Science

Gene therapy helped these children see. Can it transform medicine?

A pioneering new way to fight disease is finding success among doctors and patients. But what are its costs and dangers?

OCTOBER 19, 2017 by David Crow in New York

When Caroline Carper was 10 years old she saw rain falling from the skies for the first time. “So I was in grammar class, and it started to pour down. I was like, ‘Oh my gosh, what is that?’ And my friend goes, ‘That’s rain, you’ve never seen rain before?’ It was like a whole new world.”

Caroline’s eyesight problems emerged shortly after birth, but it was not until her younger brother Cole was also born with poor vision that doctors realised something more serious was afoot. The pair were eventually diagnosed with Leber congenital amaurosis (LCA), a rare inherited retinal disease that left them with severe impairment in both eyes. “I just told people that I was half-blind. That’s really the only way they’d understand,” says Cole.

Their parents decided not to tell them the disease was likely to progress to the point where they would go completely blind. “I just felt like there was no point in burdening them with it at that age, when they’re little,” recalls their mother Ashley. “If you’re an adult, you might be able to handle that – but as a child? I think that’s too much. Privately, sometimes, our hearts might have hurt a little bit, but we have never felt sorry for them.”

None of that heartache is evident when I meet the family at their home in Little Rock, Arkansas, on a hot and humid Saturday morning. Over home-made brownies and iced tea, Caroline and Cole tell me how they received a pioneering treatment known as gene therapy on a clinical trial in 2014, which restored much of their sight. “Basically, they take a gene and they put it in your eye,” explains Caroline, before she is interrupted by her brother, who is apparently outraged that she is leaving out the gory bits. “They put you to sleep and they slice open your eye,” he interjects with a broad grin. “And then they give you a popsicle. The popsicles are the best part.”

With giddy excitement, the pair recall the weeks and months following the treatment, when they saw things properly for the first time — stingrays at the aquarium, the intricate structure of a snowflake, a starry night sky. Cole, now 11, could not contain his excitement when he saw the toy section in the supermarket, especially when he happened upon the shelves with his favourite Nerf guns (he is fiddling with a loaded one as we speak).

I was like, “Oh my gosh, what is that?” And my friend goes, “That’s rain, you’ve never seen rain before?” It was like a whole new world

CAROLINE CARPER

Caroline, who turns 14 in January, remembers seeing herself in the mirror for the first time and still recoils with horror at the ugly protective glasses their mother made them wear after surgery. But she is glad that her eyelashes — which were cut off to prepare for surgery — have grown back fuller and stronger thanks to the post-operative steroids. “It made them look beautiful, so it’s OK,” she says with a little flutter.

Earlier this month, a committee of scientists and experts advising the US Food and Drug Administration voted unanimously in favour of approving the gene therapy used on Caroline and Cole, which is being developed by Spark Therapeutics, a biotech group based in Philadelphia. If, as expected, the agency follows their recommendation in January, the treatment will become the first of its kind to be given a green light in the US.

Spark’s product, named Luxturna, is designed to help a subset of LCA sufferers with a mutation in a gene known as RPE65 — who number about 6,000 in northern America, Europe and the other developed markets the company hopes to enter. But its approval would have much broader implications for the way we fight sickness and disease.

Drugs are designed to fight illnesses by cajoling the body, opening up one biological pathway or closing down another. Gene therapy takes a different approach, replacing the faulty or missing DNA that is causing the disease in the first place and helping the body fix itself. Because it tackles the illness at its biological root, it could offer a one-time treatment for an array of genetically driven conditions that have either had poor options or none at all, from haemophilia and Parkinson’s to Huntington’s disease, cystic fibrosis and myriad rare diseases. It opens up the possibility of that thing still so elusive in modern medicine: a cure.

“Gene therapy gives our cells the genetic capability they need to repair the illness themselves,” explains Dr Michel Sadelain, an expert in gene therapy at Memorial Sloan Kettering Cancer Center in New York. “Most current medicines are chemicals that you deliver through a pill or some other route of administration. They are active for a few hours or sometimes a few days.

“So this treatment is important not just for people with this form of blindness but for many others beyond. A demonstration like this one will encourage more scientists, physicians and industry to pursue such curative medicines, and patients and their advocates to demand them. That is what a result of this kind can produce.”

Treatments such as the one being developed by Spark are the culmination of decades of work in two branches of science. First, the Human Genome Project, which concluded in 2003, unlocked the sequence of three billion letters that make up our genetic code, giving scientists a long list of targets for gene therapies. Second, researchers found a way of shuttling the cloned genes directly into cells without making the human body go haywire.

Although the field is in its infancy, there are several biotech groups aside from Spark hoping to bring gene therapies to market in the next few years, including Paris-based , which is targeting a different type of blindness. Others, such as BioMarin and Bluebird Bio, are developing treatments for inherited blood disorders, while AveXis is running trials in spinal muscular atrophy, a childhood wasting disease. The space is dominated by smaller companies that are not household names, but big pharmaceutical groups such as Novartis, Sanofi, Bristol-Myers Squibb and Pfizer have invested billions of dollars in gene therapy in recent years.

"There are a number of people that are pretty close behind Spark, so the fact the FDA believes the safety data and the long-term efficacy is very encouraging," says Dr Cynthia Dunbar, a researcher at the National Heart, Lung, and Blood Institute.

Although many scientific questions have yet to be answered, Dunbar and others fear that affordability is the biggest obstacle to widespread adoption of gene therapies. Healthcare systems are not set up to pay for one-off treatments that are expected to cost more than $1m per patient in many cases. "The issue is going to be figuring out how you structure payment for a one-time upfront therapy that's going to be very expensive," she says, adding that while gene therapies could cut health spending in the long run, the savings will only be felt down the line.

Neither Caroline nor Cole has been cured, since some of their retinal cells had already died before treatment and could not be saved. Caroline asks her science teacher to send her handouts in advance and has trouble seeing in the dark. Cole, an aspiring golfer, struggles to follow the ball, and still has a hint of involuntary eye movement known as nystagmus. But to hear them recount their story is to understand how completely things have changed. How, in Caroline's words, they escaped from a darkened world of "outlines and shadows".

Later, while her children are out by the swings in their backyard, Ashley recounts her quest to find something that would restore their sight. Undeterred by the poor prognosis, she quickly familiarised herself with the medical literature and attended meetings devoted to retinal disorders in the hope of finding them a place on a trial. Deeply religious, she detects the hand of God in her family's good fortune. "Our faith is really strong, and when I look back, everything has been laid out in the plan," she says. "I'm not preaching but I really think God has given them something. I don't believe in coincidence. I believe everything happens for a reason."

Whether it was God or fate, someone was smiling on the Carper family. In 2006, shortly after the children were diagnosed, Ashley found herself at a medical conference sitting next to Dr Jean Bennett, a scientist at the University of Pennsylvania who specialises in the genetics of retinal degeneration. Ashley did not know it at the time, but Bennett was already working on the treatment that would change Caroline and Cole's lives.

Bennett and her husband Albert Maguire, an eye surgeon also on the staff at UPenn, started developing the therapy given to the Carper children in the 1990s, long before the culpable gene, RPE65, had been identified by the Human Genome Project. The pair knew the eye was a good candidate for gene therapy because it had a high degree of what scientists call immune privilege. In order to deliver the genes into the body, Bennett would need to package

the cloned DNA inside a delivery vehicle that would shepherd it to the intended cells. Using a modified virus, that tiny organism well known for its ability to infiltrate humans, was one option, but it was fraught with danger.

Dr Jean Bennett of the University of Pennsylvania, who, with her husband Albert Maguire, pioneered gene therapy for the treatment of retinal degeneration © Nic Defranceschi

When a virus or any other foreign biological substance is inserted directly into the body, our immune system tries to destroy what it has identified as an invader. In the best-case scenario, the virus is destroyed, rendering the intervention pointless. In some instances, the response can be so dramatic as to prove fatal.

The eye, however, is a closed system that is given the biological equivalent of a free pass by the immune system, meaning that the danger is greatly reduced. It is also among the smallest organs in the body, so Bennett did not have to produce large amounts of her experimental gene therapy for the trials.

“The eye seemed like a great target for so many reasons and so we started developing, in a naive way, the surgical expertise to deliver genes,” she recalls. “Then the field developed and the genes were identified. By 2000, we had a good model, we had a good virus, and we knew how to deliver it. It wasn’t until the dog model worked that we could be convinced: a dog’s eye is the same size as a human’s, and they are such visual animals.”

The next logical step after several years of dog trials would have been to start studying the treatment in human volunteers, but the field of gene therapy had suffered a setback many thought it would never recover from. In September 1999, Jesse Gelsinger, an 18-year-old boy suffering from a liver disease, died four days after he was given an experimental gene therapy during a clinical trial. He had suffered a catastrophic immune response to the virus used to

deliver the genetic material. The researchers running the study, also from UPenn, were sharply criticised by the FDA.

Our intention was to do it in an academic way to help people, and the whole business aspect in terms of the price tag is upsetting to us

DR JEAN BENNETT, UNIVERSITY OF PENNSYLVANIA

"Just as we were seeing our first successes, it was a time when the gene therapy field hit a huge low," Bennett recalls. "All the funding was pulled out of the area and there were restrictions and regulations put in place. We had the wind pulled out of our sails. It was very difficult to find support for a trial, let alone one for children, who we knew would be the ultimate beneficiaries."

Five bleak years passed until a lifeline appeared in the form of Dr Katherine High, a friend and colleague of Bennett's, who was working at the time as a researcher at the Children's Hospital of Philadelphia (CHOP), which has strong ties to UPenn. "She walked into my office one day in July 2005 and said, 'Jean, how would you like to run a clinical trial?'," recalls Bennett. "It was absolutely thrilling. I had to pinch myself to believe this was really happening. It took me one millisecond to say yes. The path had not been trodden — we had to build it ourselves."

Dr Katherine High, co-founder and chief medical officer of Spark Therapeutics

I meet High later in her office on the 13th floor of a skyscraper that looks out over the Philadelphia skyline. She peers at me over silver-rimmed glasses with the air of someone who is always slightly amused. A haematologist by training, she started work in the late 1980s on a gene therapy for haemophilia, an inherited disease that stops the blood from clotting properly. She was determined to find an alternative to the infusions and transfusions that sufferers must endure, in part because of a historic blood crisis that meant some of her patients had contracted HIV and Aids. But, after Gelsinger's death, the pharmaceutical company she had been working with pulled out, leaving her without a source of medical-grade virus for her research.

“When you’re working on something like that, you can almost not see everything that’s going on around you. I have to admit I fell into that category,” she recounts in her mild southern drawl. When she did finally realise that the field was in trouble, she started trying to drum up new backing for gene therapy, eventually turning to CHOP. “When things get really tense for me, I focus on logistics. There is a great quote from an American general during World War II, Omar Bradley, who said, ‘Amateurs talk strategy, professionals talk logistics.’”

High convinced the hospital to set up a unit focused on gene therapy, but the agreement came with an important caveat: the division would have to work not just on haemophilia but on a disease that primarily affected children. This prompted her to recruit Bennett.

By February 2011, after High’s team had published the results of the first human trials in academic journals, the outside world started to notice the successes they were having. Biotech investors began cold-calling High, asking if they could fund the hospital’s efforts in exchange for a stake. But she was too busy to speak to them. “I would always say, ‘Please, leave me alone.’”

Jeffrey Marrazzo, co-founder of Spark © Joe Leaenworth

Another person who would not leave her alone was Jeffrey Marrazzo, a young management consultant who had been hired by the hospital to ferret out ways of generating more revenue. “I kept cancelling my appointment with him. Every day I would look at my schedule and say to my assistant, ‘Who is this guy?’ I would say, ‘No, I can’t do it.’” Eventually she relented, and sat down for a 45-minute meeting with Marrazzo. Three hours later, the pair were still talking about the possibilities of gene therapy. He returned to the chief executive of the hospital to run through his ideas, saving the best for last. “You know those people on the fifth floor? They’re a drug company. And you should set them up.”

Marrazzo engineered the spin-off of Spark into a separate company in 2013, and two years ago the group completed an initial public offering, listing its shares on Nasdaq under the stock ticker "ONCE" — a nod to the potentially curative properties of gene therapy. High has since left her job at CHOP and joined Spark as its president and head of research and development.

For us to prove it works for ever, we have to wait for ever. Until that point, someone out there is always going to have a theory

JEFFREY MARRAZZO, CO-FOUNDER OF SPARK

Today the company is worth $3bn, though most of that value is ascribed not to the blindness therapy but to the earlier-stage haemophilia programmes, which will prove very lucrative if successful: there are almost 190,000 sufferers worldwide. Wall Street investors have snapped up shares this year, sending the stock up almost 70 per cent, in large part because of promising data from the haemophilia trials.

Marrazzo spends much of his time thinking about how the world is going to pay for gene therapies. Because while Luxturna will be heralded as a breakthrough if it is approved in January, it will also make headlines as one of the most expensive drugs of all time. Spark has not yet announced the price but the figure being whispered among scientists in the field is between $700,000 and $900,000 per eye, which would put the total cost of treating a single patient at well above $1m.

The fact that treatments such as Luxturna are only meant to be given once means that the companies who make them cannot recoup their investment in the staggered manner employed by traditional drugmakers, who produce pills or injections that are prescribed and bought on a regular basis. For a rare disease, such as the one the Carper children suffer from, it might not matter so much: healthcare systems tend to look at the cost of a treatment in aggregate rather than per person, and analysts predict that the product will generate just $120m in sales in 2018.

But when it comes to haemophilia or other diseases that are more common, gene therapy is going to put a huge strain on the system. Marrazzo points to considerable savings down the line — infusions for a single haemophilia patient can cost $500,000 per year, for example — but that is scant consolation for the UK's National Health Service or private insurers in the US that have to manage tight annual budgets. One option gaining some traction in healthcare circles is some kind of "value-based" approach, where drugmakers are paid according to results. Instalments could be handed over for as long as the drug is working, or pharma groups might pay refunds if a product is less successful than claimed.

Regardless of whether the system finds a way of paying for gene therapies, the undoubtedly high price of Luxturna does not sit well with its inventor. “Neither my husband nor I had the intention of charging a huge amount of money,” says Dr Bennett, who waived any financial gain from the product when she licensed the patents to Spark. “Our intention was to do it in an academic way to help people, and the whole business aspect in terms of the price tag is upsetting to us, but I guess it’s part of it.”

For-profit drugmakers have proven themselves to be remarkably efficient vehicles for bringing drugs to market, but they are equally good at enriching investors and employees, something Bennett finds distasteful. She recounts a recent visit to Spark’s office when one of the staff members remarked that they were waiting for the stock to hit $80 per share so they could use their options to build a swimming pool. (Today they are trading at $84.)

“It makes my skin crawl because we haven’t made a penny,” she says. “In fact we’ve lost money because we paid for the first set of [trial] dogs out of our own bank account. It rubs me the wrong way, but we waived our rights knowing we wanted to carry it through. We’re getting a different type of reward, which is seeing the benefit in the patients.”

No one denies that Luxturna has brought real change to patients like Caroline and Cole, though some scientists have raised doubts about whether the benefits of the treatment will last. In 2013, a group of researchers, many of them also from UPenn, published an article on a similar gene therapy, which showed that after a period of improvement the retina continued to deteriorate.

“In our hands, with different patients and our own [virus], we found all of the patients that benefited began to slowly lose the benefit,” says William Hauswirth, professor of ophthalmology at the University of Florida, who co-authored the article and who is also a paid consultant to Applied Genetic Technologies Corporation, a small gene-therapy company that could be classed as a competitor to Spark.

“Most of them are still somewhat above where they started out six years ago. But there is this issue of how long is it going to last?” he adds. “We all agree it’s going to last five years, maybe 10 — which is nothing to sneeze at — but whether it’s going to last for a long, long time, that’s something we don’t know. We’ll have to see.”

Whether the treatment fades is important not only because Spark is likely to charge a lot of money but also because it remains unclear whether patients like Caroline and Cole could receive another dose of gene therapy. Some scientists believe injecting patients a second time comes

with a higher risk of a dangerous reaction, as the body might have developed immunity to the virus.

Marrazzo says Hauswirth's team were testing a different gene therapy, one that used an alternative virus. Spark's earliest patient was treated five years ago and has shown no sign of deterioration, he says. "For us to prove it works for ever we have to wait for ever," he adds. "Until that point, someone out there is always going to have a theory."

Ashley, an avid reader of the medical literature, has seen the research casting doubt on the treatment's longevity. "We don't know how long it's going to last. We don't know because it's a trial," she says, describing how she and her husband Greg have been taking the children to see the wonders of America, from the Grand Canyon and Yosemite national park to New York City. "We've tried to see as many things as possible. We wouldn't go back."

Dazzling June sunshine filters into an office building in Paris's 12th arrondissement. Later, the skies will darken and it will start to rain, much to the chagrin of workers scurrying back from lunch. But for Arthur Leroy — who is trying to avoid the shards of light streaming into the room — the clouds will be a welcome arrival. He has come to loathe bright days, which aggravate his poor vision and make it harder to see. "This weather, it's very boring for me," says the 40-year-old.

French businessman Arthur Leroy, who received treatment for a progressive form of blindness as part of a trial carried out by Gensight in Paris © Charlotte Tanguy

Leroy noticed that something was wrong with his sight in 2014, when he was attending a friend's wedding. A couple of days later, he returned to Paris for an appointment at the Rothschild Foundation Hospital, where doctors told him he was suffering from some kind of unexplained optical nerve damage. Asked to read an eye chart, he realised he could not make out any of the letters using his left eye, compared with eight out of 10 lines with his right. As the medics tried to work out what was wrong, he remembered something that might be relevant: a cousin on his mother's side of the family also had a problem with his eyesight. "OK, this is urgent," he remembers being told. "You're going up to the second floor to see Dr Vignal."

Catherine Vignal-Clermont was the bearer of bad news. Leroy was suffering from Leber hereditary optic neuropathy (LHON), a rare progressive form of inherited blindness passed down the maternal line, which robs people of their eyesight in just a few months. Like the Carper children's condition, LHON is named after Theodor Leber, a German ophthalmologist who first described the illness in the 19th century.

You are losing your vision, day after day, week after week. You cannot see, you cannot cross the street . . . The world was grey for me and then, after six months, there was colour

ARTHUR LEROY, CLINICAL TRIAL PARTICIPANT

"We're going to take some time here," Leroy recalls Vignal saying. "Because there's going to be a big impact on your life." She explained he would lose the sight in his right eye too. "It's going to be very sudden," she warned. Within little more than two months, he could not make out any letters on the eye chart with his right eye either: "Zero out of 10, zero out of 10."

"You are losing your vision day after day, week after week," he says, recalling the dark period that followed his diagnosis, during which he also lost his ability to make out colour. "You cannot see. You cannot cross the street. I could not recognise myself. I could not recognise my wife. It was all so sudden."

Vignal explained that there was no treatment and gave him advice on how to adapt, something he did remarkably well. He learnt to perform his duties as a management consultant at a French conglomerate with the help of a huge interactive whiteboard. At home, he imposed "discipline and control", assigning every item a specific place and reorganising his wardrobe of smart tailored suits with white and blue shirts. "I said to myself, 'OK, you're going to have to continue. You're 40 years old. You have a wife. You have your work. Life is good.'"

Life might still have been good for Leroy but it was not always easy, not least when it came to his relationship with his mother, who blamed herself for carrying the genetic defect that caused his illness — and who now lives in fear that one of his three brothers might be next.

Dr Catherine Vignal-Clermont, a specialist in neuro-ophthalmology at the Rothschild Foundation Hospital, Paris, who has conducted gene-therapy trials © Charlotte Tanguy

“She tells me she’s sorry, that it’s all her fault. I just tell her it’s OK, it’s just something that happens in life. But she says it was inside of her. We can talk about a lot of things but we can’t talk about this.”

A keen sportsman, Leroy tried to find a physical activity he could still enjoy, settling on water-skiing because there was less chance of injury if he fell off. It was while on a water-skiing holiday on the French Caribbean island of Martinique in March 2015 that he received a call from Vignal. She wanted to know if he would take a place on a trial of an experimental gene therapy for

LHON being developed by GenSight Biologics, a French biotech group. Leroy cut short his holiday and was back in Paris within two days. “Show me where to sign,” he recalls saying.

LHON is a disorder of the compartments inside cells that provide the body with the energy it needs to survive. Because of a genetic mutation, these “mitochondria” do not produce enough fuel in the cells that form the optic nerve, resulting in their death. The disease, which is mostly diagnosed in young males, results in the rapid loss of central vision, with around 80 per cent of patients being classed as legally blind within a year.

GenSight’s treatment, codenamed GS010, aims to correct the problem by inserting a functioning copy of the responsible gene, ND4, into the eye, encouraging the mitochondria to supply power to those retinal cells that are still alive. Unlike Spark’s Luxturna, which is administered through a surgical procedure, the virus containing the ND4 gene is injected straight into the eye. The company has not said how much it is thinking of charging but the price tag is expected to be in the same range as Spark’s.

“I was given the shot in April 2015, and in May, June, July and August there was nothing. It was as normal,” recalls Leroy. “I thought it wasn’t going to happen and I was a bit sad because I had hoped it would work, just a little. But, you know, I was only person number 15 in the whole world to receive the treatment. I thought maybe it just doesn’t work.” Then, one day in late September, he realised he could make out the colours on the flipchart in his office. He started recognising people in the street. And he was able to see the green man at the pedestrian crossing.

When he returned to hospital for tests, he had made remarkable progress that continued apace over the next few months. Today, standing four metres away from an eye chart, he can make out five lines with his left eye and four with his right. But he measures his progress differently: he can interact with friends again, and pick up on cues from colleagues; he can cook now that he can tell the difference between the salt and the pepper. “The world was grey for me and then, after six months, there was colour again.”

Over a lunch of steamed dumplings in a nearby Chinese restaurant, Bernard Gilly, chief executive of GenSight, poses a question: why do you so rarely see a blind person on the street when there are more than a million registered as such in the US alone? The answer, he says, is that most of these people are consigned to a life indoors because there are so few treatments available. “This is really the first time ever that someone has been able to show a clinically significant improvement in visual acuity in patients who have lost their sight,” he says of his

company's gene therapy, pointing out that Spark's Luxturna primarily restores different types of eyesight like light sensitivity and field rather than the visual acuity that is measured by a reading chart.

Since Leroy's trial, GenSight has published the results of a second mid-stage study that shows the treatment worked in roughly two-thirds of patients. A further two late-stage trials, named Reverse and Rescue, are ongoing, with results due next year. If they are successful, the company could file for approval in the US towards the end of 2018.

A laboratory at Paris-based GenSight, a biotechnology company developing gene therapies for diseases of the eye and central nervous system © Charlotte Tanguy

Although LHON is rare — with up to 1,400 cases in the US and Europe each year — it is more common than the LCA that affects the Carper children. The commercial potential — and the undoubtedly high price tag — has encouraged backing from some of the best-known life-sciences investors and Swiss pharmaceutical group Novartis.

The success of the treatment could also give hope to patients suffering from other genetically driven mitochondrial diseases, which can affect almost every part of the body, as well as other illnesses in which the mitochondria are thought to play a role, such as Parkinson's. GenSight is working on another gene therapy for an undisclosed illness, and its description of itself as a company focused on "diseases of the eye and central nervous system" suggests it has aspirations beyond blindness.

In the coming years, gene-therapy researchers will have many questions to answer. Can the treatments be expanded outside the eye to other parts of the body without causing the kind of fatal immune reaction that killed Jesse Gelsinger? Will the effects fade, as with so many other medical interventions that were once hailed as breakthroughs? How will society afford a treatment costing more than $1m per person? And what are the long-term risks of hacking a person's biology? In the case of Spark, the FDA is so concerned about problems developing in the future that it has asked the company to follow patients until 2029.

If gene therapy does come of age, the world will have to thank not just the scientists who have devoted their lives to it but also the likes of Leroy and the Carpers, who have taken a leap into the unknown. "I've got brothers — twins and one little brother — and so I have to fight for them, and for others too," says Leroy.

"I am grateful that they've had the surgery — but, if other people can benefit too, that'd be awesome," adds Ashley Carper. "It matters to us. It really matters to us."

Arthur Leroy's name has been changed at the request of his doctors to preserve the integrity of the clinical trial.

David Crow is an FT correspondent in New York. His last feature for the magazine was 'Has science cracked the peanut allergy?'

We'd like to hear from people who might benefit from gene therapies, as well as those with novel ideas about how to afford one-time potentially curative treatments.

Photographs: Drew Nikonowicz; Charlotte Tanguy; Nic Defranceschi; Joe Leavenworth.

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