

Biotechnology / Genomic Medicine

Two sick children and a \$1.5 million bill: One family's race for a gene therapy cure

One day, gene therapy may help with the rarest of diseases. Some parents aren't waiting.

by Antonio Regalado

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Jennie and Gary Landsman launched an appeal to save their sons on Thanksgiving of 2017. By the end of the weekend the family, who live in Marine Park, Brooklyn, had raised \$200,000.



In a moving three-minute video posted online, they sit on an overstuffed leather couch. Jennie glances away from the camera, betraying little emotion, as Gary talks. “We need your help, we really do,” Gary says, his voice breaking. The Landsmans’ two sons—Benny, then 18 months, and Josh, four months—both have a fatal genetic brain disorder called Canavan disease.

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Benny, limp on his mother's lap, is already affected by nerve loss. Josh isn't yet. But he will be if nothing is done.

Canavan is an "ultra-rare" disease. So rare, in fact, that there is no reliable understanding of how many children are born with it. Relatively few researchers study Canavan, and no drugs are approved to treat it. There isn't even a single clinical trial open for some last-ditch remedy, the kind people battling cancer can turn to. Doctors told Jennie there was not much to be done. She should go home and make her boys comfortable until they died.

The Landsmans refused to accept that advice. Instead, Jennie hit Google and started e-mailing scientists. Here's what she learned: there may be a way to fix the genetic error in the boys' brains. But the family would have to pay for it themselves. And it would be expensive.

"We need one and a half million dollars, and our goal is to get it in the next six months," Jennie says in the video.

The Landsmans had discovered gene therapy, technology that uses viruses to add healthy genes to cells with defective ones. After several decades caught in scientific backwaters, gene therapy has entered a golden age. During a span of four months, from August to December 2017, the US Food and Drug Administration (FDA) approved three such therapies, two for blood cancer and one for an inherited cause of blindness. Companies are investigating treatments for hemophilia and muscular dystrophy. "Once just a theory," said the FDA's chief, Scott Gottlieb, in July, gene therapy "may have the potential to treat and cure some of our most intractable and vexing diseases."

The technology's medical logic is especially irresistible for parents of children with the rarest diseases on earth. These are the 7,000 or so conditions that typically, like Canavan, are caused by errors in a single gene. Gene therapy suggests the ultimate bug fix—just give people working DNA instructions. The problem for the Canavan kids is that there have been too few patients for anyone to bring the research out of the lab and put dollars behind it. The same is true for countless other diseases you've never heard of, some of which are known to affect fewer than 50 people on the globe.

"The simple math is that there are a very limited number of patients. That is what created this crazy, crazy paradigm," says Eric David, an executive with BridgeBio, a biotech in Palo Alto, California, that specializes in treatments for rare diseases. "Families are saying, 'Oh my God, no one is going to pay for this. I have to fund it myself.'"

Gene therapy already has a reputation as medicine's gnarliest economic case. The problem is who will pay. Even those few treatments approved for sale carry price tags as high as \$1 million. Underlying the unheard-of prices is the cost of years of research, human tests, and paperwork to win the FDA's sign-off, all in tiny markets with small pools of patients. Costly, too, is the still unwieldy process of manufacturing trillions of viruses, into each of which a gene is placed so it can be conveyed into people's cells. The result? A growing gap between the list of diseases that could be treated with gene therapy and those that actually are.

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I learned of six cases where parents financed clinical trials for gene therapy in which their own children were treated. These include Karen Aiach, who started a biotechnology company, Lysogene, based outside Paris; it funded the trial in which her daughter was treated for Sanfilippo syndrome. A connected Hollywood couple, the Grays, raised \$7 million to pay for a trial that infused gene-carrying viruses into two of their daughters and several other children with a rare form of Batten disease. More than 20 other parent-financed trials are in the planning phase.

Other families are avoiding the rigors of formal studies and trying to secure untested gene therapies as emergency treatment. In Florida, a single boy was treated with a Canavan gene therapy in 2017 after his parents paid for the experiment. They did it under an exemption in federal rules called “expanded access,” which can allow unapproved drugs to be offered to specific patients “whose life is immediately threatened.”





That experiment fell into a gray zone, not quite research and not quite medicine. It is the same pathway the Landsman family is trying to follow, with the help of Paola Leone, a gene therapist in New Jersey, and Christopher Janson, a neurologist in Chicago. Leone and Janson asked the FDA last June to permit emergency use of their own Canavan gene therapy in up to five children they have designated in advance. The first two names on the waiting list: Benny and Josh Landsman.

According to the FDA, the strategy is not as unusual as it sounds. Of the approximately 700 gene-therapy trials it oversees, 77 fall into the desperate-case category, according to an agency spokesperson. It is not known in how many of these cases the families are covering the costs, but that is entirely legal, too. “We would love to do it in a broader, systematic fashion that would lead to a drug treatment, but we don’t have the money,” says Janson, a physician at the University of Illinois College of Medicine. “Until then, we are stuck on our own trying to help a couple of kids.”

Some scientists who know of the Landsmans’ plan fear it represents a new form of boutique medicine—a way to give those with fat checkbooks or a knack for viral fund-raising campaigns special access to cutting-edge breakthroughs. A different perspective is that it’s just a preview of the personalized genetic medicine that will increasingly be available more generally.

In the future, health officials believe, it could become commonplace for scientists to detect a genetic mutation and whip up a custom DNA antidote for one person. “Those 7,000 diseases are ones where we know the molecular defect for most of them. We know exactly what the initial glitch was that has led to this outcome,” Francis Collins, the director of the National Institutes of Health (NIH), said in a speech this year. “Shouldn’t we think about ways to do that in a fashion that scales to hundreds or maybe thousands of diseases? So what would that take?”

Nobody really knows. And the Landsmans can’t wait for Washington, DC, or drug companies to figure it out. At today’s rate of new drug approvals for rare diseases—about 15 a year—it could take 1,000 years for companies to get around to all of them. With two sons slipping away at home, Jennie and Gary are measuring time in months instead. Josh has a big smile but never learned to crawl. He’ll soon become like Benny, who moves his arms only weakly and communicates by glancing at pictures Velcroed to a felt pad. “He’s never said ‘mommy,’” Jennie told me. But he can still ask for her—one of the pictures pinned up there is hers.

Jennie says she hopes that all Canavan kids will someday benefit and that the researchers helping her “will become famous.” But she did not raise all that money to fund an experiment or to become a philanthropist. “This is not a clinical trial,” Jennie told me. “This is private. This is for Benny and Josh.”

Perfect timing

Canavan disease is rare, but it's significantly more common among people of Ashkenazi Jewish descent, like the Landsmans. Like Tay-Sachs, it's enough of a threat that prospective parents in this population are tested to see if they are silent carriers of the gene error. About one in 40 are. A series of medical miscommunications, Jennie says, led her to mistakenly believe she had tested negative. Since it takes two mutated gene copies, one from each parent, to cause the illness, they saw no reason to test Gary.

Jennie and her pediatrician were slow to pick up on Benny's symptoms. Her sister said the toddler seemed “mushy,” but the Landsmans' doctor said not to worry. By then she was pregnant with Josh. The disastrous diagnoses unfolded over a few days last summer. In late July, a blood test finally showed Benny had Canavan. Two weeks later, on Gary's birthday, they learned their newborn had it, too.

As Jennie remembers it, she spent weeks in depression, staring at sunbeams coming under the awning and trying to “live in the moment.” But when I visited Leone, the gene therapist, at the Rowan University School of Osteopathic Medicine in New Jersey, she showed me e-mails Jennie had sent her between the two boys' diagnoses. “Can you help?” she had asked.

The idea of gene therapy traces back to 1970, but only recently have scientists mastered its components. In 2017, doctors at Nationwide Children's Hospital, in Ohio, described in *The Lancet* how they had prevented a group of infants from developing spinal muscular atrophy, a nerve disorder that, like Canavan, is fatal. The key elements: a virus that infects the right cells (nerves, in this case), immense doses, and timing. Give a one-month-old infant the missing gene, and the nerve damage doesn't begin. It now appears to scientists—and parents—that similar strategies must be capable of saving kids with other inherited nervous-system diseases.

Leone was a logical person for Jennie to approach. Between 2001 and 2005, Leone and Janson had, with government funding, treated 13 children with Canavan in one of the first attempts to change the genetic code inside a person's brain. At that time, scientists were unsure of the concept's potential, and their treatment, though it had some effect, was no cure.

Leone had been working toward a new Canavan gene therapy. But her last federal grant had run out in January 2018. In her lab, I saw a scientist curse at an old-model Mac that was slow to load an image. The shoestring budget is nothing new. “When I started this work,” she says, “people looked at me and said, ‘You must be out of your mind to work on a rare disease—you are never going to find any money and no one is going to be interested.’”

Leone keeps pictures and memorials to Canavan kids she has known in her office. Over the years, she had told many of their parents there was no chance at a cure. But the Landsmans' timing was perfect. By the fall of 2017, Leone had given the new gene therapy to enough mice to see what she calls dramatic effects. The disease seemed to have greatly slowed, even reversed. “Then I was prepared to say ‘Yes’ to the family that came along,” she says.

“There is a lot we can do”

Leone met the Landsmans in New York, near the 9/11 memorial, in September of 2017. Gary confessed that if he had a choice between fighting and fleeing, he would flee. He wished he could take Jennie far away and never come back. “Excruciating pain,” recalls Leone. “Eyes that had cried so much they were hard to see.”

Jennie wanted to know what they could do. Leone told her: “There is a lot we can do, but the first thing is how much it will cost. I can tell you it’s approximately \$1.5 million.”

“We can do it,” Jennie said without blinking.

Leone tallied the costs. They would need to hire a company to chemically synthesize healthy copies of the gene that’s broken in Canavan, set aside payments for neurosurgeons, and hire consultants to prepare a request to the FDA. The biggest single expenditure would be manufacturing. Making the viral particles—they’re grown in thin sheets bathed in components of cow blood—remains a delicate craft, and there are long waiting lists at production centers. Leone believed it would cost at least \$1 million just to make enough virus to treat Benny, Josh, and perhaps a few others.

The Landsmans didn’t have the money. The family is squarely middle class. “But there’s money everywhere, isn’t there?” Jennie reasoned. She was right. Their video, posted to Facebook and later GoFundMe, a crowdfunding site, went viral. By now, they’ve been on TV and in *People* magazine. Eight thousand donors have already given more than \$1.5 million. “This was all local people in a small Jewish community in Brooklyn,” says Ilyce Randell, a Canavan patient advocate who has been in contact with the Landsmans and has funded Leone’s work in the past. “It was a perfect storm—everyone rallied.”

But if the Landsman children end up benefiting, she says, it will be because of research under way long before they were born. “To make it seem like they bought a cure for a million bucks—that is misleading,” she says. “What is true is they came at the right time. Ten years ago you couldn’t say, ‘I’ll raise money and get my kid treated.’ Three years ago you couldn’t do it. The science was not ready.”

Unfair system

In August, many of the families and key researchers in the rare-disease world arrived in the security line at the NIH in Bethesda, Maryland. During a two-day meeting, cosponsored by the FDA, scientists gave talks whose topics teetered between remarkable results of tailored therapies and what the organizers called “unanswered questions” about how these could ever reach patients at affordable prices.

The event attracted parents hoping to find gene-therapy specialists who would treat their children. One, Amber Freed, wore a name tag reading “*SLC6A1*,” the scientific designation of a little-studied gene. Freed told a story that was by now becoming familiar. After months criss-crossing the country trying to diagnose her son’s unexplained symptoms, she finally had his genome sequenced. In May, she learned he had a pathological *SLC6A1* mutation. Freed had been working as an equity analyst in Denver, Colorado, but quit the day of the diagnosis. “I stood up from my desk and never looked back,” she says.

Until recently, many children with clusters of unusual symptoms would remain undiagnosed. Starting in 2010, genome sequencing became inexpensive enough to employ as a routine diagnostic tool. Now, much

of the time, even mysterious inherited disorders can be linked to a genetic misspelling. “Now you can walk out of a hospital with a genetic cause,” Freed told me. “I think pretty soon kids will walk out the door with a solution.”

At today's rate of new drug approvals for rare diseases—about 15 a year—it could take 1,000 years for companies to get around to all of them.

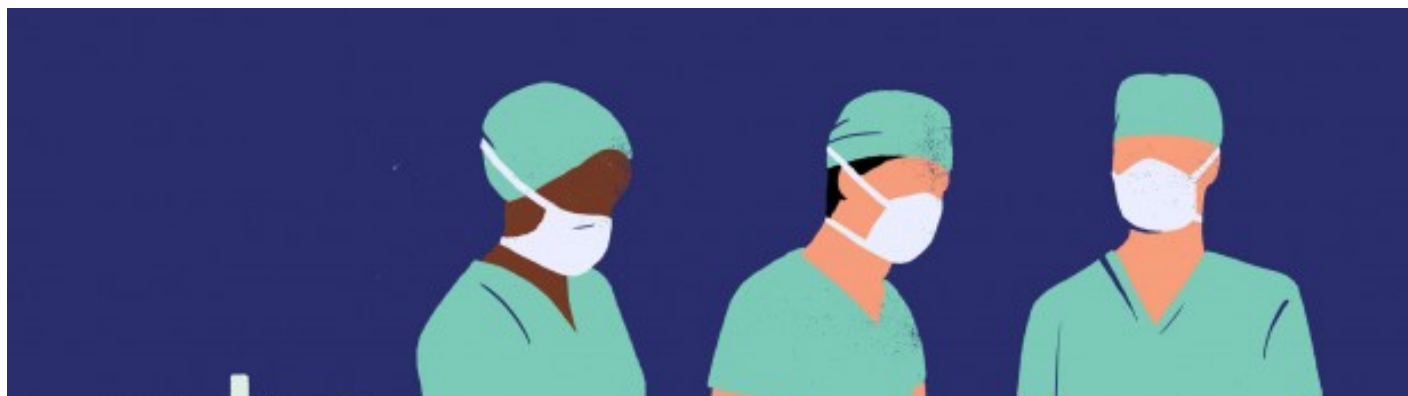
Without treatment, Freed's son will come to experience a violent form of seizure called a “drop attack.” The victim remains conscious but frozen and can topple to the ground, unable to break the impact. “It's coming, but we are going to get the cure before it gets to that point,” said Freed, who came to the meeting in a power suit and positioned herself near the stage. “We are going to find the cure for him. Our secondary mission is to help those who come after us.”

That evening I spotted Freed perched on a stool at a Bethesda eatery, speaking to a researcher named Steven Gray. A soft-spoken southerner and gene-therapy specialist at the University of Texas Southwestern Medical Center, Gray has become the go-to scientist for parents like Freed. During the conference, he showed a slide listing 23 rare diseases for which he is trying to develop genetic treatments. Gray says he finds the kids' stories tragic and a powerful motivator.

Part of Gray's job is to reset parents' expectations. Gene therapy is not as simple as packaging a gene into a virus. Many diseases can be poor candidates—for instance, those in which a gene is overactive rather than broken. Often scientists have groundwork to do, such as engineering a mouse to mimic the condition. Bypassing these steps can be perilous. If a child's body has been missing a vital molecule since birth, for example, adding it may provoke a violent immune response. “We have gotten this wrong in the lab and we have killed mice,” says Gray. “Gene therapy is not a pill you can stop taking.”

Gray's best-known client is Lori Sames, whose daughter suffers from giant axonal neuropathy. The disease affects only about 80 people in the world. Sames managed to raise \$6 million, which she funneled to Gray and into animal tests. In 2016, her daughter became the fifth child treated in a study of Gray's gene therapy at the NIH.

Gray told me that if a gene looks like a good candidate, and a family has money to support laboratory work, he will agree to take on their cause, no matter how rare the disease. “This is the most unfair system imaginable,” he admitted. “If you don't have money, it won't happen.”





To some bioethicists, when parents fund treatments it has the potential to create sharp ethical dilemmas. “There is a fairness issue if only the people who have the money get to be first in line,” says Mildred Cho, a bioethicist at Stanford University, who has consulted on similar cases. “And there is a scientific integrity issue, because those with the money may not be the most appropriate or the best candidates. These decisions should be objective.”

I asked Sames if she had created a conflict of interest by paying for research. The question makes “the hairs on my arms stand up,” she said. “Anyone who suggests it’s corrupt that parents privately fund development of a treatment for a child, in an attempt to save the child—well, I think it’s irrational and rather insane. If the parents don’t drive it, it’s never going to happen. Wake up.” Sames adds that the fundraising she did never guaranteed her daughter, Hannah, a spot in the NIH trial. Hannah had to pass a lung function test like others to get in. “We were no different than any other candidate,” she says. “I wept the day she passed the test.” Since then the trial has been moving forward at a “glacial” government pace,

according to Sames, and other parents are mad at her. “They are hurt—their child is failing before their eyes—and they are angry, angry their kid is not injected,” she says. “But there is nothing I can do.”

Some families are managing to move even faster to a treatment than Sames did. The Hollywood couple, film producer Gordon Gray and his wife, Kristen, were able to get two daughters treated at Nationwide Children’s Hospital about one year after the girls were found to have Batten Cln6, an inherited nervous-system disease believed to affect just a few hundred kids. Kristen Gray says the couple paid for the trial in its entirety. They also formed a company to take commercial rights to the treatment.

Few parents, though, are able to raise millions or start a company. On GoFundMe, hundreds of appeals mention gene therapy, but most raise only a few thousand dollars. One woman from Texas appealed for funds because she has muscular dystrophy; she has gathered just \$35. The medical possibilities are out there, “but I don’t think there is the regulatory infrastructure or the funding infrastructure to really make it happen,” says Steven Gray, the gene therapist from Texas.

Another obstacle is that most of the key components of gene therapy are patented—including the viruses, the production tricks, and engineered genes. That means parents, and the scientists who help them, are often working in a cloud of legal uncertainty. Leone says to treat the Landsman boys she will have to buy \$250,000 worth of trial insurance. “I could have been stopped with a phone call, but I wasn’t. People have been very kind,” she says. “But I will tell you, there are so many pieces in the patent puzzle ... it’s like a contemporary symphony, one that is atonal. It makes you want to scream.”

Calling Bill Gates

Of the 7,000 rare diseases, around 90% currently have no treatment whatsoever. Gene therapy could potentially help with many, and in the future, new technologies like gene editing could, in theory, make it possible to fix nearly any genetic mutation. Christopher Austin, chief of an NIH branch responsible for new therapies, says eventually there may be as many different treatments as there are unique DNA flaws. To Austin, that means made-to-order, hyper-personalized medicine isn’t some ethical mistake to avoid; it is the next step forward. “All of us need to think deeply that this is possible now,” he says. It’s something “that people have thought about for decades—and now it seems to be coming true.”

Exactly who will pay to discover, develop, and deploy this Noah’s ark of medicines is not clear. Lori Sames told me she sometimes fantasizes about approaching Bill Gates, whose foundation is trying to eradicate malaria and polio. Leone envisions a different solution: a global institute of cures, with access to manufacturing, hospital beds, and agreements in place to streamline the “biblical” work of dealing with insurers and regulators. “So any new disease, any new genetic mutation, we’d have everything set up,” she says. “We would bring patients from all over the world for treatment.”

Biotech companies have raced into gene therapy, but so far, much of their effort has been aimed at more common genetic conditions like hemophilia. The US government’s clinical-trial website lists more than 20 open studies exploring gene treatments for that disease, which could be the technology’s first blockbuster. The markets for ultra-rare diseases haven’t drawn as much commercial interest. “Imagine a company with 75 employees that exists to treat 75 people. You can see the problem,” says Eric David, the executive with BridgeBio.

“All of us need to think deeply that this is possible now. It’s something that people have thought about for decades—and now it seems to be coming true.”

In April 2018, however, something happened to make biotechnology executives take a fresh look. The Swiss drug company Novartis announced that it would buy the gene-therapy company AveXis for \$8.7 billion. AveXis had just one drug in the clinic—it owned rights to the treatment for spinal muscular atrophy that had been tested at Nationwide Children’s Hospital. The acquisition price was immense for a treatment used, at that time, on only about 15 kids, and for a disease that affects one in 10,000 births.

“My jaw hit the floor. I don’t even know what \$8 billion is,” says Jerry Mendell, the doctor who led the trial. Mendell didn’t hold shares in AveXis, but one of his center’s former employees, Brian Kaspar, did. Kaspar, who joined the company, is now \$400 million richer. “In my mind, the AveXis deal—there is a before and there is an after,” says David. “After that, people who would not have looked at gene therapy for a disease quite that rare said, ‘Wow—if I can get a trial going, maybe I can be worth a billion dollars too.’”

One reason AveXis was worth so much is that the treatment seemed to be an outright cure. That could let Novartis charge \$2 million per patient, and perhaps more. To Walter Kowtoniuk, a principal at the investment company Third Rock Ventures, in Boston, such medical successes mean diseases previously thought to affect too few people to attract companies are suddenly drawing intense interest. He says he has been “shocked” by the “massive competition” to gain control of gene-therapy programs.

That’s created a situation in which desperate bids to treat children can rapidly turn profitable. In October, the Gray family—which had helped form a virtual company around the Batten Cln6 treatment—sold the rights to another biotechnology company, Amicus, for \$100 million. Some investors are starting to think Canavan looks pretty interesting too. It’s widely known among Canavan parents that a couple in Florida spent more than \$1 million to get their child treated in a one-person study organized by the University of Massachusetts and the University of Florida. I reached the boy’s father, who asked to remain anonymous but did say his son seems to have benefited.

The Florida experiment helped launch Canavan out of the too-rare-to-care category. Early in 2018, David’s company, BridgeBio, entered an agreement to license the treatment from the University of Massachusetts and created a subsidiary, Aspa Therapeutics, which he now leads. But Kowtoniuk says other investors have been angling to take over the project because the risk seems much lower now that one boy has been treated. “There is a battle, literally a battle, to license the technology,” he says. “I think there is such a tidal-wave shift in what is going on right now.”

The growing biotech interest could mean the end of the parent-led scrambles. David told me he doesn’t think the epoch of parent-financed gene therapy will last very long. “It’s transitional,” he says. “I think it’s going to be for a limited time.”

A ticking clock

David says the formal clinical trial of his company’s Canavan treatment, different in design from Leone’s,

won't begin for another year, maybe two. For his company it's important to plan carefully and not rush, since that would jeopardize its investments and its aim of getting a treatment approved.

Jennie Landsman's children, though, can't wait that long. A self-financed experiment is probably the only way her two kids can get gene therapy in time. When I visited the Landsman home, I stood behind Josh, who was belted into a high chair, as his mother showed him pictures of lunch foods: chicken, macaroni and cheese, corn. Jennie followed his gaze.

She had hoped the boys would be treated by now. The team submitted its proposal to the FDA in June 2018, but the agency responded with a notice, called a "clinical hold," delaying the experiment. At the time of writing, in October 2018, Jennie was counting on December at the latest. Janson, the doctor running the trial, thought sometime in 2019 was more likely. He and Leone have plans to submit a new request following a meeting with FDA officials. He has also started testing the treatment on monkeys, a costly safety step he predicts regulators may insist on.

Nerves are fraying. At Benny's age, Canavan patients often have a steep decline in brain function. Even gene therapy might not reverse it. "My blood pressure is really going up," Janson says. "We probably lost at least three to four months."

When I visited her, Jennie had the idea of going to the FDA meeting and bringing her kids. She wanted to know what I thought. If the regulators saw them, how could they say no? Janson doesn't think it's a good idea. "I think we have to go within the system," he says. "We aren't a drug company. We don't have unlimited resources to lobby the FDA."

I asked Janson if he thought it was fair that the Landsmans' kids could end up getting treated while some other family without a surprise GoFundMe success would not be. "Unfortunately, there are a lot of things in society that are not fair," he said. "There are parents who want to see me in my neurology clinic and can't because they don't have insurance. We have a problem in society."

Precision medicine, it seems, is just another example: "There is no easy answer to your question, because the system is not set up to deal with this." **T**

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