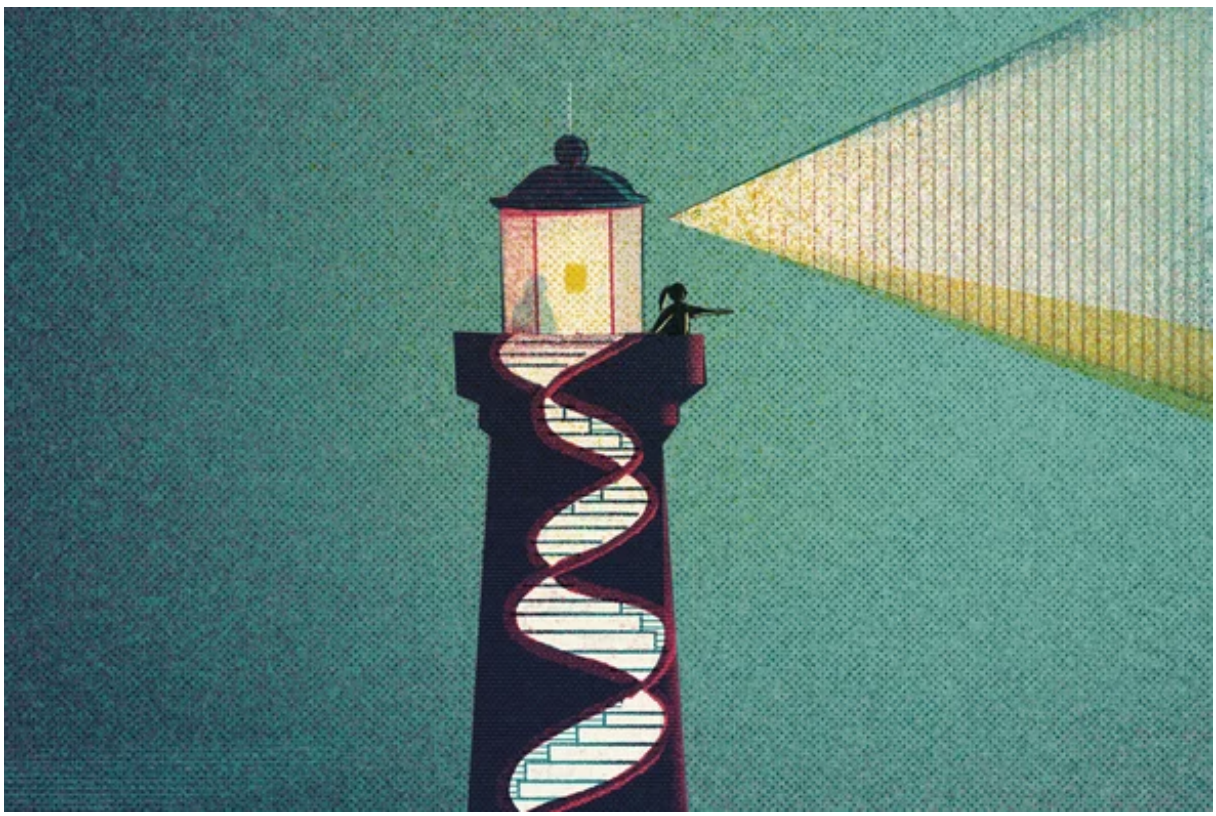
Innovations

HEALTH CARE

We Need to Ground Truth Assumptions about Gene Therapy

Researchers, practitioners and patients must balance the discipline's promise with its reality

By Marla Broadfoot on November 1, 2021



Credit: Luisa Jung

Melissa Creary was three years old when she was diagnosed with sickle cell disease. The genetic condition, which affects more than 100,000 people in the U.S., is caused

by a mutation that distorts red blood cells into sickle-shaped crescents that can get stuck in blood vessels and trigger episodes of agonizing pain. People in the thick of an episode have described the sensation as something akin to broken glass flowing through their veins. Others liken it to being electrocuted or stabbed.

Creary was in her early 40s when she developed a rare complication that turned her mild case into a severe one. Suddenly she began experiencing pain like never before. To dilute the sickle cells clogging her bloodstream, she had to undergo monthly blood transfusions. Creary felt tethered to the health-care system, literally and figuratively, in ways she had never expected.

"I remember moments where I was so angry all the time—angry at the betrayal of my body, angry at the betrayal of my genetics," says Creary, a health policy researcher at the University of Michigan. She recalls feeling resigned to the fate spelled out in her DNA. But as new gene therapies emerged, she began to see glimmers of hope.

Creary studies the biology, policy and social determinants of health related to sickle cell disease in the U.S. and Brazil. Her experience of severe sickle cell disease led her to talk with physicians about gene therapy in a new way—not as an academic exchanging ideas with colleagues but as a patient seeking answers. The dialogue progressed from talk of technology to deeper discussions about identity, history, trust, education, equity and emotion. Even now Creary is not sure what she would do if an experimental treatment were offered to her tomorrow.

A handful of gene-targeted treatments are under development for sickle cell disease, and hundreds more are being investigated for a variety of conditions, including cystic fibrosis, muscular dystrophy, hemophilia, Huntington's disease, HIV and cancer. Several gene therapies have already won FDA approval. The notion of rewriting a person's DNA is finally becoming a clinical reality.

In previous decades, conversations about gene therapy had to address and overcome the field's tragic past missteps. But today, after so much scientific progress, researchers and practitioners are dealing with an unexpected challenge: excessive hope. That hope takes different forms in different groups of people, and it alters expectations about gene therapy in ways that can have far-reaching consequences. As a result, some researchers have begun shifting their focus from the machinations of

the genetic material and viral delivery systems that make up these therapies to the perspectives of the human beings who will ultimately be affected by their deployment.

"It's crucial at this point to start to explore what patients [and the public] think they need to know and their attitudes toward these therapies because these are therapies that cost millions of dollars to develop," says Olalekan Lee Aiyegbusi, an applied health researcher at the University of Birmingham in England. If people expect too much too quickly, they will end up disappointed or distrustful of the research enterprise; if expectations are too low, not enough people will invest money, time or patient power in the cause.

TROUBLING ASSUMPTIONS

The term "gene therapy" emerged in the public consciousness nearly five decades ago. By fixing defects in our DNA, scientists speculated, gene therapy had the potential to undo thousands of inherited conditions. When gene therapy comes up in conversation, however, some people's thoughts slide from treating disease to engineering human traits such as eye color, IQ and athletic ability—a concept referred to as genetic enhancement. That association, researchers say, is not only inaccurate but harmful.

Speculation about such Gattaca-like futures swelled in 2018 after the Chinese scientist He Jiankui announced that he had created the world's first gene-edited babies by removing copies of a gene in embryos before they were implanted. He was convicted of "illegal medical practice" and sentenced to three years in prison, and scientists around the globe have called for a moratorium on genetic edits that could be passed on to future generations. Experts say that conflating such morally fuzzy research with studies focused on treating disease could derail the conversations that need to take place around the more pressing applications of gene therapy.

Juliette Delhove, a gene therapy researcher at the University of Adelaide in Australia, has examined dozens of studies of public opinion and attitudes toward gene therapy and gene editing. In 2020 she published a scientific review showing that people's support can shift depending on how gene therapy is defined. There is substantially less support for enhancement technologies—which one person likened to "playing God" and another criticized as "going against nature"—than there is for therapies for

serious or fatal diseases. In one study, only 35 percent of respondents believed it was definitely acceptable to use gene therapy to enhance memory, compared with 93 percent who supported its use to treat an inherited form of blindness known as Leber congenital amaurosis.

Delhove and others have found that people bring their life experiences to conversations about the technology, and such experiences shape their perspectives. Studies show that people with more education and some knowledge of genetics are generally more accepting of gene therapy, whereas those with strong religious ties tend to be less accepting, even when it is used to treat cancer or prevent blindness. But perhaps the biggest factor in how someone views gene therapy is whether they or someone they love is affected by a disease the innovation aims to cure. Ultimately, says Holly Peay, a social scientist and genetic counselor at the nonprofit RTI International, "a lot of what we're seeing in the literature that exists are people's emotional reactions."

THE RISKS OF HOPE

Talking about gene therapy can seem like a hypothetical exercise—for someone without anything at stake, it is a chance to explore technological progress or debate ethical principles. But for patients, such discussions have real-life implications. Every new data point is a signal that they might be just steps away from overcoming their illness. When Creary thinks about gene therapy, she considers its potential impact on her daily life. "There's a scientific innovation that will take the pain away," she says. "That is the crux of the hope conversation: I could live a day without pain."

Creary has been wary about giving herself over to that hope, but patients generally tend toward enthusiasm, often holding unrealistic expectations of benefits from treatments that have not yet proved effective in clinical trials. Researchers have a name for this: therapeutic optimism. "We are, as a species, wildly optimistic about ourselves," says Peay, who works with patients and families with the progressive muscle disorder Duchenne muscular dystrophy. Repeatedly she has heard patients

share their hopes that a clinical trial will heal them, even after they have read extensive informed consent forms and heard investigators explain that they are just as likely to receive no benefit. Peay thinks that optimism is not necessarily a bad thing. “People need hope,” she says. “Hope is important. Therapeutic optimism is an expression of hopefulness.”

The problem starts when people fail to recognize that a clinical trial is an experiment, not a treatment. Researchers have named this phenomenon, too: therapeutic misconception. They describe it as a blurring of the lines—an inability to distinguish between an approved treatment chosen and dosed specifically for a patient and a trial designed to further the science. “It’s kind of a perfect storm of the natural optimism and expectation of people who are desperate and clinical investigators who are, honestly, hyping their trials,” Peay says. She spends a lot of time trying to rectify mismatched expectations, which often arise in those facing rare diseases with unmet medical needs. According to unpublished research by bioethicist Jonathan Kimmelman of McGill University, only about one in 70 people in a phase 1 clinical trial will receive a drug at a dose that will ultimately receive FDA approval, whereas up to 15 percent of participants could experience a severe side effect.

Setbacks during the early iterations of gene therapy [see “Overcoming Gene Therapy’s Long Shadow”] showed scientists how much more they needed to learn about the underlying biology. Research has since filled in critical knowledge gaps, resulting in several FDA-approved gene therapies and dozens more likely to be approved by 2030.

Remarkable successes could lead some people to believe the field is moving faster than it really is, warns Rachel Bailey, a gene therapy researcher at the University of Texas Southwestern Medical Center. She points to one treatment, for a fatal neurodegenerative condition called Batten disease, that moved from concept to human testing in a little more than a year. Gene therapy has slowed the progression of Batten disease, but “at this point,” Bailey says, “we’re not at the cure stage yet. We are at the treatment stage.” A true cure will take much more research. “I think what’s important for patients to understand is that it takes a very large amount of time, effort and funding to develop these gene therapy products,” Bailey says.

QUESTIONS OF EQUITY

Gene therapy's rise to prominence has come with an extraordinarily high price tag. Novartis's newly approved gene therapy, a one-time treatment for spinal muscular atrophy, is now the world's most expensive drug at $2.1 million. On average, currently available gene therapies are priced at more than 30 times the average household income. "We must be thinking right now about the equity question and how we make sure that as many people as possible benefit from the technology that's built on government funding, that's built on great science," says Vence Bonham, acting deputy director of the National Human Genome Research Institute and leader of the NHGRI Health Disparities Unit.

Bonham has been talking about this issue for a while. In 2017, before the first gene-editing trial for sickle cell disease had been approved, his team interviewed more than 100 patients, families and physicians to gauge their attitudes and beliefs about the technology. Many were hopeful but cautious. "If this treatment becomes available to the public, will it be available to everyone equally?" one patient asked. "I have sickle cell. I struggle with it daily.... I don't want the reason why I can't get it done to be because, oh, your insurance, or you don't have the money."

Cost is not the only concern. In the U.S., only about one in four people with sickle cell disease receives the standard of care. These patients can be marginalized and dismissed, often having to wait longer for help in the emergency department than other pain patients. Creary herself has spent hours writhing in pain in hospital emergency rooms, misperceived by staff as drug seeking because she is Black and has sickle cell disease. She found a way to get her Ph.D. added to her medical record and learned to code switch, dropping hints about her academic titles in the hopes that health-care staff might equate her, she says, with "acceptable auspices of humanity."

Creary has noticed scientists promoting the narrative of gene therapy as social justice —a way of repairing the damage done to those living with sickle cell disease. She points to the Web site for the NIH's Cure Sickle Cell Initiative, which opens with, "It's time to rewrite the story of sickle cell." The statement seems to suggest that scientific innovation can rewrite history or at least right the wrongs wrought by historical neglect and racism. But Creary, who studies a concept she calls bounded justice, believes any justice achieved by targeting new gene therapies to marginalized populations will inevitably be limited by the very inequities that caused those groups to be marginalized in the first place.

"You let [gene therapy] out into the wild, and then all of these historical, societal and anthropological things are going to muck it up," Creary says. Her research suggests that discussions about gene therapy, at least for sickle cell disease, must address big issues such as colonialism, slavery, racism, and "all the things that come from generations and generations of oppression." Part of that is recognizing that physicians make assumptions about who may or may not be a good candidate for gene therapy. It also involves addressing social supports that could counteract the disadvantages many gene therapy patients face, such as health insurance to cover the procedure, transportation to and from the hospital, child care and paid time off for recovery. "It is tough, I think, because on some level it's this recognition that it's never enough," she says.

DEMOCRATIZING INFORMATION

One way that scientists can help their technologies land equitably in the world, Bonham says, is to center conversations on building trust, providing quality information and ensuring transparency. It is an important triumvirate that will take concerted effort from all involved.

Emily Howell, a science communication expert at the University of Wisconsin–Madison, says that the trust part happens when researchers meet people where they are by asking about their concerns, their hopes and their fears. Howell, who studies how to communicate controversial topics such as fracking and gene editing, says starting with emotions and values rather than with facts and figures can help to foster trust. People tend to trust someone when that person not only is competent but also seems to care about the same things as they do, Howell says.

Clarity of information has been another big obstacle. Patients have had a difficult time finding information that is accurate, actionable and understandable. U.T. Southwestern's Bailey says people with genetic diseases often have little choice but to try to make sense of esoteric research papers on their own or to hunt down scientific experts like her to answer their questions. She chairs the American Society of Gene and Cell Therapy's Patient Outreach Committee, which aims to foster open dialogues and easy access to information with a Web site that breaks down various aspects of gene therapy from a patient's perspective. Delhove concurs and says that accurate information empowers people to make decisions for their own health. "That's what

you want for patients," she says. "They shouldn't just be bystanders; they should be in control and know what is available for them."

The last of Bonham's trio—transparency—requires researchers to lay out precisely what is and is not possible and to be open and honest when something goes awry. In 1999 18-year-old Jesse Gelsinger died while participating in a gene therapy trial that he hoped would help others with the same rare liver disorder. In the years since, any safety scare has raised the specter of repeating history. Two gene therapy trials for sickle cell disease were temporarily suspended earlier this year after one of the participants developed cancer (it was later deemed unrelated to the treatment). Bonham says the pause was a clear sign of the scientific community's renewed commitment to engagement and transparency. "I think we've seen a really positive shift occurring with regard to our understanding that gene-based therapies have potential," he says, "but that doesn't mean that they don't have any risks."

Today, after several frank discussions buoyed by her own deep dives into the literature, Creary is well aware of those benefits and risks. She knows gene therapy might completely erase her sickle cell disease, untethering her from its pain and complications. But she has also learned how intense the procedure would be, with punishing rounds of chemotherapy and lengthy hospital stays. "I think about measuring that destabilization in that moment with what I could gain, in addition to the risks, and I'm still not sure," she says.

More than a million people could be eligible for gene therapy in the next 15 years. The conversations researchers have today, both with the general population and with their patients, may ultimately determine how the field evolves. With the right support, it could be revolutionary. Without it, an immeasurable amount of time and treasure will have been spent honing a technology that may never fulfill the hopes of the patients it was designed to help.

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