Providing Newborn Screening Specimens for Research: Legal Issues Faced by State Health Departments Webinar Series

Abbreviations Key
ANPRM – Advanced Notice of Proposed Rulemaking
CDPH - California Department of Public Health
DBS – Dried blood spots
HHS – U.S. Department of Health and Human Services
IC – informed consent
ISNS – International Society for Neonatal Screening
MDCH – Michigan Department of Community Health
MDH – Minnesota Department of Health
NBS – Newborn screening
NNSGRC - National Newborn Screening and Genetic Resource Center
QA/QI – quality assessment/quality improvement
SACHDNC - Secretary of Health and Human Services’ Advisory Committee on Heritable Disorders in Newborns and Children
TDSHS – Texas Department of State Health Services

Introduction to NBS and residual DBS

NBS is a public health program which enables early identification and treatment of infants with conditions that otherwise would go unrecognized prior to irreversible clinical damage. Pioneered in the 1960s by Dr. Robert Guthrie, NBS consists of collecting blood spots on filter paper from every newborn and sending them to a state laboratory for analysis. NBS is administered by each state and every state requires that all babies be screened. The number of conditions screened varies per state. In 2012, the SACHDNC recommended an NBS panel of 31 core conditions and identified 26 secondary conditions, part of the differential diagnosis of the core conditions, but for which no treatment is available. In 2007, Congress passed the Newborn Screening Saves Lives Act to promote and improve NBS for heritable disorders, develop population research surveillance and epidemiology, and expand research partnerships. The Newborn Screening Translational Research Network (NBSTRN) came out of this law, and our mission is to improve the health outcomes of newborns with genetic or congenital disorders by means of an infrastructure that allows investigators access to robust resource for newborn screening research. NBS is a successful program consisting of an entire system with pre-analytic, analytic (including QA/QI) and post-analytic (including follow-up) components. The primary reason for collecting DBS is for NBS. Residual DBS are the samples that remain after NBS is completed.

Secondary use of DBS

Different states retain DBS specimens for a variety of reasons, including the confirmatory diagnosis of NBS analytical results, legal accountability, QA/QI, public health needs, development and evaluation of new testing methods, epidemiological
or other public health surveys, special health-related studies for patients and families, study of medical genetics, postmortem diagnosis of genetic conditions, identification of deceased persons, and research. Among the secondary uses of DBS, the webinars specifically address the development and validation of first-tier tests, the usefulness of second-tier testing, metabolic autopsy, and research.

Public health will be served by the expansion of NBS programs to new conditions. Using residual DBS in the development and validation of new first-tier tests is the most efficient way to do this. Candidate conditions for an expanded NBS panel include X-linked adrenoleukodystrophy, lysosomal storage disorders, Duchenne muscular dystrophy, Fragile X, Pompe disease, Smith Lemli Opitz, spinal muscular atrophy and others. Test development and validation are different from research purposes, and represent the primary reason for long-term storage. Clinical validation could take decades without the collaborative, IRB-approved, informed access to historical specimens.

The use of residual DBS constitutes a cost-effective approach to second-tier testing, as it does not require additional patient contact and as a normal result for a second-tier test overrules the result of the primary screen. As such, residual DBS have been used to implement tandem mass spectrometry (MS/MS)-based second-tier tests and thereby reduce the NBS false positive rate for a variety of tests. On a national level, NBS second-tier tests for just three tests – congenital adrenal hyperplasia, maple syrup urine disease and propionylcarnitine/methionine – could reduce annual health care cost by approximately $90 million, for the 4.5 million babies born each year in the United States. These numbers do not factor in the financial and emotional costs incurred by families when they learn about their babies’ abnormal NBS results.

Several clinical cases illustrate the utility of residual DBS for metabolic autopsy. One of them, a California baby who was believed to have died of pneumonitis and otitis media, was properly diagnosed with LCHAD ten years later thanks to California’s law requiring the retention of DBS, as retrospective identification of metabolites is feasible on cards older than a decade. In another state, on the other hand, Maria Crandall died at 15 months from a likely undiagnosed/unscreened fatty acid oxidation disorder, for which definite postmortem diagnosis was not possible due to the absence of a specimen; her NBS card had been discarded. Finally the tragic case of Patricia Stallings proves the point. She was sent to jail for poisoning her infant son, when in fact he had died of methylmalonic acidemia (MMA), which could have been diagnosed if the child’s NBS card been stored.

When states use residual DBS for research, they need to keep that aim distinct from the primary goal of NBS programs. The research priorities should focus on advancing NBS activities, including knowledge of diseases and diagnosis and treatment in newborns and infants. Parents of newborns need to know their rights and to have a choice about participating in research because the NBS program is based upon public trust.

Legal and regulatory issues
For almost 50 years, residual DBS have been used for secondary purposes without major problems. However in the past decade, issues of confidentiality, privacy, control, consent, ownership, governance, and distrust of government have arisen. A variety of causes, such as the heterogeneity of state laws, advent of state genetics laws, lack of federal legislation, inadequate public education, and misleading coverage in the media, has led to state lawsuits and threats to the existence of NBS programs. In addition, many statutes related to NBS programs written decades ago lack the necessary express authority for each component of their programs.

**No national laws** comprehensively govern NBS programs; rather there are only the SACHDNC recommendations mentioned above. State-based policies govern the testing conditions, financing, facilities, confidentiality, return of results, re-contact of parents, retention and use of residual DBS. In addition, few states have addressed these issues in a comprehensive manner. In 2011, the National Coordinating Center for the Regional Genetics and NBS Service Collaboratives (NCCRGNSC) conducted a survey showing that a majority of states have policies on the retention and use of residual DBS, covering ownership and parental control of specimens.

States hold the DBS and the NBS data, and have stewardship over **privacy and confidentiality.** The privacy policies of at least half the states make NBS information confidential. Different states use different measures to protect privacy of residual DBS, such as informed consent, de-identification and anonymization of samples, an honest broker system, and program transparency.

While in most states storage and secondary uses of DBS have occurred without **parental consent,** states such as Michigan and California have developed and implemented consent policies. States with policies on the retention and use of residual samples have various opt-out regimes and parental consent requirements for research. Some specify that an IRB or particular committee must review and approve research studies. Some states allow tested individuals upon reaching the age of 18 or children’s parents to request the destruction of a residual specimen.

As far as **ownership of DBS** is concerned, some states designate residual specimens as property of the state, others have “qualified ownership” of specimens and act as a fiduciary. According to the NCCRGNSC survey, 31 of the 38 states that responded have laws stipulating the individual’s personal property rights to their DNA samples and/or their genetic information. Models discussed in the webinars include charitable trust, open results, and shared ownership.

Several **federal laws,** although not specific to NBS programs, play a role in the retention and use of residual DBS. Research activities conducted on human subjects are covered by federal regulations. A research project can be exempt from federal regulation if it involves existing data or specimens that are publicly available; or if subjects cannot be identified, directly or through identifiers. A federal policy for the protection of human subjects, the “**Common Rule,**” protects
the confidentiality of human subjects involved in research performed with federal funding or by federal institutions.

The federal government is proposing changes to the Common Rule to enhance human research protections and to reduce administrative burden. The changes would require broad, open-ended written consent for research use of biospecimens, including for de-identified or anonymized samples. If these proposed changes come into effect, NBS programs and other public health programs would have to change their practice, as IC would be required every time blood or data are collected even if de-identified. The proposal would also adopt HIPAA-like standards to be applied to all research. This proposal has received mixed responses to date.

A different federal law, the Genetic Information Non-Discrimination Act (GINA), protects individuals from discrimination based on genetic information. GINA prohibits health insurers and employers from using a person’s genetic information.

**De-identified or anonymized samples** like DBS are not traditionally considered human subjects under federal regulations, although the proposed changes to the Common Rule and recent litigation in Minnesota show that this view is changing. Under the Common Rule, all research performed on residual DBS must be approved by an IRB. Because Guthrie cards potentially contain genetic information, they could harm the individual and family members if information was communicated to employers, health insurance companies or other third parties and could lead to discrimination. The Minnesota Supreme Court interpreted DBS to be **human subjects** because of their genetic content for the first time in a state public health legal debate. Thus, DBS are regulated by federal regulations and subject to IRB approval.

**The SACHDNC developed recommendations** to protect individuals’ privacy and allow for important public health uses of residual NBS specimens. These recommendations call for all states and the federal government to establish policies addressing retention, access and disposition of residual DBS. The procedures for secondary uses of DBS should include consent or dissent requirements and privacy protections. At the same time, NBS programs should offer proactive education for parents, health care providers, and the public about NBS and potential uses of residual DBS. Finally, the utility and feasibility of establishing a voluntary national repository of residual DBS should be explored.

**State lawsuits involving ownership and control of residual DBS**

In the lawsuit *Bearder vs. State of Minnesota*, nine families sued the Minnesota NBS program in 2009 for violating their right to privacy and bodily integrity. They feared the use of their specimens and test results by government and private entities for unknown purposes. In November 2011, the Minnesota Supreme Court found that the Minnesota Department of Health (MDH) had violated the Genetic Privacy Act (GPA) of Minnesota and ruled in favor of the plaintiffs. The Supreme Court held that an individual’s blood sample is genetic information subject to
protection under the GPA of Minnesota. The DNA within the sample is the element which requires protection. The Supreme Court also treated NBS test results as genetic information, even though NBS does not test for specific genes but for metabolites. The Court further held that the state practice of retaining DBS and using them for secondary research without explicit parental consent violated the genetic privacy provisions of the State Data Practices Act. As a result of the Supreme Court decision, the use of genetic information for purposes other than NBS and for follow-up services requires informed consent. MDH, which had an opt-out choice for parents before the lawsuit, was faced with having to switch to an opt-in option. Thus, analytical validation of NBS tests in Minnesota was no longer legally possible even with IRB-approved random use of anonymized recent specimens, since MDH did not have express authority to do QA/QI. Furthermore, according to the broad definition of genetic information in the Minnesota Genetic Information Statute, almost all public health data could be interpreted to be genetic information. Thus, the litigation of NBS in Minnesota extends beyond the NBS program to other public health programs.

After this threat to its public health programs, MDH succeeded in having legislation passed in 2012 to temporarily address issues raised in the court case; the legislation required MDH to propose legislation to permanently address the concerns. The Court will study the proposed legislation program-by-program and conclude whether MDH can continue to operate these programs.

A few issues came to light as the Minnesota lawsuit unfolded. First, the plaintiffs did not distinguish between QA and research. Secondly, the plaintiffs did not care that DBS were de-identified and argued that consent was needed regardless. Up to then, the MDH relied on the federal regulation, which stipulates that research conducted on de-identified samples does not necessitate human subject protection. Thirdly, plaintiffs were under the false impression that DBS were being sold to third parties. Finally, plaintiffs argued that they had property rights to their genetic material, although no such precedent existed in Minnesota. To protect their public health programs, state health departments should be aware of these issues. A second insight gained from the Minnesota experience suggests that states should be wary of “genetic exceptionalism” as legislatures feel strongly that “genes” or “DNA” are a special concept.

Another lawsuit, in Texas, is of note. In 2009, families including the Belenos brought a class action lawsuit against the Texas Department of State Health Services (TDSHS) on behalf of all infants born in the state, Beleno vs. Tex. Dept. of State Health Servs. They claimed that the state practice of storage and use of de-identified DBS without explicit parental consent violated their right to privacy, and that samples were stored for the purpose of undisclosed research unrelated to the purposes for which blood was originally collected, without their knowledge or consent. Since DBS contain medical genetic information, plaintiffs were concerned about the potential misuse of DBS and discrimination against their children and relatives. The plaintiffs asked the court to compel the state to disclose the purposes for which the DBS were used and the related financial transactions. They did not object to the state’s NBS program as long as safeguards existed to destroy
an infant’s samples within a reasonable period of time. Parties settled with an agreement including the destruction of 5 million DBS cards and a mandate requiring TDSHS to post on its website a list of all research and QA/QI projects related to DBS use. A law was passed requiring TDSHS to ask for parental consent for the retention and use of DBS for research, and to inform plaintiffs in writing of how their child’s sample was used as well as any financial transactions involving that sample.

The Michigan experience

Michigan created a new system to regulate DBS in 2006, with the goal of making residual DBS widely available for research. The system included the Michigan BioTrust for Health (MBTH), an informed consent policy for research use for new DBS samples (with an opt-out for DBS collected prior to that date), explicit statutory language for residual DBS to be used for research as long as it preserves confidentiality, and a public awareness campaign. The state created an honest broker system that links de-identified DBS and data of the MBTH. The coded de-identified DBS are stored indefinitely for future research at the state-of-the-art Michigan Neonatal Biobank. A Community Values Advisory Board makes recommendations to the MDCH regarding acceptable uses and other policy issues to ensure that the community benefits from the use of DBS.

Combining the data already held by public health departments, such as birth defect registries, WIC, cancer registries, early hearing detection and intervention, and children’s special health care services, with the MBTH data represents a powerful tool to facilitate research. For example, the honest broker within the MDCH could find the exact cohort and provide the matching DBS to a researcher studying a specific population with a particular disorder from a certain geographic locality.

In the process of creating the MBTH, Michigan state laws were analyzed to address issues of ownership and governance of the NBS repository, and the requirement for consent for the storage and use of the residual DBS. It was concluded that the MDCH owns the DBS conditionally, and holds them in trust to benefit individual child’s health and population’s health.

As proven by the Bearder vs. State of Minnesota case, one must consider that biological samples are subject to genetic information laws when establishing the control of DBS. This determines whether consent is necessary for de-identified or anonymized DBS. Michigan requires IC for the storage and use of residual DBS. A six-month IC pilot process showed approximately 70% of the population was consenting to the secondary use of DBS. The MDCH continues to evaluate and improve the IC process. Differences in participation rates are noticed by hospitals and are correlated with the amount of support MDCH had provided the hospitals. MDCH was concerned that the establishment of the MBTH changed the parameters regarding consent, as the collection and storage of DBS would be intended for research in addition to NBS purposes. Studies show that people do not object to specimens obtained for non-research purposes being used for research, but they want to be asked. In the end, the MDCH IRB determined consent should be asked.
The Office of Human Research Protections (OHRP) did consider the MBTH to be research with human subjects and therefore consent, or a waiver, was required. Subjects in the MBTH can discontinue their participation at any time. This also applies to the legacy collection for which a waiver of consent was granted. The IRB for the MBTH requires annual renewal of approval, contingent upon reporting progress in educational efforts to support the consent process. The MDCH set up the Michigan Material Transfer Agreement that addresses intellectual property and sharing of results by requiring researchers to inform the public about research on DBS.

The California experience

In California, the Genetic Disease Screening Program includes NBS and Maternal Serum Screening. The California Health and Safety Code gives authority for the use of residual DBS for anonymous research. It stipulates that DBS become the property of the CDPH after completion of NBS. Parents have an opt-out choice to have their child’s specimen marked not for research or to be destroyed. The department maintains confidentiality of patient information and samples. The information is used only for research on children and women’s diseases. In 2008, new legislation added storage and use of prenatal maternal serum specimens and data to NBS, and updated research regulations on residual DBS and other blood samples, to form the California Perinatal Biobank, which holds the largest number of specimens of any state. This development has enabled a link between statewide data from prenatal screening, birth defects, developmental disabilities and cancer databases.

The New York experience

The New York Public Health law for NBS is very general and minimal, and allows the health commissioner to implement regulations, to screen for phenylketonuria and any other disorders that he/she finds appropriate. The law specifies the responsibilities of everyone involved in the NBS program, from parents to the health care centers providing treatment and laboratories performing the test. In addition, the NYDH dispenses online guidance and educational material for parents, primary physicians and treatment centers.

A Parental Notice on the procedures for the collection, storage and use of the residual DBS is distributed by prenatal and birth medical specialists. At discharge from the hospital, parents receive an explanation that the specimen was collected and its tracking number. They are asked to bring this number to their pediatrician and ask for the test results. Despite these efforts, the vast majority of parents claim to not know whether the NBS has been performed on their babies and not having any information on NBS.

The Parental Notice specifies that the child’s specimen will be stored by the NBS program for up to 27 years under secure conditions and strictly controlled access; that it may be used for diagnostic purposes with parental consent; that a portion of
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the specimen will be anonymized for possible use in public health research that has been approved by a Board in accordance with laws and ethical guidelines. Opting out allows parents to request the destruction of DBS or to prevent their use in public health research.

Information released by the state includes demographic data and NBS test results as an aggregate summary rather than by individual specimen. Parental consent for the use of identified specimens must be obtained for research or for a pilot study of the program.

The state Genetic Confidentiality Statute applies to DBS. This law exempts the NBS program from the consent requirement for genetic testing, as long as specimens are de-identified or anonymized. Another protection is offered by the New York anti-genetic-discrimination law, a more specific law than GINA, including employment, housing and education. New York also has unique laboratory certification requirements, by which the tests must have been validated and approved by the NYHD.

**Professional views on the use of residual DBS**

Professional groups have published statements on residual DBS. The ACMG, for example, recognizes that residual DBS constitute a valuable national resource that can contribute significantly to the health of children. ACMG states that DBS are stored with rigorous control and respect for privacy and confidentiality. It proposes that parents should have the option to store their child’s specimen in a national repository if their state does not retain DBS or does not use DBS for research.

The Genetic Alliance Biobank provides training to researchers and advocacy organizations to set up their own bioregistries in a transparent manner. It improves access to information and resources by using a cooperative or cost sharing model. An IRB approval insuring the provision of informed consent and legal protection is available for member organizations. The Genetic Alliance controls the collections of samples from the donors and their distribution to research organizations. It clarifies governance structures, provides regular research updates to donors, and uses the Bioresource Research Impact Factor (BRIF) to evaluate the usefulness and quality of the bioresource. It also prevents the creation of small and redundant collections of no use.

**Parental, public and media perception (and misconceptions) of retention and research use of residual DBS**

After the passage of the federal 2007 Newborn Screening Saves Lives Act, the media voiced concerns about the creation of warehouses storing newborns’ blood samples and their DNA indefinitely without parental consent. Fear of discrimination emerged from the idea of individual genetic codes and personal health information being owned by the government and communicated to employers and health insurance companies. Concerns persist on a variety of topics such as confidentiality, privacy, potential for discrimination, control, consent, distrust of
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government, and education. However, a number of studies show that generally the public is supportive of NBS, residual DBS retention and use for QA and important research activities. The majority of people believe it is more important to allow notification of parents if important health information is learned than to provide greater privacy protection. Most feel that with confidentiality safeguards, the risk to the baby’s privacy when using DBS for research is very small or non-existent, and almost as many would allow their samples to be used for important health research if they could not be contacted.

Along with privacy concerns, parents want to control what happens to their child’s residual DBS even when samples are de-identified or anonymized. The plaintiffs in the Texas case acknowledged thinking that NBS is good and had they been asked for consent to use their children’s samples for specific medical research, they would probably have agreed. The Bearder attorneys in the Minnesota case made a similar point. The public opinion studies mentioned above showed a clear preference for an informed permission process for parents regarding residual DBS activities, with an opt-in process. Medical professionals report that parents of children with diseases that could not be screened by NBS overwhelmingly support researchers’ access to their children’s specimens in an effort to find a screening test. Parents need clear understandable information about their options.

Conclusion and Future Research

Public health research is a balancing act between providing for the common good and respecting individuals’ rights. Storage and secondary use of DBS contribute to improving patient care and public health, even many years after the primary test, and to ensuring timely implementation of robust new tests. Test development and validation is different from the concept of “research,” and constitues the predominant reason behind the need for long-term storage.

Parents and activists have influenced legislation and their activities have been hurtful to NBS programs in states such as Texas and in Minnesota. These issues are not going away and states should take these concerns seriously. In many instances, parental concerns reflect a lack of understanding. They point to a greater need for transparency and education, particularly in the areas of QA activities, research, and benefits from the use of residual DBS.

Such education could help maintain the public trust in both primary and the secondary use of DBS, and to ensure the longevity of these programs. Media and parents need to understand that the scientific and medical value of these samples far outweigh the risk to individual privacy when appropriate precautions are taken, as proven among states that store samples for the long term (Michigan, California) while consistently maintaining individual privacy through appropriate and ethical safeguards.

Moreover, state health departments need to prioritize stewardship, establish trust, set appropriate expectations, increase dialogue with communities, and demonstrate
the value of research on DBS as a public asset. Likewise, the concept of reciprocity, including the sharing of aggregate results with the community, and the control of research results and commercial products need to be addressed.

National efforts to develop uniform and clear policies and procedures on the use of residual DBS and privacy protection, as well as to educate parents, need to be undertaken. Transparency is paramount to address many of these concerns.

Further questions regarding research on residual DBS include:

- Defining acceptable versus unacceptable research uses
- Distribution of DBS for rare diseases
- Possible amplification to increase amount of DBS material (DNA)
- What happens to DBS after research
- Reporting incidental findings to parents
- Sharing results with the scientific community and the public
- Commercial products and profits resulting from research
- Determining the beneficiaries of research
- Determining the different levels of research reviews beyond the usual IRB