Return of Results from Research Using Newborn Screening Dried Blood Samples

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Introduction

Whether research results should be returned to participants has been an ongoing debate in the research and bioethics communities for years. The debate has become more complicated as advances in technology permit the discovery through genomic sequencing of a growing number of findings that may or may not have clinical relevance for research participants. As part of the larger conversation regarding whether and under what circumstances research results should be returned to participants, research conducted using residual newborn screening dried blood samples (DBS) deserves special consideration due to the nature of newborn screening, the recent controversy regarding the retention and use of DBS, and the impact of this controversy on state newborn screening programs.

Currently, there is a disconnect between the potential benefits — both to the population at large and to individual infants and their families — of research that could be conducted using DBS and the practical capabilities of state newborn screening programs. Although as a society, we are on the cusp of being able to bring about significant improvements in health as a result of research conducted in the newborn period, budget constraints, political exigencies, and concerns about the potential negative impact on the primary public health mission of newborn screening may limit the ability and/or willingness of state newborn screening programs to support the secondary research use of DBS and the return of results to research participants.

The full value of research using DBS has not been realized previously for a variety of reasons, including the fact that population-based DBS studies can only be conducted in a limited number of states.[1] Over time, however, if state policies are amended, DBS could be utilized to develop a population-wide genomic database. Genetic information linked with clinical information over the course of a person's lifetime could provide unprecedented opportunities to learn about human health and disease from the early stages of life.[2]

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The potential benefits of research conducted with DBS can only be achieved if there is broad support from the newborn screening community and buy-in from the general public. Returning research results in some circumstances is one potential way to enhance public buy-in. If the full value of research conducted using DBS is to be achieved, results of research conducted using DBS should be returned to infants' families under some circumstances. This article will explore the circumstances under which it may be beneficial to research participants, state newborn screening programs, and the research enterprise to return a subset of research results to parents. Returning some results of research conducted using DBS will require significant changes to the newborn screening program infrastructure. We offer a starting point for discussion of these issues.

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I. Background

A. Newborn Screening

The purpose of newborn screening is to identify infants with certain serious medical conditions and allow for early interventions to avoid or ameliorate clinical symptoms and prevent disability or death. Newborn screening is mandated by state law in the District of Columbia and all 50 states, except Wyoming.[3] Shortly after birth, whether born at home or in a hospital, a newborn's heel is pricked, and several drops of blood are placed on filter paper that is sent to the state newborn screening laboratory when the blood has dried. It has been estimated that 1 in 300 newborns has one of the newborn screening conditions, and an estimated 12,500 children with metabolic, endocrine, hematologic, or functional disorders are identified through newborn screening each year.[4] After diagnostic confirmation, these infants are referred for treatment and long-term follow-up.

B. Secondary Uses of Residual Newborn Screening DBS

When the heel stick is performed, more blood is collected from each newborn than is required to perform newborn screening. This extra blood is collected so that the blood can be re-evaluated if warranted by the initial screen results and to ensure that there is sufficient blood to perform the initial screening. As a result, when newborn screening has been completed, residual DBS remain.

DBS have a broad range of potential secondary uses, including program quality assurance, test validation, and the development of new newborn screening tests. For example, DBS were used to develop a screening test for Severe Combined Immunodeficiency Disorder (SCID), a condition that was added in 2011 to the list of core conditions recommended for inclusion in state newborn screening panels by the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children.[5] DBS also have been used to evaluate the feasibility of using new technology, such as next generation sequencing, to improve upon current newborn screening methods.[6]

DBS also may be used for research unrelated to newborn screening. DBS are whole blood samples and contain a wide range of biomarkers, including DNA, RNA, and proteins.[7] DBS have been used to explore the possible etiology of a wide variety of conditions, from childhood leukemia[8] to autism,[9] and they have been used to provide evidence of exposure to infectious diseases[10] and environmental toxins. For example, in the "Mercury in Newborns from the Lake Superior Basin" study, DBS from three states were evaluated to assess prenatal mercury exposure because even small amounts of mercury can harm the developing brain and nervous system. These results were used to improve outreach to pregnant mothers and their health care providers to promote eating types of fish low in mercury.[11]

Since newborn screening is conducted on almost all of the babies born in the United States, DBS provide a nearly complete representation of the U.S. population. In the future, information derived from DBS could be integrated with other public health surveillance data, such as environmental health tracking programs or the Behavioral Risk Factor Surveillance System (BRFSS)

maintained by the Centers for Disease Control and Prevention,[12] to provide a rich resource for research.

In addition, the National Institutes of Health (NIH) have made a significant investment in newborn screening research. Under the Genomic Sequencing and Newborn Screening Disorders program, the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the National Human Genome Research Institute (NHGRI) have jointly funded pilot projects with awards of $5 million each to four grantees to assess whether "sequencing of newborns' genomes provides useful medical information beyond what current newborn screening already provides."[13] In addition, the American College of Medical Genetics and Genomics (ACMG) was awarded a 5-year, $12.5 million extension of its contract by NICHD for the Newborn Screening Translational Research Network (NBSTRN) Coordinating Center to develop an infrastructure to support newborn screening reearch.[14] One of the resources developed by the NBSTRN is a Virtual Repository of Dried Blood Spots, an open-source web-based tool that enables researchers to search over two million DBS that are available to researchers in participating states.[15] The full value of these resources can only be realized if there is broad participation in the research. Returning results of the research in some form to parents may be one way to encourage participation.

II. The Retention and Use of DBS

A. Litigation Regarding the Secondary Use of DBS

The public health benefit of newborn screening can be expanded by using residual DBS for research, but the retention and secondary use of DBS have been controversial in some states. It is important to understand the context of this controversy when considering the implications of returning or not returning results of research conducted with DBS.

The public controversy surrounding the retention and use of DBS has focused on whether explicit parental permission should be required. Until recently, informed consent was not required by federal law to release DBS for research because research conducted with de-identified DBS was not considered human subjects research under federal human subjects research guidelines. Nevertheless, the retention of DBS without parental permission led to a firestorm of negative media attention and garnered incendiary headlines such as, "The Government Has Your Baby's DNA!"[16] and "Your Child's DNA: Who Has It?"[17]

Concerns of privacy advocates and some parents about the retention and use of DBS without explicit consent resulted in lawsuits against the state health departments in Texas,[18] Minnesota,[19] and Indiana.[20] As a result of the litigation in Texas and Minnesota, millions of DBS were destroyed, and parental consent now is required to release DBS for secondary research in both states. The litigation in Indiana is ongoing at the time of this writing.

The controversy generated by these lawsuits has led to concerns that state policies regarding the retention and use of residual DBS may have a negative impact on the primary public health mission of newborn screening. The fear is that parental concerns regarding the possible research use of their children's DBS will cause parents to refuse newborn screening altogether. An editorial in *Nature* highlighted these concerns by stating that "to be unclear about how newborn blood is collected and used is the fastest route to turn the public against sampling of newborns for any purpose — including screening programs."[21] The perceived lack of transparency by state health departments that have not sought parental permission to release de-identified DBS for secondary research may undermine public trust in state newborn screening programs and the research enterprise. For this reason, consideration of any policies related to the secondary use of DBS, including whether and under what circumstances results of research conducted using DBS should be returned, must involve consideration of the impact of these policies and practices on the operation of state newborn screening programs.

B. Federal Legislation Regarding Secondary Research Use of DBS

In the past, research conducted using de-identified DBS was not considered human subjects research under federal human subjects research guidelines, and parental informed consent was not required by federal law to release de-identified DBS for biomedical research.[22] The Newborn Screening Saves Lives Reauthorization Act of 2014 changed these requirements by defining federally-funded research conducted using DBS as research on human subjects and limiting the federal provisions that permit Institutional Review Boards (IRBs) to modify or waive the requirement to obtain informed consent for research.[23]

At the time of this writing, federal regulations to implement the legislation have not been promulgated, and the impact of the legislation on research conducted using DBS is unclear, particularly with respect to whether informed consent will be required for all research conducted using DBS. As discussed above, a wide variety of activities can be conducted with DBS, and it is unclear how the term "research" will be defined in this context. For example, are pilot studies considered research that will require informed consent? Another area that needs clarification is whether

blanket consent for research conducted with DBS will be sufficient.

Given the potential policy and programmatic barriers to adequately obtaining informed consent from parents for the research use of DBS, the Newborn Screening Saves Lives Reauthorization Act of 2014 may significantly limit the use of DBS in biomedical research. When the legislation was enacted, federal law did not require parental consent to use de-identified DBS for research. Few states had mechanisms in place to solicit consent, and in those states, blanket consent for the future research use of DBS is requested rather than seeking specific consent for individual research studies.

One state that has a mechanism in place to seek blanket consent for the future use of DBS is Michigan. Michigan state law authorizes the retention of DBS.[24] All DBS are stored in the Michigan BioTrust for Health, a biobank created to make DBS more useful for medical and public health research, but parental consent is required to release DBS collected after April 30, 2010, for secondary research.[25] Blanket parental consent for health research is requested at the time newborn screening testing is performed.

Massachusetts is the only state to our knowledge with a mechanism to request consent from parents of every baby born in the state to participate in a specific study — in this case, optional screening in a state-run pilot study.[26] It is important to note that in Massachusetts, blanket consent for future research using DBS is not requested.

A requirement to obtain informed consent to use DBS for federally-funded research may have implications for whether research results could or should be returned to individual participants. Requirements to obtain consent suggest that research participants can be identified and may indicate that participants have an expectation that results will be returned.

In the past, when de-identified DBS were used for research, in many cases, the DBS were anonymized and did not retain any link to identifying information, effectively removing the possibility of returning results to research participants. However, if consent is obtained to release DBS for secondary research, DBS could have identifying information stripped but retain a link to identifying information kept by the state newborn screening program. In this way, the researcher could not easily ascertain the identity of the individual from whom the sample was obtained, but the state would have the information if necessary for the future re-identification of the child. The Michigan BioTrust has adopted this type of approach. The DBS stored in the BioTrust are double-coded, and only the Michigan Department of Community Health holds codes that identify to whom individual samples belong.[27] The intent of the double-coding is to protect the privacy of newborns and facilitate the return of research results that might impact the health of the child.

An alternative approach to releasing de-identified but linked samples would be to seek parental consent to release identifying information at the same time that parental consent is sought to release DBS for research. In this scenario, it would be possible to recontact families to provide them with research results.

When parental consent has been sought to release DBS for secondary research, parents may have a desire or expectation that research results with potential importance for the health of their children will be returned to them. Whether parents expect research results to be returned to them is an empirical question, but members of the public place high value on having research results returned. In 2011, 3,855 members of the general public were surveyed to evaluate public opinions about the policies and practices relevant to the retention and use of DBS for biomedical research. The survey addressed the potential tradeoff between removing identifiers from samples and the return of research results. Participants were informed that removing identifiers would increase privacy protections, but that if identifying information was retained with the DBS, important results about an infant's health could be returned to the infant's parents. Sixty-four percent of participants responded that allowing the return of results to parents was more important than providing greater privacy protections.[28] It should be noted that this question addressed the return of research results that may be important to the health of a child, not the return of all research results. If a research protocol that uses DBS requires informed consent but does not involve returning research results to participants' parents, it is crucial that parents be informed that research results will not be returned to them so that their understanding of what to expect from their children's participation in the research will be clear.

III. Is There a Legal Duty to Return Results from Research Conducted Using DBS?

A. State Law on Return of Results from Research Conducted Using DBS

Currently, the laws of only three states specifically address the return of results from research conducted using DBS. However, the return of results from research using DBS currently is not required by law in any state. In Massachusetts, the New England Newborn Screening Program allows parents to participate in pilot studies of new tests. The Massachusetts Department of Health Regulations define the

pilot studies as "statewide testing and related screening activities offered through a research protocol with informed consent process approved by the Department's Institutional Review Board."[29] State regulations require that the "pilot studies provide for the maintenance of specimen identifiers, allowing study results to be linked to, and reported for, specific individuals."[30] These regulations do not require that pilot study results be returned to infant's parents, but in practice, the results of the pilot studies are reported with routine newborn screening results to the infants' physicians.[31]

The DBS stored in the Michigan BioTrust for Health are double-coded in order to enable re-identification of individual infants if necessary. The BioTrust policies do not contain guidance regarding the circumstances under which research results could or should be returned to infants' families, and Michigan state law does not require that research results be returned to research participants.

South Carolina law permits the Department of Health to return results of research conducted with DBS that may be important for the health of the child.[32] However, the return of research results is not required, and no guidance is provided regarding the circumstances in which return of research results is appropriate.

B. Newborn Screening Litigation Regarding the Return of Research Results

A Lexis/Nexis search of federal and state cases conducted in February 2015 using the terms "newborn," "screening," "research," and "results" generated 127 cases. Two cases involved allegations related to a failure to return results of research conducted in the newborn period. The remaining 125 cases did not involve failure to return research results. In *Ande v. Fost*, the plaintiffs were two parents whose newborn participated in a research study to "test for the presence of factors indicative of cystic fibrosis."[33] The study was conducted prior to the inclusion of cystic fibrosis (CF) on state newborn screening panels. In one arm of the study, parents were told if their child screened positive for CF and a "nutritional plan was made available to them immediately."[34] Parents of infants in the other arm were placed in a blinded control group and were not told if their child screened positive for CF. The plaintiffs' child who participated in the study screened positive for CF, but these results were not given to the parents prior to her diagnosis with CF.

The plaintiffs sued the investigators, the hospital where the infant was born, and the Wisconsin Department of Health and Social Services. All claims except the allegation of medical malpractice were dismissed for procedural reasons. The circuit court concluded that the medical malpractice claim could not proceed because no physician-patient relationship between the plaintiffs and any of the defendants had been established. The Wisconsin Court of Appeals affirmed the lower court's decision.[35] The results of this case might have been different if any of the researchers had been involved in the clinical care of the Andes' child.

In *Dinkins v. Hutzel Hospital*,[36] the plaintiff was a mother who sued on behalf of the estate of her deceased daughter. The plaintiff gave birth to her daughter, Stephanie, at Huntzel Hospital in 1986, prior to the widespread adoption of sickle cell anemia screening as part of state newborn screening programs. At the time, the hospital cooperated "with an organization implementing a pilot program to screen for sickle cell disease, the Sickle Cell Detection and Information Program"[37] (the Sickle Cell Program).

The Sickle Cell Program had routine procedures in place to notify families and physicians of any newborn who tested positive for sickle cell disease, but the Sickle Cell Program failed to notify anyone that Stephanie had tested positive. She died when she was three years old after becoming sick with flu-like symptoms and being treated in an emergency room for a viral infection when in fact she was suffering from a sickle cell crisis.

Her mother sued Hutzel Hospital where Stephanie was born, the Sickle Cell Program, the hospital in which Stephanie died, and Stephanie's pediatrician. The physician settled out of court. A jury found the Sickle Cell Program negligent in Stephanie's death and awarded damages of $3 million. The Sickle Cell Program did not participate in the appeal. The jury found that Hutzel Hospital was negligent for failing to obtain informed consent for the sickle cell testing, but that the negligence was not the proximate cause of Stephanie's death; Hutzel Hospital was thus held blameless. The District Court opinion was affirmed on appeal.[38] In the *Dinkins* case, the Sickle Cell Program that conducted the pilot study was found liable for failing to return results because it had a protocol in place to return results but was negligent in its failure to follow that protocol. It is unclear what the results of the litigation would have been if the Sickle Cell Program's protocol had not required that positive results be reported.

These cases demonstrate that the different stakeholders involved in newborn screening research may have different legal responsibilities to the parents and infants from whom DBS are obtained depending upon the circumstances of the research. Nevertheless, there currently is no U.S. case law that establishes a legal duty to return results of research conducted

using DBS. It is important to note that both of these cases involved participation in a pilot program associated with new newborn screening tests rather than research conducted using de-identified DBS, but the significance of this distinction is unclear since the court in the *Ande* case characterized the cystic fibrosis study as a research study.

It is not surprising that there are few reported cases that pertain to the return of results from research conducted using DBS, given that much of the research conducted using DBS has been conducted using de-identified samples that have not required parental consent. If they never were asked for consent, most parents would not know that their child's DBS had been used for research and therefore would not know if potentially important results had been withheld from them.

IV. Other Reasons to Return Results from Research Conducted Using DBS

A. The Mandatory Nature of Newborn Screening

In determining whether there are other reasons to return results from research using DBS, it is crucial to consider the unique context in which these samples are collected. Since newborn screening is mandatory in most jurisdictions, the DBS used in research would not exist but for the state laws that require that they be collected. Most states allow parents to opt-out of mandatory screening, but few states require that parents be informed of their option to refuse.[39] Therefore, it is unclear whether the option to refuse screening is a real choice. The question then arises whether the state's role in collecting newborn screening samples and retaining DBS has any bearing on the decision whether to return results to research participants.

State departments of health are responsible for the retention and curation of DBS, and state resources are used to perform these functions. Although issues related to the ownership and control of individual samples are not well settled in the law, DBS comprise an important public asset that could be extremely valuable for biomedical and public health research.

As guardians of this public asset, state departments of health have an obligation to be good stewards of these samples. This stewardship entails the careful and responsible management of the samples that have been entrusted to the care of the state. This stewardship also encompasses a duty to act in the best interests of those who have entrusted the samples to the state newborn screening program. Clearly, learning research results that could have an impact on the health of a child is in the best interests of that child. It follows then that a state's return of research results that could be important to the health of the child is in the best interests of the research participant and is consistent with good stewardship practices.

B. Shifting Views about Whether Research Results Should Be Returned

In the past, the prevailing view was that individual research results should not be returned to research participants. This view has shifted in recent years, and although a consensus about which research results should be returned remains elusive, there does seem to be a consensus that investigators have a limited responsibility to disclose certain types of research findings.[40] The rapid pace of advances in the technology used in genomic research has further driven discussion in this area.[41] In the literature, the duty to return at least some types of research results has been extended to research conducted using archived data sets and samples obtained from biobanks.[42] Return of a limited subset of results from research conducted using DBS is consistent with that literature.

C. Increased Utility of DBS Research

Research conducted using DBS has value for two main reasons: (1) because samples collected after birth but before exposure to environmental factors provide information that cannot be obtained at any other time of life, and (2) because over time, DBS could provide a population-wide database that could be tremendously valuable for biomedical and public health research. No other types of biospecimens are collected on such a large scale.

DBS are the most valuable for research if there is high participation, so that the samples are representative of the population to be studied. The potential value of research conducted using DBS will be diminished if large numbers of parents refuse to allow their children's DBS to be used for secondary research.

If parental consent is now required to use DBS for research, which seems likely given the new federal legislation, more parents may refuse to participate. Returning research results that may be important for the health of their child is one way by which participation in DBS research can be promoted, since parents may be more likely to agree to the use of their child's DBS if they believe that they may potentially learn important information about their child's health. However, careful consideration must be given to the ethical implications of framing the return of individual research results as an incentive to allow samples to be used, given that the primary goal of research is not to benefit individual patients or their families.

D. Potential Positive Impact on State Newborn Screening Programs

It is important to remember that the primary function of newborn screening is to identify infants at increased risk of disease, not to perform biomedical research. It is equally important that any research activities conducted using DBS not jeopardize the public health mission of state newborn screening programs. One case in which a bad outcome for an infant could have been prevented if research results had been returned to the infant's family would be enough to cause a public relations nightmare for newborn screening programs.

In considering whether results of research using DBS should be returned to participants' families, the effect of NOT returning results on state newborn screening programs should be considered. Whether there is an obligation to return a particular result may depend upon the severity and treatability of the disease, and the obligation may decrease as the potential harm to the infant decreases.

Research conducted using DBS has been controversial. The perceived lack of transparency on the part of some state departments of health regarding the retention and use of DBS has been extremely damaging to these state newborn screening programs. It is crucial that state departments of health maintain public trust in newborn screening and the research enterprise. Apart from their potential value in other types of biomedical and public health research, DBS are a vital component in research to improve newborn screening. It is necessary to preserve states' abilities to monitor and improve their newborn screening programs.

Another factor that should be considered is the positive impact that returning results of research using DBS could have on state newborn screening programs, newborn screening research, and the research enterprise. Returning research results could enhance community engagement with the research process and allow research participants to realize personal benefit from participation in research. In this way, both the community and individuals would benefit from the research. Returning results also would promote transparency regarding the activities of state newborn screening programs and their research activities.

The potential impact of the principle of reciprocity also should be considered. In this situation, the state newborn screening program would make a promise to return research results that may be important for the health of the child in exchange for parental permission to release DBS for secondary research. This promise could enhance trust in the newborn screening program and facilitate cooperation with the research enterprise.

Although there is a growing consensus that some research results should be returned to research participants, precisely what results should be returned remains debated. Advances in genomic sequencing technology have further stimulated debate on this topic. In considering what results should be returned to pediatric patients and their families, discussions have centered around issues such as whether to return results regarding adult-onset conditions and whether the guiding standards of the best interests of the child should be expanded to include potential benefits to other family members. Commentators also have considered whether there is a duty to return incidental findings, particularly in the context of pediatric genomic research.

V. If Research Results Are to Be Returned, What Results Should Be Returned?

Although there is a growing consensus that some research results should be returned to research participants, precisely what results should be returned remains debated.[43] Advances in genomic sequencing technology have further stimulated debate on this topic. In considering what results should be returned to pediatric patients and their families, discussions have centered around issues such as whether to return results regarding adult-onset conditions[44] and whether the guiding standards of the best interests of the child should be expanded to include potential benefits to other family members.[45] Commentators also have considered whether there is a duty to return incidental findings, particularly in the context of pediatric genomic research.[46]

This is not the first time that the newborn screening community has wrestled with the question of what results should be returned to infants' parents. In 2006, when the ACMG recommended that all states adopt a core uniform panel of conditions for newborn screening, the ACMG acknowledged that testing for those core conditions would also reveal secondary conditions that did not meet the criteria for inclusion but could be detected in the differential diagnosis of core panel conditions. Adoption of the Recommended Uniform Screening Panel was encouraged, but it was left to individual states to decide whether to report any of the secondary findings.[47]

For purposes of considering what results of research conducted using DBS should be returned, the most practical initial approach would be to return only actionable results for conditions that would potentially result in an improved clinical outcome for the child. This approach would necessitate that effective treatment or prevention strategies be available. In some cases, depending upon the type of research, returning aggregate results (for example, to a community at risk due to environmental exposures) may be more appropriate.

Under an approach that returns results based on potential to benefit the child's health, whether the research results are target or incidental findings is irrelevant. Of primary importance is whether the result has clinical utility. This approach is consistent with the purpose of newborn screening, the early detection of disease to reduce morbidity or mortality for the child.

When parents are informed that their children's DBS may be used for research, they also should be informed that research results that include important health information that could potentially result in an improved clinical outcome for their child will be returned to them. Parents should be informed that if they would prefer not to receive research results that would potentially benefit their child's health, they should decline to participate in the research.

If the return of other types of research results, such as results that may have clinical utility for other family members rather than the child or results related to adult-onset conditions, is considered in the future, it may be appropriate to allow parents to refuse to receive these types of results. However, if the research results are deemed to have potential clinical significance for the health of the child during childhood, it is in the best interests of the child that parents receive these results. An approach that would allow parents to refuse to receive research results that could benefit the health of the child could be damaging to state newborn screening programs and the research enterprise.

In the future, returning research results that indicate risk of an adult-onset disorder and so do not directly benefit the health of the child during childhood may be considered, but returning these types of results should only be undertaken in the context of a research protocol to evaluate the effects of providing families with this type of information. This type of research will be particularly important since little is known about the potential harms and benefits of returning information about adult-onset disorders and what the long-term health and psychosocial effects of returning this information might be.[48]

VI. By What Mechanism Should Research Results Be Returned?

If results of research conducted using DBS are to be returned to families, there should be a mechanism in place by which research results are returned. Using the return of positive newborn screening results as a model for returning research results is problematic, because there is no single mechanism by which positive newborn screening test results are returned. State law and practice vary by state and by condition.

How results are returned to families and what type of follow-up is offered varies depending upon the urgency of the condition. The ACMG has published ACT sheets for each of the conditions included in state newborn screening panels. These ACT sheets are intended to provide primary care providers with information about the appropriate follow-up and care for patients who screen positive for a newborn screening condition. These ACT sheets recommend different courses of action depending upon the condition. For example, conditions such as congenital hypothyroidism or sickle cell anemia typically are not immediately life-threatening, and consultation with a subspecialist with timely confirmatory/diagnostic testing as recommended by the specialist are recommended. Other conditions, such as galactosemia, can be life-threatening, and immediate evaluation of the infant and referral to a metabolic subspecialist are recommended.[49] In addition, there is state-to-state variation regarding which party contacts infants' families for follow-up. Whoever receives the positive results bears the responsibility to ensure that the infant receives the appropriate care. As a result, newborn screening represents a complex network of stakeholders whose responsibilities vary by state and by condition. Consequently, development of a systematic process by which research results can be returned to families presents practical challenges.

One approach would be to require that all research protocols involving the use of DBS have a clear plan in place specifying whether and under what circum-

stances research results will be returned to parents and who is responsible for contacting the family and informing them of the research results. Clear communication of results is important to ensure that the benefit of returning results outweighs the potential harms. In addition, the research protocol should include sufficient information and procedures to ensure that infants with positive research results have access to an expert in that particular condition and receive appropriate follow-up and care in a timely manner.

VII. Practical and Ethical Barriers to Returning Results of Research Conducted with DBS

Although there may be compelling reasons to consider returning a limited set of individual results of research conducted using DBS to infants' parents, doing this in practice poses significant practical and ethical challenges. First, states arguably already are overburdened and face challenges maintaining current program activities, assuring appropriate and timely follow-up with families, and adding new conditions over time to their state newborn screening panels. Asking states to be responsible for returning research results will undoubtedly place additional burdens on state newborn screening programs, especially since much of the research conducted using DBS will not be conducted by state health departments, but rather by outside researchers, with the states then facilitating the return of results. One solution could be to require the researchers themselves to return research results to individuals; however, this requirement would entail additional consent requirements and the sharing of identifiers with researchers, something many states have avoided in order to protect the privacy of families. States are likely to view themselves as stewards of DBS, and as an honest broker between researchers and families, placing the burden of communicating results back on the state programs themselves.

Second, if research conducted using DBS is carried out on a large scale in the future, the numbers of infants whose parents may need to be contacted to have results returned may not be trivial. Communication of research results to a potentially large number of individuals and the provision of ongoing support to ensure that they receive adequate follow-up and access to treatment may not be practicable in the context of newborn screening programs.

In some cases, returning aggregate results to subpopulations or communities may be more feasible while at the same time fulfilling an obligation to share some kinds of information with families and the public. In either case, the associated costs and stress on the current newborn screening infrastructure should not be overlooked. If newborn screening programs are to be expected to facilitate the return of research results, programs will need additional funding and resources to accomplish this task. Innovative ways to keep track of mobile families, as well as additional workforce members whose task it is to locate families, may be necessary.

Given the current political and social concerns about the use of DBS, approaching the return of results in ways that are sensitive to the expectations of parents and the programmatic constraints of the newborn screening system is essential. States ultimately are responsible for the development and direction of their newborn screening practices. It is vital that states and other newborn screening stakeholders work together to address the potential challenges of returning research results and at the same time protect the public health mission and clinical benefits of state newborn screening programs.

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