BE THE SPARK

SPARK

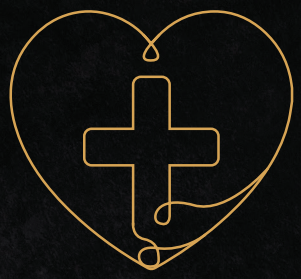
SICKLE CELL TREATMENT OPTIONS

Understanding the treatment options for sickle cell disease

WHAT YOU NEED TO KNOW ABOUT SICKLE CELL AND TREATMENT OPTIONS FOR YOU

This guide aims to explain the different types of sickle cell treatment options, so that you and your healthcare team can make informed decisions about what is right for you. It also provides education on research and development of potential future therapies.

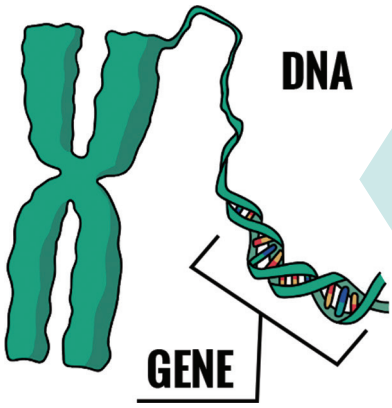
The information provided in this brochure is for educational purposes only and does not constitute medical advice. Individuals should discuss all questions about their medical care with their treating doctors.



Knowing how to manage symptoms and complications can help you or your loved ones better navigate sickle cell care.

SICKLE CELL IS A GENETIC CONDITION

Learning about the role that genes play can help you and your loved ones better understand what causes sickle cell and its symptoms.

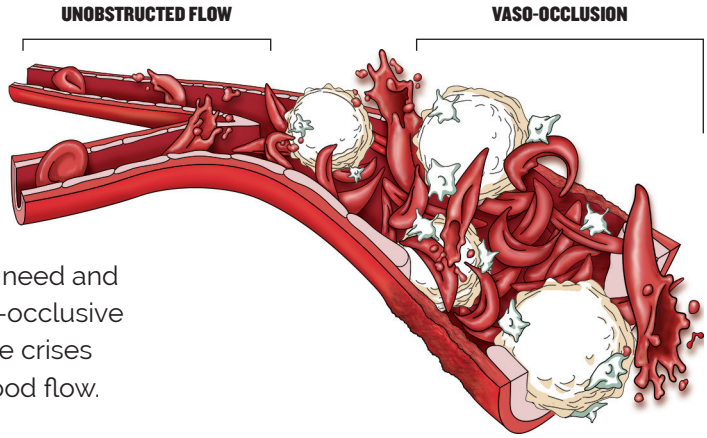


As a lifelong genetic disease, **sickle cell is an inherited condition that begins in your genes.** Your genes provide instructions for your body to create proteins that carry out different functions. Each cell in your body relies on thousands of proteins to do their jobs properly and function correctly, and a mutation in those instructions can cause those proteins or cells to malfunction.

Sickle cell is **caused by a mutation in both copies of the *HBB* gene that you inherit from your biological parents.** This causes the cell to make an abnormal form of hemoglobin called sickle hemoglobin instead of normal, adult hemoglobin. Hemoglobin is a molecule found in red blood cells that carries oxygen to your organs.

Unlike adult hemoglobin, **sickle hemoglobin molecules can change to an abnormal shape when they are low on oxygen.** When there are many sickle hemoglobin molecules in a cell they cause red blood cells to become sickle shaped.

SICKLE HEMOGLOBIN



Sickle-shaped red blood cells can damage blood vessels and block blood flow throughout your body. This blockage, known as vaso-occlusion, can prevent your organs and tissues from getting the oxygen they need and cause vaso-occlusive crises (also known as vaso-occlusive events). In addition to causing extreme pain, these crises can affect any part of the body where there is blood flow.

THERE ARE TREATMENT OPTIONS AVAILABLE

Sickle cell is a complex disease that affects everyone differently. But there has been significant progress in how we treat it, leading to current options that have the potential to help manage acute and chronic symptoms of the disease.

PHARMACOLOGIC TREATMENTS

focus on **relieving pain and managing acute symptoms**. They aim to lessen the frequency and severity of pain crises, reduce blood transfusions and hospitalizations, or improve hemoglobin levels—they also require lifelong use.

BLOOD TRANSFUSIONS

aim to help **relieve symptoms of sickle cell and potentially prevent stroke** in high-risk individuals. Blood transfusions are a common procedure, but risks can include an immune response to the donated blood, infection, and iron overload—they also require lifelong use.

HEMATOPOIETIC STEM CELL TRANSPLANT (HSCT)

(also called a bone marrow transplant or stem cell transplant) is a type of treatment that **replaces blood stem cells** with cells from a donor. This treatment option is usually reserved for people with sickle under the age of 18 who have a matched related donor available.

RESEARCH PROVIDES HOPE FOR NEW OPTIONS

Significant advancements have been made in the treatment of sickle cell, but it is not enough; serious medical and social burdens remain. There is still a need for treatments that can eliminate lifelong symptom management and its unwanted side effects.

PHARMACOLOGIC TREATMENTS

One area of study is expanding available pharmacologic treatments to **target and address symptoms and complications of sickle cell disease** throughout the body. Some methods being investigated aim to:

- stabilize sickled red blood cells to try to prevent them from breaking apart (hemolysis)
- reduce the frequency and effects of vaso-occlusion by impacting how different cells bind and stick to one another
- decrease the inflammation caused by damage from sickled red blood cells that contribute to organ damage

HEMATOPOIETIC STEM CELL TRANSPLANT (HSCT)

Scientists are also working to develop new approaches to help possibly **reduce transplant-related risks involved with HSCT**, such as finding a less-toxic regimen. Scientists are also investigating how to expand the type of donors who are available to patients, as having a human leukocyte antigen (HLA)–matched related donor is a limitation for this type of treatment.

Please note, this list is not comprehensive of all therapies currently in development for sickle cell disease.

HOW GENE THERAPY AND YOUR CELLS COULD TREAT SICKLE CELL

Gene therapy is a treatment approach that uses genetic material, like DNA, with the goal of changing the course of a disease by way of **adding, deleting, or editing genes to help address the disease at the genetic level.** Gene therapy has a long history of research.

For nearly 100 years, scientists have studied the human body and the building blocks of DNA. With each mark of progress comes a better understanding of how our bodies work at the genetic level.

Gene therapy is built on the strong foundation of decades of DNA research and aims to treat the condition at the genetic level. Gene therapies that use your body's own cells and therefore do not require a donor—eliminate some, but not all, risks known to transplant procedures, such as graft-versus-host disease.

We are constantly learning about **how changes to our DNA can prevent our genes from working correctly,** sometimes leading to diseases such as sickle cell disease.

Two examples of gene therapy in sickle cell include **gene addition** and **gene editing**. In both types, your own cells are collected, modified, and reintroduced to your body with the objective of providing new instructions to create hemoglobin.

GENE ADDITION ADDS A WORKING COPY OF A GENE TO YOUR CELLS

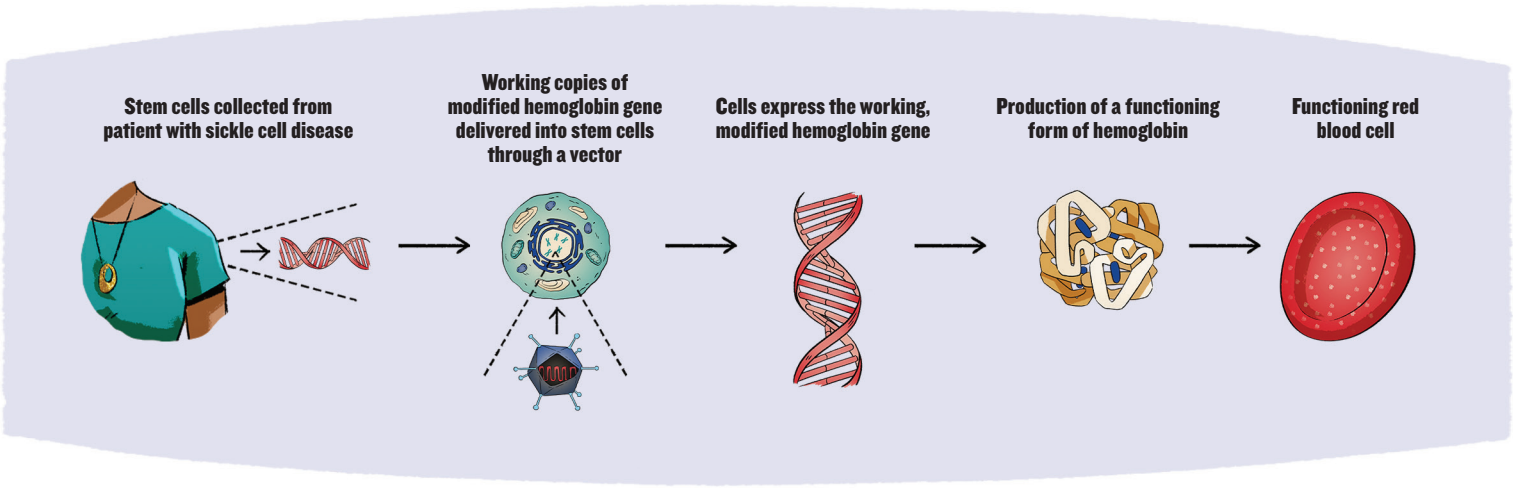
Gene addition therapy is the process of adding modified working copies of a gene to stem cells, collected from a person, to provide a new set of instructions for cells.

So, for individuals with sickle cell disease, that would be adding a working gene that instructs the body to produce a functioning form of hemoglobin that can compensate for sickle hemoglobin.

A VECTOR HELPS DELIVER THE GENE TO YOUR CELLS

The delivery system responsible for delivering the working copies of a modified hemoglobin gene to your cells is called a vector. There are viral vectors (those based on a virus) and non-viral vectors. One of the most widely used and studied viral vector types is a ***lentiviral vector***. The most well-studied lentivirus is human immunodeficiency virus (HIV), and scientists have used its blueprint to design lentiviral vectors for gene therapy. The reason scientists create vectors based on viruses is because viruses are very efficient at delivering genetic material to cells of the body. Though vectors are based on viruses, they do not contain any of the parts of the virus that can cause an infection. Vectors act as a delivery system into cells.

HOW GENE ADDITION WORKS



CAN THE LENTIVIRAL VECTOR USED IN GENE THERAPY CAUSE AN HIV INFECTION?

No; viral vectors cannot cause infection of the virus, because only a few parts of the virus are used.

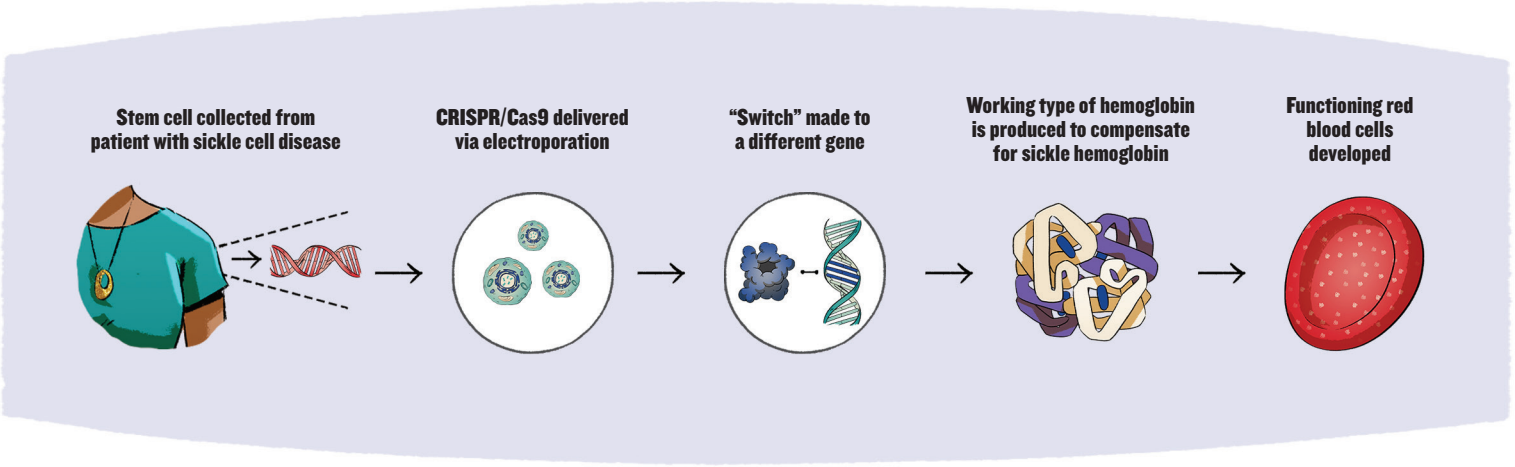
GENE EDITING MODIFIES A GENE INSIDE YOUR CELLS

Like gene addition, gene editing requires the collection of stem cells to start the process.

Gene editing **modifies a person's DNA by either changing a mutated gene directly or by changing a related gene** to compensate for the mutated one. Changing a related gene means turning the on/off switch for a different gene that regulates the production of a type of hemoglobin produced by your body. This switch helps the body increase production of a working type of hemoglobin protein.

One example of gene editing technology is known as CRISPR-Cas9 (Clustered Regularly Interspaced Short Palindromic Repeats), which is found in bacteria. CRISPR uses a delivery system called electroporation. This nonviral technology uses electricity to enable DNA to pass through cell membranes.

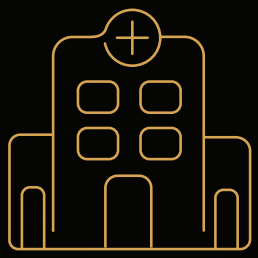
HOW GENE EDITING WORKS



In addition to gene editing and gene addition, there are other types of gene therapy being studied as part of the greater sickle cell disease treatment landscape, like gene correction and gene silencing. These different types of gene therapy continue to evolve rapidly, with many current and upcoming clinical trials to investigate their potential as treatment options for sickle cell disease.

THE GENE THERAPY TREATMENT PROCESS IS COLLABORATIVE

The treatment process for gene therapy relies on **close collaboration between a patient and their primary physician**, their treatment team, and their caregivers. It's important to keep in mind that there are a lot of things to consider when learning about gene therapy.



Gene therapy is a detailed process—**one that takes place over a long period of time**, often with many consultations and visits. That's why staying **informed and having as many conversations as needed are important aspects of the process.**

In general, there are 4 steps to the treatment process: consultation, preparation, treatment, and recovery. Let's take a quick glance at each step on the following page.

STEP 1: CONSULTATION

- **Discuss** the potential risks and benefits of the specific gene therapy
- **Ensure** appropriateness and eligibility of gene therapy. This can include discussions around your or your loved one's physical and emotional health, as well as the existing support network
- **If you or your loved one** decides to discuss or move forward with gene therapy, you or your loved one will need to go through a process called informed consent. Informed consent is where a patient actively participates in discussions with their physician and is empowered to make decisions about their medical care by deciding which treatments they do (or do not) want
- **Discuss** any short- and long-term steps to plan for gene therapy, including healthcare coverage, fertility discussions, timing of treatment, chemotherapy, side effects of gene therapy, and any potential impacts on life, family, and work
- **This consultation step** can take weeks or months, depending on discussions between you or your loved one and the treating physician/treatment team and the timing of the referral. These discussions can include multiple consultations with specialists or physicians at a specialized treatment center with an expertise on gene therapy
- **You or your loved one's** primary physician and care team at the treatment center will work with you to collectively determine if gene therapy is the appropriate treatment choice

STEP 2: PREPARATION

- **Will include** the stem cell collection needed for creating gene therapy *ex vivo* (meaning created outside your body)
- **Physician** will give instructions for any preparation procedures or regimens that your or your loved one will need to complete
- **Usually requires a few days** for the patient to stay in the hospital for stem cell collection. After the collection, it will usually take a few months for the lab to modify the patient's own stem cells to create the gene therapy

STEP 3: TREATMENT

- **Conditioning** with chemotherapy happens at this stage—conditioning is needed for all transplant-based treatments to help maximize the effects of treatment by clearing out the cells that contain the mutated hemoglobin gene and making room in the bone marrow for the modified stem cells. Treatment with chemotherapy includes certain risks, including infertility, which you should discuss with your doctor
- **Gene therapy treatment** that was prepared using your or your loved one's own cells is infused back in. Treatment is often administered by a specialist and can include a specialized care team
- **After treatment**, you or your loved one will remain in the hospital for several weeks—this time span includes a recovery period and the time needed for engraftment and monitoring. Engraftment is when transplanted stem cells enter the blood and make their way to the bone marrow to start making new blood cells

STEP 4: RECOVERY/LONG-TERM FOLLOW-UP

- **You will be discharged** once your physician has decided it is safe for you or your loved one to leave the hospital
- **May include follow-up appointments** at the specialized treatment center and with you or your loved one's physician
- **May include home healthcare** for a period of time
- **May include enrolling** in a registry to monitor long-term treatment results
- **After gene therapy is administered**, there is a critical process of recovery and a follow-up monitoring period that can last for at least 15 years. If you or your loved one is treated with gene therapy, you will work with your physician to monitor the effect of treatment during this period. You or your loved one may be asked whether you're interested in enrolling in registries to help track the long-term outcomes of treatment

THERE ARE RISKS WITH GENE THERAPY

Like any treatment, there are risks associated with gene therapy. **Some risks of gene therapy include, but are not limited to:**

- **Conditioning:** Conditioning with chemotherapy can cause a number of side effects. Some side effects can happen quickly including hair loss, rash, nausea or vomiting, and infections, some of which can be life-threatening. Other side effects that can take longer to show up are tooth and mouth issues, not being able to have children, cancers, or liver or bone damage
- **Platelet engraftment failure:** Platelets are the blood cells that help blood to clot. An engraftment failure could prevent new platelets from developing, which causes the risk for bleeding
- **Neutrophil engraftment failure:** Neutrophils are the most common type of white blood cell in your immune system, which is the reason an engraftment failure makes you more susceptible to infection
- **Insertional Oncogenesis:** In gene addition, the new genes from the vector insert into the DNA of the person's stem cell via a process called integration. With this process comes a chance that the integration of the new DNA may change the activity of nearby genes, which could cause changes like uncontrolled cell growth, resulting in blood cancer. Individuals receiving gene therapy should be monitored lifelong by their physician for the development of blood cancer
- **Off-Targeting:** In gene editing, there is a chance that the technique used could make changes at a different site than intended, posing the risk of causing changes to healthy genes
- **Unintentional Gene Inactivation:** In any type of gene therapy, there comes a risk of unexpected complications that could prevent the function of another important gene, possibly leading to tumor formation and cancer

When living with sickle cell, it's important to know you do have options for treating it. Educating yourself on currently available treatment options—as well as developing therapies—can help spark change in how you navigate your treatment journey.

Scan here to learn more about sickle cell treatment.
SparkSickleCellChange.com/Treatment

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