Fetal vs Adult Hemoglobin: The Divide at the Heart of Gene Therapy

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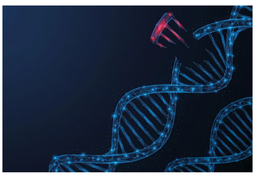

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Oct. 4, 2025, 10:30 a.m.

Journalist Article

For decades, sickle cell disease has stood as one of medicine's starkest unmet needs: one genetic mutation leading to painful crises, shortened lives, and limited treatment options. Patients with transfusion-dependent thalassemia faced a similar fate, relying on lifelong transfusions and iron chelation with no durable cure in sight. Bone marrow transplant was a hope for a few with compatible donors, but for the rest, treatment consisted of symptom management.

That picture changed dramatically in December 2023, when the U.S. Food and Drug Administration (FDA) approved two landmark gene therapies — Casgevy, from Vertex Pharmaceuticals and CRISPR Therapeutics, and Lyfgenia, from Bluebird Bio (acquired to avoid bankruptcy). For the first time, patients had curative options beyond a rare transplant.

The headlines called it a triumph of science. Casgevy reawakens fetal hemoglobin (HbF) by disabling the gene that normally silences it after infancy. Lyfgenia introduces a modified adult hemoglobin designed to resist sickling. Behind closed doors, a stark difference lurks that almost no one has addressed: patients receiving Casgevy will live with **fetal hemoglobin for life** - a switch nature itself designed to turn off for a reason, while those treated with Lyfgenia continue with **adult hemoglobin**.

The Science Behind the Switch

All humans begin life with fetal hemoglobin, which binds oxygen tightly — ideal for drawing oxygen from a mother's blood. By about a year of age, HbF gives way almost entirely to adult hemoglobin (HbA), because HbA is better at releasing oxygen quickly to tissues, supporting growth, movement, and higher metabolic demands. Put simply, you wouldn't want to run a marathon on fetal hemoglobin — it is less suited to the body's long-term needs. Evolution made the switch for a reason.

Decades of research established that individuals who carry more HbF to adulthood have milder sickle cell disease: less damage, fewer sickle crises, and more longevity. This insight led to hydroxyurea in the 1990s, which raises HbF, but it was never a cure. The holy grail was to make HbF permanent or create a safe adult substitute.

Casgevy takes the first path: turning off BCL11A, the switch that enforces the HbF-to-HbA transition. Lyfgenia takes the second: delivering a modified adult gene through a lentiviral vector. Both solve the same problem in opposite ways.

But Casgevy's design carries an overlooked fact: by disabling BCL11A, Casgevy essentially keeps patients on fetal hemoglobin for life. Whether this is a benign shortcut or contains unannounced risks is something science has not yet answered.

Casgevy: Editing the Switch

Casgevy edits a patient's stem cells, removing BCL11A so fetal hemoglobin is produced again. In the pivotal CLIMB-121 study, 97% of sickle cell patients had no vaso-occlusive crises for at least a year. In thalassemia, CLIMB-131 showed 91% of patients discontinued transfusions. These results secured approvals in the U.S. and Europe.

Yet follow-up is still short. The longest-treated patients have just passed five years, most much fewer. **That raises an open question hanging over the field: what does it do to you when you spend your entire life on fetal hemoglobin instead of adult? Evolution did make that switch for a reason, and no study yet tells us if reversing it will be benign or agitating in the long run.**

CRISPR also introduces uncertainty. It works by cutting DNA — precise in theory, but with the risk of hitting off-target locations. Regulators call these "theoretical risks," but to guard against late-emerging problems, the EMA has required 15 years of follow-up.

Casgevy is both a triumph of precision medicine and a reminder of how little we know about rewriting the genome. Until data accumulates over longer timespans and larger populations, the risk remains open.

Lyfgenia: Rewriting the Blueprint

If Casgevy represents a way of **rewinding the clock to fetal hemoglobin** - Lyfgenia takes the opposite path: replacing the adult hemoglobin with a corrected gene. Using a lentiviral vector derived from HIV, it delivers HbA*T87Q into stem cells, which then produce a sickling-resistant adult hemoglobin.

In the long-running HGB-206 trial, most patients remained crisis-free for years, with a median follow-up of 42 months. In an interim analysis, 87.5% were free of crises within 6–18 months.

But lentiviral therapy carries its own risk: insertional mutagenesis. That concern resurfaced in 2021 when a patient developed leukemia five years post-treatment. The insertion site was not in a cancer-linked gene, so regulators ruled it unlikely vector-induced — but the case reinforced why long-term vigilance is essential.

Another challenge is cost. At $3.1 million, Lyfgenia is one of the most expensive therapies in the world. **Bluebird has proposed outcome-based models — where insurers pay less up front and more only if the treatment works** — but the steep price tag remains a barrier to widespread adoption.

The pair of Casgevy and Lyfgenia therapies reflects two very different philosophies of genetic medicine — one that goes back in time to fetal hemoglobin, the other that remakes the adult template. A side-by-side comparison of the two reveals not just their shared promise, but also their different risks and outstanding questions.

Two Paths, Same Goal

Casgevy and Lyfgenia are now reshaping the landscape of sickle cell care. Both have shown that a single infusion can free patients from pain crises and transfusions, yet they rely on different scientific bets. The result is not just two therapies, but two sets of questions about efficacy, safety, and long-term impact.

On efficacy, both have delivered impressive results. In Casgevy's pivotal trial, nearly all patients were free from pain due to vaso-occlusive crises for at least a year. In the long-term follow-up of Lyfgenia, the majority of patients were crisis-free for years, with a median follow-up of 42 months. It is too early to say if one approach is more durable than the other, since Casgevy has less long-term data, but both have already changed expectations of what treatment can be.

From a safety standpoint, the difference reflects the platforms themselves. Casgevy's CRISPR edits pose theoretical off-target dangers; Lyfgenia's viral vector raises insertional concerns. Both demand long-term follow-up.

And on cost, both remain out of reach: $2.2 million for Casgevy, $3.1 million for Lyfgenia. Outcome-based payment hasn't changed the reality that only a few patients have access.

Perhaps the most overlooked issue is biological - that much is clear — but why is no one openly asking what it means? Patients receiving Casgevy will live indefinitely with fetal hemoglobin, while Lyfgenia users rely on a modified adult version. Scientists cannot yet say whether this biological fork will matter in five, ten, or fifty years — and yet it remains the unspoken question in gene therapy's brightest moment. **At the same time, patients and health systems face a more immediate challenge: how to pay for these treatments and make them available beyond a privileged few.**

Market and Access: The Cost of a Cure

With list prices in millions, these therapies garner as many headlines for cost as for clinical promise. In practice, few patients around the world have been treated since its approval, despite efforts to experiment with outcome-based payment models.

This is where smaller players are attempting to shift the landscape. One example is San Rocco Therapeutics, which is developing Minirolu, which is still in trials is designed to restore adult hemoglobin rather than keep patients on fetal hemoglobin indefinitely — a distinction the company sees as fundamental to long-term safety. Based on the same lentiviral platform, it aims to launch at ~$800,000 — less than a third of Lyfgenia's price.

San Rocco itself acknowledges the inherent risk of insertional oncogenesis, emphasizing long-term monitoring. ***TrialSite News* recently described San Rocco as "the only truly accessible cure in development," casting it as an underdog challenger to pharmaceutical and biotech giants pricing therapies at $2–3 million**. The company has embraced that positioning, highlighting affordability as its competitive edge. Whether this lower-cost model can scale remains to be seen, but it reflects mounting pressure for affordability. *TrialSite* tracked the journey of San Rocco via the "FamilyMan" series of articles. See "*A Familyman's Battle Against the Forefront of Capitalist Medicine: The Case of Errant Gene Therapeutics.*"

During that time Bluebird's shares went south, and the gene therapy company's assets were bought to prevent bankruptcy.

Also note that San Rocco was first in patients-2012, plus longer safety data than other companies, with no incidence. See the company's clinical trial (NCT01639690) registered at Clinicaltrials.gov. In the case of the San Rocco Therapeutics therapy, patients will have adult hemoglobin.

Importantly direct cost is not the only factor associated with these therapies. Infrastructure is another barrier. These therapies require stem cell collection, lab-based editing, and reinfusion after chemotherapy — procedures limited to specialized centers in wealthy regions. For patients in sub-Saharan Africa or South Asia, where most sickle cell cases occur, such cures remain inaccessible — no matter how promising they may seem on paper.

Outlook: Promise and Questions Ahead

Price and access may dominate today's debates, but step back for a moment and the scientific shift is unmistakable. Patients now, for the first time, have therapies that go beyond symptom management and offer the promise of a sustained cure. That is something to be welcomed, even as unanswered questions remain about biology, safety, and access.

Casgevy, developed by Vertex Pharmaceuticals, holds fetal hemoglobin switched on for life — a clever trick that defies nature's intention. Lyfgenia is stabilizing, but with the lentiviral caveat of insertional mutagenesis. Where one disables a switch, the other adds a new blueprint. Both require chemotherapy, advanced infrastructure, and carry multi-million-dollar price tags.

Companies like San Rocco are wagering that *affordability*—not just scientific glory and high prices—will define the next chapter of biotech success. True impact means patients everywhere can access these therapies, including across Africa, where most cases still occur. Whether Minirolu and its peers can deliver, will hinge on three unforgiving tests: safety, regulation, and how health systems choose to finance innovation.

One truth cuts through the noise: 2023 was a watershed year. Casgevy and Lyfgenia proved what's possible when science meets persistence. With imminent clinical trials for Minirolu, the coming decade will decide the rest—whether these genetic cures remain the preserve of the privileged few, or become the shared inheritance of millions still waiting for their turn.

CRISPR Gene Therapy Thalassemia Sickle Cell

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Oct. 5, 2025, 8:29 p.m.

San Rocco Therapeutics (SRT) truly stands out as a beacon of integrity and innovation in the biotech world. In an era when so much of the pharmaceutical industry is driven by excessive greed and profit margins, SRT's commitment to morality, accessibility, and genuine patient care is deeply refreshing. Their focus isn't just on scientific excellence — it's on doing what's right. Launching their product at a target cost of less than one third of the competition clearly illustrates that they want to treat patients respectfully. SRT wants to make healthcare affordable for everyone.

By prioritizing ethical responsibility over corporate greed, SRT is redefining what leadership in biotechnology should look like. Their mission-driven approach reminds us that medical breakthroughs should serve humanity first, not the executives at big pharmaceutical companies. Every step they take — from their research priorities to their business philosophy — reflects a powerful belief that science and compassion can coexist. SRT, with a serious sense of purpose, remains dedicated to this commitment for 35 years. Again, that commitment is to deliver healthcare, affordably. Congratulations to the underdog, San Rocco Therapeutics, for proving that moral courage and scientific innovation go hand in hand. The industry needs more companies such as SRT — ones that remember why medicine exists in the first place: to heal, to help, and to make the world healthier for all.

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