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Family decision maker perspectives on the return of genetic results in biobanking research

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Abstract

Purpose—There are many ethical considerations regarding the return of genetic results to biobanking participants, especially when biobanks collect samples from deceased organ and tissue donors that require the authorization of a family decision maker (FDM). This paper explores FDM knowledge and opinions regarding return of genetic results in the context the Genotype-Tissue Expression (GTEx) Project, which does not return results to participants.

Methods—Data collection included a survey completed by organ procurement organization (OPO) requesters (n=22) and semi-structured telephone interviews with FDMs (n= 55).

Results—Nearly every FDM wanted some form of genetic results returned. Information on treatable diseases (94.3%) and diseases that could affect their children (84.9%) were more desirable than untreatable diseases (71.7%). Sixty percent of FDMs understood that GTEx would not return genetic results. FDMs were 4 times more likely to have correct knowledge of the GTEx policy when their GTEx requester reported discussing the topic with them.

Conclusion—FDMs from the GTEx project were interested in receiving genetic test results. Marked changes in the infrastructure of GTEx would be required to alter the policy. Regardless, care must be taken to ensure that the return policy is clearly communicated with FDMs in order to dispel misconceptions.

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Keywords

Incidental findings; return of results; bioethical issues; genomics; whole genome sequencing; genetic research; biobanking

Introduction

For over a decade, the bioethics community has deliberated about the best ways to manage and return genetic findings. Many genetic findings from whole-exome or whole-genome sequencing (WES/WGS) and biobanking projects are not “incidental,” but are planned outcomes of genetic sequencing and subsequent study of the individual’s genotype.^{1, 2, 3} Current discussions search for an equilibrium that ensures sound research ethics, respects the wishes of the donors and ultimately acknowledges the limited capacity of researchers to follow-up on findings.^{4, 5, 6} Although disagreement persists, current dialogue is moving toward the return of analytically valid and clinically significant genetic findings with the potential to impact immediate medical care.^{4, 6, 7, 8, 9} Yet, many WES/WGS and biobanking projects choose not to return results for a variety of reasons,^{10, 11, 12} including the daunting number of results that could potentially be returned to any one individual.¹³ Additionally, in contrast to the return of findings in clinical research where individual participants are known to the research team and reasonable efforts might be made for recontact, much genetic research is conducted using secondary data – specifically, the anonymized tissue and DNA made available via biobanks and other types of biorepositories – making recontact more difficult.¹⁴ The Genotype Tissue Expression Project (GTEx), a project of the NIH Common Fund, is establishing a resource database and associated tissue bank in which to study the relationship between genetic variation and gene expression, in multiple reference tissues.¹⁵ It is one of the many studies conducted in the United States that currently will not return genetic findings to the family decision makers (FDMs) who donate the tissues of deceased family members.

Empirical studies of the American public, however, indicate support for the return of genetic results. Kaufman and colleagues’ survey of over 4,600 adults found that 9 in 10 wanted genetic risk information returned in exchange for participation in research studies, regardless of the treatability of the disease. The return of results was cited as the most important benefit of donating to a biobank; in fact, three out of four participants would be less likely to donate to a biobank that did not return results.¹⁶ Access to clinically actionable results, as well as results that may be inconclusive, difficult to interpret, or of unclear medical significance are desired. Many participants claim the information would be empowering, providing a sense of control and an opportunity to make lifestyle changes, even if the disease were untreatable.¹⁷ In fact, most laypersons maintain that researchers have an obligation to return results based on the principles of reciprocity; additionally, most perceive ownership of any results stemming from the use of their tissue.¹⁸ Indeed, another study reported that nearly ninety percent (88.8%) of respondents desired the return of hypothetical genetic findings of uncertain clinical significance.¹⁹ In the context of hypothetical pharmacogenetic testing from which incidental findings may be revealed, 69% of adult participants wanted results of uncertain risk.²⁰ Conversely, two-thirds of respondents interviewed (n=40) were

comfortable with a hypothetical biobank's policy to not return results, unless the findings were about serious health concerns.²¹ Actual biobanking participants expect findings to be returned. Of 322 surveyed ClinSeq participants, none opted-out of receiving results, citing disease prevention as the motivating factor for disclosure.²² Moreover, half expected to receive actionable, individualized results from participating in the study.²³ Nearly all study participants also wanted clinical results returned and more than 9 in 10 opted to receive future genetic results, even after learning about the potential risks and limitations of the information.²⁴

Less is known about participants' families' desire to be informed of a deceased relative's genetic results. In fact, we know of no empirical studies investigating return of genetic results to deceased donors' families. However, a precedent to returning the results to interested family members of now deceased donors exists²⁵ and some argue for the return of any clinically urgent findings to potentially impacted family members.^{26,27} One qualitative study also reported participants' relatives' affirmative perceptions of their right to access deceased donors' health information, commenting that results could be used to make health decisions.²⁸ FDMs for critically ill patients have also shown a preference for receiving genetic results.²⁹ These findings suggest that more research is needed to understand the preferences of FDMs in WES/ WGS and biobanking research.

This report focuses on whether FDMs, defined as the family members who authorized the donation of a deceased loved one's tissue, understood the GTEx policy regarding the return of results. It also explores FDMs' opinions regarding the return of genetic results from the donated tissue of deceased patients as well as FDMs' desire to receive results if they were to donate to a biobank themselves.

Materials and Methods

GTEx Project and ELSI Sub-study

In partnership with three geographically dispersed organ procurement organizations (OPO), the GTEx project requests the collection of additional tissues for research purposes from families of deceased patients who agreed to the donation of organs and tissues for transplantation. The OPO request process requires the authorization form be read out loud to the FDM. Authorizing donation to GTEx includes the release of a patient's medical and social history records, various tissue samples and the whole brain, when medically suitable. Donated tissues are placed in the Cancer Human Biobank (caHUB), the National Cancer Institute's biobank, and the donor's genome is fully sequenced and analyzed for gene expression by the Broad Institute. The sequencing information is added to the database of Genotypes and Phenotypes (dbGaP) online data resource. Cell lines may be developed from donated skin and blood.¹⁵

The GTEx ethical, legal and social issues (ELSI) sub-study examines ethical issues concerning the decision to donate a deceased next of kin's tissues to a biobank for unspecified future research purposes. Specifically, the sub-study examines FDMs' understanding of the risks and benefits of donation, as well as the possible psychosocial effects of the authorization process.¹⁵ Two of the three empanelled OPOs also participated

in this ELSI sub-study. ELSI data collection activities spanned from September 2011 to December 2012. The National Disease Research Interchange (NDRI) coordinated the GTEx tissue collection activities and provided the ELSI team access to the contact information of the FDMs. All relevant institutional review boards approved this study.

Tissue Requester and Family Decision Maker Samples

All OPO staff (referred to as ‘requesters’) who discussed GTEx donation with an FDM were recruited into the ELSI sub-study (n=37; 100%). All FDMs approached about donating to GTEx, regardless of their decision, were considered eligible for participation and invited to be a part of the research (N = 125). Invitational packets including letters explaining the ELSI sub-study and instructions for declining participation to the ELSI sub-study were mailed to eligible FDMs two months after the patient’s death. Past research examining family experiences with organ and tissue donation for transplantation has identified this as an optimal time period for recruiting grieving families.^{30, 31} Telephonic invitations were made two weeks later, providing the FDM had not opted-out. A total of 85 FDMs agreed to participate (68%). Common reasons for declines included: generally not interested in any research participation, not interested in talking about the death of a loved one, and not enough time to participate. Of the 85 who agreed, twenty-five (29.4%) FDMs reported poor or unreliable recall of the GTEx request and 5 had incomplete data, leaving a total of 55 (64.7%) cases for these analyses. Results of nonparametric tests comparing the demographic characteristics of FDMs with poor or unreliable recall to that of FDMs recalling the request revealed a significant age difference. Specifically, FDMs with poor recall were older (52.1 vs. 46.4 years of age; $z = 2.31, p < .03$). No other statistically significant differences were found between these groups.

Measures

Family Decision Makers—FDMs were asked to describe the experience of being approached for GTEx donation using a semi-structured telephone interview instrument (no qualitative data are presented herein). The interviews collected sociodemographics (e.g., age, sex, marital status, education, religious affiliation) and relationship to the patient, as well as the context and content of the donation discussion. The goal of the interview was to describe and evaluate the authorization process and explore ethical issues that surround this type of donation, including return of results. FDM understanding and attitudes toward the returning of results was determined based on questions to the following areas: 1) whether donating to GTEx would provide access to more information about the donor patient’s health; 2) desire for access to the patient’s DNA results; 3) how they felt about having results returned to them if they had donated their own tissue; and, 4) if their desire for information would change if the results told them information about diseases that are treatable, untreatable, could affect children, or could affect family members. The true/false measure assessing understanding was in the form of the following question: “If I had signed the consent form and the donated tissue were used for a research project, I would have been told what they learned about the (patient’s name) health.” Attitudes towards return of results were assessed with the item, “Donors should have access to the result of DNA testing done on their tissue samples” using a 1–5 agreement rating scale (1-strongly disagree; 5-strongly agree). FDMs

were also asked to assess if they themselves would wish to receive the results of their own genetic testing if they donated tissue to a biobank.

Respondents were presented with six hypothetical return scenarios that included a high/low likelihood of developing a potentially treatable/untreatable disease, risk related to a disease that could affect the FDM's children, and risk related to a disease that could affect the FDM's family members.

We also asked respondents to rate the quality of the GTEEx requester's communication. These items were assessed using true/false and yes/no measures and items measured by a 5-point Likert scale (*1-poor; 5-excellent*).

The major dependent variable, decision to authorize donation to the GTEEx project, was assessed from study records.

OPO Requesters—Requesters completed a paper-pencil survey capturing their sociodemographic information (i.e., age, race, ethnicity, sex, and education) upon enrollment. After each GTEEx request, the requester completed a brief, self-administered online survey that described the process of requesting tissues for GTEEx. Requesters were also asked to indicate the specific GTEEx-related topics discussed with FDMs, including one item concerning the discussion of the return of results policy, and the requesters noted whether this topic was discussed during each request (*yes/no*). We classified any form of talk about the topics as their having been brought up or discussed during the donation request.

Analytic Approach

Descriptive statistics are reported for sociodemographic information (e.g., age, race, sex, education, marital status, religious affiliation) for requesters and FDMs. Frequencies and percentages are presented for categorical-level variables and means and standard deviations are reported for interval-level variables. Bivariate associations between FDM sociodemographic characteristics, attitudes toward access to genetic results, communication quality, and knowledge of the GTEEx return of results policy was examined. The Chi-square statistic was used to evaluate significant associations for categorical data and the Wilcoxon-Mann-Whitney non-parametric analog to the independent samples t-test was used for continuous variables.

Exact logistic regression was performed to evaluate associations with variables found to have significant bivariate associations with return of results. Exact logistic regression was chosen as it is appropriate for modeling binary outcome variables when the sample size is too small for a standard logistic regression and/or when some of the cells formed by the outcome and categorical predictor variable have no observations. The estimates given by exact logistic regression do not depend on asymptotic results. The models presented here are exploratory. For all tests, significance was determined at the level of $\alpha=0.05$. Analyses were performed using IBM SPSS 21.0³² for Microsoft Windows and SAS 9.3.³³

Results

Sample Characteristics

Family Decision Makers—The majority of FDMs were white, female and as likely to be widowed as married. FDMs' averaged 47 years of age and 14 years of education; most were of self-reported Protestant religious affiliation. Of the 55 FDMs interviewed, 44 (80.0%) agreed to donate to GTE_x and 11 (20.0%) did not. It is important to note that differences related to return of results were not associated with the donation outcome.

OPO Requesters—Of the 37 requesters who made a GTE_x request, 22 (59.5%) were the requester of record for FDMs participating in the ELSI sub-study and were, therefore, included in these analyses. The majority of requesters were white, married females. (See Table 1.) 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 Attitudes and Knowledge

FDMs had imperfect knowledge (see Table 2) of the GTE_x return of results policy, with 60% correctly understanding there would be no information returned about the results of the genetic analysis of the donor's tissues. Those who answered correctly were slightly younger (45.7 vs. 48.6 years, $p < .10$) with higher education (14.6 vs. 13.6 years, $p < .07$), but neither difference reached conventional levels of statistical significance. Additionally, donors' spouses ($\chi^2 (5) = 11.3$, $p < .04$) were more likely (73.7% vs. 27.3%) than donors' parents, to understand the GTE_x policy on return of results (see table 2). White FDMs ($\chi^2 (1) = 4.76$, $p < .03$) were more likely (69.2% vs. 37.5%) to understand the GTE_x policy on return of results as compared to non-White FDMs. However, these differences may simply be an artifact of the much larger number of white persons and spouses in the sample. No other significant demographic differences were observed for this item. FDMs rated the quality of the communication with requesters very highly (see Table 2) and those who answered the knowledge items correctly rated the requester's communication even more highly (4.5 v 4.8, $p < .03$) (Table 2).

Requesters reported having discussed the policy (as opposed to just reading out loud the authorization form) with FDMs in 55.6% ($n = 30$) of cases. There was a significant association between the requester reporting discussing return of results and the FDM correctly answering the related knowledge question ($\chi^2 (1) = 4.24$, $p < .04$). The association between requesters' reports of return of results discussions during requests and family authorization to donation failed to reach conventional levels of significance ($\chi^2 (1) = 3.30$, $p = .065$).

FDMs indicated that individuals mostly favored the return of genetic results in response to the statement, '*FDMs should have access to the results of DNA testing done on tissue samples*' (Mean (M) = 3.5, median (md) = 4.0, (SD) = 1.5). Desire for genetic results of all types was strong (Table 3), with the majority desiring information on treatable and untreatable diseases, and diseases that might affect other family members and children. Only 6% expressed no desire for the return of genetic findings. Given the uniformity of responses,

no contrast analyses with return of results knowledge was performed. Participants who understood the GTEEx policy were less likely to favor the return of genetic results ($t(1) = 2.9$, $p < .05$).

Factors Predicting Understanding of GTEEx Return of Results Policy

A logistic regression was run to model the relationships between knowledge of policy concerning the return of results, race, relationship to patient, quality of the communication, and desire to have access to genetic results. Quality of the communication and FDM rating of wanting access to findings were tested individually and in conjunction with the other variables, but were not significant in any iteration of the model. White FDMs were 4.2 times (95% Confidence Interval (CI) 1.1–16.3; $p < .04$) as likely to have *correct* knowledge of the GTEEx policy compared to minorities. Additionally, FDMs whose requester reported discussing return of results were 4.1 times (95% CI 1.2–14.3; $p < .03$) as likely to have *correct* knowledge of the GTEEx policy compared to exchanges where the requester did not report the topic's discussion (see Table 4).

Discussion

Consistent with prior work examining the perspectives of donors on the return of results, families who donated a deceased's organs and tissues for transplantation, were overwhelmingly in favor of the return of the donor's genetic testing results. However, we discovered serious gaps in FDM recall and knowledge about the GTEEx project. Four in ten of our respondents incorrectly believed that GTEEx would return results, even though the nonreturn policy is stated within the authorization document. This is not an uncommon phenomenon; studies have shown that biobank participants have a limited understanding of biobanking protocols, even after the authorization process is complete.³⁴ Additionally, prior research has revealed that families expect results to be shared with them even after broad consent is given.^{34, 35, 36} Given these findings, it is imperative to clearly communicate return of results policies to FDMs to dispel the belief that personal benefits will be gained from the donation to research, a kind of biobanking "therapeutic misconception"^{37, 35, 36} and support meaningful informed decision-making.

Research regarding organ and tissue donation for transplantation has consistently demonstrated that communication variables are associated with donation decisions.^{31, 38, 39} Our examination of the discussions that occurred between tissue requesters and FDMs concerning the GTEEx biobank reinforces these claims. In this study, FDMs' understanding of the return of genetic results policy was positively associated with the requester's report that the topic was discussed. FDM understanding was also more likely when the quality of the communication with the requester was rated highly.

Effective communication is especially critical in GTEEx donation discussions as it occurs shortly after a family member's death and takes place after multiple requests for solid organ and tissue donation for transplantation. In a single conversation, a requester must develop an empathetic relationship with a grief-stricken family member and accurately communicate dense and detailed information on a complex topic. The policy regarding the return of genetic findings is one of many topics discussed, including the size and type of the tissue

requested, the potential transformation of the donation tissue into cell lines that may live indefinitely, and the small, but inherent risk of a breach of confidentiality and revelation of donors' and FDMs' identities. Even if a requester is able to successfully accomplish this task, the sheer volume of information conveyed under such stressful and chaotic circumstances is likely to result in some FDMs experiencing difficulty processing the information or suffering memory lapses. Therefore, rather than a one-way information transfer, requesters must engage FDMs in active conversations about GTE_x, and frequently check-in to confirm FDMs' understanding of what donation entails. It may be wise to follow-up with FDMs after the donation to ensure understanding of basic information about donation.

Clearly, FDMs believe they prefer access to genetic results, particularly those with significance to their health. Families' views must be considered in the ongoing debate surrounding the return of individual research results and incidental findings. Future research efforts might extend our work and add to this discussion by exploring families understanding of the consequences of full disclosure including the potential costs of returning findings to donors and/or their families, psychological distress, and the need for genetic counseling and/or additional medical care. Providing these results to all FDMs would also require significant shifts in the infrastructure and organization of the GTE_x biobank, and a substantial increase in monetary resources. GTE_x, like many other biobanking projects, is designed to support many studies of currently unknown purposes and procedures. Keeping track of every donor family over the course of many years would be logistically daunting and expensive. Given that personally identifiable information would be privy to many affiliated research organizations, it would also place donors and FDMs at greater risk of having personal genetic information compromised. It is important to consider how complex and sensitive results might best be conveyed to families. Furthermore, the question as to who should bear the responsibility of communicating genetic results back to the families – the biobank or its affiliated researchers – remains open for debate.

Another consideration is whether results should be delivered directly or mediated through a healthcare provider or genetic counselor. Genetic results are multifaceted, difficult to interpret, often inconclusive, and sometimes wrong. Moreover, because GTE_x would only in some cases be returning the results of a blood relative, the results would be indirect and may not necessarily reflect the actual genetic makeup of the donor's family, meaning greater interpretation would be required. Genetic counseling and, if necessary, follow-up care would incur substantial costs, and it is unclear who would create, support, and financially back such a system. One solution would be the creation of a decision support tool for FDMs to use when determining what, if any, results they would like returned. Clinically actionable results could be sent from the biobank directly to family physicians. If basic health insurance covered genetic counseling, the results could be disseminated to families and patients in a meaningful manner without placing additional burden on limited research resources. Another potential model to address the return of genetic results to future FDMs would be to assign the primary responsibility of genetic counseling and follow-up care to the biobank, but require researchers using the biobank's tissue and data to contribute financially to these activities. This model would prohibit affiliated researchers from accessing patient and family identities, establish a single standard for communicating results, and ultimately ensure better

data security standards around donor and family re-contact. All these models assume that the index family member will communicate with the rest of the family.

The GTEx biobank is currently neither staffed nor funded to meet the demands of returning genetic results, and will unlikely be staffed to perform this task in the future. However, other projects could consider these results and in turn accommodate the disclosure of findings to donors' families. A substantive discussion about the costs and benefits of returning research results and who should pay for the return of genomic results must continue.

As biobanking and WES/WGS research gain prominence as a medium for medical discoveries it is imperative that respective policies take into consideration donors' and families' attitudes and expectations regarding the return of genetic results. Additionally, the informed consent process must communicate all policies and protocols in a way that addresses the expectations of all involved. Given these findings, it is likely that more in-depth conversations are needed to dispel confusion about a biobank's return of results policy.

Limitations

While we found that parents of GTEx donors and FDMs of minority descent were more likely to incorrectly believe that they would receive research results, the small sample size and low variability in participant responses suggests these results be interpreted cautiously. For example, the study's small sample size may induce bias of odds ratios away from one, thereby artificially inflating the effect size.⁴⁰ It is also possible that, for whatever reason, these groups had greater expectations regarding their receipt of the donor's genetic results. Nonetheless, some individuals may have a more difficult time understanding complex biobanking concepts and extra time and care may be needed to engage those persons in conversations about the issue. More research is needed to ascertain which groups might be most susceptible to difficulties in understanding biobanking policies and protocols. Finally, this population of individuals had deeply held beliefs in the value of donation itself. Others within the more general population may have lower levels of knowledge or understanding and greater skepticism or mistrust regarding research and the healthcare industry. These caveats must be considered when considering the generalizability of the findings.

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Table 1

Family Decision Maker (FDM) and Tissue Requester (TR) Sociodemographics

Demographic Characteristic	TR (n=22)	FDM (n=55)
Age, mean years (SD)	42.6 (8.29)	46.9 (13.2)
Sex		
Female	13 (59.1)	41 (74.5)
Race		
Nonwhite	3 (13.6)	16 (29.1)
Hispanic	0 (0)	2 (3.6)
Marital Status		
Never Married	4 (18.2)	8 (14.5)
Married/Cohabit	16 (72.7)	21 (38.2)
Divorced/Separated	2 (9.1)	6 (10.9)
Widowed	0 (0)	19 (34.5)
Not reported		1 (1.8)
Religious affiliation		
Protestant	11 (50.0)	31 (56.4)
Catholic	5 (22.7)	9 (16.4)
Other	4 (18.2)	4 (7.3)
None	2 (9.1)	11 (20.0)
Household income		
<\$30,000		12 (21.8)
\$30,000-59,999		15 (27.3)
>\$59,999		26 (96.4)
Willing to donate own tissues		
Yes		52 (95.0)
Education, mean years (SD)	16.1 (1.70)	14.2 (2.4)
Degree in Health-related field		
Yes	17 (77.3)	
Job Tenure, mean months (SD)	48.14 (31.29)	

Note: Values are count (percent) unless noted otherwise.

Table 2

FDM Knowledge of Return of Results Policy by Sociodemographic, Attitudinal, and Conversation Variables

	Responding Correctly to Knowledge Item
	Count (%)
<i>FDM relationship to patient*</i>	
Spouse/Significant Other	14 (73.7)
Parent	3 (27.3)
Sibling	7 (87.5)
Child	8 (53.3)
Other	1 (50.0)
<i>FDM Race*</i>	
White	27 (69.2)
Minority/nonwhite	6 (37.5)
<i>Requester <u>did</u> discuss return of results*</i>	22 (73.3)
	Mean (SD)
<i>FDMs should have access to the results of DNA testing done on tissue samples. *† (n=54)</i>	3.27 (1.42)
<i>Quality of the communications FDM had with TR*†</i>	4.76 (.43)

Note:

* Denotes significance at $\alpha < 0.05$;

† Scale 1–5 with 5 indicating very strong agreement with the statement.

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Table 3

Types of Results Desired by FDM

Type of Result	FDM Desired Result
	Count (%)
<i>Treatable Diseases</i>	50 (94.3)
<i>Untreatable Diseases</i>	38 (71.7)
<i>Diseases that may affect donor children</i>	45 (84.9)
<i>Diseases that could affect donor's family</i>	45 (84.9)
<i>No results desired</i>	3 (5.7)

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Table 4

Bivariate Logistic Regression Models for Correct Return of Results Knowledge

Independent Variables in Model	AOR (95%CI)
<i>Participant's Race (Caucasian: African American)</i>	4.2 (1.09–16.26)
<i>Relationship to Patient (Parent: Significant Other)</i>	.85 (.552–1.352)
<i>Discussion of Return of Results (Yes: No)</i>	4.1 (1.18–14.30)

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