Factors Influencing Participation in a Population-based Biorepository for Childhood Heart Disease

WHAT’S KNOWN ON THIS SUBJECT: Understanding human disease genomics requires large population-based studies. There is lack of standardization, as well as social and ethical concerns surrounding the consent process for pediatric participation in a biorepository.

WHAT THIS STUDY ADDS: The study identifies specific barriers to pediatric participation in biorepositories relative to adults, and proposes strategies to improve ethical and responsible participation of pediatric-aged patients in large-scale genomics and biorepository-driven research without significantly increasing research burden for affected families.

abstract

BACKGROUND: Consenting minors for genetics research and biobanking involves ethical and social challenges. We examined factors influencing participation rates in a population-based biorepository for childhood heart disease.

METHODS: Individuals were prospectively enrolled across 7 centers in Ontario by using a standardized consent form. Individuals were approached for consent for the donation of blood/saliva (DNA), tissue, and skin from the affected individual for future genomics and stem cell research. Consent rates were compared between pediatric and adult patients and factors affecting consent were analyzed by using multiple logistic regression analysis.

RESULTS: From 2008 to 2011, 3637 patients were approached. A total of 2717 pediatric patients consented (90% consent rate); mean age was 8.5 ± 5.8 years (57% male; 76% white). A total of 561 adult patients consented (92% consent rate, P = .071 versus pediatric). Factors associated with lower pediatric consent rates included younger age, race, absence of complex defects, and location of consent; these were not associated with adult consent rates. Leading causes for refusal of consent were lack of interest in research (43%), overwhelmed clinically (14%), and discomfort with genetics (11%). Concerns related to privacy, insurability, indefinite storage, and ongoing access to medical records were not the leading causes for refusal.

CONCLUSIONS: The high pediatric consent rate (90%) was comparable with that of adults. Ethical, social, or legal issues were not the leading reasons for refusal of consent. Pediatrics 2012;130:1–8
Despite a growing need for population-based approaches to study disease biology, pediatric participation in biorepositories lags behind adults. Population-based biorepositories are critical for accrual of study subjects who are representative of the racial/ethnic and geographic diversity of the population under study. This is particularly true for pediatric diseases in which single-center studies may fail to capture sufficient numbers of subjects for genomics research. From a biological perspective, many adult diseases are deemed to have their origins in childhood or even to events in prenatal life. Therefore, the study of genetic and environmental influences on adult disease needs to begin in childhood. Failure to include children represents a failed opportunity to modify the course of disease in its early stages and can also result in the exclusion of patients with the most extreme phenotypes who may die before reaching adulthood.

Complex challenges surround pediatric participation in research biorepositories. Attempts to protect minors from ethical, legal, and social risks related to genomics research has been a significant barrier to pediatric participation in biorepositories. These include concerns about parental consent on behalf of a minor, “open” consent for indefinite sample storage, unspecified research on stored samples, privacy, insurability, and general ethical concerns about genetics research. The lack of standardized guidelines across institutions and research ethics boards has resulted in considerable variability in the approaches toward recruitment of minors. Restrictions on consent further compound the issue by limiting broad applicability of research findings.

To address these concerns, we developed a standardized protocol and informed consent process for pediatric participation in a disease-based biorepository. The objectives of our study were to evaluate pediatric consent rates in an Ontario province-wide biorepository for childhood-onset heart disease by using a standardized consent process, and to investigate the medical, ethical, legal, and social obstacles to pediatric participation compared with adults.

**METHODS**

The Heart Centre Biobank was established in 2008 at the Hospital for Sick Children, Toronto, and expanded to 7 centers, including 10 pediatric and adult cardiac programs across the Ontario province (Hospital for Sick Children, Toronto General Hospital, Mount Sinai Hospital, London Health Sciences Centre, Hamilton Health Sciences Centre, Kingston General Hospital, and Children’s Hospital of Eastern Ontario). Patients of all ages with congenital heart disease (CHD), cardiomyopathies, rhythm disorders, and other forms of childhood-onset heart diseases were eligible for participation. A standardized informed consent form for patients and parents was developed based on guidelines from the International Society for Biological and Environmental Repositories, National Cancer Institute, National Institutes of Health, Ontario Genomics Institute, and institutional research ethics boards. The consent form specifically addressed key ethical and social issues in genetics research identified in previous studies, and was amended as needed to meet updated international best practices. The consent form was approved by research ethics boards across all participating sites.

Subjects were ascertained through a review of outpatient clinic scheduled visits and inpatient hospitalizations. A letter notifying families about the study was sent before the clinic visits or patients were introduced to the study by their responsible physician or nurse before approach. Subjects were approached during inpatient hospitalization or outpatient visits. For patients who consented, blood was collected in conjunction with clinical blood work or a clinical procedure. For minors <16 years old and adults with mental disabilities, informed consent was obtained from parents/legal guardian and consent was explained to the subject in lay language. Assent was obtained from patients between the ages of 8 and 16 years. For teenagers older than 16 years, informed consent was obtained from the patient. Consented patients undergoing surgery at a later date were approached again to confirm their willingness to donate biospecimens during surgery. Parents of affected children were approached in those with a positive family history. The process of consenting was standardized across institutions through centralized training and site visits. Consenting was done by research coordinators, nurses, research assistants, or research trainees. A standardized material and data transfer agreement form was signed between transferring and recipient institutions to permit sample and data sharing with investigators within and outside the research network. All biospecimens and data were de-identified by using unique codes and were centrally stored at the Hospital for Sick Children. All phenotypic data were stored de-identified on a Web-based, secure, restricted access, data platform.

**Consent Form**

The following items were included in the consent form by using an “open” consent model with the participant consenting to all of the following: (1) donation of blood/saliva, tissue, or skin for genomics, biomarker, and stem cell research in heart disease and other medical conditions; (2) longitudinal collection and storage of personal
health information with ongoing medical record review and a self-administered questionnaire at enrollment; (3) indefinite storage of samples and data; (4) right to withdraw samples and/or data at any time; (5) disclosure of only clinically significant results; (6) future recontact; (7) use of samples for genome-wide studies; (8) distribution of de-identified samples to investigators within and outside participating institutions; (9) deposition of genome-wide data in federal data repositories if required; and (10) potential for commercialization of research findings. The participants were provided information about the processes for protection of sample/data. Potential benefits and risks were explained, including privacy and insurance risks, and the absence of direct medical/financial benefits. They were made aware that should they choose to withdraw from participation, only unused samples and data remaining in the biorepository would be discarded on request. Parents were made aware that should sensitive information (eg, neglect or child abuse) be revealed during the course of the study, this would need to be reported as per legally mandated reporting policies. Participants also were made aware that only research findings with known clinical significance for which a clinical genetic test and an “actionable” intervention was available would be disclosed to the participants or their physician, unless the participant chose not to be contacted. By consenting to participation, subjects were consenting to all aspects of the study as described. Any restrictions to the consent were recorded.

Statistical Analysis
Data are presented as mean/median ± SD and frequencies. The characteristics of enrolled patients were compared with that of nonconsenting patients to determine if consent rates differed by age, gender, race, type of heart disease, and timing of consent. Heart defects were divided into simple or complex defects, cardiomyopathies, or transplants. Simple defects included patients with a primary diagnosis of an isolated septal defect (ie, ventricular septal defect, atrial septal defect, atrioventricular septal defect, patent ductus arteriosus, or isolated valve anomaly). Complex heart defects included complex left- or right-sided obstructive lesions, laterality disorders, conotruncal anomalies, unbalanced atrioventricular septal defect, and single ventricles. Data were analyzed by using χ² test for categorical variables and confounding factors influencing consent were evaluated by using multiple logistic regression.

RESULTS
Subject Characteristics
From February 2008 to August 2011, 3637 individuals were approached for participation in the Heart Centre Biobank Registry; 3028 were pediatric (<18 years old) and 609 were adults. The details of patients approached and consented are shown in Fig 1. The mean age of pediatric patients approached was 8.5 ± 5.8 years (median 8.8 years; range 0–18 years); 57% were male. Racial distribution was 76% white, 4% black, 15% Asian, and 5% other. There were 36% who had simple defects. The mean age of adult patients approached was 34.7 ± 14.0 years (median 30.4 years; range 18–84 years); 50% were male. Racial distribution was similar to pediatrics (ie, 93% white, 1% black, 4% Asian, and 2% other). There were 38% who had simple defects. Consent rates across the 7 recruiting centers were Hospital for Sick Children, 89%; Toronto General Hospital, 90%; Hamilton Health Sciences Center, 92%; Kingston General Hospital, 89%; Children’s Hospital of Eastern Ontario, 90%; and London Health Sciences Center, 97%. The latter had a higher consent rate compared with the Hospital for Sick Children (P < .0001). Overall, there was no significant difference in pediatric versus adult consent rates (90% vs

FIGURE 1
Characteristics of pediatric and adult patients who were approached for participation.
92%; \( P = .071 \) ). Consent rate was 100% for parents of children with CHD.

Factors Influencing Pediatric Consent Rate

**Patient Characteristics**

Participation rate was lower in infants <2 years of age compared with those \( \geq 2 \) years (82% vs 92% respectively, \( P < .001 \)) (Fig 2A). Consent rates did not differ between male and female patients (\( P = .605 \)). The pediatric consent rates were lower in blacks (79%) and Asians (83%) compared with whites (92%, \( P < .001 \) white versus other races) (Fig 2B). Consent rates were 88% in patients with simple heart defects, 91% in those with complex defects (\( P = .061 \) versus simple), 93% in those with cardiomyopathies (\( P = .093 \) versus simple), and 95% in transplant recipients (\( P = .032 \) versus simple) (Fig 2C).

**Timing of Consent**

Consent rates varied by timing/location of consent: 93% in outpatient settings, 90% in inpatient settings, 90% in pre-catheterization clinics (\( P = .041 \) versus outpatient), and 80% in preoperative clinics (\( P < .001 \) versus outpatient). On multiple logistic regression, only younger age, race, and preoperative clinic location remained significantly associated with lower consent rate (\( P < .001 \)) (Table 1).

Factors Influencing Adult Consent

Overall participation rates did not differ between pediatric and adult cohorts (90% vs 92% respectively, \( P = .071 \)) (Fig 2A). Except for lower consent rate in adult male patients relative to female patients (\( P = .041 \)), consent rates did not differ by race/ethnicity, type of cardiac defect, and location of consent (all adults were approached only as outpatients) (Fig 2B and C). Gender remained marginally significant on multiple logistic regression (\( P = .048 \)) (Table 1).

Reasons for Nonconsent

Of the 311 families that refused consent, 8 (3%) families did not provide a reason for declining participation. Of the remaining 303 families, reasons for nonconsent are shown in Fig 3. The leading reasons for nonconsent included lack of interest in research (43%), being clinically overwhelmed (14%), not comfortable with genetics research (11%), being overwhelmed with research studies (7%), and language barrier (6%). Only 35 (12%) families declined participation because of discomfort with additional specimens being taken (5%), privacy concerns (3%), unwillingness to consent on behalf of a minor (1%), ethical concerns related to prenatal screening (2%), and insurability concerns (0.6%).
None of the families expressed the wish for the child to be reconsented at maturity. Among the adults, 48 individuals refused participation and 4 (8%) did not provide a reason for declining participation. The leading reasons for nonconsent were refusal of specimen donation (27%), not interested in research (25%), not comfortable with genetics research (11%), or being clinically overwhelmed (11%).

**Restrictions on Consent**

Only 121 pediatric participants (4%) placed restrictions on 1 or more clauses in the consent form. These restrictions were primarily related to type and timing of sample collection; 18 (0.7%) refused tissue collection, 100 (4.0%) refused skin collection in the operating room, 18 (0.7%) refused tissue collection in the operating room, and 12 (0.4%) participants restricted any additional specimen collections after initial donation. Other restrictions included 2 (0.07%) refusals for generation of lymphoblastoid cell lines, 12 (0.4%) refusals for sample use for research unrelated to heart disease, 2 (0.07%) refusals for sample use for research outside of the Hospital for Sick Children hospital, 2 (0.07%) refused consent for release of clinically significant findings, and 10 (0.4%) refused future recontact. Only 1 family withdrew consent 8 months after enrolling; the reason was not further specified. Among the adults, only 9 participants (1.6%) placed restrictions on 1 or more clauses in the consent form. These restrictions related to type of sample collection with refusal of either skin and/or tissue collection.

**DISCUSSION**

Longitudinal genetic research studies involve the collection, retention, and use of biological samples and personal health information for several years. This has raised concerns about pediatric participation in biorepositories that have hindered researchers from involving children in large-scale genomics research.\(^2\)\(^{-7}\)\(^9\) In one of the largest studies of its kind, we analyzed our experience with using a standardized open consent form and enrollment process for a multi-institutional population-based biorepository and found a high consent rate of 90% for pediatric participation, which was comparable to adult biorepositories. Several barriers to participation were identified, with only 1% of all patients approached citing ethical concerns related to genetics or biorepository-related research as a reason for refusal of consent.
In a study by Ries et al., the following were identified as key ethical and social issues in genetic research studies involving children that should be specifically addressed during consent: (1) parental authority to consent for a minor; (2) the nature of consent (ie, broad or specific); (3) reconsent at maturity; (4) protection of confidentiality; (5) handling sensitive information (eg, signs of child abuse); (6) disclosure of results to participants; and (7) withdrawal from the study. We developed an informed consent form that was based on guidelines from the International Society for Biological and Environmental Repositories, National Cancer Institute, National Institutes of Health, and Ontario Genomics Institute that addressed all these issues and that was approved by the ethics boards of all participating institutions. By using this standardized consent form, we obtained a 90% participation rate in our pediatric population with heart disease. This consent rate was comparable to our adult biorepository with a consent rate of 92% as well as adult biorepositories internationally with consent rates ranging from 99% in the Dutch CONGenital CORVitia (CONCOR) registry for CHD, and 93% in a Swedish-based biorepository.

Several factors influenced our pediatric participation rates, including age, race, complexity of disease, and location/time of consent. These obstacles to consent have been previously acknowledged in the literature for both genetics research and clinical studies and are not unique to pediatric biorepositories. There were age-related differences in consent rates with lower rates of participation among infants <2 years old relative to older children and adults. Analysis of our consent patterns allowed us to intensify our efforts to improve recruitment of younger patients, particularly unoperated newborns, to avoid biasing our repository toward survivors by failing to capture the sickest and most complex patients.

There were race/ethnicity-related differences in consent rates with higher rates among whites compared with other races, a finding that is not unique to pediatric biobanks. Racial imbalances can interfere with the genetic diversity of the enrolled cohort. These differences may reflect cultural attitudes or language barriers; it is therefore important to provide consent forms in different languages to overcome language barriers. Despite disparities in consent rates, we were able to capture patients who reflected the racial admixture of our population.

Patients with more complex heart defects or chronic cardiac conditions were more likely to participate than those with simple defects, suggesting that most families with ongoing medical issues do not perceive participation in genomics research to be a significant burden and should be offered an opportunity to participate.

Finally, families that were approached during situations of high stress, such as before cardiac surgery or catheterization procedures, had lower consent rates. The feeling of being “overwhelmed/stressed due to illness” represented the second leading reason for non-consent (14%) in our cohort, which is comparable to an adult coronary heart disease genetics biobank.

Overall, only 39 pediatric families (13%) refused consent because of discomfort with genetics research or other concerns specific to biobanking research activities, a finding similar to the adults approached in our repository and to other adult biobanks as well. This does not imply that families do not harbor concerns; however, these concerns did not outweigh families’ perceived value in participating in this research. In response to these concerns, it is important to have better community involvement to understand public perceptions toward large-scale genomics research and a need to enhance transparency and research quality, improve subject protection, and enhance public trust.

To achieve this goal, we have used a strategy to keep the community informed through annual newsletters and family education days, which helps engage the community and create better awareness of research advances.

The issue of informed consent for biorepositories is unique given the “unknown” nature of biobanks and the change in uses, risks, and benefits over time. “Open” consent implies that participants make a 1-time choice about the future use of their data and samples as opposed to specific informed consent for each use. It has been recognized that the open consent format is ideal for biobanks, as it allows for broad research applications for future studies and applications that may not be available at the time of enrollment. Others have disputed the acceptability of an open consent or accepting open consent methods on the condition of complete anonymity. We used an open consent approach because restrictions on consent limit the usability and generalizability of results generated from this resource. Only 4% of pediatric participants in our cohort placed restrictions on the consent and most were related to types and frequency of sample collection with virtually no restrictions on future uses of specimens or the need to reconsent for individual studies or reconsent into adulthood. The concept that anonymizing the samples obviates the need for consent is highly debatable, as the inability to link the sample back to the subject essentially deprives the participant of his or her right to withdraw in the future, which is a fundamental right of a research participant. Public opinions on this issue were highlighted through 2 recent examples, 1 in which newborn blood spot tests stored by the state
were being used for genetics research without parental consent, and the second
in which a native Indian tribe sued an academic university for conducting research on stored samples for which previous consent had not been ob-
tained.17,18 Our experience suggests that a fully informed consent that explains the scope of intended future research with the stored samples and data is important to build public trust and encourage responsible participation. In light of the high participation rate and extremely low withdrawal rate, our experience supports the practice of open consent that is conducted responsibly and with full disclosure. A limitation of our study is that education level or basic genetic knowledge, which can influence the understanding of ethical, legal, and social issues, were not assessed.

An unresolved issue in pediatric biobanking relates to whether children should be reconsented once they reach the age of maturity. Despite general agreement toward reconsenting at maturity,2,4,5 there are no standardized policies among research ethics boards and pediatric biobanks.7,15,19 Public opinions on this issue vary.4,5,10 Studies investigating parental attitudes toward the participation of minors in research have reported a general consensus of parental attitudes in favor of reconsent at the age of maturity.4,5 Despite being considered good practice to reconsent minors at maturity, the challenges of recontacting participants who may have moved or prefer not to be recontacted limits the practical applications of this approach. Also, opinions regarding reconsent do not appear to influence an individual’s willingness to participate in population-based genomics research, as only 4 of the total 3028 number of fami-
lies approached cited “unwillingness to consent on behalf of a minor” as a reason for nonparticipation. A recent article suggested a surrogacy model similar to advanced directives for medical decision-making to ensure that the participant’s interests are taken into account on an ongoing basis.21 In the absence of a uniform institutional policy across all participating sites requiring reconsent of minors at majority, we have opted for a knowledge-dissemination approach whereby families can be re-
contacted if needed and are reminded of their ongoing participation through annual newsletters, research updates, and family education days. This provides them with an opportunity to have concerns addressed and to exercise their right to withdraw by notifying the inves-
tigators. In addition, we have partnered with patient advocacy groups and invited community representation on our advisory committee to help us adapt to the evolving needs and values of participants over time.

CONCLUSIONS

Pediatric participation in large-scale genomics research and biorepositories should be encouraged so as to not de-
prive children from contributing to re-
search discoveries that could potentially benefit them in the long-term. Families of children with chronic disease have a high rate of participation despite perceived ethical, legal, and social concerns, which is comparable with the consent rate in an adult population. Standardizing consent forms and streamlining re-
cruitment procedures may be helpful in enhancing participation and improving the consistency and quality of population-based research.

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