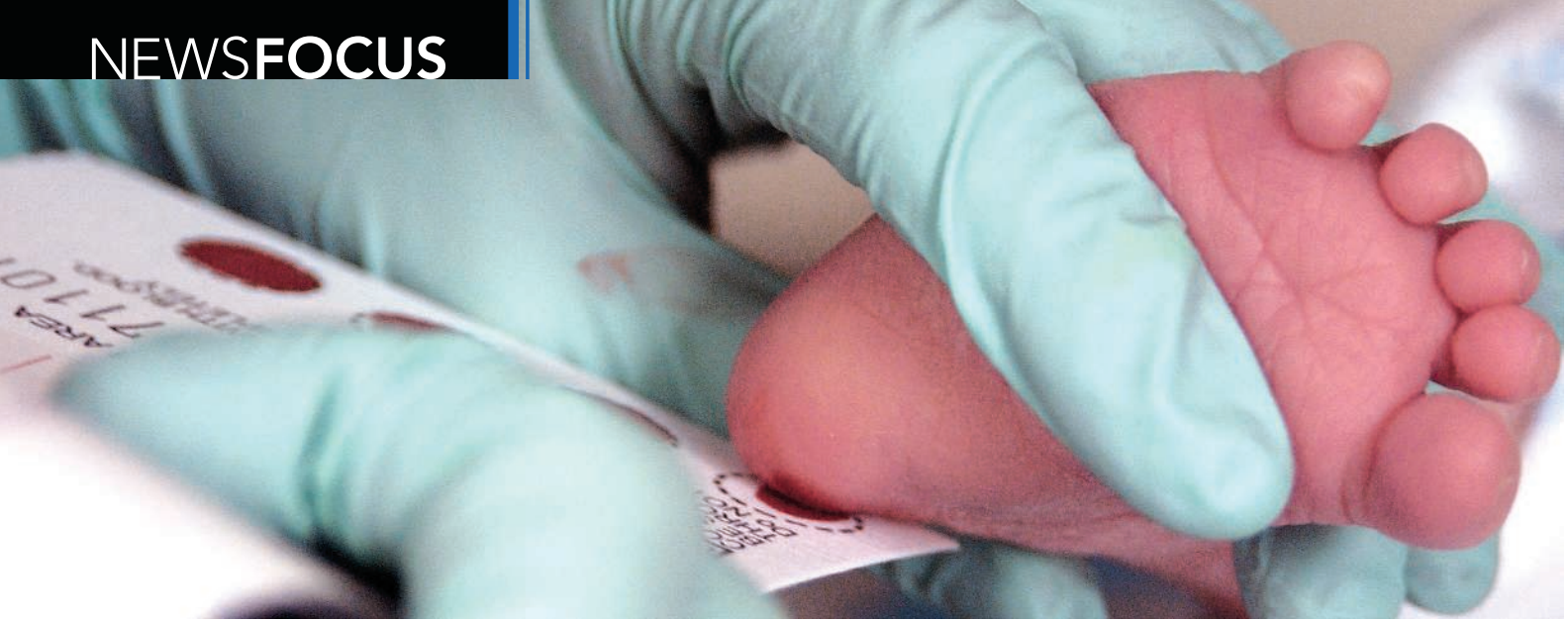

Science Gold Mine, Ethical Minefield

Health agencies launched a system 40 years ago to identify babies at risk. Now there are millions of blood samples in files that researchers want to access, raising public concern

FROM MINNEAPOLIS TO PARIS TO AUCKLAND, nearly every new baby experiences the same procedure hours after birth: a prick of the heel to draw a few drops of blood, which are applied onto filter paper. The paper is shipped off and tested for rare metabolic diseases, which can be devastating if they're not treated early.

Most parents have only the faintest idea that this testing occurs; they are even less likely to know that health agencies are storing their child's blood for years, in some cases indefinitely, in dusty file boxes or deep-frozen in giant warehouses. This growing treasure trove of samples is catching the attention of researchers, who are turning to them to study everything from the origins of childhood leukemia to toxin exposures in utero. The blood spots have been "vastly underexploited in the past," says Mel Greaves, a pediatric cancer biologist at the Institute of Cancer Research in London.

But the same feature that makes blood-spot repositories so potent—mandatory screening means that they capture entire populations—also makes them ethically and legally tenuous. Parents of newborns are rarely informed that samples will be stored and made available for research. And if studies do take place, they're likely to be done anonymously; most families will never know the findings on their child's blood.

The newborn-screening system has skirted some questions about consent in the past. But as more locales shift to long-term storage and more researchers seek access to the blood spots, it now faces direct challenges. In Minnesota, a group promoting confidentiality in health care has been engaged in a 6-year battle with the state legislature and the courts over whether its newborn-screening program violates privacy by storing and disseminating samples. Last month, a civil rights group sued the state of Texas, charging that its screening program is unconstitutional because it stores samples long-term without obtaining informed consent.

Such objections reflect a discomfort with government agencies gathering and filing away everyone's DNA without explicit notification. "It's one thing to justify the testing at the time of birth for disease," says James Harrington, director of the Texas Civil Rights Project in Austin, whose organization filed the lawsuit against the Texas screening program. "It's quite another just to keep it for something as nebulous as scientific use at a later date." Parents, he says, are "not led to think" that anything more than testing of their baby is taking place, and "that deception is troublesome."

A federal committee that advises the secretary of the U.S. Department of Health and Human Services on newborn screening is now considering the use of blood spots. Among other issues, the panel is reviewing how long samples should be stored and under what conditions they should be available to researchers. It hopes to make recommendations later this year.

Some states, such as Michigan, are trying to stay ahead of the critics, consulting bioethicists and residents as they transform their repository of 4 million blood spots into one that's friendlier to researchers. "It's become a real social and, I think, political hot potato," says Aaron Goldenberg, a bioethicist at Case Western Reserve University in Cleveland, Ohio, who has studied Michigan's efforts. "Is the use of these samples … a big enough shift to make us rethink issues of informed consent? A lot of screeners are afraid to go there because they don't want to damage the system."

More than a PKU test

Newborn screening began in the 1960s, when physicians recognized that babies with certain rare diseases, such as phenylketonuria (PKU), could be saved from a lifetime of mental retardation if they were identified immediately. Many countries initiated mass-screening programs, which have expanded dramatically as new technologies made it easier to test for many gene mutations at once. In 2005, the American College of Medical Genetics recommended that all U.S. states screen for 29 conditions. Most states quickly adopted this as a minimum, and today some test for as many as 50.

At the same time, "everyone began to see the value of these specimens in terms of future research," and many locales shifted from quickly discarding the samples to storing

Online
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Podcast interview with author Jennifer Couzin-Frankel.

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them long-term, says Brad Therrell, director of the federally funded National Newborn Screening and Genetics Resource Center, which is based at the University of Texas Health Science Center at San Antonio and provides information on newborn screening to the public and health care workers. In North Carolina, epidemiologist Andrew Olshan of the University of North Carolina, Chapel Hill, and other researchers lobbied the state health department not to throw away samples after just 1 year. Today, North Carolina stores blood spots in perpetuity. In the United Kingdom, storage varies by region from 2 months to indefinitely; at Great Ormond Street Hospital for Children in London, the blood-spot card of every child with leukemia in the area is yanked from the repository at the time of diagnosis to ensure that it will be available for studies. Normally, London-based samples are stored for 10 years.

Greaves pushed for this change, after pioneering a blood-spot technique in the mid-1990s called "backtracking." When children were diagnosed with leukemia, he and others turned to their blood spots to determine whether the signature abnormalities in their cancer cells were also present at birth. "By the time you see the patient and you characterize the mutation, it's too late" to understand when and how cancer began, says Greaves. Hunting for preleukemic DNA in the sea of 30,000 white blood cells that make up each blood spot, he found that in 50% to 100% of cases, depending on the form of leukemia, genetic mutations were present—suggesting that the cancer was seeded in utero.

Epidemiologist Gary Shaw of Stanford University in Palo Alto, California, meanwhile, has used blood spots to examine interactions between genes and the environment. For example, he's focused on the intricate dance between cigarettes, folate in the maternal diet, and birth defects such as cleft lip. By studying genes that metabolize cigarette smoke and those that code for folate, he's found that maternal smoking compromises folic acid's role in healthy fetal development and raises the risk of cleft lip—a discovery, he says, that required an enormous number of DNA samples.

Shaw is keen on another hot area as well: examining not DNA but contaminants, such as pesticides, that may be present in blood spots. By combing through hundreds or thousands of samples, epidemiologists can assess exposure levels across a population or compare different regions. Or they can match exposure with certain health problems. Henry Spliethoff, an environmental health scientist at the New York State Department of Health Center for Environmental Health in Troy, wondered whether phasing out products that contained perfluorinated compounds around the year 2000 had reduced exposure levels in utero. By comparing blood spots collected before 2000 with those collected after, he found that exposure had gone down by as much as 70% between 1999 and 2004 and had dropped further after that. Such studies are still in their infancy.

Just gaining access to the spots can be a logistical challenge because many U.S. state health departments are strapped for cash and don't have the staff to handle a growing number of requests. At Maryland's health department, Christopher Loffredo, an epidemiologist at Georgetown University Medical Center in Washington, D.C., says, "I spent 6 months of my life going through boxes and boxes and boxes of blood spots looking for the ones I needed" for a study on congenital heart disease. California, which has stored samples since 1983 and now has 14 million, gets about one research request every 2 weeks. But because it is short of staff, it hasn't been filling them for more than a year.

Safeguards and gaps

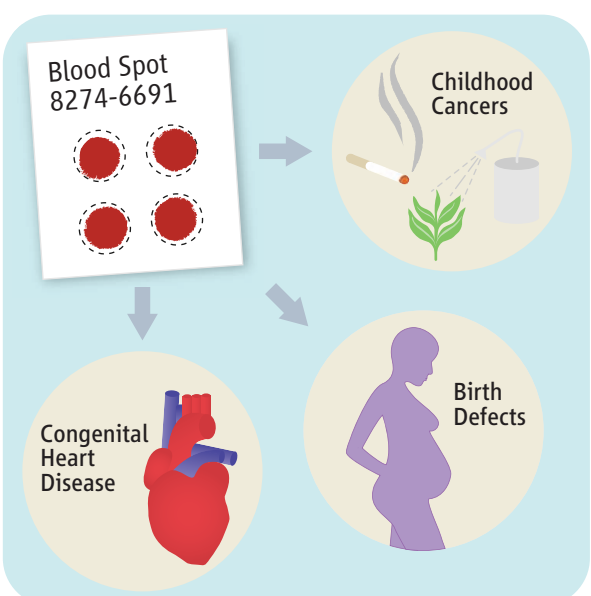
In most countries, researchers must seek approval from an ethics board before getting their hands on the blood spots they want to study. They generally obtain informed consent in cases in which a blood spot could be identified—for example, when detailed health information is needed. Greaves, for example, seeks consent from families of the children with cancer he studies. In cases without consent, the health department might provide researchers with an anonymous sampling of blood spots, offering them, say, geographic information but nothing more; or it might provide control samples for a study of a particular disease.

Many people consider such protections insufficient. In the Netherlands, where samples are kept for 5 years and sometimes used in research studies, the newborn-screening program was thrust into turmoil in 2000. A fireworks depot exploded in the Dutch city of Enschede, killing 22 people and injuring almost 1000; officials discussed using blood spots to help identify the dead. An outcry ensued, because the Dutch public hadn't realized the samples were being banked. "People were very angry. … It was never kept secret, but it wasn't clear," says J. Gerard Loeber, a member of the steering committee for the Dutch screening program and president of the International Society for Neonatal Screening. Since then, the country has incorporated informed consent for the program into its prenatal care. Midwives offer the chance to opt out of sample storage, something about 100 to 150 families do each year, says Loeber.

Consent standards vary wildly between and even within countries. In Australia, screening programs do not seek consent for sample storage; in New Zealand, practices differ from region to region. In France, where samples are stored for at least 1 year, researchers generally must have families sign their children's blood-spot card if they wish to perform a specific study, says Jean-Louis Dhondt of the Catholic University in Lille, who heads up the screening lab of one French region, Nord-Pas de Calais. "We have no right to look at other genes" beyond those

NEWBORN BLOOD'S VARIED USES

Scientific question	Researcher and Institution
Origins of childhood leukemia	Mel Greaves, Institute of Cancer Research, U.K.
Birth defects and folate	Gary Shaw, Stanford University, California
Gene-environment origins of congenital heart disease	Christopher Loffredo, Georgetown University, Washington, D.C.
Contaminant exposure in utero	Henry Spliethoff, New York State Department of Health
Genetics of preterm birth	Mads Melbye, Statens Serum Institut, Denmark



CREDIT: NEWBORN GRAPHIC: J. NEWFIELD/*SCIENCE*

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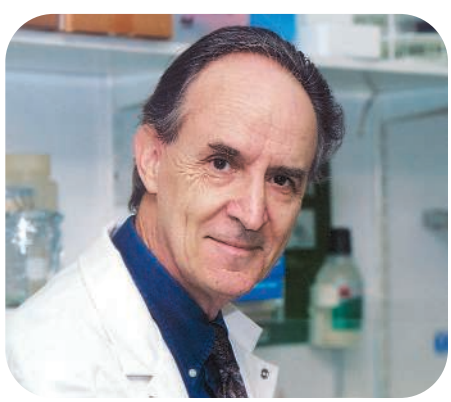
already being tested for, Dhondt says.

In Denmark, where the public enthusiastically participates in national biobanks, sample storage is discussed in newspapers and elsewhere, and residents "certainly know" that research is performed on the blood spots, says Mads Melbye, head of epidemiology at the Statens Serum Institut in Copenhagen. Individuals can opt out of having their samples used in research if they wish.

The patchwork U.S. system changes from state to state: Blood-spot cards are kept indefinitely in some places and discarded immediately after initial testing in others. A handful of states, including California and Michigan, have statutes that provide legal authority to store the blood spots.

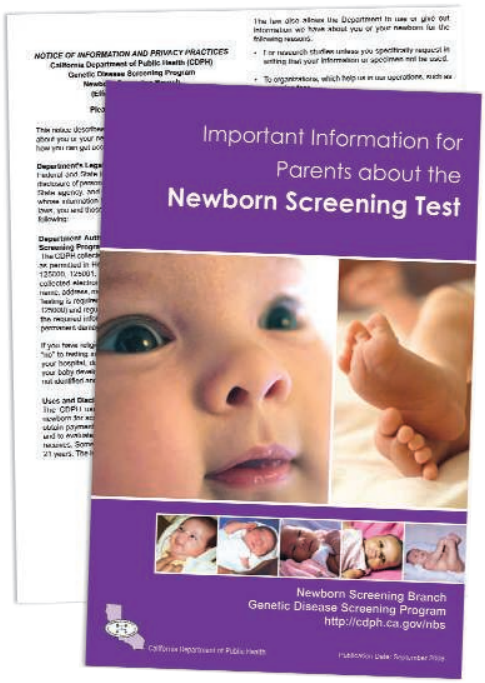
But nearly everywhere in the United States, there is no informed consent for any element of the screening program. Families can decline to participate on religious or other grounds, or accept screening but refuse to have the sample stored. But they must know to do so in advance, and most do not. Even though some states distribute information sheets at a child's birth, "many people aren't aware of the infant-screening program," says Tom Tomlinson, a bioethicist at Michigan State University in East Lansing. And "you can't do research on people without their consent."

Tomlinson was recruited to advise the Michigan Department of Community Health, which plans to make its repository more accessible to researchers and is considering the ethical minefields around doing so. Samples there are stored in perpetuity. The Michigan Neonatal BioTrust, as the effort is called, is trying to shift storage from room temperature to freezing to better preserve the samples, improve tracking of what's been distributed to researchers, and encourage community input into how samples are studied.



Research treasure. Cancer biologist Mel Greaves uses blood spots to track the trajectory of childhood leukemia.

"There's an ethical gap" in how federal rules govern protection of human subjects, says Tomlinson. "They are all about protecting individuals against risk" and guarding privacy. But "people have other [concerns about] the way in which their materials are used," for example, to study medical conditions that could stigmatize an ethnic group to which they belong.



In brief. California tells families that they must opt out if they don't want a child's blood used in research studies.

Delayed impact

Information from a baby's blood spot may pose other difficult questions. For example, should parents be told if researchers discover that their child carries a gene that increases the risk of disease? In New Zealand, one group inquired about using samples to examine the prevalence of gene mutations for long QT syndrome, a condition that can cause sudden cardiac death. "We went to an ethics committee and they said, 'It's not ethical to do this [anonymously] because you might find information that's useful to families,' " says Dianne Webster, director of the New Zealand Newborn Metabolic Screening Programme in Auckland. But gathering permission from families was deemed "too logistically difficult," and the project was abandoned.

In Denmark, Melbye and his colleagues have funding from the U.S. National Institutes of Health (NIH) to examine gene sequences that might contribute to preterm birth in 4000 mothers and their babies. (Samples were collected by the country's biobanks and a study on pregnant women.) The Danish ethics committee chose not to mandate seeking permission from the mothers, concluding that the project was unlikely to come up with genetic risk factors that would make preterm birth extremely likely in a future pregnancy. If that happens, however, says Melbye, "we will write to the scientific ethics committee and say, 'This is a very strong marker, it's important for the mothers to know—they will decide what needs to be done.' "

Obtaining consent years or decades after a blood spot was collected may not be possible, some say. Furthermore, seeking consent at any time could potentially be alarming to families. Imagine, for example, a study that finds a mutation in blood spots whose medical significance is fuzzy, says Jeffrey Botkin, a pediatrician and bioethicist at the University of Utah. "No way can you call those families up and say, 'We've found something about your child,' " because there's no guidance anyone can offer. "You're not going to do anything with that information." Botkin received NIH funding last year to examine the ethical issues and public attitudes involved in retention and research use of blood spots.

Tomlinson, however, notes that in his experience in Michigan, a "significant minority" of the people he speaks with would prefer that researchers obtain consent from individuals whose blood spots are used in a given study. That desire may be important to heed, in part to maintain good community relations.

Leaders of newborn-screening programs are sensitive to public perceptions: A misstep, they fear, could taint the entire program, leading families to decline screening altogether. "These are extremely valuable samples for public health research," says Logan Spector, a childhood cancer epidemiologist at the University of Minnesota. "That's why I would support strengthening the law to protect them from any perceived misuse"—for example, invoking a "firewall" that allows for research but not nonresearch uses, like those involving law enforcement. Botkin favors obtaining consent from a couple before a child's birth for storage and potential research. After the lawsuit in Texas was filed in March, members of the Texas House of Representatives introduced legislation to require consent.

Opening up the inner workings of the screening program is crucial to keeping samples in the world of science, says Loeber, citing his own experience after the explosion at the Dutch fireworks depot. "If you don't do that, some parents will always feel that something secret is going on. … The general population has always the sense of, 'Hmmmm, what are they doing with the blood of my baby?' "

–JENNIFER COUZIN-FRANKEL

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