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Guidelines for the Retention, Storage, and Use of Residual Dried Blood Spot Samples after Newborn Screening Analysis: Statement of the Council of Regional Networks for Genetic Services

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The Council of Regional Networks for Genetic Services (CORN) was created in 1985 to provide a forum for information exchange between groups concerned with public health and genetic services. The CORN Newborn Screening Committee includes representatives that are divided among laboratorians and administrators from each of the council's regions of the United States, and liaison members from associated federal agencies and professional groups. State and regional newborn screening programs across the United States vary widely in their approaches and policies concerning the retention, storage, release, and use of residual dried blood-spot (DBS) samples collected for newborn screening. Recognition of the epidemiologic utility of DBS samples for HIV seroprevalence surveys and the growing interest in DBSs for DNA analysis has intensified issues regarding the retention, storage, and use of residual DBS samples to prominent concern in almost all screening programs. Residual DBSs have become a valuable sample resource as scientists, administrators, and judiciary officials have recognized. Potentially these samples could provide a genetic bank for all newborns nationwide. The guidelines in this document are not intended to dictate policy or to be all inclusive but rather should be used to provide scientific guidance for developing policy to address these important DBS issues.

Background

The Council of Regional Networks for Genetic Services (CORN) is a federally funded project to improve the quantity, quality, and availability of cost-effective genetic services in the United States. CORN was developed in 1985 in response to the need for an organization that could coordinate activities among federally funded genetic service networks encompassing the entire United States and could implement programs of national significance that emerge from regional initiatives in priority areas such as quality assurance, data collection, and education. Two delegates from each defined network serve on the CORN steering committee with additional representation from the Alliance for Genetic Support Groups, national sickle cell disease programs, and certain other organizations involved in genetic services. CORN members constitute a unique organization of genetic service providers, public health personnel, and consumers. In its goals and activities, the organization focuses on the public health components of genetic services.

The Newborn Screening Committee of CORN was formed in 1987 to address national and regional issues about newborn screening. One goal of the committee is to provide guidance and resolve universal problems and concerns that affect the public health community conducting newborn screening programs. Previously, the committee developed guidelines for newborn screening systems [1]. The guidelines presented here are intended to help newborn screening programs make decisions about developing protocols and justifications for length of retention for residual dried blood spots (DBSs) once the newborn screening process has been completed. These guidelines provide specific information about 1) duration and conditions of storage, 2) elements associated with sample release and use, and 3) concerns with the potential DNA banking of samples. In all cases, newborn screening programs should have written procedures for storing, releasing, and using residual samples.

Introduction

Currently most states destroy all residual DBS samples within a year after the newborn screening analytical process has been completed. However, some states save all residual DBSs for numerous years and justify this extended retention on the basis of public health needs and concerns, but acknowledging that the courts could subpoena these samples for forensic or other legal purposes (e.g. analysis of residual sample for evidence in a law suit for failure to detect a specific

disorder). A widely disseminated belief is that saved samples can have only a negative impact on a program's legal liability. Saving residual DBSs should be justified and related protocols developed using scientific reasoning and all available information. The decision not to save the DBSs beyond a certain time should be carefully weighed against all information. The program's advisors (see Sec. 1.3 in ref. 1) should participate in any decisions and policy developments concerning residual DBSs.

Decisions concerning the length of retention of residual DBSs should be made on the basis of the stability of the analytes of interest, the potential use of the DBS samples, and technical issues concerning proper storage and ease of retrieval. An extensive search of the literature concerning stability of analytes in DBSs was performed, but was of minimal value in making decisions about long-term storage. Table 1 gives a review of the most recent or the most comprehensive published data for stability of newborn screening analytes in DBSs. These stability studies were performed using a variety of procedures and conditions, and most did not result in meaningful conclusions about long-term storage outcomes. The storage studies were performed over relatively short periods and provided sufficient data relevant only to the testing environment for identifying disorders among newborns. Interpretation of stability data was inconsistent and included evaluations based on analyte concentration either for disease classification or for recovery level. Elution schemes for DBSs were usually carried out for fixed time intervals; therefore, samples that eluted slowly could be misinterpreted as sample instability. Analytical reference points for assessing stability were often weak. The general conclusion from these published studies was that data are not available for predicting stability outcomes from long-term storage of DBSs and that, for maximum stability for most analytes, DBSs should be stored at low temperature and controlled low humidity.

Table 1. Stability of Analytes in Dried Blood on Filter Paper Stability[a] (months)

Analyte	-20°C	4°C	Ambient	Reference
Apo A-I	43d	1d(25d)	1d	3(4)
Apo B	7d	3d,(1)	3d	5(4)
ß-globin DNA	-	-	1yr	6
Biotinidase	-	-	<2d	7
Galactose	-	1.5	1wk	8
Galactose-1-phosphate	-	2	1wk	8
G-1-P uridyl transferase	-	-	<15d	9
Hemoglobins - F,A,S,C	3	-	-(1)	10(11)
Hepatitis B antigen	6	6	6	12
HIV-1 antibodies	6[b],(5)	6[b],(5)	2[b],(1,5)	13(14)
HIV proviral DNA	3.5[b]	-	3.5	15
Leucine	5	5	2wk	16
Methionine	5	5	5	16
Phenylalanine	(2yr[b])	5	5	16(17)
17a-hydroxy-progesterone	-	7[b]	7	18
Thyrotropin(TSH)	11,(1yr[b])	1,(1yr[b]	1	19(20)
Thyroxine(T_4)	-	5,(1yr[b])	5	21(20)

[a]Maximum stability may be greater than indicated but is limited to length of experiment.
[b]Desiccated conditions.

Advances in techniques for obtaining DNA from DBSs and in applying the polymerase chain reaction (PCR) technology have provided an analytical mechanism for generating numerous genetic tests from a single DBS. Scientific and forensic concerns have accelerated interest in the potential use of existing DBS sources for these genetic studies. Whole blood absorbed into filter paper and then dried offers an excellent means for creating a repository (bank) of samples for DNA investigations. Such a system is already finding a use in storing biological "dog tags" for military personnel [2]. Some researchers and public officials are considering mechanisms to require the retention of DBSs by newborn screening

laboratories as a foundation for DNA banks. Many issues have arisen surrounding the need for banking: the potential public health value; intended use; appropriate release of samples; personal privacy issues; and other ethical, moral, social, and legal concerns. The value of national DNA banks for all newborns has been debated in many scientific discussions. The impact of decisions from vested interest groups on the newborn screening systems is unclear and the final decision will probably be made with little consultation from newborn screening programs.

Scientific Issues

1.1 Retention of samples

How long are DBSs currently retained by screening programs? Among the state newborn screening programs, the length of time for storage of residual samples varies: 10 programs save samples for 21 years or more; 6 programs, for >5 to 7 years; 2 programs, for >1 to 3 years; 6 programs, for >6 to 12 months; 21 programs, for >1 to 6 months; 5 programs, for 1 to 4 week; and for 3 programs retention information is not available [22]. Only one program is known to save residual samples at low temperature (-20 ^{0}C) in sealed bags containing a desiccant. A few states have retained in excess of a million residual samples. Some states have indicated that saved residual DBSs may become a permanent collection. The cost estimates for low-temperature storage or any other storage systems have not been reported. In addition, no information is available on the myriad of storage systems used by the various programs.

Why save DBSs after newborn screening is complete? Clinical laboratories do not usually retain residual serum or blood samples after the results have been reported for the test for which the samples were originally collected. If questions arise regarding test results, fresh samples are collected to ensure integrity of the sample, and the analysis is repeated. Analogous to some newborn screening programs, pathology laboratories do retain autopsy samples for some extended periods. When a sample is retained, it should be stored carefully and appropriately for an intended purpose. The duration of storage should meet the defined purpose.

Some reasons for retaining residual DBSs include: legal accountability (e.g., number of punches taken for analysis, the existence of a sample and its adequate collection), future DNA testing, reconfirmation of analytical results, method evaluations and comparisons, epidemiologic or other public health surveys, special studies for families,
and forensic studies.

Some reasons for discarding residual DBSs include: lack or uncertainty of analyte stability, high storage cost, unavailability of suitable storage space, no defined justification for future use, no mechanism for easy retrieval, no quality assurance system to ensure integrity of stored samples, lack of informed consent, and the failure to contribute positively to legal liabilities.

Why retain residual DBSs for possible DNA testing? A policy of retaining samples for possible DNA analysis is questionable because of the expense and the unknown demand for use of the samples. Locating the required DBS within a storage facility containing millions of samples will be a problem if procedures for doing so are not planned in advance. Ownership of the DNA in a residual DBS is an issue, especially given the current informed consent by a nondissent system used by most programs. Without informed consent about specific sample use, a problem arises regarding DNA ownership and use, and this problem may arise even if informed consent is practiced. Saving DBSs for use in the identification of a person may infringe on the rights of the individual (see Sec. 2.3).

What are the concerns when using residual DBSs in method studies and evaluations? For validating new methods or for comparing methods, studies usually require fresh samples of a collection age closely approximating the age of samples intended for use in the proposed method. Compromised or potentially compromised samples from uncontrolled storage should not be used for method evaluations or comparisons.

What is the appropriate means for disposing of residual DBSs? When the length of storage specified by the program's policy on use and storage of residual DBSs is reached, the samples should be incinerated. If samples must be transported off-site for incineration, precautions should be taken to assure that confidentiality of samples during transportation and

destruction is maintained, and that appropriate disposal of samples was achieved (i.e., no identifying information should be attached). The program's specified length of retention for DBSs should be consistently met. All the information about disposal of residual samples should be documented.

1.2 Storage of samples

Usage of retained DBSs bears directly on the concern and care applied to their storage. If a newborn screening program makes the decision to store residual DBSs for long intervals, a scientifically sound and justifiable approach should be taken and carefully planned. A storage policy should be developed. Advice and consultation should be obtained from programs experienced in long-term storage of DBSs and from other organizations maintaining sample banks [e.g., the military, Centers for Disease Control and Prevention (CDC)]. Making a flow chart of the process and using barcodes or other electronic media identification should be considered in the cataloguing process. Systems for easy access and retrieval should be carefully designed, and storage conditions should be maintained and documented. Additionally, the long-term cost and logistics of maintaining the sample banks should be anticipated.

Optimal operation of a DBS storage facility requires that storage be planned and that conditions be specified and monitored. If the purpose in saving samples involves future analysis, screening programs should use data that indicate the stability of various analytes when making determinations about storage of samples. (See Table 1.) The defined purpose of storing samples should dictate the environmental conditions for storage. Ideally, residual DBSs should be stored frozen (preferably at -20^0C) in sealed bags of low-gas permeability that contain desiccant and humidity indicator. Samples retained only for DNA testing should be stored at least refrigerated (preferably at 4^0C) in sealed bags of low-gas permeability and contain a desiccant for humidity control. In all situations, precautions should be taken to avoid possible contamination from sample-to-sample contact. During storage, the humidity indicator should be periodically monitored and appropriate action taken to reactivate the desiccant when humidity exceeds 30% [13,17] or some other designated level of action. Every DBS should be properly identified. An index or catalog should be maintained so that any individual sample can be located. Whenever a sample is retrieved, an entry should be made in the record indicating 1) who had access to the sample, 2) the purpose for which the sample is to be used, 3) the authorization, 4) the chain-of-custody, 5) the amount of sample released, and 6) the results of any analysis of the sample or correction of any demographic or descriptive data. Appropriate and secured records should be maintained in a manner similar to that required for maintaining legal requirements in forensic laboratories. A quality assurance system is necessary for documenting the integrity of the saved DBS. At least two newborn screening programs have recently developed detailed sample storage policies and planned systems.

A quality assurance system should be designed to ensure validity of stored samples for their intended purpose. If the analytes for which the DBSs are being saved are known, then appropriate assayed DBS quality control samples should be included in the storage. All control samples must be handled and maintained under identical processing conditions as the stored samples. In order to prevent location bias, control samples should be randomized in the storage system. Compromised or potentially compromised samples have limited scientific value.

1.3 Use of stored samples

What studies and applications have been identified for using stored residual DBSs? The DBS material remaining after newborn screening has been completed can be used effectively for epidemiologic studies and for method development, comparison, and validation. These uses are important public health applications for these residual samples. For example, the HIV seroprevalence survey among childbearing women [23] that provides important public health data on the spread of HIV infections was predicated on the use of residual DBSs. Each use also leads to specific requirements (e.g., the need for fresh samples [within a short time after collection] and the need for specific demographic information linked to the sample). To date few studies have required samples older than a few months. Most screening programs have no laws or regulations governing the use of residual DBSs (see Sec. 2.3).

Should residual DBS samples be provided for public health epidemiologic studies, for assessing the use in detecting new disorders, and for the validations of new methods? Screening programs should establish a review board to process all requests for DBSs and to ensure valid use of these samples before their release. The laboratory should have a written

policy for release of residual DBSs (see Sec. 2.3). Samples should not be released from the laboratory with personal identification data (or demographic data that could potentially identify a person) without signed consent from the parents of the newborn. Further, all studies using residual DBSs should be reviewed and cleared by a Human Subjects Review process. The screening program's advisors (see Sec. 1.3 in ref. 1) should be involved in the decision process. When samples are released, the recipient of the sample should be advised that, although low in potential biological hazards, DBSs are nevertheless biological materials and appropriate precautions should be exercised in their use.

1.4 Financial elements

Costs are associated with storage and retrieval of DBS samples. Most epidemiologic studies and method evaluations have available funds, and the laboratory should consider the logistics of reimbursement for costs in cataloguing, storage, and retrieval, including any specialized processing such as removing personal identification, retrieving special sample sets of specific categories, and providing demographic data bases. Laboratories should also consider reimbursement for providing DBSs to manufacturers of diagnostic products for research applications. Small sets of anonymous residual DBSs might be provided free of charge to individual researchers at the discretion of the program director. Potential authorship or acknowledgment on the study publication should be negotiated in advance by the program director, on the basis of the workload required of the laboratory staff in retrieving the requested sample sets and providing specific demographic information.

Legal and Ethical Issues

2.1 Retention of samples

When appropriately used, retained DBSs may be valuable resources with potential benefits for individuals and society. Solutions to the legal and ethical concerns about the retention of residual DBSs are unclear. As more and more screening programs consider retaining DBSs and as DNA technology expands rapidly in detecting genetic disorders, a more formal approach to legal and ethical concerns should be taken. Some of the questions to be addressed include 1) the stability and suitability of DBSs analytes (see Table 1.) for analysis, 2) the length of time DBSs should be retained and for what purposes, 3) the requirement of legal consent, 4) the removal of identifiers, 5) a Human Subjects Review process, and 6) the ownership of the DBS. A recently published review [2] describes the importance of retaining sample collection cards and the importance of DNA banks. The existence of these unplanned DNA banks for newborns has raised concerns regarding the privacy of medical records because of an increase in the amount of DNA information available (such as disease susceptibility) through technologic advancements [2].
An ethical concern is retaining DBSs with the capability of linking them to patient information. Currently, the trend is for states to either retain DBSs for longer periods or to be increasingly concerned about destroying them in a specified period. Because of the claimed value of these samples, it is becoming more difficult to justify not retaining and storing them for longer periods. However, in an Institute of Medicine report, the statement is made that DBSs should be made available for research "only if identifiers have been removed" [24]. This major concern for confidentiality continues to be part of the ethical debate over the issue of public health benefits versus personal privacy.

Retained DBSs may be useful in certain legal situations. Because of the proliferation of DNA studies, DBSs are increasingly being considered for DNA analysis. One of the main areas of consideration is forensic use. Many states are enacting or have enacted legislation in this area. Two reviews have recently been published on this subject [25,26]. State, territorial, or federal departments of justice may maintain individual DNA banks. Nevertheless, residual newborn screening samples or other potential DNA samples collected for public health purposes should be used only as a last resort in any legal cases, and samples should be released only under subpoena and then only if the requestors can show that there is no suitable alternative source.

2.2 Privacy protection

Formal procedures, documentation, and written policies should be considered when planning for DBS sample storage. Because of the increasing number of requests for DBSs, the procedures and regulations regarding the release and use of DBSs should be formalized [27]. In a previously cited study [2], only 13% of the states indicated that there were

written regulations from state departments of health about third party access to samples. Of all state laboratories reporting, 19% had some internal written policies [2]. One state has established rules and regulations requiring that all requests for samples should be in writing and should include information about project goals and intended use of results. A committee within the state agency must review all these requests and can then accept or reject them. State newborn screening programs usually do not have sample storage systems or policies for DBSs that meet the legal chain-of-custody requirements for samples used for forensic purposes. Procedures should be appropriate for their intended uses.

2.3 Use of samples

Appropriate consent is an important issue. Most state screening programs use informed refusal, or dissent, meaning that parents may refuse the DBS collection and test or may refuse to allow the DBSs to be used for purposes other than newborn screening. In one state, agreeing to the test also implies consent to use the residual DBSs for anonymous program evaluation and research, in addition to all tests required to complete the original screening intent. With the proliferation of other uses for samples, the type of consent or refusal obtained should be clarified [28]. The collection form and educational material for parents could indicate that the sample becomes the property of the state and that, unless the parents object in writing, the sample may be used without personal identifiers in studies related to preventing birth defects and disorders of the newborn or for protecting the public health. In such cases, a protocol for obtaining parental consent for any studies that are not anonymous may be needed. Some legal experts have proposed, however, that proper informed consent is impossible since it is not possible to adequately inform or educate a parent about all potential uses and outcomes associated with the consent. Release of identifying information requires review by a Human Subjects Review Board and written consent if there is any possibility for the identification of adverse outcomes. Whenever DBSs are released, a minimum quantity of a sample should be released and at least one spot should be retained for program purposes. The use of this remaining spot should be a matter of program policy. A possible accepted use might be for further testing at a family's request when clinical problems exist concerning health issues. When providing residual DBSs for any use, the screening program, its advisors (see Sec. 1.3 in ref. 1), or its review board must be cognizant of any local or state laws or regulations that take precedence for sample use.

The issue of counseling parents when test results are released should be addressed. DBSs should not be released to the parents; however, with the parent's written permission, the samples may be released directly to a laboratory or a physician. This suggestion is justified on the basis of possible contamination of the sample in the hands of the parent, a situation that would complicate the clinical picture. Therefore, a state agency cannot protect itself from legal problems if DBSs are released directly to parents. Limited, aggregate demographic data may be considered for release in epidemiologic studies on anonymous samples with the approval of a Human Subjects Review Board. Care should be taken with unlinked studies to ensure that small cell sizes of demographic data cannot lead to personal identification through demographic data. Anonymous test results directly related to the screening program itself should not require such a review.

Many different types of requests for DBSs will be received by the newborn screening program. One broad category of requests includes special studies for which significant numbers of DBSs are requested and for which the approval of a Human Subjects Review Board is required. A second category includes individual requests from families or family physicians in order to identify a possible disorder contributing to a family member's morbidity or mortality. If identifiers are required for a study, or contact of patients or families is needed, there should be no release of DBSs or data without using an approved Human Subjects Review Board protocol, including consent, terms of release, and confidentiality protection. Strict documentation should be applied for all uses of DBSs, including to whom and for what purpose the samples were released and whether or not special consent was obtained. Some examples of specific types of requests are cited below:

> Subpoena -- In most instances, a subpoena should be required for all releases of DBSs or test results relating to a legal case, especially where chain-of-custody must be documented. However, there may be some instances in which a mutual agreement between the screening program and the requestor results in obtaining the DBS without a subpoena.
>
> Special cases/family studies -- A common altruistic type of release (with written permission of parents or closest living relative) involves testing a DBS from a deceased child to determine a previously unknown cause of death.

For example, testing for Medium Chain Acyl-CoA Dehydrogenase Deficiency (MCADD) and Cystic Fibrosis (CF) may be requested. Knowledge of previous test results may be useful in making subsequent decisions about pregnancy or in treating living siblings. In one instance, a mother was unjustly charged with the murder of her child by poisoning the child with antifreeze when actually the infant died of methylmalomic acidemia [29]. Only after the same diagnosis was made through testing of another of her children was the mother cleared of the charge. This unfortunate situation might have been avoided if a residual DBS had been available. In most of these instances, the screening program's advisors (see Sec. 1.3 in ref.1) should be consulted before a sample is released.

Research Studies -- These studies may be an appropriate use of residual DBSs if the following criteria are met:

Anonymous testing -- Anonymity negates the need for obtaining parental consent since no possible physical or psychological harm to the parents or child could result and because the sample can provide population data that is important in public health studies. An argument might arise that under certain conditions, population studies may be detrimental. Controversy regarding anonymity may arise when significant, treatable problems are found in the sample of a person who cannot be identified. For example, many states are currently struggling with the issue of the anonymity of HIV testing of DBSs since research indicates that transmission of the virus can be reduced by up to 65% through infusions of zidovudine (3'-azido-3'deoxythymidine, ZDV, AZT) during late pregnancy and delivery [30]. By the time of testing, it is too late to affect the outcome (since corrective measures do not currently exist for completely eradicating the virus in the newborn), but releasing the information to a mother who could use it to prevent transmission during a subsequent pregnancy would be important.

Reanalysis -- Retrieval of a sample may be needed to attempt the confirmation of an original analytical results. Confirmatory testing might contribute to the resolution of a legal issue (e.g., to attempt to prove misidentification of a sample by DNA testing, to confirm late onset of disease, or to verify an original test result) if the DBS was not compromised during storage (see Sec.1.2). Specific samples may be retrieved also to verify the adequacy of storage conditions or to provide documentation for a quality assurance assessment of stored DBSs.

Limitations -- Since the amount of blood spot material is limited and finite, its potential use should be of significant impact, especially if large numbers of DBSs are required. Inherent in any proposed use of DBSs should be some element of contribution to public or family health or some contribution to goals for genetic screening. Prioritizing possible uses of DBSs should be considered by each screening program in its written procedures.

The following examples represent special types of requests for residual DBSs that have been received by some newborn screening programs:

Individual requests -- In one state, there were approximately 20 requests for access to individual DBSs for testing in 1 year. These are some specific examples of requests: to study MCADD and sudden infant death syndrome (SIDS), to rule out mitochondrial DNA mutations, to study carbohydrate-deficient glycoprotein syndrome, to confirm an initial negative T_4 value in a legal case, to perform Werdnig-Hoffman disease linkage analysis, to study DiGeorge's syndrome (transfused infant), and to rule out galactosemia after an original screening result was reported negative for the disorder (see Sec. 1.2).

Large-scale requests for DBSs or data bases -- Most of the research studies requested fewer than 1000 samples of known cases and approximately equal numbers of control samples. Studies for which large numbers of DBSs have been retrieved include these: MCADD, SIDS, HIV seroprevalence study, conotruncal heart malformations, oral cleft malformations, genetic basis for cerebral palsy, hypothyroidism (test results only), sickle cell trait and SIDS (test results only), childhood leukemia,

cancer-gene studies, miscellaneous hemoglobin results for new test development, and folate-receptor variants.

2.4 Privacy and other ethical concerns

The potential for permanent storage of DBSs in DNA banks and the availability of genetic information in DBSs raises ethical concerns. Although significant benefits may be gained from the storage of DBSs for genetic testing, the general public still has many concerns. An uneasiness exists about the possible misuse of these samples leading to discrimination, psychological harm, identification of incorrect assignment of paternity, and potential social injustices [27]. Widespread testing for genetic factors (e.g. susceptibility) is not recommended for newborns when no clear indication of disease exists [31], or no medical intervention exists.

Conclusion

Currently, most state and territorial newborn screening programs have few or no procedures for retaining, storing, retrieving, and using residual DBMS. In reaction to continued questions about these issues, some newborn screening programs have used weak justification for their handling of residual DBMS as stop-gap measures; but few scientifically sound procedural systems currently exist. Each state has its own opinions, laws, concerns, and rationale for handling residual DBMS; and most programs are seeking nationwide guidance from the screening community. The ethical concerns of the public and the judiciary about issues related to discrimination and privacy may ultimately dictate policies about retaining or destroying residual DBMS. Since it is likely that conclusive decisions regarding DBS banking of samples from all newborns for possible DNA analysis will be determined by the judicial system [26], it is hoped that the basis for such decisions will be the potential benefit or harm to society. Any decisions should include reflections on the numerous considerations presented in this guideline. Programs should begin now to promulgate policies and rules for retention and use of residual newborn screening DBS samples. These guidelines are intended to establish the groundwork for these important decisions that must be made by the screening program.

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