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Confidentiality in Biobanking Research: A Comparison of Donor and Nondonor Families' Understanding of Risks

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Aims: Confidentiality of personal identifiers potentially linking the genetic results from biobanking participants back to the donor and donor relatives is a concern. The risks associated with a breach of confidentiality should be ascertained when biobanks collect samples requiring the consent of a family decision maker (FDM) from deceased organ and tissue donors. This article explores FDM knowledge and opinions regarding risks associated with participation in biobanking research in the context of the Genotype-Tissue Expression (GTEx) Project.
Methods: Data collection included a survey completed by organ procurement organization requesters ($n = 37$) and semistructured telephone interviews with the FDMs ($n = 85$).
Results: Donor families were more likely to know that there was a risk that a patient's identity could be revealed through a breach of confidentiality ($p < 0.05$). They also were more likely to understand that researchers using biobanked tissue would not have access to the patient's exact identity ($p < 0.05$). FDMs who refused donation were more concerned about risks than donors and reported lower levels of support for medical research in general. Finally, families were frequently interested in the return of results and willing to trade absolute confidentiality for participation.
Conclusions: Clear discussion of the risk of breach of confidentiality is needed during the consent process. The risk and benefit equation could be equalized if studies such as GTEx offered genomic results to interested participants.

Keywords: informed consent, tissue donation, biobanking, genomic research

Background

There are in excess of 500 million human biospecimens containing genetic material stored in public and private biobanks in the United States (Eisman and Haga, 1999; Henderson *et al.*, 2013). These specimens can contribute to research on gene variations associated with diseases, leading to advancements in our understanding of how to target therapies for many illnesses (Witt, 2011; Visscher *et al.*, 2012; O'Reilly and Elphick, 2013; Takahashi *et al.*, 2013; Maitland *et al.*, 2015). Collecting and storing this volume of biospecimens raise ethical concerns, including adequate protection of confidentiality and ensuring prospective donors are properly informed of the implications of potential data breaches.

Informed consent for the collection and analysis of biospecimens gives precedence to individual autonomy. For studies such as the Genotype-Tissue Expression (GTEx) Project, a National Institutes of Health (NIH) study linking complete genetic information from tissue samples and health information obtained from deceased donors' medical records, the risks of participation extend from individual participants, that is, the proband, to their genetic relatives (GTEx Consortium, 2013). A breach of confidentiality is the greatest potential risk to GTEx donors and their families. A breach could result in public disclosure of donors' identities and genetic and private health information and the associated possibility of psychological harm, familial discord, or discrimination by employers or insurers (Lowrance and Collins, 2007).

Evidence regarding public awareness of confidentiality risks is conflicting (Kaufman *et al.*, 2009; Brothers *et al.*, 2011; Oliver *et al.*, 2011; Trinidad *et al.*, 2012; Rogith *et al.*, 2014). A survey study ($N = 1041$) about consent to a hypothetical biobank found that 75% of participants disapproved of using their genetic material because of security concerns

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(Kerath *et al.*, 2013). Another large study surveyed 4659 adults, of whom 90% expressed privacy concerns about biobanking and 37% worried that they could be harmed from results (Kaufman *et al.*, 2009). Interestingly, donors report lower levels of concern about potential risk compared with the general public; only 34.6% of actual donors report that the greatest risk to biobanking participation is revealing their identity (Oliver *et al.*, 2011). While recent studies have not found elevated privacy concerns within minority groups (Rodriguez *et al.*, 2013; Gao *et al.*, 2014; Hagiwara *et al.*, 2014), mistrust about privacy protection does affect consent. African Americans especially demonstrate a preference for defined uses of their tissue samples (Ewing *et al.*, 2015).

New genomic analysis technologies are outpacing currently available protections in large often public datasets, making breaches of confidentiality a growing concern (Rodriguez *et al.*, 2013). Although no actual breaches have been documented, the capability exists to identify participants in genetic research studies using available data (Craig, 2016). The increased possibility of future breaches impels more attention be paid to biobanking participants' understanding of confidentiality in this context. We report on a sample of families asked to donate a deceased patient's tissues and medical records to the GTEx project (GTEx Consortium, 2013; Keen and Moore, 2015). We examine both donor and nondonor families' understanding of the risks to confidentiality and associated attitudes.

Methods

GTEx project and ethical, legal, and social issues substudy

GTEx, a project of the NIH Common Fund, requires biospecimens from many individuals and collects multiple reference tissues from each donor to explore the relationship between genetic variation and gene expression. In partnership with three geographically dispersed organ procurement organizations (OPO), GTEx requests the collection of tissues for research purposes from families who agreed to donate deceased relatives' organs and/or tissues for transplantation. GTEx authorization includes the release of patients' medical and social histories, various tissue samples, and, when medically suitable, the whole brain. Families' consent to GTEx is inclusive of possible future, unspecified research projects (referred to as blanket consent). Donated tissues are managed by the study biobank; the donor's genome is fully sequenced and analyzed for gene expression by an independent academic institute. All sequencing information is added to the NIH database of Genotypes and Phenotypes (dbGaP) online data resource. dbGaP restricts access to the full dataset to qualified researchers who promise to never try to identify donors (Keen and Moore, 2015).

The ethical, legal, and social issues (ELSI) substudy examines the social and ethical issues concerning the decision to donate deceased tissue to the GTEx project and policy implications. The substudy assesses family decision maker (FDM) understanding of donation risks and benefits and possible psychosocial consequences of donation (GTEx Consortium, 2013). The National Disease Research Interchange (NDRI) coordinated all tissue collection activities and provided the ELSI team access to contact information of FDMs approached for GTEx donation from September 2011 through December 2012. All relevant institutional review boards approved this study.

Tissue requester and FDM samples

All OPO staff who discussed GTEx donation with FDMs participated in the ELSI substudy ($n = 37$). FDMs asked to donate to GTEx, whether or not they consented, were considered eligible for ELSI substudy participation. Invitational packets were mailed to eligible FDMs 2 months after the patient's death using a protocol developed for past research with similar subject populations (Siminoff *et al.*, 2001, 2010). Telephonic invitations were made 2 weeks later to FDMs who had not declined participation. Verbal consent to participate in the ELSI study was given by 85 (68%) of the total 125 FDMs invited.

Measures

FDM variables. A semistructured interview captured FDM sociodemographic information, relationship to the patient, as well as the context and content of the donation discussion, and understanding and perception of risk as described below.

Knowledge of risk. Four true/false items gauged FDM knowledge of risk to confidentiality associated with donation of their family members' tissues.

Risk/benefit discussions. Six items assessed FDM understanding of potential risks and benefits of donation (yes/no).

Risk perceptions. FDM perceptions of the risk of a breach of confidentiality were measured for five items along 7-point Likert scales.

Attitudes. Attitudes toward medical research were assessed using a 7-point Likert scale with seven items adapted from the Research Attitudes Questionnaire (Rubright *et al.*, 2011). Global support for biobanking was measured using a single item on a 5-point scale. Five items assessed attitudes regarding the process of conducting biobanking research using a 5-point Likert scale. Higher responses on all items/scales indicate higher levels of agreement or support.

OPO requester variables. Requesters completed a self-administered paper–pencil survey capturing sociodemographics upon enrollment.

Donation decision. FDM GTEx donation decision (authorized/refused) was ascertained from NDRI records.

Analytic approach

Descriptive statistics are reported for demographic information for requesters and FDMs by consent status. Frequencies and percentages are presented for categorical-level variables and means and standard deviations for interval-level variables. Bivariate associations between FDM sociodemographic characteristics, knowledge, and perceptions of risk and consent status are examined. Discussion of desire to know about and whether the risk to the family associated with donation influenced the decision were also compared for

Table 1. FDM Sociodemographics by Consent Status

Demographic characteristic	*Authorized donation,* n = *55 (64.7%)*	*Refused donation,* n = *30 (35.3%)*	*Total sample,* N = *85*
Age, years, mean (SD)	49.1 (14.3)	47.9 (13.8)	48.9 (13.9)
Education, years, mean (SD)	14.8 (2.6)	13.9 (2.3)	14.4 (2.4)
Sex			
Female	36 (65.4)	23 (76.7)	59 (70.0)
Race			
African American	12 (21.8)	9 (30.0)	21 (24.0)
White	42 (76.4)	19 (63.3)	61 (72.6)
Other	1 (1.8)	2 (6.6)	3 (3.5)
Marital status			
Never married	6 (10.9)	5 (16.7)	11 (12.5)
Married/cohabit	19 (34.5)	8 (26.7)	27 (32.0)
Divorced/separated	5 (9.1)	4 (13.3)	9 (10.7)
Widowed	25 (45.4)	11 (36.7)	36 (42.9)
Not reported	0 (0)	2 (6.7)	2 (2.4)
Religious affiliation			
Protestant	35 (63.6)	16 (53.3)	51 (60.7)
Catholic	8 (14.5)	8 (26.7)	16 (19.0)
Other	6 (11.0)	3 (10.0)	9 (10.7)
None	6 (11.0)	3 (10.0)	9 (10.7)
Relationship to patient			
Spouse	23 (41.8)	11 (36.7)	34 (40.5)
Parent	11 (20.0)	8 (26.7)	19 (22.6)
Sibling	10 (18.2)	3 (10.0)	13 (15.5)
Offspring	9 (16.4)	8 (26.7)	17 (20.0)
Other	2 (3.6)	0 (0)	2 (2.4)
Willing to donate own tissues			
Yes	53 (96.4)	17 (56.7)	70 (83.0)

Values are count (percent) unless noted otherwise.
FDM, family decision maker; SD, standard deviation.

donor and nondonor families. The chi-square statistic was used to evaluate significant associations for categorical data, and GLM (controls for unbalanced cell sizes) was used to compare means for continuous variables.

Exploratory exact logistic regression, the appropriate choice for modeling binary outcome variables when the sample size is too small for a standard logistic regression, was used to assess predictors of FDM authorization. Analyses were performed using SPSS 21.0 (2012) for Microsoft Windows and SAS 9.3 (2011); significance was determined at $\alpha = 0.05$ for all tests.

Results

FDM and requester characteristics

The majority of FDMs self-identified as white, female, and as likely to be widowed as married. FDMs averaged ~47 years of age and 14 years of education; most reported Protestant religious affiliation (Table 1). Of the 85 FDMs interviewed, 55 (64.7%) agreed to donate to GTEx and 30 (35.3%) did not. No statistically significant differences were found in FDM demographic characteristics by consent status.

The majority of OPO requesters (data not tabled) were married ($n = 16$, 70%), self-identified as white ($n = 19$, 83%), female ($n = 14$, 61%), and of self-reported Christian faith, that is, Protestant or Catholic ($n = 18$, 82%). On average, requesters were 41 years of age (SD = 7.6), with at least a college degree and 4 years of experience making requests for donation.

Knowledge of GTEx study risks

FDMs exhibited low to moderate knowledge of the risks associated with the donation of tissues to GTEx; six FDMs (10.0%) answered none of the four questions correctly. Fifteen participants reported nonexistent or poor recall of the GTEx request and were excluded from the analyses.

FDMs authorizing GTEx exhibited higher levels of understanding than nondonors. While most donors understood that researchers would not know the donor's identity, less than half of those refusing donation answered this question correctly [69.6% vs. 42.8%; χ^2 (1) = 4.19, $p < 0.05$]. Donor families were also more likely to be aware of the risk that patients' identities could be revealed through a breach of confidentiality [58.7% vs. 28.7%; χ^2 (1) = 3.91, $p < 0.05$] and to know that genetic results would not be returned [65.2% vs. 35.7%; χ^2 (1) = 10.87, $p < 0.001$]. No statistically significant difference was detected in the proportions of consenting and refusing families who understood there was a risk that family members could be identified through accidental release of the patient–donor genetic information [43.5% vs. 28.7%; χ^2 (1) = 0.99, $p = 0.30$].

Although just over half of all FDMs reported a desire for information regarding risks to families associated with the accidental release of the donor's genetic information ($n = 48$; 56.5%), less than half of FDMs reported discussing family-level risks with the requester ($n = 35$, 41.7%). When discussed, it was significantly associated with consent status [51% vs. 23%; χ^2 (1) = 5.59, $p = 0.02$]. Moreover, less than a third of FDMs acknowledged that the potential risks of a breach of confidentiality influenced their donation decision ($n = 24$, 28%); however, this was not significantly associated with FDM authorization [χ^2 (1) = 3.2, $p = 0.07$]. Nearly half of FDMs reported a desire to know that the family would receive no direct benefits for participation ($n = 39$, 46.4%); this was significantly associated with GTEx donation [χ^2 (1) = 6.32, $p = 0.02$].

Just over half ($n = 46$; 53.7%) of FDMs reported discussing that there was no direct benefit to the family from participation in GTEx (Table 2). Consenting FDMs were more likely to report discussing this topic with the requester [67.3% vs. 27.6%; χ^2 (1) = 12.0, $p = 0.0005$]. Authorizing FDMs were more likely to want information about the lack of a direct benefit from participation (56.4% vs. 27.6%). Few FDMs reported that knowledge of no direct benefit from participating influenced the donation decision ($n = 10$, 11.9%); the perceived influence was not significantly associated with FDM authorization [χ^2 (1) = 0.15, $p = 0.07$].

Perception of risk

FDMs who refused donation indicated a lower tolerance for risk than authorizing FDMs [$F(1, 59) = 3.7$, $p < 0.05$]. Compared with donor families, nondonor families were more frightened by the thought of a breach of confidentiality and

Table 2. Risk Knowledge and Risk to Family by Consent Status

Risk knowledge items	*Authorized donation,* n = *46*	*Refused donation,* n = *14*
Researchers using the donated tissue will know the patient's exact identity	32 (69.6)	6 (42.8)*
There is a slight risk that the patient's identity could be found out	27 (58.7)	4 (28.7)*
There would have been a slight risk that the identity of my family could be found out	20 (43.5)	4 (28.7)
If I signed the consent form and the donated tissue were used for a research project, I would have been told what they learned about patient's health	30 (65.2)	5 (35.7)
Risk to family	*Authorized donation,* n = *55*	*Refused donation,* n = *30*
Was the topic of risk to family associated with the release of genetic information discussed with the requester?	28 (51.0)	7 (23.3)
Was risk to family a topic you wanted to know about?	35 (63.6)	13 (43.3)
Did risk to family influence your decision to donate tissue for research purposes?	13 (23.6)	11 (36.7)
Was the topic of no direct benefits of participation discussed with the requester?	37 (67.3)	8 (27.6)
Was no direct benefits of participation a topic you wanted to know about?	31 (56.4)	8 (27.6)
Did no direct benefits of participation influence your decision to donate tissue for research purposes?	6 (10.9)	4 (13.8)

Risk knowledge values expressed as count (percent) answering correctly. Knowledge questions were not administered to 15 FDMs who reported poor or unreliable recall of the GTEx request. Risk to family values expressed as *n* (%) endorsing ''yes.''

*$p < 0.05$.

GTEx, Genotype-Tissue Expression Project.

considered a breach more serious and more of a risk to family members. Notably, both donor and nondonor FDMs found a 1 in 100,000 risk of a breach of confidentiality acceptable (4.9 vs. 5.6) and expressed moderate levels of certainty about their understanding of these risks (4.0 vs. 3.8). These differences did not reach levels of statistical significance (Table 3).

Attitudes toward medical research and the biobanking process

Compared with FDMs who declined GTEx donation, consenting FDMs held more positive attitudes regarding medical research [$F(1, 82) = 8.87$, $p < 0.001$] and expressed greater levels of support for biobanking [$F(1, 82) = 12.41$, $p < 0.001$].

GTEx donors' and nondonors' attitudes toward the process of biobanking were similar [$F(1, 82) = 3.25$, $p = 0.07$], with the exception that donors were more likely to endorse scientists' unrestricted access to unidentified personal samples for research [$F(1, 82) = 9.21$, $p < 0.005$] (Table 4).

Associations between risk knowledge, perceptions, and consent status

Exact regression analysis simultaneously modeled the relationships between risk perceptions, research attitudes and reported communication regarding risks (both by FDM and requester), and FDM authorization to GTEx donation. This model was significant [χ^2 (6) = 38.0, $p < 0.0001$] and demonstrated that lower perceptions of risk (odds ratio [OR] = 0.60; confidence interval [CI] = 0.36–0.99; $p = 0.02$) and more positive attitudes toward research (OR = 3.6; CI = 1.1–15.5; $p = 0.02$) were independently associated with FDM authorization.

Discussion

This study is the first to examine FDM knowledge and perceptions of risk in a whole genomic sequencing biobanking project. The data reveal that many FDMs have an inaccurate understanding of the confidentiality risks related to donation. These gaps in knowledge are consistent with prior research conducted with living biobanking participants (Ormond *et al.*, 2009; Oliver *et al.*, 2011). We also found that donors and nondonors differed in their knowledge and perceptions of risks. Most notably, donors were more likely to report actually discussing the issue with requesters and had more accurate knowledge about and less fear of a breach than nondonors. The exact regression model demonstrated that lower risk perceptions and more positive attitudes toward research predicted GTEx donation. Overall, the data demonstrate that conversations about risks do not inhibit donation, but are associated with a greater understanding of and comfort with tissue donation for genetic research.

A notable finding was that 15/85 FDMs had virtually no recollection of the GTEx request. In this study, FDMs were first asked to donate a deceased patient's organs for transplantation and then were asked to donate tissue to GTEx. These conversations occur during an emotionally heightened and stressful time, circumstances that challenge families' ability to fully comprehend complex medical and risk-related information. Alternative ways to convey this information to families are needed. GTEx OPO requesters read verbatim from densely worded consent documents. We advocate the use of concise informational document bulleting points about different aspects of the research and potential use of the tissue and use of conversational techniques such as repetition and checking for understanding to ensure FDM comprehension. Provision of visual aids (e.g., short videos or infographics) might also aid comprehension (Kardia and Platt, 2015; Overby *et al.*, 2015).

Table 3. Perceptions of Risk by Consent Status

Risk perception items	*Authorized donation, n = 55 (64.7%)*	*Refused donation, n = 30 (35.3%)*
Risk Perception Scale	3.7 (1.5)	4.7 (2.1)*
How much does the chance of a breach of confidentiality frighten you?	2.7 (2.1)	4.2 (2.9)
If the patient's identity were revealed, how serious would the consequences of that breach of confidentiality be?	3.7 (2.1)	4.8 (2.4)
To what extent does a breach of confidentiality pose a risk to your family members?	3.0 (2.2)	4.3 (2.8)
What level of risk of a breach of confidentiality is acceptable?	4.9 (2.4)	5.6 (2.0)
How sure are you about what the risk of a breach of confidentiality is?	4.0 (2.4)	3.8 (2.8)

Values are expressed as mean (standard deviation). Higher values represent greater risk aversion (lower tolerance for risk).
*$p < 0.01$.

Currently, few large-scale genomic research projects in the United States routinely return results to participants (Bledsoe *et al.*, 2012; Johnson *et al.*, 2012; McGuire *et al.*, 2013). Even fewer have taken steps to incorporate return of results to family members of deceased donors (Chan *et al.*, 2012; Wolf *et al.*, 2015). One difficulty with returning results is that participants do not generally opt in or out of ongoing communication in studies obtaining blanket consent from donors. Moreover, the complexity of finding and contacting subjects repeatedly over the course of many years makes the return of results challenging and costly. In contrast, broad consent, wherein participants release their sample for future research, but retain the possibility of contact after donation, may not only be an ethically preferable framework to blanket consent but also requires expensive and long-term logistical support (Grady *et al.*, 2015). Rather than providing donors with tangible benefits to encourage participation, such as the return of results, most research projects rely on altruism and the acceptance of risk without any anticipated benefits. While altruism can be a significant motivator for participation, the notion that it is the only legitimate reason for participation in research is neither realistic nor desirable. Studies have demonstrated that altruism is not always the main factor driving participation in medical research and that subjects frequently have more than one reason for participation (McCann *et al.*, 2010; Hunter *et al.*, 2012; Godskesen *et al.*, 2014). Relying only on altruism may be especially problematic for communities with a history of experiencing research abuses who may demand more tangible benefits from participation in genetic studies (Corbie-Smith *et al.*, 1999).

Given the potential to improve the health and welfare of probands and their genetically related family members, the return of results could be an incentive and ameliorate concerns about risks and potential exploitation. Our data indicate

Table 4. Attitudes Toward Medical Research by Consent Status

Attitude items	*Authorized donation, n = 55 (64.7%)*	*Refused donation, n = 30 (35.3%)*
Research Attitudes Scale Summative	4.5 (0.4)	4.2 (0.6)**
I have a positive view about medical research in general.	4.6 (0.6)	4.5 (0.7)
Medical researchers can be trusted to protect the interests of people who take part in their studies.	4.4 (0.6)	3.9 (1.1)
We all have some responsibility to help others by volunteering for medical research.	4.4 (0.6)	4.1 (1.2)
Society needs to devote more resources to medical research.	4.5 (0.7)	4.3 (1.1)
Participating in medical research is generally safe.	4.5 (0.6)	4.2 (0.8)
If I volunteer for medical research, I know my personal information will be kept private and confidential.	4.4 (0.6)	4.0 (1.0)
Medical research will find cures for many major diseases during my lifetime.	4.5 (0.7)	4.2 (0.9)
In general, I support biobanking.	4.6 (0.9)	4.1 (1.1)**
Process of Conducting Biobanking Scale	3.8 (0.7)	3.5 (0.6)
There is no risk to participants who donate tissue to biobanks.	3.9 (1.3)	3.5 (1.4)
The confidentiality of personal medical information is critical in any circumstance where research is being conducted.	4.4 (1.1)	4.5 (1.1)
I do not care if the donated tissue is connected with the donor's name and medical information.	2.8 (1.7)	2.6 (1.6)
Scientists should have access to all unidentified personal samples for research.	4.3 (0.9)	3.6 (1.4)*
It is more important for the donor tissue to remain identifiable so the donor can be informed of important research results.	3.3 (1.6)	3.2 (1.7)

Values are expressed as mean (standard deviation).
*$p < 0.01$, **$p < 0.001$.

that the majority of participants would welcome the opportunity to receive at least some results as a tangible benefit of participation, particularly if the results were validated and clinically actionable (Murphy-Bollinger *et al.*, 2014; Siminoff *et al.*, 2016). In fact, 40% of participants erroneously believed that they would receive information about their loved one's health from the GTEx project (Siminoff *et al.*, 2016). Returning results must be an endeavor embarked on by more than a handful of investigators; it requires a national commitment of time, resources, and assurances that recipients could understand the results (Berg *et al.*, 2011; Jarvik *et al.*, 2014; Pinxten and Howard, 2014). However, returning results are not without complication and risk. In the United States, there are no regulations requiring the return of results and doing so could open researchers up to unforeseen legal issues (Clayton and McGuire, 2012). Potential recipients would also need to be made aware of the risks related to receiving results, including evidence of misattributed paternity, psychological distress, and receipt of medical information of unknown significance. There is also debate about the need to only return immediately clinically actionable results (Evans and Rothschild, 2012). Nonetheless, emerging ethical principles guiding biobanking and WES/WGS research may lead us in the direction of returning all possible results so that participants will be in possession of information that could be actionable in the future (Green *et al.,* 2013; Jarvik *et al.*, 2014).

Limitations

This study has two notable limitations. Individuals approached about a GTEx donation may have received more than one request to donate tissue for research. They also had already agreed to donate for transplantation and therefore are not representative of the general population. We also note the higher than average educational attainment and the low number of minorities in the sample, making it difficult to interpret the meaning of differences between groups. Second, the FDM interviews occurred at least 2 months after the event, so some degree of recall error and/or bias is expected. Replication of this research in a larger and more diverse sample is required to validate these findings.

Conclusion

The collection of tissues from deceased donors for genomic research will continue to be a valuable resource for researchers. It is important to consider how scientists can earn trust and generate enthusiasm for genomic research from a large and diverse population. We see an opportunity for FDMs who made the decision to donate tissues for research to become ambassadors and educators for genomic research within their own social networks and beyond. Continued research into the perspectives of potential donors regarding the risks and benefits of participating in genomic research is critical to providing an evidence base for future policies and ensuring continued public support of and participation in these efforts.

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Author Disclosure Statement

No competing financial interests exist.

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