IN THE LAB

CRISPR is used in landmark treatment to correct genetic misspelling of a single patient

Treatment of baby with rare disease could usher in era of personalized genome editing

Baby KJ with two of the researchers who treated him, Kiran Musunuru (left) and Rebecca Ahrens-Nicklas. Children's Hospital of Philadelphia

By Jason Mast May 15, 2025

General Assignment Reporter

For the first time, scientists say they have reached into the genome of a severely ill child and rewritten the unique misspelling in his DNA.

The results, published in the New England Journal of Medicine on Thursday, are a landmark in the 50-year quest to read and repair the code of life. The boy, a now 9.5-month-old named KJ, was diagnosed days after birth with an ultra-rare disease that impairs his liver's ability to process ammonia, which can build up and cause permanent brain damage or death.

KJ had been living in the hospital, waiting until he was old enough to receive a liver transplant. Instead, at 6 months, doctors administered the first dose of the gene editing treatment. They have since been able to loosen a strict low-protein diet and reduce his daily ammonia-lowering medications by half.

Plans for a transplant have, for the moment, been scrapped, although investigators remain cautious about declaring success.

"It is still early days to be able to make definitive statements about how well this worked," said Rebecca Ahrens-Nicklas, the Children's Hospital of Philadelphia physician who administered the therapy. "I think we can say this has been shown to be safe and well tolerated, and there's hints that this has been a benefit to him, but we just need more time."

Some outside researchers were less reserved. Clinical trials using CRISPR gene editing have been underway for nearly a decade. But like most trials, they focused on broad groups of patients. If early findings hold up, KJ's therapy will mark the first time CRISPR has been successfully calibrated to fix a single patient's unique genetic typo.

"It's terrific work," said Erik Sontheimer, a gene editing researcher at UMass Chan Medical School. "It truly brings CRISPR genome editing into the n-of-1 regime."

The results may offer hope of treatment for thousands of patients with deadly or disabling mutations that are unique or too rare to interest traditional for-profit drug developers.

At the same time, they will ignite long-simmering questions about how to safely and equitably scale personalized treatments.

In their paper, Ahrens-Nicklas, University of Pennsylvania geneticist Kiran Musunuru, and the other researchers behind KJ's treatment concluded patient-specific genetic surgery "will become routine for many genetic diseases." Eventually, perhaps. But KJ's treatment was a remarkable endeavor, requiring collaboration of researchers and companies working at breakneck speed, for free or reduced rates in Philadelphia, Boston, North Dakota, California, Maine, and Vancouver, British Columbia. No one will say how much it cost.

Applying it to more than a tiny handful of patients may require not just scientific advances, but sweeping changes to how the U.S. regulates and pays for genetic medicine.

Chasing CRISPR's promise

Both the need and the possibility for such concierge DNA repair emerged a few years ago, as gene editing tools became more precise. Early on, CRISPR was best at breaking genes, not fixing them. But in the late 2010s, Harvard biochemist David Liu debuted two CRISPR-based tools, base editing and prime editing, that allowed researchers to swap individual letters and make other small changes to DNA.

If early CRISPR was a molecular scissors, base and prime editing was like taking a pencil and eraser to the genome.

The challenge is that single genetic diseases can be caused by up to thousands of different mutations. Companies were not going to spend tens of millions of dollars developing a therapy for each. Musunuru began warning about "mutational discrimination": a world in which only patients with the most common and lucrative variants for a particular disease receive treatment.

There was an alternative path, though. Since 2018, academics and nonprofits have been crafting treatments calibrated to children's particular mutations using antisense oligonucleotides (ASOs), small stretches of DNA or RNA that change how genes function without changing the genome itself.

Some in the n-of-1 movement, as it's called, wanted to use gene editing as well. ASOs required lifetime treatment, but CRISPR could provide a permanent fix. And whereas ASOs were used primarily for neurological diseases, gene editing could help patients with liver and blood conditions, the easiest organs to reach with CRISPR.

“This is the critical next step we’ve been waiting for,” said Julia Vitarello, whose late daughter Mila became the first patient to receive an n-of-1 ASO and who has since been working on making such medicines broadly available.

A nurse’s hunch

Nicole and Kyle Muldoon’s fourth child was born at the University of Pennsylvania premature but seemingly healthy. After birth, Nicole went for a surgery to deal with a complication and Kyle went to watch his other three kids, leaving KJ in the NICU.

Within two days, though, a nurse showed Kyle his son’s arm. When you lifted it, the arm stayed rigid, shuddering on its way down, a possible sign of sepsis or meningitis. But one nurse thought to also check ammonia levels. They should have been under 40. KJ’s were in the thousands.

He was rushed across the street to CHOP, where doctors put him on dialysis to clear the ammonia in time, hopefully, to prevent brain damage. Ahrens-Nicklas had his genome sequenced. The test showed CPS1 deficiency, one of the most severe of a cluster of conditions, called urea cycle disorders, that prevent the liver from breaking down ammonia.

Kyle and Nicole tried to learn all they could. It was “trauma,” he told reporters, “parenthood trauma.”

Ahrens-Nicklas, meanwhile, sent the sequence to Musunuru. The two had been collaborating for three years, preparing, with support from the National Institutes of Health, for a moment like this. But for now, she told the family nothing.

“I was very nervous about giving any false hope,” she said.

‘What diseases would we tackle?’

KJ’s wasn’t the first mutation Musunuru and Ahrens-Nicklas tried to solve. Soft-spoken, lanky, and supremely confident, Musunuru had spent much of the 2010s trying to convince the world of a single idea: CRISPR could be used to break cholesterol genes in perhaps billions of people, staving off the heart disease he saw as a practicing cardiologist.

Around 2020, investors finally started listening and backed a company, Verve Therapeutics, he co-founded to take the idea into clinical trials. In summer of 2021, Musunuru returned from a sabbatical there itching for a new challenge.

He wanted to focus on fixing, instead of breaking, genes. The same summer, the first human data emerged proving you could deliver CRISPR to the liver with lipid nanoparticles, the same tiny soap bubbles used in mRNA vaccines. He reached out to Ahrens-Nicklas, who specializes in treating children with inborn errors of metabolism.

“We started brainstorming, you know, if we make any change we want in the liver, what diseases would we tackle?” he said.

They eventually homed in urea cycle disorders. The need felt particularly acute. The disorders were generally quite rare and severe. Many patients would need to be treated as infants, meaning researchers would have to craft an editor in a number of months.

Musunuru and Ahrens-Nicklas began running what they called “time trials.” Ahrens-Nicklas picked a variant, informed by her clinical experience, and they tested to see how fast they could design an editor.

The first one took over a year. But over five or six tries, the team got faster and faster.

The six-month sprint

When Musunuru got the sequence, one evening in early August, it kicked off a stripped-down, hair-on-fire version of a process that usually takes years and tens of millions of dollars.

KJ had two mutations, one from each parent. One was amenable to prime editing, which is versatile but cumbersome. The other was amenable to base editing, which is limited but simpler. Musunuru would likely be able to craft a base editor, but several pins would have to be lined up immediately if it was going to be ready for KJ in time.

The editor would have to be tested in mice bearing KJ’s mutation. But mice need time to be born, so they immediately placed an order from the Jackson Laboratory in Maine. The drug, they believed, needed to be tested in monkeys for safety. But waiting lists for lab

monkeys can resemble queues for a rent-controlled apartment in New York City. So they reserved them immediately.

They needed to manufacture the drug at human quality and confirm that it didn't accidentally also nick another part of KJ's DNA in a location that could cause cancer or other issues. For that, Musunuru emailed, among others, Fyodor Urnov, a director at the University of California-Berkeley's Innovative Genomics Institute, who had become the country's most vocal advocate for pushing custom gene editors into patients.

Urnov had struck a partnership with Danaher, a $134 billion biomedical conglomerate, to fund and provide services for his institute to create such treatments for blood disorders. Both now agreed to help.

"We've been preparing this, full time, for the past few years of our lives," said Urnov.

Back at Penn, a graduate student, Sarah Grandinette, created cell lines bearing KJ's mutations. Base editors contain two parts — a letter-swapping enzyme, called the editor, and a homing sequence, called guide RNA — and she created 30 different combinations to test. She picked one after four weeks and then swapped it out for a better one, built with machine learning at Harvard.

The following months were chaotic, nerve-wracking, but largely hitch-free. There were no significant off-target edits. The monkeys, dosed around month 5 with funds from the NIH, appeared unharmed. The editor was shown to work in mice around the same time.

The FDA authorized a trial a week after submission. Because it was for a single, desperate patient, some testing could be skipped. KJ's therapy was produced in Fargo, N.D., with a guide RNA supplied from California and lipid nanoparticles brought from Vancouver. Vials were flown, frozen, to Philadelphia.

When they were sure a committed group was in place, Ahrens-Nicklas had informed Kyle and Nicole. It "was such a foreign concept," said Kyle. But it was compelling compared to the invasiveness of a liver transplant. And they trusted Ahrens-Nicklas.

They named the drug kayjayguran abengcemeran, or k-abe, after KJ. It was injected into KJ's IV bag mid-morning in late February. He lay sleeping as a crowd watched in excitement and fear.

Ahrens-Nicklas and Musunuru picked an ultra-low dose to minimize risk, and the first shot showed little efficacy. But after a second treatment, they saw results. KJ has now received his third — and final — dose, though researchers have not yet reported whether that's allowed him to fully come off daily medicines. Ahrens-Nicklas said she would consider KJ to have a "milder form" of his disease, not cured.

Researchers won't know exactly how well they were able to edit the liver. To do so, they would need to biopsy KJ's liver, which would be unsafe given his condition. But outside researchers were impressed.

It's "groundbreaking," said Julien Baruteau, who develops treatments for urea cycle disorders at the University College of London.

Nicole, KJ's mom, has her own measure of efficacy: walking into his hospital room one morning and seeing him sitting up in his crib. "We didn't know if that was going to be something he was able to do," she said.

KJ, in his father's lap, with his mother and siblings. Children's Hospital of Philadelphia

Will there be more n-of-1s?

Researchers dearly want to correct the genetic misspellings in other children like KJ, but the hurdles are high. It's not just cost. Several technical factors made KJ's mutation particularly easy to treat. Other treatments may require further customization, though researchers may save time in other ways.

Although Ahrens-Nicklas and Musunuru wanted to run through as much of the usual drug development process as possible for the first patient, they hope to eventually be able to treat new mutations after just testing cells in a lab. The goal would be to build a "platform" where you can develop an editor for one mutation, prove it works, and then tweak it slightly to go after the next mutation.

Under longtime biologics chief Peter Marks, the FDA had shown openness to that idea. But Marks' forced resignation in March casts doubt over the future of the agency's efforts. So, too, do the Trump administration cuts at the NIH, which has been spending hundreds of millions of dollars to enable gene-targeted treatments.

Researchers involved in KJ's therapy were eager to underline the government's involvement. "This is what the engine of American innovation does for American health care," said Urnov.

Musunuru and Ahrens-Nicklas are planning to return to the agency in the next couple years to start a "platform" trial, going after multiple mutations in a more common rare disease. In the meantime, they hope KJ's case will encourage others to try curing another child with an n-of-1 disease.

Sontheimer, the UMass gene editing researcher, said he assumes the pair are already working on the next patient. "I'm willing to bet that there are already other patients," he said.