Considerations and Recommendations for a National Policy 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 / DRAFT
# DRAFT

## TABLE OF CONTENTS

I. Executive Summary iii

II. Introduction 1

III. Policy, Ethical and Legal Issues 1

- Ownership 4
- Stewardship 5
- Privacy Protections 6
- Awareness and Education 8
- Consent/Dissent 9
- Position Statements 11

IV. Financial Considerations 12

- Storage and Retrieval 13
- Associated Costs 14

V. Conclusion 14

VI. Recommendations 15

Appendix A. 20

Appendix B. 25
EXECUTIVE SUMMARY

In recognition of the tremendous potential to advance science and clinical care through the use of residual newborn screening blood specimens for newborns, children and their families, the Advisory Committee on Heritable Disorders in Newborns and Children calls upon policymakers, the public health community, health care providers and families to work together to protect this valuable resource for the public good.

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

Newborn screening is a highly successful public health program that identifies rare genetic, congenital and functional disorders and ensures early management and follow-up for those affected. States are responsible for oversight and implementation of newborn screening, and each state has a law that either requires or allows newborn screening. Newborn screening policies are usually developed with input from multi-disciplinary advisory committees that include consumers, health care and public health professionals and others. While state administration of newborn screening programs fosters local control and accountability, it also gives rise to wide variation in practices across the country, including policies on the retention and use of dried blood spot specimens after newborn screening.

All newborn screening programs in the United States obtain dried blood specimens on a special filter paper designed for laboratory testing in newborn screening. States generally retain portions of these specimens (residual specimens) for some period of time 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 and family. Residual specimens also may be used for result verification and quality assurance activities for the laboratory and program (including new test validation). A collection of stored specimens is often referred to as a “biobank.”

Newborn screening specimens are usually the first blood specimen drawn in a baby’s life and are collected on essentially all newborns. Testing of the specimens yields critical information about risk for certain inherited conditions. 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.

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

This document is designed to review the issues facing newborn screening programs and to develop a national guidance for programs that retain and use dried blood specimens after newborn screening is complete.

CONCLUSION AND RECOMMENDATIONS

Since the newborn screening community first published guidance regarding the retention, storage and use of residual dried blood spots in 1996, noticeable improvements in policy development have occurred.1 In state newborn screening programs, there are currently two distinct philosophies regarding the storage and use of residual dried blood spots: 1) short-term storage (<3 years), presumably for program quality
assurance and test improvement; and 2) long-term storage (> 18 years), presumably for public health research. Heightened awareness exists in the research and consumer communities concerning both the potential value of specimens and the possible privacy concerns. Some characteristics of the current policy environment complicate these privacy issues, including differing state policies on the need for consent or dissent, potential uncertainty about legal ownership of residual blood specimens in states without a well-defined policy, and minimal public awareness of newborn screening.

Because newborn screening is the only medical screening program that reaches the entire population of newborns in the U.S., it is unique, and the processes surrounding it must be thoughtfully approached. Residual blood specimens provide an excellent opportunity for storage in a biobank for approved uses after screening is complete and the results have been validated. However, at the present time, this is a secondary purpose that may not be adequately addressed in some existing state laws or policies. Newborn screening programs should approach the use of residual specimens use carefully, anticipating both the potential benefits and risks. To assist in this process, the Secretary’s Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) 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 addressing the disposition of dried blood specimens remaining after newborn screening. The policy should specify appropriate use and storage after the completion of newborn screen testing and verification of results according to laboratory QA procedures. Parties responsible for drafting the policy should consider whether consent from families is necessary for uses other than newborn screening. Multidisciplinary input, including from consumers, should be solicited and thoughtfully considered in developing such a policy. The specimen disposition policy should include the length of time for which specimens will be stored and storage conditions. Compliance with storage processes included in NCCLS/CLSI Standard LA4-A5 or its current edition is recommended. Any data linkages should be carefully addressed, and privacy and confidentiality should be ensured.

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 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. Parties responsible for drafting the policy should consider whether consent from families is necessary for uses other than newborn screening and if the consent policy varies depending on the purpose. Multidisciplinary input, including from consumers, should be solicited and thoughtfully considered in developing such a policy. The specimen access policy should address any uses prior to and after the newborn screening laboratory testing and validation process. Policies that permit the approved use of dried blood spot specimens for purposes other than newborn screening should address handling and disposition of the specimen and measures to protect the privacy and confidentiality of any associated patient information.

3) All state newborn screening programs should work proactively to ensure that all families receiving prenatal care are educated about newborn screening. 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 dried blood specimens. This activity should include appropriate steps to inform and train prenatal care providers regarding their educational responsibilities within the newborn screening system. Processes should be in place to evaluate the extent, timing and understanding of prenatal education with an eye towards educational program improvement. Where long-term storage
policies or other options exist relative to storage of residual dried blood spots, such information should be included in prenatal education materials.

4) **If residual blood specimens are to be available for any purpose other than the legally required newborn screening process for which they were obtained, an indication of the parents’ awareness and willingness to participate should exist in compliance with federal research requirements** (45CFR46[http://ohsr.od.nih.gov/guidelines/45cfr46.html]). A consent (opt in) or a dissent (opt out) process may meet this requirement depending on purposes for which specimens will be used. The state attorney general or other appropriate legal authority should review this process. The use of residual specimens for program evaluation (e.g., repeat testing as a quality check) or process improvement (e.g., non-commercial, internal program new test development) are valid components of the public health newborn screening program, and, therefore, should not require additional consent if the studies are conducted using anonymized samples. However, once the use of a bloodspot moves beyond the state mandated uses of program evaluation, treatment efficacy and test refinement, each state should consider whether separate or blanket consent for approved studies is required from parents, legal guardians or individuals screened upon the age of majority for the use of bloodspots. It is recommended that the Secretary, HHS consider the assessment of the necessity and efficacy of utilizing additional consent/dissent processes for the use and storage of newborn screening residual dried blood specimens. In addition, if the Secretary, HHS desires these studies, that she provide funding for utility assessment projects over the next 5 years.

5) **It is recommended that the Secretary, HHS provide administrative support and funding to the state programs to develop:**

- Model consent/dissent processes for the use of residual newborn screening specimens, including the advantages and disadvantages of particular approaches;
- National data on the utility of any additional consent/dissent processes implemented relative to potential research uses of residual newborn screening specimens;
- Model educational programs for the general public on the importance of newborn screening and the potential uses of residual specimens to generate population-based knowledge about health and disease; and
- Educational materials for use in such programs with facts about potential uses of residual newborn screening specimens for both consumers and prenatal healthcare providers.

**Note:** During the vetting process (webinars) to the stakeholder community, questions and discussions led to development of the following proposed (optional) recommendation. Since this proposed recommendation was not shared with the stakeholders in the webinars and not unanimously embraced by all members of the ACHDNC Work Group, it is listed here separately for your consideration and discussion.

**Optional Recommendation—Where state newborn screening programs elect to maintain a long-term newborn screening biobank of residual newborn screening specimens, a secure third party key holder system ("honest broker"), with appropriate consent, should be used to allow for emergency linkages in de-identified specimen studies.** The key holder would have the ability to reveal critical health information to a study subject should such information be discovered during the course of the research, and the ability to obtain and reveal personal information from a subject to a researcher, if such information were deemed to be of critical importance. In either case, consent from the study participant or appropriate parent or guardian would be required.
BRIEFING PAPER

In recognition of the tremendous potential to advance science and clinical care for newborns, children and their families through the use of residual newborn screening blood specimens, the Advisory Committee on Heritable Disorders in Newborns and Children calls upon policymakers, the public health community, health care providers and families to work together to protect this valuable resource for the public good.

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

INTRODUCTION

Newborn screening is a highly successful public health program that identifies rare genetic, congenital and functional disorders and ensures early management and follow-up for those affected. States are responsible for oversight and implementation of newborn screening, and each state has a law that either requires or allows newborn screening. Newborn screening policies are usually developed with input from multi-disciplinary advisory committees that include consumers, health care and public health professionals and others. While state administration of newborn screening programs fosters local control and accountability, it also gives rise to wide variation in practices across the country, including policies on the retention and use of dried blood spot specimens after newborn screening.

All newborn screening programs in the United States obtain dried blood specimens on a special filter paper designed for laboratory testing in newborn screening. States generally retain portions of these specimens (residual specimens) for some period of time 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 and family. Residual specimens also may be used for result verification and quality assurance activities for the laboratory and program (including new test validation). A collection of stored specimens is often referred to as a “biobank.”

Newborn screening specimens are usually the first blood specimen drawn in a baby’s life and are collected on essentially all newborns. Testing of the specimens yields critical information about risk for certain inherited conditions. 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.

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

This document is designed to review the issues facing newborn screening programs and to develop national guidance for programs that retain and use dried blood specimens after newborn screening is complete.

POLICY, ETHICAL AND LEGAL 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. DNA and RNA can be extracted from the dried blood specimens used for newborn
DRAFT

screening, and there is increasing bioinformatics capability allowing the linkage of DNA information with clinical data.\textsuperscript{7} International guidelines have been suggested as a means of emphasizing the importance of preserving newborn blood specimens in repositories for the benefit of future generations,\textsuperscript{iii} but none currently exist. The issues and possibilities surrounding national, regional or state repositories of residual newborn screening specimens have been discussed in at least two national meetings with no clear resolution. Appropriate stewardship and public trust have been repeatedly identified as essential elements of a successful repository, but no consensus model for a repository has emerged.\textsuperscript{iii}

All states require that any baby born within the state’s jurisdiction be screened for certain inherited or congenital conditions that can result in catastrophic consequences if left undetected and unmanaged. As part of the screening process, a blood specimen is collected, usually by a heel stick, and the blood is absorbed onto a special blood collection device—a specialized filter paper—air dried and submitted to the state’s designated newborn screening laboratory. Most (but not all) states provide a mechanism for opting out of the screening process for any reason or for religious objections, but consent for screening is almost universally not required.\textsuperscript{iv} In some programs, the rules accompanying the state’s newborn screening statute define ownership of the specimen, once collected and submitted, as residing with the state, and there is at least one supporting legal decision that might apply (see Ownership discussion below). Nonetheless, potential uncertainty about legal ownership of specimens remains, and ethical questions persist about specimen use following screening. Despite awareness of the issues and previously published guidance encouraging state policy development, some states still lack clear policies regarding retention time, storage conditions and possible uses of the blood specimen remaining after screening.\textsuperscript{v} Among states with such policies, the content varies considerably between programs.

There are important newborn screening program uses for residual specimens that may remain after screening \textit{per se} is complete. These include:

1. Program quality assurance and test validation; (Residual newborn screening specimens are valuable evidence that appropriate testing has occurred. The existence of a residual specimen proves that the screening laboratory received it and assumed responsibility for analyzing it correctly.)
2. Parental requests for other testing, particularly in cases where an infant has died without an obvious cause and when future pregnancies may be contemplated;\textsuperscript{vi} (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, perhaps through environmental interactions.)
3. Court ordered forensic uses; and
4. Population research; (Newborn screening programs have reported numerous additional requests for specimen usage over the years including public health research projects.\textsuperscript{5} As one example, the Centers for Disease Control and Prevention-sponsored 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 public health educational and other resources.\textsuperscript{vii} Additionally, case control studies also possible using residual specimens to determine concentrations of biomarkers in children who develop certain disorders in comparison with similar markers in healthy children—controls. Such studies have the potential to provide insight into the mechanisms behind the origin of diseases and their potential screening biomarkers.)\textsuperscript{viii}

Increased public awareness of stored residual newborn screening specimens has raised concerns for some individuals about personal medical information that the bloodspots might reveal such as disease susceptibility through current and future technological advances.\textsuperscript{iv} In addition to the federal privacy laws
that exist and state laws that specifically pertain to newborn screening, other state privacy laws may impact specimen storage and use.\textsuperscript{x,xii} Most of the legal and ethical questions surrounding retention of residual newborn screening specimens have been reviewed in depth elsewhere and will not be revisited here.\textsuperscript{xii} 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 accession 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 dried blood spots regardless of the approach, for example, would provide greater uniformity among the states. Despite prior efforts at the national level at the Institute of Medicine, President Clinton’s National Bioethics Advisory Commission and President Bush’s Council on Bioethics to explore these issues over the last two decades, many questions remain unanswered.

Because of the increasing number of requests for residual dried blood specimens, the procedures and regulations regarding their release and use should be formalized.\textsuperscript{xi} A 2002 study of the storage and usage practices in U.S. newborn screening programs revealed that almost all programs stored their residual specimens with identifiers present.\textsuperscript{xiv}

- Only 2 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 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).

The mechanisms for using aggregate data obtained from newborn screening also were reported to vary. In some cases researchers were required to have institutional review board (IRB) approval at their own institution although some 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.\textsuperscript{xv} A slightly later study showed that 74% of states used residual specimens for newborn screening test evaluation, and 28% used them for epidemiological and pathophysiological research studies.\textsuperscript{xvi} Only 57% reported having internal written policies for specimen usage.

In order to determine current storage practices, online data reported by the states to the National Newborn Screening and Genetics Resource Center (NNSGRC) was reviewed and validated through email contacts with 100% response rate.\textsuperscript{xvii}

- Currently, 67% (34 of 51) of state programs and Washington, D.C., retain residual blood specimens for less than 3 years accounting for approximately 46% of all U.S. newborns (see Figure 1).
- The remaining 33% save their residual blood spots for eighteen or more years (~54% of births) with at least 6 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°C and long-term storage at -20°C, with desiccant in both cases, storage conditions vary from ambient to –20°C with variable uses of desiccant.\textsuperscript{xviii}
Ownership
Two of the more important legal and ethical questions that arise concern ownership of the blood specimen and ownership of the information gathered, produced or potentially revealed as part of newborn screening or related processes. Bioethics advisory bodies for both President Clinton and President Bush reviewed policy issues around residual blood specimens but offered no recommendations for their use and storage.xix,xx

State laws and regulations pertaining to newborn screening specimen and information storage vary, and their impact or potential impact on specimen use were extensively reviewed in 2006 by Therrell, et al.xxix At that time only 9 states had specific statutory or regulatory requirements for retaining newborn screening information and specimens. Prescribed retention periods varied from 1 month to indefinitely (then as now). In some state/territorial jurisdictions, parents may choose the return or destruction of their newborn’s specimen after a specified time period (e.g., 2 years in South Carolina, 60 days in Minnesota and 45 days in Texas), or they may allow it to be stored and used for research. The report noted in Florida, Idaho and Ohio it was unclear whether retention requirements addressed newborn screening specimens themselves or merely newborn screening related information collected by the department, but in California, Maine, Michigan, and Washington, newborn screening specimens were declared to be the property of the state. In Maine a parent may object to state ownership in writing.xxii The state of Utah has since identified specimens as property of the state, and related rules there address education and specimen use.xxiii

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. Since all states require newborn screening with an opportunity for refusal (opt out) in most cases, the state would appear to have ownership of the screening specimens for purposes of newborn screening and related uses.

Even so, the legal and ethical communities continue to debate specimen ownership, and programs will likely require clarification on an individual 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 specimen collection.
Stewardship
State public health departments strive to exercise the highest care in receiving, storing and protecting newborn residual blood specimens from unauthorized use. It is understood that the public has a right to expect that newborn screening 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. Appropriate and secured records should be maintained in a manner similar to that required for maintaining legal evidence in forensic laboratories.”xxiv

Despite a reluctance of many in the newborn screening field to label newborn screening specimen storage facilities as biobanks, the public and the media routinely use this terminology. As a result, comparisons with other biobanks are often made. Since little experience with formalized long-term storage of residual newborn screening specimens exists in the U.S., a review of other national programs such as that of Denmark is informative.

The Danish government initiated a national newborn screening biobank in 1993 (see the Appendix for further information). This biobank was established for three stated 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.xxv The Executive Order that initiated the Danish biobank was replaced in 2004 by detailed operational guidelines that require strict compliance with laws on processing personal data and management responsibilities, patient’s rights, including the option to decline participation and request destruction or retrieval of the specimen, scientific ethics, and confidential health information. In addition, the guidelines prescribe a complaint procedure. These strict regulations are considered necessary tools to ensure appropriate accountability and to gain public trust. To date, there have been no reported misuses of the Danish Newborn Screening-Biobank or its associated Register, and public acceptance is high.xxvi

In the U.S., recent attention has turned to the ‘Michigan Neonatal BioTrust,’ a developing long-term newborn screening specimen repository for expanded research use.xxvii The state newborn screening program currently stores residual newborn screening specimens for 21.5 years and are accessible for approved uses on a case-by-case basis. Early in the development of the repository, a bioethicist was recruited to advise 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.xxviii The result was 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 (see Appendix for further information).xxix 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 anonymous research while offering the possibility of access to additional information for the researcher if critical findings require such or the transmittal of critical information to the patient. In either case, consent for information sharing will be required.xxx
While national or state biobanks such as that in Denmark or Michigan provide useful models, they also represent a possible first step to a global consortium of such biobanks. These consortia might serve two primary purposes. First, joint analyses of important, but uncommon, gene variants could generate more definitive results than could be generated from individual and likely underpowered studies. Second, reasonable expectations from funders and beneficiaries with respect to knowledge sharing could perhaps result in more efficient and effective collaborations similar to the mapping of the human genome and the Global HIV Vaccine Enterprise. In turn, this could lead to accessible and affordable studies in diverse populations that allow imaginative search for common and rare genetic and other biological correlates of global diseases. Indeed, the National Women’s and Children’s Study and Newborn Screening Translational Research Network established by the National Institutes of Health (NIH) provides the impetus for a U.S. national biobank based on similar hypotheses. A few research biobanks have already been established in some developing countries. The Chinese Kadoorie study and the Mexican biobank were both designed primarily to discover correlates of non-communicable diseases in adults, and a smaller national DNA bank exists in Gambia.

In at least 4 states laws exist that define the details of procedures and processes for storage of and access to residual newborn screening specimens (see Appendix for further information on policies in Michigan, Minnesota, South Carolina and Texas). 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. The state may provide opt out information through pamphlets and websites (e.g., Michigan, available at http://www.mnbb.org/). While the exact processes vary somewhat, the intended consequences are the same—utilization of residual newborn screening specimens only with the agreement of the parents or guardian of the newborn. 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).

**Privacy Protections**

The issue of privacy and the use of residual blood spots are closely linked to parental education and informed decision-making (see section on Consent/Dissent Issues). There continues to be some public mistrust about the possible uses of newborn screening specimens. Concerns focus on possible discrimination, psychological harm, identification of paternity, and social injustices; however, there are no documented cases of harm resulting from these concerns relative to use of newborn screening specimens. While some state statutes specifically address newborn screening privacy, there are additional broader health laws, regulations and medical standards of practice that may also affect newborn screening. Five states (Alaska, Colorado, Florida, Georgia, and Louisiana) have defined genetic information explicitly as personal property, and Alaska has extended this property right to 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 a covered entity. 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 itself such as research that involve genetic testing or the use of genetic information.

Federal privacy regulations (the ‘Privacy Rule’) have been in place since April 2003 (45 CFR Parts 160 and 164). These regulations provide specific exemptions and allowances for public health activities and to individuals providing services associated with those activities. Under this exemption, newborn screening programsmay use and disclose information for treatment, payment, or health care operations without the individual’s consent or authorization. ‘Operations’ include most routine program activities.
except for research. Research conducted by state or federal programs as mandated by relevant law is permitted as a public health activity. For research by private researchers or research not mandated by law (e.g., a prevalence study using identifiable names), both the privacy and the research rules apply. Research with human subjects conducted with federal funding or involving researchers otherwise covered by federal law is regulated by 45 CFR Part 46 — or the ‘Common Rule.’ Because research is not considered by the federal privacy rule to be part of treatment, payment, or operations, a researcher wishing to access identifiable personal health information (also called Protected Health Information — PHI) must either:

“(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 number; fax number; electronic mail address; Social Security number; medical record number; health plan beneficiary number; 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 says 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. For research using DNA derived from dried blood spots: a. there must be de-identification, which can most easily be accomplished by simply snipping off a piece of the specimen and providing no other information; or b. there must be parental or legal guardian written authorization on a Privacy Rule compliant form; or c. there must be a waiver of the need for authorization properly granted by a Privacy Board or IRB; or d. there must be a Limited Data Set containing only general geographic information and relevant dates, coupled with a data use agreement signed by the researcher (see privacyrulesandresearch.nih.gov/xlii

In addition to the privacy considerations above, newborn screening laboratories are also governed by the Clinical Laboratory Amendments of 1988 (CLIA), which require confidentiality of patient information throughout all phases of the testing process under laboratory control (42 CFR §493.1231).xliii Additional state licensure or contract requirements may also exist. The CDC has recommended that laboratories performing molecular genetic testing, which may include 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.xliv
Awareness and Education

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 samples. A recent study by Goldenberg has determined that only 12 states currently include mention of specimen storage in their newborn screening educational pamphlet. Regardless of the content, studies have shown that there is little effort currently ongoing to involve prenatal care providers in the newborn screening system. 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.

So while the role of the obstetrician as an educator in the newborn screening process has been defined, 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. The need for 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 it, 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.

While these studies validate the need for better physician education to meet the educational needs of the screening program, 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. 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. 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. 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), and there are important variations between programs in the information provided to parents. The most common educational mechanism remains a brochure provided in the hospital package of informational materials for the mother. 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.

With respect to specimen storage, typically a newborn screening educational program will need to: (1) inform prenatal and other healthcare providers and policy makers about the issues related to residual newborn screening specimen storage; and (2) inform parents about the issues related to newborn screening specimen storage and potential use and their options. While models of informational brochures for newborn screening programs exist, they do not generally address residual specimen storage issues. 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.\textsuperscript{viii}

A recent study of the attitudes of women towards a hypothetical pediatric biobank showed that Caucasians were the most willing to enroll their children, while non-Black minorities were the most uncertain about what they would do.\textsuperscript{lix} 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 consented 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. This study found a general understanding of research, but there were significant misperceptions about what participation in a biobank entailed. These 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 more clearly explain what information researchers or others might access.\textsuperscript{lx}

Information sharing has been shown to positively correlate 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.\textsuperscript{lxi} 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.\textsuperscript{lxii} A 2008 hypothetical biobank study also found potential participants would place restrictions on the type of research to be performed with over 90\% supporting all conditions proposed. In addition to their willingness to enroll, potential participants were also 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.\textsuperscript{35}

Community engagement to help relevant programs understand public privacy concerns has been identified as a useful step in helping recruit and retain biobank participants.\textsuperscript{lxiii} It has also been suggested that researchers should translate community knowledge and concerns about children into responsive and realistic study protocols. A longitudinal study of children (who eventually transition to adulthood) should retain some degree of flexibility to account for differing rights as children transition to adults. Clear communication at the outset about consent, dissent and re-consent, as well as the scope, risks and benefits of studies are considered to be essential.\textsuperscript{lxiv} Commentators have noted that the best way to ensure that new tests are introduced in a rational manner that promotes 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.\textsuperscript{lxv} It also has been noted that fundamental ethical concerns around individual and societal risk should ultimately drive how research regulations are interpreted and used.\textsuperscript{lxvi} 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.\textsuperscript{lxvii}

Consent/Dissent

The use of residual newborn screening specimens represents perhaps the most visible example of the need for consensus on the ethical tenets and legal rules governing the use of bodily tissues, including the concept of ‘meaningful’ consent.\textsuperscript{lxviii} Some form of consent or formal IRB waiver of consent appears to be necessary if 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.\textsuperscript{lxix} Medical privacy advocates and
Ethicists argue that parents must be asked for consent before residual newborn screening specimens are retained, but others contend that meaningful consent is impossible because parents cannot be adequately educated about all potential uses and outcomes.

Residual dried blood spots 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. 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 for anticipated, anonymized research, questionable and a threat to public trust in research endeavors with such specimens. 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. 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. Subject to ethical review board approval and parental consent, the use of identified or coded specimens also has been deemed acceptable if researchers can demonstrate that newborn screening specimens are the best specimens available and that similar data could not be obtained from adults. If the research study does not require that donors be re-contacted or identified, some have suggested that existing medical records and stored specimens that contain identifying information can be made available for research without explicit individual consent or ethical review board approval.

Various experts and organizations in the U.S. and abroad have contemplated the issue of consent for the use of newborn screening specimens in research studies. The AAP Newborn Screening Task Force recommended that archived dried blood 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 blood spots. A 2004 German National Ethics Council opinion states 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." Length of storage and use of data were regarded similarly with neither limited in advance. 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.” 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.

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 for discussion of 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 (e.g., PatientsLikeMe, Private Access). In this way, consenting individuals participate for the public good while maintaining personal values and autonomy and may ultimately enhance research activities and
Successful models for opting out (dissent) also exist such as the Danish newborn screening biobank uses (see Appendix).

In the United States, consent for research is usually for a single project, and researchers must re-consent 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. Since retention and use policies for residual dried bloodspots cannot anticipate all future research proposals, newborn screening program 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 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. A more recent ACMG position statement 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.

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 dried blood specimens following newborn screening analysis. 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. There may be other reasons other reasons to save residual dried blood specimens, including test development, research, and forensic identification. To retain residual for such purpose 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.

The Clinical and Laboratory Standards Institute (CLSI) – The CLSI guideline states that, “Beyond the usual medico-legal considerations that determine advisable durations for retention of all clinicopathologic 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.

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 blood samples 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.”

FINANCIAL CONSIDERATIONS

Understanding that policymakers need to weigh benefits of newborn screening system against the costs of the system, policy guidance should address the costs associated with the infrastructure for the storage and use of residual blood spots and the financing of the system. The sources of funding for newborn screening vary across states depending on local infrastructure resources available, monies from external sources that can be used for newborn screening, and the definition of system components that require financial support. A recent review of newborn screening financing reported that 90% of all newborn screening programs have a fee paid by parents or a third party payer, 61% utilize some funding from the Maternal and Child Health Services Title V block grant, 33% receive some funding from state general revenue/general public health appropriations, and 24% obtain direct reimbursement from Medicaid without passing through a third party. Although this report noted that 64% of newborn screening programs received budget increases between 2002 and 2005 (72% from fees and to a lesser extent from Medicaid, the Title V block grant, and state general revenues), the effect of recent national financial difficulties on newborn screening programs is not accurately known at present.

A fiscal impact analysis of a specimen storage program requires careful and comprehensive definition of the components of the program. 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, researcher costs and other issues. Because many newborn screening programs view a national position that encourages better education, control and facilitation of residual blood specimens as an unfunded mandate, consideration of federal financial support is needed.
Storage and Retrieval
All newborn screening programs retain residual blood 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. The national blood spot collection standard recommends that specimens should be refrigerated for up to six months until they are either destroyed or stored frozen for a longer-term. Desiccation also is recommended to prevent adverse effects of moisture. The majority of programs currently maintain specimen storage under standard laboratory conditions—room temperature without desiccant. Thus, most programs will incur additional expenses if residual newborn screening specimens are stored properly. Programs anticipate further expenses for computerized specimen, data and permission tracking.

Increased costs are expected when residual specimens are maintained long-term. Published reports of storage and related costs are rare; therefore, the formulation of cost estimates relies on anecdotal reports of expenses. Proper long-term storage requires the desiccant to be monitored and replaced periodically to maintain ‘dry’ storage. Programs may use a manual or automated filing system to facilitate specimen access. Automated systems will identify exact storage location instantaneously, while a manual system may take longer depending on the volume of stored cards. The level of sophistication of storage methods affects pricing, which may include bar coding and the additional expense of bar code reading. Specimen volume dictates storage capacity and security, which may vary from a small walk-in freezer to a small warehouse. Storage capacity impacts electrical cost and security costs, which may include expenses for security personnel.

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 on the basis of 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.

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.

SeraCare is a commercial storage company dealing in individual specimen storage. Residual blood specimens are currently stored in freezer boxes with 25 cards to a box. Each specimen is stored in a separate storage bag with desiccant. Specimens are typically stored at -20°C or -80°C. Current charges
include: ambient, $0.03; +4°C or -20°C, $0.35; -80°C, $0.57; and liquid nitrogen, $0.32 per specimen per year.

For the Danish Healthcare Biobank, residual specimen retention occurs at a government-owned storage facility and contains about 2 million specimen cards. The freezer (-20 °C) contains space for ~ 3 million collection cards. Specimens are kept in small boxes containing 400 cards each and these small boxes are located in larger boxes for more efficient retrieval. No desiccant is required since the humidity is very low, and specimens are not kept in plastic bags. No contamination has been noted in large studies using specimens maintained by this storage procedure. A contingency freezer is available. Specimen retrieval is manual, and a database maintains permission records that enable easy specimen identification and location using the personal identity number of the mother or child. Automated retrieval is considered excessively expensive and unnecessary. Only authorized personnel have access to the locked freezer. A central unit at the institution monitors the freezer operation constantly. There is a specimen retrieval charge of approximately $20 per specimen to recover storage and operating cost of $20,000 per year. Storage costs are considered to be low, and specimens are efficiently stored and retrieved.

Associated Costs
In order to supply information about specimen use and to obtain proof of understanding and acceptance by parents, blood spot collection kit modifications may be necessary. In some programs, specific wording requirements already exist, and specific forms and wording must be used [see newborn screening statues for Texas (Texas Health and Safety Code, Title 2 Ch 33 Sec 011-012.); Minnesota (Minnesota Statutes, Ch 144 Sec 125); South Carolina (South Carolina Code of Laws, Title 44 Ch 37 Sec 30.); Missouri (Missouri Revised Statutes, Ch 191 Sec 331.); and Michigan (Michigan Compiled Laws, Public Health Code Act 368 of 1978 Ch 333 Sec 5430)]. South Carolina modified their blood collection card to create multi-layer tear-off forms for the specimen retention information and consent document attached to the reverse side of the blood collection card. This change added an approximate cost of $5 per 100 collection cards. A legislative requirement in Texas has resulted in the need to add a page to the collection card. Other printed materials also may be required as part of the consent/dissent process. Residual newborn screening specimens must be placed in storage and then retrieved and shipped if research uses are approved. Costs for these activities will vary depending on local salary schedules, the manner of specimen storage, the location of the storage facility, the number of specimens required for a project, the de-identification or other specimen preparative processes, method of transport to and from the research facility, and method of specimen destruction. Environmental control and possible chain of custody requirements for specimens in transit may add expenses. Although individually these costs may be minimal, collectively they may result in substantial costs for a program and, therefore, should not be dismissed.

CONCLUSION
Since the initial guidance for retention, storage of use of residual blood specimens in 1996, noticeable improvements in policy development among state newborn screening programs have occurred. Nevertheless, there remain two distinct philosophies regarding the storage and use of residual blood specimens: 1) short-term storage (<3 years), presumably for program quality assurance and test improvement; and 2) long-term storage (> 18 years), presumably for public health research. While two-thirds of state programs maintain the philosophy that specimens should not be stored long-term for research, the number of newborns affected by these policies totals less than 50% of the newborn population.

Heightened awareness exists in the research and consumer communities concerning both the potential value of specimens and the possible privacy concerns. Some characteristics of the current policy
environment complicate these privacy issues, including differing state policies on the need for consent or dissent, potential uncertainty about legal ownership of residual blood specimens in states without a well-defined policy, and minimal public awareness of newborn screening. 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, protection of parental choice, an informed process for consent/dissent, and stricter enforcement of genetic privacy and confidentiality. All programs seeking to store residual newborn screening specimens should strive for public trust and transparency of operations. Public health organizations should encourage open and informed dialogue with the public that they serve as part of the screening process.

Because newborn screening is the only medical screening program that reaches the entire population of newborns in the U.S., it is unique, and the processes surrounding newborn screening must be thoughtfully approached. Residual blood specimens provide an excellent opportunity for storage and use in a biobank after screening is complete and the results have been validated. However, at the present time, this is a secondary purpose that may not be adequately addressed in some existing state laws or policies. Therefore, newborn screening programs must craft residual specimen policies carefully and anticipate both the potential benefits and risks.

RECOMMENDATIONS

To assist in providing guidance to states and towards harmonizing the storage and use of residual NBS specimens, the Secretary’s Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) makes the following recommendations to the Secretary, HHS and requests action 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 addressing the disposition of dried blood specimens remaining after newborn screening.** The policy should specify appropriate use and storage after the completion of newborn screen testing and verification of results according to laboratory QA procedures. Parties responsible for drafting the policy should consider whether consent from families is necessary for uses other than newborn screening. Multidisciplinary input, including from consumers, should be solicited and thoughtfully considered in developing such a policy. The specimen disposition policy should include the length of time for which specimens will be stored and storage conditions. Compliance with storage processes included in NCCLS/CLSI Standard LA4-A5 or its current edition is recommended. Any data linkages should be carefully addressed, and privacy and confidentiality should be ensured.

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 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.** Parties responsible for drafting the policy should consider whether consent from families is necessary for uses other than newborn screening and if the consent policy varies depending on the purpose. Multidisciplinary input, including from consumers, should be solicited and thoughtfully considered in developing such a policy. The specimen access policy should address any uses prior to and after the newborn screening laboratory testing and validation process. Policies that permit the approved use of dried blood spot specimens for purposes other than newborn screening should address handling and disposition of the specimen and measures to protect the privacy and confidentiality of any associated patient information.
3) All state newborn screening programs should work proactively to ensure that all families receiving prenatal care are educated about newborn screening. 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 dried blood specimens. This activity should include appropriate steps to inform and train prenatal care providers regarding their educational responsibilities within the newborn screening system. Processes should be in place to evaluate the extent, timing and understanding of prenatal education with an eye towards educational program improvement. Where long-term storage policies or other options exist relative to storage of residual dried blood spots, such information should be included in prenatal education materials.

4) If residual blood specimens are to be available for any purpose other than the legally required newborn screening process for which they were obtained, an indication of the parents’ awareness and willingness to participate should exist in compliance with federal research requirements (45CFR46[http://ohsr.od.nih.gov/guidelines/45cfr46.html]). A consent (opt in) or a dissent (opt out) process may meet this requirement depending on purposes for which specimens will be used. The state attorney general or other appropriate legal authority should review this process. The use of residual specimens for program evaluation (e.g., repeat testing as a quality check) or process improvement (e.g., non-commercial, internal program new test development) are valid components of the public health newborn screening program, and, therefore, should not require additional consent if the studies are conducted using anonymized samples. However, once the use of a bloodspot moves beyond the state mandated uses of program evaluation, treatment efficacy and test refinement, each state should consider whether separate or blanket consent for approved studies is required from parents, legal guardians or individuals screened upon the age of majority for the use of bloodspots. It is recommended that the Secretary, HHS consider the assessment of the necessity and efficacy of utilizing additional consent/dissent processes for the use and storage of newborn screening residual dried blood specimens. In addition, if the Secretary, HHS desires these studies, that she provide funding for utility assessment projects over the next 5 years.

5) It is recommended that the Secretary, HHS provide administrative support and funding to the state programs to develop:

- Model consent/dissent processes for the use of residual newborn screening specimens, including the advantages and disadvantages of particular approaches;
- National data on the utility of any additional consent/dissent processes implemented relative to potential research uses of residual newborn screening specimens;
- Model educational programs for the general public on the importance of newborn screening and the potential uses of residual specimens to generate population-based knowledge about health and disease; and
- Educational materials for use in such programs with facts about potential uses of residual newborn screening specimens for both consumers and prenatal healthcare providers.

Note: During the vetting process (webinars) to the stakeholder community, questions and discussions led to development of the following proposed (optional) recommendation. Since this proposed recommendation was not shared with the stakeholders in the webinars and not unanimously embraced by all members of the ACHDNC Work Group, it is listed here separately for your consideration and discussion.

Optional Recommendation—Where state newborn screening programs elect to maintain a long-term newborn screening biobank of residual newborn screening specimens, a secure third party key
holder system ("honest broker"), with appropriate consent, should be used to allow for emergency
linkages in de-identified specimen studies. The key holder would have the ability to reveal critical health
information to a study subject should such information be discovered during the course of the research,
and the ability to obtain and reveal personal information from a subject to a researcher, if such
information were deemed to be of critical importance. In either case, consent from the study participant
or appropriate parent or guardian would be required.

1 Kharaboyan L, Avard D, Knoppers BM. Storing newborn blood spots: modern controversies. J Law, Med and Ethics
2004;Winter:741-748.
2 Norgaard-Pedersen B, Hougaard DM. Storage policies and use of the Danish Newborn Screening Biobank. J Inherit Metab Dis
2007;30:530-536.
10, 2009.
blood spot samples after newborn screening analysis: statement of the Council of Regional Networks for Genetic Services.
6 Ibid, 2.
8 Ibid, 2.
12 Ibid, 9.
14 Mandl KD, Feit S, Larson C, Kohane IS. Newborn screening program practices in the United States: notification, research, and
15 Ibid, 14.
16 Olney RS, Moore CA, Ojodu JA, Lindegren ML, Hannon WH. Storage and use of residual dried blood spots from state
17 National Newborn Screening and Genetics Resource Center, National Newborn Screening Information System, available at:
http://www2.uthscsa.edu/nnsis.
18 Clinical and Laboratory Standards Institute (CLSI). Blood collection on filter paper for newborn screening programs;
20 The President’s Council on Bioethics. The Changing Moral Focus of Newborn Screening: An Ethical Analysis by the
22 Ibid, 19.
24 Ibid, 5.
26 Ibid, 2.
27 Michigan Neonatal Biobank (BioTrust), Available at http://mmbb.org/index.html; Michigan Neonatal BioTrust, Business Plan
2008 (Draft).
28 Ibid, 4.
29 Ibid, 27.
31 Ibid, 27.
32 Ibid, 2.
667.
DRAFT


xxxv Global HIV Vaccine Enterprise, www.hivvaccineenterprise.org/


xli Ibid, 19.

xlii ACMG Newborn Screening Working Group. Newborn screening: toward a uniform screening panel and system. Genetics in Medicine 2006;8(suppl 1):1S-252S.


xliv MMWR, Good laboratory practices for molecular genetic testing for heritable diseases and conditions, June 12, 2009/58(RR06);1-29. Available at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5806a1.htm?s_cid=rr5806a1_e


xlvi Personal communication, Aaron Goldenberg, Case Western Reserve University, September 1, 2009, manuscript in preparation.


xlviii ACOG Committee Opinion, Newborn Screening, Number 393, Obstet Gynecol 2007;110:1497-1500.


lii Ibid, 44.

liii Ibid, 47.

liv Ibid, 47.

lv Ibid, 39.


lxii Ibid, 58.


Ibid, 5.


Ibid, 45.

German National Ethics Committee (Nationaler Ethikrat), Biobanks for Research, Opinion (German National Ethics Committee, 2004) (available in English at kontakt@ethikrat.org).

Ibid, 72.

Ibid, 1.


Ibid, 77.


Ibid, 79.


Ibid, 45.


Ibid, 18.

Personal communication, John Reddic, South Carolina NBS Program, June 12, 2009.

Personal communication, Fred Lorey, California Newborn Screening Program, June 11, 2009.

Personal communication, Kathi Shea, Seracare, June 15, 2009.

Ibid, 2.


Ibid, 2.

Ibid, 5.


Ibid, 1.

Ibid, 18.
APPENDIX A. Examples of Residual Dried Blood Specimen Biobanks

1. Danish Newborn Screening Healthcare Biobank, http://www.ssi.dk

For more than 25 years, residual dried blood 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 blood specimens are stored at -20 °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 blood 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 blood 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 °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

2. Michigan Newborn Screening Program and Michigan BioTrust for Health

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

The newborn screening laboratory routinely saves all residual blood 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 blood 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. 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. 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 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 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°C. Specimens tested after September 2008 requires informed consent for use of residual specimens in research studies. MDCH’s residual blood specimens that have authorized permission for research use are currently being moved to the Michigan Neonatal BioTrust (see below).


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.”

A not-for-profit organization, the Michigan Neonatal BioTrust, is being created to implement the business plan and to prepare and make available the archived specimens for research. The BioTrust will provide stewardship of residual newborn screening specimens, but MDCH will retain ownership of the specimens and oversee the research use of the specimens. Full implementation of the Michigan Neonatal BioTrust 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—will maintain the storage facility and will provide 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 blood 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 will be implemented for the Michigan Neonatal BioTrust 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 will be responsible for identifying optimal specimen storage conditions and assisting with implementation. Residual blood 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 by first linking to the test results from the MDCH’s newborn screening laboratory and later to different registries and databases that detail disorders, diseases, treatments and outcomes. The data currently associated with newborn screening specimens will be developed into a searchable database. Linking information from other databases is important to increase the value of the specimens for epidemiologic and genetic research; therefore, the BioTrust will establish business use agreements with other programs whenever possible in order to access their data;

and (Phase 3) An “Honest Broker” function will be introduced to enhance and pilot the merging and de-identification of data from multiple sources. The “honest broker” acts as the intermediary between the specimen source (biobank) and the research investigator, and a researcher cannot serve as his/her “honest broker.” The “honest broker” assigns each specimen and corresponding information a unique code and maintains the linkage to individual identities. The specimens are stored and distributed with this unique code. In this way only coded specimens and information can be used anonymously for research, but mechanisms still exist for additional information to be relayed in both directions (e.g., medical record information to broker to researcher; researcher to broker to medical record information). The link should not be accessible to research investigators unless a) the source has explicitly consented to having their directly-identifiable specimen and data used by researchers; and b) the research cannot practicably be carried out with coded specimens. The intermediary is the gatekeeper who ensures that the scope and preferences of the informed consent are honored. This model allows for secondary and future users to proceed with minimal regulatory burden.


South Carolina law requires the Department Health and Environmental Control to store a child’s residual newborn screening blood specimen in a specified manner. After screening tests are completed, the residual blood specimens are stored with no humidity control in a freezer (-20 °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 blood 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 °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.

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

Beginning with specimens stored since 2002, the state will store the residual specimens from all newborns for 25 years. Before 2002, specimens were discarded after 6 months. 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 that seeks more effective ways to test, treat and cure serious
colchildhood diseases [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. Over 5.4 million residual specimens are in storage.

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 earlier in
2009) allows parents to instruct DSHS to destroy their child’s residual blood specimen 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. 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.


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 blood specimens since
July 1, 1997. By August 1, 2008, approximately 792,000 newborn screening specimens were in storage.
Specimens 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; however, residual specimens obtained after 2005 are stored at -20 °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 blood spots 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.
APPENDIX B. TECHNICAL CONSIDERATIONS

Specimen Quality
The national standard for blood collection on filter paper currently in use defines the characteristics of residual dried blood spots required for analysis. 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. 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° from each other to avoid specimen contact unless physical barriers are present (e.g. fold-over flaps or non-absorbent paper). 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.

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. Personal data on the information portion of collection cards should be kept separate from stored blood specimens, with secure access restricted to authorized personnel.

Analyte Stability
Assorted stability studies have demonstrated the extractability and stability over time of DNA in residual blood 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. 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. A study of 70 well-residual blood specimens stored for 19 months at ambient temperature gave adequate forensically useful DNA. Likewise, whole genomic amplified DNA from residual blood 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. The quantitative RNA stability in residual blood specimens has also been demonstrated for specimens stored at 4 °C with controlled relative humidity maintained at 30% for up to 20 years.

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. No significant loss of phenylalanine, leucine, tyrosine, methionine and valine was observed in analyte-enriched blood spots during 1 year of storage at -20 °C, whereas all amino acids showed degradation at 37 °C within 30 days. Methionine was the least stable of the amino acids tested. Although acylcarnitines have shown stability for at least 330 days at -18 °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. 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. 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.\textsuperscript{21} Free carnitine increased during the first 5 years with the largest increase in the first year during which it rose 40%. Phenylalanine, alanine, arginine and leucine decreased exponentially. Citrulline, glycine and ornithine decreased markedly during the first 5 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.\textsuperscript{22}

Storage Conditions
Optimal operation of a residual blood specimen storage facility requires that storage be carefully planned and that storage conditions be specified and monitored. If the purpose for saving residual blood specimens involves future analysis, screening programs should investigate data that address the stability of various analytes when making decisions about storage conditions.\textsuperscript{23,24,25,26} The defined purpose of storing samples should dictate the environmental parameters for storage. Ideally, residual blood 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.\textsuperscript{27} In all storage situations, precautions should be taken to ensure that possible contamination from specimen-to-specimen contact is not a problem.\textsuperscript{29} Several publications have demonstrated the recovery of quality DNA from residual blood specimens stored at ambient conditions.\textsuperscript{29,30,31} During storage, a humidity indicator should be periodically monitored and appropriate action taken to reactivate the desiccant when humidity exceeds 30%\textsuperscript{32,33} or some other designated level of action. Every residual blood 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 blood specimens.\textsuperscript{34}

Retention Conditions
Laboratory genetic testing guidelines exist and appear to be applicable to newborn screening testing.\textsuperscript{35} 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.\textsuperscript{36} 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.\textsuperscript{37} 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.\textsuperscript{38} It has been recommended that at a minimum, stable 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.\textsuperscript{39}

Specimen retention times vary widely among state newborn screening programs as demonstrated in Figure 1. At least 10 programs have indicated their intention to maintain archives of specimens indefinitely.\textsuperscript{40} 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.\textsuperscript{41} 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. Safe disposal of samples no longer required for examination should be accomplished in accordance with local regulations regarding waste disposal. Care should be taken to dissociate patient identifiers from the blood spots. 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). The program’s specified length of retention for residual blood specimens should be consistently met, and all disposal activities should be documented.

**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. Residual blood 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. “Standard precautions” and compliance with local regulations and institutional policies are required in preparing newborn screening specimens for shipment. 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. U.S. transport standards are harmonized with the World Health Organization’s Guidance on Regulations for the Transport of Infectious Substances and the International Civil Aviation Organization’s Technical Instructions for Safe Transport of Dangerous Goods by Air.

Residual blood 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 blood 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).

6 Ibid, 5.
8 Ibid, 2.
12 Ibid, 1.
17 Ibid, 4.
18 Ibid, 1.
23 Ibid, 8.
24 Ibid, 4.
25 Ibid, 10.
26 Ibid, 11.
27 Ibid, 1.
30 Ibid, 8.
31 MMWR. Good laboratory practices for molecular genetic testing for heritable diseases and conditions, June 12, 2009/58 (RR06):1-29. Available at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5806a1.htm?ss_cid=rr5806a1_e
34 Ibid, 37.
37 Ibid, 8.
38 Ibid, 8.
44 Ibid, 4.
46 Ibid, 4.
48 Ibid, 23.
49 Ibid, 37.
51 Ibid, 4.
52 Ibid, 4.
53 Ibid, 50.
55 Ibid, 4.