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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

their written consent, and 3) recognition of risks and benefits of participation. Examples of these questions include: "Do you think that your relatives might benefit from participating in this study?"; and "What are the potential risk(s)/benefit(s) from providing information about your relatives?" All interviews were tape-recorded, transcribed, and content-analyzed to identify themes across cases. Subjects had no major health impairment that would impede their participation. The Institutional Review Board at UTHSCSA approved the study protocol, and all participants gave informed consent before being interviewed. Findings are presented as percentages in the results section. Percentages for those giving no response are found in Table 1.

Data analysis. Descriptive statistics such as frequency distribution and means were applied to continuous variables such as participants' age and years of education. Associations between categorical variables in the form of contingency tables were examined using a χ^2 test. Content analysis involved: 1) building matrices with blocks of text for each subject, 2) reviewing the matrices to identify recurring themes, and 3) summarizing data into higher-level matrices. All phases of the content analysis were cross-checked to determine the appropriate method for applying coding categories and to resolve any anomalies or discrepancies. Inter-rater reliability was established by having a second researcher recode 50% of the case materials and then check for discrepancies. The software packages SPSS and Atlas.ti were used for analyzing quantitative and qualitative data, respectively.

TABLE 1. Participants' attitudes toward contacting relatives for genetic family studies

	Frequency (%) (N = 246)
Researchers contact relatives directly	
Yes	84 (34%)
No	110 (45%)
No difference	52 (21%)
Willingness to contact relatives	
Yes	192 (78%)
No	19 (8%)
Maybe	35 (14%)
Contacting immediate vs. extended relatives	
Prefer to contact immediate relatives	178 (73%)
Prefer to contact extended relatives	7 (3%)
Does not make a difference	39 (16%)
No response	22 (9%)
Why contact relatives	
Awareness/help future generations	200 (81%)
Appreciation for research	11 (4%)
Learn more about ill relatives	10 (4%)
No response	25 (10%)
Reasons not to contact relatives	
Not close family relationship	106 (43%)
Geography (far residence)	17 (7%)
Busy	48 (20%)
Health condition	11 (4%)
Privacy concerns	32 (13%)
No response	32 (13%)

RESULTS

Sociodemographic Characteristics

The sociodemographic characteristics of subjects are presented in Table 2. Fifty-three percent of probands were females. Probands' average age was 56 years (range, 33–76 $\pm$ 9.04). Relatives were 68% female and averaged 54 years old (range, 32–86, $\pm$ 11.25). The majority of participants were not formally educated beyond high school (78%). Eighty percent of probands and 65% of relatives reported a household income of $\leqslant$ $20,000. This difference in household income reflects the fact that 84% of the probands were unemployed due to dialysis or related disabilities. A total of 220 (89%) participants were at least second-generation, US-born Mexican Americans. Another 26 (11%) were first-generation Mexican Americans, born in Mexico.

Participants' Attitudes toward Relatives' Enrollment in GFS

Contacting relatives (Table 1). Thirty-four percent of participants indicated a preference that the researcher contact their relatives directly, while 45% preferred to contact their relatives prior to a researcher. One patient said: "I would rather talk to them (relatives) first; then I can tell you if they will participate, then give you their

TABLE 2. Socio-demographic characteristics of probands and relatives

	Probands (N = 105) Frequency (%)	Relatives (N = 141) Frequency (%)	Total (N = 246) Frequency (%)
Education			
High school or below	70 (67%)	107 (76%)	177 (72%)
Technical school	12 (11%)	3 (2%)	15 (6%)
College (no degree)	11 (10%)	17 (12%)	28 (11%)
College (degree)	2 (2%)	9 (6%)	11 (5%)
Graduate school	3 (3%)	5 (4%)	8 (3%)
No answer	7 (7%)	0 (0%)	7 (3%)
Gender			
Female	56 (53%)	96 (68%)	152 (62%)
Male	49 (47%)	45 (32%)	94 (38%)
Household income			
$\leqslant$ $10,000	56 (53%)	47 (33%)	103 (42%)
$10,000–$20,000	28 (27%)	45 (32%)	73 (30%)
$20,001–$30,000	8 (7%)	27 (19%)	35 (14%)
$30,001–$40,000	3 (3%)	8 (6%)	11 (4%)
> $40,000	1 (1%)	12 (9%)	13 (5%)
No response	9 (9%)	2 (1%)	11 (4%)

addresses." Twenty-one percent of subjects felt that it made no difference whether their relatives were contacted by them or by the researcher.

The majority of probands and their relatives (78%) reported that they were willing to contact other family members to invite them to participate. Fourteen percent were undecided and 8% were unwilling to invite family members to participate. Additionally, most (73%) probands and relatives preferred to contact immediate but not extended family members. One healthy sister said: "Brothers and sisters are easier to contact because all (her sibs) want to know why my brother is on dialysis." Sixteen percent of probands and their relatives indicated that they would contact any member of their family, while 3% indicated a preference for contacting extended family members. Eight percent did not respond to this question.

Eighty-one percent of participants indicated that their main reason for contacting relatives was to enhance relatives' awareness of diabetes and kidney disease. Four percent of participants felt that they appreciate research, while 4% like to learn more about ill relatives. Ten percent of the participants did not respond to this question. Among participants who provided reasons for not contacting relatives, 43% felt that they did not have a close family relationship with their relatives, 7% would not contact relatives due to geographical barriers, 20% indicated that relatives were too busy to participate, 4% specified that their relatives were sick, and 13% expressed that their relatives may have concerns regarding disclosing private information. Thirteen percent of participants gave no response. There were no statistically significant differences between probands and relatives regarding attitudes towards family members' enrollment and participation in GFS (χ^2 test, $p > 0.05$).

Disclosing information (Table 3). The overwhelming majority of probands and relatives (89% and 86%, respectively) indicated that they would disclose information about relatives regarding physical diseases, while others indicated that they would not (9% and 11%, respectively). One patient indicated: "I think we should give all the

TABLE 3. Participants' attitudes toward disclosing information about relatives

	Probands (N = 105) Frequency (%)	Relatives (N = 141) Frequency (%)	Total (N = 246) Frequency (%)
Disclosing information on physical diseases			
Yes	93 (89%)	122 (86%)	215 (87%)
No	9 (9%)	15 (11%)	24 (10%)
I do not know	3 (3%)	4 (3%)	7 (3%)
Disclosing information on mental diseases			
Yes	68 (65%)	88 (62%)	156 (63%)
No	29 (28%)	38 (27%)	67 (27%)
I do not know	8 (8%)	15 (11%)	23 (9%)
Disclosing demographic information/age, gender, and education			
Yes	91 (87%)	117 (83%)	208 (85%)
No	8 (8%)	14 (10%)	22 (9%)
Maybe	6 (6%)	10 (7%)	16 (6%)
Disclosing identifiable information/name, address, and telephone number			
Yes	71 (68%)	89 (63%)	160 (65%)
No	28 (27%)	38 (27%)	66 (27%)
Maybe	6 (6%)	14 (10%)	20 (8%)
Disclosing information on income			
Yes	34 (32%)	39 (28%)	73 (30%)
No	65 (62%)	88 (62%)	153 (62%)
Maybe	6 (6%)	14 (10%)	20 (8%)
Relatives' response to probands disclosing information			
Don't mind	47 (45%)	90 (64%)	137 (56%)
Upset	15 (14%)	10 (7%)	25 (10%)
I do not know	43 (41%)	41 (29%)	84 (34%)
Risks related to disclosing information			
Yes	10 (10%)	14 (10%)	24 (10%)
No	71 (68%)	117 (83%)	188 (76%)
I do not know	24 (23%)	10 (7%)	34 (14%)
Benefits related to disclosing information			
Yes	56 (53%)	100 (71%)	156 (63%)
No	26 (25%)	25 (18%)	51 (21%)
I do not know	23 (22%)	16 (11%)	39 (16%)

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information you need to help other people. I do not have a problem with it. I will answer as much as I can."

The majority of probands and relatives stated that they would disclose information on relatives regarding mental diseases (65% and 62%, respectively), while over a quarter indicated that they would not (28% and 27%, respectively). Eighty-seven percent of probands and 83% of relatives would provide information on relatives' age, gender, and education, while 8% of probands and 10% of relatives would not provide such information. Sixty-eight percent of probands and 63% of relatives were willing to provide identifiable information such as names, addresses, and phone numbers of relatives without their family members' prior notification and consent, while 27% of probands and relatives would not disclose such information. Six percent of probands and 10% of relatives indicated that they might provide identifiable information on relatives. Approximately one-third of probands and relatives stated that they would disclose information regarding relatives' income (32% and 27%, respectively), while 62% of probands and relatives indicated that they would not. With regard to relatives' responses to probands disclosing information, 56% of participants felt they wouldn't mind, 10% indicated that they would be upset, and 34% were unsure.

Risks and benefits. Fifty-three percent of probands and 71% of relatives felt that there were direct benefits associated with disclosing information about family members. Twenty-five percent of probands and 18% of relatives indicated that there were no direct benefits to providing information about relatives. Twenty-two percent of probands and 11% of relatives indicated that they did not know whether there were any direct benefits resulting from disclosing information about relatives. Ten percent of both probands and relatives believed that there were risks associated with disclosing information (e.g., confidentiality of genetic information or discrimination) compared with 68% of probands and 83% of relatives who felt that there were no risks. Twenty-three percent of probands and 7% of relatives indicated that they did not know of any risks related to disclosing information.

Qualitative Analysis

The following cases represent recruiters' actual experiences using CAA to gain in-depth understanding of cultural and ethical issues associated with GFS participation. The first case illustrates how CAA was used to identify risks and ethical issues associated with subjects' participation. The second shows how applying CAA helps to provide additional important information to enhance enrollment and address issues associated with subjects' privacy and confidentiality of genetic information. These cases are examples of common perspectives we have encountered during this investigation.

Case 1: Ethical issues of enrolling relatives without going through the probands. A middle-aged Mexican-American proband on dialysis stated that although he would like to participate in the study, he felt that the siblings would not, because they would feel that by asking them to provide a blood sample (for the genetic analysis), researchers would test them for kidney donation compatibility. For this reason, the proband was reluctant to contact relatives.

It became apparent from interviewing the proband that kidney donation was a sensitive issue and source of tension within the family. It was only by applying a subject-centered approach in which probands were active in asking and receiving information that recruiters were able to identify this issue within the family.

Case 2: Privacy and confidentiality—sociocultural and familial risks associated with GFS participations. A proband reported being the youngest of five children born to the same parents. The mother died of kidney failure while on dialysis and the father was alive but did not seem very involved in the family's life. One of the siblings had kidney failure due to DN (on dialysis) and the other two were reported as not having either diabetes or kidney disease.

The proband indicated that siblings were willing to participate and gave the phone number of a sibling to the recruiter. When the recruiter contacted the sibling and explained that the FIND staff was recruiting full siblings, the sib revealed that only two of the five children were full siblings, but the proband believed that all of the siblings had the same parents.

In-depth interviews with family members revealed that they all shared the same mother, who had children from three different men. This case presented many ethical concerns regarding the disclosure of information related to blood relationships among family members. Recruiters cannot assume that all family members have an equivalent degree of awareness regarding family relatedness. Recruiters should assess the potential risk and ethical issues that could be imposed on this family by trying to obtain more accurate information for the purpose of confirming genotype/phenotypic inclusion criteria for research. The results of this case were never disclosed to any family members.

DISCUSSION

Several risks and ethical issues of enrolling subjects in GFS have been identified and described previously (2, 11, 30, 31). We explored how subjects recognize ethical issues associated with their participation in the FIND study and examined how this recognition affects their informed and voluntary participation once they decided to participate.

Our findings highlighted some ethical issues that might be encountered while enrolling GFS subjects, including:

1) Relatives should be contacted through probands to avoid undue pressure on probands and to respect unique family issues. Probands may feel pressure if family members are contacted directly by researchers. Subjects' enrollment in GFS is more complicated than a simple yes or no response to researchers or relatives (1). We also found that among participants who provided reasons for not contacting relatives, about half felt that they did not have a close family relationship with their relatives. Case 1 and 2 unfold some of the familial and ethical issues that can be encountered while enrolling relatives without going through the probands. 2) Our findings showed that extended family members are difficult to enroll. The majority of probands and relatives preferred to contact immediate family members, however, some GFS require enrolling extended family members for linkage analysis. Additional caution should be exercised when enrolling members from extended families. Further studies are needed to explore how to enroll extended family members while avoiding undue pressure on probands. 3) The majority of subjects in our study believed that there were no risks associated with disclosing information (i.e., confidentiality of genetic information or discrimination). While discussing potential risks, subjects did not consider these to influence their decision to participate in GFS. Both probands and relatives in our study indicated that they would disclose information on relatives regarding physical and psychiatric diseases. Subjects' underestimation of familial as well as potential group risks raises questions about their ability to provide true informed consent and voluntarily participate in studies. No major differences were documented between probands and relatives in recognition of risks and ethical issues associated with GFS participation. This is probably due to our participants having similar demographic characteristics. However, data showed (Table 2) that a higher percentage of female (152, 62%) than male (94, 38%) subjects was enrolled in the study ($\chi 2$ test, $p < 0.05$). Other researchers have also observed gender differences in attitudes towards participation (1, 2). Therefore, we anticipated that female participants might be more vulnerable to potential risks because they are more willing to participate. Recruiters should pay special attention to communicating risks and ethical issues when enrolling female subjects.

Subject-centered Approach: A New Paradigm in Genetic Research

The conceptual framework driving this study evolves from our previous and ongoing research, which focuses on the exploration of cultural and ethical issues associated with enrolling subjects in GFS (28, 32–34). Communicating risks and ethical issues to subjects is essential, yet presents a major challenge to current regimens employed in enrolling subjects in genetic research. Wendler et al. (23) indicated that the current consent practices might not minimize the subjects' risks of genetic research. The risks of genetic research are often not apparent until after the subject's research participation has ended. Genetic studies often take several years to complete and findings may have implications for subjects many years after their enrollment. Besides, recognition of risks and declining to participate in a study by individuals is not likely to reduce group harms unless other group members do not also decline.

Previously, we have shown that incorporating the CAA before enrolling subjects enhances communication between recruiters and subjects regarding risks and ethical issues specific to participation in GFS. Findings about the impact of the CAA on participation in the FIND study are published elsewhere (33). Previous research found that CAA increased enrollment rates, facilitated a family enrollment rate of 88%, and reduced recruitment efforts by 32%.

As indicated in Fig. 1, our approach views enrollment as an active process in which both subjects and recruiters give and receive information about the genetic study and ethical issues associated with participation. CAA is a subject-centered approach to improve information exchange between subjects and recruiters concerning enrollment that allows for the exploration of circumstances influencing subjects' participation in GFS (28). This approach is different from the traditional approach currently employed in enrolling subjects in GFS. If subjects are not active in the consent discussion, individual risks and concerns may be overlooked. The goal is to ensure that subjects are able to make informed decisions about their participation, and recruiters are able to help subjects within the context of subjects' experiences.

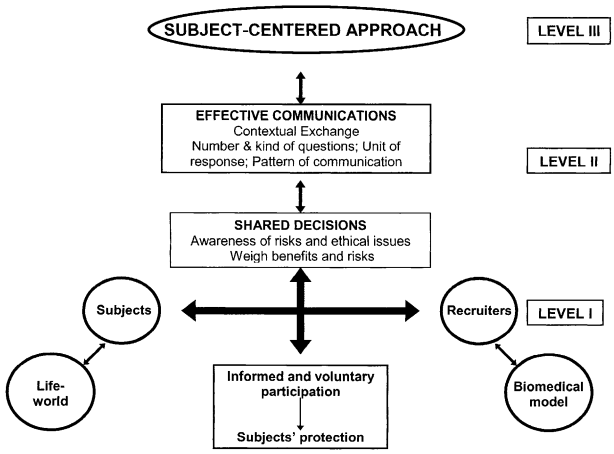

FIGURE 1. Contextual Assessment Approach to place subjects-centered enrollment in practice.

During interviews (Fig. 1, Level I), recruiters and subjects discuss issues related to participation in GFS; each has a distinct set of goals and methods for pursuing and evaluating these issues. While subjects' goals and perspectives about participating in GFS are influenced by their life-world factors (such as level of education and age), researchers/recruiters perspectives are affected by their training and plans related to GFS. Effective contextual exchange can narrow the divergence between subjects and recruiters by improving communication regarding risks and ethical issues (Fig. 1, Level I). The CAA means enhancing partnership and assigning subjects a central role in providing informed decisions about their own participation (Fig. 1, Level II, cases 1 and 2); it views effective exchange as a reflection of the quantity and types of questions asked by subjects or recruiters, as well as responses pertaining to ethical issues associated with participation in GFS. Using a subject-centered approach to explore, document, educate, discuss, and evaluate ethical issues related to enrollment can facilitate informed and voluntary participation (Fig. 1, Level III).

Although our research has focused on Mexican Americans, the ethical concerns apply to all potential participants. All subjects in GFS have unique family issues that will affect their participation and cooperation with researchers. Potential enrollees should be made aware of possible risks and ethical implications of the research. In a previous study among Ashkenazi Jews, understanding the benefits as well as awareness of community support of the project predicted participation in research activities (35). A study involving African-American women found that participation in genetics studies is strongly influenced by cultural beliefs and values (36). By incorporating CAA into recruitment strategies, researchers can more thoroughly explore participant understanding of risks, benefits, and cultural issues.

The need for exploring and addressing ethical issues is especially crucial when enrolling ethnic minority subjects. History has documented consequences when social constructs of racial and ethnic differences are permitted to penetrate the biological sciences (14, 37, 38). From the well-known eugenics movements of the early twentieth century to the infamous Tuskegee Syphilis Study, the dangers inherent in failing to assure that full understanding of GFS risks and ethical issues are evident (39–42).

New discoveries in genetic research will lead to more emphasis on racial and ethnic interpretations, which will be integrated into health research (43, 44). With the completion of the human genome sequencing in April 2003, many efforts are being directed toward utilizing this fundamental source of knowledge about human biology to apply genomics to improve human health and prevent disease (17, 45). Currently, the First Genetic Trust (FGT) provides comprehensive genetic data processing and bioinformatics services to pharmaceutical companies, medical researchers, and health care providers engaged in GFS and its application in clinical practice (http://www.firstgenetic.net). It is especially urgent that the risks and ethical issues associated with genetic research be made explicit and precise to subjects and researchers involved in such research (46).

While the broader implications of our findings remain to be demonstrated, we believe they provide the basis for building on other studies that advocate putting human protection into practice. One important future research area is to investigate how subjects across ethnic groups weigh benefits and risks regarding participation in GFS.

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