1.0 PURPOSE

1.1 The purpose of this procedure is to provide a protocol for the uniform histologic analysis of tissue sent to the cancer Human Biobank (caHUB) Pathology Resource Center (PRC) from the Comprehensive Biospecimen Resource (CBR) and generate a Case Summary Report of tissues received.

2.0 SCOPE

2.1 This procedure is applicable to all GTEx tissues that are procured at Biospecimen Source Sites (BSS) and processed at the CBR, whereby digital images, glass slides and DVDs are shipped by the CBR to the PRC for review.

2.2 The procedure applies to all caHUB PRC staff involved in the handling of materials and microscopic interpretation of the tissues for project use. This includes receipt of slides and images, reviewing of slides and images, resolution of issues, managing data collection into CDR, producing a case summary report, final storage, and inventory of slides and images.

2.3 This standard operating procedure (SOP) refers to specimens collected in post mortem, organ donor, and surgical cases.

3.0 RESPONSIBILITY

caHUB Pathologist	American Board of Pathology certified pathologist responsible for histological analysis and annotation of specimens and subsequent notification of results to all relevant parties
Comprehensive Biospecimen Resource (CBR)	Responsible for creating the slides and shipping them to the PRC, creating digital images, and maintaining the image management system.
Contracting Officer Technical Representative (COTR)	Responsible for overall interface and supporting operational issues among BSSs
Director, Pathology	American Board of Pathology certified pathologist responsible for oversight of histologic analysis of specimens and assignment of caHUB pathologists to incoming cases.
Pathology Resource Center (PRC)	Staff or representatives involved in activities for case reviews for the project.
Program Manager	Assigned to lead overall management of program and ensure the procedures and operational connections between parties with responsibilities in this procedure are met.

4.0 ACRONYMS & DEFINITIONS

Aperio	Whole Slide Image system

Bio4D	CBR Inventory Management System
BSS	Biospecimen Source Site
caHUB	cancer Human Biobank
CBR	Comprehensive Biospecimen Resource
CDR	Comprehensive Data Resource
CID	Case Identification Number
CoC	Chain of Custody
COTR	Contracting Officer Technical Representative
CSR	Case Summary Report
DVD	Digital Versatile Disc
IMS	Imaging Management System
LDACC	Laboratory, Data Analysis and Coordinating Center
PDF	Portable Document File
PM	Project Manager
PMT	Project Management Team
PRC	Pathology Resource Center
QA	Quality Assurance
QC	Quality Control
SOP	Standard Operating Procedure
WSI	Whole Slide Image

5.0 ENVIRONMENTAL HEALTH & SAFETY

Not Applicable

6.0 MATERIALS/EQUIPMENT

6.1 Materials provided by caHUB:

- Nikon microscope
- Nikon Camera
- Computer with Internet access
- Slide/DVD storage cabinets
- Secured storage area

6.2 Materials provided by CBR:

- Glass microscope slides
- Digital images
- Web access to digital images from CBR using their image viewer
- DVD with images

6.3 Materials provided by PRC:

- PRC Tissue Review SOP
- Attachments to SOP (TBD Guidance documents)
- caHUB Pathology Resource Center Case Summary Report

6.4 Informatics support provided by CDR

7.0 PROCEDURE

NOTE: CBR receives, processes and generates digital slide images from tissue specimens received from the Biospecimen Source Sites (BSS). Slides and/or images will be ready for PRC review approximately within five (5) working days of tissue receipt at the CBR or within the designated timeframe as approved by the PMT. The CBR assigns a status of "Quarantine/In process" in the inventory management system to indicate that the slides have been processed and have been sent to the PRC for review and images have been made available for viewing in the CBR Image Management System (CBR IMS).

In most cases, whole slide images from stained glass slides will often be available to the PRC before the glass slides are received. This is due to the fact that images may be accessed and reviewed virtually while slides must be sent via a courier service. Images from each case are also copied onto a DVD(s) at the CBR and shipped with the glass slides. This serves as a backup for digital images, if the CBR IMS is unavailable.

When the CBR has a set of images from a case ready for the PRC to review via the CBR IMS, an alert is sent to the PRC team stating that the images are ready and glass slides and DVDs are in process of being shipped. CoC documents are sent with the slides/DVD.

7.1 PRC RECEIPT AND INVENTORY OF SLIDES, DVDS AND IMAGES

7.1.1 The Data Management Team acknowledges the email from the CBR that the images and slides have been made available.

7.1.2 When the slides are received by the PRC, the materials are inventoried into BIO4D by logging into the system and receiving the slides into inventor. This process includes verifying the manifest shipped with the slides and DVDs against what is listed in Bio4D in conjunction with performing a visual check for any damaged slides or DVDs.

7.1.3 PRC representative completes the CoC form that accompanies the shipment and files the information into the GTEx Cases Folder in the designated Shared Drive. The external case ID and barcode ID for each tissue are on the shipping manifest that accompanies the CoC. The slides are inventoried in Bio4D.**NOTE:** DVD's are permanently stored at caHUB with the microscope slides. Archiving and storage will be in a secure, controlled room, limited to approved personnel.

7.1.4 A PRC Pathologist is assigned to review the case by the Director or his delegate.

7.2 Whole Slide Image Review

NOTE: Cases may be reviewed solely based on the WSI Images in the CBR IMS once made available to the PRC from the CBR. DVDs are used if the CBR IMS is unavailable. Please note, DVDs cann**ot** be annotated. Glass slides may be used when WSI or DVDs are insufficient to interpret the case findings completely (see SOP PR-9001 v1.0.0 Operations Manual for caHUB Nikon Microscope).

7.2.1 The pathologist reviews and annotates the images in the CBR IMS, as appropriate. See guidance document, PR-0001-W1 Annotating Digitally Scanned Microscope Slides, regarding annotation.

NOTE: Pathologists review all tissues primarily to confirm the following but not limited to: a) the presence of the intended morphology, b) presence and degree of autolysis, c) presence of pathological findings (for e.g. inflammation, hemorrhage, neoplams), and d) verification of aliquot numbers provided by the CBR.

7.2.2 If issues have been identified, the PRC will work with the relevant parties to ensure complete resolution of issues prior to assigning a final specimen status. Issues may include: requests for recuts for verification, mislabeled slides, broken slides, extraneous tissues, and unexpected findings.

7.2.3 The pathologist can, on request, also assess the suitability of the tissue for further analyses by the CBR, project analysis facilities, and other end users.

7.3 **Pathology Case Summary Report**

7.3.1 All findings and issues identified from the WSI review are documented in the electronic PRC CSR. In instances where the electronic system is unavailable, the paper based PRC CSR may be used and distributed electronically via pdf.

7.3.2 Each tissue reviewed per case is assigned an inventory status on the PRC CSR based on the review. These statuses are implemented at the CBR in the inventory management system and include the following:

7.3.2.1 *Acceptable:* Biospecimens that have been processed by the CBR and reviewed by the PRC and deemed acceptable for quality and for use in the GTEx Project.

7.3.2.2 *Unacceptable:* Biospecimens that have been processed by the CBR, reviewed by the PRC and are deemed unacceptable for GTEx project use.

7.3.2.3 *Quarantine/Issues Pending:* Biospecimens that have been processed by the CBR, reviewed by the PRC and issues have been identified that require resolution.

7.3.2.4 *Invalidated:* a) Biospecimens that have not been consented for by the donor or donor family and have been verified by the data management team (samples may either be destroyed or returned to the BSS per the request of the donor or donor family) OR b) Biospecimens that have been withdrawn by the donor or donor family (samples may either be destroyed or returned to the BSS per the request of the donor or donor family).

7.3.3 Once completed, the PRC releases the PRC CSR to all approved parties to include the BSS that collected the tissues, the CBR and other project approved parties within the designated timeframes.

7.4 **Case Quality Control**

7.4.1 At a minimum, 10% of the images per cases will receive a second review by a second caHUB pathologist (QC pathologist) as a quality control measure. This review takes place after the primary review, but need not be carried out before release of the PRC Case Summary Report.

7.4.2 The QC pathologist provides concurrence or reports any discrepancies on the images reviewed.

7.4.3 The QC pathologist provides signature to the primary PRC CSR, if no issues are reported.

7.4.4 All discrepancies are resolved by the PRC pathology team by reviewing and coming to a mutual agreement on case findings. The PRC Director has final responsibility for the resultion of the problem.

7.4.5 For issues identified and resolved, a revised version of the PRC CSR will be generated to reflect any changes to the original PRC CSR.

7.4.6 If a new PRC CSR is generated, relevant parties, may be notified electronically (automatic alert or email) for their review.

7.5 **ARCHIVAL**

7.5.1 All WSI images will be stored in the CBR IMS and made accessible to the PRC for review.

7.5.2 All glass slides and DVDs will be at the PRC location at caHUB.

7.5.3 PRC Case Summary Reports will be stored within the electronic CDR-DS system (Comprehensive Data Resource for the GTEx Project).

8.0 REFERENCES

None

9.0 ATTACHMENTS

PR-0002-F1, PRC GTEx Case Report Form
PR-0002-F2, PRC GTEx Request for Clarification-Recuts
PR-0001-W1 Annotating Digitally Scanned Microscope Slides
PR-9001 Operations Manual for caHUB Nikon Microscope

APPROVALS		
NAME / TITLE	**SIGNATURE**	**DATE**

INITIATION/REVISION HISTORY			
REV #	**DESCRIPTION OF CHANGE**	**AUTHOR**	**EFFECTIVE DATE**