Newborn screening residual dried blood spot use for newborn screening quality improvement

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Abstract: The outcomes of a meeting that focused on the role of the residual dried blood spots from newborn screening for uses in the improvement of newborn screening are reported. Discussions of policy development, such as this one, begin by identifying the problem to be solved; in this case, it is achieving common ground to develop consistent policies for the use of residual dried blood spots, such that their benefits to the public's health and the health of children are amplified, and harms are minimized. Similarly, the issue must be considered contextually. The example of newborn screening for phenylketonuria was used to highlight the issues in the context of the condition with the longest history in newborn screening. Principles and recommendations for the use of the residual dried blood spot were developed. ***Genet Med*** **2010:12(12):S269–S272.**

Key Words: *newborn screening, dried blood spots*

On April 6–7, 2009, the National Coordinating Center for the Regional Genetic and Newborn Screening Service Collaboratives convened a meeting (jointly funded by the Health Resources and Services Administration [HRSA], Maternal and Child Health Bureau [MCHB], Genetic Services Branch, and the Eunice Kennedy Shriver National Institute of Child Health and Human Development [NICHD], National Institutes of Health) to discuss state newborn screening (NBS) programs and provide collaboration to improve NBS. The purpose of the meeting was to provide a forum and starting point for on-going discussions related to the usage and storage of the residual NBS dried blood spots (RDBS) for NBS quality improvement. These activities are in concert with the goals of the federal Newborn Screening Saves Lives Act of 2007 (PL-110-204).[1] Meeting attendees included representatives from state NBS programs, state screening laboratories, state legal departments, academic institutions, consumer advocacy organizations, and federal agencies (HRSA/MCHB/Genetic Services Branch, NICHD, the Centers for Disease Control and Prevention, and the Office of the Assistant Secretary for Planning and Evaluation, Department of Health and Human Services). The meeting format was designed to establish common ground through presentations that explained the history of RDBS use and related policies, outlined ethical issues, and described current and future ways of using and storing the RDBS. Through an open forum, participants identified and discussed the myriad considerations regarding future policy development. This included the rapidly changing NBS environment, variability in state program policies regarding dried blood spot retention and use, and secondary uses of the information and data derived from the NBS process. As there is currently no national standard for programs around the country, the varying RDBS storage methods and policies from state to state present challenges to creating a national system. Consequentially, there is much room for debate over the privacy and ethical issues regarding policy changes. This document represents an initial step in fostering a broader ongoing public discussion. Over the course of the meeting, the group discussed the rapidly changing NBS environment and began to consider the variability in state program policies regarding dried blood spot retention and use, and secondary uses of the information and data derived from the NBS process. Although many issues and policy implications exist, the group recognized not only the value of residual blood spots as a unique resource but also the importance of balancing public good with research interests and ensuring that privacy and confidentiality remain a central focus.

BACKGROUND

NBS has developed since the 1960s to become a highly valued public health program. Screening for phenylketonuria (PKU) was the first to be introduced. Because of the very important health benefits to those identified, it evolved from a hospital-based program to a public health program for which screening is now legislatively mandated in every state in the United States and in many other countries.

From the outset of PKU NBS, it was apparent that a subset of individuals with significant hyperphenylalaninemia (H-phe) responded differently to the low-phenylalanine (Phe) diets than did the great majority. Further, a group of patients with more intermediate levels of H-phe was identified. Although typically placed on restricted diets while diagnostic confirmation was pursued, their diets were gradually normalized while their H-phe was monitored. It became apparent in the ensuing years that conditions defined by quantitative variations in particular metabolites could have multiple genetic etiologies resulting from either specific enzyme deficiencies, from abnormalities in the enzyme's cofactors, or from other abnormalities within the same metabolic pathways.

Many of these conditions and variants such as H-phe were ultrarare and neither appreciated when screening for the primary target condition began nor likely to be identified without detection in population-based screening programs such as NBS. With rare conditions, it took entire populations to give meaningful sample size to the data. Since the introduction of NBS in the 1960s, overlaid by a vast increase in our knowledge of genetics, there has been a continuous improvement in approaches to (1) screening tests and technologies; (2) our understanding of the conditions being screened or that are candidates for screening; (3) the diagnostic tools available; and (4) treatment strategies. This recurring phenomenon points to the need for ongoing research and monitoring of the outcomes of patients identified by population screening.

Four features of a disease (knowledge of the condition, performance characteristics of the screening tests, methods of diagnosis, treatment and outcome, and knowledge of costs and

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Disclosure: The authors declare no conflict of interest.

DOI: 10.1097/GIM.0b013e3181fea489

potential harms) are central to decision making about what is appropriate for introduction to NBS. Going back to the original prototype, PKU screening was predicated on the finding that those with a metabolic defect in the metabolism of the amino acid Phe accumulated excess Phe in their blood (H-phe) and that individuals with these elevations could be detected as newborns by a simple, easily reproducible assay.[2] When untreated, individuals with PKU developed severe mental retardation and autism spectrum disorders. However, the ways by which we are able to expand our understanding of NBS conditions and improve outcomes varies between these features. The RDBS strengthens evidence and provides data to support what we know about each parameter, as elucidated later.

Knowledge of the condition

Inherent biases of genetics ascertainment can lead to misperceptions about the burden of a genetic disease, its incidence, and variability in its presentation. It is only through population-based clinical investigation that the true clinical history of a genetic condition is appreciated. This requires aggregating clinical information from significant numbers of patients (because of the rarity of the conditions in NBS), often from many states or nationally to identify sufficient numbers of patients for statistically informative analysis. However, a subset of questions (e.g., incidence) can be answered from anonymized or de-identified dried blood spots samples.

Performance characteristics of existing and new screening tests

The rarity of many of the genetic diseases or their subtypes combined with the lack of quality control and assurance materials from patients with these diseases makes the use of a RDBS a critical part of NBS. Specimens can be used as positive controls in high-throughput testing systems to ensure the accuracy of the results of all specimens being tested. Although this is used beyond the screening of that individual, it is critical to the quality of results for all newborns screened by the program.

The development of new tests and technologies for NBS and their validation occur at many levels. A new test or technology might offer an improvement over a prior test or technology in identifying the same analytes in the same patients. The use of the de-identified or anonymized RDBS is the most efficient and practical way to compare the performance of the new test with the predicate test. No new clinical information is generated, and the risks to those whose specimens are used in this way are nonexistent. However, a new test or technology for a condition already in NBS that generates new information of potential utility about a patient requires that more formal institutional review board (IRB) processes be used. Similarly, new tests and technologies for the identification of individuals with conditions not already included in NBS would also require formal IRB processes.

RDBS have also been used to address important public health questions. For instance, during the early years of the spread of human immunodeficiency virus, anonymized RDBS provided a unique population-based resource for the determination of rates of human immunodeficiency virus seropositivity in the general population.

Methods of diagnosis

New methods of diagnosis of genetic diseases typically operate outside of the public health environment of NBS programs and within the clinical services provider community. However, in time, these may become the basis on which new screening tests or technologies are based. RDBS could be a key aspect of informing this process in the future.

Knowledge of costs and potential harms

During the early stages of introduction of any new test, costs and harms are still being learned and assessed. Although there were anecdotal reports with respect to early PKU screening and some limited controversy related to possible harms from dietary overrestriction of an essential amino acid,[3] there was broad consensus that the benefits of NBS for PKU greatly outweighed the possible harms. However, recent reviews of the medical literature have shown little evidence of death or disability from inappropriate treatment of well children identified in NBS programs.[4] Given that the RDBS provide the only general population biospecimen resource in the United States and that appropriate privacy and confidentiality protections can be applied that are specific to their planned use, it is important that they be retained and the NBS programs continue their stewardship.

There are many positive aspects of RDBS use, as evidenced by their contributions to the ongoing improvements in NBS. It is a distortion of the facts to argue that all potential uses of a RDBS are a violation of one's civil rights or a governmental intrusion into an individual's privacy. Many uses involve de-identified or anonymized RDBS for which the potential for individual harms are negligible to zero and for which additional consent is typically waived by IRBs. Other uses may be of such low risk as to require an expedited IRB review. Some uses clearly involve the need to have the identity known and a full consent process engaged. A better understanding of these many uses and reflection on the documented benefits from these uses can allow a more balanced discussion. It was the purpose of this meeting to consider the range of potential uses of RDBS and to explore mechanisms for safety, of both personal information and physical retention of RDBS.

MEETING SUMMARY

The meeting began with an overview by Brad Therrell of the issues and historic perspectives, including the storage, retention period, uses, policies, and the privacy implications of RDBS usage. The trends, practices, and history of attempts at policy development were introduced. He also discussed the concept of a national (or multistate) RDBS repository, whether this could be virtual, and the implications associated with it. Peter van Dyck presented the long-term activities of the Heritable Disorders Program (HRSA/MCHB) and the NBS services activities funded through the program. Existing long-term follow-up activities are critical to discussions of current policies and their future development, with the seven HRSA Regional Genetic and Newborn Screening Service Collaboratives cited as a major resource for these activities. Duane Alexander discussed NICHD's related activities, specifically goals and plans for the Newborn Screening Translational Research Network. These included an organized network of state NBS programs and clinical centers as well as a national research informatics system for investigators and policy makers that links with the already present national clinics network.

The meeting quickly moved to an overview of the history of the ethical issues surrounding the storage and use of newborn blood spots, as sources of data, and their potential implications. The preliminary and overarching theme was the question of how to balance the public good and children's health with individual rights. Not only do the physical collection and storing of RDBS raise these issues, so does the continued use of the data. The fine line and tension between NBS as a public health

service and NBS as a public health resource will need to be addressed as part of policy development. This again raises the issue of what is "research" in this light and as it relates to RDBS and was discussed by Aaron Goldenberg who presented work done in collaboration with Shlomit Zuckerman.

State regulations and educational materials regarding the storage and use of RDBS were also presented. There is wide variability between current state policies regarding RDBS, in particular, the materials and policies put out by individual states are not the same. This raises ethical issues for patients and their neighbors in other parts of the country. With policies differing widely regarding duration of RDBS retention, how much they can be used for research purposes, and necessity of consent, parents and ethicists are left in search of common ground. There is a distinct need for discussion regarding unifying the states under a single plan, and Goldenberg emphasized that this plan must benefit both the public and the science.

The points discussed in the February 2009 meetings of the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children (SACHDNC) regarding RDBS were subsequently reported by Rodney Howell. The SACHDNC discussion of residual blood spot policies and uses was a keystone in fostering continuing dialog. Susan Berry presented a proposed way of storing RDBS and focused on the interplay between clinical care and research and how that affects the relationship between patient and scientist. Specifically, she discussed the relationship between public health and providers in the collection and eventual sharing of NBS data. Frances Downes brought forward Michigan's BioTrust Initiative regarding RDBS and their proposal to make it more useful for medical and public health research. This information was key to the debate regarding future policies. Fred Lorey followed with a presentation of the long-term aspects of data storage, using California's long-term follow-up data system as a model.

MEETING CONCLUSIONS

Although not everyone agreed to every point, the following vision, principles, and recommendations, which form the Meeting Statement, were the majority view of the meeting attendees. There are several overarching principles, which include a more specific statement and related recommendations. The rationales are an attempt to describe the thinking behind each recommendation.

Consensus statement

NBS is a valuable public health prevention activity that continuously evolves to improve and optimize the health of our children. One product of the multifaceted NBS process, the residual dried blood spots, serves as an additional valuable resource, whose benefits were discussed at length. Their overall use includes facilitating the improvement and evolution of NBS programs nationwide. It is envisioned that their uses will improve and change as scientific advances occur in the coming years. It is the desire of the group to encourage these developments with the continuation of appropriate stewardship to assure privacy and confidentiality.

Meeting attendees agreed that moving forward, policy needs to recognize the three classes of residual RDBS use. These include (1) improvement of current screening programs; (2) introduction of new screening tests; and (3) expanding medical knowledge related to NBS.

RDBS retention: Rationale

Meeting participants identified and reached consensus on the following as rationale to underpin policies promoting RDBS retention:

- Quality improvement
- Accountability to the public
- Epidemiologic research to benefit public health
- Basic research to benefit general medical knowledge
- New test method evaluation
- Legal accountability of the program (e.g., quality control and documentation)
- Individual self-directed use (e.g., forensics and postmortem examination)

RDBS retention: Points to consider

To realize the benefits listed earlier in the text, the group acknowledged that there are scientific and societal provisions, safeguards, and considerations that must be taken. Although the policy development and decision making regarding these provisions may take place on a national level, many are implemented by the individual programs. The group acknowledged that how these provisions are addressed may vary with the class of RDBS use being considered. The group identified the following as an important preliminary list that may expand as the field evolves:

- Consideration of human subjects' protections
  - Protect confidentiality
  - Protect privacy
  - Access (who has it)
  - Consent issues
    - When is it needed?
    - Opting out
    - Reconsenting
- Prioritization of use for this finite and valuable resource (RDBS)
  - Resource allocation
  - Resource identification
  - Access (who has it)
    - Biomarker longevity
    - Data integrity
    - Commercialization

RDBS retention: Use of the SACHDNC

SACHDNC advises the Secretary of Health and Human Services regarding the most appropriate application of universal NBS tests, technologies, policies, guidelines, and standards for effectively improving public health, particularly newborns and children having, or at risk for, heritable disorders. The Advisory Committee is currently addressing the issue of retention and use of residual RDBS. The conversations and products of this meeting have informed their deliberations.

Moving forward

The April 2009 meeting was a major catalyst toward fostering further discussion between states and with the public. One of the main points reiterated throughout the meeting was a dedication to keeping the process transparent to the public. It was the group consensus at this point that, as this policy conversation moves forward, ongoing education of the public, patients, and providers will be a critical component. Time did not permit the group to agree on definitions of "privacy" and "de-identification" with respect to data sharing; however, these are critical future steps. Once agreed on, these definitions should be followed to assure continuity within and between

programs and activities, along with maintaining the privacy of all human subjects involved. Furthermore, it is the hope that this meeting is the stepping stone for future interactions to streamline the way NBS research and program improvement occurs and to foster discussions within individual states and with the public. We believe that establishing this foundation and conducting these activities should be transparent and engage the public at all levels.

In response to the meeting, the Board of Directors of the American College of Medical Genetics issued a statement addressing the value of RDBS to NBS research and program improvement.[5] In addition, the Association of Public Health Laboratories reaffirmed their existing statement on the same issue.[6] A follow-up policy forum in September 2009 will engage the public in continuing discussions of this issue.[7] These tangible results of the meeting affirm the importance of these issues to ongoing and continued work within the field and indicate the field is ready for future policy changes.

ACKNOWLEDGMENTS

This meeting was partially supported by HRSA/MCHB Cooperative Agreement U22MC03957-05-02 (National Coordinating Center for the Regional Genetic and Newborn Screening Service Collaboratives) and NIH/NICHD Contract HHSN27520080001C (Newborn Screening Translational Research Network Coordinating Center). Dr. Michael Watson raises money from industry to support the education programs of the American College of Medical Genetics Foundation.

Meeting Participants

Federal and ACMG Participants: Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health: Duane Alexander, MD; James Hanson, MD; and Melissa Parisi, MD. Health Resources and Services Administration, Maternal and Child Health Bureau: Alaina Harris, MSW, MPH; Michele Lloyd-Puryear, MD, PhD; Marie Mann, MD, MPH; Jill Shuger, MS; Bonnie Strickland, PhD; and Peter van Dyck, MD, MPH. Office of the Assistant Secretary for Planning and Evaluation, Department of Health and Human Services: Contanze Coon and Alan Zuckerman, MD. Centers for Disease Control and Prevention: Coleen Boyle, PhD and William Hannon, PhD. American College of Medical Genetics: Judith Benkendorf, MS, CGC; Taylor Goodspeed; Alisha Keehn, MPA; Barry Thompson, MD, Michael Watson, PhD; and Meredith Weaver, ScM, CGC.

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