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Democracy Dies in Darkness

Opinion Too many treatable diseases go unnoticed. This could change that.

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The day a young boy ends up in the hospital with liver failure is not the best time for his parents to find out they might have prevented the problem by giving him a zinc supplement from an early age. The day a small girl has a seizure that results in irreversible brain damage is the wrong time to learn she has a genetic mutation that, if diagnosed at birth and managed with a high-fat diet, would not have meant lifelong intellectual disability. And no one wants to find out that a baby who died in her crib could have been saved with a DNA test and an inexpensive medication.

Yet, most people in the United States today who have Wilson's disease, a rare genetic condition that overloads the body with copper, poisoning the liver; glucose transporter deficiency, which triggers seizures; or Long QT syndrome, which causes sudden infant cardiac arrest, get a diagnosis only after something goes seriously wrong. Hundreds of treatable genetic diseases go unnoticed for years — not because they cannot be diagnosed, but because newborn screening for them is not routine in the United States. If biomedical breakthroughs are to benefit the millions of children afflicted with rare diseases, genetic testing of babies needs to expand.

This is an urgent problem for families now, but its solution could also pave the way for a future in which doctors can treat many more rare, intractable diseases. By screening newborn genomes for currently known genetic diseases, patients and scientists could gain insights that lead to the treatment and prevention of thousands of illnesses that currently lack cures.

Today, most families with children who suffer from rare diseases embark on what researchers and patient advocates call "the diagnostic odyssey." The average time from the appearance of mysterious symptoms to getting an accurate diagnosis for a rare disease is, by some estimates, about six years — a time during which children get no potentially lifesaving care and families know too little to participate in policy advocacy or clinical trials that might bring forth new treatments. Whether a child gets tested for a genetic disorder often depends on whether a doctor recognizes the signs of a rare disease and if families can afford extensive tests when insurance doesn't foot the bill.

I know firsthand the frustration this causes. My sister's youngest child, Ayoni, an ebullient 7-year-old, was diagnosed just before her fifth birthday with a rare disease called Prader-Willi syndrome, which stunts her growth and will make her hunger insatiable. Had she been diagnosed at birth as some newborns are, she could have benefited from years of growth hormone injections that would have supported her cognitive development and muscle mass.

Rare diseases fall through the cracks at every stage of the biomedical research pipeline and in every corner of the health-care system. Researchers and patients are left doing what Anna Greka, a professor at Harvard Medical School, calls "hand-to-hand combat" with some 8,000 rare diseases, each with its own unique symptoms and genetic mechanics. Whether any one of them gets attention often depends on the power and persuasiveness of its patient advocacy group — the cystic fibrosis community's successful push for diagnosis and therapies is a preeminent example — and whether an academic researcher or biotech company takes an interest in helping a small number of patients.

Taken as a whole, rare diseases are common, afflicting more than 30 million people in the United States and more than 300 million globally. Researchers such as Greka are looking for common threads among them, to categorize them so they can be studied and, ideally, treated more efficiently.

One crosscutting tool is already here, but not being used to its potential: genomic sequencing. It can uncover known rare diseases in patients and also reveal new ones in the population. DNA sequencing can help doctors diagnose treatable diseases and help researchers discover patterns in the data that match incurable illnesses with genetic mutations. The more widespread newborn genome sequencing becomes, the better the data — and the easier it becomes to study the genetics of thousands of diseases.

Currently, the U.S. government recommends screening newborns for only 63 conditions. Even for this limited set, states decide which ones are actually screened for within their borders, so a child's chances of being accurately diagnosed at birth could depend on whether the family lives in Billings or Boston.

But a pioneering study underway in New York City that is sequencing the genomes of 100,000 newborns to screen for 238 treatable conditions points to the future of rare-disease diagnosis. Babies enrolled in the study are being screened for Wilson's disease, glucose transporter deficiency, Long QT syndrome and other conditions, says Wendy Chung, the head of pediatrics at Boston Children's Hospital who is leading the research. Parents of children in the study have the option to also screen for 100 additional neurogenetic conditions that could be helped by early physical and speech therapy or seizure treatments.

Getting a disease added to the government's universal screening list, even in cases where a cure exists, right now is a painstaking process. Patient advocates recently got a test for spinal muscular atrophy added to the list after a roughly two-year effort. Chung calls this "remarkably quick." These tests are finally being administered to newborns across most of the country, which means more afflicted children can be treated earlier to prevent the loss of motor function that results in death.

As scientists rapidly discover new genetic diseases, the gap between which ones are being diagnosed at birth and which ones *can* be diagnosed widens. And as more advances are made in treating once-deadly genetic diseases — consider the new gene therapies for Duchenne muscular dystrophy and spinal muscular atrophy — failure to diagnose becomes a greater tragedy. But routine genomic screening would make it technically feasible to add hundreds of diseases to the screening list.

And what of the thousands of rare diseases that still lack treatments? Failing to screen for them is tragic, too, because it keeps patient groups from advocating for research into cures, taking part in clinical trials and demonstrating to biotech companies that there is a market for experimental therapies. "If we could change the diagnostic odyssey, we could actually change the power balance of patients in the health-care system," said Tania Simoncelli, who as vice president for science in society at the Chan Zuckerberg Initiative supports a network of rare disease patient organizations.

In the absence of universal screening, the children who get treatment for rare diseases tend to be those whose families can afford and have access to genetic testing. "If you are living in a rural community, or if you don't know how to navigate the health-care system because of language or other barriers, you may go year after year without a diagnosis or with a misdiagnosis," Simoncelli said.

Newborn genome sequencing won't entirely ease the diagnostic odyssey faced by patients with rare diseases. (Some syndromes, including my niece's, are best diagnosed with narrower genetic testing, which requires greater recognition of symptoms by doctors. Others are not caused by singular gene mutations.) But even in mysterious cases, it could go a long way by ruling out diagnoses.

It is expensive: In the New York study, the cost per child is $1,000. But DNA sequencing to diagnose newborns could end up saving much more money — especially if done for babies who are sick. In a study funded by the state of California called Project Baby Bear, researcher Stephen Kingsmore found that sequencing the whole genomes of 178 infants hospitalized in intensive care saved $2.5 million. The screening yielded a diagnosis for more than 40 percent of the babies and improved care for almost one-third. Later this year, the United Kingdom is launching a program to screen 100,000 babies' genomes for rare diseases, driven by the potential to improve care and research.

In the United States, a federally funded mandate to screen infant genomes, allowing families to opt out, or widespread state adoption of routine genetic screening could lead to a future where fewer families have to live with the scourge of rare diseases and fewer patients die or become disabled. Chung suggests states might repurpose coronavirus testing labs to do genetic sequencing.

Some people fear a future of widespread genomic sequencing; they're not wrong to worry about the potential for misuse of information about individuals' predisposition to disease. Researchers are right to take precautions to secure patient data, but patients themselves and the broader public also need to remain vigilant about privacy and the ways that data can be legally used. It's critical to monitor political attempts to revise the 2008 law that bars employers and health insurers from discriminating based on people's genetic information, and to expand those protections to more spheres.

Newborn screening also presents an ethical conundrum for parents: They have to decide on behalf of their children whether to risk creating a record of their genomes and, in some cases, facing a devastating diagnosis.

The danger of not learning more about human genetics, however, might be worse. For those of us who have seen a child suffer from a rare disease, the most urgent concern is to help children survive, to find and treat those whose suffering can be prevented, and to shorten the path to new cures.

This column is the first in an occasional series on the future of rare diseases and what it will take to unlock better treatments.