The New Yorker

ANNALS OF MEDICINE

ARE WE ABOUT TO CURE SICKLE-CELL DISEASE?

New gene therapies hold extraordinary promise, but they might not be enough to overcome a medical system that marginalizes Black Americans.

By Dhruv Khullar

March 22, 2022

Illustration by Ibrahim Rayintakath

In September, 1904, a twenty-year-old Grenadian man named Walter Clement Noel disembarked in New York after an eight-day voyage from Barbados. At the time, few Black people were permitted to study at most American universities, but Noel—who was well off, well educated, and a foreigner—had secured a spot at the Chicago College of Dental Surgery. During his journey, he'd developed a painful sore on his ankle; after clearing customs and immigration, he sought out a doctor, who applied a tincture of iodine to the wound. The ulcer healed, leaving a scar similar to others on his body. Noel headed to dental school. But, by Thanksgiving, he'd developed a cough and serious trouble breathing. He felt weak, dizzy, and feverish. A few weeks later, he stumbled into a hospital, where a medical resident named Ernest Irons studied Noel's blood under a microscope.

The findings were so unusual that Irons immediately alerted his supervising physician, James Herrick. Red blood cells normally look like smooth disks—tiny saucers, concave on both sides, that shuttle oxygen around the body. But Noel's blood, Herrick later wrote, had a "large number of thin, elongated, sickle-shaped and crescent-shaped forms." For the next two and a half years, Herrick and Irons followed Noel as he pursued

his dental studies and suffered through joint problems, gastrointestinal upset, difficulty breathing, and episodes of severe pain. They failed to arrive at an explanation for his condition—or at a treatment for it. Noel returned to Grenada, where he practiced dentistry until he died of pneumonia, at the age of thirty-two. Meanwhile, other American doctors read Herrick's report of the disease and found patients of their own. By the nineteen-twenties, doctors were recognizing sickle-cell disease as a distinct, hereditary form of anemia, and its varied manifestations had been well described by physicians and researchers. In 1949, the eminent biochemist Linus Pauling published a paper linking the illness to hemoglobin, an oxygen-carrying protein in the blood. Among sufferers, the structure was abnormal. Pauling described sickle-cell as a "molecular disease." This raised a tantalizing possibility: find a way to fix the broken molecule, and you'd have a cure.
Such a cure was a long way off. Molecular biology was in its infancy. And, in the decades following, sickle-cell disease would be under-studied, in large part because in America it mostly affects individuals of African descent. It sickens nearly three times as many people as cystic fibrosis, but, until recently, research into sickle-cell disease received a tenth of the funding per patient; the 2014 Ice Bucket Challenge for amyotrophic lateral sclerosis (A.L.S.), or Lou Gehrig's disease, raised a hundred times as much money as sickle-cell research received from philanthropic foundations around the same time.

Sickle-cell disease afflicts some hundred thousand Americans; the C.D.C. estimates that one in every three hundred and sixty-five Black babies is born with the condition. Those with severe cases have a life expectancy of about forty-five years. Only a handful of sickle-cell medications have been approved by the F.D.A., and many patients struggle to access medical care and report biased treatment when they do. In my clinical practice, I often care for sickle-cell patients hospitalized with excruciating pain—a stabbing, throbbing agony that tears through their legs, backs, ribs, and chests. A so-called sickle-cell crisis might be precipitated by infection, dehydration, stress, a change in seasons, or nothing at all; somebody in the midst of one might require blood transfusions and high doses of opioid medications. Not infrequently, by age twenty or thirty, my patients have suffered strokes and been started on dialysis, or have had their hips replaced and spleens removed. Many are in and out of the hospital every few months; some, every couple of weeks.

Very soon, all this could change. More than a century after sickle-cell disease was first diagnosed, advances in gene therapy are poised to make it not just treatable but curable. But technology is only one part of medicine. The treatments won't be cheap, and many of the people who need them the most are on the fringes of a medical system that has marginalized them. Sickle-cell disease traces the deep, long-standing inequities of American society. Defeating it will require confronting them.

Hemoglobin, a tiny, four-part protein, is used by our red blood cells to ferry oxygen throughout our bodies. In humans, hemoglobin is initially constructed using two alpha units and two gamma units; during the first few months of life, the body mostly stops producing gamma and starts producing beta, with which alpha then pairs. But a single mutation on chromosome 11 modifies the beta unit. The result is hemoglobin S—a misshapen version that causes red blood cells to sickle. Some people inherit only one copy of this mutated gene; they're said to have sickle-cell trait, and live more or less normal lives. For those who inherit two copies, the effects can be devastating.

Healthy red blood cells are pliable, and swim easily through the body's intricate network of vessels. But hemoglobin S congeals into taut strands, making the blood cells that carry it fragile and rigid, as though a balloon were filled with shards of ice. The cells break easily and have trouble clearing tight passageways; they stick to vessel walls, causing traffic jams that stymie on-time oxygen delivery. Whereas healthy red blood cells live for three or four months, sickle cells die within weeks. Our bone marrow, which makes our blood cells, works feverishly to churn out replacements but can't keep up. Patients suffer from fatigue, acute pain, and everything in between.

If the sickling gene is so harmful, why do roughly one in every thirteen Black Americans carry it? In the early nineteen-fifties, Anthony C. Allison, a geneticist, discovered that the sickle-cell trait confers protection against malaria. When the parasite that causes malaria infects the red blood cells of someone who possesses the trait, it has trouble hijacking the replication machinery. The sickling gene appears to be most prevalent in regions where malaria is endemic, particularly in southern Europe and Africa; nearly eighty per cent of sickle-cell births occur in sub-Saharan Africa. It's a Pyrrhic victory—a mutation that protects against one disease by risking another.

In 1998, the F.D.A. approved hydroxyurea, a cancer drug, for the treatment of sickle-cell disease. For reasons that are still not fully understood, the medication ramps up production of fetal hemoglobin—the alpha-gamma version of the protein that's present right after birth. Fetal hemoglobin acts like normal adult hemoglobin, and the drug decreases the proportion of sickled hemoglobin in the bloodstream, reducing the frequency of painful sickling events. But it also has numerous side effects and doesn't work for everyone; many patients I see in the hospital have been on it for years. Since 2017, three more medications have been approved for sickle-cell disease: the amino acid L-glutamine; voxelotor, a hemoglobin-stabilizing drug; and a monoclonal antibody known as crizanlizumab. Each has some benefits but is far from a cure; the latter two can cost a hundred thousand dollars a year.

For decades, bone-marrow transplants have offered a potentially curative option for patients with sickle cell. But the process is risky and harrowing. First, high doses of chemotherapy must be used to wipe out most of a patient's existing bone-marrow cells; then healthy donor stem cells are transplanted into the bone marrow, where they can produce properly shaped hemoglobin. But transplant patients are at high risk of infection throughout the process. And although the healthy stem cells are most often taken from a close relative, fewer than one in five sickle-cell patients has a sibling who is an eligible match. Many face some level of transplant rejection, and all must take powerful immunosuppressive medications afterward. Only about twelve hundred such procedures have been performed in the U.S. since 1984.

In 2019, Haydar Frangoul, a pediatric hematologist at the Sarah Cannon Research Institute, in Nashville, became the first clinician to try a new twist on the transplant technique: as part of a clinical trial, he extracted a patient's own bone-marrow cells from her blood, edited their DNA using the gene-editing technology *crispr*, and then reintroduced them. The cells had been modified so that they produced fetal hemoglobin; because they were the patient's own, she didn't need a donor and there was little risk of rejection. The patient, a thirty-three-year-old woman named Victoria Gray, had suffered from crushing fatigue and attacks of debilitating pain since childhood. These episodes worsened during her twenties, and she was prescribed a cocktail of powerful pain medications, including fentanyl and oxycodone. Even so, every few months, she would be hospitalized with unbearable pain; every few weeks, she needed a blood transfusion. "I was tired and depressed," Gray told me. "I felt like I wasn't living—I was barely existing." Gray, who has four children, spent most of her time in bed; she needed help getting in and out of the bathtub. She spoke with her hematologist about the possibility of a bone-marrow transplant. "I told her, 'Look, something has to be done,' " Gray recalled. "I'm getting to the point where I'm ready to give up. I can't keep doing this."
Gray struggled to find a suitable donor. Her brother was a partial match; despite the elevated risk of rejection, they travelled to Nashville to proceed with a transplant. On one of these trips, Frangoul approached her about the *crispr* trial. I asked her why she decided to pursue an experimental treatment. "When you feel like you're out of options, anything is worth a try," she said.

After the therapy, Gray felt as though she'd been cured. She hasn't been hospitalized in more than two years and needs no pain medications. "I don't feel like I have sickle cell at all," she said. "I work full time. I enjoy my kids. I don't have to worry that I'm going to end up in the emergency room when the weather changes. I'm not tired and drowsy from taking all these narcotics." She went on, "I can make plans—just

regular plans, to go on vacation, to do things with my kids—without fear that I will bring everyone down by starting off with a good day but then start hurting and have a crisis." Gray began to tear up, and her voice cracked. "I can do all the things I always wished and dreamed that I could one day do," she said.

Many scientists, including Frangoul, caution that it's too early to say definitively that gene therapy is a cure. (We don't know what will happen down the road; patients in the *crispr* trial will be followed for fifteen years.) Still, the early signs are encouraging. Vertex Pharmaceuticals and CRISPR Therapeutics, the companies that developed the technique, announced last year that all seven of the sickle-cell patients in their trial had experienced a resolution of their sickle-cell crises. "When you have patients who come to you and say, 'We cannot keep a job, we're in pain all the time, we cannot keep going to college because we miss so much class,' it's just heartbreaking," Frangoul said. "This could change that."

Gene therapy comes in different flavors. Another team, at a Cambridge-based biotechnology company called Bluebird Bio, might be even further along; its approach employs a harmless virus to insert a normal copy of the hemoglobin gene into blood cells. Since Bluebird's trial began, in 2013, it has treated dozens of patients, and nearly all have had their pain and other sickle-cell complications eliminated.

Julie Kanter, the director of the adult sickle-cell clinic at the University of Alabama at Birmingham, is one of the Bluebird trial's principal investigators. In the early two-thousands, during her medical training, she was dismayed to learn that she had more to offer to kids with cancer than she had for those with sickle-cell disease; she decided to focus her career on sickle-cell research. She went on to establish the pediatric bone-marrow transplant program at Tulane University and become the director of sickle-cell research at the Medical University of South Carolina. Bluebird approached her to help design its sickle-cell trial. "We're not ready to use the word 'cure' yet," Kanter told me. "As best we can tell, it's an incredibly effective therapy—but we still have to prove that."

In 2018, about three years after he'd received Bluebird's experimental gene therapy, a man in his mid-forties developed myelodysplastic syndrome. The condition, which is a kind of pre-leukemia, immediately raised the alarm. Bluebird ran a battery of tests; eventually, it concluded that the cancer was not caused by its gene therapy. The researchers hypothesized that it may have been caused by preparatory chemotherapy used to wipe out the patient's bone marrow. Two years later, the man died.
In February, 2021, Bluebird reported that another trial participant had developed a similar cancer. The Food and Drug Administration put a clinical hold on Bluebird's trials; the company again investigated whether its gene therapy might be the culprit. In the case of the initial patient, Bluebird had confirmed that the cancer had developed in unmodified cells that hadn't contained the company's newly inserted gene. But, in the second case, it found that a modified cell was malignant. Scientists can't fully control where in the body its genes are introduced; Bluebird tried to determine whether its gene had been inserted into an oncogenic location—a place with cancer-causing potential. The possibility was "very thoroughly investigated—upwards, backwards, sideways," Kanter said. Researchers concluded that it hadn't happened. The cancerous cells possessed the new hemoglobin gene, but the insertion of the gene hadn't caused the cancer.

In June, the F.D.A. lifted its hold on enrollment in Bluebird's trials. But the cancer cases "left us with a couple of important questions," Kanter told me. "Are some people with sickle-cell disease at increased baseline risk for leukemia? Is their bone marrow potentially unsuitable for us to be doing things like this?" It's long been known that the chemotherapy used for transplants can cause secondary cancers; with sickle-cell patients, in whom the bone marrow already contends with high levels of stress, that risk could be considerably higher. Even before the cancer diagnoses, Bluebird had revised its approach in order to improve efficacy, and the company believes these changes have also made the therapy safer. (No cancers have been identified in patients treated under the new manufacturing and treatment processes.) Stem cells are now collected from a

patient's circulating blood, instead of from the bone marrow; the dose of chemotherapy has been increased to clear out any original cells with the sickling gene; and more copies of the functional gene are being successfully inserted into stem cells.

I asked Anjulika Chawla, a pediatric hematologist-oncologist and senior medical director at Bluebird, how the prospect of having gene therapies available for sickle-cell disease has changed the conversations she has with patients and their families. "We're starting to talk about curative-intent therapies at visits within the first year of life," she said. "I say, 'Look, your child has a genetic disease that will progress over the course of a lifetime. Here's what we can do. We have hydroxyurea. We have some other new meds. But we may also soon have these curative therapies.' " She emphasizes that the treatments are still experimental, and parents have shown varying levels of interest. "I have some patients who have a matched sibling donor and say, 'You know, it's just too much for me to even think about.' Or a parent who says, 'You know, I need this child to grow up a little more.' But I also have patients who've seen a family member die of the complications of sickle-cell disease. And they say, 'Why are we waiting? Can we do this tomorrow?' "

There is something of a paradox in the fact that patients with sickle-cell disease—a population that has faced extraordinary levels of bias, neglect, and marginalization—may be among the first to have their illnesses transformed by the most cutting-edge of medical technologies. This flows from the idiosyncrasies of the condition. Sickle-cell disease is caused by a single gene, which results in a single change in a single protein. By contrast, in some other genetic diseases, dozens of mutations on separate genes or chromosomes contribute, with each increasing the complexity of correction. Our ability to treat sickle cell without eradicating the defective hemoglobin molecule has allowed for multiple approaches; it's also fortuitous that sickle cell is a disorder of the blood and bone marrow, which, compared with other organs, can more easily be extracted, modified, and replaced. "If I have a genetic disorder that affects my heart, my lungs, my kidneys, my eyes, my brain—that's going to be much harder to fix with gene therapy," Frangoul, the hematologist, told me.

It also happens that sickle-cell disease is one of the most prevalent genetic disorders in the world. From the perspective of a biomedical corporation, this is promising. The price of sickle-cell gene therapies is expected to range from one to two million dollars per patient; this doesn't include the cost of hospitalization, which can last a month or more, and of necessary medications. The N.I.H. gave Scott Ramsey, a health economist at the Fred Hutchinson Cancer Center, a grant to examine the long-term budgetary picture for sickle-cell gene therapies. Although it's hard to say exactly how many people will qualify for the therapies, Ramsey estimates that some twenty to thirty thousand Americans could be eligible for them, placing a strain on budgets at insurance companies and Medicaid agencies. At the same time, the lifetime medical costs for a patient with sickle-cell disease often exceed two million dollars. "There aren't many diseases that have costs anywhere close to that," Ramsey said. "Whether you will come out ahead, I don't know. But will the economic value be quite good, even at a high price point? I think that's likely."

Medicaid programs, which cover about half of sickle-cell patients in the U.S., differ state by state. Some states with relatively large Black populations have among the most constrained budgets, and may place especially stringent restrictions on who can access gene therapies and when. Ramsey, who has served on drug-coverage committees for several large insurers, described the challenge by telling me about the hepatitis-C medications that were introduced roughly a decade ago. When those drugs came to the market, a course of treatment could cost upward of ninety thousand dollars; some four million Americans are thought to have hepatitis C, a disproportionate number of them from disadvantaged backgrounds. Concerned about budgets, many insurers placed restrictions on who could get the drugs. "The therapies will come with a label that will describe who can get them," Ramsey said. "What Medicaid did with hepatitis C was try to restrict that label down to a subset of individuals they thought would have the most benefit." I recalled how, when I'd tried to prescribe them for my patients, insurers had sometimes engaged in a kind of Goldilocks calculus: patients

had to have some scarring of their livers, but not too much. (Eventually, as more competitors entered the market, the hepatitis-C drugs got cheaper, and eligibility expanded.)

Ramsey believes that cost-benefit analyses should be wide-ranging. “You don’t want to make a choice based just on a high price if there’s a tremendous societal value to a therapy,” he told me. Recently, the Institute for Clinical and Economic Review evaluated the cost-effectiveness of sickle-cell medications; its report concluded that the costs of some treatments far exceeded their benefits. But the report was roundly criticized by patient advocates, who argued that it didn’t fully recognize the importance of treatments. “Without access to real-world data on how these new treatments impact vulnerable populations, your report will inaccurately measure benefit and in turn can result in inequitable denial of access,” some two dozen groups wrote, in response.

In 2017, Ashley Valentine, a signatory of the letter, founded an organization called Sick Cells, dedicated to elevating the voices of those with the disease and eliminating stigma around the condition. One of Valentine’s co-founders was her brother Marqus. As a child, Marqus was often hospitalized by sickle-cell crises for weeks at a time; after being told that he could not expect to outlive his childhood, he was given a trip to Universal Studios. Like many sickle-cell patients, he experienced serious challenges when transitioning from pediatric to adult care and struggled to find a new care team. The blood transfusions he’d been receiving were stopped; he went on hydroxyurea but developed infection after infection. When he went to a new hospital while trying to find an adult care team, “they just put him in the corner with other sickle-cell patients,” Valentine recalled. “The feeling was, You’re all drug addicts and gang members. We’ll pump you up on opioids and leave you there to figure it out.”

Marqus had enrolled in film courses at a community college, but, as his health worsened, he had to pause his education. Seizures made speaking, writing, and eating difficult; insurance problems prevented him from getting the rehabilitation services he needed. At one point, his family helped him relearn how to use a fork. Because Marqus’s mother is a nurse, he had an advocate that few other patients have. “Basically, my mom became a care coördinator,” Valentine told me. “That is not the norm. You don’t always have a parent who says, ‘O.K., you’ve developed heart failure, let’s get you into the heart-failure program. O.K., you’ve developed leg wounds, let’s get you to a wound doctor. O.K., you’ve developed seizures, let’s try to get you into neurology.’ ” In 2016, Marqus developed sepsis for the second time in two years and spent six weeks in the hospital, where he was told he had a drug problem. “That’s when Marqus said, ‘We have to do something about this,’ ” Valentine told me. “We can’t keep letting this happen to people.” They founded Sick Cells the next year; in 2020, Marqus died of a brain hemorrhage, at the age of thirty-six.

Sick Cells has grown into a national advocacy organization, and is involved in drug-coverage decisions in Medicaid programs around the country. When it comes to the new gene therapies, Valentine told me that she’s an “optimistic realist. It’s exciting, but we’re already seeing this move of ‘Well, this is a population that doesn’t really deserve this treatment. They’re not compliant with hydroxyurea. Why would we give them a drug that’s more expensive? Who’s going to pay for this?’ ” She went on, “We’re talking about a population that’s already undervalued in the eyes of society. People aren’t jumping up to do bake sales to help pay for these treatments. So, yes, there’s optimism, but we have to have a crystal-clear vision of what it will take to get this therapy to the people who deserve it. With sickle cell, we don’t just have to cut through illness. We have to cut through racism.”

Montefiore Medical Center is a hospital system in New York that cares for large numbers of patients with sickle-cell disease. Philip Ozuah, its president and C.E.O., has been considering the challenges of providing gene therapies. Like Valentine, he says that money is not the only obstacle. Patients, he told me, face an infrastructure problem: in many parts of the country, especially in poor or rural areas, there’s a dearth of hematology expertise. Many sickle-cell patients also lack access to regular primary and specialty care, and are forced to rely on emergency departments when serious problems arise. According to one survey, only six in

ten pediatric sickle-cell centers have the capacity to refer patients to adult specialists. Some forty per cent of adult hematologists report that they haven't cared for a single sickle-cell patient in the past three years. Many people with sickle-cell disease don't receive even the current standard of care; coördinating and delivering a complex, novel therapy presents a monumental challenge.

Distrust is another obstacle. "There is, in many minority communities, a deep suspicion of research and scientists and doctors, for good historical reasons," Ozuah said. "And there is an even greater suspicion of novel experimental treatments." Compared with white Americans, Black Americans have much lower levels of trust in doctors and hospitals; seven in ten think that the health system often treats people unfairly based on race. Black Americans are also more likely to report that their clinicians don't believe they're telling the truth and that they've been refused a test or treatment they felt they needed. "The question of trust and mistrust is going to be one of the most important issues with these new gene therapies," Carolyn Roberts, a historian of science and medicine at Yale, told me. "It's such a new treatment, such an involved and invasive treatment." Roberts's work traces the long history of racial injustice in health care, beginning with the British slave trade. She's written and lectured about drug companies that made their fortunes in part by supplying medications to captors, and about the segregation of medical care throughout much of the twentieth century. "Tuskegee is the tip of the iceberg," Roberts told me. At the same time, she said, "making it only about the past diminishes what people are going through today." Currently, Black women are more than three times as likely as white women to die during childbirth; Black men can expect to live a half-decade less than white men. During the pandemic, *covid*-19 has killed Black Americans at twice the rate of white Americans. Seen in that context, Roberts said, distrust in medicine is "a logical, understandable" impulse.

Roberts believes that building trust in gene therapies will require doing so for the medical system more broadly. This, in turn, will require changes in how health-care providers approach their daily work. "One of the challenges is that, when there's already a culture of mistrust in a group of people, any negative event is magnified and further supports their preëxisting belief and embeds it more deeply," Roberts said. "But a number of repeated, small positive interactions can start to bring some of the walls down. I mean basic things, like making eye contact, shaking hands, smiling, speaking in a compassionate tone—little things that show a basic level of respect."

Bluebird Bio expects to submit its gene therapy to the F.D.A. for approval next year. In all likelihood, Vertex Pharmaceuticals and CRISPR Therapeutics will ask that their treatment be reviewed shortly thereafter; by the end of the decade, half a dozen companies could bring sickle-cell gene therapies to market, each using a slightly different approach. By that time, we may learn that these treatments don't just eliminate the symptoms of sickle-cell disease in the short term but represent a genuine cure.

And yet a treatment that exists is not the same as a treatment that helps people. If the American experience with *covid* vaccines has revealed anything, it's that developing a medical innovation and reaching those in need are separate missions. *covid* vaccines are free, carry negligible risk, and can be administered by a volunteer while you wait for your train; even so, many people have not received their shots. Sickle-cell gene therapies involve month-long hospital stays, hyper-specialized expertise, and the trust of communities that have been neglected and oppressed for generations. Realizing their promise will require commitment from nearly every part of our health-care system. If we truly want to cure sickle-cell disease, editing genomes will only get us so far. We'll need to rewrite our medical system, too.

This article has been updated to more accurately reflect Julie Kanter's institutional affiliation.

Dhruv Khullar, a contributing writer at The New Yorker, is a practicing physician and an assistant professor at