

Hemophilia gene therapy: **your questions answered**

Pre-gene therapy
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Short-term post-gene
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Pre-gene therapy information seeking

Questions	Answers
What is gene therapy?	<p>Gene therapy is a treatment that provides a corrected version of a missing or changed gene. In hemophilia A this is the Factor VIII (or <i>F8</i>) gene and in hemophilia B this is the Factor IX (or <i>F9</i>) gene. The most common way to introduce gene therapy into your body is to package the corrected gene into a carrier, called a vector, which is a virus. This virus is not dangerous to humans. It can target certain cells in your body, like the liver cells, and deliver the corrected version of the gene.</p> <p>This newly introduced gene contains “instructions” which are then handled by the cell like other genes to make the clotting factor.¹ Current gene therapy treatments provide a healthy copy of a gene, but the new gene does not become a part of your DNA. For that reason, current gene therapy is different than gene editing, which is a treatment to directly change the poorly functioning gene within your DNA.</p>
How does gene therapy work in my body compared to how my usual treatment works in my body?	<p>Although regular factor therapy replaces the missing factor in your blood, the factor is not produced by your body and needs to be given regularly to maintain effective levels.</p> <p>Gene therapy helps your body make the clotting factor that is low or missing, which is much like regular factor replacement therapy. They both help your blood to clot, but they work in different ways. Gene therapy is designed to enter your cells and enable your body to produce clotting factor on its own at a fairly stable level.¹ When you use factor concentrate therapy, there are highs and lows to your factor level, which does not happen with gene therapy.</p>
How is gene therapy given to patients?	Gene therapy is given at a special center by a single infusion into a vein. The dose is based on your weight. The infusion usually takes at least one hour but may take longer based on how you feel during the infusion. After the gene therapy treatment, you need to stay in the infusion area to be watched for at least 3 hours, but this could be longer based on how you feel.
What gene therapy treatments are available to use?	Gene therapy is a new form of therapy for hemophilia. Researchers continue to test different gene therapy products in clinical trials. At this time, there is one gene therapy product that is available to treat hemophilia B called Hemgenix®.
What information is currently available on how safe and effective gene therapy is?	<p>Effectiveness: Many people who take Hemgenix® have increased FIX levels. Studies have shown an average FIX activity level of 41.5% one year after treatment, and 36.7% at two years after taking Hemgenix®.³³ People who are treated with Hemgenix® may need fewer or no additional factor infusions. Their bodies are making more FIX, so they have fewer bleeding symptoms.^{13,33} The level of FIX activity after taking Hemgenix® may be different for each person. Not everyone will have improvements up to the average level reported in the studies.</p> <p>Safety: The most common side effects reported in the clinical studies occurred during the treatment (infusion) and were face getting red and hot (flushing), feeling cold, shivering, rise in blood pressure, stomach discomfort, tight feeling in throat, itching, headache, feeling dizzy, and a tight feeling in chest. Your treatment center will have a physician available to monitor your symptoms and treat you as needed. After treatment in clinical trials, 24 out of 54 (44%) people had an increase in their liver function tests, and 9 out of 54 (17%) people needed treatment with steroids as a result.³⁴ These 9 people needed steroid treatment for an average of 81 days.³⁴</p>
Who is eligible for gene therapy?	<p>People in Hemgenix® studies with moderate or severe Hemophilia B had FIX levels of $\leq 2\%$ before taking Hemgenix®. Your insurance company needs to approve this treatment for you. You must be over 18 with Hemophilia B and not have an inhibitor. You must also meet one of these conditions:</p> <ul style="list-style-type: none"> • use FIX factor prophylaxis, or • have current or historical life-threatening bleeding, or • have had repeated, serious bleeding episodes with no known cause

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Pre-gene therapy information seeking (continued)

Questions	Answers
Who is not eligible for gene therapy?	<p>You cannot take Hemgenix® if any of the following apply to you:</p> <ul style="list-style-type: none"> • Are younger than age 18 • Have significant liver problems • Have an inhibitor against FIX • Cannot take steroids • Have been exposed to the virus vector in the past and have a high level of immunity to the virus vector • Cannot come to frequent follow up visits and get lab draws, either at your treatment center or locally if you live at a distance. If you have side effects, you may need to come in for visits or lab draws more often.
What will I need to do after the gene therapy treatment to make sure I have the best chance of it working?	<p>You need to be seen for regular lab draws and check-ups before and after treatment. You will need to be seen most often in the first 4-6 months and the first year after gene therapy infusion. Afterwards, the number of appointments will be based on your body's response to the treatment. Blood tests will be taken at least weekly to look at your liver function tests and FIX level for a few months after treatment. These tests are to determine your response, if treatment with steroids is needed, and the details of your steroid treatment.</p> <p>To protect your liver health, you cannot drink alcohol for at least 1 year after treatment. After a year, you may resume only light use, which means a maximum of 3 drinks per week with no more than 1 drink in a single day. You will also need to use a condom during all sexual activity for at least 6 months after treatment.</p> <p>It is also important that all people with hemophilia who use gene therapy commit to long term follow-up and data collection to gather long-term information. This data collection may be done through a mobile app or through other ways.^{10,14}</p>
Am I a good candidate for gene therapy?	<p>Your doctor will discuss with you if you are a good candidate and if this treatment is right for you. They will review your medical records and speak with you in detail about eligibility, needed tests, and the need for your commitment to post-treatment requirements to determine together what is best for you.</p>
How will my quality of life be affected after gene therapy?	<p>After gene therapy you may enjoy increased freedom. You most likely will not need regular prophylaxis and you may be able to be more physical active.¹⁶ You will need to use a condom during all sexual activity for at least 6 months after treatment, which may cause a delay in family planning.</p> <p>Although you likely may no longer need weekly treatment, you will need to be prepared for long-term monitoring. To protect your liver health, you cannot drink alcohol for at least 1 year after treatment. After a year, you may resume only light use, which means a maximum of 3 drinks per week with no more than 1 drink in a single day.</p>
Will I still need medicine after gene therapy?	<p>The response to gene therapy may be different between each person. Regular factor replacement therapy will stop once your factor levels after gene therapy reach a level where most bleeds stop.^{17,18} How long gene therapy lasts is not known and that is why ongoing follow-up and data collection is needed. It is unknown if at some point in the future, you may need to restart your regular medicine (factor infusions).</p>
How long are the effects of gene therapy likely to last?	<p>The goal of gene therapy is for it to last a lifetime. Although this is the goal, we do not have enough long-term follow-up data to say this is the case for each person. A small number of patients have shown lasting levels of missing factor for about 8 years for hemophilia B.^{19,20,33} However, a decrease in your FIX may occur over many years. Currently, re-treatment is not possible with current gene or cell therapies.</p>
Where can I go for more information? Who do I call if I have 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 resources for more 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
<p>What is the experience of other people with hemophilia who have undergone gene therapy?</p>	<p>Many patients treated with hemophilia gene therapy in clinical trials have reported decreased bleeding events and have been able to stop taking their regular prophylaxis. However, patients have also experienced some short-term side effects, most of which are related to the use of steroids which are given to control the immune response against the vector (carrier virus) and treat the liver inflammation.</p> <p>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 Some patients after treatment have had improved feelings about their future while some were worried about how long the treatment will last.¹⁶</p>
<p>How likely is it the therapy will work?</p>	<p>Information from the clinical study of Hemgenix[®] showed that 2 out of 54 people did not respond and were unable to stop their prophylaxis. One of these people had a high level of vector immunity and the other received 10% of the dose which was stopped because of some symptoms of a reaction. Studies have shown an average FIX activity level of 41.5% one year after treatment, and 36.7% two years after taking Hemgenix[®]. The factor level achieved after treatment varies between people so each person's response cannot be predicted or guaranteed. Although the factor levels appear consistent over the course of the study we do not know if factor levels will drop over time. Long-term information is needed to fully answer this question.¹</p>
<p>What are the potential risks and side effects?</p>	<p>Short-term risks include immediate reactions to infusion or possible temporary liver changes. Steroids are commonly used to treat many disorders that are due to inflammation and may be required after Hemgenix[®] if your liver function (enzymes) increase or your FIX level decreases. Steroids may be associated with side effects such as increased appetite, weight gain, elevated blood sugar, nausea, reflux, and trouble sleeping.²¹ Some less common side effects may be discussed with you by your physician. Steroid use usually stops once the liver changes return to baseline or factor IX reaches expected levels. This is usually within a few weeks or months but could be longer for some people.²² In clinical trials, 24 out of 54 (44%) people had an increase in liver function tests, and 9 out of 54 (17%) people needed treatment with steroids as a result. On average, these 9 people needed steroid treatment for 81 days.³⁴</p> <p>Long-term risks of gene therapy treatment may include lasting impacts on liver health.¹⁸ Hemophilia gene therapy is not thought to contribute to a risk of cancer, but this will need to be carefully followed over time.²³</p>
<p>Will my day-to-day life be affected?</p>	<p>Your day-to-day life will be affected in a few ways. Some will be positive changes. You may be able to participate in more or different types of sports or activities and you likely will not need to have regular factor infusions. With a decrease in chronic joint bleeding, your joint health could be maintained as you grow older.</p> <p>It is important to understand that the success of this therapy requires a commitment on your part to make sure you get the required follow-up visits and frequent lab tests needed to monitor your response. During the first 4-6 months after treatment, you should be prepared for at least weekly lab tests. You may need lab tests more often to monitor your safety and response to the infusion. Between 6 to 12 months, you will have at least monthly lab tests, but these could also be more frequent. After 1 year, you will likely only need lab tests every 1 to 3 months. Talk to your physician about developing a roadmap for your labs and visits. You may also need treatment for any side effects if these occur.</p> <p>In addition, you cannot drink alcohol for at least 1 year after treatment. After a year, you may resume only light use, which means a maximum of 3 drinks per week with no more than 1 drink in a single day.</p> <p>You will also need to use a condom during any sexual activity for at least 6 months after treatment. This is not only to prevent pregnancy but to prevent exposing your sexual partner to the vector in your semen.</p>

Pre-gene therapy decision-making (continued)

Questions	Answers
Will my day-to-day life be affected? (continued)	<p>It is important to collect long term data on outcomes for all people. This can be done by enrolling in the ATHN gene therapy registry which requires follow-up for at least 15 years, and potentially lifelong monitoring.^{10,14}</p> <p>A project called The World Federation of Hemophilia Gene Therapy (WFH GT) Registry will collect similar information on all hemophilia gene therapy patients. This information will be available to all doctors treating patients with gene therapy. For patients in the United States, this data will also be entered into the American Thrombosis and Hemostasis Network (ATHN) system and shared with the WFH GT registry.</p>
I have heard I might need to take steroids – should this worry me?	Corticosteroids, often just called steroids, are a type of medicine that reduce inflammation and suppress your immune response. Steroids are given to many patients undergoing gene therapy to manage side effects. ²² Possible side effects of steroid can include nausea, weight gain, increase in blood sugar, mood changes, reflux, increased blood pressure, or increased risk of infection. ^{21,24} If you need steroid treatment, it could last for a few weeks or months, but it could be longer for some patients. How long you will need to take steroids will depend on your individual response and your liver health.
Will gene therapy heal existing joint damage?	No, gene therapy does not heal existing joint damage. However, by achieving and maintaining a higher factor level to prevent bleeds, joint health may be maintained. ²⁵
Will I still have hemophilia after treatment?	Yes, you will still have hemophilia because gene therapy does not change your body's DNA. Gene therapy is not the same as gene editing. Although you will still have hemophilia, gene therapy should improve your low factor levels to a moderate or mild level. Some people's levels after gene therapy were in the normal range. ^{13,33}
What do we not know about gene therapy?	At this point, long-term experience with gene therapy in hemophilia is limited. ^{20,26} We cannot say how long gene therapy will continue to work, what the long-term risks are, or how long protection from bleeds will last. With the current treatment options, if gene therapy fails or your factor levels decrease over time, you will not be able to receive gene therapy again with the same agent.
Where will treatment be administered, where and how will follow-up be undertaken? How often will I need to visit the hospital?	Gene therapy is administered at a hemophilia treatment center (HTC) that has the experience to safely administer a gene therapy product. Depending on your gene therapy product 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 the 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 to determine if this is the right treatment for you. Your team has patient education and a roadmap to safely guide your treatment before, during, and after gene therapy. Being well-informed and having a care team you trust is essential to understand the process and prepare you for lifestyle changes that may be required.
When does regular medicine stop?	Your regular prophylaxis treatment should stop once you have a measurable, protective level of missing factor from your gene therapy. ³⁻¹³ Your HTC care team will discuss this target range with you. It will depend on things like your joint health and previous bleeding patterns.
How will I know if my treatment has worked?	At first, you will have weekly lab tests to check your missing factor levels and liver health. You and your team will discuss these levels and what they mean. Over time, you will need these lab tests checked less often. It will not be known until after your treatment what factor level you will achieve, how soon you will get to that level, or how long that will last.
How does bleeding risk change after gene therapy?	Bleeding risk is related to your factor levels. There is good evidence that higher factor activity levels are associated with less bleeding. ²⁷ Each patient is different and there may be other things that contribute to your bleeding risk, like your joint health, weight, and physical activity level. Your HTC team will discuss this with you before you start gene therapy.
How long will monitoring continue for?	Monitoring will be life-long. You will need frequent visits during the first year and continued visits with your HTC. It is important to track your factor level and general health over time, as with any hemophilia patient.
Can I drink alcohol after gene therapy?	You should not drink alcohol for the first year after treatment. After the first year, you may resume only light use (maximum total 3 drinks per week with no more than 1 drink per day). You should discuss this with your physician if you have concerns. There is not much information on the safety of drinking alcohol after gene therapy. ²⁴ Alcohol use can affect your liver health. Because the liver is the target for hemophilia gene therapy, it is very important to maintain and monitor liver health before and after treatment. It is recommended in the long-term to reduce or eliminate alcohol after gene therapy.
Do I need to use a condom after gene therapy?	For the first 6 months after gene therapy, you need to use a condom during all sexual activity. ²⁴ This is not only to prevent pregnancy but to prevent exposing your sexual partner to the vector in your semen.
Will I need liver tests (biopsies)?	The need for liver function tests, liver ultrasounds, or other tests such as a liver sample (biopsy) will be based on each person's history and present situation. If you had past liver problems or any type of hepatitis, you will be screened before treatment and monitored more closely if you get treatment. If you have abnormal scans or worsening liver health, your care team will discuss whether a small tissue sample (biopsy) should be taken for closer examination.

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Short-term post-gene therapy follow-up (<1 yr)

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

Useful websites

References

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

Questions	Answers
What are the immediate follow-up requirements?	The most frequent follow-up will be in the first 4 to 6 months after treatment, but regular follow-up will continue through the first year. This may include checking your temperature, pulse rate, breathing rate, weight, and laboratory tests like your factor level and liver function. More may be needed based on each person's circumstances and health. Other checks may include heart health, joint health, review of side effects, questionnaires about your quality of life, and your bleeding events. It is important for you to communicate with your treatment center about any bleeding episodes or factor infusions.
What are the ATHN Transcends Gene Therapy Registry follow-up requirements?	<p>The registry will work together with your HTC to collect your baseline information before you get gene therapy. After treatment, they will collect information at months 3, 6, 12, 18, 24, and once per year after that.</p> <p>The baseline information 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 such as any side effects, illnesses, or other medications you need to take. Even things that may seem unrelated to your gene therapy will need to be recorded. • Information about how well the gene therapy worked for you based on your factor levels, bleeding events, and need for treatment <p>Questionnaires about your quality of life after treatment and other self-reported information. These can be collected on paper or using a mobile app.</p>
Can I exercise/play sports whenever I want?	<p>Exercise is good for general health and wellbeing.^{28,29} Because of the risk for bleeding, doing contact sports and other high intensity activities after gene therapy is a personal decision you need to make with your HTC. This decision will be based on how well gene therapy works for you and things like your current joint health.</p> <p>As with any hemophilia treatment, your ability to safely play sports and do physical activity over your lifetime after gene therapy will depend on the factor levels achieved.</p>
What are "quality of life questionnaires" and what parts of my life will they ask about?	<p>Quality of life questionnaires ask you about your feelings about your health and treatment. These may ask how you feel about your future, work and social life, pain, fatigue, and sexual health. They also ask about other physical or mental health issues, such as anxiety. You may be asked to rate your answer on a scale.</p> <p>Your answers are confidential, which means no one will share them without your permission. Your answers will be help assess how gene therapy treatment affected your life personally and may help us understand how gene therapy could affect the lives of others.</p>
What happens in the event of a bleed?	Gene therapy may not prevent bleeds in the first few weeks after treatment. It takes some time for factor levels to reach a protective level. There are no guarantees that gene therapy will protect you from all bleeds because each person's response will be different. If a bleed occurs at any time after gene therapy treatment, you should let your HTC know and treat it with your usual factor replacement product. You should record all the details of any bleed and factor infusions in an infusion log or app.

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Short-term post-gene therapy follow-up (<1 yr)

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

Useful websites

References

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

Questions	Answers
What happens if I need surgery after gene therapy?	If you need surgery after gene therapy, you may need additional factor replacement treatment. If you have a planned surgery after gene therapy, your factor level will be checked to determine your treatment plan. For an emergency surgery, treatment may be recommended based on your most recent factor level.
Whom do I contact for information/support if I am unsure about anything?	After receiving gene therapy at an HTC, your center may arrange to have follow-up tests done at a different center or at a lab outside of your center. Your HTC care team will be your first point of contact for questions or concerns, and they will help you keep track of your appointments and follow-up. There are also online educational resources like those provided by the National Hemophilia Foundation.
What happens if I need other therapy or medications at the same time as gene therapy (either related to my hemophilia or not)?	Both before and after gene therapy, any medicine or supplements you take on a regular basis will be reviewed and followed closely. This includes all prescription drugs, over-the-counter medications, herbal products, vitamins, minerals, and vaccines. If you start taking any kind of new medication or supplement before or after gene therapy, tell your HTC doctor the name, the reason for taking it, the dose, and how long you will need to take it.

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

Useful websites

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Long-term post-gene therapy follow-up (>2 years)

Questions	Answers
What is known about long-term safety after gene therapy?	As of now, there is not very much long-term safety information about hemophilia gene therapy. Right now, the longest clinical trial data follow-up for hemophilia B gene therapy is 8 years. ^{19,33} There have been no major safety concerns yet in hemophilia gene therapy trials, but there have been safety concerns about gene therapies for other conditions. ^{31,32} It is important to continue collecting safety information and other data to make sure no issues come up over time. ^{10,14} Long-term safety information on people that have received gene therapy will include how many of those people experience side effects, details about those side effects, illnesses, and deaths--even if they seem unrelated to gene therapy.
What are the requirements for long-term follow-up?	After gene therapy, it is recommended to have lifetime follow-up and continued monitoring. This will include blood tests, physical exams, and questionnaires.
What are the requirements for registry participation and other long-term study needs?	Long-term follow-up is not required but is strongly recommended. This is to make sure that patients receive the best care after gene therapy, to learn about how well gene therapy works, and to study how safe it is. The ATHN Transcends gene therapy registry will follow you for at least 15 years after gene therapy treatment, but ideally over your whole lifetime. It will ask you questions about your quality of life after gene therapy. ^{10,14}
What are the treatment options if my missing factor level drops too low for protection from bleeds?	<p>If your missing factor levels drop too low, you will be able to return to your previous or a new factor replacement therapy or another non-factor replacement product. There are no reports of people being unable to return to these treatments after unsuccessful gene therapy.²⁴ If this happens to you, your care team will discuss your treatment options and insurance approval.</p> <p>Currently, if you get a gene therapy or cell therapy treatment, you would not be able another similar treatment after. After you receive a current gene therapy product, your immune system will recognize the delivery vector and it will not work for you again. However, researchers are testing other treatment options including vectors that are different from the one you received.</p>

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

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

Useful websites

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Useful Websites

Resource name	Description	Website access
ASGCT	<p>American Society of Gene and Cell Therapy</p> <ul style="list-style-type: none"> Gene and cell therapy 101 Disease treatments ASGCT clinical trials finder 	https://patienteducation.asgct.org/
EAHAD	<p>European Association for Haemophilia and Allied Disorders</p> <ul style="list-style-type: none"> <i>Haemophilia</i> (official journal) EAHAD annual congress 	https://eahad.org/
EHC	<p>European Haemophilia Consortium</p> <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	<p>International Society on Thrombosis and Hemostasis</p> <ul style="list-style-type: none"> ISTH Academy ISTH annual congress 	https://www.isth.org/
NHF	<p>National Hemophilia Foundation</p> <ul style="list-style-type: none"> Online education Information center Patient assistance programs 	https://www.hemophilia.org/
WFH	<p>World Federation of Hemophilia</p> <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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