MICHELE COHEN MARILL SCIENCE 03.09.2020 03:00 AM

Ultra-Fast Genome Sequencing Could Save the Lives of Newborns

Whole genome tests can help identify the cause of a baby's mysterious illness. But ethicists say it's still too soon to use them for all infants.

PHOTOGRAPH: MARVIN JOSEPH/THE WASHINGTON POST/GETTY IMAGES

Maverick Coltrin seemed like any other newborn when he first came home from the hospital, wearing his beanie cap with bear ears and blue-and-gray onesie and following the typical around-the-clock cycle of sleeping and breastfeeding. But within a couple of days, his parents noticed something was off. At 6 days old, Maverick completely stopped feeding. His arms and legs would stiffen and then release, the spasms punctuated by his cries.

His parents rushed him to Rady Children's Hospital in San Diego, where EEG monitors recorded that he was having as many as 30 seizures an hour. Doctors scrambled to find the

cause. Anti-seizure medicines didn't work, so he was sedated to stop the damage to his brain. His organs started to fail, and his skin turned a dusky blue. His mother, Kara Coltrin, walked into his empty nursery at home and cried.

So when doctors from Rady's Institute for Genomic Medicine asked for permission to sequence Maverick's genome as part of a clinical trial of ultra-rapid sequencing for newborns who are critically ill from an unknown cause, Maverick's parents didn't hesitate. The doctors cautioned that they couldn't guarantee that they would pinpoint a genetic disorder or, if they did, that it could be treated. They gave the standard caveat about genetic testing—that identifying a genetic disorder could affect Maverick's eligibility for life insurance someday. But even if the sequencing didn't help him, his participation would contribute to a study that could benefit other babies. "Obviously, the pros outweighed the cons manyfold," his mother says. "We just wanted his pain to stop."

COURTESY OF KARA COLTRIN

Within 36 hours, the Coltrins had an answer: Maverick has pyridoxine-dependent epilepsy, caused by a rare mutation of the ALDH7A1 gene, which codes for the enzyme antiquitin. By giving him high doses of vitamin B6 and controlling a couple of amino acids in his diet,

doctors stopped the seizures. Maverick, now 2 years old, runs around like a normal, rambunctious toddler. He has hit all his developmental milestones, although they have been somewhat delayed. He hasn't had a seizure since his treatment began. "Every once in a while, I think back on him being dusky blue and super skinny and hooked up to all these tubes," says Kara Coltrin. "I look at him and it's hard to believe that happened to him. People who see him on a normal basis would never know he was ever sick."

The technology that saved Maverick's life stretched the limits of bioinformatics, returning results far sooner than is typical for genetic testing. Rapid sequencing typically takes about seven days for a preliminary diagnosis, while Rady completes ultra-rapid sequencing in three days or less. (In 2018, Rady set a Guinness World Record by sequencing a baby's genome in 20 hours and 10 minutes.)

But now ultra-rapid sequencing is moving from an investigational tool to a standard of care. Blue Shield of California is the first insurer to cover rapid and ultra-rapid sequencing of babies and children who have life-threatening and unexplained medical conditions. Since the new policy began in July 2019, 28 babies or children in California have received the testing through Blue Shield, which is just beginning to promote the new coverage.

Blue Shield expects that 250 to 500 newborns will be eligible for the whole genome sequencing each year, which represents about 10 percent of their insured babies treated in neonatal intensive care units in California. Company executive vice president Terry Gilliland said he will encourage other Blue Cross and Blue Shield plans around the country to adopt a similar policy. "When you think about all the pain and suffering families go through with sick babies, this is going to be an enormous benefit," he says.

Medi-Cal, California's Medicaid program for low-income children and adults, is also considering coverage of the new technology after funding a $2 million pilot project that screened 154 newborns at five hospitals over two years. Of the babies who were screened, 66 received a diagnosis, or 43 percent. Based on the results, physicians changed the treatment for 45 babies, or 29 percent—including for some babies who weren't diagnosed with a genetic condition, says David Dimmock, senior medical director of the Rady Institute for Genomic Medicine, which conducted and analyzed the sequencing. Dimmock and his colleagues estimated that the sequencing conducted in the pilot project, dubbed Project Baby Bear, led physicians to order 103 fewer diagnostic tests and avoided 400 days of hospitalization, including dozens of surgeries and other procedures.

COURTESY OF KARA COLTRIN

"If you take children where there is a suspected genetic disorder, and you do rapid whole genome sequencing and return the results within part of a system of care, you actually save more money on health care costs than you pay for sequencing," says Dimmock. "Oh, and by the way, we saved a kid's life."

Timing is critical because some disorders, such as the one that caused Maverick's seizures, can lead to brain damage. "We feel we have to continue to push the boundaries of doing this faster. We probably would have had a better outcome with Maverick if we'd known sooner," says Dimmock, who notes that Maverick had seizures for about three days before he was diagnosed. On the other hand, Dimmock says, "he probably would have been dead within a couple of days if we hadn't made this diagnosis."

Still, this isn't a first-line test. A baby with severe symptoms with no obvious cause, such as an infection, will likely get a targeted screening test for more common genetic disorders. If that is negative, and doctors suspect a genetic cause, the Blue Shield policy authorizes them to move forward quickly with whole genome sequencing.

In one case in the Medi-Cal pilot project, a newborn girl had a life-threatening irregular heartbeat, but cardiologists didn't know the underlying cause. Within two days, sequencing detected Timothy syndrome, a rare genetic disorder that affects the heart. Doctors were able to target a medicine to control the heartbeat and then implant a pacemaker. "That's the kind of power these tests can provide," says Henry Garlich, director of health care value solutions and enhanced clinical programs at Blue Shield.

Ultimately, as many as 40,000 newborns each year in the US may be candidates for this whole genome sequencing to find a diagnosis, Dimmock says. Even in cases in which the sequencing doesn't uncover a diagnosis and the baby dies, the testing adds value, he says. "Knowing something treatable wasn't missed makes a huge difference for the parents and providers," he says.

Saving the lives of newborns afflicted with mysterious disorders provides a compelling and even heroic case for advancing the science of genomic sequencing of babies. But the technology used to diagnose an urgent case also can be used to foresee potential future health problems, a more ambiguous realm. Whole genome sequencing of healthy babies could detect some rare genetic disorders that haven't yet caused symptoms—or may never manifest. It could be used in precision medicine—for example, to gauge how well a child is likely to respond to certain medicines or to identify their risk of developing high cholesterol.

But DNA is not a biological fortune teller. Parents might worry about potential health problems that never arise.

Anticipating that the genomic sequencing of newborns could raise difficult questions, the National Institutes of Health set up an Ethics and Policy Advisory Board when it funded the Newborn Sequencing in Genomic Medicine and Public Health (NSIGHT) project, run by a consortium of research institutions. (Maverick received his test as part of an NSIGHT trial.) The experts weighed the value of detecting genetic variants—those differences associated with symptoms and disorders and those that suggest future health risks. The ethicists recommended whole genome sequencing for sick newborns and some targeted sequencing as a part of newborn screening. For example, some states already use DNA tests to enhance detection of cystic fibrosis along with the blood tests used in routine newborn screening for dozens of metabolic and genetic diseases.

But the ethicists called broader use of genomic sequencing of babies "premature," lacking enough evidence that the benefits outweigh the possible drawbacks, including confusion or anxiety over ambiguous or even misleading results. They advised against direct-to-consumer tests that enable parents a cheap and easy way to swab their baby's mouth and test for genetic conditions and genetic differences in their response to medications. Those tests might not be as reliable and definitive as parents may believe, the ethicists concluded.

"You don't screen unless you have a really good test that has a clear outcome, and you don't screen unless you have a very serious condition in which, once you discover the condition, you can change the outcome dramatically," says Barbara Koenig, director of bioethics at the University of California San Francisco and a member of the advisory board.

Robert Green, a medical geneticist at Harvard Medical School and Brigham and Women's Hospital in Boston, aims to build the evidence that genome sequencing can improve the lives of even healthy babies. In a project dubbed BabySeq, Green and his colleagues found a disease-causing gene in one in 10 of the 257 healthy babies whose genomes the BabySeq team sequenced. For example, one healthy baby had a genetic mutation associated with narrowing of the aorta. A follow-up echocardiogram showed a small but distinctive abnormality that had not previously been detected, Green says. Although the baby's heart doesn't require any immediate treatment, it is a condition that could be monitored later in life, Green says.

Green also studied the parents' response to getting genetic results from the project's sequencing. They didn't experience increased anxiety, distress, or problems bonding with their child, he says. (BabySeq did not report findings that were of "uncertain significance," he says.)

For now, Green doesn't advocate replacing the routine blood tests for newborns provided through state public health programs. The current tests have a strong track record of effectively screening the 4 million babies born each year in the US—for example, to detect sickle cell disease or phenylketonuria (PKU), a rare but treatable metabolic disorder. But he envisions a day when parents can opt to sequence their child's genome to learn about future health risks so they can alter their child's diet or take other protective measures. "At the very start of your life, we could start thinking about ways to prevent disease, rather than just respond to it," he says. "Doesn't our entire health care system have to address this sooner or later?"

Perhaps. But for now, health care providers seem ready just to take the first step—harnessing the emerging capabilities of whole genome sequencing to help babies with dire symptoms and no diagnosis.

Updated 3-10-20: This story was updated to reflect the correct spelling of the Coltrin family's last name.

More Great WIRED Stories

- Wikipedia is the last best place on the internet
- Do fans of cartoon porn stars hate (real) women?
- Want to fight climate change? Stop believing these myths
- Michael Bloomberg, the original tech bro
- Uber changes its rules, and drivers adjust their strategies
- 👁 The secret history of facial recognition. Plus, the latest news on AI
- 📱 Torn between the latest phones? Never fear—check out our iPhone buying guide and favorite Android phones