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'Transformative' gene therapies for sickle cell disease spur cautious hope in Mich. patients

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Detroit — Pain is familiar and far from predictable for people such as Medjie Pascal-Harris, a Detroiter who lives with sickle cell disease, an inherited blood disorder that cuts 20-30 years off the average person's lifespan.

"Living with sickle cell feels like the pain is like a friend," said Pascal-Harris, 37. "A friend that you're really close with, and you don't know when they're going to come over to see you."

The pain can range from dull and achy to sharp, stabbing and pulsating, said Clifton Kirkman, 36, who also grew up in Detroit and, like Pascal-Harris, has lived with sickle cell disease his entire life.

But a pain crisis, which people living with sickle cell disease are all too familiar with, truly cannot be explained, Kirkman said.

"You just are in a complete state of pain, so much so that you have to try and be out of your body in order to soothe your body," Kirkman said. "Every time you take a breath, it intensifies with the beat of the heart and the beat of inhaling and exhaling."

But hope may be on the horizon for patients such as Pascal-Harris and Kirkman. After decades of what experts say has been an under-investment in sickle cell disease research and patients, two new gene therapy treatments that could potentially cure the painful genetic condition might be approved this month by the Food and Drug Administration.

The treatments involve extracting the stem cells of those living with sickle cell, genetically manipulating those cells and then putting them back into the patient. Early results have shown that patients have seen a marked improvement in symptoms.

Asif Alavi, a sickle cell hematologist with Detroit-based Henry Ford Health, has already treated two sickle cell patients with gene therapy, similar to the protocol that the FDA is considering. His study targeted the same mutation but used a different gene editing technique. Since his clinical trials' cutoff date in 2022, both of those patients have had "marked responses" in symptom improvements, he said.

"I've seen firsthand how effective these therapies can be," Alavi said.

In June, the FDA accepted biologics license applications for two gene therapies for sickle cell disease for priority review, which means it is expedited: exagamglogene autotemcel, or exa-cel, produced by Switzerland-based CRISPR Therapeutics and Boston-based Vertex Pharmaceuticals, and Lovotibeglogene autotemcel, or lovo-cel, which is made by Bluebird Bio, based in Somerville, Mass.

The FDA must respond to each application by Dec. 8 and Dec. 20, respectively. Thirty-five people with sickle cell disease had received exa-cel treatment as of June, and 36 had been given the most up-to-date lovo-cel treatment.

For Kirkman, who has a 10-year-old daughter who also carries the sickle cell trait, the new treatments have sparked cautious optimism about the road ahead. People with the sickle cell trait typically do not experience any symptoms of the disease, but can pass the trait on to their children.

“Are we hopeful? Absolutely. But only time will tell if that is going to be a story of hope for all of us,” Kirkman said. “Are we going to get there before our time runs out?”

Michiganians live with sickle cell

Sickle cell disease affects roughly 100,000 people in the United States and over 4,000 in Michigan. Most individuals living with the disease in the United States are Black, and it affects one in every 365 Black births, according to the Centers for Disease Control and Prevention. Its roots can be traced to the transatlantic slave trade when millions of enslaved Africans who carried the trait were brought to the United States against their will. The mutation arose in Africa because it protects against malaria infection.

Most people with sickle cell disease in Michigan live in the southeast portion of the state. More than 1,000 live in Wayne County, which is home to Detroit, one of the nation’s largest majority Black cities.

Sickle cell disease refers to a group of inherited red blood cell disorders. Patients with sickle cell disease can’t produce normal hemoglobin, a protein that carries oxygen, due to a single-point mutation in their genetic code. The condition causes red blood cells to become crescent-shaped like a sickle, according to the CDC.

These red blood cells die prematurely, so patients have a perpetual shortage. They can also get stuck more easily in blood vessels, affecting any organ and causing severe pain, clots and strokes.

New treatments

As of June, 71 patients had received one of the new gene therapies.

“The numbers are growing, but it’s still a relatively small number of people,” said Alavi at Henry Ford Hospital in Detroit. “Over time, we’re going to have to see … what’s the long-term efficacy of the types of treatments.”

The treatments both involve autologous transplants, a process in which a patient’s stem cells are removed, genetically manipulated and transplanted back into the patient, said Ghada Abusin, a physician who treats

pediatric sickle cell patients at Michigan Medicine in Ann Arbor. They differ in the method used to genetically modify the stem cells.

Initial results show that gene editing of stem cells using both techniques raises normal hemoglobin levels and lowers sickle hemoglobin levels, reducing or eliminating the painful symptoms of sickle cell disease and the need for transfusions.

Patients receiving either treatment have to undergo chemotherapy to wipe out their old cells before the genetically edited stem cells can be infused back into their bodies, Alavi said.

A lack of funding

Institutional racism has contributed to the historic lack of funding and resources for people with sickle cell disease, said Wanda Whitten-Shurney, the CEO and medical director of the Sickle Cell Disease Association of America's Michigan chapter, which provides services to roughly 900 people annually, including every child screened for sickle cell disease since 1987.

Despite being the most common inherited blood disorder in the United States, research shows that sickle cell disease patients receive less federal funding per patient than other inherited diseases that affect mostly White populations, such as cystic fibrosis.

"Every large medical center will have a comprehensive cystic fibrosis center. … If you look at it with sickle cell disease, it's almost the opposite," Alavi said.

A drug approved by the FDA in 2017 marked the first new treatment for sickle cell disease in nearly two decades. Two more have been approved in recent years, said Wanda Whitten-Shurney, who was a pediatrician at the Children's Hospital of Michigan sickle cell clinic for 30 years.

Currently, the only curative treatment available is a stem cell transplant, but only around 20% of patients have a matched sibling donor for this and the process includes significant risks, experts said.

"It's so important for our (sickle cell) warriors to have access to care so that they can have access to these medications," Whitten-Shurney said. "That's what's important, of course, about the genetic cure for sickle cell disease. … It would be aimed at what actually is going on, rather than just trying to treat the symptoms."

Hope for the future

Sickle cell disease typically only manifests in people who inherit two abnormal hemoglobin genes, one from each parent.

For Kirkman, his sickle cell journey has included years of monthly blood transfusions, at least one surgery and a stroke. He was 10 when he already had gallbladder surgery; excess bleeding caused a stroke.

He has been receiving blood transfusions monthly since then to reduce the chances of having another stroke. Having sickle cell disease often leads to organ damage, and decades of transfusions have caused cirrhosis in

Kirkman's liver.

Kirkman, whose daughter, Crystal, carries only one copy of the flawed hemoglobin gene, is excited for younger generations living with sickle cell to have new treatment opportunities and not experience the chronic pain, transfusions and other challenges he's faced. He is also optimistic that older adults with the condition will have access to the treatments.

Kirkman said he has had three friends pass away from sickle cell disease, two while going through the process of a bone marrow transplant.

"It rushes us to live life because we don't know when that time may come," Kirkman said.

Pascal-Harris of Port-au-Prince, Haiti, moved to Detroit when she was 8 and remembers learning she had sickle cell around the same time. It took her eight years to earn her undergraduate degree from Wayne State University, where she is currently a second-year medical school student, because of frequent hospitalizations.

"The reason why it took me so long to get here is because of the sickle cell," Pascal-Harris said. "I would have crises, and I would have to go to the emergency room. To be gone so many times, going in and out of the hospital, it caused me to not be able to graduate in four years."

She is now strongly considering emergency medicine because that's where she's spent the most time hospitalized for sickle cell disease. She is excited by the prospect of new genetic treatments and finding out whether she'll be eligible for them.

"I have two children. I have two boys. And since I had my second baby in 2022, sickle cell crises for me have basically gotten worse," Pascal-Harris said. "Literally, I'm in the hospital every six weeks."

The boys don't have sickle cell anemia, she added.

While Pascal-Harris' brother was only a half match for a bone marrow transplant, she's already started talking with her physician about gene therapy.

"If it's something that will cure the sickle cell ..., I believe we should all at least seek and try to figure out if it's something that is possible for every patient," Pascal-Harris said.

Increasing access, building trust

But the new treatments have raised concerns. Whitten-Shurney, the medical director of the Sickle Cell Disease Association of America's Michigan chapter, wonders who will pay for the treatment and what the long-term risks and results are.

"So much is unknown, but we will know more and more as time goes on," Whitten-Shurney said. "It's a question of who's going to be the first one to do the long-term follow-up."

Resistance to the gene editing treatment also could be an issue. Trying to get people to genetically modify their stem cells may prove difficult when many don't even want to eat genetically modified food, Whitten-Shurney added.

"You're dealing with a race of people who have been known … in this country to have been testing guinea pigs," Kirkman said. "That is always going be something that's in the back of our mind."

While the treatments are overdue, physicians can never have 100% confidence in their safety and efficacy, Michigan Medicine's Abusin said.

"We are serving a population who have been marginalized for a very, very long time, and so we should not rush them," Abusin said.

Trust is affected by prior experiences with health care providers, Kirkman added. Many people with sickle cell disease are treated as drug seekers when they end up in the emergency room during a pain crisis.

"I've been called a drug seeker before; I've been called a drug addict," Pascal-Harris said. "Sometimes they don't believe that you're in pain. They think that you're making it up."

Sickle cell coverage

Despite the existence of treatments now that can reduce the risk of strokes and infection in people with sickle cell disease, gaps in care continue to persist, said Sarah Reeves, an assistant professor in the departments of pediatrics and epidemiology at Michigan Medicine.

"When you merge a very complex, chronic condition to manage with being consistently underserved in health care historically, and currently — that really creates a difficult situation to receive high-quality care," Reeves said. "Access doesn't just mean health insurance. It means there's a provider you can go to."

Most Michigan residents with sickle cell disease are enrolled in Medicaid, the government health care program for mostly low-income residents. Those under the age of 21 historically received coverage through the Michigan Department of Health and Human Services' Children's Special Health Care Services Program. In 2021, coverage was expanded to include adults with sickle cell disease.

Michigan Medicaid and the Children's Special Health Care Services Program have an established process for reviewing new FDA-approved therapies to be considered for coverage, state Department of Health and Human Services spokeswoman Lynn Sutfin said. There is also a process to evaluate new therapies for coverage based on individual medical necessity before they are officially added to the state's coverage policies.

Price information for lovo-cel and exa-cel, the gene editing treatments the FDA is considering, is not available yet, but analysts estimate the treatments could cost around $2 million each and the total price of treatment and other costs of care to be over $2.5 million, according to the Institute for Clinical and Economic Review, a Boston-based independent nonprofit research organization. At this price, the gene therapies would be more expensive than the average cost of care throughout a person with sickle cell's lifetime.

While Henry Ford was not a recruitment site for either clinical trial of the new gene editing treatments, the hospital is already working with the companies providing lovo-cel and exa-cel and will probably be one of the first centers offering them, Alavi said.

“The biggest challenge when getting going is figuring out how it’s going to get paid for,” Alavi said.

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