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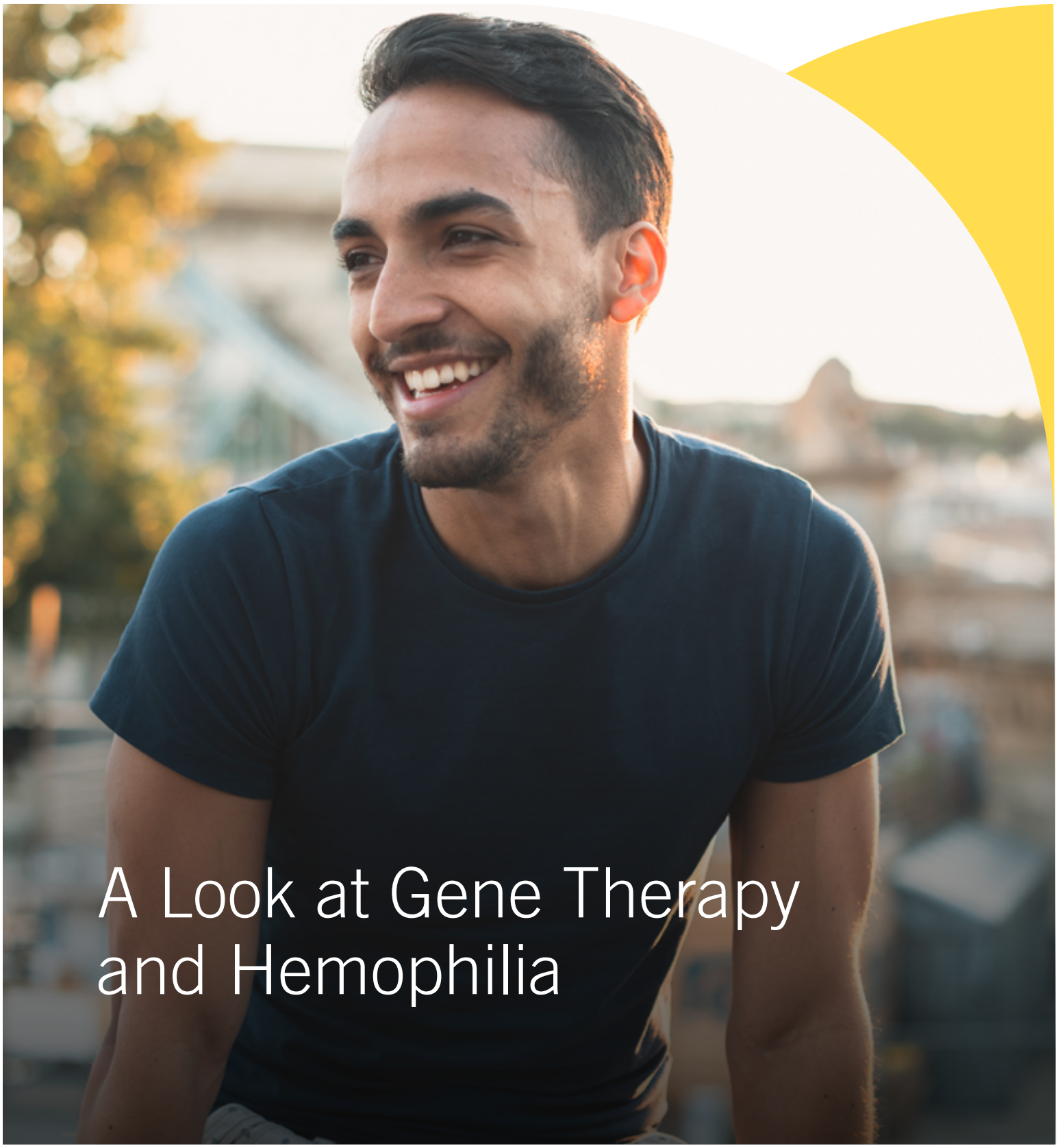

A Look at Gene Therapy and Hemophilia

The treatment of hemophilia has had tremendous highs and lows throughout its history

Since the 1970s, factor products have been available for self-infusion treatment. In subsequent years, new breakthrough treatments evolved, giving the hemophilia community many different options and individualized choice of treatments. We are now stepping into new treatment opportunities that have the potential to change the course of hemophilia for years to come.

The decision to change your treatment is very personal. Not every individual will be a candidate for gene therapy, and not every individual will want to pursue it. Accredo has created this guide for you and your loved ones to aid in discussions on available treatment options. The choice to consider gene therapy or continue with current treatment is personal and should be made in consultation with your physician and healthcare team. It will be a unique experience for everyone — there is no wrong decision.

This book will provide you with an overview of gene therapies, administration, post-therapy management, and future considerations. The back of this book has areas to take notes. Write down your questions or thoughts. Use your notes as a guide to have discussions with your **hemophilia** healthcare providers. Regardless of your decision, Accredo is ready to support you and your family's needs through our established dedicated bleeding disorders clinical and support teams.

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Gene therapy overview

Genes and DNA

Genes carry the information that determine what is passed on, or inherited, from your parents, like blue eyes or brown hair. Genes are made up of **DNA**, the genetic material that gives instructions for making **proteins**, like in a cookbook recipe. These proteins form tissues. Tissues form organs, **blood vessels**, bone and much more. These pieces all come together to make you.

Each cell in the human body has about 25,000 genes.[1] A gene that is faulty, missing, or isn't working correctly can cause disease.

Explanation of gene therapy

Gene therapy treatment means changing genes already inside the body, or adding new genes to treat or stop disease, but sometimes these genes do not deliver a cure. In hemophilia, gene therapy refers to adding working genes that can help the body make more clotting factor.[2] That means factor therapy to prevent or treat bleeding may not be needed in the future, but hemophilia gene therapy does not "cure" the disease. We explain this more in the coming paragraphs.

How gene therapy works: three different ways

Replacing
a disease-causing gene with a healthy copy of the gene[3]

Inactivating
a disease-causing gene that is not functioning properly[3]

Introducing
a new or modified gene into the body to help treat a disease[3]

Gene therapy in hemophilia

In gene therapy for hemophilia, a faulty factor VIII (eight) or IX (nine) gene is replaced by a functional factor VIII or IX gene. This is called gene transfer.

Gene transfer is carried out by **vectors**. Think of a vector as a vehicle to carry a biologic substance from one place to another. Vectors can be created from inactivated **viruses**. In gene therapy, viral vectors are changed so they cannot infect you. They act like taxis, driving and carrying the new, functional genes into the body.

Special viruses are used as vectors because they can deliver the new, functional genes into the body and then go directly into the **cells** where they are needed. There, they can start working right away.

Current gene therapy programs for hemophilia focus on using a **lentivirus** or an **adeno-associated virus (AAV)** made in a lab as a vector.

Lentiviruses are especially popular due to their ability to have an effect on both dividing and non-dividing cells.[4] Lentiviruses can permanently stay inside the body's genes.

Adeno-associated viruses (AAVs) are like adenoviruses — common viruses that may cause mild cold- or flu-like illness, or no illness at all. Most adenovirus-related illnesses will go away on their own with time. The AAVs used in gene therapy do not cause viral illnesses. In gene therapy, AAVs act like a taxi and drive a functional factor VIII or IX gene into the body's genes. AAVs do not permanently stay inside the body's genes.

Neutralizing antibodies

Many people with hemophilia may understand neutralizing **antibodies** by comparing them to inhibitors. Inhibitors are **neutralizing antibodies** to clotting **factor proteins**. Antibodies are proteins produced by the body when it detects harmful things like germs (which is a common term for viruses), in order to protect you. Sometimes the body gets confused and makes antibodies to attack clotting factor proteins. This destroys the clotting factor proteins and makes them useless in clotting blood.

Antibodies to the AAV work in the same way. Even though the virus has been changed and cannot make you sick, the body could become confused and both attack and destroy the AAV "taxi" carrying the functional gene.

This could stop the gene therapy infusion from working correctly. As a result, testing for neutralizing antibodies before gene therapy treatment is very important.

Understanding if gene therapy is right for me

There are many reasons why gene therapy may or may not be right for you. Current **clinical trials** do not include males under 18*, women**, or those with an active inhibitor to clotting factor proteins (in nearly all trials). Not every person who wants gene therapy will be a candidate. Not everyone who is a candidate may want gene therapy. It is important to remember that standard treatments for hemophilia have improved over the years, and other non-gene therapy drugs are currently in development. Accredo is committed to providing you optimal specialty pharmacy services for the prescribed treatment that is right for you.

**Males under 18 are still actively growing, and as a result, the gene therapy may not work as it would in adults.*

***Hemophilia primarily affects males, it is very rare for females to have hemophilia.[6]*

Things to consider about gene therapy (after FDA-approval)

- More time is needed to study people who have received gene therapy to understand long-term outcomes.
- People may need short- or long-term medication to keep the body from attacking the new genes inside the body.
- Some clinical trials exclude those who have developed antibodies to the vector, or "taxi," used in the gene therapy. People with antibodies to the specific type of AAV used in the gene therapy product may not be eligible for AAV gene therapy.
- Children may need more than one dose of AAV carrier gene therapy, because AAV does not change the body's genes permanently; however, there may be limitations on which gene therapy can be used, based on antibody response. At this time, gene therapy drugs approved by FDA will likely not be approved for use in people under the age of 18.
- For children, use of lentiviral vectors may be more permanent or long-lasting. More research is needed.
- Nearly all of the gene therapies currently in clinical trials include factor proteins that would be **inactivated** by inhibitors. Because of this, people with inhibitors were excluded from clinical studies to date. There is one gene therapy product in early clinical trials, which uses **nanoparticles**, designed to also treat people with inhibitors.[5]
- Follow-up after gene therapy may take a lot of time and may require travel for appointments. Know what the expectations are before agreeing to treatment.
- People may have previously developed antibodies to AAV "taxis" that transport hemophilia gene therapy into the body, making it ineffective. Additionally, a person may have to take medicines, like prednisone, for a short period of time to keep the body from attacking the virus "taxi" that transports gene therapy.
- People with **liver** disease may not qualify for gene therapy, because it may cause additional stress to the liver.
- People with other chronic health issues that are not well-controlled may not qualify for gene therapy.
- There may be unexpected or unknown side effects from gene therapy.
- An appropriate support system is required to manage stress and follow-up.
- Environmental limitations (for example, inability to travel to the clinic for follow-up, long time periods spent at the clinic, or lots of appointments) may impact your decision.
- Those living with hemophilia who receive gene therapy may experience a resetting of their bleeding system much like someone who doesn't have hemophilia. For example, they may get blood clots. As such, they may experience cardiovascular events like patients without hemophilia. People with significant family **cardiovascular** history (heart attack, ischemic heart disease, high cholesterol, high blood pressure, or obesity), particularly in first-degree relatives (parent, sibling, or child), will need to watch for possible new or existing issues.

Gene therapy administration

Gene therapy is administered as a single intravenous (IV) infusion

Preparing for gene therapy infusion

Accredo will provide dedicated nursing, pharmacist, and insurance support to all patients on gene therapy. You will have access to highly skilled resources to help throughout your gene therapy journey.

If pre-infusion medication is prescribed, like prednisone, it is very important to take this medication. Be sure to follow the instructions from your hemophilia treatment center (HTC).

During gene therapy infusion

You will receive an infusion of the gene therapy into your vein. A gene therapy infusion allows billions of functioning factor VIII or IX genes packaged in viral vector "taxis" to enter your bloodstream. Several of the first gene therapies to be approved will package the functional gene in an adeno-associated virus (AAV) vector "taxi," which targets the liver. These "taxis" holding the functional genes find their way to the liver cells, where the gene is delivered and begins to make new clotting factor.

After gene therapy treatment

You can expect close follow-up for the first 12 months, with many visits and lab tests. You can also expect some continued visits long term.

The goal of gene therapy for hemophilia is to increase your body's own clotting factor; however, you should expect to keep your HTC relationship.

Ensure your body is creating factor

Your factor levels will be checked after your gene therapy treatment for a period of time decided by your HTC. If your body is making more factor, you may be instructed by your HTC to decrease or stop regular doses of your hemophilia medication. You may still need to keep clotting factor in your home in case you have a bleed. Follow all specific directions from your prescriber and hemophilia treatment team.

Post-gene therapy and future considerations

Future use of factor

Some, but not all, people who receive gene therapy will reach normal or near-normal factor levels. Others may move from "severe" hemophilia to "moderate" or "mild" hemophilia factor levels following gene therapy. If your factor levels are not in the normal range after gene therapy, you may need to continue other hemophilia treatments at specific times of increased need, like surgery.

How long gene therapy lasts

It is unknown how long the gene therapy treatment will last. Each person who receives gene therapy will not have the same result. The goal is to increase clotting factor levels. Your clotting factor level and how long the increased factor level lasts in you may look different from someone else who has received gene therapy.

Inheritance of hemophilia

People with hemophilia who have received gene therapy will still carry the abnormal factor VIII or factor IX gene, which can be passed on to your children.

Maintaining good health

Continue any follow-up appointments recommended by your HTC

Go to scheduled healthcare visits, as your prescriber recommends, to keep you healthy and prevent illness

Keep an eye on your blood pressure and cholesterol levels

For more information on good health, read Accredo's "Living with Hemophilia" book at hemophilia.com/resources.

Additional gene therapy treatments

More research is needed to understand if children are good candidates for gene therapy in the future. Because children grow and change quickly, one dose of gene therapy may not be enough. Even for adults, factor levels may decline over time after receiving gene therapy; however, it is unclear at this time if a second dose of the same gene therapy, or a dose of a different gene therapy, will be possible or available. There are still many unknowns about the possibility of subsequent gene therapy doses.

Future treatments for hemophilia[7]

In the future, other potential treatments for hemophilia may include:

- **Anti-tissue factor pathway inhibitor (TFPI) or anti-TFPI (monoclonal antibody)[8]**: An antibody therapy that blocks TFPI, so it cannot work normally. TFPI keeps the blood from clotting. If TFPI is blocked, it can help clotting to occur.
- **Antithrombin interference RNA therapy (RNAi or iRNA)[9]:** A therapy that blocks antithrombin. Antithrombin keeps the blood from clotting. If antithrombin is blocked, it can help clotting to occur.

Learning about gene therapy options for hemophilia may feel overwhelming

Although you may still have some outstanding questions, we at Accredo hope the information in this book has given you a starting point for additional discussions with your healthcare providers and your family to determine whether gene therapy may be an option for you.

Whether you and your family, with the guidance of your healthcare provider, decide to pursue gene therapy options or continue your current treatment, Accredo is here to support your decision. Through dedicated teams in the Bleeding Disorders Therapeutic Resource Center, Accredo will support your needs as you continue your path to thriving. It is our commitment to you and to the hemophilia community to adapt and improve through these times of change as new treatment opportunities become available.

More information and resources are available at hemophilia.com/resources

Notes

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Glossary and helpful terms

Adeno-associated virus (AAV)
(*ade*·*no* uh·sow·see·ay·tuhd vai·ruhs)
Viruses that are similar to adeno viruses, but are changed and cannot make people sick.

About half of all living people have been exposed to some form of adenovirus in their lifetime. After the body has detected an adenovirus infection, it remembers the virus and produces antibodies to fight the virus if the body sees it again. Antibodies are proteins produced by the body's immune system when it detects harmful things like germs. Any prior antibodies made from the body fighting off adenovirus can get confused and attack the AAV "taxi" carrying the healthy gene and destroy it, so that it won't work for treatment of hemophilia.

Antibodies (an·ti·baa·dees)
Proteins in the body, produced in order to fight disease.

Anti-tissue factor pathway inhibitor (TFPI or anti-TFPI)
(an·tee·*tish*·oo fak·tr path·way uhn·hi·buh·tr)
A monoclonal antibody therapy that blocks TFPI, so it cannot work normally. TFPI keeps the blood from clotting. If TFPI is blocked, it may help clotting occur.

Antithrombin interference RNA therapy (iRNA)
(an·tee·thraam·bn in·tr·fee·ruhns r·n·a theh·ruh·pee)
A therapy that blocks antithrombin. Antithrombin keeps the blood from clotting. If antithrombin is blocked, it may help clotting occur.

Blood vessels (blud ves·uhlz)
The tubes that carry blood in the body.

Bone marrow (bohn marr·oh)
A thick kind of jelly inside the bones. Bone marrow makes all kinds of special cells, for example: blood cells, brain cells, skin cells or heart cells.

Cardiovascular (kaar·dee·ow·va·skyuh·lr)
About the heart (cardio) and the blood vessels (vascular).

Cells (selz)
The very small units that make up all living things. The body is made of billions of cells. Each cell in the human body contains about 25,000 genes.

Chromosome (kro·moh·some)
Come in sets of two and might contain hundreds of genes. In humans, a cell contains 46 individual chromosomes or 23 pairs of chromosomes (remember, chromosomes come in pairs). Half of these chromosomes come from one parent and half come from the other parent.

Clinical trials (kli·nuh·kl trai·uhlz)
Where research about a treatment is tested on people.

Clotting factor proteins (klo·ting fak·tr prow·teenz)
Proteins made in the liver that help the blood to clot when needed.

DNA (deoxyribonucleic acid)
(dee·ox·see·ri·bo·nyoo·clay·ik *as*·id)
The genetic information inside the cells of the body that helps make people who they are. Chromosomes and genes are made of DNA. Inside of the cells, the DNA in a gene gives instructions for making the proteins, which make up the entire body — like in a cookbook recipe or the code to a video game.

Endothelial cells (*en*·doh·thee·lee·uhl selz)
The main type of cells found on the inside of blood vessels and the heart.

Factor proteins (fak·tr pro·teenz)
Refers to clotting factor proteins.

Gene (jeen)
Each cell in the human body contains about 25,000 to 35,000 genes. Genes come in pairs. Genes carry the information that decides what is passed on to someone (inherited) from their parents, like blue eyes or brown hair. Each parent passes along just one copy of genes to make up the genes their child has. Genes are found on tiny spaghetti-like structures called chromosomes and chromosomes are found inside cells. Genes are so small they can't be seen with just the eyes.

Hemophilia (hee·mo·**fee**·lee·uh**)**
A bleeding disorder, usually inherited, in which the blood does not clot properly. This can lead to bleeding without a cause and/or bleeding following injury or surgery. Blood contains many proteins called clotting factors that can help to stop bleeding.

Immune response (uh·**myoon** re·**spaans)**
How the body recognizes and fights against bacteria, viruses, something that doesn't belong in the body, or seems harmful.

Inactivate (in·**ak**·tuh·vayt**)**
To change something that can cause illness, like a virus, into something that cannot cause illness; or to attack clotting factor protein so it doesn't work inside the body.

Inactivated virus (in·**ak**·tuh·vaytud **vi**·ruhs**)**
Usually made by taking a virus that can make someone sick and changing it so it can no longer make someone sick, but can still be used for other things, like gene therapy transport.

Intravenous infusion (in·truh·**vee**·nuhs in·**fyoo**·zhn**)**
One way of putting fluids, including medicine, into the bloodstream, by using a vein.

Lentivirus (len·tuh·**vi**·ruhs**)**
A type of virus that can actually put its DNA inside the genes of the body. A lentiviral vector is a type of virus that can infect both dividing and non-dividing cells because their virus "shell" can get through to the nucleus or "control center" of the cells that need help.

Liver (li·vr**)**
An organ inside the body. It does many jobs, such as making clotting factor proteins that help the blood to clot.

Modified (maa·duh·fide**)**
Something that has been changed.

Monoclonal antibody
(maa·nuh·**klow**·nuhl **an**·ti·baa·dee**)**
A type of protein that is made in a laboratory and can bind to certain targets in the body, like cells. These antibodies might help a cell work better or block it from working.

Nanoparticles (na·no·paar·tuh·klz**)**
A small particle that ranges between 1 to 100 nanometers in size. Nanoparticles are so small they can't be seen with just the eyes.

Neutralizing antibodies
(noo·truh·lai·zeeng **an**·ti·baa·dees**)**
Proteins the body produces in order to fight disease, but they may also accidently attack clotting factor protein or gene therapy inside the body.

Plasma (plaz·muh**)**
The liquid part of the blood. It is mostly made of water and holds things like proteins, clotting factor, or blood cells.

Proteins (pro·teens**)**
The building blocks for everything in the body. Skin, hair, muscles, bones, teeth, and blood, are made up of proteins. Those proteins help the body stay healthy, grow, and work properly.

Recombinant (ree·**kom**·bih·nunt**)**
Something that was changed and made in a lab, like factor.

Reservoir (reh·zr·vwaar**)**
A place where anything is collected or accumulated in large amount.

RNA (ribonucleic acid) (ri·bo·nyoo·**clay**·ik ***as***·id**)**
A copy of DNA. Inside of the cells, the DNA in a gene gives instructions for making the proteins, which make up the entire body — like in a cookbook recipe or the code to a video game. The RNA is the one that goes out to do work throughout the cell.

Stem cells (stem selz)
Cells in the body that can change and turn into any cell with a special job. These cells are made inside of the bones, in the bone marrow.

Vector (vek·tr**):** A biological vector is a living thing that carries a disease-causing agent from reservoirs to the host.

Virus (vai·ruhs**):** A type of germ. They are very tiny, and when they get inside the body, can make someone sick. Viruses cause colds, chicken pox, measles, flu, and many other diseases. The viruses used to move hemophilia gene therapy into the body do not cause illness.

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This guide is provided for informational purposes only. Please contact Accredo or your healthcare provider if you have any questions or need specific instructions on how to administer your medication.

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