

Gene therapy trial shows promise for treating ‘bubble boy’ syndrome. Now comes the hard part



By [Brittany Trang](#) Dec. 21, 2022



H.T. Begay, age 4, with UCSF Child Life Specialist Courtney Dellings.

BARABARA RIES / UCSF

H.T. Begay is a happy kid. He’s smiley, silly, and definitely trying to make you laugh. The four-year-old’s two neat braids of dark hair wave behind him as he runs

among the dust, dogs, and sheep near his family's ranch on their Navajo reservation in Arizona.

On a table inside the family's sweat lodge is a little altar, as shown in a [video](#) shared by the University of California, San Francisco. Next to a pair of tiny baby booties is a certificate that reads, "The first patient in the world to receive Autologous Gene Therapy for Artemis-deficient SCID 06/23/2018."

Even though he was born without an immune system, H.T. can play with "all those animals and the diseases that those animals carry" and be completely fine, his doctor Morton Cowan says with a chuckle. That's thanks to a new gene therapy that corrected the mutated gene called Artemis that prevented H.T. from being able to form T cells and B cells.

On Wednesday, the results of the clinical trial in which H.T. participated were [published](#) in the New England Journal of Medicine. H.T. has severe combined immunodeficiency, more popularly known as "bubble boy disease," so named because of the sterile environment to which babies and young children were once confined in order to avoid infection. Led by Morton Cowan and Jennifer Puck, both professors of pediatrics from the UCSF, the new Phase 1/2 trial is the first gene therapy for one of the rarest and hardest-to-treat forms of the disease, Artemis-deficient SCID. All of the patients survived the therapy, and four of them have stopped requiring immunoglobulin treatment. Some have even received childhood immunizations and created protective antibodies — a resounding success.

But while the results make this gene therapy look like a sleek sports car speeding toward a cure for an incredibly rare disease, there are problems with the road ahead. Several companies have already bailed on gene therapies for more prevalent forms of SCID, leaving patients without a pathway for treatment.

The commercialization failures have been "extremely disappointing," said Sung-Yun Pai, a senior investigator at the National Cancer Institute. "These therapies take so many years to design, get regulatory approval, and conduct the studies, and then to have all those years of investment be wasted without moving to the next step of bringing the therapies as licensed therapies to the public, it's devastating."

Cowan and Puck are toying with the idea of offering the therapy as a not-for-profit institution if no company comes through on commercialization, but that territory is uncharted and extremely uncertain. As gene therapies for rare diseases start pushing on the boundaries of what was previously possible, more cracks are appearing in the current

regulatory and commercialization models, and it's not clear what it will take to get much-needed treatments to more patients.

What is Artemis-deficient SCID, and why is it hard to treat?

There are several different mutations that can lead to severe combined immune deficiency, or SCID, but they all have the same outcome: no functional T cells or B cells, which equals no ability to fight common infections. The 1976 John Travolta movie “The Boy in the Plastic Bubble” was inspired by the life of David Vetter, the most famous SCID patient. Vetter lived in a sterile, enclosed environment until his death at age 12, which popularized the term “bubble boy disease.” Many children with SCID do not survive their first year of life unless treated.

Artemis-SCID, which occurs disproportionately in Navajo and Apache populations, is so rare that only two to three babies with the mutation are born each year in the U.S. The Artemis gene codes for a protein that repairs broken DNA strands, and without it, the body can't complete the process of making B and T cells. The fact that Artemis-SCID patients can't repair broken DNA also makes it difficult to treat them with the standard treatment for SCID: a bone marrow transplant, ideally from a matched sibling. Cowan, who's treated “probably over 30 babies with Artemis-SCID over the years,” said that Artemis patients don't respond as well to bone marrow transplants, which often rebuild their immune systems less successfully compared to other SCID patients. Another common complication from bone marrow transplants is [graft-versus-host disease](#), which results from the transplanted cells recognizing the host cells as foreign and attacking them. This happens more often with Artemis patients than with other SCID patients, and can sometimes be fatal.

“Ten patients, ten alive”: The promise of gene therapy

One way to overcome graft-versus-host disease is to use the patient's own cells, which is the genius conceit of [gene therapy](#). Researchers harvest the patients' bone marrow and separate out the stem cells. In Puck and Cowan's new study, they introduced the correct gene to the stem cells via a lentiviral vector before giving the cells back to the patient.

[Lentiviruses](#), a family of viruses that includes HIV, hijack cells by inserting their own piece of genetic code into the host cell's. That infected cell's descendants also carry the inserted gene. Taking advantage of this machinery, the UCSF researchers emptied a lentivirus of its dangerous genes and instead filled it with the corrected Artemis gene and an accompanying strand of genetic code called a promoter, which they borrowed from the normal, healthy Artemis promoter to ensure that the gene was expressed at normal levels. The lentivirus carrying the corrected gene was then stuffed inside an “envelope”

from another cell that could easily attach to the surface of stem cells and deposit its cargo inside.

Because the corrected stem cells came from the patient's own body, the possibility of graft-versus-host rejection is eliminated, said Cowan, but the new stem cells still need room to graft in the patient's bone niches. To make room, patients were treated with a light course of chemo—only 25% of the normal amount, which is the lowest amount a clinical trial has used, said Puck. After two days of chemo, the patients were re-injected with their corrected stem cells and waited for them to graft. The entire process — from harvesting to re-injection — takes about two weeks.

One of the goals of the study was to see evidence of the corrected genetic sequence in the patients' blood within six weeks, but Puck says they found it in every patient by the four-week mark. Of the nine patients that were followed for 12 months, four of them met the other goal of the study, getting to a “normal” range of T-cells by the 12-month mark.

There's still hope that over time, the remaining SCID patients' immune systems will balance out, according to Anne Galy, director of the Accelerator of Technological Research in Genomic Therapy at Inserm, the French equivalent of the NIH. She explained that with gene therapies for Wiskott-Aldrich syndrome, patients' T cells recover quickly, but their B cells take almost two years. Here, the opposite is happening, but this precedent gives hope that the remaining patients' T cells may recover yet.

Galy also pointed out that some of the patients developed an auto-immune complication called autoimmune hemolytic anemia. She agreed with the authors that the sample size was too small to determine whether this complication was due to the treatment or to the disease itself. But she was pleased with how well the therapy treated a disease whose patients are even more fragile than those with other forms of SCID. “Ten patients, ten alive, so it's good in terms of success and in terms of tolerance to the treatment,” said Galy, who was not involved with the study.

Pai, who was uninvolved with the study but authored an accompanying NEJM [editorial](#), pointed out that even though the number of B cells varied a lot across all the patients in the study, four of the six patients who were observed after 24 months were able to go off immunoglobulin infusion therapy, which meant that their B cells were working well enough to produce their own immunoglobulin. “Sure, it would be nice to have more B cells,” she said. “But it's not really necessary. I think the most important clinical parameter, or a clinical risk to the patient, has been fixed.”

Besides documenting long-term followup, Cowan says the research team is trying to get the therapy approved by the FDA, which has already given the therapy a Regenerative Medicine Advanced Therapy designation. The team will conduct a pivotal study that would involve another ten patients, which will take another four to five years. The team is also in discussions with a company about commercialization, but researchers across the field are unhappy about how companies have treated other SCID gene therapies.

Hurdles in commercializing SCID gene therapies

Multiple companies have tried to commercialize gene therapies for a less rare type of SCID called ADA-SCID, and most of them have given up. In 2000, Maria Grazia Roncarolo, co-director of the Institute for Stem Cell Biology and Regenerative Medicine at Stanford University, led the first-in-human trial for an ADA-SCID gene therapy. This therapy was approved in Europe as Strimvelis in 2016, but only [17 patients](#) have been treated with the drug. In 2018, GSK sold off Strimvelis to Orchard Therapeutics when the company decided to [get out of rare diseases](#). Orchard had a second ADA-SCID therapy in the pipeline from Donald Kohn, a researcher at the University of California, Los Angeles, but Orchard too has given up on both the therapies, [terminating](#) its license of Kohn's therapy in 2021 and announcing in early 2022 it would [discontinue investment](#) in Strimvelis.

“It’s been extremely disappointing to me individually, to the community of investigators that I belong to, and to the patient population, that industry, when it comes to lentiviral-based gene therapy for immune deficiency, has essentially abandoned the field,” said Pai at the NCI.

Because there aren’t any companies commercializing ADA-SCID gene therapies, Kohn has now taken it into his own hands to try to treat patients. However, the financial aspect of offering the therapy as a not-for-profit procedure is hard. Kohn has estimated that the \$4 million in grants he got back from Orchard would only be enough to cover the cost of treating three patients, according to an [Insider story earlier this year](#).

Many researchers across the field have talked about similar approaches, including the UCSF team. If the talks with the company fall through for the new Artemis-SCID gene therapy, said Cowan, “we’ll probably keep it at UCSF and offer it through UCSF as a nonprofit procedure, because the results so far look so good that it’s almost unconscionable to not be able to offer this type of treatment to these patients.”

However, this route of bringing treatment to patients won’t be easy — such a nonprofit model has [rarely](#) been attempted before, and it’s unclear what the FDA approval pathway will look like. Additionally, “whether any academic center can provide the level of quality

control over manufacturing that the FDA would accept for a licensed therapy [is] one of the big barriers,” said Pai, especially because these are individualized therapies, not one drug.

Puck also reiterated points made by many experts in the gene therapy and rare disease field: The [cost of clinical trials](#) has to come down for it to become more feasible to offer therapies at a reasonable price, and federal regulations for [approving treatments for rare diseases](#) will have to look different than for diseases in which there are hundreds or thousands of patients who can participate in trials.

Roncarolo says that the efforts of Kohn as well as Italian philanthropic organization [Telethon](#), which is trying to give Strimvelis new life through non-commercial routes, are “commendable” but unsustainable. The government needs to incentivize companies to invest in therapies for rare diseases despite the low return, she said, because industry is the only group that has the resources to continue developing and distributing therapies for the long term.

“I think that this is really an alarm bell for all of us, because if we spend an enormous amount of technology, energy, money to bring these therapies to patients and then there is no biotech or big pharma that are interest[ed] to commercialize this product because they are for rare genetic diseases, then we need really to ask to ourselves, what are we doing?” said Roncarolo. “What are we doing for the patient? What are we doing for society?”

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