

Genotype-Tissue Expression (GTEx) Legacy Specimen Access and Distribution Plan

I. Overview of the collection and the access process.

Purpose

The purpose of this document is to describe the process to be followed to allow researcher access to samples from the Genotype-Tissue Expression (GTEx) collection stored at the Broad Institute (GTEx LDACC, Laboratory, Data Analysis and Coordination Center). This process will be followed when specimens, slides, aliquots and derivatives are requested and the requests are reviewed, granted, and samples are shipped.

This process is applicable to all case-specific materials collected by the GTEx project.

The GTEx collection

The National Institutes of Health (NIH) Common Fund Genotype-Tissue Expression (GTEx) project aims to provide to the scientific community a resource with which to study human gene expression and regulation and its relationship to genetic variation. The project collected and analyzed multiple human tissues from post mortem donors who were also densely genotyped, to assess genetic variation within their genomes. By analyzing global RNA expression within individual tissues and treating the expression levels of genes as quantitative traits, variations in gene expression that are highly correlated with genetic variation were identified as expression quantitative trait loci, or eQTLs.

Correlations between genotype and tissue-specific gene expression levels have helped to identify regions of the genome that influence whether and how much a gene is expressed. GTEx resources will continue to help researchers to understand inherited susceptibility to disease and will be a resource database and tissue bank for many studies in the future.

In addition to primary data and analyses available through NIH's database of Genotypes and Phenotypes (dbGaP) and the GTEx Portal, banked, residual GTEx biospecimens and derivatives (cell lines, DNA, RNA) will be made available to scientists for additional research. The goal of this policy is to facilitate the efficient use of this valuable biospecimen resource. All GTEx samples, whether renewable (e.g. fibroblast and lymphoblastoid cell lines) or non-renewable (e.g. DNA, RNA, Tissues, etc.), are subject to this policy.

The GTEx protected raw datasets can be downloaded from dbGaP here:

(https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000424.v1.p1).

The public, derived and analyzed datasets, along with many data visualization tools, are available on the GTEx Portal (<https://www.gtexportal.org/home/>). Histological images are available both on the GTEx Portal and from the NCI Biospecimen Research Database (<https://brd.nci.nih.gov/brd/image-search/searchhome>). The Standard Operating Procedures

under which the biospecimens were collected are available at <https://biospecimens.cancer.gov/resources/sops/default.asp>.

II. GTEx biospecimens access policy

The residual GTEx biospecimens and derivatives (cell lines, DNA, RNA) are under the custodianship of the Broad Institute of Harvard and MIT. This document governs the processes by which biospecimens and derivatives will be made available to scientists for research.

The GTEx Portal (<https://www.gtexportal.org/home/>) hosts a sample request feature that will trigger the processes for biospecimen requests, approval, and sample distribution.

Requests for access to the GTEx biospecimens will be reviewed by an Access Committee (GTEx-AC). The GTEx-AC will be composed of individuals from the Broad Institute and the NIH, with collective expertise in biology, genomics, proteomics, bioinformatics, statistical analysis, human subjects research, and deep knowledge of the GTEx collections of biospecimen and associated data. The Committee will meet once a month to review requests. The GTEx-AC will have a chair from the Broad Institute and an assigned point of contact from the Broad Institute. Appendix A lists the current members of the GTEx-AC.

The GTEx-AC will consider Institutional Review Board (IRB) issues for researcher requests as well as MTAs. Management of the workflow for request and access will be focused on ensuring timely and appropriate access based on demand. Handling of competing applications will be done on a first come/first serve basis. Once the sample requests are approved, the requestors will be notified, and the samples will be retrieved and prepared for shipment. The receiving party will be contacted to confirm that the shipment can be received and stored appropriately within a specified timeframe. Once the confirmation is received, the samples will be packaged and shipped typically via FedEx Overnight.

Factors that will be considered in evaluating requests for access to GTEx biospecimens include:

- 1) The potential for the project to address an important question/problem or a critical barrier to progress in the field;
- 2) The level of experience and expertise of the investigators to conduct the proposed analyses;
- 3) The degree to which the requested samples are uniquely suited for the proposed study or whether other samples are equally appropriate;
- 4) The degree to which the proposed research takes advantage of existing data associated with the samples;
- 5) The degree to which the quantity of sample requested matches the intended use and the impact on remaining amounts;
- 6) The degree to which the proposed study increases the overall value of the GTEx resource;

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- 7) Whether the proposed research is redundant, complementary, or synergistic to ongoing or past research using the GTEx samples;
- 8) Whether there are sufficient funds to support the proposed research;

Process for Accessing GTEx biospecimens

Step 1 – Request access to GTEx biospecimens

Investigators wishing to access GTEx biospecimens will make a request using the GTEx web portal, answering the following questionnaire:

- 1) Provide a title of the proposed project
 - 2) Describe the proposed use of the biospecimens, including goals of the study, justification for using GTEx specimens over other sources (with reference to the evaluation factors listed above), molecular assay details, statistical analysis plans, etc.
 - 3) Describe the types (DNA, RNA, fixed tissue, paraffin-embedded fixed tissue, frozen tissue, cell lines, etc.), the number of samples, and the amounts (number of nanograms or milligrams, etc.) of material required
 - 4) Describe which tissues are planned for study and how they were selected (e.g. lung, skin, those with associated RNA-Seq data, etc.)
 - 5) Describe how the proposed project will select donors (e.g. age, sex, etc.)
 - 6) Describe how you plan to share the data and resources that are generated, including whether you will share and make the data available and integrated on the GTEx portal
 - 7) Indicate the source of funds to be used to carry out the work
 - 8) Please indicate if your request is for an NIH grant application you plan to submit.
 - 9) Please provide a one paragraph summary of your work to be shared on a website.
- Your request will be made public only when approved and the samples are sent.

Access requests will be accepted on a continuing basis. The GTEx-AC will review each request for completeness and follow up as necessary until all the required information is received.

Step 2 –Review of access requests by the GTEx Access Committee and eligibility criteria for sample access

Once complete, the GTEx-AC will review the request, taking into consideration factors such as the size and scope of the request, whether existing funding is already in place, and whether the proposed use is within scope of an existing grant or contract.

There are at least 4 situations in which requests to access GTEx biospecimens can be expedited:

- 1) Technical feasibility studies that will require $N \leq 24$ of a given sample type and will use $\leq 1/10$ th of the material available.
- 2) Studies involving exclusively renewable resources (e.g., cell lines).
- 3) Studies involving work that is within scope of an existing funded, peer-reviewed grant (NIH R01/U01 or equivalent, e.g. NSF, MRC-UK) or contract. The funded grant or contract does not have to have specified use of GTEx samples in the original application, but the proposed assays must be within scope of the peer reviewed grant and GTEx samples must be an appropriate choice for the given scientific question. The

determination of whether the proposed work is within scope will be determined by the GTEx-AC.

- 4) When seeking a letter of sample availability for an NIH R01 or similar grant application (access to samples will be dependent of outcome of review process)

If a study involves one of the above situations, the requestors will be asked to make this clear in their access request.

More extensive review of access requests may be required in situations where funding is already in place to conduct the proposed study, but one of the above situations does not apply. In these situations, *ad hoc* review by experts outside of the GTEx program may be required.

Access Requests will be reviewed at least once a month by the GTEx-AC, supplemented by additional *ad hoc* reviewers, as required. Decisions are expected within 4 weeks in most cases, with expedited decisions expected within 2 weeks.

After review by the GTEx-AC, the final decision is made about which projects are approved. Investigators will be notified by email of the decision. This decision is final and there is no appeal process. Investigators may submit revised requests.

Step 3 – MTA, cost recovery, and sample shipment

A Material Transfer Agreement (MTA) is required and needs to be in place before delivery of the samples. The current version of the MTA is attached as Appendix B.

No onward transfer shall be permitted; i.e., an approved investigator may not forward GTEx biospecimens and/or derivatives on to other investigators.

Reasonable cost recovery fees may be assessed by the Broad Institute to cover the cost of reviewing requests with investigators, processing approved samples as needed to provide to researchers, and shipping of approved samples.

Requests that involve shipping materials outside of the U.S. at other than ambient temperature (e.g., frozen) will be considered on a case-by-case basis and may not be able to be fulfilled.

Step 4 - Post-shipment requirements

Investigators must follow the data analysis and sharing plan agreed to in their Access Request. A yearly progress report is expected. Continued communications from investigators is important for reporting on the usefulness of the GTEx collection to the research community and to provide a rationale for the continued cost of maintaining and distributing the materials.

GTEx portal sample request feature

The sample request feature on the GTEx portal will allow users to request GTEx samples. This feature will be implemented on the Biobank Search page on the GTEx Portal. Users will be able

to click a checkbox for their desired sample(s), which will place their desired samples in a shopping cart. Users will then be able to review and modify their shopping cart. Once they are satisfied with their sample request, they will be able to submit the request.

Once a sample request has been submitted, the GTEx Portal will create a corresponding sample request in a dedicated issue tracking project, using the software package JIRA. That JIRA project will be used to track the status of each sample request. Each sample request will be monitored by the AC point of contact and the status update and progress of the request will be visible to the requester. If there are any issues with the request (e.g. further clarification is needed, or additional help is required to find appropriate samples), the AC point of contact will reach out via email to discuss.

The workflow for the sample requests is attached as Appendix C. The potential sample status includes (at any given status, further information could be pending):

1. New (i.e. a new request or even a query received)
2. Sample search in progress (this is where we are involved in helping to do the back and forth of the search request with them)
3. In Review (refers to the committee approval)
4. Approved (refers to the committee approval)
5. Rejected/returned for revision (not related to searching but to committee response)
6. Processing
7. Shipped
8. Received (here we should indicate that we received an acknowledgement of the receipt and condition of the samples)

The Broad Institute will configure a JIRA Dashboard for the project to allow the reviewers to easily see an overview of the progress of sample requests.

III. Monitoring of compliance

The Broad Institute, as custodian of the GTEx biospecimens and derivatives, reserves the right to audit the recipient's use of samples as deemed necessary by the Broad Institute. Recipients found to be in breach of the MTA may be denied future access to the collection and their institutions and funders informed.

IV. Withdrawal of consent

GTEx biospecimens were collected from deceased individuals with the written research authorization of family decision makers. If the NIH or the Broad Institute is notified that consent is withdrawn, any affected specimens will be destroyed and will be excluded from a searchable database. Investigators who have already received affected specimens will be asked to destroy the samples and send verification of such to the Broad. Appendix D outlines the Standard Operating Procedure to be followed after notification of withdrawal of consent.

V. Data identifiability and protection of anonymity

As outlined in the MTA

VI. Publication

The recipient investigator and institution will comply with the GTEx policy for publications and presentations, details of which are available on the GTEx Portal.