BABY'S FIRST TEST

It is now feasible to test babies for several lysosomal storage disorders, but this goes against the gold standard for screening that was established nearly 50 years ago. The ethical issues raised are forcing a rethink of the way that newborns are screened.

BY SUJATA GUPTA

In January 2005, spurred by the tragic story of a local sports star's young son, the governor of New York State, George Pataki, signed an executive order mandating that every newborn baby is screened for a rare disorder known as Krabbe disease. Pataki's decision effectively turned the state into a laboratory. The experiment entailed testing and then processing samples from millions of babies for this particular lysosomal storage disorder (LSD), and determining how best to follow those who screened positive. It was a massive undertaking, and a test case for the wider issue of how to implement newborn screening in the modern age.

Krabbe disease is caused by a defect in the *GALC* gene, which normally produces an enzyme that helps to make the myelin that surrounds and protects nerve fibres. Babies with the most severe form of Krabbe have trouble swallowing, experience seizures, and quickly lose their sight and hearing. Such children are unlikely to live beyond two years of age.

Pataki hoped that screening newborns for this devastating disorder would lead to early diagnosis and treatment — in this case, a bone-marrow transplant in the first few months of life, before symptoms emerge. Transplants can prolong and improve the lives of those with Krabbe disease. But not everyone with Krabbe develops full-blown symptoms, and transplants are extremely risky. Screening babies for rare diseases that may not develop, and which do not yet have simple, effective treatments, is ethically fraught.

"Many of these conditions may present at different stages of life. So if we start treating early, we can do harm," says Lainie Ross, a physician and bioethicist at the University of Chicago in Illinois. But, she adds, "we can also do great benefit."

Over the past few years, people have grown more comfortable with genetic testing. Some researchers now argue that even when the benefits of diagnosis remain unclear, identifying babies with LSDs serves several purposes, from advancing research into such diseases to connecting the parents of children with rare disorders. At the very least, a diagnosis can save time and heartache later if symptoms start to manifest.

"There is an advantage in knowing the baby has a disorder," says Giancarlo La Marca, head of the newborn-screening lab at the University of Florence in Italy, even if no therapy is available. But testing for it means rethinking decades of 'best practice' in screening newborns.

CLASSIC CASE

In 1961, US physician and microbiologist Robert Guthrie wrote to the *Journal of the American Medical Association* outlining a method to test newborns for phenylketonuria (PKU). Those with the disorder lack the

enzyme needed to break down the amino acid phenylalanine, which then builds up in the blood, where it can cause developmental problems. Guthrie suggested pricking a newborn's heel and testing a small spot of blood for PKU. By identifying affected newborns, the family could adopt a restrictive diet before the onset of symptoms, giving their child a better chance to live a healthy life.

Similar medical screenings quickly became so popular that towards the end of the decade the World Health Organization (WHO) established some guiding principles. Among the criteria were that the disease must have a clear test and an acceptable treatment, and that the cost of finding cases should be weighed against the expense of treating them, often for life. The document soon became the 'gold standard' for determining which disorders to include in universal newborn screening.

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Jennifer Kwon, a paediatric neurologist at the University of Rochester in New York, says that PKU is the classic case for newborn screening. The test is straightforward, the benefits are clear, and the treatment is accessible, even though the diet is difficult to follow. "Those are the disorders we want most to detect in newborns," Kwon says.

HUNTER'S LEGACY

Screening (determined in the United States on a state-by-state basis) now includes dozens of blood, endocrine and metabolic disorders, such as sickle-cell anaemia and hypothyroidism. But conditions such as Krabbe and many other rare diseases are increasingly being considered for screening, despite failing several of the WHO's criteria.

So why did Pataki change the rules on screening? It all began when Hunter Kelly was born on Valentine's Day — his father's birthday — in 1997. The son of the Buffalo

Bills' quarterback Jim Kelly and his wife Jill, Hunter initially seemed healthy, but he soon began crying incessantly and was diagnosed with colic. Over the next few months, his body began to stiffen, and the diagnosis was changed to cerebral palsy. When Hunter began to have trouble swallowing, doctors conducted more thorough tests. At the age of four months, Hunter was diagnosed with Krabbe disease, but by then his symptoms were too severe for a bone-marrow transplant.

Hunter's relatives then created the Hunter's Hope Foundation, a non-profit organization, to raise awareness of Krabbe, to encourage research into the disorder, and to connect affected families. Central to its mission was increasing the early detection of Krabbe by screening newborns. By chance, the timing of Hunter's diagnosis coincided with the rise of tandem mass spectrometry, which makes it possible to test a baby for several rare but related disorders at the same time. This technique allows researchers to identify newborns that have abnormally low levels of the various enzymes implicated in LSDs. Newborns who screen positive then undergo more detailed testing for confirmation.

The foundation's efforts paid off when Pataki added Krabbe disease to the state's newborn screening panel in 2005 — the same year that Hunter died, at the age of eight.

For the families whose newborns screen positive, there have been profound, and often unexpected, consequences. According to a study published by the New York State Krabbe Consortium — a group of neurologists, paediatricians, metabolic specialists and geneticists — the state screened nearly 2 million newborns for Krabbe disease between August 2006 and August 2014.

The screen and subsequent genetic testing identified 51 infants as being at moderate or high risk for the disease. Of these, five seemed to be showing early symptoms, and doctors advised the parents to move ahead with a bone-marrow transplant. One baby, who received a transplant at one month, has age-appropriate language skills but significant developmental delays and cannot walk unaided. A second has severe developmental and motor delays, owing perhaps to a logistical snag that postponed the transplant until the baby was two months old. Two others died shortly after the procedure from complications. The fifth child, whose family opted against transplantation, died at the age of 18 months.

The cohort is too small to draw firm conclusions about the value of the screen and early bone-marrow transplants, says Kwon, who is a member of the consortium. "When you have only done it in four infants, it's hard to know what to make of any outcomes."

But Anna Grantham, director of programmes at the Hunter's Hope Foundation,

DIFFERENT DISEASES

Not all LSDs are the same

A simple heel prick allows doctors to screen newborn babies for a range of conditions.

Four years ago, Missouri began screening for Pompe disease. As with Krabbe disease, most newborns diagnosed with Pompe do not yet show any symptoms. But unlike Krabbe, Pompe can be treated with enzyme-replacement therapy. Although still problematic, enzyme-replacement therapy is much safer than a bone-marrow transplant, making Pompe disease more suitable to include in the screening schedule. Indeed, a federal advisory panel recommends against screening newborns for Krabbe, but is in favour of screening for Pompe.

In general, the United States has been considerably more liberal in expanding the scope of its screenings than elsewhere. Most other countries prefer to focus on LSDs that can be treated pharmaceutically, or with enzyme-replacement therapies. Although they are expensive and do not

provide a cure, enzyme-replacement therapies do seem to be safe and effective for young children.

In Italy, researchers are about halfway through a three-year pilot screening project for three LSDs that can be treated with enzyme replacements: Pompe disease, Fabry's disease and Hurler syndrome. Giancarlo La Marca, a clinical chemist and head of a screening lab at the University of Florence, is hopeful that these three disorders will make it into Italy's mandatory newborn-screening panel at the end of the pilot study.

There is no single solution for all LSDs. "Each disease has to be thought of for the ethical issues that it raises," says Lainie Ross, a physician and bioethicist at the University of Chicago in Illinois. "To lump them together is a little unfair." [S.G.](#)

says that the nationwide statistics tell a more positive story. Across the United States, dozens of babies, mostly the younger, asymptomatic siblings of children with Krabbe disease, have now received transplants.

Grantham tells the story of two brothers from Oregon. The older boy was not diagnosed with Krabbe until 12 months old when he started showing symptoms, at which point he could no longer benefit from a bone-marrow transplant. When his baby brother also tested positive, the boys' parents quickly moved ahead with a transplant. The older child died of the disease at the age of six, but the younger boy remains asymptomatic. Grantham says she has talked to other parents who have similar stories. "These kids

are living," Grantham says. "They're able to speak. They're able to walk. They're able to do all these things that no child with Krabbe can do."

But no one knows if, without the transplant, the younger Oregon sibling would have developed the same severe form of Krabbe disease as his brother. So far, none of the remaining 46 moderate-to-high-risk children in the consortium study are showing symptoms — they are, in essence, patients-in-waiting. Unsure of how to track and treat such individuals, and wary of giving unnecessary, risky transplants, doctors have been taking a wait-and-see approach.

Despite the uncertainties, screening for Krabbe disease is forging ahead. Following

New York's lead, Missouri added the disease to its newborn-screening schedule in 2012, and Kentucky followed suit earlier this year. Seven other states have passed legislation mandating Krabbe screenings and are now sorting out the logistics. And it's not just Krabbe — other LSDs are in their sights too (see 'Different diseases').

SPLIT DECISION

With so much data now available on babies who screen positive for Krabbe disease, the ethical issues surrounding it have come into sharper focus. A crucial point for many bioethicists hinges on the word 'consent'. Under the current system, parents must either agree to all the screenings conducted in their home state or opt out entirely — picking and choosing is not an option. What's more, new parents are often too exhausted or overwhelmed to grasp the implications of their baby's heel prick, and as such might be unaware that screening has even taken place.

All this puts the screening system in a privileged position. "We don't let researchers take blood samples from people without their permission," Ross says, by way of analogy.

Instead, Ross envisages a two-tier system in which screening for conditions such as PKU that fulfil the WHO's gold standard remain mandatory, but screening for conditions that fail to meet the criteria become optional. Others think that screenings for all disorders should remain compulsory, mainly because there is a dearth of information. "To give parents the option of opting in for something they don't really know anything about, I think it's dangerous," says Grantham. She fears that a two-tier system would delay diagnosis for too many high-risk babies.

It is likely that most parents will consent to screenings when given the choice. Researchers at Brigham and Women's Hospital in Boston, Massachusetts, asked more than 500 parents of newborns if they would be interested in receiving genomic testing for their healthy babies. Fewer than 7% said they would not be interested at all, whereas 46% said that they would be very or extremely interested in the testing.

But Bridget Wilcken, an expert on newborn screening at the University of Sydney in Australia, views these results cautiously. Hypothetical questions about screening may not reflect how parents feel when faced with the reality of a possible positive diagnosis for a disorder that lacks a clear point of onset or treatment, she says.

Nevertheless, parents' willingness to agree to screenings suggests that Ross's two-tier testing system would mean that most newborns get tested. "Some parents won't consent, and they have that right," says Ross. "But many parents will consent, because even if it can't help their kid, it will help the next generation." ■

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