Abstract

Title of Thesis: A Comparative Analysis of the Governance and Use of Residual Dried Blood Spots from State Newborn Screening Programs and Neonatal Biobanks

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Newborn screening (NBS) using dried blood spots is a public health testing program for metabolic or genetic disorders that involves approximately four million newborns in the United States each year. Historically, the governance of each state's screening program has been left to individual states. However, in recent years, there have been movements to standardize various aspects of the programs, including collection and storage procedures and the set of disorders on the screening panel. In 2009, two lawsuits brought the uses of residual dried blood spots (rDBS) to public attention; since, a vigorous debate has developed around the use of rDBS in research. The objective of this study was to assess the current procedures for the governance and research use of rDBS from state NBS programs. This mixed-methods social science research study involved five main sources of information from both consumer and regulatory sources. The policies from two neonatal biobanks were included for comparison purposes, and content analysis was used to identify the major themes of research governance that were addressed by each policy. It was found that 38 state newborn screening programs, as well as the two neonatal biobanks, addressed the research use of rDBS in one or more of the data sources analyzed. Discoverable state research policies were outlined in an internal policy and/or a state law in 23 states, but 15 states lacked any written law or policy. Important differences between the NBS programs and biobanks included the type and number of research reviewers, the agreements required of the researcher, and the evaluation criteria used. None of the policies explained how the listed evaluation criteria would be applied during the evaluation process. Overall, this study demonstrates that there are different ways that research policies have been structured, and the highlighted features of these policies could be useful during future policy evolution and creation with respect to the governance and use of rDBS. The creation of a model policy or template, developed with cooperation between the states and input from other experts, might be the next step in addressing this issue.

A Comparative Analysis of the Governance and Use of Residual Dried Blood Spots from State Newborn Screening Programs and Neonatal Biobanks

by
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LIST OF ABBREVIATIONS

AAP: American Academy of Pediatrics

ACMG: American College of Medical Genetics

APHL: Association for Public Health Laboratories

CDC: Centers for Disease Control and Prevention

CFR: Code of Federal Regulations

CLIA: Clinical Laboratory Improvement Amendments

CORN: Council of Regional Networks for Genetic Services

DBS: dried blood spot(s)

DNA: deoxyribonucleic acid

GINA: Genetic Information Nondiscrimination Act

HIPAA: Health Insurance Portability and Accountability Act

HHS: U.S. Department of Health and Human Services

IRB: institutional review board

NBS: newborn screening

NBSTRNCC: Newborn Screening Translational Research Network Coordination Center

NCSL: National Conference of State Legislatures

NIH: National Institutes of Health

NNSGRC: National Newborn Screening and Genetic Resource Center

OHRP: Office of Human Research Protections

PKU: phenylketonuria

rDBS: residual dried blood spot(s)

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

BACKGROUND AND LITERATURE REVIEW

History and Components of Newborn Screening

Newborn screening (NBS) is one of the United States' most notable and reliable public health efforts for children with approximately four million newborns screened each year.[1, 2] NBS began in the early 1960s with the development of the Guthrie bacterial inhibition assay that tested for phenylketonuria (PKU).[3-5] A 1962 pilot study in Massachusetts showed that mass screening for PKU was feasible, and by 1965, 45 states had passed state statutes mandating newborn screening.[5] These state NBS laws were based on public health models for disease screening and came to rely upon the population screening principles developed by Wilson and Jungner in 1968 to determine which genetic conditions were prevalent, treatable, and severe enough to warrant screening.[5, 6]

The first federal legislation for NBS was passed in 1994 with the "Screening for Heritable Disorders" amendment to the Public Health Service Act, which provided federal funding for state and local public health agencies to conduct newborn screening.[7] More recently, the "Newborn Screening Saves Lives Act" was passed by Congress in 2007 and amended in 2008, which provided additional funding for NBS, established the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children (SACHDNC), mandated laboratory quality assurance evaluation, created an Internet clearinghouse to distribute information about NBS, and started the Hunter Kelly Research Program to conduct and expand research in NBS.[8] This Act has been criticized for not including parental consent requirements for testing and for allowing research on the residual dried blood spots (rDBS) remaining after clinical testing has been completed.[9]

The primary objective of NBS is to ensure that every newborn receives appropriate services.[1] Thus, there are five components of NBS programs: screening, follow-up, diagnosis, management, and evaluation.[10, 11] First, the screening function of NBS is the most widely-recognized part of a program as it includes the education of parents, sample collection, transport of the sample to a designated laboratory, and sample testing. The second component of a NBS program is the ability of the lab to report and follow-up on results with hospitals, physicians, and parents. Many states do some form of long-term follow-up on medical care, treatments, and services received in addition to short-term follow-up until a diagnosis is reached.[12] Next, the diagnosis and management functions of NBS are performed by the newborn's physician and other members of the health care team, and the NBS program may help families to coordinate services and to obtain the medical foods necessary for disease management. Finally, evaluation is an important part of NBS because programs must ensure that they are meeting their public health goals and using financial resources wisely.[10, 13]

Standardization of Newborn Screening

Historically, each state has held the authority to set the regulations and policies that align with community values, political and economic situations, and public health capabilities.[1] However, there is a growing recognition that national standardization is important from the perspective of distributional justice because without uniform guidelines, not all newborns will have equal access to the benefits of screening.[1] Thus, over the past 10 to 15 years, there have been a number of initiatives to standardize aspects of NBS such as storage requirements, the screening panel, collection procedures, and consent processes. The standardization of storage procedures and the screening panel will be discussed next.

One of the first NBS policies to undergo standardization was the storage recommendations for rDBS. rDBS are typically retained for a period of time for program evaluation and quality assurance purposes, to test treatment efficacy, to refine tests, and to verify results as a form of legal accountability.[1, 14, 15] Each state's retention and storage procedures were surveyed by McEwen and Reilly in 1994.[16] They found that most state programs had limited or no written policies for the retention, storage, retrieval, and usage of rDBS, so they called for the formation of a set of national guidelines.

In response, the Council of Regional Networks for Genetic Services (CORN) proposed a set of guidelines in 1996 that set the optimal temperature, time period, and conditions for rDBS storage.[14] CORN also recognized that there were a number of reasons to discard rDBS: uncertain analyte stability, storage space and costs, ill-defined future uses, retrieval difficulties, lack of quality assurance for sample integrity, lack of informed consent for retention, and little contribution to legal liabilities. However, the decision of whether or not to retain and store rDBS was left to each individual state.

The push for standardization can also be clearly seen in an influential report published by the American Academy of Pediatrics (AAP) in 2000, "Serving the family from birth to the medical home; Newborn screening: A blueprint for the future. A call for a national agenda on state newborn screening programs." This article drew attention to the wide variations in the number of conditions that each state screened for in addition to PKU, congenital hypothyroidism, and in most states, galactosemia.[1]

In 2006, an committee of experts convened by the American College of Medical Genetics (ACMG) recommended mandated screening for a core panel of 29 conditions with an additional 25 secondary targets consisting of less reliable tests and tests to rule out other metabolic conditions in the differential diagnoses of core panel disorders.[17] Although almost all states now require testing for the core panel, there are still national and international variations in testing for the secondary target conditions as well as in test criteria, such as the cutoff points to determine positive results.[6, 18, 19]

At present, the discussions of standardization have moved beyond issues of storage and testing panels to the uses of rDBS, especially the use of rDBS by third parties such as law enforcement, the military, researchers, insurance companies, and employers. The AAP Newborn Screening Task Force recommended the development of model legislation or regulations for the use of anonymous or identifiable rDBS for research and public health.[1] But ten years later, this issue has yet to be resolved, as evidenced by a SACHDNC briefing published in September 2010 that also highlighted the need for explicit statements on rDBS retention and use.[15]

Third-party use of rDBS is an issue of increasing importance because, as the SACHDNC briefing suggested, the status of current state policies sends an unclear message to the general public about the purposes behind rDBS storage and use. The differing state consent requirements, uncertainty over who possesses the decision-making authority to decide on rDBS uses, and low public awareness about NBS contribute to a lack of confidence in the governmental management of rDBS.[15]

The debate surrounding rDBS retention and use has also been brought to public attention by ongoing legal disputes in Texas and Minnesota beginning in 2009, as well as by the surrounding news articles, including CNN's provocatively-titled article, "The Government Has Your Baby's DNA."[20] In both states, parents filed civil complaints against their state health departments claiming that the government had no right to retain or use their children's rDBS for research without consent.[21-24] In *Bearder v Minnesota* (788 N.W.2d 144 [Minn. Ct. App. 2010]), a judge dismissed the complaint on the grounds that the Minnesota state statutes allowed the Minnesota Department of Health to retain and use rDBS.[21-24] In *Beleno v Texas Department of State Health Services* (TDSHS) (No. SA-09-CA-0188-FB [W.D. Tex. 2009]), the parties reached a settlement in which TDSHS would destroy the 4.5 to 5.3 million samples obtained between 2002 and May 2009, as well as post information on online about research projects using rDBS.[21-24]

The Biobank Paradigm

Beginning in 1995, similar issues arose in response to the research use of clinical tissue samples stored without consent.[25] Stored human biological materials obtained during clinical procedures were frequently collected by pathology labs at public and private institutions. During the mid 1990s, the National Institutes of Health (NIH) discussed the problems surrounding the research use of stored tissues, and they published a consensus statement.[26] However, before the issue could receive further discussion, Dolly the sheep was cloned in 1996, and the resulting controversy overshadowed the use of stored tissue samples.[27]

More recently, the development of genetic research biobanks has brought up some of the same concerns. Research biobanks were developed as large-scale repositories that "can be linked to medical, genealogical or lifestyle information about a specific population gathered using a specific consent process" (p. 539).[28] A number of genetic biobanks currently exist with national and institutional collections. National biobanks exist in eight countries as shown in Table 1. Large U.S. biobanks include those held by the Marshfield Medical Clinic, Northwestern University (NUgene), Duke University, University of Alabama, Mayo Clinics, Vanderbilt University (BioVU) and Howard University (African American Population Biobank).[29-31] The collections obtained by large cohort studies and NIH projects could also be considered as biobanks.

Table 1. Countries with national biobanks, the approximate number of samples in each biobank, and the entity or entities that review research requests.

Country	Biobank	No. of Samples	Research Reviewing Entity
Estonia	Estonian Genome Project	1 million samples	unspecified
Canada	CARTaGENE	60,000 samples	External advisory committee
Iceland	Icelandic Biobank	270,000 samples	Data protection and national bioethics committees
Japan	Biobank Japan	300,000 samples	Japanese Medical Association
Latvia	Latvian Genome Project	60,000 samples	Central medical ethics committee and state data inspection
Singapore	Singapore Tissue Network	unspecified	Bioethics advisory and central steering committees
Sweden	Medical Biobank	70,000 samples	Swedish Medical Research Council
United Kingdom	UK Biobank	500,000 samples	Ethics and governance council and scientific committee

Source: Swede H, Stone CL, Norwood AR. National population-based biobanks for genetic research. *Genet Med*. 2007;9:141-149.

The development of these large biobanks has changed the context of research away from the "traditional 'one study/one informed consent' paradigm to something more suitable to the broad impact biobanking might have on society" (p. 782).[32] In the past, genetics has been studied as a science in itself, but increasingly, genetics is seen as a means to obtain products and technologies that can improve life through research conducted by the government, pharmaceutical companies, and other ventures.[33]

This shift in the purpose of genetic research has led to a number of changes in the way research is conducted.[25, 32, 34, 35] In the past, genetic research was conducted by one or a small group of researchers who were known to the research subjects. Personal, informed consent was obtained based on individual risks and benefits and for a specific disease. Biobanks, however, act as suppliers by gathering and storing specimens for use in many projects with many diseases and are not directly involved in the research.

Additionally, biobanks find it necessary to ask for a general (or blanket) consent to unspecified future research and broad sharing of samples, which means that participants are unable to provide fully informed consent to research projects. The principles of autonomy and informed consent developed under the Belmont Report in 1979 form the basis of human subject research protections, but they were conceptualized to primarily protect *individual* autonomy, benefits and risks. Biobanks, though, have found it problematic to rely on traditional ethical principles because the research done with samples has *social* benefits and risks with each individual sample having a minimal impact on the research outcome, although individual rights must still be protected.[25, 34] Issues surrounding informed consent in the context of large-scale research studies and biobanks are currently being debated in the ethics literature.

Newborn screening is facing a similar paradigm shift as programs address issues of rDBS storage, retention and use in ways that allow for new research possibilities. As it was stated above, typical uses of rDBS include program evaluation, quality assurance/ quality control, treatment efficacy testing, test refinement, and result verification; they are also sometimes used for forensic identification of remains and special studies requested by a patient's physician or family.[1, 14, 15] However, NBS programs, by retaining and storing a large number of human biological specimens, can be thought of as biobanks, and rDBS can be useful in research to develop new genetic tests or to conduct population studies for clinical medicine or public health purposes.[1, 15] Thus, the biobank model could provide helpful insights when discussing the research uses of rDBS.

Research Uses of rDBS

Although a limited number of studies to date have used rDBS for population-wide screening studies,[36] there is a growing scientific interest in accessing this resource for large-scale genetic research projects. Hannelius suggested that one 3mm punch from a DBS theoretically contains 230ng of DNA,[37] and other studies have confirmed that "a standard 6mm Guthrie card punch could…become the basis for genome-wide neonatal testing" (p. 43).[38] A series of articles in the last several years has determined that DNA can successfully and reliably be extracted from DBS using whole-genome amplification techniques and that this DNA is reliable for genotyping and microarray analysis.[37-40]

Although there are currently prohibitive technical limitations, there might eventually be some practical benefits to using whole-genome techniques for NBS screening and research.[41] Whole-genome techniques might become more efficient and specific than the variety of techniques currently used in NBS because they could theoretically provide better quality data and testing could be automated.[41] In addition, some disorders with problematic analyte or protein analysis could be more accurately detected. At this point in time, metabolite analysis has a greater sensitivity to detect individuals with many metabolic disorders, but sequence data could provide more detailed information about disorders for which we currently have limited knowledge, such as regarding the allelic spectrum, genotype-phenotype correlations, and gene interactions.

Some authors have suggested that it might be premature to analyze concerns about the use of DNA sequencing techniques in NBS when the technology has not yet progressed to a point where whole-genome sequencing is practical (although the costs are rapidly declining).[42] Users of whole-genome sequencing techniques must overcome challenges such as high implementation costs, unrefined quality assurance tests, and difficulties in interpreting unknown genetic variants and uncertain genotype-phenotype correlations. In addition, the characteristics of a blood spot can vary with collection procedures and filter paper quality.[43] Not all genetic disorders that are detectable by traditional NBS methods can be identified by DNA techniques, and DNA-based methods would not replace the tests for non-genetic diseases such as congenital hypothyroidism.[41] Given these concerns, it appears that whole-genome techniques for NBS testing purposes are not currently feasible because of the limited clinical or practical benefits.

Support for rDBS Storage Using a Biobank Model

At present, the storage of rDBS as a biobank appears to be supported by politicians, researchers and the general public. The PREEMIE Act of 2006 (Public Law 109-450) appropriated funds to develop a neonatal biobank that would research the genetic and environmental contributions to preterm birth.[29] In addition, as part of the Newborn Screening Saves Lives Act in 2007, the NIH was directed to coordinate and expand research in NBS through the Hunter Kelly Research Program.[8] The resulting Newborn Screening Translational Research Network Coordination Center (NBSTRNCC) was formed by a $13.5 million-dollar grant to the ACMG to assist state NBS programs in evaluating newly-proposed screening tests.[44]

Research has been conducted to assess public and healthcare provider reactions to the formation of a national neonatal biobank and the use of rDBS for population research. A Japanese study found that the attitudes of the general public were more conservative on issues of rDBS storage and use than either patients with PKU and their families or medical professionals.[45] Another study found that 38% of Canadian geneticists felt that including statements about rDBS retention and research use in educational brochures would reduce participation in NBS,[46] but a focus group study in British Columbia showed that 67% of adults were not very concerned about hypothetical situations involving the continued use of their childhood Guthrie cards, even though 46% wanted to provide separate consent for research.[47]

Focus groups in the U.S. tended to prefer giving a separate consent for rDBS storage and research, even if research samples would be anonymous.[48] In another U.S. study, the majority of parents (75%) would provide consent for research if asked, and 77.9% would permit storage of their child's rDBS, which included 38.5% who would permit indefinite storage.[49] Similarly, a study of New Zealand maternity service providers found that provider opinions on consent for testing and storage of rDBS tended to be consistent with local policies requiring separate consents for each NBS function.[50]

There appears to be a general consensus that parents would be willing to give permission for the storage and use of their child's rDBS if they are asked for consent. However, there is no agreement on the structure of a model repository, and no international or federal guidelines have been proposed.[15] A joint meeting of the Centers for Disease Control and Prevention (CDC) and the Association for Public Health Laboratories (APHL) concluded that the wide variations in state storage policies formed a substantial barrier for the consolidation of rDBS into a specimen bank.[51]

One reason why NBS programs “seem not yet to be fully prepared to…manage a population-based genomic databank while addressing issues of human subjects and patient confidentiality” (p. 272)[52] is that U.S. privacy laws and regulations (including GINA, HIPAA, HHS/ORHP, and CLIA [see list of abbreviations]) provide contradictory and vague guidance on research using anonymized rDBS. Most noticeably, anonymous studies are exempt from Institutional Review Board (IRB) review under 45 CFR 46 regulations.[53, 54] Research often takes place in commercial or institutional settings rather than the clinical sites that are HIPAA-covered entities, and many research labs are not CLIA approved to be authorized to return results to research participants.

Given the research potential of rDBS and the lack of regulatory guidance for the retention and use of rDBS, this study aimed to survey the research oversight procedures developed through state regulations and the internal policies of NBS labs. Furthermore, the oversight structures from two neonatal biobanks were included in this study for comparison purposes.

<u>Relevant Research Involving Biobanks</u>

In a review of national biobanks, Swede highlighted the fact that each biobank has formed a different model for oversight (Table 1 above).[29] Even with this variation in reviewing entities, biobanks have tended to centralize the research review process in a form that is independent from the funding and managing organizations as well as researchers.[55] Deschenes described three critical areas to biobank governance: 1) the project and protocol assessment process, 2) the overall research platform management (the physical specimens and the databank), and 3) data privacy protections.[55] In addition, "accountability, transparency, and monitoring are fundamental components of a good governance strategy" (p. 40).[55]

Few studies have looked at the governance structures for research involving rDBS. The earliest study in 1994 by McEwen and Reilly found that of the 40 states that retained rDBS, 11 had written regulations regarding retention and 29 states had internal retention policies.[16] In terms of rDBS usage, they found that seven out of 53 states had written regulations on third-party access to rDBS with another 10 states having internal policies. Finally, McEwen and Reilly assessed the actual use of rDBS to find that over the previous five years, 28 states had received none or up to six requests for specimens, seven states had 6-20 requests, two states had 21-100 requests, and one state had more than 100 requests.

In 2002, Mandl found that 36 states retained rDBS, of which 31 states stored identified samples, two stored rDBS completely de-identified and three states stored coded samples.[52] This study also surveyed the approval procedures of the 25 state labs that allowed research access to aggregate data (not rDBS). Most states (16) required research requests to be approved through the institutional review board (IRB) at the state lab. Six states required IRB approval from the researcher's institution; five states had proposals reviewed by the lab director; two states reviewed proposals in a committee of the senior staff members; and four states required no special permissions since aggregate data was publicly available. Interestingly, for public health officials to access the aggregate data, fourteen states required approval from the state lab IRB, three states required approval from the researcher's institutional IRB, in four states the lab director reviewed requests, in two states a committee of senior staff members reviewed proposals, and six states required no special permissions.

A study by Olney in 2003 found that 15 states had written rDBS usage policies, 28 states had no written policy and six states did not know.[56] A few years later, in 2006, Therrell observed that 19 states had statutes or regulations that allow research access to rDBS, with 10 states specifically addressing access.[51] There were 37 states that had written storage policies, but only nine state statutes specifically addressed rDBS retention and storage.

The most recent data from 2010 reported to the National Newborn Screening and Genetic Resource Center (NNSGRC) on laboratory specimens showed that 47 states now have written policies for the storage and disposal of rDBS. Only four states have no written policy, and among the five U.S. territories, only Puerto Rico has a written policy.[57]

Similarly, two recent studies have surveyed the content of state NBS statutes for references to the retention and use of rDBS.[15, 58] The SACGHDC commissioned a review of state statutes and regulations, finding that 19 states had relevant legislation,[15, a] and Haga reported that ten states had legislation on the storage and/or use of rDBS.[58, b] Haga also surveyed state NBS websites and educational brochures to find that only 14 states provided public information about rDBS retention and use.

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[a] California, Idaho, Indiana, Iowa, Maine, Massachusetts, Michigan, Minnesota, Mississippi, Missouri, Nebraska, New Hampshire, North Dakota, Oklahoma, South Carolina, Texas, Utah, Washington and Wisconsin

[b] California, Indiana, Iowa, Michigan, Minnesota, Missouri, Nebraska, North Dakota, South Carolina and Wisconsin

Finally, in March 2011, Lewis published a review of legislation addressing issues of retention and use of rDBS.[59] She used state statutes and regulations accessed between November 2008 and December 2009 and found that 20 states addressed retention and/or use of rDBS.[c] This is a similar result to the previous two studies, but her content analysis is more detailed than that of the SACGHDC or Haga. This paper also categorized which state statutes had references to the release of information related to NBS, parental or state control over rDBS, the purposes for which rDBS may be used, and information that must be provided to parents about these issues.

Relevance of the Proposed Study

The research mentioned above has mainly provided dichotomous information on the presence or absence of storage and use policies, but it has not provided information about the governance of research using rDBS. The process of research oversight is an important issue to examine because the persons who evaluate research proposals hold considerable power to define risks and benefits, and the failure to explicitly address the oversight process of rDBS research may contribute to the lack of public trust in NBS.[60] Even as early as 1999, Nørgaard-Pedersen pointed out that “an international consensus policy among neonatal screening institutions is important to aid individual screening facilities in mounting the necessary regulatory framework to protect the integrity of the individual, while at the same time granting investigators conditioned rights to targeted use of samples for the greater good” (p. 108).[61]

To this investigator’s knowledge, no studies have looked beyond state legislation to determine how research uses of rDBS are regulated by NBS programs. The studies

[c] California, Hawaii, Indiana, Iowa, Maine, Maryland, Michigan, Minnesota, Mississippi, Missouri, Nebraska, New Hampshire, North Dakota, Oklahoma, South Carolina, Texas, Utah, Washington, West Virginia and Wisconsin

mentioned above highlight the growing number of states developing statutory or written policies on rDBS retention and use, and the paper by Mandl was the only one to describe the approval processes for research use of aggregate data from NBS.[52] Thus, the objective of this study was to assess the current procedures for governance and use of rDBS from state newborn screening programs and neonatal biobanks.

This study aimed to ascertain and describe the nature of research oversight policies from each state NBS program and compare them to neonatal biobank governance structures. In addition, this project characterized the current research uses of rDBS in the United States. Finally, the acquired data was used to highlight features of well-developed governance models that could be beneficial to future policy creation with respect to governance and use of rDBS.

METHODOLOGY

This mixed-methods social science research study involved five main sources of information (from both secondary and primary sources) to collectively address the study objectives related to the use of residual dried blood spots (rDBS) from newborn screening (NBS) in research. Two sources, NBS websites and educational brochures, contained information designed for the general public and parents of newborns. Three sources contained regulatory and program governance information: state legislation, NBS program internal policies, and survey responses from key informants.

Secondary Data Collection

Newborn metabolic and genetic screening state laws are found in two places: state statutes and state administrative codes. The relevant NBS state statute citations were available online in a list compiled by the National Conference of State Legislatures (NCSL; www.ncsl.org). Administrative code citations regarding NBS were published by Therrell in 2006.[51] The citations used in this study can be found in Appendix A.

The current version of each statute and administrative code, including 2010 updates when available, was obtained from state legislative websites during January 2011. In some states, relevant information about research uses of rDBS was also available in genetic privacy statutes or in public health laboratory sections of the administrative code; however, these were excluded so that this study would be comparable to previous studies that only used NBS legislation. Since Lewis (2011) recently published an article about the content of state NBS laws,[59] her results were verified, and any discrepancies investigated.

Links to the state NBS websites were available through the National Newborn Screening and Genetic Resource Center (NNSGRC) website (genes-r-us.uthscsa.edu). Each program's website was thoroughly searched for pages containing information about the retention, storage and use of rDBS; these pages were downloaded in January 2011. Educational brochures to be given to parents of newborns, if available, were also retrieved from the program websites for analysis.

Biobank Data Collection

To compare NBS policies to biobank policies, information about two neonatal biobanks was included in this study. These biobanks store only NBS samples taken during screening, which makes them comparable to NBS programs. Information about the Michigan Neonatal Biobank (Michigan BioTrust for Health), the only neonatal biobank in the U.S., was located from the NBS program and biobank websites (www.michigan.gov/mdch; www.mnbb.org).

The Danish Neonatal Screening Biobank (PKU biobank) was included because its storage and use policy has been publicly described in the scientific literature.[62] It was the first neonatal biobank to be established (in 1982), so it is likely to be a highly developed model for using rDBS in research. Information in English was located from the biobank website (www.ssi.dk), and translations were also provided by a key informant at the biobank. Danish legislation was not included in this study due to the differences in social and political structures between Denmark and the U.S.

Key Informant Survey

To confirm and expand upon the information acquired from the secondary data sources mentioned above, a survey was administered to key informants at state NBS programs, as well as to biobank representatives. Informants from NBS programs were identified through the contact list available on the NNSGRC website. Informants from the two biobanks were identified through personal communication and recommendations of other biobank representatives.

A total of 57 people were initially approached to participate in the survey: one person from each of the 51 state NBS programs and the District of Columbia; one person from each of the four U.S. territories with NBS programs (Puerto Rico, Guam, the Northern Mariana Islands, and the Virgin Islands; American Samoa does not have a NBS program); and one person from each of the two neonatal biobanks. An introductory letter requested that the survey be forwarded to a more knowledgeable person if appropriate.

The introductory letter and the electronic version of the survey in Microsoft Word format were emailed to the key informants on March 31, 2011, and printed copies of the same materials (with a return envelope provided) were subsequently sent via the U.S. Postal Service. About one week after the emails were sent, each person received a phone call to personally invite them to participate and to answer any questions they might have. Participants were given slightly over two weeks to return the survey, at which time a reminder email was sent. If there was still no response, a follow-up phone call was made. After two months, data collection was closed and non-responsive states were assumed to be not participating.

If a participant returned his or her survey form with complete, clear information, he/she was sent a thank you email. If information was missing or needed to be clarified, the specific questions were sent in an email to the participant, or if preferred, a brief phone interview was arranged. Following the phone interview, the participant received a copy of the researcher's notes about the interview with a thank you email. A copy of the thesis was also offered to all participants, pending its completion. This study was reviewed and assessed to be exempt by the University of Maryland, Baltimore IRB on March 17, 2011.

Survey Instrument

A set of quantitative and qualitative survey questions was developed based on the study's research objectives. Some of the questions were also based upon those developed by Liz Horn and the Genetic Alliance Biobank for their "Registry and Repository Vendor Assessment Worksheet" (www.resource repository.org).[63] The survey included questions in four main categories: 1) qualities and quantities of rDBS currently stored, 2) extant policy governing research use of rDBS, 3) description of state or biobank policies and procedures, and 4) the number and types of research requests for rDBS that were received during 2010. Each state or biobank that possessed a formal, written policy regarding the research uses of rDBS was asked to include a copy of it with their survey responses. The introductory letter (Appendix B) and survey (Appendix C) were reviewed by three experts in NBS and biobanking and were revised in response to their comments before being sent to participants.

Data Analysis

Information from each of the five sources (state laws, internal policies, survey responses, websites, and brochures) was imported into the ATLAS.ti computer program for qualitative content analysis. ATLAS.ti is a program for textual analysis that allows the user to organize multiple documents and then to highlight and code the concepts of interest.

In the first step of analysis for this study, a pre-defined codebook (Appendix D) was developed based upon the codes used by Lewis,[59] and further codes were added based on the study's aims. In particular, codes were added to characterize information specifically related to the research use of rDBS and the evaluation of research proposals. Primary categories of interest are shown in Figure 1.

In the second step, quotations for each particular code were extracted and viewed as a group to determine patterns and common themes. A process of emergent coding (a systematic method of coding that establishes new codes as they arise) identified the major themes present within each code. The codebook was revised iteratively as new themes were identified, and materials were re-coded accordingly.

Once the codebook had been finalized, all materials were reviewed and coded one final time, and the information was cross-checked with an assistant to ensure consistency. Results were analyzed using Microsoft Excel to produce descriptive statistics and to identify statistical correlations between various categories. Quantitative survey data were categorized for analysis so that individual participants would not be readily identifiable.

Categories of Interest

- Retention and/or use of residual DBS*
    - State or departmental control over the use of rDBS
        - rDBS become property of the state *
    - Parental control over the use of rDBS*
    - Purpose for which rDBS may be used*
    - Form in which rDBS are allowed to be released*
- Research use of rDBS
    - Research using rDBS is prohibited*
    - rDBS may be used for research
    - Type of researchers/entities that are allowed*
    - Types of research that are allowed
    - Review of research requests
        - Entity or person that reviews proposals
        - Criteria considered in the evaluation of requests
        - Agreements made by researcher
        - State may charge a fee for use of rDBS*
        - Lab responsibilities regarding research
- Use of NBS information*
    - Purpose of information use*
    - Entities that may receive NBS information
    - Statistical data from NBS*
    - Confidentiality*
    - Information provided to parents*

Figure 1. Categories of interest used during coding and content analysis.
* Categories were used in Lewis MH, Goldenberg A, Anderson R, Rothwell E, Botkin J. State laws regarding the retention and use of residual newborn screening blood samples. *Pediatrics*. 2011;127:703-712.

RESULTS

As mentioned in the methodology, this study used data collected from five main sources. Consumer-oriented information regarding the retention and use of residual dried blood spots (rDBS) was found on 21 out of 56 websites (37.5%) and in 11 out of 41 educational brochures (26.8%). Regulatory and program governance information related to this topic was obtained from 32 surveys (56.1% response rate), 39 state laws (n=55, 70.9%), and 14 internal policies (13 policies provided with surveys; four were available online). A few states declined to participate based on legal advice, and several did not wish to provide information before their policies were finalized. Although the four U.S. territories with newborn screening (NBS) programs were included in the data collection, the Virgin Islands, Northern Mariana Islands, and Guam, as well as six other states (AL, KY, NC, SD, VT, WY), did not have or provide any information about retention or the research uses of rDBS through the sources used in this study.

This study was able to verify Lewis's results[59] regarding state NBS laws, as well as to identify additional state laws, many of which were enacted during 2009 or 2010 (Table 2). Recent changes to state laws included the addition of information about state retention and control of rDBS (three and four states respectively), the potential purposes of rDBS use (five states), and the form in which rDBS may be released (three states).

Although Lewis's coding system identified only legislative references to the use of NBS information for research, this study coded for legislation regarding the general use of NBS information. Thus, Table 2 shows 25 additional states that described the use of NBS information as well as nine more states that described the purposes of releasing NBS information.

Table 2. Comparison of Lewis's state NBS legislation data with data from January 2011.

	Coding of state NBS laws	Lewis's total no. of states	States with relevant laws from Lewis	Preslan's total no. of states	States with additional references	States with absent references
rDBS specimens	Retention and/or use of rDBS	**20**	CA, HI, IN, IA, ME, MD, MI, MN, MS, MO, NE, NH, ND, OK, SC, TX, UT, WA, WV, WI	**21**	CT, ID, OH	MD, WV
	rDBS become property of the state	**4**	CA, ME, UT, WA	**4**	none	none
	State retains control over use of rDBS	**10**	CA, IN, IA, ME, MO, NE, ND, UT, WA, WI	**14**	MI, MN, SC, TX	none
	Research using rDBS prohibited	**1**	MS	**1**	none	none
	State may charge a fee for use of rDBS	**4**	CA, MO, NE, ND	**4**	none	none
	Purpose for which rDBS may be used specified	**13**	CA, HI, IN, IA, ME, MI, MO, NE, ND, SC, UT, WA, WI	**18**	ID, MA, MS, NH, TX	none
	Form in which rDBS may be released	**7**	CA, IA, ME, MO, SC, UT, WA	**9**	IN, NE, OK	MO
	Parental control over rDBS	**11**	CA, IA, ME, MN, MO, NE, NH, SC, TX, UT, WA	**12**	ID	none
	Information provided to parents	**12**	CA, DC, IA, MD, MI, MN, MO, NE, SC, TX, UT, WA	**11**	none	MO
NBS Information	Uses of information related to NBS [a]	**13**	AZ, AR, CO, DE, FL, ID, LA,MA, NJ, OR, PA, TN, VA	**38**	CA, DC, HI, IA, IL, IN, KS, ME, MD, MI, MN, MS, MO, NE, MH, MD, OH, OK, PR, SC, TX, UT, WA, WV, WI	none
	Confidentiality	**26**	AZ, AR, CA, CO, DE, DC, HI, ID, IA, LA, MD, MA, MI, MO, NH, NJ, ND, OK, PA, SC, TN, TX, VA, WA, WV, WI	**28**	IL, PR, UT	MI, MO
	Purpose for releasing NBS information	**10**	CA, HI, ME, MD, MO, NE, ND, OK, TX, VA	**19**	AR, IN, MA, NH, NJ, OH, OR, TN, WV	none
	Information released with parental consent	**14**	CA, CO, DC, IA, LA, MD, MA, MO, NH, PA, TX, UT, VA, WA	**13**	none	MO
	Statistical data not considered confidential	**11**	CA, CO, DE, DC, MO, NE, ND, TX, UT, VA, WI	**14**	MD, NJ, OK, TN	MO

Source: Lewis MH, Goldenberg A, Anderson R, Rothwell E, Botkin J. State laws regarding the retention and use of residual newborn screening blood samples. *Pediatrics*. 2011;127:703-712.

[a] Per personal communication, Lewis lists only research-related uses of NBS information

Storage and Retention of rDBS

To assess how suitable the currently-stored rDBS might be for research purposes, key informants were surveyed about how many and what types of rDBS were stored. The 32 states returning surveys accounted for approximately 2.8 million of the newborns screened during 2010 (Table 3). These data had a 92.7% correlation with the 2009 screening information that was reported to the National Newborn Screening and Genetic Resource Center (NNSGRC),[57] indicating that the number of newborns screened has remained constant over the last two years.

Sixty-five percent of the survey respondents reported collecting one screening sample from each full-term newborn, and of those that collected two samples, none stored the two samples together. The oldest cards reported to be in storage were from 1982, but 17 of the responding states only maintained samples taken during or after 2010 (i.e., samples are stored for one year or less). This finding is supported by the required retention times for rDBS (taken from all data sources): 21 out of 51 states (42.2%) retain rDBS for less than one year (Figure 2); 14 states (27.5%) retain rDBS for one to less than five years; and about 25% percent of the states (13) retain rDBS for more than 20 years.

The respondents' data on the approximate number of stored rDBS as of January 1, 2011, resulted in a total of about 10 million stored rDBS cards, with five states currently storing more than one million rDBS each. The number of stored rDBS correlates 69.3% with the retention time for each state.

Over half of the survey respondents reported storing their rDBS with all demographic information attached to the blood specimen; the rest coded the rDBS using a barcode or another numbered identification system (Table 3). No states reported storing anonymous samples.

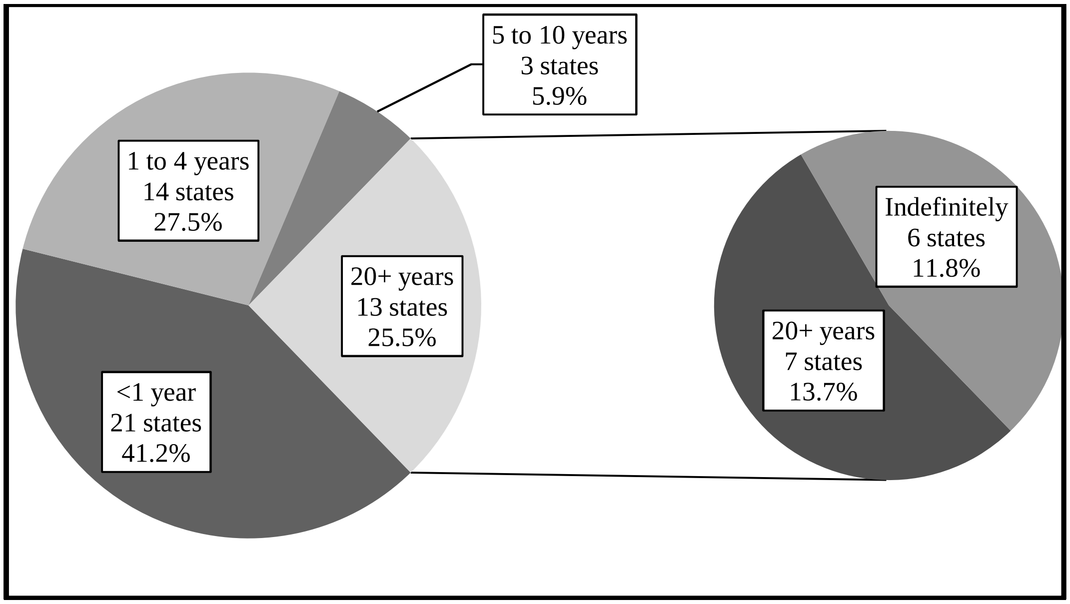

Figure 2. rDBS retention times in the 50 U.S. states and the District of Columbia. Data were obtained and verified from survey data, state laws, internal policies, websites and brochures.

Only one state reported not having electronic records, but 34.5% of those employing electronic records also had data linkages with other databases or registries. The most common linkages were to vital statistics databases, birth defects registries, and hearing screening databases. One biobank reported having data linkages to four other databases and disease registries.

The Michigan Neonatal Biobank and the Danish Neonatal Screening Biobank tended to provide similar answers to questions related to the storage of rDBS (Table 3). Both biobanks stored only one sample per newborn, and all the samples were barcoded for storage. They currently retain rDBS indefinitely and store a combined total of approximately 6.5 million samples.

Table 3. Survey data about the characteristics of the rDBS stored by state NBS programs and neonatal biobanks.

	State NBS Programs Returning Surveys (n=32)	Neonatal Biobanks (n=2)
Number of newborns screened in 2009 (as reported to the NNSGRC) [a]	n=44	--
<50,000	20 (45.5%)	--
50,000-100,000	11 (25.0%)	--
>100,000	13 (29.5%)	--
Total	*4,644,973*	--
Approximate number of newborns screened in 2010 (survey data)	n=30	n=2
<50,000	15 (50.0%)	0
50,000-100,000	8 (26.7%)	1
>100,000	9 (30.0%)	1
Total	*2,790,678*	*177,986*
Approximate number of stored rDBS cards as of Jan. 1, 2011	n=30	n=2
No answer	3 (10.0%)	0
<10,000	2 (6.67%)	0
10,000-49,999	7 (23.3%)	0
50,000-99,000	8 (26.7%)	0
100,000-499,999	4 (13.3%)	0
500,000-999,999	1 (3.33%)	0
>1 million	5 (16.7%)	2
Total	*26,314,755*	*6,500,000*
Year of oldest stored rDBS card	n=29 [b]	n=2
1980s	2 (6.90%)	2
1990s	4 (13.8%)	0
2000s	6 (20.7%)	0
2010s	17 (58.6%)	0
Storage of personal info with rDBS card	n=29 [b]	n=2
Identified	18 (62.1%)	0
Coded	10 (34.5%)	2
Other storage type	1 (3.45%)	0
Data linkages	n=29 [b]	n=2
No	19 (65.5%)	1
Yes	10 (34.5%)	1
Vital statistics database	4	1
Birth defects registry	3	1
Cancer registry	1	1
Immunization database	2	1
Hearing screening database	3	0
Child health database	2	0
Other state health database	1	0

[a] Source: National Newborn Screening and Genetic Resource Center. National newborn screening information system: Laboratory specimen information report. 2011 Accessed 5/2/2011.
[b] Not all respondents provided this information.

General Findings about the Retention and Use of rDBS

Using data from all five data sources, an observed total of 40 entities (38 states and two biobanks) had information about the research use of rDBS (Table 4). An additional two states talked about the retention and non-research uses of rDBS without discussing research uses. Forty-two states (77.8%) and both biobanks addressed the use of NBS information.

Table 4. The general retention and non-research use of rDBS

	No. of biobanks (n=2)	No. of states (n=54) [a]	Percent of all states (n=54)	No. of entities with consumer information [b] (n=56) [d]	No. of entities with regulatory information [c] (n=56)
Retention and use of rDBS	**2**	**40**	**74.1%**	**24**	**41**
Retention/non-research uses	2	40	74.1%	23	39
Research use	2	38	70.4%	17	40
Use of NBS information	**2**	**42**	**77.8%**	**24**	**43**

[a] 49 U.S. states (excluding MI) + DC + 4 U.S. territories
[b] Websites and brochures designed for the general public and parents/individuals
[c] State legislation, internal policies, and survey responses designed to provide regulatory guidance
[d] 49 U.S. states + Michigan Neonatal Biobank + DC + 4 U.S. territories + Danish Neonatal Biobank

Policies about the Research Use of rDBS

Qualitative information about the research use of rDBS was available for 38 states, the Danish Neonatal Screening Biobank, and the Michigan Neonatal Biobank. Twenty-six states were found to allow research while 12 did not permit research. Both biobanks and 12 states that returned the survey had an internal, written policy (Table 5); however, two of those internal policies were actually non-NBS legislation. Six states that allow research, and nine of those 12 states that do not allow research, did not have any governing law or policy regarding research that was discoverable by or available to this study. In addition, states that permit research tended to include information about research in multiple sources, but states that do not allow research tended to discuss the topic mainly in the survey rather than in any other source (Figure 3).

Table 5. The current status of state NBS program research policies, among states with information that was discoverable or available to this study. Additional states may also have laws or policies regarding research.

State research policy	Allow research (n=26 states)	Do not allow research (n=12)
Outlined in law or policy	**20**	**3**
Outlined in a written, internal policy	11	1
Outlined in state law	14	2
Not outlined in law or policy	**6**	**9**

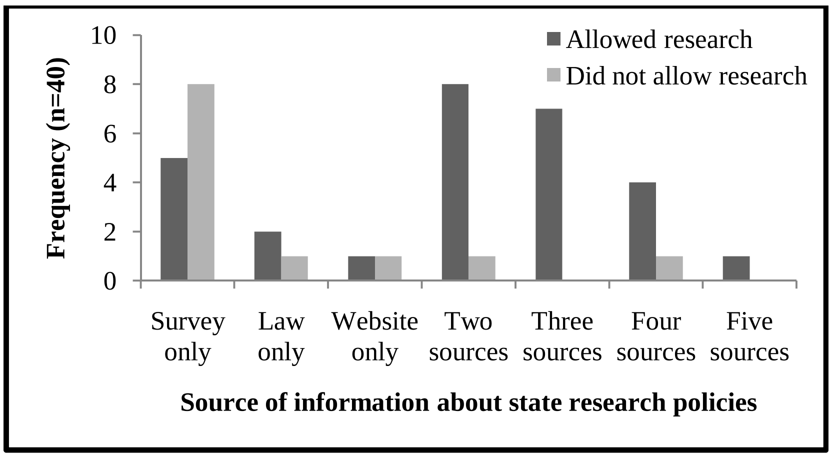

Figure 3. The frequency of states with single or multiple sources of research information for the states and biobanks with available or discoverable information.

Research Review Process

Research Reviewer

Among the 38 states that had information available about the research uses of rDBS, 27 (71.1%) listed one or more persons or committees that reviewed research requests (Table 6). Nineteen states required some form of institutional (IRB) review, most commonly by the public health department's IRB, and 16 states had proposals reviewed by a state official, such as the NBS program director or a health department official. Seven states mentioned in their surveys that they require some form of legal review, but this was only confirmed in two of the states' internal policies.

States with more detailed policies tended to have proposals reviewed by multiple persons and committees. Similarly, both biobanks require that proposals be reviewed by four separate entities. The biobanks more specifically required both a state committee and an advisory committee to review proposals, and only one state was found to require both of these committee reviews.

Research Type

Twenty-one NBS programs specified the types of research that were permissible or impermissible (Table 6). Most states and both biobanks generalized to allow public health or medical research. Seven states and both biobanks explicitly allowed other study types, such as toxicology, environmental exposure, or vaccine studies, and one state allowed research that would align with the health department's mission statement. Only two states and one biobank excluded certain types of research, such as military research or research related to cosmetics, abortion, or non-health topics.

Table 6. The research reviewers and the types of research permitted.

	No. of biobanks (n=2)	No. of states (n=54) [a]	Percent of all states (n=54)	Percent of states that address research (n=38)	No. of entities with consumer information [b] (n=56) [d]	No. of entities with regulatory information [c] (n=56)
Research reviewer	**2**	**27**	**50.0%**	**71.1%**	**11**	**27**
Any IRB review	1	19	35.2%	50.0%	8	17
Department's IRB	1	16	29.6%	42.1%	7	15
Researcher's IRB	1	8	14.8%	21.1%	2	8
Unspecified IRB	0	6	11.1%	15.8%	2	5
State official/director	1	17	31.5%	44.7%	7	17
State committee	2	5	9.26%	13.2%	3	7
Department/manager	0	7	13.0%	18.4%	2	7
NBS advisory committee	2	5	9.26%	13.2%	3	6
Legal review	0	6	11.1%	15.8%	1	7
Other reviewer [e]	1	1	1.85%	2.63%	2	2
Research type	**2**	**21**	**38.9%**	**55.3%**	**12**	**20**
Public health topics	2	12	22.2%	31.6%	8	13
Medical topics	2	5	9.26%	13.2%	5	6
NBS study	0	6	11.1%	15.8%	6	3
Pilot studies	0	6	11.1%	15.8%	5	2
Certain populations [f]	2	8	14.8%	21.1%	5	5
Certain study designs [g]	1	2	3.70%	5.26%	1	3
Excluded studies topics [h]	1	2	3.70%	5.26%	1	3
Other research topics [i]	2	7	13.0%	18.4%	4	6

[a] 49 U.S. states (excluding MI) + DC + 4 U.S. territories
[b] Websites and brochures designed for the general public and parents/individuals
[c] State legislation, internal policies, and survey responses designed to provide regulatory guidance
[d] 49 U.S. states + Michigan Neonatal Biobank + DC + 4 U.S. territories + Danish Neonatal Biobank
[e] Other reviewers included Data Protection Agency, birthing facility's IRB, offsite storage facility review
[f] Children, mothers, or families; birth defects; chronic diseases; disorders of interest to the regional program
[g] Case/control studies; small (<100 person) pilot studies of a new testing tool; anonymous studies
[h] Chemical, biological or nuclear warfare research; cosmetics research; non-health research except if for injury or medical conditions; non-public health studies; law-enforcement studies; abortion research
[i] Other topics included commercial, academic, or national public health studies; research about toxicology/toxic chemical effects, infections (CMV, HIV/AIDS), vaccines, environmental exposures (lead, mercury); bacterial surveillance studies; maternal smoking research; research recruitment studies; rDBS inclusion in a forensic mtDNA database or cancer neonatal biobank; research that supports the dept.'s mission statement

Researcher Agreements

In 16 states (42.1% of states that addressed research uses), the researcher is required to make certain agreements before rDBS can be released. The most common agreements included those related to data protection, disposal or return of the surplus DBS, and the fees the researcher would pay (Table 7). One state required the researcher to assist with retrieving the rDBS from storage, and one state required that the researcher be able to provide study documentation during the research project, rather than after the research was written up. One agreement used by a biobank and not by the state NBS programs was a Material Transfer Agreement.

Program Responsibilities

Only 12 states specified program or laboratory responsibilities in their research policies (Table 7). Six states required some form of communication with the researcher, either during the review process or following the release of the rDBS. Five states and both biobanks permitted the releasing entity's participation in research projects approved by the state. This could be in a formal collaborative arrangement, or by doing specific rDBS-related tasks for the researcher, such as obtaining consent or doing any necessary data linkage to minimize the release of personal information.

Table 7. Researcher agreements and program responsibilities for research using rDBS.

	No. of biobanks (n=2)	No. of states (n=54)	Percent of all states (n=54)	Percent of states that address research (n=38)	No. of entities with consumer information (n=56)	No. of entities with regulatory information (n=56)
Researcher agreements	**2**	**16**	**29.6%**	**42.1%**	**6**	**16**
Data protection	2	11	20.4%	28.9%	4	12
Disposition of rDBS	2	10	18.5%	26.3%	1	12
Fees	1	9	16.7%	23.7%	1	10
Compliance	1	6	11.1%	15.8%	3	5
Publication	2	5	9.26%	13.2%	2	6
Study documentation	0	1	1.85%	2.63%	0	1
Assist to retrieve rDBS	0	1	1.85%	2.63%	1	1
Material Transfer Agreement	1	0	0%	0%	0	1
Program responsibilities	**2**	**12**	**22.2%**	**31.6%**	**9**	**12**
Contact with researcher	1	6	11.1%	15.8%	2	7
rDBS coding or anonymizing	1	5	9.26%	13.2%	2	6
Doing some of the research [a]	2	5	9.26%	13.2%	6	4
Documentation of research	2	4	7.41%	10.5%	0	6
Returning research results	0	3	5.56%	7.89%	2	2
Other responsibilities [b]	1	1	1.85%	2.63%	1	2

[a] Obtaining consent, collaboration with researcher, data linkage

[b] Other responsibilities included writing a letter of support for a grant application or an action memo to a reviewer

State vs. Parental Control of rDBS

All of the 38 states that addressed research uses of rDBS also addressed issues of state vs. parental control over rDBS (Table 8). State control was defined as cases in which the rDBS were specifically declared as state property, instances of unclear authority over rDBS (such as when consent was unspecified), or when rDBS are released without parental consent. Parental control over rDBS comprised consent or dissent (opting out) to a proposed use, or of requesting destruction of the rDBS.

Six states established rDBS as state property. Fourteen states use broad statements that rDBS could be released for research without defining what type of rDBS or whether consent would be required. Eight states specified that anonymous or de-identified rDBS could be released without consent. However, two states also included that they would release identifiable rDBS if an IRB approved or waived the consent requirements for a study, or if a court or law required that the rDBS be released.

Regarding consent to rDBS uses for research, parents in 23 states must provide consent (Table 8). Nineteen states require consent for any research use, and the release of identified rDBS for research require consent in seven states. Six states have provisions for parents to opt-out of research or other uses of rDBS, and seven states allow individuals to request the destruction of the rDBS.

Table 8. State and parental control over the use of rDBS.

	No. of biobanks (n=2)	No. of states (n=54)	Percent of all states (n=54)	Percent of states that address research (n=38)	No. of entities with consumer information (n=56)	No. of entities with regulatory information (n=56)
State control of rDBS	**2**	**38**	**70.4%**	**100.0%**	**16**	**23**
Research allowed	2	26	48.1%	68.4%	15	28
Research not allowed	0	12	22.2%	31.6%	2	11
DBS are state property	1	6	11.1%	n/a	5	5
General research use	2	14	25.9%	36.8%	12	12
Unidentified rDBS	2	8	14.8%	21.1%	7	7
Anonymous rDBS	0	6	11.1%	15.8%	5	3
De-identified rDBS	2	2	3.70%	5.26%	3	3
Identified rDBS	0	0	0%	0%	0	0
Use without consent	2	7	13.0%	18.4%	4	8
Unidentified rDBS	2	2	3.70%	5.26%	1	3
Anonymous rDBS	0	4	7.41%	10.5%	1	3
De-identified rDBS	0	1	1.85%	2.63%	0	1
Identified rDBS [a]	1	2	3.70%	5.26%	2	1
Parental control of rDBS	**2**	**25**	**46.3%**	**65.8%**	**16**	**23**
Consent to rDBS use	2	23	42.6%	60.5%	14	22
Unidentified rDBS	2	12	22.2%	31.6%	5	2
Anonymous rDBS	0	1	1.85%	2.63%	0	1
De-identified rDBS	0	0	0%	0%	0	0
Identified rDBS	1	7	13.0%	18.4%	6	4
Other uses of rDBS	2	17	31.5%	n/a	10	15
Dissent to rDBS use	2	6	11.1%	15.8%	7	3
Unidentified rDBS	2	4	7.41%	10.5%	5	3
Anonymous rDBS	0	1	1.85%	2.63%	1	0
De-identified rDBS	0	0	0%	0%	0	0
Identified rDBS	0	0	0%	0%	0	0
Other uses of rDBS	1	3	5.56%	n/a	3	1
Destruction of rDBS	2	7	13.0%	n/a	7	8

[a] If research is IRB approved/waived or if release is legally required or court ordered

Evaluation Criteria for Research Proposals

Table 9 shows the 14 criteria for the review of research proposals that emerged from an examination of the practices of 26 states and two biobanks. The most commonly cited criteria included the following: data protection/privacy considerations, the type of research study, regulatory compliance (with federal regulations, HIPAA, CLIA, etc.), qualities of the rDBS being requested (number, type, etc.), and the "appropriateness" of the research. The biobanks also appeared to emphasize the risks and benefits of the research, the scientific merit of the research, and the protection of their rDBS as a valuable and finite resource. Less common criteria included consideration of the technology used in the study, the study's funding, whether the study would return results to individuals, and the public favorability of the research.

Table 9. The criteria used by state NBS programs and biobanks when evaluating research proposals.

	No. of biobanks (n=2)	No. of states (n=54)	Percent of all states (n=54)	Percent of states that address research (n=38)	No. of entities with consumer information (n=56)	No. of entities with regulatory information (n=56)
Evaluation criteria	**2**	**26**	**48.1%**	**68.4%**	**14**	**27**
Data protection	2	21	38.9%	55.3%	13	21
Research type	2	20	37.0%	52.6%	12	19
Regulatory compliance	2	16	29.6%	42.1%	10	13
rDBS characteristics	2	15	27.8%	39.5%	6	14
Appropriateness	2	13	24.1%	34.2%	4	14
Feasibility for program	1	10	18.5%	26.3%	5	16
Investigator qualities	1	9	16.7%	23.7%	3	10
Risks/benefits of research	2	9	16.7%	23.7%	7	7
Scientific merit	2	6	11.1%	15.8%	6	4
Technology used	1	4	7.41%	10.5%	3	2
Study funding	1	3	5.56%	7.89%	0	4
Returning research results	0	3	5.56%	7.89%	0	3
Resource protection	2	2	3.70%	5.26%	4	3
Public favor	0	1	1.85%	2.63%	2	1
Other criteria [a]	1	7	13.0%	18.4%	2	7

[a] Other criteria included the consideration of ethical standards and integrity, legality, and the use or publication of research results.

<u>Retention, Non-Research Uses of rDBS, and Information Provided to Parents</u>

This study also characterized the non-research uses of rDBS that were mentioned in the five data sources, as well as the information available to parents about the retention and research use of rDBS (Table 10). Forty states communicated information about the retention, storage, and/or disposal of rDBS. One important non-research use of rDBS is for quality control and quality assurance for individual newborn and/or laboratory purposes. Only seven states talked about using rDBS for medico-legal purposes, such as when rDBS are requested by a court or a medical examiner. Three states referred to using rDBS in cases of missing children, accidents, crimes, or paternity testing, but both neonatal biobanks included these less common uses in their policies.

Eleven states' laws and policies required NBS programs to inform parents about the retention and use of rDBS after testing (states expected to provide parents with information about retention), and four states required information to be provided about the research use of rDBS (Table 10). These expected states were all observed to provide the required information in their brochures and websites. Furthermore, eight additional states voluntarily provided parents with retention information, and 11 additional states provided information about research uses of rDBS.

Table 10. Retention and non-research uses of rDBS, and the information provided to parents about retention and research.

	No. of biobanks (n=2)	No. of states (n=54)	Percent of all states (n=54)	No. of entities with consumer information (n=56)	No. of entities with regulatory information (n=56)
Retention and non-research uses of rDBS	**2**	**40**	**74.1%**	**24**	**40**
General retention, storage, disposal of rDBS	2	40	74.1%	20	39
Testing and retesting uses	2	20	37.0%	11	16
QA/QC/new test development uses	2	19	35.2%	12	16
General public health uses	1	9	16.7%	6	6
Legally-ordered uses	2	7	13.0%	7	5
Other uses [a]	2	3	5.56%	2	4
Information provided to parents	**2**	**25**	**46.3%**	**24**	**13**
Expected information about retention	2	11	20.4%	0	13
Expected information about research	2	4	7.41%	0	6
Observed information about retention	2	19	35.2%	21	0
Observed information about research	2	15	27.8%	17	0

[a] Other uses included identification after accidents, crimes, natural disasters, or of missing children; retesting for previously-conducted tests; paternity testing; and commercial uses.

Overall Transparency of State NBS Programs and Neonatal Biobanks

Tables 4 through 10 above also contained statistics about the sources of information (consumer-oriented vs. regulatory information) that supplied the listed data for each analyzed category. A comparison of the frequencies of information being covered in the consumer vs. regulatory sources for each topic provides a rough measure of the overall degree of transparency about rDBS policies.

All of the main categories examined in this study, with one exception, had more research information available in regulatory sources than in consumer sources (Figure 4). In Table 4 above, statements about the research use of rDBS were observed in 17 consumer-oriented sources and 40 regulatory sources (n=56). Similarly, the categories related to research reviewer and evaluation criteria showed large discrepancies in regulatory vs. consumer sources of information.

In the category about information provided to parents, there was more consumer information than regulatory guidance. Twenty-four consumer and 13 regulatory sources provided or required that parents be given information about the retention and/or research use of rDBS (Table 10 and Figure 4).

Figure 4 also shows that although 40 states had regulatory information available about the general retention and non-research uses of rDBS, fewer than half of the states and biobanks had regulatory guidance available about topics related to the research use of rDBS. Fewer than 20 entities had information available about the permitted research types, how requests are evaluated, and the releasing laboratory's responsibilities regarding research.

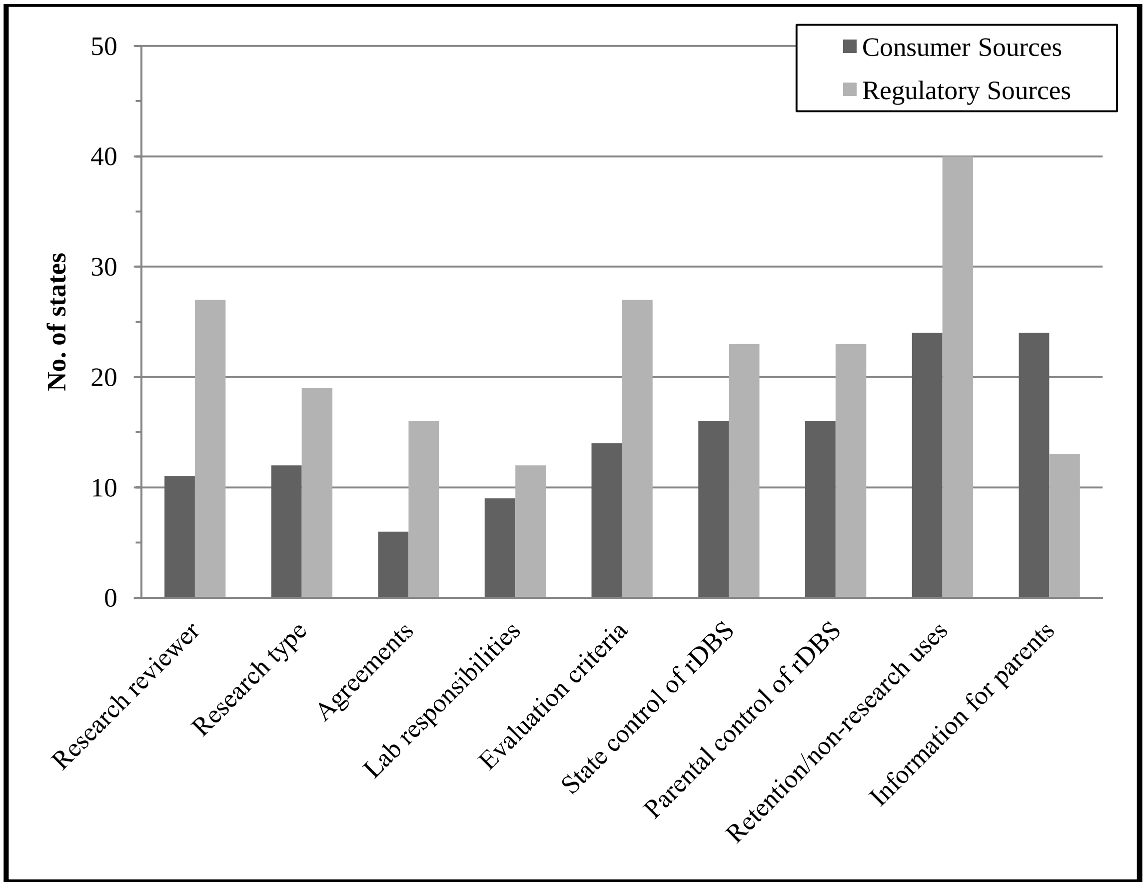

Figure 4. The overall transparency of the studied entities regarding each category of research governance. Consumer-oriented sources of information were program websites and educational brochures. Regulatory sources included state laws, available internal policies, and survey data (from 32 states).

2010 Research Uses of rDBS

Finally, the survey used in this study collected information about the current research uses of rDBS. Of the 21 states that responded to the survey and allowed research, five states received a total of seven research requests during 2010 (Table 11). However, one large state that is known to receive many requests did not provide data. Five of the seven requests reported here were approved. The two neonatal biobanks received 12 requests and approved 11 proposals with one still being reviewed.

Characteristics of the 2010 research studies that used rDBS are shown in Table 11. Many of the requests for rDBS were from academic researchers, but five were from commercial researchers. Only four studies were for the purposes of investigating genetic variation or disease incidence, and only one biobank request proposed testing for environmental exposures. Eight of the reported studies (five from state programs, three from the biobanks) were for new test development or quality control purposes. Three of the reported biobank studies requested less than 50 samples each, and no studies requested more than 5,000 rDBS. This trend is reversed for state NBS programs, which received no requests for less than 100 rDBS, and two studies requested more than 5,000 rDBS.

Table 11. The number and types of 2010 research requests for rDBS.

Research requests for rDBS	State NBS Programs (n=21) [a]	Neonatal Biobanks (n=2)
Total requests during 2010	**7**	**12**
Requests approved	5	11
Requests not approved	1	0
Request was withdrawn	1	0
In review process	0	1
Researcher affiliations	**n=7**	**n=11**
Academic	4	8
Commercial	2	3
State	0	0
Federal	0	0
State/academic collaboration	1	0
Multi-state studies	**n=7**	**n=11**
Yes	3	2
No	4	9
Types of research	**n=7**	**n=6** [b]
New test development	4	3
Public health product testing	1	0
Genetic variation	1	2
Disease incidence	1	0
Environmental exposure	0	1
No. of rDBS requested	**n=5** [b]	**n=6** [b]
<50 rDBS	0	3
50-99 rDBS	0	0
100-999 rDBS	1	1
1000-4999 rDBS	2	2
5000+ rDBS	2	0
Forms of rDBS requested	**n=6** [b]	**n=11**
Anonymous rDBS	3	0
Coded or de-identified rDBS	2	11
Identified rDBS	1	0
Specific rDBS	3	4
Random rDBS	3	7

[a] 21 states return a survey and allowed research. However, one large state that receives many requests did not provide this information.
[b] Not all respondents provided this information.

DISCUSSION

The objective of this study was to assess the current governance policies and use of residual dried blood spots (rDBS) from state newborn screening (NBS) programs and neonatal biobanks. The specific aims were: 1) to ascertain and describe the nature of research oversight policies from each state NBS program and compare them to neonatal biobank governance structures; 2) to characterize the current research uses of rDBS in the United States; and 3) to highlight features of well-developed governance models.

This study determined that 38 state NBS programs, as well as the two neonatal biobanks, addressed the research use of rDBS in one or more of the five data sources used by this study (consumer-oriented information in websites and brochures; regulatory information in state laws, internal policies, and survey responses). State research information was outlined by an internal policy and/or a state law in 23 states, and 15 states lacked any written law or policy on the topic.

Research using rDBS was permitted in 26 states and prohibited in 12 states. The most commonly discussed aspects of research governance were the identification of the reviewers and allowable research types. The most common evaluation criteria included data protection, research type, regulatory compliance, rDBS characteristics, and "appropriateness."

General Form of Internal Policies

This is the first study of NBS policy to date to include data from internal policies, as previous work has tended exclusively to utilize more readily available sources of information, such as publicly available legislation. Although only 14 internal policies were obtained, the represented NBS programs include many key states that are actively addressing this issue.

There does not appear to be a single model policy in use or circulation, as there were striking differences in the internal policies analyzed here. Some states combined research use with their retention policies; however, the states with separate research policies tended to include more details. Texas's policy took a tabular approach by outlining the types of quality control/quality assurance and research uses of rDBS (program evaluation, test development, research, etc.), examples of each usage, and the approval requirements for each.

In contrast, one of the Michigan Neonatal Biobank's multiple policy documents focused on the responsibilities of different managers involved with the biobank and how each person would contribute to the overall review process. Michigan also had a policy that outlined the research process in terms of the biobank's guiding principles and the actions that would demonstrate those principles.

The policies from Maryland, Oregon and Utah were good examples of a straight-forward, concise approach that list the proposal requirements and evaluation processes and criteria. Finally, Iowa's policy was very comprehensive in accounting for both research and non-research uses of rDBS, as well as many associated issues like confidentiality and access to NBS information.

<u>Research Reviewer</u>

Of the 38 states with information about research, Table 6 showed that 19 included an IRB review, and 17 states had proposals reviewed by a state official or program director (a single person rather than a committee). While most states tended to involve one to three separate types of reviews/reviewers, Texas and Iowa mentioned four and five reviewers, respectively. It is also important to point out that, while not formally analyzed in this study, several state policies and surveys referred to an informal review by the department or director prior to the submission of a formal proposal or request.

In contrast, the neonatal biobanks used three to four separate reviews/reviewers. The Danish Neonatal Biobank required approval from the Danish Data Protection Agency (coded as “other reviewer”), the Scientific Ethical Committee System (a “state committee”), and the Steering Committee for Scientific Use of the Biobank (an “advisory committee”). The Michigan Neonatal Biobank required approval from the researcher’s IRB as well as the Michigan Department of Community Health IRB; a review panel from the BioTrust Scientific Advisory Board (coded as a “state committee”); a DBS Program Representative, which the policy defines as “the State Registrar, Director of the Bureau of Laboratories and Director of Bureau of Epidemiology or designee” (a “state official”); and a description is provided to the BioTrust Community Values Advisory Board (an “advisory committee”).

The combination of a scientific/state committee and an advisory committee appeared to be a distinctive feature of the reviewers used by the biobanks but not by state NBS programs (taking into account that only two neonatal biobanks were studied here). Only one state, Iowa, had this same combination of reviewers.

Since research reviewers have the power to make decisions about risks and benefits, scientific potential, and property rights, [60] the use of multiple reviewers reduces the power and responsibility of each individual reviewer, while potentially increasing the quality of the overall review by soliciting diverse perspectives on each research proposal.

Multiple reviews could also help to reassure parents that research proposals are thoroughly scrutinized, especially when an advisory committee, that should always include members from outside the department or biobank, is involved and has public and parental interests in mind.

State vs. Parental Control of rDBS

The results of this study suggest that, in general, states may have some hesitation about discussing state control over rDBS in information sources aimed at parents. Fourteen states addressed the general release of rDBS for research (Table 8), and they did so by using statements such as "may be released for anonymous research," in which the state's control could be inferred rather than being explicitly acknowledged.

In addition to general statements about releasing rDBS for research, three other common situations were considered: 1) release of rDBS only if a parent consents to the release, meaning the rDBS are strictly under parental control; 2) state-controlled release of rDBS unless a parent dissents or opts-out, meaning the use of rDBS is administered by the state unless a parent actively states his or her desires; and 3) state-controlled release of rDBS without parental consent or dissent, meaning the use of rDBS is directed by the state alone. One final form of parental control would be through a request that the state destroy the rDBS in question. Twenty-five states had statements about parental consent, dissent, or the destruction of rDBS. In comparison, only seven states specified when rDBS could be released without parental consent.

Except in the situation of using rDBS without consent, the states have a relatively higher overall transparency about state and parental control over rDBS, in comparison to other research categories. This may indicate that states are motivated to protect parental autonomy. Or, since five states have added legislative provisions in these areas within the last one to two years (Table 2), NBS programs could be adding consent requirements for research in response to the lawsuits in Texas and Minnesota. It is interesting to note that Texas amended their state statute following the 2009 lawsuit to include all probable reasons why rDBS would be released. Similarly, Minnesota's lawsuit was dismissed because the NBS program had statutory authority to retain and use rDBS, and the parental brochure specifically mentioned research uses of rDBS. Thus, at least in the cases of these two states, there appear to be legal advantages to being open and clear about how rDBS will be used.

It is commendable that certain states have been explicit and transparent about the situations in which rDBS could be released without consent. The specific situations mentioned included: the general release of anonymous or de-identified rDBS for research, if an IRB waived the consent requirements for a research study, if the release were ordered by a court, or if the release were required by law. No entities discussed consent in the context of using rDBS for identification purposes (e.g., accidents, missing children, natural disasters), but in certain emergency situations, it might be reasonable for rDBS to be released without consent.

Evaluation Criteria

Finally, an important outcome of this study is the observation that none of the research policies included a great deal of detail on the subject of exactly how proposals are evaluated. Policies listed or implied *what* criteria they would use, but they did not define exactly *how* each criterion would be used (Table 9). For example, if one consideration is the feasibility of supplying the requested rDBS, then many questions arise about how feasibility is defined: how many or few rDBS could be requested, how much personal information could potentially be released with the rDBS, which staff members could retrieve the rDBS, how much time could be afforded away from other duties, and other similar questions. Or, if “appropriateness” is a criterion, who defines what is appropriate, and how would that definition reflect the diversity of community values within a state?

Due to the clinical context, as well as the storage of both biological samples and personal and medical information, one might expect these official state policies to have a level of detail similar to the regulations protecting personal health information or genetic privacy, which are written in very careful legal language so as to avoid ambiguities. Since DBS can be used to discover an individual’s unique DNA sequence, some may consider the release of these spots to be similar to the release of other personal information and meriting greater formal protections than are currently found in the research policies studied here.

The open communication of detailed, legally drafted research policies might help to build public trust and support for research, especially since recent events indicate that transparency regarding the operation of NBS programs and policies is a critical public concern. The fact that six states talked about a legal review of research requests for rDBS (Table 6) suggests that there is some concern about avoiding the lawsuits that Texas and Minnesota have been, and still are, facing (see literature review: p. 5). Furthermore, there are recent or pending bills in Oklahoma (SB 1250, passed 2010) and Texas (HB 2110, pending House Public Health Committee) that prohibit any unauthorized storage or use of DNA, and these bills do not appear to exempt NBS programs. Even though the “legalese” of official documents may be difficult to read and comprehend, having each nuance of a research policy fully defined would result in a greater level of transparency and trust because all parties involved would understand their rights and responsibilities.

Limitations of This Study

First, it was not possible to obtain complete data for all the states, so the full range of use and governance policies is not known. The survey had a 56% response rate, so the non-participating states could differ significantly from those that did return the survey. Some states expressed a reluctance to participate in this study due to concerns in the field related to the ongoing lawsuits. Furthermore, at least five states, including two nonparticipating states, commented that they were currently creating or revising their research policies. Also, this study did not include all possible legislation, since relevant information that was found in genetic privacy statutes or laboratory regulations was excluded to make this study similar to prior research that only looked at NBS laws.

Next, the data from the neonatal biobanks are not completely analogous to NBS programs. Biobanks are designed to supply biological specimens for research projects, and NBS programs are primarily clinical testing programs. While certain NBS-specific concerns, such as returning research results to participants, are not as pertinent in a biobank context, the majority of the biobanks' policy information was mirrored in NBS programs, suggesting that the policies of these neonatal biobanks would be good models for NBS programs. Also, the Michigan Neonatal Biobank was only recently created, and it is not fully operational for research use at this time.

Finally, there is a degree of subjectivity to this study since a second reviewer was not used during content analysis. This limitation was somewhat mitigated by using an assistant to help verify and cross-check the data used in analysis.

Future Directions

Since this study did not elicit a large number of research projects that used rDBS during 2010 (only five successful proposals were identified out of 21 state NBS programs), this is an opportunity to address issues related to the research uses of rDBS and to build capacities before there are more requests for rDBS.

The next step to moving this conversation forward might be the creation of a model and/or template policy, developed with cooperation between and among the states, and with input from other experts and stakeholders. Some topics might be best addressed using a prescriptive policy model, which could strongly recommend or require certain actions by states. For example, some human subject protections, such as IRB review of research protocols or data confidentiality, have been generally agreed upon and are widely utilized in biomedical research, so these might be elements that all states could feasibly implement. This would ensure some degree of national consistency and a standard, baseline level of protection for all U.S. research uses of rDBS.

However, many of the topics identified in this paper, such as evaluation criteria and allowable types of research, would need further discussion and investigation, and these issues might be appropriately addressed using a template form of model policy. For instance, some states with a larger Native American presence might decide that population genetics research is not compatible with local beliefs regarding creation and identity. Each state must be able to address the concerns unique to its constituents, and the creation of a template model policy would allow states to focus on modifying certain elements to meet their needs, rather than on creating a policy from scratch.

By characterizing the current policies for research uses of rDBS, this study could help to start future conversations into the form and content of NBS policies. However, it will be also important to expand on the themes identified in this study as well as to consider what elements might be missing. A strong, comprehensive research policy will better protect the interests of the newborns and their families. Ultimately, a greater level of transparency and trust might be achieved through open discussion and the collaboration required to address this important issue.

CONCLUSION

This thesis contributes to the literature a detailed comparative analysis of information available from consumer-oriented and regulatory sources that describe the current governance policies for the research use of rDBS. It characterizes the research studies that used rDBS during 2010, compares the policies of state NBS programs and neonatal biobanks, and highlights the features of well-developed policies. These results could help to inform future policy creation by suggesting features to be included in a model policy format or template.

APPENDIX A – CITATIONS OF STATE NBS LEGISLATION

State	Newborn Screening Statute [a]	Newborn Screening Public Health Regulation [b]
ALABAMA	Ala. Code § 22-20-3	Ala. Admin. Code 420-10-1
ALASKA	Alaska Stat. § 18-15-200 and 210	Alaska Admin. Code 07§ 27.510 to 590
ARIZONA	Ariz. Rev. Stat. § 36-694	Ariz. Admin. Code § R9-13-201 to 208
ARKANSAS	Ark. Code § 20-15-301 to 304	Ark. Admin. R. § 007.16.07-001
CALIFORNIA	Cal. Health & Safety Code § 124975 to 125001	Cal. Code Regs. 17 § 6500 to 6510
COLORADO	Colo. Rev. Stat. §25-4-1001 to 1006	Colo. Code Regs. 5 § 1005.44
CONNECTICUT	Conn. Gen. Stat. 368a § 19a-55 and § 19a-55a	Conn. Public Health Code § 19a-55-1 to 3
DELAWARE	Del. Code § 16.2.201 to 206	Del. Admin. Code 16 § 4107
DISTRICT OF COLUMBIA	D.C. Code § 7-831 to 840	D.C. Mun. Regs. § 22-B2101
FLORIDA	Fla. Stat. 29 § 383.14	Fla. Admin. Code § 64C-7
GEORGIA	Ga. Code § 31-12-5 to 7	Ga. Comp. R. & Regs. 290-5-24
HAWAII	Hawaii Rev. Stat. § 321-291	Haw. Admin. Rules § 11-143-1 to 100
IDAHO	Idaho Stat. 39-909 to 912	Idaho Admin. Rules § 16.02.12
ILLINOIS	Ill. Comp. Stat. 410, § 240/0.01 to 3	Ill. Admin. Code § 77-661.10 to .70
INDIANA	Ind. Code § 16-41-17	Ind. Admin. Code 410 § 3-3-1–8
IOWA	Iowa Code § 136A.1 to .9	Iowa Admin. Code § 641-4.1 to 4.7
KANSAS	Kan. Stat. § 65-180 to 183	Kan. Admin. Regs. § 28-4-501 to 521
KENTUCKY	Ky. Rev. Stat. § 214.155	Ky. Admin. Regs. 902 § 4:030
LOUISIANA	La. Rev. Stat. § 40:1299	La. Admin. Code 48 §5-63
MAINE	Me. Rev. Stat. 22, § 261A-1531 to 1533	Code Me. Regs. 10-144 § 283
MARYLAND	Md. Health Code § 13-101 to 112	Code Md. Regs. 10.52.12
MASSACHUSSETTS	Mass. Gen. Laws 111 § 3, 4E, 5, 6, 24A, 110A	Code of Mass. Regs. 105 § 270.000
MICHIGAN	Mich. Comp. Laws § 333.5430 to 5431	None
MINNESOTA	Minn. Stat. § 144.125, .1255, .128	Minn. R. § 4615.0300 to .0760
MISSISSIPPI	Miss. Code. § 41-21-201 to 205	Code Miss. R. 15-4-01 § 38
MISSOURI	Mo. Rev. Stat. § 191.331 to 333	Mo. Code Reg. Ann. 19 § 25-36.010
MONTANA	Mont. Code §50-19-201 to 212	Mont. Admin. R. 37.57.301 to 321
NEBRASKA	Neb. Rev. Stat. 71-519 to 524	Neb. Admin. R. & Regs. 181-2 §001 to 010
NEVADA	Nev. Rev. Stat. § 442.008	Nev. Admin. Code § 442.020 to .050
NEW HAMPSHIRE	N.H. Rev. Stat. § 132:10	N.H. Admin. R. He-P3008
NEW JERSEY	N.J. Rev. Stat. § 26:2-110 and 111	N.J. Admin. Code §8:18-1.1 to .14
NEW MEXICO	N.M. Stat. § 24-1-6	N.M. Admin. Code 7 § 30.6.1–.9

State	Newborn Screening Statute [a]	Newborn Screening Public Health Regulation [b]
NEW YORK	N.Y. Public Health Laws § 2500-a	N.Y. Comp. Codes 10 § 69-1.1–1.9
NORTH CAROLINA	N.C. Gen. Stat. § 130A-125	N.C. Admin. Code 10A § 43H.0314
NORTH DAKOTA	N.D. Cent. Code § 23-01-03.1 and § 25-17-00.1 to .05	N.D. Admin. Code § 33-06-16-01 to 05
OHIO	Ohio Rev. Code § 3701.50 to 509	Ohio Admin. Code § 3701- 55-01 to 20
OKLAHOMA	Okla. Stat. § 63-1-533 and 534	Okla. Admin. Code § 310:550
OREGON	Or. Rev. Stat. § 433.285 to .295	Or. Admin. R. § 333-024-0210 to 0235
PENNSYLVANIA	Pa. Consol. Stat. 35 § 621-625	Pa. Code 28 § 28.1–.41
PUERTO RICO	P.R. Laws 24 § 7-135-3151 to 3158	None
RHODE ISLAND	R.I. Gen. Laws § 23-13-14	Code R.I. R. § 23-13 MET/HRG
SOUTH CAROLINA	S.C. Code § 44-37-30	S.C. Code Regs. § 61-80
SOUTH DAKOTA	S.D. Codified Laws § 34-24-17 to 25	Admin. R. S.D. § 44:19
TENNESSEE	Tenn. Code § 68-5-401 to 506	Tenn. Comp. R. & Regs. §1200-15-1-.01 to .06
TEXAS	Tex. Health & Safety Code §33.001 to .038	Tex. Admin. Code 25 § 37.51 to .65 and § 73.21
UTAH	Utah Code § 26-10-6	Utah Admin. Code § 398-1
VERMONT	Vt. Stat. 18, § 115	Code Vt. R. § 13-140-057
VIRGINIA	Va. Code § 32.1-65 to 69	Va. Admin. Code 12 § 5-71 and § 5-191-260
WASHINGTON	Wash. Rev. Code § 70.83.020 to .050	Wash. Admin. Code 246-650
WEST VIRGINIA	W.Va. Code § 16-22-1 to 6	W. Va. R. 64 § 91-1 to 11
WISCONSIN	Wis. Stat. § 253.13	Wis. Admin. Code HFS §115.01 to .06
WYOMING	Wyo. Stat. § 35-4-801 to 802	Wyo. R. & Regs. HLTH 6959-1 to 8

[a] National Conference of State Legislatures. Newborn Genetic and Metabolic Disease Screening. Accessed 1/2011.
[b] Therrell BL, Johnson A, Williams D. Status of newborn screening programs in the United States. *Pediatrics*. 2006;117:S212-S252.

APPENDIX B – COVER LETTER TO SURVEY

March 31, 2011

Elicia Preslan
[Researcher's Address]

[Recipient's Address]

Dear [Recipient's Name]:

My name is Elicia Preslan, and I am a master's student in the human genetics program at the University of Maryland, Baltimore. I am writing to ask you to participate in a research study for my master's thesis.

The purpose of my study is to learn about the research oversight procedures used by each of the United States' newborn screening programs and by two neonatal biobanks. I also want to find out how residual dried blood spots are currently being used in research studies. You were selected for this study because you are listed by the National Newborn Screening and Genetic Resource Center's website as the contact person for newborn screening follow-up in your state or territory, or because you are an administrator for a neonatal biobank. However, if someone else who would be more knowledgeable about how your state or biobank handles research requests for dried blood spots, please forward this survey on to them.

To participate in this study, please complete and return the attached survey. You will be asked questions about the dried blood spots that are currently being stored by your program or biobank, the policies and regulations that govern research uses of dried blood spots, and the research requests that your program or biobank received during 2010. You will also be asked to send me a copy of any internal policy, separate from laws and regulations, that would address how your state or biobank handles research requests for dried blood spots.

The total time for participation in this study will be approximately 25 minutes. The amount of time will vary depending on how accessible the requested information is, if your program allows research, and if your program has a written policy about research uses of dried blood spots. If you choose to participate, you may return the survey form at any time before Monday, April 18, 2011.

Once I have received your completed survey, I will schedule a brief (15-minute) follow-up telephone interview to clarify any answers that I do not completely understand. All interviews will be recorded to ensure accuracy. However, any personal information will be deleted from the transcript, and the recordings will be destroyed at the end of the study.

This study has been designated as a minimal risk study and exempted from review by the University of Maryland Institutional Review Board. I do not think that participation in this study poses any major risk to you, and it will not cost you anything to take part. The main risk to you is the possibility of loss of confidentiality. Your name and contact information are available on publicly-accessible websites, so it might be possible for someone to infer your participation in this study based on references to your state's newborn screening program or to your biobank. For this reason, the survey has been designed to gather factual data about the policies and procedures of your program, and your responses, as a representative of your program, are not anticipated to reveal any sensitive information. This risk will also be minimized by destroying audio recordings and survey forms at the end of the study, and by coding your responses for analysis. Data will be stored in a secure location in a locked office and locked cabinet, and electronic data will be password-protected. The data from the study may be published; however, you will not be identified by name. Everyone using study information will work to keep your personal information and survey responses confidential, and your personal information will not be given out unless required by law.

You will not directly benefit from your participation in this study. However, the results of this project will highlight features of well-developed research oversight models that are currently being used by state newborn screening programs and neonatal biobanks. This information could be beneficial to future policy creation concerning the research uses of residual dried blood spots.

Your participation in this study is voluntary. You do not have to take part in this research, and you do not have to answer any question that you do not want to answer. If you do join and later change your mind, you may quit at any time. Your decision to participate or not participate in this research study will involve no penalty or loss of benefits to which you are otherwise entitled, and will not affect your employment status or any current or future care you receive at University of Maryland, Baltimore, University of Maryland Medical System. If you decide to stop taking part, or if you have any questions or concerns about the study please feel free to contact me at [researcher's email] or [phone number], or my advisor, Dr. Debra Mathews, at [phone number].

I appreciate your time and consideration in completing the survey. It is only with your help that we can provide information about how dried blood spots are currently being used in research and how that research is being governed. You will be receiving a paper copy of this letter and the survey within the next several days, and I will call you in about a week to personally invite you to participate and to answer any questions you might have. Thank you for participating in this study!

Sincerely,

Elicia Preslan
Master's student at the University of Maryland, Baltimore

Enclosures (2): University Statement Concerning Research Risks
Survey form

APPENDIX C – SURVEY

POLICIES FOR THE RESEARCH USE OF DRIED BLOOD SPOTS

In September 2010, the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children (SACHDNC) published a briefing that highlighted the need for states to develop individual policies addressing dried blood spot retention and use. Currently, no international or federal guidelines have been proposed. To contribute to this topic of discussion, I would like to learn more about the research oversight procedures used in each of the state newborn screening programs and by neonatal biobanks. I also want to find out how residual dried blood spots are currently being used in research studies. This information is important because it will help to highlight the features of well-developed models of research oversight.

The survey that follows will ask you questions about the policies that govern the research use of residual dried blood spots in your state newborn screening program or biobank. Your responses are extremely valuable to me. However, if you feel that you do not want to answer a particular question, I will accept your decision.

As part of my background research, I have systematically reviewed and read the statute and administrative code citations relevant to newborn screening in each state, and I have reviewed each program and biobank's website. I am aware that certain states and biobanks have made some of the requested information publicly available. Consequently, I am grateful for your participation since your answers will ensure that I have up-to-date, comparable data.

This form will only allow you to respond in certain, highlighted places. The small, grey text boxes will expand to fit any size of response, but if you decide to change your response to a question that uses check boxes, you will need to uncheck your previous response manually. You may save your work to continue it later by saving this document to your computer. When you are finished with the survey, save or print this file and return it to me. If you have any questions or concerns, please feel free to call me at [phone number], or my advisor, Dr. Debra Mathews, at [phone number].

If you are affiliated with a newborn screening program, please begin with section 1A.
If you are with a neonatal biobank, please begin with section 1B.

Thank you for your participation!

Return completed surveys and state policies by:

Postal mail to Elicia Preslan
[researcher's address]
Email to [researcher's email]
Fax to the UMB Program in Epidemiology and Human Genetics
attn: Elicia Preslan at [fax number]

1A. NEWBORN SCREENING CARDS STORED BY NEWBORN SCREENING PROGRAMS

First, I would like to ask some questions about how many newborn screening cards (Guthrie cards) are being stored and what information is linked to the physical samples. This information is relevant to determining if the dried blood spots are suitable for use in research studies.

1. Approximately how many newborns did your state screen during the year 2010?

2. How many newborn screening samples are routinely collected from each full-term newborn in your state?

- ☐ One blood sample
- ☐ Two blood samples: Are both samples stored together? ☐ Yes ☐ No

3. How long does your state currently allow newborn screening cards to be retained?

4. Approximately how many total newborn screening cards did your state have in storage (at your own facility and in any other locations) as of January 1, 2011?

5. The oldest newborn screening cards currently in storage were collected in what year?

6. How is personal information stored with each newborn screening card?

- ☐ Stored with no personal information (stored anonymously)
- ☐ Stored with coded personal information (de-identified or barcoded)
- ☐ Stored with identifying personal information
- ☐ Other:

7. What identifying personal information, if any, is physically retained in storage with each newborn screening card?

8. Does your program keep electronic records (i.e. records of personal information or screening results)?

- ☐ No, my program does not keep electronic records.
- ☐ Yes: Are those records linked to medical records or to any other databases (such as immunization or birth records)?
  - ☐ No, my program's electronic records are not linked to any other databases.
  - ☐ Yes: Which records or databases?

1B. DRIED BLOOD SPOTS STORED BY NEONATAL BIOBANKS

If you are affiliated with a neonatal biobank, this section contains similar questions to those in section 1A about how your biobank stores newborn screening cards (Guthrie cards) and what information is linked to the physical samples.

1. Is your biobank a "virtual" biobank that stores information but few physical samples?

- ☐ No
- ☐ Yes

2. Does your biobank store samples other than those resulting from newborn screening?

- ☐ No, my biobank stores only newborn screening samples.
- ☐ Yes: What other types of biological materials do you store (e.g. tissue specimens, additional blood samples, etc.)?

3. Approximately how many newborn screening cards, if any, did your biobank receive during the year 2010?

4. Approximately how many total newborn screening cards, if any, did your biobank have in storage as of January 1, 2011?

5. In what year were the oldest newborn screening cards currently in storage collected?

6. When you receive multiple samples from the same individual, are the samples stored together?

- ☐ No, multiple samples from the same person are not stored together.
- ☐ Yes, multiple samples from the same person are stored together.

7. How is personal information stored with each newborn screening card?

- ☐ Stored with no personal information (stored anonymously)
- ☐ Stored with coded personal information (de-identified or barcoded)
- ☐ Stored with identifying personal information
- ☐ Other:

8. What identifying personal information, if any, is physically retained in storage with each newborn screening card?

9. Does your biobank keep electronic records?

- ☐ No, my biobank does not keep electronic records. *(Please go to section 2)*
- ☐ Yes, my biobank does keep electronic records. *(Please answer the next two questions)*

9a. Are your electronic records linked to medical records or to any other databases (such as immunization or birth records)?

☐ No, my biobank's records are not linked to any other databases.

☐ Yes: Which records or databases are linked with yours?

9b. Do your electronic records incorporate additional information beyond what is available from newborn screening (information separate from any database linkages that is systematically added into your records)?

☐ No, my biobank's records do not include additional information.

☐ Yes: From what sources do you incorporate information into your records?

2. RESEARCH OVERSIGHT POLICY

Now, I would like to find out if your state or biobank has a written policy about the research uses of dried blood spots. I am interested in the topics and requirements that are described by the policy, so I would greatly appreciate it if you would send me a copy of the document, if one is available.

Does your newborn screening program or neonatal biobank have an internal, written policy, or a state law or regulation, that governs the research uses of dried blood spots?

☐ My state's laws do not allow any research using dried blood spots. *[Go to next section]*

☐ No, my program or biobank has NEITHER an internal, written policy NOR a relevant state law or regulation. *[Go to next section]*

☐ Yes, my program or biobank has an internal, written policy, AND/OR the policy is defined by state law or regulation. *[Answer questions A and B, then go to section 4]*

A) What is the reference citation of the governing law or regulation?

B) I am sending a copy of the relevant internal policy by:

☐ Postal mail to Elicia Preslan
[researcher's address]

☐ Email to [researcher's email]

☐ Fax to the UMB Program in Epidemiology and Human Genetics
attn: Elicia Preslan at [fax number]

☐ My state's policy is available online at:

3. FACTORS IN POLICY DECISIONS

This question asks about some of the factors previously discussed in scientific articles that were found to be important concerns in newborn screening programs. Please select one answer per row.

1. How much, if at all, did the following factors influence your state's decision not to have a formalized law or policy at this time or not to permit any research using dried blood spots?

	No influence	**Small influence**	**Moderate influence**	**Large influence**	**Very large influence**
Inadequate staffing to support research uses of DBS	☐	☐	☐	☐	☐
Inadequate funding to support research uses of DBS	☐	☐	☐	☐	☐
Possible litigation over appropriate uses of DBS	☐	☐	☐	☐	☐
Risk of greater non-participation in newborn screening	☐	☐	☐	☐	☐
Possible adverse media coverage	☐	☐	☐	☐	☐
Local attitudes that would disapprove of research uses	☐	☐	☐	☐	☐
Research uses of DBS are not an issue at this time	☐	☐	☐	☐	☐
Other factor(s):	☐	☐	☐	☐	☐

4. DESCRIPTION OF EVALUATION PROCESS

If your state allows research or if you represent a neonatal biobank, whether or not you have laws, regulations, or internal policies regarding research uses of dried blood spots, please describe how your state or organization handles research requests. If you have specific laws, regulations or policies that provide the answer, you may write, "see XXX" as appropriate, but please be as specific as possible about who makes decisions, how decisions are made, and what criteria or requirements must be met.

What happens when your program or biobank receives an initial inquiry from a potential researcher about using dried blood spots?

What guidelines, if any, does your program or biobank have about what research requests will be considered (e.g. type of research study, number or type of samples, researcher affiliations, etc.)?

What information must be submitted by the researcher as part of a formal request for dried blood spots?

What are the steps in your program or biobank's evaluation process? To whom is the researcher's request submitted? Specifically what is evaluated at each step in the process?

Does your program or biobank have any obligations that the researcher must comply with in order to receive the dried blood spots (e.g., data access agreements, storage, disposal, etc.)?

5. RESEARCH USING DRIED BLOOD SPOTS

If your state allows research or if you represent a neonatal biobank, I would like to ask some questions about the research requests for dried blood spots that your state or biobank received during 2010.

1. What was the total number of research requests for dried blood spots that your state or biobank received during 2010?

2. How many of those requests were approved, or are currently in the process of being reviewed?

Please fill in the following table with information about each research request for dried blood spots (DBS) that your state or biobank received during 2010. The first line provides an example of how to complete the table. If your state had many requests and more lines are needed, please copy the next page and continue, or if the information is already compiled in a similar table, that can be sent to me instead.

1. What type of institution or corporation (e.g., academic, commercial, state, federal etc.) made the request for dried blood spots (DBS)?
2. Did the institution or corporation request DBS from multiple states or just from your state/biobank?
3. What general type of study was it (e.g., test development, genetic variation, pharmacogenetics, etc.)?
4. How many DBS were requested?
5. Did the researchers request anonymous DBS, coded DBS or DBS with identifying information?
6. Did the researchers request DBS from specific individuals or years, or a random sampling?
7. Was this study approved to receive the requested DBS?

	1. Type of institution or corporation (e.g., academic, commercial, state, federal)?	**2. Multiple states involved?**	**3. General type of study (e.g. test development, genetic variation)?**	**4. How many DBS?**	**5. Requested anonymous, coded or identifiable DBS?**	**6. Requested specific or random DBS?**	**7. Request approved?**
e.g.	academic	☐ Yes ☒ No ☐ Unsure	new test development	25	☒ Anonymous ☐ Coded ☐ Identifiable	☒ Specific ☐ Random	☒ Approved ☐ Not approved ☐ Other decision
1		☐ Yes ☐ No ☐ Unsure			☐ Anonymous ☐ Coded ☐ Identifiable	☐ Specific ☐ Random	☐ Approved ☐ Not approved ☐ Other decision
2		☐ Yes ☐ No ☐ Unsure			☐ Anonymous ☐ Coded ☐ Identifiable	☐ Specific ☐ Random	☐ Approved ☐ Not approved ☐ Other decision

3		☐ Yes ☐ No ☐ Unsure			☐ Anonymous ☐ Coded ☐ Identifiable	☐ Specific ☐ Random	☐ Approved ☐ Not approved ☐ Other decision
4		☐ Yes ☐ No ☐ Unsure			☐ Anonymous ☐ Coded ☐ Identifiable	☐ Specific ☐ Random	☐ Approved ☐ Not approved ☐ Other decision
5		☐ Yes ☐ No ☐ Unsure			☐ Anonymous ☐ Coded ☐ Identifiable	☐ Specific ☐ Random	☐ Approved ☐ Not approved ☐ Other decision
6		☐ Yes ☐ No ☐ Unsure			☐ Anonymous ☐ Coded ☐ Identifiable	☐ Specific ☐ Random	☐ Approved ☐ Not approved ☐ Other decision
7		☐ Yes ☐ No ☐ Unsure			☐ Anonymous ☐ Coded ☐ Identifiable	☐ Specific ☐ Random	☐ Approved ☐ Not approved ☐ Other decision
8		☐ Yes ☐ No ☐ Unsure			☐ Anonymous ☐ Coded ☐ Identifiable	☐ Specific ☐ Random	☐ Approved ☐ Not approved ☐ Other decision
9		☐ Yes ☐ No ☐ Unsure			☐ Anonymous ☐ Coded ☐ Identifiable	☐ Specific ☐ Random	☐ Approved ☐ Not approved ☐ Other decision
10		☐ Yes ☐ No ☐ Unsure			☐ Anonymous ☐ Coded ☐ Identifiable	☐ Specific ☐ Random	☐ Approved ☐ Not approved ☐ Other decision
11		☐ Yes ☐ No ☐ Unsure			☐ Anonymous ☐ Coded ☐ Identifiable	☐ Specific ☐ Random	☐ Approved ☐ Not approved ☐ Other decision
12		☐ Yes ☐ No ☐ Unsure			☐ Anonymous ☐ Coded ☐ Identifiable	☐ Specific ☐ Random	☐ Approved ☐ Not approved ☐ Other decision
13		☐ Yes ☐ No ☐ Unsure			☐ Anonymous ☐ Coded ☐ Identifiable	☐ Specific ☐ Random	☐ Approved ☐ Not approved ☐ Other decision
14		☐ Yes ☐ No ☐ Unsure			☐ Anonymous ☐ Coded ☐ Identifiable	☐ Specific ☐ Random	☐ Approved ☐ Not approved ☐ Other decision
15		☐ Yes ☐ No ☐ Unsure			☐ Anonymous ☐ Coded ☐ Identifiable	☐ Specific ☐ Random	☐ Approved ☐ Not approved ☐ Other decision
16		☐ Yes ☐ No ☐ Unsure			☐ Anonymous ☐ Coded ☐ Identifiable	☐ Specific ☐ Random	☐ Approved ☐ Not approved ☐ Other decision
17		☐ Yes ☐ No ☐ Unsure			☐ Anonymous ☐ Coded ☐ Identifiable	☐ Specific ☐ Random	☐ Approved ☐ Not approved ☐ Other decision
18		☐ Yes ☐ No ☐ Unsure			☐ Anonymous ☐ Coded ☐ Identifiable	☐ Specific ☐ Random	☐ Approved ☐ Not approved ☐ Other decision
19		☐ Yes ☐ No ☐ Unsure			☐ Anonymous ☐ Coded ☐ Identifiable	☐ Specific ☐ Random	☐ Approved ☐ Not approved ☐ Other decision

ADDITIONAL COMMENTS

Please share any additional comments your may have about research oversight and the use of dried blood spots.

PERSONAL INFORMATION

The following spaces ask for your name and contact information so that I can get in touch with you to schedule a brief (15-minute) follow-up interview by phone to clarify any answers that I do not completely understand. There is no obligation to provide this information, though I assure you that your personal information will be protected and used for follow-up purposes only.

<table>
<tr><td colspan="2">First Name:</td><td>Last Name:</td></tr>
<tr><td>State:</td><td colspan="2">Title:</td></tr>
<tr><td colspan="3">Mailing
Address:</td></tr>
<tr><td colspan="2">Telephone:</td><td>Email:</td></tr>
</table>

Would you like to receive a copy of the final thesis before publication?

☐ Yes, please send me a copy of the thesis when it is completed.

☐ No, do not send me a copy of the thesis.

Thank you for taking the time to fill out this survey. Your input is greatly appreciated!

***Please save or print your work** and return your completed survey, along with any requested policies or documents, using one of the methods listed on the first page.*

APPENDIX D – CODEBOOK

1. **<u>Retention and/or use of rDBS</u>:** Broad category for any information related to retention, storage, disposal, rDBS use (research and non-research), etc.
    a. <u>Other rDBS uses</u>: Non-research purposes of using rDBS (Note: Lewis [a] included research use in a similar category of "Purpose for which DBS may be used")
    b. <u>Form in which rDBS may be released</u>: Whether rDBS are anonymous, coded, identified, etc.
    c. <u>Information provided to parents</u>: Information educating parents about retention, use, disposal, etc.
        i. <u>Expected information about retention</u>: The regulatory requirements about notifying parents on retention and/or use of rDBS
        ii. <u>Observed information about retention</u>: Information actually provided to parents in brochures and websites about retention and/or use of rDBS
        iii. <u>Expected information about research</u>: The regulatory requirements about notifying parents on research uses of rDBS
        iv. <u>Observed information about research</u>: Information actually provided to parents in brochures and websites about research uses of rDBS
2. **<u>Research use of rDBS</u>:** Broad category for any information related to the research use of rDBS
    a. <u>Research reviewer</u>: The entity/committee/person that reviews research proposals
    b. <u>Research type</u>: The kinds of research that are permitted or not permitted
    c. <u>Evaluation criteria</u>: What factors should be considered when evaluating research proposals
    d. <u>Researcher agreements</u>: Agreements made by researcher in order to receive DBS, including fees the state may charge for the use of DBS
    e. <u>Laboratory responsibilities</u>: The releasing laboratory/department's research-related duties
    f. <u>State control of rDBS</u>: State/departmental authority over retention, disposal, use of rDBS, including whether research is allowed and use of DBS without consent
        i. <u>rDBS are state property</u>: rDBS clearly defined as property of the state
        ii. <u>Research not allowed</u>: Research using rDBS is not allowed
        iii. <u>Research allowed</u>: rDBS may be used for research
    g. <u>Parental control of rDBS</u>: Consent or dissent to DBS use, destruction of DBS
3. **<u>Use of information related to NBS</u>:** Broad category for any reference to the use of information derived from NBS, including case registries (Note: In a personal communication, Lewis [a] defined this category to be the research use of NBS info)
    a. <u>Confidentiality</u>: Confidentiality of NBS information
    b. <u>Purpose for releasing NBS information</u>: The reason for which NBS information may be used
    c. <u>Entities receiving NBS information</u>: The person(s) to whom NBS information may be released
    d. <u>Statistical data</u>: Statistical data are not considered confidential and may be released without consent

[a] Lewis MH, Goldenberg A, Anderson R, Rothwell E, Botkin J. State laws regarding the retention and use of residual newborn screening blood samples. *Pediatrics*. 2011;127:703-712.

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