Want a glimpse of baby's future?

If you were offered the chance to unravel your child's whole genome just after birth to see what may lie in the years to come, would you say yes? In 2015, a groundbreaking trial asked parents to do exactly that. Now, seven years down the line, **Katharine Gammon** discovers the consequences

ALYSSA CARTER had just given birth when a doctor asked if she would like to find out more about her baby's genes. With a few spots of blood, researchers could sequence her son's whole genome. She would receive a report that predicted various aspects of her baby's future health. "I eagerly signed up," says Carter. But although she had been briefed on the possible outcomes, it hadn't occurred to her that there might be bad news. When she saw the results, her stomach lurched.

In the 21 years since whole-genome sequencing was first applied to humans, it has become a powerful tool – instrumental in tracking disease outbreaks and diagnosing mysterious conditions. But as the technology evolved, so too did an extraordinary idea. What would happen if we knew the intimate details of our entire genome from birth?

The implications are a minefield, said ethicists. Who will have access to the data? Will it be useful? How will it affect parents and children over the course of their lives? The benefits could be worth the risk, said others. What if we could spot diseases before they took hold or help someone avoid a risky behaviour? Could it even mean the difference between life and death? The way to find out was to run a unique trial. That trial, in which Carter's child is a participant, is now seven years old and is finally starting to provide answers to these fundamental questions.

The human genome contains about 25,000 genes, and the first (almost) complete sequence of it was achieved in 2001, costing about $1 billion. Last year, it was completed for real, with the additional sequencing of 2000 genes that had been hard to place. Back in 2001, Francis Collins, then director of the US National Human Genome Research Institute in Maryland, predicted that it would be feasible within 20 years to use this type of genetic data to produce a "kind of report card analysis" for every newborn baby's health.

Before this could happen, though, researchers spent decades exploring the use of whole-genome sequencing in adults. As the technology dropped in price, they slowly revealed the medical, behavioural and economic impacts of incorporating such sequencing into everyday medicine. Among the many projects designed to do this was MedSeq, which began in 2012 and was the first study to examine the use of whole-genome sequencing in people with suspected genetic cardiac disease. It also looked at people who were in good health with no family history that suggested they were at risk of a genetic disease.

One of the most surprising outcomes of this work was the discovery that a significant percentage of the latter group carry deleterious mutations – gene variants that increase a person's susceptibility to a certain condition. "We found 20 per cent of healthy adults carrying something that might put them at risk of a disease," says Robert Green at Brigham and Women's Hospital in Boston, Massachusetts, who led the project.

It was then that he wondered whether it might be time to put Collins's prediction into action. "We thought, we want to sequence people as soon as possible in life," he says, rather than wait until the diseases may have already started to develop.

The UK already routinely screens babies for nine rare conditions that can affect long-term health by looking for biomarkers in a few drops of blood from the newborn's heel. States in the US screen for at least 29 conditions.

Adding whole-genome sequencing to the mix could allow doctors to potentially identify hundreds more conditions that might affect a child's life. But testing this idea hasn't been easy. For a start, it wasn't clear what conditions should be included, how results might be interpreted and how knowing this information might affect the parents or long-term health of a baby. Only two things were certain: speculating wasn't going to provide any answers and private companies weren't going to wait to start offering the service.

Predicting the future

Green felt a scientific responsibility to begin a trial sequencing the genes of newborn babies, so that any challenges could be mitigated and understood before whole-genome sequencing was launched onto an unsuspecting public. "We wanted to do it really well and understand the process," he says.

First, he and his team deliberated on which conditions to include. With a whole genetic landscape at their fingertips, there needed to be some ground rules. They decided that each condition had to have solid evidence of how genes affected it. They also questioned whether to return results related to adult-onset conditions – problems that couldn't be treated in childhood, such as Alzheimer's.

Eventually, they focused on 954 genes that were related to childhood diseases and included a limited list of adult-onset conditions in the study. It meant that some ›

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of the results could indicate a parent was at risk, too. "Our logic was that there isn't much better for the baby than saving the life of the parent," says Green. The trial, called BabySeq, started enrolling up to 500 participants in 2015.

There were a few teething problems. Preliminary surveys suggested that 70 to 80 per cent of people would want to join. But when the team actually went to maternity wards to enrol volunteers, only 7 per cent of the parents they asked signed up.

Another issue was figuring out how to break bad news to parents whose results showed their newborn was at risk of a severe disease. Carter was a case in point. A counsellor shared that her son had a rare disease-causing variant of the *ELN* gene. The variant is associated with supravalvular aortic stenosis, which is characterised by a narrowing of the aorta. It can lead to heart failure. However, severity differs and not all those with the variant will go on to develop the disease.

Families under the microscope

Carter wasn't emotionally prepared for the "word salad" of information about her son's potential condition and for what it all meant. "We have to navigate medical care for something that exists in theory, that could be a big deal, but might not happen," she says. More tests showed that her baby had inherited the disease-causing variant from his father. How would this information affect them all?

That was exactly what BabySeq researchers wanted to explore. Their study involved getting parents of 325 newborns to complete surveys when they enrolled in the trial, immediately after their child's results were disclosed, three months later and 10 months later. Half of the children received standard newborn screening plus a family history report, the rest received standard newborn screening plus a report based on whole-genome sequencing.

The surveys examined the parent-child relationship, the parent-parent relationship and the parents' psychological distress. An analysis of the results, published last year, found no long-term negative psychological harm in a parent having knowledge about their child's genome, even in families where the sequencing found an increased risk for a disease. Perhaps surprisingly, parents of babies who had received genetic sequencing scored lower on a test of self-blame for passing potentially harmful genes onto their baby.

There are limitations, the researchers say: it could be that the parents who agreed to participate are already interested in the research outcomes, or that the results only reflect a small portion of the population. A second project, BabySeq2, is now enrolling a more diverse set of families across the US.

BabySeq's first cohort was comprised of babies born in intensive care and babies without any overt health conditions. Genetic sequencing of ill babies has a long history of having a positive impact on health. And as the technology is getting faster and cheaper, the impacts are even greater. For instance, in 2018, doctors were able to sequence a child's genome and diagnose a disease in 7 hours and 18 minutes – a world record for fastest genetic diagnosis.

John Gorzynski at Stanford University in California, part of the team that carried out the rapid diagnosis, says that babies used to spend months in hospital if they had a condition that couldn't be explained. Now that they can have their genomes sequenced faster, it means fewer tests, less time in hospital and a speedier treatment for genetic-based illnesses.

But while genetically screening sick babies has obvious benefits, the consequences of screening healthy babies has been less clear until now. BabySeq's latest results, posted earlier this year ahead of formal publication, show that 18 per cent of 159 babies with no current medical problems who had their genome sequenced at birth had a mutation for a childhood-onset or adult-onset genetic condition. All of the conditions had available clinical interventions. In eight cases, the results prompted screening for at-risk family members, too. For instance, the maternal

Should you get your whole genome sequenced?

Private companies already offer whole-genome sequencing for adults. The price has come crashing down, falling from thousands of pounds to just a few hundred in the past five years. But is it worth it and can it really tell you anything that your family medical history can't?

To find out, a 2017 study recruited nine primary care doctors and 100 of their patients who had no history of cardiovascular disease or diabetes and were deemed generally healthy. The aim was to see how whole-genome sequencing affected the health of the patients. Half of them received a family history report and whole-genome sequencing; the rest received a family history report alone. The sequencing revealed a high rate of increased risk for rare, monogenic diseases – conditions caused by a variation in a single gene. Yet the participants themselves had no sign of the illnesses their genes showed. It turns out, markers for genetic disease are far more common than expected.

Most of the people who received genetic information didn't panic over the results, and the doctors in the study generally advised them to do the right things (as judged by an independent panel of geneticists). Six months later, the people who received genetic results were more likely to have made positive changes to their health, when compared with the control group. But the genome sequencing was more expensive than a family history and had no significant impact on health outcomes during the study period.

"Whole-genome sequencing can offer up a lot of information for adults," says John Gorzynski at Stanford University in California, which may make them change their behaviour in a positive way. But there are things that we can do now to make our lives healthier, he says – and an awful lot of them we know we should do without having to sequence our genomes.

The cost of sequencing a whole genome has plummeted in recent years to just a few hundred pounds

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grandfather of a child in the study had been previously diagnosed with a heart condition. The baby was shown to carry the variant that predisposes them to the same heart condition. Consequently, the child's mother now has routine echocardiography.

Changing behaviour

Gorzynski says it is likely that a lot of children and adults will have their genome sequenced in the next decade (see "Should you get your whole genome sequenced?", left). Indeed, the UK government recently launched its own newborn genome screening project, enrolling 200,000 newborns to explore whether it accelerates diagnoses and access to treatment. "If we can know more about a person's genome in terms of how it may affect their health, I think that is really beneficial," says Gorzynski.

Not everyone agrees, however. Josephine Johnston at the Hastings Center, a think tank in Garrison, New York, has published a report on the ethics of newborn genome screening, listing some of the problems. One is that sequencing the entire genome has the potential to give results that aren't significant or actionable, causing worry without any pay-off. And although BabySeq has been running for a while now, there is limited understanding of how such early knowledge of your genes affects your life over the long term.

We know from a 2019 study, for instance, that being given genetic information can change behaviour. When people were told they had a genetic propensity for either obesity or lower exercise capacity, it altered the way their body responded to a meal and exercise (even though the result was, in fact, fake). And of course, when screening newborns, you are making these decisions on behalf of an individual who, as an adult, may not want to know about them. A paper co-authored by Green, published last year, found that more than a third of people whose genetic information showed a disease-causing variant with an actionable outcome chose not to receive the information.

David Curtis at the University College London Genetics Institute says that privacy and consent are his biggest concerns. An individual's medical information is private, he says. If a child is sick and must be treated without their consent, the parents may get information about the child's health. But it isn't the case that our parents have the right to total knowledge about our health, he says. "We're talking about basically subjecting all members of society to a medical investigation that will yield huge amounts of private information, which will be somewhere, available to whoever, without the individual's consent." It isn't clear to Curtis who will hold the genetic information, how it will be tied to public health records or how often each genetic risk leads to actual disease. "The potential benefits are absolutely minuscule, and we can deliver them in other ways," he says.

BabySeq's data is held by a lab in Massachusetts and parents have consented to its use for research, says Green. "The whole purpose of BabySeq is to understand precisely what are the benefits, harms and costs of implementing this."

Knowing your genes from birth could influence behaviour

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"Would you want to know whether your baby is predisposed to having a high IQ?"

It is also unclear how a baby's genetic data could be used in the future, adds Curtis. Indeed, although researchers are currently focused on the medical outcomes of newborn genetic screening, it may be possible to correlate the data with other outcomes in the future. Would you want to know whether your baby is predisposed to having a high IQ or excellent sporting ability? It is too early for this kind of prediction, but research is progressing in these areas. A 2018 study of 1.1 million people found correlations between certain genes and educational attainment, for instance.

These are all questions that need to be explored. For Carter, though, the information from her newborn's sequencing was ultimately a good thing. Her son is now 6 years old and is assessed every six months. He is doing great, she says: no symptoms have developed. There are little things she pays more attention to than she would have – she would immediately go to the doctor if he had any chest pain, for instance, however minor.

Carter hopes that genome sequencing will be more accepted in the future. "I would much rather know than not know. I think of the pain and suffering information like this could help ease," she says. "There's power in knowledge." ▮

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