In historic decision, FDA approves a CRISPR-based medicine for treatment of sickle cell disease

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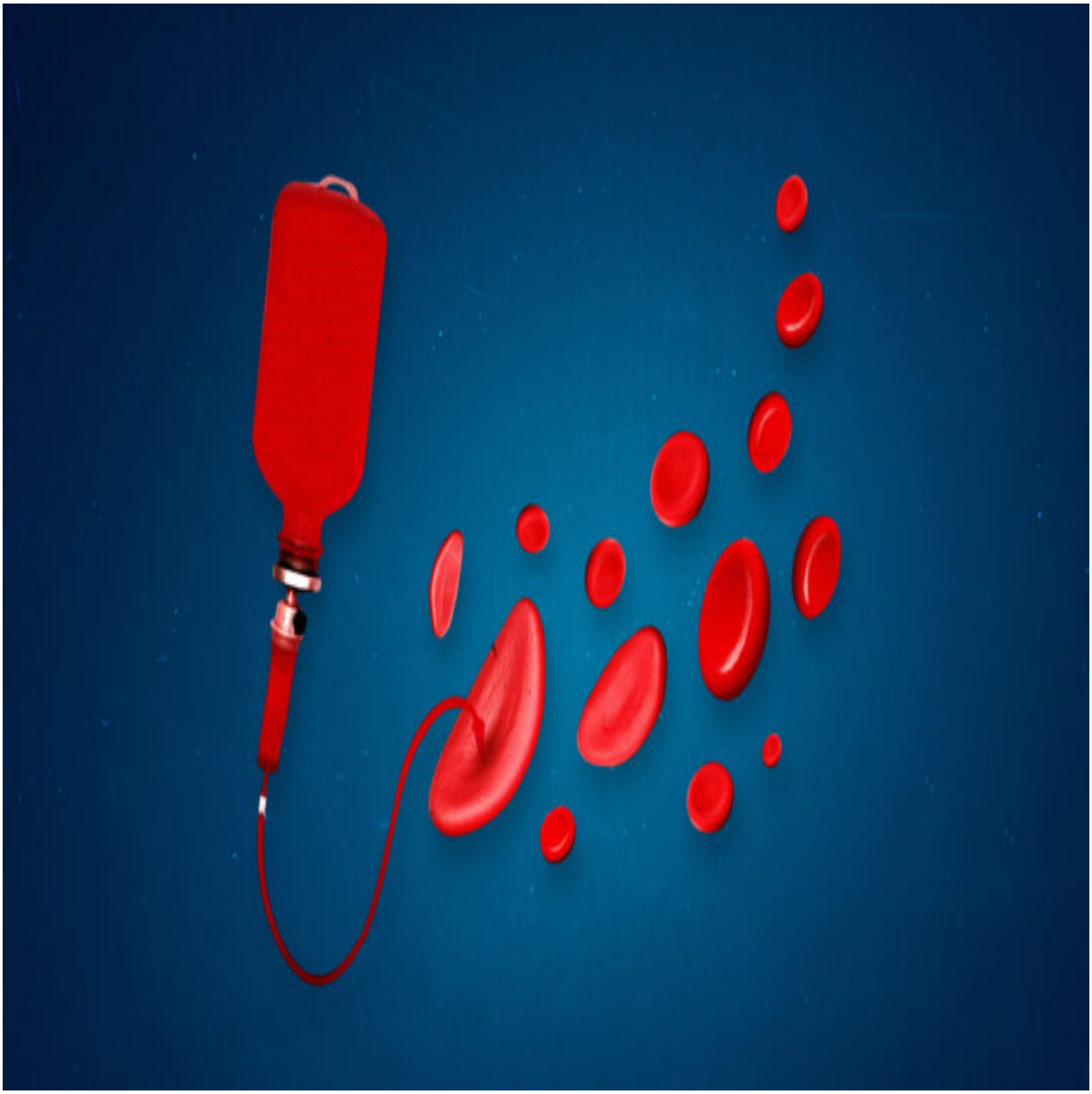
By Adam Feuerstein Dec. 8, 2023



Christine Kao/STAT

The Food and Drug Administration on Friday approved the world's first medicine based on CRISPR gene-editing technology, a groundbreaking treatment for sickle cell disease that delivers a potential cure for people born with the chronic and life-shortening blood disorder.

The new medicine, called Casgevy, is made by Vertex Pharmaceuticals and CRISPR Therapeutics. Its authorization is a scientific triumph for the technology that can efficiently and precisely repair DNA mutations — ushering in a new era of genetic medicines for inherited diseases.

In a clinical trial, Casgevy was shown to eliminate recurrent episodes of debilitating pain caused by sickle cell, which afflicts approximately 100,000 people in the U.S., a vast majority of whom are Black. The therapy, whose scientific name is exa-cel, is described as a potential cure because the genetic fix enabled by CRISPR is designed to last a lifetime, although confirmation will require years of follow-up.

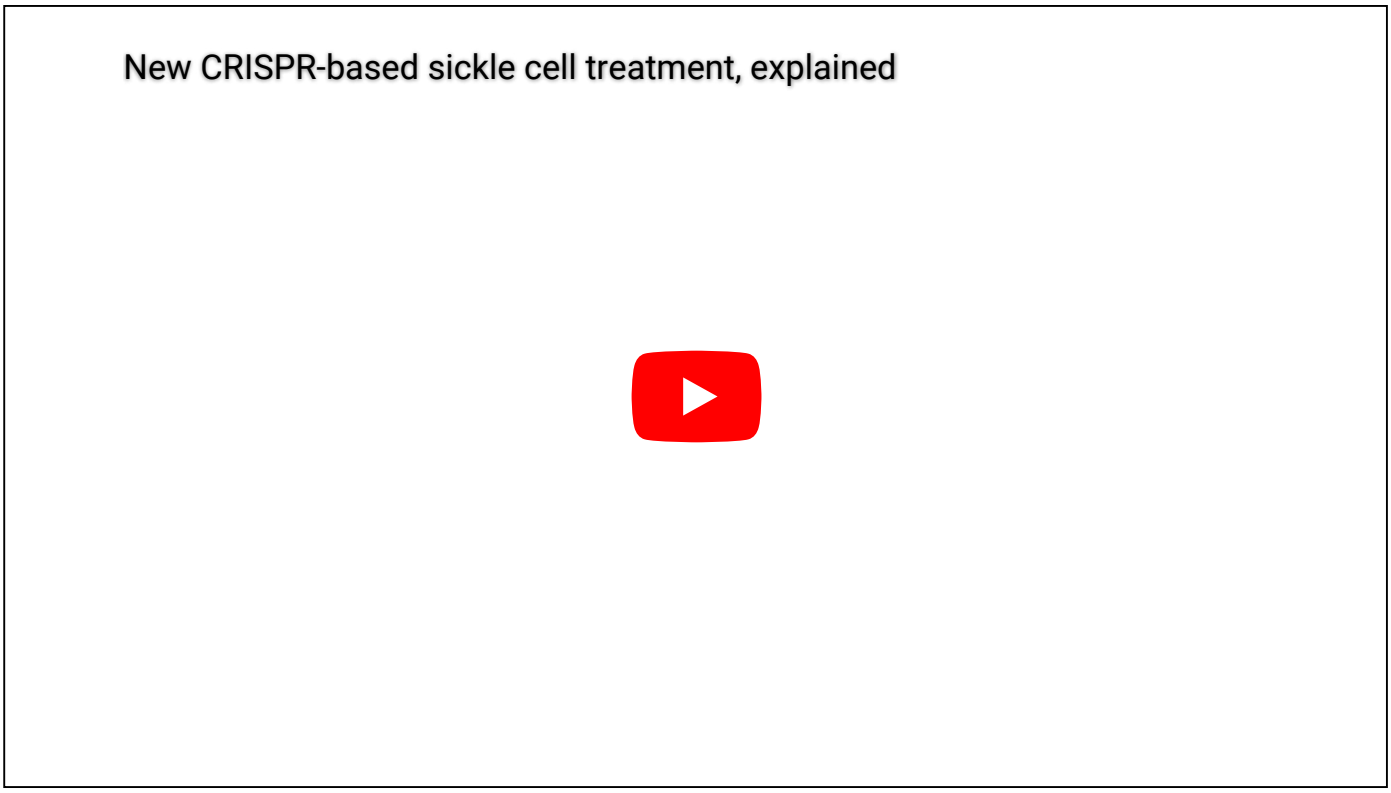
The FDA decision comes three weeks after regulators in the U.K. were the first to clear the drug. Approval in the European Union is expected next year. The FDA is also expected to rule on exa-cel as a treatment for beta thalassemia, another inherited blood disorder, by March 30.

The FDA on Friday also approved another sickle cell treatment, a gene therapy from Bluebird Bio called Lyfgenia. Patients will now have the option of two cutting-edge therapies that provide potentially curative benefits.

“We are celebrating,” said Lewis Hsu, chief medical officer at the Sickle Cell Disease Association of America and director of the pediatric sickle cell program at the University of Illinois at Chicago. “This decision has been a long time coming, pretty much since the first description of sickle cell as a genetic disease some 70 years ago.”

Scientists Emmanuelle Charpentier and Jennifer Doudna published their first CRISPR paper just over a decade ago. In 2020, the research won the pair a Nobel Prize. Reflecting on the approval of Casgevy, Charpentier told STAT via email that she was “excited and pleased” for what it means for patients and their families.

“This milestone certainly underscores the importance of fundamental research in the field of microbiology,” added Charpentier, who is also a scientific co-founder of CRISPR Therapeutics. “I am truly amazed at the speed at which CRISPR research and applications have developed to get us to this historic moment.”



The biotechnology era began in the 1980s with the invention of protein-based drugs made from genetically modified animal cells. Four decades later, the arrival of the first CRISPR therapy establishes a new industry benchmark that could deliver cures for an array of inherited diseases.

“Casgevy’s approval by the FDA is momentous: It is the first CRISPR-based gene-editing therapy to be approved in the U.S.,” Vertex CEO Reshma Kewalramani said. “As importantly, Casgevy is a first-in-class treatment that offers the potential of a one-time transformative therapy for eligible patients with sickle cell disease. I want to convey my deepest gratitude to the patients and investigators whose trust in this program paved the way for this landmark approval.”

But for all its virtues, whether or not Casgevy, as well as Lyfgenia, becomes a widely used treatment for people living with sickle cell — undoing decades of scientific neglect and medical racism — remains an open question.

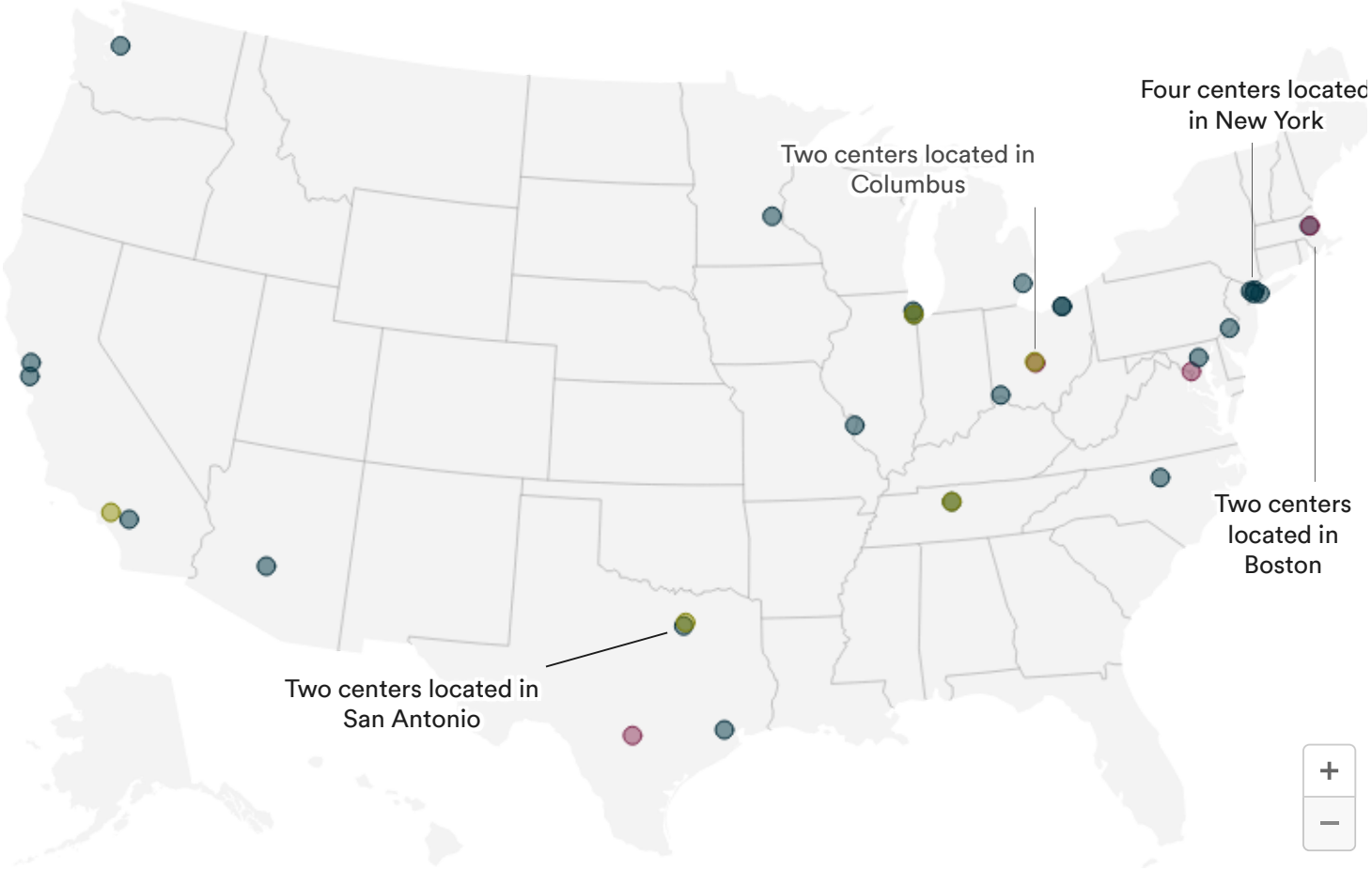
Vertex set the price of Casgevy at $2.2 million compared to $3.1 million for Bluebird’s Lyfgenia. Bluebird’s gene therapy for thalassemia, approved last

year, has a list price of $2.8 million.

The therapies are also not easy to receive. Patients must spend weeks, even months, in the hospital before and after the therapy is administered. And some of the preparatory steps can cause serious side effects, including severe infections, nausea, painful mouth sores, and infertility.

“I think there will be immediate uptake in some portion of the patients who have more severe disease — frequent pain episodes that cause hospitalization and require opioids for the treatment of pain,” David Williams, chief of the division of hematology-oncology at Boston Children’s Hospital and an expert in treating sickle cell disease, said ahead of the anticipated approval of Casgevy. “But there could be bumps in the road,” he added, if Vertex and CRISPR Therapeutics run into trouble making the complicated treatment, or if its high price tag erects barriers to reimbursement and access.

Where initial sickle cell gene therapy treatment centers are located



Map: J. Emory Parker/STAT • Source: Vertex Pharmaceuticals, Bluebird

“I’m skeptical that this will open the floodgates, as some people are predicting,” said Akshay Sharma, a physician who treats children with sickle cell at St. Jude Children’s Research Hospital. Casgevy has the potential to be a “transformative therapy,” Sharma added, but “I would expect physicians and patients to be nervous and hesitant” until its long-term efficacy and safety are better defined.

Sickle cell disease is caused by a mutation in the gene responsible for the production of oxygen-carrying hemoglobin, a protein in red blood cells. The mutation causes red blood cells to become misshapen. Under a microscope, they look like crescents or sickles, which gives the disease its name. When sickled red cells clump together, they clog blood vessels, robbing tissues of oxygen and causing bouts, or “crises,” of extreme pain, hospitalizations, organ damage, stroke, and early death.

Physicians who treat people with sickle cell today prescribe a number of medicines that can reduce the frequency of pain crises, increase hemoglobin levels, or ameliorate symptoms, but none targets the underlying genetic cause of the disease. Stem cell transplants can be curative, but the procedure requires patients to have a donor with matched immune cells, which occurs infrequently.

Further reading

More on CRISPR sickle cell therapies

- How sickle cell became the first disease treated by CRISPR.
- Watch a short explainer on how Casgevy works.
- New gene therapies confront many sickle cell patients with an impossible choice.
- Key questions (and answers) about the CRISPR-based medicine.
- Sickle cell patients ask hard questions about who can access CRISPR therapies.

This is what makes Casgevy different. It edits a patient's own blood stem cells to produce high levels of fetal hemoglobin — the healthy, oxygen-carrying form of the protein that is produced during fetal development but normally shuts down soon after birth. Researchers had previously identified a certain genetic mutation that causes fetal hemoglobin to persist into adulthood. When this happens to people with sickle cell, their disease is mild and outcomes are greatly improved.

Casgevy uses the CRISPR-Cas9 enzyme to mimic this protective genetic mutation. It makes a cut at a specific spot in a gene called BCL11A. The edit, in turn, disables a DNA brake on the production of fetal hemoglobin.

Bluebird's gene therapy works through another route, delivering, with the help of a virus, a copy of a gene into patients' cells that enables them to produce healthy hemoglobin. In a clinical trial, 28 out of 32 patients lived free of pain crises during the study period after receiving Lyfgenia.

The clinical trial conducted by Vertex and CRISPR Therapeutics that supported Casgevy's approval enrolled 30 people with sickle cell, aged 12 to

35, who were, on average, experiencing four severe pain episodes per year and just under three hospitalizations per year.

Victoria Gray, seen here in a 2019 photo, was the first person treated with Casgevy in the clinical trial of the treatment. *Anthem Pictures/Sarah Cannon Research Institute via AP*

Within three months of receiving a single Casgevy infusion, all of the study participants began producing protective levels of fetal hemoglobin. All but one of the participants achieved the main goal of the study — freedom from severe pain episodes for at least one year following treatment. Twenty-eight participants remained free of pain episodes for an average of 22 months. The first person treated with Casgevy in the clinical trial, a woman named Victoria Gray, has now gone more than four years without a severe pain episode.

The FDA recently held a meeting with outside experts about Casgevy, which focused on "off-target" editing — that is, any potential inadvertent changes the medicine may make in patients' cells — underscoring how scientists and regulators are adapting to this new class of genetic medicines. On Friday, the FDA said the treatment's label will include a caution about the "potential" risk of off-target edits.

“Genome editing is something special and it may redefine the paradigm of medicine over the next 30-40 years,” said CRISPR Therapeutics CEO Samarth Kulkarni. “Exa-cel’s approval represents the start of it. “We can fundamentally alter the genes that cause disease to create a functional, lifelong solution with a single administration. That’s a new paradigm, and it’s only powered by genome editing.”

CRISPR Therapeutics was founded in 2013 soon after Charpentier and Doudna published their seminal CRISPR paper. Work on what is now Casgevy started in earnest two years later, with Vertex on board as a partner and investor. The first clinical trial involving patients with sickle cell began in 2019.

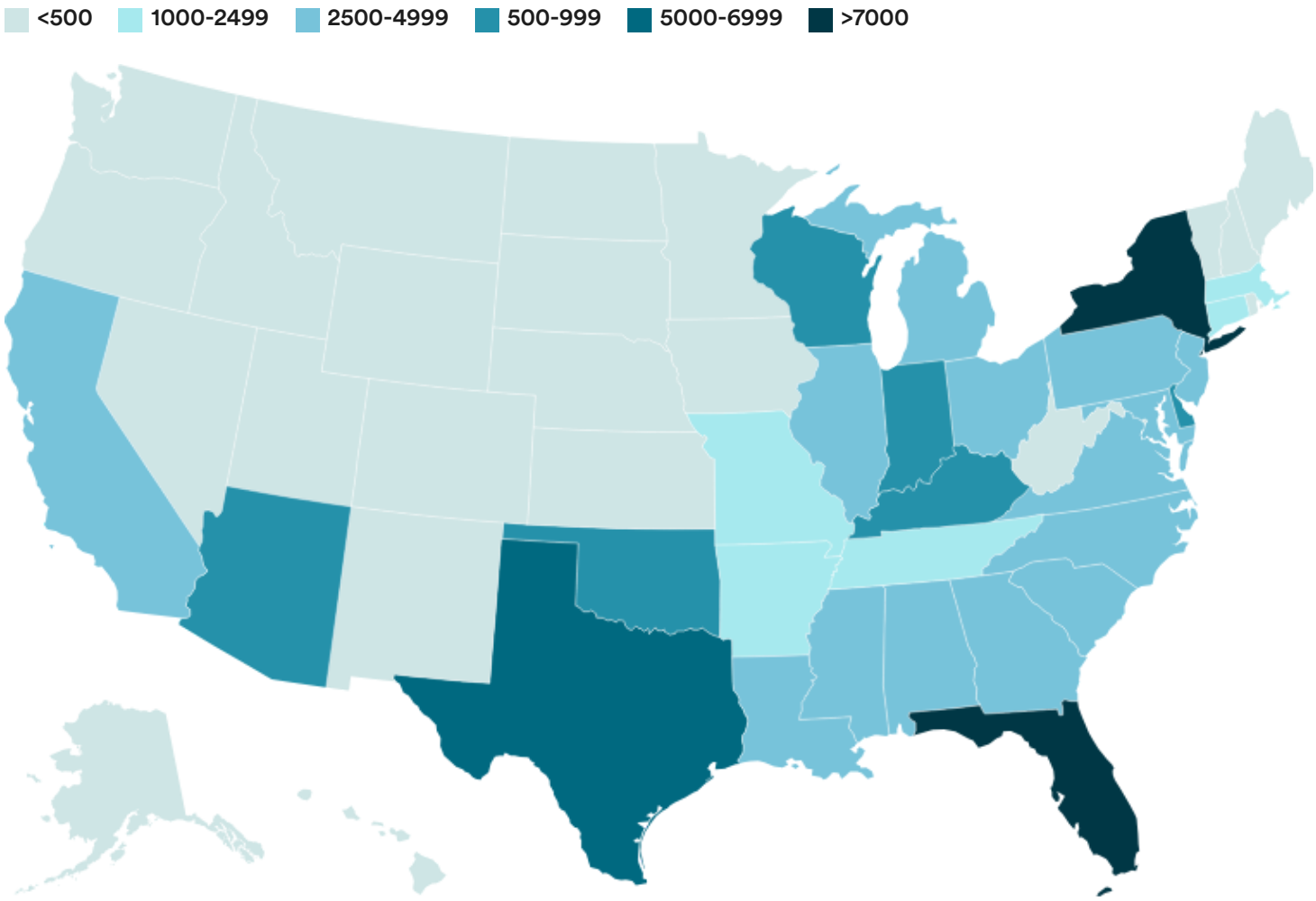
Casgevy is often described as a one-time treatment, but that convenience underrepresents the arduous and lengthy steps required before it’s administered. Patients first have their blood stem cells removed through a process called apheresis; the cells are then shipped off to a company-run manufacturing lab where they are edited. While cells are prepared, patients must undergo a preparatory treatment with a chemotherapy drug to remove any native stem cells that might remain in their bone marrow.

This “conditioning” step is crucial because it provides space in the bone marrow for the functional, CRISPR-edited cells to engraft and grow. But the chemotherapy drug used, called busulfan, wipes out germ-fighting immune cells and can cause serious side effects, including infertility — a particularly troublesome risk factor for people who wish to have children.

The actual injection of Casgevy is quick, but patients must remain in the hospital for weeks until their immune system recovers and the risk of serious infection abates.

Where sickle cell is most prevalent

Estimated number of people with sickle cell disease in 2018 in the U.S.



Map: J. Emory Parker/STAT • Source: Lee et al. (2019) Public Health Rep.

Vertex estimates about 25,000 people in the U.S. and Europe might be good candidates for Casgevy — consisting mostly of people with more severe disease who are willing to undergo the arduous procedure and accept the risks.

“The initial patients will be motivated because they’ve been following, they’re interested, and they believe the benefits outweigh the risks and the current challenges,” said David Altshuler, Vertex’s chief scientific officer. “But I think the other thing that will happen is a sort of community aspect, where patients will be watching other patients in their care centers and in their community. Over time, that will build confidence and trust.”

Both regulators in the U.K. and the FDA approved Casgevy for people as young as 12.

"We've heard consistently from physicians that they are interested in treating patients who are younger," said Stuart Arbuckle, Vertex's chief operating officer. "The disease has taken hold less, and so these patients have fewer complications and more of a lifetime of benefit to gain. And they tend to be able to schedule this procedure into their life a bit easier than a working adult. They also tend to do really well versus older people."

Sharma, the sickle cell expert at St. Jude's, intends to take a more cautious approach.

"As long as we don't have evidence of long-term safety, I would be hesitant to expose young children to this therapy, which is still so novel," he said. "I think the ideal patient is an adult who has severe disease not controlled by currently available treatments."

Hsu, the University of Illinois physician, has already started speaking to his patients about undergoing treatment with Casgevy. Patients with more severe sickle cell disease "who have seen how bad it can be, especially as they grow older" are likely to be the first to seek out treatment, he said.

He's also counseled some adolescent patients who expressed initial interest in Casgevy but have since decided to wait because the medicines they take today to control their disease are working. "These are younger people whose organs are in good enough shape that they could go through this, and their disease severity is high enough that they would be eligible."

Vertex, which is running point on Casgevy's commercial launch, has said previously that it expects a slow uptake, given the complexity of treatment and the need to sort out reimbursement and access.

Lyfgenia's approval came with a black box warning about the possibility that patients who receive the therapy might later develop blood cancer and should be monitored for that risk. Two patients in trials of the drug died of blood

cancers, and studies concluded that the cancers were caused by the chemotherapy conditioning regimen for the treatment, not Lyfgenia itself.

Andrew Joseph and Brittany Trang contributed reporting.

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