Tomorrow's children

What would genome editing really mean for future generations?

BY ERIKA CHECK HAYDEN

Ruthie Weiss's basketball team seemed to be minutes away from its fourth straight loss. But even as she stood on the sidelines for a brief rest, the nine-year-old had not given up. She convinced the coach to put her back in the game. Then, she charged out onto the court, caught a pass from a teammate and drove straight to the basket. Swish! Ruthie scored a quick two points, putting her team in the lead. As the game clock wound down, she scored again, clinching the victory. The team had earned its first win of the season, and celebrated as if it had just taken the national championship. A couple of parents from the opposing team even stopped by to congratulate Ruthie, who had scored all of her team's 13 points: "Wow, she's unbelievable!" they told her mum and dad.

What makes Ruthie's performance even more extraordinary is her DNA. Because of a misspelling in one of her genes, she has albinism: her body produces very little of the pigment melanin, which means that her skin and hair are fair, and that she is legally blind. Her visual acuity is ten times worse than average. She is still learning to read

Ruthie Weiss walks home from playing basketball with her father (centre) and uncle. Her sight problems have not prevented her from excelling at sport.

PRESTON GANNAWAY

and will probably never be able to drive a car, but she can make out the basket and her teammates well enough to shoot, pass and play.

In January, Ruthie's dad Ethan asked her whether she wished that her parents had corrected the gene responsible for her blindness before she was born. Ruthie didn't hesitate before answering — no. Would she ever consider editing the genes of her own future children to help them to see? Again, Ruthie didn't blink — no.

The answer made Ethan Weiss, a physician–scientist at the University of California, San Francisco, think. Weiss is well aware of the rapid developments in gene-editing technologies — techniques that could, theoretically, prevent children from being born with deadly disorders or with disabilities such as Ruthie's. And he believes that if he had had the option to edit blindness out of Ruthie's genes before she was born, he and his wife would have jumped at the chance. But now he thinks that would have been a mistake: doing so might have erased some of the things that make Ruthie special — her determination, for instance. Last season, when Ruthie had been the worst player on her basketball team, she had decided on her own to improve, and unbeknownst to her parents had been practising at every opportunity. Changing her disability, he suspects, "would have made us and her different in a way that we would have regretted", he says. "That's scary."

Ethan and Ruthie are not the only people pondering these kinds of questions. The emergence of a powerful gene-editing technology, known as CRISPR–Cas9, has elicited furious debate about whether and how it might be used to modify the genomes of human embryos. The changes to their genomes would almost certainly be passed down to subsequent generations, breaching an ethical line that has typically been considered uncrossable.

But emerging technologies are already testing the margins of what people deem acceptable. Parents today have unprecedented control over what they pass on to their children: they can use prenatal genetic screening to check for conditions such as Down's syndrome, and choose whether or not to carry a fetus to term. Preimplantation genetic diagnosis allows couples undergoing *in vitro* fertilization to select embryos that do not have certain disease-causing mutations. Even altering the heritable genome — as might be done if CRISPR were used to edit embryos — is acceptable to some. Mitochondrial replacement therapy, which replaces a very small number of genes that a mother passes on with those from a donor, was approved last year in the United Kingdom for people who are at risk of certain genetic disorders.

Many safety, technical and legal barriers still stand in the way of editing DNA in human embryos. But some scientists and ethicists say that it is important to think through the implications of embryo editing now — before these practical hurdles are overcome. What sort of world would these procedures create for those currently living with disease and for future generations?

So far, little has been heard from the people who could be first affected by the technology — but speaking with these communities reveals a diverse set of views. Some are impatient, and say that there is a duty to use genome editing quickly to eliminate serious, potentially fatal conditions. Some doubt that society will embrace it to the degree that many have feared, or hoped. Above all, people such as Ethan Weiss caution that if policymakers do not consult people with disabilities and their families, the technology could be used unthinkingly, in ways that harm patients and society, today and in the future.

"Hearing the voices of people who live with these conditions is really important," says Tom Shakespeare, a medical sociologist at the University of East Anglia in Norwich, UK.

THE CASES FOR

John Sabine, now 60, was once described as one of the brightest legal minds of his generation in England. Now, he is in the advanced stages of Huntington's disease: he cannot walk or talk, is incontinent and requires constant care. Charles Sabine, his younger brother, carries the same genetic glitch that causes Huntington's disease, and therefore knows that, like his brother and his father before him, he is destined to undergo the same deterioration of brain and body.

Charles and his brother have five children between them, each of whom as a 50% chance of having inherited the mutation that causes Huntington's disease. To Charles — and to many others who live with the mutation that causes Huntington's — there is no legitimate ethical argument about whether gene editing should be used, either to treat people living with the condition now or to spare their children from it.

"Anyone who has to actually face the reality of one of these diseases is not going to have a remote compunction about thinking that there is any moral issue at all," Sabine says. "If there was a room somewhere where someone said, 'Look, you can go in there and have your DNA changed,' I would be there breaking the door down."

Matt Wilsey, a technology entrepreneur in San Francisco, would be there too. His daughter Grace was one of the first people in the world to be diagnosed with a disease caused by a mutation in the gene *NGLY1*, which makes it difficult for her cells to get rid of misshapen proteins. Grace, now six years old, has severe movement and developmental disabilities.

She can barely walk and cannot talk. Because her condition is new to medicine, doctors cannot even predict how long she might live.

Wilsey is bullish on CRISPR. He says that if he had had the chance to detect and fix the mutation in Grace's genome before she was born, he would have. But he is frustrated that the debate over editing embryos seems to have monopolized discussions about the technology. He is hopeful that a gene-therapy-like approach using CRISPR, which would be free of the ethical concerns about altering the genes she passes on, could help Grace within several years. And he wonders whether a temporary moratorium on embryo editing might allow the field to focus on such approaches sooner.

"As a parent with an incredibly sick child, what are we supposed to do — sit by on the sidelines while my child dies? There's zero chance of that," Wilsey says. "CRISPR is a bullet train that has left the station — there's no stopping it, so how can we harness it for good?"

A meeting convened in December 2015 by the US national academies of sciences and medicine, the Chinese Academy of Sciences and the Royal Society of London recommended such a moratorium in light of multiple safety and ethical concerns. Still, many bioethicists and scientists have argued that if defects in single genes causing fatal and debilitating conditions could be corrected in an embryo, then they should be. Shakespeare notes that embryo editing for conditions that cause major disability and death are likely to raise less concern and criticism in the long term. But, he says: "As soon as you get away from the archetypal terrible condition, then you've got a debate about whether a condition makes life unbearably hard."

"These kinds of interactions significantly change our attitudes about what kinds of people matter in the world."

SOCIAL CONSEQUENCES

Many people are concerned about where that line would be drawn. Although it may seem now that only a few, very severe conditions should be subject to gene editing, disability activists point out that the list of conditions considered as illnesses, and possibly subject to medical treatment, is expanding. "More and more, people think of obesity or predisposition to alcoholism as disease," says Carol Padden, a linguist at the University of California, San Diego. She herself is deaf, and points out that many deaf people do not consider it a disability. This stance has led to controversy when, for instance, deaf parents decline technologies such as cochlear implants for their children, or even go so far as to select, through processes such as preimplantation genetic diagnosis, children who will be deaf.

Like Padden, some disability-studies researchers do not oppose the idea of gene editing, but do think that society needs to understand that it is not possible to eliminate all disability, and that humans might lose something important if they try to do so.

Padden points out that accommodations originally intended for people with disabilities often end up benefiting everyone. For example, the development of closed captioning — subtitles for the hearing-impaired on television — required major advocacy from the deaf community and legislative action to get off the ground in the United States in the 1970s. Today, people rely on it in ways that no one could have foreseen, such as in noisy airports and sports bars. Some people use it to learn to read or to learn a language.

Rosemarie Garland-Thomson, a literature scholar and co-director of the Disability Studies Initiative at Emory University in Atlanta, Georgia, adds that legislative mandates, such as the 1990 Americans with Disabilities Act in the United States, have helped to integrate people with disabilities into society — in workplaces, schools and other public spaces. As a result, the world is much more humane for everyone, says Garland-Thomson. "These kinds of interactions significantly change our attitudes about what kinds of people matter in the world."

The idea that parents should edit out characteristics that are considered debilitating goes against this drive towards inclusion, Garland-Thomson warns, and could create a harsher social climate for everyone. The experience of disability, she adds, is universal; all people inevitably experience sickness, accidents and age-related decline. "At our peril, we are right now trying to decide what ways of being in the world ought to be eliminated," she says.

Padden says that ethicists, patients and disabilities-studies researchers must work urgently to make a broad societal case in favour of greater acceptance of diversity. This has been a long-fought battle, and many see evidence of progress — for instance, in the 'neurodiversity' movement, which champions the idea that medical conditions such as autism are part of the spectrum of human variation. "We do have to start coming up with more arguments for diversity, and quickly, because CRISPR is coming upon us faster than some of us are thinking about this issue," she says.

MAKING CHOICES

The prospect of editing the genome of a human embryo is still in its early stages, but the ability to prevent the inheritance of some conditions already exists. Prenatal screening, which has advanced to the point that doctors can sample a developing fetus's DNA through its mother's blood, has given parents the option to terminate pregnancies when a disease or disability is diagnosed. This has already started to show limited effects on the population.

In Europe, for example, the prevalence of a Down's syndrome diagnosis during pregnancy has risen from 20 cases per 10,000 in 1990 to 23 cases per 10,000 today, as the average age of women having babies has increased. But the number of children born with the syndrome has stayed level at about 11 per 10,000, because many women whose fetuses are diagnosed with the condition terminate their pregnancies. In the United States, pregnancies in which a Down's syndrome diagnosis is made are terminated in 67–85% of cases.

By surveying women whose fetuses and babies are diagnosed with Down's syndrome, and by compiling similar surveys from around the world, medical geneticist Brian Skotko of the Massachusetts General Hospital in Boston has found that doctors sometimes advise women to terminate or give up for adoption babies diagnosed prenatally with Down's syndrome. They can influence the decision by using phrases such as "I'm sorry", or "I have some bad news to share"[1]. For instance, 34% of 71 Dutch women who terminated their pregnancy after a Down's syndrome diagnosis said that their doctors did not even mention the possibility of carrying the pregnancy to term when discussing their options[2].

Mark Leach, a lawyer in Louisville, Kentucky, whose 11-year-old daughter has Down's syndrome, says that he and his wife have been asked many times — especially when his wife was pregnant with their second child — whether they "knew beforehand" that Juliet would be born with Down's. (They didn't.) Some people are simply curious, Leach says, but for others, there's judgement in that question. "The ability to do something beforehand imposes a sense of, 'You should do not only what's right for you, but what's right for society'," Leach says. It bothers him, he says, that although government and private health insurers routinely pay for prenatal diagnosis, he recently learned that his school system is discontinuing support for the learning specialist who had been helping Juliet to thrive in mathematics and reading.

Dorothy Roberts, a professor of law and sociology at the University of Pennsylvania in Philadelphia, says that this kind of pressure is troubling and that it could get worse if embryo editing were to become readily available. "Women should not be given the responsibility of ensuring the genetic fitness of their children based on lack of support for children with disabilities."

Leach knows that children with disabilities can live rich lives. Juliet likes ballet dancing and horse-riding, and she is especially attuned to the names of people and animals whom she knows. And Leach says that she helps to remind other people how to care for others. "The main

thing that would be lost if Down's syndrome continues to diminish is a diminishment in the amount of compassion that is shown in this world," he says.

Even among people who already have life-threatening conditions, many choose not to interfere with the way the genetic cards are dealt. Edward Wild, a neurologist who cares for people with Huntington's disease at University College London, estimates that fewer than 5% of patients in the United Kingdom use preimplantation genetic screening to select embryos that lack the disease-causing mutation and so avoid passing it to their children. Some people do not know that they have the mutation; some decide against screening because of the costs or risks involved; some have personal or moral objections to the technique; and some just have a sense that 50–50 odds of passing down the disease are not so bad.

"Having kids the fun way is still much more popular than having kids the science way, even though the latter is how you guarantee the kid is free of Huntington's disease," Wild says.

Even if gene editing were safe, effective and everyone opted to use it, it would not eliminate genetic diseases, because researchers still have a long way to go to understand the genes involved. Even Huntington's, which is fairly well characterized, is no easy target. The glitch that causes it is a repeat of a particular genetic sequence; the more repeats, the more severe the symptoms, and repeats are added with each successive generation. New families are diagnosed with Huntington's all the time, either because the disease is misdiagnosed in older generations or because symptoms worsen, and become recognizable, in subsequent generations. Although he is working on genetic techniques to treat Huntingon's, Wild doesn't hold out high hopes for a future free of the disease. "Although it's nice to think about, it's little more than a dream," he says.

> "Prediction: my grandchildren will be embryo-screened, germline-edited. Won't 'change what it means to be human'. It'll be like vaccination."

Human biology can complicate things in other ways. Padden notes, for instance, that some mutations that predispose to genetic disease, such as the sickle-cell mutation, confer population-level benefits, such as resistance to malaria. So editing out one disease could backfire by increasing the risk of another. She argues that very little is known about the potential benefits of other mutations associated with disease, and applying genome editing too freely could have unintended consequences.

And if it were adopted, the technology would almost certainly be applied unevenly around the world. Aleksa Owen, a sociologist at the University of Illinois at Chicago, predicts that genome editing would be used first in countries that approve of and support assisted reproductive technologies, such as the United Kingdom, some other European Union countries, China and Israel. But it would probably be too expensive for many people in developing countries.

UNEVEN ACCESS

Still, some scientists predict that editing human embryos could have transformative effects. During the National Academies' summit on gene editing in December, Harvard University geneticist Dan MacArthur tweeted, "Prediction: my grandchildren will be embryo-screened, germline-edited. Won't 'change what it means to be human'. It'll be like vaccination."

Sandy Sufian, a historian of medicine and disability at the University of Illinois, agrees with MacArthur that CRISPR has the potential to become widely adopted, both because of the perception that it would save money that would otherwise be spent caring for disabled people and because of people's fear of disability. But she questions the idea that eliminating such conditions will necessarily improve human life. Sufian has cystic fibrosis, a disease caused by mutations that render her lung cells more vulnerable to infection and disease. She spends 40 hours a week inhaling medicine to clear her lungs of mucus, exercising and undergoing physical therapy; others have to quit their jobs to make sufficient time for treatments. Yet given the option to edit cystic fibrosis out of her bloodline, Sufian wouldn't do it. "There are some great things that come from having a genetic illness," she says.

Garland-Thomson echoes that sentiment; she has one and a half arms and six fingers because of a condition called limb-reduction disorder. She says that she values traits in herself that she may have developed as adaptations to the condition: she is very sociable and wonders if that is because she's had to learn to work hard to make others feel comfortable around her. "Any kinds of restrictions or limitations have created the opportunity for me to develop work-arounds," Garland-Thomson says.

Shakespeare, who has achondroplasia, a genetic condition that causes shorter than average stature, says that people with disabilities are just as able to attain life satisfaction as others. "I have achieved everything I hoped for in life, despite having restricted growth: career, children, friendship and love." He wouldn't want to have altered his own genes to be taller, he says.

DISABILITY RIGHTS

People without disabilities consistently underestimate the life satisfaction of those with them. Although people with disabilities report a slightly lower overall quality of life than those without, the difference is small. One study[3] found that half of people with serious disabilities ranked their quality of life as 'good' or 'excellent'.

People also overestimate how severely health affects their happiness compared with other factors, such as economic or social support. One 1978 study[4], for instance, compared people who had recently become paralysed as a result of accidents with people who had recently won between US$50,000 and $1 million in a state lottery. Although people who had had accidents ranked their happiness lower than lottery winners, both groups predicted that their future happiness would be roughly equal, and people who had accidents derived more pleasure from everyday activities, such as eating breakfast or talking to a friend.

"A lot of this terrific science and technology has to take into account that the assumption of what life is like for people who are different is based on prejudice against disability," says Lennard Davis, a disability-studies researcher at the University of Illinois, who was raised by two deaf parents.

There is a common saying among people in the disability-rights community: "Nothing about us without us." People with disabilities argue that scientists, policymakers and bioethicists should take steps to ensure that the CRISPR debate reflects what is best for patients and their families, to ensure its most humane use now and for future generations.

At a minimum, they say, the investment in developing CRISPR should be matched by investments in innovations to help people who are already living with conditions that cause disability. And it is essential that people with the conditions that are up for consideration as possible CRISPR targets should be included in the decision-making processes.

For their part, Ruthie Weiss and her dad have already made up their minds. Ruthie must work harder than her classmates to do some routine activities. But when she is dominating the basketball court, or practising the piano, or skiing down a mountain, Ethan Weiss doesn't see a child with a disability. He sees his daughter making the most of her life, given all her strengths and challenges. And he knows that he wouldn't change a thing. ■

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