CURE SICKLE CELL.

National Heart, Lung, and Blood Institute

SICKLE CELL DISEASE TRANSFORMATIVE THERAPIES

A Resource from the Cure Sickle Cell Initiative

Sickle cell disease (SCD) is a genetic disorder that affects hemoglobin, the major protein in red blood cells that carries oxygen throughout the body. In SCD, red blood cells are misshaped or "sickle"-shaped due to a faulty hemoglobin protein, called hemoglobin S. The sickled cells can block blood flow and cause pain and organ damage.

Thanks to advances in research and care through the years, there are more ways to manage sickle cell disease. These include blood transfusions, as well as medications that can prevent sickling, reduce complications, prevent or treat pain, and lower risk of infection.

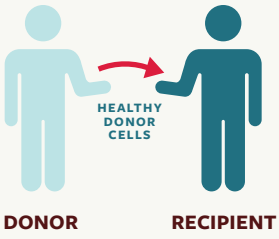
For some people living with SCD, transformative therapies—including **blood and bone marrow transplants** and **gene therapies** may also be options.

There are a number of similarities and differences between the two treatments, including the following:

"There are several ways blood and bone marrow stem cells can be used to reduce the symptoms of sickle cell disease. Gene therapies use a person's own stem cells, while bone marrow transplants use the stem cells of a matched donor." [1]

Bone marrow transplants

A blood or bone marrow transplant, also called a hematopoietic stem cell transplant (HSCT), replaces blood-forming stem cells that aren't working properly, with healthy donor cells.[2]



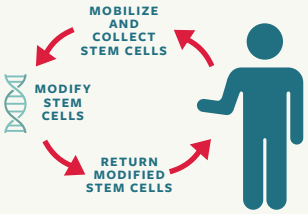
Requires a well-matched donor, usually a close blood relative.[4] But with recent advances, the donor can also be a half-matched (haploidentical) or even a well-matched unrelated donor.[5]

A provider infuses the donor's cells into the recipient's blood. The cells travel in the bloodstream to the marrow spaces inside the bones.

Gene therapies

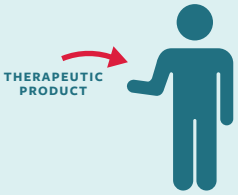
Gene therapies aim to treat or cure conditions by correcting problems in a person's DNA.[3] This involves replacing a gene (gene correction), turning off a gene (gene silencing), or adding a new gene (gene addition).[4]

Uses the patient's own stem cells, "mobilized" from the bone marrow with medication. These cells are then collected and taken to a lab for modification.[1]



The stem cells are then returned to the patient's body.[1] The cells travel in the bloodstream to the marrow spaces inside the bones. Currently this is done "ex-vivo" which means the technique is done outside of the body.

Researchers are also studying "in-vivo" approaches where the therapeutic product is delivered directly into a patient's cells while they are still inside the body.



In both procedures, once inside the bone marrow, the stem cells can produce healthy red blood cells that have hemoglobin that doesn't sickle.[4]

Below is a list of common questions about blood and bone marrow transplants and gene therapies. Consider using this resource to help discuss these options with your provider so you can make an informed decision about whether transformative therapies may be right for you.

BLOOD AND BONE MARROW TRANSPLANTS	GENE THERAPIES
▸ What is done to prepare the body for the therapy?	
In both blood and bone marrow transplants and gene therapies, simple or exchange transfusions are usually performed as a first step. Then, the patient's bone marrow needs to make space for the new stem cells. This is done with a chemotherapy drug or radiation through a process called "conditioning."[6]	
▸ How long is the process?	
First, a suitable donor must be found, which can take a long time. Once the donor is identified, the process can take weeks to months. A provider will monitor the patient's recovery, usually for up to one year or more.[2]	The process can take months to years. Gene therapy involves a series of steps over a long period of time. Learn about the steps and timing.[7]
▸ How have patients with SCD benefited from these therapies?	
Because the transplanted cells from the donor will produce the normal hemoglobin, the red cells will not sickle, so the majority of SCD-related symptoms should be greatly reduced. However, the damage to the patient's organs caused by SCD before the transplant may not be reversed. A blood and bone marrow transplant is a potential curative therapy for some people with sickle cell disease.[4] Research has shown a 92% to 94% five-year overall survival rate of patients who have received allo-HSCT from an HLA-identical sibling donor.[8]	Because the patient's own cells have been modified and now produce a non-sickling hemoglobin, or enough fetal hemoglobin that will reduce sickling, the majority of SCD-related symptoms should be greatly reduced. However, the damage to the patient's organs caused by SCD before the procedure may not be reversed. Clinical trials have shown that patients who participate in gene therapy have less sickled hemoglobin, less hemolysis (red blood cell breakdown) and little to no vaso-occlusive pain events.[7]
▸ What are some potential risks or complications from these therapies?	
Possible complications of blood and bone marrow transplants include: graft-versus-host disease (GVHD) caused by transplanted cells attacking the recipient's organs, higher risk of some cancers later in life, infertility, seizures, serious infections, and transplant failure.[4] Both therapies have the same risk of cancer from the conditioning process.	Gene therapies are newer and were approved for SCD in 2023. Gene therapies do not have the risk of GVHD. They can increase a person's risk of cancer—from either the conditioning process or the gene therapy vector which could affect nearby cancer-causing genes. Experts believe that it is a small risk; however, the exact likelihood is still not known.[7]
▸ What treatments may be necessary after the procedure?	
Following bone marrow transplants, patients may need immunosuppressive drugs[9] to reduce the risk of the body rejecting the transplanted cells.	Patients who receive gene therapy would not need immunosuppressive drugs because they are receiving their own modified cells.[9]
▸ Can the sickle cell gene still be passed on to a person's children?	
Yes, even if a person with SCD is treated with a blood and bone marrow transplant or gene therapy, they still can pass the sickle cell gene to their children.[4]	
▸ Do I need to consider fertility preservation?	
Chemotherapy is used during the conditioning process for both procedures so there is a risk of infertility. Patients should consider discussing fertility preservation options, such as freezing eggs or sperm, with their provider.[7]	
▸ What are the potential long-term effects of these therapies?	
Possible long-term risks include: organ damage, abnormal growth of lymph tissues, infertility, and hormone changes, among others.[10]	Gene therapies are newer and potential long-term effects are still being identified. Experts recommend that people who have gene therapy be followed for 15 years after the procedure to examine the treatment over time and learn more about long-term risks.[7]
▸ Are these therapies accessible?	
Currently, only a few medical centers do transplants and gene therapies for people with sickle cell disease. However, providers and U.S. government programs are working to make these therapies available to more people. Although these treatments may be costly, they are designed to only be given once.[4]	

For more information about transformative therapies, visit:

Cure Sickle Cell Initiative

NHGRI: Understanding gene therapy approaches

ASGCT: Gene Therapy Approaches

[1] https://www.genome.gov/research-at-nhgri/Projects/Democratizing-Education/understanding-gene-therapy-approaches
[2] https://www.nhlbi.nih.gov/health/blood-bone-marrow-treatments
[3] https://www.nhlbi.nih.gov/health/genetic-therapies
[4] https://www.nhlbi.nih.gov/health/sickle-cell-disease/treatment
[5] Akshay Sharma; How I treat sickle cell disease with gene therapy. Blood 2024; 144 (26): 2693–2705. doi: https://doi.org/10.1182/blood.2024024519
[6] https://curesickle.org/sites/default/files/CSC_Conditioning_Patient_Bi_FOLD_FactSheet_042321_Digital_CenterSpread.pdf
[7] https://www.genome.gov/research-at-nhgri/Projects/Democratizing-Education/sickle-cell-disease-gene-therapy-FAQ
[8] Rostami T, Rad S, Rostami MR, Mirhosseini SA, Alemi H, Khavandgar N, Janbabai G, Kiumarsi A, Kasaeian A, Mousavi SA. Hematopoietic Stem Cell Transplantation in Sickle Cell Disease: A Multidmentional Review. Cell Transplant. 2024 Jan-Dec;33:9636897241246351. doi: 10.1177/09636897241246351. PMID: 38680015; PMCID: PMC11057353.
[9] https://www.chop.edu/centers-programs/sickle-cell-and-red-cell-disorders-curative-therapy-center-cured/blood-and-marrow-transplant-vs-gene-therapy
[10] https://www.cancer.org/cancer/managing-cancer/treatment-types/stem-cell-transplant/transplant-side-effects.html