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**

In the United States, type 1 diabetes mellitus has an annual incidence of 15 per 100,000 younger than 18 years, making it the most common metabolic disease of childhood. Of major concern is that type 1 diabetes is increasing at a yearly rate of 2.5%. In January 2002, a Florida newspaper proclaimed that “Florida had taken a progressive step in becoming the first state offering to screen newborns for the risk of developing juvenile diabetes.” The newborn screening involves identifying children with a genetic predisposition to type 1 diabetes. It will be offered as a voluntary test in conjunction with the mandatory newborn metabolic screening. Infants discovered to be at increased risk will be recruited for follow-up studies to determine whether and when the child develops autoantibodies (preclinical disease) or overt diabetes. This article examines the ethics of predictive diabetes screening research in newborns.

**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...
genetic screening, and 14.8% of the children are found to be at increased risk.12 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.13 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 screening10, 94% of mothers consent.16 The Florida newspaper report3 refers to the Prospective Assessment in Newborns for Diabetic Autoimmunity (PANDA) study in which infants at increased genetic risk will be observed for antibody development to uncover possible environmental triggers such as breastfeeding, immunizations, and viral infections.14

To date, the only combined prediction-prevention study in newborns is a prevention trial in Finland (the Trial to Reduce IDDM in the Genetically at Risk [TRIGR]). After encouraging results of a pilot study in 1992 to 1993,1 the second TRIGR pilot study was launched in 1995 to examine whether avoiding cow’s milk protein for the first 6 to 8 months of life prevents diabetes in infants with an affected first-degree relative.15 The diet was effective in non-obese diabetic mice,19 although some preliminary data suggest that it is ineffective in humans.17,19 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).15 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.10,22 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 NEWBORN

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.10,23 When psychosocial risks and benefits of predictive identification are mentioned, it is presumed that the risks outweigh the benefits.19,21,23

However, there are scant empiric data regarding the psychosocial risks and benefits of predictive screening with disclosure of results of children generally,20,27 let alone for newborn screening for a specific condition like type 1 diabetes. Although the NOBADIA study plans to do ex-tensive psychological follow-up,19 there are very few data on the psychosocial risks associated with identifying newborns for a genetic predisposition to diabetes.25 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).29,31 These studies found that families were initially quite anxious, but most of the anxiety dissipated by 4 months.29,33 However, anxiety persisted in some subgroups (eg, those who relied on self-blame and wishful thinking as coping strategies31,32), such that the researchers concluded that some participants may experience greater distress than others.32,33

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.35–38 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.38–41 The data showed that parents initially had strong negative emotional reactions to the diagnosis,38 and yet, most parents had positive feelings that the screening program identified their child’s risk.37

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.38 Follow-up data found increased smoking by fathers of affected children46 and negative long-term effects in the mental and physical health of the mother40,41,42, in mother-child but not father-child interactions41, in parents’ long-term emotional adjustment to their children’s α1-antitrypsin status60, and in the parents’ view of their children’s health,39 although this improved over time.40 However, the children, as young adults, were aware of the dangers of smoking and smoky environments and were positive about α1-antitrypsin deficiency screening.43 In 1997, the World Health Organization reviewed the data and published a memorandum in support of implementing newborn screening for α1-antitrypsin deficiency.44 Although Sweden remains somewhat ambivalent,45 Oregon had a similar program in the 1970s46 and supports reimplementation.47

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.45 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.48,107 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 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).31

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 unneces-sarily, 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.50 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 co-factors.52 It may also adversely affect the parent-child relationship.45,53,54 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.50 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 stress30,53,54 and may be stigmatizing for the family, as reflected in difficulty procuring health insurance.32,24,29

The concerns about genetic discrimination in health insurance are serious. Several studies have documented that genetic information leads to discrimination in health insurance.60,61 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

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.64 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 years10,75 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 to screen 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 rescreen 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-
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.
10. Flanders G, Graves P, Rewers M. Review: prevention of type 1 diabetes from labor-
53. Headings

54. Lefcourt HM.

55. Andrykowski MA, Lightner R, Studts JL, Munn RK. Hereditary cancer risk noti-

56. Geller LN, Alper JS, Billings PR, Barash CI, Beckwith J, Natowicz MR. Individual,

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


59. Medical Research Council of Canada, Natural Science and Engineering Re-


61. Psychosocial Effects of Screening for Disease Prevention and Detection

62. Andrykowski MA, Lightner R, Studts JL, Munn RK. Hereditary cancer risk noti-


64. Schatz DA, Krischer JP, Syler JS. Therapeutic controversy: now is the time to

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

67. Department of Health and Human Services (45 CFR 46 Subpart A). Final regu-


69. World Medical Association Declaration of Helsinki.

70. Medical Research Council of Canada, Natural Science and Engineering Re-

71. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Report and Recommendations: Research Involving Chil-


73. Department of Health and Human Services (45 CFR 46 Subpart A). Final regu-

74. EURODIAB ACE Study Group. Variation and trends in incidence of childhood

75. Fellbauer RG, McKinney PA, Bodansky HJ. Rising incidence of childhood dia-
betes is seen at all ages and in urban and rural settings in Yorkshire, United King-

76. Entwistle V. The potential contribution of decision aids to screening pro-


78. Escolar DM, Scacheri CG. Pharmacologic and genetic therapy for childhood mus-

79. Concepts. 46

80. Protections for Children Involved as Subjects in Research, 48

81. Veijola R, Reijonen H, Vahasalo P, et al. HLA-DQB1–defined genetic suscepti-

82. Buzzetti R, Quattrocchi CC, Nistico L. Dissecting the genetics of type 1 diabetes:

83. Rewers M, Bugawan TL, Norris JM, et al. Newborn screening for HLA markers

84. EURODIAB ACE Study Group. Variation and trends in incidence of childhood

85. EURODIAB ACE Study Group. Variation and trends in incidence of childhood

86. Veijola R, Reijonen H, Vahasalo P, et al. HLA-DQB1–defined genetic suscepti-

87. Rewers M, Bugawan TL, Norris JM, et al. Newborn screening for HLA markers

88. Buzzetti R, Quattrocchi CC, Nistico L. Dissecting the genetics of type 1 diabetes:

89. Veijola R, Reijonen H, Vahasalo P, et al. HLA-DQB1–defined genetic suscepti-

90. Concepts. 46

91. Veijola R, Reijonen H, Vahasalo P, et al. HLA-DQB1–defined genetic suscepti-


96. Veijola R, Reijonen H, Vahasalo P, et al. HLA-DQB1–defined genetic suscepti-

97. Department of Health and Human Services (45 CFR 46 Subpart D). Additional

98. Ortho. Ox-


100. World Medical Association Declaration of Helsinki.


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

103. Entwistle V. The potential contribution of decision aids to screening pro-

104. Concept. 46

105. Concepts. 46

106. World Medical Association Declaration of Helsinki.

107. Concepts. 46

108. World Medical Association Declaration of Helsinki.

109. Concepts. 46

110. World Medical Association Declaration of Helsinki.

111. World Medical Association Declaration of Helsinki.

112. Concepts. 46

113. Concepts. 46

114. World Medical Association Declaration of Helsinki.

115. World Medical Association Declaration of Helsinki.


117. World Medical Association Declaration of Helsinki.

118. World Medical Association Declaration of Helsinki.

119. World Medical Association Declaration of Helsinki.

120. World Medical Association Declaration of Helsinki.

121. World Medical Association Declaration of Helsinki.

122. World Medical Association Declaration of Helsinki.

123. World Medical Association Declaration of Helsinki.

124. World Medical Association Declaration of Helsinki.

125. World Medical Association Declaration of Helsinki.

126. World Medical Association Declaration of Helsinki.

127. World Medical Association Declaration of Helsinki.

128. World Medical Association Declaration of Helsinki.

129. World Medical Association Declaration of Helsinki.

130. World Medical Association Declaration of Helsinki.

131. World Medical Association Declaration of Helsinki.

132. World Medical Association Declaration of Helsinki.

133. World Medical Association Declaration of Helsinki.

134. World Medical Association Declaration of Helsinki.

135. World Medical Association Declaration of Helsinki.

136. World Medical Association Declaration of Helsinki.

137. World Medical Association Declaration of Helsinki.

138. World Medical Association Declaration of Helsinki.

139. World Medical Association Declaration of Helsinki.

140. World Medical Association Declaration of Helsinki.

141. World Medical Association Declaration of Helsinki.

142. World Medical Association Declaration of Helsinki.

143. World Medical Association Declaration of Helsinki.

144. World Medical Association Declaration of Helsinki.

145. World Medical Association Declaration of Helsinki.

146. World Medical Association Declaration of Helsinki.

147. World Medical Association Declaration of Helsinki.

148. World Medical Association Declaration of Helsinki.

149. World Medical Association Declaration of Helsinki.

150. World Medical Association Declaration of Helsinki.

151. World Medical Association Declaration of Helsinki.

152. World Medical Association Declaration of Helsinki.

153. World Medical Association Declaration of Helsinki.

154. World Medical Association Declaration of Helsinki.

155. World Medical Association Declaration of Helsinki.

156. World Medical Association Declaration of Helsinki.