

An Introduction to Gene Therapy for Genetic Diseases

Exploring the gene addition approach



This information has been provided in response to an unsolicited request.

What Are Genetic Diseases?

Genetic diseases are caused by changes (or mutations) in one or more genes.¹ **Genes** are the instructions the body uses to make the proteins it needs to function properly. Genes are made of a substance called **DNA** that carries information in the body's cells.² Changes in the DNA can prevent a gene from working properly and can sometimes lead to genetic disease.¹

How Are Genetic Diseases Treated?

For some genetic diseases, there are treatments available that can help manage the symptoms of the disease. These treatments help patients deal with existing signs of disease and may also be used to help prevent future complications.³

Another approach for treating certain genetic diseases is called **bone marrow transplant (BMT)**, also called **stem cell transplant** or **hematopoietic stem cell transplant (HSCT)**.^{4,5}

BMTs for genetic diseases address the disease at the gene level. They introduce blood stem cells that have a functional (or working) copy of the defective gene into the patient's body.⁴

Stem cells are used in transplants because they have the ability to form many other types of cells in the body.^{4,6} **Blood (or hematopoietic) stem cells** are found in the bone marrow and circulating blood.⁷



Stem cells have the ability to form many other types of cells.⁶

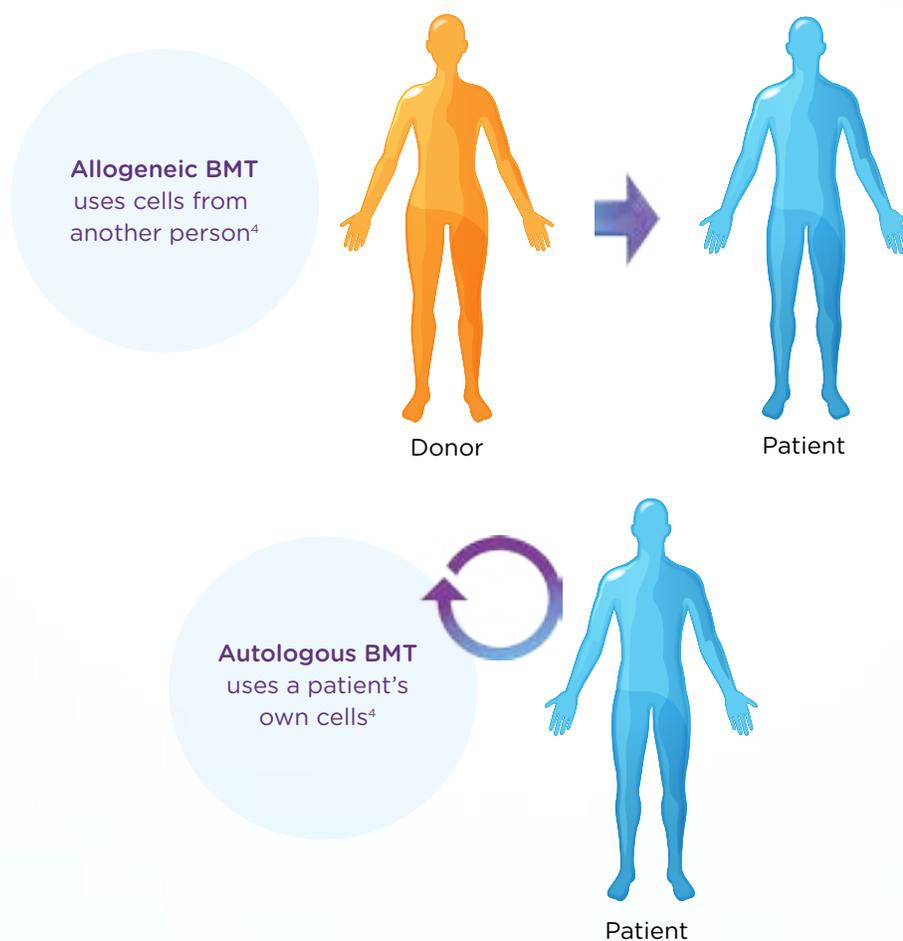
Types of Bone Marrow Transplant

There are two types of BMT, **allogeneic** and **autologous**.⁴

Allogeneic transplant for genetic diseases uses cells from another person, or a **donor**, who does not have the disease to introduce cells with the functional gene into the patient's body.⁴

Autologous BMT uses a patient's own cells for the transplant, so no donor is required.⁴

There are serious risks associated with a BMT. The patient should discuss their specific situation and all risks with their doctor.



What Is Gene Therapy?

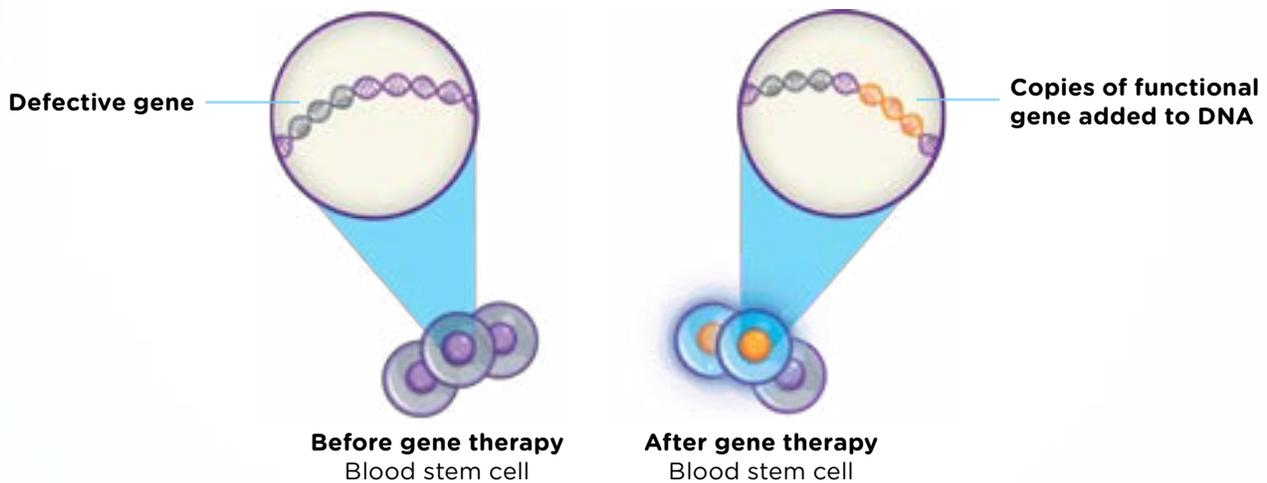
Gene therapy can describe many things. Today, there are a few different approaches to gene therapy being studied⁸:

- Turning off genes that are causing problems
- Replacing a defective gene with a functional gene
- Adding functional genes to help do the work of a defective gene

For approaches using the gene addition method, addition of a functional gene can take place either outside (ex vivo) or inside (in vivo) the body.⁸ Here, we discuss one of the procedures used for gene addition outside the body.

How Are Genes Added?

Gene addition uses a delivery system, called a **vector**, to insert the new genes directly into cells. Vectors can be selected parts of viruses that have been genetically modified so they can deliver the new genes into the cells without causing an infectious disease. Viruses are used because they have a natural ability to deliver genetic material into cells.⁸



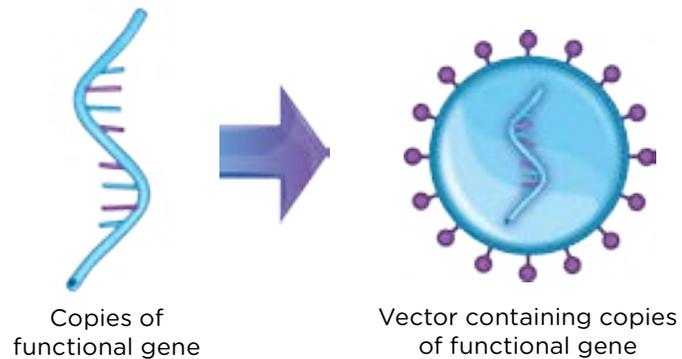
The goal of gene therapy is to change or replace faulty genes with functional ones in order to prevent, treat, or cure a disease.⁸

What Happens During Gene Therapy?



1 Copies of the Functional Gene Are Added to the Vector

Before a patient begins gene therapy treatment, copies of the functional gene are added to a vector (delivery system) that will carry the gene into the patient's cells. The copies of the functional gene are the template (or instructions) the patient's cells will use to create their own gene. This step is done in a laboratory.



Collection of Patient's Cells



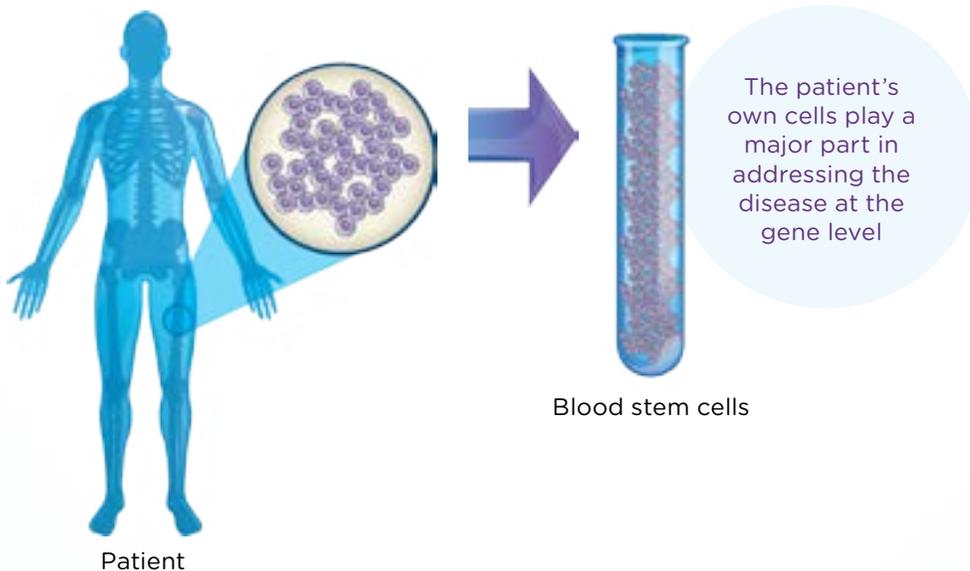
2 The Patient's Cells Are Collected

Next, blood stem cells are collected from the patient. Blood stem cells can be collected from a vein in the patient's arm using a special machine through a process called **apheresis**. For this process, the patient will first receive medicine to get more of the stem cells into the circulating blood for collection.⁹

There may be some risks with the cell collection and the medicines received during the process. The patient should discuss these and all risks with their doctor.

Stem cells can also be collected directly from the patient's bone marrow through a process called **bone marrow harvest**.⁹ The stem cell collection procedure used depends on the patient and the type of disease being treated.⁴

The collection process is performed in a hospital setting.⁹ After the collection process is complete, the patient is discharged from the hospital.



The Gene Therapy Is Created

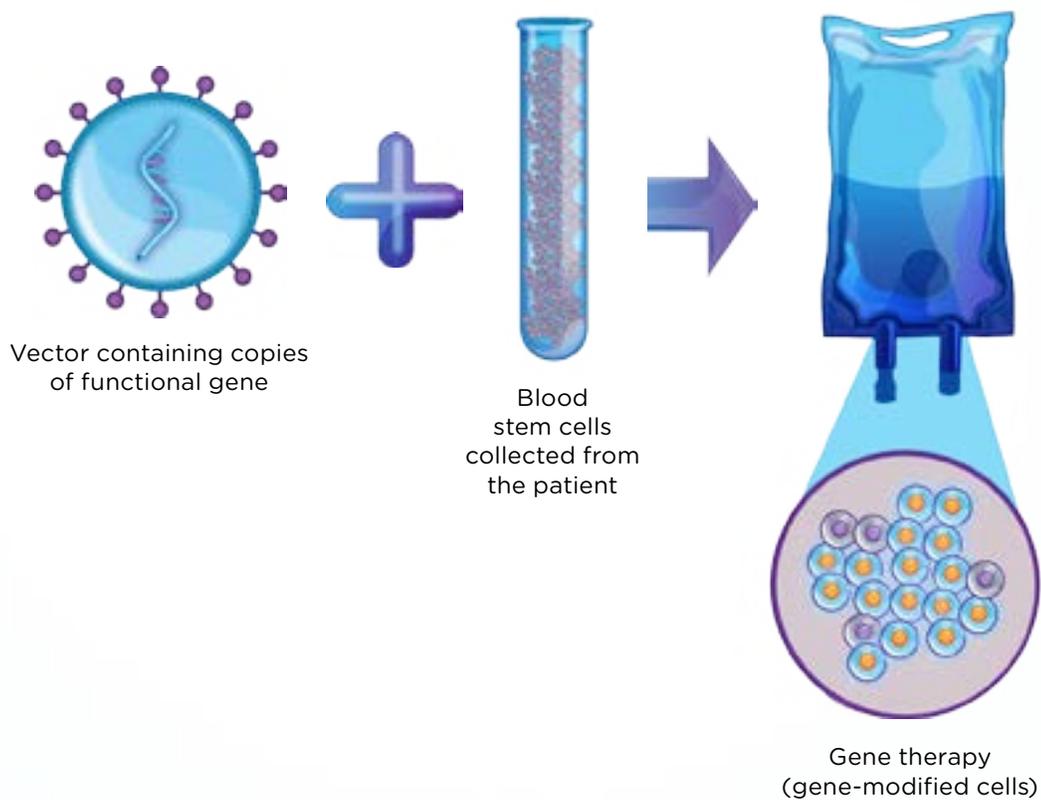


3

Vector With Copies of the Functional Gene Is Added to the Patient's Cells

The copies of the functional gene are then added into the patient's blood stem cells that were collected to make the **gene therapy**. The cells that now have functional copies of the gene are referred to as **gene-modified cells**.

After going through several tests to ensure that there are plenty of cells and it is ready for use, the gene therapy can be used in the patient.



Preparing for Gene Therapy Administration

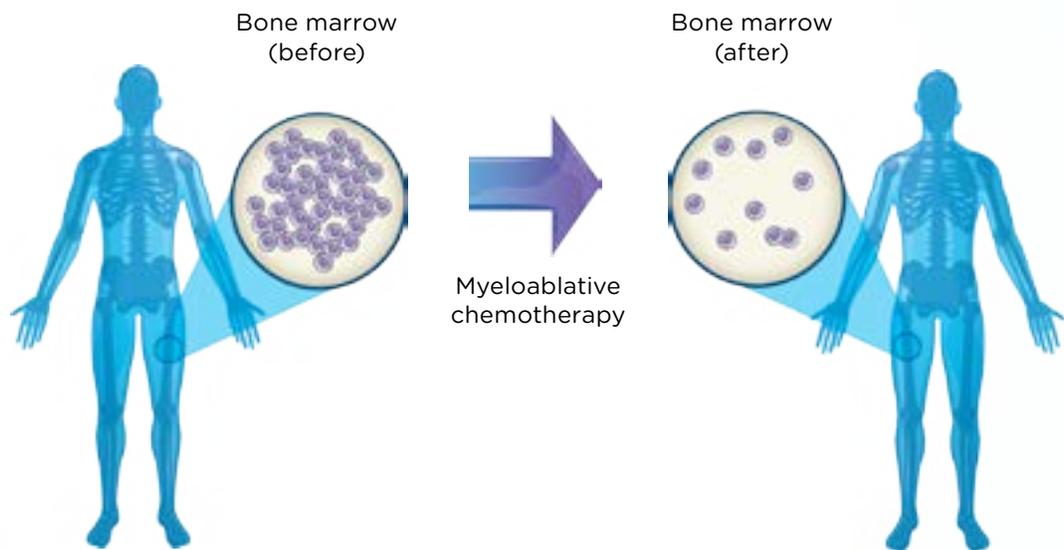


4 The Patient Is Prepared to Receive Gene Therapy

The patient's body is prepared to receive gene therapy using **chemotherapy**. This type of chemotherapy is administered in the hospital and may also be referred to as **myeloablative conditioning** or **myeloablation**.

Chemotherapy is used for nearly all types of stem cell transplant. This process clears out the patient's faulty bone marrow cells to make room for the gene therapy.⁴ This helps the gene therapy engraft successfully and produce a robust amount of new cells with copies of the functional gene.

There are serious risks with this type of chemotherapy, so the patient must remain in the hospital following chemotherapy until after the gene therapy has been infused and bone marrow cells and immune system cells have recovered.



Risks of Myeloablative Chemotherapy

Chemotherapy can affect the immune system and may cause other serious side effects. The patient should discuss their specific situation and all risks with their doctor.

Infusion

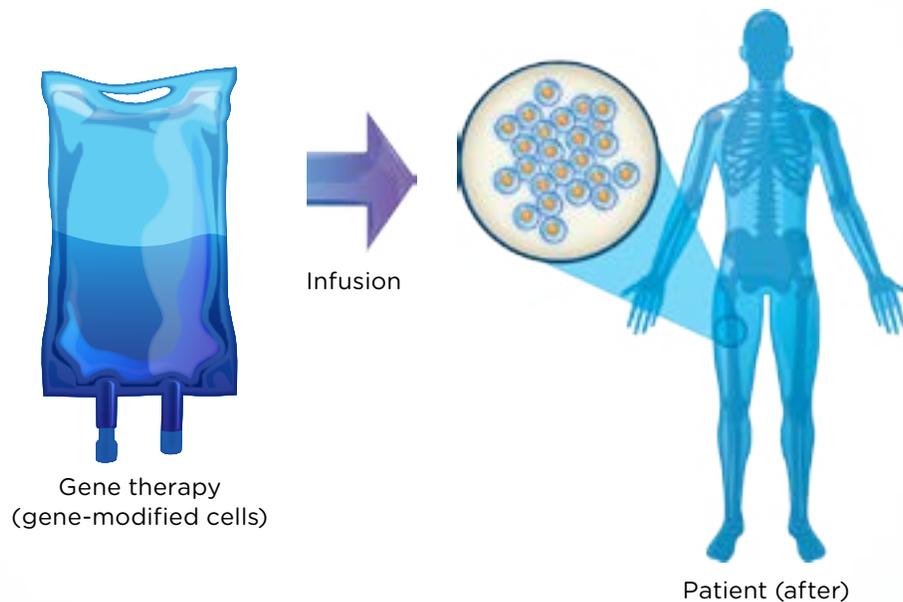


5 The Gene Therapy Is Infused Into the Patient

After chemotherapy is complete and the patient is ready, the gene therapy is usually delivered by intravenous (IV, or into the vein) **infusion**. This is done at the hospital.

After the gene therapy has been infused, the patient's cells will need time to multiply and produce new cells so the patient's body has enough cells with the functional gene. This process is called **engraftment**. There is a risk that the patient's cells may not multiply. This is known as failure of engraftment. If this occurs, the patient will be given unmodified backup or reserve cells to help them to form blood cells again.

The patient remains in the hospital until they have enough new cells, their key immune cells have returned to adequate levels, and their doctor determines that it is okay for them to be discharged. Until the patient's cells have recovered, they will have increased risk for bleeding and serious infections. The patient should discuss these and all risks with their doctor.



Follow-up Care

After the patient is ready to be discharged from the hospital, they will require follow-up monitoring. To monitor gene therapy safety, how well the gene therapy is working, and to collect information that may help other patients who are considering gene therapy, follow-up may extend over a period of years. The extent and length of follow-up required for each patient will be determined by the patient's healthcare team.

Important Terms

All Important Terms are defined within the context of gene therapy and are specific to gene therapy procedure and administration.

Allogeneic hematopoietic stem cell transplant (allogeneic HSCT or allo HSCT) [also allogeneic bone marrow transplant or allogeneic stem cell transplant]—transplant in which the patient receives blood stem cells or bone marrow cells from another person called a donor

Apheresis—in gene therapy, a process of separating stem cells from blood cells

Autologous hematopoietic stem cell transplant (autologous HSCT or auto HSCT) [also autologous bone marrow transplant or autologous stem cell transplant]—transplant in which the patient's own blood stem cells are used as the source for the procedure

Blood stem cells (also hematopoietic stem cells or blood-forming cells)—cells found in the bone marrow and circulating blood that can develop into blood cells, such as red blood cells, white blood cells, and platelets

Bone marrow harvest—a process of removing stem cells from the bone marrow

Bone marrow transplant (BMT) [also stem cell transplant or hematopoietic stem cell transplant]—the process of infusing blood stem cells to correct or restore normal cell function in a patient with a genetic disease or in a patient whose bone marrow or immune system is defective or damaged

Chemotherapy—the use of medicines to destroy or stop the growth of certain types of cells

DNA (deoxyribonucleic acid)—the substance (or molecule) that carries genetic information in a human cell

Donor—for hematopoietic stem cell transplant, a person who donates their blood stem cells

Engraftment—the process of transplanted cells being accepted by the patient's body and producing enough new cells to reach an adequate level

Gene—the instructions made of DNA that the body uses to make the proteins it needs to function properly

Gene-modified cells—stem cells in which functional copies of a defective gene have been added to the DNA to help correct the function of the cell

Gene therapy—a method of addressing genetic disease at the gene level with the goal of changing the course of the disease

Genetic disease—a disease caused by a mutation (or problem) in one or more genes

Important Terms (Cont)

Hematopoietic stem cell transplant (HSCT) [also bone marrow transplant or stem cell transplant]-

the process of infusing blood stem cells to correct or restore normal cell function in a patient with a genetic disease or in a patient whose bone marrow or immune system is defective or damaged

Infusion-in gene therapy, the process of delivering cells into the body through a vein (or intravenously)

Myeloablative conditioning [also myeloablation or myeloablative chemotherapy conditioning regimen]-

the process of clearing out bone marrow cells using chemotherapy

Stem cells-cells in the body in which all other cells are formed and become different cell types with specific functions, such as blood cells, brain cells, muscle cells, or bone cells

Stem cell transplant [also bone marrow transplant or hematopoietic stem cell transplant]-the process of infusing stem cells to correct or restore normal cell function in a patient with a genetic disease or in a patient whose bone marrow or immune system is defective or damaged

Vector-a modified (or changed) virus used as a vehicle to deliver functional (or working) copies of a gene into the patient's blood stem cells

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