

ETHICAL ISSUES IN NEWBORN SCREENING RESEARCH: LESSONS FROM THE WISCONSIN CYSTIC FIBROSIS TRIAL

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Newborn screening (NBS) is a well-established approach to genetic testing, with a 40-year history of improving public health.¹ With advances in technology, the number of diseases that are included in NBS programs is anticipated to expand over the next decade.² With the technological advances, a consensus, supported by a number of national expert groups, has been emerging that clinical trials to assess clinical validity and utility are important before the introduction of new genetic tests (including NBS tests) into clinical practice.³⁻⁸ In fact, randomized trials of early interventions for sickle cell anemia and cystic fibrosis (CF) commenced in the 1980s influenced the rapid introduction of NBS in the former case⁹ and a more conservative approach in the latter case.¹⁰ Thus, proposals for randomized, clinical trials may be anticipated for conditions for which NBS has been suggested, including Duchenne muscular dystrophy,¹¹ fragile X syndrome,¹² severe combined immune deficiency,¹³ and organic acidemias.¹⁴ Newborn screening research raises complicated ethical issues related to risk/benefit assessment, use of control groups, withholding of information, and informed consent.¹⁵ Although the design of future NBS trials will depend on the specific disorder under study and the outcome of interest, we believe that the randomized, controlled trial, despite the large sample and time investment required when studying relatively rare disorders, can be scientifically and ethically justified to determine the utility of NBS tests before their introduction into clinical practice.

We will describe the ethical issues that confronted the randomized, controlled trial of CF NBS conducted in Wisconsin between 1985 and 1998. Fost and Farrell¹⁶ initially discussed the ethical issues related to the design of this trial in 1989. Subsequently, a civil suit was filed by the parents of a child with CF who was in the control group.¹⁷ Although the suit has been discussed in the popular press,¹⁸ there has not been a recent analysis of the ethical issues published in the medical literature. We examine how the study design and approach to parental permission would be considered by the current federal research regulations (the Common Rule). This analysis will provide ethical guidance to investigators, health departments, institutional review boards (IRB), and funding agencies that may be considering clinical trials of NBS for other conditions.

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THE WISCONSIN CYSTIC FIBROSIS NEWBORN SCREENING TRIAL

The trial involved more than 650,000 infants and was one of the largest public health studies ever conducted.¹⁹ The primary empirical question was whether children with CF had improved health outcomes from early diagnosis and intervention that would outweigh any risks from NBS.²⁰ Although it was possible that early intervention may improve nutritional status or pulmonary function, there was concern that more frequent medical evaluations and antibiotic use might result in earlier acquisition of respiratory pathogens, such as *Pseudomonas aeruginosa*. The psychologic risks of early diagnosis to CF children and to families of children who had false-positive screening results were also of concern.

Beginning in April 1985, all children born in Wisconsin (approximately 70,000 per year) were screened by means of immunoreactive trypsinogen (IRT) analysis performed on dried blood spots that had been routinely collected for standard newborn screening tests.¹⁹ Infants were alternatively assigned to a "screening diagnosis group" or a "symptom diagnosis group."

In the "screening diagnosis group," elevated IRT results were forwarded to parents by their primary physician within 6 weeks after birth. Parents of children whose IRT was

CF	Cystic fibrosis	IRT	Immunoreactive trypsinogen
IRB	Institutional review board	NBS	Newborn screening

greater than 180 ng/mL (99.8th percentile) were asked to bring their children to a CF center for a diagnostic sweat chloride test (7 of 8 children with an elevated IRT did not have an elevated sweat chloride and were considered false-positives). In 1991, an IRT/DNA approach was implemented that reduced the number of false-positives to 5 children per patient with CF identified.²¹ Parents of children diagnosed with CF were asked to participate in a longitudinal epidemiologic study in which their children were provided with routine cystic fibrosis care,²² including pancreatic enzymes, vitamins, and antibiotics, thereby increasing the number of children treated earlier.

The blood samples assigned to the “symptom diagnosis group” were analyzed for IRT but not processed fully and not reported to the investigators, providers, or parents. The raw IRT data were retained in a computer database and reported to the parents when either the child was subsequently diagnosed with CF, the fourth birthday was reached, or a request was made by the parent (to be discussed below). It was the case at the time the study was initiated and remains true today that approximately 50% of children are diagnosed with CF on the basis of symptoms by 6 months of age and 90% are diagnosed by age 4 years.²³ When children in the “symptom diagnosis group” were diagnosed with CF, they were also offered enrollment in the longitudinal study.

A number of arguments were put forth to justify a “symptom diagnosis” control group: The children assigned to the control group were not denied an effective standard of care (there was professional uncertainty regarding the benefits and risks of screening and early intervention), the interventions to which the children in the study group were exposed had potential risks, and the validity of the study would be reduced in the absence of a control group.¹⁶

Additional considerations prompted the specific design, which involved the testing and then nondisclosure of IRT results to half of the parents. It was necessary to completely identify the asymptomatic patients to avoid a selection bias that would have occurred if only symptomatic children were included in the “symptom diagnosis group.” This included the “unblinding” of newborn IRT results of children in the “symptom diagnosis” group when each child reached 4 years of age to identify any children with CF who had not yet been diagnosed. This study design was developed through interactions with several IRBs, ethics consultants, focus groups of parents, the CF Foundation, and NIH study sections.¹⁶

A randomized, controlled trial for CF NBS was justified. When faced with a screening test for a condition in which the clinical value of early intervention is uncertain, there is an ethical imperative to conduct an adequate trial to determine both the benefits and harm of early intervention. Furthermore, it is important to assess the utility of a NBS program to deliver this benefit.²⁴ The alternative, the widespread adoption of NBS in absence of reasonable evidence of efficacy of early intervention and the utility of the NBS approach, might expose children and families to unnecessary harm. Additionally, such adoption could be a significant cost to society without compensating benefits. Given the potential

for many more tests to be included in NBS without empirical evidence of benefits and harm, this justification is even more salient today.

WAIVING DOCUMENTATION OF PARENTAL PERMISSION

Despite the justification of the trial design, the approach used to address the issue of parental permission could be improved in future NBS research. The investigators maintained that given the barriers to obtaining permission from more than 70,000 parents per year, that “meaningful consent could not be relied on as an essential condition for conducting the study.”¹⁶ A brochure was provided at the time of birth that “explained the research project along with background information on CF and disclosing options available to parents (including the option to refuse CF screening test).”¹⁹ However, parents were not asked to sign a permission form. It appears that the IRBs waived *documentation* of permission,²⁵ although this was not explicitly stated in the study publications.^{16,19}

To waive documentation, the Common Rule requires that the risks of a study must not be greater than minimal, defined at the time of the study as the “probability and magnitude. . . . ordinarily encountered in daily life or during performance of routine physical or psychologic examinations.”²⁶ The IRB would have had to determine that the risk to infants in each group was not more than minimal risk. For the “symptom diagnosis” group, there were no additional risks in comparison to infants in states without screening. As noted above, the primary risk to children randomly assigned to the “screening diagnosis” group was early acquisition of respiratory pathogens and the psychologic risk of early diagnosis of CF. In addition, there was some psychologic risk to the families who received false-positive screening results. For the IRBs to have assessed the risks to the “screening diagnosis” group as no more than minimal, they must have concluded that for the CF subjects, these risks would be ordinarily encountered, but just encountered earlier compared with infants in states without screening. For the false-positive subjects, they must have concluded that the probability and magnitude of harm of a false-positive test result was similar to that experienced by infants in routine newborn screening. In the absence of such a conclusion, written documentation of permission could not have been waived.

The second criterion to waive documentation is that permission is not routinely obtained outside of the research setting. In the 1980s, there was no standard for obtaining documentation of “informed consent” for routine NBS.²⁷ In fact, a recent report from the Newborn Screening Task Force of the American Academy of Pediatrics and the Health Services Research Administration still maintains that documentation is not necessary for tests of proven validity and utility, although parents should be informed about testing and be able to refuse testing.²⁸

Although both criteria may have been satisfied to waive documentation at the time the study was conducted, the current Task Force Report recommendations explicitly state that screening done in a research context should be accompanied by written documentation.²⁸ This recommendation is misguided because it focuses on documentation rather than permission per se. A signature does not guarantee understanding.²⁹ In contrast to the recommendation from the Task Force Report, CF NBS was begun in Massachusetts in 1999 as a research study, and the permission process developed intended to get permission from all parents but did not require a written signature.³⁰ Assessment of the Wisconsin investigators' assertion that "meaningful" consent cannot be relied on in NBS research may depend on future evaluation of the Massachusetts experience. Although it may not be feasible to ensure that all parents fully understood the research, it does not follow that it is impracticable to attempt disclosure.

ETHICAL ISSUES WITH THE PERMISSION PROCESS AND CONTENT OF DISCLOSURE

A waiver of documentation of permission for investigational NBS may be justified ethically. However, it is not ethically justified to waive *any attempt* to disclose the study. A *reasonable attempt* should be made to disclose information about the research to parents. In fact, although the Wisconsin investigators did not obtain written documentation, an effort was made to disclose key features of the study. However, the manner in which parents were notified about the CF study and what they were told may not have reached the "reasonable attempt" threshold that should be met in future studies.

Parents were notified about the CF study at the time of childbirth, when they were given a brochure about NBS. Given that disclosure coincided with delivery, parents may not have had adequate time to review and understand the information provided nor make a thoughtful decision about their participation in the trial. Furthermore, the cover of the brochure included only a title such as, "Neonatal Screening in Wisconsin." Information about CF testing was embedded inside the brochure, so only those parents who opened the brochure would realize that a study was underway. Finally, although most of the information in the brochures is clear, including a statement that parents had the option to refuse CF testing, information provided about the way in which the blood samples were to be handled and parental notification of results was ambiguous. The following language appeared in the 1986, 1988, and 1989 versions of the Wisconsin Division of Health newborn screening brochure:

... Wisconsin currently is including research to test whether early treatment of CF (detected during the newborn screening) is better than treatment begun after a child develops certain symptoms. The CF test does not require any extra blood, and will be performed at no added cost to parents. The CF test will be done on alternate blood specimens, with positive results reported to your baby's doctor by a CF specialist doctor. The remaining blood specimens

will be partly tested with the CF test, with the final results completed and reported to your doctor in 4 years. The reason diagnosis and treatment are not offered to all babies at the time of birth is that it is not known whether early treatment is helpful."

This was an attempt to accurately convey the study design, and one of the authors (B. W.) was involved in some revisions of the brochure. However, to parents not familiar with the study, these statements are ambiguous. The language could have been improved to clarify that the complete CF test would be done on samples from every other *child* rather than on every other *specimen* to make it more clear to parents that there was a 50% chance that positive results would not be disclosed to them.

Data from the study provide evidence that parents either failed to read the brochure or failed to understand the research nature of the CF testing. Tluczek et al³¹ surveyed parents of children with false-positive results (n = 104), and although 73% were aware that Wisconsin sponsored a neonatal screening program, 73% were unaware that CF was included.

To attempt to increase the number of parents who read and understood the brochure, each parent could have been asked to review and sign a permission form. However, written consent has become so "routinized" that this approach probably would have limited value in improving parent understanding.^{32,33} Furthermore, written materials may be insufficient for the 20% of the population that is not medically literate.³⁴ For individuals with limited education, face-to-face discussion may be necessary.³⁵

The key for future studies of NBS will be careful attention to crafting the language for brochures, letters, and discussions that is not ambiguous. Written materials should undergo rigorous evaluation to ensure that individuals can easily understand the meaning. We would anticipate that with clear information about the nature of the research and the need for the use of control groups, most parents would not object to the research nor ask for results. As a practical advantage, providing clear information might diminish the likelihood of a lawsuit (to be discussed below). More importantly, it is a respectful way to treat parents. It allows those few parents who might want to opt out or obtain results to do so. However, for the vast majority of parents, it will be an expression of respect for their role as the steward of their child's interests^{27,36} and an opportunity for education about NBS research.

With the goal of improving the way in which information is shared with future parents asked to participate in clinical trials of NBS, we recommend a number of alternative approaches to increase the likelihood of meaningful disclosure. The Task Force Report recommends that standard NBS information be conveyed before labor and delivery, whenever possible.²⁸ Because research tests have more ambiguous clinical validity and utility, it is even more compelling to use this approach for NBS research. We would recommend that pregnant women be notified of routine NBS and any research study in their State during the third trimester of pregnancy. This will increase the likelihood of meaningful disclosure and

allow for discussion with health care professionals. Second, a separate brochure can be developed for a specific NBS study or a simple notation on the cover of a more generic NBS brochure that highlights the fact that a clinical trial is being conducted (eg, "Study about Cystic Fibrosis underway. Look inside for details"). Additionally, a follow-up letter can be sent to each family after the sample is obtained, to remind them about the trial, offer an opportunity to opt out, and to inform them when they will obtain results. Finally, information about the trial can be disclosed in person some time after delivery by a designated health care professional (ie, pediatrician or nurse). Obviously, such efforts are unlikely to result in 100% parental understanding, since research concepts, such as randomization, are not understood by all parents even after written descriptions and face-to-face discussion.³⁷ It will be important to include empirical assessments of the efficacy of such disclosure efforts in concert with the conduct of future NBS trials. The development of effective communication strategies to improve parents' understanding of participation in newborn screening research is a worthwhile objective.^{27,36}

LEGAL OBLIGATION TO INFORM PARENTS ABOUT THE TRIAL

The issue of whether a greater effort should have been made to inform parents in the Wisconsin study that they may be in the control group was the subject of a civil suit.¹⁷ The parents of a child who was diagnosed with symptoms at age 23 months in 1995 alleged (1) the screening test was done without their informed consent, (2) treatment was withheld when investigators had knowledge that nutritional treatment would decrease the severity of her condition, and (3) the test results were withheld. They claimed that they were harmed because if they had the results (1) they would have accepted treatment, and (2) they would not have conceived a second child (who also had CF). There were state, federal, and medical malpractice claims dismissed in summary judgment by the circuit court. The plaintiffs appealed the federal and malpractice claims to the appellate court, which affirmed the circuit court's judgment. The malpractice claims were dismissed on the grounds that the investigators did not have a physician-patient relationship with the research subject. The court never clearly addressed the substantive claim that the child was harmed because an effective treatment was withheld. However, the initial report of nutritional benefit from this trial was not reported until 1997,³⁸ and a subsequent CDC Workshop still concluded that there was not sufficient evidence for routine CF NBS in all states.¹⁰

When addressing the question of disclosure of the test results, the court maintained that the plaintiffs did not have a responsibility to explicitly disclose the test results because statutory duty to disclose results is limited to the tests explicitly included in the Wisconsin Administrative Code. CF was not one of the routine NBS tests specified by statute. Additionally, the study protocol stipulated that *results would be disclosed*,

upon request, for infants in the "symptoms diagnosis" group. The court did not address the question of whether there was any obligation to *inform parents that results would be disclosed*, upon request. Even if this judicial opinion did not define a legal duty, we argue that there is a moral duty to make a reasonable effort to inform parents.

IMPLICATIONS FOR FUTURE STUDIES

The Wisconsin CF trial typifies the fundamental ethical challenges in the design and conduct of NBS research. The presence of a control group, and the necessity of "testing" and then "withholding" results for the control group was not only justified, but necessary. Randomized, controlled trials for NBS should be advocated, on both scientific and ethical grounds, particularly when there are significant questions about the clinical value of early interventions, or about the clinical utility of NBS to achieve this value. However, the permission process used in future studies should be more robust to respect parents who might wish to know that their child is enrolled in research, including the presence of the control group, and if results are available upon request. The solution is not asking parents to sign one more unread form, but to develop and use approaches to effectively communicate with parents.

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