Rewriting the Blood: How CRISPR Gene Editing Is Transforming Sickle Cell Disease

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Executive Summary: Although the genesis of sickle cell disease occurs due to one mutation in the DNA, the consequences may affect almost all organs of the body. This mutation affects the hemoglobin – protein that transports oxygen within the red blood cells. If there is not enough oxygen in the blood cells, abnormal hemoglobin may cause sticking and change the shape of cells into a rigid sickle. This type of cells may clog blood vessels leading to pain, anemia, stroke, and organ damage. In December 2023, the United States Food and Drug Administration (FDA) approved Casgevy, the first gene therapy that uses CRISPR/Cas9 technology. In July 2026, the agency approved this treatment for patients aged two years and older that experience recurring pain crises. Casgevy is not the treatment that fixes sickle cell mutation. Casgevy edits the control region of the BCL11A gene to allow the production of fetal hemoglobin that stops much sickling. During the clinical trials of Casgevy, 29 of 30 patients had no vaso-occlusive crisis for twelve consecutive months. Despite such impressive results, Casgevy requires preparation, chemotherapy, a lengthy hospitalization period, and many years of follow-up. This case study will describe the technology itself, the importance of results, and safety, financial, and access issues (FDA, 2026; Frangoul et al., 2024).

Background: The condition is transmitted from parents to their offspring where they inherit two defective copies of the HBB gene from each parent. The change involves the substitution of an amino acid called beta-globin in the gene, whereby the glutamic acid is substituted by the valine. This leads to the formation of long chains by the sickle hemoglobin also known as HbS whenever there is less oxygen. The red blood cells consequently become rigid, sticky, and crescent shaped. CDC states that an estimated 100,000 people suffer from the disease in the USA, with millions suffering worldwide. In the USA, people from African descent or of African-American origin are the most commonly affected with the disease, although it affects individuals of all races and ethnicities. Treatment for the disease ranges from oral medication such as hydroxyurea, blood transfusions, and newer medications that prevent the complications associated with the disease. Bone marrow stem cell transplant from a matched donor could cure the disease, however, lack of donors and risk of graft-versus-host disease makes it difficult for many.

The Casgevy Case: From a One-Letter Mutation to an Approved Therapy

The uniqueness of Casgevy stems from the fact that scientists decided not to target the HBB mutation directly. Scientists found inspiration in something natural in human physiology. In an unborn fetus, hemoglobin is made in its fetal form known as HbF. The fetal hemoglobin lacks the beta-globin chain which is affected in sickle cell disease. In the first months of life, a particular protein called BCL11A works to turn off the fetal hemoglobin production to make room for the adult one. Patients suffering from sickle cell disease typically do not develop severe manifestations until their level of HbF decreases. Furthermore, scientists noticed that people who naturally retain HbF in large amounts do not suffer from the disease as severely.

Enhancers are regions in DNA responsible for regulating the activity of genes at certain times. An enhancer was found to exist in BCL11A, and the enhancer is specifically crucial in red-blood-cell formation. CRISPR/Cas9 technology is able to edit the BCL11A enhancer by making cuts to the enhancer region in hematopoietic stem cells. This results in deletions and insertions as the cell repairs itself, rendering the enhancer defective, hence reducing the activity of the BCL11A,

increasing fetal hemoglobin, and decreasing sickling. Due to the specific activity of the enhancer in the red-blood-cell pathway, the technique tries to keep BCL11A's other functions intact (Canver et al., 2015; Frangoul et al., 2021).

How the Treatment Works

1. COLLECT	2. EDIT	3. TEST	4. CONDITION	5. RETURN
Blood-forming CD34+ stem cells are collected from the patient.	CRISPR/Cas9 disrupts the BCL11A enhancer outside the body.	The edited cells are checked, frozen, and prepared as Casgevy.	Busulfan chemotherapy clears space in the bone marrow.	Edited cells are infused and begin making HbF-rich blood cells.

Figure 1. Simplified ex vivo treatment pathway. The gene editing happens outside the patient's body.

This technique is referred to as ex vivo editing since the cells undergo the editing process outside the body. Initially, medical professionals assist in mobilizing blood-forming stem cells from the bone marrow to the bloodstream via a procedure known as apheresis. Subsequently, in a manufacturing facility, guide RNA directs Cas9 enzyme to the BCL11A enhancer. Guide RNA serves as an address, whereas Cas9 serves as molecular scissors. The edited cell product is analyzed for identification, purity, and edit quality prior to being sent back to the treatment center. At this point, the individual is administered with busulfan chemotherapy. The therapy helps kill numerous bone marrow cells and pave the way for the edited cells. Lastly, the edited cells are infused through an intravenous line. In case of successful engraftment, the edited cells will go on generating blood cells for several years (FDA, 2023; Frangoul et al., 2024).

Clinical Results and What They Mean

In the phase 3 trial, participants were aged between 12 and 35 years old and had undergone at least two vaso-occlusive crises in each of the last two years before screening. Out of 44 participants, 30 people got exagamglogene autotemcel which is the technical name of Casgevy. During the time of the final analysis, there were 30 participants in the primary effectiveness population. Among these 30 participants, 29 did not have any severe vaso-occlusive crises for twelve consecutive months which was 97%. Moreover, all 30 participants avoided hospitalization for severe crises for twelve consecutive months. All of the treated participants had neutrophil and platelets engraftment and there were no cancers found. These findings were particularly significant since participants had gone through severe crises in the past (Frangoul et al., 2024).

Not being a randomized clinical trial comparing Casgevy to a placebo means that there are limitations on what the study conclusions may state. However, the difference between recurring events of pain crisis and a whole year without any such incidents was significantly larger than expected as random variance. In addition, the follow-up revealed that the stem cells with the edits retained high production of HbF. A subsequent study discovered improvement in quality-of-life parameters for the participants of the initial study; specifically, those related to pain, physical functioning, and activities of daily living. The procedure has been characterized as a potential functional cure, as it allows elimination of the symptoms but does not eliminate all copies of the sickle mutation. Further studies are needed to establish long-term outcomes (Sharma et al., 2025).

Why This Gene-Editing Strategy Works

- **It edits stem cells, not mature red blood cells:** A red blood cell survives for only about four months and has no nucleus to edit. A blood-forming stem cell can self-renew and create many generations of red blood cells, making long-term benefit possible.
- **It copies a protective natural condition:** People who keep producing fetal hemoglobin because of naturally occurring variants can have much milder sickle cell disease. Casgevy tries to recreate part of that biology.

It avoids a donor mismatch: The patient's own cells are used, so there is no risk that donor immune cells will attack the patient's tissues. This removes graft-versus-host disease, one major problem with donor transplants.

It targets a control switch: The edit does not have to repair the same HBB mutation in every cell. It only has to disrupt enough copies of the enhancer to raise HbF to a protective level.

Risks, Limits, and Ethical Questions

The words one-time treatment can make Casgevy sound like a simple injection, but the full process resembles a bone marrow transplant. Busulfan conditioning can cause severe drops in blood cells, infections, mouth sores, nausea, liver complications, and infertility. Patients may need fertility preservation before treatment. They must also spend weeks in or near a specialized hospital while their immune system and blood counts recover. In the clinical trial, the overall safety pattern was mostly consistent with busulfan conditioning and autologous stem cell transplantation, meaning that much of the immediate danger came from preparing the body for the edited cells rather than from CRISPR alone (Frangoul et al., 2024; CMS, 2026).

CRISPR creates a double-strand break in DNA. Most cuts occur at the intended BCL11A enhancer, but a guide RNA can sometimes direct Cas9 to a similar sequence elsewhere. These off-target edits could damage an important gene. Repairing a double-strand break can also create large deletions, rearrangements, or unexpected changes near the target. No editing-related cancer was identified in the main trial, but that does not prove the lifetime risk is zero. The FDA therefore required long-term monitoring, including a postmarketing study that follows recipients for fifteen years (FDA, 2023).

Access may be the largest ethical challenge. Casgevy was listed at $2.2 million per patient, not including fertility services, hospitalization, chemotherapy, or travel. Treatment is available only at trained centers with stem-cell transplant and cell-processing experience. This is especially important because many people with sickle cell disease are covered by Medicaid, and most people with the disease worldwide live in countries that do not have enough advanced treatment centers. A technology can be scientifically successful and still fail many patients if it cannot be delivered fairly. The Centers for Medicare & Medicaid Services created an outcomes-based access model to help states cover gene therapies, but long-term solutions will also require simpler manufacturing, safer conditioning, and lower prices (CMS, 2026).

The Next Generation of Editing

Casgevy proves that edited human stem cells can become an approved medicine, but it is probably not the final form of the technology. Base editing changes one DNA letter into another without cutting both DNA strands. In 2021, researchers used an adenine base editor to convert the sickle variant into a naturally occurring, non-sickling hemoglobin variant called HbG-Makassar in cells and mice. In 2026, an early clinical study of risto-cel used base editing on the HBG1 and HBG2 promoters to raise fetal hemoglobin. At six months, the mean HbF level was above 60% among 13 patients with available data. However, the follow-up was still short, and one of the 31 treated patients died from idiopathic pneumonia syndrome, showing that the transplant process remains serious even when the edit itself is more precise. Base editors may reduce some risks connected to double-strand breaks, although they can still cause unwanted bystander or off-target changes (Gupta et al., 2026; Newby et al., 2021).

Prime editing is another possibility. It uses a modified Cas protein, a reverse transcriptase enzyme, and a specialized guide RNA to write a new DNA sequence. In patient-derived stem cells and mouse studies, prime editing corrected the sickle HBB variant back to the normal sequence and reduced sickling without requiring a double-strand break or a donor DNA template. The method is more complex, and scientists must improve editing efficiency, manufacturing, and stem-cell survival before it can become routine. Another major goal is nontoxic conditioning. If antibodies or other targeted

drugs could clear only the necessary bone marrow cells, patients might avoid chemotherapy and infertility (Everette et al., 2023).

Comparing Curative and Gene-Editing Strategies

Approach	What Changes	Main Advantage	Main Limitation	Status in 2026
Matched-donor stem cell transplant	Replaces the patient's blood system with donor stem cells.	Long experience and can eliminate sickle blood production.	Needs a suitable donor; risks rejection and graft-versus-host disease.	Established curative option for selected patients.
CRISPR/Cas9: Casgevy	Disrupts the BCL11A enhancer to reactivate fetal hemoglobin.	Uses the patient's own cells; strong clinical results.	Double-strand breaks, busulfan conditioning, cost, and complex care.	FDA approved for recurrent VOCs in patients age 2+.
Base editing	Changes selected DNA letters in HBB or fetal-hemoglobin control regions.	No double-strand break; can make precise protective variants.	Bystander edits, off-target changes, and limited long-term data.	Early clinical or preclinical development, depending on method.
Prime editing	Rewrites the sickle HBB sequence back toward the normal sequence.	Direct correction without a double-strand break or donor template.	More complicated system and currently lower or variable efficiency.	Preclinical research in patient cells and animal models.

Table 1. Major curative and experimental approaches for sickle cell disease. Only Casgevy uses approved CRISPR gene editing.

Conclusion

Casgevy is an important turning point in biotechnology because it moved CRISPR from a laboratory tool to an approved treatment. Its design also shows that gene editing does not always have to repair a mutation directly. By changing the BCL11A control system, scientists used a second biological pathway to protect red blood cells. The trial results show that this strategy can stop severe pain crises for many patients, but the treatment's risks and difficult delivery prevent it from being a simple cure for everyone. The next challenge is not only to make editing more precise. Researchers also need to remove toxic chemotherapy, shorten manufacturing, lower costs, and build treatment systems that reach the populations most affected by sickle cell disease. Casgevy may be the first chapter of clinical gene editing, but its long-term impact will depend on whether the science can become safer and more accessible.

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