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Consent to a Postmortem Tissue Procurement Study: Distinguishing Family Decision Makers' Knowledge of the Genotype-Tissue Expression Project

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Tissues from postmortem transplantation donors are a viable and productive option for genomic research. This entails obtaining authorization from the family decision makers (FDMs) of deceased donors. This study examined best practices for making such requests within the context of the Genotype-Tissue Expression (GTEx) project, a large national effort to collect reference tissues to establish a genomic biobank and database. Our study interviewed 413 FDMs about their donation experiences. We assessed FDM understanding of important consent concepts varied such as ability to withdraw tissues, the risks of donation, and return of results. Using latent class analysis applied to a subgroup of 188 FDMs who had agreed to participate in GTEx, three groups emerged, representing distinct patterns of comprehension of the GTEx project. Tissue requester gender and use of a GTEx brochure were associated with group membership. Results indicate that more research is needed to improve consent processes with FDMs to facilitate informed decision-making.

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

Introduction

Organ Procurement Organizations (OPOs) that obtain family authorization for postmortem deceased donation of organs and/or tissues for transplantation are now asking families to donate tissues for research.[1] This source of tissues for research has growing importance in biomedical research initiatives, especially genetic research.[2–4] Postmortem tissue donation provides several advantages to living donations, including the opportunity to obtain larger amounts of high-quality tissues, access to normal (not diseased) tissues, and a wider variety of tissue types, all of which are essential to increase our understanding of disease onset and progression, and eventual treatments.[5] Deploying OPOs to obtain multiple reference tissues with high-quality RNA and DNA maybe be the single best source for genomic research.[6]

In keeping with standard research practices, consent must be obtained to secure tissue from living donors and, for deceased donors, authorization is sought from family decision makers (FDMs). Guidance regarding informed consent for genomic biobanking, as outlined in the common rule, recommends that the collection process, data access, and risks associated with donation be described in detail.[7] These recommendations informed the creation of the Genotype-Tissue Expression (GTEx) project, which was funded by the National Institutes of Health's (NIH) common fund, to examine the relationship between gene expression and common diseases by collecting multiple reference tissue from >900 healthy organ and/or tissue donors.[5,8]

To meet this goal, the NIH partnered with six geographically dispersed OPOs and the collections accomplished by a tightly regulated protocol implemented by trained OPO staff.[8] Potential donors were deceased individuals, whose families first authorized donation for transplantation, a process that occurs immediately following the death of their loved one and can be time-consuming.[6,9] Partner OPOs approached family members of deceased organ and/or tissue donors and requested an additional anatomical gift of tissues for the GTEx project. When medically suitable, families were asked to donate the whole brain.[10]

Agreeing to the donation of tissues for GTEx research included authorization to release the patient's medical records and social history, the full sequencing of the donor's genome, and blanket consent for all future research using

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the donated tissue and resultant data.[10] Authorization also permits use by secondary researchers, in the United States and internationally, gaining access to the genomic data through the NIH database of Genotypes and Phenotypes online data resource. The full dataset (medical and social history, and tissue) is restricted to qualified researchers who must follow the standard NIH ethical guidelines for use and promise never to identify the donors.[11]

Very little work had been accomplished regarding specific goals for consent conversations in projects like GTEx. Consensus-based guidelines for adequate comprehension of these and other elements of informed consent for biobanking had been suggested.[12] These guidelines covered a range of topics to be disclosed to both living donors and the families of deceased donors, and imply a relatively detailed and lengthy discussion. However, the guidelines did not anticipate or fully consider the context of consent conversations with the FDMs of postmortem donors, which occur at the end of the extremely wrenching experience of losing a loved one and making a prior decision to donate organs and/or tissues for transplantation. These decisions were made over many hours, if not days, leaving FDMs physically and emotionally exhausted.

With this context in mind, the GTEx project set forth a narrower goal for FDMs to understand seven essential consent elements about the project, as outlined in Table 1.[6] GTEx's Ethical, Legal, and Social Implications (ELSI) substudy was created to explore FDM perceptions of tissue donation for biobanking/research and evaluate the adequacy of the authorization process for GTEx tissue donation. Five of the six partnering OPOs participated in the ELSI substudy, which included measurement of FDM knowledge of GTEx at a single time point after the donation. Tissue collections at all five sites were coordinated by the National Disease Research Interchange (NDRI) located in Philadelphia, Pennsylvania.

OPOs were selected as collection partners because of the large number of high-quality normal tissues needed for the project.[5] NDRI provided the ELSI team with contact

Table 1. Mapping of Genotype-Tissue Expression Essential Consent/Authorization Topics and Ethical, Legal, and Social Implications Knowledge Questions

Brief title	*GTEx specific essential consent topics*	*ELSI knowledge questions*
Biobank purpose	A description that genetic and genomic research may be conducted on the donated biospecimens	Agreeing to donate [patient's name]'s tissues to a biobank. Donated tissue to be used for medical research. Donated tissue to be used for genetic research. Agreeing to include patient's medical records in the biobank.
Biobank access	The donated biospecimens may be shared with researchers who are approved by an access committee, including international researchers	Donated tissues would be stored in a government biobank. Donated tissues could be used in research outside United States.
Biobank use	The donated biospecimens may be used for broad future research	Agreeing to indefinite storage of tissue. Donated tissues can be used for any research study. Donated tissues would be used for just one study.
For profit use	Commercial products may be developed using the donated biospecimens; however, the donor families will not financially profit from these products	Donated tissues could be used for research by for-profit companies.
Risks	There may be a risk of loss of privacy and confidentiality	Slight risk that [patient's name]'s identity could be found out. Slight risk that the identity of my family could be found out. Researchers who would use the donated tissue would NOT know [patient's name]'s exact identity. Researchers who would use the donated tissue would NOT know [patient's name]'s exact identity.
Withdrawal from study	Biospecimens can be withdrawn, but molecular data cannot be ''retrieved''	Can remove from the storage facility whenever he or she wants to. Request donated tissues be deleted from a project in which it is actively being used. Request donated tissues not be used in future research studies.
Return of results	No individual genetic information will be returned to the next of kin or legal representative; however, results from the collective GTEx biospecimen set will be available on the GTEx portal and the NIH's National Center for Biotechnology Information's dbGaP	FDM would NOT have been told what they learned about [patient's name]'s health.

dbGaP, database of Genotypes and Phenotypes; ELSI, Ethical, Legal, and Social Implications; FDM, family decision maker; GTEx, Genotype-Tissue Expression; NIH's, National Institutes of Health's.

information of FDMs approached for GTEx donation and the donation status of each case. Detailed descriptions of the ELSI substudy data collection methodology have been published elsewhere.[13,14] All relevant institutional review boards approved this study.

This article examines FDMs' comprehension of consent–critical topics as part of the informed authorization process for the donation of postmortem tissue samples and medical records data to the GTEx project and to distinguish between individuals who had different levels of comprehension and knowledge. This study seeks to identify variation between and gaps in FDM understanding of tissue donation for biobanking and research purposes, and inform efforts to improve the authorization process.

Methods

Study samples

Potential GTEx donors were newly deceased adults between the ages of 21 and 70 years, whose families agreed to donate the patient's organs and/or tissue for transplantation. Potential donors were without significant morbidities, such as a history of drug use or active cancer, which would have precluded donation for transplantation.[6]

All FDMs asked to donate to GTEx had already agreed to donate for transplantation. After FDMs authorized donation for transplantation, some were also asked to donate for research in general or other research projects before being asked to donate tissue samples to GTEx. FDMs were later invited to participate in this study of the consent process, whether they had agreed to donate to GTEx or not. All families were mailed invitational packets to the consent study 2 months after the patient's death. This is a well-established protocol for approaching families who have made decisions about donations after the death of a family member.[15,16] In the absence of an explicit refusal (opt-out card), FDMs were telephoned to further discuss the study and their potential participation. The median interval between the patient's death and interview was 3 months. A total of 724 FDMs were invited to participate in the interviews and 413 (68.0%) agreed.

OPO staff who discussed GTEx donation with FDMs were also consented into this substudy, comprising the tissue requester (TR) sample. In all, 99 TRs participated over the course of the study.

Measurement

Semistructured telephone interviews were conducted with 317 (76.8%) FDMs who donated to GTEx and 96 (23.2%) who refused donation to GTEx. The interviews took 45–60 minutes and captured FDMs' sociodemographic information, the content of the donation discussion, and attitudes concerning research and biobanking. Seventeen questions gauged FDMs' knowledge of the specific tissues requested, the use of the tissues, confidentiality, and other the potential uses. The seventeen questions map to the seven essential GTEx consent elements outlined by GTEx (Table 1) and were covered by the GTEx authorization form. Responses were scored as incorrect (0) or correct (1). There were a total of 207 cases with complete knowledge data. The majority of this sample agreed to GTEx donation ($n = 188$, 90.8%) and were included in this analysis.

TRs completed a demographic questionnaire on enrollment into the study, including date of birth, gender, race/ethnicity, religious preference, years working as a TR, and whether she or he held a health-related degree. After each GTEx approach, TRs also completed a brief online survey that assessed perspectives of the GTEx authorization process for the case and noted whether a GTEx brochure was provided to the FDMs. The geographic location of the TR's OPO was also collected. Ninety-nine surveys with corresponding FDM interviews were completed over the course of the study, with each TR submitting an average of 2.8 (range 1–13) surveys.

Analytic plan

Descriptive statistics are reported for sociodemographic information for TRs and FDMs. Frequencies and percentages are presented for categorical-level variables and means and standard deviations (SDs) are reported for interval-level variables.

A three-step latent class analysis (LCA) was employed to identify meaningful subgroups of FDM regarding knowledge of biobanking/research and to examine the associations between these subgroups and FDM and TR predictors.[17] The first step is a regular LCA using only the latent class indicators (e.g., knowledge items). In the second step, the most likely class variable is created using the latent class posterior distribution obtained during the LCA estimation for each observation. In the third step, the most likely class variable is used as latent class indicator to examine associations between assigned class and covariates (e.g., auxiliary variables). FDM responses to the 17 knowledge items were used in a latent class model to identify subgroups based on participants' patterns of response (e.g., correctly answered knowledge items).

Model-based measures of fit, including the Likelihood ratio chi-square test and Likelihood Ratio Chi-Square (LRT) model comparison measures, including Akaike information criteria (AIC), Bayesian information criteria (BIC), and entropy (measure of classification certainty), were used to evaluate the quality of latent class solution and optimal number of classes.[18,19] For both chi-square tests, a small p-value (<0.05) suggests poor model fit as the data do not fit the model; for AIC and BIC, the model with the lowest AIC or BIC should be considered to have the best fit. The entropy statistic ranges from 0 to 1, with values near one indicating high certainty in classification (strong solution) and values near zero indicating low certainty.

The LCA solution returns the percentage of the individuals in each class, who answered each individual item correctly. It was therefore necessary to set a threshold for labeling the response for the class as correct. Responses that would be considered correct beyond the chance (or 50%) were determined to be 70% or more of the participants in the class answering correctly. This 70% cutoff corresponds to other ''beyond chance'' threshold definitions in the literature.[20]

Once the number of optimal classes was determined and patterns of knowledge responses examined, the third step was to rerun the LCA analysis, including covariates, and conduct a multinomial logistic regression comparing the classes on these variables. Two separate models using the MPlus R3STEP command were run, one for FDM

characteristics (age, race, gender, religion, and donor/nondonor) and one for TR characteristics (geographic location, tenure, race, gender, age, and exchange characteristics such as the provision of a GTEx brochure).[21] The full information maximum likelihood estimation method was employed to handle missing data.[22]

Results

The majority of FDMs were white (73%), female (70%), and as likely to be widowed as married. FDMs averaged 50 years of age (SD = 14.2) and 14 years of education, most self-reported as being Protestant.

The majority of TRs were also white (82%) and married females (78%). On average, requesters were 43 years of age, with at least a college degree and 4 years of experience discussing donation with bereaved families.

FDM knowledge

Responses to the knowledge items were examined for the participants who agreed to GTEx donation. Four items had nearly universally correct responses: agreeing to donate patient's tissues to a biobank (99%), donated tissue to be used for medical research (99%), donated tissue to be used for genetic research (98%), and donated tissues can be used for any research study (98%). As these items did not contribute variation in terms of responses, they were not included in subsequent analyses.

Using the remaining 13 items from the participants who agreed to GTEx donation, a three-class model provided the best fit with good convergence and a strong classification solution reflected by entropy = 0.81 (Table 2). The percentage of participants in each class who correctly answered each knowledge item is presented in Table 3; bolded values indicate which items were not answered correctly by that class. Each of the three classes represents the overall level of knowledge of the individual included FDMs.

The first and largest class was composed of 89 subjects. These individuals were the most knowledgeable about GTEx and correctly answered 8 of the 13 knowledge items, including understanding patient's medical records would be abstracted, specifics of the storage of tissues, who can use the tissue and for how many studies, and two of the three confidentiality risk questions. There was confusion about five items, including the potential to identify donor families, expectation that they would be provided with results from the genetic analyses, and what happens if they withdrew from the study in the future.

The second class of 62 individuals responded correctly to only six items, such as understanding patient's medical records would be abstracted, knowing the tissues could be stored indefinitely, that they would not get information back about the patient's health, and what happens to samples if they withdraw from the study. This class did not answer correctly seven questions, including specifics of the storage of tissues, who can use the tissue, and confidentiality risks and future use of tissues in multiple research studies.

The third class of 37 participants had one fewer item correct than the second class. The main differences between the second and third class are that the third class had a better understanding of the risks of donation and a worse understanding of the ability to withdrawal from the project. Specifically, the five correct items that included agreeing to include patient's medical records in the biobank, indefinite storage of tissue, donated tissues would (not) be used for just one study and could be used in for-profit research, and that there existed a slight risk that patient's identity and or family identity could be found out.

The remaining eight items were answered incorrectly by the participants in group 3 (donated tissues would be stored in a government biobank, could be used in research outside United States, researchers would not know patient's exact identity, can remove tissues from the storage facility whenever he or she wants to, [cannot] request donated tissues be deleted from a project in which it is actively being used, and can request donated tissues not be used in future research studies).

Using Mplus, we conducted a multinomial logistic regression by the three-step procedure to test whether the three classes differed on sociodemographic characteristics that commonly distinguish donors from nondonors. This analysis indicated that the three classes did not differ on FDM age, race, education, gender, or religion. We next examined whether the TRs differed across the three groups. The TR model found differences in TR gender (female) and whether the TR provided the FDM with a GTEx brochure ($p < 0.001$) were associated with greater knowledge. We note that the latent class solution did not change significantly with the inclusion of the covariates, suggesting a stable classification solution.

Discussion

This study examined FDM comprehension of the components of critical elements of informed consent when making decisions about donating a deceased family member's tissues to a biobank for genomic research.

Most FDMs understood that consent meant agreement to donate tissues to a biobank and that these would be used for medical and genetic research. There was also moderate understanding that information from the patient's medical record would be abstracted, that the tissues would be stored in a biobank for an indefinite period of time, and that they could be used for any one of a number of unspecified studies.

Other knowledge areas had very low levels of understanding. FDMs struggled to comprehend that the tissues could be used for research done by a for-profit company and that the research could be conducted outside of the United

Table 2. Latent Class Model Fit Indices

Model	*Loglikelihood*	*AIC*	*BIC*	*Adj. BIC*	*LRT* χ^2	*df*	*Entropy*
1-class	−1189.793	2405.586	2447.660	2406.483	524.212	8168	
2-class	−1114.351	2282.702	2370.086	2284.564	398.270	8158	0.705
3-class	−1093.476	2268.952	2401.646	2271.780	389.377	8147	0.809

AIC, Akaike information criteria; BIC, Bayesian information criteria; LRT, Likelihood Ratio Chi-Square.

TABLE 3. LATENT CLASS ANALYSIS FOR FAMILY DECISION MAKER CORRECT RESPONSES TO DONATION KNOWLEDGE ITEMS

	Donated to GTEx	*LCA class 1*	*LCA class 2*	*LCA class 3*
	N = *188*	n = *89*	n = *62*	n = *37*
Biobank purpose				
Agreeing to donate [patient's name]'s tissues to a biobank				
Incorrect (%)	0.01			
Correct (%)	0.99			
Donated tissue to be used for medical research				
Incorrect (%)	0.01			
Correct (%)	0.99			
Donated tissue to be used for genetic research				
Incorrect (%)	0.02			
Correct (%)	0.98			
Agreeing to include patient's medical records in the biobank				
Incorrect (%)	0.23	0	0.225	0.259
Correct (%)	0.77	100	0.775	0.741
Biobank access				
Donated tissues could be used in research outside United States				
Incorrect (%)	0.62	0.282	0.825	0.897
Correct (%)	0.38	0.718	**0.175**	**0.103**
Donated tissues would be stored in a government biobank				
Incorrect (%)	0.30	0.171	0.383	0.537
Correct (%)	0.70	0.829	**0.617**	**0.463**
Biobank use				
Agreeing to indefinite storage of tissue				
Incorrect (%)	0.12	0.02	0.050	0.037
Correct (%)	0.88	0.98	0.950	0.963
Donated tissues can be used for any research study				
Incorrect (%)	0.02			
Correct (%)	0.98			
Donated tissues would be used for just one study				
Incorrect (%)	0.22	0.249	0.101	0.099
Correct (%)	0.78	0.751	0.899	0.901
For profit use				
Donated tissues could be used for research by for-profit companies				
Incorrect (%)	0.62	0.185	0.506	0.756
Correct (%)	0.38	0.815	**0.494**	**0.244**
Risks				
Slight risk that [patient's name]'s identity could be found out.				
Incorrect (%)	0.35	0.274	0.665	0.058
Correct (%)	0.65	0.726	**0.335**	0.942
Slight risk that the identity of my family could be found out.				
Incorrect (%)	0.50	0.500	0.763	0.201
Correct (%)	0.50	**0.500**	**0.237**	0.799
Researchers who would use the donated tissue would NOT know [patient's name]'s exact identity.				
Incorrect (%)	0.41	0.238	0.904	0.702
Correct (%)	0.59	0.762	**0.096**	**0.298**
Withdrawal from study				
Can remove from the storage facility whenever he or she wants to.				
Incorrect (%)	0.66	0.507	0.205	0.706
Correct (%)	0.34	**0.493**	0.795	**0.294**
Request donated tissues be deleted from a project in which it is actively being used.				
Incorrect (%)	0.39	0.523	0.204	0.436
Correct (%)	0.61	**0.477**	0.796	**0.564**
Request donated tissues not be used in future research studies.				
Incorrect (%)	0.59	0.501	0.710	0.355
Correct (%)	0.41	**0.499**	**0.290**	**0.645**
Return of results				
FDM would NOT have been told what they learned about [patient's name]'s health.				
Incorrect (%)	0.41	0.828	0.281	0.464
Correct (%)	0.59	**0.172**	0.718	**0.536**

Bolded values are below the threshold (70% correct) to be considered correctly answered by that class.

States. They did not exhibit understanding of the risks that the patient and/or family identities could be revealed or clear understanding regarding request for removal of the tissues from the study sample. FDMs widely and incorrectly believed that the resultant genetic testing would be conveyed to the family and that they would learn more about the patient's health conditions.

This is consistent with our pilot GTEx research, which found gaps in knowledge about return of results and risks of breach of confidentiality.[13,14] Similar false beliefs have been shown to be held by living donors to genetic research.[23–26] There is special concern about these misunderstandings because our research has shown that these issues play a significant role in the decision as to whether or not to donate.[15,16] Future genomic research projects collecting tissues from both living and deceased donors should consider highlighting the risks and benefits of donation carefully during the authorization process to support informed decision-making.

The LCA demonstrated that there were different identifiable groups of individuals who had more or less comprehension. For example, participants in class one understood that donated tissues could be used for research outside of the United States and by for-profit companies, but the participants in groups two and three did not. These variations were not linked to the FDM characteristics, but to the characteristics and behaviors of TRs. The requester's gender and provision of a brochure to the FDM were each associated with group membership. In organ and tissue studies, the gender of the TRs has been shown to have an impact on FDM understanding of donation for transplantation, providing confidence in our similar finding in this dataset.

These findings suggest that more studies are needed to understand the impact of the quality of the conversation with TR on FDM understanding of the authorization. Our pilot research shows that when the TR reported talking with the FDM regarding the risks of donation, the FDM demonstrated greater knowledge of the subject.[14]

Conclusion

One limitation of this project was sample size. It is possible that more predictors of group differences could be found in larger studies. Predictors of FDM group differences may also be found in studies that measure recall of the donation decision or knowledge of the authorization concepts overtime to see if changes in group membership occur. The lack of understanding demonstrated by all GTEx FDMs makes a strong case for improving the future of authorization process of future deceased donation biobanking projects to increase FDM knowledge, especially the concepts of risk and return of results.

GTEx FDMs in the scale-up encountered more problems with comprehension and knowledge of those concepts than the FDMs in the pilot.[13,14] The findings suggest a need for tests of an enhanced consent process that consider the context of these types of requests within an emotionally stressful environment. The use of visual or multimedia aids may increase FDM understanding.[27–29] In addition, FDMs should be provided with supplemental and tailored informational materials. Consideration of follow-up informational materials related to tissue donation for research purposes may also be of value in strengthening the information provided and in keeping with the ideal of informed consent as a process.

These materials may provide the FDMs the opportunity to retain critical information about their donation. Not only is donor comprehension an ethical imperative, it is important for the success of complex biobanking projects as understanding increases willingness to donate.[30] Given the incredible generosity of FDMs to donate during a period of significant distress, the biobanking community must respond by improving the current standard consent processes.

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