Including ELSI Research Questions in Newborn Screening Pilots Studies

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Abstract

Background: The evidence review process for adding new conditions to State Newborn Screening (NBS) panels relies on data from *pilot studies* aimed at assessing the potential benefits and harms of screening. However, the consideration of ethical, legal and social implications (ELSI) of screening within this research has been limited. This paper outlines important ELSI issues related to newborn screening policy and practices as a resource to help researchers integrate ELSI into NBS *pilot studies.*

Methods: Members of the Bioethics and Legal Workgroup for the Newborn Screening Translational Research Network facilitated a series of professional and public discussions aimed at engaging NBS stakeholders to identify important existing and emerging ELSI challenges accompanying NBS.

Results: Through these iterative engagement activities we identified a set of "key ELSI questions" related to 1) the types of results parents may receive through of newborn screening and 2) the implementation and initiation of NBS for a condition within the NBS System.

Conclusion: Integrating ELSI questions into pilot studies will help NBS programs to better understand the potential impact that screening for a new condition may have for newborns and families and to make crucial policy decisions aimed at mitigating the potential negative health and/or social implications of screening.

Introduction

Newborn screening (NBS), a population-based screening program, is required for every newborn in the United States[1] [2]. For over fifty years, NBS has led to the identification and early treatment of tens of thousands of newborns for selected birth defects[3] [4]. US state-based NBS programs began with screening for phenylketonuria in the 1960's and expanded to include a variety of other conditions as screening technologies developed, clinical understanding improved, and treatments became available. Each state ultimately decides which conditions to include, or exclude, in their statewide NBS program. In addition, the Secretary of Health and Human Services, considering the advice of the Advisory Committee for Heritable Disorders of Newborns and Children (ACHDNC), recommends conditions for screening, termed the Recommended Uniform Screening Panel (RUSP). ACHDNC and state decisions to recommend the addition of new conditions include processes that examine the evidence of the potential net benefit of screening, the ability of states to screen for the disorder, and the availability of effective treatments[5]. Historically, the consideration of ethical, legal and social implications (ELSI) within these evidence review processes has been limited, generally because researchers have not included a systematic study of ELSI issues within NBS research studies. The goal of this paper is to systematically outline important ELSI issues related to NBS policy and practices as a resource to help researchers integrate ELSI into NBS *pilot studies,* or "systematic investigations or public health activities that are designed to evaluate the efficacy and safety of incorporating a new test or condition on a population-based level into state NBS programs"[6].

As researchers, clinicians, NBS policy makers, and federal agencies have reviewed evidence related to the harms and benefits of mandating screening of newborns for a new condition, some of their deliberations have included ELSI issues including discussions of

permission, the availability of treatments and their costs, and the disparity caused by state-based variability in the number and types of conditions screened. Within the context of NBS, previous NBS ELSI research studies have examined issues such as the impact of false positives or uncertain results on families and the ethical implications of storing and using residual blood spots for future research.[7] [8] [9] [10] [11] However, the extent of this research has been limited and except in a few cases[12] [13] most ELSI studies associated with NBS have not been conducted as part of pilots investigating the benefits and harms of adding a new condition. Policy decisions at the federal and state levels to recommend and/or add new conditions to routine NBS rely on the data generated during pilots, and the lack of an ELSI focus in pilots has led to a paucity of empirical data related to ELSI within the NBS setting. Pilots that explore ELSI components could contribute important data for the evidence review process designed to evaluate new conditions for NBS. Any systematic evaluation of benefits or harms regarding expanding NBS panels is hindered by this ELSI research gap. Additionally, continued advances in our understanding of disease and the introduction of new screening technologies raise new ELSI concerns, such as when to report carrier status, when to offer testing to additional family members, or the possible psychosocial impact of false positives, that warrant further research to improve understanding of these issues and provide a basis for policy decisions.[14] [15] [16] [17] [18]

This paper systematically outlines the crucial ELSI issues related to NBS and to help researchers *integrate a robust consideration of these issues into NBS pilot studies.* To do so, we have identified nine **"key ELSI questions"** that represent important ethical or social challenges for NBS policy and practice. Our goal is to promote the incorporation of these questions when implementing NBS pilot studies to add to the evidence base for making

informed policy and practice decisions. We posit that ELSI data that are collected as part of pilot studies can allow the ACHDNC and state NBS programs to better address ELSI systematically within their evidence review processes, and mitigate potential negative impacts on newborns, their families, and the public health system through empirically informed policy and practice changes. We recognize that there are also a number of research ethics challenges related to the design and implementation of NBS pilot studies themselves, including human research subjects protections issues related to recruitment and study design, However, these important research process questions are beyond the scope of this paper. For example, while ELSI questions related to the potential need for parental permission for new screened conditions are raised here, the permission requirements for enrolling participants in a pilot study are not. Future work in this area will be needed to address these important, yet distinct, research ethics questions.

Deliberative Approach

The key questions presented in this paper were developed through a series of professional and public discussions aimed at engaging multiple NBS stakeholders to help identify important existing and emerging ELSI challenges accompanying NBS. These questions began with activities of a *Parent Project Muscular Dystrophy (PPMD)*[19] workgroup focused on ELSI issues raised by piloting NBS for Duchenne Muscular Dystrophy (DMD). Members of the National Institute of Health's (NIH) *Eunice Kennedy Shriver's* National Institutes of Child Health and Human Development's (NICHD) Newborn Screening Translational Research Network's (NBSTRN)[20] Steering Committee and the Bioethics and Legal Workgroup then discussed these questions, developing a series of general ethical

issues that should be addressed by any NBS pilot study. This workgroup is made up of more than twenty NBS stakeholders whose goal is to provide expert advice on issues pertaining to newborn screening research, and includes NBS Program Officials, Bioethicists and Social Scientists, Geneticists, Laboratory Officials, Layers, and biomedical researchers. An early draft of these key questions was presented and discussed at the NBSTRN's annual network meeting in Fall 2016. This meeting included an additional 100 NBS stakeholders including NBS program officials, laboratory directors, NBS researchers, and representatives of disease advocacy organizations. Finally, these questions were posted and discussed on a public forum, the *NBS Public Square* hosted by *Genetic Alliance* through *Babies First Test*[21], the *National Newborn Screening Clearinghouse,* and funded by Health Resources and Services Administration (HRSA). Each of the engagement exercises was meant to solicit informed opinions from NBS stakeholders to iteratively refine and enhance the content of this paper. For example, stakeholders from the NBSTRN Network Meeting aided significantly in defining the potential harms of false positives and false negatives, while responses from our online discussion forum led to the addition of questions related to equity health disparities.

Essential ELSI Research Questions

The following sections review nine key ELSI questions divided the into two main categories: 1) ELSI issues associated with the results of screening, and 2) ELSI issues anticipated in the implementation and initiation of NBS for a condition within the NBS System. Specific examples of possible research questions are provided in **Table 1**. Each of these sets of questions may impact one or more NBS stakeholder groups including: 1)

newborns, 2) families, 3) state NBS programs, 4) clinicians and the larger health care delivery system, and 5) the general population. We also recognize that ELSI issues vary depending on the specific condition, and some may raise unique challenges for families and other NBS stakeholders. Additionally, not all pilot studies will need, or be able, to answer every question from each of these sets of ELSI issues.

ELSI Questions Raised by NBS Results related to a Screening for a Condition

The *result-related ELSI questions* focus on outcomes related to the analytical and clinical validity or utility of the screening test or of the subsequent diagnostic tests. From any screen there are a number of possible results including positive, negative, false positive or false negative. NBS programs continually work to minimize the potential ambiguity or negative implications of screening results. For example, programs strive to reduce the number of false positive and false negative results to mitigate any potential physical or psychosocial harm to newborns and families. Nevertheless, as NBS programs add conditions and utilize new technologies, there will be need for ongoing ELSI research to continually understand the potential impacts, including benefits and harms, that NBS results may have for families, and utilize that data to make crucial policy decisions aimed at mitigating the potential negative physical or social implications of screening. Results of ELSI studies may, for example, lead to improved screening algorithms, raise difficult decisions about what kinds of results physicians or the NBS program should return to parents, how those results may impact the screened infants and their families, and whether or how to insure that the information from the screening and diagnosis processes becomes a part of the child's health care record.

Key Question 1: What are the potential ELSI implications of positive screening results related to a condition?

Screening tests do not provide a diagnosis, but rather detect indicators of increased risk. A diagnostic test establishes the presence (or absence) of a disorder. When the screening test result is positive and the diagnosis is confirmed, the family may receive a diagnosis before the infant's disease is clinically observable—this is one of the primary goals of NBS.

ELSI: The ethical or social issues associated with a positive result relate primarily to assessing the benefits of screening as well as the potential physical harms and financial burdens associated with the diagnostic process following the screen. These concerns are especially salient for conditions where diagnostic testing and treatments are more invasive or where long term medical impact or benefits of interventions are less clear. Additionally, as programs have expanded, there are increasing numbers of conditions with later and adult onset variants, further complicating diagnostic and treatment decisions.[22] While these issues are a core concern for NBS programs generally, they raise a number of important ethical concerns related to the harms and benefits of screening. Additionally, an out of range result may bring worry, confusion, anger, depression, and even despair to a family.[23,24,25] However, to date there are few published studies that look at the potential adverse psychosocial or emotional impacts of non-NBS health screening results for most individuals and families. Pilot studies that include an ELSI focus are needed to evaluate screening protocols for new conditions and compare the net benefits of screening with the potential harms of screening and diagnostic procedures and help to address this gap in the

context of NBS.. These studies could also address the impact of different approaches to education and communication aimed at helping families understand screening information, and identify those at most-risk for distress who may need further psychological support.

Key Question 2: What are the potential ELSI implications of <u>false positive</u> screening results related to a new condition?

Screening tests, unlike diagnostic tests, generate relatively large numbers of patients needing further evaluation to clarify screening results. The need for such re-assessment may have implications for many stakeholders, particularly since the recall rate can vary significantly from state to state, depending on the screening protocol and the adherence to quality assurance by the state NBS laboratory. While the goal is to minimize the number of patients recalled who do not have the screened condition, some patients, with further testing, will be shown to not have the disease and will therefore considered to be a false positive screen.

ELSI: Too many false positives could potentially weaken public confidence in NBS programs and diminish the ability of health departments to provide accurate and helpful information.[26] Other ELSI issues include concerns about the possible impact of false positive screening results on the stress of parents and the bonding between a parent and their newborn, as well as the increased cost and inconvenience of medical procedures needed to establish a diagnosis.[27] Previous research suggests relatively limited psychosocial implications for most individuals and families, and studies have not shown increased health care utilization by parents with newborns who receive false positive screening results[28] [29]. However, the existing empirical research on false positives has been

somewhat limited with regard to the diversity of populations included, lack of subgroup analyses, and the need for more generalizable quantitative data. Further research is needed to assess whether specific subgroups within the screened population may be at increased risk for higher levels of stress or other familial impacts of false positive results. Excessive numbers of false positive screening results may also put demands on state NBS program resources and the capacity of the health care system to respond. Studies of the financial costs of false positives could provide estimates of system-wide impact.

Key Question 3: What are the potential ELSI implications of <u>false negative</u> screening results related to a new condition?

When implementing screening technology for a new condition, NBS programs must balance between testing approaches that maximize preventable death or disabilities that limit false negatives (cases that might be diagnosed at a later time) and unwarranted reassurance from a false negative result, as some confuse a negative screen as a negative diagnosis. The potential impact of a false negative result will greatly depend on the condition screened and the implications of post symptomatic diagnosis. Nevertheless, once the testing procedures (its analytical and clinical validity and utility) for a new condition reach the level of evidence necessary to justify using it in a state NBS program, the potential for false negative screening results should be very low since current approaches maximize test sensitivity.

ELSI: The primary ELSI of false negative results relate to the potential false reassurance that these results cause for parents along with the potential physical harm from delayed diagnosis. Subsequently, like false positives, increased numbers of false negative screens

may erode public trust and support for NBS programs. Including ELSI issues in pilot studies should help to understand the impact of a false negative finding relative to public trust. A key outcome of pilot studies aimed at assessing the potential for false negative screens could focus on creating policies and educational materials to help increase awareness about the potential for false negatives and mitigate the potential harms to newborns and families if conditions are detected and diagnosed late.

Key Question 4: What are the potential ELSI implications of obtaining and reporting carrier status related to a new condition?

Many of the conditions that may be piloted in NBS programs are inherited in a recessive manner, where both the mother and father are carriers of the condition. Thus, screening for these conditions may identify newborns who are also carriers of a condition and who may not be clinically affected. As a result, unique ELSI questions arise when a newborn's carrier status is identified as part of the NBS process. As a practical matter, NBS already detects carrier status for many of the screened conditions including sickle cell disease, cystic fibrosis and others[15].

ELSI: The core ELSI issues center on debates regarding disclosure and potential benefits and harms of carrier status information for newborns and families, and their implications for state policy decisions to disclose or not disclose carrier results as part of their screening program.[30] Being a carrier for conditions screened may have health implications for individuals either in childhood or as an adult, including reproductive decision making. Additionally, there are arguments for assessing the social implications of screening for families as well as newborns. For example, carrier results may be important for parents

considering their own future reproductive choices.[30] NBS laboratories may report carrier findings as part of their perceived ethical obligation to disclose all testing results. Similarly, parents may also lose trust in the NBS system if they perceive that the programs are withholding of information, such as carrier status from them.

Alternatively, arguments could be made that there may be less of an ethical obligation to disclose carrier status, or even an obligation to not disclose, if the information would have no immediate impact on the health of a newborn. This debate raises important questions about how we assess the social implications of screening and the impact of NBS information on newborns and families.

Pilot studies could give researchers and states the opportunity to collect data on the impact of reporting carrier status to families, and then develop more informed policies regarding decisions to report carrier status results to health care providers and whether parents should have a choice about receiving carrier results. For example, studies could investigate parental perceptions on how carrier information identified as part of NBS may be of significant value for the child across their lifespan. Therefore, aside from programmatic decisions about reporting protocols, it is important to consider the ELSI issues for individuals and their families who might receive carrier information.[31]

Key Question 5: What are the potential ELSI implications of <u>indeterminate results</u> related to a condition?

In NBS there are sets of results for which the implications of the information obtained through screening may be unclear. This may be especially true as more complex conditions are added to panels. The addition of conditions to NBS panels with an unknown

age of onset, variable phenotypic features, unknown penetrance, or undetermined severity creates a situation in which parents or screened individuals, once subjected to diagnostic testing, might have uncertain knowledge concerning the presence or absence of disease.[32]

ELSI: When indeterminate results are returned to parents, there may be increased anxiety and stress related to when, or if, symptoms will occur in their children or themselves (for example, as with Krabbe Disease or Cystic Fibrosis Transmembrane Conductance Regulator-related Metabolic Syndrome[33]). Delayed onset of a condition has the potential for labeling newborns as "diseased" before any actual manifestation of the disease, and without knowledge of potential morbidity. Such newborns may become "patients-in-waiting" as families and affected individuals embark on an uncertain future or lengthy diagnostic odyssey.[9] Pilot studies of conditions with variable penetrance or variable phenotypic features can document the potential emotional and financial costs before such conditions are considered for inclusion in the RUSP. For example, a pilot could assess the potential impact that receiving indeterminate or unclear results may have on families, including reassurance that they would be able to intervene at the earliest possible moment if symptoms arise, or exploring whether these results increase anxiety with regard to an unknown future and raise concerns about even minor symptoms.

ELSI Questions Related to the NBS System

The *NBS System ELSI Issues* focus on the impact of initiation and implementation of a new condition on a state NBS program or a State's public health or health care delivery systems. These questions begin with the decision to initiate screening for a particular condition and represent the implications that adding a condition (and its associated

screening and diagnostic tests) could have on the state health department (medical foods, child health insurance programs, etc.), the NBS program, screening laboratory, or health care delivery systems.

Key Question 6: What are the cost or resource allocation implications for adding a new condition to the RUSP or a state panel?

NBS programs require a great deal of resources to run an effective screening program for all infants born within their state. Costs to state programs are not merely associated with the screening process itself, but also cover a number of crucial components of the entire NBS system including parent education, laboratory needs, and follow-up services.[34] If the addition of a condition to the program's NBS panel would be costly to the state NBS programs (equipment, training, personnel and other resources), and implementation might impact the program's ability to function effectively in other areas, then assessing the net harms and benefits of screening for a particular condition is crucial to the decision-making process.

ELSI: If adding a new condition to a NBS program disrupts its ability to maintain an effective NBS program, then expansion may prevent states from fulfilling their social and ethical obligation to assure that all newborns born within a state have the opportunity to be screened. Therefore, program costs/resources related to new condition implementation should be an integral part of the piloting process. These cost evaluations should include assessing the cost of educating parents, policy makers, health professionals and laboratory specialists; building or incorporating results reporting infrastructure, and

supporting public relations activities, including development of related materials (pamphlets, videos, etc.). For some resource-poor programs, addition of new conditions for NBS may be more difficult than for resource-rich programs, and additional support may be necessary.

Key Question 7: What are the <u>health disparities or equity considerations</u> related to adding a new condition to the RUSP or a state panel?

Distributive justice questions in NBS include the availability and accessibility of short-term and long-term follow-up services and treatments. While a NBS program may have a variety of resources available for newborns and their families, there may be challenges for medically underserved and/or geographically isolated families to access condition-related healthcare services at either the state or local levels.

ELSI: Like resource allocation, equity considerations in NBS center on the ethical duty to assure that all newborns in a State have the opportunity to be screened and have appropriate follow up services.[2] Barriers to services may include a lack of access to medical foods and formulas not covered by insurers[35], expensive drugs, and difficulty obtaining expensive diagnostic procedures or medical interventions associated with a condition. All have the potential to increase inequities for families and populations. In some locations, sufficient subspecialty physician services may not exist and regional resources may be required. Pilots should include an assessment of how NBS programs and the larger health care system could mitigate medical and related service inequities using approaches like telemedicine and regional service networks.

Key Question 8: What are the potential implications for <u>public/parental trust</u> in the NBS system or health department that might arise because of adding a new condition?

Knowledge about NBS and its requirement is low among parents and families.[36] This awareness is exacerbated by the poor communication practices between NBS programs and prenatal health care practitioners. Therefore, improving awareness and education about the NBS system is a key area of concern for state programs as patients become more active in their own healthcare and especially, as programs grow to include more conditions. Trust in the NBS system is crucial to the success of screening and follow up services.

ELSI: When developing pilots to study the implementation of a new condition, it is important to assess the potential impact that expanding a state NBS panel may have on public trust and other public perceptions. [37] [38] Such assessments may require examining perceptions about program transparency and the decision-making process for adding new conditions, including how best to promote and manage input from parents, advocacy organizations, and other stakeholders. Considerations should include the potential for public engagement and education concerning the addition of a new condition. It is vital to assess whether unique characteristics of a new condition will merit special considerations when returning screening results to individuals who are members of populations already exhibiting mistrust of the government or the health care system. For example, if a subgroup of the population has a higher risk of false positive screens, targeted educational and engagement activities may be required to that build greater trust in the NBS system as part of the larger health care community. In addition, due to the complexity of NBS

technologies, treatments and disorders, communicating the purpose of, and results for, a pilot must include language and dialogue understandable to parents and families.

Key Question 9: Does a condition raise any concerns regarding <u>parental permission</u> or challenges to the ethical or social justification for requiring population-based screening?

Because NBS is a public health requirement, parents can opt-out of screening in most states (although not all) only for religious and/or philosophical reasons.[39] Justification for the screening requirement is predicated on the principle that requiring active parental permission about NBS is not necessary because the potential harm(s) from screening are outweighed by the benefits from screening. . As genetic diseases are better understood as a result of population screening, some may argue that parents should be asked to "opt-in" for NBS that may include conditions for which clinical symptoms arise later in life and not during childhood. That is, unless conditions need emergent diagnosis and treatment, there is less justification for a requirement to have NBS. For example, an abnormal result for some lysosomal storage disorders (LSDs) might mean that the baby is an asymptomatic carrier, or that he (she) will experience late onset of the disease with milder symptoms, or that he (she) needs treatment immediately to prevent serious outcomes, depending on the LSDs. Insurance companies may not pay for the additional testing required for a definitive diagnosis.

ELSI: There are a number of different approaches programs can take with regard to parental permission, including a variety of opt-out and opt-in options.[34] ELSI issues surrounding parental permission center on the need to weigh the public health necessity and benefits of screening with parental choice. These ELSI questions are compounded

when interventions for diagnosed infants are not medical treatments. As an example, early interventions may be initiated to minimize a cognitive delay in a condition such as Fragile X rather than working to eliminate the underlying defect in cognition.[11] Obtaining parental permission for some NBS conditions while not requiring permission for others (thereby combining opt-in and opt-out processes) could create a tiered screening approach.[40] Thus, the benefits of universal screening for conditions where the need for early detection and the availability of effective interventions are more certain would exist while allowing parents to choose screening for conditions that are in a pilot study or do not meet accepted criteria required for a universal mandate. The potential harms for a two-tiered approach requires closer examination particularly with respect to the potential for creating an overly complicated system that might lead increased processing errors or decreased patient participation and social inequities. Pilot studies could include questions and methodological designs that could test different types of parental permission and help programs assess the impact of different approaches.

Applying Key ELSI Questions in Pilots

These questions are intended to help research teams systematically consider the kinds of empirical ethics questions that can be assessed within pilot studies. However, the utilization of these questions within the development of pilot studies will ultimately be shaped by the condition being studied. It is our hope that research teams will develop a set of condition-specific ELSI questions to guide their own inquiry into the benefits and harms of population screening for their proposed condition. The purpose of **Table 1** is to provide teams of clinicians, advocates, and investigators with sample empirical questions that could

aid in identifying and assessing ELSI issues related to a specific condition.

In addition to the use of this tool, we also encourage researchers designing pilot studies to include researchers engaged in ELSI related work in the planning and implementation of NBS pilots. Doing so will allow for more robust identification of ELSI challenges related to a condition, or sets of conditions, and will aid in the integration of ELSI research methodologies into pilots, including surveys, interviews and other quantitative and qualitative research methods.

Finally, it is also important to recognize the current challenges facing NBS pilots to integrate ELSI questions. Generally, the disconnect stems from a lack of direction from funding agencies for NBS pilots to include specific ELSI concerns within the pilot study design. Additionally, federal initiatives often lack sufficient funding or resources to include ELSI aims in pilot studies. Rather, federal initiatives often target examination of the analytical and clinical validation of the screening test during the pilot without including specific ethical or legal questions. Engaging NBS stakeholders to create new innovative approaches to NBS research will be vital in expanding the size, scope and quality of pilot studies, and could create new opportunities for integrating ELSI questions.

Conclusion

NBS pilot studies provide an invaluable opportunity to explicitly address the ELSI issues of screening by assessing the potential benefits and harms of screening and follow up, including diagnostic procedures, and medical interventions/treatments for newborns and their families. We have delineated important questions for researchers to help in determining which ELSI should be included in pilot studies with the goal of identifying

research gaps, increasing the evidence base for assessing net benefits and harms of population based screening for newborn conditions, and promoting enhanced collaboration between researchers, state NBS programs, clinicians, advocacy organizations, ethicists, and social scientists to develop new approaches to assessing these difficult questions.

It is also crucial to acknowledge that NBS is constantly evolving. For example, some conditions being considered for NBS may have interventions that fall outside "traditional medical treatments". While screening for these conditions may provide net benefit to newborns and families, they may challenge the traditional metrics that have been used to determine when a condition is appropriate for addition to NBS panels. Additionally, adding new testing technologies, such as genomic sequencing as an alternative or adjunct screening modality, also provides NBS programs with an opportunity improve the speed and quality of screening. It will be essential that as screening programs evolve, the ELSI questions asked in pilot studies also reflect the changing landscape of NBS.

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