Retention and Research Use of Residual Newborn Screening Bloodspots

abstract

The storage and use of residual newborn screening dried blood specimens has generated significant controversy in the past 5 years, primarily because of public concerns over the lack of parental knowledge and consent for these activities. State policies addressing the management of these specimens vary widely, and there is currently little guidance to aid new state policy development to address the concerns of program professionals, investigators, and the general public. This article offers guidance for state policy based on multiple sources of data, including public attitudes, professional statements, state experience, and an analysis of the ethical, social, legal, and biomedical issues from a multidisciplinary group of scholars. This guidance will be useful for state programs that seek to develop policies that are informed by a contemporary analysis of the key ethical, legal, and social aspects of this practice. This article represents the work of the authors and does not represent American Academy of Pediatrics policy. *Pediatrics* 2013;131:120–127

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KEY WORDS

newborn screening, policy, research, ethics, biobank

ABBREVIATIONS

AAP—American Academy of Pediatrics
DBS—dried bloodspots
IRB—institutional review board
MTA—Material Transfer Agreement
NBS—newborn screening
QA—quality assurance
WG—working group

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Newborn screening (NBS) is conducted on almost all of the 4 million infants born in the United States each year. After the completion of clinical screening, many state programs store the residual bloodspots for various lengths of time. Currently, 20 states have policies that address the retention and use of residual dried bloodspots.¹ Potential uses of these residual dried bloodspots (DBS) fall into 3 categories.² Bloodspots are commonly used for quality assurance (QA) purposes within NBS programs to improve existing tests. QA applications of residual samples have not been controversial. A second use of residual NBS dried blood samples (DBS) is for forensic purposes. Rarely, the residual NBS sample will be the best source of DNA from a child when there is a need to identify remains or for post-mortem examination. The third use of residual bloodspots is biomedical research.

From a research perspective, the primary value of these DBS is that they represent a single repository of specimens from infants across all demographic and geographic segments of a state population. A particular focus of research using DBS has been genetic epidemiology. DNA is stable in DBS for long periods of time, making these specimens particularly useful for genetic research.^{3–6} However, a wide variety of research projects can be conducted with DBS, including infectious disease epidemiology, population-based studies of pharmacologic exposures, etiologic studies of birth defects and developmental disabilities, environmental agent epidemiology, and research related to the introduction of new screening tests.^{7–10}

The ethical concerns with the retention and use of DBS are significant.¹¹ Informed permission of parents for NBS is required by law only in Wyoming and the District of Columbia.² Parents have the ability to refuse NBS in all but 5 states for religious or philosophic reasons, but

parents are not effectively informed of this option.¹² Parents in all states are provided brochures or information sheets about NBS during the peripartum period, but these materials often are intermingled with other educational materials and samples, so parents often do not attend to this information. Furthermore, many brochures do not conform with professional recommendations for content and quality,¹³ nor do they consistently address retention and use of residual DBS. A 2005 survey found that only 11% of the brochures from all state programs addressed the issues of storage and use of residual samples.¹³ A recent study found that only 14 program websites contain any information for parents about the storage and/or use of DBS.¹⁴

The state health departments in Minnesota and Texas were sued in recent years by families who objected to the retention of DBS without parental permission. In Minnesota, the suit successfully claimed that the state genetic privacy law prohibited retention of DBS without explicit consent. The Texas lawsuit alleged that the retention and use of DBS violated constitutional privacy rights. The Texas lawsuit was settled, and 5 million archived DBS were destroyed pursuant to the settlement. The legal issues were never adjudicated.

Despite the interest in DBS for research and the ethical complexities involved, professional organizations have not promulgated a comprehensive set of policy recommendations. The Secretary's Advisory Committee on Heritable Diseases in Newborns and Children published a statement in 2011 that encouraged states to develop policies and procedures to address the retention of NBS samples.¹⁵

The purpose of this article is to provide guidance for states to consider in the development of policies related to the retention and research use of residual

NBS specimens. For the purposes of this discussion, we define “retention” to mean storage beyond that period of time necessary to conduct clinical NBS services.

SOURCES OF SUPPORT FOR THE GUIDANCE

To develop guidance for this complex domain, we drew on multiple resources including (1) recent empirical studies that assessed public or parental attitudes, (2) guidelines or statements from other professional bodies, (3) examples of current state of NBS policies, and (4) an expert working group convened to assess policy issues related to the storage and retention of DBS.

A key source of support for this guidance is our own 4-part project that involved (1) a comprehensive analysis of state NBS laws on the retention of residual NBS specimens,¹ (2) focus groups involving NBS advisory committee members,¹⁶ and interviews with NBS program employees in the Mountain States region, (3) a national survey of public attitudes,^{17,18} and (4) a working group involving national and international experts in NBS.

A working group (WG) was convened in January 2011 in Salt Lake City, Utah, for a 2-day meeting to address state policy issues regarding the storage retention of DBS. There were 43 participants in the WG including experts in NBS, public health, biomedical ethics, research ethics, health law, public policy, pediatrics, and laboratory medicine. Three lay advocates with backgrounds in NBS issues also participated. The meeting consisted of 7 hours of background presentations and discussion by participants followed by 4 hours of breakout group discussion. The breakout groups were titled Utility, Transparency, and Trust following the broad issues identified by the Institute of Medicine Roundtable.¹⁹ Each group was given a set of questions related to

these broader themes addressing specific issues and challenges. The task of each group was to achieve consensus on each question or, alternatively, to articulate majority and minority opinions.

The final 3 hours of the meeting consisted of presentations of group conclusions by the group leaders and a general discussion of the key issues. Because of the range and complexity of the issues, the WG was not organized with the intent to achieve consensus on all issues but to provide guidance to the authors who take responsibility for the conclusions presented here. Neither the project nor the WG were convened under the auspices of the American Academy of Pediatrics (AAP), and the following guidance does not represent AAP policy or guidance.

GUIDANCE

General Considerations

Through this work, we perceive that health departments, NBS program professionals, investigators, and members of the public want clear public policies on the retention and use of DBS.

Conclusions

- States should develop policies and procedures regarding the retention and research use of residual DBS whether specimens are retained for purposes other than clinical services and QA.
- State policies must be consistent with other state legislation and policy regarding research and genetic privacy.

Utility of DBS Retention

This guidance addresses some of the core practice and programmatic questions related to DBS storage and use. The questions that follow correspond to the questions posed to the WG breakout groups. The focus of the questions in this

domain is to evaluate the utility of DBS for various potential uses while addressing ethical concerns.

Question 1: How Long Should Residual Specimens Be Retained for Clinical and QA Purposes?

Background and Support: We identified no professional consensus on how long specimens should be retained for clinical purposes or QA activities. Screening and diagnostic testing is generally complete within a few weeks to months after birth. For a child who is screen negative, the only reason to retain a bloodspot for a longer period of time is the possibility of a false-negative result. False-negative screens in NBS occur, although the lack of long-term surveillance systems can make it difficult to determine their incidence.^{20–22} Indefinite storage of all screen-negative specimens might be useful for QA purposes in anticipation of false-negative cases, although such storage could be a substantial burden to many programs with uncertain benefit. In contrast, true-positive specimens are highly valuable for QA purposes. As new testing platforms or protocols are developed, true-positive specimens can be extremely useful to evaluate test analytic sensitivity and specificity.

Conclusions

- State programs should stipulate the length of time specimens are retained for clinical purposes. A minimum of ~3 months for core services for screen negative specimens is recommended.
- True positive specimens should be saved indefinitely or as long as the target analytes are known to be stable in a stored specimen.

Question 2: Should State Health Departments Retain Residual NBS Specimens for Research Use?

Background and Support: As noted, there is wide variety of state policies

with respect to whether residual specimens are retained.¹ The retention of DBS for reasons other than to maintain high-quality clinical services is beyond the core missions of most programs. However, residual NBS specimens are an extraordinarily valuable resource for the conduct of research that has provided significant benefits to children, pregnant women, and the general public's health, and will continue to do so with proper management. Data from our focus groups and surveys and the work of others show that the public is supportive of specimen retention and research use with appropriate safeguards.^{17,18,23} These data confirm the findings of previous studies on public perspectives regarding bloodspot use.²⁴ States that choose not to retain specimens will lose opportunities to address state-level concerns over infectious agents, environmental exposures, and population genetics.

Conclusions

- We strongly encourage states to consider the retention of residual NBS specimens and to make retained specimens available to qualified investigators, consistent with the guidance to follow.
- State partnerships with academic or other not-for-profit research institutions should be considered to enhance the feasibility of retention and the utility of the specimens.

Question 3: Should Residual Specimens Be Retained With or Without Individual Identifiers?

Background and Support: Deidentification of specimens is a useful strategy to reduce the risk of adverse consequences from research, although there have been no reported cases of harm from breaches in privacy or confidentiality from use of stored DBS. Current federal regulations do not

consider research with deidentified tissue specimens to be human subjects research, and such projects can be conducted without institutional review board (IRB) oversight. Many potential research projects using DBS can be conducted with deidentified samples. However, in rare circumstances, it may be appropriate to return research results to families.²⁵ In addition, deidentifying specimens in a repository makes it impossible to withdraw specimens at the request of parents. The majority of respondents in our survey preferred to enable return of a significant clinical result to families rather than enhance privacy protections through anonymization of specimens.¹⁷

Conclusions

- Residual specimens should be retained in a linked or coded fashion that permits the identity of the source individual to be determined.
- Research should be conducted with deidentified specimens unless specific approval is obtained from an IRB for use of identifiable specimens.

Question 4: How Long Should Residual Specimens Be Retained for Research Use?

Background and Support: Many current NBS tests target products of intermediary metabolism. Research is currently inadequate to determine the stability of these analytes over years or decades under different storage conditions.²⁶ However, DNA is stable over many years, as are other potential targets of testing such as heavy metals and some environmental toxins.⁹ Infectious agents are likely to be detectable over many years because of stable DNA or RNA strands.²⁷ Therefore, specimens may be useful for research purposes for decades. There are 2 considerations that limit storage time. Storage expense and space will limit reasonable storage time for most programs, particularly if

specimens are refrigerated. Second, storage into the adult years of the bloodspot source raises the question of whether the consent of the now adult should be obtained.¹⁵ Finding and contacting large numbers of individuals after 18 to 21 years would not be feasible even if identifiers are retained, but systems should be responsive to individuals who contact the state with a request to have their DBS destroyed.

Conclusions

- Specimens should be retained until the legal age of adulthood in the state, resources permitting.
- If specimens are retained into the adult years of the source individuals, an opt-out mechanism should be in place for the source individuals.

Question 5: Should Specimens Be Made Available for Research by Commercial Entities and Out-of-State Partners?

Background and Support: Our survey found that the public has moderate trust in academic institutions and somewhat less trust in commercial companies to use the specimens in an ethical manner.¹⁷ However, commercial partners are essential in bringing health care products to market. An ethical concern with access by commercial research organizations can be the use of public resources for narrow proprietary interests. Nevertheless, projects with a variety of partners can be acceptable under appropriate agreements and IRB oversight, consistent with the guidance to follow. With respect to out-of-state partners, the National Institutes of Health has funded a Newborn Screening Translational Research Network to foster multistate collaboration on NBS research. One initiative by the network is a virtual repository of DBS from participating states that entails sharing of DBS with investigators nationally.²⁸ This type of national platform with access to

large numbers of DBS will be essential in addressing screening issues for rare conditions for which it may be difficult to obtain sufficient numbers of samples from any single state.

Conclusions

- States should require that research using public resources be published in the public domain. Communication of research results should not be restricted on the basis of the proprietary interests of commercial or private partners.
- Given the rare nature of many NBS conditions, sharing of specimens across state lines should be anticipated and acceptable with appropriate agreements and safeguards.

Transparency With Parents and the Public

This guidance addresses transparency among public health programs, parents of newborns, and the general public. As noted, controversies over the retention and use of residual DBS have arisen largely based on claims of lack of public transparency. Our survey respondents and WG participants strongly support parent and public education and notification regarding these practices.

Question 6: How Should Parents Be Involved in Decision-Making About the Retention and Research Use of Their Child's Sample?

Background and Support: There was strong consensus in the public survey, the WG, and other literature that parents should be offered choice over whether their newborn's specimen would be retained for purposes beyond the clinical analysis and associated QA activities. Choice can be provided through an "opt-in" approach that would consist of an informed choice documented with a signed consent document. Alternatively, an "opt-out" approach could be used that informs parents about the

retention of the samples and affords them the opportunity to refuse but does not require explicit, written consent.

The opt-in and opt-out approaches each have strengths and weaknesses. The major advantage of the opt-in approach is that it requires an interaction with parents to obtain a signature and therefore enhances the possibility that parents would make an informed choice. However, opting-in requires substantially more effort by staff and, given the hectic environment of the newborn nursery, a large portion of the specimens would not be retained simply because parents are not approached for permission.²⁹ Furthermore, signatures can become perfunctory in this environment, undermining the primary value of the opt-in approach.

Opting-out has the primary advantage of offering choice with an ease of administration. Opt-out approaches typically have high levels of participation because it takes initiative from the parents to withdraw their newborn's specimen. The primary weakness of the opt-out approach is that it can undermine efforts to ensure that parents are adequately informed about the issues and their choice.

Our public survey indicated that the general public prefers the opt-in approach. This is consistent with some other surveys and recommendations regarding bloodspot use and biobanking generally.^{23,30–32} Nevertheless, we argue that an opt-out approach can be ethically justified in this context provided that certain criteria are met. These include ensuring that (1) parents are informed about the retention and use of residual samples in a meaningful way that permits an informed decision, (2) parents understand that they have the option to refuse, and (3) the ability to opt-out entails a process that is not unduly burdensome. If parents are adequately educated about DBS policy and their options, then we believe it makes

little difference from an ethical perspective whether the approach is opt-in or opt-out. Furthermore, the risks to infants and parents through residual sample retention and research use is extremely low with no reported cases of misuse or harm over the past 3 decades. Therefore, it is not clear that the permission process plays any significant role in protecting children or families from harm.

Conclusions

- Either an opt-in or an opt-out approach for enabling parental choice can be ethically acceptable. In either case, parental education and public transparency are central to the ethical conduct of the program and must be effectively implemented to justify DBS retention and research use.

Question 7: What Information Should Be Provided to Parents, and When Should It Be Provided?

Background and Support: Research has been conducted by Davis et al³³ to determine what parents want to know about NBS generally. Their results indicate that most parents want a simple explanation of key aspects of the program.³⁴ Similar work has yet to be done with respect to what parents want to know about the retention and use of residual DBS.

There is a growing consensus that the best timing for parental education about NBS is during the prenatal period.^{18,35} Our focus groups strongly advocated education about NBS and DBS retention during the prenatal period when new parents have more time to receive and review the information. This is consistent with the recommendations of professional and advocacy groups including the AAP, the American College of Obstetrics and Gynecology, the Secretary's Advisory Committee on Heritable Diseases in

Newborns and Children, the Institute of Medicine Roundtable, the New York State Task Force for Life and the Law, and the Genetic Alliance.^{2,15,35–38} Although conceptually attractive, prenatal education about NBS raises a number of challenges including the development of effective educational tools, professional education, and professional time constraints.

Conclusions

- Professionals and programs should work toward a goal of providing information about the retention and use of residual DBS in both the prenatal and postnatal periods.
- Information for parents should be simple with an emphasis on key points regarding state policy.
- Parents should be informed about their choice regarding DBS retention and how that choice can be exercised.
- Information should be made readily available to the general public regarding state policy through the department of health website.

Trust in Public Health Programs

Public trust will be earned and maintained through transparency and through procedural mechanisms that ensure the specimens are managed in safe and appropriate ways. This section addresses procedural mechanisms that states might use to manage residual DBS.

Question 8: What Privacy and Confidentiality Protections Should Be in Place?

Background and Support: The public is concerned about genetic privacy issues and there has been debate about whether biospecimens can be deidentified given the unique nature of individual DNA sequences.³⁹ As outlined earlier, we recommend that DBS be retained with links to identifiers,

although most common research uses will be with specimens that are deidentified to the investigator. Some states double code DBS to limit the risk of reidentification of specimens without the appropriate authorization.⁴⁰ In this way, only the state program would retain links to identifying information.

An important question is whether access to the specimens should be permitted for non-health-related purposes. A specific issue is whether DBS should be accessible to the criminal justice system. DBS on a large segment of the population over time could be an extremely valuable resource for identifying potential perpetrators when biological materials are left at a crime scene. Despite the potential value of this use, access by criminal justice system would be a serious concern for many individuals in the general population and might threaten the efficacy of the NBS program through suspicion and distrust.

Conclusions

- State policies should have robust systems to protect the privacy and confidentiality of source individuals for residual DBS. Information about these systems should be clearly communicated to the public.
- We discourage policies that permit ready access to DBS by the justice system. Any access should be permitted only with appropriate authorization and under carefully considered protections for privacy and other legal rights.

Question 9: What Should the Approval and Oversight Process Be for Research Within the Health Departments?

Background and Support: The oversight process for access to DBS should address 3 issues: (1) human subjects protections, (2) scientific validity, and (3) public transparency. With respect to

human subject protections, a health department IRB should have oversight responsibility for the creation and function of the repository as a research resource and for all projects using DBS. The federal regulations do not require IRB oversight for projects that use deidentified biospecimens, although IRBs have the prerogative to develop more stringent policies than the regulations require. Given the potential sensitivity of research in this domain, we recommend that all projects undergo IRB review and approval. In addition, the federal regulations do not adequately address potential harms or wrongs to racial or ethnic groups that may occur through the use of specimens that are individually deidentified but retain demographic information that associate them with racial or ethnic groups.⁴¹ IRBs should be alert to potential group harms or wrongs in this context.

Given the limited nature of DBS, research use should be restricted to projects with a high level of scientific value and validity. The IRB or public health professionals may lack the necessary expertise to judge all proposals on scientific merit. Accordingly, a scientific review panel should be used to review protocols.^{42,43}

The third issue is public transparency. The oversight process and approval process for research access to DBS should have substantial and meaningful public participation to meet the dual goals of ensuring that community values and perspectives are considered and making clear that research is being conducted “in the light of day.” These issues are particularly important given the finding by Rothwell et al¹⁶ that state NBS advisory committee members in the Mountain States region did not consider themselves to be adequately representative of their lay communities. In addition to transparency about research access and oversight, states

should also consider providing the public with information regarding research projects using DBS. This practice has already been implemented in Texas and Minnesota.^{43,44}

Conclusions

- All research seeking access to DBS should be reviewed and monitored by an IRB whether the proposed projects meet the definition of human subjects research or meet criteria for an IRB exemption.
- IRBs should address, when appropriate, potential group harms or wrongs that may occur from DBS research.
- Because DBS are a limited resource, scientific review panels should be convened to assess the scientific merit of research proposals.
- States should develop mechanisms to ensure public engagement in the oversight of research with DBS.
- States should consider posting information about research projects using DBS on a publically available website.

Question 10: What Are the Obligations of the Health Department After the Transfer of Samples to Investigators?

Background and Support: Specimens will be transferred to investigators for research use under an approved IRB protocol. Research protocols rarely address potential secondary uses of specimens or the fate of the specimens after the research has ended. Academic institutions often enter a Material Transfer Agreement (MTA) between specimen sources and recipients to address these issues.

Conclusions

- States should develop and implement a MTA between the state and the recipient research organization when transferring DBS.

- MTA's should address, at a minimum, the following:
- destruction or return of specimens upon completion of the research,
- prohibitions on secondary transfer of DBS without state authorization,
- prohibitions on secondary research on DBS without state authorization,
- data sharing back to the state program,
- intellectual property rights,
- publication requirements, and
- acknowledgment of state resource use in publications.

DISCUSSION

Residual DBS represent a valuable resource for promoting the welfare of children and their families. However, as demonstrated in Texas and Minnesota, the lack of adequate public transparency and parental choice can lead to controversy, legal challenges, and the loss of these valuable resources. Research on public attitudes on these issues demonstrates that the public is supportive of retention and research use under appropriate safeguards and with an element of parental choice. States may continue to vary widely on their policies in this domain, but in all

cases, a formal public policy to address these issues will maximize their utility and the public's trust.

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