New consent requirements for newborn screening raise concerns

Each year, nearly 4 million babies are born in the US, and their dried blood samples have been used by scientists to study the severity and prevalence of rare genetic diseases that are being considered for addition to routine newborn screening panels. However, researchers no longer have ready access to these millions of samples since the country's Newborn Screening Saves Lives Reauthorization Act was signed into law late last year and went into effect on 16 March. Although the reauthorization renewed government funding to support newborn screening programs—allotting about $20 million per year from 2015 to 2019—updates to the law are stalling research on metabolic conditions such as Pompe disease and spinal muscular atrophy, and they are also slowing the development of new tests to identify these rare diseases in newborns.

Newborn screening research can inform clinicians and families about the true prevalence of rare diseases at a population level. For example, a study published last year using blood samples from more than 3 million babies in the US showed that the incidence of severe combined immunodeficiency (SCID) was nearly twice as prevalent as previously thought (*J. Am. Med. Assoc.* **312**, 729–738, 2014). Although it was estimated that SCID affected 1 in 100,000 newborns, the study found the incidence to be closer to 1 in 58,000 births. SCID babies are born without a developed immune system, which makes them susceptible to a range of life-threatening infections very early on life. The sooner these babies are diagnosed and their immune systems restored by stem cell transplantation, the better the chances are of their survival.

The changes to the Newborn Screening Saves Lives Reauthorization Act now stipulate that research on newborns' dried blood spots—blood collected from a baby at birth to screen for a panel of diseases—is considered "research carried out on human subjects." Therefore, informed consent must be obtained before a newborn's blood spot can be used for federally funded research through the US National Institutes of Health (NIH), and institutional review boards can no longer waive consent requirements for research, as they previously had.

Michael Watson, executive director of the Bethesda, Maryland–based American College of Medical Genetics (ACMG), believes that the NIH is using a "very conservative interpretation of the law" when considering projects to fund, and this might be putting babies' lives on the line by hampering research into how to screen for rare, life-threatening conditions in these newborns.

Consent conundrum

The changes to the Newborn Screening Saves Lives Act grew out of policy makers' privacy concerns about giving researchers automatic access to newborn blood spots, because these contain the infants' DNA. One strong nongovernmental champion for the changes was the Citizen's Council for Health Freedom, a health advocacy group based in St. Paul, Minnesota, that in 2003 found that states were keeping newborn samples long after the routine screening tests were done—meaning that the DNA in these samples was also kept on file. When the Newborn Screening Act was to be reauthorized, the Council helped Republican Senator Rand Paul of Kentucky, a former physician, craft the language surrounding these new consent policies.

"Parents didn't know that first of all, newborn screening is being done and second of all, that states are keeping the child's DNA," says Twila Brase, president of the Citizen's Council for Health Freedom. "A lot of researchers presume that a child's DNA can be used for research without the parents' consent. It's just a false presumption that our private genetic information can be used for public purposes. If there are now studies that have been put on hold as a result of not having parental consent, that's just a logical outcome of the legislation that is now law, and researchers have to make that kind of consideration in advance."

Watson counters that the consent requirements are currently being interpreted in a very restrictive manner. "We're very conscious of not wanting to do something that would make a family uncomfortable having their baby screened, but right now we're just in this disproportionate discussion of the risks compared to the benefits," he says. "The risks to the baby's health and privacy are pretty minimal."

The US Office for Human Research Protection (OHRP) now has up to two years to decide the best way to consent to research done on dried blood spots from newborns. "There's a lot of concern that newborn screening research will be put on hold until the two-year mark," Watson says. "Right now we estimate there to be 40 disease candidates that require multi-state pilot studies that are on hold."

Reasons to screen

Newborn screening is done at birth to test infants for a range of conditions that may not be discernible by eye. According to the March of Dimes, 1 in 300 newborns have a disease that can be detected by routine newborn screening, such as cystic fibrosis or SCID. Upon delivery, a blood sample from each infant is obtained and analyzed by the state's government laboratory. Nearly 4 million newborns were screened in the US in 2013.

The federal government has a list of 32 blood spot tests, for which there is clinical evidence showing the conditions are reliably detected and medically actionable, that it recommends states should implement as part of routine newborn screening. However, although the government makes these suggestions, it is ultimately up to the states to incorporate tests in pilot or normal screens.

Researchers are concerned that because of the updates to the Newborn Screening Saves Lives Act, government-funded research to define the prevalence of rare diseases in the general population of newborns has been halted. This prevents research from being done on how many infants are truly affected by rare diseases, and on whether these new screens are necessary and should be implemented broadly.

For example, Pompe disease, a potentially fatal genetic condition that causes detrimental sugar buildup in muscles if not treated, was being studied as part of a multi-state pilot prior to 16 March. It is now one of the 40 pilot studies put on hold owing to the revised law. Infants with this disorder can die from heart failure, and a study of the natural history of the disease found that fewer than 25% of babies diagnosed with Pompe survive to their first birthday.

Some researchers argue that the Pompe pilot isn't actually considered research, but rather additional testing to understand its prevalence in newborns. Ronald Scott, a clinical geneticist at the University of Washington, has developed and validated tests that detect Pompe disease and similar lysosomal storage disorders. He can no longer continue developing novel newborn screening tests with federal funding. "Because of the reauthorization, we have lost $1.2 million in NIH funding toward research for newborn screening tests," says Scott. "It's really unfortunate that well-trained physicians like Rand Paul—who introduced much of the language in the reauthorization—compromise running good public health programs for rare diseases."

Researchers like Scott are beginning to turn to pharmaceutical companies for additional sources of funding to develop new tests or to study the prevalence of disease in a particular state. However, if all states turn to private companies, competition for research funds would inevitably increase.

Finding funding

Given the new regulations, Watson agrees that it will certainly take a fair bit of money to get all disease candidates examined in multi-state pilots, but that the payoff is worth it. "Right now we're having a disproportionate discussion of the risks of research as compared to the benefits. The risks to privacy are pretty minimal. Each test ranges between $1 to $5 each, and the return on screening is really on the child not becoming sick and requiring very expensive health care."

To facilitate access to newborn blood spots, scientists are also contemplating how to make the consent process easier. One way to obtain consent from mothers and work with the new law is to explain what newborn screening is in the prenatal stage, where women will be "far more receptive" to that type of information, as opposed to when they are in labor and rushed to the hospital, or after they have just given birth, according to Watson.

Some lessons might be taken from Michigan and Texas, which both already had an opt-in process analogous to the one required by the reauthorization of the Newborn Screening Saves Lives Act when those changes went into effect. Michigan implemented its statewide consent policy in October 2010, according to Carrie Langbo, coordinator of Michigan BioTrust for Health. Based in Lansing, the BioTrust is a program that oversees the state's stored blood spots and their use in research. Langbo and the BioTrust worked extensively with prenatal care providers through discussion and on-site training to ensure the smooth adoption of consent regulations for newborn research.

Training and educating the birthing staff allowed the hospitals in Michigan to swiftly adopt opt-in consent. "Setting up the whole consent process was not a trivial matter," Langbo says. "It's optimal to receive education on newborn screening prenatally and then ensure that after delivery, all birthing attendants and staff have the information to provide prior to discharge." It took Michigan over two years to conduct this sort of training before the consent policies were adopted as law.

"We did really intensive training with the hospital staff back when we were first implementing the new [consent] regulations in Michigan, but it never really ends," says Jennifer Smith, a spokeswoman at the BioTrust for Health. "Continual reinforcement of the importance of newborn screening is really needed."

Wudan Yan

Microbiome models, on computers and in lab dishes, see progress

In the three years since the completion of the first phase of the Human Microbiome Project, the number of scientific papers linking the microbes that live in our gut to diseases ranging from diabetes and colitis to anxiety and depression has grown exponentially. Yet, these tantalizing connections have yielded few benefits from a therapeutics standpoint.

A major reason for this may be because researchers exploring the gut flora have struggled to find effective model systems within which to study the nature of these gut microbes. Now, however, mouse models and *in vitro* systems, along with new computational modeling, are being used by scientists to better observe how microbial populations influence the onset and progression of disease. Additionally, some models now look beyond bacterial populations to also include fungi and viruses that reside within hosts. The hope is that these updated models will shed light on microbiome mechanisms in a controlled laboratory environment and enable testing of therapeutics, ultimately leading to effective interventions in humans.

In recent years, the field of microbiome research has relied on metagenomics, which allows scientists to directly analyze genetic material from organisms without culturing in the lab. However, even though metagenomics gives researchers an impression of a microbial population's potential capabilities based on the genes the bacteria possess, it doesn't offer much information about when and where these genes produce proteins and how the bacteria actually interact with the human body.

One answer to this problem comes from the related field called integrated omics. Integrated omics combines metagenomics with metatranscriptomics, metaproteomics and metabolomics, which look at the relative abundance of RNA transcripts, protein products, and metabolites, respectively. "Integrated omics can put metagenomics results in a different light," says Willem de Vos, a microbiologist at Wageningen University in the Netherlands. He recalls a study in which the authors showed that obese people had a low abundance of *Bacteroidetes*, a major bacterial phylum[1]. "With metaproteomics we showed that these *Bacteroidetes* compensate their low abundance by being very metabolically active," says de Vos, about recent work that has yet to be published. This activity component is crucial, as the protein products and metabolites produced by microorganisms in the body largely mediate their influence.

To study causal effects between the gut microbes and their hosts, experimental models that can be manipulated and controlled are needed. For example, the Simulator of the Human Intestinal Microbial Ecosystem (SHIME), a model intestinal system consisting of glass bioreactors connected with tubes simulates the stomach, small intestine and three compartments of the large intestine. Developed at Belgium's Ghent University, it allows researchers to study how food compounds metabolize over a period of several weeks. Initially, SHIME, like other *in vitro* models, lacked human cells, ruling out the researchers' ability to study the interactions between the human host and its resident microbes, but recently a layer of human mucosal and intestinal cells was added to the system. The system is also seeded with bacteria from the human gut[2].

Another promising tool is the organoid model, a three-dimensional bud made from mouse or human cells that often mimics the function of a full-fledged organ, in this case the small intestine. As such, researchers are able to observe, albeit on a smaller scale, the mechanisms that govern how microbes influence the environment in which they live. Specific bacterial populations can be injected into the organoids to study the interaction of these microbes with the intestinal wall, as was done recently with two species of bacteria commonly found in the human gut[3]. The researchers measured which genes were switched on in the mouse organoid and found that one of the species, *Akkermansia muciniphila*, switched on fatty acid metabolism. This, they believe, gives this bacterial species potential value as a weight loss probiotic. Similarly, organoids can also be used to study the effects of pharmaceutical and nutritional compounds on the gut epithelium.

These models, however, lack full-scale blood circulation and an immune system within which to record responses. One tool being developed to address this issue comes from a team led by Paul Wilmes at the University of Luxembourg. They developed a microfluidics-based *in vitro* model that has three distinct culture chambers separated by semipermeable membranes: one for microbial cells, one for human epithelial cells and the third for human immune cell cultures. The system allows for control of environmental factors, including nutrient concentrations, pH and mucin compositions, in an attempt to mimic the conditions in the human body[4].