term study needs?	Long-term follow-up is not compulsory but is highly recommended to ensure the best level of care, as well as to record important information on how well gene therapy works and how safe it is. The WFH GT registry will follow-up for 15 years, or ideally over your lifetime, and will involve the use of a mobile app to self-report your individual quality of life outcomes. ^{10,14}
What are the treatment options if factor expression drops too low to reliably offer protection?	<p>If your factor levels drop too low, you will be able to return to your previous factor replacement therapy or non-factor replacement product (eg, emicizumab). There are no reports of patients not being able to return to standard of care treatment if gene therapy proves unsuccessful.²⁴ However, any implications this might have on your insurance are not currently known. Please discuss this with your HTC team.</p> <p>Currently, you would not be able to have cell therapy or another similar gene therapy treatment, due to your immune system's response to the delivery vector. However, researchers are testing other approaches (ie, not based on the same type of vector) in clinical trials that you might be eligible for in the future.</p>

Useful websites

Resource name	Description	Website access
ASGCT	American Society of Gene and Cell Therapy <ul style="list-style-type: none">• Gene and cell therapy 101• Disease treatments• ASGCT clinical trials finder	https://patienteducation.asgct.org/
EAHAD	European Association for Haemophilia and Allied Disorders <ul style="list-style-type: none">• <i>Haemophilia</i> (official journal)• EAHAD annual congress	https://eahad.org/
EHC	European Haemophilia Consortium <ul style="list-style-type: none">• Resources on bleeding disorders• Conferences, fellowship programs and virtual community building• Youth Leadership and New Technologies workshops	https://www.ehc.eu/
The Haemophilia Society	<ul style="list-style-type: none">• Support resources• Publications, videos, member stories• Diagnosis and management guidelines• Volunteering and local groups (UK)• Events (UK)	https://haemophilia.org.uk/
ISTH	International Society on Thrombosis and Hemostasis <ul style="list-style-type: none">• ISTH Academy• ISTH annual congress	https://www.isth.org/
NHF	National Hemophilia Foundation <ul style="list-style-type: none">• Online education• Information center• Patient assistance programs	https://www.hemophilia.org/
WFH	World Federation of Hemophilia <ul style="list-style-type: none">• E-learning platform• Treatment guidelines• World Hemophilia Day	https://www.wfh.org/en/resources-education/educational-materials

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