Minimizing Risks

The Ethics of Predictive Diabetes Mellitus Screening Research in Newborns

Lainie Friedman Ross, MD, PhD

Type 1 diabetes mellitus is the most common metabolic disease of childhood. Two states offer newborn screening to identify children with a genetic predisposition to it. It is a voluntary test offered in conjunction with the mandatory newborn metabolic screening. There are no preventive treatments, but children discovered to be at increased risk may participate in follow-up studies to determine whether and when the child develops autoantibodies (preclinical disease) or overt diabetes. This study examined the ethics of predictive genetic research in newborns for type 1 diabetes. Prediction research has serious psychosocial implications, and research designs must account for them. The study concluded that, to minimize harm to infants and their families, (1) if the research does not incorporate a prevention strategy, studies should avoid disclosure of results; and (2) if disclosure is necessary, then the research should be restricted to newborns with an affected first-degree relative.

Arch Pediatr Adolesc Med. 2003;157:89-95

DIABETES PREDICTION STUDIES IN NEWBORNS

Florida’s interest in diabetes prediction research in newborns is not unique. The BABY-DIAB studies in Germany and Australia are prospective studies from birth of children who have at least 1 parent with diabetes mellitus. The studies are designed to perform serial blood tests on the children for evidence of autoantibody development and its relationship with environmental triggers.

Although newborns with an affected first-degree relative have a 10-fold higher incidence of developing type 1 diabetes, most newborn studies do not focus on these children because they account for only 10% of type 1 diabetes cases. The Diabetes Prediction and Prevention (DIPP) study in Finland seeks to identify all newborns with HLA-DQB1 genotypes that confer a high (~8%) or moderate (1.7%-2.6%) risk of developing type 1 diabetes (compared with a national average risk of 0.7%). Approximately 94.4% of parents consent to

From the Department of Pediatrics and MacLean Center for Clinical Medical Ethics, The University of Chicago, Chicago, Ill.
genetic screening, and 14.8% of the children are found to be at increased risk. The Norwegian Babies Against Diabetes (NOBADIA) study seeks to identify the 4% of newborns in the general population with the highest genetic risk (12%) of developing insulin-dependent diabetes mellitus. Begun in 1998, this study will follow these infants for 15 years. In Colorado, the Diabetes Autoimmunity Study in the Young (DAISY) seeks to identify newborns with the highest genetic risk alleles (2.3%) to participate in serial antibody screening to prevent diabetes in infants with an affected first-degree relative. The diet was effective in non-obese diabetic mice, although some preliminary data suggest that it is ineffective in humans. After weaning from breast milk, infants enrolled in TRIGR receive exclusively either a casein-hydrolysate formula that lacks intact cow’s milk (Nutramigen; Mead Johnson & Co, Evansville, Ind) or another formula (Enfamil [Mead Johnson & Co], with 20% Nutramigen to control for taste and smell). No results are available yet.

All of the studies described above include disclosure of the child’s genetic risk to the parents. Contrast such disclosure with the consensus in the medical and medical ethics communities against clinical predictive genetic testing of children when no treatment exists. Yet, despite the medical and ethical consensus against clinical predictive testing, more than 90% of parents consent to research predictive screening of their newborns for diabetes. In the next 3 sections, I address the following questions: (1) What are the risks and benefits of such newborn research screening? (2) What is required for newborn research screening to be ethical? (3) Do current newborn research screening projects fulfill these ethical requirements?

THE RISKS AND BENEFITS OF DIABETES SUSCEPTIBILITY RESEARCH IN NEWBORNS

The expert consensus against isolated predictive identification of newborns and children for increased genetic susceptibilities when no preventive measures are available is based on the lack of therapeutic benefit. When psychosocial risks and benefits of predictive identification are mentioned, it is presumed that the risks outweigh the benefits. However, there are scant empiric data regarding the psychosocial risks and benefits of predictive screening with disclosure of results of children generally, let alone for newborn screening for a specific condition like type 1 diabetes. Although the NOBADIA study plans to do extensive psychological follow-up, there are very few data on the psychosocial risks associated with identifying newborns for a genetic predisposition to diabetes. The data that do exist regarding predictive diabetes identification are from studies in families who were notified that children (beyond infancy) or adults had islet cell antibodies (a marker of β-cell destruction). These studies found that families were initially quite anxious, but most of the anxiety dissipated by 4 months. However, anxiety persisted in some subgroups, such as those who relied on self-blame and wishful thinking as coping strategies, such as the researchers concluded that some participants may experience greater distress than others.

In addition, whether the anxiety will remain low needs to be determined. Psychological follow-up from other newborn screening programs suggest that harms can accrue over a much longer period, and that they can wax and wane. Consider, for example, α1-antitrypsin deficiency screening begun in Sweden in the early 1970s. α1-Antitrypsin deficiency is an autosomal recessive predisposition to chronic lung disease in young adulthood with variable penetrance and expressivity. Parents of at-risk children were counseled that smoking and smoky environments could hasten or worsen their children’s pulmonary symptoms. Psychological data were procured for 20 years on a subset of families with a child who screened positive. The data showed that parents initially had strong negative emotional reactions to the diagnosis and yet, most parents had positive feelings that the screening program identified their child’s risk.

The α1-antitrypsin deficiency screening program was stopped after 5 years because of the psychological stress it had caused in some families whose child had tested positive. Follow-up data found increased smoking by fathers of affected children and negative long-term effects in the mental and physical health of the mother in mother-child but not father-child interactions, in parents’ long-term emotional adjustment to their children’s α1-antitrypsin status, and in the parents’ view of their children’s health, although this improved over time. However, the children, as young adults, were aware of the dangers of smoking and smoky environments and were positive about α1-antitrypsin deficiency screening. In 1997, the World Health Organization reviewed the data and published a memorandum in support of implementing newborn screening for α1-antitrypsin deficiency. Although Sweden remains somewhat ambivalent, Oregon had a similar program in the 1970s and supports reimplementation. α1-Antitrypsin deficiency and type 1 diabetes are not completely analogous. First, as noted by the α1-antitrypsin deficiency researchers, some of the psychological stress might have been avoided if the parents had been informed about the testing and given the opportunity to consent to or refuse testing, which was not the case when α1-antitrypsin deficiency testing was incorporated into universal screening programs in the 1970s. All of the predictive diabetes newborn screening programs described above include a separate informed consent process. Yet, even if a special informed consent is required, it may not be enough, in part because “the pressure of the hospital setting, the parents’ physical and emo-
tional condition immediately after birth, and the cultural belief that ‘medical testing is good for you’ will lead most parents to consent.**4849** A second dissimilarity between the 2 conditions is that there are preventive measures that can be taken for α1-antitrypsin deficiency that improve the benefit-harm ratio for α1-antitrypsin deficiency screening. One would hypothesize greater harm in predictive information about type 1 diabetes when subjects and their families have no control over the development of diabetes.49,50

What, then, are the risks and benefits of predictive identification of newborns at increased risk for type 1 diabetes? One potential clinical benefit is that parents can be taught the signs and symptoms of clinical disease so that their children are diagnosed early, and avoid being diagnosed in the emergency setting of diabetic ketoacidosis. The risk, however, is that parents may overreact and interpret a child’s normal urination habits as a sign of polyuria. A second potential clinical benefit is that the parents will be familiar with a diabetes center and will make the transition to clinical care more easily. However, a high-risk allele does not confer certainty of disease, and parents may become very anxious and make life plans based on an increased susceptibility, a susceptibility that has less than a 20% probability of fruition; and a low-risk allele may give parents false reassurance of their child’s health because some children with low-risk genetic alleles do develop diabetes.

The most serious clinical risk, however, is that parents will conflate the experimental and nontherapeutic nature of diabetes screening with the therapeutic newborn screening programs geared to detect metabolic and endocrine disorders that require immediate treatment. Parents may decide that all newborn screening is experimental and refuse phenylketonuria and diabetes screening, despite the high medical benefit of the former. Alternately, parents may conflate the experimental and therapeutic screening and consent to both without understanding that the former is nontherapeutic. This will leave them unprepared for a positive test result. Data show that the receipt of a positive test result has more negative effects than anticipated in population-based screening (vs fewer negative effects than anticipated in testing of high-risk families).51

There are also potential psychosocial benefits and risks to newborn diabetes screening programs. One potential psychosocial benefit is that the parent can prepare. Yet, given the high rate of false-positive results (the highest-risk allele confers less than a 20% risk of developing diabetes), many parents will prepare unnecessarily, and the danger is that they may begin treating their child as being ill, when the child has at most an increased risk of becoming ill in the future.52 This is particularly true when the genetic factor is but one contributor to a higher relative risk of an illness that also depends on unknown individual or environmental cofactors.52 It may also adversely affect the parent-child relationship.53,54 This risk may be exaggerated in the newborn period, which is a particularly vulnerable time in parent-child relationships.54,55 Even families who have received a positive screening test that is quickly confirmed to be negative (eg, false-positive hypothyroid screen) report greater strain on marriage and difficulties in their relationships with their children.56 Imagine, then, a positive screening test that reflects only increased susceptibility over a lifetime! These children may spend their childhood as neither healthy nor ill but “at risk.”57,58 Such labeling may cause familial stress59,60 and may be stigmatizing for the family, as reflected in difficulty procuring health insurance.53,54,55

The concerns about genetic discrimination in health insurance are serious. Several studies have documented that genetic information leads to discrimination in health insurance.50,63 The institutional review board guidebook prepared by the Office for Human Research Protections specifically states that subjects in genetic research must be made aware of the potential for discrimination in health and life insurance.52,54,55

If the benefits do not clearly outweigh the risks, why do 94% of parents consent to screening for type 1 diabetes? In part, the high uptake can be explained by our culture’s unequivocal support of testing generally.48,63 The low frequency of positive results in the general population makes it attractive to individuals who seek reassurance.64,65 The high uptake may also be explainable, in part, because of how the test is offered. Data show that uptake is highest when requested in person and when testing can be done immediately.50 In the case of newborn screening for type 1 diabetes, the blood may already have been procured (DAISY) or will be procured for traditional newborn screening.

**MINIMIZING RISKS TO CHILDREN**

Although the diabetes community clearly supports diabetes research in the general population of newborns,66 the question remains whether current study designs minimize risk, a requirement enumerated by various reports on what is required for research to be ethical in general,67-70 as well as in reports focusing on research with children.71,72 In the United States, this requirement was adopted into the federal regulations regarding the protection of human research subjects (§46.111).73 Several reports also note that, because of the vulnerability of children, research should be conducted when possible on animals, then adults, and then older children.69,71,72 Unfortunately, the demographics of type 1 diabetes1,2,74 and the increasing number of new cases of children younger than 4 years2,75 mean that such research must be done on young children.

One question is whether it matters if the research is done on newborns or older infants. Newborns are attractive for population genetic screening research because (1) virtually all newborns in developed countries are born in hospitals (captive population); (2) virtually all undergo screening for phenylketonuria and hypothyroidism, making screening already accepted; and (3) large amounts of blood can be obtained from the placenta at delivery without any physical risk to the infant. A delay of 3 months would not interfere with predictive research, as autoantibodies and overt disease rarely develop before then.12 The advantage of such a delay is that it would distinguish this research study from current metabolic newborn screening. The major drawback of such a
study design would be lower participation. Attempting to enroll children at primary care clinics is much less efficient than enrollment in the hospital. It requires the active recruitment by many primary care physicians who may not have a vested interest in the project and may not be willing to spend the time to get consent from the parent. It would also require a separate blood sample, which both increases the physical riskiness of the study (albeit minimally) and could result in a lower rate of parental consent.

Whether such a precaution is necessary would depend on whether the increased vulnerability of newborns and the newborn-parent relationship is significantly reduced by 3 months. However, even if this is not the case, one could argue, at minimum, in support of decision aids to improve the consent process or a more active parental consent process. Consider, for example, the suggestion by Clarke, one of the principal investigators of a voluntary newborn screening program for Duchenne muscular dystrophy, a progressive neuromuscular disorder for which no treatment exists. Duchenne muscular dystrophy screening has been offered in Wales for the last decade, and it also has a 94% uptake rate. Clarke suggested that requiring more active parental involvement (eg, requiring parents to mail the blood spot for the Duchenne muscular dystrophy screening) may lead to a lower, “more appropriate” uptake rate: “To suggest that a lower uptake rate for a screening test would be preferable, that we should set a threshold of motivation so that infants are not screened unless their parents actively choose it, is certainly unusual but is perfectly appropriate in the context of an untreatable disease.”

Again, the analogy is not perfect. Duchenne muscular dystrophy is uniformly fatal, whereas type 1 diabetes is treatable, although currently there does not exist a treatment for either condition that can be provided presymptomatically that will prevent or delay the onset of the disease. Duchenne muscular dystrophy is also virtually 100% penetrant (the likelihood of developing the disease if one has the gene), in contrast to the genetic markers for type 1 diabetes that result only in an increased susceptibility. This means that many newborns identified as being at increased risk for type 1 diabetes will not develop the disease. There are many dangers in creating awareness and labeling individuals “at risk” in a low-risk population, leading to vulnerable child syndrome, inappropriately treating the child as being “ill” even before symptoms develop, or trying unproven and potentially dangerous preventive measures. Thus, because the genetic markers for type 1 diabetes offer only predispositional information and no preventive measures are available, one could make an argument, similar to Clarke’s, that infants should not be screened unless the parents actively choose it; 94% uptake seems too high.

Another way to reduce risk in genetic susceptibility research is to design studies that do not require disclosure of individual results because nondisclosure eliminates the psychosocial harms of classifying an individual as “at risk.” In such a study, one would request parental permission (1) to procure a blood sample of the infant and (2) to track whether the infant develops diabetes by annual contact with local hospitals, pediatric endocrinologists, diabetes registries, or the families themselves. In Sweden, long-term studies have been done in this way. Critics might object to this study design requirement for 3 reasons. First, they may object on the grounds that parents will not consent to genetic testing of their newborns under these conditions, but that is an empiric question for which there are no data. Second, critics might also object because a policy of nondisclosure in the general population means that follow-up autoantibody screening studies will be more expensive because the researchers cannot target those at high risk. This concern is valid and will require innovative study designs. At minimum, consent should be sought not only for procuring the blood sample but also for permission to obtain follow-up data from third parties. Third, critics may object that my solution is overly paternalistic. They will point to the fact that 94% of parents consent to research participation. I have already tried to explore why the uptake is higher than it would be if parents truly understood the risks and benefits of such research before they consented. But even if only 20% of informed parents consented, the critics’ cry of paternalism must be addressed.

Paternalism is “the intentional overriding of one person’s known preferences or actions by another person, where the person who overrides justifies the action by the goal of benefiting or avoiding harm to the person whose will is overridden.” However, the situation at hand is not about interfering with an individual’s decision about whether to participate in research, but whether to interfere in a parent’s autonomy about whether to enroll his or her child in research. The issue, then, is about whether to respect not individual autonomy but parental autonomy. Proxy decision making is more restricted than individual autonomy because individuals may take risks that they cannot authorize others to take. As such, it is morally justifiable to require that risk status not be disclosed to minimize the research risks for individuals who cannot consent for themselves.

If one wants to focus one’s research on the development of autoantibodies in individuals with increased genetic susceptibility, these individuals need to be identified for periodic retesting, or one would need to re-screen entire sample populations periodically. The latter becomes cumbersome and expensive, given that one is often interested in a small percentage of the population. For example, in DAISY, the researchers identified 2.3% of the population as high risk (meaning that the individual infant has a 1 in 15 chance of developing type 1 diabetes by the age of 20 years) vs a 1 in 250 chance in the general population.

If one assumes that the research has scientific merit, and that it is unrealistic to assume that it can be done without identifying individuals “at risk,” the question remains who is the appropriate subject population. Given the demographics of the disease, it will require the participation of young children. However, there is also the question of whether such research should be done on the general population, or only in newborns from high-risk families (ie, a family with an affected first-degree relative). The scientific advantage of screening the low-yield gen-
eral population is that it will increase the number of infants identified. The advantage of selectively screening the high-risk community is that one will identify a larger number of individuals “at risk” with a smaller sample. The major disadvantages of recruiting only from high-risk families are that the total number identified may be too small for some research and fear that this sample population may be biased. For example, most studies have concluded that islet cell antibodies are less predictive in the general population than in high-risk families, with the exception of Schatz et al in the United States.

The answer becomes clearer if one uses the criteria that research must be designed to minimize risks, including psychosocial risks. There is some empirical evidence to support restricting the identification of risk to children in high-risk families. Children in these families are often viewed as “at risk” even before genetic markers were discovered and are often labeled as such by their families even if they do not undergo genetic testing. The parents’ behavior is not without merit: Siblings have a 15-fold increased chance of developing type 1 diabetes compared with an individual from the general population. In addition, although the data are anecdotal, parents in families in which either a parent or child has diabetes frequently do monitor their other children for signs of glycosuria or hyperglycemia. The exact percentage is unknown because this fact is rarely shared with physicians. Given the baseline anxiety that already exists within these families, genetic and immunologic testing does not induce the anxiety but rather either confirms or refutes these concerns, albeit only probabilistically.

A policy that distinguishes newborns in high-risk families from newborns in the general population may also be more consistent with current regulations regarding children as research subjects. The federal regulations permit minimal-risk research to be done on all children, but they restrict research that entails a minor increase over minimal risk to subjects who have the disease or condition being studied. If “disease or condition” is understood to include children at risk for the particular disease or condition, then one could justify restricting more than minimal risk research to children from high-risk families because these children are at risk as a result of the genetic basis of diabetes. I argue for this interpretation elsewhere (L.F.R., unpublished data, 2002).

Finally, one must consider prediction research that is coupled with prevention. Clearly, the children need to be identified for the prevention strategy to be used. Both the concern of introducing the “at-risk” status into the healthy population and the high false-positive rate have led many ethicists to conclude that initial studies should be restricted to children from high-risk families, despite their therapeutic potential.

**DO CURRENT RESEARCH DESIGNS MINIMIZE RISK?**

Population studies are important to understand incidence, prevalence, and gene-environment interactions of type 1 diabetes in the general population. However, the identification of at-risk newborns in the general population and the disclosure of these results to unsuspecting parents fail to minimize risks, an ethical requirement for all research involving human subjects. Population studies that are designed to disclose the results to parents in order to follow up subjects prospectively need to be redesigned. This includes many of the studies being done today, including DIPP, NOBADIA, DAISY, and PANDA.

Even if one focuses on infants from high-risk families, the ethical requirement to minimize risk would support designing predictive studies that do not require disclosure of the results. Virtually all of the German and Australian BABY-DIAB data could have been procured without disclosing results (except for 13 children from whom the German researchers requested more frequent testing because they had more than one positive antibody while this additional information may have been valuable, it greatly increased the potential psychosocial harms of the research and could have been omitted).

If it is necessary to disclose the risk status of infants, then the study population ought to be restricted to infants from families with an affected first-degree relative. For example, if the research includes a prevention strategy, identification of at-risk children will be necessary. Given the potential harms of introducing at-risk status into the healthy population, initial studies should recruit only children from high-risk families, as TRIGR did.

**CONCLUSIONS**

Type 1 diabetes is a significant health problem in children, and accurate prediction in infancy will be necessary to prevent or delay its onset. However, prediction research in the newborn period has potentially serious psychosocial implications, particularly when it is being introduced into the unsuspecting general population, and research designs must account for them. To minimize harm to infants and their families, I propose 2 recommendations. First, if the research is solely predictive (ie, it does not incorporate a prevention strategy), studies should be designed, when possible, to avoid disclosure of increased susceptibility results. Second, if disclosure is necessary, then the research should be restricted to children with an affected first-degree relative, and this would hold even for prediction-prevention protocols.

---

**What This Study Adds**

Although there is wide consensus against predictive genetic screening in children for adult-onset conditions when no treatments can be implemented in childhood, there is virtually no discussion about the ethics of predictive genetic screening in infants and children for conditions that present in childhood when no treatments can be implemented before symptoms appear. There is also scant discussion on how to perform predictive screening research in children ethically. This article argues that such research must conform to the ethical principle that research should be designed to minimize risk to children and their families. It then considers whether current research fulfills this criterion.
Accepted for publication September 18, 2002.

Dr Ross’s research on genetics is supported by a Harris Foundation (Chicago) grant, “Ethical and Policy Implications of Genetic Testing of Children.” Dr Ross’s research on children in research is funded by grant NLM 1 G13 LM07472-01 from the National Institutes of Health, Bethesda, Md. Dr Ross is also a member of the Internal Organizational Advisory Group for the Policy and Ethics Section of the Collaborative Network for Clinical Research on Immune Tolerance, also known as Immune Tolerance Network, sponsored by the National Institutes of Health. The opinions expressed in this article represent her own views, and do not necessarily reflect the views of the National Institutes of Health, the Immune Tolerance Network, or the Harris Foundation.

Corresponding author: Lainie Friedman Ross, MD, PhD, Department of Pediatrics, The University of Chicago, 5841 S Maryland Ave, MC 6082, Chicago, IL 60637 (e-mail: lross@uchicago.edu).

REFERENCES


3. Infant diabetes test is good start [editorial]. St Petersburg Times. January 8, 2002:8A.


45. Sveger T, Tellin T. A future for neonatal alpha-antitrypsin screening? Acta Paedi- 

46. O’Brien ML, Buist NRM, Murphey WH. Neonatal screening for alpha-1- 

248-251.


49. Senior V, Marteau TM, Peters TJ. Will genetic testing for predisposition for 
disease result in fatalism? a qualitative study of parents responses to neonatal screen- 

50. Lefcourt HM. Locus of Control: Current Trends in Theory and Research. 2nd ed. 

51. Michie S, Marteau TM. Predictive genetic testing in children: the need for psy- 

Psychosocial Effects of Screening for Disease Prevention and Detection. New 

53. Headings VE. Counselling in a hospital-based newborn screening service. Pa- 

54. Clayton EW. What should be the role of public health in newborn screening and 

55. Fyto K. Neonatal screening: life-stress scores in families given a false-positive 

56. Tymstra T. False positive results in screening test: experience of parents of chil- 

57. Davison C, Macintyre S, Smith GD. The potential social impact of predictive 
 genetic testing for susceptibility to common chronic disease: a review and pro- 


59. Reilly PR, Boshar MF, Holtzman SH. Ethical issues in genetic research: disco- 

60. Billings PR, Kohrn MA, de Cuevas M, Beckwith J, Alper JS, Natowicz MR. Dis- 
crimination as a consequence of genetic testing. Am J Hum Genet. 1992;50: 
476-482.

61. Geller LN, Alper JS, Billings PR, Barash CI, Beckwith J, Natowicz MR. Individual, 
family, and societal dimensions of genetic discrimination: a case study analysis. 

62. Office for Human Research Protections. Institutional Review Board Guidebook, 

63. Nelkin D, Tancredi L. Dangerous Diagnostics: The Social Power of Biological In- 

64. Andrzykowski MA, Lightner R, Studds JL, Munn RK. Hereditary cancer risk noti- 
fication and testing: how interested is the general population? J Clin Oncol. 1999;17: 
2139-2148.

65. Marteau TM, Croyle RT. The new genetics: psychological responses to genetic 

66. Schatz DA, Krischer JP, Syler JS. Therapeutic controversy: now is the time to 
address the ethical principles. In: Burley J, Harris J, eds. A Companion to Genetics. 

67. Clarke AJ. The genetic dissection of multifactorial disease: the implications of 
susceptibility screening. In: Harper PS, Clarke AJ, eds. Genetics, Society and Cli- 

68. Samuelsson U, Sundqvist G, Borg H, Farnlund P, Ludvigsson J. Islet auton- 
2001;51:51-57.

69. Beauchamp TL, Childress JF. Principles of Biomedical Ethics. 4th ed. New York, 

70. Buchanan AE, Brock DW. Deciding for Others: The Ethics of Surrogate Decision 

Oxford University Press; 1998.

72. Revers M, Bugawan TL, Norris JM, et al. Newborn screening for HLA markers 
associated with IDDM: Diabetes Autoimmunity Study in the Young (DAISY). 

73. Buzzetti R, Quattrocchi CC, Nistico L. Dissecting the genetics of type 1 diabetes: 
relevance for familial clustering and differences in incidence. Diabetes Metab Rev. 

74. Veijola R, Reijonen H, Vahasaalo P, et al. HLA-DQB1-defined genetic suscepti- 
bility, beta cell autoimmunity, and metabolic characteristics in familial and non- 


insulin autoantibodies for type 1 (insulin-dependent) diabetes mellitus in a popula- 


78. Orth R. Psychological and ethical aspects of prevention trials. J Pediatr Endo-

©2003 American Medical Association. All rights reserved.