

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

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

**BRIEFING PAPER**

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## EXECUTIVE SUMMARY

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

This document is designed to review the issues facing state newborn screening programs related to the retention and use of residual newborn screening specimens. It will lay the foundation for developing national guidance to states in this area, and encourage an approach to future policymaking that enables residual specimens use to advance science and clinical care for newborns, children and their families. The core principles of protecting patient privacy, confidentiality and ensuring public trust are at the core of these recommendations.

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

All newborn screening programs in the United States obtain dried blood specimens on a special filter paper designed for laboratory testing. States generally retain the unused 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, quality assurance activities for the laboratory and program (including new test validation) and research. 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 represent a unique timeframe without byproducts of either medical interventions or environmental effects. These are collected on nearly all of the more than 4 million babies born annually in the U.S. Testing of the specimens yields critical information about risk for certain inherited conditions and the status of the infant shortly after birth. The specimens also present an opportunity to generate population-based knowledge that can improve the health of children, support families, and provide information critical to understanding the antecedents of both child and adult diseases. State policies related to retention of specimens seek to protect the privacy and confidentiality of newborns and their families, secure the specimens, and ensure public trust. State policies also emphasize transparency of administrative practices, and create supporting information that encourages informed public participation.

## CONCLUSION AND RECOMMENDATIONS

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.<sup>1</sup> In state newborn screening programs, there are currently two distinct practices regarding the storage and use of residual newborn screening specimens: 1) short-term storage (<3 years), primarily for program quality assurance and test improvement; and 2) long-term storage (> 18 years), which allows for the above program needs and additionally for public health research. Heightened awareness exists in the research, pediatric and consumer communities concerning both the potential value of the residual newborn screening specimens and the possible privacy concerns. The previously successful research uses of residual newborn screening specimens have included the development of new or improved screening tests such as for Cystic Fibrosis,<sup>2</sup> for Severe Combined Immunodeficiency Disease,<sup>3</sup> and Sickle Cell Disease.<sup>4</sup> Some parents equate the storage of residual newborn screening specimens as banking deoxyribonucleic acid (DNA) and are concerned about protecting the privacy of their infant. Some characteristics of the current public policy environment complicate these privacy issues, including differing state policies on the need for explicit consent (an opt in approach to secondary use of residual dried blood specimens) or dissent (an opt out approach to secondary use of residual dried blood specimens that presumes consent unless explicitly refused),<sup>5</sup> 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 public health 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 research uses after screening and validating are complete. However, at the present time, research 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 carefully, anticipating both the potential benefits and risks.

The SACHDNC believes that national guidance on the retention and use of residual newborn screening specimens for research would help states to navigate these complex issues.

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

**1) All state newborn screening programs should have a policy in place that has been reviewed by the state attorney general or other appropriate legal authority addressing the disposition of dried blood specimens remaining after newborn screening. Policymakers should consider the value of the specimens as a promising resource for research, the importance of protecting the privacy and confidentiality of families and the necessity of ensuring the public's trust.** The policy should specify appropriate use and storage after the completion of newborn screen testing and verification according to laboratory Quality Assurance (QA) procedures. Parties responsible for drafting the policy should consider whether consent or dissent from families is necessary for uses other than newborn screening and, if so, under what circumstances. 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.<sup>6</sup> 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.* 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 develop a well-defined strategy to educate health care professionals who provide patients with pre-and post-natal care about newborn screening and the potential use of residual dried blood specimens for research.** The strategy should include steps to inform and train health care professionals about the newborn screening system, the state's policy on the potential use of residual newborn screening specimens, and their educational responsibilities with respect to expectant parents and parents of newborns. Educational programs should take steps to educate professionals treating new parents who did not have ready access to prenatal care, and, therefore, did not receive information about the newborn screening system at that time.

**4) All state newborn screening programs should work proactively to ensure that all families of newborns are educated about newborn screening as a part of prenatal and postnatal care.** As part of the educational process, all state newborn screening programs should maintain and distribute educationally and culturally appropriate information that includes basic information about the use or potential use of the residual newborn screening specimens. Processes should be in place to evaluate the extent, timing and understanding of parental education with an eye towards educational program improvement. While prenatal care should serve as the primary target of educational programs, they also should be designed to reach parents that do not have access to those services and require postnatal education about newborn screening. Educational materials should address potential uses of residual newborn screening specimens, long-term storage policies, procedures for withdrawal of consent, opting-out of future research use, requesting the destruction of samples, limitations with regard to consent once samples have been distributed for research, and information on stewardship of specimens.

**5) 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, if applicable.**<sup>7</sup> Depending on the purposes for which specimens will be used, a parental consent (opt-in) or a dissent (opt-out) process may meet this requirement, if necessary, or a waiver of consent may be appropriate. The state attorney general or other appropriate legal authority should review this process. The use of residual newborn screening specimens for program evaluation (e.g., repeat testing as a quality check) or process improvement (e.g., non-commercial, internal program new test development or refinement) are valid components of the public health newborn screening program, and, therefore, should not require additional consent. However, once the use of a residual newborn screening specimens moves beyond the state mandated uses of program evaluation and quality assurance, treatment efficacy and test refinement, each state should consider whether separate or blanket consent/dissent processes for approved studies is required from parents, legal guardians or individuals screened upon the age of majority for the use of residual newborn screening specimens.

**6) Provide administrative support and funding to the SACHDNC to:**

- Facilitate a national dialogue among federal and state stakeholders about policies for the retention and use of residual newborn screening specimens, including model consent and dissent processes;
- Develop national guidance for consent or dissent for the secondary use of specimens and mechanisms to ensure privacy and confidentiality, including methods for opting in or out of repositories; and
- Collect and analyze national data on the utility of any additional consent or dissent processes implemented relative to potential research uses of residual newborn screening specimens;

**7) Provide administrative support and funding to the Health Resources and Services Administration - Maternal and Child Health Bureau to award grants to states to:**

- Develop model educational programs for the general public on the importance of newborn screening and the potential uses of residual newborn screening specimens to generate population-based knowledge about health and disease; and
- Create educational materials directed to health care professionals and consumers with facts about potential uses of residual newborn screening specimens and other related issues, including those outlined in Recommendation 4).

1 Guidelines for the Retention, Storage, and Use of Residual Dried Blood Spot Samples after Newborn Screening Analysis: Statement of the Council of Regional Networks for Genetic Services. Therrell BL, Hannon WH, Pass KA, Lorey F, Brokopp C, et al., *Biochem Molec Med* 1996;57:116-24

2 Farrell PM, Aronson RA, Hoffman G, Laessig RH. Newborn screening for cystic fibrosis in Wisconsin: first application of population-based molecular genetics testing. *Wis Med J.* 1994 Aug;93(8):415-21.

3 Baker MW, Grossman WJ, Laessig RH, Hoffman GL, Brokopp CD, Kurtycz DF, Cogley MF, Litsheim TJ, Katcher ML, Routes JM. Development of a routine newborn screening protocol for severe combined immunodeficiency. *J Allergy Clin Immunol.* 2009 Sep;124(3):522-7. Epub 2009 May 31.

4 Jinks DC, Minter M, Tarver DA, Vanderford M, Hejtmancik JF, McCabe ER. Molecular genetic diagnosis of sickle cell disease using dried blood specimens on blotters used for newborn screening. *Hum Genet.* 1989 Mar;81(4):363-6.

5 Saunders, B. Normative consent and opt-out organ donation. *J Med Ethics.* 2010 Feb;36(2):84-7.

6 Clinical and Laboratory Standards Institute (CLSI). Blood collection on filter paper for newborn screening programs; approved standard—fifth edition. CLSI document LA4-A5. Wayne, PA: Clinical and Laboratory Standards Institute; 2007.

7 45 CFR 46

## INTRODUCTION

Newborn screening is a highly successful public health program that identifies rare genetic, congenital and functional disorders, ensures early management and endeavors to ensure follow-up for those affected. Each state has a law that either requires or allows newborn screening and states are responsible for oversight and implementation of their respective newborn screening programs. State newborn screening policies are usually developed with input from multi-disciplinary advisory committees that include consumers,<sup>1</sup> health care and public health professionals and others stakeholders. 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 disparate policies on the retention and use of dried blood spot specimens after newborn screening. Given the tremendous potential to advance science and clinical care for newborns, children and their families, the Secretary’s Advisory Committee on Heritable Disorders in Newborns and Children (SACHDNC) calls upon policymakers, the public health community, health care providers and families to work together to protect this valuable resource for the public good.

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Newborn screening specimens are usually the first blood specimen drawn in a baby’s life representing a unique timeframe where the only influences on the contents of the blood are the in utero exposures. These specimens are collected on nearly all of the more than 4 million babies born annually in the U.S. Testing of the specimens yields critical information about risk for 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.

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

This SACHDNC document is designed to review the issues facing state newborn screening programs related to the retention and use of residual newborn screening specimens, including research uses, lay the foundation for developing national guidance to states in this area, and

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<sup>1</sup> Consumers refers to the definition in the Newborn Screening American Health Information Community Detailed Use Case: “Members of the public that include patients as well as caregivers, patient advocates, surrogates, family members, emergency contacts, and other parties who may be acting for, or in support of, a patient receiving or potentially receiving healthcare services.” Available at <http://healthit.hhs.gov> under Regulations and Guidance/Standards and Certification.

encourage an approach to future policymaking that enables residual newborn screening specimen use to advance science and clinical care for newborns, children and their families, while maintaining the core principles of benefiting the infant, protecting patient privacy, confidentiality and ensuring public trust.

## **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. Deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) can be extracted from the dried blood filter paper specimens used for newborn screening, and there is increasing bioinformatics capability allowing the linkage of DNA information with information that could be used to identify an individual.<sup>i</sup> These scientific advances also have raised public concerns about the potential misuse of genetic information by employers, insurers or others. Congress passed the Genetic Information Nondiscrimination Act of 2008 (GINA) in an effort to alleviate these concerns,<sup>ii</sup> and many states have enacted measures to safeguard genetic information over the last two decades.

International guidelines have been suggested as a means of emphasizing the importance of preserving residual newborn blood specimens in repositories for the benefit of future generations,<sup>iii</sup> 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 for a model repository has emerged.<sup>iv</sup> The Organization for Economic Co-operation and Development and the International Society for Biological and Environmental Repositories have developed best practices and guidelines for repositories that do not focus specifically on newborn screening but may be useful in furthering the discussion in this area.<sup>v, vi</sup>

All states either require or allow 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.<sup>vii</sup> 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 are several supporting legal decisions that apply (see Ownership discussion below). Nonetheless, potential uncertainty about legal ownership of specimens remains, and ethical questions persist about residual newborn screening 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 newborn screening.<sup>viii</sup> Among states with such policies, the content of the policies varies considerably between programs.

## DRAFT

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

1. Program quality assurance and test validation; [Residual newborn screening specimens are valuable evidence that appropriate testing has occurred, and newborn screening programs may require use of residual specimens for various quality assurance and test validation purposes. Quality assurance and test validation activities are needed to demonstrate that the laboratory received and assumed responsibility for analyzing the specimen correctly, and to establish evidence-based interpretations of screening results, and may be the state's regulatory requirements for the newborn screening program.]
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;<sup>ix</sup> [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.]
3. Family requested identification of remains for criminal investigation; and
4. Population surveillance. [Newborn screening programs have reported numerous additional requests for residual newborn screening specimen usage over the years including public health research projects.<sup>x</sup> As one example, the Centers for Disease Control and Prevention (CDC)-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.<sup>xi</sup> States have used the residual newborn screening specimens to build newborn screening programs for Cystic Fibrosis<sup>xii</sup> and Severe Combined Immunodeficiency Disease<sup>xiii</sup> and to refine testing for Sickle Cell Disease.<sup>xiv</sup> Additionally, case control studies are also possible using residual specimens to determine concentrations of biomarkers in children who develop certain disorders in comparison with similar markers in healthy children. Newborn screening specimens have provided insight into the mechanisms behind the origin of diseases and their potential screening biomarkers.]<sup>xv</sup>

Increased public awareness of stored residual newborn screening specimens has raised concerns about personal medical information that the specimens might reveal such as disease susceptibility through current and future technological advances.<sup>xvi</sup> In addition to the federal privacy laws that exist and state laws that specifically pertain to newborn screening, other state privacy laws may impact residual newborn screening specimen storage and use.<sup>xvii,xviii</sup> 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 in detail here.<sup>xix</sup> 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 newborn screening specimens, regardless of the approach, would facilitate greater uniformity among the states. Despite prior efforts over the last two decades to explore these issues at the national level (Institute of Medicine, President Clinton's National Bioethics Advisory Commission and President Bush's Council on Bioethics), many questions remain unanswered.<sup>xx,xxi,xxii</sup>

## DRAFT

The use of residual newborn screening specimens in research already has generated significant findings. Examples of test development that have resulted from research on these unused portions of the specimens include the use of T-cell receptor excision circles (TREC) assay to identify infants with T-cell lymphopenia<sup>xxiii</sup> and the use of real-time quantitative polymerase chain reaction to quantitate TRECs from DNA to screen for severe combined immunodeficiency (SCID).<sup>xxiv</sup> Research studies to improve the quality of testing also has led to more accurate and affordable means of screening for disorders.<sup>xxv,xxvi</sup> Ongoing research involving the use of residual newborn screening specimens includes a CDC project being conducted by Emory University to develop a new testing method for Fragile X syndrome. Residual newborn screening specimens also have proven useful in other studies unrelated to the screening process. For example, specimens collected in New York were used in a temporal biomonitoring study to assess changes in population exposures to contaminants,<sup>xxvii</sup> and forensic scientists have tested residual newborn screening specimens to identify a kidnapped child or determine whether a genetic condition contributed to a child's death.<sup>xxviii</sup>

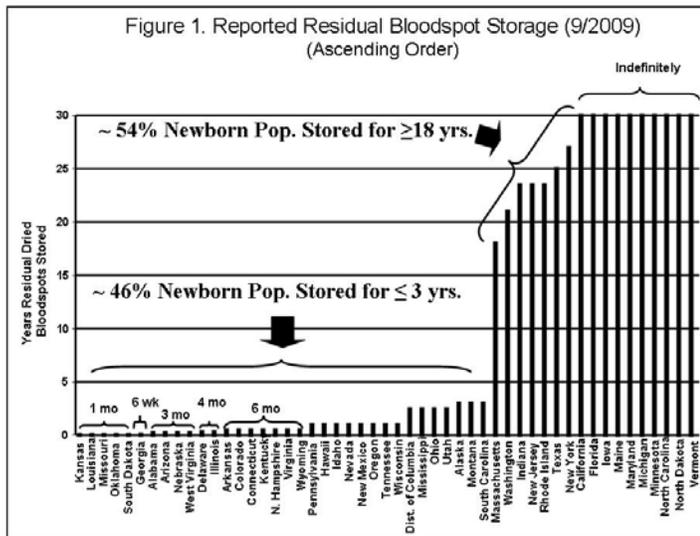
Because of the increasing number of research requests for residual newborn screening specimens, the SACHDNC recommends that procedures and regulations regarding their release and use should be formalized.<sup>xxix</sup> A 2002 study of the storage and usage practices in U.S. newborn screening programs revealed that almost all programs stored their residual newborn screening specimens with identifiers present.<sup>xxx</sup>

- 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).<sup>xxxi</sup>

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 also required IRB approval at the state health department. Submission of individual requests to the newborn screening program director for review were required in other instances, and in a few cases requests were individually reviewed by senior newborn screening staff members.<sup>xxxii</sup> Another study showed that 74% of states used residual specimens for newborn screening test evaluation, and 28% used them for epidemiological and pathophysiological research studies.<sup>xxxiii</sup> Only 57% reported having internal written policies for specimen usage.

In order to determine current storage practices, information on practices was solicited via email by the National Newborn Screening and Genetics Resource Center (NNSGRC). NNSGRC reviewed the state reports and validated answers through email contacts with 100% response rate.<sup>xxxiv</sup>

- Currently, 67% (34 of 51) of state programs and Washington, D.C., retain residual newborn screening specimens for less than 3 years accounting for approximately 46 % of all U.S. newborns (see Figure 1).



- The remaining 33% of state programs save their residual newborn screening specimens for eighteen or more years (~54% of all births in the United States) with at least 6 programs saving them indefinitely (others indicating 18-21 yr. storage may eventually save them indefinitely, but currently they are extending their policy on a year-by-year basis).

Despite the recommendations of a national standard suggesting that short-term specimen storage occur at +4 °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.<sup>xxxv</sup> Storage conditions may affect the reliability of subsequent analyses of residual newborn screening specimens, for example amino acid levels are affected by storage practices (See Appendix B).

### 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 newborn screening specimens but offered no recommendations for their use and storage.<sup>xxxvi,xxxvii</sup>

State laws and regulations pertaining to newborn screening specimen and information storage vary, and their impact or potential impact on specimen use were reviewed in 2006 by Therrell, et al.<sup>xxxviii</sup> At that time only nine 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 residual newborn screening 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 2006 report noted in Florida, Idaho and Ohio it was unclear whether retention requirements addressed residual newborn screening specimens themselves or merely newborn screening related information collected by the department. In California, Maine, Michigan, and Washington, residual newborn screening specimens were declared to be the property of the state. In Maine a parent may object to state ownership in writing,<sup>xxxix</sup> and in Michigan the state holds qualified ownership of specimens, in that the state must still act on the best interest of the individual from whom the specimen was collected, protecting privacy and providing specimens for research that the community endorses. The state of Utah has since identified residual newborn screening specimens as the property of the state and has related rules addressing education and specimen use.<sup>xl</sup>

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

### ***Stewardship***

State newborn screening programs are charged with the important task of stewardship—the caretaking responsibility where roles, responsibilities, and policies are clearly defined for ensuring appropriate use—of newborn screening specimens. State public health departments strive to exercise the highest care in receiving, storing and protecting newborn residual newborn screening 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.”<sup>xlii</sup>

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

The Danish government initiated a national newborn screening biobank in 1993 (see Appendix A 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.<sup>xliii</sup> The operational guidelines for the biobank 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. 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.<sup>xliv</sup>

In the U.S., recent attention has turned to the 'Michigan BioTrust for Health' a developing long-term newborn screening specimen repository for expanded research use (see Appendix A for further information).<sup>xlv</sup> 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.<sup>xlvi</sup> The result was the creation of a detailed business plan for a phased-in, research accessible biobank that—within a framework that protects patient information privacy and promotes public health research—would address specimen storage issues, increase health research, provide linkages to related public health data, allow greater access to research results, and be self sustaining after 5 years.<sup>xlvii</sup> The 'BioTrust' will house specimens in an appropriately controlled environment with privacy safeguards and will control specimen access through an 'honest broker' (third party key holder) system. In this model, the 'honest broker' will have access to specimens and their linked information in order to facilitate research requests. The broker will provide limited, necessary information to researchers and ensure the privacy and confidentiality of patients. This linkage system will allow de-identified research while offering the possibility of access to additional information for the researcher if critical findings require such.<sup>xlviii</sup>

Examples of four states' (Michigan, Minnesota, South Carolina and Texas) laws that define the details of procedures and processes for storage of and access to residual newborn screening specimens are presented in Appendix A. In each of these states, parents are given the opportunity to allow long-term storage of the residual newborn screening specimen through an informed process that allows refusal. The state also may provide opt out information through pamphlets and websites, e.g., Michigan, available at [www.michigan.gov/newbornscreening](http://www.michigan.gov/newbornscreening). Examples of consent and dissent forms for research use of residual newborn screening specimens are provided in Appendix C (Examples are for descriptive purposes only and not intended as an endorsement of the particular forms or approach to consent or dissent.) Although the exact processes vary somewhat, the principle in practice is the same: residual newborn screening specimens are utilized 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).

The SACHDNC recommends the establishment of a voluntary U.S. national repository. Such a repository would facilitate more rapid and meaningful scientific advances. 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.<sup>xlix,l</sup> In turn, this could lead to accessible and affordable studies in diverse populations that could allow for an imaginative search for common and rare genetic and other biological correlates of global diseases.<sup>li,lili,liv</sup>

The National Women's and Children's Study established by the National Institutes of Health (NIH) provides the impetus for a U.S. national biobank based on similar hypotheses. In order to make larger collaborative studies feasible, for instance, through HRSA's Genetic and Newborn Screening Regional Collaborative groups and the National Institute for Child Health and Human Development's Newborn Screening Translational Research Network, a national IRB may be necessary to expedite studies because working with an IRB at every participating institution may be impractical. For example, to simplify the IRB process for collaborative studies at the National Cancer Institute (NCI), NCI established a central IRB in 2002. Subsequently, NIH and the Office of Human Research Protections have explored the expanded use of alternative IRB models with other institutions.<sup>lv,lvi</sup>

### ***Privacy Protections***

The issue of privacy and the use of residual newborn screening specimens are closely linked to parental education and informed decision-making. There continues to be some public mistrust about the possible uses of residual newborn screening specimens. Concerns focus on possible discrimination, psychological harm, identification of paternity, and social injustices.<sup>lvii</sup> However, there are no documented cases of harm resulting from these concerns relative to use of residual 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 law further clarifies that an individual has a personal property right to his or her DNA. As of 2006, eight of 30 states/territories with genetic privacy laws were reported to have laws that might extend to newborn screening while the remainder had exemptions for this public health program or did not name newborn screening programs as covered entities. In those eight states, depending on the definition of genetic information or genetic testing in the statute, technologies used in newborn screening may not fall within the scope of the law if they are not deemed "genetic." The 22 states with genetic privacy laws that were reported to exempt newborn screening may still apply to the use of newborn screening specimens for purposes other than newborn screening (such as research that involves genetic testing or the use of genetic information).<sup>lviii</sup>

Compliance with federal privacy regulations, the Health Information Portability and Accountability Act of 1996 (HIPAA) Privacy Rule (the 'Privacy Rule') has been required since April 2003 (45 CFR Parts 160 and 164). These regulations govern the permitted uses and disclosures of individually identifiable protected health information (PHI) by HIPAA covered

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entities, which includes genetic information as specified under GINA.<sup>lix</sup> Newborn screening facilities that are HIPAA covered entities may use and disclose an individual's PHI for treatment, payment, or health care operations without the individual's authorization. 'Operations' include most routine program activities except for research that contributes to generalizable knowledge.

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

*“(1) de-identified health information. De-identification may be achieved by statistical methods or by removal of all identifiers of the individual (and the individual's relatives, employers and household members): names; all geographic subdivisions smaller than a state, including address, except for the initial 3 digits of a zip code (there are special rules for zip codes containing 20,000 or fewer people); all dates, except the year including birth date; telephone numbers; fax numbers; electronic mail addresses; Social Security numbers; medical record numbers; health plan beneficiary numbers; account numbers; certificate/license numbers; vehicle identification and serial numbers; device identifiers and serial numbers; URLs; IP address numbers; biometric identifiers; full-face photos or comparable images; and any other unique identifying number, characteristic or code; or*

*(2) patient authorization to access the PHI, or waiver of authorization by a Privacy Board or an IRB 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) a Limited Data Set, and sign a Data Use Agreement. A Limited Data Set can include dates and geographic information, but not street addresses or other direct identifiers listed above. A Data Use Agreement establishes the permitted uses of the limited data set and stipulates that the researcher will not further use or disclose the information, will protect it, and will not identify or contact the individuals whose data are in the set.”<sup>lix</sup>*

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

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

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).<sup>lxii</sup> Additional state licensure or contract requirements may also exist. Through CLIA-CMS, the CDC have 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.<sup>lxiii</sup>

### ***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 newborn screening specimens.<sup>lxiv</sup> A recent study by Goldenberg has determined that only 12 states currently include mention of specimen storage in their newborn screening educational pamphlet.<sup>lxv</sup> Regardless of the content, studies have shown that there is little effort currently ongoing to involve prenatal care providers in the newborn screening system.<sup>lxvi</sup> 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.<sup>lxvii</sup>

Studies validate the need for better physician education to meet the educational needs of the screening program. While the role of the obstetrician as an educator in the newborn screening process has been defined,<sup>lxviii</sup> 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.<sup>lxix</sup> The need for improved provider education was confirmed by a California study that found most prenatal care providers believed that newborn screening participation was important. However, 25% reported not discussing it with any of their patients,

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and most who did discuss newborn screening, did not discuss it with all patients. Prenatal care providers seemed to believe hospital staff or pediatricians would discuss newborn screening with their patients. Nearly 1/3 of patients never received newborn screening educational materials from their prenatal care provider, even though prenatal care providers in California are legally required to provide them.<sup>lxx</sup>

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.<sup>lxxi</sup> 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.<sup>lxxii</sup> 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.<sup>lxxiii</sup>

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),<sup>lxxiv</sup> and there are important variations in the information provided to parents between programs.<sup>lxxv</sup> The most common educational mechanism is a brochure provided in the hospital's package of informational materials for mothers. Focus groups of parents have shown that written information should be presented in a user-friendly and easy-to-read format, and parents are most interested in information that they deem relevant and practical<sup>lxxvi</sup> and that emphasizes what they need to know and do.

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

A recent study of the attitudes of women towards a hypothetical pediatric biobank found significant variations in women's willingness to enroll their children and misperceptions about what participation in a biobank entailed.<sup>lxxviii</sup> Women with only one previous child were the most willing to enroll their child, while women with no previous children were the most uncertain. When women were asked why they would or would not enroll their child into a biobank, 26% of the 207 responders did not feel that they had enough information, 10% were concerned about risks, and 8% were concerned about privacy. Consent issues were a concern in

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

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.<sup>lxxx</sup> 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.<sup>lxxx</sup> A 2008 study of hypothetical enrollment in the University of Chicago's obstetrics biobank program found potential participants would place few restrictions on the type of research to be performed, with over 90% supporting all conditions proposed.<sup>lxxxii</sup> In addition to their willingness to enroll, potential participants also were optimistic that the research would achieve significant clinical results in the near future. Trust and belief that the research would be integrated fairly into clinical care were also found to correlate with enrollment.<sup>lxxxiii</sup> Community engagement to help relevant programs understand public privacy concerns has been identified as a useful step in helping recruit and retain biobank participants.<sup>lxxxiv</sup>

It has also been suggested that researchers should translate community knowledge and concerns about children into responsive and realistic study protocols. Longitudinal studies of children who eventually transition to adulthood should retain some degree of flexibility to account for the differing consent rights of children as compared 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.<sup>lxxxv</sup>

Commentators have noted that the best way to ensure new tests are introduced in a rational manner and promote appropriate communication with families, is to rely on a research approach that is flexible with respect to (1) how parental permission is acquired; and (2) methods for the rigorous evaluation of harms and benefits associated with screening.<sup>lxxxvi</sup> It also has been noted that fundamental ethical concerns around individual and societal risk should ultimately drive how research regulations are interpreted and used.<sup>lxxxvii</sup> 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.<sup>lxxxviii</sup>

### ***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.<sup>lxxxix</sup> 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.<sup>xc</sup> Some medical privacy advocates contend that parents must be asked for consent before residual newborn screening specimens are retained,<sup>xc<sup>i</sup></sup> but others assert that meaningful consent is impossible because parents cannot be adequately educated about all potential uses and outcomes.<sup>xc<sup>ii</sup></sup>

**Types of Data Storage**

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

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

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

**Directly Identifiable** - Any information that includes personal identifiers.

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

**Linked** - See Coded.

Source: Partners Human Research Committee, <http://healthcare.partners.org/phsirb/hipaaglos.htm>  
(NOTE: Permission to publish pending.)

Residual newborn screening specimens can be stored unidentified (anonymized), linked, or with identifiers. Anonymization of data is generally thought to set aside the requirement to obtain explicit consent. If specimens are not identifiable, then they are not considered "personal," and data-subjects are at very low risk of being harmed.<sup>xc<sup>iii</sup></sup> However, anonymization is not as risk-proof as it was once thought to be as a result of advances in genetic technology.<sup>xc<sup>iv</sup>,xc<sup>v</sup></sup> 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.<sup>xc<sup>vi</sup></sup> 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.<sup>xc<sup>vii</sup></sup> 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.<sup>xc<sup>viii</sup>,xc<sup>ix</sup></sup> If the research study does not require that donors be re-contacted or identified, some have suggested that existing medical records and stored specimens containing identifying information can be made available for research without explicit individual consent or ethical review board approval.<sup>c</sup>

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

A 2004 German National Ethics Council opined that different options do not need to be offered in the informed consent process for samples obtained during medical care, and informed consent may be waived when samples and data are completely anonymous, unless a prior contrary wish has been expressed: “Donors should be able to give generalized consent to the use of their samples and data for the purposes of medical, including genetic – research.”<sup>cii</sup> Length of storage and use of data were regarded similarly with neither limited in advance.<sup>ciii</sup> 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.”<sup>civ</sup> 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.<sup>cv</sup>

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

In the United States, consent for research is usually for a single project, and researchers must request re-consent of individuals if they wish to undertake another project. Occasionally, consent is broader and open-ended, in which case study participants agree to specimen storage and use for future unspecified purposes. This broad or ‘blanket’ consent is not as common and is problematic under the federal privacy regulations, which call for specific consent for specific research projects (see federal privacy rule 08-14-02 preamble 53231); therefore, institutional review boards are reticent to approve such consent processes.<sup>cvi</sup> Since retention and use policies for residual newborn screening specimens cannot anticipate all future research proposals, newborn screening programs will likely consider blanket consent. States must approach blanket consent carefully, balancing maximum specimen use for valid study with potential objections of consenters and state and federal consent and privacy requirements, if applicable, such as those set forth in the Health Insurance Portability and Accountability Act.

***Position Statements – Professional Groups***

The American College of Medical Genetics (ACMG) - In a previous position statement for clinical genetic laboratories, ACMG took the position that testing facilities should establish laboratory policies regarding specimen retention and appropriate storage conditions.<sup>cxix</sup> A more recent ACMG position statement<sup>cx</sup> 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.<sup>cxii</sup>

The Association of Public Health Laboratories (APHL) - APHL has a position policy that supports the development of national consensus policies, procedures, and standards for retaining residual newborn screening specimens following newborn screening analysis.<sup>cxiii</sup> The position policy specifically calls for the following: “These policies and procedures must recognize existing federal regulations for clinical testing, state laws, professional guidelines, and ethical and legal precedents. The policies should allow for introduction of new analytes and techniques into the newborn screening arena. To meet recognized laboratory quality assurance practices, dried bloodspot specimens must be retained for a time period and under conditions that permit analytical validation. Other reasons to save residual newborn screening specimens include test development, research, and forensic identification. To retain residual newborn screening specimens for such 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.”<sup>cxiiii</sup>

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 clinico-pathologic specimens, molecular genetic specimens – particularly the DNA contained therein – have potential importance for family studies and distant 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.<sup>cxiv</sup>

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

## **FINANCIAL CONSIDERATIONS**

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

### ***Storage and Retrieval***

All newborn screening programs retain residual newborn screening specimens for some period of time, usually with at least one identification number. Linkage to demographic information usually continues until de-identification may be initiated for privacy protection and preparation for some research uses. Most programs will incur additional expenses if residual newborn screening specimens are stored in compliance with established standards.. Increased costs are also expected for the long-term maintenance of residual specimens.

As one cost example, the South Carolina public health screening laboratory uses a dedicated walk-in freezer to store residual specimens (~55,000/year) for up to three years (depending on the disbursement option chosen by the guardian at the time of collection). Retrieval costs include a database that provides physical location information to facilitate a manual searching process. The retrieval process cannot be realistically separated into component parts and has been estimated on the basis of employee time. Approximately 0.67 FTE is required for an annual

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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.<sup>cxvii</sup>

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.<sup>cxviii</sup>

## CONCLUSION

Since the 1996 guidance for retention, storage of use of residual newborn screening specimens,<sup>cxix</sup> noticeable improvements in policy development among state newborn screening programs have occurred. Nevertheless, there remain two distinct practices regarding the storage and use of residual newborn screening specimens: 1) short-term storage (<3 years), for program quality assurance and test improvement; and 2) long-term storage (> 18 years), which includes the above program development and longer-term storage for possible public health research.

Heightened awareness exists in the research, pediatric and consumer communities concerning both the potential value of the residual newborn screening specimens and the possible privacy concerns. For example, the research uses of residual newborn screening specimens have included the development of new or improved screening tests, such as for Cystic Fibrosis, for Severe Combined Immunodeficiency Disease, and Sickle Cell Disease. Yet some parents equate the storage of residual newborn screening specimens as banking Deoxyribonucleic acid (DNA) and are concerned about protecting the privacy of their infant. Some characteristics of the current public policy environment complicate these privacy concerns, including differing state policies on the need for explicit consent (an opt in approach to secondary use of residual dried blood specimens) or dissent (an opt out approach to secondary use of residual dried blood specimens that presumes consent unless explicitly refused),<sup>cxx</sup> potential uncertainty about legal ownership of residual newborn screening specimens in states without a well-defined policy, and minimal public awareness of newborn screening.

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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.<sup>cxxi</sup> 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 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 it must be thoughtfully approached. Residual newborn screening specimens provide an excellent opportunity for storage in a biobank for approved uses, such as research after screening and validation of results are complete. However, at the present time, research 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 for research carefully, anticipating both the potential benefits and risks. The SACHDNC believes that national guidance on the retention and use of residual newborn screening specimens for research would help states to navigate these complex issues.

## RECOMMENDATIONS

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

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

The policy should specify appropriate use and storage after the completion of newborn screen testing and verification according to laboratory Quality Assurance (QA) procedures. Parties responsible for drafting the policy should consider whether consent or dissent from families is necessary for uses other than newborn screening and, if so, under what circumstances. 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.<sup>cxxii</sup> Any data linkages should be carefully addressed c, 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.***

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 residual newborn screening 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 develop a well-defined strategy to educate health care professionals who provide patients with pre-and post-natal care about newborn screening and the potential use of residual newborn screening specimens for research.***

The strategy should include steps to inform and train health care professionals about the newborn screening system, the state's policy on the potential use of residual newborn screening specimens, and their educational responsibilities with respect to expectant parents and parents of newborns. Educational programs should take steps to educate professionals treating new parents who did not have ready access to prenatal care, and, therefore, did not receive information about the newborn screening system at that time.

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

As part of the educational process, all state newborn screening programs should maintain and distribute educationally and culturally appropriate information that includes basic information about the use or potential use of the residual newborn screening specimens. Processes should be in place to evaluate the extent, timing and understanding of parental education with an eye towards educational program improvement. While prenatal care should serve as the primary target of educational programs, they also should be designed to reach parents that do not have access to those services and require postnatal education about newborn screening. Educational materials should address potential uses of residual newborn screening specimens, long-term storage policies, procedures for withdrawal of consent, opting-out of future research use, requesting the destruction of samples, limitations with regard to consent once samples have been distributed for research, and information on stewardship of specimens.

- 5) ***If residual newborn screening 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, if applicable.*<sup>cxiii</sup>

Depending on the purposes for which specimens will be used, a parental consent (opt-in) or a dissent (opt-out) process may meet this requirement, if necessary, or a waiver of consent may be appropriate. The state attorney general or other appropriate legal authority should review this process. The use of residual newborn screening specimens for program evaluation (e.g., repeat testing as a quality check) or process improvement (e.g., non-commercial, internal program new test development or refinement) are valid components of the public health newborn screening program, and, therefore, should not require additional consent. However, once the use of a residual newborn screening specimens moves beyond the state mandated uses of program evaluation and quality assurance, treatment efficacy and test refinement, each state should consider whether separate or blanket consent/dissent processes for approved studies is required from parents, legal guardians or individuals screened upon the age of majority for the use of residual newborn screening specimens.

**6) *Provide administrative support and funding to the SACHDNC to:***

- Facilitate a national dialogue among federal and state stakeholders about policies for the retention and use of residual newborn screening specimens, including model consent and dissent processes;
- Develop national guidance for consent or dissent for the secondary use of specimens and mechanisms to ensure privacy and confidentiality, including methods for opting in or out of repositories; and
- Collect and analyze national data on the utility of any additional consent or dissent processes implemented relative to potential research uses of residual newborn screening specimens;

**7) *Provide administrative support and funding to the Health Resources and Services Administration - Maternal and Child Health Bureau to award grants to states to:***

- Develop model educational programs for the general public on the importance of newborn screening and the potential uses of residual newborn screening specimens to generate population-based knowledge about health and disease; and
- Create educational materials directed to health care professionals and consumers with facts about potential uses of residual newborn screening specimens and other related issues, including those outlined in Recommendation 4.

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APPENDIX A.

## Examples of Residual Newborn Screening Specimen Biobanks

### 1. Danish Newborn Screening Healthcare Biobank,

<http://www.ssi.dk>

For more than 25 years, residual newborn screening specimens from the Danish newborn screening program have been stored in a healthcare biobank. The storage has taken place according to regulations from the Danish Ministry of Health (1993) and recently according to new guidelines for the establishment and operation of biobanks in general (2004). After routine newborn screening, residual newborn screening specimens are stored at -20 °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.<sup>1</sup>

Prior to collecting the blood specimen, parents are informed about newborn screening and residual newborn screening specimen storage by local health professionals using program-prepared educational pamphlets ([www.ssi.dk/nyfoedte](http://www.ssi.dk/nyfoedte)) and through information available on the homepage of the Staten Serum Institute (SSI) (<http://www.ssi.dk>). Information about storage of residual newborn screening specimens focuses on possible uses for: 1) documentation, retesting and diagnosis later in infancy; 2) quality assurance and assay improvement; and 3) research. The parents may opt-out of biobank storage at the time of blood sampling by marking the data portion of the specimen collection card, by a written letter to the SSI at any time, or by registering in the central Use of Tissue Registry. Several safety procedures also exist for both the data registry and the biobank. The residual specimens are stored in a separate freezer facility (-20 °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

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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.<sup>2</sup>

## 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 newborn screening specimens after testing is complete unless otherwise directed by a parent or guardian. The program's brochure and website provides information about retention of residual newborn screening specimens. In accordance with state law, some leftover de-identified specimens may be used for medical research after all directly identifying information (name, address, etc.) has been removed. However, the newborn screening laboratory always retains one full circle of the blood specimen in case it is ever needed for the child or family. 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  $-20^{\circ}\text{C}$ . Specimens tested after September 2008 requires informed consent for use of residual specimens in research studies. MDCH's residual newborn screening specimens that have authorized permission for research use are currently being moved to the Michigan Neonatal BioTrust (see below).

*Michigan BioTrust for Health, <http://mnbb.org/index.html>*

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

A not-for-profit organization, the Michigan BioTrust for Health, is being created to implement the business plan and to prepare and make available the archived specimens for research. The BioTrust for Health will provide stewardship of residual newborn screening specimens but will not maintain a copy of the newborn screening database and linkages to all other follow-up data. MDCH will retain ownership of the specimens and oversee the research use of the specimens. Full implementation of the Michigan BioTrust for Health is expected to require \$3.9 million in

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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 newborn screening specimens for research and in studying the ethical, legal and social implications of genetics research and practice. Each of these universities is expected to contribute substantially to a unified and effectively operated specimen repository. The BioTrust management also is exploring the possibility of a fee structure system to recover storage and linkage costs.

A multi-phased approach will be implemented for the Michigan BioTrust for Health as follows:

(Phase 1) The Van Andel Research Institute in Michigan has considerable experience with evaluating and identifying ideal storage conditions for biospecimens, and they will be responsible for identifying optimal specimen storage conditions and assisting with implementation. Residual newborn screening specimens currently stored will be identified with bar code labels, repackaged and moved to a secure location in TechTown;

(Phase 2) As part of the repository design to achieve self-sustainability, the BioTrust will increase the research value of the residual newborn screening specimens, through the use of an honest broker, by having the ability to link to NBS test results as well as to different state-based health registries and databases that detail disorders, diseases, treatments and outcomes. The ability to perform such linkages significantly increases the value of the specimens for epidemiologic and genetic research; therefore, the BioTrust will establish business agreements with other programs whenever possible in order to access their data; and (Phase 3) An "Honest Broker" function 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 with this unique code and prior to distribution are assigned and released to researchers with a different unique code. 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.

### **3. South Carolina Newborn Screening Program,**

<http://www.scdhec.gov/health/mch/nbs/index.htm>

South Carolina law requires the Department Health and Environmental Control to store a child's residual newborn screening specimen in a specified manner. After screening tests are completed,

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the residual newborn screening 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 newborn screening specimen for approved research without any identifying information to learn new information about diseases. The law allows the parent or guardian to choose one of three options. If they do not want the specimen handled in this way, however, they are not required to select an option. The options are: 1) specimen stored by state but not used for research; 2) specimen destroyed two years after testing; and 3) specimen returned to parents two years after the testing date if requested in writing. Parents must check a box and sign a consent form on the reverse side of blood collection card. If no boxes are checked and/or the form is not signed, then specimen is retained at -20 °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 childhood 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 newborn screening specimens after the newborn screening testing is complete. The law also requires distribution of an informational disclosure form that discusses allowable post-test uses of the blood spots so that the parents can make an informed decision on the matter. 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

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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.

### **5. Minnesota Newborn Screening Program,**

<http://health.state.mn.us/newbornscreening/research.html>

Parents have the option to decline newborn screening by signing a Refusal of Newborn Screening form. Following newborn screening, the Minnesota Department of Health (MDH) securely stores leftover blood specimens and newborn screening results. The MDH has securely stored residual newborn screening specimens since July 1, 1997. By August 1, 2008, approximately 792,000 newborn screening specimens were in storage. Specimens 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 newborn screening specimens in research efforts are provided on the MDH website.

Specimens received by MDH beginning September 8, 2005 are stored onsite in a locked storage room. Only MDH employees who have received extensive data privacy training are allowed access to this area. MDH stores these specimens securely and in accordance with strict data and genetic privacy standards. The following reasons for storage are paraphrased from the website: 1) to provide results or specimens upon the request of the family or the baby's healthcare team; 2) to repeat testing if needed without obtaining another blood specimen; 3) to conduct other

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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 newborn screening specimens required for analysis.<sup>4</sup> 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.<sup>5</sup> 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).<sup>6</sup> 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.<sup>7</sup>

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.<sup>8</sup> Personal data on the information portion of collection cards should be kept separate from stored blood specimens, with secure access restricted to authorized personnel.<sup>9</sup>

***Analyte Stability***

Assorted stability studies have demonstrated the extractability and stability over time of DNA in residual newborn screening specimens on filter paper. Although genomic DNA was shown to be stable under tropical conditions for at least 11 years at ambient temperature, the DNA quality for amplification of larger DNA fragments decreased when specimens were stored for longer than 10 years.<sup>10</sup> 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.<sup>11</sup> A study of 70 well- residual newborn screening specimens stored for 19 months at ambient temperature gave adequate forensically useful DNA.<sup>12</sup> Likewise, whole genomic amplified DNA from residual newborn screening specimens archived for 15 to 25 years was used for reliable genome-wide scans and was found to be a cost-effective alternative to collecting new specimens.<sup>13</sup> The quantitative RNA stability in residual newborn screening specimens has also been demonstrated for specimens<sup>14,15</sup> stored at 4 °C with controlled relative humidity maintained at 30% for up to 20 years.<sup>16</sup>

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.<sup>17</sup> 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

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within 30 days. Methionine was the least stable of the amino acids tested.<sup>18</sup> 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.<sup>19</sup> 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.<sup>20</sup> 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.<sup>21</sup> 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.<sup>22</sup>

### ***Storage Conditions***

Optimal operation of a residual newborn screening specimen storage facility requires that storage be carefully planned and that storage conditions be specified and monitored. If the purpose for saving residual newborn screening specimens involves future analysis, screening programs should investigate data that address the stability of various analytes when making decisions about storage conditions.<sup>23,24,25,26</sup> The defined purpose of storing samples should dictate the environmental parameters for storage. Ideally, residual newborn screening specimens should be stored frozen (preferably at -20°C) in sealed bags of low gas permeability containing a desiccant and a humidity indicator. Specimens retained only for DNA testing may be stored at ambient conditions (preferably refrigerated at 4°C) in sealed bags of low gas permeability and containing a desiccant for humidity control.<sup>27</sup> In all storage situations, precautions should be taken to ensure that possible contamination from specimen-to-specimen contact is not a problem.<sup>28</sup> Several publications have demonstrated the recovery of quality DNA from residual newborn screening specimens stored at ambient conditions.<sup>29,30,31</sup> During storage, a humidity indicator should be periodically monitored and appropriate action taken to reactivate the desiccant when humidity exceeds 30%<sup>32,33</sup> or some other designated level of action. Every residual newborn screening specimen should be properly identified. An index or catalog should be maintained so that any individual sample can be easily located. A quality assurance system is necessary for documenting the integrity of the stored residual newborn screening specimens.<sup>34</sup>

### ***Retention Conditions***

Laboratory genetic testing guidelines exist and appear to be applicable to newborn screening testing.<sup>35</sup> 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.<sup>36</sup> 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.<sup>37</sup> 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.<sup>38</sup> It has been recommended that at a minimum, stable tested patient specimens should be retained after testing

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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.<sup>39</sup>

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.<sup>40</sup> 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.<sup>41</sup> 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.<sup>42,43</sup> Safe disposal of samples no longer required for examination should be accomplished in accordance with local regulations regarding waste disposal.<sup>44,45</sup> Care should be taken to dissociate patient identifiers from the blood spots.<sup>46</sup> 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).<sup>47</sup> The program's specified length of retention for residual newborn screening specimens should be consistently met, and all disposal activities should be documented.<sup>48</sup>

### ***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.<sup>49</sup> Residual newborn screening specimens can be shipped or transported by mail or other carrier with no reasonable expectations of occupational exposure to blood or other potentially infectious material.<sup>50</sup> "Standard precautions" and compliance with local regulations and institutional policies are required in preparing newborn screening specimens for shipment.<sup>51</sup> 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.<sup>52</sup> U.S. transport standards are harmonized with the World Health Organization's Guidance on Regulations for the Transport of Infectious Substances<sup>53</sup> and the International Civil Aviation Organization's Technical Instructions for Safe Transport of Dangerous Goods by Air.<sup>54</sup>

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Residual newborn screening specimens must not be packaged in airtight, leak-proof sealed containers (e.g., plastic or foil bags) because the lack of air exchange in the inner environment of a sealed container causes heat buildup and moisture accumulation. Heat, direct sunlight, humidity, and moisture are detrimental to stability of residual newborn screening specimens and analyte recovery. The inclusion of desiccant packs will aid in preventing moisture accumulation. However, shipping conditions are uncontrolled, and desiccant has limited effectiveness. Local postal, courier, and other transport regulations must be followed. If local regulations require enclosure in airtight, leak-proof sealed containers (plastic or foil bags) for transportation, then sufficient numbers of desiccant packages must be included to ensure minimal exposure of specimens to excessive moisture. Indicator cards may be used to monitor humidity. Specimens known to contain an infectious agent should be transported with special precautions according to local regulations (e.g., required packaging and outside warning label).<sup>55</sup>

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APPENDIX C.

## Examples of Consent/Dissent for Research Use of Residual Newborn Screening Specimens

### 1. South Carolina<sup>56</sup>

Blood Sample Storage Options Form: DHEC 1812, Blood Sample Storage Options, Screening for Inborn Metabolic Errors and Hemoglobinopathies

Child's complete legal name: \_\_\_\_\_

Child's date of birth: \_\_\_\_\_

Parent or legal guardian's complete name: \_\_\_\_\_

Parent or legal guardian's complete address: \_\_\_\_\_

South Carolina law requires the Department of Health and Environmental Control to store your child's blood sample in a manner required by law. The blood sample is collected on a special piece of filter paper. This is called "newborn screening." The blood is tested to see if your child has one of the "newborn screening" diseases that can cause mental retardation, abnormal growth or even death. After the tests are done, the filter paper is stored in a freezer at the state laboratory. This storage is highly protected, and each sample is held under strict confidentiality. A child's blood sample can only be released for approved research, without any identifying information, to learn new information about diseases. The law allows you to choose one of the options below, if you do not want your child's blood sample handled this way. **However, you are not required to check one of the boxes below.**

I want my child's blood sample stored by the South Carolina Department of Health and Environmental Control, but I do not want my child's blood sample to be used for research.

I want my child's blood sample destroyed by the South Carolina Department of Health and Environmental Control two years after the date of testing.

I want my child's blood sample to be returned to me two years after the date of testing. I understand that it is my responsibility to notify the South Carolina Department of Health and Environmental Control, 2600 Bull Street, Columbia, SC, 29201, of address or name changes. I have been given the brochure produced by the South Carolina Department of Health and Environmental Control that describes the conditions for which testing is currently available and explains the benefits of testing and blood sample storage.

Parent: \_\_\_\_\_ Date: \_\_\_\_\_

I have given the brochure produced by the South Carolina Department of Health and Environmental Control to the parent/legal guardian of the child named above.

Name: \_\_\_\_\_ Date: \_\_\_\_\_

*DHEC can store your baby's blood sample for special study. Studies help DHEC find out new information about diseases. If a study finds something in your child's blood sample that can help your child, DHEC can confidentially notify you (or your child if he/she is 18 years or older).*

IF THIS FORM IS NOT SIGNED BY A PARENT/LEGAL GUARDIAN AND/OR NONE OF THE ABOVE BOXES ARE CHECKED, THE BLOOD SAMPLE WILL BE STORED AS REQUIRED BY SC CODE ANN. Section 44-37-30 AT -20 DEGREES CENTIGRADE AND MAY BE RELEASED ONLY FOR CONFIDENTIAL, ANONYMOUS SCIENTIFIC STUDY.

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NOTE TO PROVIDERS: The parent or legal guardian is not required to sign this form. However, the person who gives the brochure that explains neonatal testing and blood sample storage to the parent or legal guardian must sign this form.

**2. Michigan<sup>57</sup>**

*Michigan Department of Community Health*

**Directive to Remove Residual Newborn Screening Blood Specimen from Possible Research Uses**

*This form should be completed and signed by the legal representative\* to request removal from any research uses of the remaining newborn screening blood specimen on the individual named below:*

Child's Name at Birth:

Date of Birth:

Child's Current Name:

Circle Order if Multiple Birth: A B C D E

Mother's Name at Time of Child's Birth:

Hospital of Birth:

I am the legal representative of the child named above. By signing below, I hereby request the Michigan Department of Community Health, after newborn screening has been completed, to **not** use this child's blood specimen for possible future research. I understand that the specimen will be retained by the laboratory but not used for research of any kind unless directed otherwise in writing by a legal representative.

Signature of mother, guardian, or other legal representative:

Relationship to child:

Printed name:

Date:

Street Address:

City:

Zip: Phone:

Signature of father, guardian, or other legal representative:

Relationship to child:

Printed name:

Date:

Street Address:

City:

Zip: Phone:

\* **“Legal representative”** means the parent or guardian of a minor who has authority to act on behalf of the minor, or the individual from whom the specimen was collected if 18 years or older or legally emancipated.

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