CHALLENGES AND OPPORTUNITIES IN USING RESIDUAL NEWBORN SCREENING SAMPLES FOR TRANSLATIONAL RESEARCH

WORKSHOP SUMMARY

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

ROUNDTABLE ON TRANSLATING GENOMIC-BASED RESEARCH FOR HEALTH

CHALLENGES AND OPPORTUNITIES IN USING RESIDUAL NEWBORN SCREENING SAMPLES FOR TRANSLATIONAL RESEARCH

W O R K S H O P S U M M A R Y

Steve Olson and Adam C. Berger, *Rapporteurs*

Roundtable on Translating Genomic-Based Research for Health

Board on Health Sciences Policy

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Willing is not enough; we must do."
—Goethe

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This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the process. We wish to thank the following individuals for their review of this report:

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Although the reviewers listed above have provided many constructive comments and suggestions, they did not endorse the final draft of the report before its release. The review of this report was overseen by **Elena O. Nightingale,** Scholar-In-Residence, Institute of Medicine, Washington, DC. Appointed by the Institute of Medicine, she was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the rapporteurs and the institution.

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The Roundtable wishes to express its gratitude to the expert speakers whose presentations highlighted the challenges that need to be resolved in order to make newborn screening samples accessible for research without compromising the function of the newborn screening program. These speakers were Wylie Burke, Michele Caggana, Ellen Wright Clayton, Anne Comeau, Kelly Edwards, Alan Fleischman, Alissa Johnson, Sharon Kardia, Kenneth Pass, Sharon Terry, and Ann Waldo.

The Roundtable also wishes to thank the members of the planning committee for their work in developing an excellent workshop agenda. Planning committee members were Wylie Burke, Ellen Wright Clayton, Sharon Kardia, Michael Katz, Allen Roses, and Martha Turner.

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Abbreviations and Acronyms

CDC	Centers for Disease Control and Prevention
CHI^2	Child Health Information Integration
GINA	Genetic Information Nondiscrimination Act
HIPAA	Health Insurance Portability and Accountability Act
IRB	institutional review board
PKU	phenylketonuria
RHIO	regional health information organization
SACHDNC	Secretary's Advisory Committee on Heritable Disorders in Newborns and Children
SCID	severe combined immunodeficiency
TIES	Trust, Integrity, and Ethics in Science

1

Introduction

Residual newborn screening samples represent a significant, though largely untapped, resource that could improve the health and welfare of the public, said Wylie Burke, if these samples could be used for translational research (Box 1-1). However, there are important ethical, legal, and social issues surrounding such use which must be addressed. As biological research uncovers new links between genetic variants and disease susceptibilities these issues will only become more pressing.

In the 1960s, states began collecting blood samples from babies to test for rare diseases such as phenylketonuria (PKU) that could be prevented if affected infants were identified at birth. Since then these public health programs have expanded dramatically as new tests and technologies have made it possible to screen for a large number of preventable diseases. Today most states require that all infants be screened for at least 29 of the 30 conditions[1] recommended by the Secretary's Advisory Committee on Heritable

BOX 1-1
Definition

Translational Research Defined here as the use of residual dried blood spots in basic laboratory, clinical, or public health research in order to transform the relevant findings into clinical applications and reduce disease burdens.

[1] SCID was officially added to the Recommended Uniform Screening Panel core conditions on May 21, 2010.

Disorders in Newborns and Children (SACHDNC). Newborn screening programs collect samples through traditional heel pricks from more than 4 million infants per year in the United States, leading to the prevention of thousands of illnesses and premature deaths.

Screening programs collect more blood samples than are necessary to complete screening tests in most infants. Once screening is completed, the remaining samples often are stored for future uses. Many of these uses are directly related to improving screening programs, such as the development of new methods and tests. But over the years, researchers have become increasingly aware that residual dried blood spots from newborn screening programs constitute an unparalleled resource for public health and biomedical research. These residual samples have been used to study childhood leukemia, exposure to environmental toxins, the prevalence of HIV infection, birth defects, and many other topics. The potential research uses of residual dried blood spots are limited only by the amount of residual blood on the card.

Yet many questions—and considerable controversy—surround the use of these materials. Most parents know very little about the testing of their children and are unaware that samples can be stored for years afterward. Since the collection of blood spots from each infant is mandated by state laws, informed consent is not routinely obtained from the parents or guardians of the children and legal challenges have recently shed light on when, or if, these samples can be used for purposes other than those known to the donors. In Minnesota a group of families sued the state, claiming that the Minnesota Department of Health was violating a Minnesota privacy statute that requires "written informed consent [for the] collection, storage, use, and dissemination of genetic information." In Texas, a group of parents also asked that the state obtain parental consent before collecting samples. Although the case in Minnesota was summarily dismissed, the settlement reached in the Texas case resulted in the state destroying 5.5 million samples (Bearder et al., 2009; Beleno et al., 2009).

On May 24, 2010, the Roundtable on Translating Genomic-Based Research for Health held a workshop to examine the challenges and opportunities in using residual newborn screening samples for translational research. The workshop examined such questions as:

- What are the benefits of making residual newborn screening samples available for research?
- How can the privacy and rights of individuals be protected while allowing access to residual newborn screening samples?
- How can these samples be made available for other uses without compromising the main function of the newborn screening program?

The workshop was held during the public comment period for a draft report from the SACHDNC that contained recommendations directed to the Secretary of Health and Human Services. In particular, their draft report contained several recommendations related to issues discussed extensively at the workshop. The SACHDNC recommended that state newborn screening programs have legally vetted policies on the disposition of newborn screening samples and on who should have access to residual samples after screening is completed. It observed that state newborn screening programs should have strategies to ensure the education of health-care professionals and families about the newborn screening process. The draft report recommended that if residual newborn screening samples are made available for research, there should be an indication of parental awareness and willingness for those uses in compliance with federal research requirements.

Unlike the SACHDNC, the Roundtable on Translating Genomic-Based Research for Health is not a body designed to generate recommendations. Rather, the roundtable seeks to ensure that the viewpoints of different stakeholders are identified and heard. By providing a forum where potentially opposing viewpoints can be considered, the roundtable tries to identify common ground and foster innovation, partnerships, coordination, and collaborative problem solving.

The issue of using residual newborn screening samples for research fits well with the charge of the roundtable, said Burke. This is an issue for which different points of view need to be compared, explored, and at least harmonized, if not resolved. For this reason, the workshop contained ample time for discussion and comment. In this regard, said Burke, the roundtable hopes that this summary of the presentations and discussions at the workshop will be a valuable complement to the comments submitted on the draft report from the secretary's advisory committee.

The workshop also looked beyond newborn screening. Participants at the workshop discussed some of the most urgent issues in health care today, including autonomy, confidentiality, privacy, and informed consent. As researchers continue to explore the biological bases of diseases and disease susceptibilities, these issues will only become more significant. Because fundamental questions concerning newborn screening can be examined within the context of specific public health programs, newborn screening offers lessons that can be applied much more broadly in health care.

2

Newborn Screening as a Public Health Program

Important Points Highlighted by Speakers

- Newborn screening programs in the United States have been extremely successful, preventing thousands of premature illnesses and deaths per year.
- The residual dried blood spots that remain once screening is complete have a variety of uses, from quality control and the development of new tests to a very wide range of research applications (discussed in Chapter 3).
- Secondary uses of residual dried blood spots should not be allowed to interfere with the public health mission of newborn screening programs.
- Newborn screening programs cannot succeed without public trust.

BENEFITS AND PREREQUISITES OF NEWBORN SCREENING

Newborn screening programs identify children who are born with serious genetic, metabolic, hematologic, infectious, or auditory disorders (Sahai and Marsden, 2009; Wilcken and Wiley, 2008). These children generally appear normal at birth but have an inherent condition that will lead to disability or death without intervention. Screening is performed on blood samples that have been collected shortly after birth and dried on filter paper. To ensure

that the specimens can be re-evaluated if warranted by the initial screening results, extra samples are collected in the form of multiple blood spots on a standardized form. Individual states may store these extra samples for use in the quality control of current tests and the development of new tests. In addition, residual dried blood spots also have many potential uses in public health and biomedical research. (These uses are discussed in Chapter 3.)

Newborn screening programs have been highly successful, said Dr. Anne Comeau, deputy director for the New England Newborn Screening Program and associate professor in the Department of Pediatrics at the University of Massachusetts Medical School. They provide an opportunity for early identification and treatment of infants with conditions that otherwise would go unrecognized prior to irreversible damage. In New England, about 1 in 600 children is found to have one of the conditions being looked for by the screen (Figure 2-1). But newborn screening programs include much more than just a laboratory test, Comeau said. To provide parents with information and get infants into treatment, her program has pre-analytic, analytic, and post-analytic components. Every baby needs to be screened and every affected infant needs to get treatment and follow-up care.

Quality people and quality systems are essential to the success of newborn screening, Comeau said. The people running screening programs need to be well trained and competent. Quality systems need to be in place for the analysis and storage of residual dried blood spots. "It is not just the robotics of running a laboratory test," she said.

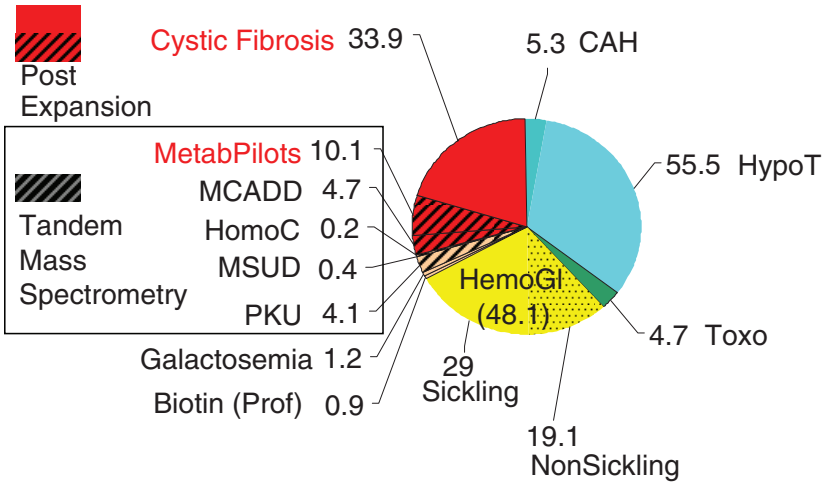

FIGURE 2-1 The number of cases detected (169)/100,000 screened through the New England newborn screening program.
SOURCE: Comeau, 2010.

Quality programs in turn build public trust. Newborn screening programs are authorized through the legal doctrine known as *parens patriae*, which gives the state the right to assume certain roles of parents based on benefits to the child and to society as a whole. But such programs cannot succeed without public trust.

PRINCIPLES BEHIND NEWBORN SCREENING

There is a lot at stake in newborn screening, said Dr. Alan Fleischman, senior vice president and medical director at the March of Dimes Foundation and professor at the Albert Einstein College of Medicine. Extrapolating the experiences of individual states to the United States as a whole, it is estimated that more than 6,000 children are identified each year with a metabolic, endocrine, hematologic, or functional disorder (CDC, 2008). Because these tests are directly in the interest of infants, this gives states the right to mandate the tests without first obtaining informed consent from the parents, Fleischman said, although all new parents should be educated about the process. Some states allow parents to opt out of screening for various reasons, he said, although "if any form of parent consent is required, including opting out, it should be addressed only after the blood sample has been obtained." (Issues of consent are discussed in more detail in Chapter 5.)

Newborn screening programs have changed significantly in just the past five years, Fleischman said. Currently 42 states and the District of Columbia screen for 29 of the 30 recommended disorders, and all states screen for 26 or more of these disorders. New technologies have made it possible to screen for many more disorders than in the past and the number will continue to increase. This represents, Fleischman said, "a public health success story of this decade."

Newborn screening is based on certain fundamental principles, Fleischman explained. Screening should be directed at serious diseases or disorders that significantly impair health. Conditions tested should be identifiable before symptoms appear. There need to be valid, reliable, sensitive, and specific screening methods available that can be performed shortly after birth. The benefits of early detection, including timely intervention and efficacious treatment, need to be documented. This set of requirements explains why newborn screening programs entail much more than gathering samples and testing, Fleischman said. In addition to sample collection, submission to the laboratory, and testing, the programs include the reporting of results, diagnostic confirmation, referral for treatment, long-term support of patients and families, and program evaluation.

The samples left after screening is complete have a variety of potential uses in addition to the use of residual specimens in research. The first such

use is program quality assurance and test validation. Samples are needed to ensure that tests are accurate. "It is not heartening to hear some legislators or programs in some states discarding samples after a few weeks or 30 days," Fleischman said, since this makes it more challenging to fulfill quality assurance needs in those states.

Second, residual samples are needed to develop new screening methods. This is part of the public health program and should be seen as an essential component of the mandatory screening process, according to Fleischman.

Third, parents are increasingly requesting additional testing, particularly in the case of sudden or unexpected death. Such testing is not possible if samples have been destroyed.

Fourth, samples have the potential to be used for forensic purposes by the police, the Federal Bureau of Investigation, Homeland Security, and other governmental bodies. The possibility of such use raises many difficult questions, Fleischman said.

The challenge, Fleischman said, is to balance respect for parental involvement in decisions about the storage and use of residual blood spots with the importance of the newborn screening public health program. Residual blood spots are an "incredibly important resource," and their secondary uses, including research, should not be allowed to interfere with the public health mission of the screening itself. "The public health program is mandatory in this country. Research, though laudable, is optional."

STAKEHOLDERS IN NEWBORN SCREENING

Many individuals and groups are stakeholders in the use of blood spots. The child is the first and most important stakeholder with regard to the screening process itself, since it is in the child's interest to have the program. The importance to the child is why parents should not be allowed to opt out of newborn screening, Fleischman said, even if they are allowed to opt out of subsequent uses of samples.

The family is also a stakeholder in newborn screening, since the use of residual dried blood spots can have implications for the privacy and identity of family members. When parents attend meetings about the use of residual dried blood spots, Fleischman said, they often express concerns about how the use of those samples will affect not only their children but other members of the family.

Scientists and clinicians are stakeholders in the use of residual blood spots for research, because their job is to use this important resource to generate new knowledge in ways that will help all children and families. And governments and the public health departments are also similar stakeholders because they are the stewards of this important resource. Taken together, these are the primary stakeholders, Fleischman said, and each needs to have a voice in how newborn screening samples are used.

3

Uses of Residual Newborn Screening Samples in Research

Important Points Highlighted by Speakers

- A feedback exists between the service of providing newborn screening and subsequent research for biomedical and public health purposes.
- Residual newborn screening samples have been used in the past for a wide range of useful and productive research.
- The number of potential uses of residual specimens has increased dramatically as new technologies have developed. Future research will only increase the value of these specimens.
- Combining information from newborn screening programs with other health data could greatly improve the delivery of health care, although difficult issues of privacy, security, and technological coordination need to be resolved.

THE CONTINUUM FROM SERVICE TO RESEARCH

There is a feedback from service to research and back to service, said Anne Comeau, in which research to improve newborn screening, public health, or basic science has led to advances in the other endeavors. A well-known example of this type of beneficial relationship was the study of HIV seroprevalence in childbearing women, a national study that started

in Massachusetts (Gwinn et al., 1991; Hoff et al., 1988). In the study, the state was divided into nine regions with the residual dried blood spots being identified only by the region where they were collected. All of the blood spots were analyzed simultaneously to determine the seroprevalence of HIV in the nine regions, which ranged from 11.6 percent to 0.3 percent. Thus, by performing research on the dried blood samples collected for the purpose of newborn screening, public health programs in Massachusetts were able to use this information to determine where to locate HIV services for women of childbearing age.

Research to benefit the service of providing improved newborn screening can also lead to a direct public health benefit. One recent study on expanding newborn screening in Massachusetts was aimed at identifying children with severe combined immunodeficiency (SCID). The treatment for SCID is quite effective, so a screen to identify such babies is easily justified. However, the practical issues of instituting such a screen on a population-wide level at the time were unknown. To date, Comeau said, the program has screened more than 75,000 infants for SCID, with less than 1 percent of parents declining to participate. Researchers also retrieved residual dried blood spots from storage after having received consent from the parents of infants who had previously been identified with SCID in order to demonstrate the clinical validity of the screening test. "Without the input from our program to save these [residual] dried blood spots, this would not have happened," Comeau said. The program provided data to the SACHDNC so that the committee could make evidence-based decisions, and ultimately it helped to add SCID to the national uniform screening panel.

This interplay between service and research is reflected in the several rationales for retaining residual specimens that Comeau cited from the Massachusetts Department of Public Health Policy on the Purpose, Storage, and Use of Specimens Residual to Those Collected for Newborn Screening Services.

- These samples provide legal accountability for reconfirmation of newborn screening test results and for the existence of a specimen and its adequate collection.
- They allow for continuous improvements in the quality of screening and testing methodologies.
- They enable the comparison and validation of new analytical methods.
- They provide for research that can advance newborn screening efforts as well as other areas of public health medicine.
- They make possible basic research to enhance general medical knowledge.

However, there are certain issues that need to be taken into account in order to make it feasible to perform this type of translational research. It is not cheap to develop and maintain repositories of dried blood spots, Comeau observed. Specimens need to be stored properly and studies need appropriate quality control. Intensive data management is needed to ensure that the proper consent is obtained and that consent is matched with the correct dried blood spot. State rules for review by independent boards need to be observed and studies sometimes need to be redesigned in response to input from newborn screening personnel.

Comeau recommended against establishing central, regional, or national repositories for newborn screening specimens. The states have good track records of stewardship, she said. Control should reside within the communities that have put forth the effort to store specimens so that they can be of value to research. "Just storing specimens is not good enough," Comeau said. "Do you want quality research? It is a lot of work to have appropriate repositories, with appropriate linkages, and with appropriate [institutional review board] (IRB) evaluation." As an alternative to centralized repositories, Comeau suggested a virtual repository model in which the physical location of samples, the location of information about samples, and the stewardship or control of the samples are distributed among individuals, the state, and the federal government.

PAST AND PRESENT USAGE

According to Kenneth Pass, senior research scientist with the New York State Department of Health's Wadsworth Center, the range of uses for and the population coverage of newborn screening samples make the samples irreplaceable. More than 160 uses have already appeared in the scientific literature and many more will be developed in the future. Residual dried blood spots have been utilized for research with informed consent, with an opportunity to opt out, as anonymized, and as de-identified (consent is discussed in Chapter 5). "Are there ways to use them? Have they been used? Have they been reported? Yes, yes, and yes," Pass said.

Sharon Kardia, professor and chair of epidemiology at the University of Michigan and co-director of the Michigan Center for Genomics and Public Health, listed some of the key attributes of residual dried blood spots. They provide a nearly complete representation of the population. They can be integrated with existing public health data. Because they consist of whole blood samples, they also contain a very wide range of biomarkers, including DNA, RNA, proteins, metabolites, and evidence of exposures to environmental or infectious agents. Although some analytes, such as proteins, degrade over time, Kardia said that, in general, the extent of preservation is astonishing.

The potential for residual newborn screening samples to be used in research has been recognized for many years, Pass noted. While no genetic tests are currently performed as part of the initial newborn screening process, many research applications could make use of the inherent genetic matter present in these samples. In 1996, he and a group of colleagues wrote, "Potentially these samples provide a genetic material 'bank' for all newborns nationwide. Their value as a resource for other uses has already been recognized by scientists, administrators, and judicial officials" (Therrell et al., 1996). Since then, as the field of human genetics has developed, the value of these samples has become even more apparent. They represent an unbiased sample of biological materials from the entire United States and much of the industrialized world. They cover nearly the entire population and often are the only remaining tissue sample for a particular individual. "Each of us has his or her own story about how a blood spot was used postnatally [or] after death to help with the diagnosis of a child," Pass said.

Samples have been particularly useful in public health studies, Pass said. They were used to identify PCB hazards for children born near Love Canal in New York and research on this topic is still under way at the Wadsworth Center. They provide markers for fetal alcohol syndrome, drugs that the mother might have taken during pregnancy, and environmental exposures that the mother may have experienced. (For examples, see Burse et al., 1997; Henderson et al., 1997; and Spliethoff et al., 2008.) In particular, they can be used to detect exposures to perfluorinated compounds, cocaine, nicotine, caffeine, hepatitis B, toxoplasmosis, syphilis, rubella, pesticides, *E. coli*, and other harmful drugs and infectious organisms.

The DNA that can be extracted from residual dried blood spots is also valuable. It can be used as a second-tier screening mechanism to confirm results from other biomarkers in diagnosing such disorders as cystic fibrosis, sickle cell disease, and galactosemia. DNA samples can be used to determine how common a particular genetic variant is in the population and enable new discoveries related to specific diseases. For example, Pass and his colleagues recently published a paper on new candidate biomarkers for autism and nine of the markers were identified in residual dried blood spots. Blood spots also have found applications in forensics. "Again, we all have a story of how these specimens have been used in natural disasters or terrorist attacks to establish a positive identification," Pass said.

Alan Fleischman also commented on the wide range of uses for residual newborn screening samples, both for public health purposes and for research directed toward individuals. The gradual expansion of these uses has had a major effect on public health programs, he said. Newborn screening programs were originally small. Departments of public health did not have a sense of being powerful, but they had high-quality people dedicated to their work in the midst of a complex state public health structure.

The first research applications were consistent with the agencies' efforts to improve public health. Surveillance for threats to public health using residual newborn screening samples was a natural part of what a department of health would do. Such surveillance was based in its mission and was not controversial.

As researchers outside departments of health began to recognize the value of residual newborn screening samples, they began to seek access to these samples. And because the people in these departments were thoughtful and believed in research, and because the questions being asked by researchers were reasonable, they began to build relationships with the researchers.

Today, the most important question regarding residual dried blood spots, according to Fleischman, is whether they can be stored and used for future research without jeopardizing the important public health goals of newborn screening programs. "My answer is yes, as long as we are careful," he said.

RESEARCH POTENTIAL OF RESIDUAL NEWBORN SCREENING SAMPLES

Kardia noted that modern technologies make it possible to measure and evaluate many different molecules and genes simultaneously. Genetic material can be amplified, turning tiny samples into samples large enough for analytic techniques. Thousands of genetic variants can be detected in residual dried blood spots collected years before. Dried blood spots represent "a huge repository of information about biomarkers and molecules that are associated with health," Kardia said.

As an aside, Kardia noted that dried blood spots have proven so useful that they are being used outside of newborn screening. Pharmaceutical companies are beginning to collect dried blood spots as opposed to venous blood samples to test for the presence of particular molecules and to determine the efficacy or toxicity of drugs. Vaccine trials in developing countries use them for monitoring. Some epidemiological researchers are moving to dried blood spots for measuring environmental exposures. Dried blood spots are even being used to gather biological information about animals used as model organisms for medical research.

Very valuable forms of research can be conducted using only anonymized samples, but the information in a dried blood spot can be particularly valuable when it is combined with other sources of data, Kardia said. Birth records, death records, immunization data, hearing test results, nutrition programs, cancer registries, Medicaid records, and other types of public health information can all be integrated with the information derived from dried blood spots. Data based on geographic zones, such as water quality,

air quality, environmental hazards, disease outbreaks, or hospital discharge records, can also be combined with the information available from dried blood spots. "The integration of these provides real grist for research advances," Kardia said.

Residual blood spots from newborn screening offer a continuum of research opportunities, Kardia said. They can be used for case studies of rare diseases, cross-sectional studies of the prevalence of a particular condition or exposure, case-control studies, and birth cohort studies. These last two are particularly promising, she said, because residual dried blood spots make it possible to do such studies across large populations and for many diseases. "Just about any disease that is found in a population could be, in a case-control format, evaluated," she added.

Cross-sectional studies can assess patterns of genetic variations or environmental exposures geographically and assess trends over time. For example, some people have particular genetic dispositions that make them highly susceptible to diseases such as familial hypercholesterolemia. These individuals could be identified and efforts could be made within communities to get them access to care or other interventions. Trends also could be assessed over time using objective measures rather than the recollections of the people in the study, which may not be accurate. "Being able to assess time changes in a population is a huge benefit," Kardia said.

Hundreds or even thousands of diseases and health outcomes could be studied using residual dried blood spots in case-control studies. Examples include cerebral palsy, hearing loss, severe combined immunodeficiency, sudden cardiac death, drug allergies, and childhood cancers. Today, the controls in a study are usually not random and cases have to be painstakingly identified and contacted. Residual dried blood spots offer a way to identify robust and reliable sources of both cases and controls in large populations.

Today, birth cohort studies are typically tremendously expensive and difficult to perform, though they offer a powerful way to investigate a population's health. Residual dried blood spots, if combined with information in public health registries, could provide an integrated picture of the health of entire populations, starting from birth. Such a study would offer a unique opportunity to look at the effects of health policies on health outcomes, for example. Public health registries could be combined with electronic health records to track the development of particular conditions across a person's lifetime and across generations as well as to determine the effects of interventions. It would also allow for the long-term investigation of environmental accidents and hazards. "There is huge potential," Kardia said. "We don't know what next week will bring," Pass added. "If we have those spots, we are ready to go."

However, Kardia acknowledged that many ethical questions need to be addressed before many of these steps could be taken. "Relationships to the

participants or to departments of health are incredibly important, because this whole endeavor is about helping people," Kardia said. "If I alienate either the participants or the department of health, then I really haven't done any service at all."

AN INTEGRATED RECORD OF CHILD HEALTH

Michele Caggana, chief of the Laboratory of Human Genetics, director of the Newborn Screening Program, and head of the Genetic Testing Section of the New York State Department of Health's Wadsworth Center, observed that health information technology has progressed to the point where it is possible to have a single health record containing many forms of public health data, such as the results of newborn screening, immunizations, hearing tests, childhood diseases, hospitalizations, medications, exposures, and so on. Today, however, much of this information is kept in separate records. Newborn screening data and vital records data, for example, are not often combined.

New York State has begun to take steps to eliminate this separation and establish a unified health record for each child. Known as the Child Health Information Integration (CHI^2) project, the effort is being led by representatives in different bureaus of the health department involved in child health. "We want to create a virtual child health profile," Caggana said. Authorized users involved with the health of a child would have access to certain views of comprehensive information on each child. This information could include newborn screening results, hearing screening results, admissions to a neonatal intensive care unit, immunizations, early intervention programs, other specialized care, testing results, and needs for follow-up (see Figure 3-1).

Such a system would have many benefits, Caggana said. It would provide comprehensive, timely, and accurate child health information to support the provision of health-care services. It would ensure that newborn screening tests have accurate diagnoses and that children receive treatment and short- and long-term follow-up as needed. It would help coordinate medical care and public health activities and services. The timely sharing of accurate data would give clinicians a full picture of a child's medical history and ensure that children receive needed preventive, screening, therapeutic, and follow-up services as well as eliminating duplicate work and services. Such a system would also allow for population-based decision making and would enable evaluations of the newborn screening program. Better policies could be developed, and programs could be better planned and implemented.

Over the long term, the CHI^2 program will allow clinicians and public health officials to engage in meaningful exchanges of health information. Such exchanges will reduce the reporting burden, help track infants over

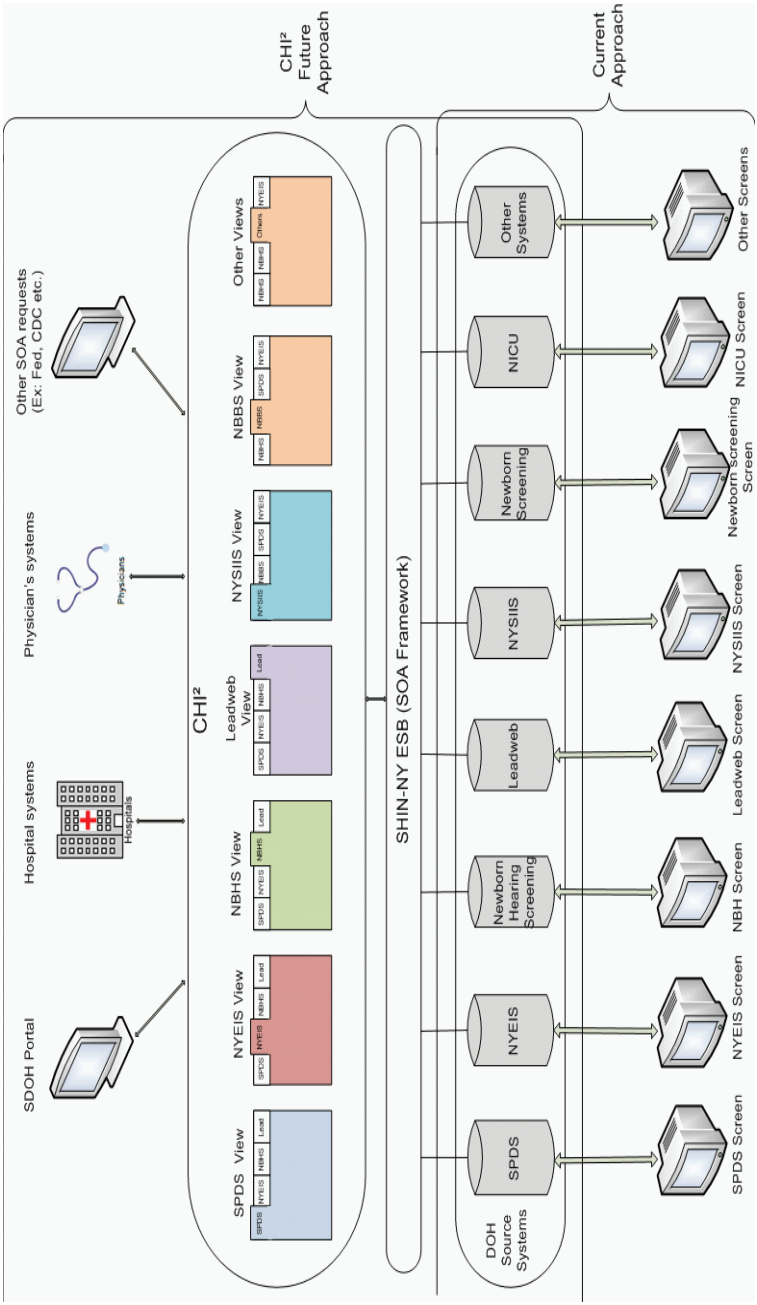

FIGURE 3-1 The CHI² vision of integrating public health databases (top) is juxtaposed with the current separated systems approach (bottom) used in New York State.
SOURCE: NYSDOH Child Health Information Integration Project; current as of May 2010.

time, improve diagnoses, help standardize data and diagnostic criteria, improve public health communication, and improve the quality of care. It could also help in locating missing children and detecting environmental exposures. In the short term, such a system could determine how many infants were born and not screened in New York State as well as how many babies who were screened in New York were not actually born in New York. It could also improve the quality of demographic data, improve tracking and follow-up measures, better track infant deaths, and provide for integrated childhood medical records (see Box 3-1 for an example of the potential use of the CHI^2 approach).

BOX 3-1
A Use Case for Integrated Information

To guide the CHI^2 project, a use case was developed to show the system in action.

A child is born and admitted to the neonatal intensive care unit (NICU) because of transient rapid shallow breathing and poor oxygen saturation upon delivery. Information about the child is entered into the hospital's systems and into all of the Department of Health systems that capture NICU and screening data. The child is determined to have no recurrent problem and is transferred to the newborn nursery for routine hospital care. A hepatitis B vaccine is administered, and this information is also logged into the system.

Shortly after that, a newborn heel stick is performed, a vital statistics workbook is prepared, and the child receives a hearing screen. The dried blood spot which was obtained is sent to the Wadsworth Center for testing and Dr. Goodfriend, the child's pediatrician, schedules a one-week checkup in her office to see the baby.

At approximately 1 week, Dr. Goodfriend is advised that the child had a positive screen for hypothyroidism. She tells the family about this positive result at the baby's 1-week visit and orders a follow-up test. The necessary blood samples are drawn and sent to the lab for testing. While the baby is in her office, Dr. Goodfriend accesses the CHI^2 data system and verifies that the hepatitis B vaccine was administered in the hospital.

The test results show that the baby does not have hypothyroidism. Her office calls the family to let them know that the follow-up laboratory tests were within normal limits and that the baby does not have hypothyroidism. The outcome is documented in the CHI^2 system.

After a few months the family moves to a different county. The child is taken to a new pediatrician, Dr. Wellness, for a 6-month visit. Dr. Wellness accesses the CHI^2 system and determines that the child has missed one set of vaccinations, which are then administered.

This use case reflects "our perfect-world scenario," Caggana said. Technology would be used to combine all the sources of information with all the support systems that a patient might require over a lifetime.

However, linking information systems raises major challenges in the areas of privacy, legal and regulatory considerations, and technology, Caggana said. The system needs to be secure and to comply with federal and state regulations. Only appropriately authorized personnel should be able to access the data and only for the information which is proper for them to retrieve. New regulations may be needed, said Caggana, to allow data exchange while still protecting patient privacy and security. For example, people working with the CHI^2 project have discussed how to maintain security, role-based access, and privacy if records are opened up to parents. Finally, many current technology systems cannot communicate easily with one another.

Despite these challenges, *not* instituting such a system would have much greater drawbacks, Caggana said. Data from electronic health records and regional health information organizations (RHIOs) would be more difficult and costly to use for public reporting purposes. The continued lack of a coordinated approach would make it more difficult for the Department of Health to share integrated child-related data with health-care providers. And practicing clinicians and public health programs would be unable to use existing Department of Health information to improve the clinical and public health outcomes of New York's children.

The long-term outcomes of having such a system are largely unknown, yet the system offers sufficient promise that New York State is vigorously pursuing it.

4

Concerns About the Use of Residual Newborn Screening Samples

Important Points Highlighted by Speakers

- Concerns about the use of residual newborn screening samples center on discrimination, inadequate security, loss of autonomy, unfair economic returns, the potential for abuses by law enforcement, and inappropriate governmental control.
- Recent events have increased the visibility of newborn screening programs and have demonstrated the potential for standard practices to raise concerns and generate opposition.
- Concerns about privacy are especially prevalent and need to be resolved in order for research to progress.
- State laws and regulations address some of these concerns but leave others unresolved and vary greatly from state to state.
- Transparency and oversight are essential to counter concerns about the use of residual newborn screening samples.

SEPARATING CONCERNS FROM ISSUES

The concerns that people feel about newborn screening should be separated from the issues surrounding screening, said Ann Waldo, senior counsel at Genetic Alliance. The concerns need to be understood first and then they can be analyzed to identify the issues that need to be addressed.

The number one concern that parents feel, in Waldo's opinion, is protectiveness toward children. "Every parent understands this, particularly if you have a newborn," she said. "If you see something that you think might harm your children, you are going to immediately feel opposition to that." Some of the fears about potential harm to children are vague and inchoate, but that does not mean that they are invalid. Sometimes people have a vague sense of unease for a good reason.

The sense of the unknown that surrounds newborn screening and genetic testing in general can generate suspicion and distrust. "If I were a parent trying to make this decision myself, that would be one of my bigger concerns," Waldo said. "I don't know what I don't know and I'm a little afraid of what I don't know." Furthermore, science and society have been changing dramatically in recent years and these changes can raise new issues that were not previously foreseen.

A specific concern cited by parents in informal discussions is the fear of discrimination. Perhaps if genetic or biological information about a child exists in a database, they say, it will be used to discriminate against that child. The Genetic Information Nondiscrimination Act (GINA) protects against some forms of discrimination, but it has limitations and is not widely known, so it does not eliminate the fears that people have. Furthermore, even if it were possible to guarantee that a child would never be discriminated against—which is not guaranteed under GINA—sensitive information could still be used to embarrass, humiliate, or ostracize a child.

Parents have raised many other concerns regarding newborn screening programs. The question of a child's paternity can become an issue if the results of tests are made known. Or, if a first child is born with a disorder and a family makes strenuous efforts to avoid having another child with the same condition, what message does that give to the first child? "Is it in effect telling the child that he is a regrettable mistake and you are going to redouble your efforts to make sure you don't have another one like him or her?" Waldo asked. "What does that do to a child's self-esteem?" Genetics research has the potential to make many decisions surrounding reproduction difficult. But "the train is unstoppable," Waldo said. "Even if all newborn screening programs disappeared, which would be a tragedy, genetics is going to be advancing, and we are going to have to face these tough questions about what to do with knowledge."

Newborn screening programs also raise difficult issues concerning autonomy, control, and choice. In the preface of the Texas lawsuit, one of the plaintiffs was repeatedly quoted as saying, "If they'd only asked me for permission, I would have said yes." Waldo expressed some puzzlement over this statement. If parents fear harm to their children from information being stored, then why would they consent to storage? Nevertheless, the desire for choice and control can take precedence in decision making. "People want to

be asked. Whether someone else thinks it's reasonable or not, [consent is] a very real concern." (Issues of consent are discussed in Chapter 5.)

Some state health departments have been accused, rightly or wrongly, of being overly cavalier about the use of residual dried blood spots, according to Waldo. Even if completely unfounded, such attitudes can easily fuel antigovernment sentiment.

Forensic uses of residual dried blood spots are another focus of attention and concern. People sometimes ask in public meetings whether dried blood spots can be used to obtain convictions—or exonerations—of family members. The expressed interest of some government agencies in using remaining newborn screening samples for forensics has raised the profile of this issue, said Waldo.

Waldo expressed reservations, as a former privacy officer at two large companies, about inadequate security. Making information secure takes considerable thought and effort. When samples are being used for research, either the state or the recipients of samples might have inadequate information security. Even if a university researcher is careful not to share information about the samples, for example, someone else at the university might hack into the researcher's database.

The use of residual newborn screening samples and information generated from those samples are not subject to clear-cut standards or laws, Waldo said. Repositories of residual newborn screening samples may or may not be covered under the Health Insurance Portability and Accountability Act (HIPAA), depending on whether the holder is within HIPAA's scope, so HIPAA provisions that were developed to balance competing needs, such as access to data in litigation, do not always protect newborn screening samples and information. Although there are constitutional limits on the use of newborn screening samples, in general the laws governing these materials are "unclear and not prescriptive," Waldo said.

The proprietary rights surrounding residual newborn screening samples also remain largely undefined. As has been discussed with the case of Henrietta Lacks, some people ask who will benefit from the research being done with their biological materials. If the public and sick children are the primary beneficiaries, people may have no concerns. But when large amounts of money and proprietary research are involved, people sometimes raise questions about the disposition of intellectual property and flows of money.

Related to questions concerning money are payments that states might receive from outside entities for furnishing blood spots for research or other purposes. This issue has been raised in media reports from Texas. Although the payments in Texas were very small—amounting to somewhere between $2 and $4 a blood spot, which the state considered nominal handling fees used to recover part of the taxpayers' expenses in providing samples to others—perceptions can be damaging. "That nomi-

nal administrative fee gets presented as, 'You sold my baby's blood. You bartered my [baby's] blood.' Headline writers have been doing a great job of finding these mellifluous headlines in Texas," Waldo said.

CONCERNS AND THE POTENTIAL FOR HARM

Other speakers also cited concerns raised by members of the public about newborn screening programs. Sharon Kardia said that whenever she meets with parents or other members of the public, she gets "a whole storm of questions and concerns that indicate we haven't done the necessary education," such as: Who owns the spots? Who is going to make money from them? Why didn't you ask me for permission to use them? What will we get in return for their use? (Parental and public education is the topic of Chapter 6.) Kardia also noted that in Michigan a frequent concern is that the use of residual dried blood spots will undermine community-based research networks, which are very active in investigating local health concerns in that state. If information is centralized, Kardia asked, will these networks disband and no longer have a say in health research?

Kelly Edwards, associate professor in the Department of Bioethics and Humanities at the University of Washington School of Medicine, also used a storm metaphor in describing public concerns. A "perfect storm" of stories in the media has focused public attention on this issue, Edwards said. A recent article in the *New York Times* was entitled, "Where'd You Go with My DNA?" (Harmon, 2010). The recent publication of a book about Henrietta Lacks (Skloot, 2010) and the return of genetic samples to the Havasupai tribe in Arizona, though both unrelated to newborn screening, have raised the public profile of screening. The family of Henrietta Lacks was proud that cells taken from their mother had led to immense contributions to science and medicine, but they were angry that no one had talked to them about what was happening and that many people were benefiting from this research while they could not afford health care. In the Havasupai case, there was a disconnect between the expectations of the different parties, Edwards said. Members of the tribe expected the samples to be used only for diabetes research, while the researchers expected that they would be able to do other kinds of research if the samples could not be linked to individuals. Thus, these two experiences illustrate what can happen when people manage genetic samples for purposes that the donors and their families do not understand and with no communication about what is happening to those samples.

Several important lessons can be drawn from these episodes, Edwards said. First, regulations currently provide the floor for what can be done, not the ceiling. Other standards may be needed to provide additional guidance. The researchers who were involved in the Henrietta Lacks and Havasupai

cases were following current regulations, "but clearly we need to go beyond that if we are going to build and sustain public trust."

Another lesson is that "business as usual" practices can cause harm. Researchers are not bad people who have intention to harm. Yet their research and public health practices can cause harm that was unanticipated or overlooked.

The way to avoid such harm, Edwards said, is to get a more diverse group of people offering input into decisions about how to manage samples and what kind of work should go forward. These decisions should not be made by a narrow group of people, because a narrow group cannot imagine what harm looks like to other people at other times.

CONCERNS ABOUT PRIVACY AND SECURITY

Sharon Terry, president and CEO of Genetic Alliance, elaborated on the many concerns involving privacy and security associated with residual newborn screening samples. Privacy is being redefined in the digital age, she said, when information about people is readily accessible on social networking sites. People are interested in sharing such information, but most are also interested in controlling it.

Perspectives on privacy vary widely. Terry cited the views of James Heywood, co-founder of the organization PatientsLikeMe, who contends that people have a moral imperative to share their health information. PatientsLikeMe has created a platform for collecting and sharing outcome-based patient data in order to benefit people with life-changing diseases. From Heywood's perspective, as members of the human family, all of us should care enough about others to share our health information and privacy should be a secondary concern.

On the other hand, Terry observed, many people have a protectionist view of their health information. She shared a quote by a nurse and new mother: "We were appalled when we found out. Why do they need to store my baby's DNA indefinitely? Something on there could affect her ability to get a job later on, or get health insurance." According to Terry, "we need to hear the spectrum [of opinion]. We also need to figure out how to balance all the needs."

Many parents are interested in being involved in research, especially translational research designed to yield advances in health, Terry has learned from her own evaluation of studies. But these parents also express concerns about the privacy implications of participating in research. According to a survey conducted by Harris/Westin,[1] 63 percent of people would permit

[1] The Harris Poll® March 26, 2007, "Many U.S. Adults Are Satisfied with Use of Their Personal Health Information—Significant minority still withholds information from health providers due to worries about security of medical data" Harris Interactive Inc. All rights reserved.

their personal health information to be used for research only if various privacy-oriented conditions are met. The message people give, Terry said, is that "we need to have some say about what happens."

The context of information is critical, Terry added. It is important where the information is created, where it exists, and who sees it. People make calculated decisions about their privacy, as when they are posting information on a social networking site or doing online banking. People do not understand all of the risks, but they decide that the benefits are worth the risks that they do understand. An additional factor for newborn screening is that parents are making decisions for their children, raising the question of whether children should be able to revisit those decisions and make different ones when they turn 18.

The Genetic Information Nondiscrimination Act protects people from employment and insurance discrimination. It does not protect them from discrimination in the areas of long-term care or life insurance. It thus offers some protections, Terry said, but not blanket protections.

Privacy and security will always depend in part on trust. This factor is hard to measure, regulate, or codify, yet it is essential for public health departments and researchers to do their jobs. Trust also influences how people interact and the messages they take away from those interactions. Wild rhetoric and blanket statements may reveal how someone feels, but they also can undermine trust, Terry said. Public health departments are not running amok and betraying people's trust. They are not blatantly violating privacy policies. Researchers do not care only about samples. The conversation needs to be nuanced and people need to trust each other if they are to move toward a solution that does not abandon research.

Privacy issues can make translational research difficult, but addressing them is essential. "There is dying going on right now," Terry said. "Every one of us knows somebody who could have benefited by research having been sped up." Yet difficult trade-offs arise. Is one dying child worth the privacy risks to many others, or even one other? Should privacy protection preferences be allowed to delay translational research for a given number of years? What are the responsibilities of individuals, nations, and all human beings? "Those are all really, really hard questions," Terry said, "and translational research runs into them all the time."

STATE LAWS AND PRACTICES

As of May 2010, at least 18 states had laws or regulations that specifically addressed both the storage and use of newborn screening samples: California, Indiana, Iowa, Maine, Massachusetts, Michigan, Minnesota, Mississippi, Missouri, Nebraska, New Hampshire, North Dakota, Oklahoma, South Carolina, Texas, Utah, Washington, and Wisconsin. Alissa Johnson of Johnson Policy Consulting provided an overview of state poli-

cies and practices and described several legislative initiatives directed toward newborn screening programs.

State policies and practices regarding the storage and use of residual dried blood spots vary widely. Some allow research uses if the research is conducted in accordance with established requirements. Others ban some research uses, while one—Mississippi—strictly prohibits the use of residual dried newborn screening specimens for research or purposes other than confirmation of test results. Other states probably have positions regarding the use of residual newborn screening samples, Johnson said, but these policies are not readily obtainable from available materials.

Some states allow parents to determine how samples from their infants may be used. For example, in California and Maine, where researchers may have access to specimens for approved studies, a person can prohibit the use of samples for program evaluation or research by submitting a written request. Parents in several states, including Michigan, Minnesota, South Carolina, Texas, and Washington, can also request the destruction of residual dried blood specimens after a defined period when the samples are no longer needed for screening purposes. Most state policies that permit research use of residual dried blood samples employ an opt-out approach, with samples being released for approved research unless parents indicate otherwise, but in Nebraska and New Hampshire researchers must obtain written consent from the parents of individuals whose specimens are being requested. In some states children, once they reach the age of 18, can request the destruction or return of a specimen.

Some states limit secondary use of residual dried blood specimens to research in specific study areas. A few permit research only on issues related to newborn screening. Wisconsin confines secondary use of samples to research and evaluation purposes related to congenital and metabolic disorders or laboratory procedures. Massachusetts offers participation in pilot studies of conditions that may be added to the state newborn screening panel in the future. Other states permit a slightly broader range of research. Iowa, for example, allows studies related to newborn screening, studies that can affect the health of a child from whom no other specimens are available, and studies that can inform existing public health surveillance activities. In some states, the language of policies or laws refers simply to medical research as a permissible use of newborn screening samples (see Box 4-1 for examples of permitted uses).

State laws or regulations on the secondary use of residual newborn screening samples typically only allow access by health department personnel, laboratory personnel, or researchers and other individuals who have been granted departmental approval. When access to specimens is granted to researchers, policies often state that the health department is responsible for the preparation of specimens and other information approved for the study. In California, Missouri, Nebraska, and North Dakota, the state

BOX 4-1
Example of Permitted Uses

In the state of Michigan, the Michigan Department of Community Health publishes a booklet that explains newborn screening and describes the kinds of research permitted with dried blood samples. It states, "The only studies that have been done and are allowed in the future are for medical or public health research. Some examples of studies that have been done include: (1) studying the incidence of different gene variants for an inherited condition (hereditary hemochromatosis); (2) developing additional laboratory screening methods (sickle cell diseases); and (3) searching for new disease markers (childhood leukemia)."[a]

[a] From "Newborn Screening Dried Blood Spots and Michigan's BioTrust Initiative." Available at www.michigan.gov/documents/mdch/FAQbooklet_269087_7.pdf (accessed May 20, 2010).

health department may bill researchers for these services. States that address research use also may require approval by an IRB and adherence to federal regulations governing the protection of human subjects.

Some states prohibit access to personally identifiable information if specimens are released, including Indiana, South Carolina, and Texas. Policies in Iowa and North Dakota require researchers to include in their study proposals a justification for accessing personally identifiable information. In California, Maine, Texas, Utah, and Washington, researchers who wish to access personally identifiable information associated with specimens may need to obtain consent from parents. In California, an IRB may modify the usual informed consent requirements for the release of personal information if it determines that the research has such public health value that the waiver is justifiable. State laws and policies may also dictate the use of anonymized or coded and double-blinded studies in research using residual newborn screening samples. In Michigan, for example, samples are sent to a biotrust and then are coded before they go to researchers.

Some laws and regulations dictate how long samples are to be stored, with retention periods ranging from about one month to an indefinite length of time. Similarly, policies in at least eight states require that information provided to parents regarding the newborn screening program discuss storage and use of residual dried blood specimens.

LEGAL CONCERNS REGARDING THE USE OF RESIDUAL DRIED BLOOD SPOTS

The issues surrounding state laws have become more prominent, said Ellen Wright Clayton, the Rosalind E. Franklin Professor of Genetics and Health Pol-

icy and director of the Center for Biomedical Ethics and Society at the Vanderbilt University Medical Center, because the types of research that can be done using residual dried blood spots have increased dramatically in recent years. Research done in the past to develop new and better tests could be considered quality improvement in newborn screening. However, new technologies have made it possible to do much more with residual newborn screening samples, such as longitudinal epidemiological studies with links to other sources of data. "It is a very different kind of research that we're talking about, moving away from the traditional issues that exist just within newborn screening to much broader and more expansive research," Clayton said.

The Office for Human Research Protections does not consider research that involves only coded private information or coded specimens to involve human subjects, as defined by federal regulations, as long as the following conditions are met: (1) The private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; and (2) the investigators cannot readily ascertain the identity of the individuals to whom the coded private information or specimens pertain because of such factors as an agreement with a key holder or IRB or legal limits. These two factors are critical considerations for newborn screening programs, Clayton said. Human subjects research requires one to consider the risks and benefits as well as whether informed consent is required and whether it can be waived or limited in any way. If these provisions do not apply, research using residual newborn screening samples need not take these steps.

Clayton used Utah as an example of a state where several issues are associated with state law. State regulations in Utah assert that dried blood spots become the property of the Department of Health. However, Clayton pointed out that property is not a unified thing. It is a body of rights and responsibilities that depend on context. "Just because I have a property interest in my house does not mean that I am free to burn it up to the ground. There are limits on what I am free to do." The argument that blood spots belong to someone and are property is "unhelpful and obfuscating," Clayton said.

The Utah regulation also requires the department to tell parents about its policy on retention and use, allows the use of residual blood spots for newborn screening quality assessment activities, and permits the release of blood spots for research if the following conditions are met[2]:

1. The person proposing to conduct the research applies in writing to the department for approval to perform the research. The application shall include a written protocol for the proposed research,

[2] Utah Admin. Code § R398-1-15 (2010) available at www.rules.utah.gov/publicat/code/r398/r398-001.htm (accessed August 26, 2010).

the person's professional qualifications to perform the proposed research, and other information if needed and requested by the department. When appropriate, the proposal will then be submitted to the department's internal review board for approval.

2. The department shall de-identify blood spots it releases unless it obtains informed consent of a parent or guardian to release identifiable samples. (De-identification is discussed in the next chapter.)
3. All research must first be approved by the department's internal review board.

These kinds of limitations are useful, Clayton said, because they address issues of oversight and transparency. In Texas, for example, a lawsuit made claims based on search and seizure, privacy, and liberty provisions in the U.S. Constitution, and a settlement was reached in part because of a determination that at least some of these claims were going to go forward as a matter of law. In this case, information released under a Freedom of Information Act request revealed that a proposed transfer of samples to the Armed Forces Institute of Pathology was not publicized because it raised ethical issues. "Anytime you don't want to talk about something, you had better think about it," said Clayton. "That's a life message that I give to everybody every day."

The Havasupai case is another example where oversight and transparency were slighted. In this case, the samples had been collected to do research on diabetes, but they were also used to study schizophrenia and, ultimately, ancestry. The investigator was quoted in the *New York Times* as saying that she was just doing good science. But Native American populations have always been sensitive about using their blood samples for ancestry testing, Clayton observed. "There needs to be oversight and accountability to make sure that those kinds of decisions—which are just not good decisions—do not happen." Most of the decisions made about the use of residual dried blood spots would be sustained with oversight. "But all it takes is one screw-up and you're toast."

Finally, Clayton raised the issue of using DNA for forensics, which she described as "the elephant in the middle of the room." Sometimes states have suggested that they would like to retain samples in order to help identify abducted children. "As a family law professor for many years, I have a really clear sense that the overwhelming majority of children who are abducted, are abducted in the context of messy divorces," Clayton said. "So if that is what your concern is, the answer is to collect DNA at that point, not on everybody."

Some have suggested that residual newborn screening samples could be collected for a comparison database. But this raises issues of having a genetic database of the entire populace that could be accessed by the police,

by Homeland Security, or by other entities. There is a general consensus that it is not appropriate to demand DNA from people for a general database that will be used for forensics purposes, Clayton said.

People working with residual newborn screening samples need to be very clear about what they are going to use samples for and what they will not use them for, Clayton said. "I am not surprised that people are not happy about the idea of the state holding on to DNA samples for a long time and not telling them what they're going to do with them." It would be legally complicated for a state to design a mechanism that would forbid the use of samples for forensic purposes. For example, it would be difficult for a legislature to pass a law requiring newborn blood spots to be retained for quality assurance and research but did not allow law enforcement to access them under any circumstances. Or it is possible that the Department of Homeland Security might claim to have a right to access whatever samples a state holds. Some people argue that the police ought to have access to newborn blood spots to identify someone who is guilty. "Whether the states are going to be able to navigate that territory in a way that protects them both from the police in their own states as well as from federal agents is a tough, tough issue."

Waldo added that states do have some ways of protecting sensitive information from law enforcement use. For example, a state can adopt an official policy to never honor an informal law enforcement request for data, which is where most of the abuses occur. Repositories and other biobanks can also do what HIPAA requires. Under HIPAA, if an institution gets a request for data, one of two things must be done before the request is honored. Either the patients must be notified with sufficient time to go to court and seek an order to quash or limit the request themselves, or the institution must take legal action to quash the request. This is not an illusory protection, Waldo said. Hospitals and insurance companies have challenged law enforcement agencies in court with great success.

In the legal sense, Clayton concluded, "to take the research issue out of context and not look at all the other concerns about DNA collections [would be] a mistake" which could jeopardize the entire newborn screening system.

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Review and Consent in the Use of Residual Newborn Screening Samples

Important Points Highlighted by Speakers

- An important distinction exists between anonymous samples that cannot be linked to an individual and de-identified samples for which linkage can be made by an outside party if research uncovers a finding of use to an individual.
- The process of review and consent needs to become more dynamic and flexible.
- Giving parents an option to opt out of long-term storage of samples rather than consenting for storage is less likely to jeopardize the public health newborn screening process.
- IRBs and other oversight authorities need to have a strong community representation.

DISTINGUISHING BETWEEN ANONYMIZED AND DE-IDENTIFIED SAMPLES

Alan Fleischman drew a crucial distinction between anonymized and de-identified samples, a distinction that is usually not appreciated by the public (and sometimes not even by researchers). Making this distinction is essential, he said, because it allows different rules to be set for different types of research.

Anonymous samples do not have identifiers that enable the samples to be linked with individuals. As an example, Kenneth Pass described the use of such samples in a blinded seroprevalence study for HIV in New York. The only identifiers retained with the samples were the mother's age, the gender of the child, and the ZIP code. "Using those three pieces of information, it would be literally impossible to go back and identify an individual specimen," he said. By the same token, however, anonymized data would, at least theoretically, make it impossible to find a subject who needs to be treated for a life-threatening disease.

By contrast, de-identified samples are coded and separated from identifiers. These identifiers are not held by the researchers themselves, but are instead kept by an "honest broker." In this case, the identifier can be retrieved and linked to a sample if necessary, allowing the person who donated the sample to be re-contacted if something is discovered that could be beneficial to his or her health.

Fleischman and several other speakers raised the issue of whether anonymous samples containing DNA could be linked to individuals. They acknowledged that this could occur. For example, Terry pointed out that additional data could be obtained to link the DNA in an anonymized sample to a particular person and such identification will become increasingly possible in the future. Fleischman observed, however, that creating such linkages would require the use of other databases. Careful data and sample access agreements with researchers can make it inappropriate and unethical for people to make such linkages. Other speakers pointed out that legal provisions can also be used to prohibit the identification of anonymized samples.

A SENSE OF STEWARDSHIP

Public health programs are the stewards of newborn screening samples, Kelly Edwards said, in the sense that these programs are responsible and accountable for the fair use of samples and for follow-up with the public. Stewardship implies program-level decisions about who has access to samples, for what purpose, and relative to what expenditures of resources. Stewardship is also related to accountability for fair use, ethical practices, and follow-up with dissemination where appropriate, Edwards said.

More broadly, stewardship means taking responsibility for the care and well-being of something that is valued, Edwards added. It entails the science, art, and skill of responsible and accountable management of resources. A steward assumes responsibility for the donor's intent, the manner in which resources are used, and the outcomes from their use. Achieving these objectives requires that stewardship be built into governance strategies, Edwards said.

In the case of residual newborn screening samples, it is not enough to rely on bare minimum safety standards. What is needed is a standard of excellence that goes well beyond the minimum standards. For example, Edwards said, when genomic samples are identifiable, they should be traceable so that research participants can learn who has their samples and how they are being used. Similarly, the research loop needs to be closed so that people know how their samples contributed to a published paper or to changes in research or health care. "Those are very simple things to keep track of," she said, "and we are at risk if we cannot let people know how we are using their information."

MAINTAINING PUBLIC TRUST

Trustworthy practices will be key to the long-term success of newborn screening programs and research, said Kelly Edwards, but current regulatory systems and practices may not be sufficient to sustain the trust of the public. The current system relies largely on upfront review and consent. Review traditionally consists of an IRB or a department of health reviewing a proposal for the use of residual newborn screening samples. Consent traditionally consists of telling people up front what will happen to them and to their sample and asking for their permission. "As long as we tell you everything up front and you sign that piece of paper, we are ethically in the clear," Edwards said.

These processes place a very heavy burden on review and consent. They offer little or no opportunity for ongoing follow-up, for checking on how samples were used, or for determining what outcomes happened as a result of a project.

Traditional forms of consent can be especially problematic. People cannot easily absorb such large amounts of information at once. They often do not completely understand what they are consenting to, much less the detailed risks and benefits relevant to the decision. Furthermore, while consent focuses on individual privacy and autonomy, there are also harms to groups that can result from research. Alternatives such as anonymization that reduce reliance on consent can reduce the amount of regulatory review, but the resulting lack of identifiers may cause researchers to forgo richer research results, forfeit valuable connections with research subjects, and have less control over ethical issues. Furthermore, one-time consents do not allow appropriate responses and modifications that reflect the rapidly changing nature of research and of society.

The use of residual newborn screening samples in research raises special considerations. Newborn samples are collected for a public health purpose, which places an even greater onus on the people who collect and use these samples, Edwards said. If plans change about how a sample will be used,

that information needs to be communicated to the public. These are mandatory programs, which means that the bar needs to be set especially high when engaging people about their participation and about secondary uses of their materials.

Consent should not be abandoned, Edwards said. The challenge is to build a responsive system that would be more dynamic and flexible as circumstances change over time. The result could be a transformation of research practices and oversight that brings benefits to both researchers and research subjects.

NEW WAYS OF THINKING ABOUT CONSENT

Consent is sometimes confused with the idea that people must have control over their own data, Edwards said. But the more important issue is conveying respect. Researchers must have enough respect for members of the public to have a conversation with them about what is happening. Consent conveys respect by asking questions and inviting participation. It permits the expression of diverse beliefs, values, and preferences. And it provides an opportunity for education and outreach (which are discussed in Chapter 6). "The consent process is a perfect place for education to happen," Edwards said.

A range of consent options needs to be available for use with residual newborn screening samples. Some states and research repositories use a community consent model in which town hall meetings are held to let people know about research using their samples. Blanket consent at birth releases a sample for any and all research purposes in the future. Tiered consent at birth gives individuals some choices about how a sample is managed. A waiver of consent may be used with identified, de-identified, or anonymized samples. Potential research subjects can be notified that work is being planned and be given an opportunity to opt out or to withdraw a sample if they do not wish to participate. Finally, each individual can be reconsented for each new use of a sample.

Edwards argued that two of these options satisfy the goals of maintaining public trust and keeping the community engaged in the research enterprise: recontacting and reconsenting.

Recontacting and reconsenting have many advantages in the review and consent process, Edwards said. They can help create partnerships, relationships, and opportunities for public education. They keep participants engaged and informed about research activities. They can contribute to science literacy and create good will toward public programs and the research enterprise. "You are enlisting people into the excitement of the work that you're doing, [letting them know] why you think this is a good idea, and getting them on board with you," she said. "This is a real opportunity."

Edwards cited Washington State as an example of a state that has sought to maintain public trust through a stewardship model using reconsent. Data are released to researchers with written informed consent from parents and IRB approval from the Department of Health and Department of Social and Health Services. Anonymous samples may be released if the department determines that the intended use has significant potential health benefits and that each of the following criteria has been met[1]:

- The investigation design is adequate to ensure anonymity.
- All newborn screening tests have been completed.
- At least one fully adequate spot will remain after the anonymous sample has been taken.
- Sufficient resources, including personnel, are available for sampling.
- The Department of Health/Department of Social and Health Services human subjects research review board has reviewed and approved the investigation.

Residual newborn screening samples have been used in Washington State to study type 1 diabetes, hearing loss, maternal smoking, H1N1 infection, and lysosomal storage diseases. Participation rates for reconsented studies have been as high as 90 percent. (For example, in the type 1 diabetes study, approximately 104,000 of the 116,000 people contacted agreed to be in the study.) Since 2004, out of 450,000 births, there have been fewer than 10 requests for destruction of blood spots.

"People are worried about privacy, yes, but they are willing to take those risks if the payoff is worth it," Edwards said. "So the onus comes back to us to say, 'What kind of research is going on? Is it worthwhile research from the health benefit point of view? And is this something that we can keep the public excited about?'"

THE USE OF TECHNOLOGY IN CONSENT

Edwards pointed out that technology-based ways of managing consent can provide people with a dynamic interface with which to make choices and, in particular, smart informatics tools can help cope with diverse beliefs. "We are not going to be smart enough to anticipate all of the harms and how they might be perceived by others," she said. "We are going to need informatics help to make this feasible."

Sharon Terry elaborated on the ways in which technology can contribute to thinking about consent in new ways. Social networking sites

[1] Criteria available at www.doh.wa.gov/ehsphl/phl/newborn/privacy.htm (accessed August 23, 2010).

and other new applications of information technologies, though not yet prominent in medicine or biomedical research, can yield very strong privacy protections. People in all socioeconomic classes can interact with the health-care system through such means as cell phones and computers in libraries or other public places. But different people need to be reached in different ways, so reliance on a single system is not optimal.

One new technology cited by Terry is a system called PrivateAccess (privateaccess.com). It provides parents with "dynamic consent," allowing them to provide different kinds of consent at the time of pregnancy, at the time of the birth, and later as well as giving them the option of changing their preferences through an online system. The preferences can be very specific. For example, a parent could give permission for a blood spot to be used for quality control for the newborn screening lab but not for behavioral research. In addition, new technologies can generate audit trails of requests for information, so that the uses of information can be monitored and controlled. Newborn screening would make an excellent test case for such a system because of how it would let parents change their consent declarations over time.

The issues associated with newborn screening are exciting because they are going to push the system, Terry said. If states decide, as Texas did, to destroy their samples, a great public treasure will be lost. Parents will lose the opportunity to have choices about how their child's blood spot is used. Terry expressed confidence that a poll of parents in Texas would have led to a different result. "The case was decided by a few parents and their representatives," she said.

ISSUES WITH EXPANDED CONSENT

The issues associated with consent generated the longest and most detailed discussions of the workshop. In particular, several speakers and participants raised questions about whether the consent process should differ in form or substance from what is typical today. Ann Waldo pointed to a study by the University of Michigan establishing that roughly three-fourths of people would be willing to have their children's residual newborn screening samples stored and used in research if a consent mechanism existed. If there is no consent mechanism, roughly three-fourths say no. Terry pointed out that not asking for consent for the use of residual newborn screening samples can open the door to lawsuits. "So consent really does matter," said Waldo.

Requiring retention of residual dried blood spots would necessitate making storage as compulsory as the census or newborn screening according to Terry. These are programs that have been implemented on a national scale and require mandatory participation. Terry expressed doubt that every

state would be able to mandate storage, since the public in at least some states would not agree to such a provision.

Asking for consent to store residual dried blood spots may also pose a risk if parents interpret such a request as consent to be screened. If parents in large numbers began to refuse screening, an extremely valuable program could be destroyed. For this reason, Alan Fleischman argued that parents should be offered the choice to opt out of long-term storage of samples for research unrelated to the newborn screening program, but only after the blood samples have been obtained and screened. Offering the choice of opting out of storage is less likely to jeopardize the public health program than asking for full and informed consent for storage, Fleischman said. This is a consequentialist argument based on believing that the processes of committee review ought to be able to reassure families that opting out is a sufficient protection for their families' interests. Although research involving identified subjects requires an appropriate and informed consent process, the vast majority of research now being done with specimens requires only that families be asked whether they want to opt out after their babies have been screened, Fleischman said. In the best of all possible worlds, families would be engaged in a comprehensive consent process, he added, "but opting out after full informing seems to me to be a very reasonable process for most of the research we're talking about, until we reach those types of research that require identified subjects."

Families need to understand that they may benefit from having their specimens stored in case something happens with the family, Fleischman said. They also need to understand that the research to which they are being asked to consent will not have identifiers. They should also be reassured that if any identifiable research is done with individuals in the family, permission will be asked. "We should support those models and study them, and then we ought to develop some practices across the country that will emulate the best practice models," he said.

Anne-Marie Comeau objected to giving families a choice to opt out of storage, however, because half of the population could say that they do not want their specimens stored. "Consenting to storage is possibly throwing away the national resource that we are all trying to protect for individual and societal benefits," she said. Families should be reassured about the use of their samples by storing and treating specimens responsibly and appropriately. Edwards added that a research repository governance system needs to have built-in accountability mechanisms that track the research uses of repository samples and data, that incorporate plans for risk management, and that establish recourse or consequences if breaches occur. "It is not satisfying to the public to say, 'Well, they won't get to use the data again if somebody violates this agreement.' That is not good enough." Transparency about accountability systems will help build trust, she added.

Wylie Burke pointed out that an important distinction exists between the storage necessary for maintaining a high-quality newborn screening program and storage for research unrelated to the newborn screening program. Even if the storage process is the same, the distinction is material to parents. Programs should be able to label certain samples that have been stored as not available for secondary research. Laboratorians would then determine how long samples should be stored for purposes related to the public health program and storage for that length of time ought to be part of the mandatory public health program. If half of parents still opted out of de-identified or anonymized research, more deliberation would be needed, Burke said. But a distinction needs to be made between maintaining a good public health program and supporting secondary research uses.

Fleischman expressed the opinion that with the proper public education very few families would choose to opt out. He pointed to the experience in states like South Carolina and Michigan where people are not opting out and are accepting anonymized research. Conversations should be held with the small number of families that do choose to opt out so that the families understand the consequences of their decision. "If they continue to believe that that is best for their family, then they have opted out," he said, "and I think you have to destroy the sample after the testing and the public health program." In states where the samples have already been gathered without a consent process, he said, there should be a dialogue with the public in order to decide on the appropriate policies.

Fleischman also argued that it is important to make distinctions between different kinds of research. In fact, he argued that the word "research" should not be used as an overarching concept for how the samples are used because it can sometimes be seen as a pejorative term. Comeau agreed that consenting to different kinds of research is acceptable, but she maintained that consenting to storage should not be an option.

Edwards emphasized that people should always have the right to say that they do not want their samples to be in a study. So far, the newborn screening program in Washington State has used anonymized samples only for test development. The samples have not been used for epidemiological research. "The Washington State newborn screening program directors are taking their job as stewards of this public health program very seriously," Edwards said. They have chosen to maintain high standards to meet public expectations and have insisted on proactive consent if research samples are identifiable.

If people in Washington State were told that samples would be retained for future research, a review process would be carried out to determine if people need to be re-consented, Edwards said. The usual IRB reviews would then come into play. What she would advocate is an ongoing communications strategy that would inform people what is being done with

de-identified samples. Fleischman suggested that governors annually sponsor a public forum to discuss what has happened with the newborn screening program during the past year, although several workshop participants thought that such a forum could become a venue for expressing skepticism and particular viewpoints.

Even if it is not possible to recontact and reconsent everyone involved in a given research study, Edwards said, there should be an ongoing review or oversight process that would help build trust in the process. For instance, a community advisory board could help researchers make decisions about the use of samples in a biorepository. Such a board could also help determine when it is necessary to recontact potential research participants and enhance transparency—for example, by keeping a running database of what has been done and what results have emerged.

Consent can be problematic when it is taken to either extreme, Waldo said. If the claim is made that the government can do virtually anything with IRB approval, "my autonomy buzzer ... is going to go off." On the other hand, requiring consent for each and every use of residual dried blood spots, even if the research does not involve personal identifiers and has very little risk, is excessive and would severely constrain this kind of research.

Waldo suggested that thresholds of risk could be established beyond which consent would be necessary. New technologies could be a game changer for such an approach. If dynamic consent forms could be accessed through cell phones or an e-mail account and people could be in regular communication with the holder of their preferences, then granting consent could be done quickly and efficiently.

On the other hand, altering consent preferences or adding new consent options could lead to a significant resource constraint for state programs. The director of one state public health laboratory stated that a law or regulation to track consent or dissent in the use of existing residual dried blood spots would be impossible to adhere to with current budgets. States have enough trouble tracking their citizens for more immediate purposes; tracking them for consent to research would be much harder. Alissa Johnson agreed that in her discussions with state newborn screening programs, the issue of resources came up repeatedly. A few states allow the program to charge researchers for the preparation of specimens, but that clearly does not cover the expense of tracking consents and the extra burden which is put on these public health agencies.

The cost of obtaining consent need not be borne fully by the departments of health. Edwards suggested, for instance, that departments should issue a notice to researchers saying that they should set aside extra resources for the recruitment and consent process and for health department staff to prepare and deliver samples. Isn't the investment in open communications worth the ability to keep using this resource?, asked Edwards. However,

academic researchers at the workshop suggested that they would not be able to do their research if they had to contact the thousands of people who are involved in their studies and ask for consent. Confounding this issue is the potential for adding bias into the results by only evaluating samples from consenting individuals.

Terry disagreed and said that dynamic consent need not be expensive and could eventually become as practical as online banking or the use of credit cards. As a system becomes more familiar to people and is more widely used, she noted, it becomes less expensive. Furthermore, there is a business incentive because pharmaceutical companies are interested in enlisting research subjects with dynamic forms of consent. People can decide whether to consent just for quality control experiments, for all disease research, or even for forensic research. And they could change their minds. If a friend or acquaintance gets a disease, a person could update his or her consent to participate in a study that would help that person. Research would be participatory.

In addition, Ellen Wright Clayton pointed out that money tends to follow good ideas. Partnerships with federal and state agencies, communities, disease advocacy groups, or philanthropies can bring in resources.

Given the prospect of future uses, residual newborn screening samples should not be destroyed, Clayton and several other workshop participants urged. Nor is it necessary to enroll research participants retrospectively. "We can enroll more than 4 million a year in the country," she said, "so it would be much better to be prospective about all of this."

Having a diverse set of state policies, said Fleischman, could be useful because the experiences of different states will reveal valuable lessons. At the same time, however, Waldo urged the federal government to generate guidelines and standards that states can use in developing policies.

THE ROLE OF REVIEW BOARDS

Several speakers emphasized that the involvement of review boards is very important in building and maintaining public trust. These boards can assure compliance with laws and regulations and can identify and explore issues that may not be immediately apparent.

Comeau recommended that approvals from review boards be project-specific. "The idea of a general consent for general access to newborn screening specimens is only going to cause problems," especially in the area of public trust, she said. Just because a project has been funded does not necessarily mean that it has been completely thought through. If review boards are appropriately educated to understand the pros and cons of such research, review can produce benefits for everyone involved in a project.

In universities and departments of health, IRB review is necessary but not sufficient, Fleischman said. Once an IRB review is complete, there should be a secondary review by a group more oriented toward stewardship and with a stronger community influence. Review by groups with multiple people who represent the community from which samples have come can make sure that the interests of all stakeholders are represented.

A number of states, such as Michigan and South Carolina, have already taken initial steps to involve communities in the review process in more substantive ways, Fleischman said. "In South Carolina, in a brochure, parents are told what happens to [their] baby's blood sample after the lab test and they are told they can decide. Similarly, in Michigan, they can make a [choice]."

Community-oriented review boards may also be able to help make some of the tough decisions involving prioritization of research projects with residual newborn screening samples. Blood spots are finite resources, and newborn screening programs will not reduce the sample to zero, according to Ken Pass, because they are saving a certain part for the family. He continued by saying that research results are not foreseeable, and it is not known what future scientific advances will make possible. "We have to make decisions and set priorities about how those resources are going to get used," said Kelly Edwards.

TRANSPARENCY IN SCREENING PROGRAMS AND RESEARCH

Review boards offer one way to increase transparency in the uses of residual newborn screening samples, but other steps are necessary as well.

Clayton asked that departments of health be more specific and open about what they are claiming and what they are not claiming. If states want to claim the royalties from intellectual property developed with residual newborn screening samples, she said, they should state that explicitly.

States also need to be proactive in making information available about the options for parents. In Minnesota, for example, an opt-out provision was established that enables parents to control the use of their children's screening samples for research, but, said one workshop participant, the state and hospitals did not do an adequate job of making parents aware of the provision.

Burke read a letter to the workshop from Logan Spector, chair of the Epidemiology Steering Committee of the Children's Oncology Group, who wrote, "While the scientific value of residual newborn screening samples is unquestionable, their long-term storage creates an undeniable tension between public health research and personal autonomy. It is our position that this tension can be alleviated through proper research protocols which include transparency and explicit declaration of the possible future uses of

the samples." He also wrote that "to allay concerns about the potential misuse of samples held by states, we support a strong firewall between legitimate research uses and their use for law enforcement, litigation, commercial, or insurance purposes."

Transparency may in some cases extend to the data generated from samples. Sharon Kardia, for example, observed that the procedures used and the data generated in research need to be transparent to the public. When researchers can see the data but the public cannot, that situation creates mistrust. Participants at the workshop also discussed the Personal Genome Project, in which participants who enroll must be willing to share their genome sequences and personal health information with the scientific community and the general public. According to Waldo, the people who are participating in the project are told, "We have no idea what will happen to your data and we offer you nothing in terms of protections, and if you want to do it anyway, go ahead." Yet a large number of people are agreeing to those terms.

Waldo drew a parallel between transparency and the concept of materiality in consumer protection laws. Advertisements are required to make clear and conspicuous disclosures of everything that a reasonable person would find material to the transaction. Following this consumer protection principle, the transaction of collecting a blood spot would include a disclosure of what kinds of research the sample might be used for and what sorts of protection would be applied. If the subject objected, an opt-out mechanism would be available. Where consent is required, "you need to make sure [parents] know how [a sample] is going to be used and saved and give them some sense of the risks," Waldo said. "I think that is only fair."

People also have a reasonable expectation of privacy, Waldo said. This can boil down to a judgment call—and legal arguments—about what is reasonable and what is not. But this expectation can lead to greater transparency by encouraging the disclosure of which information will and will not be confidential and secure.

Waldo also urged that samples not be destroyed, pointing out that the process in Texas that led to the destruction of samples was far from transparent. The decision to destroy the samples was made behind closed doors without legislative hearings or public input, which in turn raised objections from members of the public. At a recent hearing in Texas, Waldo said, a father came forward to say, "My child's blood was destroyed and I'm really unhappy about that. My child died of a rare disease and I wanted that blood made available so that other children wouldn't go through what my child went through."

A large amount of valuable epidemiologic research goes on without patient or parental consent, Clayton said, and this is generally appropriate.

Transparency can make possible the oversight and accountability needed for this research to proceed.

BUILDING RELATIONSHIPS

Review and consent are not necessarily ends in themselves, several speakers noted. They should instead be part of the process of building relationships. Consent is not just about risk disclosure. It is more about the shared expectations that everyone will be on the same page and that public communication will be incorporated into the research process. If the reasons for retaining samples have changed—because, for example, they are going to be used in new forms of research—then people need to be informed. This new information may be passed along in the form of a written consent process or via a public information campaign, but the public needs to be brought along, Edwards said.

Relationships are based in part on trust. For that reason consent and review need to be more inclusive. "Consent is actually a symbol for something else," said Kardia. The consent and review process is equally about assurance and building relationships over time.

Trust involves concern for others. The use of a residual blood spot for research is, in essence, the first altruistic gift that an individual makes to society, Fleischman said. It is an optional gift, but it is made in the interests of future children whose health will be better than if that gift were never made.

6

Parental and Public Education

Important Points Highlighted by Speakers

- Education for parents and the public is essential to inform people about the collection of newborn screening samples and how those samples are used.
- Communication requires mechanisms for listening and gathering information as well as for speaking about and disseminating information.
- Making the benefits of newborn screening programs more apparent would help build public support for these programs.
- States may need financial support from the federal government to establish the necessary infrastructure for parental and public education.

THE NEED FOR OUTREACH

As Sharon Kardia observed, people tend not to know much about newborn screening programs. They also know very little about how residual dried blood spots are used after they are collected and tested. The fact that newborn screening has occurred largely "under the radar" is a vulnerability, Kardia said. Many researchers will forego studies using residual newborn screening samples if the pressure from the public gets too high. Yet the research opportunities are so great that efforts need to be made to bridge

the divide between the research community and the public. According to Kardia, educating the public about the public health infrastructure will be necessary so that people will be informed about the collection of data and the way that this information is used on their behalf.

The parents and others who have raised questions about this topic are not necessarily anti-science, Kelly Edwards noted. The Havasupai people were deeply interested in health research that was going to benefit their community. Many of the Texas parents involved in the lawsuits were also supportive of research. They were angry because they were not asked before samples were used outside of their original scope or intentions.

Edwards participated in a working group of the Trust, Integrity, and Ethics in Science (TIES) Project, which has convened representatives from a number of industries that require the public's trust (Yarborough et al., 2009). Rebuilding trust that has been lost involves two basic actions, she said: fostering multiple types of relationships and developing accountability practices that exceed those required by external regulators. In particular, in building relationships it is important to engage the public proactively rather than in response to an adverse event. "Be out there early and often so they know you and you are a trusted face." Then, if something does happen, people will be willing to listen to what you have to say.

Screening programs need to direct their educational efforts to health-care providers as well as the public. "The average pediatrician in his or her office today and the average obstetrician knows little, if anything, about this program," Alan Fleischman said. Pediatricians may appear to be somewhat unconcerned about initial positive results from newborn screening because they know that true positives are relatively rare. One consequence is that health-care providers are unprepared when they encounter a negative response about screening programs from patients. Fleischman added that ways need to be found to provide education to health-care providers without burdening obstetric or midwife professionals.

State legislators, some of whom have expressed considerable suspicion and distrust about newborn screening programs, should be another target for education, Fleischman said. But Anne-Marie Comeau countered by noting that legislators are responding to what they see as pressure from constituencies. Education that is targeted at legislators, unless complemented by public education that defuses political pressure, may not do the job, she said.

FORMS OF OUTREACH

Only eight of the states whose laws and regulations could be identified require that information provided to parents regarding newborn screening programs discuss the storage and use of residual dried blood spots, said

Alissa Johnson in her review of state policies and programs. Any education for parents should cover not just how the samples are used but the screening program in general, Michele Caggana said. "When we talk to parents and they get an understanding of the entire program, it really does help them to say, 'Okay, this is helping my child, it's helping other kids.'" Many different forms of parent education are possible, Kardia said. Public service announcements can be effective and new ways of educating community members about the process of obtaining consent offer great promise. Caggana observed that one effective approach is to describe state policy in a very brief form in either a brochure for parents or on the screening form itself. In New York State, the brochure that parents receive has contact information and gives parents a number to call if they want to opt out of any research use or have a screening specimen destroyed. Kenneth Pass added that one-time programs are not effective. Education has to be a continuing process, he said, "because the babies are continuing to come."

Caggana also pointed out that coverage of newborn screening programs in the media can have both positive and negative consequences. Media coverage has helped the New York State Department of Health's Wadsworth Center review and formalize its policies, she said. "It helped us to write things down and make sure that we were doing things to the best of our abilities. And it opened dialogues between the parents in our state and the screening program." Caggana always makes sure to invite parents to visit when they call her department and parent groups, genetic foundations, and advocacy groups have all expressed interest in visiting the facility.

As an example of a system that could generate considerable good will among parents, Caggana pointed to a familiar problem: getting a child's immunization chart for a school, summer camp, or extracurricular activity. If parents had access to the immunization registry in New York State, they could go online, print out their child's chart, and deliver it wherever it was needed. "[Parents] would not have to call the pediatrician, go over there, drop the form off, go back, and pick it up. On that very simple level, this could only result in a useful thing for parents." Kardia added that such a system would also help parents understand the public health system by involving them directly with it. This is important because parents have many ideas about newborn screening that are seriously off base. "When we went to these town halls, the first half of the conversation was about the conspiracy theories that they had," Kardia said. "They were deep and they were wide, and they were getting nods from across the room in terms of what was happening and why it was happening. It was a huge wake-up for me." If parents had access to their children's immunizations, Kardia said, it might generate a lot of social capital.

Ann Waldo urged that the benefits of newborn screening programs be made more transparent, with more visible and tangible links to parents.

Perhaps a newborn screening program could send information directly into an individual's public health record, or maybe a blood spot could be reserved indefinitely for possible future uses that could improve an individual's health.

Comeau agreed that providing the public with services that they see as beneficial would be useful to newborn screening programs. But she cautioned that the first priority of these programs still needs to be newborn screening.

Kardia asked where the money will come from for education. Ensuring that research can continue requires education, but finding funds for education is difficult. Several speakers pointed out that newborn screening programs have a common interest with research institutions, universities, biobanks, and other organizations in assuring and explaining the trustworthiness of the research enterprise. Partnerships directed toward broad public education campaigns could have specific benefits for newborn screening programs.

The states may need some help from the federal government to set up the necessary infrastructure for communication, Fleischman said. Resources are not easily obtained within the states to offer educational programs, enhance transparency, and strengthen oversight.

In addition, new and creative approaches to education are needed. For instance, Facebook or Google ads could let people know about the existence of newborn screening, since so many parents do not know that their babies were screened. Baby expos could be used to reach out to prospective and new parents. Viral networks, social networking sites, and other new media can enhance transparency and education. "It will be much, much easier than trying to tell us something with billboards," Sharon Terry commented.

THE LIMITS OF EDUCATION

Parents have a limited motivation to absorb this information, Comeau said, particularly when the information concerns a program that will find only rare instances of harmful conditions. "To spend a lot of money and time designing specific newborn screening [educational materials], I think all of us have been through that at some level, and I am just not sure about [its effectiveness]."

Clayton said that the period of labor and delivery is the wrong time to try to educate pregnant women about newborn screening. A much better time would be during pregnancy. Obstetricians may object that they are too busy to provide such education, but "that's nonsense," Clayton said. "If we're going to talk with parents or potential parents about newborn

screening, the time to do it is when they're prepared to listen, which is not in the 24 to 48 hours postpartum." And even prenatal education is not enough, Comeau added, because 20 to 30 percent of pregnant women do not access prenatal services.

The time lines for education and for research are different, Terry pointed out. Research can take a long time, whereas decisions about newborn screening often have to be made quickly. "How do we both keep up the energy and the urgency but also temper it, knowing that we need to be mindful and thoughtful?" Terry asked. The approach she urged is one of tempered urgency. Virtual communities might accelerate social change, but the "people part" of change still tends to be slow.

7

Workshop Overview and Wrap-Up

Residual newborn screening samples represent an unparalleled resource for translational research, said Wylie Burke in her concluding overview of the workshop. These samples are gathered from almost the entire population; they yield multiple measures of health and disease, both genetic and non-genetic; and information derived from them can be linked to other health databases, allowing a very wide variety of useful research to be undertaken.

Yet people are concerned about the use and retention of residual newborn screening samples, expressing concerns about discrimination, security, and use in forensic investigations. As one speaker at the workshop noted, parents have a fundamental desire to protect their children against unknowns that they cannot fully define. These concerns point to very important policy issues.

Newborn screening is a highly successful public health program. It provides important benefits to children and families. The core mission of this program needs to be safeguarded stressed Burke. Yet this resource also offers tremendous opportunities for translational research if the potential tensions and problems can be addressed.

Some newborn screening programs have exhibited a lack of transparency and accountability. If parents do not know that newborn screening is being carried out, they cannot access information about the program. Only 18 states have policies transparent enough to analyze, and state politics remain highly variable.

The variability among states means that important lessons can be learned from different experiences in different states. On the other hand,

national guidelines might be helpful in identifying good models and asking how these models might be further disseminated. For example, a uniform definition of "de-identified" could help ensure that security measures are appropriate to the associated level of risk.

Not enough has been done to bring families and physicians along in understanding newborn screening, Burke said. Stakeholders need to think about how to move forward proactively. Clear measures for accountability need to be in place, with appropriate steps to be taken when inappropriate actions are performed.

Trust is essential, but trust requires trustworthiness. Building trust requires dialogue to identify common ground among researchers, the public health officials who implement newborn screening programs, and the public that is affected.

Tough issues require additional deliberation. The right thing to do cannot be determined in advance for every circumstance. For example, the use of residual newborn screening samples in forensics has generated considerable concern. But forensics use can take on many different forms, from looking for the cause of death in DNA to creating databases that will be available to the FBI for criminal investigation. Burke called attention to the need for further discussion and clarification of the use of samples for forensics in order to determine appropriate and inappropriate uses and the corresponding policies that are needed.

Another difficult issue involves the destruction of samples after parents opt out. Different stakeholders may come to different conclusions. National deliberations involving all of the stakeholder groups could help identify more robust models.

The need for quality assurance in various areas, from the public health programs at one end of the spectrum to the reporting and use of research results at the other, raises many issues. For example, at what point do researchers cross a line between moving forward with appropriate IRB review alone and receiving formal individual consent? Different kinds of research have different needs and demands and these differences need to be communicated effectively to the public, said Burke.

Large sets of samples have been gathered without consent. These samples have great value for research. For example, Michigan has created and incorporated a nonprofit biobank that holds the residual dried blood spots collected in that state over the past 25 years, about 4 million altogether, for which the state has no plans of getting consent. Under what conditions and circumstances can these samples be used?

Education has to occur at multiple levels—both before and after a woman gives birth, for instance, and with mothers, families, and the general public. People need to be much more aware of newborn screening programs and the potential for secondary research emphasized Burke. Public service

announcements as well as more targeted outreach could play an important role in accomplishing this.

Health professionals also need enhanced levels of education, especially those who are involved in pre- and post-natal care. But what works? How can information best reach people? What kinds of media and message should be used? How can these issues be clearly explained? How will this information dissemination be funded?

Resource constraints are a major problem, Burke said. One must have resources in order to store samples properly, to implement appropriate opt-out and informed consent procedures, and to develop policies on tough issues and ensure that all stakeholders are engaged in that policy development. Public health agencies will have a very hard time taking on all of these tasks on their own.

Finally, trust requires good stewardship of samples. Yet it is not clear what good stewardship entails in this setting. Who should be involved, how should the public be involved, how should information be communicated to the public, what kinds of access policies are consistent with good stewardship, and who gets access to the data?

All these various questions lead to one final tough question: How can priorities be set for doing research on these precious resources? The samples were collected under a mandate for public health, yet they have a rapidly expanding array of potential research uses. What kind of responsibilities for reporting back to the public does an honest steward assume?

In a final comment, Ellen Wright Clayton emphasized the distinction between newborn screening for public health and the secondary uses of residual newborn screening samples for research. These two activities raise different kinds of concerns. It is easy to be defensive about criticisms of newborn screening programs and associated research activities. But it is also important to look into the issues behind the criticism, Clayton said. "Almost always there is something that we need to attend to, that needs to be paid attention to, and I would caution us to do this. Our job as people who care about science and about improving health is to help people understand what research is about and the idea that research in fact is not something that is done in everybody else's backyard. I think we have to take on that mantle and do that work."

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Appendix A

Workshop Agenda

Challenges and Opportunities in Using Residual Newborn Screening Samples for Translational Research: A Workshop

May 24, 2010

The Keck Center of the National Academies
500 Fifth Street, NW
Washington, DC 20001

MEETING OBJECTIVE

To examine and explore the access to, use of, and storage of dried blood spots that have been collected for newborn screening purposes through questions such as:

- What are the benefits of making these resources available for translational research?
- How do we protect the privacy and rights of individuals while allowing access to newborn screening samples?
- How can we make these samples available without compromising the main function of the newborn screening program?

8:00–9:00 A.M. **WORKING BREAKFAST**

9:00 A.M. **PUBLIC WORKSHOP BEGINS—KECK 100**

9:00–9:10 A.M. **Welcome**
Wylie Burke, Roundtable Chair, and Professor and Chair of the Department of Bioethics and Humanities, University of Washington

9:10–10:20 A.M.	**CURRENT STATUS REGARDING STORAGE OF NBS SAMPLES**
9:10–9:30 A.M.	**Current state practices and policies** *Alissa Johnson, Johnson Policy Consulting*
9:30–9:50 A.M.	**Rationale for storing newborn screening samples** *Kenneth Pass, Senior Research Scientist, New York State Department of Health Wadsworth Center*
9:50–10:20 A.M.	**Discussion**
10:20–10:30 A.M.	**BREAK**
10:30 A.M.–12:20 P.M.	**RESEARCH OPPORTUNITIES ON NBS SAMPLES**
10:30–10:50 A.M.	**Continuum from service to research** *Anne Comeau, Deputy Director New England Newborn Screening Program; Associate Professor, Department of Pediatrics, University of Massachusetts Medical School*
10:50–11:10 A.M.	**Opportunities for broader research** *Sharon Kardia, Professor and Chair of Epidemiology; Director, Public Health Genetics Program; Director, Life Science and Society Program; Co-Director, Center for Genomics and Public Health School of Public Health, University of Michigan*
11:10–11:30 A.M.	**Implications of dataset linkage** *Michele Caggana, Deputy Director Division of Genetics; Chief, Laboratory of Human Genetics; Director, Newborn Screening Program; Head, Genetic Testing Section, New York State Department of Health Wadsworth Center*

11:30 A.M.–12:20 P.M.	**Discussion**
12:20–1:20 P.M.	**WORKING LUNCH**
1:20–3:30 P.M.	**SURMOUNTING CHALLENGES**
1:20–1:40 P.M.	**Importance of retaining the core mission of newborn screening programs** *Alan Fleischman, Medical Director, March of Dimes Foundation*
1:40–2:00 P.M.	**Balancing issues from the patient/parent perspective** *Sharon Terry, President and CEO, Genetic Alliance*
2:00–2:20 P.M.	**Informed consent and stewardship** *Kelly Edwards, Associate Professor Department of Bioethics and Humanities, University of Washington School of Medicine*
2:20–2:40 P.M.	**Legal issues related to the usage of newborn screening samples** *Ellen Wright Clayton, Rosalind E. Franklin Professor of Genetics and Health Policy; Director, Center for Biomedical Ethics and Society, Vanderbilt University*
2:40–3:30 P.M.	**Discussion**
3:30–3:45 P.M.	**Break**
3:45–4:45 P.M.	**WEIGHING THE VALUE**
3:45–4:45 P.M.	**Panel discussion examining the potential benefits that could be derived from the use of dried blood spots for translational research versus the issues that need to be overcome** *Ann Waldo, Senior Counsel, Genetic Alliance*

Michele Caggana, New York State Department of Health Wadsworth Center
Alan Fleischman, Medical Director, March of Dimes Foundation

4:45–5:30 P.M. **SUMMARY AND WRAP-UP DISCUSSION**

4:45–5:30 P.M. **Summary and wrap-up discussion**
Wylie Burke, Roundtable Chair and Professor and Chair of the Department of Bioethics and Humanities, University of Washington

Appendix B

Speaker Biographical Sketches

Wylie Burke, M.D., Ph.D., is Professor and Chair of the Department of Bioethics and Humanities at the University of Washington. She received a Ph.D. in genetics and an M.D. from the University of Washington and completed a residency in internal medicine at the University of Washington. She was a medical genetics fellow at the University of Washington from 1981 to 1982. Dr. Burke was a member of the Department of Medicine at the University of Washington from 1983 to 2000, where she served as Associate Director of the Internal Medicine Residency Program from 1988 to 1994 and as founding Director of the University of Washington's Women's Health Care Center from 1994 to 1999. She was appointed Chair of the Department of Medical History in October 2000. She is also an Adjunct Professor of Medicine and Epidemiology and an Associate Member of the Fred Hutchinson Cancer Research Center. She was a Visiting Scientist at the Centers for Disease Control and Prevention in 1998 and is a fellow of the American College of Physicians. She has served on the NIH National Advisory Council for Human Genome Research and the Secretary's Advisory Committee on Genetic Testing. Dr. Burke's research addresses the social, ethical, and policy implications of genetic information, including genetic test evaluation, the development of practice standards for genetically based services, and genetics education for health professionals. She is also the Director of the University of Washington Center for Genomics and Healthcare Equality, a center of excellence in ethical, legal, and social implications research funded by the National Human Genome Research Institute.

Michele Caggana, Sc.D., received her doctoral degree from the Harvard School of Public Health in cancer, cell, and radiation biology and completed postdoctoral work in clinical molecular genetics at the Mt. Sinai School of Medicine. She is board certified in clinical molecular genetics by the American Board of Medical Genetics and a fellow of the American College of Medical Genetics. Dr. Caggana has been employed by the Wadsworth Center since 1996. She is Deputy Director of the Division of Genetics, Chief of the Laboratory of Human Genetics, and Director of the Newborn Screening Program. In addition, she serves as the Section Head for genetic testing at the Wadsworth Center. In this capacity she conducts regulatory reviews for technical and clinical validity of all genetic test methods conducted by laboratories performing testing on specimens taken in New York State. Dr. Caggana's laboratory uses molecular genetics techniques to study frequencies of specific gene mutations in dried blood spots received as specimens for newborn screening. Her laboratory also performs DNA analysis in the context of newborn screening and works on new molecular technologies. She is also an Assistant Professor in the Department of Biomedical Sciences in the School of Public Health at the State University of New York at Albany. Dr. Caggana also serves on the institutional review board at the Department of Health and the Clinical and Molecular Devices Panel at the Food and Drug Administration.

Ellen Wright Clayton, M.D., J.D., received a bachelor's degree from Duke, a master's degree from Stanford, her law degree from Yale, and her medical degree from Harvard. A member of the Vanderbilt faculty since 1988, she is currently the Rosalind E. Franklin Professor of Genetics and Health Policy and co-Director of the Center for Biomedical Ethics and Society at the Vanderbilt University Medical Center. She is also Professor of Pediatrics and Professor of Law. At Vanderbilt, she directs the law emphasis program and teaches the Patient, Profession, and Society course in the medical school and teaches the interdisciplinary course in Bioethics and Law in four schools of the University.

Dr. Clayton has focused primarily on issues surrounding the ethical, legal, and social implications of advances in genetics and genomics as both a scholar and a policy maker. She has served on Tennessee's Genetics Advisory Council since the early 1990s, has participated in numerous policy and academic groups that have considered newborn screening, and is currently conducting research on the impact of false positive results in newborn screening. She has been very involved with the Human Genome Project in the United States, serving as a member of the National Advisory Council for Human Genome Research and more recently as co-Chair of the Ethical, Legal, and Social Implications Working Group of the International Haplotype Mapping Project. She has also been very involved in ethical

issues raised by genetics and genomics research, working with investigators and deliberative bodies around the world. She has been instrumental in the development of Vanderbilt's DNA biobank and is currently co-Chair of the Consent and Community Consultation Working Group of the eMERGE consortium, which is studying the use of electronic medical records in genome-wide association studies. She has also written about a variety of issues regarding children's and women's health. She is currently a member of the advisory council for the National Children's Study. A member of the Institute of Medicine (IOM) since 2006, she has served on the Health Sciences Policy Board, its advisory council, and on several IOM committees, chairing committees to evaluate Title X family planning and to evaluate the safety of vaccines.

Anne Comeau, Ph.D., is Deputy Director of the New England Newborn Screening Program and Associate Professor of Pediatrics at the University of Massachusetts Medical School. The principal focus of Dr. Comeau's work has been the identification and epidemiology of disease that is detectable in neonates through population-based newborn screening. Technical advances from her laboratory have made sophisticated molecular assays available to patients and providers working in domestic centers and international centers that would otherwise be unable to access such technology. Her early publications include work on the identification of HIV sequences in infected newborns for early diagnosis, the study of mother-to-infant transmission, and evaluation of the efficacy of treatment. More recent publications include evaluations of newborn screening for cystic fibrosis, implications of expanded newborn screening on the healthcare community, and recommendations for successful implementation of newborn screening programs such as cystic fibrosis and now including severe combined immunodeficiency (SCID). Dr. Comeau continues as the project leader for the HRSA-funded Priority Focus on Long-Term Follow Up in New England and is the principal investigator of one of two Centers for Disease Control and Prevention grant awards to study the feasibility of newborn screening for SCID and has overseen the implementation of the pilot SCID NBS program for Massachusetts.

Dr. Comeau authored the human subjects research protocols that facilitated the 1999 Massachusetts expansion of newborn screening services and 2009 screening for SCID and additional biochemical conditions. She has presented on the special considerations for research use of data held under public health stewardship and is the author of two book chapters describing such: Newborn Screening Expansion: Massachusetts Research Models Encompass Public Health Service Responsibility in *Genomics and Public Health: Legal and Socio-Ethical Perspectives* (B. M. Knoppers, Ed., 2007) and Population-Based Research within a Public Health Service:

Two Models for Compliance with the Common Rule in the Massachusetts Newborn Screening Program in *Ethics and Newborn Genetic Screening: New Technologies, New Challenges* (M. A. Bailey and T. H. Murray, Eds., 2009).

With respect to the issue at hand, Dr. Comeau has been an avid advocate for responsible stewardship of residual newborn screening specimens. She coined the phrase "virtual repository," proposing the model in September 2002 at CDC meeting on use of dried blood spots.

Kelly Edwards, Ph.D., is an Associate Professor in the Department of Bioethics and Humanities at the University of Washington School of Medicine and core faculty for the Institute for Public Health Genetics. She received an M.A. in medical ethics and a Ph.D. in philosophy of education from the University of Washington, Seattle. Research and program responsibilities include serving as Director of the Ethics and Outreach Core for the NIEHS-funded Center for Ecogenetics and Environmental Health, co-Director of the Regulatory Support and Bioethics Core for the Institute for Translational Health Sciences, and lead investigator with the NHGRI-funded Center for Genomics and Healthcare Equality. Special interests include community-based research practices, biobank governance, environmental justice, everyday ethics in research practice, feminist and narrative approaches to bioethics, and integrating ethics into training programs, public conversations about science, and public policy.

Alan R. Fleischman, M.D., is Senior Vice President and Medical Director of the March of Dimes Foundation and Clinical Professor of Pediatrics and Clinical Professor of Epidemiology and Population Health at the Albert Einstein College of Medicine in New York.

Born in New York City, Dr. Fleischman graduated Phi Beta Kappa from the City College of New York and Alpha Omega Alpha from the Albert Einstein College of Medicine. He continued his education in pediatrics at the Johns Hopkins Hospital in Baltimore, Maryland, and completed a fellowship in perinatal physiology at the National Institutes of Health and through a Royal Society of Medicine Foundation Scholarship at Oxford University in England. He joined the faculty at the Albert Einstein College of Medicine and the Montefiore Medical Center in 1975, where he became Professor of Pediatrics and Professor of Epidemiology and Social Medicine and served as Director of the Division of Neonatology until 1994.

In 1994, he became Senior Vice President of the New York Academy of Medicine, where he catalyzed the Academy's growth into a research-intensive institution in areas related to urban health, medical education, public policy, bioethics, and public health. In 2004 Dr. Fleischman became ethics advisor to the National Children's Study at the National Institutes

of Health and was Chair of the federal advisory committee to the study from 2005–2010.

In the academic area, he has published and lectured extensively in many areas of perinatal medicine and has been a pioneer in the field of bioethics, emphasizing the rights of individual patients and the responsibilities of health-care professionals and organizations. This work has resulted in more than 150 publications in peer-reviewed journals and book chapters, including a book edited with Robert Cassidy, entitled *Pediatric Ethics—From Principles to Practice*, published by Harwood Press.

He was a member of the American Academy of Pediatrics Bioethics and AIDS Committees, a member of the National Human Research Protections Advisory Committee for the Office for Human Research Protections of the Department of Health and Human Services, an expert advisor to the Institute of Medicine's Committee on Ethical Conduct of Clinical Research Involving Children and a member of the National Research Council/Institute of Medicine Committee on Ethical Issues in Housing-Related Health Hazard Research Involving Children, Youth, and Families. He was a founding member and is currently still a member of the New York State Governor's Task Force on Life and the Law, and a member of the Department of Health and Human Services Secretary's Advisory Committee on Human Research Protections' Subcommittee on Research Involving Children.

Alissa Johnson is a consultant with Johnson Policy Consulting (JPC) where she examines and reports on health policy issues for the public, private, and non-profit sectors. On behalf of clients, Ms. Johnson has explored policy issues around newborn screening, genetic discrimination, genetic privacy, and e-health. Prior to starting JPC in January 2008, she was a Program Principal with the National Conference of State Legislatures' (NCSL's) Health Program. At NCSL Ms. Johnson served state legislators and legislative staff and managed the organization's Genetic Technologies Project. Ms. Johnson holds bachelor's and master's degrees in political science.

Sharon Kardia, Ph.D., is Professor and Chair of Epidemiology at the University of Michigan. She is Director of the Public Health Genetics Program, co-Director of the Michigan Center for Genomics and Public Health, and Director of the Life Sciences & Society Program housed in the University of Michigan School of Public Health. Dr. Kardia received her doctoral degree in human genetics from the University of Michigan, was a postdoctoral fellow in the Department of Microbiology and Immunology and continued postdoctoral work in the Department of Human Genetics. Dr. Kardia's main research interests are in the genomic epidemiology of cardiovascular disease and its risk factors. She is particularly interested in gene–environment, gene–gene interactions and in modeling complex relationships

among genetic variation, environmental variation, and risk of common chronic diseases. Her work also includes using gene expression and proteomic profiles for molecular classification of tumors and survival analysis in lung and ovarian cancers. As a part of her center's activity, Dr. Kardia is also actively working on moving genetics into chronic disease programs in state departments of health. Dr. Kardia was a member of three National Academy of Sciences committees (Genomics and the Public's Health in the 21st Century; Assessing Interactions Among Social, Behavioral, and Genetic Factors and Health; and Applications of Toxicogenomics Technologies to Predictive Toxicology).

Kenneth Pass, Ph.D., was Director of the New York State Newborn Screening Program for 28 years. During that time he introduced screening for biotinidase deficiency, congenital adrenal hyperplasia (CAH), and Krabbe disease. The program was the first to use a call-in system by which physicians could obtain test results on any day at any time, the first to provide a portion of the specimen form for the mother to facilitate acquisition of test results, the first to implement HIV testing of all newborns, and the first to test for the lysosomal storage disorders. He has published more than 80 peer-reviewed papers and eight book chapters and has delivered lectures all over the world on many different aspects of newborn blood screening. With funding from the National Institute of Child Health and Human Development he has developed multiplex assays that screen for congenital hypothyroidism/cystic fibrosis/CAH (5-plex), severe combined immunodeficiency (2-plex), and autism (7-plex), all using a single 3-mm spot. Currently his laboratory is developing a multiplex assay for hemoglobin variants that can be added to each of the above, thereby allowing calculation of the hematocrit and normalization of test results.

Sharon Terry is President and CEO of the Genetic Alliance, a coalition of more than 600 disease-specific advocacy organizations working to increase capacity in advocacy organizations and to leverage the voices of the millions of individuals and families affected by genetic conditions. She is the founding Executive Director of PXE International, a research advocacy organization for the genetic condition pseudoxanthoma elasticum (PXE). She is at the forefront of consumer participation in genetics research, services, and policy and serves as a member of many of the major governmental advisory committees on medical research, including the Food and Drug Administration Cellular, Tissue and Gene Therapies Advisory Committee and the Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children. She is a member of the board of directors of the Biotechnology Institute and on the advisory board of the Johns Hopkins Genetics and Public Policy Center funded by the Pew Charitable Trusts. She is the chair of the

Coalition for Genetic Fairness, composed of advocates, health-care providers, and industry working to enact effective federal policy to prohibit genetic information discrimination. She is also chair of the Social Issues Committee of the American Society of Human Genetics. In 2005 she received an honorary doctorate from Iona College for her work in community engagement and haplotype mapping. Ms. Terry is a co-founder of the Genetic Alliance Biobank and serves as president of its board. It is a centralized biological and data (consent/clinical/environmental) repository catalyzing translational genomic research on rare genetic diseases. The BioBank works in partnership with academic and industrial collaborators to develop novel diagnostics and therapeutics to better understand and treat these diseases. Along with the other co-inventors of the gene associated with PXE (ABCC6), she holds the patent for the invention. She co-directs a 19-lab research consortium and manages 52 offices worldwide for PXE International.

Ann Waldo, J.D., joined Genetic Alliance in November 2009 as Senior Counsel. She advises on public policy matters, including privacy, gene patenting, genetic discrimination, newborn screening, and health information technology. She also serves as Partner in the law firm of Oldaker, Belair & Wittie, LLP, providing counsel and advocacy on privacy and information management, with special focus on the Health Insurance Portability and Accountability Act (HIPAA) and consumer protection health privacy. Ms. Waldo has extensive experience in privacy. She served as Global Chief Privacy Officer for Lenovo, a worldwide computer manufacturer, where she led privacy compliance in human resources, marketing, and product development and served as a public policy advocate on national and international privacy issues. She was also the Chief Privacy Officer at Hoffmann-La Roche, handling privacy compliance and best practices in U.S. marketing, human relations, HIPAA, and clinical research. She was actively involved with the International Pharmaceutical Privacy Consortium. She worked in public policy at GlaxoSmithKline, providing legislative support on privacy, infectious disease, and other health policy issues. Previously she served as in-house counsel at IBM, working on consumer protection, marketing, and e-business. Before working at IBM, she had been a commercial litigator and had handled tax legislation for the Ohio Legislative Service Commission. A frequent public speaker, Ms. Waldo is active in the International Association of Privacy Professionals and the Carolina Privacy Officials Network, has consulted with foreign governments regarding privacy laws, and has represented the U.S. government in APEC privacy talks in Korea and Australia. She is a Certified Information Privacy Professional. Ms. Waldo graduated from the University of North Carolina School of Law with high honors in 1995. A member of Phi Beta Kappa, she holds a B.A. degree in religion from Ohio Wesleyan University (summa cum laude).