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Public Attitudes Regarding a Pilot Study of Newborn Screening for Spinal Muscular Atrophy

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Abstract

A population-based pilot study of newborns screening for a rare genetic condition, spinal muscular atrophy (SMA), is being conducted with funding from the National Institutes of Health. The first component of the study is to assess the ethical, legal and social implications of population-based pilot studies with a focus on public engagement and parental decision-making for the proposed opt-out approach in this research. We conducted focus groups with members of the general public to ascertain attitudes about the pilot study and acceptability of an opt-out approach in two states, Colorado and Utah, where the pilot screening is being proposed (N = 70). We developed an informational video for the project and showed it to the groups prior to the discussion in order to inform participants about population-based research, newborn screening, permission/consent models, and SMA.

Results indicated support for the conduct of pilot studies that is consistent with the current standard of practice for similar population-based programs. There was support for an opt-out approach for parental decision-making; however there was limited parental knowledge about population-based research, newborn screening and SMA. In general, our participants considered this pilot study to be low risk and of potential benefit to infants and families. The majority of participants were supportive of an opt-out approach with information delivered through various avenues

Keywords

Newborn screening; population-based research; public health; spinal muscular atrophy; research ethics; focus groups

INTRODUCTION

The nature of parental decision-making for population-based pilot studies, particularly for newborn screening (NBS), has been the focus of debate [Botkin, 2009; Tarini et al., 2008]. Approaches to pilot NBS research have spanned the spectrum from a clinical research model with written permission to a public health model in which state authorization is obtained for

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including the new condition on the mandatory panel [Pass et al., 2006; Taylor and Wilfond, 2004]. Experience suggests that permission models that entail a signed form are inefficient and largely ineffective for population-based pilot studies involving hundreds of thousands of new parents [Feuchtbaumet al., 2007]. For example, in a California NBS pilot program to evaluate tandem mass spectrometry (MS/MS), only 47% of the new parents during the study provided permission. This was not because parents refused to participate for the most part but because hospitals were unable or unwilling to engage parents and this resulted in many not benefiting from the screening and infants with potentially treatable diseases were missed [Feuchtbaumet al., 2007]. Most NBS conditions have been added to state NBS panels with limited formal evidence demonstrating that screening for these conditions leads to improved outcomes [American College of Medical Genetics, 2006; Botkinet al., 2006]. Only one condition on the current NBS panel, cystic fibrosis, has been evaluated through a randomized trial before most states mandated it to be included on NBS panel [Farrell et al., 2001].

The addition of new conditions to the NBS panel without valid and reliable evidence of the outcomes of early identification and treatment at a population level has drawn criticism. The Children's Health Act of 2000 created an advisory committee within the U.S. Department of Health and Human Services to bring greater uniformity to the nation's NBS efforts [American Academy of Pediatrics, 2000]. A primary function of this committee, the Secretary's Advisory Committee on Heritable Diseases in Newborns and Children (SACHDNC), is to conduct evidence based reviews of proposed conditions to be added to a uniform NBS panel [Kemper et al., 2008]. When appropriate, the SACHDNC will recommend pilot studies to develop the evidence on which recommendations can be made.

Spinal Muscular Atrophy (SMA) was nominated for formal consideration to SACHDNC in 2008 by a collaborative group of physicians, scientists and support organizations led by Families of SMA. This effort was motivated by the tremendous progress in therapeutics development for SMA over the past decade, with several promising treatments or therapies either in clinical trials or expected to reach the clinical trial stage in the next several years [Butchbach et al., 2010; Foust et al., 2010; Hua et al., 2010; Passini et al., 2010; Riessland et al., 2010; Swoboda et al., 2009; Tsai et al., 2008]. The SACHDNC reviewed the proposal to add SMA to the uniform panel. But given the lack of a population-based data on SMA screening, they recommended pilot research to further evaluate the feasibility and efficacy of NBS for SMA.

SMA is one of the most common lethal recessive genetic conditions with an incidence of 1 in 10,000 births [Hendrickson et al., 2009; Jedrzejowska et al., 2010]. The condition is associated with significant motor disability, respiratory and nutritional compromise, and death in infancy or childhood in more than 50% of affected children [Rudnik-Schoneborn et al., 2009]. Epidemiologic data indicates that symptom onset before 18 months of age occurs in more than 80% of affected children. There is significant neuronal loss within the first six months in infants with SMA type I, the most severe form of SMA [Swoboda et al., 2007; Swoboda et al., 2005]. The majority of undiagnosed affected infants who present in their first 12 months do so in medical crisis with acute respiratory failure [Chung et al., 2004; Rudnik-Schoneborn et al., 2009]. By the time a diagnosis is made, these infants are often severely nutritionally compromised, potentially exacerbating irreversible loss of neurologic function and the resulting compromised respiratory reserve. Often families have little time to cope with the complex decisions they must make, particularly when they are under great stress at this time of crisis in the intensive care unit setting. Early diagnosis during the newborn period could avoid these crises and improve outcomes for affected children and their families, prompting interest in the possibility of NBS for SMA.

A pilot study of SMA screening has been initiated with funding from the National Institutes of Health. The first component of the study was to evaluate the ethical, legal, and social issues of a population-based pilot study of newborn screening for SMA. An important question in the conduct of the trial was the appropriate approach to parental decision-making in a pilot newborn screening trial. Despite improvements to the nomination process for new NBS screens, uncertainty remains in the conduct of population-based pilot studies due to an ethical conflict between attention to individual decision-making about research participation and the need to efficiently screen large numbers of participants when the target condition is rare [Beskow et al., 2011]. Two commentaries in the literature support the conclusion that NBS pilot studies can qualify for a waiver of parental permission under the federal human subjects regulations, but clearly IRBs and investigators remain uncertain about the most appropriate approach [Botkin, 2009; Tarini et al., 2008]. Conducting population-based NBS research with parental informed permission creates unique barriers to evaluate new conditions for screening that may prevent the research itself from being conducted [Taylor and Johnson, 2007]. Others have also argued that utilizing an individual informed permission model for pilot research fails to model the program under study because almost all NBS programs do not require informed permission of the parents [Botkin, 2009].

We proposed a waiver of traditional informed permission in our IRB application (i.e. a waiver of the need for a signed permission from parents for participation). Our proposed approach would be to provide information to all new parents regarding the SMA pilot study and enable parents to opt-out of participation for their child. This approach is consistent with the model of parental participation used in the CF screening study in Wisconsin [Farrell et al., 2001]. The primary purpose of the focus groups was to present our preferred model for conducting the SMA pilot study and to ascertain public response to this model. Therefore, our educational materials for the focus groups were designed to present information regarding SMA, the pros and cons of different parental permission models, and to present our preferred approach, that is, the opt-out approach. Our question to the focus groups participants was not, “What decision-making model would you prefer?” but, rather, “For these reasons, we are considering an “opt-out” approach to parental decision-making; is this acceptable?” In this respect, questions to the focus group participants mirrored the decision-making approach in clinical research projects [Jefford and Moore, 2008]. Investigators present a preferred approach to conduct the research to an IRB and receive approval for this specific protocol. Subsequently, potential participants are then asked if they are willing to participate in the study as designed. In our context, we have a preferred approach to parental decision-making based on a variety of considerations and we wished to know whether our preferred approach for the SMA pilot study is acceptable to the general public. The first aim of this pilot screening study was to determine an approach acceptable to the public and feasible for the conduct of such a project through focus groups.

MATERIALS AND METHODS

IRB approval was obtained before beginning research. A total of 70 people participated in six focus groups (three groups within each state). (See Table I for an overview of demographic data on the participants.) Participants were recruited through a professional agency within each of the two states and to target individuals of the general public with variability in age, gender, income and education. The only requirement was to be a parent. An informational video was created by the University of Utah Genetic Science Learning Center to inform participants about SMA and NBS, population-based research, and options for parental decision-making in research. The video was validated using a separate set of respondents on appropriateness of content, length and understanding. This approach of educating participants prior to the focus group discussion through a narrative video has been successfully used in several studies [Botkin et al., 2012; Rothwell et al., 2012]. The video is

available online (http://learn.genetics.utah.edu/sma/), and outlined the challenges of parental decision-making for population-based research with residual NBS samples if written informed permission was required among hundreds of thousands of new parents. It is important that the video provided both the cons and pros of decision-making approaches (e.g., decreased chance that communication about the study will occur with the opt-out approach, false positives, no direct benefits to most participants) along with the benefits and the preference of the investigators for an opt-out approach.

There were two moderators for each of the focus groups and one observer. One moderator led the focus group discussion and another moderator, with expertise in NBS and research ethics, answered questions and posed additional questions as they arose within the emerging discussions. Open-ended questions invited participants to identify and explain their attitudes and opinions toward a pilot NBS study for SMA. The questions for the focus groups were created from a review of the literature, and input from experts in NBS (See Table II). The moderators used nondirective probes to seek additional detail and description from the participants [Frazier et al., 2010]. On average, each focus group lasted 1.5 to 2 hours. The audio recordings were transcribed and verified by one of the researchers.

A qualitative content analysis was used to analyze the data [Morgan, 1993; Sandelowski 2011]. All the transcripts were read and re-read by one of the researchers. Then codes were generated from the semi-structured interview guide and reading of the transcripts. This coding template was applied to all of the transcripts with the ability for open coding to capture emerging categories that might have been missed with the coding template [Morgan, 1993; Elo and Kyngäs, 2008]. Consistent with our other work, the codes were summarized to identify the most frequently reported codes across and within each of the groups [Rothwell et al., 2012; Rothwell, 2011]. We then returned to the transcripts and recontextualized the data for development of themes [Polit and Beck, 2004]. The frequency of codes was not used to assess data saturation but rather the content of the data [Morse and Field, 1995]. Repetitive data emerged, and no new codes were generated after coding of the third focus group, indicating data saturation [Krueger and Casey, 2009]. However, all six transcripts were coded and included in the analyses.

RESULTS

In general, findings were consistent within and across the focus groups, with the majority of participants reporting little to no knowledge about NBS, SMA, or population-based research. Almost all participants expressed agreement with an opt-out approach compared to written informed permission for conducting population-based research for this candidate NBS condition. However, there were numerous questions from the participants indicating the complexity of the topic and the need to provide opportunities for participants to obtain more information.

General Knowledge and Attitudes

Only a handful of participants had heard about NBS and even fewer participants had heard about SMA. Most of the participants recognized the benefits of NBS for children. (*"You have to weigh that it is for the health of my child."*). Furthermore, many of the participants remembered the "*poke on the foot*," and "*prick on the heel*", but they were unaware that there were so many conditions screened for on the bloodspots ("*I never knew there were 30 things, my initial reaction was why?"*). In regard to NBS research with children, participants were supportive if the blood samples were already collected for another purpose (non-invasive and did not require an additional heel prick), did not risk harm emotionally or physically, and parents were informed about it ("*It should always be cleared with the parent."*) Some of the positive outcomes of the NBS research with children stated by

participants included: development of effective treatments, early interventions, improving the quality of life, prolonging life, and for the benefit of the family and future generations.

Opt-Out Preference and Education

There was strong agreement among the participants that for population-based research, such as the pilot screening for SMA, giving parents a choice was important and necessary. Most participants indicated that it did not matter whether a pilot study was conducted with an opt-out or an opt-in approach but rather providing sufficient information to make a decision about participation was the key factor. Most of the participants expressed support for an opt-out approach for population-based research ("*Opt-out is pretty simple and straightforward*"). The most common reasons provided by the participants for why they were supportive of an opt-out approach were that the blood was already collected for NBS (*"This is not an invasive study. The blood has already been drawn."*), and that the study would benefit children (*"There's a lot you can do with early intervention. I think it's real important for children."*). Other comments for why most of the participants agreed with an opt-out approach included: there are finite resources and they should be used more efficiently, such as for the conduct of the research; there are limits to education and people are not going to take the time to sufficiently inform themselves (*"The human race really doesn't pay a whole lot of attention to details."*); and research goes through a systematic review and it can be assumed that the best interests of helping the public are driving the research (*"I'm just going to trust the professionals looked at this and they're not going to be using me as a guinea pig and I have no problem."*).

Additionally, there were numerous comments about how an opt-in approach does not necessarily ensure more understanding and that people often do not sign things because they do not want to take the time to read (*"A lot of people will just kind of glance at something and then if there's a line for a signature, they'll assume well most people sign this and will just keep on signing.";* and *"I think a lot of people just wouldn't sign something because they're like "I don't want to sign that." They wouldn't read about it."*). When the moderators asked participants to make a choice "assuming time and resources were unlimited," between opt-out versus written informed permission many participants were still supportive of an opt-out approach for this population-based study. Similarly, when the moderators asked participants what is more important, "to conduct the research or to obtain informed consent," most of the participants stated it was more important to conduct the research.

However, it is important to note that there were a few participants in our focus groups who stated a preference for opt-in and that a signature was important for any type of research (*"I like the consent form."*). Conversely, there were also a few participants who stated that the study should be conducted without parental permission due to the importance of conducting population-based research. (*"You don't give them an opt in or opt out. I don't see the point in doing that."*)

Approaches to Parent Education

Education was a significant topic of discussion within all focus groups. There was no consensus on the best way to inform people about this research. The most common suggestion was a brochure with a link to a website with more information. Many of the participants stated that information about this study should be added to the existing NBS brochure, but should highlight that this was a new screen and more information could be found at a website. Other participants stated a separate brochure should be created. Some of the suggestions for the type of information that could be included in the new brochure included: benefits of this research, use of already collected blood sample, what is SMA, SMA treatment options, genetic aspects of the condition, probability, accuracy of the screen,

and what happens if the infant has a positive screen. Other suggestions for how to educate people about this study included: commercials, flyers, and interactions with hospital staff during the birth of the baby. Participants also stated that efforts to educate parents about the pilot study should be similar to how NBS is currently communicated and parents should be targeted as opposed to the general public. Many participants stated that more should be done to improve current communication about NBS itself ("*You go to the education. Most of us didn't even know what it was* [NBS] *so you've got to educate the parents."*)

Benefits and Risks

Another topic of discussion was the benefits and risks of a pilot study. Overall, most of the comments focused more on the benefits, which included early intervention and the importance of knowledge and preventative treatment (*"Treat the symptoms early on."*; and *"You can't deal with something if you don't know about it."*). In general, many of the participants stated that because the blood was already collected, that this research was an additional benefit to NBS. The primary risk mentioned by the participants was the growing influence of government in their lives and the potential storage of residual newborn screening samples by the government. For example, *"The government is going to have my kids' DNA. How is that going to affect them in the future?"* A few participants stated that too much attention on this study would highlight the current lack of education about NBS and that, in itself, might have negative consequences on NBS participation. Other risks mentioned by participants were false positive results, insurance discrimination, and unethical pharmaceutical company profit (*"It's a stepping stone for the pharmaceuticals."*). Some participants stated that this study did not entail any risks for families or participating children. The moderators also asked participants whether an earlier diagnosis (due to NBS) would be viewed as a risk because the knowledge of the child having the condition before symptoms appear might impact their parental experience. Most participants stated that the benefit of knowledge outweighed this risk and that engaging in preventative treatments was significantly more important. However, a few participants stated that if a parent did not want to know "*that could be difficult.*"

Public Health Implications

For this specific pilot study, many participants stated that another reason they supported the opt-out approach was that the NBS program is already utilizing an opt-out approach. Others said that the pilot study should be consistent with this approach because it is gathering data for a new NBS screen, the pilot might be confused for NBS itself, and if an individual is going to opt-out of this pilot study it is because they would opt-out of NBS already. In addition, there could be misconceptions about what the pilot study would entail, such as an additional heel prick *("People see 'pilot study' and they go 'oh no.'"*; and *"Would this require any additional heel pricks?"*). In general, most of the participants stated that they were supportive of public health agencies and newborn screening and that this study will not influence them to decline NBS. ("*I can't imagine people would opt out over adding one new test when there's already 30 of them").* Participants also stated that this pilot study was another preventative measure to help children and that they viewed it as an additional screen along with the other thirty-plus conditions screened. Many of the participants stated that they did not see any difference in pilot screening program for SMA and the already established NBS program. This pilot study would not require additional blood to be drawn, there are already over thirty conditions screened for by NBS programs, and parents would be notified if the DBS screened positive for SMA. ("*Because of the scope of the project and the simplicity of adding it onto the blood draw that's already being done and the minimal risks, I am comfortable with the opt out.")* In addition, some participants stated they did not want to pose any additional risk to individuals opting-out of the NBS program if too much attention was placed on this specific study. ("*But you're also concerned that if they opt out, there's*

this spotlight on the screening test [NBS] *that they didn't know anything about and now people are just going to say, 'I don't want any of it.'")*

Types of Questions

One of the most interesting aspects of the focus groups was the high number of questions. The most commonly occurring code in the data was the participant questions. There were over 240 questions coded within the six focus groups. The next most frequently occurring code was ways to educate and inform people about this research, with 137 incidences. An additional content analysis was conducted on the questions that were coded. Table III contains an overview of the categories and representative examples of the questions asked by the participants. The co-moderator answered questions as they arose in the discussion.

DISCUSSION

NBS is a complex topic, as are the research ethics involved in conducting pilot studies of population screening for conditions like SMA. This project attempted to provide substantial information to focus group participants by incorporating the use of an informational video as well as an extensive, interactive question and answer session with an expert in the field of NBS and research ethics. Many focus group participants commented on the utility of the movie in fostering their understanding of the issues. We believe this approach enabled more informed discussion and opinions by focus group participants and therefore increased the value of those opinions for informing public policy.

A central question for the focus groups was the nature of the permission process for parents. The literature tends to indicate that individuals want an active decision-making role when their records or tissues might be used in research [Hull et al., 2008]. However, there are distinct differences between the risk and information needs of participants in most clinical research projects involving dozens or hundreds of participants, and population-based pilot research involving tens or hundreds of thousands participants [Taylor and Johnson, 2007]. In addition, the newborn screening pilot study under discussion would not involve additional blood draws or burdensome procedures for the infants or families, although there are some risks, primarily in the form of false positive results, as is for other newborn screens. The fact that research could be conducted on existing bloodspots was important for many focus group participants.

In this study, when the researchers presented to the participants the opt-out approach compared to individual written permission for population-based research, the participants were supportive of an opt-out approach. We believe several factors influenced the attitudes and opinions of the participants in this study. Of primary importance is our stated preference for an opt-out approach. For the reasons noted above, we considered it justified to present a particular model that was otherwise preferable for logistical and financial reasons and, arguably, justified under the human subject regulations. When provided with some education about the issues, we found that a large majority of participants were comfortable with a parental education and opt-out approach to this research. The important element for participants was the parents to be informed of the research and that they have a choice. The method of choice (opt-in or opt-out) was much less important.

Many of the participants stated that the pilot study should be conducted in a similar manner as NBS, because it was a pilot study for a candidate condition for NBS. Also, the participants in this study were able to articulate a much higher number of benefits than participants in a study that assessed attitudes and opinions about the general use of residual dried blood spots (DBS) for research [Rothwell et al., 2012]. This may be in part due to the specific nature of this study, which has a clear beginning and end point for the research and

that parents would be notified if a screen for SMA was positive. In contrast, participants would not know what type of research the residual DBS would be used for, the results of the research and how long they would be stored [Olney et al., 2006]. Finally, the focus groups allowed participants to ask a number of questions. NBS and population-based research are complex topics and the ability to ask questions clarifying the purpose of the project appeared to be a significant factor in all of the group discussions and appeared to increase transparency about the research.

In general, our participants considered the proposed research to be low risk and of potential benefit to infants and families. The majority of participants stated a preference for information being made available to parents through various avenues and with parents being offered the option to refuse participation. Limitations of the study include focus groups from only two states, Colorado and Utah (states in which the pilot screening is being proposed). Attitudes may differ in other states or other regions of the country, although a recent assessment of public attitudes regarding the research use of residual bloodspots did not find differences between the mountain states region and a national sample [Botkin et al., 2012]. Furthermore, our novel approach with an informational movie and expert discussion could bias the conversation. Another limitation of the study was the hypothetical nature of the discussion. That is, participants were not making real-time decisions about their own infants, however our target population was pregnant women, their partners and parents of children less than 5 years of age.

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Table I

Demographics of Participants(n = 70)

Characteristic	n or Mean	% or SD
Age (years)		
18–29	12	17%
30–39	22	31%
40–49	13	19%
50–64	18	26%
65+	5	7%
Gender		
Male	36	51%
Female	34	49%
Ethnicity		
Non-Hispanic	62	89%
Hispanic	8	11%
Race		
Asian/Native Hawaiian/Other	2	3%
White	57	81%
African American	2	3%
Other	1	1%
Income(1 not reported)		
Less than $25,000	10	14%
26 to $35,000	13	19%
36 to $45,000	8	12%
46 $65,000	17	25%
66 to $100,000	14	20%
$100,000 or more	7	10%
Education		
Some High school	1	1%
High school diploma or GED	8	11%
Some college	24	34%
Associates degree	3	4%
Technical	2	3%
Bachelor’s degree	26	37%
Graduate degree	6	9%

Table II

Questions in the Semi-Structured Interview Guide

1	In general, what are your thoughts and opinions about NBS?
2	How much did you know about NBS before this group?
3	Have you heard about this disease [SMA] before?
4	What are some of your opinions about research with children?
5	What kinds of risk do you think this pilot study entails for families and their newborns?
6	What kinds of benefits do you this pilot study entails for families and their newborns?
7	What information should new parents receive about the pilot study and their option to refuse?
8	Departments of health are concerned that people may opt out of NBS because of this research. What are your thoughts about this risk?
9	What are your thoughts about the option to not participate for this study? (opt-out)
10	What are some ways that you feel would be acceptable for parents to notify the pilot study about the option to refuse? (i.e. call in, email).
11	If time and resources were not an issue, would you prefer (a) signed informed consent or (b) option to not [opt-out] participate for this project?
12	Explain what you think is more important: to conduct this research or to have informed consent?
13	Overall, do you think it is acceptable to do this kind of pilot study using the “option to refuse” approach? Why?

Table III

Questions Asked by Participants

Category of Questions	Representative Examples
NBS-related questions	What do they screen for? When did it begin? How many screens? Who pays for NBS? Do they get consent for NBS? Do they test for carriers? What is the accuracy of NBS? Did each of the NBS tests undergo population-based pilot study before being included? Why are they not educating about NBS prenatally? Is this supported by state legislatures? What about home births? Has any test been removed from NBS? How are tests added to NBS? Do you test for cancer? How do they educate parents about NBS now? Can you opt out of NBS?
SMA-related questions	Is SMA genetically linked? How long have they known about SMA? Why is it now being researched? What are the treatments? Is there a cure? How is this passed on to kids? Do boys and girls get this? What happens if they test positive for type 3 SMA? What is the incidence of SMA to the other tests on NBS? What is the difference between SMA and muscular dystrophy? Will you identify carriers? When and how are you typically diagnosed with SMA? How effective is drug therapy and physical therapy? Are there any risk factors?
Population-based research related questions	What if they identify more kids before the study ends? Why is it so hard for hospitals to talk to people about this? Why include only two states for this research? What are examples of other population-based research? What are the risks to population-based research? How do you compensate participants in this type of research? How do you notify people if you found something typically? What are the legal obligations to inform people about this type of research?
Risks	Are drug companies funding this? How will my insurance be affected if my child is diagnosed with this? How likely is it to get a false positive? What are the health laws to protect us?
Pilot study specific questions	If my child tests positive, what type of services will I get? Are you keeping any identifying information with the samples during the pilot study? How should one opt-out? What is the timeframe of this study? Who approves this study? How can you use leftover blood? What if you get more false positives than anticipated? How accurate is the test? How many kids do you anticipate identifying? How will the researchers double check if you get an initial positive result? Is there treatment included in this study? Can you tell which type of SMA you have from the blood test?