

## GENE THERAPY DEFINED:

### What is gene therapy?

Gene therapy is designed to introduce genetic material into cells to compensate for abnormal genes or to make a beneficial protein. If a mutated gene causes a necessary protein to be faulty or missing, gene therapy may be able to introduce a normal copy of the gene to restore the function of the protein. <https://ghr.nlm.nih.gov/primer/therapy/procedures>

### What is a vector? Are there different types of vectors?

A vector is a carrier; the DNA of an agent (virus or plasmid) used to transfer the desired gene to a cell. There are a variety of different types of vectors currently used in gene therapy including retroviruses, adenoviruses, adeno-associated viruses & the herpes simplex virus.

### What are the differences among the various approaches to gene therapy: gene editing, gene transfer and cell therapy?

Gene therapy involves the transfer of genetic material utilizing a vector. Cell therapy refers to the transfers of cells with the necessary function into the patient. Gene editing targets a specific gene in order to correct its mutation. For more information please go to: <https://www.asgct.org/education>

### What is CRISPR?

Clustered Regularly Interspaced Short Palindromic Repeats is a term used to describe a gene editing technique that can identify and modify specific DNA sequences in the genome of an organism. There is a wide variety of uses for this type of technology including repairing specific disease-causing gene mutations as well as the ability to increase a plant's nutritional value and resistance to climate change.

### What vectors are being used in gene therapy for hemophilia?

Gene Therapy that is focused on treating hemophilia currently utilizes viral vectors. The most commonly used are the adeno-associated viruses or AAV. These viruses are modified so they don't cause viral infections and are able to safely deliver the gene of interest into specific cells so that they can start producing factor.

## WHAT CAN I EXPECT:

### Is gene therapy a cure for hemophilia?

Gene therapy holds the potential for longer term, durable treatments for hemophilia and gives promise for improvements to quality of life. Clinical trials are still underway so there is no definitive answers to length of durability which could determine if it is a cure.

### Are there gene therapy treatments for both Hemophilia A and Hemophilia B?

Yes, currently there are several different clinical trials underway at various stages for both types of hemophilia.

### What can I expect my factor level to be once I undergo gene therapy?

This depends on many factors. Response to gene therapy is very individual and it can vary over time. Clinical trials to date have demonstrated an increase in baseline factor levels. However, it is hard to predict if it will work on everybody and, if it does, how much it will increase and for how long.

### Will my factor level fluctuate in the future if I undergo gene therapy?

Current clinical trials data have shown fluctuations in factor levels over time.

### When is gene therapy for hemophilia realistically going to happen?

Currently there are several ongoing clinical trials underway for both Hemophilia A and B which are showing promising results. These trials will continue to be closely monitored to determine safety and efficacy of the therapy. At least one of these trials is nearing completion and is expected to file an NDA New Drug Application with the FDA which means the therapy could be available to patients as early as late 2020.

### How long can I expect the effects of gene therapy to last?

At this time, no one really knows the answer to this question. There are several clinical trials underway with data that suggests the possibility of some factor expression in excess of 7 years.

### Will I still need factor if I receive gene therapy? What if I have an accident, injury or need surgery?

The need for factor post gene therapy will be dependent upon the amount and duration of factor expression. Each person's response to gene therapy will likely be different and will require an individualized approach. This is a question best discussed with your provider.

### If I am deemed ineligible for a particular gene therapy will this mean I am ineligible for any type of gene therapy in the future?

There are many reasons why a person could be deemed ineligible for gene therapy. Current clinical trials do not include males under 18, women, or those with an active inhibitor. Some trials exclude those who have developed antibodies to the vector used in the gene therapy. As the technology matures we will learn more about ways to make this technology available to more patients.

### If I undergo gene therapy and it stops working can I try again in the future?

Currently, gene therapy for hemophilia is indicated as a one-time intravenous infusion. There is a possibility that the science will advance and increase options for the future.

### Once I receive gene therapy will I still need annual checkups at my HTC?

Yes, you still need to follow up with your health care team after having completed gene therapy at least yearly.

### Can I stop or turn off gene therapy?

No, gene therapy is a one-time intravenous infusion which once administered cannot be reversed or undone.

## RISKS ASSOCIATED WITH GENE THERAPY:

### What is vector shedding?

It is the process by which the viral vector leaves the body through bodily fluids after it is no longer needed by the body.

### What are the risks associated with gene therapy?

Some possible risks associated with gene therapy include but are not limited to: an unwanted immune system reaction, targeting of the wrong cell, an infection caused by the virus and the possibility of hepatic carcinomas.

### What happens if I undergo gene therapy and my resulting factor levels are higher than the normal range?

In some cases, gene therapy has resulted in factor levels well over the normal ranges. Although this may be associated with increased clotting risks no adverse effects have been reported. However, you need to know that this can happen and if it does you will need to be closely supervised by your hemophilia treatment center.

## GENE THERAPY AND REPRODUCTION:

### Can I pass the effects of gene therapy to my children?

No. Gene therapy for hemophilia is designed to correct the genetic defect only in the person who receives it. That is, it delivers a functional (or working) copy of the factor VIII or factor IX gene to the liver cells providing them with the instructions of how to produce the missing factor. Gene therapy does not correct the genes that are passed onto the next generation.

### Should patients who undergo gene therapy bank sperm?

After the administration of gene therapy the body takes several weeks to months to get rid of the vector used in gene therapy through different bodily fluids including semen, blood, urine, feces and saliva. Although the risk for the vector to integrate into the sperm cell is low, men who undergo gene therapy are being asked to use a barrier contraceptive method (such as condoms) to prevent pregnancies for an extended period of time after the infusion. If you are considering having a baby in the near future, it might be reasonable to think about banking sperm before undergoing gene therapy.

### **Will gene therapy impact my ability to have children?**

No, gene therapy will not impact your ability to have children in the future. However, because the vector will be found in semen for a period of time after the infusion, you will need to use a barrier contraceptive method (such as condoms) to prevent pregnancies for an extended period of time.

### **GENE THERAPY CLINICAL TRIALS:**

#### **Can I get gene therapy today outside a clinical trial?**

Currently, there are no gene therapy treatments for Hemophilia A or B that have been approved by the FDA. The high costs of gene therapies, the supply and demand for the therapies and the stringent regulatory environment could result in non-FDA approved therapies becoming available. It is imperative that you work with your HTC to ensure the safety and efficacy of any gene therapy treatment for Hemophilia.

#### **How can I find out about on-going gene therapy clinical trials for hemophilia?**

The primary source of information on clinical trials can be found at [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov). Your HTC provider can direct you to current clinical trials and can answer specific questions you may have.

### **GENE THERAPY AND INHIBITORS:**

#### **Can I develop an inhibitor to gene therapy?**

Currently only patients with long-standing regular clotting factor administration on record are eligible to participate in gene therapy trials. Therefore, the likelihood to develop an inhibitor for those patients appears low. This is because the body is already used to factor. However, it is too early to tell and has to be studied further.

#### **Will gene therapy cause me to develop an inhibitor to my factor?**

Probably not. Although this is not yet known, receiving gene therapy should not put you at a higher risk to develop an inhibitor.

#### **Can I receive gene therapy if I have an inhibitor?**

No. At this time, all clinical trials exclude individuals with a history of an inhibitor or those who might still be in the window of risk to develop one.

### **PSYCHO/SOCIAL ISSUES AND GENE THERAPY:**

#### **What are the Psycho/Social issues to be expected if I undergo gene therapy?**

It is completely normal to have conflicting feelings after you undergo gene therapy or any other major life change. It is important that you speak with your HTC or primary care provider who can help you understand these feelings.

#### **Will I still be part of the bleeding disorders community?**

The Bleeding Disorders Community is one that is warm and welcoming and regardless of a change in your health status you will always be a member of the community. You have much to offer others as a member of the community and your experience and knowledge can be very beneficial to others.

#### **Will I still have hemophilia if I have normal factor levels?**

Gene therapy for hemophilia is a relatively new concept as a treatment option and is still in the clinical trial phase. This means that we don't know how durable it will be (aka how long will it last) and the level of factor expression will vary among individuals. Factor levels may be in the moderate, mild or normal range and may fluctuate over time.

These gene therapies are targeted to somatic cells (ex. cells that control biological processes within your tissues, organs, blood) not germline or reproductive cells so you can still pass hemophilia to your offspring. While you may rarely need to do infusions or maybe not at all, you will need to remain diligent with your healthcare to ensure you are on top of things.

#### **Will I still be able to go to the HTC?**

Most definitely, in fact please do. It will be important to continue to be monitored to assess any changes in overall health including emotional health as well as factor levels. Any underlying issues you had prior to gene therapy (ex. joint issues) will need to be monitored as well. Your HTC will be an important partner in your follow-up care post gene therapy.

### **ELIGIBILITY:**

#### **Who is eligible for gene therapy?**

Currently gene therapy for Hemophilia A and B are in the clinical trial phases. Eligibility criteria varies somewhat between studies but for the most part the criteria is as follows: healthy (no diabetes, history of malignancies, heart disease, glaucoma, high blood pressures etc.) males, age 18 and older, with severe Hemophilia A or B, without inhibitors, no evidence of hepatitis or HIV, no evidence of liver dysfunction and no detectable neutralizing AAV antibodies. Your healthcare provider can explain the exclusion criteria in more detail.

#### **At what age can my child have gene therapy?**

Currently gene therapy for hemophilia is not indicated for individuals under 18. Gene Therapy for Hemophilia is targeted towards the liver which continues to grow in humans until they reach at least age 12. As the science is perfected the age could be lowered in the future.

#### **Can females with Hemophilia receive gene therapy? If not why?**

Currently gene therapy for Hemophilia is not indicated for female patients. Most female patients who are affected are classified as carriers with mild hemophilia and their factor levels are not low enough to qualify.

### **GENERAL INFORMATION:**

#### **How is gene therapy administered?**

Similar to a factor infusion, gene therapy is a one-time intravenous infusion which can last anywhere from minutes to a few hours. However, unlike factor, it is currently being done in a medical facility by healthcare providers.

#### **Where will I receive gene therapy? An HTC?**

Gene therapy is currently being offered to eligible participants who are enrolled in a clinical trial. Currently, infusions occur only in pre-determined sites participating in the clinical trial.

#### **Will my insurance company pay for gene therapy?**

This is an important question and much work is being done to determine alternative financing and reimbursement strategies to enable patients to access these promising therapies. The current healthcare system as we know it is not equipped to handle large one-time payments. Additionally, these new treatment options have short treatment regimens (one-time infusion) and benefits that create challenges. These challenges include uncertainty around how long the therapy will last (insurance plans don't want to pay for things that don't work long-term) and uncertainty around an individual remaining on a given insurance plan (think about how often you might change insurance plans - new job, employers change types of plans offered, etc.). We have seen some gene therapies for rare diseases being reimbursed by insurance companies and that is great news for hemophilia patients. The creation of other conditions or comorbidities due to the gene therapy is also an unknown.

We do not currently know if the out-of-pocket costs will continue to be a challenge for the consumer like it is now in our current health care system. For those consumers with comorbidities or lasting physical effects of their primary disease, the out-of-pocket costs could and probably will continue to pay on an ongoing basis as out-of-pocket costs from high deductible health insurance continue to rise year over year.

Some suggested strategies include milestone-based contracts (payments are made when milestones are achieved) and performance-based annuities (a plan would pay an agreed upon amount if the therapy continues to perform well year to year) to name a few. This will require significant changes to our existing healthcare system. Additionally, there will be a need for policy changes at the Federal level to enable these strategies to work. NHF and other rare disease organizations are working with payers and policy makers to ensure access to these therapies becomes a reality. First dollar coverage is one component being discussed to address the affordability from the patient's side of things. Academic entities like the MIT NEWDIGS consortium bring together stakeholders that are working collaboratively (payers, providers, patient advocacy organizations, pharmaceutical developers, academics and others) to come up with innovative solutions.

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