ELSEVIER

Ethical Issues Associated with Conducting Genetic Family Studies of Complex Disease

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PURPOSE: To examine subjects' recognition of the risks and ethical issues associated with enrollment in genetic family studies (GFS) and explore how this recognition affects their informed and voluntary participation.
METHODS: A cross-sectional study design including both quantitative and qualitative data was employed. Structured interviews using the Contextual Assessment Approach Questionnaire (CAA-Q) were conducted with 246 Mexican American (MA) participants. To gain in-depth understanding of questionnaire responses, semi-structured interviews with 30 participants were conducted. All participants were interviewed before their enrollment in the Family Investigation of Nephropathy and Diabetes (FIND).
RESULTS: Subjects' average age was 56 years; 62% were females. Seventy-eight percent of participants were not formally educated beyond high school and 72% reported an annual household income of $\leqslant$ $20,000. Eighty-five percent agreed to provide researchers with information on relatives' ages, gender, and education. Sixty-five percent of participants were willing to provide identifiable information such as names, addresses, and phone numbers of relatives. Sixty-three percent of participants indicated that there were direct benefits (i.e., supporting research) to disclosing relatives' information. Seventy-six percent stated that there were no risks associated with participation in GFS (e.g., discrimination or confidentiality of genetic information) compared with 10% who said that there were such risks. While discussing potential risks, subjects did not consider these to influence their decision to participate.
CONCLUSIONS: Subjects enrolled in GFS did not recognize and tended to underestimate the social and cultural risks associated with their participation in GFS. If subjects do not fully comprehend the risks, this raises questions concerning their ability to provide informed consent and to voluntarily participate. We propose a subject-centered approach that views enrollment as an active process in which subjects and recruiters give and receive information on risks and ethical issues related to participation, which enhances protection of the rights and welfare of subjects participating in GFS.
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KEY WORDS: Genetic Family Studies, Ethical Issues, Contextual Assessment Approach, Subject-centered Approach.

INTRODUCTION

In conducting genetic family studies (GFS), researchers face several ethical obligations. Protecting the rights and welfare of subjects participating in genetic family studies (GFS) is a critical, yet complicated issue, particularly challenging to the traditional approach of protecting human subjects participating in research (1–3). Basic ethical principles identified by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research and their application are summarized in the Belmont Report (4). The application of these principles through the informed consent process gives individuals the opportunity to decide if they want to participate as subjects in a research project, thus ensuring that such participation is informed and voluntary. Informed participation entails full understanding of the research procedure, purpose, and risks/benefits of participation. However, this approach of obtaining informed consent will not adequately protect the rights and welfare of persons involved in GFS (5–7). The individual-based approach fails when researchers use the family as the basic unit of analysis. In the family studies model: 1) subjects have ties to other research participants through shared genetic heritage, 2) information learned from the research may affect the entire family, and 3) family members may become part of the study without their

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Selected Abbreviations and Acronyms

CAA = contextual assessment approach
CAA-Q = Contextual Assessment Approach-Questionnaire
DN = diabetic nephropathy
FGT = First Genetic Trust
FIND = Family Investigation of Nephropathy and Diabetes
GFS = genetic family studies
MA = Mexican Americans
UTHSCSA = University of Texas Health Science Center, San Antonio

consent (8, 9). Some have argued that the current policy of the Federal Office for Human Research Protection, based on an interpretation of the definition "human subject," is incoherent and needing change (10).

Several social, cultural, and ethical issues associated with subjects' participation in GFS have already been identified—familial issues; stigmatization; stored tissue samples; discrimination due to genetic data in employment and in life and medical insurance; privacy and confidentiality of subjects' health information; and DNA research and ownership of the genetic information (2, 11–18). Communicating these risks and ethical issues to enrolled subjects is vital to ensure informed and voluntary participation (19–21). Obtaining informed consent for GFS participation is particularly challenging because it requires a level of comprehension beyond that required for consent to other studies (22). The current consent process was developed prior to the advent of genetic research, and is not sufficient to minimize the risks that these individuals face (23–26). The Washington University (St Louis, MO) Human Studies program developed a separate informed consent document for participation in genetic research that requires acknowledgement of risks and ethical issues associated with participation (22). Initiatives to better safeguard the rights and welfare of research subjects require a broader vision. Research volunteers should be accurately and effectively educated about their involvement (27).

Effective communication and broadening the perspectives to include families are crucial components to ensure informed decisions to participate in GFS. In the present study, we explored subjects' recognition regarding risks and ethical issues associated with their participation in the Family Investigation of Nephropathy and Diabetes (FIND) and examined how this recognition influenced their informed and voluntary participation. We also presented a new analytical framework (Contextual Assessment Approach) that has informed the content analysis presented herein.

METHODS

Subjects and Procedures

Participants were recruited from families potentially eligible to be enrolled in the multicenter FIND at UTHSCSA. The major goal of the FIND study in San Antonio is to identify gene(s) involved in the development and progression of diabetic nephropathy (DN) in Mexican-Americans (MA). A total of 246 subjects were interviewed using the CAA questionnaire (CAA-Q), including 105 DN probands (first DN affected and enrolled subject) and 141 of their relatives. Relatives such as parents, siblings, and children were contacted by the probands. Separate consent was obtained and all interviews for this substudy were conducted before enrolling subjects in FIND. We elected to use this approach because: 1) preliminary analysis indicated that by using the CAA-Q, recruiters were able to identify and address important ethical issues associated with subjects' participation in FIND, and 2) although the FIND consent form did not include any emphasis on social and cultural risks associated with participation, recruiters may explain these issues when obtaining consent. Subjects were interviewed before enrollment in FIND to avoid potential bias and to capture subjects' general recognition of the sociocultural risks and ethical issues associated with their GFS participation.

Study Design and Procedures

A cross-sectional study design including both quantitative and qualitative approaches was employed.

Structured interviews. A culturally-sensitive quantitative questionnaire was developed, tested, and modified to elicit participants' perceptions regarding ethical issues associated with participation in GFS and gather data on subjects' perceptions of the benefits/risks associated with their participation, such as discrimination in employment and privacy of genetic information, and ethical issues associated with relatives' enrollment, such as disclosure of health and identifiable information. The questionnaire also gathered basic demographic data on participants, such as gender, age, education level, income, and marital status, Additionally, a detailed description of the method employed to develop the questionnaire was published elsewhere (28). On average, administering the CAA-Q requires 30 minutes; it was conducted in English or Spanish based on the participant's preference. In order to achieve linguistic, conceptual, and contextual equivalence, translation/back-translation procedures were applied (28, 29).

Semi-structured interviews comprised of open-ended questions were conducted with a convenience sample of 30 subjects. These interviews entail the least control over subjects' responses and provide in-depth understanding of the subjects' views of the domains of interest. Interviews with probands and their relatives collected information on the following ethical issues: 1) contacting relatives to participate in GFS, 2) revealing health, demographic, and identifiable information about relatives without first obtaining