Considerations and Recommendations for National Guidance Regarding the Retention and Use of Residual Dried Blood Spot Specimens after Newborn Screening

Secretary's Advisory Committee on Heritable Disorders in Newborns and Children

BRIEFING PAPER

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EXECUTIVE SUMMARY

Considerations and Recommendations for National Guidance Regarding the Retention and Use of Residual Dried Blood Spot Specimens after Newborn Screening

This briefing paper has two principal purposes. The first purpose is to review the issues facing state newborn screening programs related to the retention and use of residual dried blood spot specimens. The second purpose is to lay the foundation for developing national guidance to states in this area. The Secretary's Advisory Committee on Heritable Disorders in Newborns and Children (SACHDNC) encourages an approach to guidance that maintains the standard uses of the residual blood specimens by newborn screening programs and upholds the core principles of benefiting infants, families and society, protecting privacy and confidentiality, and ensuring the public's trust while recognizing the research value of residual newborn screening specimens and their potential for advancing science and clinical care. The recommendations related to the retention and use of residual dried blood spot specimens are intended to work in concert with – and not to weaken – longstanding and highly effective state newborn screening programs.

Newborn screening is a highly successful public health program that identifies rare genetic, congenital and functional disorders, ensures early management and endeavors to ensure follow-up for those affected. All states require newborn screening. State public health agencies generally are responsible for oversight and implementation of their respective newborn screening program. States develop their newborn screening policies usually with input from multi-disciplinary advisory committees that include consumers, health care and public health professionals and other interested stakeholders. While state administration of newborn screening programs fosters local control and accountability, it also sometimes gives rise to wide variation in practices across the country, including disparate policies on the retention and use of dried blood spot specimens after newborn screening has been finished. Given the potential to advance science and clinical care for newborns, children, their families and society through the use of residual newborn screening blood specimens, SACHDNC calls upon policymakers, the public health community, health care providers and families to work together to protect this valuable resource for the public good.

All newborn screening programs in the United States obtain dried blood specimens on a filter paper collection device. States generally retain the unused portions of these specimens (residual specimens) for some period after testing is complete. A collection of stored specimens often is referred to as a "biobank" or "biorepository." The primary justification for retention of residual specimens is to document that a specimen was collected, received, and properly analyzed for the benefit of the child. Standard uses of residual dried blood specimens include program evaluation and quality assurance, treatment efficacy, test refinement and result verification activities for the laboratory and program. The use of specimens for research also is possible.

Newborn screening specimens are usually the first blood specimen drawn in a baby's life and represent a unique timeframe with few byproducts of medical interventions or environmental effects. These blood spots are collected on nearly all of the more than 4 million babies born annually in the U.S. Testing of the specimens yields critical information about risk for inherited conditions and the status of the infant shortly

after birth. The specimens also present an opportunity to generate population-based knowledge that can improve the health of children, support families, and provide information critical to understanding the antecedents of both child and adult diseases. State policies related to retention of specimens seek to protect the privacy and confidentiality of newborns and their families, secure the specimens, and ensure public trust. State policies also emphasize transparency of administrative practices and create supporting information that encourages informed public participation.

CONCLUSION AND RECOMMENDATIONS

In state newborn screening programs, there are now currently two distinct practices regarding the storage and use of residual newborn screening specimens: 1) short-term storage (<3 years), primarily for program quality assurance and test improvement; and 2) long-term storage (> 18 years), which allows for the standard program needs and uses and public health research. Since the newborn screening community first published guidance regarding the retention, storage and use of residual dried blood spots in 1996,[1] improvements in policy development among state newborn screening programs have occurred. Nevertheless, aspects of the current public policy environment, including differing or lacking state policies on the need for explicit consent (an opt-in approach to secondary use of residual dried blood specimens) or dissent (an opt-out approach to secondary use of residual dried blood specimens that presumes consent unless explicitly refused),[2] potential uncertainty about authority over decision-making with regard to residual blood specimens in states without a well-defined policy, and minimal public awareness of newborn screening, send an unclear message to the public about the purpose of storage and use of residual blood specimens. This has engendered some public concern about the storage of residual newborn screening specimens even for standard newborn screening program uses.

Because newborn screening is the only public health screening program that reaches the entire population of newborns in the U.S., it is unique, and the policies governing it must be thoughtfully approached. The storage and use of residual blood specimens for non-standard uses such as research may not be adequately addressed in current state laws or policies. Policies developed for the storage and use of residual dried blood specimens for research should not harm longstanding and highly effective state newborn screening programs, including their ability to store and use specimens for program activities. Rather, these policies should strengthen these well-established public health programs through increased public education and engagement. The SACHDNC believes that national guidance on the retention and use of residual newborn screening specimens would help states to navigate these complex issues.

To assist in this process, the SACHDNC makes the following recommendations to the Secretary of the Department of Health and Human Services (HHS) and requests action by the Secretary where applicable:

1) ***All state newborn screening programs should have a policy in place that has been reviewed by the state attorney general or other appropriate legal authority that specifies who may access and use dried blood specimens once they arrive at the state-designated newborn screening laboratory, including further access after newborn screening tests are completed.***

2) ***All state newborn screening programs should have a policy in place that has been reviewed by the state attorney general or other appropriate legal authority addressing the disposition of dried blood specimens remaining after newborn screening. Policymakers should consider the value of the specimens as a promising resource for research, the protection of the privacy and confidentiality of families and the necessity of ensuring the public's trust.***

3) ***All state newborn screening programs should develop a well-defined strategy to educate health care professionals who provide patients with prenatal and postnatal care about newborn screening and the potential uses of residual dried blood specimens.***

4) ***All state newborn screening programs should create policies that are in compliance with federal research regulations, assure that parents are aware of these activities, and consider whether documentation of parents' wishes and willingness to participate are required.***[3]

5) ***All state newborn screening programs should work proactively to ensure that all families of newborns are educated about newborn screening as a part of prenatal and postnatal care.***

6) ***The Secretary of Health and Human Services should help improve efforts to educate the public and health care providers about newborn screening and the retention and use of specimens.***

7) ***The Secretary of Health and Human Services should facilitate a national dialogue among federal and state stakeholders about policies for the retention and use of residual newborn screening specimens, including model consent and dissent processes.***

8) ***The Secretary of Health and Human Services should explore the utility and feasibility of establishing a voluntary national repository of residual dried blood specimens, in which families may choose to participate.***

1 Guidelines for the Retention, Storage, and Use of Residual Dried Blood Spot Samples after Newborn Screening Analysis: Statement of the Council of Regional Networks for Genetic Services. Therrell BL, Hannon WH, Pass KA, Lorey F, Brokopp C, et al., Biochem Molec Med 1996;57:116-24
2 Saunders, B. Normative consent and opt-out organ donation. J Med Ethics. 2010 Feb;36(2):84-7.
3 45 CFR 46

INTRODUCTION

Newborn screening is a highly successful public health program that identifies rare genetic, congenital and functional disorders, ensures early management and endeavors to ensure follow-up for those affected. All states require newborn screening. State public health agencies are responsible for oversight and implementation of their respective newborn screening programs. State newborn screening policies are usually developed with input from multi-disciplinary advisory committees that include consumers,[I] health care and public health professionals and others stakeholders. While state administration of newborn screening programs fosters local control and accountability, it also sometimes gives rise to wide variation in practices across the country, including disparate policies on the retention and use of dried blood spot specimens after newborn screening. Given the potential to advance science and clinical care for newborns, children, their families and society, the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children (SACHDNC) calls upon policymakers, the public health community, health care providers and families to work together to protect this valuable resource for the public good.

Standard Newborn Screening Program Uses
Residual Newborn Screening Specimens

Program Evaluation and Quality Assurance

Treatment Efficacy

Test Refinement

Result Verification

All newborn screening programs in the United States obtain dried blood specimens on a filter paper collection device. These specimens are collected on nearly all of the more than 4 million babies born annually in the U.S. States generally retain the unused portions of these specimens in a biobank or biorepository (residual specimens) for some period after testing is complete. The primary justification for retention of residual specimens is to document that a specimen was collected, received, and properly analyzed for the benefit of the child. Examples of standard and required uses of residual dried blood specimens include program evaluation, quality assurance, treatment efficacy, test refinement and result verification. The use of specimens for research also is possible.

This briefing paper has two principal purposes. The first purpose is to review the issues facing state newborn screening programs related to the retention and use of residual dried blood spot specimens. The second purpose is to lay the foundation for developing national guidance to states in this area. The SACHDNC encourages an approach to guidance that maintains the standard uses of the residual blood specimens by newborn screening programs and upholds the core principles of benefiting infants, families and society, protecting privacy and confidentiality, and ensuring the public's trust while recognizing the research value of residual newborn

[I] Consumers refers to the definition in the Newborn Screening American Health Information Community Detailed Use Case: "Members of the public that include patients as well as caregivers, patient advocates, surrogates, family members, emergency contacts, and other parties who may be acting for, or in support of, a patient receiving or potentially receiving healthcare services." Available at http://healthit.hhs.gov under Regulations and Guidance/Standards and Certification.

screening specimens and their potential for advancing science and clinical care. The recommendations related to the retention and use of residual dried blood spot specimens are intended to work in concert with – and not to weaken – longstanding and highly effective state newborn screening programs.

USES OF NEWBORN SCREENING RESIDUAL SAMPLES

Standard Uses

There are standard uses for residual newborn screening specimens after screening is complete. These include:

- Program evaluation and quality assurance, treatment efficacy, test refinement and result verification activities for the laboratory and program; [Residual newborn screening specimens are valuable evidence that appropriate testing has occurred, and newborn screening programs may require use of residual specimens for various quality assurance and test validation purposes. Quality assurance and test validation activities are needed to demonstrate that the laboratory received and assumed responsibility for analyzing the specimen correctly, and to establish evidence-based interpretations of screening results, and may be the state's regulatory requirements for the newborn screening program.]

Newborn screening programs can carry out these activities using anonymized specimens (see page 20 of the report for an explanation of types of data storage).

Other Uses

Some newborn screening programs may use residual newborn screening specimens for other activities, including one or more of the following:

- New test development; [States have used the residual newborn screening specimens to build newborn screening programs for Cystic Fibrosis[1] and Severe Combined Immunodeficiency Disease[2] and to refine testing for Sickle Cell Disease.][3]
- Population surveillance; [Newborn screening programs have reported numerous additional requests for residual newborn screening specimen usage over the years including public health research projects.[4] As one example, the Centers for Disease Control and Prevention (CDC)-sponsored a state-based HIV Seroprevalence Survey among Childbearing Women utilized fully anonymized residual newborn screening specimens to evaluate the extent of HIV infections in child-bearing women nationally as an aid to better targeting state and national public health educational and other resources.][5]
- Parental requests for other testing, particularly in cases where an infant has died without an obvious cause and when future pregnancies may be contemplated; [6] [Should the child develop inexplicable symptoms or neurodevelopmental delay later in life, the residual specimen could be reanalyzed or other tests applied to determine whether the condition was congenital or acquired.]
- Family requested identification of remains for criminal investigation; and
- Research.

Newborn screening programs can use anonymized specimens for new test development and population surveillance. Research may involve the use of anonymized, coded/linked or identifiable specimens depending on the parameters set forth for the approved study, which may require consent for access to identifiable specimens (see page 20 of the report for an explanation of types of data storage).

Research Uses. Because newborn screening specimens are usually the first blood specimen drawn in a baby's life, they represent a unique timeframe where most influences on the contents of the blood are *in utero* exposures. Testing of the specimens also may yield critical information about risk for inherited conditions. In addition, the specimens present an opportunity to generate population-based knowledge that can improve the health of children, support families, and provide information critical to understanding the antecedents of both child and adult diseases.

The use of residual newborn screening specimens for test development and research has generated significant findings and has resulted in direct public health benefits.[7,8] For example, a study in Massachusetts, which aimed to identify children with Severe Combined Immune Deficiency (SCID), also provided previously unavailable data to SACHDNC in order to make an evidence-based decision about whether to add SCID to the recommended uniform newborn screening panel.[9] The condition was added to the panel in January 2010. Examples of tests that have been developed from studies on these unused portions of the specimens include the use of T-cell receptor excision circles (TREC) assay to identify infants with T-cell lymphopenia[10] and the use of real-time quantitative polymerase chain reaction to quantitate TRECs from DNA to screen for severe combined immunodeficiency (SCID).[11] Research studies to improve the quality of testing also have led to more accurate and affordable means of screening for disorders.[12,13] Ongoing research involving the use of residual newborn screening specimens includes a CDC project being conducted by Emory University to develop a new testing method for Fragile X syndrome.[14]

Residual newborn screening specimens also have proven useful in other studies unrelated to the screening process. For example, specimens collected in New York were used in a temporal biomonitoring study to assess changes in population exposures to contaminants.[15] Forensic scientists also have tested residual newborn screening specimens to identify a kidnapped child or determine whether a genetic condition contributed to a child's death.[16]

ETHICAL, LEGAL AND SOCIAL ISSUES

The mapping of the human genome and other advances in genetic medicine have heightened awareness among the public health community and others concerning the research value of residual newborn screening specimens. Deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) can be extracted from the dried blood filter paper specimens used for newborn screening, and there is increasing bioinformatics capability allowing the linkage of DNA information with demographic or medical information that could be used to identify an individual.[17] These scientific advances also have raised public concerns about the potential misuse of genetic information by employers, insurers or others.

Legal and ethical questions surrounding retention of residual newborn screening specimens that are reviewed in depth in other literature will not be revisited in detail here.[18, 19, 20] It suffices to say that the potential research value of residual newborn screening specimens has increased the need for national harmonization of certain aspects of specimen storage and access policies for both ethical and legal reasons. The identification of a standard set of key issues to be addressed in a comprehensive policy for residual newborn screening specimens, regardless of the approach, would facilitate greater uniformity among the states as they develop their policies**.**

International Policy

International guidelines have been suggested as a means of emphasizing the importance of preserving residual newborn blood specimens in repositories for the benefit of future generations,[21] but guidelines currently do not exist. Appropriate stewardship and public trust have been repeatedly identified as essential elements of a successful repository, but no consensus for a model repository has emerged.[22] The Organization for Economic Co-operation and Development and the International Society for Biological and Environmental Repositories have developed best practices and guidelines for repositories that do not focus specifically on newborn screening but may be useful in furthering the discussion in this area.[23, 24]

Federal Policy

Despite efforts over the last two decades to explore the issues and possibilities surrounding national, regional or state repositories of residual newborn screening specimens at the national level through meetings[25] and publications (Institute of Medicine, President Clinton's National Bioethics Advisory Commission and President Bush's Council on Bioethics),[26,27,28] many questions remain unanswered. Although federal guidance to states on the storage and use of newborn screening residual dried blood specimens is absent, several federal laws and regulations provide privacy protections to individuals whose specimen may be stored or used for purposes other than screening itself.

Genetic Information Nondiscrimination Act of 2008 (GINA). Congress passed GINA in an effort to alleviate the public's fears about the misuse of genetic information by employers and health insurers.[29] Specifically, the law prevents employers from making employment-related decisions such as hiring or termination based on genetic information, and employers may not intentionally acquire genetic information.[30] Under GINA health insurers may not determine eligibility or charge higher premiums based on genetic information and health insurers also may not request or require that an individual or his or her family member undergo a genetic test.[31] Greater public understanding of the protections mandated by GINA could mitigate parents' concerns about possible risk of genetic discrimination if their children's bloodspots are retained.

The Health Information Portability and Accountability Act of 1996 (HIPAA) Privacy Rule. Compliance with federal privacy regulations known as the HIPAA Privacy Rule has been required since April 2003 (45 CFR Parts 160 and 164). These regulations govern the permitted uses and disclosures of individually identifiable protected health information (PHI), which includes genetic information as specified under GINA, by HIPAA covered entities.[32] Newborn screening facilities that are HIPAA covered entities may use and disclose an individual's PHI for

treatment, payment, or health care operations without the individual's authorization. 'Operations' include most routine standard program uses, except for research that contributes to generalizable knowledge.

The Privacy Rule also provides specific allowances for secondary uses of PHI, including public health activities and research. Public health activities (as mandated by relevant laws) conducted by state or federal programs are permitted, without individual authorization or other permission. However, researchers wishing to access PHI held by a HIPAA covered entity must do one of the following:

> *"(1) de-identify the health information so that the patient cannot be determined. De-identification occurs once the following items are redacted from the data to be used by the researcher: names; all geographic subdivisions smaller than a state, including address, except for the initial 3 digits of a zip code (there are special rules for zip codes containing 20,000 or fewer people); all dates, except the year including birth date; telephone numbers; fax numbers; electronic mail addresses; Social Security numbers; medical record numbers; health plan beneficiary numbers; account numbers; certificate/license numbers; vehicle identification and serial numbers; device identifiers and serial numbers; URLs; IP address numbers; biometric identifiers; full-face photos or comparable images; and any other unique identifying number, characteristic or code; or*
>
> *(2) have the patient authorize access to the PHI, unless a Privacy Board or an IRB waives the need for authorization in accordance with specific requirements designed to protect privacy. Those requirements include a finding that the research could not practicably be conducted without the waiver, that data will not be reused or disclosed to a third party, and that there is an adequate plan to protect privacy (164.512(i)); or*
>
> *(3) construct a Limited Data Set, where the data are provided to a researcher who has signed a Data Use Agreement. A Limited Data Set can include dates and geographic information, but not street addresses or other direct identifiers listed above. A Data Use Agreement establishes the permitted uses of the limited data set and stipulates that the researcher will not further use or disclose the information, will protect it, and will not identify or contact the individuals whose data are in the set."*[33]

For research using genetic material derived from dried blood spots, the HIPAA Privacy Rule requires one of the following actions: a) de-identification of the health information associated with the sample, which can most easily be accomplished by simply snipping off a piece of the specimen and providing no other information; b) parental or legal guardian written authorization for access to the PHI associated with the sample on a Privacy Rule compliant form; c) a waiver of the need for authorization properly granted by a Privacy Board or an institutional review board (IRB); or d) a Limited Data Set containing only general geographic information and relevant dates, coupled with a data use agreement signed by the researcher (see *http://privacyrulesandresearch.nih.gov/).*"[34]

HHS regulations for the protections of human subjects. In addition to the privacy considerations above, research involving the use of residual newborn screening specimens are

subject to HHS regulations for the protections of human subjects, or 45 CFR Part 46 (the 'Common Rule'). The Common Rule applies to HHS-funded studies and others if the institution engaged in the research activity voluntarily elects to apply the regulations to all research it performs through the institution's Federal-wide Assurance. Furthermore, the HHS regulations only apply to research activities that are considered human subjects research, as defined in the regulations, and do not meet one of the categories of research that are exempt. Assuming the above criteria are met, the Common Rule may apply to a particular study involving residual newborn screening specimens depending on further criteria. Such criteria include whether the specimen collection for newborn screening is modified in any way for a research purpose and whether associated individually identifiable information is retained with the specimen. Additional regulatory protections for children involved in research (45 CFR 46, subpart D) also apply if the research is conducted before the subject reaches the age of majority.

The Clinical Laboratory Improvement Amendments of 1988 (CLIA). Newborn screening laboratories are also governed by CLIA, which requires confidentiality of patient information throughout all phases of the testing process under laboratory control (42 CFR §493.1231).[35] Additional state licensure or contract requirements may also exist. The Clinical Laboratory Improvement Amendments Advisory Committee (CLIAC) recommended that laboratories performing molecular genetic testing (which includes both newborn screening laboratories, diagnostic laboratories working in collaboration with the newborn screening program, and research laboratories) should establish and follow procedures and protocols that include defined responsibilities of all employees to ensure appropriate access, documentation, storage, release, and transfer of confidential information and prohibit unauthorized or unnecessary access or disclosure.[36]

Future National Policy Considerations. There are compelling reasons for promoting some national or population-based research endeavors through facilitated access to specimens and data. Joint analyses of important but uncommon gene variants could generate more definitive results than could be generated from individual and likely underpowered studies. Furthermore, reasonable expectations from funders and beneficiaries with respect to knowledge sharing would result in more efficient and effective collaborations similar to the mapping of the human genome and the Global HIV Vaccine Enterprise.[37,38] In turn, these collaborations could lead to accessible and affordable studies in diverse populations that could allow for an imaginative search for common and rare genetic and other biological correlates of global diseases.[39,40,41,42] Recent federal funding has supported infrastructure to facilitate collaborations among investigators interested in studies of newborn and childhood health such as the Health Resources and Services Administration's (HRSA) Genetic and Newborn Screening Regional Collaborative Groups and the Eunice Kennedy Shriver National Institute for Child Health and Human Development's Newborn Screening Translational Research Network.

The establishment of a **voluntary** U.S. national biological repository for research, in which families may choose to participate, specific to promoting the health of infants and children might facilitate more rapid and meaningful scientific advances. One method for establishing a voluntary repository under discussion that could be accomplished without the collection of de novo specimens involves the use of newborn screening biobanks to develop a national newborn research biobank. There are challenges to the establishment of any non-newborn screening

repository comprising residual newborn screening specimens, and significant issues would need to be addressed, including variations in state law, regulation and policies.

However, the practicalities of ensuring appropriate human subjects review for collaborative studies when the subjects and investigators are at multiple institutions is a challenge. In addition, a locally structured IRB lacking public health expertise may not suffice to serve a national biorepository being used for public health research. Therefore, the establishment of a national IRB may help to expedite these studies. For example, to simplify the IRB process for collaborative studies at the National Cancer Institute (NCI), NCI created a central IRB in 2002. NIH and the Office of Human Research Protections have explored the expanded use of alternative IRB models with other institutions.[43,44]

State Policy

State processes for residual newborn specimen storage strive to secure the specimens, protect the privacy of the newborn and their families, and promote public trust. State policies also emphasize transparency of administrative practices and create supporting information that encourages informed public participation.

Storage Practices. There have been several studies looking at state practices for storage, length of storage times and manner of storage. A 2002 study of the storage and usage practices in U.S. newborn screening programs revealed that almost all programs stored their residual newborn screening specimens with identifiers present. [45]

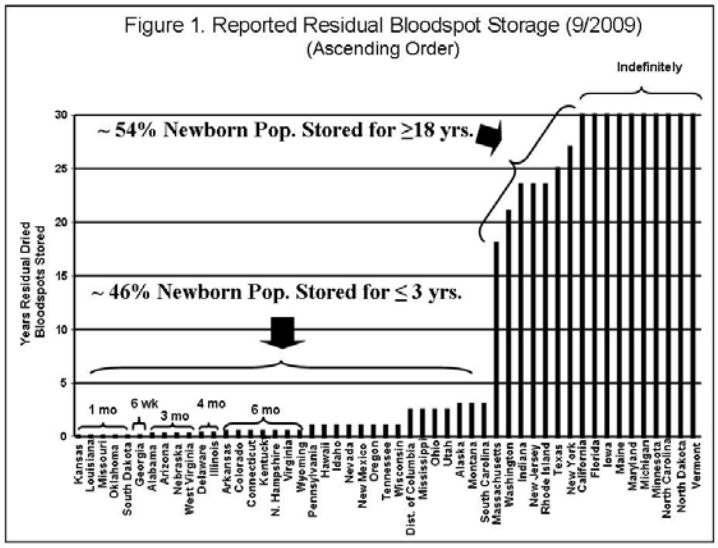
- Only two of the 36 programs that reported their short-term storage practices kept specimens completely de-identified.
- Three programs reported using a coding system that kept information private unless decoded.
- One-third of the reporting programs stored residual specimens for no officially stated reason. The remainder reported storage for one or more specific purposes, including future testing (13 of 36), special testing at the request of the family after the death of the child (7 of 36), quality control to check errors in testing (8 of 36), and research (5 of 36).[46]

The mechanisms for using aggregate data obtained from newborn screening also were reported to vary.[II] In some cases, researchers were required to have IRB approval at their own institution although some also required IRB approval at the state health department. Submission of individual requests to the newborn screening program director for review were required in other instances, and in a few cases requests were individually reviewed by senior newborn screening staff members.[47] Another study showed that 74% of states used residual specimens for newborn screening test evaluation, and 28% used them for epidemiological and pathophysiological research studies.[48] Only 57% reported having internal written policies for specimen usage.

[II] Under federal regulations governing the protection of human subjects, known as the Common Rule, the use of aggregate data only requires IRB approval if the data is individually identifiable.

In 2009, the National Newborn Screening and Genetics Resource Center (NNSGRC) solicited information on state practices for the manner and length of storage. NNSGRC reviewed the state reports and validated answers through email contacts with 100% response rate.[49]

- As of September 2009, 67% (34 of 51) of state programs and Washington, D.C., retain residual newborn screening specimens for less than 3 years accounting for approximately 46 % of all U.S. newborns (see Figure 1).
- The remaining 33% of state programs save their residual newborn screening specimens for eighteen or more years (~54% of all births in the United States) with at least 6 programs saving them indefinitely (others indicating 18-21 yr. storage may eventually save them indefinitely, but currently they are extending their policy on a year-by-year basis).



Despite the recommendations of a national standard suggesting that short-term specimen storage occur at +4 ^{o}C and long-term storage at -20 ^{o}C, with desiccant in both cases, storage conditions vary from ambient to –20 ^{o}C with variable uses of desiccant.[50] Storage conditions may influence the reliability of subsequent analyses of residual newborn screening specimens. For example, storage practices affect amino acid levels (See Appendix B), and improper storage conditions could result in the cross-contamination of DNA.

State laws and regulations pertaining to newborn screening specimen and information storage vary, and their impact or potential impact on specimen use were reviewed in 2006 by Therrell, et al.[51] At that time only nine states had specific statutory or regulatory requirements for retaining newborn screening information and specimen. Prescribed retention periods varied from one month to indefinitely (then as now). In some state and territorial jurisdictions, parents may choose the return or destruction of their newborn's residual newborn screening specimen after a specified time period (e.g., two years in South Carolina, 60 days in Minnesota), or they may allow the specimen to be stored and used for research. The 2006 report noted in Florida, Idaho

and Ohio it was unclear whether retention requirements addressed residual newborn screening specimens themselves or merely newborn screening related information collected by the department. Some states such as Idaho, Oklahoma and Texas have revised policies in recent years. (see Appendix C for an updated list of state statutes and regulations that specifically address the storage and use of residual newborn screening specimens)

Ownership. Uncertainty about who has the authority to make decisions with regard to specimens and the information gathered, produced or revealed as part of newborn screening or related processes may exist. Some state statutes or regulations, including those in California, Maine, Michigan, Utah and Wisconsin, define ownership of the specimen, once collected and submitted, as residing with the state, but the legal ramifications of state ownership vary from state to state.[52] In Maine, a parent may object to state ownership in writing.[53] In Michigan, the state holds qualified ownership of specimens, meaning that the state must still act on the best interest of the individual from whom the specimen was collected by protecting privacy and providing specimens for research that the community endorses. Utah's law that identifies residual newborn screening specimens as the property of the state is accompanied by rules addressing education and specimen use.[54] There are several legal decisions that support the state's assertion of ownership of residual newborn screening specimens.

In a 1990 decision, the Supreme Court of the State of California held, in Moore v. Regents of the University of California (51 Cal. 3d 120; 271 Cal. Rptr. 146; 793 P.2d 479), that there were no property rights in one's own body parts after medical removal. Decisions in Greenberg v. Miami Children's Hospital Research Institute [264 F. Supp. 2d 1064 (S.D. Fla. 2003)] and Washington University v. Catalona (4:03-cv-01065-SNL) supported the notion that individuals who donate biological samples to research do not retain ownership of the specimens.[55] Even so, scholars and experts in law and ethics continue to debate residual newborn screening specimen ownership, and programs will likely require clarification on a state-by-state basis. This may prove especially true if research was not the original intended use and when consent for research was not obtained at the time of newborn screening specimen collection.

Stewardship. State newborn screening programs are charged with the important task of stewardship—the caretaking responsibility where roles, responsibilities, and policies are clearly defined for ensuring appropriate use of newborn screening specimens. State public health departments strive to exercise the highest care in receiving, storing and protecting residual newborn screening specimens from unauthorized use. It is understood that the public has a right to expect that specimens are cared for in a manner that protects personal information and eliminates misuse and mistrust. Previous U.S. guidelines noted that, "Whenever a sample is retrieved, documentation should be kept indicating: (1) who had access to the specimen; (2) the purpose for which the specimen was accessed; (3) the authorizing authority; (4) the chain-of-custody from retrieval to analysis; (5) the amount of specimen released; (6) the results of any analysis of the sample; and (7) changes to any demographic or descriptive data."[56]

Despite a reluctance of many in the newborn screening field to label residual newborn screening specimen storage facilities as biobanks, the public and the media routinely use this terminology. Little experience with formalized long-term storage of residual newborn screening specimens is present in the U.S., but Michigan has a developing state repository - the 'Michigan BioTrust for

Health' a long-term newborn screening specimen repository for expanded research use (see Appendix A).[57] During the development of the repository, multiple bioethicists and other key stakeholders, including community representatives, advised the Michigan Department of Community Health on ways to make the archived specimens more accessible to researchers while considering and addressing the many ethical issues.[58] The result was the creation of a detailed business plan for a phased-in, research accessible biobank that—within a framework that protects patient information privacy and promotes public health research—would address specimen storage issues, increase health research, provide linkages to related public health data, allow greater access to research results, and be self sustaining after 5 years.[59] The 'BioTrust' will house specimens in an appropriately controlled environment with privacy safeguards and will control specimen access through an 'honest broker' (third party key holder) system. In this model, the 'honest broker' will have access to specimens and their linked information in order to facilitate research requests. The broker will provide limited, necessary information to researchers and ensure the privacy and confidentiality of patients. This linkage system will allow de-identified research while offering the possibility of access to additional information for the researcher if critical findings require such.[60]

DENMARK: AN INTERNATIONAL PERSPECTIVE The Danish government initiated a national newborn screening biobank in 1993 (see Appendix A). This biobank was established for three purposes: (1) diagnosis and treatment of phenylketonuria (PKU) and congenital hypothyroidism (CH), including repeat testing, quality assurance and group statistics; (2) diagnostic use later in infancy, which requires informed consent from the parents; and (3) research, which requires approval of the scientific ethics committee system.[61] The operational guidelines for the biobank require strict compliance with laws on processing personal data and management responsibilities, patients' rights, including the option to decline participation and request destruction or retrieval of the specimen, scientific ethics, and confidential health information. These regulations are considered necessary tools to ensure appropriate accountability and to gain public trust. To date, no misuses of the Danish Newborn Screening-Biobank or its associated Register have been reported, and public acceptance is high.[62]

Examples of procedures and processes for storage of and access to residual newborn screening specimens from four states (Michigan, Minnesota, South Carolina and Texas) are presented in Appendix A. In each of these states, parents are given the opportunity to allow long-term storage of the residual newborn screening specimen through an **informed** process that allows refusal or requires consent. Other models of storage and access exist (e.g., Maryland, in which a research review committee examines and recommends which projects requesting the use of residual newborn screening specimens should proceed to IRB approval). The state may provide information to help parents make informed decisions through pamphlets and websites, e.g., Michigan, available at www.michigan.gov/newbornscreening. Although the exact processes vary somewhat, the principle in practice is the same: residual newborn screening specimens are utilized only without objection of or with consent of the parents or guardian of the newborn (depending on the process for engaging parents/guardians).

Privacy Protections. With increased public awareness of stored residual dried blood newborn screening specimens, concerns have emerged that personal medical information such as disease susceptibility might be revealed from these specimens through current and future technological

advances.[63] Concerns focus on possible discrimination, psychological harm, identification of paternity, and social injustices.[64] However, there are no documented cases of harm resulting from these concerns relative to use of residual newborn screening specimens. In addition to the federal privacy laws and state policies specific to the storage and use of newborn screening specimens (see Appendix C) discussed previously, state genetic privacy laws, other broader state health privacy laws and regulations and medical standards of practice may affect the storage and use of residual newborn screening specimens.[65,66, 67]

Five states (Alaska, Colorado, Florida, Georgia, and Louisiana) have defined genetic information explicitly as personal property, and Alaska law further clarifies that an individual has a personal property right to his or her DNA. As of 2006, eight of 30 states/territories with genetic privacy laws were reported to have laws that might extend to newborn screening while the remainder had exemptions for this public health program or did not name newborn screening programs as covered entities.[68] In those eight states, depending on the definition of genetic information or genetic testing in the statute, technologies used in newborn screening may not fall within the scope of the law if they are not deemed "genetic." The 22 states with genetic privacy laws that were reported to exempt newborn screening may still apply to the use of newborn screening specimens for purposes other than newborn screening such as research that involves genetic testing or the use of genetic information.[69]

EDUCATION, AWARENESS AND ENSURING THE PUBLIC TRUST

The issue of privacy and the use of residual newborn screening specimens are closely linked to parental education and informed decision-making. In 2000, the American Academy of Pediatrics (AAP) Newborn Screening Task Force recommended developing educational materials for parents that include information about the storage and use of residual newborn screening specimens.[70] A recent study by Goldenberg has determined that only 12 states currently include mention of specimen storage in their newborn screening educational pamphlet.[71] States considering the addition of information about specimen retention and use to educational materials may want to make other changes simultaneously that could improve the effectiveness of patient and provider education about the newborn screening system overall.

Engaging Providers and the Public

Better public understanding and acceptance of state policies on the possible storage and use of residual dried blood specimens depends heavily on the involvement of health care providers. Studies validate the need for better physician education to meet the educational needs of the screening program. The role of the obstetrician as an educator in the newborn screening process has been defined,[72] and the American College of Obstetricians and Gynecologists (ACOG) has published a position paper—ACOG Committee on Genetics Opinion—that encourages its members to become aware and involved in state newborn screening efforts.[73] However, most obstetricians still do not educate their patients about newborn screening. A 2005 questionnaire study of Hawaii obstetricians showed that less than 15% could correctly answer knowledge questions about newborn screening. Fewer than 20% reported discussing newborn screening with patients, and, of those, only 1/4 correctly answered the newborn screening questions.[74] The need for improved provider education was confirmed by a California study that found most

prenatal care providers believed that newborn screening participation was important. However, 25% reported not discussing it with any of their patients, and most who did discuss newborn screening, did not discuss it with all patients. Prenatal care providers seemed to believe hospital staff or pediatricians would discuss newborn screening with their patients. Nearly 1/3 of patients never received newborn screening educational materials from their prenatal care provider, even though prenatal care providers in California are legally required to provide them.[75]

Studies have also shown that the responsibility for informing parents about the screening process has not been clearly defined in many programs. A 2005 survey about educational responsibility indicated that only 25% of programs encouraged prenatal care providers to educate parents about newborn screening and less than 50% felt that primary care providers had some educational responsibility for informing parents about newborn screening.[76] A recently published Canadian study reported that virtually all midwives and almost half of the nurses reported discussing newborn screening with parents whereas less than one sixth of the physicians did so.[77] Providers who perceive a responsibility to inform parents were three times more likely to report discussing newborn screening with parents. Those who lacked confidence to inform parents were 70% less likely to discuss newborn screening.[78]

Research also has shown that the educational materials developed for parents often do not meet the standard recommended by the American Academy of Pediatrics (AAP),[79] and there are important variations in the information provided to parents between programs.[80] The most common educational mechanism is a brochure provided in the hospital's package of informational materials for mothers. Focus groups of parents have shown that written information should be presented in a user-friendly and easy-to-read format, and parents are most interested in information that they deem relevant and practical and that emphasizes what they need to know and do.[81]

With respect to specimen storage, models of informational brochures for newborn screening programs exist, yet they do not generally address residual specimen storage issues. Typically, a newborn screening educational program will need to: (1) inform prenatal and other healthcare providers and policymakers about the issues related to residual newborn screening specimen storage; (2) inform parents about the issues related to newborn screening specimen storage and potential use and their options; and (3) inform parents about privacy protections. For some programs, filling gaps in basic program educational efforts coupled with the addition of complex information related to specimen storage may pose a significant cost, at least at start-up. Birthing facilities also will incur costs associated with providing information at the point-of-care. A California pilot program for tandem mass spectrometry (MS/MS) found that the labor cost required to have each parent sign an informed consent form upon specimen collection resulted in many parents never being approached or having their decision documented.[82]

A recent study of the attitudes of women towards a hypothetical pediatric biobank found significant variations in the willingness of women to enroll their children and misperceptions about what participation in a biobank entailed.[83] Women with only one previous child were the most willing to enroll their child while women with no previous children were the most uncertain. When women were asked why they would or would not enroll their child into a biobank, 26% of the 207 responders did not feel that they had enough information, 10% were

concerned about risks, and 8% were concerned about privacy. Consent issues were a concern in 8% of cases, including a desire to have the father included or to have the child consent at a later age. Of 90 women explaining why they would enroll their child, 53% expressed altruistic reasons to benefit society and 20% described the potential to benefit their own child or family. The study also showed that Caucasians were the most willing to enroll their children while non-Black minorities were the most uncertain about what they would do. This study found a general understanding of research, but significant misperceptions confirmed a need for increased public education about research participants' general rights to privacy in research, and the implications of enrollment in a biobank for donors. In particular, there was a need to explain more clearly what information researchers or others might access.[84]

Information sharing has been shown to correlate positively with participation in research. A 1998 study of 93 subjects showed a high percentage of willingness to participate in hypothetical biobank research studies with only 13% placing some restrictions on the type of research to be done.[85] Similarly, analysis of 1670 consent forms from clinical research participants at the National Institutes of Health showed 87% agreement to authorize research on any medical condition.[86] A 2008 study of hypothetical enrollment in the University of Chicago's obstetrics biobank program found potential participants would place few restrictions on the type of research to be performed with over 90% supporting all conditions proposed.[87] In addition to their willingness to enroll, potential participants also were optimistic that the research would achieve significant clinical results in the near future. Trust and belief that the research would be integrated fairly into clinical care were also found to correlate with enrollment.[88] Community engagement to help programs understand public privacy concerns has been identified as a useful step in helping recruit and retain biobank participants.[89] Commentators also have noted that the best way to promote appropriate communication with families is to rely on a research approach that is flexible with respect to (1) how parental permission is acquired; and (2) methods for the rigorous evaluation of harms and benefits associated with screening.[90]

Ensuring the Public Trust Through Empowerment

Clear communication at the outset about the authority of parents or guardians to control specimen storage and use through consent or dissent, as well as the scope, risks and benefits of studies are essential.[91] The use of residual newborn screening specimens represents perhaps the most visible example of the need for consensus on the ethical principles and legal rules governing the use of bodily tissues, including the concept of 'meaningful' consent.[92] Some form of consent or formal IRB waiver of consent appears to be necessary if identifiable newborn screening specimens are to be placed into a repository for research purposes since creation of a research repository is, in and of itself, research.[93] Some medical privacy advocates contend that parents must be asked for consent before residual newborn screening specimens are retained,[94] but others assert that meaningful consent is impossible because parents cannot be adequately educated about <u>all</u> potential uses and outcomes.[95]

Newborn screening programs may utilize several methods to provide parents or guardians with alternatives regarding specimen storage and use. The alternatives involve an opt-in or opt-out process whereby individuals are informed of the potential storage and use of specimens, and either one of the following occurs: (1) A newborn's specimen is not stored or available for

allowable, approved uses after screening is complete unless the parent/guardian opts into the biobank. Parental *consent* is sought and possibly formalized through a signed document; or (2) A newborn's specimen is stored and available for allowable, approved uses unless the parent/guardian objects or indicates *dissent.*[96] The decision to opt out also may be formalized through a signed document. Consent/dissent processes for longitudinal studies of children who eventually transition to adulthood should take into account the decision-making authority of children as compared to adults.

Residual newborn screening specimens can be stored unidentified (anonymized), linked, or with identifiers. Anonymization of data is generally thought to set aside the requirement to obtain explicit consent. If specimens are not identifiable, then they are not considered "personal," and data-subjects are at very low risk of being harmed.[97] However, anonymization is not as risk-proof as it was once thought to be as a result of advances in genetic technology.[98,99]

Although consent is waived when archived specimens are anonymized, some observers consider the anonymization of newborn screening specimens without obtaining consent at the time of collection questionable and a threat to public trust in research endeavors with such specimens.[100] When investigators need access to linked or coded specimens, renewed consent from the parents (or from the subject, if the latter has reached the legal age to consent) is often required.

Types of Data Storage

Anonymized - Previously identifiable data that have been deidentified and for which a code or other link no longer exists. An investigator would not be able to link anonymized information back to a specific individual.

Anonymous - Data that were collected without identifiers and that were never linked to an individual. Coded data are not anonymous.

Coded - Data are separated from personal identifiers through use of a code. As long as a link exists, data are considered indirectly identifiable and not anonymous or anonymized.

Directly Identifiable - Any information that includes personal identifiers

Indirectly Identifiable - Data that do not include personal identifiers, but link the identifying information to the data through use of a code

Linked - See Coded

Source: Partners Human Research Committee, http://healthcare.partners.org/phsirb/hipaaglos.htm

In rare circumstances and when specific criteria are met, ethical review boards have authority to waive consent requirements. This generally happens when research is of minimal risk, when it will not adversely affect the subject's rights and welfare, when it is impracticable to obtain consent and, whenever appropriate, subjects will be provided with pertinent information after participation.[101] A balanced consideration of concerns justifies waiving informed consent for population-based newborn screening research using de-identified specimens when a clinically well-defined test and an effective therapy are present.[102] It has been noted that fundamental ethical concerns around individual and societal risk should ultimately drive how research regulations are interpreted.[103]

Subject to ethical review board approval and parental consent, it is common practice to use identified or coded specimens if researchers can demonstrate that newborn screening specimens are the best specimens available and that similar data could not be obtained from adults.[104,105]

Various experts and organizations in the U.S. and abroad have contemplated the issue of consent for the use of residual newborn screening specimens in research studies. The AAP Newborn Screening Task Force recommended that archived residual newborn screening specimens should be made available for research only if identifiers are removed, and in the case of linked or identified specimens, the Task Force noted that parents should be informed of the specimen retention policy and asked for consent for storage of residual newborn screening specimens.[106]

A 2004 German National Ethics Council opined that different options do not need to be offered in the informed consent process for samples obtained during medical care, and informed consent may be waived when samples and data are completely anonymous, unless a prior contrary wish has been expressed: "Donors should be able to give generalized consent to the use of their samples and data for the purposes of medical, including genetic – research."[107] Length of storage and use of data were regarded similarly with neither limited in advance.[108] Published guidance from Canadian investigators stressed the importance of educating parents: "Information pamphlets should describe the reasons for storage, specifying whether dried blood spots will be used for diagnostic testing and treatment, for control and documentation of previously performed analyses should suspicion of diseases arise later in life, quality assurance of screening programs, for the development of new and better assays, in epidemiological studies, for specific disease testing if unexpected events occur during the newborn's first year of life or after, or for research projects."[109] The authors also suggested providing information to parents about security measures, access to specimens, and whether separate consent will be required from parents or an ethical review board for researchers to access samples.[110]

The German approach exemplifies a gradual move towards allowing biobanks to obtain a broad consent for future secondary research. To minimize privacy concerns, anonymized or double coded specimens/data [with a third party key holder (see Appendix A for discussion of the Michigan 'honest broker') controlling release and use of information] are sometimes used. Further, there are a number of systems in development that would allow individuals to determine consent in a more dynamic manner such as PatientsLikeMe and Private Access. [111] In this way, consenting individuals participate for the public good while maintaining personal values and autonomy, and this approach may ultimately enhance research activities and outcomes.[112] Successful models for opting out (dissent) also exist such as the Danish newborn screening biobank uses (see Appendix A).

In the United States, consent for research is usually for a single project, and researchers must request re-consent of individuals if they wish to undertake another project. Occasionally, consent is broader and open-ended, in which case study participants agree to specimen storage and use for future unspecified purposes. This broad or 'blanket' consent is not as common and is problematic under the federal privacy regulations, which call for specific consent for specific research projects (see federal privacy rule 08-14-02 preamble 53231); therefore, institutional review boards are reticent to approve such consent processes.[113] Since retention and use policies for residual newborn screening specimens cannot anticipate all future research proposals,

newborn screening programs that pursue an opt-in rather than an opt-out approach will likely consider blanket consent. States must approach blanket consent carefully, balancing maximum specimen use for valid study with potential objections of consenters and state and federal consent and privacy requirements, if applicable, such as those set forth in the Health Insurance Portability and Accountability Act.

POSITION STATEMENTS—PROFESSIONAL GROUPS

The American College of Medical Genetics (ACMG)

In a previous position statement for clinical genetic laboratories, ACMG took the position that testing facilities should establish laboratory policies regarding specimen retention and appropriate storage conditions.[114] A more recent ACMG position statement[115] on newborn screening noted that: "1) residual newborn screening specimens are a valuable national resource that can contribute significantly to the health of our children; 2) newborn screening blood spots are stored with rigorous control and respect for privacy and confidentiality to protect the public; and 3) if a state decides that newborn screening blood spots should not be retained or used for anything more than the screening test, it is critical that individuals have the option of having their children's dried blood spots deposited in a national repository which will allow for necessary studies under appropriate privacy and confidentiality protections." ACMG Standards and Guidelines state that the retention of a patient's DNA should be in compliance with state and federal laws. Re-use of patient DNA specimens, i.e., subsequent use and retention is as allowed by the patient.[116]

The Association of Public Health Laboratories (APHL)

APHL has a position policy that supports the development of national consensus policies, procedures, and standards for retaining residual newborn screening specimens following newborn screening analysis.[117] The position policy specifically calls for the following: "These policies and procedures must recognize existing federal regulations for clinical testing, state laws, professional guidelines, and ethical and legal precedents. The policies should allow for introduction of new analytes and techniques into the newborn screening arena. To meet recognized laboratory quality assurance practices, dried bloodspot specimens must be retained for a time period and under conditions that permit analytical validation. Other reasons to save residual newborn screening specimens include test development, research, and forensic identification. To retain residual newborn screening specimens for such purposes requires clear guidelines that are incorporated into national consensus policies that state public health departments can follow in carrying out their authorized newborn screening programs."[118]

<u>The Clinical and Laboratory Standards Institute (CLSI)</u> – The CLSI guideline states that beyond the usual medico-legal considerations that determine advisable durations for retention of all clinico-pathologic specimens, molecular genetic specimens – particularly the DNA contained therein – have potential importance for family studies and distance descendants long after the present patient is deceased. The patient's DNA could prove essential for either linkage studies or direct mutation identification, perhaps involving tests not yet developed. A primary issue regarding specimen retention involves ethical and legal considerations, such as specimen

ownership, confidentiality, and informed consent. Until universal recommendations are adopted or until regulations are implemented, each laboratory should establish its own policy regarding specimen retention and the use of archived specimens or stored DNA. A laboratory specimen retention policy should consider the following factors: 1) type of specimens retained (e.g., dried blood on filter paper), 2) analytes tested (e.g., DNA, RNA, or both), 3) test results or the genotypes detected. (If only abnormal specimens are retained, identifying false-negative results at a later date will be difficult. This practice also might introduce bias if a preponderance of specimens with abnormal test results is used to verify or establish performance specifications for future testing.), 4) test volume, and 5) new technologies that might not produce residual specimens."[119]

The American Academy of Pediatrics (AAP)

The AAP Newborn Screening Task Force made the following recommendations concerning residual newborn screening specimen storage and use: "1) Using national recommendations, each state program should develop and implement policies and procedures for retention of residual newborn screening specimens that articulate the rationale and objectives for storage, the intended duration of storage, whether storage is with or without identifiers, and guidelines for use of identifiable and unlinked samples; 2) Develop educational materials for parents that include information regarding the storage and uses of residual specimens; 3) Develop model consent forms and informational materials for parental permission for retention and use of newborn screening specimens (to date these models have not been developed for newborn screening program use); 4) Develop policies and procedures for unlinked/linked residual specimens in research/surveillance; and 5) Organize collaborative efforts to develop minimum standards for storage and database technology to facilitate appropriate storage of residual newborn screening blood specimens at the state level and consider creating a national or multi-state population-based specimen source for research in which consent is obtained from the individuals from whom the tissue (blood) is obtained."[120]

FINANCIAL CONSIDERATIONS

Understanding that policymakers need to weigh the benefits and costs of newborn screening, guidance should address the costs associated with the infrastructure for the storage and use of residual newborn screening specimens and the financing of the system. [121] At a minimum the newborn screening program will incur costs associated with the storage and retrieval process, professional and consumer education, consent/dissent forms and processes, if required, and preparing specimens for research use. In addition, there may be costs related to counseling associated with the return of results, ongoing oversight, and honest broker systems.

Storage and Retrieval

All newborn screening programs retain residual newborn screening specimens for some period of time, usually with at least one identification number. Linkage to demographic information usually continues until de-identification may be initiated for privacy protection and preparation for some research uses. Most programs will incur additional expenses if residual newborn

screening specimens are stored in compliance with established standards. Increased costs are also expected for the long-term maintenance of residual specimens.

As one cost example, the South Carolina public health screening laboratory uses a dedicated walk-in freezer to store residual specimens (~55,000/year) for up to three years (depending on the disbursement option chosen by the guardian at the time of collection). Retrieval costs include a database that provides physical location information to facilitate a manual searching process. The retrieval process cannot be realistically separated into component parts and has been estimated based on employee time. Approximately 0.67 FTE is required for an annual cost of $40,500 (salary + fringe + indirect + health services support). Primary laboratory non-personnel expenses include the cost of freezing and storage. Annual freezing costs include: freezer rental at $6,000/yr (200 sq. ft. at $30 sq. ft.); maintenance at $500 (assuming no equipment failures); and electricity at $6,850 (3 hp compressor = 3450 watts/yr; electric rate = .09355/KW/hr). Packaging/storage supplies add approximately $850 to the overall cost for a total of approximately $14,000 for laboratory non-personnel storage costs. Thus, the annual cost for specimen storage and retrieval in South Carolina is approximately $54,500 for storage of ~165,000 specimens with minimal retrieval.[122]

The much larger California program (~560,000/year) currently maintains the largest newborn screening storage facility with a total of approximately 15 million residual specimens kept frozen and desiccated. Regulations specify the process for specimen retrieval and usage requests. Specimens are stored in a rental facility at a cost of approximately $150,000/yr through a contract that provides for backup contingencies and security. There are additional charges for forklift operations when a pallet of specimen storage boxes must be moved, but this cost is insignificant compared to the total contract. Retrieval costs have been calculated to be approximately $30/specimen based on the personnel time required for accessing, labeling, and shipping. Accessing involves cutting out an already punched circle and asking the user to return the remainder following their project use.[123]

CONCLUSION

In state newborn screening programs, there are currently two distinct practices regarding the storage and use of residual newborn screening specimens: 1) short-term storage (<3 years), primarily for program quality assurance and test improvement; and 2) long-term storage (> 18 years), which allows for standard program needs and uses and public health research. Since the newborn screening community first published guidance regarding the retention, storage of use of residual newborn screening specimens,[124] improvements in policy development among state newborn screening programs have occurred. Nevertheless, aspects of the current public policy environment, including differing or lacking state policies on the need for explicit consent (an opt in approach to secondary use of residual dried blood specimens) or dissent (an opt out approach to secondary use of residual dried blood specimens that presumes consent unless explicitly refused),[125] potential uncertainty about authority over decision-making with regard to residual newborn screening specimens in states without a well-defined policy, and minimal public awareness of newborn screening, send an unclear message to the public about the purpose of storage and use of residual blood specimens. This has engendered some public concern about

the storage of residual newborn screening specimens even for standard newborn screening program uses.

In light of growing use of residual newborn screening specimens, and their potential secondary applications, proactive solutions should be envisaged to ensure proper public education, parental choice, including an informed process for consent or dissent, and protection of genetic privacy and confidentiality.[126] All programs seeking to store residual newborn screening specimens should strive for public trust and transparency of operations and policies. Public health organizations should encourage open and informed dialogue with the public as part of the screening process.

Because newborn screening is the only public health screening program that reaches the entire population of newborns in the U.S., it is unique, and the policies governing it must be thoughtfully approached. The storage and use of residual blood specimens for non-standard uses such as research may not be adequately addressed in current state laws or policies. Policies developed for the storage and use of residual dried blood specimens for research should not harm longstanding and highly effective state newborn screening programs, including their ability to store and use specimens for program activities. Rather, these policies should strengthen these well-established public health programs through increased public education and engagement. The SACHDNC believes that national guidance on the retention and use of residual newborn screening specimens would help states to navigate these complex issues.

RECOMMENDATIONS

To assist in this process, the Committee makes the following recommendations to the Secretary, HHS and requests action by the Secretary where applicable:

1. ***All state newborn screening programs should have a policy in place that has been reviewed by the state attorney general or other appropriate legal authority that specifies who may access and use dried blood specimens once they arrive at the state-designated newborn screening laboratory, including further access after newborn screening tests are completed.***

   Multidisciplinary input, including from consumers, should be solicited and thoughtfully considered in developing such a policy. The public should have access to information about the state policy.

2. ***All state newborn screening programs should have a policy in place that has been reviewed by the state attorney general or other appropriate legal authority addressing the disposition of dried blood specimens remaining after newborn screening. Policymakers should consider the value of the specimens as a promising resource for research, the importance of protecting the privacy and confidentiality of families and the necessity of ensuring the public's trust.***

   The policy should include the standard program uses [program evaluation and quality assurance, treatment efficacy, test refinement and result verification activities for the

laboratory and program] after the completion of newborn screen testing, according to laboratory Quality Assurance (QA) procedures and SACHDNC. The specimen disposition policy also should include the storage conditions and length of time for which specimens will be stored, as per NCCLS/CLSI Standard LA4-A5 or its current edition. Linkage of data to personally identifiable information should be carefully addressed, and privacy and confidentiality should be ensured. Parties responsible for drafting the policy should consider whether consent or dissent from families is necessary for uses (such as research) other than the newborn screen and the program's associated standard program uses, and, if so, under what circumstances. Families and the public should have access to information about the state policy. Multidisciplinary input, including from consumers, should be solicited and thoughtfully considered in developing such a policy.

3. ***All state newborn screening programs should develop a well-defined strategy to educate health care professionals who provide patients with prenatal and postnatal care about newborn screening and the potential uses of residual newborn screening specimens.***

   The strategy should include steps to inform and train health care professionals about the newborn screening system, the state's policy on the potential use of residual newborn screening specimens, and their educational responsibilities with respect to expectant parents and parents of newborns. Educational programs primarily should focus on prenatal care providers. Education of postnatal care providers should instruct them to follow-up on prenatal educational efforts and be cognizant of new parents who did not have access to prenatal care, and, therefore, did not receive prior information about the newborn screening system.

4. ***All state newborn screening programs should create policies that are in compliance with federal research regulations, assure that parents are aware of these activities, and consider whether documentation of parents' wishes and willingness to participate are required.***[127]

   The state attorney general or other appropriate legal authority should review this process. The SACHDNC emphasizes that the use of residual newborn screening specimens for standard program uses are valid components of the public health newborn screening program, and, therefore, do not require additional consent. Once the use of a residual newborn screening specimens moves beyond the state mandated and related standard program uses, each state should consider whether separate or blanket consent/dissent processes for approved studies are required from parents, legal guardians or individuals screened upon the age of majority for the use of residual newborn screening specimens.

5. ***All state newborn screening programs should work proactively to ensure that all families of newborns are educated about newborn screening as a part of prenatal and postnatal care.***

   As part of the educational process, all state newborn screening programs should maintain and distribute educationally and culturally appropriate information that includes basic

information about the use or potential use of the residual newborn screening specimens. Processes should be in place to evaluate the extent, timing and parental comprehension of newborn screening education with an eye towards educational program improvement. While educational programs should focus on the prenatal period, they also should be designed to reach parents that do not have access to those services and require postnatal education about newborn screening. Educational materials should address potential uses of residual newborn screening specimens, long-term storage policies, options for parents regarding storage and use of specimens, and information on stewardship of specimens.

6. ***The Secretary of Health and Human Services should help improve efforts to educate the public and health care providers about newborn screening and the retention and use of specimens.***

   Educational programs should be developed that take into account existing resources for the public on the importance of newborn screening and the potential uses of residual newborn screening specimens to generate population-based knowledge about health and disease. Educational materials directed to health care professionals and consumers with facts about potential uses of residual newborn screening specimens and other related issues should be developed. Administrative support and funding should be provided to the Health Resources and Services Administration (HRSA), Maternal and Child Health Bureau (MCHB) to award grants to states to develop these programs and materials.

7. ***The Secretary of Health and Human Services should facilitate a national dialogue among federal and state stakeholders about policies for the retention and use of residual newborn screening specimens, including model consent and dissent processes.***

   National guidance should be developed for consent or dissent for the secondary use of specimens and mechanisms to ensure privacy and confidentiality, including methods for opting in or out of repositories and options for children whose specimens are stored upon reaching the age of majority. In addition, data should be collected and analyzed nationally on the utility of any additional consent or dissent processes implemented relative to potential research uses of residual newborn screening specimens. The Secretary should encourage states to defer making permanent policy changes that would result in the premature destruction of specimens until national guidance is available for their consideration and use in establishing such policies. Administrative support and funding should be provided to SACHDNC to facilitate this dialogue and develop this guidance.

8. ***The Secretary of Health and Human Services should explore the utility and feasibility of establishing a voluntary national repository of residual dried blood specimens, in which parents may choose to participate.***

   Additional funding should be made available to the Centers for Disease Control and Prevention and the National Institutes of Health to draft policies and guidelines addressing the support and maintenance of the repository, stewardship of the collection, establishment of oversight systems, access and retention policies, and how legal and ethical issues would be addressed, including variations in state laws.

Secretary's Advisory Committee on Heritable Disorders in Newborns and Children
Workgroup on Residual Blood Spots

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APPENDIX A.

Examples of Residual Newborn Screening Specimen Biobanks

Danish Newborn Screening Healthcare Biobank (http://www.ssi.dk)

For more than 25 years, residual newborn screening specimens from the Danish newborn screening program have been stored in a healthcare biobank. The storage has taken place according to regulations from the Danish Ministry of Health (1993) and recently according to new guidelines for the establishment and operation of biobanks in general (2004). After routine newborn screening, residual newborn screening specimens are stored at -20 ^{o}C in a secure cold room inside a secure building. The Danish Biobank and Register contains residual newborn screening specimens from virtually all newborns in Denmark since 1982—about 1.8 million specimen cards. The stated purpose of the storage is: (1) diagnosis and treatment of congenital disorders, including documentation, repeat testing, quality assurance, statistics and improvement of screening methods; (2) diagnostic use later in infancy after informed consent; (3) legal use after court order; and (4) the possibility of research projects after approval by the Danish Scientific Ethical Committee System, The Danish Data Protection Agency and the Newborn Screening -Biobank Steering Committee.

An executive order from the Danish Ministry of Health from 1993 until 2004 regulated the operation of and use of the newborn screening Biobank. During this time, the Ethical Council, the Central Scientific Ethical Committee and the National Board of Health also were involved in regulation of the biobank. Detailed General Operational Guidelines for Biobanks in Denmark in compliance with Acts on Processing of Personal Data, Patient's Rights, Health 546/2005 and the Biomedical Research Ethics Committee System have now replaced the earlier regulations. The Danish government has not passed legislation specific to biobanks, but the 2004 regulations and guidelines instill security measures in the operations of the Danish Newborn Screening-Biobank. The Danish Newborn Screening-Biobank has been used in several research projects for etiological studies of a number of disorders, recently employing new sensitive multiplex technologies and genetic analyses utilizing whole-genome amplified DNA.[1]

Prior to collecting the blood specimen, parents are informed about newborn screening and residual newborn screening specimen storage by local health professionals using program-prepared educational pamphlets (www.ssi.dk/nyfoedte) and through information available on the homepage of the Staten Serum Institute (SSI) (http://www.ssi.dk). Information about storage of residual newborn screening specimens focuses on possible uses for: 1) documentation, retesting and diagnosis later in infancy; 2) quality assurance and assay improvement; and 3) research. The parents may opt-out of biobank storage at the time of blood sampling by marking the data portion of the specimen collection card, by a written letter to the SSI at any time, or by registering in the central Use of Tissue Registry. Several safety procedures also exist for both the data registry and the biobank. The residual specimens are stored in a separate freezer facility (-20 ^{o}C), and they are linked to the individual data forms only by a unique specimen number. The database archive is located in another building and access to both facilities is restricted to authorized health personnel only. The Newborn Screening-Biobank has been included in the International Organization for Standardization (ISO) 17025 accreditation of the screening laboratory since 1998. Yearly inspections by DANAK, a Danish accreditation authority, ensure

that the biobank adheres to this certification concerning traceability, documentation, and quality assurance.[2]

Michigan Newborn Screening Program and the Michigan BioTrust for Health

Michigan Department of Community Health (http://www.Michigan.gov/newbornscreening)

The newborn screening laboratory routinely saves all residual newborn screening specimens after testing is complete unless otherwise directed by a parent or guardian. The program's brochure and website provides information about retention of residual newborn screening specimens. In accordance with state law, some leftover de-identified specimens may be used for medical research after all directly identifying information (name, address, etc.) has been removed. However, the newborn screening laboratory always retains one full circle of the blood specimen in case it is ever needed for the child or family. For samples collected through September 30, 2010, parents who wish to have their newborn's leftover specimen stored by the laboratory but unavailable for possible medical research may complete the Directive to Remove Newborn Screening Specimen from Research and mail or fax the completed/signed form to the laboratory. Beginning October 1, 2010, the program will transition to an opt-in process for future research uses by obtaining written permission from parents using a form attached to the back of the newborn screening kit. Parents who wish to have their newborn's screening specimen destroyed after completion of the screening tests may fill out the Directive to Destroy Newborn Screening Specimen and mail or fax the completed/signed form to the laboratory. The Directive to Remove form remains available at any time to parents or individuals who want to change a prior decision to allow research uses. The directives to save or to destroy specimens require signatures of the requestor and the form requesting destruction requires authentication of identity (driver's license, passport, etc.) of the requestor. Once the individual from whom the specimen was collected reaches 18 years of age, they may make the request themselves. The Michigan Department of Community Health (MDCH) owns the residual 3.5 million specimens collected over many years and has recently changed storage conditions and retention period from ambient storage for 21.5 years to indefinitely at $-20\ ^{0}C$. MDCH's residual newborn screening specimens are currently being moved to the Michigan Neonatal Biobank (see below).

Michigan BioTrust for Health (http://michigan.gov/biotrust)

[Text extracted from the Executive Summary, Business Plan 2008, Michigan Neonatal BioTrust] A draft business plan (2008) for the Michigan residual newborn screening specimen repository was produced at the request of the MDCH. "*The objectives were: (1) to identify alternative storage conditions and space for their archive of dried blood spots that creates more opportunities for health research; (2) to provide linkages between the specimens and other public health data sources; (3) to make the results of research available to the broad research community; and (4) to accomplish these within a framework that protects the identity and ethical treatment of participants, and promotes a public health research agenda.*"[3]

The resulting Michigan BioTrust for Health is an initiative that encompasses educational outreach and community engagement, policy development, residual dried blood specimen storage, and data linkages to create a resource for future research that will benefit the public's health.[4] MDCH retains ownership of the dried blood specimens and holds them "in trust" for future research use. MDCH contracts with the Michigan Neonatal Biobank, a non-profit

organization, for specimen storage after all directly identifying information is removed and labeled with a code.[5] The current governance structure for the BioTrust includes a Community Values Advisory Board and Scientific Advisory Board for review of research proposals. In addition, the MDCH IRB reviews all blood spot requests for research use. The Biobank has a Board of Directors with representatives from each of the partner organizations (Michigan State University, University of Michigan, Van Andel Institute, and Wayne State University) that oversee its operations.

According to the 2008 business plan, full implementation of the Michigan BioTrust for Health is expected to require $3.9 million in funding over a five-year period. From year six onward the BioTrust is expected to be self-sustaining. The BioTrust will achieve self-sustainability with support from Michigan's three major research universities: Wayne State University, Michigan State University (MSU), and the University of Michigan. Wayne State University's TechTown—a growing center of excellence in biobanking with expertise in archiving, retrieving, shipping and handling biological specimens for research—maintains the storage facility and provides the capability to amplify DNA as needed to ensure that this resource is available and sustainable. MSU provides extensive experience and expertise in assembling de-identified data from other Michigan data warehouses and linkage to the National Children's Study and its related data. MSU medical ethics researchers have initiated projects to determine public acceptance of research uses for archived specimens. The University of Michigan's School of Public Health has extensive experience in community engagement and public education concerning the use of residual newborn screening specimens for research and in studying the ethical, legal and social implications of genetics research and practice. Each of these universities is expected to contribute substantially to a unified and effectively operated specimen repository. The BioTrust management also is exploring the possibility of a fee structure system to recover storage and linkage costs.

A multi-phased approach is being implemented for the Michigan BioTrust for Health as follows:
(Phase 1) The Van Andel Research Institute in Michigan has considerable experience with evaluating and identifying ideal storage conditions for biospecimens, and they are responsible for identifying optimal specimen storage conditions and assisting with implementation. Residual newborn screening specimens currently stored will be identified with bar code labels, repackaged and moved to a secure location in TechTown;
(Phase 2) As part of the repository design to achieve self-sustainability, the BioTrust will increase the research value of the residual newborn screening specimens through the use of an honest broker, which will allow linkage of stored specimens to newborn screening test results as well as to different state-based health registries and databases that detail disorders, diseases, treatments and outcomes. The ability to perform such linkages significantly increases the value of the specimens for epidemiologic and genetic research; therefore, the BioTrust will establish business agreements with other programs whenever possible in order to access their data; and
(Phase 3) An "Honest Broker" function has been introduced to enhance and pilot the merging and de-identification of data from multiple sources. Selected newborn screening and vital records staff members at MDCH serve in this role. MDCH assigns each specimen and corresponding information a unique code and maintains the linkage to individual identities. The specimens are stored with this unique code by the Biobank. Should samples meeting specific demographic criteria be needed for a particular research study, the honest broker identifies these samples through established data linkages at MDCH and instructs the Biobank which samples to release to the researcher. If necessary, the honest broker also will conduct appropriate database

queries and prepare a flat file with de-identified data for use by the researcher. Before samples are released by the Biobank, they are labeled with a new unique code. If samples from specific, identified individuals are required for a particular study, the researcher must submit release forms signed by the legal representative (parent, guardian or individual if 18 years or older). MDCH also requires the researcher to sign a Materials Transfer Agreement that specifies allowable uses of the specimens and data before any samples are released.

Minnesota Newborn Screening Program
(http://health.state.mn.us/newbornscreening/research.html)

Parents have the option to decline newborn screening by signing a Refusal of Newborn Screening form. Following newborn screening, the Minnesota Department of Health (MDH) securely stores leftover blood specimens and newborn screening results. The MDH has securely stored residual newborn screening specimens since July 1, 1997. By August 1, 2008, approximately 792,000 newborn screening specimens were in storage. Specimens that were received between July 1, 1997 and September 7, 2005 are stored securely in an offsite protected record center. MDH employees do not have direct access to these specimens. Requests for specimens housed at the offsite record center go through both a trained records coordinator and the outside record management and document storage facility. Residual specimens retained before 2005 are stored at ambient temperature, but, residual specimens obtained after 2005 are stored at -20^{o}C with desiccant. Educational information about retention of residual specimens is available on the MDH Newborn Screening Information brochure and at the MDH website provided above.

The parent or guardian may choose to have the screening results and the blood specimen destroyed. This request can be made at birth or at any future time. In the case of the Directive to Destroy Form neither a permanent record of the test nor the leftover blood are kept by MDH. When a request to destroy is received, the blood specimen is destroyed within 45 days, and results are destroyed 24 months after the initial screen took place. The Directive to Destroy Form and examples of past uses of residual newborn screening specimens in research efforts are provided on the MDH website.

Specimens received by MDH beginning September 8, 2005 are stored onsite in a locked storage room. Only MDH employees who have received extensive data privacy training are allowed access to this area. MDH stores these specimens securely and in accordance with strict data and genetic privacy standards. The following reasons for storage are paraphrased from the website: 1) to provide results or specimens upon the request of the family or the baby's healthcare team; 2) to repeat testing if needed without obtaining another blood specimen; 3) to conduct other health-related testing upon parental request; 4) to help identify a missing or deceased child upon parental request; and 5) to provide a permanent record that MDH completed the screening. In other cases specimens with all identifying information removed may be used: 1) to ensure high quality testing (quality control); 2) to develop new tests for more disorders; and 3) to contribute to public health studies and research for a better understanding of diseases to benefit the general public.

South Carolina Newborn Screening Program
(http://www.scdhec.gov/health/mch/nbs/index.htm)

South Carolina law requires the Department Health and Environmental Control to store a child's residual newborn screening specimen in a specified manner. After screening tests are completed, the residual specimens are stored with no humidity control in a freezer (-20^{o}C) at the state laboratory. The storage is highly protected, and each specimen is held under strict confidentiality. The newborn screening program only can release a child's residual newborn screening specimen for approved research without any identifying information to learn new information about diseases. The law allows the parent or guardian to choose one of three options. If they do not want the specimen handled in this way, however, they are not required to select an option. The options are: 1) specimen stored by state but not used for research; 2) specimen destroyed two years after testing; and 3) specimen returned to parents two years after the testing date if requested in writing. Parents must check a box and sign a consent form on the reverse side of blood collection card. If no boxes are checked and/or the form is not signed, then specimen is retained at -20 ^{0}C for up to 3 years (typically 2 and a half years — space/staff dependent) and may be released only for anonymous confidential studies. Specimens also may be released with parental consent or with a court order/subpoena.

Texas Newborn Screening Program (http://www.dshs.state.tx.us/lab/nbsBloodspots.shtm)

Specimens received by the department since May 27, 2009 have been kept onsite in secure storage at ambient temperature unless a specimen destruction request was received from the child's parent, managing conservator or legal guardian. Once the newborn screening test is complete, the specimen card is securely stored for public health uses such as on-going quality assurance/quality control and research purposes, if approved by an IRB or privacy board of the health department [see Health & Safety Code Sec. 33.017(b)-(c)]. For any use outside of the Department of State Health Services (DSHS), identifying information must be removed from the blood spot card so that it cannot be connected to the identity of the child. Identifying information that links a child to a blood spot card is not allowed outside of DSHS without advance consent of the child's parent, managing conservator or legal guardian unless otherwise provided by law. The residual specimens are stored in the DSHS laboratory for one year at ambient temperature in containers with no humidity control. After one year the residual blood spot portion of the collection cards with a unique identifier are transported to a facility for storage off-site at the Texas A&M University where they are stored in boxes at ambient temperature with no humidity control. The majority of previously collected specimens were destroyed in spring 2010 as part of a lawsuit settlement; therefore, the transport of additional specimens to Texas A&M will not begin until 2011.

Physicians, nurses and other medical professionals must disclose to parents or guardians that blood taken from their newborn to screen for various disorders will be stored by the state and could be used for beneficial public health uses such as quality control or research. If the child's parent (legal guardian or managing conservator) decides that they do not want the child's blood spot card to be used for any other purpose after the newborn screening test results have been determined, Texas state law (changed in 2009) allows parents to instruct DSHS to destroy their child's residual newborn screening specimens after the newborn screening testing is complete. The law also requires distribution of an informational disclosure form that discusses allowable post-test uses of the blood spots so that the parents can make an informed decision on the matter,

and in June 2010 the program began distributing newborn screening specimen collection kits that include the disclosure and destruction request form. DSHS has placed the disclosure information at the top of the destruction request form, which is provided at birth and is available on the DSHS website, as directed by the new law. If the parent wishes to take advantage of this option, they completely fill out and submit the form, Directive to Destroy. Upon receipt of a completed Directive to Destroy form, the department will destroy the blood spot within 60 days. Some health care providers upon initial implementation of the new requirements have mistakenly labored under the impression that each parent must sign the destruction request form. As a result, many forms are being returned ultimately targeting the newborn screening specimen card for destruction when this may not be the intent of the parent. A study to determine the exact impact of this process and a method of improving it must be completed by December 2010.

The law requires providers to give the disclosure/destruction request form to the parents at the birth and at any subsequent newborn screen specimen collection (two specimens are currently required in Texas), but there is no legal obligation for healthcare providers to have the parents sign the form or for the providers to return signed forms to DSHS. The decision to sign the form is entirely up to the parent after they read the disclosure statement, and it is up to the parent to return a signed form to DSHS if they decide to request destruction of their blood spot card. The law requires DSHS to develop a mechanism for the providers to verify that they have provided the disclosure information to the parent. This was accomplished in the interim by adding a label to the cards with a check box that the healthcare provider can mark to indicate that the disclosure information was provided to the parent. In the future, this will become a permanent feature of the newborn screening specimen collection kit.

APPENDIX B.

TECHNICAL CONSIDERATIONS

Specimen Quality

The national standard for blood collection on filter paper currently in use defines the characteristics of residual newborn screening specimens required for analysis.[6] Because the collection cards constitute federally approved specimen collection devices, careful handling to prevent contamination is essential, particularly from extraneous DNA, which may be transmitted by touching. Lightly abrasive contact between specimens on filter paper has been shown to result in DNA cross-contamination; however, where contamination was detected, levels were insufficient to affect most routine molecular genetic newborn screening assays.[7] Since cross-contamination by contact (leaching) is possible, specimen-to-specimen contact should be avoided. It is standard practice to submit newborn screening specimens in transport envelopes rotated 180^{o} from each other to avoid specimen contact unless physical barriers are present (e.g., fold-over flaps or non-absorbent paper).[8] Should punching and cutting tools be used for DNA specimen procurement, they must be cleaned before each use to avoid carry-over contamination between specimens.[9]

Since the amount of residual specimen material that remains after newborn screening tests are completed is limited, if used for other purposes, its use should be of significant impact, especially if a relatively large amount of specimen is required. Previous U.S. guidance suggested that policies should prioritize the possible uses of residual specimens and should ensure that at least one blood spot is retained for possible use for the specific benefit of the patient.[10] Personal data on the information portion of collection cards should be kept separate from stored blood specimens with secure access restricted to authorized personnel.[11]

Analyte Stability

Assorted stability studies have demonstrated the extractability and stability over time of DNA in residual newborn screening specimens on filter paper. Although genomic DNA was shown to be stable under tropical conditions for at least 11 years at ambient temperature, the DNA quality for amplification of larger DNA fragments decreased when specimens were stored for longer than 10 years.[12] Studies in Washington state showed that storage for 25 years, at times without air conditioning, yielded successful genotyping results. However, the investigators noted that the climate in Washington is moderate, and study assays primarily used short amplicons - genotype might not be determinable for all subjects for assays requiring long amplicons.[13] A study of 70 well-residual newborn screening specimens stored for 19 months at ambient temperature gave adequate forensically useful DNA.[14] Likewise, whole genomic amplified DNA from residual newborn screening specimens archived for 15 to 25 years was used for reliable genome–wide scans and was found to be a cost-effective alternative to collecting new specimens.[15] The quantitative RNA stability in residual newborn screening specimens has also been demonstrated for specimens stored at $4\ ^{0}C$ with controlled relative humidity maintained at 30% for up to 20 years.[16, 17, 18]

Stability of non-DNA biomarkers commonly used in newborn screening has been shown to vary across analytes with many showing degradation within a few months.[19] No significant loss of phenylalanine, leucine, tyrosine, methionine and valine was observed in analyte-enriched blood spots during one year of storage at -20 ^{0}C, whereas all amino acids showed degradation at 37^{0}C within 30 days. Methionine was the least stable of the amino acids tested.[20] Although acylcarnitines have shown stability for at least 330 days at -18^{0}C, at room temperature, they are readily hydrolyzed to free carnitine (with its level increasing during storage) and the corresponding fatty acids. The velocity of decay is logarithmic and depends on the chain length of the acylcarnitines.[21] Studies have shown that stored blood spots should only be used for retrospective quantitation of acylcarnitines if appropriate correction for sample decay during storage is applied.[22] A tandem mass spectrometry evaluation of the long-term stability of acylcarnitines and amino acids in dried-blood stored for 15 years at ambient conditions showed that, with the exception of free carnitine and valine, all metabolite concentrations decreased.[23] Free carnitine increased during the first five years with the largest increase in the first year during which it rose 40%. Phenylalanine, alanine, arginine and leucine decreased exponentially. Citrutilline, glycine and ornitihine decreased markedly during the first five years. Methionine was the least stable of the amino acids. Many of the acylcarnitines decrease significantly during the first 5 years and more gradually thereafter. Tyrosine was relatively stable compared to most other amino acids in that it decreased more gradually during the first 5 years. Valine was considered stable since no significant change was found during the 15 years. Medium and long-chain acylcarnitines could not be analyzed because of low physiological concentrations.[24]

Storage Conditions

Optimal operation of a residual newborn screening specimen storage facility requires that careful planning of storage under specified and monitored storage conditions. If the purpose for saving residual newborn screening specimens involves future analysis, screening programs should investigate data that address the stability of various analytes when making decisions about storage conditions.[25,26,27,28] The defined purpose of storing samples should dictate the environmental parameters for storage. Ideally, residual newborn screening specimens should be stored frozen (preferably at -20°C) in sealed bags of low gas permeability containing a desiccant and a humidity indicator. Specimens retained only for DNA testing may be stored at ambient conditions (preferably refrigerated at 4°C) in sealed bags of low gas permeability and containing a desiccant for humidity control.[29] In all storage situations, precautions should be taken to ensure that possible contamination from specimen-to-specimen contact is not a problem.[30] Several publications have demonstrated the recovery of quality DNA from residual newborn screening specimens stored at ambient conditions.[31,32,33] During storage, a humidity indicator should be periodically monitored and appropriate action taken to reactivate the desiccant when humidity exceeds 30%[34,35] or some other designated level of action. Every residual newborn screening specimen should be properly identified. An index or catalog should be maintained so that any individual sample can be easily located. A quality assurance system is necessary for documenting the integrity of the stored residual newborn screening specimens.[36]

Retention Conditions

Laboratory genetic testing guidelines exist and appear to be applicable to newborn screening testing.[37] Additionally CLIA requires laboratories to establish and follow written policies and procedures that ensure positive identification and optimum integrity of a patient's specimen from

time of collection through completion of testing and reporting of results.[38] ACMG Standards and Guidelines state that the laboratory should retain the original patient sample until all testing is completed, and the report has been completed.[39] Depending on specimen stability, technology, space, and cost, tested specimens for molecular genetic tests for heritable conditions should be retained as long as possible after the completion of testing and reporting of results.[40] It has been recommended that, at a minimum, stabile tested patient specimens should be retained after testing until the next proficiency testing or the next alternative performance assessment to allow for identification of problems in patient testing and for corrective action to be taken. [41]

Specimen retention times vary widely among state newborn screening programs. At least 10 programs have indicated their intention to maintain archives of specimens indefinitely.[42] Because of the cost and complexity of specimen storage, only a few programs are known to store their residual newborn screening specimens frozen (-20°C) in sealed bags containing a desiccant. Notwithstanding storage challenges, some states have retained large numbers of residual specimens, often exceeding 1 million. Where specimen storage exists, a quality assurance system should ensure validity of stored samples for their intended purpose.[43] Where a defined purpose exists such that a control specimen can be stored, the control should be stored under identical conditions. In order to prevent location bias, control samples should be randomized in the storage system. Specimens that may be analytically unacceptable for newborn screening analysis may still contain usable analytes, including DNA, and should be stored under similar conditions to specimens that were analytically acceptable.

Specimen storage must be carefully planned such that specimens are kept readily accessible, secure, and environmentally sound. A storage policy should exist with input from others with experience and newborn screening stakeholders, including researchers and the public. The long-term cost and technical logistics of maintaining a specimen bank should be anticipated. Systems for easy access and retrieval should be carefully designed, and storage conditions should be maintained with careful documentation. Flow charting the specimen retrieval process and electronic specimen identification should be a part of the cataloging process.[44,45] Safe disposal of samples no longer required for examination should be accomplished in accordance with local regulations regarding waste disposal.[46,47] Care should be taken to dissociate patient identifiers from the blood spots.[48] If samples must be transported off-site for incineration or destruction, precautions should be taken to ensure that confidentiality of samples during transportation and destruction is maintained and that appropriate disposal of samples is achieved (i.e., no identifying information should be attached).[49] The program's specified length of retention for residual newborn screening specimens should be consistently met, and all disposal activities should be documented.[50]

Transport to/from Researchers

Handling and transport of residual newborn screening specimens should conform to the established processes for transport of specimens to the screening laboratory in accordance with Occupational Safety and Health Administration (OSHA) guidelines and with the understanding that any human tissue and fluids may harbor infectious agents.[51] Residual newborn screening specimens can be shipped or transported by mail or other carrier with no reasonable expectations of occupational exposure to blood or other potentially infectious material.[52] "Standard precautions" and compliance with local regulations and institutional policies are required in preparing newborn screening specimens for shipment.[53] The identified packaging system must meet the basic triple

packaging system, i.e., blood absorbed into paper, an inner envelope or other protective cover, and an outer envelope of high quality paper.[54] U.S. transport standards are harmonized with the World Health Organization's Guidance on Regulations for the Transport of Infectious Substances[55] and the International Civil Aviation Organization's Technical Instructions for Safe Transport of Dangerous Goods by Air.[56]

Residual newborn screening specimens must not be packaged in airtight, leak-proof sealed containers (e.g., plastic or foil bags) because the lack of air exchange in the inner environment of a sealed container causes heat buildup and moisture accumulation. Heat, direct sunlight, humidity, and moisture are detrimental to stability of residual newborn screening specimens and analyte recovery. The inclusion of desiccant packs will aid in preventing moisture accumulation. However, shipping conditions are uncontrolled, and desiccant has limited effectiveness. Local postal, courier, and other transport regulations must be followed. If local regulations require enclosure in airtight, leak-proof sealed containers (plastic or foil bags) for transportation, then sufficient numbers of desiccant packages must be included to ensure minimal exposure of specimens to excessive moisture. Indicator cards may be used to monitor humidity. Specimens known to contain an infectious agent should be transported with special precautions according to local regulations (e.g., required packaging and outside warning label).[57]

APPENDIX C.

State Statutes and Regulations on the Retention and Use of Residual Newborn Screening Blood Specimens[3]

State	Citations	Research Use Provisions[4]	Consent (opt-in) and Dissent (opt-out) Provisions[5]
California	Health and Safety Code §124980 et seq.	Research to identify risk factors for children's and women's diseases and to develop and evaluate screening tests, prevention strategies, or treatment that is approved by the department permitted	Informed consent requirements may be modified for research that allows an approved custodian to access personal information, only if the proposal is reviewed and approved by an IRB, which certifies that the research project is of potentially substantial public health value such that the modification is justified.
Idaho	IDAPA 16.02.12.050	Uses other than routine calibration of newborn screening lab equipment and quality assurance permitted only with consent	Express written consent of a parent or guardian required for any purpose other than those described under research use provisions
Indiana	IC 16-14-17-10	Epidemiological survey and research purposes on specimens that are not identifiable permitted	None, but research is allowed on specimens that do not identify the individual.
Iowa	IAC 641-4.3	Research approved by an IRB, the congenital and inherited disorders committee, and the health department that would further screening activities, the health of infant/child for whom other specimens are not available or readily attainable, or general medical knowledge for existing public health programs permitted	Parental informed consent is required to access confidential information for research purposes.

[3] This table ONLY includes statutes and regulations that specifically address BOTH storage and use of residual dried blood spot specimens. Policies that only discuss the period of time specimens are stored or storage conditions and broader laws such as those pertaining to genetic privacy are not listed. States may have policies in guidelines or practices on retention and use of specimens (such as guidelines in Arizona) that are not found in the official statutes and regulations.

[4] This column provides a brief description of the research use provisions. Please see the text of the statutes and regulations for a full understanding of the requirements placed on research applicants, including privacy and confidentiality protections, and the types of research allowed, if approved.

[5] This includes consent/dissent provisions related to secondary use but does not include consent/dissent for screening itself.

State	Citations	Research Use Provisions[4]	Consent (opt-in) and Dissent (opt-out) Provisions[5]
Maine	10-144 CMR Ch. 283	Research by the health department or approved researchers to improve the health of mothers and children permitted	Consent of a parent or guardian is required to release specimens with identifiers intact.
Massachusetts	CMR 270.004	Pilot studies offered through a research protocol approved by the health department IRB for conditions that do not meet the criteria for mandatory screening, for which screening may provide more information on incidence, natural history and treatment or testing and which may, based on this information, meet criteria for mandatory screening	Informed consent is required for pilot studies.
Michigan	MCL 333.5431	Medical research conducted in a manner that preserves confidentiality and is consistent with the Common Rule permitted	The health department will switch to a consent approach for storage and use of specimens through the Biotrust on October 1, 2010. An opt-out method was previously used.
Minnesota	MS §144.125	Statutes require the health department to provide parents an explanation of the benefits of retaining specimens (the resulting information provided discusses public health studies and research, including guidelines for these uses).[6]	Parents may request destruction of specimens 24 months after testing.
Mississippi	MAR Title 15 Ch. 38	Research or use for purposes other than confirmation of previous test results prohibited	N/A
Missouri	MRS §191.331	Use for public health purposes and in compliance with applicable provisions of federal law	None

[6] Minnesota Department of Health, http://www.health.state.mn.us/newbornscreening/storage_QA.html.

State	Citations	Research Use Provisions[4]	Consent (opt-in) and Dissent (opt-out) Provisions[5]
Nebraska	NRS 71-519 NAC Title 181 Ch. 2	Use for approved public health research (including but not limited to quality assurance and improvement of newborn screening practices) and in compliance with applicable provisions of federal law is permitted. The Chief Medical Officer, Newborn Screening Advisory Committee, and a Human Subject Review or IRB must review and approve public health research projects.	Written consent is required from parent or guardian of individuals whose specimen is requested for research.
New Hampshire	NHRSA 132:10-a	Research permitted with consent.	Consent required for research or DNA testing purposes.
North Dakota		Research projects concerning medical, psychological, or sociological issues sponsored by specified entities and reviewed and approved pursuant to human subjects policies and procedures by an IRB or equivalent panel is permitted.	None
Oklahoma	2010 SB 1250	Use permitted with consent	Parental consent required to store, transfer, use or database DNA from any newborn child
South Carolina	SCCL 44-37-30	Use for confidential, anonymous scientific study approved by the health department IRB permitted unless directed otherwise by a parent or guardian	Parents (or child if 18 or older) may direct the department to return a blood sample two years after testing, destroy a blood sample two years after testing or store a blood sample but not release the sample for research.
Texas	Health and Safety Code §33.0111	Other uses permitted unless limited by a parent or guardian	Parents or guardians may limit the use of genetic material by providing a written statement that prohibits the health department from retaining or using the material for any purpose other than newborn screening.

State	Citations	Research Use Provisions[4]	Consent (opt-in) and Dissent (opt-out) Provisions[5]
Utah	R398 1-15 and 16	Use for newborn screening quality assessment and research approved by the health department and an IRB using de-identified blood spots permitted	Informed consent required for research if specimens are not de-identified
Washington	WAC 246-650-050	Research reviewed and approved by the departmental human subjects review board (and the secretary of the health department for projects involving the use of identifiable information) is permitted. Research using anonymous samples is permitted if the use has significant public health benefit.	Parents may request destruction of specimen form after screening is completed. Written, informed consent required for research involving samples and specimen information.
Wisconsin	WAC DHS 115.05	Use for research and evaluation purposes related to congenital and metabolic disorders or laboratory procedures is permitted. All applicable laws and human subjects research protections must be observed.	None

Source: Johnson Policy Consulting, www.policyconsult.com (September 2010)

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