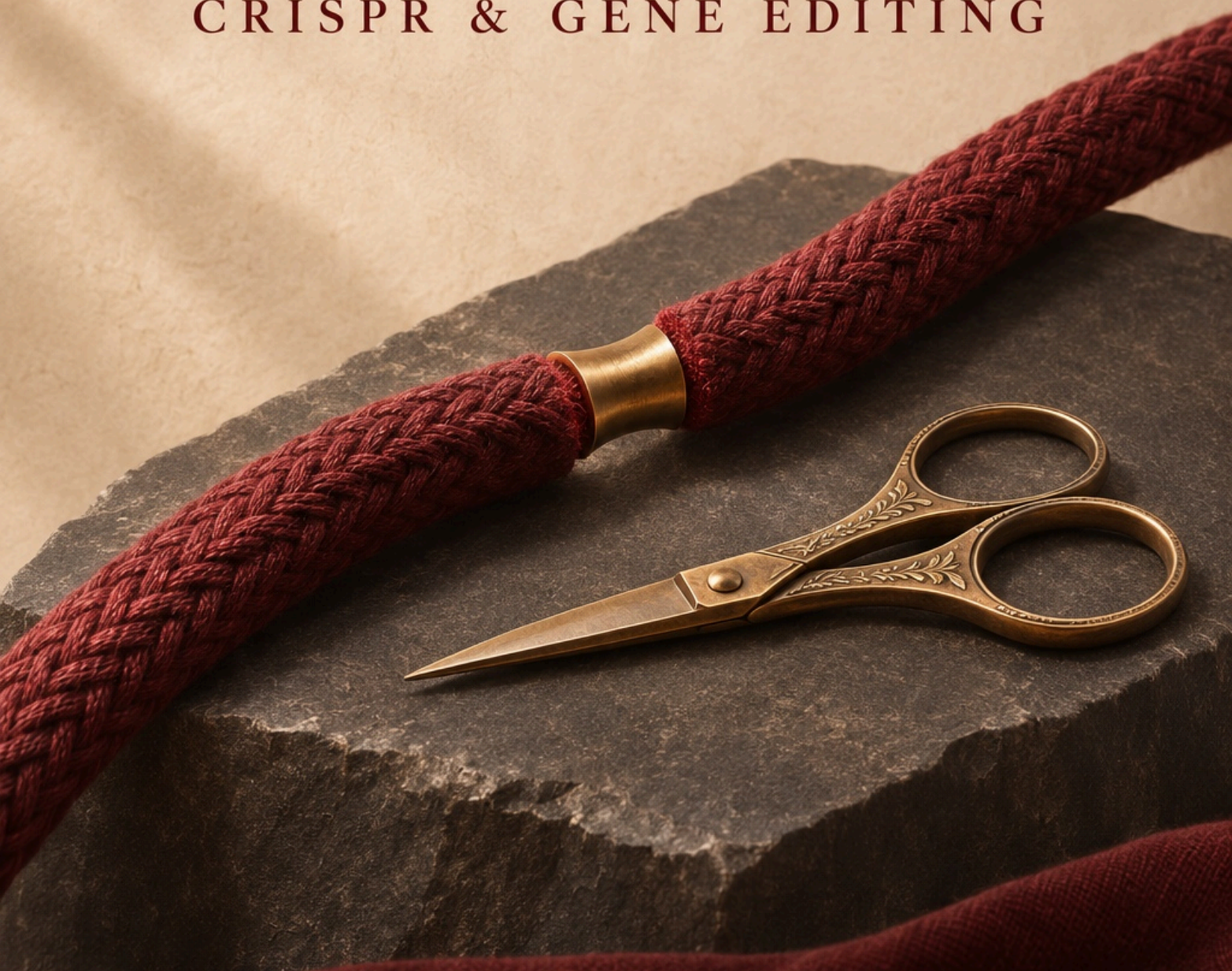
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# When an Edit Changes a Life

CRISPR & GENE EDITING



NOVEMBER 2026

# When an Edit Changes a Life

## CRISPR, sickle cell disease, and the whole treatment

The Arising · Gene editing & sickle cell disease · November 2026 · John Griffin, MD

The achievement becomes easier to understand when we start with the illness, rather than the tool.

For someone living with severe sickle cell disease, a painful crisis can interrupt work, school, family plans and ordinary life. The possibility of a sustained period without those crises is not an abstract improvement in a laboratory number. It is a change in what a person might be able to count on.

A 2024 study of an edited-cell treatment called exagamglogene autotemcel, or exa-cel, reported that 29 of 30 participants with enough follow-up met its main goal: at least 12 consecutive months without a severe vaso-occlusive crisis. Forty-four people had received the treatment overall. [1]

That is a striking result. Understanding it properly means keeping the achievement together with the treatment's demands, the denominator and the length of observation.

This story is not about editing every cell or solving aging. It is about a specific change in a particular group of cells, for a defined disease, with a meaningful clinical outcome.

## Why sickle cell disease causes crises

Hemoglobin is the protein inside red blood cells that carries oxygen. In sickle cell disease, an inherited change can cause hemoglobin to behave abnormally and red blood cells to become rigid and sickle-shaped. Blood flow can be obstructed, contributing to painful episodes and other serious complications. [1]

“Vaso-occlusive” means involving blocked blood vessels. A severe vaso-occlusive crisis is more than an inconvenience. The study defined qualifying events using specific clinical criteria, rather than counting every ache or pain as the same outcome.

The question was whether treatment could prevent those severe events for a sustained period. That makes the result different from a study showing only that a biological marker moved in a favorable direction.

## What was changed, and where?

The treatment used each participant's own blood-forming stem and progenitor cells. These are cells capable of helping rebuild the blood-cell supply. They were collected and edited outside the body, then infused back after preparative treatment. Editing outside the body is called ex vivo editing. [1]

The CRISPR-Cas9 system targeted a regulatory region associated with a gene called BCL11A. More specifically, it targeted an enhancer active in the red-blood-cell lineage. An enhancer is a stretch of DNA that helps control how a gene is used. [1]

The aim was to increase fetal hemoglobin, a form normally prominent before birth. This helps protect against the sickling process. The strategy did not repair the inherited sickle-cell mutation. It edited a separate regulatory region in collected blood-forming cells to increase fetal hemoglobin. [1]

That difference is worth understanding. “Gene editing” is not one interchangeable medicine. The target, cells, delivery method and surrounding care determine what an intervention can do.

## The people in the 2024 report

The phase 3 study was single-group and open-label. Everyone who received the study treatment was in the same treatment group, and participants and clinicians knew what was being given. There was no randomized group receiving a different treatment for comparison. [1]

Participants were 12 to 35 years old and had experienced at least two severe vaso-occlusive crises in each of the two years before screening. These were the study's selection criteria, not a statement of current eligibility for treatment. [1]

Forty-four participants received exa-cel. At the time of the report, follow-up was long enough for 30 to enter the main efficacy evaluation. That evaluation required at least 16 months after infusion. The crisis-free assessment window began 60 days after the last transfusion used for support or sickle cell disease management. [1]

These details explain why “44 treated” and “30 evaluable” are both correct. They describe different groups for different questions.

## What 29 of 30 means

Twenty-nine of the 30 evaluable participants were free from severe vaso-occlusive crises for at least 12 consecutive months. All 30 were free from hospitalization for those crises for at least 12 consecutive months. Median follow-up across the treated group was 19.3 months. [1]

The finding is not the same as saying that 97% of everyone treated was permanently cured. Some treated participants had not yet been followed long enough to enter that endpoint analysis. Meeting a 12-month goal also does not guarantee that no crisis can ever occur afterward.

The paper illustrates that distinction: one participant who had met the response goal later experienced a severe crisis during a parvovirus B19 infection, around 22.8 months after infusion. That later event does not erase the preceding crisis-free interval, but it matters when describing what the endpoint proves. [1]

A useful reading holds both ideas together. Sustained freedom from severe crises is a meaningful outcome. Its durability over a lifetime requires longer observation.

## A strong signal without a randomized comparison

The results were tested against a prespecified statistical threshold. That asks whether the observed response is sufficiently strong relative to a benchmark chosen for the study. It is not the same as directly comparing treatment with another option in randomly assigned groups. [1]

A single-group study can still produce important evidence, especially when the outcome represents a substantial change in a severe disease. But it cannot answer every comparative question on its own.

How does the complete treatment compare with other available approaches for different patients? Which people are most likely to benefit, and who faces greater risk? How do long-term outcomes, practical burdens and access compare?

Those questions need their own evidence and a specialist discussion. The 2024 report should not be made to answer questions it was not designed to settle.

## The treatment is more than the edit

Before receiving the edited cells, participants underwent myeloablative conditioning with busulfan. In everyday language, this is intensive chemotherapy used to prepare the bone marrow for the infused cells. It is a major part of the treatment, not a small preliminary step. [1]

The process includes collecting cells, manufacturing and checking the edited product, preparing the patient, infusing the cells and supporting recovery while blood-cell production becomes established. The scientific precision of the edit does not make the surrounding procedure simple.

It also uses the patient's own cells, which is what “autologous” means. That feature does not eliminate the need for intensive care, monitoring or a careful assessment of risk.

For a person considering treatment, the relevant question is not only “Does the edit work?” It is “What does the whole process ask of me, and what might it make possible?”

## What the safety results showed

In the 44 treated participants, 42 had grade 3 or 4 adverse events, about 95%. These grades describe severe or life-threatening events. Twenty participants, about 45%, had serious adverse events, a separate category that includes outcomes such as hospitalization or life-threatening illness. [1]

The investigators did not attribute any serious adverse events to exa-cel itself. They described the overall safety pattern as generally consistent with busulfan conditioning and transplantation using a person's own stem cells. That distinction is relevant to understanding causes. It does not mean the complete treatment was harmless. [1]

One participant died on day 268 from respiratory failure during COVID-19 infection. The case also involved busulfan-associated lung injury and pre-existing lung disease. Investigators attributed the relevant events to infection and busulfan, not to exa-cel. A balanced account includes the death and that attribution, rather than using either to erase the other. [1]

No cancers had been observed by the report's June 14, 2023 data cutoff. That is reassuring within the observation available. It cannot establish that rare or delayed risks are absent over a lifetime. [1]

## Safety continues after the paper

Current official prescribing information for CASGEVY, the product containing exa-cel, helps place the treatment burden in context. It includes concerns about blood-cell recovery, infection and bleeding, allergic reactions, and uncertainty about unintended editing outside the target site. Conditioning can impair fertility, making fertility-preservation counseling an important part of preparation. [2]

This is not a complete list of risks or a substitute for the prescribing information. The practical point is that follow-up, recovery planning and reproductive goals belong in the discussion before treatment, not only after a decision has been made.

A specialist team can explain how the current label and available evidence apply to a particular person's disease, organ health and circumstances. The ages and outcomes in the historical trial should not be mistaken for a current eligibility checklist.

## Editing DNA is not the same as every form of reprogramming

The exa-cel study concerns an engineered change in a regulatory DNA region in collected blood-forming cells. Other experimental approaches use different mechanisms.

For example, the registered ER-100 study concerns controlled expression of reprogramming factors in retinal cells using a gene-delivery vector. That is a different target, tissue and strategy from editing the BCL11A enhancer outside the body. The registry describes a research protocol, not evidence that ER-100 produces the outcomes reported for exa-cel. [3]

The comparison is useful because sophisticated terms can make unlike technologies sound interchangeable. They are not. A success in one set of cells does not demonstrate that the same result can be achieved in every organ or that aging as a whole has been reversed.

Nor is the exa-cel intervention germline editing. It is not designed to alter eggs or sperm or to pass an engineered change to future generations.

## Who supported the research?

The study was supported by Vertex Pharmaceuticals and CRISPR Therapeutics. The sponsors co-designed the study with its steering committee. Vertex participated in data collection and analysis and supported writing assistance; company employees were among the authors. Those relationships belong alongside the methods and results when readers assess the evidence. Independent follow-up and transparent long-term reporting remain important. [1]

## Four questions worth keeping together

**What exactly changes?** Here, a particular regulatory DNA region is edited to increase fetal hemoglobin. The mechanism should be described as specifically as the result.

**In which cells?** Collected blood-forming cells are edited outside the body. This is not an edit of every tissue or a general claim about all gene-editing methods.

**What improves for the person?** The study measured sustained freedom from severe crises and related hospitalization, not a biological-age score or a promise of universal health.

**What comes with the whole treatment?** Conditioning, recovery, monitoring, possible fertility effects, risks and practical support are part of the decision.

These questions work together. Leaving out any one can turn an accurate fact into a misleading overall story.

## Three ways to read the next headline

**“CRISPR cured 97% of patients.”** Look for the denominator, the endpoint and the follow-up. In this report, 29 of 30 evaluable participants met a defined sustained crisis-free goal; 44 had received treatment. Permanent cure is a stronger claim.

**“It uses your own cells, so it is straightforward.”** Ask about conditioning and recovery. Using a person's own cells does not make intensive chemotherapy or transplantation support disappear.

**“This proves gene editing can reverse aging.”** Ask which disease and cells were studied. A meaningful success for severe sickle cell disease is important without borrowing a claim about every other condition.

These are illustrative reading situations, not individual treatment recommendations.

## A frontier made concrete

The power of this study is that it connects a molecular strategy to an outcome people can recognize: a sustained interval without severe crises.

That achievement does not become smaller when its limits are stated. It becomes clearer. The denominator tells us whose outcomes were evaluated. The treatment burden tells us what the result required. Continued follow-up tells us what still needs to be learned.

The code can sometimes be changed in a way that changes a life. The details define the achievement, and the whole person remains the reason it matters.

## Sources and further reading

[1] Haydar Frangoul, Franco Locatelli, Akshay Sharma and colleagues. Exagamglogene Autotemcel for Severe Sickle Cell Disease. New England Journal of Medicine. 2024;390(18):1649-1662. Primary publication record. Full paper.

[2] CASGEVY prescribing information. Official DailyMed label.

[3] ER-100 registered study, NCT07290244. ClinicalTrials.gov record.

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