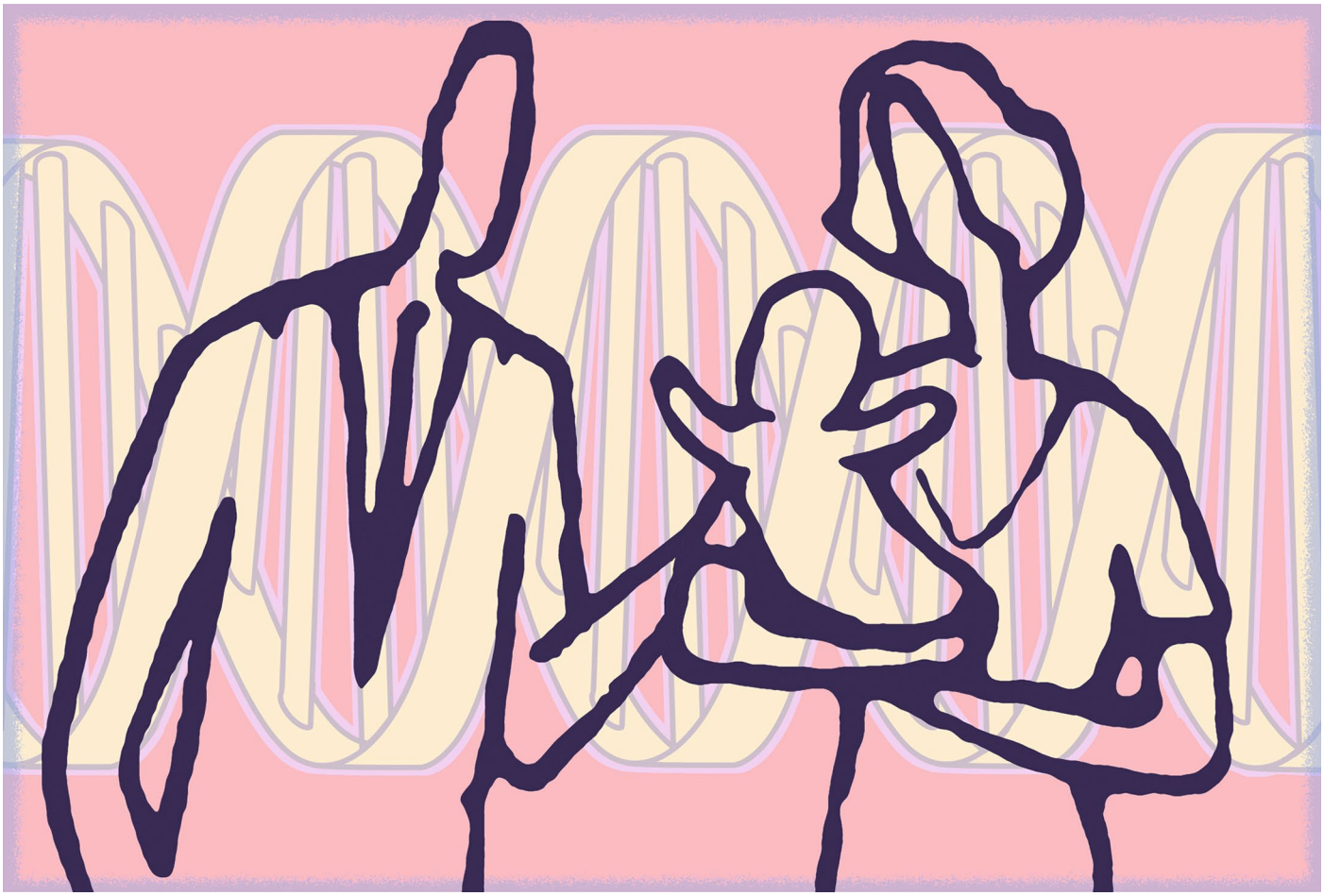

Credit: Westend61 GmbH / Alamy Stock Photo

Baby's first genome

Whole-genome sequencing may be the fastest way to diagnose rare complex diseases, but should it be incorporated into healthy newborn screening?

Caroline Seydel

In January, a team at Stanford University set a new record by sequencing a human genome in just 5 hours and 2 minutes. Among the 12 patients whose genomes they sequenced were those of a 3-month-old experiencing seizures and a 13-year-old with myocarditis. In both cases, the genetic diagnosis helped the families obtain timely treatment. Stanford plans to offer ultrarapid sequencing to patients in intensive care units at their hospitals and, eventually, to other hospitals.

Advances in speed, portability and interpretation are spurring new initiatives to expand sequencing's reach, both geographically and functionally. A new program called iHope Genetic Health aims to bring genomic medicine to tens of thousands of patients with genetic diseases around the world, specifically in areas where clinical resources are limited. At the same time, projects underway in the United Kingdom and United States are testing the waters for using whole-genome sequencing (WGS) as a screening tool for healthy newborns—and a lifelong medical reference for families.

But this practice raises a host of ethical questions about exactly what information would be most useful to the families of these babies, what kind of information to share and how it should be presented to a public unfamiliar with nuances of genetic screening.

Going global with genetic screening

The iHope Genetic Health program, recently announced by the sequencing giant Illumina in partnership with the non-profit Genetic Alliance, aims to enable access to clinical whole-genome sequencing in low- and middle-income countries. This is an outgrowth of an Illumina program, iHope, which since 2016 has sequenced samples from over 1,000 children and their parents to diagnose genetic disease at 24 sites in 9 countries, including the

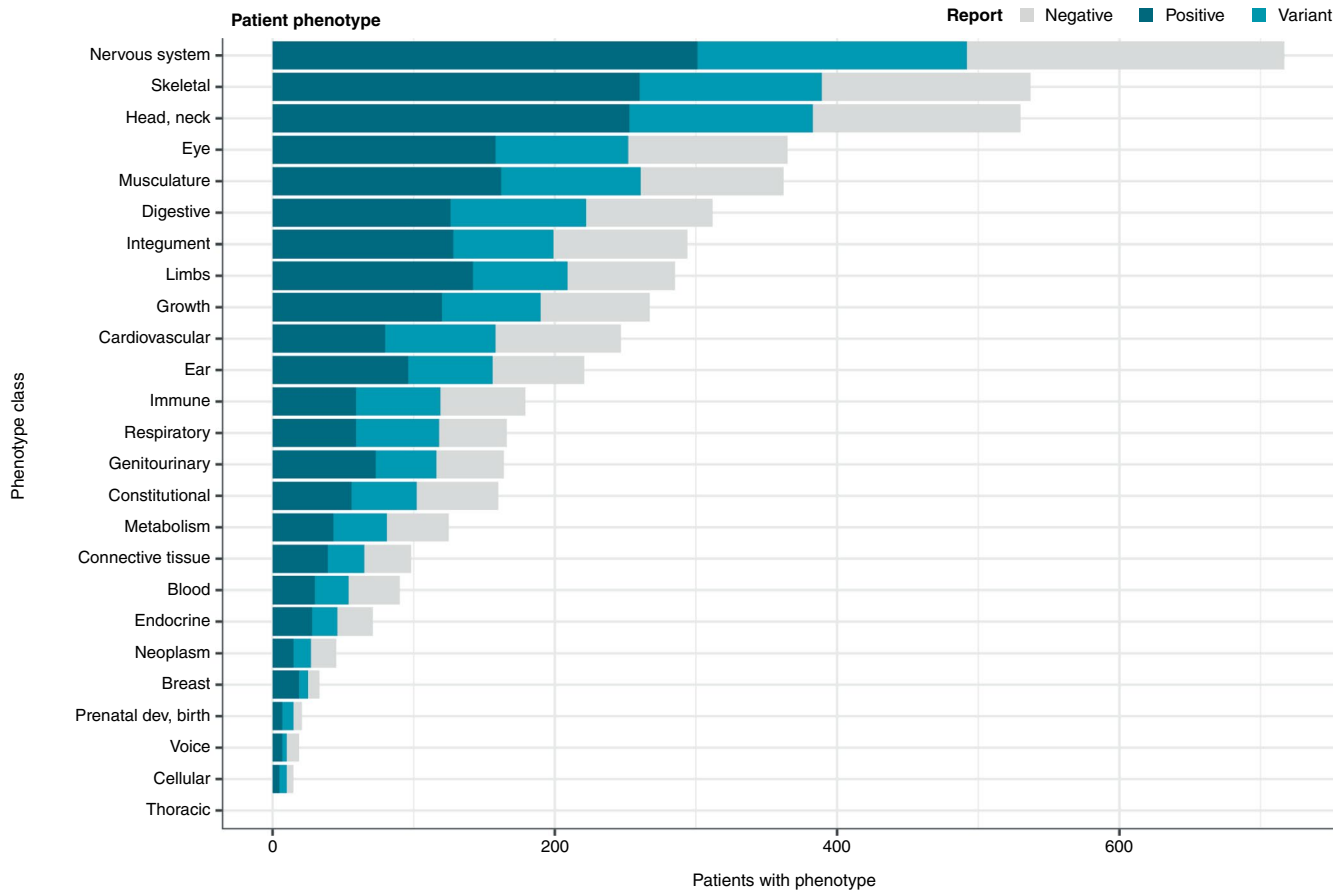

Fig. 1 | Cohort characteristics. Illumina's iHope program sequenced the genomes of over 1,000 newborns with a genetic disease from low-resource countries. The graph shows the breakdown by phenotype. "Negative" indicates no genetic findings; "positive" indicates a pathogenic or likely pathogenic finding that is likely and/or confirmed to be explanatory of the condition; "variant reported" indicates that a variant of unknown significance was reported back that has suspected clinical relevance. Source: Illumina.

United States, Mexico, Peru, Ghana and the Democratic Republic of the Congo. At the 2021 American Society of Human Genetics meeting, iHope reported diagnostic findings in 40% of patients, nearly two-thirds of whom experienced a change of disease management thanks to the new diagnosis (Fig. 1).

Whereas iHope was run entirely by Illumina, Genetic Alliance heads the new effort, with materials and equipment donated by Illumina and other corporate partners. Julia Ortega, who ran the daily operations of the iHope program at Illumina, joined Genetic Alliance in January 2022 to helm iHope Genetic Health. "We quickly realized that we wanted to scale it, and this is how iHope Genetic Health was born," Ortega says. The clinical report provided by iHope was a major step forward, but Ortega says she soon realized that families would benefit from more help connecting with specialists, finding treatment options and getting involved in the rare disease community.

Illumina has pledged $120 million in equipment, reagents and software over the next five years to Genetic Alliance, who has committed to deploying at least a third of this in Africa. Ryan Taft, Illumina's iHope lead and vice president, scientific research, compares the project to the spread of cell phones in regions of Africa that had never developed landlines. Through iHope Genetic Health, he says, resource-limited communities may be able to forgo conventional genetic testing and jump straight to genome sequencing.

One might ask whether diagnosing rare genetic diseases is a top public health priority in countries where malaria, HIV and other infectious diseases remain pressing problems. Ortega points out that worldwide some 250–300 million people have rare diseases. "Collectively, they're not rare," she says. "HIV has around 40 million, and malaria has about 200 million. This surpasses those numbers, and it also requires the same type of imperative to find solutions and treatments."

In addition to Illumina, iHope Genetic Health is working with other technology partners to build out the patient support and logistics components. Site selection is underway, and Genetic Alliance has released a request for information, to be followed by a request for proposals to determine how the resources will be awarded. "We can't just give out genomes and then leave —that's not a solution," says Ortega. The key to making the program successful, she says, will be to build networks within the local communities, both patients and clinicians, to understand how they define their needs.

Finally, patients will retain ownership of their genetic data and control access to it through a platform called LunaDNA. As part of LunaDNA, participants can find out about research studies they may be eligible for, which could benefit the research community by providing a more diverse collection of genomes. For sharing their genomes, patients receive shares of the company (data are not bought or sold), depending on the securities regulations in their country. "We want to make sure those communities are empowered," says Taft. "The idea is to ensure that the patients are the ones saying yes, you can have access to my data, or not."

Table 1 | Recommended Uniform Screening Panel

Propionic acidemia	Trifunctional protein deficiency
Methylmalonic acidemia (methylmalonyl-CoA mutase)	Argininosuccinic aciduria
Methylmalonic acidemia (cobalamin disorders)	Citrullinemia, type I
Isovaleric acidemia	Maple syrup urine disease
3-Methylcrotonyl-CoA carboxylase deficiency	Homocystinuria
3-Hydroxy-3-methyglutaric aciduria	Classic phenylketonuria
Holocarboxylase synthase deficiency	Tyrosinemia, type I
β-ketothiolase deficiency	Primary congenital hypothyroidism
Glutaric acidemia type I	Congenital adrenal hyperplasia
Carnitine uptake or transport defect	Sickle cell disease, S/S genotype
Medium-chain acyl-CoA dehydrogenase deficiency	β-thalassemia
Very-long-chain acyl-CoA dehydrogenase deficiency	Sickle cell disease, S/C genotype
Long-chain L-3 hydroxyacyl-CoA dehydrogenase deficiency	Biotinidase deficiency
Cystic fibrosis	Severe combined immunodeficiencies
Classic galactosemia	Mucopolysaccharidosis type 1
Glycogen storage disease type II (Pompe disease)	X-linked adrenoleukodystrophy
Hearing loss	Spinal muscular atrophy due to homozygous deletion of exon 7 in SMN1

Source: Health Resources and Services Administration https://www.hrsa.gov/advisory-committees/heritable-disorders/rusp/index.html

"I was excited to see the announcement [about iHope Genetic Health]," says Gregory Costain, clinical geneticist at the Hospital for Sick Children in Toronto. Although it remains to be seen how exactly the program will support patients, providers and families, Costain says that it potentially could address global inequities in access to genomic medicine. "If the genetic information from one of these tests is paired with empathic genetic counseling and some context, I think that these results have the potential to do good."

Sequencing gains steam in the clinic

However, even in wealthy countries, WGS is not yet a universal component of routine healthcare. Payers have been slow to embrace clinical genome sequencing, although more and more evidence is emerging that sequencing can both save money and improve patient outcomes. The National Health Service (NHS) in England leads the pack, having recently announced its intent to become the first national health care system to offer WGS as part of routine care for patients, particularly children, who have cancer or are suspected of having a rare genetic disease.

In the United States, the Rady Children's Institute for Genomic Medicine conducted a study of 184 newborns, funded by California's Medicaid program, to evaluate the clinical and economic effects of rapid WGS for critically ill children in intensive care. The study, called Project Baby Bear, published its findings last September, showing that rapid WGS saved an average of $12,041 to $15,786 per child's genome sequenced, compared with the $9,492 per child cost of the procedure, for around $1.2 million net savings. Similarly, Florida's Project Baby Manatee enrolled 50 critically ill babies and children, and it reported a return on investment of $2.88 million. In September 2021, Michigan's Medicaid program became the first to cover rapid WGS for critically ill infants up to age one, and Medicaid in California followed suit in January 2022. And in March 2020, Blue Shield of California became the first private insurer to cover rapid WGS for sick children, from birth through age 18. "It's difficult to get a genome clinically, because insurance companies call it 'research' and they don't want to cover it," says Jerry Vockley, chief of Genetic and Genomic Medicine at University of Pittsburgh Medical Center Children's Hospital. "But that's only pertinent for outpatient procedures, because inpatient care is paid by the hospital. So if the hospital wants to say it's too expensive, it's up to me to convince them." Different hospitals are more or less receptive to adopting whole-genome sequencing, he says. "Our hospital administration is very receptive to new things, as long as we're providing them documentation as to why we're doing it, how we're doing it and what the impact is on the bottom line."

Making genome sequencing routine could help increase equity for patients who would not otherwise be recommended for genetic testing. The SeqFirst project, a research collaboration between the University of Washington, GeneDx and others, performed rapid whole-genome sequencing for 97 patients in the NICU. In 51 cases, sequencing provided at least a partial explanation for their symptoms. Only 35 of these patients had been referred by the NICU team for genetic testing, however, suggesting that the conventional workflow is missing a substantial fraction of patients who could benefit from genetic information. "Moreover, when we look at what we call 'self -identified or provider-assigned racial construct,' or SPARC, we see that many of the kids in whom a genetics consult was not sought but who had an explanatory variant were non-white," says Michael Bamshad, chief of genetic medicine in the pediatrics department at University of Washington, who led the study. "That's one of the other reasons for pursuing SeqFirst. We know that access in general to sequencing for those kids who deserve to be offered sequencing is low. But it's even lower in under-represented minority communities."

In China, the Children's Hospital of Fudan launched a neonatal sequencing project in 2016 with the goal of performing focused medical exome sequencing or whole-genome sequencing on 100,000 critically ill babies by 2021. So far, they have enrolled 30,000, and the project has been extended to 2025. In addition to establishing a standard workflow for sequencing in the natal intensive care unit (NICU), the project aims to create a Chinese neonatal genome database that can be used to create more effective panel tests for rapid genetic testing of babies with unknown illnesses. Wenhao Zhou, the lead investigator on the project, says the project will only enroll patients in the NICU, not healthy babies. Although WGS for newborn screening seems "more feasible than ever," Zhou wrote in an e-mail, "this prospect raises economic, ethical and even legal issues that need to be discussed and fully addressed" before offering the procedure to parents.

From diagnosis to screening

In the United States and United Kingdom, however, studies are underway to explore the feasibility of genome sequencing for healthy newborn screening. The rationale is that sequencing can identify rare diseases before symptoms arise, shortening the diagnostic odyssey and allowing doctors to initiate treatment or other interventions, such as a specialized diet, before permanent damage occurs. This year, Genomics England and the

NHS are launching the Newborn Genomes Programme, which aims to sequence 200,000 newborns to test for childhood-onset genetic diseases. "I'm excited to see such an ambitious effort," says Costain. "I think it has the potential to answer a lot of the questions that until now, we've been debating back and forth as a field, but we have not had any strong evidence to go on."

The overarching question is whether genome sequencing provides substantial medical benefits over conventional newborn screening. The United States has a robust newborn screening program that uses tandem mass spectrometry to test for 30–70 different conditions, depending on the state. By comparison, the United Kingdom screens infants for just nine conditions. In either case, these conventional tests cover only a fraction of known treatable genetic diseases.

"We are missing the opportunity to address an increasing number of treatable conditions," says Robert Green, a medical geneticist at Brigham and Women's Hospital and professor at Harvard Medical School who runs the Preventive Genomics Clinic at Brigham and Women's Hospital and co-founded Genome Medical. He points out that it can take months or years to get new conditions added to the Recommended Uniform Screening Panel (RUSP), a list maintained by the US Department of Health and Human Services (Table 1), and even then, not every state will add the condition to its newborn panel. "That process is working great for the 35 conditions that are on the RUSP," he says. "A few states have expanded it to 60. But it's not working well nationwide because there are more and more conditions for which treatments are getting discovered," but families can't seek out those treatments unless they know the baby carries the disease mutation.

The BabySeq study, co-led by Green and Alan Beggs of Boston Children's Hospital, set out to evaluate screening-by-sequencing in a randomized clinical trial. Among 127 apparently healthy newborns and 32 who were in a NICU, all of whom received exome sequencing, the sequencing identified childhood-onset disease-associated variants in 10 well-nursery newborns and 5 in the NICU, none of which was predicted by the clinical or family history.

In the United Kingdom, upon the request of England's chief medical officer, an international group of researchers evaluated which genes and conditions a newborn program should screen for. "As we started looking into treatable conditions, we kept finding more and more," says David Bick, a physician formerly of HudsonAlpha Institute for Biotechnology in Huntsville, Alabama and clinical advisor to what was to become the UK's Newborn Genomes Programme. To keep track of them all, Bick created the website http://Rx-genes.com, which catalogues the available data on genetic diseases and their treatments. So far, he says, the site includes more than 700 treatable genetic diseases. Some are adult-onset conditions, but many are diseases for which prompt intervention could minimize or avoid severe symptoms in childhood.

Though sequencing can capture more conditions in a single test, it still misses some conditions that would be caught by the current biochemical analyte screening tests, where those are available. "Conventional, state-mandated newborn screening has been by any measure a public health triumph," says Green. "We should never be suggesting that sequencing can in any foreseeable future replace newborn screening. We can only suggest there might be opportunities to expand it."

This is one reason the UK's strategy seems misguided, says bioethicist Lainie Friedman Ross of the University of Chicago. "It's fascinating to me that they're looking at the genetics, rather than starting with tandem mass spectrometry," Ross comments. "There's a lot more they could be testing for using technology that's already in use successfully in many countries, rather than going the genetic route." Although genome sequencing can screen for hundreds of potential disorders in one test, Ross remains skeptical of how much that benefits an asymptomatic newborn. "You can find genetic variants, but if we don't know their significance, we can create 'worried well'," she says. "They're waiting for the other shoe to drop, but sometimes it doesn't drop. Until we understand a lot more, I don't think we're ready to be doing it in the newborn period."

WGS isn't yet part of routine newborn screening in the United States, but it is available for those who seek it out and are willing to pay for it. ViaCord, PerkinElmer's cord blood banking business, offers parents the opportunity to sequence their newborn's entire genome, at a cost of $1,900. When reporting the results, the company follows the ethical and sequencing interpretation guidelines laid out by the American College of Medical Genetics & Genomics (ACMG), says Madhuri Hegde, senior vice president and CSO, Global Lab Services, PerkinElmer. Parents can choose which information they want reported back; they can choose to receive only diagnostic findings or include information about the child's carrier status and pharmacogenetic findings. Hegde stresses that the service is not direct-to-consumer, but is ordered by a physician and includes pre- and post-test genetic counseling for the family. "At times, the parents will also get their genome sequenced, and in some situations extended families have also got sequenced," says Hegde.

Ross, however, believes that even if they benefit adult relatives, returning genetic results found in children who did not consent to the testing about adult-onset conditions is outside the bounds of ethical medical practice. If adults wish to know their genetic risk of disease, Ross says, they should get themselves tested, rather than using the baby as a means to learn about their own genomes. "Children are vulnerable, and we give information that we don't fully understand and we give it as absolutes," she says. By sequencing the baby's genome before they can consent, "we're taking away their right to make health decisions, particularly where our knowledge is evolving and we may just be creating worry about something that may never be an issue. You might make some very specific life choices based on information that, ten years later, we realize we didn't fully understand."

False positives — or early warning signs?

Interpreting genetic variants isn't always as straightforward as measuring levels of a blood analyte. Without symptoms, geneticists must consider a variant's penetrance — the percentage of people who have that variant and go on to develop the disease. Some variants have complete penetrance, whereas in other cases, a variant leads to disease only sometimes. For instance, 55–72% of women who inherit a harmful *BRCA1* variant will develop breast cancer before age 70.

"Genomics is a process that challenges the distinction between diagnosis and screening," says Josephine Johnston, a bioethicist with the Hastings Center who served on the Ethics and Policy Advisory Board of the Newborn Sequencing in Genomic Medicine and Public Health Consortium. "Now you have a technology that promises to be able to prediagnose people before they get sick. That's the vision of personalized medicine, but there are lots of reasons why the vision is a bit more complicated to actualize."

While there are obvious benefits to earlier diagnosing of serious health problems, Johnston says, screening by its nature will always generate false positives. If WGS is going to be widely deployed for screening, it's essential that families be provided adequate education and counseling to understand the results that they receive. In a 2018 paper calling for a "nuanced approach," Johnston and the other members of the Ethics and Policy Advisory Board point out that, for many variants, the impact on health is not fully understood. Genomic, epigenetic, and environmental factors

influence gene expression — factors that can't be evaluated from sequencing results.

Despite these challenges, Green says that knowing what variants a child carries can still provide useful context as the baby grows up. "The way I think of it, these unanticipated findings are risk stratifiers," he says. For instance, variants discovered in some of the BabySeq participants led to further testing that could provide early warning of possibly dangerous conditions later on. He cites a case where a baby was carrying an elastin mutation, which is associated with supravalvular aortic stenosis, a narrowing of the aorta. The baby's heart sounded normal, but follow up testing revealed a very mild narrowing of the aorta. "A perfectly healthy baby, no heart sound abnormalities, nothing," Green says. Because the mutation was discovered, doctors did an echocardiogram and found a very mild narrowing of the aorta. "Mild, but definitely abnormal," Green says. "Now if that baby goes out, and maybe at age five or six starts fainting on the playground, you have a very different prior probability of understanding what's going on than you would if you did not have this information."

It can also work the other way around. Instead of collecting variants at birth and watching for symptoms, the genome can be kept on file to be referenced if symptoms arise later on. This approach can lower the threshold for flagging variants, says Vockley. Variants are categorized as pathogenic, likely pathogenic, and "variants of unknown significance," or VUS. (A single gene can have multiple VUS.) "If you just say, 'tell me everything,' you're going to get 20,000 variants," Vockley says. "There are maybe 500 genes you can look at for immediately actionable things in the newborn period. Now you've reduced your number of VUS from 20,000 to maybe less than 2,000." If symptoms arise later in life, he says, they can be cross-referenced with the list of VUS that have been compiled, and that can speed up a diagnosis. "So sequencing by itself is not the answer," Vockley says. "It's part of the platform."

Even if no troubling symptoms arise, keeping the genome on file could be useful for what Vockley calls age-appropriate genome screening. Just as the pediatrician does blood tests and checks for developmental markers at each visit, the genome could also be checked for variants that might be relevant at that stage. "If you don't find anything in the newborn period, just put it aside, and then you look at it at intervals over the course of a lifetime," he says. "Say you have a family history of colon cancer, and the youngest person in your family was diagnosed at age 40. Current guidelines will tell you that you should start having your colonoscopy 10 years before that. So, at age 30, you look at your genome to see if you've got any colon cancer genes. And that's something that now is relevant to you at that age."

The stress of knowing — or not knowing

Finding out that your perfect newborn carries potentially dangerous genetic variants could understandably cause parents stress and anxiety, and the BabySeq study tried to address this by measuring psychosocial effects. They found that having information about a potential disease mutation caused no significant increase in anxiety, health spending, or harm to the parent–child relationship, although there was some increase in spending. However, the BabySeq population was self-selected, and only 8% of the families offered the opportunity to participate opted in. "In the 8% who volunteered, they found no harm," Ross says. "Maybe the other 92% were smart enough to know they might have been harmed by it."

Also, the study was small, only 519 parents. "While data has shown that families are resilient, that shouldn't discount the potential anxiety that complex genetic information may cause," says Aaron Goldenberg, a bioethicist at Case Western Reserve University. "We need to study a larger population to really understand whether or not that exists."

As part of the planning process for the Newborn Genomes Programme, NHS England conducted an extensive public dialogue to understand the public's concerns and wishes with regard to newborn sequencing. From that public engagement, Bick says, the NHS developed a few core principles for how it would conduct the genome sequencing study. First was a commitment to transparency, so that all decisions are being made in a public way, and including members of the public on all committees throughout the process. Second, the ethics committee is integral to every step of the project, to make sure that issues of ethics, consent and patient engagement are considered throughout.

"Population-scale initiatives like this have always relied on some degree of public trust," says Costain. "We are at a critical time where trust in medicine and in the healthcare system is being challenged in many quarters."

Based on the public feedback, NHS states that they will not report on any adult-onset conditions, but don't explicitly rule out looking for these variants later on. That's not always as simple as it sounds. BabySeq also pledged to report on only a certain slate of actionable, childhood-onset genetic diseases. Then they discovered one of the infants was carrying a *BRCA2* mutation. "We found ourselves in an ethical dilemma, because we thought that mother ought to know that she was at risk for breast cancer," said Green. The BabySeq team went back to the institutional review board and received permission to amend the study protocol to avoid creating "moral distress" when laboratory personnel learn something potentially actionable that they cannot share with the parents. The amended protocol required parents to consent to receive results for an additional list of genes: the ACMG 59. The ACMG considers these genes to be highly penetrant and medically actionable, and they recommend that incidental or secondary findings discovered by clinical sequencing be returned to the patient.

After sequencing, what next?

Whatever variant information is ultimately deemed appropriate to share with the family, Goldenberg points out that not everyone may have access to follow-up care after the variant is discovered. "Equity matters," he says. "What I fear is that screening programs may assure universal access to screening, then not adequately address equity beyond screening." For instance, sequencing may return a result that warrants follow-up testing to confirm, or maybe there are interventions that should start before symptoms arise. If families can't afford these next steps or lack access to transportation, child care, or other support, it calls into question the value of the screening test as a public health measure.

The newborn screening program in the United States was created as a way to improve health equity, Ross points out. In theory, screening every child would provide a safety net for families who lack access to high-quality healthcare, but in practice, it hasn't worked out that way. Take the newborn hearing screen, for example. "The outcomes show a lot of socioeconomic disparity," Ross says. "Rural families aren't getting the hearing aids and the adaptive resources that the children need as quickly as families who have resources and can efficiently navigate the system. So to the extent that we believe that newborn screening should be about improving equity in this country, we need to focus on that. Screening for conditions which we're going to have to follow over a lifetime — and we're not even sure it's ever going to present — isn't necessarily where I want to be putting my resources." ❐

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