Hemdifferently

A guide to understanding the science behind gene therapy research

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What is gene therapy?

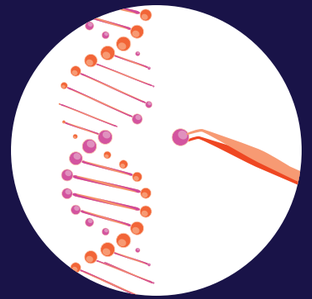
A POTENTIAL GENETIC SOLUTION BEING RESEARCHED

A **genetic** condition could potentially have a genetic solution. This logical thinking has led to more than 50 years of gene therapy research. Today, gene therapy is being evaluated in multiple clinical trials to determine benefits and risks for a range of genetic conditions, including hemophilia A and B.

50+ YEARS OF RESEARCH

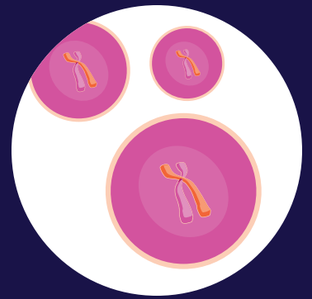
- Gene therapy has been explored as a potential treatment approach for more than 50 years
- More than 2500 gene therapy studies have been completed, are ongoing, or have been initiated worldwide

THREE METHODS OF GENE THERAPY ARE BEING EXPLORED



Gene Editing

Repairing or replacing a **mutated gene**



Cell Therapy

Removing **cells** from the body, modifying them, then delivering them back into the body

Gene Transfer

Introducing a working copy of the gene into the body

To explore current research in gene therapy, visit **ClinicalTrials.gov**.

The 5 steps of investigational gene therapy

GENE TRANSFER

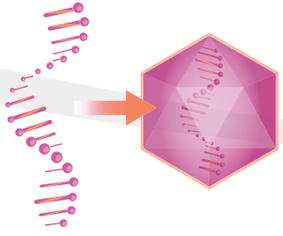
One method of gene therapy currently being explored in clinical trials is called **gene transfer**. This approach aims to introduce a working, or functional, **gene** into the body to research if it can produce a needed **protein**.

1

CREATING A WORKING GENE

2

BUILDING A THERAPEUTIC VECTOR



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DETERMINING ELIGIBILITY

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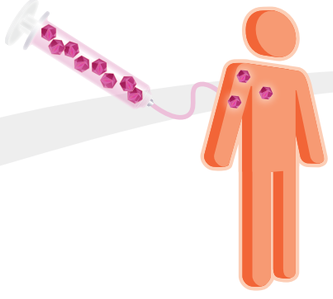
DELIVERING THE WORKING GENE



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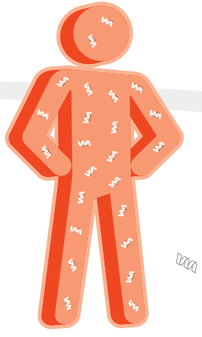
MONITORING SAFETY AND EFFICACY



=New proteins

No gene therapies for hemophilia A or B have been determined to be safe or effective or approved for use.

For more about how gene therapy is designed to work, visit **HemDifferently.com**

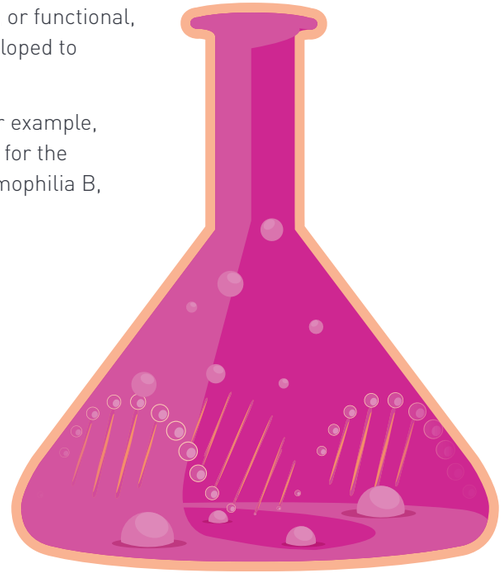
See pages 6-11 for more detailed information about each step of gene transfer therapy.

STEP 1: CREATING A WORKING GENE

The **gene transfer therapy** process begins when a working, or functional, **gene** is created in the laboratory. The **working gene** is developed to contain the instructions for making a needed **protein**.

Scientists design working genes to meet specific needs. For example, in patients with hemophilia A, an F8 gene is needed to code for the **factor VIII** protein, which is essential for clotting, and in hemophilia B, an F9 gene is needed to code for the **factor IX** protein.

Gene transfer therapy has been evaluated in more than 900 clinical trials



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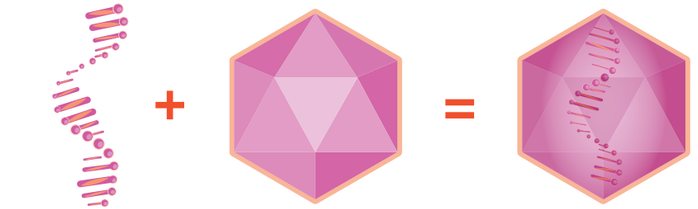
STEP 2: BUILDING A THERAPEUTIC VECTOR

The **working gene** now has to be delivered into the body. To do so, a **therapeutic vector** is used. This therapeutic vector is created by modifying a naturally occurring virus; the shell of the virus is created without the viral **DNA** and the working gene is put inside the empty shell. No longer a virus, the therapeutic vector is designed to deliver the working gene to the **cells** in the body where it is needed.

How is a therapeutic vector made?



WORKING GENE DNA | EMPTY VIRAL SHELL | THERAPEUTIC VECTOR

Therapeutic vectors
The working gene DNA is protected and transported into the body via a therapeutic vector.

More about therapeutic vectors

Like a working gene, a therapeutic vector is created in the laboratory. Trillions of vectors are created by scientists who build the empty outer shell of the virus. Because the body has a natural defense against external **proteins**, the shell is needed to protect the working gene and serves as a transport vehicle to guide it to the proper cells within the body. The viral shell is sometimes called a **neutralized virus** because viral DNA is absent.

STEP 3: DETERMINING ELIGIBILITY

As part of gene therapy research, a healthcare provider must determine whether a patient is eligible. Factors such as age, gender, and organ health may be considered.

Additional eligibility criteria

Therapeutic vectors being used in research are commonly made from **adeno-associated viruses (AAVs)**. These viruses are not known to make people sick. They are found naturally around the world, so some people will have already developed immunity to them via exposure at some point in the past. Having pre-existing immunity to the AAV used in gene therapy could reduce or eliminate its effectiveness. Because of this, candidates may have to be screened with a blood test to ensure that they do not have immunity.

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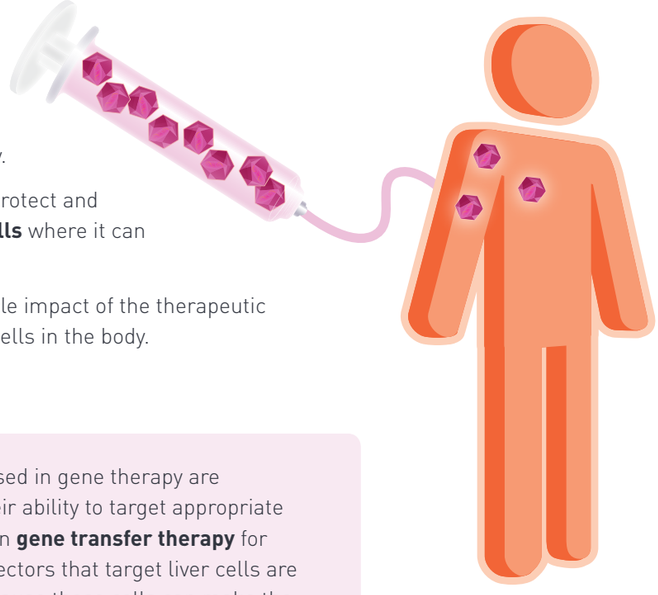
STEP 4: DELIVERING THE WORKING GENE

Once the patient is determined to be eligible, the gene therapy is ready for administration to evaluate its safety and impact.

A single, one-time infusion in an appropriate clinical setting delivers large numbers of therapeutic vectors into the body.

The **therapeutic vector** is designed to both protect and guide the **working gene** toward preferred **cells** where it can be used to make the needed **proteins**.

Research is ongoing to determine the possible impact of the therapeutic vector delivering the working gene to other cells in the body.



The specific vectors used in gene therapy are chosen because of their ability to target appropriate cells within the body. In **gene transfer therapy** for hemophilia A and B, vectors that target liver cells are being investigated because these cells can make the proteins required for blood to clot.

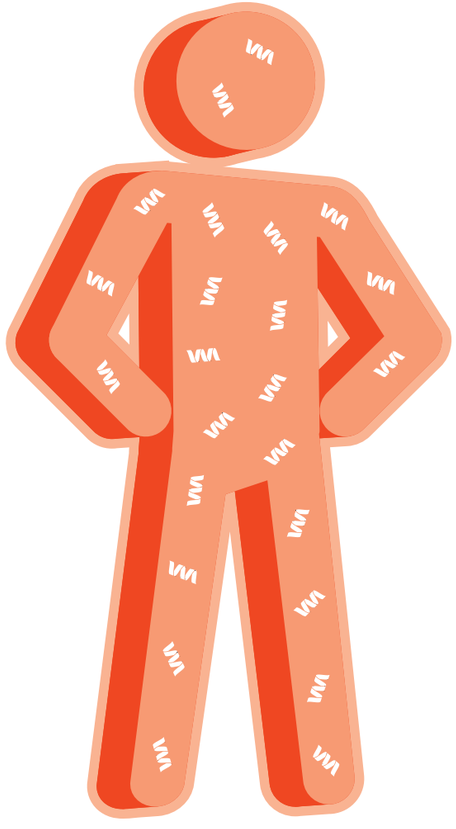
STEP 4 CONTINUED: DELIVERING THE WORKING GENE

Once in the body, the new **gene** is designed to do the work of the gene that is missing or isn't functioning properly. The goal is to provide instructions for the body to make the **protein** it needs on its own, and ongoing research is evaluating the risks and impact of introducing the new gene.

Does it replace the mutated or non-working gene?

Because the new, **working gene** is not intended to become part of your **DNA**, the original missing or **mutated gene** is left unchanged. **Gene transfer therapy** is not designed to replace or edit the existing gene, which means that the mutated gene could still be passed to future generations.

For more about how gene therapy is designed to work, visit **HemDifferently.com**



STEP 5: MONITORING SAFETY AND EFFICACY

Regular monitoring after gene therapy is important because it allows researchers to understand any risks and what impact the gene transfer is having. Patients in clinical trials meet with their care teams for blood tests and to discuss their medication regimen and lifestyle to collect data as part of the study.

As with all medications, response to gene therapy may vary. How long gene therapy might keep working is being evaluated in ongoing clinical trials with researchers aiming to create a long-lasting therapy.

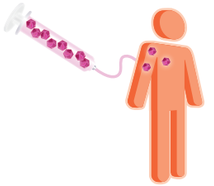
=New proteins

What are the goals of gene transfer therapy in clinical trials?

Clinical trials are underway to determine the risks and whether there is a need for further treatment. They are also determining if the burdens of chronic disease could be reduced or eliminated for some people. It's important to remember that the long-term effects of **gene transfer therapy** are also being studied and have not been determined.

Many gene therapies are under investigation for a range of conditions. No gene therapies for hemophilia A or B have been determined to be safe or effective or approved for use.

POSSIBLE GOALS BEING RESEARCHED



Introducing working genes

One goal of **gene transfer therapy** being investigated is to introduce **working genes** into the body to function in place of the **mutated genes** responsible for the **genetic** condition.

Producing protein

Also being researched is whether the new, working gene helps the body produce the **protein** it needs to function properly. For example, in hemophilia A or B, the goal is to allow the body to produce **factor VIII** or **factor IX**, respectively, on its own.

Eliminating or reducing treatment burdens

Ongoing research is trying to determine whether gene therapy can help the body produce the proteins it needs, possibly lessening or eliminating the need for other treatment and routine disease management. Research is also looking at whether it might increase or lessen the physical, mental, and emotional burdens of a disease. Although gene therapy may not be able to address preexisting damage, trials are also testing whether it may be able to slow progression of any future damage.

What are the possible risks of gene therapy?

Many forms of gene therapy are being researched in adults, at least initially. Some gene therapies may not work in patients with certain antibodies or other preexisting conditions. Ongoing clinical trials are being conducted across a variety of **genetic** conditions to determine the possible risks of treatment with gene therapy.

SAFETY IS KEY

It's important to know that many safety precautions are taken when developing gene therapies. **Clinical trials in the United States are closely monitored by the FDA and the National Institutes of Health. Patient safety is the top priority.**

POSSIBLE RISKS

Gene transfer that uses **AAV vectors** to deliver new genetic material may have several risks:

- As with any gene therapy, the body's immune system could respond to the newly introduced **therapeutic vector** as if it were an intruder. An immune system reaction can lead to inflammation and other serious risks
- While the objective of using a particular vector is to direct the new **gene** to a specific tissue type, vectors can travel to other **cells** that weren't targeted. Scientists are studying the potential safety impact of therapeutic vectors traveling to other tissue types
- After delivery of the gene therapy, the remaining vector particles can be released from the recipient's body. Called **vector shedding**, this can occur through bodily fluids such as urine, saliva, or semen. Vector shedding raises the possibility of passing those remaining materials on to untreated individuals through close contact. The significance of vector shedding is currently being evaluated in gene therapy clinical trials
- Whether gene therapy may have an adverse impact on the health of the organ or tissues targeted is being evaluated in long-term studies
- Gene therapy may result in creation of too much of the protein. The effect of this overproduction, or overexpression, could vary based on the type of protein being created. The significance of overproduction is currently being evaluated in gene therapy clinical trials
- For some people, gene therapy may not work at all. It is not yet clear how long the effects of gene therapy may last

Gene Therapy Research Glossary

Adeno-associated virus – A type of virus that occurs in nature, but is not believed to cause illness in humans. It requires another virus, such as an adenovirus or herpesvirus, in order to reproduce. It is currently being researched in gene transfer therapy as part of a therapeutic vector to introduce functional genes into cells.

Cell – The fundamental, structural, and functional unit of living organisms. Gene transfer therapy research is evaluating whether it can target specific cells in order to evaluate the safety risks and impact with the body.

DNA (deoxyribonucleic acid) – The molecular basis of heredity in humans. Mutations in DNA can cause genetic conditions like hemophilia.

Factor VIII – A blood-clotting protein encoded by the F8 gene. Coagulation factors are essential in the formation of stable blood clots. Factor VIII is missing or not working in people with hemophilia A. Research is ongoing to determine if gene therapy may help people with hemophilia A produce their own factor VIII.

Factor IX – A blood-clotting protein encoded by the F9 gene. Coagulation factors are essential in the formation of stable blood clots. Factor IX is missing or not working in people with hemophilia B. Research is ongoing to determine if gene therapy may help people with hemophilia B produce their own factor IX.

Gene – A part of a DNA molecule that tells your body how to make a protein. A mutation within certain genes can lead to lacking or missing proteins, which can lead to genetic conditions. Gene therapy aims to help the body produce the protein it needs.

Gene Transfer Therapy – One method of gene therapy currently being explored in clinical trials. This approach aims to introduce a working gene into the body to evaluate whether it can produce a missing or deficient protein.

Genetics – The study of genes and their heredity.

Mutation – A change in the structure of a gene that then becomes a non-working form, which may cause problems (or damage) and may be passed along to future generations. It is caused by the alteration, deletion, insertion, or rearrangement of parts of DNA.

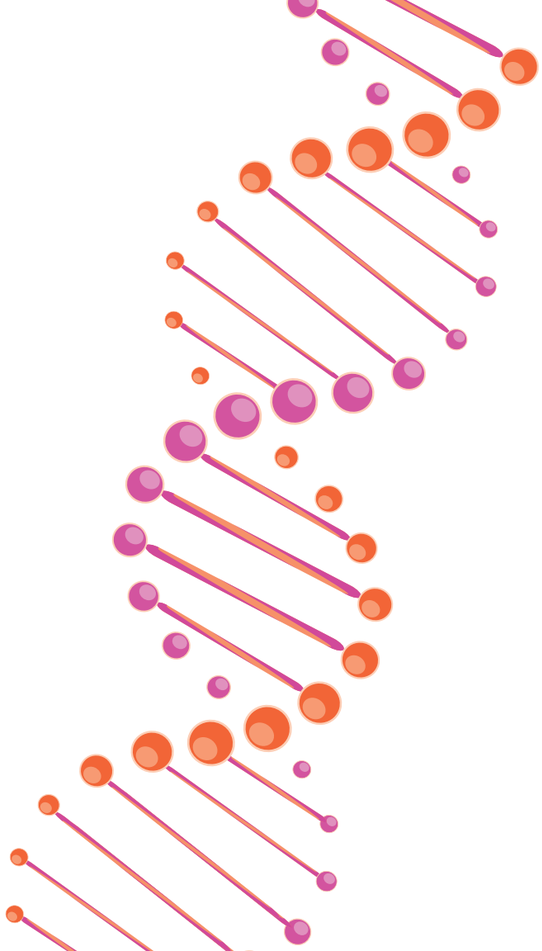
Neutralized virus – The shell of a virus without any viral DNA inside. In gene transfer therapy, the shell is used to protect and transport the functional gene DNA.

Protein – A substance created by a gene that performs various biological functions. Examples include enzymes, hormones, and antibodies. Proteins also make up our bones, organs, and tissues.

Therapeutic vector – A vehicle used to deliver the working, or functional, gene into the body.

Vector shedding – The release of vector particles from the body of the person who has received gene therapy. Scientists are studying clearance of these materials from the body and whether they could pose any risk to others or to the environment.

Working gene, or functional gene - A piece of DNA designed by scientists to make a desired protein. It is intended to supplement the functionality of a mutated or missing gene to target the specific needs of different genetic conditions.



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MOISTEN, FOLD, SEAL, AND MAIL.

GET AN INSIDER'S LOOK AT THE SCIENCE BEHIND ONGOING GENE THERAPY RESEARCH

Gene therapy is being researched in multiple clinical studies for a range of genetic conditions—including hemophilia A and B.

Whether you're a person with hemophilia, a caregiver, or a healthcare provider looking to help educate the bleeding disorders community—HemDifferently is here to keep you in the know.

Scan the QR code now or visit **hemdifferently.com/contact** to sign up digitally to receive the latest updates on gene therapy research. Prefer snail mail? Fill out the form below.

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Which best describes you?

☐ I have Hemophilia A
☐ I have another bleeding disorder
☐ I am a caregiver
☐ I am an advocacy team member
☐ I am a healthcare provider
☐ None of the above apply

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