

Type 1 Diabetes Mellitus: Ethical Issues in Research with Children

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Key Points

Genetics

- Risk for type 1 diabetes mellitus is associated with certain HLA genotypes.
- As a result, HLA genotyping can be used to identify children at increased risk for type 1 diabetes mellitus; research studies to evaluate this testing strategy are currently being implemented.

Ethics

- Research involving children raises significant questions, and families may need guidance in considering the risks and benefits of participation.
- In some research studies, results are provided to the patient. However, results are not disclosed to the patient's physician unless the patient chooses to disclose them.

Learning Objectives

Participants will:

- Gain an awareness of the potential implications of genetic testing to identify an increased risk of type 1 diabetes mellitus;
- Be able to consider the issues raised by participation of children in research studies;
- Be able to guide parents in considering the risks and benefits of participation in a genetic research study.

Family History Issues: Type 1 Diabetes Mellitus

Individuals in the general population have approximately a 0.3% chance of developing type 1 diabetes mellitus; the risk increases to about 2% for individuals with an affected mother and 6% for individuals with an affected

sibling or father. However, most individuals with type 1 diabetes mellitus (~90%) have no other affected relatives.

Red Flags



Type 1 diabetes mellitus

Symptoms of diabetes mellitus include frequent urination, excessive thirst or hunger, unusual weight loss, increased fatigue, irritability, or blurred vision.

Children as human subjects in research

Federal guidelines identify factors that should be considered in the protection of children as human subjects. These include:

- The degree of risk to the child, the direct benefit to the child, and the direct benefit to other children.
- The process for soliciting the assent of children and the permission of parents and guardians.
- The nature of the health problem under study. The more serious the problem for children, the greater the claim that research could be justified. This is particularly true when research provides the only means to identify health care strategies to address important health problems of children [[DHHS Protections for Children Involved as Subjects in Research](#)].

Case 19. Question about a Child Participating in Research Related to Type 1 Diabetes Mellitus

Mrs. J asks for advice about enrolling her four-year-old daughter in a research study. She has been notified that her daughter is eligible to participate as a subject in a study of newborn screening for type 1 diabetes mellitus. The study utilizes the blood sample that was taken for routine newborn screening. As part of the research study, the blood sample would be tested for genetic predictors of type 1 diabetes mellitus (HLA genotypes). She has been informed that this study will help researchers to determine the

ability of such testing to identify those individuals who will eventually develop type 1 diabetes mellitus. Mrs. J wants to know whether participation in the study would provide a medical benefit to her daughter.

Clinical Care Issues

Will Mrs. J's daughter receive medical benefits from participation in the study?

Medical benefit is unlikely. Clinical research addresses questions for which there is no clear answer. Benefits to participants may occur but cannot be promised; most often, clinical research studies provide benefits in the form of generalizable knowledge rather than specific benefits to individual participants in a particular study. In this study, participants will be tested for HLA genotypes that identify increased risk for diabetes mellitus. The benefits and risks of such information are not established. (See further discussion under [Risk Assessment](#).)

If Mrs. J enrolls her daughter in the study, is her study participation coordinated with her medical care?

No. Research procedures will be coordinated by the study and all results are confidential; therefore, the physician will not receive information regarding the patient's results. If some clinically relevant information about her daughter is identified by the study and disclosed to Mrs. J, she may decide to share it with her daughter's physician. Mrs. J and the physician can then decide whether and how much information should be included in the medical record.

Risk Assessment

HLA genotyping to identify risk for type 1 diabetes mellitus

In the general population, 1/300 children develop type 1 diabetes mellitus. Both genetic and non-genetic risk factors contribute to risk.

- Polymorphisms in the genes encoding HLA proteins can be used to identify individuals with an increased risk of type 1 diabetes mellitus. The majority of children who develop type 1 diabetes mellitus have specific HLA genotypes. In particular, variants of two tightly linked genes in the HLA region, HLA-DQA1 and HLA-DQB1, are associated with either increased or decreased risk of developing type 1 diabetes

mellitus. Specific genotypes are estimated to be present in more than half of individuals with type 1 diabetes mellitus, with the attributable fraction ranging from 53% to 75% in different ethnic groups. As a result, tests to assess HLA genotypes have been proposed for newborn screening, to identify infants at increased risk for type 1 diabetes mellitus.

- However, current data suggest that the chance of developing diabetes mellitus in individuals who have HLA genotypes associated with type 1 diabetes mellitus is approximately 2-12%, depending on whether only high-risk genotypes are included or whether moderate-risk genotypes are also included in the newborn screening program; thus positive predictive value for HLA genotyping is at best 12%.
- Environmental exposures such as enteroviruses are thought to be important co-factors in the development of the disease.
- Other genetic factors contribute to risk. Variation in the insulin gene may play a role, and extensive gene-mapping efforts are underway to identify other genetic contributors.

Risks of study participation

Researchers are obligated to provide potential participants with information about the study, including potential benefits (if any) and risks, as part of the informed consent process. Mrs. J can ask to review an informed consent document before deciding whether to have her daughter participate.

The risks of study participation should be clearly outlined in the study's informed consent form. In genetic research studies, the physical risks are usually minimal, typically limited to the risks associated with a blood draw. However, if study information is shared with participants, the risks associated with determining genetic susceptibility could be significant. In the type 1 diabetes mellitus study, parents of children who are found to be at "increased risk" may experience worry or anxiety about the possibility of diabetes in their child. Because most children at increased risk will not develop diabetes, there is a potential concern that parents might prepare unnecessarily or prematurely treat their child as being ill. Concern might also arise over the potential risk of discrimination by insurers or future employers of a child known to carry a genetic predisposition. In considering these risks, Mrs. J may want to ask about confidentiality protections for the research data.

Conversely, some parents may view risk information of this kind as a benefit. In considering the potential value of any risk information provided

by the study, Mrs. J may want to ask about recommendations or follow-up that will be provided to children identified as having increased risk.

Mrs. J may also want to consider other factors, including:

- **Voluntary nature of research participation.** Participation in human subjects research is voluntary. Because children cannot consent to participate in research, parents must make the decision in the best interests of their child. (Adolescents age 14-15 may assent, as they are deemed mature minors. In some cases, adolescents are considered legally competent to consent as "emancipated minors.")
- **Convenience.** Mrs. J may want to consider personal convenience, and to assure herself that study procedures will not be unduly burdensome or uncomfortable either for her daughter or her family.
- **Level of interest.** She may also want to consider the level of her family's interest in contributing to science by participating in this research study.

Genetic Counseling and Testing

Counseling about participation in research studies is not a routine component of genetic counseling. Although genetic providers frequently refer interested families to research studies, there are clear boundaries between genetic counseling as a component of clinical care and discussions of potential participation in research studies.

When a study involves genetic testing, as in this case, the research study procedures may or may not involve disclosure of test results. The disclosure policy should be discussed during the informed consent process. Potential participants (or parents, in the case of research involving children) should be encouraged to ask whether disclosure will occur and if so, what the nature of the information to be disclosed will be. If genetic test results are to be disclosed, they must be obtained in a laboratory certified by [CLIA](#) (Clinical Laboratory Improvement Act), a regulatory process which has the objective of ensuring quality laboratory testing. Genetic testing results obtained through non CLIA-certified labs should not be released or used in clinical management unless a CLIA-certified lab has confirmed the results.

In studies of newborn screening for type 1 diabetes mellitus, test results are typically provided to families, and study procedures may involve additional medical follow-up of children at increased risk.

Interventions

Since research activities occur separately from the patient's medical care, the primary care provider's role is limited to discussing general principles related to research participation and encouraging the patient to ask study personnel about specifics of the study before deciding whether to participate.

Ethical/Legal/Social/Cultural Issues

Discussions with patients about research participation

Patients may appreciate advice from their primary care provider about research participation. In a discussion of this issue, the primary care provider needs to emphasize that research participation is voluntary and will not affect the patient's medical care. The physician may be able to help the patient (or in this case, the patient's parents) to clarify the questions about the research study that will be most helpful in determining whether to participate. Patients should be encouraged to ask questions concerning the risks (physical or psychological) and the goals of research for which they are eligible to participate. Other questions may include how long samples will be stored, whether they may be used in any other research projects, and what confidentiality procedures are in place. Because studies vary greatly in design and duration, participants also need to understand the commitment that is being asked when participating in a study.

Will research participation provide a clinical benefit to the family?

Often people are interested in participating in clinical research because of they perceive that the research may provide a clinical benefit. Yet clinical research often provides no guarantee of clinical benefits to participating subjects, either because the research is addressing preliminary questions about a technology (e.g., is it feasible?) or because the research is testing a possible but unproven benefit, for which risks are not fully characterized. Potential subjects and their families may need help in determining whether a particular research project has any realistic possibility of offering benefit, or whether participation will provide only the opportunity of contributing to clinical knowledge that may benefit future patients (as is usually the case). In this case, the study has a small chance to benefit the individual, based on the hypothesis that knowledge of increased risk could lead to a more timely diagnosis if type 1 diabetes occurs. However, the benefit of such knowledge has not been proven. This type of research study has the potential to help future patients by producing additional information about associations

between HLA genotypes and risk for type 1 diabetes mellitus, and also by generating a pool of high-risk individuals who may be candidates for diabetes prevention trials.

Will research participation pose a risk to the family?

Because there are no preventive measures that have been proven to reduce the risk of type 1 diabetes mellitus, knowledge of "increased risk" status may cause the child's parents to experience increased unnecessary stress or worry related to the possibility that their child may develop diabetes. In considering whether to participate in the diabetes screening study, Mrs. J may wish to ask about the availability of counseling to discuss her daughter's results. She also may wish to ask about the specific follow-up measures that will be recommended if her daughter is found to have increased risk, and whether these follow-up measures will be provided as part of the study.

Resources

- **Ambulatory Pediatric Association Policy Statement on Research with Children**
- **American Society of Human Genetics Report: Statement on Informed Consent for Genetic Research**
- **CDC Brochure: Informed Consent: Taking Part in Population-Based Genetic Research**
- **Federal Government Regulations: The Protection of Human Subjects (2004)** Search term: 34CFR97 AND protection of human subjects
- **IRB Guidebook Chapter on Human Genetics Research**
- **GeneTests Online Medical Genetics Information Resource**
- **GeneReviews, GeneTests Online Medical Genetics Information Resource**

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