BABY STEPS

Sequencing every newborn's genome to detect diseases faces ethical and practical obstacles, but the United Kingdom is pushing ahead with a major test

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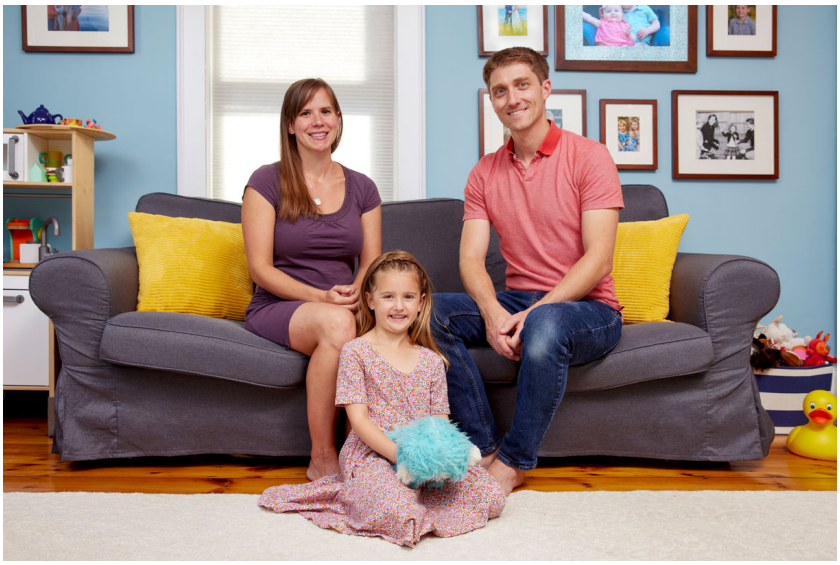
In 2016, a girl named Cora Stetson was born in Boston. Within 48 hours, hospital staff pricked her heel to get a drop of blood to look for molecules that signal dozens of rare genetic diseases—a test required for all U.S. newborns. Because Cora's parents had agreed to enroll her in a study, a researcher also took blood for a much broader test—one that scoured her genome for about 1500 disease genes.

The genetic information proved crucial. Although the standard test flagged a disorder involving a B vitamin–processing enzyme called biotinidase, a follow-up test was negative, and her pediatrician concluded Cora did not have the disorder. But the genome test revealed she indeed had mutations causing biotinidase deficiency—a mild form that nonetheless could result in "bad eyesight and struggling in school," says Cora's mother, Lauren Stetson, a theater educator. Cora now takes a daily biotin tablet and is a "spunky, crazy, sassy" kindergartner, Stetson says.

Cora's case illustrates the promise of sequencing the entire genomes of newborns: uncovering a bounty of genetic information that could identify infants needing treatment and improve health later in life. "Five to 7% of people are born with a rare disease, and many could be treated very early in their life" if the disease is detected, says Richard Scott, chief medical officer of Genomics England, a government-funded company. Genome sequencing could help. "The costs have come down so much that we're now at a tipping point where it's wrong not to."

Genomics England hopes to test that promise in a pilot research project involving up to 200,000 babies. Though it would initially look for the genes of rare childhood diseases, it would also store the genome data for later, when it could help predict drug sensitivities and risks for adult diseases such as cancer. Some U.S. researchers are also eager to add genomewide sequencing to newborn screening. One impetus is to find babies who could benefit from a growing wave of gene-based treatments for devastating, often fatal childhood diseases, such as Sanfilippo syndrome, a metabolic disorder that causes brain damage.

But the U.K. program has an advantage: The country's national health care system already uses whole genomes in clinical care. In the United States, sequencing every newborn's genome is probably still a long way off. Even with inexpensive technology, newborn genome screening on a countrywide scale could take complex infrastructure and hundreds of millions of dollars, if not billions. Some companies already market newborn tests that sequence many genes or the whole genome, at a cost of several hundred to a couple thousand dollars. But those tests are likely to benefit only relatively well-off families.



Genome sequencing showed Cora Stetson (center) inherited an enzyme deficiency from her parents. Now 5, she takes a supplement and is thriving. KEN RICHARDSON

In every country, ethical and practical questions abound, including which disease genes to test for and whether testing should be done by default. In fact, an ethics group funded by the U.S. National Institutes of Health (NIH) warned in a 2018 report that the evidence to date "does not support genome-wide sequencing of all babies at birth." The report noted that the health consequences of many mutations are unknown, and many genetic diseases remain untreatable. Instead of genomewide sequencing, U.S. disease advocacy groups and clinical geneticists have focused on speeding up the sluggish existing national system for screening newborns.

Newborn genome sequencing may become attractive as costs come down, but it's not easy or straightforward, says bioethicist Barbara Koenig of the University of California, San Francisco, a co-author of the 2018 report. "The genome is so, so much more complicated than it appears."

THE IDEA OF READING a newborn's genome dates back at least to the first draft of the human genome, released in 2001. In a TV interview aired that year, Francis Collins, then director of the National Human Genome Research Institute, predicted it would be "feasible" within 20 years to produce a "kind of report card analysis" from a baby's DNA sequence. In 2010, NIH held a workshop to plan four pilot projects to explore newborn genome sequencing.

One project, led by Stephen Kingsmore, now at Rady Children's Hospital-San Diego, has proved an overwhelming success: sequencing critically ill newborns to find out whether they have a genetic disease. For example, in October 2020, a couple brought its inconsolable 5-week-old boy to the Rady emergency room; a computerized tomography scan showed brain abnormalities. Kingsmore's team then found in the baby's genome a mutation for a severe B vitamin metabolic disorder, and soon the boy was quietly drinking vitamin-spiked formula; he's now healthy. The condition likely explained his sister's death as an infant 9 years earlier, Kingsmore's team reported on 3 June in *The New England Journal of Medicine*.

In June, Kingsmore reported at an online NIH-sponsored meeting on gene therapy that across 23 studies in the past decade by his and other groups, genome sequencing led to a genetic diagnosis for 36% of 1839 seriously ill children, mostly infants. In 533 patients—29% of the total—the findings led to changes in medical care, which saved some babies' lives.

Because of results like those, several countries, including Australia and England, are making genome sequencing for very sick newborns routine, and California and Michigan have approved Medicaid coverage for the test. Genome sequencing "is becoming a new form of care for critically ill neonates," said Diana Bianchi, director of the National Institute of Child Health and Human Development, at the meeting.

Other NIH pilot studies tested genome sequencing as a screening tool for all babies, healthy and sick, comparing it with standard newborn screening. That program began in the United States in the 1960s to identify phenylketonuria (PKU), a metabolic disorder that leads to intellectual disability unless infants eat a special diet. States now screen for PKU and about 30 to 70 other treatable disorders, using mostly biochemical tests. Whole-genome sequencing could look for those single-gene diseases and hundreds more that don't now have a biochemical test, such as neonatal diabetes, hemophilia, and a kidney condition called cystinosis.

But the technique is not infallible. The NIH-funded research and related studies found that sequencing the

A bigger net

Standard newborn screening using biochemical tests flags several dozen genetic disorders. Genome

whole genome or protein-coding DNA misses 12% or more of cases detected by newborn screening. That's because the sequencing misses some genetic changes, and analysts may disregard others—even ones associated with a newborn disease—if that change hasn't been shown to be harmful. But the studies also suggested the two methods could be powerful if combined because sequencing could confirm an ambiguous biochemical test result, as it did with baby Cora.

sequencing could screen for thousands more.

	STANDARD SCREENING	GENOME SEQUENCING
What is analyzed?	Mostly metabolites that reflect a disease	All 3 billion DNA base pairs or the 1% encoding proteins
Number of disorders	Ranges from two to about 70 depending on country or U.S. state	Potentially more than 5000 known single-gene diseases
Method	Mass spectrometry. Additional tests for some disorders	Next-generation DNA sequencing
Drawbacks	Can only detect diseases that result in a biochemical change	Misses some cases found with standard screening
Cost (in the U.S.)	About $30 to $200	Up to $900, not including analysis

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Cora was part of a pilot project called BabySeq that highlighted another complication of newborn sequencing: It turns up mutations that may never affect health. A team co-led by Robert Green of the Harvard University–affiliated Brigham and Women's Hospital looked for disease mutations in some 1500 genes in 127 healthy babies and 32 sick babies. About 8% of apparently healthy babies and 9% overall had mutations for a childhood genetic disorder—"startling" proportions, Green says. And 88% of the babies were carriers of a genetic disease, a finding that might unsettle parents even though their babies only had one of the two copies of the mutation necessary to get sick.

Among the 10 healthy babies with disease genes, only Cora later had clinical test results indicating she had the condition and should be treated. Seven others had risk genes for heart disease, and a few with slightly abnormal results on heart function tests will be monitored. But many people with those mutations never develop symptoms. "We are plowing new ground here," Green says, by finding mutations whose effects don't always cause illness.

Despite that uncertainty, BabySeq parents, including the 15 families whose babies had an unexpected risk gene for childhood disease, did not experience substantial anxiety or disrupted family bonding from learning that result, according to survey results published in August in *JAMA Pediatrics*. "Many parents would much

rather know about these risk factors than not know," Green says. That finding comes with a large caveat, however: Only 7% of parents invited to participate in BabySeq accepted, and—like Cora's parents—most were white and well-educated. To learn how a broader population responds to newborn sequencing, NIH is funding BabySeq2, which will enroll 500 ethnically and socioeconomically diverse families in Boston, New York City, and Birmingham, Alabama.

IN THE UNITED KINGDOM, which has embraced using whole-genome sequencing in routine health care, the public has already weighed in on newborn sequencing. This summer, Genomics England and the U.K. National Screening Committee released the results of a consultation with 130 diverse members of the public. They supported newborn sequencing if parents gave consent—and if they received results only for treatable or preventable childhood diseases.

Genomics England intends to follow those principles in its large pilot project, which could screen for up to 600 genetic diseases that can cause symptoms in early childhood. Those diseases will all have treatments, if not cures, and may include vitamin B6–dependent epilepsy and familial Diamond-Blackfan anemia, a red blood cell disorder. Planners hope to enroll as many as 200,000 newborns over several years, Scott says—a sizable fraction of the 600,000 babies born annually in the country.

The pilot project has the support of Genetic Alliance UK, which includes many groups advocating for patients with rare diseases. Director of Policy Nick Meade says the groups see whole-genome sequencing as a way to rev up the United Kingdom's current screening program, which only tests for nine diseases.

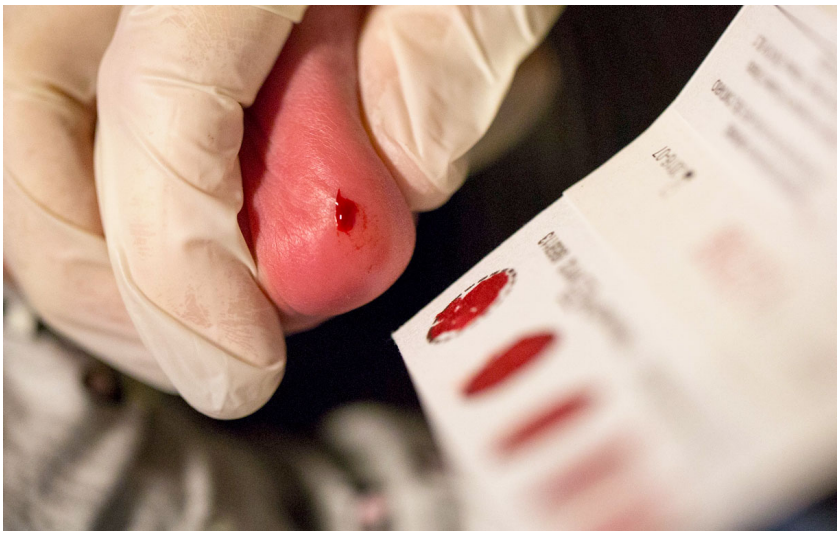
To critics, however, "There are massive ethical and cost issues," as psychiatric geneticist David Curtis of University College London puts it. He is concerned that identifying disease variants that will never make some babies seriously ill will lead to needless testing and family anxiety. He also worries the cost of newborn genome screening—perhaps $900 per baby, or $540 million per year—would be too high for the potential payoffs, and notes newborns can't give consent to storing their genome where it could potentially be accessed by companies as part of agreements with Genomics

England. "That baby, in 18 years' time, is he going to be happy that somebody took his whole-genome sequence and put it in a database?" Curtis asks.

ADVOCATES OF GENOMEWIDE screening agree that plenty of uncertainties need to be resolved, including whether to give parents results for mutations that may not be pathogenic and whether to test for incurable diseases, such as fragile X syndrome, which causes intellectual disability. One parent told the U.K. consultation that he was glad *not* to know his son had Duchenne muscular dystrophy before symptoms appeared—they had four happy, worry-free years.

Still, says Tiina Urv, of the National Center for Advancing Translational Sciences, basically everyone at NIH's June meeting on gene therapy "recognized that whole-genome sequencing [of all infants] is the way to go in the future." They discussed stories like that of a San Diego couple who came home from the hospital in June 2019 with a seemingly healthy baby and then got a phone call that brought terrifying news: Standard newborn screening had found that little Fitz Kettler lacked a functioning immune system. Fitz was referred to Kingsmore's group for genome sequencing, which revealed he had Artemis-deficient severe combined immunodeficiency (SCID), a rare disease that could kill him within a year.

Fortunately, in San Francisco, researchers were testing a gene therapy for Artemis-deficient SCID. Fitz was enrolled in the trial and received a transplant of his own bone marrow cells, genetically modified to correct the mutation. His family still isolates him to avoid COVID-19, but he now has functioning immune cells and is "flourishing," his mother, Christina Eagle-Kettler, said at the June meeting. Early diagnosis through sequencing was key, she said. "I can't imagine not wanting to help make that happen" for other families.



Standard newborn screening, done with blood from a heel prick, could vastly expand with DNA sequencing. RANDY RISLING/*TORONTO STAR* VIA GETTY IMAGES

Yet adopting newborn sequencing in the United States has practical obstacles. One is that adding a single new disease to the current screening program takes years, followed by more time to move the disease to state screening lists, dimming prospects for adding hundreds of diseases that genome sequencing could screen for. University of North Carolina, Chapel Hill, clinical geneticist Cynthia Powell chairs the committee that oversees the national list. She says the committee is looking at ways to move more quickly—for example, by adding classes of diseases at once.

Some researchers also fear adding genome sequencing to U.S. newborn screening could cause a backlash against the existing program. Newborn screening is essentially mandatory, like childhood vaccinations. (Only rarely do parents opt out.) The goal of preventing severe childhood diseases across the population "is so important," Koenig says. Adding genes that don't always lead to serious disease or that lack a clearly effective treatment, along with storing the baby's entire genome, could turn parents off the program, Powell says. "I can just see potentially jeopardizing the whole newborn screening system and not even being able to identify conditions such as PKU. I think we have to be very careful," she says.

The United States also lacks the infrastructure for universal newborn sequencing, such as an obvious place to store the genome data for the 3.7 million babies born each year, says clinical geneticist Marc Williams of the Geisinger Health System. And the

state labs that perform newborn screening today may not be capable of interpreting whole genomes. The process "would have to be superstreamlined," says clinical geneticist Melissa Wasserstein of the Albert Einstein College of Medicine.

In the United Kingdom, by contrast, much of the infrastructure is already in place. Thanks to the 100,000 Genomes Project, a study that over the past decade used sequencing to diagnose or treat patients with rare diseases, the country already has a research database and seven laboratories that offer whole-genome tests within the National Health Service.

The U.S. health care system would also need to provide genetic counseling and possibly treatment to families who receive alarming sequencing results. "Our health care system is already overwhelmed with the conditions currently tested for with standard newborn screening," Powell says.

For now, U.S. researchers are pushing ahead with demonstration projects. Starting next year, for example, researchers plan to seek parental consent to screen as many as 20,000 North Carolinian newborns for 100 or more genetic diseases by using a DNA test that only sequences specific genes. Wasserstein heads a study called ScreenPlus that over 5 years will test 175,000 babies born at hospitals in ethnically diverse New York City neighborhoods for 14 severe disorders not on the standard screening list. One goal is to see whether the estimated 20 to 40 babies with the diseases have better health outcomes than those diagnosed later. The project will also ask parents for their views on newborn screening, including the use of genomewide sequencing. That input "will hopefully inform how to roll out newborn whole-genome sequencing in a sensitive way," Wasserstein says.

Lauren Stetson says she understands the high stakes. Newborn genome sequencing "has a gravity and weight to it," she says, because it can deliver life-altering news. But the information is important to have. "I want to be part of it. We want to sequence Cole," Cora's 1-year-old brother. "I was like, Dr. Green, I have another one!"

But she cautions that treatment must be easy to find after newborn sequencing. When she and her husband learned Cora's genetic results, they were immediately referred to a genetic counselor and a

specialist in biotinidase deficiency. "The doctors, the information was all lined up for us. It made all the difference in the world," she says. If newborn sequencing "does become commonplace, the support system needs to be there."

See more on the human genome in our special issue.

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