Parental Permission for Pilot Newborn Screening Research: Guidelines From the NBSTRN

abstract

There is broad recognition of the need for population-based research to assess the safety and efficacy of newborn screening (NBS) for conditions that are not on current panels. However, prospective population-based research poses significant ethical, regulatory, and logistical challenges. In the context of NBS, there have been a variety of approaches that address parental decision-making in pilot studies of new screening tests or conditions. This article presents an ethical and legal analysis of the role of parental permission by the Bioethics and Legal Work Group of the Newborn Screening Translational Research Network created under a contract from the National Institute of Child Health and Human Development to the American College of Medical Genetics and Genomics. Circumstances are outlined in which a waiver of documentation of permission or a waiver of permission may be ethically and legally appropriate in the NBS context. These guidelines do not constitute American Academy of Pediatrics policy. *Pediatrics* 2014;133:e410–e417

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KEY WORDS

newborn screening, research, research ethics, informed consent, parental permission

ABBREVIATIONS

IRB—institutional review board

NBS—newborn screening

NBSTRN—Newborn Screening Translational Research Network

PCP—primary care provider

SACHDNC—Secretary's Advisory Committee on Heritable Diseases in Newborns and Children

Dr Botkin conceptualized and designed the project and drafted portions of the manuscript; Dr Lewis was involved in project concept and design and drafted portions of the manuscript; Drs Watson and Swoboda were involved in project concept and design and edited the manuscript; Ms Anderson, Dr Berry, Ms Bonhomme, Drs Comeau and Goldenberg, Ms Levy-Fisch, and Drs Therrell, Tarini, and Wilfond were involved in project conference and edited the manuscript; Drs Brosco and Goldman discussed and edited the manuscript; and all authors approved the final manuscript as submitted.

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Newborn screening (NBS) is widely recognized as one of the nation's most effective public health programs. Despite this success, NBS programs continue to be challenged by a lack of adequate data on which to make policy decisions.¹ The Secretary's Advisory Committee on Heritable Diseases in Newborns and Children (SACHDNC) was established in 2004 to advise the Secretary of Health and Human Services on issues relevant to the screening of newborns and children. The SACHDNC developed an evidence-based process for additions to the NBS panel and to promote greater uniformity across the nation in state NBS panels.² In 2006, the American College of Medical Genetics issued an influential report that advocated a uniform panel of 29 conditions for NBS.³ The recommended panel was supported by the SACHDNC and the American Academy of Pediatrics and has been adopted by most US states as the core panel.

Nevertheless, challenges remain regarding the conduct of appropriate population-based studies of new NBS tests or conditions to support an evidence review process.⁴ After a new candidate for population screening is identified on the basis of smaller-scale studies, a population-wide pilot study is desirable to assess the analytical feasibility, clinical predictive values of the test technology, assess the ability of the screening system to conduct high-volume screening and short-term follow-up, and evaluate the efficacy of early intervention for improving clinical outcomes in affected children.

Population-based pilot studies are difficult to perform because of their high cost and organizational challenges. A significant, recurring problem is how to appropriately engage parents in decision-making in the context of population-based pilot studies. Under federal human subjects regulations, the informed permission of parents for the

enrollment of their children in research is a basic requirement in all research unless the research is deemed by an institutional review board (IRB) to fall within 1 of several categories: (1) human nonsubject research, (2) exempt from the federal regulations, or (3) meeting the criteria for a waiver of parental permission. How these categories apply in the context of population-based research has not been settled.

The federal regulations governing human subjects research were not developed with population-based screening research in mind, so it is not surprising that various studies in this domain have been approved under different approaches to parental permission. The Wisconsin cystic fibrosis NBS study was initiated in the mid-1980s.⁵ This study was IRB-approved to provide new parents with information about the study in written form and to enable parents to opt out of participation. Written documentation of permission was not required. The Massachusetts pilot studies evaluating NBS for an expanded set of metabolic conditions and for cystic fibrosis was IRB-approved and required parents to "opt in" to screening.^{6,7} However, the protocol involved educational brochures distributed prenatally and at birth and verbal permission from parents. Written documentation was only required if parents declined to participate. This approach led to a high level of study participation and was used again for implementation of a pilot evaluation of NBS for severe combined immunodeficiency in Massachusetts, beginning in 2009. In Wisconsin, a recent pilot study of severe combined immunodeficiency screening was conducted under a waiver of parental permission. In contrast, for the California pilot study of tandem mass spectrometry, the state IRB required a signed consent form for participation, in addition to approval by individual hospital IRBs. This study was severely

hampered by recruitment rates that were <50%, due primarily to a refusal by many hospitals and individual staff members to present the research opportunity to parents.^{8,9} An alternative approach to a pilot conducted on a research basis is for states to mandate addition of a new condition to the routine panel. This approach has been taken by New York state in its program for screening for Krabbe disease.^{10,11} The Krabbe addition was not reviewed by an IRB, and parents are not asked for permission for their child's participation in the screening.¹²

These experiences illustrate that approaches to new additions to state panels have spanned a spectrum from a clinical research model with written permission to a legislative mandate model without parental permission. Experience also indicates that a permission model that entails a signed consent form poses serious challenges for pilot studies involving tens or hundreds of thousands of individuals. Two commentaries in the literature support a determination that NBS pilot studies can qualify for a waiver of parental permission in certain circumstances, but clearly IRBs and investigators remain uncertain about the appropriate approach.^{13,14}

This report is a result of a consensus conference sponsored by the Newborn Screening Translational Research Network's (NBSTRN's) Bioethics and Legal Issues Work Group to assess questions related to parental permission for NBS pilot studies. The Work Group anticipates that concerns over parental permission for pilot NBS studies will be a recurring problem as new conditions are considered for inclusion in NBS programs. The Work Group did not formally discuss permission models for specific conditions. The question addressed by the Work Group was, "Is a waiver of written informed permission ethically and legally appropriate

in some circumstances in pilot studies of new newborn screening tests or conditions?"

METHODS

The NBSTRN was created under a contract from the Eunice Kennedy Shriver National Institute of Child Health and Human Development to the American College of Medical Genetics and Genomics to develop a comprehensive research infrastructure that allows investigators access to robust resources for NBS research. In its development phase, the NBSTRN comprised a Standing Committee and 4 main work groups: Clinical Centers, Laboratories, Bioethics and Legal Issues, and Information Technology.

There were 35 participants in the meeting, including experts in NBS, public health, biomedical ethics, research ethics, health law, public policy, pediatrics, medical genetics, and laboratory medicine. Two of the participants were lay advocates with expertise in NBS issues. The findings and guidelines discussed in this article represent the views of the Bioethics and Legal Issues Work Group of the NBSTRN and do not necessarily reflect the views of all participants. These guidelines do not reflect American Academy of Pediatrics policy or guidance.

The meeting was held on September 15 and 16, 2011, in Salt Lake City, Utah. An attempt was made to articulate a consensus position on key points in the discussion. Subsequently the manuscript was reviewed and revised by the Bioethics and Legal Issues Work Group.

Principles and Underlying Assumptions Used to Develop the Guidelines

Several key principles and underlying assumptions were identified:

- Pilot studies are vital to the development of a strong evidence base

to support decision-making regarding the addition of new conditions to the uniform panel, or state NBS panels, or to adopt new technologies for NBS.

- Participants recognized the need for state departments of health to conduct quality assurance/quality improvement activities to continue to provide high-quality NBS services.
- Any research activities designed to improve NBS must not jeopardize the public health mission of state NBS programs.
- Maintaining the public's trust in NBS is of paramount importance.

POINTS OF GENERAL AGREEMENT

Definition of "Pilot Studies"

Point 1. For purposes of this statement, NBS "pilot studies" are defined as research 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.

In general, "pilot studies" for the purposes of this statement are studies conducted before approval for inclusion in the national Recommended Uniform Screening Panel by SACHDNC or approval by authorities at the state level. Because of the need to evaluate outcomes for screened newborns, pilot studies under this definition involve identifiable participants. This definition excludes quality assurance/quality improvement projects.

Point 2. Pilot studies should be considered "research" and therefore should be subject to human subjects research protections.

The federal regulations to protect human research subjects define "research" as "a systematic investigation, including research development, testing and evaluation, designed to develop

or contribute to generalizable knowledge."¹⁵ Pilot studies as defined here fit within this definition.

Framework for Screening for Conditions When the Evidence Base Is Incomplete

Advocacy for the inclusion of certain conditions on state panels has led to state legislative mandates for screening despite an incomplete body of supporting evidence.

Point 3. Pilot studies should be conducted under a research paradigm rather than through public health authority when there are insufficient data for evidence review bodies such as the SACHDNC to make an informed recommendation regarding inclusion on NBS panels.

Parental Education Regarding Pilot NBS Research

It is imperative that pilot research be conducted in a manner that is ethical and consistent with human subjects research protections. Education of parents about NBS and the pilot study was considered essential regardless of the permission model used.

Point 4. Parental education and choice are essential regarding participation in pilot NBS protocols. Regardless of the specific approach taken, substantial efforts should be made to inform parents about pilot protocols and to enable a decision-making process.

Parents should be informed of the pilot study and their choices regarding participation through high-quality, linguistically appropriate educational materials. Multiple avenues and levels of information should be made available to parents, including informational brochures and information on the state NBS Web site. These educational materials should be provided prenatally, when possible, and during the

immediate postpartum period. In addition, prenatal and postnatal care providers should be informed about the research protocol and where to refer parents for additional information.

Waivers of Parental Permission

IRBs can make a determination to waive informed consent entirely, to alter or modify the requirements for informed consent, or to waive only the documentation of informed consent. We discuss waivers of informed consent in this section and waivers of documentation of informed consent subsequently.

Federal human subjects research regulations require that legally effective informed consent be obtained from a research subject or the subject's legally authorized representative to involve a human being as a subject in research covered by the regulations.¹⁶ Except under certain circumstances, informed consent must be documented by the use of a written consent form signed by the research subject or the subject's legally authorized representative.¹⁷ The regulations permit an IRB to waive the requirement to obtain informed consent if 4 criteria are met:

1. the research involves no more than minimal risk to the subjects,
2. the waiver of consent will not adversely affect the rights and welfare of the subjects,
3. the research could not practicably be carried out without the waiver, and
4. whenever appropriate, the subjects will be provided with additional pertinent information after participation.

Working group participants concluded that each of these criteria may be met in the context of NBS pilot studies in certain circumstances. However, we emphasize that a potential waiver of parental permission is only relevant to the screening portion of a pilot study.

The infants who screen positive may be recruited for additional studies involving treatment interventions and/or long-term surveillance that would typically involve written parental permission.

Each criterion for a waiver of permission is discussed separately.

1. Minimal Risk

For the requirement to obtain informed consent to be waived, proposed research must involve no more than minimal risk. Under the federal regulations, "*Minimal risk* means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."¹⁸ Research may be considered minimal risk if the prior probability of significant adverse outcomes is considered to be low.

Several factors should be considered when making the determination whether a research protocol would involve more than minimal risk. In general, the risks of pilot studies involve the impact of false-positive and true-positive results. False-positive results are expected in screening for rare conditions, and determining the incidence of false-positive results may be an important outcome in a pilot study. True-positive results could be considered a risk rather than a benefit only if the early identification and treatment of a condition through screening is worse for the infant than a diagnosis after symptoms. This risk can be minimized if appropriate studies have been conducted before a population study.⁴ False-negative results are not considered a significant research risk in this situation because affected children would not have been identified in the absence of a pilot protocol, although the risk of false reassurance of clini-

cians in the event of a false-negative result should be considered and addressed in professional education materials.

The following factors relate to the risk of true- and false-positive results and should be considered individually and collectively.

- What is known about the analytic validity and clinical validity of the screening test? A pilot study should not be considered minimal risk if there is limited evidence of test characteristics in the population under study. There are known psychological burdens of false-positive results.^{19–21} Furthermore, in some circumstances, a positive screen may require a family to travel long distances for subspecialty evaluations to make a definitive diagnosis. Limited specificity for some tests also means that results may yield findings of uncertain clinical significance, incidental findings related to other conditions, or carrier status. Research has shown that these types of results can be distressing for parents and confer risks associated with labeling and additional diagnostic testing.²² Therefore, a pilot study using a test with a poor positive predictive value should not be considered minimal risk.
- How invasive or costly is diagnostic testing after a positive screening test? This issue is of particular concern for newborns with false-positive results who otherwise would not undergo diagnostic testing. Burdensome or costly diagnostic testing is also a consideration for affected children if early detection and treatment prove not to be beneficial for the infant.
- What are the risks of a loss of privacy or confidentiality and

secondary stigma or discrimination? Participation in NBS research can increase the risk of the loss of confidentiality of patient information. Privacy and confidentiality protections must be in place and are necessary for a pilot study to be considered minimal risk.

- How will research results be disclosed to parents? NBS programs typically rely on primary care providers (PCPs) to disclose initial positive results. However, research shows that many PCPs have limited understanding of many NBS conditions and are often uncomfortable with this role.^{23,24} Therefore, disclosure of pilot research results by PCPs may increase the risk of misinformation. A carefully designed protocol to disclose results through the investigators or knowledgeable clinicians will reduce the risk of misinformation.

Point 5. A protocol for pilot NBS research may involve no more than minimal risk if the following criteria are met:

- on the basis of reasonable evidence, the screening test is considered to have a relatively high positive predictive value (meaning the risk of false-positives or results of unknown significance, etc is acceptably low),
- diagnostic confirmation of the condition is of low risk to participants and will not subject them to substantial additional burdens, and
- research results will be disclosed to participants in a manner that maximizes efficient and accurate disclosure.

2. Rights and Welfare of the Subjects

For the requirement to obtain informed consent to be waived, the waiver of

consent must not adversely affect the rights and welfare of the research subjects. This criterion has not been further defined within the federal regulations. State laws may create additional rights with respect to research participation and informed consent that must be considered. In addition, screening for conditions that might be considered culturally sensitive to subgroups within the population could threaten the welfare of some individuals or groups.

3. Impracticability

For the requirement to obtain informed consent to be waived, it must not be practicable to conduct the research without the waiver. The federal regulations do not define “practicable,” but guidance by the Secretary’s Advisory Committee on Human Research Protections suggests that the bar for impracticability should be set relatively high.²⁵ That is, informed consent should not be considered impracticable just because obtaining consent is difficult or somewhat more expensive. However, consent can be considered impracticable if low recruitment rates secondary to a written permission process are likely to prevent valid conclusions from being drawn for the pilot study. Accordingly, recommendations from Secretary’s Advisory Committee on Human Research Protections suggest that scientific validity is relevant to a determination of practicability, including circumstances such as when “The sample size required is so large (e.g., population-based studies, epidemiology trials) that including only those samples/records/data for which consent can be obtained would prohibit conclusions to be drawn or bias the sample such that conclusions would be skewed.”²⁵

Furthermore, obtaining meaningful written informed consent to participate in research from parents of tens or

hundreds of thousands of infants at dozens or hundreds of birthing centers within a typical project timeline can be an enormous logistical challenge, as well as expensive. Although a determination of whether the research could not practicably be carried out without the waiver should rarely be based on resources alone, the substantial resources required to obtain written-informed consent in this arena are relevant to a determination of practicability. If a formal permission process is to be meaningful, staff must act as investigators to present the information in a knowledgeable fashion. When pilot studies involve dozens or hundreds of birthing facilities with hundreds or thousands of nursery staff, the logistical challenges of this approach are evident.

Point 6. Written informed permission for pilot NBS research may be considered impracticable in certain circumstances. Several factors are relevant to this determination. A key factor is the number of newborns necessary to enroll to draw valid study conclusions. Furthermore, the number of institutions in which permission would be sought and the number of personnel who would be involved in recruiting are relevant considerations.

4. Providing Research Subjects With Pertinent Information After Participation

For the requirement to obtain informed consent to be waived, the research subjects must be provided with additional pertinent information after participation in the research, when appropriate. This information may include the results of the research conducted under the pilot study. Returning both positive and negative results in this context may be part of an assessment of how to incorporate the condition into the NBS program. However,

return of positive and negative results pose different considerations.

Point 7. It will be necessary to return all positive results in all circumstances in which the clinical efficacy of screening is being evaluated. Several factors should be considered regarding how to return positive results:

- Only results of tests that have been conducted in a laboratory certified under the Clinical Laboratory Improvement Amendments (a CLIA-certified laboratory) may be provided to participants for clinical decision-making.
- The individuals returning the results should be able to accurately interpret the test results, respond to the information, and provide informed counsel to parents.
- Any additional workload associated with the return of results on the NBS programs must be considered and minimized.
- Whether, how, and when to return test results that are not the target of the research (ie, ancillary or unanticipated findings such as carrier status) must be considered, and information should be provided to parents about the approach being used.

The return of negative test results was the subject of considerable discussion by our meeting participants. There was a strong opinion expressed by some that parents have a right to all research results, particularly if research is conducted under a waiver of permission. Others felt that the logistical problems of returning large numbers of negative results could threaten the feasibility of population-based pilot studies. Although the small number of positive test results can be disclosed by investigators or selected specialists, negative test results would need to be disclosed by PCPs because of the large

numbers involved. Enabling PCPs to serve this role in an appropriate fashion is a substantial logistical challenge for a pilot study and entails the risk that some parents would not receive accurate information. No consensus was achieved on this point.

Point 8. Whether and how positive and negative results of pilot studies will be returned to families should be included in the information provided to parents about the pilot study.

Waiver of Documentation of Consent

It may be appropriate in some circumstances to waive the requirement to document informed permission rather than to waive the requirement to obtain informed permission. An IRB may waive the requirement to obtain written informed permission if it finds “that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.”²⁶ Because NBS does not require informed permission outside of the research context in almost all states, it may be appropriate to waive the requirement to document informed permission if it is determined that participation would involve no more than minimal risk to research participants.

For a waiver of documentation to be effective, newborn nursery staff members or others who are obtaining the verbal consent must be sufficiently trained and motivated to conduct this dialogue with new parents. The lack of a requirement to document informed permission may facilitate population-based research by reducing logistical challenges, but this approach does not guarantee that the research will be conducted with parental knowledge and permission if staff give cursory attention to information and the permission process.

Use of an “Opt-Out” Approach

Alternatively, in certain circumstances, it may be legally and ethically appropriate to waive the requirement to obtain informed permission but maintain the obligation to inform parents of the study and to enable parents to opt out at their discretion. This approach is conceptually distinct from the situation in which a waiver to document informed consent has been granted because if an opt-out approach is used, there is no affirmative obligation to obtain verbal permission from parents for participation in the pilot study. Rather, parents must be provided with information about the research and their option to refuse, but their infant will participate unless the parents decide otherwise.

Point 9. The Working Group participants determined that an opt-out approach can be justified when a pilot study meets the criteria for a waiver of informed permission. However, the opt-out approach is only ethically and legally appropriate if the ability to opt out is clearly communicated to parents in the educational information provided to them, and if the mechanism through which they can exercise their choice is not unduly complex or burdensome.

Under an opt-out approach, greater emphasis typically is placed on the education of parents through informational media such as brochures or short videos in the postpartum hospital environment rather than through dedicated time with staff. This is the approach used for educating parents about NBS generally, including their ability to opt out in most states. However, the quality of NBS brochures has generally been considered to be suboptimal.²⁷ In the context of a pilot study, use of high-quality supplemental educational materials in appropriate languages and levels of complexity is appropriate.

CONCLUSIONS

Research is an essential component of safe and effective NBS programs. The contemporary standard is for decisions regarding the inclusion of new conditions on NBS panels to be evidence based, although it is recognized that evidence for the inclusion of rare conditions may not be as robust as is often desired. When screening for rare conditions, a population-based pilot study is often necessary to develop evidence for policy decisions that will affect millions of children and families each year. Tension exists between this imperative to conduct research and the ethical standards required to promote informed decision-making by parents for the enrollment of their children in research. Our broad conclusion is that a waiver of a formal permission process with a signed consent document is

appropriate in some circumstances in which the criteria for waiver of permission are met. However, parental information and choice about newborn participation are essential to the ethical conduct of pilot studies in NBS.

ACKNOWLEDGMENTS

Members of the Bioethics and Legal Work Group of the National NBSTRN are as follows: Steve Dobrowolski, PhD, Children's Hospital of Pittsburgh; Amy Brower, PhD, American College of Medical Genetics; Felipe Vizcarrondo, MD, Uniformed Health Services University

Conference participants were as follows: Don Bailey, PhD, RTI; Paul Levy, MD, Children's Hospital and Montefiore; Nancy Green, MD, Columbia University Medical Center; Richard Harward, Utah Health Department; Jeff Galinkin, MD, University of Colorado; Ann Johnson,

University of Utah; Tara Newcomb, MS; Sara Copeland, MD, Health Resources and Services Administration; Leslie Francis, PhD, JD, University of Utah; Debra Skinner, PhD, University of North Carolina; Richard Olney, MD, MPH, Centers for Disease Control and Prevention; Alan Fleischman, MD, March of Dimes; Erin Rothwell, PhD, University of Utah School of Medicine; Harper Randall, MD, Utah Health Department; Marci Sontag, PhD, University of Colorado, Denver; Ellen Clayton, MD, JD, Vanderbilt University; Iona Thraen, ACSW, University of Utah; John Stillman, University of Utah; Rebecca Anderson, BSN, RN, University of Utah

We thank the American College of Genetics and Genomics and the following individuals for their support of this work: Amy Hoffman, Rebecca Anderson, Sara Copeland, Heather Sudbury, and Irina Smotrich.

REFERENCES

1. American Academy of Pediatrics. Serving the family from birth to the medical home. Newborn screening: a blueprint for the future—a call for a national agenda on state newborn screening programs. *Pediatrics*. 2000;106(2 pt 2):389–422
2. Perrin JM, Knapp AA, Browning MF, et al. An evidence development process for newborn screening. *Genet Med*. 2010;12(3):131–134
3. American College of Medical Genetics Newborn Screening Expert Group. Newborn screening: toward a uniform screening panel and system—executive summary. *Pediatrics*. 2006;117(5 pt 2):S296–S307
4. Botkin JR. Research for newborn screening: developing a national framework. *Pediatrics*. 2005;116(4):862–871
5. Taylor HA, Wilfond BS. Ethical issues in newborn screening research: lessons from the Wisconsin cystic fibrosis trial. *J Pediatr*. 2004;145(3):292–296
6. Atkinson K, Zuckerman B, Sharfstein JM, Levin D, Blatt RJ, Koh HK. A public health response to emerging technology: expansion of the Massachusetts newborn screening program. *Public Health Rep*. 2001;116(2):122–131
7. Comeau AM, Levin D. Population-based research within a public health system: two models for common rule compliance in the Massachusetts Newborn Screening Program. In: Bailey M, Murray T, eds. *Ethics and Newborn Genetics Screening: New Technologies, New Challenges*. Baltimore, MD: Johns Hopkins Press; 2009:274–291
8. Feuchtbaum L, Cunningham G, Sciortino S. Questioning the need for informed consent: a case study of California's experience with a pilot newborn screening research project. *J Empir Res Hum Res Ethics*. 2007;2(3):3–14
9. Pass K, Green NS, Lorey F, Sherwin J, Comeau AM. Pilot programs in newborn screening. *Ment Retard Dev Disabil Res Rev*. 2006;12(4):293–300
10. Kemper AR, Knapp AA, Green NS, Comeau AM, Metterville DR, Perrin JM. Weighing the evidence for newborn screening for early-infantile Krabbe disease. *Genet Med*. 2010;12(9):539–543
11. Duffner PK, Caggana M, Orsini JJ, et al. Newborn screening for Krabbe disease: the New York State model. *Pediatr Neurol*. 2009;40(4):245–252, discussion 253–255
12. Ross LF, Waggoner DJ. Parents: critical stakeholders in expanding newborn screening. *J Pediatr*. 2012;161(3):385–389
13. Botkin JR. Parental permission for research in newborn screening. In: Bailly MA, Murray TH, eds. *Ethics and Newborn Genetic Screening*. Baltimore, MD: Johns Hopkins University Press; 2009:255–273
14. Tarini BA, Burke W, Scott CR, Wilfond BS. Waiving informed consent in newborn screening research: balancing social value and respect. *Am J Med Genet C Semin Med Genet*. 2008;148C(1):23–30
15. Code of Federal Regulations, Title 45, Public Welfare. 45CFR46.102(d)
16. Code of Federal Regulations, Title 45, Public Welfare. 45CFR46.116
17. Code of Federal Regulations, Title 45, Public Welfare. 45CFR46.117
18. Code of Federal Regulations, Title 45, Public Welfare. 45CFR 46.102(i)
19. Gurian EA, Kinnamon DD, Henry JJ, Waisbren SE. Expanded newborn screening for biochemical disorders: the effect of a false-positive result. *Pediatrics*. 2006;117(6):1915–1921
20. Tarini BA, Christakis DA, Welch HG. State newborn screening in the tandem mass

- spectrometry era: more tests, more false-positive results. *Pediatrics*. 2006;118(2):448–456
21. Tluczek A, Kosciak RL, Farrell PM, Rock MJ. Psychosocial risk associated with newborn screening for cystic fibrosis: parents' experience while awaiting the sweat-test appointment. *Pediatrics*. 2005;115(6):1692–1703
 22. Timmermans S, Buchbinder M. Patients-in-waiting: living between sickness and health in the genomics era. *J Health Soc Behav*. 2010;51(4):408–423
 23. Hayeems RZ, Miller FA, Little J, et al. Informing parents about expanded newborn screening: influences on provider involvement. *Pediatrics*. 2009;124(3):950–958
 24. Kemper AR, Uren RL, Moseley KL, Clark SJ. Primary care physicians' attitudes regarding follow-up care for children with positive newborn screening results. *Pediatrics*. 2006;118(5):1836–1841
 25. Office for Human Research Protections, Department of Health and Human Services. SACHRP letter to HHS secretary. Available at: www.hhs.gov/ohrp/sachrp/sachrpletter013108.html. Accessed March 21, 2012
 26. Code of Federal Regulations, Title 45, Public Welfare. 45CFR46.117(c)
 27. Fant KE, Clark SJ, Kemper AR. Completeness and complexity of information available to parents from newborn-screening programs. *Pediatrics*. 2005;115(5):1268–1272

(Continued from first page)

www.pediatrics.org/cgi/doi/10.1542/peds.2013-2271

doi:10.1542/peds.2013-2271

Accepted for publication Oct 31, 2013

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development contract HHSN275200800001C and the National Institutes of Health grant R01HD069045. Funded by the National Institutes of Health (NIH).

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.