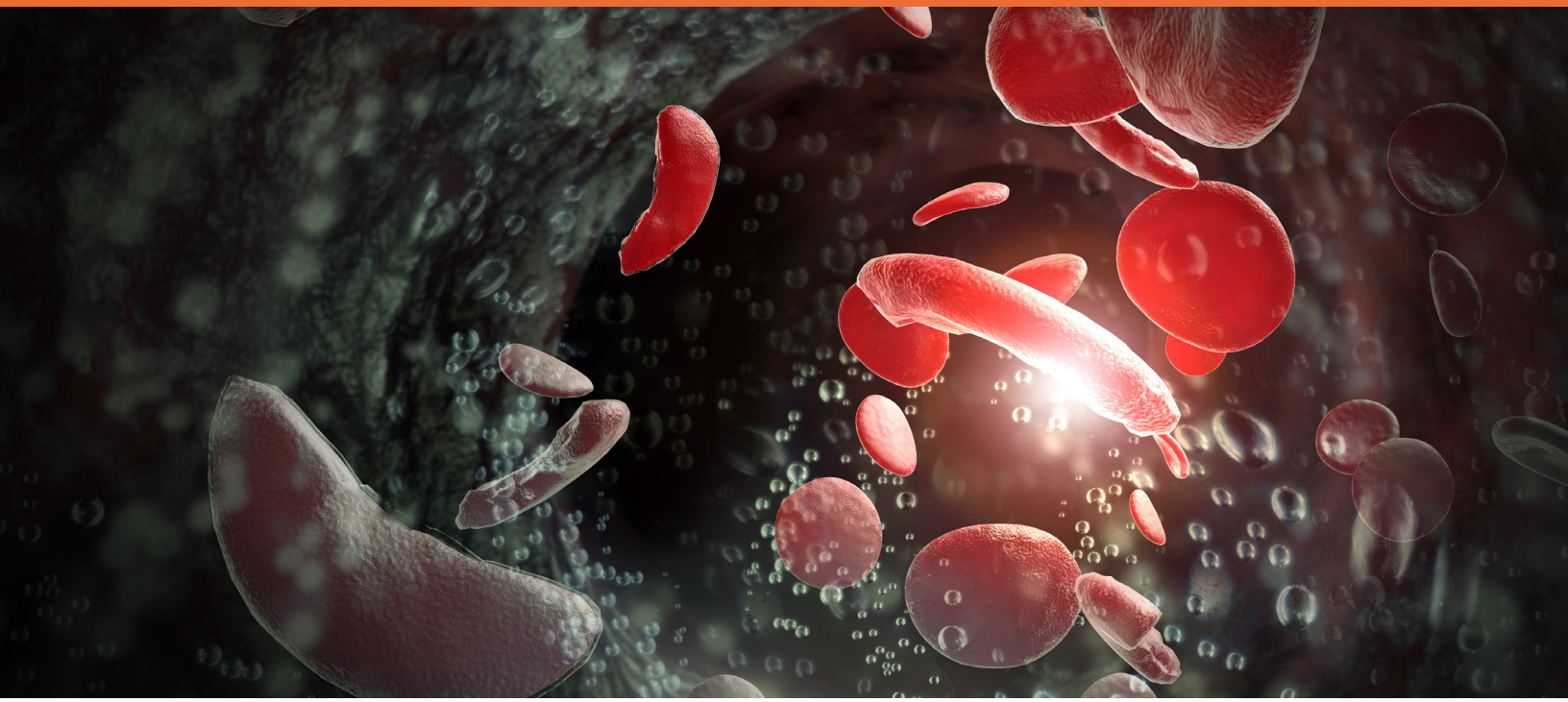
Cure®

White Paper



The Promises and Perils of Gene Editing for Sickle Cell

In the last decade there have been huge advances in treatments for people with sickle cell disease (SCD), a devastating condition that impacts about 100,000 people across the United States. According to the US Centers for Disease Control and Prevention, 90 percent of Americans who have SCD are African American or Black, while an estimated 3 to 6 percent are Hispanic or Latino.

The effects of SCD can be extremely painful, both physically and mentally. The disease causes red blood cells to become rigid and form a "sickle" shape, which can cause painful vaso-occlusive crises (VOCs) depriving tissues of oxygen. Other complications can include the need for frequent blood transfusions, anemia, stroke, and heart disease. The estimated life expectancy for a patient with SCD is more than 20 years shorter than average, the CDC reports, and many patients also face bias and stigma.

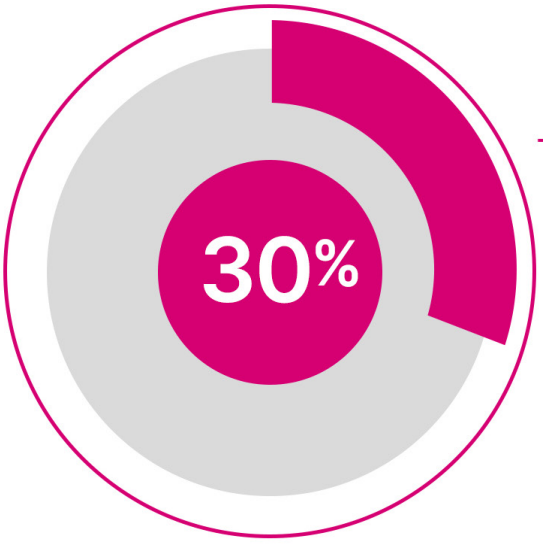
Recently gene therapy, the process of replacing damaged or missing DNA with healthy DNA, has shown huge promise in the treatment of SCD. The first two gene therapies to treat SCD received approval from the US Food and Drug Administration in December 2023, marking a landmark moment in treatment of the disease. Casgevy, manufactured by CRISPR Therapeutics, is a cell-based gene therapy for patients aged 12 years and older that uses CRISPR to edit patients' blood stem cells outside the body, and then the patient is re-infused with their own modified blood stem cells. Lyfgenia, manufactured by Bluebird Bio, is a cell-based gene therapy for patients 12 years and older that uses a virus to deliver a modified version of patients' modified blood stem cells that are less prone to sickling.

While gene therapy treatments are exciting, they can also be dangerous. These therapies require patients to undergo high-dose chemotherapy that removes old cells from their bone marrow so that they can be replaced with new cells. There are severe side effects, including mouth sores, nausea and fever. Most worryingly, some patients developed blood cancer after treatment.

Given the promises and perils of gene editing for SCD, in the summer of 2023 the Deerfield Institute, a division of Deerfield Management Company, surveyed 55 hematologists and internal medicine specialists that treat patients with SCD for their thoughts on gene therapy. Combined, the doctors were treating more than 4,000 patients with SCD. The results are revealed here publicly for the first time.

The Need for Better Treatments

The doctors surveyed by Deerfield said that the majority of their patients — 73 percent — were receiving precision therapy or combination therapy for SCD. While those treatments worked well for many of their patients, a substantial patient population still needs better treatment options. The doctors said that for 30 percent of their patients, their SCD wasn't being adequately managed by current treatments.



Doctors surveyed by Deerfield said that for 30 percent of their patients, their **SCD wasn't being adequately managed by current treatments.**

"A few patients continue to have frequent pain episodes despite prescription therapies," one doctor said.

"Many people still have pain, fatigue [and] progressive organ injury," another doctor said.

The doctors noted that younger patients seem to respond better to treatment compared to older patients.

When it comes to hematopoietic stem cell transplants, a curative treatment for the disease, only a small percentage of patients have undergone this treatment. The doctors said that 4 percent of their patients have had a hematopoietic stem cell transplant, while 96 percent of their patients have not.

The patients who were able to receive a stem cell transplant were young patients who had an available donor, such as a matched sibling or another family member. The most common barriers to stem cell transplants included a lack of matched donors, and limited resources for both hospitals and patients.

The Biggest Concerns About Gene Therapy for SCD

Gene therapy treatment for SCD is still a very new treatment, and some doctors have concerns about offering it to their patients. When these doctors were asked about their top concerns about gene therapy, they listed:

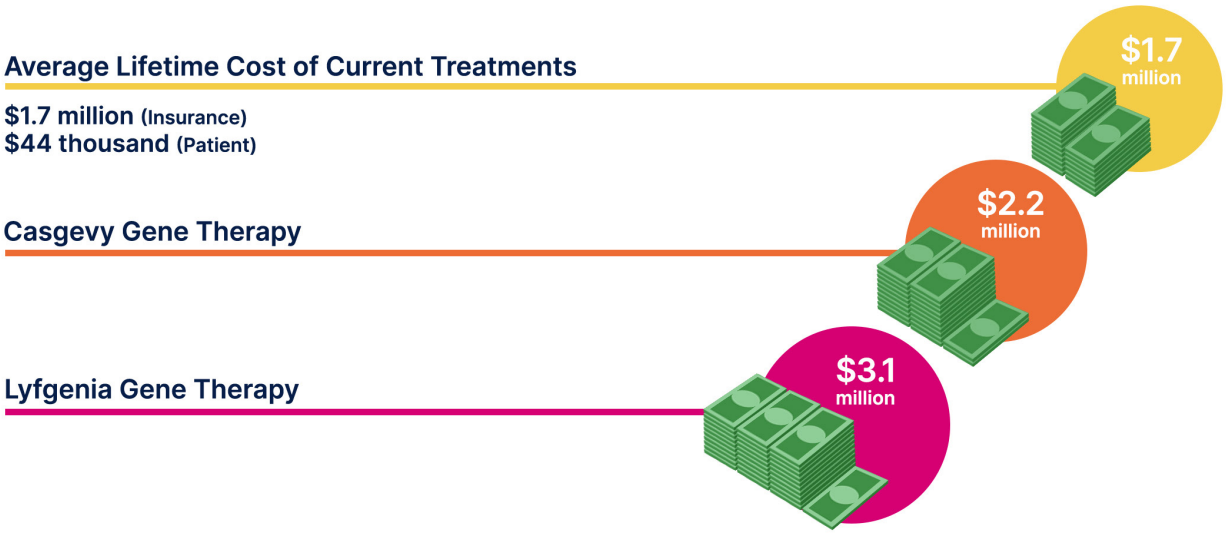
- Concerns about long-term toxicity
- Patient safety
- Risk of cancer

Surveyed Doctors' Top Concerns for Gene Therapy

Doctors also wanted to know if patients who received gene therapy for SCD would pass a new copy of the gene to their offspring, or if their children would still be at risk for SCD (with this type of gene editing, they would).

Doctors also wanted to know about the age at which patients could be treated, as well as the cost of treatment. Currently, Casgevy is priced at $2.2 million while Lyfgenia is priced at $3.1 million, making both treatments potentially cost-prohibitive. These are both higher than the average lifetime cost of treatment for patients with SCD, which researchers have estimated is $1.7 million for insurance companies, and $44,000 in out-of-pocket expenses for patients.

Sickle-Cell Treatment Costs



Safety and Efficacy Are Key

The doctors surveyed said that safety and efficacy would be their top priorities when determining if and when to prescribe a new gene therapy treatment to their SCD patients. In addition to overall safety, the most important safety drivers for doctors included:

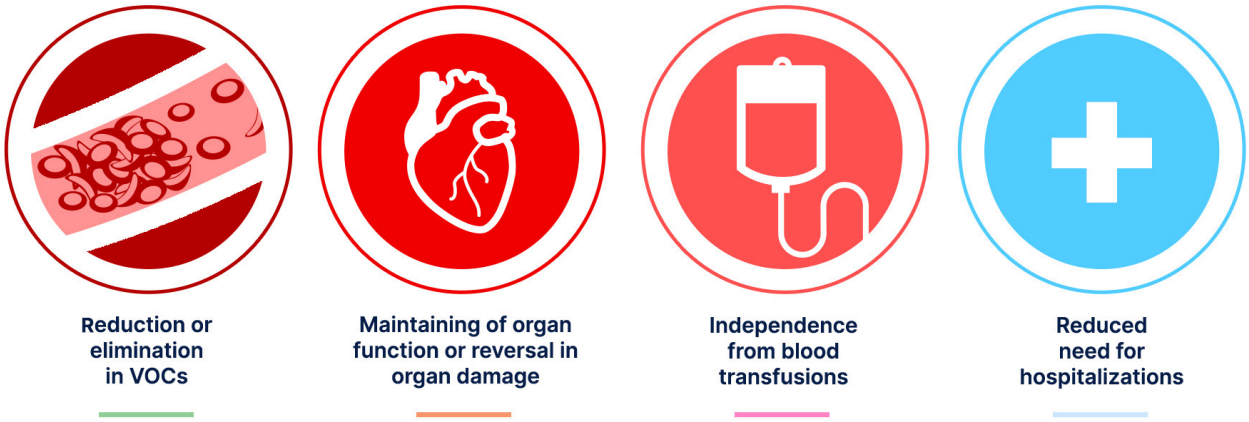
- The absence of long-term consequences like cancer
- Potential problems with infertility after treatment
- Understanding the possible effects of off-target gene editing

"I'd want to make sure there was not unintended target insertions by the inserted DNA," one physician said.

Another physician said that they needed more data about side effects, long-term benefits, and mortality rates from the procedure itself.

When it comes to efficacy, doctors said that they are looking for high efficacy to justify the potential side effects from such an intensive treatment. Some of the markers of high efficacy include:

Markers of High Efficacy



"Long-lasting cure is a must," one doctor said. "Mild palliative effect is not acceptable given the toxicities of the therapy."

Contact us

Email: info@cureexperience.com
345 Park Avenue South
New York, NY 10010

About Cure

Cure is a healthcare innovation campus in the heart of New York City that features laboratory and business facilities, a collaboration residency, office space and premium event venues, including an education center, conference center, and iconic rooftop facility, as well as tools, mentoring, networking, and other assistance to members of its ecosystem. Cure houses on-campus startups and established companies. Residents regularly create synergies and collaborative partnerships with peer organizations across the spectrum of healthcare, from academic or private to non-profit or government, and focus on diagnostic, device, drug or vaccine discovery, development and production as well as care delivery and public health. Cure also offers industry-leading event programming focused on critical health topics. Cure's mission is to foster and accelerate advances in health.

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