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Genomic Research with Organs and Tissues Originating from Transplant Donors: Ethical Considerations for the GTEx Project

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Human biospecimens are essential to uncovering the basis of human health and disease. Each year, millions of biospecimens are collected from both living and deceased donors for a variety of research purposes.[1] Biospecimen collection for research in postmortem settings such as in autopsies or organ or tissue transplantations is particularly challenging given the difficulty of obtaining an informed authorization from the next of kin, who is most often in a situation of extreme emotional distress.[2] Since comprehension of informed consent language for biobanking studies is variable at best in a typical research setting,[3] the stress and emotional turmoil following the loss of a loved one complicates an already difficult process.

The Genotype-Tissue Expression (GTEx) project is funded by the U.S. National Institutes of Health (NIH) Common Fund to study human gene expression and regulation in multiple organs and tissues (e.g., liver, skeletal muscle, and skin) from individual biospecimen donors.[4] The GTEx project aims to understand how genetic variation between individuals affects differences in gene expression levels.[5] The scientific design of the GTEx project requires the collection of small samples from up to 36 different organs and tissues from a single biospecimen donor.[6] This study design necessitates collection from deceased individuals, because living individuals simply could not donate so many organs and tissues. Ultimately, the GTEx project aims to establish a resource with centralized data on genetic variation and gene expression in multiple human organs and tissues as well as a biobank with additional biospecimens that can be accessed by approved researchers for future research studies.[7]

Unique aspects of the GTEx project led to the decision to require explicit authorization from a deceased individual's next of kin to use the decedent's biospecimens for research. These unique project aspects include the collection of a greater number of tissues per donor than in a typical research project, the extensive genomic analysis that results in potentially sensitive private information, the sharing of both data and biospecimens through a quasi-public resource, and broad future research use of collected biospecimens. All sites collecting biospecimens as part of the GTEx project were required to submit a research protocol to their institutional review boards (IRBs). Some collection sites' IRBs chose to undergo full or expedited review, while others determined that the research did not constitute human subjects research and did not require further review.

Case Description

Prior to GTEx donation, the collection site ensures that next-of-kin authorization has been obtained and that the donor meets basic eligibility criteria for the research project.[8] In order to preserve DNA and RNA quality, biospecimens are removed as quickly as possible after death and after removal of any organs and tissues for transplantation. The collection site subsequently submits more detailed clinical data about each donor routinely obtained from medical-social chart reviews and/or next-of-kin interviews within 10 business days of the collection. A data management team reviews all of the data for completeness and accuracy. To date, GTEx has collected samples from over 800 donors. Following data management review, it was determined that at least 24 GTEx donors had been the recipients of an organ or tissue transplant needed for therapeutic purposes (henceforth we use the term "therapeutic donor" to describe any of the unknown individuals who donated an organ or tissue to these 24 GTEx donors). In such cases, the next of kin of the GTEx donor would be providing authorization to conduct extensive genomic analysis on organs and tissue originally derived from the therapeutic donor, someone most probably unrelated to the GTEx donor. We questioned whether, in a case where the therapeutic donor was still alive, the consent of the therapeutic donor would be required before the organ or tissue could be used for research in GTEx. This article describes the legal, regulatory, and ethical considerations related to this case study.

Legal and Regulatory Considerations

 Revised Uniform Anatomical Gift Act. The original Uniform Anatomical Gift Act (UAGA) was endorsed by the National Conference of Commissioners on Uniform State Laws in 1968 in response to the first successful heart transplant in 1967.[9] The UAGA created a right for individuals to donate their or their next of kin's eyes, other organs, and tissue and established an "opt-in" system requiring an affirmative choice to donate by the donor or someone authorized to act on the donor's behalf.[10] The 2006 version of the UAGA has been adopted in all but four states (Delaware, Florida, Pennsylvania, and New York).[11] The 2006 revision provides default rules about how to interpret gifting documents that lack specificity about the purpose of the gift.[12] If a donor's gift does not specify the purpose of the gift, as would occur if the driver's license indicated only that the individual was an "organ donor," the gift may be used only for "transplantation or therapy," not research or education.[13] States are quite variable in the degree of choice they offer donors regarding both donation of specific organ and tissue types as well as possible uses for those tissue types.[14] The variability in how states have enacted and implemented the UAGA makes clear that it would be exceedingly difficult to determine what the original therapeutic donor or his/her next of kin may have authorized in regards to use of the tissue in question. While in most states (i.e., those that have adopted the 2006 version of UAGA)

the default uses are transplantation and therapy when further specification is not provided, many states provide online registries that allow donors to authorize or prohibit research use of their tissue.[15] In addition, the privacy of donors is generally protected so that it would not be feasible to determine the circumstances of the original therapeutic donation, particularly if the transplant was performed long ago or in a different state.

 Human subjects regulations. Under the federal human subject regulations at 45 CFR 46 (the Common Rule), a human subject is defined as "a living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information."[16] Under this definition, the individuals from whom multiple organs and tissues were donated by next of kin to GTEx would not be considered human subjects since they are deceased, and therefore 45 CFR 46 would not apply. Depending on the type of organ or tissue originally transplanted, however, it is possible that a therapeutic donor who donated an organ or tissue to the GTEx donor could be living when research is conducted with the GTEx donor's organs or tissues. For example, over 40% of transplanted kidneys are from living donors.[17] The intervention to remove the organ or tissue for therapy would not be considered a research intervention under the regulatory standard. However, could the data resulting from analysis conducted in GTEx be considered to be "identifiable private information" about the therapeutic donor? Under the current provisions of the Common Rule, information is identifiable if "the identity of the subject is or may readily be ascertained by the investigator or associated with the information." To date, this standard has not been interpreted to include coded genomic information.[18]

The merits of a regulatory standard based on whether data are "identifiable" has been called into question both due to researchers' reidentifying data that were presumed to be deidentified as well as the bioethics and policy communities' highlighting the difficulties with this model.[19] Evolving capabilities in informatics make possible the reidentification of deidentified genomic and even epigenetic data stored in aggregated databases.[20] Acknowledging the tide of such developments, the U.S. Department of Health and Human Services (DHHS) released in July 2011 an Advanced Notice of Proposed Rulemaking (ANPRM) to revise the Common Rule in a way that would categorize all biomedical research involving biospecimens as research involving identifiable human subject information and therefore to require explicit consent for such research.[21] Various stakeholders who submitted comments during the public comment period were largely against requiring consent for research involving deidentified archived tissue.[22] In September 2015 the DHHS released a Notice of Proposed Rulemaking (NPRM) in which it responded to the public comments submitted in response to the 2011 ANPRM and sought additional comment on revised proposals to protect human subjects involved in research. The NRPM proposes expanding the definition of "human subject" to include "a living individual about whom an investigator (whether professional or student) conducting research . . . obtains,

uses, studies or analyzes biospecimens."[23] Under the proposal in the NPRM, research involving biospecimens would require informed consent for most research uses or analyses of biospecimens, whether or not identifiable information is accessible or even available.

If the HHS issues a final rule that requires consent for research with deidentified archived tissue, would the consent of the original therapeutic donor who is still alive be required before the tissue or organ taken from the deceased transplant recipient can be donated for research? If the research project were genomic in nature, then the identifiable data generated from the donated organ would be about the therapeutic donor, not the GTEx donor. Arguably, this living therapeutic donor has an autonomous right to determine whether his or her tissue is used in research. The DHHS proposal to revise the Common Rule would essentially implement such a right in federal regulation, by considering all tissue from a living human being "identifiable."

 Ownership and control of donated therapeutic tissue. In considering this case, one could assess whether the research donor "owns" or "controls" the donated therapeutic tissue as a means of determining whether the research donor is legally empowered to re-donate such tissue to research. In the organ donation context, courts have declined to find an ownership right to donated tissue, deeming it against public policy to recognize a property interest in deceased body tissue in cases brought by both organ donors[24] and potential organ recipients.[25] In the research setting, attempts to recognize a research participant's property right in his or her biospecimens following donation have thus far been unsuccessful.[26] Collectively, these cases suggest common-law reluctance to find any property interest granting an individual an enforceable right to direct how his or her donated organs or tissues are used.

In lieu of property ownership, the concept of "control" could be a useful construct in this context. The UAGA of 2006 provides that an anatomical gift for one or more purposes does not limit the ability to make a later gift of the part for other purposes by the donor or any other person authorized to act on the donor's behalf.[27] However, because the biospecimen donor in the GTEx project who is also an organ recipient was never empowered to act on behalf of the therapeutic donor, he or she has no authority to make a subsequent gift of tissue for research use on the therapeutic donor's behalf. Yet, while not authorized to act on the therapeutic donor's behalf, the organ recipient by necessity is clearly empowered to act on behalf of his or her own body. The law can and does view decisions that affect the body of the organ recipient, including the donated organ, as legitimately within the organ recipient's purview. For example, an organ recipient can choose to lead an unhealthy lifestyle even though this decision may have a negative effect on the donated organ. The therapeutic organ donor has no say in the matter and cannot legally prohibit the recipient from damaging the donated organ during life. By analogy, one might argue that a therapeutic organ donor cannot legally restrict a decision by an organ recipient, or by other persons authorized to act on the donor's behalf, to donate the organ to

research upon death. By this line of reasoning, once the recipient acquires the organ via donation, the recipient (and not the therapeutic donor) legally controls its destiny.

Ethical Considerations

A key tenet included in the principle of respect for persons—one of the foundational principles of bioethics[28]—is that individuals should be treated as autonomous agents.[29] In application, the principle of respect for persons leads to the requirement for informed consent prior to participation in research. In this case, it is not practicable to discover whether the therapeutic donor or the next of kin provided consent for the research use of the donor's tissue. Even if the therapeutic donor or next of kin provided consent or authorization for research purposes, such consent would have been general in nature without consideration of the specific GTEx project.

One could argue that if the therapeutic donor is deceased, then the requirement to protect autonomy is diminished since that donor is no longer able to make autonomous choices. However, this approach seems to confound enforceable rights, a legal concept, and enforceable duty, an ethical concept. While there is no regulatory requirement to comply with the wishes of a deceased therapeutic donor, that does not imply absence of an ethical obligation to honor the donor's wishes regarding contribution to a research study. Respect for persons is a mandate that, unlike the regulatory obligation to obtain informed consent, extends beyond the death of a research participant.

The therapeutic donor could be viewed as relinquishing control of the organ at the time of donation and therefore ceasing to have a protected interest in the organ after that point.[30] Although this argument has some appeal on legal grounds, it neglects the fact that the therapeutic donor may have previously made an autonomous choice about the purposes for which his or her organ could be used. To negate the expressed choice of a therapeutic donor seems inconsistent with the ethical mandate of respect for persons. Importantly, in this specific case, it is also possible that the therapeutic donor could be living, in which case the individual may have a continuing privacy interest in how his or her genomic material is used and shared.

The principle of beneficence requires that research be justified on the basis of a favorable risk-benefit assessment.[31] Although the proposed research in GTEx poses no physical risks, both informational and psychosocial risks should be considered. Due to the extensive and multifaceted analyses that will be performed in GTEx, one possible risk is loss of confidentiality and/or privacy. While this risk is reduced by the absence of individually identifiable health information[32] and by placement of sensitive data types in controlled access in the National Institutes of Health Database of Genotypes and Phenotypes, breaches or misuse by authorized users may still be possible.[33] Since the research project includes genomic data, risk of loss of confidentiality or privacy and possible discrimination apply both to the living therapeutic donor as well as any genetically related family members of either living or deceased therapeutic

donors. Although the Genetic Information Non-discrimination Act prohibits discrimination in employment or health insurance, it does not protect against discrimination in life insurance or long-term care insurance.[34] Third-party risks to relatives generally are not primary factors in IRB review of research. However, IRBs can and should consider risks to third-party subjects in the research,[35] and it is becoming increasingly common to disclose the potential risks for genetically related family members in consent documents for genetic or genomic research.[36] While these risks are likely quite low, the therapeutic donor or next of kin would not have received an explanation of such risks at the time of organ donation.

In addition, the therapeutic donor may have "nonwelfare" interests (i.e., interests that go beyond privacy or other practical concerns) in the types of research conducted with his or her biospecimens and data.[37] Possible nonwelfare interests related to future use of biospecimens include, among others, those concerning moral or religious objections to particular research uses of tissues, group-identity harms, and the distribution of potential benefits.[38] Surveys utilizing hypothetical scenarios have demonstrated an association between moral concerns and decreased willingness to donate to a biobank.[39] The use of biospecimens in secondary research studies has led to lawsuits in cases where donors felt their biospecimens were used against their nonwelfare interests for objectionable research not included in the consent form or the consent process.[40] In the case of GTEx, the project involves both the creation of cell lines as well as distribution of biospecimens to approved researchers for additional research studies.[41] While the next of kin providing authorization for the GTEx project is informed about these aspects of the project, the therapeutic donor whose tissue and genomic material would be studied is not. The fact that both cell lines and additional biospecimens could be studied for years to come for many different scientific purposes increases the risk posed to nonwelfare interests.

The possibility of nonwelfare interests on the part of the therapeutic donor could be compared to the debate over whether gamete donors' consent is required prior to the donation of embryos for human embryonic stem cell research. Although either case could lead to research performed without the original donor's knowledge and consent, in the case of therapeutic donation, the donation's primary purpose was met prior to donation for research. However, donated gametes could be used to create an embryo that is then donated for research without the intent of the donation (i.e., to assist in reproduction) ever having been fulfilled and without the gamete donor's consent. Recent proposals to grant gamete donors "dispositional authorization" or to require explicit informed consent for research from them do not readily translate to the case of therapeutic donation; this is true not only because the primary purpose of the donation (i.e., therapy) was met prior to possible research use but also because the number of organs or tissues utilized in research following transplantation is low and there are additional operational difficulties given that many therapeutic donors may be deceased.[42]

To fully assess the risk-benefit ratio in the context of therapeutic donation, one must also consider the extent of benefit to the donor. In the GTEx project, the inclusion of tissue from the therapeutic donor offers no apparent benefit to the donor. There is clearly no medical benefit, as GTEx would not be able to link any information to a living donor even if useful information were discovered. Moreover, there is relatively little benefit to society in terms of advancing scientific knowledge to include the therapeutic donor tissue in the GTEx study. Since the design of the GTEx project is to study human gene expression and regulation in multiple tissues from a single individual, inclusion of tissue from the therapeutic donor could serve as a confounder. The genomic background for the tissue from the therapeutic donor would differ from that of tissues from the GTEx donor, despite the tissues' purportedly being from the same individual. Since the GTEx project plans to recruit approximately 900 donors and collect over 25,000 tissues, loss of a small subset of tissues would not detract from the scientific validity or power of the study.[43] While inclusion of such tissues could allow for innovative studies related to the effect of organ or tissue transplantation on gene expression within a single individual, GTEx was not designed or powered to address this question, and any conclusions would likely be preliminary based on the small number of individuals who had prior transplants. In sum, the risk-benefit ratio does not favor using the therapeutic donor's tissue in the GTEx project, at least not on beneficence grounds.

Case Outcome

The purpose of the GTEx project is to evaluate the correlation between genotype and gene expression in multiple tissues from a single individual. Since inclusion of the organs and/or tissues from the therapeutic donors could not be supported based on ethical or scientific grounds, NIH staff members unanimously agreed that the tissue should be withdrawn from the GTEx project prior to genomic sequencing analysis and future research use. The approved standard operating procedure for withdrawal of biospecimens was followed once these decisions were made. Study procedures related to eligibility and tissue collection were revised to prevent the collection of tissues from prior therapeutic transplants wherever possible. In addition, procedures were developed to rapidly identify and remove from the biobank any tissues resulting from a prior therapeutic transplant in the event that prior transplant history was unknown at the time of collection.

Discussion

The scenario described in this case study was ethically complex and unanticipated. It must be noted that the ethical analysis was case specific; there could be situations with more favorable risk-benefit ratios. For example, studies more narrowly focused and directly related to organ and/or tissue transplantation might be acceptable in some cases. Such studies might have lower

risks related to nonwelfare interests and breach of confidentiality than a public resource like GTEx and would be more scientifically justifiable if the study required the use of previously transplanted organs.

To date, about 3.8% of GTEx cases were recipients of organs or tissues from human therapeutic donors. These cases might initially seem like rare events, yet they raise important operational issues for research biobanks, as well as ethical issues for IRBs about the right to control future research uses of tissues and data. Biobank collection and withdrawal policies will need to address these issues, and consent forms must be transparent in communicating them. Such policies are particularly important for biobanks or projects involving patient populations with a higher incidence of organ transplants (e.g., diabetics). In some biobanks there is a tendency to collect limited clinical data and/or to anonymize tissues to protect patient privacy and limit regulatory burden. In such cases the data revealing a prior transplant may not be collected by the biobank. The realization that the tissue was from a prior transplant may not occur until analysis is performed and inconsistencies are uncovered, or it may never occur.

Given the complexity of the system governing organ and tissue donation in the United States, more research is warranted to address some of the legal and ethical issues raised by this and related cases. A comparison of state laws related to organ and tissue donation as well as state donor registries may help to elucidate and document some of the most significant differences between states. Qualitative and quantitative data are needed to determine donors' and donor families' attitudes about the custodianship and stewardship of donated organs, and who possesses the right to determine the ultimate use of a donated organ upon the death of the organ recipient. The GTEx project includes a study on the ethical, legal, and social implications (ELSI) of the project and in particular the attitudes of family decision-makers related to the consent process and other aspects of the GTEx project.[44] Projects such as the GTEx ELSI study could shed light on these and other important policy questions pertaining to the ethically appropriate use of postmortem tissue in research in an era when the "-omic" sciences comprise an expanding and significant portion of the federally funded medical research portfolio.

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Human Subjects Protection Statement

The GTEx project involves deceased individuals who are not considered to be human subjects. One biospecimen source site conducted an expedited IRB review, while the second biospecimen source site had its Office for Research Protections review the protocol. In both circumstances, it was determined that the GTEx study is nonhuman subjects research.

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