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Development of a Consensus Approach for Return of Pathology Incidental Findings in the Genotype-Tissue Expression (GTEx) Project

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Contributors:

BB conducted the bioethics consult described in this manuscript. NL, CW, LC, SK, ARL, SV, and HM all participated in the development of the approach to pathology incidental findings described herein. The initial draft of the manuscript was produced by NL, CW and BB with significant contributions from all authors.

Competing Interests:

The authors declare no competing interests with the work described in this manuscript.

Ethics Approval Statement:

This research was reviewed by the University of Pennsylvania Institutional Review Board and the Roswell Park Cancer Institute Review Board. In the United States, deceased individuals are not considered human subjects. However, since the GTEx project involved significant genomic analysis, project-specific authorization was received from the next-of-kin of all deceased donors. All sites collecting biospecimens as part of the GTEx project were required to submit a research protocol to their institutional review board (IRB). Some collection site IRBs chose to undergo full or expedited review, while others determined the research did not constitute human subjects research and did not require further review

Data Sharing Statement:

All clinical and molecular data from the GTEx project are available at either the GTEx Portal <https://www.gtexportal.org/home/> or the NIH database of Genotypes and Phenotypes (dbGaP) <https://www.ncbi.nlm.nih.gov/gap>. Histological images are available at <https://brd.nci.nih.gov/brd/image-search/searchhome>. Standard Operating Procedures for the program including pathology operations are available at <https://biospecimens.cancer.gov/resources/sops/default.asp>.

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Abstract

The active debate about the return of incidental or secondary findings in research has primarily focused on return to research participants, or in some cases, family members. Particular attention has been paid to return of genomic findings. Yet, research may generate other types of findings that warrant consideration for return, including findings related to the pathology of donated biospecimens. In the case of deceased biospecimen donors who are also organ and/or tissue transplant donors, pathology incidental findings may be relevant not to family members, but to potential organ or tissue transplant recipients. This paper will describe the ethical implications of pathology incidental findings in the Genotype-Tissue Expression (GTEx) project, the process for developing a consensus approach as to if/when such findings should be returned, possible implications for other research projects collecting post-mortem tissues, and how the scenario encountered in GTEx fits into the larger return of results/incidental findings debate.

Keywords

Donation/Procurement of Organs/Tissues; Clinical Ethics; Human Tissue; Pathology; Research Ethics

INTRODUCTION

In 2010 the National Institutes of Health (NIH) launched the Genotype-Tissue Expression (GTEx) Project to understand the complex interplay between genetic variation and gene expression in various tissues.(1, 2) The GTEx project collected small samples from an average of 27 different organs and tissues that appeared to be disease-free from each of almost 1000 deceased donors. Each biospecimen was examined by a pathologist prior to sequencing. During this effort, some previously unknown disease processes were discovered. While these findings were unlikely to be relevant to the deceased subjects' families, some GTEx research donors could also be organ or tissue donors. Thus, the GTEx project confronted questions of whether pathology incidental findings could be of possible medical significance to transplant recipients and, if so, whether the benefits of making information about such findings available to the affected parties outweighed any potential harm.

DESCRIPTION OF THE GTEx PROJECT

The GTEx project funded Organ Procurement Organizations (OPOs) and Rapid Autopsy Programs who conducted family decision maker authorization, donor eligibility screening, clinical data collection and biospecimen collection.(3) A board-certified pathologist reviewed a sample of each GTEx biospecimen(4) to validate tissue origin, content, and integrity before further analysis. In some cases, the pathologists observed evidence of a

medical condition that was not reflected in the clinical data for that donor. A minority of these pathology incidental findings indicated serious diseases or infections. It was not clear whether these pathology incidental findings could have clinical implications for organ and tissue transplant recipients. GTEx pathologists felt the return of pathology incidental findings deemed to be clinically relevant to transplant recipients would uphold their duty of care and support their professional ethic. A bioethics consult was requested from the NIH Department of Bioethics to help the program determine a path forward.

DID GTEx HAVE A DUTY TO RESCUE?

Unlike prior discussions about return of incidental findings, the GTEx case involved not whether to return pathology incidental findings to a research participant or a family member, (5–9) but instead to the medical provider for an unrelated transplant recipient. The medical provider and transplant recipient would have no prior relationship, expectation or knowledge about the GTEx project. Without any applicable role-based obligations, NIH considered three questions that are generally employed to analyze whether a duty to rescue exists.(10, 11) First, were the pathology incidental findings generated by GTEx of sufficient clinical significance that they plausibly would provide significant benefit or prevent a significant harm? Second, was GTEx uniquely situated to provide the clinically important information? Finally, to what extent did providing that information pose a burden on the GTEx program, or its participants?

Transplant recipients generally have a very low (0.012%) risk of donor-transmitted malignancies, but a much higher risk (> 10%) when donors have either a history or current evidence of highly aggressive tumors.(12) Further, liver and heart transplants from organ donors with a history of cancer have significantly lower 5-year patient and graft survival.(13) In the first 479 donors, GTEx pathologists identified 12 cases of cancer. Three of these cases generated a clinical concern for transplant recipients because they involved either a hematological malignancy or a high-grade carcinoma with the potential to spread aggressively. At the time the pathologic findings became known, any planned organ transplants would have already occurred and the removal of transplanted organs would be unlikely. However, potential clinical impact included possible changes in monitoring, screening, or treatment. GTEx received informal feedback from transplant surgeons that they would want to know about these types of findings to incorporate this information into their own medical assessments, and to alert the patients and their other providers. While this feedback was obtained informally from a limited number of surgeons, it was consistent with the opinion of the pathologists and other clinicians on the GTEx team. For future transplant recipients of banked tissues, return of pathology incidental findings could lead to additional pathology evaluation prior to transplantation to improve safety outcomes, or those tissues could be discarded. The consensus was that this small subset of cases was sufficiently clinically significant to warrant consideration for return.

Further, GTEx was uniquely positioned to provide this potentially relevant clinical information. The GTEx analysis was beyond the typical assessment performed prior to organ donation.(4) The pathology incidental findings resulted from the analysis of remote organs not involved in the transplant and it is highly unlikely that this information would be

discovered through alternate means. Since GTEx excluded donors with a known history of metastatic cancer or chemotherapy or radiation within two years, the potential malignancy would not be included in the donor's medical history and the OPO would be unaware of any potential risks.(14)

Based on the initial cases reviewed, the number of cases that would qualify for reporting incidental findings was estimated to be quite low, which suggested that the GTEx project and investigators would not be unduly burdened. While the benefit of returning pathology incidental findings remained unclear because of the uncertainty of how these findings would fit within the overall context of screening or management for transplant recipients, the NIH Bioethics Consult Service felt it reasonable to infer from the strong preferences for notification indicated by transplant surgeons and pathologists and oncologists on the GTEx team that the information could potentially be clinically useful. In addition, return of pathology incidental findings could prevent transplantation of banked tissues from donors with previously unknown malignancies or other serious findings.

A duty to disclose these findings could be counterbalanced by considerations related to protecting the confidentiality of organ donors. The GTEx project had a responsibility to ensure that donor confidentiality was protected and that the authorization document was upheld. However, the proposed information to be shared would not divulge any identifiable information. The GTEx authorization document stated that research results would not be shared with the donor's family, but was silent on the issue of return of pathology incidental findings for the care of organ or tissue recipients.(15) GTEx biospecimen collection sites were concerned about the identification of incidental findings outside of a Clinical Laboratory Improvement Amendment (CLIA) certified laboratory and the burden of processing and confirming research results.(16) Since return of deidentified pathology incidental findings would not pose significant risks to the deceased donors or donor families and was not prohibited by the authorization document, and GTEx was in a unique position to provide a significant potential benefit to organ recipients, a process was developed to return a subset of findings.

DEVELOPING AND IMPLEMENTING A CONSENSUS APPROACH

The NIH created the GTEx Incidental Findings Evaluation Group to review the rare cases in which unexpected pathology findings could have a potential adverse impact on organ or tissue transplant recipients. Such cases included malignancy and potential infectious processes unrelated to serology testing. The Evaluation Group consisted of experts in oncology, transplantation medicine, pathology, and bioethics, none of whom were associated with the GTEx project. The GTEx Project Team developed a detailed description of the scope, composition and operation of the Evaluation Group. In cases where the Evaluation Group recommended return of the pathology incidental finding to the biospecimen collection site, the result would first be confirmed in a CLIA-certified laboratory. If the CLIA certified review did not correlate with the result found by the GTEx pathologists, then the Evaluation Group would reevaluate the case and make a final recommendation. The confirmation of all findings in a CLIA-certified laboratory and careful vetting by the

Evaluation Group helped assure the validity of findings and limit the number of returned findings.

DISCUSSION

While return of clinical and research incidental findings is an area of active consideration in such fields as genomics and imaging,(5–9, 17–20) this case highlights the need for a broader perspective. The GTEx case shows how innovative research programs can produce findings that blur the space between research and clinical care and challenge our assumptions about investigators' duties to disclose information that could prevent harm to individuals. As this case demonstrates, such findings could have relevance not only for the research donor but for third parties with significant clinical interest, such as organ or tissue transplant recipients. An important, but unavoidable, limitation of this case is that due to the privacy protections in place, the NIH team does not know the identity of the organ and/or tissue recipients and therefore cannot assess the eventual outcome of return of this information. Further research about the utility of returning incidental findings to organ recipients is warranted.

While the scale of the GTEx biospecimen collection is unique, the research use of biospecimens from post-mortem donors is prevalent in many fields(21, 22) and the proportion of research donors who may also be transplant donors is likely unknown. In addition to post-mortem biospecimen donors, any research project that assesses the pathology of biospecimens should develop policies and processes related to pathology incidental findings or discrepancies in diagnosis that may be discovered.(23) Our experience demonstrates the feasibility of a consensus approach to develop a strategy for novel incidental findings that is both ethically permissible and practicable.

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